The stray magnetic fields in Magnetic Resonance Current Density Imaging (MRCDI)

Purpose: MR Current Density Imaging (MRCDI) involves weak current-injection into the head. The resulting magnetic field changes are measured by MRI. Stray fields pose major challenges since these can dominate the fields caused by tissue currents. We analyze the sources and influences of stray fields. Methods: First, we supply validation data for a recently introduced MRCDI method with an unprecedented noise floor of ∼0.1 nT in vivo. Second, we assess the accuracy limit of the method and our corresponding cable current correction in phantoms ensuring high signal-to-noise ratio (SNR). Third, we simulate the influence of stray fields on current flow reconstructions for various realistic experimental set-ups. Fourth, we experimentally determine the physiological field variations. Finally, we explore the consequences of head positioning in an exemplary head coil, since off-center positioning provides space for limiting cable-induced fields. Results: The cable correction method performs well except near the cables. Unless correcting for cable currents, the reconstructed current flow is easily misestimated by up to 45% for a realistic experimental set-up. Stray fields dominating the fields caused by tissue currents can occur, e.g. due to a wire segment 20 cm away from the imaged region, or due to a slight cable misalignment of 3°. The noise is increased by 40% due to physiological factors. Minor patient movements can cause field changes of ∼40 nT. Off-centered head positioning can locally reduce SNR by e.g. 30%. Conclusions: Quantification of stray fields showed that MRCDI requires careful field correction. After cable correction, physiological noise is a limiting factor.
Alginate Trisaccharide Binding Sites on the Surface of β-Lactoglobulin Identified by NMR Spectroscopy: Implications for Molecular Network Formation

β-lactoglobulin (BLG) is a promiscuous protein in terms of ligand interactions, having several binding sites reported for hydrophobic biomolecules such as fatty acids, lipids, and vitamins as well as detergents. BLG also interacts with neutral and an ionic oligo- and polysaccharides for which the binding sites remain to be identified. The multivalency offered by these carbohydrate ligands is expected to facilitate coacervation, an electrostatically driven liquid–liquid phase separation. Using heteronuclear single quantum coherence NMR spectroscopy and monitoring chemical shift perturbations, we observed specific binding sites of modest affinity for alginate oligosaccharides (AOSs) prepared by alginate lyase degradation. Two different AOS binding sites (site 1 and site 2) centered around K75 and K101 were identified for monomeric BLG isoform A (BLGA) at pH 2.65. In contrast, only site 1 around K75 was observed for dimeric BLGA at pH 4.0. The data suggest a pH-dependent mechanism whereby both the BLGA dimer–monomer equilibrium and electrostatic interactions are exploited. This variability allows for control of coacervation and particle formation of BLGA/alginate mixtures via directed polysaccharide bridging of AOS binding sites and has implications for molecular network formation. The results are valuable for design of polyelectrolyte-based BLG particles and coacervates for carrying nutraceuticals and modulating viscosity in dairy products by use of alginites.
Can Transcranial Electrical Stimulation Localize Brain Function?

Transcranial electrical stimulation (TES) uses constant (TDCS) or alternating currents (TACS) to modulate brain activity. Most TES studies apply low-intensity currents through scalp electrodes (<= 2 mA) using bipolar electrode arrangements, producing weak electrical fields in the brain (< 1 V/m). Low-intensity TES has been employed in humans to induce changes in task performance during or after stimulation. In analogy to focal transcranial magnetic stimulation, TES-induced behavioral effects have often been taken as evidence for a causal involvement of the brain region underlying one of the two stimulation electrodes, often referred to as the active electrode. Here, we critically review the utility of bipolar low-intensity TES to localize human brain function. We summarize physiological substrates that constitute peripheral targets for TES and may mediate subliminal or overtly perceived peripheral stimulation during TES. We argue that peripheral co-stimulation may contribute to the behavioral effects of TES and should be controlled for by "sham" TES. We discuss biophysical properties of TES, which need to be considered, if one wishes to make realistic assumptions about which brain regions were preferentially targeted by TES. Using results from electric field calculations, we evaluate the validity of different strategies that have been used for selective spatial targeting. Finally, we comment on the challenge of adjusting the dose of TES considering dose-response relationships between the weak tissue currents and the physiological effects in targeted cortical areas. These considerations call for caution when attributing behavioral effects during or after low-intensity TES studies to a specific brain region and may facilitate the selection of best practices for future TES studies.

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Combined Rapid Injection NMR and Simulation Approach to Probe Redox-Dependent Pathway Control in Living Cells
Dynamicresponse of intracellular reaction cascades to changing environments is a hallmark of living systems. As metabolism is complex, mechanistic models have gained popularity for describing the dynamic response of cellular metabolism and for identifying target genes for engineering. At the same time, the detailed tracking of transient metabolism in living cells on the sub-minute timescale has become amenable using dynamic nuclear polarization enhanced 13C-NMR. Here, we suggest an approach combining in-cell NMR spectroscopy and perturbation experiments and modeling to obtain evidence that the bottlenecks of yeast glycolysis depend on intracellular redox state. In pre-steady-state glycolysis, pathway bottlenecks shift from downstream to upstream reactions within few seconds, consistent with rapid decline in the NAD+/NADH ratio. Simulations using mechanistic models reproduce the experimentally observed response and help identify unforeseen biochemical events. Remaining inaccuracies in the computational models can be identified experimentally.
The combined use of rapid injection NMR spectroscopy and in silico simulations provides a promising method for characterizing cellular reactions with increasing mechanistic detail.

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Compact, low-cost NMR spectrometer and probe for dissolution DNP
The desire for higher magnetic resonance sensitivity has led to the development of multiple home-built and commercial dissolution dynamic nuclear polarization polarizers. The emergence of polarizers capable of variable magnetic field strengths desires a versatile standalone spectrometer and NMR circuit to fulfill detection needs at different frequencies. We present a benchtop NMR spectrometer with duplexer capable of serving high-field solid and liquid state NMR applications up to 450 MHz. A detailed view of the employed probe is discussed. Tuning and matching schemes are investigated yielding and experimentally verifying closed-form equations to estimate nutation frequency for a remotely tuned and matched sample coil.

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Correction of stray magnetic fields caused by cable currents is essential for human in-vivo brain magnetic resonance current density imaging (MRCDI)

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Cryogenic-free dissolution dynamic nuclear polarization polarizer operating at 3.35 T, 6.70 T, and 10.1 T
A novel dissolution dynamic nuclear polarization (dDNP) polarizer platform is presented. The polarizer meets a number of key requirements for in vitro, preclinical, and clinical applications. It uses no liquid cryogens, operates in continuous mode, accommodates a wide range of sample sizes up to and including those required for human studies, and is fully automated. It offers a wide operational window both in terms of magnetic field, up to 10.1 T, and temperature, from room temperature down to 1.3 K. The polarizer delivers a $^{13}$C liquid state polarization for $[^{1-^{13}}$C]pyruvate of 70%. The build-up time constant in the solid state is approximately 1200 s (20 minutes), allowing a sample throughput of at least one sample per hour including sample loading and dissolution. We confirm the previously reported strong field dependence in the range 3.35 to 6.7 T, but see no further increase in polarization when increasing the magnetic field strength to 10.1 T for $[^{1-^{13}}$C]pyruvate and trityl. Using a custom dry magnet, cold head and recondensing, closed-cycle cooling system, combined with a modular DNP probe, and automation and fluid handling systems, we have designed a unique dDNP system with unrivalled flexibility and performance.

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Cryogenic Single and Array Coils for Magnetic Resonance Systems
The annual cost of cancer treatment in the United States of America and the European Union exceed 100 billion euro. Using a combination of magnetic resonance imaging (MRI) and dissolution dynamic nuclear polarization (dDNP) the potential worldwide savings are in the billions of euro annually. To make the techniques clinically viable an essential aspect is the design and implementation of radio frequency (RF) receive hardware optimized for maximal signal-to-noise ratio (SNR). This work investigates three primary topics within receiver hardware for MRI systems utilizing dDNP of $^{13}$C at
Design of a local quasi-distributed tuning and matching circuit for dissolution DNP cross polarization

Dynamic nuclear polarization (DNP) build-up times at low temperature for low-gamma heteronuclei can be unfavorably long and can be accelerated by transfer of polarization from protons. The efficiency of the cross polarization (CP) depends on the B1-field strengths, the pulse sequence chosen for cross polarization and the sample composition. CP experiments rely on high B1-fields, which typically lead to electrical discharge and breakdown in the circuit. This problem is particularly severe in the low pressure helium atmosphere due to easily ionized helium atoms. The purpose of this study is to identify strategies to minimize voltages across components in a tuning and matching circuit of the coil to avoid electrical discharge during CP experiments. Design equations for three tuning and matching network configurations are derived. The results of the study are then used in the design of a single coil double resonance DNP probe operating at 71.8MHz (13C frequency) and 285.5MHz (1H frequency). In the current setup we achieve 28% polarization on 13C in urea with a build-up time of 11.6min with CP compared to 14% and 53min by direct polarization using TEMPO as the radical. Different cross polarization sequences are compared.
Dynamic Imaging of Glucose and Lactate Metabolism by C-13-MRS without Hyperpolarization

Metabolic reprogramming is one of the defining features of cancer and abnormal metabolism is associated with many other pathologies. Molecular imaging techniques capable of detecting such changes have become essential for cancer diagnosis, treatment planning, and surveillance. In particular, $^{18}$F-FDG (fluorodeoxyglucose) PET has emerged as an essential imaging modality for cancer because of its unique ability to detect a disturbed molecular pathway through measurements of glucose uptake. However, FDG-PET has limitations that restrict its usefulness in certain situations and the information gained is limited to glucose uptake only. $^{13}$C magnetic resonance spectroscopy theoretically has certain advantages over FDG-PET, but its inherent low sensitivity has restricted its use mostly to single voxel measurements unless dissolution dynamic nuclear polarization (dDNP) is used to increase the signal, which brings additional complications for clinical use. We show here a new method of imaging glucose metabolism in vivo by MRI chemical shift imaging (CSI) experiments that rely on a simple, robust and efficient, post-processing procedure by the higher dimensional analog of singular value decomposition, tensor decomposition. Using this procedure, we achieve an order of magnitude increase in signal to noise in both DNP and non-hyperpolarized non-localized experiments without sacrificing accuracy. In CSI experiments an approximately 30-fold increase was observed, enough that the glucose to lactate conversion indicative of the Warburg effect can be imaged without hyper-polarization with a time resolution of $12s$ and an overall spatial resolution that compares favorably to $^{18}$F-FDG PET.

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Hyperpolarized $^{13}$C MRI: Path to Clinical Translation in Oncology

This white paper discusses prospects for advancing hyperpolarization technology to better understand cancer metabolism, identify current obstacles to HP (hyperpolarized) $^{13}$C magnetic resonance imaging's (MRI's) widespread clinical use, and provide recommendations for overcoming them. Since the publication of the first NIH white paper on hyperpolarized $^{13}$C MRI in 2011, preclinical studies involving [1-$^{13}$C]pyruvate as well a number of other $^{13}$C labeled metabolic substrates have demonstrated this technology's capacity to provide unique metabolic information. A dose-ranging study of HP [1-$^{13}$C]pyruvate in patients with prostate cancer established safety and feasibility of this technique. Additional studies are ongoing in prostate, brain, breast, liver, cervical, and ovarian cancer. Technology for generating and delivering hyperpolarized agents has evolved, and new MR data acquisition sequences and improved MRI hardware have been developed. It will be important to continue investigation and development of existing and new probes in animal models. Improved polarization technology, efficient radiofrequency coils, and reliable pulse sequences are all important objectives to enable exploration of the technology in healthy control subjects and patient populations. It will be critical to determine how HP $^{13}$C MRI might fill existing needs in current clinical research and practice, and complement existing metabolic imaging modalities. Financial sponsorship and integration of academia, industry, and government efforts will be important factors in translating the technology for clinical research in oncology. This white paper is intended to provide recommendations with this goal in mind.

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MR-skanning til diagnostik af nonalkoholisk fedteoversygdom

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PIN diode driver for NMR and MRI

Designing custom coils for magnetic resonance systems, such as nuclear magnetic resonance (NMR) spectrometers and magnetic resonance imaging (MRI) scanners, often entails using non-standard configurations of the transmit-receive (T/R) switch and Q-spoiling circuits. The built-in drivers of commercial NMR and MRI systems are, typically, only reconfigurable within a narrow application range (if at all). Thus, the built-in driver may not be able to properly control the custom T/R switches and Q-spoiling circuits when using custom built coils. We present a PIN diode driver which functions in both an MRI scanner and NMR spectrometer. The PIN diode driver is based on readily available discrete components and achieves switching times for the reverse and forward bias states (transmit on and off) of 2 μs and 0.4 μs respectively. Hence, this work enables a higher degree of customization of the RF switching circuits in an MR system and is potentially of interest for designers of custom coils for both NMR spectrometers and MRI scanners.

Real-Time Detection of Intermediates in Rhodium Catalyzed Hydrogenation of Alkynes and Alkenes by Dissolution DNP

The hydrogenation of alkynes and alkenes using a Shrock-Osborn catalyst was followed in-situ with dissolution dynamic nuclear polarization (dDNP) NMR. Natural abundance and $^{13}$C labeled dimethyl acetylenedicarboxylate was hyperpolarized prior to hydrogenation using (1,4-bis{diphenylphosphino}butane)(2,5-norbornadiene) rhodium(1) perchlorate, [Rh(NBD)(DPPB)]ClO4. The increased signal-to-noise ratio of dDNP compared to conventional $^{13}$C NMR allowed real-time detection of substrate and products as well as the modeling of the hydrogenation kinetics. The build-up of an intermediate was observed during interruption in hydrogen flow, substantiating the current view of the reaction mechanism. Selective inversion of the carbonyl NMR signal of the substrate was applied to demonstrate unequivocally that the new peak appearing in the spectrum originates from a reaction intermediate. The scope of the dDNP method for following reaction dynamics in real time was further demonstrated by substrate competition experiments.
Core-Shell Structure of Organic Crystalline Nanoparticles Determined by Relayed Dynamic Nuclear Polarization NMR

The structure of crystalline nanoparticles (CNPs) is determined using dynamic nuclear polarization (DNP) enhanced NMR spectroscopy experiments. The CNPs are composed of a crystalline core containing an active pharmaceutical ingredient (compound P), coated with a layer of PEG (DSPE-PEG 5000) located at the crystal surface, in a D$_2$O suspension. Relayed DNP experiments are performed to study $^1$H-$^1$H spin diffusion and to determine the size of the crystalline core as well as the thickness of the PEG overlayer. This is achieved through selective doping to create a heterogeneous system in which the D$_2$O contains glycerol and organic radicals, which act as polarization sources, and the CNPs are exempt of radical molecules. We observe features that are characteristic of a core-shell system: high and constant DNP enhancement for components located in the surrounding radical solution, short build-up times for the PEG layer, and longer build-up times and time dependent enhancements for compound P. By comparing numerical simulations and experimental data, we propose a structural model for the CNPs with a core-shell organization and a high affinity between the radical and the PEG molecules.

Cryogenic Preamplifiers for Magnetic Resonance Imaging

Pursuing the ultimate limit of detection in magnetic resonance imaging (MRI) requires cryogenics to decrease the thermal noise of the electronic circuits. As cryogenic coils for MRI are slowly emerging cryogenic preamplifiers are required to fully exploit their potential. A cryogenic preamplifier operated at 77 K is designed and implemented for C imaging at 3 T (32.13 MHz), using off-the-shelves components. The design is based on a high electron mobility transistor (ATF54143) in a common source configuration. Required auxiliary circuitry for optimal cryogenic preamplifier performance is also presented.
consisting of a voltage regulator (noise free supply voltage and optimal power consumption), switch, and trigger (for active
detuning during transmission to protect the preamplifier). A gain of 18 dB with a noise temperature of 13.7 K is achieved.
Performing imaging experiments in a 3 T scanner showed an 8% increased signal-to-noise ratio from 365 to 399 when
lowering the temperature of the preamplifier from 296 to 77 K while keeping the coil at room temperature. This paper thus
enables the merger of cryogenic coils and preamplifiers in the hopes of reaching the ultimate limit of detection for MRI.

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Radiative MRI Coil Design Using Parasitic Scatterers: MRI Yagi
Conventionally, radiofrequency (RF) coils used for magnetic resonance imaging (MRI) are electrically small and designed
for nearfield operation. Therefore, existing antenna design techniques are mostly irrelevant for RF coils. However, the use
of higher frequencies in ultrahigh field (UHF) MRI allows for antenna design techniques to be adapted to RF coil designs.
This study proposes the use of parasitic scatterers to improve the performance of an existing 7T MRI coil called the single-
sided adapted dipole (SSAD) antenna. The results reveal that scatterers arranged in a Yagi fashion can be applied to
reduce local specific absorption rate (SAR) maxima of a reference SSAD by 40% with only a 6% decrease in the
propagated B1 + field at the tissue depth of 15 cm. The higher directivity of the proposed design also decreasing
the coupling with additional elements, making this antenna suitable for use in high density arrays. These findings show the
potential of parasitic scatterers as an effective method to improve the performance of existing radiative MRI coils.

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3D Hyperpolarized C-13 EPI with Calibrationless Parallel Imaging

With the translation of metabolic MRI with hyperpolarized $^{13}$C agents into the clinic, imaging approaches will require large volumetric FOVs to support clinical applications. Parallel imaging techniques will be crucial to increasing volumetric scan coverage while minimizing RF requirements and temporal resolution. Calibrationless parallel imaging approaches are well-suited for this application because they eliminate the need to acquire coil profile maps or auto-calibration data. In this work, we explored the utility of a calibrationless parallel imaging method (SAKE) and corresponding sampling strategies to accelerate and undersample hyperpolarized $^{13}$C data using 3D blipped EPI acquisitions and multichannel receive coils, and demonstrated its application in a human study of $[1-^{13}$C]pyruvate metabolism.

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3-Fold SNR Enhancement of Small Animal 13C MRI using a Cryogenically Cooled (88 K) RF Coil
SNR in hyperpolarized 13C MRI is often limited by the low sensitivity of the receive RF chain at the low Larmor frequency of 13C. In this study we present an RF transparent (non-metallic) cryostat designed for small animal imaging, which allows a coil temperature of 88 K, with a coil-to-sample distance below 3 mm. Performance of the cryostat equipped with a 30 x 40 mm2 13C surface coil (3 T, 32 MHz) was tested and 3-fold SNR gain over room temperature coil was achieved.

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Accurate Noise Figure Measurements for Highly Mismatched Preamplifiers

A method reducing the uncertainty of noise figure measurements of highly mismatched preamplifiers is presented. In many cases when measuring the noise figure of preamplifiers for MRI receive arrays the uncertainty is approximately ±0.4 dB. Since the noise figure of the preamplifier is also in this range, a more accurate method is needed. Here we show an increase of 59% in noise figure accuracy by adding an attenuator between the noise source and preamplifier.

A comprehensive study of cryogenic cooled millimeter-wave frequency multipliers based on GaAs Schottky-barrier varactors

The benefit of cryogenic cooling on the performance of millimeter-wave GaAs Schottky-barrier varactor-based frequency multipliers has been studied. For this purpose, a dedicated compact model of a GaAs Schottky-barrier varactor using a triple-anode diode stack has been developed for use with a commercial RF and microwave CAD tool. The model implements critical physical phenomena such as thermionic-field emission current transport at cryogenic temperatures, temperature dependent mobility, reverse breakdown, self-heating, and high-field velocity saturation effects. A parallel conduction model is employed in order to include the effect of barrier inhomogeneities which is known to cause deviation from the expected I--V characteristics at cryogenic temperatures. The developed model is shown to accurately fit the I--V - T dataset from 25 to 295 K measured on the varactor diode stack. Harmonic balance simulations using the model are used to predict the efficiency of a millimeter-wave balanced doubler from room to cryogenic temperatures. The estimation is verified experimentally using a 188 GHz balanced doubler cooled down to 77 K. The model has been further verified down to 14 K using a 78 GHz balanced doubler.
Analysis of dDNP NMR metabolic data from cancer cells

With the rise of the field of systems biology, metabolomic data have been integrated with the data for other -omic sciences, and these gigantic collections of correlated data have with the ever improving computing power, been data mined to locate biomarkers and motifs.[1] In this project the metabolic fingerprint of four prostate cancer cell lines, with different levels of aggression were analyzed. Metabolic data were obtained by incubating the cells with 13C6-d7 isotope labeled glucose, then quenching the metabolism, removing the cell debris and hyperpolarizing the metabolite extracts with dissolution Dynamic Nuclear Polarization (dDNP).

By integrating the peaks of the resulting NMR spectra, a collection of metabolic data was obtained without the need for identification of specific compounds. On this data, data mining was applied, with the aim to identify biomarkers of cancer and to classify the aggressiveness of the cancer. The illustrations below show examples of obtained NMR spectra for the different cell types (on the left) and Principal Components-Discriminant Function Analysis (PCDFA) results from the four prostate cancer cell types and a breast cancer cell line, in red, (on the right). The PC-DFA is clearly able to separate the cell types, with the most aggressive clustering together (blue and green). As dDNP MNR have been shown to be quantitative and reproducible,[2] it could be an important tool in the future for cancer diagnostics.

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Analysis of dDNP NMR metabolic data from cancer cells (- poster)

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A narrow line UV-induced non-persistent radical to generate highly polarized transportable glucose solid samples

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Association and Dissociation of Optimal Noise and Input Impedance for Low-Noise Amplifiers

For magnetic resonance imaging (MRI) receive coil arrays, an ideal low-noise amplifier (LNA) is noise matched while exhibiting a high-input reflection coefficient of unity or slightly higher. For this purpose, we present a design approach allowing to manipulate the optimal noise impedance and input impedance. The method is based on noise and S-parameters, hence technology independent. As an example, the method is used to design an LNA for MRI receive coil arrays operating at 32.1 MHz. The design demonstrates the highest coil decoupling published so far of 54 dB. The measured noise figure of 0.44 dB is also better than other published designs. The measured gain is 22 dB with a 1-dB compression point of -14.5 dBm. The power consumption is 81 mW. We expect this method to enable better MRI receive coil array designs resulting in lower examination time and cost due to higher quality images.

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A virtual scanner for teaching fundamental magnetic resonance in biomedical engineering

A virtual scanner for introductory teaching in magnetic resonance imaging in biomedical engineering is presented and evaluated in a randomized trial of ultra-short and short-term learning. The results show similar performance, but indicate high motivation, when compared with a classical approach, when class duration was identical.

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Combined Hyperpolarized $^{13}$C-pyruvate MRS and $^{18}$F-FDG PET (HyperPET) Estimates of Glycolysis in Canine Cancer Patients

$^{13}$C Magnetic Resonance Spectroscopy (MRS) using hyperpolarized $^{13}$C-labeled pyruvate as a substrate offers a measure of pyruvate-lactate interconversion and is thereby a marker of the elevated aerobic glycolysis (Warburg effect) generally exhibited by cancer cells. Here, we aim to compare hyperpolarized $[{1-^{13}}$C$]$pyruvate MRS with simultaneous $^{18}$F-2-fluoro-2-deoxy-D-glucose (FDG) PET in a cross-sectional study of canine cancer patients. Methods: Canine cancer patients underwent integrated PET/MRI using a clinical whole-body system. Hyperpolarized $[{1-^{13}}$C$]$pyruvate was obtained using dissolution-DNP. $^{18}$F-FDG PET, dynamic $^{13}$C MRS, $^{13}$C MRS Imaging (MRSI) and anatomical $^{1}$H MRI was acquired from 17 patients. Apparent pyruvate-to-lactate rate constants were estimated from dynamic $^{13}$C MRS. $^{18}$F-FDG Standard Uptake Values and maximum $[{1-^{13}}$C$]$lactate-to-total-$^{13}$C ratios were obtained from tumor regions of interest. Following inspection of data, patients were grouped according to main cancer type and linear regression between measures of lactate generation and $^{18}$FFDG uptake were tested within groups. Between groups, the same measures were tested for group differences. Results: The main cancer types of the 17 patients were sarcoma (n = 11), carcinoma (n = 5) and mastocytoma (n = 1). Significant correlations between pyruvate-to-lactate rate constants and $^{18}$F-FDG uptake were found for sarcoma patients, whereas no significant correlations appeared for carcinoma patients. The sarcoma patients showed a non-significant trend towards lower $^{18}$F-FDG uptake and higher lactate generation than carcinoma patients. However, the ratio of lactate generation to $^{18}$F-FDG uptake was found to be significantly higher in sarcoma as compared to carcinoma. The results were found both when lactate generation was estimated as an apparent pyruvate-to-lactate rate constant from dynamic $^{13}$C MRS and as an $[{1-^{13}}$C$]$lactate to total-$^{13}$C ratio from $^{13}$C MRSI. Conclusions: A comparison of hyperpolarized $[{1-^{13}}$C$]$pyruvate MRS with simultaneous $^{18}$F-FDG PET indicate that lactate generation and $^{18}$F-FDG uptake in cancers can be related and that their relation depend on cancer type. This finding could be important for the interpretation and eventual clinical implementation of hyperpolarized $^{13}$C. In addition, the differences between the two modalities may allow for better metabolic phenotyping performing hybrid imaging in the form of hyperPET.
of the thesis, dDNP is used to probe slow biochemical reactions in combination with Stable Isotope-Resolved Metabolomics (SIRM). By application of this method, the timeframe of the experiment can be extended from minutes to hours or longer. The dDNP-SIRM approach is applied to investigate early handling of excess fuel in insulin producing β-cells before they reach a glucotoxic state which is a pathogenic factor in type 2 diabetes. Glucose-derived pyruvate is found to correlate with a high fuel burden for the cells and is hypothesized to be a potential biomarker in the development of insulin impairment. In conclusion, this study shows that -cells actively use different metabolic pathways to reduce excess metabolites formed due to uncontrolled glycolysis. Glycerol- and fatty acid metabolism is the most likely candidate for this deviation pathway. Further studies are needed to elucidate this fundamentally important and relatively overlooked defense mechanism important for protecting the -cell against glucotoxicity. In the second part of the thesis, dDNP is applied to study real time kinetics using hyperpolarized [1-13C] pyruvate to visualize metabolism in cancer cells. The biological model represents pancreatic cancer, demonstrated by different cell lines representing various stages of the cancer. For this purpose, a bioreactor with a home-built flow cell was constructed and tested. It was demonstrated that the cells grown on microcarriers showed pyruvate to lactate conversion in the flow cell. Furthermore, the bioreactor was found suitable for longitudinal cell studies over several hours, but also revealed that flow stress is an important limitation for many cell systems on microcarriers.

The third part of the thesis concerns three different bioprobes for novel applications, in vivo and in vitro. The sample formulation and solid-state DNP polarization were optimized for each bioprobe. Biological applications are discussed for each probe, and initial studies were performed to assess potential for hyperpolarization studies. In summary, this thesis shows the versatility of dDNP for metabolic research and potential diagnostic applications demonstrated by the polarization of 13C labeled substrates in vitro.

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**Development of a Symmetric Echo-Planar Spectroscopy Imaging Framework for Hyperpolarized 13C Imaging in a Clinical PET/MR Scanner**
Here, we developed a symmetric echo-planar spectroscopic imaging (EPSI) sequence for hyperpolarized 13C imaging on a clinical hybrid positron emission tomography/magnetic resonance imaging system. The pulse sequence uses parallel reconstruction pipelines to separately reconstruct data from odd-and-even gradient echoes to reduce artifacts from gradient imbalances. The ramp-sampled data in the spatiotemporal frequency space are regridded to compensate for the chemical-shift displacements. Unaliasing of nonoverlapping peaks outside of the sampled spectral width was performed to double the effective spectral width. The sequence was compared with conventional phase-encoded chemical-shift imaging (CSI) in phantoms, and it was evaluated in a canine cancer patient with ameloblastoma after injection of hyperpolarized [1-13C]pyruvate. The relative signal-to-noise ratio of EPSI with respect to CSI was 0.88, which is consistent with the decrease in sampling efficiency due to ramp sampling. Data regridding in the spatiotemporal frequency space significantly reduced spatial blurring compared with direct fast Fourier transform. EPSI captured the spatial distributions of both metabolites and their temporal dynamics in vivo with an in-plane spatial resolution of 5 × 9 mm2 and a temporal resolution of 3 seconds. Significantly higher spatial and temporal resolution for delineating anatomical structures in vivo was achieved for EPSI metabolic maps than for CSI maps, which suffered spatiotemporal blurring. The EPSI sequence showed promising results in terms of short acquisition time and sufficient spectral bandwidth of 500 Hz, allowing to adjust the trade-off between signal-to-noise ratio and encoding speed.

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Discovery of Intermediates of lacZ β-Galactosidase Catalyzed Hydrolysis Using dDNP NMR
Using dissolution dynamic nuclear polarization, the sensitivity of single scan solution state 13C NMR can be improved up to 4 orders of magnitude. In this study, the enzyme lacZ β-galactosidase from Escherichia coli was subjected to hyperpolarized substrate, and previously unknown reaction intermediates were observed, including a 1,1-linked disaccharide. The enzyme is known for making 1,6-transglycosylation, producing products like allolactose, that are also substrates. To analyze the kinetics, a simple kinetic model was developed and used to determine relative transglycosylation and hydrolysis rates of each of the intermediates, and the novel transglycosylation intermediates were determined as better substrates than the 1,6-linked one, explaining their transient nature. These findings suggest that hydrolysis and transglycosylation might be more complex than previously described.

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Dynamic coronary MR angiography in a pig model with hyperpolarized water

To investigate dynamic coronary MR angiography using hyperpolarized water as a positive contrast agent. Hyperpolarization can increase the signal by several orders of magnitude, and has recently been translated to human cardiac application. The aim was to achieve large 1 H signal enhancement to allow high-resolution imaging of the coronary arteries. Protons in D2 O were hyperpolarized by dissolution dynamic nuclear polarization. A total of 18 mL of hyperpolarized water was injected into the coronary arteries of healthy pigs (N=9; 3 injections in 3 animals). The MRI images were acquired with a gradient-echo sequence in an oblique slab covering the main left coronary arteries with 0.55 mm in-plane resolution. The acquisition time was 870 ms per frame. A more than 200-fold signal enhancement compared with thermally polarized water at 3 T was obtained. Coronary angiographic images with a signal-to-noise ratio from the left main stem of 269±169 and coronary sharpness from the proximal left anterior descending coronary artery of 0.31±0.086 mm-1 were obtained. Dynamic images were acquired over a 10 s time window. Hyperpolarized water MR angiography of the coronary arteries in a large animal model with high signal-to-noise ratio and high spatial and temporal resolution was obtained. Magn Reson Med, 2018. © 2018 International Society for Magnetic Resonance in Medicine.

Efficient Hyperpolarization of U-13 C-Glucose Using Narrow-Line UV-Generated Labile Free Radicals

Free radicals generated by UV-light irradiation of a frozen solution containing a fraction of pyruvic acid (PA) have demonstrated their dissolution dynamic nuclear polarization (dDNP) potential, providing up to 30% [1-13C]PA liquid-state polarization. Moreover, their labile nature has proven to pave a way to nuclear polarization storage and transport. Herein, differently from the case of PA, the issue of providing dDNP UV-radical precursors (trimethylpyruvic acid and its methyl-deuterated form) not involved in any metabolic pathway was investigated. The 13C dDNP performance was evaluated for hyperpolarization of [U,13 C6,1,2,3,4,5,6-d7 ]d-glucose. The generated UV-radicals proved to be versatile and highly efficient polarizing agents, providing, after dissolution and transfer (10 s), a 13 C liquid-state polarization of up to 32%.

Logically, this text presents two distinct research articles. The first article focuses on dynamic coronary MR angiography using hyperpolarized water, demonstrating significant signal enhancement for imaging coronary arteries. The second article discusses the efficient hyperpolarization of U-13 C-glucose using UV-generated labile free radicals, showcasing a new method for nuclear polarization with potential applications in magnetic resonance imaging.
Encoding of non-MR Signals in Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is widely used for both clinical and research purposes, and offers non-invasive imaging of tissues within the head and body of patients. Generation of the magnetic resonance (MR) signal relies on the presence of a large, static, main magnetic field, and temporally varying gradient and radio-frequency fields, that typically alternate at kilohertz and megahertz frequencies. During scanning, other signals than the MR signal are often of interest, e.g., biomedical signals from the imaged patient for multi-modal studies, and precise characterization of the scanner’s electromagnetic fields for improving image quality. The static magnetic field, however, prevents having typical measuring equipment in the vicinity of the scanner, and the oscillating fields induce unwanted currents in cabling and transducers, causing artefacts in acquired non-MR signals. Using the scanner to acquire both the MR and the non-MR signals partially alleviates these challenges, as the scanner’s fields are typically not alternating during MR acquisition periods. In addition, this yields a high degree of synchronization between the scanner and the acquisition of the non-MR signals, which for most applications is highly beneficial. Such acquisition is, however, challenged by filters of the scanner attenuating signals with frequencies far from those of the MR signal. This thesis evolves around solving the engineering challenges arising from using an MR scanner for acquisition of non-MR signals. Custom circuitry is presented, which facilitates this through real-time signal processing, and digital synthesis of scanner-recorded signals. The applicability of the circuitry is exemplified by emulation of a point-shaped MR source from real-time measurements of the scanner’s electromagnetic fields. For demanding sequences, reconstruction based on nominal gradient fields, and thereby nominal k-space trajectories, leads to degradation and artefacts in MR images, which can be avoided if the actual k-space trajectory is determined. In a second study, an inductively generated k-space trajectory measure is generated and acquired by an MR scanner concurrently with MRI. Initial results from a solely inductive measure are improved by regularization using a measure of the current driving the gradient field. Minimal artefacts are observed when reconstruction is based on the measured k-space trajectory, and improved image quality compared to reconstructions based on the nominal trajectory is obtained. Lorentz forces induced in generation of the gradient field lead to loud acoustic noises that challenge speech recording in the MR environment. In a third study, an induction-based transducer and amplitude modulation are used to facilitate concurrent MRI and audio sampling. The resulting synchronization between gradient field shifting and speech signal sampling facilitates simple removal of the scanner-induced noise, and audible speech recordings are obtained.
**Gamma-aminobutyric acid edited echo-planar spectroscopic imaging (EPSI) with MEGA-sLASER at 7T**

**Purpose:** For rapid spatial mapping of gamma-aminobutyric acid (GABA) at the increased sensitivity and spectral separation for ultra-high magnetic field strength (7 tesla [T]) an accelerated edited magnetic resonance spectroscopic imaging technique was developed and optimized for the human brain at 7 T.

**Methods:** A MEGA-sLASER sequence was used for GABA editing and volume selection to maximize editing efficiency and minimize chemical shift displacement errors. To accommodate the high bandwidth requirements at 7 T, a single-shot echo planar readout was used for rapid simultaneous encoding of the temporal dimension and 1 spatial. B0 and B1 field aspects specific for 7 T were studied together with correction procedures, and feasibility of the EPSI MEGA-sLASER technique was tested in vivo in 5 healthy subjects.

**Results:** Localized edited spectra could be measured in all subjects giving spatial GABA signal distributions over a central brain region, having 45- to 50-Hz spatial intervoxel B0 field variations and up to 30% B1 field deviations. MEGA editing was found unaffected by the B0 inhomogeneities for the optimized sequence. The correction procedures reduced effects of intervoxel B0 inhomogeneities, corrected for spatial editing efficiency variations, and compensated for GABA resonance phase and frequency shifts from subtle motion and acquisition instabilities. The optimized oscillating echo-planar gradient scheme permitted full spectral acquisition at 7 T and exhibited minimal spectral-spatial ghosting effects for the selected brain region.

**Conclusion:** The EPSI MEGA-sLASER technique was shown to provide time-efficient mapping of regional variations in cerebral GABA in a central volume of interest with spatial B1 and B0 field variations typical for 7 T.

**General information**

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Ideal Coil Decoupling in Receive Arrays using Negative Resistance Preamplifiers

This work presents the method of achieving ideal decoupling between elements in a receive coil array. Generally, preamplifier decoupling is limited by nonidealities of the implemented components. It is shown analytically and numerically, that for the ideal (lossless) matching circuits the input resistance of the preamplifier should be zero, while for the realistic lossy case a small negative resistance can be used to achieve ideal decoupling. Here we use a negative input resistance preamplifier (NIRP) to compensate for the loss of the circuit. The analysis is verified experimentally showing a decoupling of -62 dB when a NIRP with an input resistance of -0.023 ? is used.

Identification of Intracellular and Extracellular Metabolites in Cancer Cells Using 13C Hyperpolarized Ultrafast Laplace NMR

Ultrafast Laplace NMR (UF-LNMR), which is based on the spatial encoding of multidimensional data, enables one to carry out 2D relaxation and diffusion measurements in a single scan. Besides reducing the experiment time to a fraction, it significantly facilitates the use of nuclear spin hyperpolarization to boost experimental sensitivity, because the time-consuming polarization step does not need to be repeated. Here we demonstrate the usability of hyperpolarized UF-LNMR in the context of cell metabolism, by investigating the conversion of pyruvate to lactate in the cultures of mouse 4T1 cancer cells. We show that 13C ultrafast diffusion–T2 relaxation correlation measurements, with the sensitivity enhanced by several orders of magnitude by dissolution dynamic nuclear polarization (D-DNP), allows the determination of the extra- vs intracellular location of metabolites because of their significantly different values of diffusion coefficients and T2 relaxation times. Under the current conditions, pyruvate was located predominantly in the extracellular pool, while lactate remained primarily intracellular. Contrary to the small flip angle diffusion methods reported in the literature, the UF-LNMR method does not require several scans with varying gradient strength, and it provides a combined diffusion and T2 contrast. Furthermore, the ultrafast concept can be extended to various other multidimensional LNMR experiments, which will provide detailed information about the dynamics and exchange processes of cell metabolites.
Improved Decoupling for Low Frequency MRI Arrays using Non-conventional Preamplifier Impedance

Objective: In this study, we describe a method to improve preamplifier decoupling in low frequency MRI receive coil arrays, where sample loading is low and coils exhibit a high Q-factor. Methods: The method relies on the higher decoupling obtained when coils are matched to an impedance higher than 50 Ω. Preamplifiers with inductive (and low resistive) input impedance, increase even further the effectiveness of the method. Results: We show that for poorly sample loaded coils, coupling to other elements in an array is a major source of SNR degradation due to a reduction of the coil Q-factor. An 8-channel 13C array at 32 MHz for imaging of the human head has been designed following this strategy. The improved decoupling even allowed constructing the array without overlapping of neighboring coils. Parallel imaging performance is also evaluated demonstrating a better spatial encoding of the array due to its non-overlapped geometry. Conclusion: The proposed design strategy for coil arrays is beneficial for low frequency coils where the coil thermal noise is dominant. The method has been demonstrated on an 8-channel array for the human head for 13C MRI at 3 T (32 MHz), with almost 2-fold SNR enhancement when compared to a traditional array of similar size and number of elements. Significance: The proposed method is of relevance for low frequency arrays, where sample loading is low, and noise correlation is high due to insufficient coil decoupling.

Integrated B_{1+} Mapping for Hyperpolarized 13C MRI in a Clinical Setup using Multi-Channel Receive Arrays

For hyperpolarized ^{13}C MRI acquisitions aimed at metabolic rate constant estimation, the Bloch-Siegert shift enables encoding of the transmit field (B_{1+}-field) amplitude within a single hyperpolarized substrate injection. This ability is needed since most clinical hyperpolarized MRI studies use inhomogeneous transmit coils, and because kinetic modeling based on incorrect flip angles can lead to incorrect rate constant estimations. This study demonstrates the feasibility of integrated B_{1+} mapping for large volume thermal and hyperpolarized phantoms in a clinical setup using a clamshell transmit coil and a 16-channel receive array, and a 3D stack-of-spirals sequence. Phase-sensitive coil-combination was achieved using
**Kinetic Analysis of Hexose Conversion to Methyl Lactate by Sn Beta: Effects of Substrate Masking and of Water**

Simple sugars bear promise as substrates for the formation of fuels and chemicals using heterogeneous catalysts in alcoholic solvents. Sn-Beta is a particularly well suited catalyst for the cleavage, isomerization and dehydration of sugars into more valuable chemicals. In order to understand these processes and save resources and time by optimising them, kinetic and mechanistic analyses are helpful. Herein, we study substrate entry into the Sn-Beta catalysed methyl lactate process using abundant hexose substrates. NMR spectroscopy is applied to show that the formation of methyl lactate occurs in two kinetic regimes for fructose, glucose and sucrose. The majority of methyl lactate is not formed from the substrate directly, but from methyl fructosides in a slow regime. At 160 °C, more than 40% of substrate carbon are masked (i.e. reversibly protected in situ) as methyl fructosides within few minutes when using hydrothermally synthesised Sn-Beta, while more than 60% methyl fructosides can be produced within few minutes using post synthetically synthesised Sn-Beta. A significant fraction of substrate thus is masked by rapid methyl fructose formation prior to subsequent slow release of fructose. This release is the rate limiting step in the Sn-Beta catalysed methyl lactate process, but can be accelerated by the addition of small amounts of water at the expense of maximum methyl lactate yield.

**Liquid-State Polarization of 30% through Photo-Induced Non-Persistent Radicals on 13C Pyruvic Acid**

Simple sugars bear promise as substrates for the formation of fuels and chemicals using heterogeneous catalysts in alcoholic solvents. Sn-Beta is a particularly well suited catalyst for the cleavage, isomerization and dehydration of sugars into more valuable chemicals. In order to understand these processes and save resources and time by optimising them, kinetic and mechanistic analyses are helpful. Herein, we study substrate entry into the Sn-Beta catalysed methyl lactate process using abundant hexose substrates. NMR spectroscopy is applied to show that the formation of methyl lactate occurs in two kinetic regimes for fructose, glucose and sucrose. The majority of methyl lactate is not formed from the substrate directly, but from methyl fructosides in a slow regime. At 160 °C, more than 40% of substrate carbon are masked (i.e. reversibly protected in situ) as methyl fructosides within few minutes when using hydrothermally synthesised Sn-Beta, while more than 60% methyl fructosides can be produced within few minutes using post synthetically synthesised Sn-Beta. A significant fraction of substrate thus is masked by rapid methyl fructose formation prior to subsequent slow release of fructose. This release is the rate limiting step in the Sn-Beta catalysed methyl lactate process, but can be accelerated by the addition of small amounts of water at the expense of maximum methyl lactate yield.
Liquid-State $^{13}$C Polarization of 30% through Photoinduced Nonpersistent Radicals

Hyperpolarization via dissolutiondynamic nuclear polarization (dDNP) is crucial to significantly increasing the magnetic resonanceimaging (MRI) sensitivity, opening up in vivo real-time MRI using $^{13}$C-labeled substrates. The range of applications, however, is limited by the relatively fast decay of the nuclear spin polarization together with the constraint of having to polarize the spins near the MRI magnet. As recently demonstrated, the employment of UV-induced nonpersistent radicals represents an elegant solution to tackling these drawbacks. Nevertheless, since its introduction, the spread of the technique has been prevented by the relatively low achievable polarization, slow buildup time, and time-consuming sample preparation. In the present work, thanks to a thorough investigation of the radical generation step, we provide a robust protocol to enhance the efficiency and performance of the UV-radical technique. Under optimal conditions, it was possible to produce up to 60 mM radical in less than 5 min and reach maximum DNP enhancement with a buildup time constant of approximately 25 min at 6.7 T and 1 K, resulting in 30% $^{13}$C liquid-state polarization.

Low microwave attenuation and low thermal loss waveguides for dDNP probes

Low microwave attenuation and low thermal loss waveguides for dDNP probes...
**Molecular imaging of tumor photoimmunotherapy: Evidence of photosensitized tumor necrosis and hemodynamic changes**

Near-infrared photoimmunotherapy (NIR PIT) employs the photoabsorbing dye IR700 conjugated to antibodies specific for cell surface epidermal growth factor receptor (EGFR). NIR PIT has shown highly selective cytotoxicity in vitro and in vivo. Cell necrosis is thought to be the main mode of cytotoxicity based mainly on in vitro studies. To better understand the acute effects of NIR PIT, molecular imaging studies were performed to assess its cellular and vascular effects. In addition to in vitro studies for cytotoxicity of NIR PIT, the in vivo tumoricidal effects and hemodynamic changes induced by NIR PIT were evaluated by C-13 MRI using hyperpolarized [1,4-C-13(2)] fumarate, R-2* mapping from T-2*-weighted MRI, and photoacoustic imaging. In vitro studies confirmed that NIR PIT resulted in rapid cell death via membrane damage, with evidence for rapid cell expansion followed by membrane rupture. Following NIR PIT, metabolic MRI using hyperpolarized fumarate showed the production of malate in EGFR-expressing A431 tumor xenografts, providing direct evidence for photosensitized tumor necrosis induced by NIR PIT. R2* mapping studies showed temporal changes in oxygenation, with an accompanying increase of deoxyhemoglobin at the start of light exposure followed by a sustained decrease after cessation of light exposure. This result suggests a rapid decrease of blood flow in EGFR-expressing A431 tumor xenografts, which is supported by the results of the photoacoustic imaging experiments. Our findings suggest NIR PIT mediates necrosis and hemodynamic changes in tumors by photosensitized oxidation pathways and that these imaging modalities, once translated, may be useful in monitoring clinical treatment response.

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**Multichannel Hyperpolarized 13C MRI in a Patient with Liver Metastases using Multi-slice EPI and an Alternating Projection Method for Denoising**

Hyperpolarized 13C-pyruvate for monitoring metabolism of liver metastases in vivo is being investigated for clinical trials of new therapeutics. This study applied advances in multichannel receive arrays and sequence design for human 13C liver imaging and investigated a new denoising method. The method is based on an alternating projection method to enforce structuredness and low-rankness, and is applied with automatic threshold estimation. In vivo data demonstrate improved quality of kinetic modeling after denoising. However, simulations revealed certain unresolved pitfalls.

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Photogenerated Radical in Phenylglyoxylic Acid for in Vivo Hyperpolarized $^{13}$C MR with Photosensitive Metabolic Substrates

Whether for $^{13}$C magnetic resonance studies in chemistry, biochemistry, or biomedicine, hyperpolarization methods based on dynamic nuclear polarization (DNP) have become ubiquitous. DNP requires a source of unpaired electrons, which are commonly added to the sample to be hyperpolarized in the form of stable free radicals. Once polarized, the presence of these radicals is unwanted. These radicals can be replaced by nonpersistent radicals created by the photolysis of pyruvic acid (PA), which are annihilated upon dissolution or thermalization in the solid state. However, since PA is readily metabolized by most cells, its presence may be undesirable for some metabolic studies. In addition, some $^{13}$C substrates are photosensitive and therefore may degrade during the photogeneration of a PA radical, which requires ultraviolet (UV) light. We show here that the photolysis of phenylglyoxylic acid (PhGA) using visible light produces a nonpersistent radical that, in principle, can be used to hyperpolarize any molecule. We compare radical yields in samples containing PA and PhGA upon photolysis with a broadband and narrowband UV–visible light sources. To demonstrate the suitability of PhGA as a radical precursor for DNP, we polarized the gluconeogenic probe $^{13}$C-dihydroxyacetone, which is UV-sensitive, using a commercial 3.35 T DNP polarizer and then injected this into a mouse and followed its metabolism in vivo.

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Probing cardiac metabolism by hyperpolarized $^{13}$C MR using an exclusively endogenous substrate mixture and photoinduced nonpersistent radicals
To probe the cardiac metabolism of carbohydrates and short chain fatty acids simultaneously in vivo following the injection of a hyperpolarized $^{13}$C-labeled substrate mixture prepared using photo-induced nonpersistent radicals. Droplets of mixed [1-$^{13}$C]pyruvic and [1-$^{13}$C]butyric acids were frozen into glassy beads in liquid nitrogen. Ethanol addition was investigated as a means to increase the polarization level. The beads were irradiated with ultraviolet light and the radical concentration was measured by ESR spectroscopy. Following dynamic nuclear polarization in a 7T polarizer, the beads were dissolved, and the radical-free hyperpolarized solution was rapidly transferred into an injection pump located inside a 9.4T scanner. The hyperpolarized solution was injected in healthy rats to measure cardiac metabolism in vivo. Ultraviolet irradiation created nonpersistent radicals in a mixture containing $^{13}$C-labeled pyruvic and butyric acids, and enabled the hyperpolarization of both substrates by dynamic nuclear polarization. Ethanol addition increased the radical concentration from 16 to 26 mM. Liquid-state $^{13}$C polarization was 3% inside the pump at the time of injection, and increased to 5% by addition of ethanol to the substrate mixture prior to ultraviolet irradiation. In the rat heart, the in vivo $^{13}$C signals from lactate, alanine, bicarbonate, and acetylcarnitine were detected following the metabolism of the injected substrate mixture. Copolarization of two different $^{13}$C-labeled substrates and the detection of their myocardial metabolism in vivo was achieved without using persistent radicals. The absence of radicals in the solution containing the hyperpolarized $^{13}$C-substrates may simplify the translation to clinical use, as no radical filtration is required prior to injection.
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Organisations: Center for Hyperpolarization in Magnetic Resonance, Department of Electrical Engineering, Center for Magnetic Resonance, Lausanne University Hospital, Swiss Federal Institute of Technology Lausanne, University of Florida, University of Lausanne
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**Signal to noise comparison of metabolic imaging methods on a clinical 3T MRI**
MRI with hyperpolarized tracers has enabled new diagnostic applications, e.g. metabolic imaging in cancer research. However, the acquisition of the transient, hyperpolarized signal with spatial and frequency resolution requires dedicated imaging methods. Here, we compare three promising candidates for 2D MR spectroscopic imaging (MRSI): (i) multi-echo balanced steady-state free precession (me-bSSFP), (ii) echo planar spectroscopic imaging (EPSI) sequence and (iii) phase-encoded, pulse-acquisition chemical-shift imaging (CSI)

**General information**
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Organisations: Center for Hyperpolarization in Magnetic Resonance, Department of Electrical Engineering, Center for Magnetic Resonance, University of Freiburg, University of Copenhagen, Kiel University
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**Slice-wise motion tracking during simultaneous EEG-fMRI**
Slice-wise motion tracking during combined electroencephalography (EEG) and echo planar imaging (EPI) is developed. Using gradient-induced noise on the EEG for tracking, no interleaved navigator modules or additional hardware is needed. The motion parameters are determined after a calibration and training scan. The method is explored in a phantom and in vivo.

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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Department of Applied Mathematics and Computer Science, Cognitive Systems, Center for Hyperpolarization in Magnetic Resonance, Philips Danmark A/S, Copenhagen University Hospital, Chinese Academy of Sciences
Stable isotope-resolved analysis with quantitative dissolution dynamic nuclear polarization

Metabolite profiles and their isotopomer distributions can be studied non-invasively in complex mixtures with NMR. The advent of dissolution Dynamic Nuclear Polarization (dDNP) and isotope enrichment add sensitivity and resolution to such metabolomic studies. Metabolic pathways and networks can be mapped and quantified if protocols that control and exploit the ex situ signal enhancement are created. We present a sample preparation method, including cell incubation, extraction and signal enhancement, to facilitate reproducible and quantitative dDNP (qdDNP) NMR-based isotope tracer analysis. We further illustrate how qdDNP was applied to gain systematic and novel metabolic phenotypic insights into aggressive cancer cells.

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Ultra-low power transmitter for encoding non-MR signals in Magnetic Resonance (MR) recordings

Advancing Magnetic Resonance Imaging (MRI) technology requires integration of the MRI scanners with sensors and systems for monitoring various non-MRI signals. In this paper, we present design and integration of a low power AM radio transmitter into a 3T MRI scanner, which can be used for efficient collection of data from non-MRI sensors. The transmitter consumes only 1.3mW while transmitting 2.7µW at 120MHz with high frequency stability. The presented design is useful in low power applications requiring high frequency stability and is intended for wireless transmission of non-MR signal recordings during MRI scanning.

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Organisations: Center for Hyperpolarization in Magnetic Resonance, Department of Electrical Engineering, Center for Magnetic Resonance, Electromagnetic Systems
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Versatile polarizer NMR spectrometer

General information
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Organisations: Department of Health Technology, Center for Magnetic Resonance, Department of Electrical Engineering, Electromagnetic Systems, Center for Hyperpolarization in Magnetic Resonance
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A cryogenic measurement setup for characterization microwave devices

A cryogenic measurement setup for characterization microwave devices from room to cryogenic temperatures is presented. The setup allows testing microwave devices at variable temperatures ranging from 300 to 77 K. Frequency doubler (94/188 GHz) has been cooled to 77 K and peak efficiency of 32% at an input-power level of 207 mW is achieved. For verification experimental results the millimeter-wave GaAs Schottky barrier diode model is developed for CAD simulator. The simulated peak efficiency is 37% at 77 K. The estimation of simulated and measured data of the doubler efficiency versus temperature has the same trend from 77 to 300 K which confirmed the cryogenic measurement setup applicability.

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Contributors: Rybalko, O.
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A microwave window for K band electromagnetic systems

This article proposes a solution for microwave window at K band. Properties of the window such as performance (transparency) at microwave frequencies, dimensions, and mounting place are discussed. The dimensions of the window were optimized in a full-wave simulator. To verify the design and simulation results the prototype of the window is realized.
by implementing into transition section and tested experimentally. The microwave window provides low return loss \(|S11|\) below −30 dB, low insertion loss \(|S21|\) below −0.5 dB and can be used for electromagnetic systems where vacuum sealing is required. © 2017 Wiley Periodicals, Inc.
[13C]alanine levels, indicating an intact glucose-alanine cycle, or [13C]bicarbonate, indicating normal flux through the Krebs cycle. In conclusion, this study demonstrates that diabetes-induced pseudohypoxia, as indicated by an increased lactate-to-pyruvate ratio, is significantly attenuated by antioxidant treatment. This demonstrates a pivotal role of oxidative stress in renal metabolic alterations occurring in early diabetes.
Detecting Elusive Intermediates in Carbohydrate Conversion: A Dynamic Ensemble of Acyclic Glucose-Catalyst Complexes

The role of acyclic carbohydrates in pathways towards value-added chemicals has remained poorly characterized due to the low population of acyclic forms, and due to their instability under reaction conditions. We conduct steady-state and pre-steady state measurements by direct reaction progress monitoring with sensitivity-optimized NMR spectroscopy in the molybdate-catalyzed epimerization of glucose to mannose. We detect an exchanging pool of at least five acyclic glucose-catalyst complexes under near-optimum reaction conditions. In the presence of catalyst, the acyclic glucose population increases within few seconds prior to reaching a steady state. Exchange between the acyclic intermediates increases at conditions that favor epimerization. Species accounting for less than 0.05% of total glucose can be monitored with sub-second time resolution to allow kinetic analysis of intermediate formation and catalytic conversion. Epimerization occurs 2-3 orders of magnitude-fold faster than the binding of acyclic glucose to the catalyst at near-optimum reaction conditions. The current study brings insight in to the nature of acyclic intermediate-catalyst complexes of very low population and into experimental strategies for characterizing very minor intermediates in carbohydrate conversion to value-added compounds.
DNP NMR of carbohydrate converting enzymes

Dissolution dynamic nuclear polarization (DNP) NMR can be used to increase the sensitivity of $^{13}$C NMR signal by up to four orders of magnitude. This allows for real time monitoring of reactions and observation of intermediates. The biggest drawback of the method is the loss of polarization with $T_1$ relaxation, but even with this limitation, it is possible to obtain detailed reaction parameters in less than one minute. The enzyme investigated was β-galactosidase from E. coli (E.C. 3.2.1.23). It is well described and the mechanism is generally accepted to be a double displacement with a covalently bound intermediate, however, this evidence is based on mutant of X-ray crystallography and simulations. As the natural substrate lactose does not have any quaternary carbon with long $T_1$, the unnatural substrate o-nitrophenyl β-D-galactopyranoside was used (figure 1) as the quaternary positions have $T_1$ relaxations of ca. 15 s instead of <2 s. The DNP NMR monitoring of the hydrolysis of this substrate can be seen in figure 2, and another use of this substrate is for optimizing the conditions for a labelled substrate (figure 1), which would further increase the signal and allow monitoring of the carbohydrate instead of the aglycon. This is, however, not commercially available and had to be synthesized from doubly labelled galactose.
Effect of a treat-to-target strategy based on methotrexate and intra-articular betamethasone with or without additional cyclosporin on MRI-assessed synovitis, osteitis, tenosynovitis, bone erosion, and joint space narrowing in early rheumatoid arthritis: results from a 2-year randomized double-blind placebo-controlled trial (CIMESTRA)

Objectives: To investigate whether a treat-to-target strategy based on methotrexate (MTX) and intra-articular (IA) betamethasone suppresses magnetic resonance imaging (MRI)-determined measures of disease activity and reduces joint destruction in early rheumatoid arthritis (eRA) patients, and to investigate whether concomitant cyclosporin A (CyA) provides an additional effect.

Method: In the 2-year randomized, double-blind, treat-to-target trial CIMESTRA, 160 patients with eRA (<6 months) were randomized to MTX, intra-articular betamethasone and CyA, or placebo CyA. A total of 129 patients participated in the MRI substudy, and had contrast-enhanced MR images of the non-dominant hand at months 0, 6, 12, and 24. MR images were evaluated for osteitis, synovitis, tenosynovitis, bone erosion, and joint space narrowing (JSN), using validated scoring methods.

Results: Significant reductions were seen at 6 months in all inflammatory parameters [synovitis, mean change -1.6 (p...
Forming of space charge wave with broad frequency spectrum in helical relativistic two-stream electron beams: Paper

We elaborate a quadratic nonlinear theory of plural interactions of growing space charge wave (SCW) harmonics during the development of the two-stream instability in helical relativistic electron beams. It is found that in helical two-stream electron beams the growth rate of the two-stream instability increases with the beam entrance angle. An SCW with the broad frequency spectrum, in which higher harmonics have higher amplitudes, forms when the frequency of the first SCW harmonic is much less than the critical frequency of the two-stream instability. For helical electron beams the spectrum expands with the increase of the beam entrance angle. Moreover, we obtain that utilizing helical electron beams in multiharmonic two-stream superheterodyne free-electron lasers leads to the improvement of their amplification characteristics, the frequency spectrum broadening in multiharmonic signal generation mode, and the reduction of the overall system dimensions.

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Organisations: Center for Hyperpolarization in Magnetic Resonance, Department of Electrical Engineering, Center for Magnetic Resonance, Sumy State University
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Renal ischemia/reperfusion injury (IRI) is a leading cause of acute kidney injury (AKI), and at present, there is a lack of reliable biomarkers that can diagnose AKI and measure early progression because the commonly used methods cannot evaluate single-kidney IRI. Hyperpolarized \([1,4-C \text{-}^{13}(2)]\) fumarate conversion to \([1,4-C \text{-}^{13}(2)]\) malate by fumarase has been proposed as a measure of necrosis in rat tumor models and in chemically induced AKI rats. Here we show that the degradation of cell membranes in connection with necrosis leads to elevated fumarase activity in plasma and urine and secondly that hyperpolarized \([1,4-C \text{-}^{13}(2)]\) malate production 24 h after reperfusion correlates with renal necrosis in a 40-min unilateral ischemic rat model. Fumarase activity screening on bio-fluids can detect injury severity, in bilateral as well as unilateral AKI models, differentiating moderate and severe AKI as well as short-and long-term AKI. Furthermore after verification of renal injury by bio-fluid analysis the precise injury location can be monitored by in vivo measurements of the fumarase activity non-invasively by hyperpolarized \([1,4-C \text{-}^{13}]\) fumarate MR imaging. The combined in vitro and in vivo biomarker of AKI responds to the essential requirements for a new reliable biomarker of AKI.
GABA-edited echo-planar spectroscopic imaging (EPSI) with MEGA-sLASER at 7T

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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Center for Hyperpolarization in Magnetic Resonance, Copenhagen University Hospital
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Gradient distortions in EEG provide motion tracking during simultaneous EEG-fMRI
Conference abstract, selected for oral presentation by Malte Laustsen.

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Contributors: Laustsen, M., Andersen, M., Madsen, K. H., Hanson, L. G.
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Hyperpolarized $^{133}$Cs is a sensitive probe for real-time monitoring of biophysical environments

$^{133}$Cs NMR is a valuable tool for non-invasive analysis of biological systems, where chemical shift and relaxation properties report on changes in the physical environment. Hyperpolarization can increase the liquid-state $^{133}$Cs NMR signal by several orders of magnitude and allow real-time monitoring of physical changes in cell based systems.

**Hyperpolarized Water Perfusion in the Porcine Brain – a Pilot Study**

Dynamic Contrast-Enhanced MR (DCE-MR) perfusion assessment with gadolinium contrast agents is currently the most widely used cerebral perfusion MR method. Hyperpolarized water has recently been shown to succeed $^{13}$C probes as angiography probe. In this study, we demonstrate the feasibility of hyperpolarized water for visualizing the brain vasculature of a large animal in a clinically relevant setting. In detail, reference perfusion values were obtained and large to small arteries could be identified.
Hyperpolarized xenon by d-DNP using the clinical GE SpinLab polarizer system

Hyperpolarized (HP) 129Xe have been demonstrated as a useful probe for magnetic resonance (MR) lung imaging and show promise for in vivo perfusion imaging and brown adipose tissue characterization. Reports of large polarization enhancements for 129Xe using dynamic nuclear polarization (DNP) have raised expectations that DNP can be an alternative to the standard spin exchange optical pumping (SEOP) method. We show that it is possible to produce HP 129Xe gas using the clinical GE SpinLab polarizer, thus extending the practical use of the system beyond the primary purpose of hyperpolarizing liquid biomolecules.

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Organisations: Center for Hyperpolarization in Magnetic Resonance, Department of Electrical Engineering, Center for Magnetic Resonance, Aarhus University
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Imaging regional metabolic changes in the ischemic rat heart in vivo using hyperpolarized(1-13C)Pyruvate

We evaluated the use of hyperpolarized 13C magnetic resonance imaging (MRI) in an open-chest rat model of myocardial infarction to image regional changes in myocardial metabolism. In total, 10 rats were examined before and after 30 minutes of occlusion of the left anterior descending coronary artery using hyperpolarized [1-13C]pyruvate. Cardiac metabolic images of [1-13C]pyruvate and its metabolites [1-13C]lactate, [1-13C]alanine, and [13C]bicarbonate were obtained before and after ischemia. Significant reduction in the [1-13C]alanine and [1-13C]lactate signals were observed in the ischemic region post ischemia. The severity of the ischemic insult was verified by increased blood levels of troponin I and by using late contrast-enhanced MRI that showed enhanced signal in the ischemic region. This study shows that hyperpolarized MRI can be used to image regional metabolic changes in the in vivo rat heart in an open-chest model of ischemia reperfusion. Hyperpolarized MRI enables new possibilities for evaluating changes in cardiac metabolism noninvasively and in real time, which potentially could be used for research to evaluate new treatments and metabolic interventions for myocardial ischemia and to apply knowledge to future application of the technique in humans.

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This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
**Improved Decoupling for 13C coil Arrays Using Non-Conventional Matching and Preamplifier Impedance**

In this study, we describe a method to obtain improved preamplifier decoupling for receive-only coils. The method relies on the better decoupling obtained when coils are matched to an impedance higher than 50. Preamplifiers with inductive imaginary impedance and low real impedance, increase the effectiveness of the decoupling. A 2-channel 13C array of 50 mm loop coils show an increase of Q-factor of the coils from 247 to 365. The measured SNR, using two small phantoms, demonstrated a similar improvement.

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**Improved reconstruction for IDEAL spiral CSI**

In this study we demonstrate how reconstruction for IDEAL spiral CSI (spectroscopic imaging scheme developed for hyperpolarized dynamic metabolic MR imaging) can be improved by using regularization with a sparsity constraint. By exploiting sparsity of the spectral domain, IDEAL spiral CSI can achieve chemical shift encoding by acquisition of only few time-shifted echoes. The minimum number of echoes required to avoid noise amplification can be decreased by means of regularization enforcing spectral sparsity, hereby reducing scan time. Improvements achieved by using regularized reconstruction are demonstrated for in vivo data from a hyperpolarized cardiac study of a pig.

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Contributors: Hansen, R. B., Mariager, C., Laustsen, G., Schulte, R. F., Ardenkjær-Larsen, J. H., Hanson, L. G.
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**Low conversion loss 94 GHz and 188 GHz doublers in InP DHBT technology**

An Indium Phosphide (InP) Double Heterostructure Bipolar Transistor (DHBT) process has been utilized to design two doublers to cover the 94 GHz and 188 GHz bands. The 94 GHz doubler employs 4-finger DHBTs and provides conversion loss of 2 dB. A maximum output power of nearly 3 dBm is measured while the doubler is not entirely saturated. The DC power consumption is 132 mW. The 188 GHz doubler utilizes a 1-finger DHBT. Conversion loss of 2 dB and a maximum output power of ~1 dBm are achieved at 188 GHz with on-wafer measurements. The DC power consumption is 24 mW under saturated conditions. Both doublers operate over a broad bandwidth. The total circuit area of each chip is 1.41 mm².
Low cost, compact, two-channel NMR spectrometer for CP-DNP

Low-Noise Active Decoupling Circuit and its Application to 13C Cryogenic RF Coils at 3T
Low RF-field strength cross polarization combined with photo-induced non-persistent radicals for clinically applicable dDNP

Mary had a little Lamb: Scanner-recorded speech during MRI without gradient-induced sound

Measuring glucose cerebral metabolism in the healthy mouse using hyperpolarized C-13 magnetic resonance

The mammalian brain relies primarily on glucose as a fuel to meet its high metabolic demand. Among the various techniques used to study cerebral metabolism, C-13 magnetic resonance spectroscopy (MRS) allows following the fate of C-13-enriched substrates through metabolic pathways. We herein demonstrate that it is possible to measure cerebral glucose metabolism in vivo with sub-second time resolution using hyperpolarized C-13 MRS. In particular, the dynamic C-13-labeling of pyruvate and lactate formed from C-13-glucose was observed in real time. An ad-hoc synthesis to produce [2,3,4,6,6-H-2(5), 3,4-C-13(2)]-D-glucose was developed to improve the 13C signal-to-noise ratio as compared to experiments performed following [U-H-2(7), U-C-13]-D-glucose injections. The main advantage of only labeling C3 and C4 positions is the absence of C-13-C-13 coupling in all downstream metabolic products after glucose is split into 3-carbon intermediates by aldolase. This unique method allows direct detection of glycolysis in vivo in the healthy brain in a noninvasive manner.
Microstrip Resonator for High Field MRI with Capacitor-Segmented Strip and Ground Plane

High field MRI coils are often based on transmission line resonators. Due to relatively short wavelength of RF fields, such coils produce uneven field patterns. Here we show, that it is possible to manipulate magnetic field patterns of microstrip resonators in both planes (sagittal and transverse) segmenting stripe and ground plane of the resonator with series capacitors. The design equations for capacitors providing symmetric current distribution are derived. The performance of two types of segmented resonators are investigated experimentally. To authors’ knowledge, a microstrip resonator, where both, strip and ground plane are capacitor-segmented, is shown here for the first time.

Monitoring Cancer Response to Treatment with Hyperpolarized $^{13}$C MRS

Monitoring the cancer response to treatment, non-invasively, by medical imaging is a key element in the management of cancer. For patients undergoing treatment, it is crucial to determine responders from non-responders in order to guide treatment decisions. Currently, PET is the most widely used technique for imaging tumor function by measuring the uptake of the glucose analogue FDG. FDG-PET can visualize changes in metabolic activity and indicate if a patient will respond to a particular therapy, sometimes within hours of the first treatment. However, PET is not effective in all tumor types, and the patient is exposed to ionizing radiation. The introduction of hyperpolarized $^{13}$C MRS has opened completely new possibilities to study the biochemical changes in disease processes. Numerous $^{13}$C-labeled compounds were proposed to interrogate various aspects of cancer cell metabolism. The aim of this study is to investigate the relevance of $[1-^{13}$C]pyruvate and $[1,4-^{13}$C$_2$]fumarate in monitoring the changes in cellular metabolism and necrosis that may occur as a result of cancer therapy. This project also aims to improve existing $^{13}$C MRSI methods to efficiently utilize the signal from hyperpolarized 13C substrates. Firstly, we investigate the effectiveness of hyperpolarized $[1-13]$Cpyruvate in detecting the
treatment response in two types of NSCLC xenografted in mice, in comparison with FDG- and FLT-PET. We show here a significant reduction in tumor lactate levels, obtained by MRS, in HCC-827 tumors, as well as lower FLT- and FDG-PET uptake with erlotinib treatment. These findings were validated ex vivo, where LDH activity level and Ki-67 IHC staining was significantly lower in treated HCC-827 tumors. Furthermore, the reduction in LDH activity levels correlated with the lactate levels found using 13C MRS. These findings indicate the hyperpolarized [1-13C]pyruvate can be an alternative to FDG-PET.

In the second study, a polarization scheme for [1,4-13C2]fumarate in the SPINlab polarizer is presented. The feasibility of using [1,4-13C2]fumarate as marker for monitoring induced necrosis is demonstrated in vivo in two rat models; ischemia/reperfusion induced necrosis in kidneys and turpentine induced necrosis in muscle. High polarization was achieved for [1,4-13C2]fumarate in the SPIN lab and high [1,4-13C2]malate signal was observed from the necrotic tissue in both models. The elevated malate signal observed in the ischemia/reperfusion induced injury in kidney showed high correlation with well-known blood and urine bio-markers used to characterize acute kidney injuries. Moreover, simultaneous assessment of metabolism and necrosis was achieved using dual polarization of [1,4-13C2]fumarate and [1-13C]pyruvate. Finally, a symmetric echo planar spectroscopic imaging sequence for hyperpolarized 13C spectroscopic acquisition in clinical scanners is presented with a reconstruction algorithm that separately reconstruct the data from odd and even echoes in order to reduce artifacts from gradient imbalances. The reconstruction algorithm employs re-gridding in the spatio-temporal frequency space to compensate for the chemical shift displacements. The sequence is compared with conventional phase-encoded chemical shift imaging on a clinical PET/MRI system in phantoms and a large animal model. The SNR per unit time of EPSI for 13C at thermal equilibrium was comparable to CSI. The reconstruction pipeline improved the localization compared to direct FFT, which resulted in spatial blurring. The encoding speed of EPSI allowed dynamic imaging of tumor metabolism with high spatial and temporal resolutions and reduced blurring due to T1 decay.

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MRI
This chapter discusses principles of nuclear magnetic resonance (NMR) and MRI followed by a survey on the major classes of MRI contrast agents (CA), their modes of action, and some of the most significative applications. The two more established classes of MRI-CA are represented by paramagnetic metal complexes (i.e., Gd(III) and Mn(II)) and iron oxide particles, acting on T1 and T2* of the water protons signals, respectively. Along the years many efforts have been devoted to endow these relaxation enhancement agents with improved sensitivity, targeting, and responsive properties that have markedly broadened the range of applications in respect to the clinically used systems. CEST agents represent innovative frequency-encoding probes that yield negative contrast in the MR images upon transfer of saturated magnetization from the agent to the “bulk” water signal. Interesting developments have been attained that markedly increase the number and topology of systems with CEST properties. Currently much attention is also devoted to hyperpolarized molecules that display a sensitivity enhancement sufficient for their direct exploitation for the formation of the MR image. A real breakthrough is provided by the use of molecules (such as pyruvate) that report about the cellular metabolism, thanks to the maintenance of the hyperpolarization in the derived species.

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Editors: Kiessling, F., Pichler, B. J., Hauff, P.
Non-Cartesian Parallel Imaging Reconstruction of Undersampled IDEAL Spiral 13C CSI Data
The short-lived nature of hyperpolarization places high demands on signal acquisition. To acquire large FOVs with high spatial resolution, and to fully capture substrate uptake and metabolic conversion, fast data acquisition is crucial. Parallel imaging uses multi-channel coils to achieve reduced scan times based on spatial information inherent to each coil element. In this work, we explored the combination of non-cartesian parallel imaging reconstruction and spatially undersampled IDEAL spiral CSI1 acquisition for efficient encoding of multiple chemical shifts within a large FOV with high spatial resolution.

Plural three-wave resonances of space charge wave harmonics in transit section of klystron-type two-stream FEL with helical electron beam
We have carried out the research of plural three-wave resonances of space charge wave (SCW) harmonics in the transit section of the klystron type two-stream superheterodyne free-electron laser (TSFEL) with helical electron beam in cubic non-linear approximation. We have found out that two-stream instability critical frequency increases with increasing of two-stream electron beam input angle in the focusing longitudinal magnetic field. Due to this fact, the frequency domain in which plural three-wave parametric resonances of SCW harmonics take place increases. The two-stream instability growth rate also increases in helical electron beams with increasing of the beam input angle. Therefore, the saturation lengths in TSFELs with helical electron beams are shorter compared to TSFELs utilizing straight electron beams. We have shown that SCWs with broad frequency spectrum form in two-velocity helical relativistic electron beam due to plural three-wave parametric resonances. We have demonstrated that klystron-type TSFEL with helical electron beam can be used as a source of powerful multiharmonic electromagnetic waves in millimeter-infrared wavelength ranges.
Practical Aspects of Preamplifier Designs for $^{13}$C Imaging.

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Preparation of Radical-Free Hyperpolarized Water using Photo-induced non-persistent Radicals on a "SpinLab-like" dissolution-DNP Polarizer

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Probing of biochemical pathways in clonal pancreatic $\beta$-cells by quantitative dDNP of metabolite extracts

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Organisations: Department of Electrical Engineering, Center for Hyperpolarization in Magnetic Resonance, University of Copenhagen
Contributors: Malinowski, R. M., Ghiasi, S. M., Mandrup-Poulsen, T., Jensen, P. R., Ardenkjær-Larsen, J. H.
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Quantifying Biochemical Activities in Living Cells with $^{13}$C dDNP NMR

General information
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Renal MR angiography and perfusion in the pig using hyperpolarized water

Purpose: To study hyperpolarized water as an angiography and perfusion tracer in a large animal model.

Methods: Protons dissolved in deuterium oxide (D2O) were hyperpolarized in a SPINlab dissolution dynamic nuclear polarization (dDNP) polarizer and subsequently investigated in vivo in a pig model at 3 Tesla (T). Approximately 15 mL of hyperpolarized water was injected in the renal artery by hand over 4–5 s.

Results: A liquid state polarization of 5.3 ± 0.9% of 3.8 M protons in 15 mL of deuterium oxide was achieved with a T1 of 24 ± 1 s. This allowed injection through an arterial catheter into the renal artery and subsequently high-contrast imaging of the entire kidney parenchyma over several seconds. The dynamic images allow quantification of tissue perfusion, with mean cortical perfusion of 504 ± 123 mL/100 mL/min.

Conclusion: Hyperpolarized water MR imaging was successfully demonstrated as a renal angiography and perfusion method. Quantitative perfusion maps of the kidney were obtained in agreement with literature and control experiments with gadolinium contrast.
with a chemical shift imaging sequence (16 × 16) with a resolution of 3.1 × 5.0 × 25.0 mm³. The 13 C spectroscopic images were acquired in 12 s, followed by an 8-min 18 F-2-fluoro-2-deoxy-d-glucose (18 F-FDG) PET acquisition with a resolution of 3.5 mm. \[1,4-13 \text{C}_2\text{] Malate was observed from the tissue injected with turpentine indicating necrosis. Normal [1-13 C]pyruvate metabolism and 18 F-FDG uptake were observed from the same tissue. The proposed co-polarization scheme provides a means to utilize multiple imaging agents simultaneously, and thus to probe various metabolic pathways in a single examination. Moreover, it demonstrates the feasibility of small animal research on a clinical PET/MR scanner for combined PET and hyperpolarized metabolic MR.

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**Towards new vistas in preamplifier design for MRI**
High signal to noise ratio (SNR) in magnetic resonance imaging is vital for ensuring accurate diagnosis and treatment. Arrays of surface coils for receive only purposes is a well established way to increase SNR. However, due to crosstalk between the array elements, the SNR can be severely degraded. For that reason, arrays often do not exploit their full potential. By using a series decoupling network with non-conventional matching and preamplifier impedances the decoupling between elements can be increased significantly. In the presented design example, almost 6 dB additional decoupling can be achieved with no impairment of preamplifier noise figure. The decoupling changes as a function of both coil and preamplifier performance. Thus, the fundamental trade-off between noise and decoupling is discussed. This work embarks on the path towards new vistas in design of preamplifiers for surface coil arrays for magnetic resonance imaging.

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16-Channel surface coil for 13C-hyperpolarized spectroscopic imaging of cardiac metabolism in pig heart

Magnetic resonance spectroscopy (MRS) of hyperpolarized 13C pyruvate and its metabolites in large animal models is a powerful tool for assessing cardiac metabolism in patho-physiological conditions. In 13C studies, a high signal-to-noise ratio (SNR) is crucial to overcome the intrinsic data quality limitation due to the low molar concentration of certain metabolites as well as the low flux of conversion. Since 13C-MRS is essentially a semi-quantitative technique, the SNR of the spectra acquired in different myocardial segments should be homogeneous. MRS coil design plays an important role in achieving both targets. In this study, a 16-channel receive surface coil was designed for 13C hyperpolarized studies of the pig heart with a clinical 3-T scanner. The coil performance was characterized by phantom experiments and compared with that of a birdcage coil used in transmit/receive mode. Segmental signal distribution in the left ventricle (LV) was assessed by experiments on six healthy mini pigs. The proposed coil showed a significant increase in SNR for the LV wall close to the coil surface with respect to that for the birdcage but also significant segmental inhomogeneity. Hence, the use of the 16-channel coil is recommended for studies of septal and anterior LV walls.

A novel MR contrast agent for angiography and perfusion: Hyperpolarized water

Magnetic Resonance Imaging (MRI) is an important tool in medical imaging, and is widely used for its high spatial and temporal resolution, and low safety concerns. However, the technique has its limitations due to the inherent low sensitivity, making it inferior to Computed Tomography (CT) in terms of spatial and temporal sensitivity and to nuclear medicine methods in terms of molecular imaging sensitivity. By hyperpolarization, the available signal can be enhanced by several orders of magnitude, and potentially close some of these gaps. In this thesis work, the purpose is to demonstrate that water, hyperpolarized by dissolution Dynamic Nuclear Polarization (d-DNP), can be applied as an MRI contrast agent for angiography and perfusion. The first part of the project focuses on development of a protocol for production of large samples of hyperpolarized protons in D2O. The samples are polarized and dissolved in a fluid path compatible with the installed base of commercial polarizers developed for clinical research. The solidstate DNP is optimized at 6.7 T and 1.2 K by microwave frequency modulation. A solid-state polarization of 70% is obtained. The dissolution procedure is optimized by introduction of a fluorinated solvent to accelerate the transition from solid to liquid state, and efficient radical extraction is obtained with a two-phase system of water and heptane. A final liquid state polarization of 13% in samples of 16 mL is obtained, suitable for large animal experiments. In second part of the project, hyperpolarized water is applied for angiographic imaging and perfusion measurements in a pig model. Renal angiography of 0.55 mm in-plane isotropic resolution is demonstrated and perfusion measurements provides values comparable to conventional Gd-T1-DCE analysis. Finally, it is demonstrated that the method can be applied to acquire dynamic coronary MR angiography with temporal resolution of less than 1 s, apparent Signal-to-Noise Ratio of 269±169 and coronary sharpness of 0.31±0.086 mm⁻¹, which is superior to coronary MRA available in today’s clinical practice.
Decoupling Scheme for a Cryogenic Rx-Only RF Coil for 13C Imaging at 3T

In this study we evaluate the different active decoupling schemes that can be used to drive an Rx-only coil, in order to determine the optimal design for 13C MRI at 3T. Three different circuit schemes are studied: two known ones (with regular series and parallel tuning respectively), and a novel one which we found to be optimal for this case. The circuits have been cooled to 77K to reduce coil noise. Preliminary tests with the preamplifier cooled to 77K for reduction of noise figure, are also reported.

Difference between Extra- and Intracellular T1 Values of Carboxylic Acids Affects the Quantitative Analysis of Cellular Kinetics by Hyperpolarized NMR

Incomplete knowledge of the longitudinal relaxation time constant (T1) leads to incorrect assumptions in quantitative kinetic models of cellular systems, studied by hyper-polarized real-time NMR. Using an assay that measures the intracellular signal of small carboxylic acids in living cells, the intracellular T1 of the carboxylic acid moiety of acetate, keto-isocaprate, pyruvate, and butyrate was determined. The intracellular T1s shown to be up to four-fold shorter than the extracellular T1. Such a large difference in T1 values between the inside and the outside of the cell has significant influence on the quantification of intracellular metabolic activity. It is expected that the significantly shorter T1 of the carboxylic moieties inside cells is a result of macro-molecular crowding. An artificial cytosol has been prepared and applied to predict the T1 of other carboxylic acids. We demonstrate the value of this prediction tool.
Dissolution Dynamic Nuclear Polarization capability study with fluid path
Signal enhancement by hyperpolarization is a way of overcoming the low sensitivity in magnetic resonance; MRI in particular. One of the most well-known methods, dissolution Dynamic Nuclear Polarization, has been used clinically in cancer patients. One way of ensuring a low bioburden of the hyperpolarized product is by use of a closed fluid path that constitutes a barrier to contamination. The fluid path can be filled with the pharmaceuticals, i.e. imaging agent and solvents, in a clean room, and then stored or immediately used at the polarizer. In this study, we present a method of filling the fluid path that allows it to be reused. The filling method has been investigated in terms of reproducibility at two extrema, high dose for patient use and low dose for rodent studies, using [1-13C]pyruvate as example. We demonstrate that the filling method allows high reproducibility of six quality control parameters with standard deviations 3–10 times smaller than the acceptance criteria intervals in clinical studies.

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Educational simulator app and web page for exploring Nuclear and Compass Magnetic Resonance
A graphical app and browser-based simulator, CompassMR, was developed for initial Magnetic Resonance (MR) education. It is available at http://drcmr.dk/CompassMR/ and executes directly in most browsers with no further need for software. Easy access and a simple user interface invite student experimentation that improves understanding of basic MR phenomena. The simulator is used to introduce and explore electromagnetism, magnetic dipoles, static and radiofrequency fields, Compass MR, the free induction decay (FID), relaxation, the Fourier transform (FFT), the resonance condition, spin, precession, the Larmor equation, Nuclear MR, resonant excitation (linear and quadrature), and off-resonance effects.
Methods and implementation:
The simulator is a complete HTML5/JavaScript rewrite of the JavaCompass so it now executes in modern browsers with no additional software needed. Spin dynamics and enhanced responsiveness was added. Android App conversion was accomplished using Adobe PhoneGap. The basis for the graphical spin simulation is the semi-classical Bloch vector equation for a proton in combined stationary and oscillating magnetic fields, B0 and B1. For providing intuitive insight, the corresponding classical equation of motion for a compass needle in similar fields is used to simulate Compass Magnetic Resonance (CMR) that is similar to NMR except for needle vibration substituting nuclear precession. The nuclear Bloch vector moves like the magnetic moment of a classical rotating charge distribution as shown in the simulator. Spin is a consequence of Quantum Mechanics (QM) and not all aspects of spin and nuclei are represented in this naive picture. Beyond spin, the consequences of QM for proton MR are largely not observable, however, and the QM Bloch vector moves as shown in the simulator. Hence, it demonstrates nuclear dynamics more accurately than typical QM-inspired "cone" pictorial representations aimed at giving better representations of MR than classical mechanics, while often doing the opposite. This justification of the classical perspective is discussed in detail in [7].

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Efficiency Analysis of Magnetic Field Measurement for MR Electrical Impedance Tomography (MREIT)
MREIT is an emerging method to measure the ohmic tissue conductivities, with several potential biomedical applications. Its sensitivity depends on the magnitude of the applied current, which is limited to 1-2 mA in the human brain [1, 2]. This renders in-vivo applications challenging. Here, we aim to analyze and optimize the efficiency of two MREIT pulse sequences for in-vivo brain imaging.

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High-field dissolution dynamic nuclear polarization of [1-13C]pyruvic acid
[1-13C]pyruvate is the most widely used hyperpolarized metabolic magnetic resonance imaging agent. Using a custom-built 7 T polarizer operating at 1.0 K and trityl radical-doped [1-13C]pyruvic acid, unextrapolated solution-state 13C polarization greater than 60% was measured after dissolution and rapid transfer to a spectrometer magnet, demonstrating the signal enhancement attainable using optimized hardware. Slower rates of polarization under these conditions can be largely overcome with higher radical concentrations.
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Organisations: Department of Electrical Engineering, Center for Magnetic Resonance, Center for Hyperpolarization in Magnetic Resonance, Aarhus University, Aarhus University Hospital
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Hyperpolarised Organic Phosphates as NMR Reporters of Compartmental pH
Organic phosphate metabolites contain functional groups with pKa values near the physiologic pH range, yielding pH-dependent 13C chemical shift changes of adjacent quaternary carbon sites. When formed in defined cellular compartments from exogenously hyperpolarised 13C substrates, metabolites thus can yield localised pH values and correlation of organelle pH and catalytic activity.

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Hyperpolarized 13C MR angiography

Magnetic resonance angiography (MRA) is a non-invasive technology that can be used for diagnosis and monitoring of cardiovascular disease, the number one cause of mortality worldwide. Hyperpolarized imaging agents provide signal enhancement of more than 10,000 times, which implies large reduction in acquisition time and improved spatial resolution. We review the role of hyperpolarized 13C agents for MR angiography and present the literature in the field. Furthermore, we present a study of the benefit of intra-arterial injection over intravenous injection of hyperpolarized agent for cerebral angiography in the rat, and compare the performance of two standard angiographic pulse sequences, the gradient echo (GRE) sequence and the balanced steady-state free precession (bSSFP). 2D coronal cerebral angiographies using intra-arterial injections were acquired with a GRE sequence with in-plane resolution of 0.27 mm and matrix size 256x128, and 2D coronal cerebral angiographies were acquired with a bSSFP sequence with in-plane resolution of 0.55 mm and matrix size 128x64. The bSSFP sequence provides higher SNR in phantoms than the GRE sequence. Similarly, intravenous injections are imaged with higher SNR with the bSSFP sequence, where the signal destruction of the GRE sequence is avoided. However, for intra-arterial injections, the bSSFP sequence results in strong artefacts, and the GRE sequence is preferred. Hyperpolarized MRA presents many challenges and cannot currently compete with conventional contrast enhanced MRA. Further research may change this since hyperpolarization is still an immature methodology.

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Hyperpolarized 13C Urea Relaxation Mechanism Reveals Renal Changes in Diabetic Nephropathy

Purpose: Our aim was to assess a novel 13C radial fast spin echo golden ratio single shot method for interrogating early renal changes in the diabetic kidney, using hyperpolarized (HP) [13C,15N2]urea as a T2 relaxation based contrast bio-
probe. Methods: A novel HP 13C MR contrast experiment was conducted in a group of streptozotocin type-1 diabetic rat model and age matched controls. Results: A significantly different relaxation time (P=0.004) was found in the diabetic kidney (0.49±0.03 s) compared with the controls (0.64±0.02 s) and secondly, a strong correlation between the blood oxygen saturation level and the relaxation times were observed in the healthy controls. Conclusion: HP [13C,15N2]urea apparent T2 mapping may be a useful for interrogating local renal pO2 status and renal tissue alterations.

**Imaging Renal Urea Handling in Rats at Millimeter Resolution using Hyperpolarized Magnetic Resonance Relaxometry**

In vivo spin spin relaxation time (T2) heterogeneity of hyperpolarized [(13)C,(15)N2]urea in the rat kidney was investigated. Selective quenching of the vascular hyperpolarized (13)C signal with a macromolecular relaxation agent revealed that a long-T2 component of the [(13)C,(15)N2]urea signal originated from the renal extravascular space, thus allowing the vascular and renal filtrate contrast agent pools of the [(13)C,(15)N2]urea to be distinguished via multi-exponential analysis. The T2 response to induced diuresis and antidiuresis was performed with two imaging agents: hyperpolarized [(13)C,(15)N2]urea and a control agent hyperpolarized bis-1,1-(hydroxymethyl)-1-(13)C-cyclopropane-(2)H8. Large T2 increases in the inner-medullar and papilla were observed with the former agent and not the latter during antidiuresis. Therefore, [(13)C,(15)N2]urea relaxometry is sensitive to two steps of the renal urea handling process: glomerular filtration and the inner-medullary urea transporter (UT)-A1 and UT-A3 mediated urea concentrating process. Simple motion correction and subspace denoising algorithms are presented to aid in the multi exponential data analysis. Furthermore, a T2-edited, ultra long echo time sequence was developed for sub-2 mm(3) resolution 3D encoding of urea by exploiting relaxation differences in the vascular and filtrate pools.
Interactive web site and app for early magnetic resonance education

Teaching and understanding basic Magnetic Resonance (MR) is a challenge. This is clear from the educational literature that often repeats misinterpretations of quantum mechanics reminiscent of its earliest formulations (see www.drcmr.dk/MR that also links to the developed software). Modern quantum formulations of MR are much closer to classical descriptions than to typical quantum inspired myths frequent in literature. This opens for intuitive educational computer simulation using modern web technologies offering excellent interactive possibilities for experimentation.

Investigating tumor perfusion by hyperpolarized (13) C MRI with comparison to conventional gadolinium contrast-enhanced MRI and pathology in orthotopic human GBM xenografts: Correlation of 13C Perfusion Imaging and Gd-Enhanced Contrast MRI

Dissolution dynamic nuclear polarization (DNP) enables the acquisition of (13) C magnetic resonance data with a high sensitivity. Recently, metabolically inactive hyperpolarized (13) C-labeled compounds have shown to be potentially useful for perfusion imaging. The purpose of this study was to validate hyperpolarized perfusion imaging methods by comparing with conventional gadolinium (Gd)-based perfusion MRI techniques and pathology. Dynamic (13) C data using metabolically inactive hyperpolarized bis-1,1-(hydroxymethyl)-[1-(13) C]cyclopropane-d8 (HMCP) were obtained from an orthotopic human glioblastoma (GBM) model for the characterization of tumor perfusion and compared with standard Gd-based dynamic susceptibility contrast (DSC) MRI data and immunohistochemical analysis from resected brains. Distinct HMCP perfusion characteristics were observed within the GBM tumors compared with contralateral normal brain tissue. The perfusion parameters obtained from the hyperpolarized HMCP data in tumor were strongly correlated with normalized
peak height measured from the DSC images. The results from immunohistochemical analysis supported these findings by showing a high level of vascular staining for tumor that exhibited high levels of hyperpolarized HMCP signal. The results from this study have demonstrated that hyperpolarized HMCP data can be used as an indicator of tumor perfusion in an orthotopic xenograft model for GBM. Magn Reson Med, 2016. © 2016 Wiley Periodicals, Inc.

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**Large dose hyperpolarized water with dissolution-DNP at high magnetic field**
We demonstrate a method for the preparation of hyperpolarized water by dissolution Dynamic Nuclear Polarization at high magnetic field. Protons were polarized at 6.7T and 1.1K to >70% with frequency modulated microwave irradiation at 188GHz. 97.2±0.7% of the radical was extracted from the sample in the dissolution in a two-phase system. 16±1mL of 5.0M (1)H in D2O with a polarization of 13.0±0.9% in the liquid state was obtained, corresponding to an enhancement factor of 4000±300 compared to the thermal equilibrium at 9.4T and 293K. A longitudinal relaxation time constant of 16±1s was measured. The sample was polarized and dissolved in a fluid path compatible with clinical polarizers. The volume of hyperpolarized water produced by this method enables angiography and perfusion measurements in large animals, as well as NMR experiments for studies of e.g. proton exchange and polarization transfer to other nuclei.

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Large field-of-view transmission line resonator for high field MRI

Transmission line resonators is often a preferable choice for coils in high field magnetic resonance imaging (MRI), because they provide a number of advantages over traditional loop coils. The size of such resonators, however, is limited to shorter than half a wavelength due to high standing wave ratio, which leads to inhomogeneous field distribution along the resonator. In this work, it is demonstrated that the resonator length can be extended to over half a wavelength with the help of series capacitors. The approach allows for reduced standing wave ratio and improved field homogeneity. Achieved magnetic field distribution is compared to the conventional transmission line resonator. Imaging experiments are performed using 7 Tesla MRI system. The developed resonator is useful for building coils with large field-of-view.

Measuring Motion-Induced B0-Fluctuations in the Brain Using Field Probes

Purpose: Fluctuations of the background magnetic field (B0) due to body and breathing motion can lead to significant artifacts in brain imaging at ultrahigh field. Corrections based on real-time sensing using external field probes show great potential. This study evaluates different aspects of field interpolation from these probes into the brain which is implicit in such methods. Measurements and simulations were performed to quantify how well B0-fluctuations in the brain due to body and breathing motion are reflected in external field probe measurements. Methods: Field probe measurements were compared with scanner acquired B0-maps from experiments with breathing and shoulder movements. A realistic simulation of B0-fluctuations caused by breathing was performed, and used for testing different sets of field probe positions. Results: The B0-fluctuations were well reflected in the field probe measurements in the shoulder experiments, while the breathing experiments showed only moderate correspondence. The simulations showed the importance of the probe positions, and that performing full 3rd order corrections based on 16 field probes is not recommended. Conclusion: Methods for quantitative assessment of the field interpolation problem were developed and demonstrated. Field corrections based on external field measurements show great potential, although potential pitfalls were identified.
Microwave-gated dynamic nuclear polarization

Dissolution dynamic nuclear polarization (D-DNP) has become a method of choice to enhance signals in nuclear magnetic resonance (NMR). Recently, we have proposed to combine cross-polarization (CP) with D-DNP to provide high polarization $P(^{13}\text{C})$ in short build-up times. In this paper, we show that switching microwave irradiation off for a few hundreds of milliseconds prior to CP can significantly boost the efficiency. By implementing microwave gating, $(^{13}\text{C})$ polarizations on sodium [1-(13)C]acetate as high as 64% could be achieved with a polarization build-up time constant as short as 160 s. A polarization of $P(^{13}\text{C}) = 78\%$ could even be reached for [(13)C]urea.

Muscle growth is reduced in 15-month-old children with cerebral palsy

Aim Lack of muscle growth relative to bone growth may be responsible for development of contractures in children with cerebral palsy (CP). Here, we used ultrasonography to compare growth of the medial gastrocnemius muscle in children with and without CP. Method Twenty-six children with spastic CP (15 males, 11 females; mean age 35mo, range 8-65mo) and 101 typically developing children (47 males, 54 females; mean age 29mo, range 1-69mo) were included. Functional abilities of children with CP equalled levels I to III in the Gross Motor Function Classification System. Medial gastrocnemius muscle volume was constructed from serial, transverse, two-dimensional ultrasonography images. Results In typically developing children, medial gastrocnemius volume increased linearly with age. Among children
with CP, medial gastrocnemius volume increased less with age and deviated significantly from typically developing children at 15 months of age (p

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On the present and future of dissolution-DNP
Dissolution-DNP is a method to create solutions of molecules with nuclear spin polarization close to unity. The many orders of magnitude signal enhancement have enabled many new applications, in particular in vivo MR metabolic imaging. The method relies on solid state dynamic nuclear polarization at low temperature followed by a dissolution to produce the room temperature solution of highly polarized spins. This work describes the present and future of dissolution-DNP in the mind of the author. The article describes some of the current trends in the field as well as outlines some of the areas where new ideas will make an impact. Most certainly, the future will take unpredicted directions, but hopefully the thoughts presented here will stimulate new ideas that can further advance the field. (C) 2016 Elsevier Inc. All rights reserved.

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Optimal Value of Series Capacitors for Uniform Field Distribution in Transmission Line MRI Coils

Transmission lines are often used as coils in high field magnetic resonance imaging (MRI). Due to the distributed nature of transmission lines, coils based on them produce inhomogeneous field. This work investigates application of series capacitors to improve field homogeneity along the coil. The equations for optimal values of evenly distributed capacitors are derived and expressed in terms of the implemented transmission line parameters. The achieved magnetic field homogeneity is estimated under quasistatic approximation and compared to the regular transmission line resonator. Finally, a more practical case of a microstrip line coil with two series capacitors is considered.

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Oxygen metabolic competition in the lactic acidotic diabetic kidney: A point of no return?
Diabetic nephropathy is directly related to renal hypoxia, with an increased mitochondrial uncoupling and increased energy demand to maintain normal renal function. Lowering the oxygen content in inspired air has shown to worsen the prognostic outcome of diabetic patients independent of glycemic control. We therefore tested the hypothesis that acutely altered renal oxygen availability alters metabolic pathways related to cellular energy production.

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Probing treatment response of glutaminolytic prostate cancer cells to natural drugs with hyperpolarized [5-13C]glutamine

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Prospective motion correction for MRI using EEG-equipment
A new prospective motion correction technique is presented that is based on signals from gradient switching, in an EEG-cap with interconnected electrodes the subject wears during scanning. The method has no line-of-sight limitations as optical methods, requires no interleaved navigator modules or additional hardware for sites already doing EEG-fMRI. Instead a training scan is performed were signals recorded with the EEG-system are correlated with motion parameters estimated by image realignment. Initial results from application of the method in a phantom are promising.

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Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression

Objective: To investigate the role of hippocampal plasticity in the antidepressant effect of electroconvulsive therapy (ECT).

Method: We used magnetic resonance (MR) imaging including diffusion tensor imaging (DTI) and proton MR spectroscopy (1H-MRS) to investigate hippocampal volume, diffusivity, and metabolite changes in 19 patients receiving ECT for severe depression. Other regions of interest included the amygdala, dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and hypothalamus. Patients received a 3T MR scan before ECT (TP1), 1 week (TP2), and 4 weeks (TP3) after ECT.

Results: Hippocampal and amygdala volume increased significantly at TP2 and continued to be increased at TP3. DLPFC exhibited a transient volume reduction at TP2. DTI revealed a reduced anisotropy and diffusivity of the hippocampus at TP2. We found no significant post-ECT changes in brain metabolite concentrations, and we were unable to identify a spectral signature at 1.30 ppm previously suggested to reflect neurogenesis induced by ECT. None of the brain imaging measures correlated to the clinical response. Conclusion: Our findings show that ECT causes a remodeling of brain structures involved in affective regulation, but due to their lack of correlation with the antidepressant effect, this remodeling does not appear to be directly underlying the antidepressant action of ECT.

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Simultaneous PET/MRI with 13C magnetic resonance spectroscopic imaging (hyperPET): phantom-based evaluation of PET quantification

Background: Integrated PET/MRI with hyperpolarized 13C magnetic resonance spectroscopic imaging (13C-MRSI) offers simultaneous, dual-modality metabolic imaging. A prerequisite for the use of simultaneous imaging is the absence of interference between the two modalities. This has been documented for a clinical whole-body system using simultaneous 1H-MRI and PET but never for 13C-MRSI and PET. Here, the feasibility of simultaneous PET and 13C-MRSI as well as hyperpolarized 13C-MRSI in an integrated whole-body PET/MRI hybrid scanner is evaluated using phantom experiments.

Methods: Combined PET and 13C-MRSI phantoms including a NEMA [18F]-FDG phantom, 13C-acetate and 13C-urea sources, and hyperpolarized 13C-pyruvate were imaged repeatedly with PET and/or 13C-MRSI. Measurements evaluated for interference effects included PET activity values in the largest sphere and a background region; total number of PET trues; and 13C-MRSI signal-to-noise ratio (SNR) for urea and acetate phantoms. Differences between measurement conditions were evaluated using t tests. Results: PET and 13C-MRSI data acquisition could be performed simultaneously without any discernible artifacts. The average difference in PET activity between acquisitions with and without simultaneous 13C-MRSI was 0.83 (largest sphere) and −0.76 % (background). The average difference in net trues was −0.01 %. The average difference in 13C-MRSI SNR between acquisitions with and without simultaneous PET ranged from −2.28 to 1.21 % for all phantoms and measurement conditions. No differences were significant. The system was capable of 13C-MRSI of hyperpolarized 13C-pyruvate. Conclusions: Simultaneous PET and 13C-MRSI in an integrated whole-body PET/MRI hybrid scanner is feasible. Phantom experiments showed that possible interference effects introduced by acquiring data from the two modalities simultaneously are small and non-significant. Further experiments can now investigate the benefits of simultaneous PET and hyperpolarized 13C-MRI in vivo studies.
Single-Shot-RARE for rapid 3D hyperpolarized metabolic ex vivo tissue imaging: RF-pulse design for semi-dense spectra
MRS of hyperpolarized (HP) 13C-enriched compounds is a promising method for in vivo cancer diagnosis. Sentinel lymph node ex vivo tissue sample histology used in clinical routine for breast cancer metastasis diagnosis requires time consuming sample analysis. 3D-HP-MRSI can potentially speed up the diagnosis given a sensitive marker that can be efficiently imaged in tissue after homogenous injection. The entire sample can be confined within the imaged volume giving the possibility of complete spatial non-selectivity of the radio frequency (RF) pulses in the RF pulse design with no chemical shift localization errors. Since only a few product signals are of interest for this application, a combination of under-sampled temporal encoding, frequency selective excitation and the Single-Shot-RARE sequence offers favourable SNR characteristics. Small peak separations are challenging, however, since they require narrow excitation transition-bands. We have designed a 3D-MRSI pulse sequence for hyperpolarized ex vivo sample imaging for semi-dense compound spectra (few components, relatively small separations), ultimately aimed to be used for metastasis detection in excised lymph nodes.
Spectroscopic approaches to resolving ambiguities of hyper-polarized NMR signals from different reaction cascades

The influx of exogenous substrates into cellular reaction cascades on the seconds time scale is directly observable by NMR spectroscopy when using nuclear spin polarization enhancement. Conventional NMR assignment spectra for the identification of reaction intermediates are not applicable in these experiments due to the non-equilibrium nature of the nuclear spin polarization enhancement. We show that ambiguities in the intracellular identification of transient reaction intermediates can be resolved by experimental schemes using site-specific isotope labelling, optimised referencing and response to external perturbations.

TE01 mode converter for highly overmoded circular waveguide at 188 GHz

A design of a G-band TE01 mode converter is presented in this work. It consists of a TE01 mode launcher followed by a tapered waveguide section. Full-wave simulated reflection coefficient of stainless steel converter is better than −15 dB and transmission coefficient is better than −1.5 dB in a frequency range from 173 GHz to 193 GHz. The design is useful in applications employing highly overmoded circular waveguides.
Transmission Line Resonator Segmented with Series Capacitors

Transmission line resonators are often used as coils in high field MRI. Due to distributed nature of such resonators, coils based on them produce inhomogeneous field. This work investigates application of series capacitors to improve field homogeneity along the resonator. The equations for optimal values of evenly distributed capacitors are presented. The performances of the segmented resonator and a regular transmission line resonator are compared.

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Tunable 13C/1H dual channel matching circuit for dynamic nuclear polarization system with cross-polarization

In this paper we report initial results of design and practical implementation of tuning and matching circuit to estimate a performance of Dynamic Nuclear Polarization (DNP) at a magnetic field of 6.7 T. It is shown that developed circuit for signal observation is compact, easy to make and provides low return loss (typically better than −45 dB) at a tuning range ±3 MHz for both resonant frequencies. In addition, transmission parameters measured between 13C and 1H channels are less than −17 dB and −50 dB for 71.8 MHz and 285.5 MHz, respectively showing a good isolation between the two channels. Measurement results with a tuning and matching circuit prototype are presented including obtained spectra (13C and 1H) and estimation of the signal-to-noise ratio.

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Ultrashort electromagnetic clusters formation by two-stream superheterodyne free electron lasers

A cubic nonlinear self-consistent theory of multiharmonic two-stream superheterodyne free electron lasers (TSFEL) of a klystron type, intended to form powerful ultrashort clusters of an electromagnetic field is constructed. Plural three-wave parametric resonant interactions of wave harmonics have been taken into account. An amplitude, phase and spectral
analyses of the processes occurring in such devices have been carried out. The conditions necessary for the forming of the ultrashort clusters of an electromagnetic field have been found out. The possibility of the ultrashort electromagnetic cluster formation in the multiharmonic TSFEL-type systems has been demonstrated.

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Waveguide transition with vacuum window for multiband dynamic nuclear polarization systems
A low loss waveguide transition section and oversized microwave vacuum window covering several frequency bands (94 GHz, 140 GHz, 188 GHz) is presented. The transition is compact and was optimized for multiband Dynamic Nuclear Polarization (DNP) systems in a full-wave simulator. The window is more broadband than commercially available windows, which are usually optimized for single band operation. It is demonstrated that high-density polyethylene with urethane adhesive can be used as a low loss microwave vacuum window in multiband DNP systems. The overall assembly performance and dimensions are found using full-wave simulations. The practical aspects of the window implementation in the waveguide are discussed. To verify the design and simulation results, the window is tested experimentally at the three frequencies of interest.

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A 282 GHz Probe for Dynamic Nuclear Polarization

Introduction: In DNP, microwave irradiation of a sample facilitates the transfer of spin polarization from electrons to nuclei. One of the ways to improve the DNP enhancement is to transfer microwave power from the mm-wave source to the sample more effectively. Several methods and techniques to efficiently transport microwave energy from the microwave source to the sample have been developed. For example, a corrugated waveguide allows to deliver mm-wave energy from external source to the probe with minimum losses. The conventional approach at high frequencies is to irradiate the sample directly from the waveguide, while at low frequencies the cavity of the probe is used as a microwave resonator. It is important to optimize the arrangement of microwave, RF and sample handling components. In this paper a solution for the double channel microwave probe for operation at 10.1 T (13C frequency is 108 MHz, 1H frequency is 430 MHz, electron frequency is 282 GHz) is developed. The construction of the probe is detailed. Probe configuration: The analysis of the probe structure is performed using a full-wave electromagnetic simulator (CST Microwave Studio 2014). Structurally, the probe consists of two sections: microwave can with RF coil; the rest of the probe consists of a waveguide, sample tube and coaxial transmission line. The probe is designed to study cylindrical samples with diameter - 9 mm, and height – 2-20 mm. An RF coil which is housed in cylindrical Macor coil form (dielectric with ε=5.64 and tangent δ is 0.0025) surrounds the sample. The RF coil has a saddle form and was made of two current loops run on opposite sides of a cylinder (in parallel). Material of the coil is copper wire with diameter equal to 0.7 mm. Coil dimensions are: diameter - 13 mm; height - 22.0 mm. The self resonant frequency of the coil is 976 MHz. A magnetic field distribution at 108 MHz and 430 MHz was calculated for the RF coil, the results revealed good homogeneity and intensity along x,y,z axes. Figure 1 shows the general view of the probe and cross section through the microwave container with field distribution. Operating frequency is 282 GHz to drive DNP. On the top of the model is mounted a corrugated, circular waveguide. To avoid losses and to maintain the constraint that the RF coil surrounding the sample should not be close to metal parts. An additional advantage of using the corrugated waveguide is that the losses and power dissipation in free space are negligible. In our construction of the probe we have optimized relevant parameters of the probe. Conclusion: We have demonstrated the feasibility of the probe design for DNP applications at 10.1 T from the microwave and RF point of view. The performance simulations of the microwave cavity have demonstrated that the electromagnetic field is effectively concentrated at the sample location.
A fast and simple method for calibrating the flip angle in hyperpolarized 13C MRS experiments

Hyperpolarized 13C magnetic resonance represents a promising modality for in vivo studies of intermediary metabolism of bio-molecules and new biomarkers. Although it represents a powerful tool for metabolites spatial localization and for the assessment of their kinetics in vivo, a number of technological problems still limit this technology and need innovative solutions. In particular, the optimization of the signal-to-noise ratio during the acquisitions requires the use of pulse sequences with accurate flip angle calibration, which is performed by adjusting the transmit power in the prescan step. This is even more critical in the case of hyperpolarized studies, because the fast decay of the hyperpolarized signal requires precise determination of the flip angle for the acquisition. This work describes a fast and efficient procedure for transmit power calibration of magnetic resonance acquisitions employing selective pulses, starting from the calibration of acquisitions performed with non-selective (hard) pulses. The proposed procedure employs a simple theoretical analysis of radiofrequency pulses by assuming a linear response and can be performed directly during in vivo studies. Experimental MR data validate the theoretical calculation by providing good agreement.

A setup for measuring characteristics of microwave electric vacuum devices with open resonance structures

A new modification of the universal experimental setup for measuring electrodynamic characteristics of microwave generators with open resonance structures of the orotron–diffraction-radiation-generator type is described. To expand the functional capabilities and the electronic frequency-tuning range, an additional periodic metal–dielectric structure is introduced into the open resonator. The experimental results of investigations of the energy, volt–ampere, and frequency characteristics of the modified diffraction-radiation generator prototype are compared to the characteristics of the generator without a metal–dielectric structure.

The intrinsic physicochemical properties of the sample formulation are the key factors for efficient hyperpolarization through dissolution dynamic nuclear polarization (dissolution-DNP). We provide a comprehensive characterization of the DNP process for Na-[1-13C]acetate selected as a model for non-self-glassing agents: the solid-state polarization dynamics of different formulations and the effect of the paramagnetic agent (trityl radical) on the pattern of polarization and the relaxation profile were extensively analyzed. We quantified the effects of the glassing agent and Gd3+-chelate on DNP performance. The results reported here describe the constraints of the acetate formulation useful for future studies in this field with non-self-glassing enriched molecules.

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Facing and Overcoming Sensitivity Challenges in Biomolecular NMR Spectroscopy

In the Spring of 2013, NMR spectroscopists convened at the Weizmann Institute in Israel to brainstorm on approaches to improve the sensitivity of NMR experiments, particularly when applied in biomolecular settings. This multi-author interdisciplinary Review presents a state-of-the-art description of the primary approaches that were considered. Topics discussed included the future of ultrahigh-field NMR systems, emerging NMR detection technologies, new approaches to nuclear hyperpolarization, and progress in sample preparation. All of these are orthogonal efforts, whose gains could multiply and thereby enhance the sensitivity of solid- and liquid-state experiments. While substantial advances have been made in all these areas, numerous challenges remain in the quest of endowing NMR spectroscopy with the sensitivity that has characterized forms of spectroscopies based on electrical or optical measurements. These challenges, and the ways by which scientists and engineers are striving to solve them, are also addressed.

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Improved Field Homogeneity for Transmission Line MRI Coils Using Series Capacitors

High field magnetic resonance imaging (MRI) systems often use short sections of transmission lines for generating and sensing alternating magnetic fields. Due to distributed nature of transmission lines, the generated field is inhomogeneous. This work investigates the application of series capacitors to improve the field homogeneity. The resulting magnetic field distribution is estimated analytically and evaluated numerically. The results are compared to a case of a conventional transmission line coil realization.

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In Vivo Phenotyping of Tumor Metabolism in a Canine Cancer Patient with Simultaneous (18)F-FDG-PET and Hyperpolarized (13)C-Pyruvate Magnetic Resonance Spectroscopic Imaging (hyperPET): Mismatch Demonstrates that FDG may not Always Reflect the Warburg Effect
In this communication the mismatch between simultaneous (18)F-FDG-PET and a (13)C-lactate imaging (hyperPET) in a biopsy verified squamous cell carcinoma in the right tonsil of a canine cancer patient is shown. The results demonstrate that (18)F-FDG-PET may not always reflect the Warburg effect in all tumors.

**Magnetic Resonance Angiography in the Pig using Hyperpolarized Water**

Introduction Magnetic Resonance Angiography (MRA) is an important tool in diagnostics of medical conditions such as emboli, stenosis and aneurysms. Sub-millimetre resolution can be obtained with proton imaging, and further optimization can be obtained with Gd-based blood pool agents. However, the acquisition time is several minutes, and conventional MRA methods thus fail to image within a single respiration or heartbeat and therefore suffers from motion artefacts. We demonstrate that hyperpolarized (HP) water can be used as an imaging agent to provide subsecond angiographies in pigs. Previous work on hyperpolarization for imaging agents in large animals has mainly been focused of 13C, but small volumes of hyperpolarized water with lower polarization has been demonstrated. Injection of hyperpolarized protons allows for the use of MRI coils and pulse sequences already existing in the clinic. Secondly, the magnetization achievable with hyperpolarized water is superior to other nuclei. Methods A 1 mL sample of 50% water and 50% glycerol with 30 mM TEMPO is polarized in a Spinlab (GE Healthcare) at 5 T, 0.9 K, 139.9 GHz for an hour. The sample is rapidly dissolved in 16 mL deoxygenated dissolution medium (DM) consisting of 1 mM EDTA, 50 mM sodium L-ascorbate, 1.9 mM NaH2PO4 and 8 mM Na2HPO4 dissolved in D2O. The DM is filled in the syringe with 7.6 g nonafluorobutyl methyl ether, which will accelerate the dissolution process and extract radical from the polar phase, and hence extend the T1. 10 mL HP substance is injected over 5 s, initiated 15 s after dissolution through a catheter in the right renal artery of a 40 kg pig. Results The protons are polarized by dissolution DNP to an enhancement of more than 2000 times at 9.4 T, corresponding to a polarization of 13% at time of injection. T1 of ~20 s is achieved in vitro for a 1H concentration of 4.5 M. A zoom of a renal MRA is shown in Figure 1. The image maps minor branches of the renal arteries, and the perfusion can be traced over time (time series not shown).
Modeling of Schottky Barrier Diode Millimeter-Wave Multipliers at Cryogenic Temperatures

We report on the evaluation of Schottky barrier diode GaAs multipliers at cryogenic temperatures. A GaAs Schottky barrier diode model is developed for theoretical estimation of doubler performance. The model is used to predict efficiency of doublers from room to cryogenic temperatures. The theoretical estimation is verified experimentally using a 78 GHz doubler cooled down to 14 K. The observed efficiency improvement due to cooling is approximately 4 % per 100 degrees.

Quantified pH Imaging with Hyperpolarized 13C-bicarbonate: Quantified pH Imaging with Hyperpolarized Bicarbonate

Because pH plays a crucial role in several diseases, it is desirable to measure pH in vivo noninvasively and in a spatially localized manner. Spatial maps of pH were quantified in vitro, with a focus on method-based errors, and applied in vivo. In vitro and in vivo 13C mapping were performed for various flip angles for bicarbonate (BiC) and CO2 with spectral-spatial excitation and spiral readout in healthy Lewis rats in five slices. Acute subcutaneous sterile inflammation was induced with Concanavalin A in the right leg of Buffalo rats. pH and proton images were measured 2 h after induction. After optimizing the signal to noise ratio of the hyperpolarized 13C-bicarbonate, error estimation of the spectral-spatial excited spectrum reveals that the method covers the biologically relevant pH range of 6 to 8 with low pH error (<0.2). Quantification of pH maps shows negligible impact of the residual bicarbonate signal. pH maps reflect the induction of acute metabolic alkalosis. Inflamed, infected regions exhibit lower pH. Hyperpolarized 13C-bicarbonate pH mapping was shown to be sensitive in the biologically relevant pH range. The mapping of pH was applied to healthy in vivo organs and interpreted within inflammation and acute metabolic alkalosis models. Magn Reson Med 73:2274–2282, 2015. © 2014 Wiley Periodicals, Inc.
Real-time cardiac metabolism assessed with hyperpolarized [1-13C]acetate in a large-animal model
Dissolution-dynamic nuclear polarization (dissolution-DNP) for magnetic resonance (MR) spectroscopic imaging has recently emerged as a novel technique for noninvasive studies of the metabolic fate of biomolecules in vivo. Since acetate is the most abundant extra- and intracellular short-chain fatty acid, we focused on [1-13C]acetate as a promising candidate for a chemical probe to study the myocardial metabolism of a beating heart. The dissolution-DNP procedure of Na[1-13C]acetate for in vivo cardiac applications with a 3 T MR scanner was optimized in pigs during bolus injection of doses of up to 3 mmol. The Na[1-13C]acetate formulation was characterized by a liquid-state polarization of 14.2% and a $T_1^{\text{Eff}}$ in vivo of 17.6 ± 1.7 s. In vivo Na[1-13C]acetate kinetics displayed a bimodal shape: [1-13C]acetyl carnitine (AcC) was detected in a slice covering the cardiac volume, and the signal of 13C-acetate and 13C-AcC was modeled using the total area under the curve (AUC) for kinetic analysis. A good correlation was found between the ratio AUC(AcC)/AUC(acetate) and the apparent kinetic constant of metabolic conversion, from [1-13C]acetate to [1-13C]AcC (kAcC), divided by the AcC longitudinal relaxation rate ($r_1$). Our study proved the feasibility and the limitations of administration of large doses of hyperpolarized [1-13C]acetate to study the myocardial conversion of [1-13C]acetate in [1-13C]acetyl-carnitine generated by acetyltransferase in healthy pigs.

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Simulation and comparison of coils for Hyperpolarized 13C MRS cardiac metabolism studies in pigs
Hyperpolarized 13C Magnetic Resonance represents a promising modality for in vivo spectroscopy since it provides a unique opportunity for the non-invasive assessment of regional cardiac metabolism. Although it represents a powerful tool for the study of the heart physiology in pig models, by permitting metabolic activity mapping, a number of technological problems still limit this technology and need innovative solutions such as the design of suitable radiofrequency (RF) coils, capable to provide a large sensitivity region. This work describes the simulation and the comparison of different 13C coil configurations, constituted by various arrangement of circular, butterfly and birdcage coils designed for hyperpolarized
studies of pig heart with a clinical 3T scanner. The coils characterization is performed by developing a Signal-to-Noise Ratio (SNR) model, previously validated with experimental results, for coils performance evaluation in terms of coil resistance, sample induced resistance and magnetic field pattern. In particular, coil resistances were calculated from Ohm's law, while magnetic field patterns and sample induced resistances were calculated using a numerical Finite-Difference Time-Domain (FDTD) algorithm. Theoretical SNR-vs-depth profiles were calculated for each coil configuration. We believe the paper could be interesting for graduate students and researchers in the field of magnetic resonance coil design and development, especially for 13C studies.

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Simultaneous Hyperpolarized 13C-Pyruvate MRI and 18F-FDG PET (HyperPET) in 10 Dogs with Cancer
With the introduction of combined PET/MR spectroscopic (MRS) imaging, it is now possible to directly and indirectly image the Warburg effect with hyperpolarized (13)C-pyruvate and (18)F-FDG PET imaging, respectively, via a technique we have named hyperPET. The main purpose of this present study was to establish a practical workflow for performing (18)F-FDG PET and hyperpolarized (13)C-pyruvate MRS imaging simultaneously for tumor tissue characterization and on a larger scale test its feasibility. In addition, we evaluated the correlation between (18)F-FDG uptake and (13)C-lactate production. Ten dogs with biopsy-verified spontaneous malignant tumors were included for imaging. All dogs underwent a protocol of simultaneous (18)F-FDG PET, anatomic MR, and hyperpolarized dynamic nuclear polarization with (13)C-pyruvate imaging. The data were acquired using a combined clinical PET/MR imaging scanner. We found that combined (18)F-FDG PET and (13)C-pyruvate MRS imaging was possible in a single session of approximately 2 h. A continuous workflow was obtained with the injection of (18)F-FDG when the dogs was placed in the PET/MR scanner. (13)C-MRS dynamic acquisition demonstrated in an axial slab increased (13)C-lactate production in 9 of 10 dogs. For the 9 dogs, the (13)C-lactate was detected after a mean of 25 s (range, 17-33 s), with a mean to peak of (13)C-lactate at 49 s (range, 40-62 s). (13)C-pyruvate could be detected on average after 13 s (range, 5-26 s) and peaked on average after 25 s (range, 13-42 s). We noticed concordance of (18)F-FDG uptake and production of (13)C-lactate in most, but not all, axial slices. In this study, we have shown in a series of dogs with cancer that hyperPET can easily be performed within 2 h. We showed mostly correspondence between (13)C-lactate production and (18)F-FDG uptake and expect the combined modalities to reveal additional metabolic information to improve prognostic value and improve response monitoring.

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Simultaneous hyperpolarized 13C-pyruvate MRI and 18F-FDG-PET in cancer (hyperPET): feasibility of a new imaging concept using a clinical PET/MRI scanner

In this paper we demonstrate, for the first time, the feasibility of a new imaging concept - combined hyperpolarized 13C-pyruvate magnetic resonance spectroscopic imaging (MRSI) and 18F-FDG-PET imaging. This procedure was performed in a clinical PET/MRI scanner with a canine cancer patient. We have named this concept hyper PET. Intravenous injection of the hyperpolarized 13C-pyruvate results in an increase of 13C-lactate, 13C-alanine and 13CCO2 (13C-HCO3) resonance peaks relative to the tissue, disease and the metabolic state probed. Accordingly, with dynamic nuclear polarization (DNP) and use of 13C-pyruvate it is now possible to directly study the Warburg Effect through the rate of conversion of 13C-pyruvate to 13C-lactate. In this study, we combined it with 18F-FDG-PET that studies uptake of glucose in the cells. A canine cancer patient with a histology verified local recurrence of a liposarcoma on the right forepaw was imaged using a combined PET/MR clinical scanner. PET was performed as a single-bed, 10 min acquisition, 107 min post injection of 310 MBq 18F-FDG. 13C-chemical shift imaging (CSI) was performed just after FDG-PET and 30 s post injection of 23 mL hyperpolarized 13C-pyruvate. Peak heights of 13C-pyruvate and 13Clactate were quantified using a general linear model. Anatomic 1H-MRI included axial and coronal T1 vibe, coronal T2-tse and axial T1-tse with fat saturation following gadolinium injection. In the tumor we found clearly increased 13C-lactate production, which also corresponded to high 18F-FDG uptake on PET. This is in agreement with the fact that glycolysis and production of lactate are increased in tumor cells compared to normal cells. Yet, most interestingly, also in the muscle of the forepaw of the dog high 18F-FDG uptake was observed. This was due to activity in these muscles prior to anesthesia, which was not accompanied by a similarly high 13C-lactate production. Accordingly, this clearly demonstrates how the Warburg Effect directly can be demonstrated by hyperpolarized 13C-pyruvate MRSI. This was not possible with 18F-FDG-PET imaging due to inability to discriminate between causes of increased glucose uptake. We propose that this new concept of simultaneous hyperpolarized 13C-pyruvate MRSI and PET may be highly valuable for image-based non-invasive phenotyping of tumors. This methods may be useful for treatment planning and therapy monitoring.
The Ups and Downs of Classical and Quantum Formulations of Magnetic Resonance

This chapter describes typical misunderstandings frequently encountered in introductions to nuclear magnetic resonance (NMR), for example, as used for chemical analysis and for magnetic resonance imaging (MRI). It is aimed at those users who are familiar with the basics but have an interest in the connection between the seemingly very different classical and quantum descriptions. Such understanding is needed by students, authors, and lecturers, in particular. With limited complexity, the text introduces probabilistic classical and quantum mechanics with emphasis on similarities and differences. It describes important concepts and the roles of measurement, eigenstates, superpositions, entanglement, and interference, all discussed with reference to spin dynamics for both isolated nuclei and ensembles. The dynamics of basic NMR are shown to be similar to those of coupled oscillators (e.g., pendulums), which gives insight into the resonance phenomenon itself as well as spectral features resulting from intramolecular J-coupling of atomic nuclei. It is discussed how classical and quantum mechanics give rise to similar expectations for basic NMR and why a classical understanding is central.

Design of a broadband passive X-band double-balanced mixer in SiGe HBT technology

In this paper, a passive double-balanced mixer in SiGe HBT technology is presented. Owing to lack of suitable passive mixing elements in the technology, the mixing elements are formed by diode-connected HBTs. The mixer uses lumped element Marchand baluns on both the local oscillator (LO) and the radio frequency (RF) port. A break out of the Marchand balun is measured. This demonstrates good phase and magnitude match of 0.7° and 0.11 dB, respectively. The Marchand baluns are broadband with a measured 3 dB bandwidth of 6.4 GHz, while still having a magnitude imbalance better than 0.4 dB and a phase imbalance better than 5°. Unfortunately with a rather high loss of 2.5 dB, mainly due to the low Q-factor of the inductors used. The mixer is optimized for use in doppler radars and is highly linear with a 1 dB compression point above 12 dBm IIP2 of 66 dBm. The conversion gain at the center frequency of 8.5 GHz is −9.8 dB at an LO drive level of 15 dBm. The whole mixer is very broadband with 3 dB bandwidth from 7 to 12 GHz covering the entire X-band. The LO–IF, RF–IF, and RF–LO isolation is better than 46, 36, and 36 dB, respectively, in the entire band of operation.
Fluid path system for dissolution and transport of a hyperpolarized material

A fluid path system (10) includes a vial (28) containing a frozen pharmaceutical product (12). A dissolution fluid path (36) is also included in the fluid path system (10), the dissolution fluid path (36) having an output end (42) in fluid communication with the vial (28) and an input end (38) attached to a pressure vessel (32) containing a dissolution medium (34). A delivery fluid path (44) has a first end (46) hermetically attached to the vial (28) to transport therefrom a mixture of dissolved pharmaceutical product (12) and dissolution medium (34) and a second end (50) connected to a receiving vessel (55) to receive the mixture. A dissolution fluid path valve (40) is positioned between the pressure vessel (32) and the dissolution fluid path (36) to control flow of the dissolution medium (34), and a delivery fluid path valve (52) is also included in the fluid path system (10) to control flow of the mixture from the delivery fluid path (44) to the receiving vessel (55).

Method and apparatus to hyperpolarize materials for enhanced MR techniques

A system for polarizing a material to be used in techniques employing magnetic resonance (MR) is provided. The polarizer system includes a cooling chamber having a cryogenic refrigerant (26) therein for use in polarizing a substance (22). A sorption pump (46) is connected to the cooling chamber to reduce a pressure therein to allow for hyperpolarizing of the sample. The sorption pump is cooled by a refrigeration system (14, 72, 90) to promote molecular adsorption in the sorption pump. The cooling chamber, sorption pump, and refrigeration system are arranged in a closed system.
Method of producing a composition, composition and its use
The invention relates to a method of producing a composition comprising hyperpolarised 13C-pyruvate, the composition and its use as an imaging agent for MR imaging.

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Method and apparatus for producing contrast agents for magnetic resonance imaging
The present invention relates to an arrangement and a method for providing contrast agent for e.g. MRI (Magnetic Resonance Imaging) and NMR (Nuclear Magnetic Resonance) applications. The method according to the invention comprises the steps of obtaining (100) a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of a substrate compound, hydrogenating (110) the substrate with hydrogen gas (H2) enriched in para-hydrogen (p-1H2) to form a hydrogenated contrast agent and exposing (120, 305) the contrast agent to a sequence of pulses of magnetic field. The apparatus comprises a magnetic treatment unit (240) equipped with means for producing pulses of magnetic field.

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Method and apparatus for producing contrast agents for magnetic resonance imaging

The present invention relates to an arrangement and a method for providing contrast agent for e.g. MRI (Magnetic Resonance Imaging) and NMR (Nuclear Magnetic Resonance) applications. The method according to the invention comprises the steps of obtaining (100) a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of a substrate compound, hydrogenating (110) the substrate with hydrogen gas (H2) enriched in para-hydrogen (p-H2) to form a hydrogenated contrast agent and exposing (120) the contrast agent to an oscillating magnetic field in combination with a stationary magnetic field. The apparatus comprises a magnetic treatment unit (240) equipped with means for producing an oscillating and a stationary magnetic field.

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Contributors: Goldman, M., Axelsson, O., Jóhannesson, H., Ardenkjær-Larsen, J. H.
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Method and arrangement for producing contrast agent for magnetic resonance imaging

The present invention relates to an arrangement and a method for providing contrast agent for e.g. MRI (Magnetic Resonance Imaging) and NMR (Nuclear Magnetic Resonance) applications. The method according to the invention comprises the steps of obtaining (100) a solution in a solvent of a hydrogenatable, unsaturated substrate compound and a catalyst for the hydrogenation of a substrate compound, hydrogenating (105) the substrate with hydrogen gas (H2) enriched in para-hydrogen (p-H2) to form a hydrogenated contrast agent and exposing (110: 705) the contrast agent to a magnetic field cycling profile adapted for enhancing the contrasting effects of the contrast agent. The magnetic field cycling profile comprises an initial decrease of the magnetic field followed by at least one increase of the magnetic field, which increase should be arranged as to give a non-adiabatic (diabatic) remagnetisation of the contrast agent.

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Contributors: Ardenkjær-Larsen, J. H., Axelsson, O., Goldman, M., Jóhannesson, H.
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**Multidimensional nmr spectroscopy of a hyperpolarized sample**

The present invention relates to methods of performing Nuclear Magnetic Resonance (NMR) spectroscopy adapted for a hyperpolarized sample. The methods comprise the steps of hyperpolarizing a sample using DNP, wherein at least a portion of the NMR active nuclei receives hyperpolarization; performing NMR spectroscopy on the sample with the use of sequences of rf-pulses, wherein the pulse sequences comprises at least two rf-pulses, either on the same nuclei or on different nuclei, and wherein the pulse sequence is adapted for a hyperpolarized sample; and analysing at least two of the NMR spectra to obtain a characterization of the sample, or to obtain an interim result to be used in the NMR spectroscopy step.

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**Methods and devices for dissolving hyperpolarised solid material for nmr analyses**

The present invention relates to devices and method for dissolving solid polarised material while retaining a high level of polarisation. In an embodiment of the present invention a material is polarised in a strong magnetic field in a cryostat and then brought into solution while still inside the cryostat.

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Method of magnetic resonance investigation
This invention provides a method of magnetic resonance investigation of a sample, preferably of a human or non-human animal body, said method comprising: (i) producing a hyperpolarised solution of a high T1 agent by dissolving in a physiologically tolerable solvent a hyperpolarised solid sample of said high T1 agent; (ii) where the hyperpolarisation of the solid sample of said high T1 agent in step (i) is effected by means of a polarising agent, optionally separating the whole, substantially the whole, or a portion of said polarising agent from said high T1 agent; (iii) administering said hyperpolarised solution to said sample; (iv) exposing said sample to a second radiation of a frequency selected to excite nuclear spin transitions in selected nuclei e.g. the MR imaging nuclei of the high T1 agent; (v) detecting magnetic resonance signals from said sample; and (vi) optionally, generating an image, dynamic flow data, diffusion data, perfusion data, physiological data (e.g. pH, pO2, pCO2, temperature or ionic concentrations) or metabolic data from said detected signals, wherein said high T1 agent in said hyperpolarised solution has a T1 value (at a field strength in the range 0.01-5T and a temperature in the range 20-40 °C) of at least 5 seconds.

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