KARL-FRIEDRICH BONHOEFFER AWARD LECTURE


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β-Amyloid, Microwaves and the Magic Angle

Nuclear magnetic resonance (NMR) is the prime tool for structure elucidation of molecules that are difficult to study with other methods for structural biology, such as cryo-EM or X-ray crystallography. Methodological development as well as improved instrumentation have revolutionized what is currently possible with this method. This presentation will selectively cover three closely related sets of experiments that have become possible because of emerging techniques: NMR with very fast magic angle spinning (MAS), dynamic nuclear polarization (DNP) to enhance signals by orders of magnitude, and their application to structural determination of $A\beta_{1\text{-}42}$, $A\beta_{1\text{-}40}$ and β_2-microglobulin amyloid fibrils.

Approximately 120 years ago, Auguste Deter, the first patient diagnosed with Alzheimer's disease, passed away and fibrils composed of the $A\beta_{1\text{-}42}$ protein, the toxic species in AD, were found postmortem in her brain. Since that time there have been numerous attempts to understand the structure of these fibrils, but, since these species do not diffract to high resolution and are insoluble, a true atomic resolution structure was lacking. Accordingly, we developed a suite of MAS dipolar recoupling experiments that permit the measurement of multiple ^{13}C-^{13}C and ^{13}C-^{15}N distances and the determination of atomic resolution structures of fibrils. We demonstrate the methodology with a description of the high-resolution structure of fibrils of monomorphic $A\beta_{1\text{-}42}$, constrained by measurement of over 500 distance restraints. We have also used these techniques to determine the structure of $A\beta_{1\text{-}40}$, the second major component of Alzheimer's disease, and β_2-microglobulin associated with dialysis related amyloidosis.

Second, to increase the signal-to-noise in MAS spectra and to better determine molecular structures, we developed methods to perform high field dynamic nuclear polarization (DNP) experiments. The experiments utilize sub terahertz microwaves (~150-600 GHz) generated by gyrotron microwave sources together with paramagnetic polarizing agents to enhance the sensitivity of MAS NMR experiments. Specifically, we irradiate electron-nuclear transitions that transfer the large electron polarization to nuclear spins via the Overhauser, cross and solid effects. In addition, we have recently initiated time domain DNP in order to circumvent the field dependence of CW DNP. We show that spin locking the electrons and chirping the microwave frequency serves as an effective approach to time domain DNP. Enhancements of 500 can be achieved, and we present applications of DNP to $A\beta_{1\text{-}42}$. Future structural biology DNP experiments will likely be performed at high spinning frequencies using MAS rotors fabricated from diamond single crystals.

Wednesday, 11.12.2024, 11:00 am

Host: Holger Stark

Manfred Eigen Lecture Hall
Fassberg Campus

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