Highlighted Research: Professor Christian L. Degen

Christian Degen joined the Department of Chemistry as a new faculty member in the fall of 2009. He carried out his Ph. D. in Physical Chemistry under Professor Beat H. Meier at ETH Zurich, Switzerland, and subsequently worked as a post-doctoral associate at the IBM Almaden Research Center in San Jose, CA. His research focuses on the application of magnetic resonance imaging and spectroscopy at the extreme nanoscale in structural biology and for chemical surface identification. Funding for Christian Degen's appointment was provided in part by the ***Paul and Marcia Cook Fund for Innovation in Chemistry, established by Mr. Paul Cook '47, in 2001.***

Magnetic resonance imaging, MRI, is mostly known from its application within medical diagnostics. MRI reveals concealed organs in the interior of our body, and worldwide, millions of investigations with MRI are performed each year. MRI is often superior to other imaging techniques, because it is highly chemically specific and does not cause any damage to tissue.

Scientists would love to have a similar method at hand to non-invasively determine the three-dimensional structure of viruses or complex proteins. In this way they could gain new insight into causes and mechanisms of many diseases.

Unfortunately, the spatial resolution of MRI – which is a few micrometers at best – is far too crude for such endeavors. Despite considerable effort, attempts to push this resolution into the realm of high-resolution microscopy have been stymied by fundamental limitations, especially detection sensitivity.

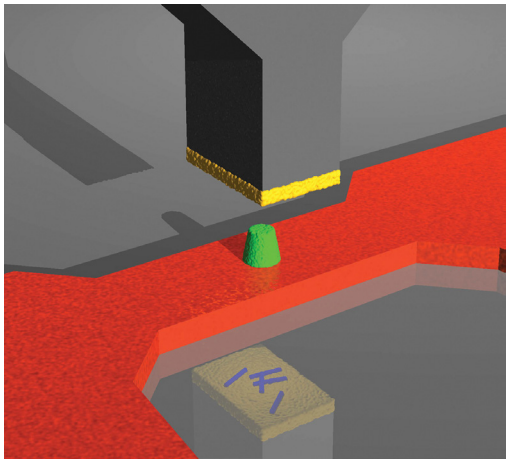

Fig 1: An artistic view of the magnetic tip (green) interacting with virus particles (blue) at the end of the cantilever arm (dark grey).

MRI takes advantage of the faint magnetic signal of atomic nuclei in the sample. Using radio-waves of suitable frequency (which varies for different chemical elements), the nuclei can be excited into resonance. After turning off the radio-frequency field, the nuclei send out a signal which can be collected by an antenna and turned into a three-dimensional distribution of the particular atomic species, often hydrogen. The nuclear signal is, however, very weak: More than a trillion atoms are typically needed to generate a detectable signal. This presumes certain sample volumes and limits the resolution of the image.

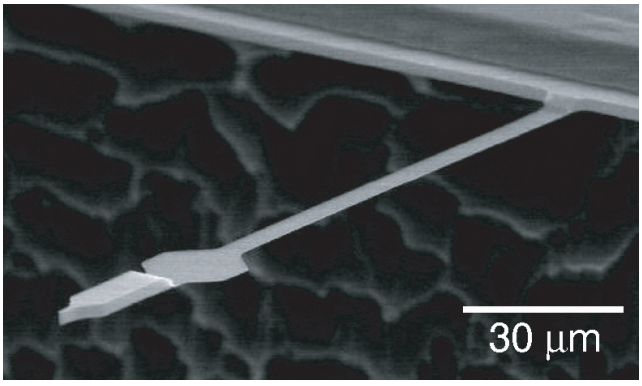

Fig 2: Ultra force sensitive silicon cantilever

Pioneering advances have over the last decade been made by combining the advantages of MRI with the extraordinary sensitivity of scanning force microscopy. Magnetic resonance force microscopy, or MRFM, exploits the small magnetic forces nuclei experience in an inhomogeneous magnetic field. Typically, the sample is attached to the arm of a silicon cantilever and brought into close proximity of a miniature magnetic tip (see Figure 1). An image is then acquired by three-dimensional scanning of the sample with respect to the tip and measuring the magnetic force at each point.

The cantilever is the most critical component to the setup. It needs to be as long and skinny as possible to achieve highest force sensitivity (Figure 2). Currently, such cantilevers can measure forces as small as one Attonewten (10^{-18} N), which is roughly one-billionth of the force needed to break a chemical bond.

MRFM has over the last years led to a dramatic increase in MRI imaging resolution. Recently, Christian Degen and his co-workers at IBM Almaden demonstrated that three-dimensional MRI of individual tobacco mosaic virus particles can be taken, at a spatial resolution approaching 5 nm (Figure 3) [1]. This is roughly 1,000 times finer than conventional MRI such as used in clinical medicine, and it is within a factor of ten of the resolution of cryo-electron tomography, the highest resolution imaging technique used by structural biologists today.

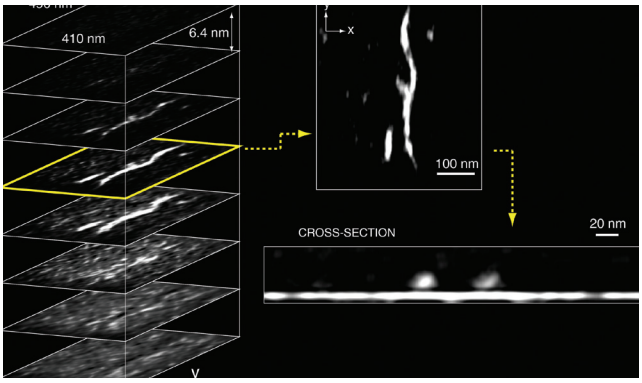

Fig 3: Three-dimensional MRI of several viral fragments lying on a surface covered by a thin film of organic molecules. Pictures to the right show a horizontal and a vertical cut through the 3D image.

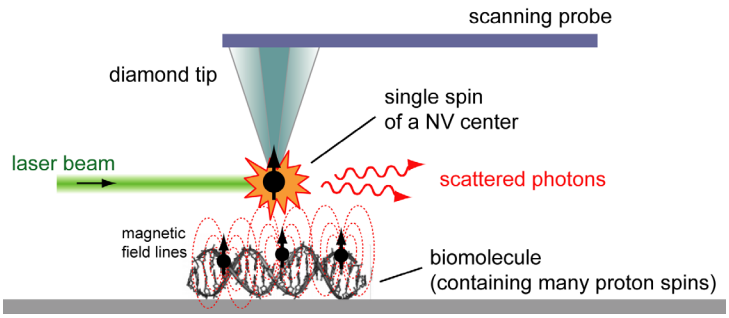

Fig 4: Basic principle of magnetic sensing with a diamond defect

In his research, Christian Degen wants to build on these advances and to apply MRFM for the imaging of complex biomolecular assemblies, like enveloped viruses (such as HIV), Amyloid fibrils (implicated in Alzheimer's disease), or functional cellular units. "Imagine that one could label specific proteins within such an complex, and then take a series of pictures revealing the location of each type of protein in the interior of the complex." As a further advantage, all of these studies can in principle be done on a single entity, which is important for large assemblies as they often show morphology.

Maybe that force detection is not even the best method to detect tiny spin signals. For the past two years Christian Degen has been pursuing a completely different approach to "Nano-MRI" based on optically-active diamond defects. In contrast to a force sensor, it's the electronic spin associated with a certain lattice defect in diamond which functions as a point-like magnetic sensor. This so-called nitrogen-vacancy defect (a substitutional nitrogen atom paired with a vacancy) is fluorescent and shows a spin-dependent optical scattering rate. In this way, magnetic fields can be measured locally and very precisely via the Zeeman effect. Combination with a scanning probe then permits one doing microscopy (Figure 4) [2].

Most importantly for biological imaging, sensing with a diamond spin can in principle be done under ambient conditions. Also, no inhomogeneous field is required, important for chemical spectroscopy by nuclear magnetic resonance (NMR). Indeed, one of the more visionary goals is the full chemical analysis of surfaces, potentially with atomic resolution. Also, nanodiamonds hosting diamond defects could find application as chemically-sensitive biomarkers in cells. This would not only help structural biologists, but would also boost surface science and materials research in general.

[1] C. L. Degen et al., PNAS 106, 1313 (2009). (doi:10.1073/pnas.0812068106).
[2] C. L. Degen, Nature Nanotechnology 3, 643 (2008). (doi:10.1038/nnano.2008.328).