Slow Spin Magnetic Resonance Spectroscopy
01-07

Summary Value Proposition

Obtaining "in vivo" information on biological processes is believed to be a key element of improving the efficacy and efficiency of the drug discovery process. Slow spin magnetic resonance spectroscopy offers a new tool for obtaining such information in live animals that may eventually be extended to human clinical applications. In addition, it can improve the resolution of magnetic resonance spectroscopy in extracted "ex vivo" samples.

Background Needs and Drivers

It has been estimated that the cost of bringing one new successful therapeutic to market is on the order of $800 million. However, there is increasing evidence that the number of new therapeutics successfully introduced into the marketplace is declining, and the industry is seeking new analytical techniques to help it reverse this trend. It is believed that analysis of the efficacy and toxicity of the therapeutics in extracted "ex vivo" organs and tissues does not accurately reflect these measures in live animals and humans. As one pharmaceutical industry representative was quoted as saying "We have done a great job of developing drugs for dead people." In addition, analysis of extracted samples from live samples (blood, urine, etc.) is not adequate in many applications.

Technology Description

Metabolism involves the cell- and organism-level chemical processes that are necessary for life. A metabolite is any substance participating in metabolism, either as a precursor, intermediate, catalyst or product. Metabolites include a large range of substances such as organic acids, carbohydrates, amino acids, nucleosides, peptides, and so on. Changes in the metabolic profiles are the earliest cellular response to environmental or physiological changes such as toxin exposure or disease state, so metabolomics, i.e. the measurement and analysis of metabolism in biological systems, may be capable of, e.g., detecting and diagnosing a disease or evaluating the efficacy of drugs in an early stage. Magnetic resonance spectroscopy has been utilized for measuring the metabolic composition of biological objects for sometime (see Figure 1 for an example of stationary MRS providing metabolite spectra for specific imaging areas of the brain). However, a phenomenon known generally as "line broadening" limits MRS resolution and resulting utility for many types of analyses in biological objects, including the liver and the lungs.

Magic angle spinning (MAS) was developed as a means of addressing this line broadening problem. However, conventional MAS is conducted at spin speeds of several kHz, which is too fast to be used in many "ex vivo" biological applications and in all "in vivo" applications. Through the development and application of novel pulse sequences (i.e. PASS and PHORMAT) and other techniques, Battelle scientists have been able to demonstrate the efficacy of using MAS to enhance spectral resolution at spin speeds as low as 1 Hz (see Figure 2 below). [1] This development opens up a whole new range of

[1] The slow-MAS technique is protected under U.S. Patents 6,653,832; 6,670,811 and 6,836,165; one additional pending U.S. patent; and several non-U.S. pending counterpart patents.

potential biological applications for MR spectroscopy, including live animals and eventually humans.

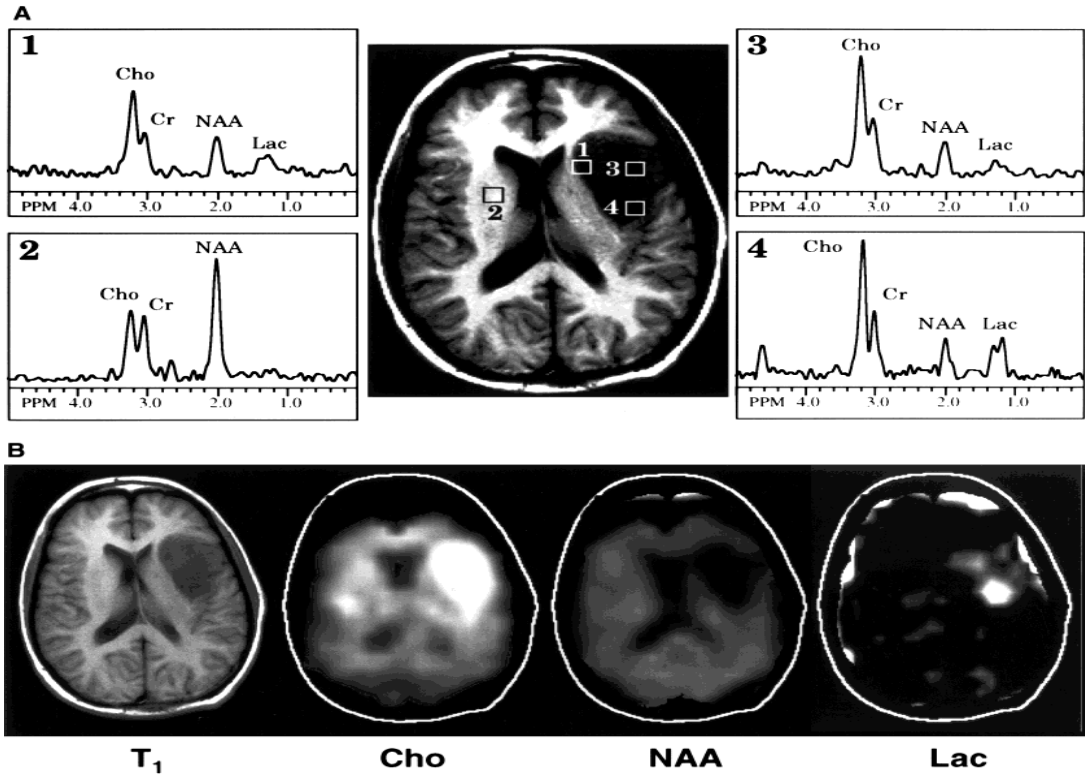

Figure 1. CSI: Heterogeneous metabolism of brain tumor. A: Local concentrations of each of the four principal metabolites to be recorded during a single MRS-examination. B: Results are displayed as metabolite-images (courtesy of Dr. P.B. Barker). From Magnetic Resonance Spectroscopy of the Human Brain, Brian Ross and Stefan Bluml, THE ANATOMICAL RECORD (NEW ANAT.) 265:54–84, 2001

The Battelle developers of slow-MAS believe that slow-MAS can be used to obtain the full range of metabolite information obtained by conventional MAS at rotation speeds compatible with living biological samples (see example comparison in Figure 2). In addition, the scientists have recently developed several generations of a localized slow-MAS technique that is needed in order to analyze specific areas of a subject's body. Work on localized MR spectroscopy using slow-MAS is on-going. However, as illustrated in Figure 3, initial results indicate that similar spectral resolution can be obtained on the liver of a live mouse similar to those obtained on an excised liver. Figure 4 presents the most recent results in "localizing" slow-MAS to a voxel size of 4×4×4mm3. The developers are optimistic that with additional effort, the voxel size can be further reduced to 2×2×2mm3. This would allow one to follow changes over time in the metabolite spectra in the individual organs of a test animal, which should be valuable complement to MRI imaging and other techniques in a wide variety of applications.

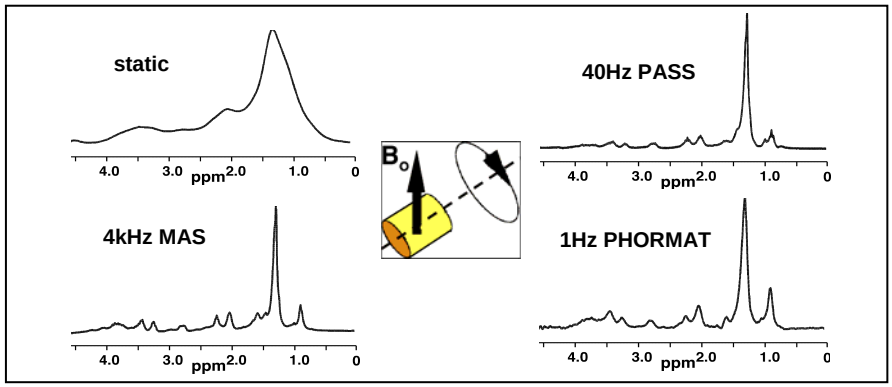

Figure 2. The 300 MHz ^{1}H NMR spectra of untreated fresh excised rat liver acquired by the various methods. Left top: by conventional liquid state NMR on a static sample; Left bottom: Conventional MAS with a sample spinning rate of 4kHz; Right top: ^{1}H PASS spectrum using a sample spinning rate of 40Hz; Right bottom: ^{1}H PHORMAT spectrum using a sample spinning rate of 1Hz. The insert picture illustrates the magic angle sample spinning of the sample.

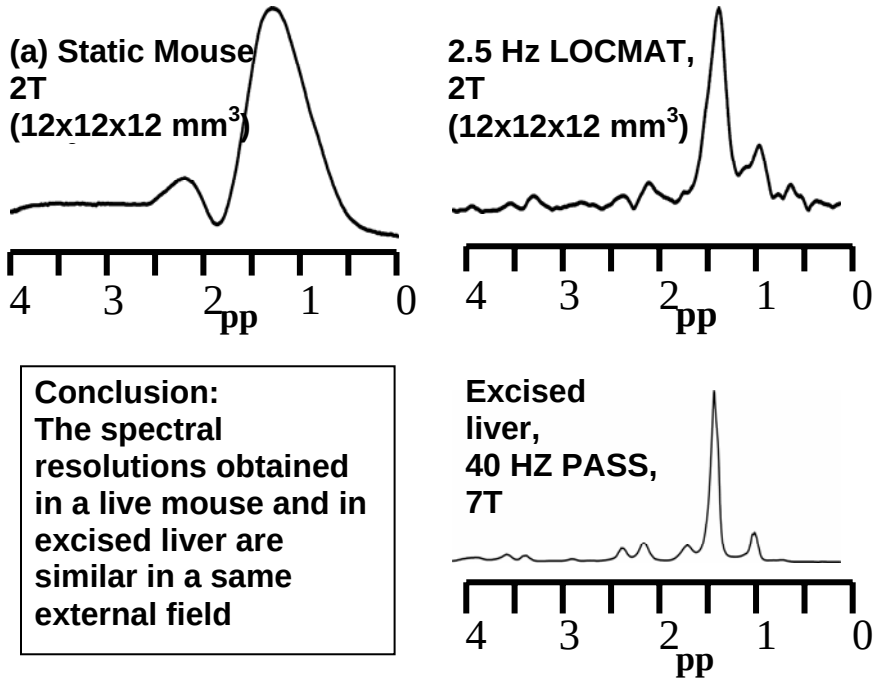

Figure 3 - Localized PHORMAT (LOCMAT) in the liver area of a live mouse and in an excised liver

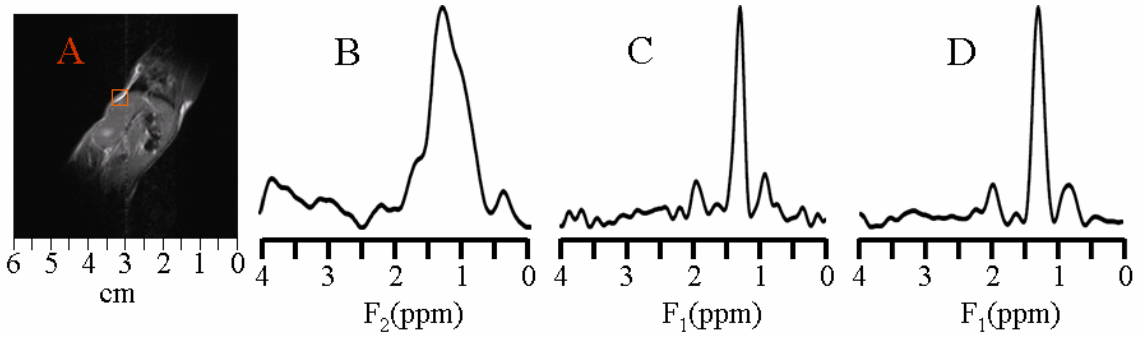

Figure 4 - 85 MHz in vivo 1H LOCMAT on a live mouse with voxel size 4×4×4mm3. A: Planning imaging, showing the location of the localized voxel; B: Anisotropic projection; C: isotropic spectrum from 1H LOCMAT with 40 evolution increments, incremented by 1.666ms. D: 20 evolution increments.

Note that in the longer term, the slow-MAS technique could eventually be applied to humans. Concepts for the implementation of this idea are shown in Figure 5. Although human applications would require substantial engineering development and are believed to be a number of years away, they reinforce the substantial potential value of the slow-MAS technique. Human applications of slow-MAS would provide an invaluable complement to MRI studies by allowing clinicians to understand the metabolic composition of individual areas of the body as well as imaging these areas.

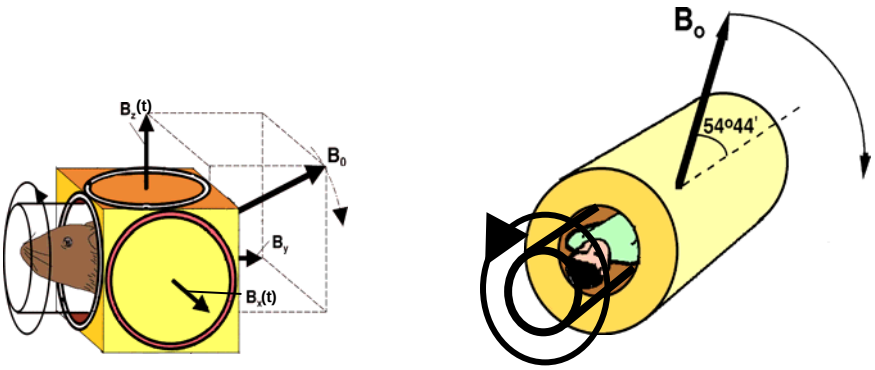

Figure 5 – Concepts for Future Development of Slow-MAS Illustrating Rotation of the Magnetic Field or Rotation of the Magnet as an Alternative to Sample Rotation