Round Table Discussion Session 4:

Science Drivers for Ultrahigh Field NMR/MRI in the US

Discussion leader: *Angela M. Gronenborn*
Scribe: *Jean Baum*

Discussion panel:
Ad Bax, Brad Chmelka, Chris Jaroniec, Ann McDermott, Gerhard Wagner, Peter Wright and all participants of the workshop

Session Agenda

3:45 – 4:00 pm

Introduction – setting the stage

4:00 – 4:30 pm

Structural, Molecular, Cell, Chemical Biology

4:30 – 5:00pm

Chemistry, Catalysis, Materials Science

5:00– 5:25 pm

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

5:25 – 5:50 pm

Biomedical Sciences and Physiology, Particularly Brain and Developmental Biology

5:50 – 6:00 pm

Summary

Examples of Integrative Transformational Science: The Marriage of NMR and MRI

Science at a Crossroads: Integrative NMR/MRI Transformational Research Requires UHF

I. Molecular basis of neurodegeneration

Alzheimer's, Parkinson's, Lewy body dementia, traumatic brain injury, and age-related vision impairments are associated with the conversion of proteins from soluble to insoluble states. UHF **solution** and **solid-state NMR** and human brain and eye **MRI** needs to be integrated to understand and develop possible treatments for these diseases.

NMR based molecular studies, in solution and in the solid state, allow characterization of the structure and dynamics of biomolecules, including **disordered and highly dynamic proteins (IDPs)**, which are of central importance in neurodegenerative disorders. These biomolecules cannot be studied by most analytic techniques, other than NMR. The utmost sensitivity and resolution afforded by high magnetic fields is required to overcome limited chemical shift dispersion and low concentrations.

MRI is able to identify alterations in brain neuronal architecture and inflammation associated with neurodegeneration. UHF - beyond 7 T - MRI can also detect protein aggregates, including Abeta and tau, associated with dementias and brain trauma (e.g. concussion) because of the magnetic susceptibility contrast associated with aggregates less than 100 micrometers.

Science at a Crossroads: Integrative NMR/MRI Transformational Research Requires UHF

II. Energy-related materials

Efficient, environmentally friendly and sustainable materials for solid-state lighting, electrochemical energy generation and storage (batteries, fuel cells, and supercapacitors), and non-precious-metal automotive emission catalysts are vital to prevent depletion of natural resources, decrease pollution, and ultimately curtail climate change. UHF **solution** and **solid-state NMR MRI** needs to be integrated to chemically and spatially characterize these materials

NMR permits non-invasive, site-specific characterization of these materials and provides unprecedented level of information on the local structure, dynamics, and chemical transformations that occur in these systems. The dramatically enhanced sensitivity and resolution at UHF is required for detection of signals from quadrupolar nuclei and those displaced paramagnetically.

MRI enables non-invasive characterization of these materials, including visualization, of structural changes in real-time, and in a spatially-resolved manner. Stray field imaging at ultrahigh fields provides opportunities for both increased gradients, resulting a higher spatial resolution (now at 100 μm) and increased sensitivity for a wide range of materials.

Structural, Molecular, Cell, Chemical Biology

Intrinsically disordered biomacromolecular systems, including low-population transient states involved in catalysis, molecular recognition and many regulatory processes

- ✓ A new frontier for which only NMR is capable of characterizing structure and dynamics of minor/transient states.
- ✓ Spectral dispersion is critical for this technology.
- ✓ Direct X-nucleus (^{13}C, ^{15}N) detection becomes important for these kinds of systems, e.g. in per-deuterated molecules for which back-exchange of amide protons is difficult or impossible.
- ✓ TROSY selection in large and complex systems.
- ✓ **UHF is a requirement for direct X detection because of low sensitivity.**

Structural, Molecular, Cell, Chemical Biology

Integral and peripheral membrane proteins (including receptors and transporters in signaling pathways) in native-like or native environments.

- ✓ In addition to the determination of native structures, the characterization of dynamics and conformational exchange will permit the mapping of allosteric pathways, elucidation of mechanisms, and will lead to unique functional insights into critical signaling events disrupted in disease.
- ✓ Membrane proteins represent the majority of important drug targets, including CNS drugs, antimicrobials, and anti-cancer agents.
- ✓ These systems, because of theirs size and complexity, need the improved resolution and sensitivity of UHF for full characterization of their structure and dynamics in solution and in the solid states.

Structural, Molecular, Cell, Chemical Biology

Large and/or heterogeneous non-crystalline biological assemblies

- ✓ Amyloid fibers and oligomeric assemblies that are critical in Alzheimer's and related protein deposition diseases.
- ✓ Multicomponent assemblies of viral and bacterial pathogens whose properties need to be elucidated for understanding of infectious diseases.
- ✓ Large nucleic acid assemblies and their alignment in the magnetic field based on magnetic susceptibility anisotropy.
- ✓ These systems need UHF for increased alignment, and improved resolution and sensitivity for thorough characterization of their structure and dynamics.

Structural, Molecular, Cell, Chemical Biology

Metallobiomolecules and pharmaceuticals: **structure, dynamics, chemical reactivity via measurements of previously inaccessible quadrupolar nuclei.**

- ✓ Assessment of physiological processes or identification of metal binding sites and protonation states in biomolecules.
- ✓ Structural and dynamics analysis of pharmaceutical polymorphs and quality control studies.
- ✓ The use of UHF enables quadrupolar spectroscopy for many of such systems. Particularly impressive gains are expected for the measurements of rare nuclei, such as ^{43}Ca, ^{17}O, $^{37/39}Cl$, ^{41}K as well as for other half-integer quadrupolar transition metals.

Structural, Molecular, Cell, Chemical Biology

Metabolomics, in-cell spectroscopy and imaging

- ✓ This is a rapidly expanding frontier in biochemical research.
- ✓ Physiological states become accessible in real time – phosphorlylation and other PTM processes.
- ✓ The biggest payoffs of UHF are expected in this area where sensitivity and resolution directly enhance the ability to quantify metabolic changes and identify intracellular processes.

Chemistry, Catalysis, Materials Science

Heterogeneous catalysts (active sites) for improved activities and selectivity; Processing natural gas, petroleum, or biomass into high-value hydrocarbon products, polymers, or fine chemicals

- ✓ The information on these systems is obtained through direct measurements of quadrupolar nuclei with non-integer spins.
- ✓ *In situ* NMR measurements of chemical and physical processes permit monitoring of material compositions and structures during hydrothermal syntheses of catalysts, cements, and high-performance ceramics and under industrially realistic operating conditions.
- ✓ UHF is critical to provide enhanced sensitivity and resolution.

Chemistry, Catalysis, Materials Science

Materials for solid-state lighting, electrochemical energy generation and storage (batteries, fuel cells, and supercapacitors) and non-precious-metal automotive emission catalysts

- ✓ Detailed studies of their structure and molecular mechanisms requires detection of paramagnetically displaced NMR signals.
- ✓ UHF enables measurements of such species, through enhanced resolution and sensitivity.

Chemistry, Catalysis, Materials Science

Carbon sequestration materials, biominerals, cementitious materials, heterogeneous catalysts

- ✓ Detailed analysis of their structure and reactivity requires detection of low-gamma or dilute nuclei, such as ^{17}O and ^{33}S (heterogeneous catalysts), ^{13}C and ^{25}Mg (carbon sequestration materials), ^{43}Ca NMR (biominerals, bone and teeth, and cementitous materials).
- ✓ Detection of these nuclei is enabled by UHF providing enhanced sensitivity and resolution.

Chemistry, Catalysis, Materials Science

In situ characterization of chemical and physical processes for monitoring material compositions and structures

- ✓ During hydrothermal syntheses of catalysts, cements, and high-performance ceramics.
- ✓ Under industrially realistic operating conditions of catalysts, batteries, or photovoltaic materials.
- ✓ During fluid transport in microscale chemical reactors, microfluidic devices, membrane separations, or polymer manufacturing processes.
- ✓ UHF is necessary for the detection of minor potentially detrimental processes.

Chemistry, Catalysis, Materials Science

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

Membrane-bound protein-protein complexes at interfaces with synthetic host materials and in biofilms

- ✓ Characterization of structure and dynamics of these systems is essential for biotechnology applications and safe biomedical device development.
- ✓ UHF are required for enhanced sensitivity and resolution.

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

Proteins and inorganic species in bone matrices and biomineralization processes

- ✓ Understanding structure-function relationships and role of natural and synthetic biomaterials in bone diseases is required for advancing bioengineering applications.
- ✓ Structural analysis of molecules involved in bone health is critical for preventing age-related biomineralization-associated pathologies.
- ✓ Studies of these complex systems require UHF for analysis of dilute/low-gamma/half-integer quadrupolar nuclei (e.g., ^{43}Ca, ^{17}O, and ^{25}Mg) and low abundance species in the bone matrix.

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

Identification of dilute metal ions or organic pollutants in soils and minerals and their transport mechanisms

- ✓ Direct detection of these low-concentration species in solid pools and liquid phases of soil is required for in-depth analysis in environmental engineering applications and in biogeochemistry.
- ✓ Assessment of heavy metal mobility and transfer between soil phases permits the determination of plant-available amounts for environmental impact studies.

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry

Biomedical Sciences and Physiology, Particularly Brain and Developmental Biology

Metabolism of drugs and mapping of neuronal responses.

- ✓ Direct detection of drug-drug interactions *in vivo* is critical in pharmacokinetic studies to prevent severe side effects.
- ✓ Measurements of drug/prodrug amounts at the desired site of action necessitates the sensitivity afforded by UHF.
- ✓ UHF was required to map the auditory response of the primary cortex in humans to sound of different frequencies by fMRI (7 Tesla).

Biotechnology, Bioengineering, Environmental Engineering, Biogeochemistry