Advanced NMR & Imaging

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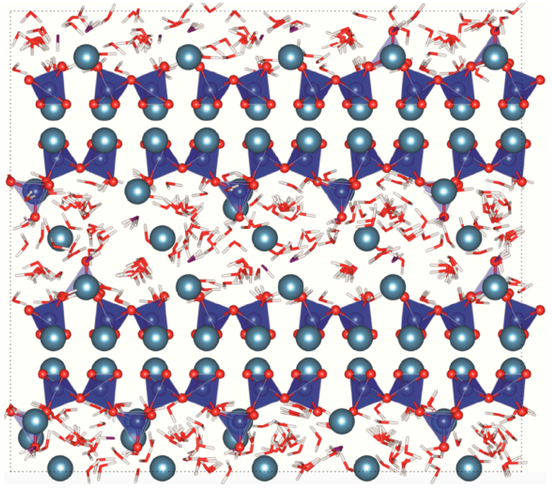
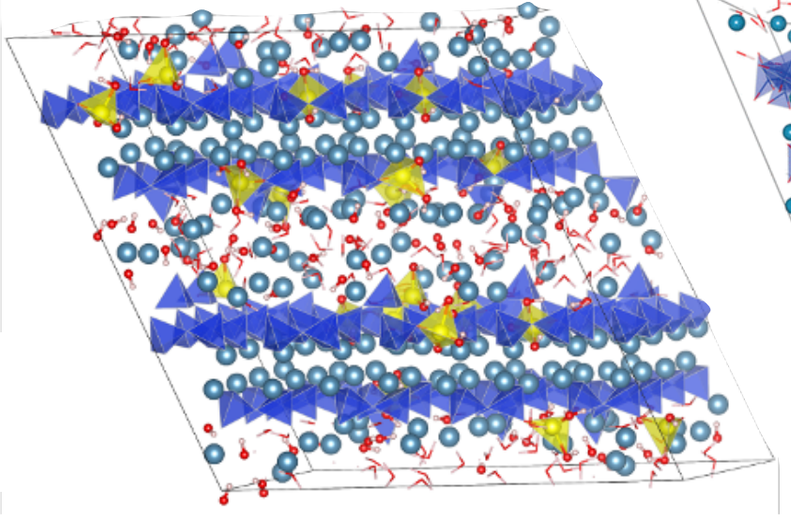
Atomic-Level Structures of C-S-H, C-A-S-H & C-S-H-Zn

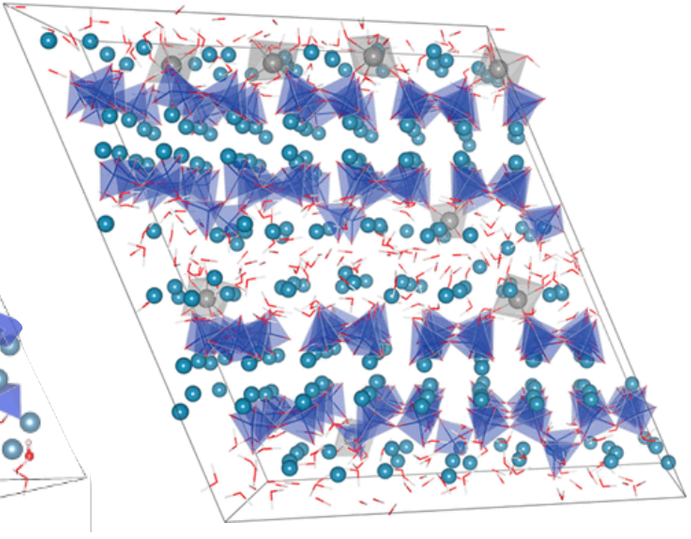
Cementitious Calcium Silicate Hydrate



Cementitious Zinc-Modified Calcium Silicate Hydrate



Cementitious Calcium Aluminate Silicate Hydrate



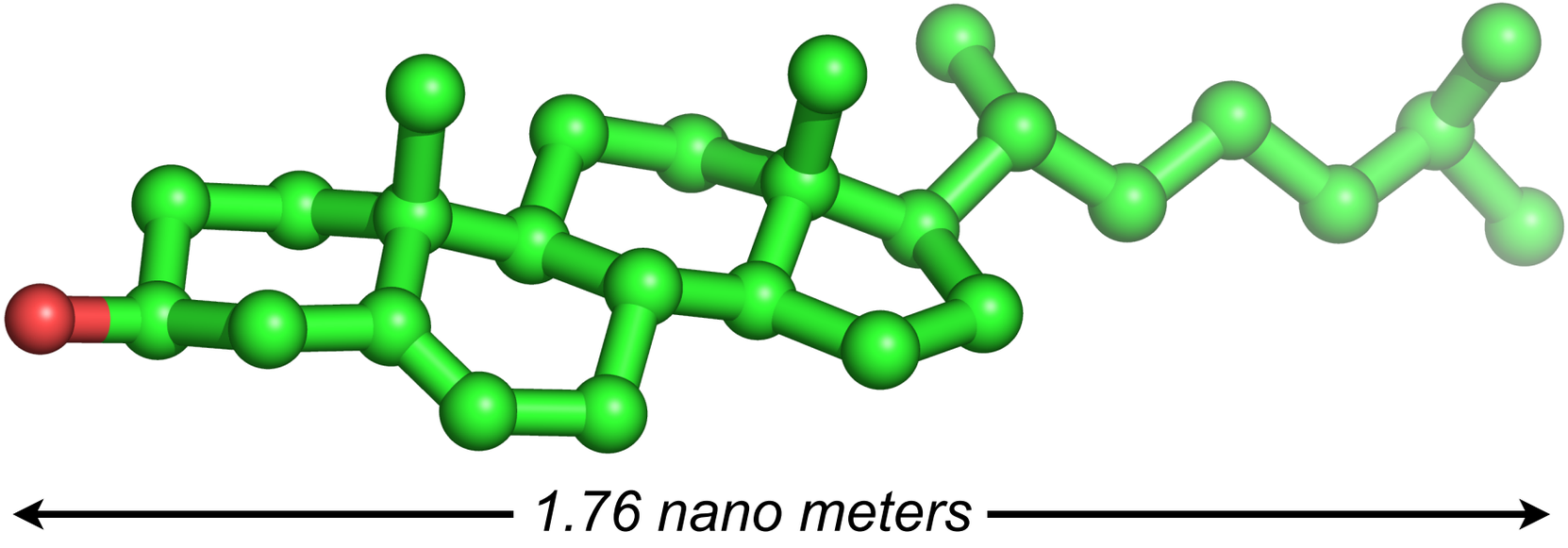
Sangodkar, Smith, Gajan, Rossini, Roberts, Funkhouser, Lesage, Emsley, Chmelka, J. Am. Chem. Soc. **137**, 32, 8096 (2015)

Kumar, Walder, Mohamed, Hofstetter, Srinivasan, Rossini, Scrivener, Emsley, Bowen, J. Phys. Chem. C **121**, 32, 17188 (2017)

Mohamed, Moutzouri Berruyer, Walder, Siramanont, Harris, Negroni, Galmarini, Parker, Scrivener, Emsley, Bowen, J. Am. Chem. Soc. **142**, 25, 11060 (2020)

Morales-Melgares, Casar, Moutzouri, Venkatesh, Cordova, Mohamed, Scrivener, Bowen, Emsley, J. Am. Chem. Soc. **144**, 50, 22915 (2022)

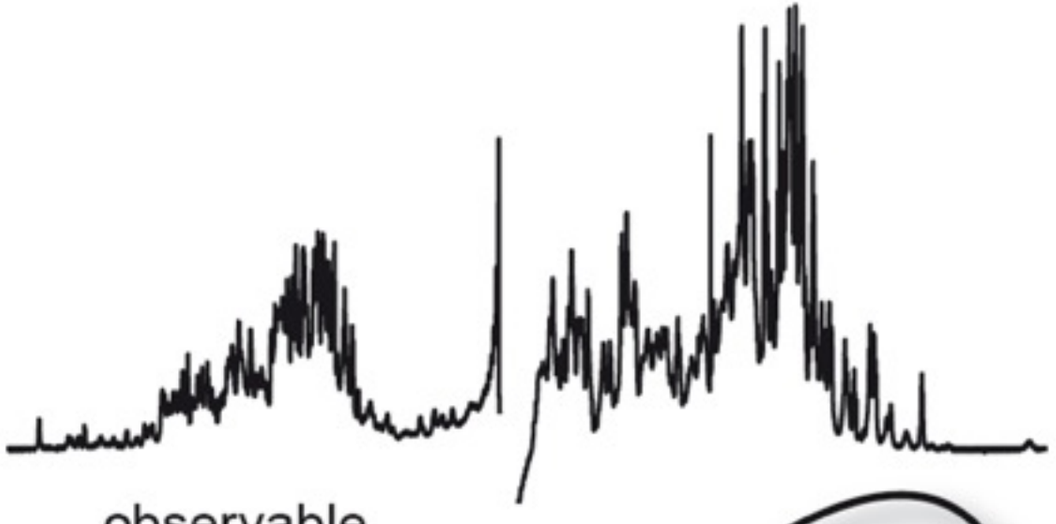
Representation of a Molecule of Cholesterol (Actual Size)



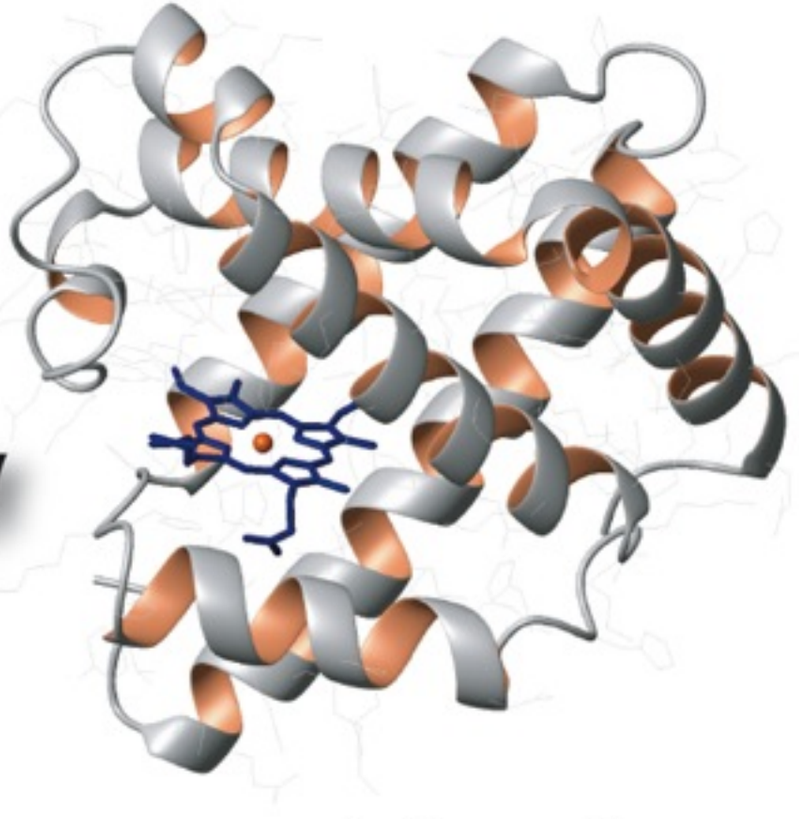
(reminder: 1 nano meter = 0.000000001 meters)

How can we “see” the invisible?

*we need spies... **observables** that are more or less direct reporters of molecular structure.*



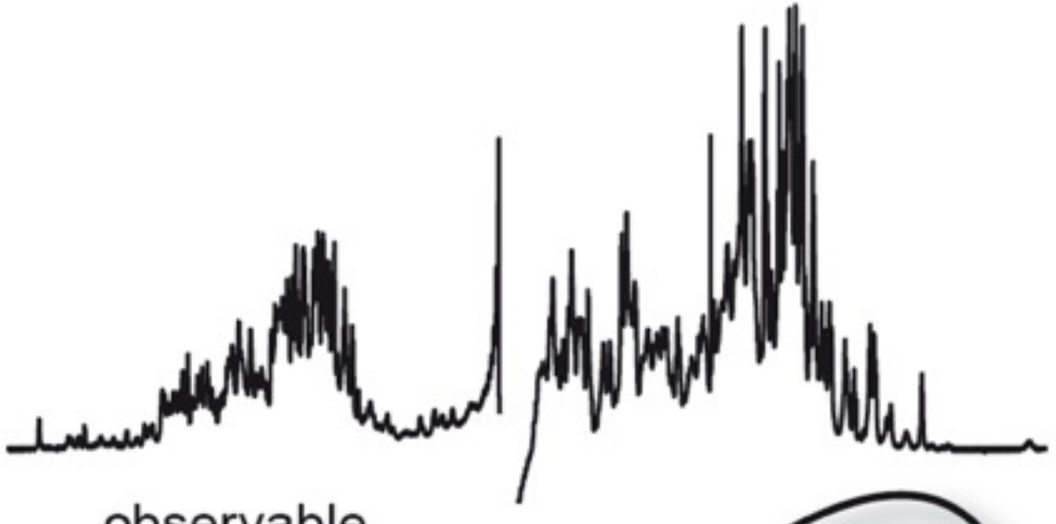
observable



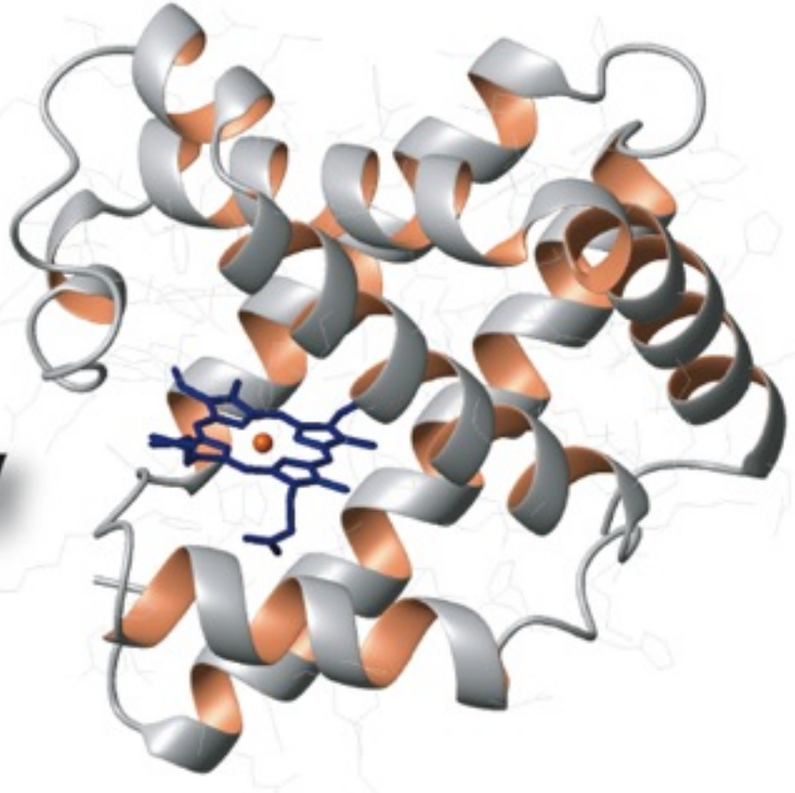
inobservable

How can we “see” the invisible?

*We will **interpret** the **observables** to construct **a model** of the molecular structure.*



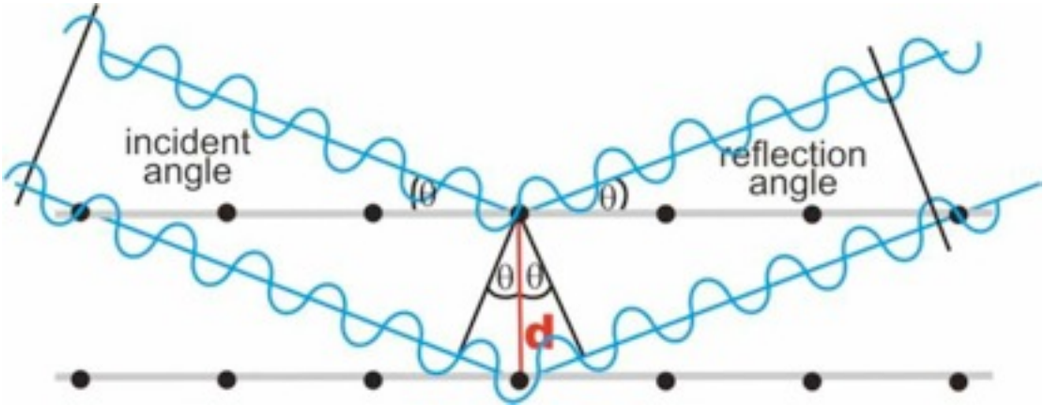
observable

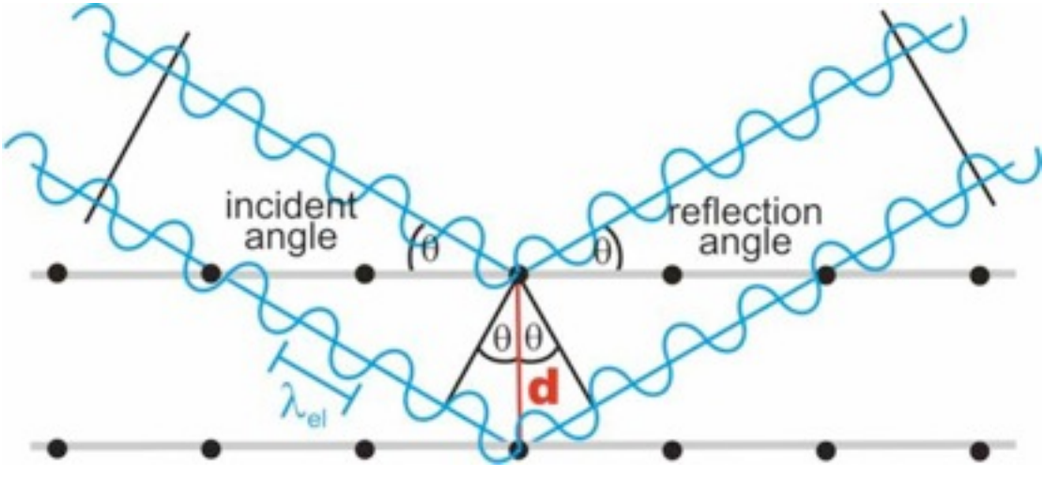


inobservable

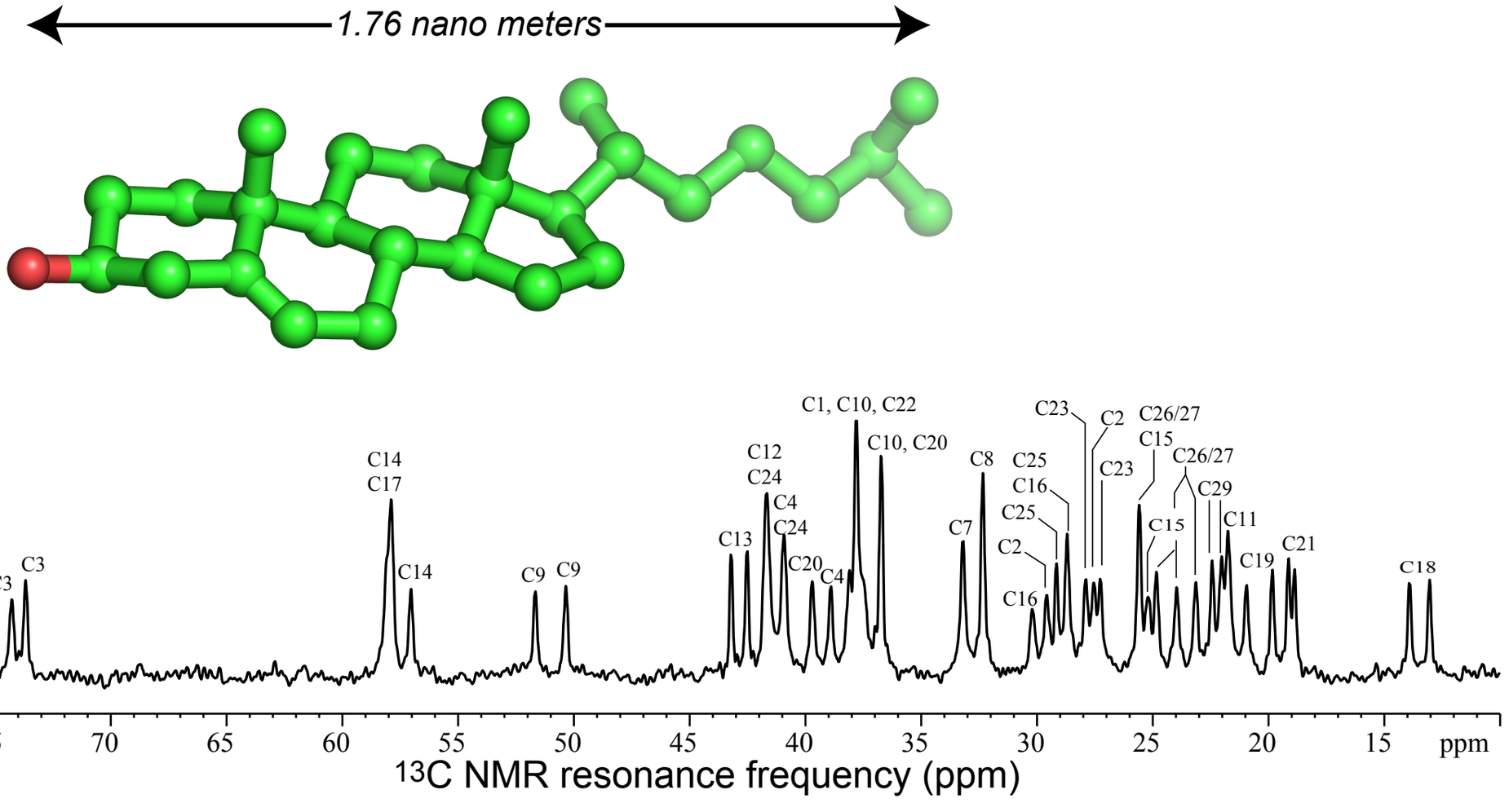
Observable N° 1:
Bragg Diffraction of X-Rays

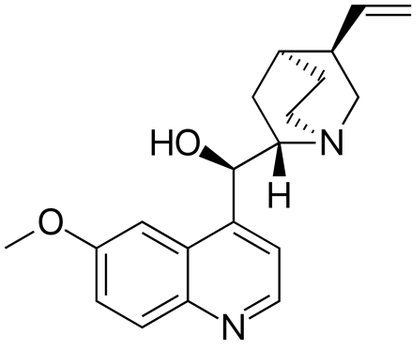
$$n\lambda = 2d\sin\Theta$$





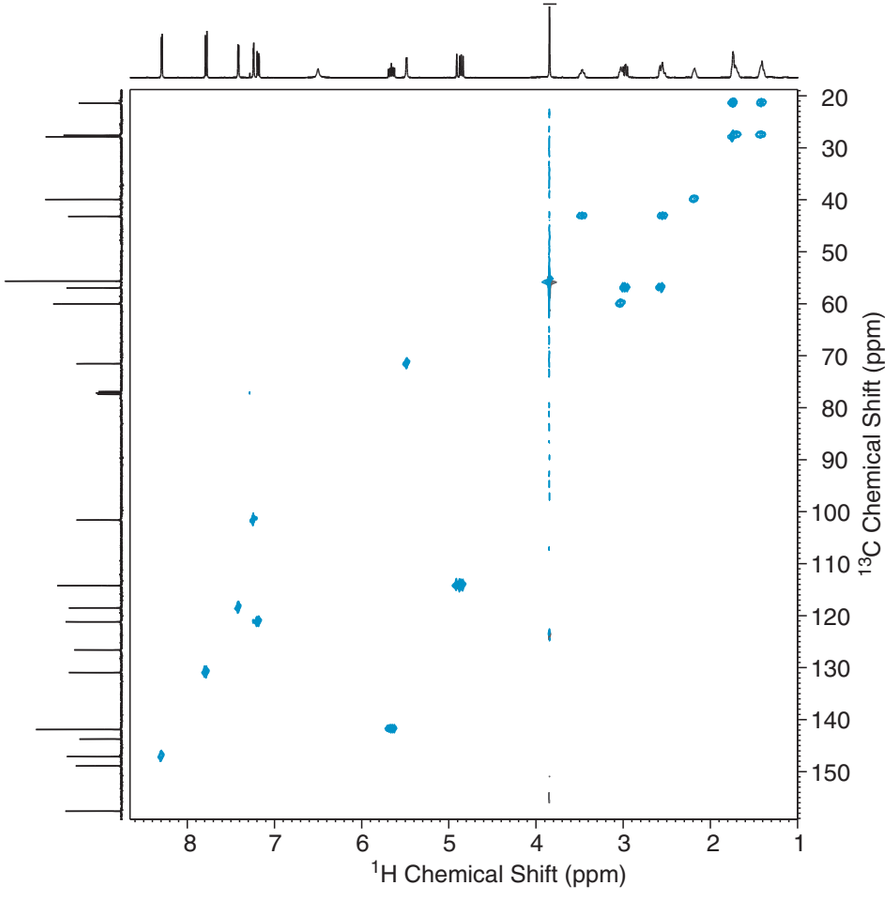
Spectroscopy Provides Eyes for Molecular and Materials Sciences

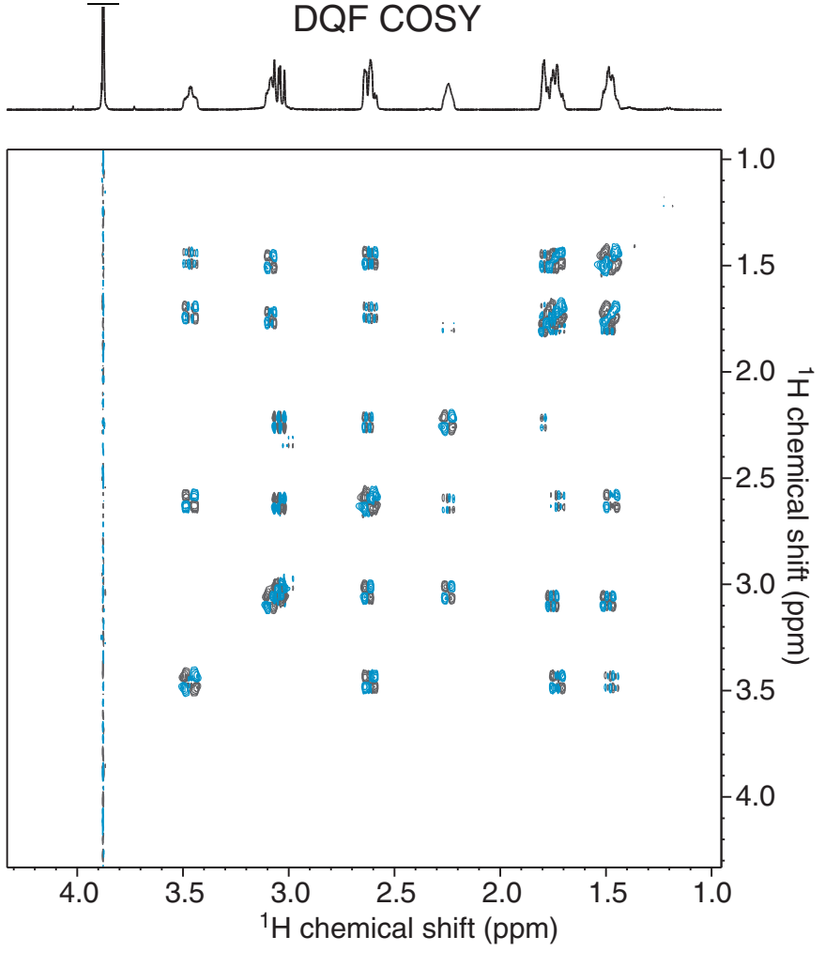




Observable N° 2: NMR correlation spectra

$$\omega = -\gamma(1-\sigma)B_0$$

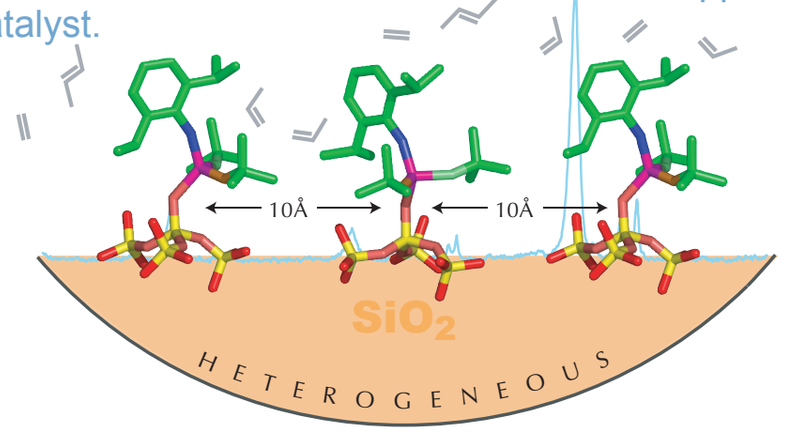




Chemical shift correlations provide a unique fingerprint to discover structural formula

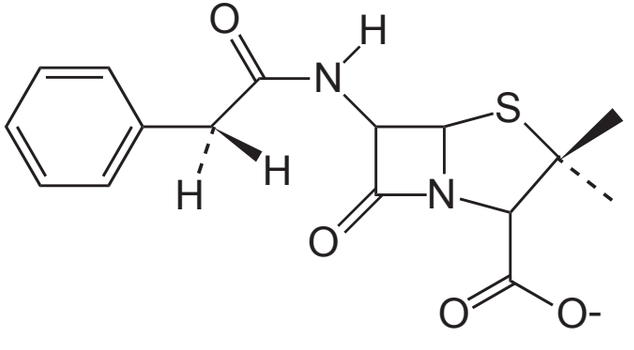
basic chemistry and catalysis

The first spectra from catalysts are recorded in the 1970s, as NMR revolutionizes the way chemists approach multi-step synthesis. In 2006 Schrock wins the Nobel Prize in Chemistry for his development of meta-thesis, which has become central to basic industrial chemistry. In the same year he uses high-field solid-state NMR to validate the mechanism of olefin meta-thesis on a supported catalyst.

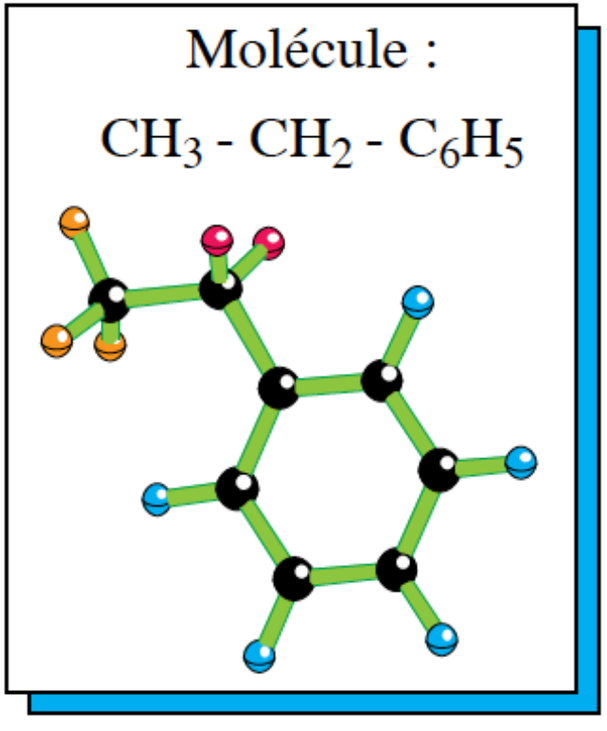


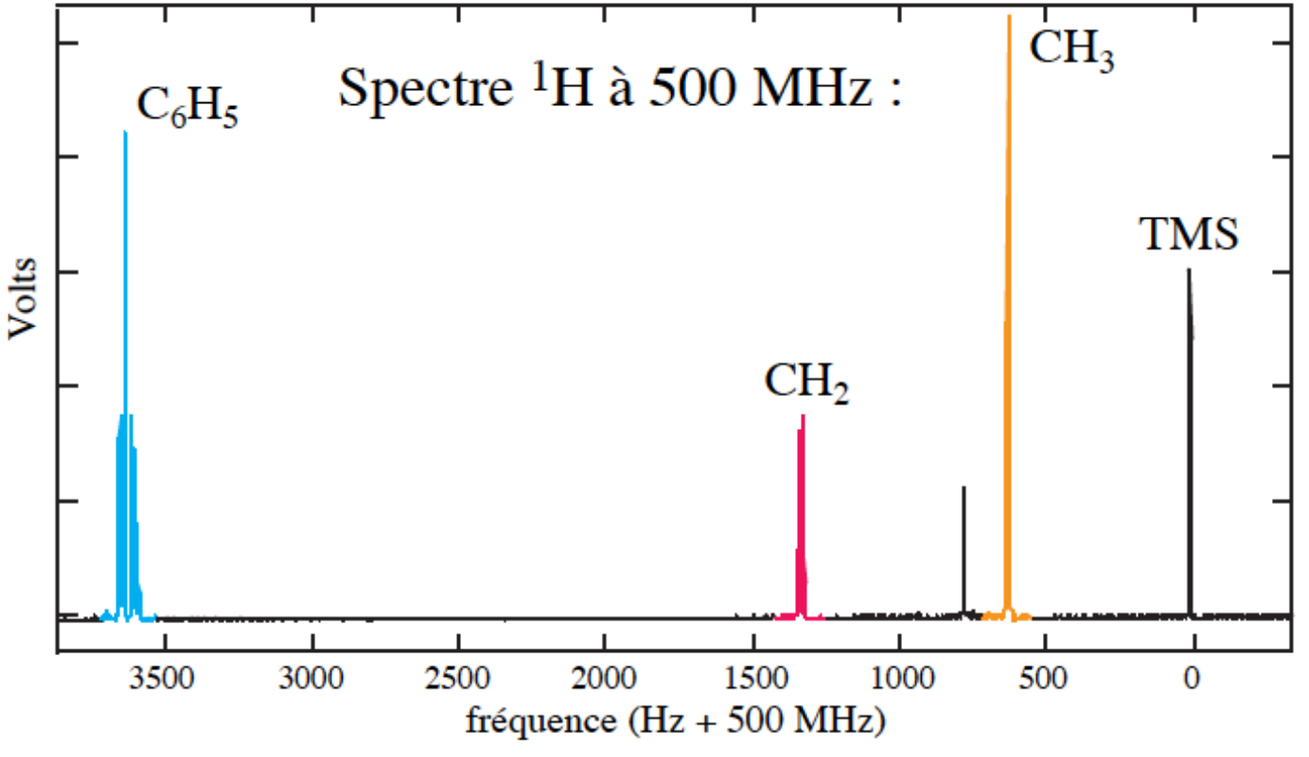
from penicillin to taxol: stereochemistry in the drug industry

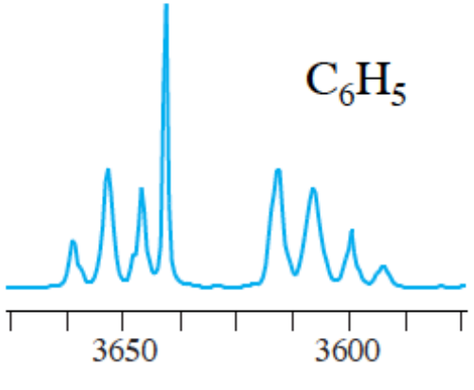
In 1959 Karplus proposes a dependence of H-H coupling constants on dihedral angles. Today this forms the basis for the determination of the stereochemistry of many of the therapeutic drugs on the market, crucial to both their safety and efficiency.

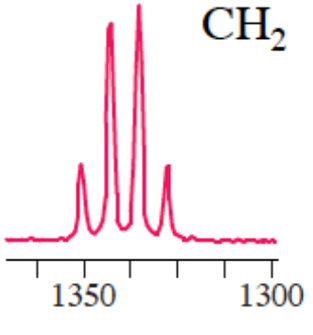


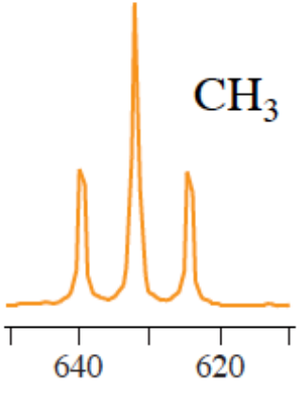
NMR: Is this it?



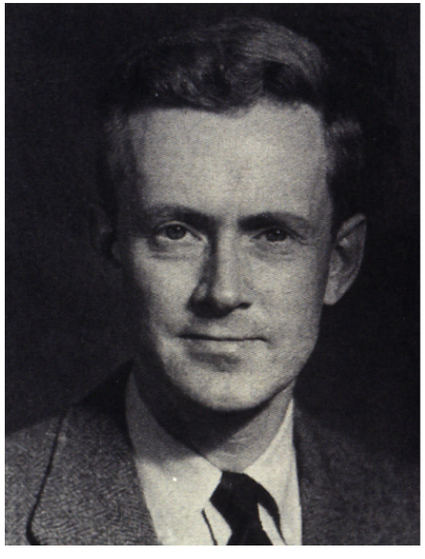




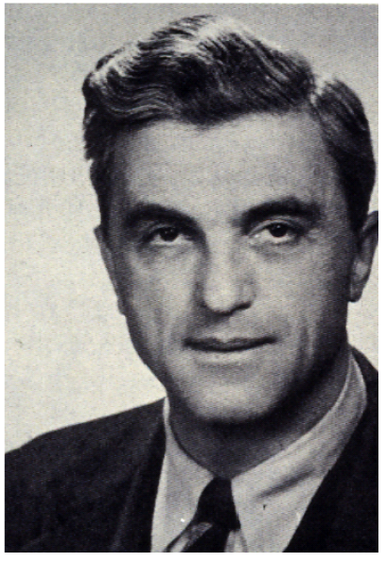




High Field NMR in Condensed Matter

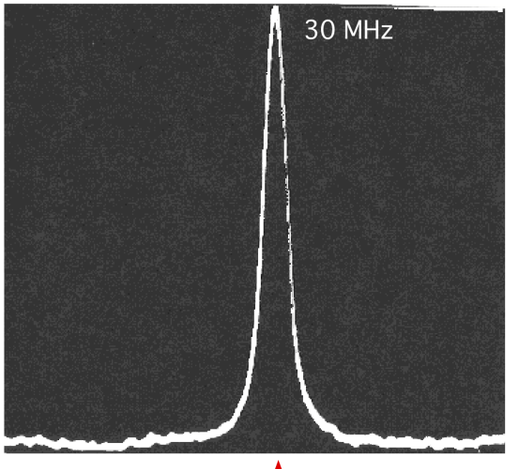


Edward Purcell
at Harvard

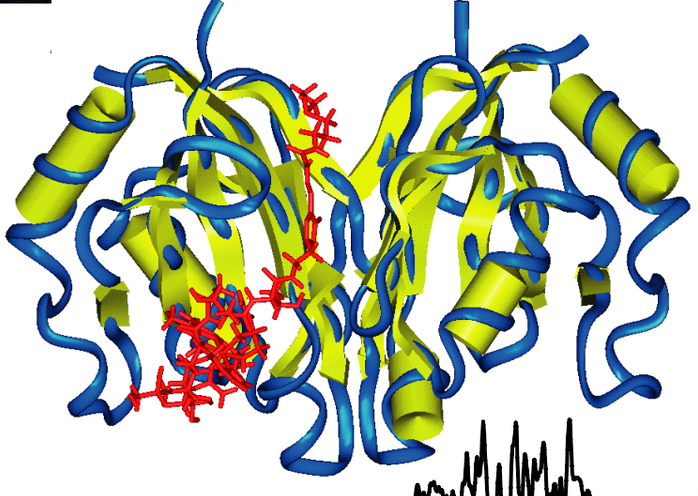


Felix Bloch
at Stanford

$$\omega_0 = -\gamma B_0$$



30 Mhz, 1948



courtesy of M. Blackledge, B. Brutscher, *et al.*, IBS-Grenoble

800 MHz, 2000

The Nobel Prize in Physics 1952

"for their development of new methods for nuclear magnetic precision measurements and discoveries in in connection therewith"

Observable N° 2:
The chemical shift

The NMR Hamiltonian contains several terms, linked to atomic coordinates, electronic structure, or to molecular dynamics.

As an example we remark the chemical shift, which is a modification of the resonance frequency with respect to the Larmor frequency, due to the shielding of the nucleus by the electrons.

$$\omega = -\gamma(1-\sigma)B_0$$

By measuring the chemical shifts of all the spins, **we could deduce the coordinates of the atoms**, **if we knew** the relation between chemical shift and structure....

Observable N° 3:
The dipolar interaction between spins

The NMR Hamiltonian contains several terms, linked to atomic coordinates, electronic structure, or to molecular dynamics.

As another example we remark the magnitude of the dipolar interaction between two nuclear spins j and k is:

$$b_{jk} = -\frac{\mu_0}{4\pi}\frac{\gamma_j \gamma_k \hbar}{r_{jk}^3}$$

If we could measure the dipolar interactions between all pairs of spins, **we could deduce the coordinates of the atoms**....

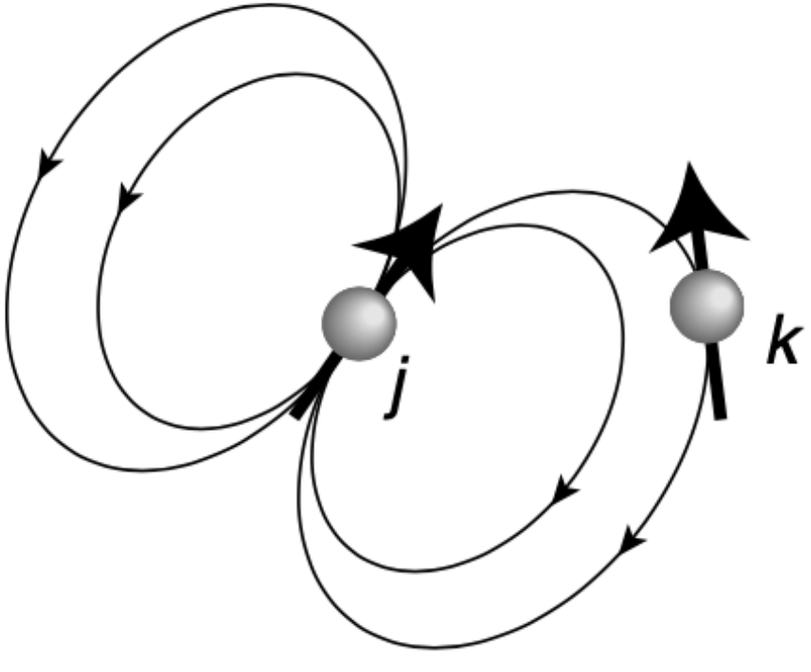
Observable N° 2:
Direct dipole-dipole coupling between spins

The direct dipole–dipole coupling between spins is conceptually simple. Since each nuclear spin is magnetic, it generates a magnetic field in the surrounding space depending on the direction of the spin magnetic moment. A second nuclear spin then interacts with this magnetic field (and vice-versa). This interaction is called the through-space dipole–dipole coupling, or direct dipole–dipole coupling, because the fields between the nuclear spins propagate through the intervening space, without involving the electron clouds.

The interaction Hamiltonian is:

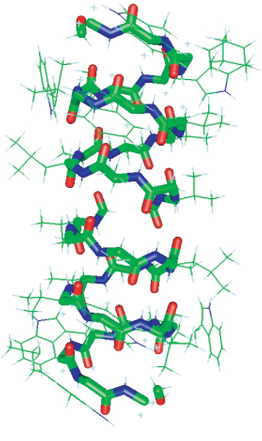
$$\widehat{\mathcal{H}}_{jk}^{\mathrm{DD,full}} = b_{jk}\left(3(\hat{\mathbf{I}}_j \cdot \mathbf{e}_{jk})(\hat{\mathbf{I}}_k \cdot \mathbf{e}_{jk}) - \hat{\mathbf{I}}_j \cdot \hat{\mathbf{I}}_k\right)$$

where $\hat{\mathbf{I}}_j$ and $\hat{\mathbf{I}}_k$ are the spin angular momentum operators which are proportional to the magnetic moments ($\boldsymbol{\mu}$) of the nuclei, and where $\mathbf{e}_{jk}$ is the unit vector parallel to the line joining the centres of the two nuclei.

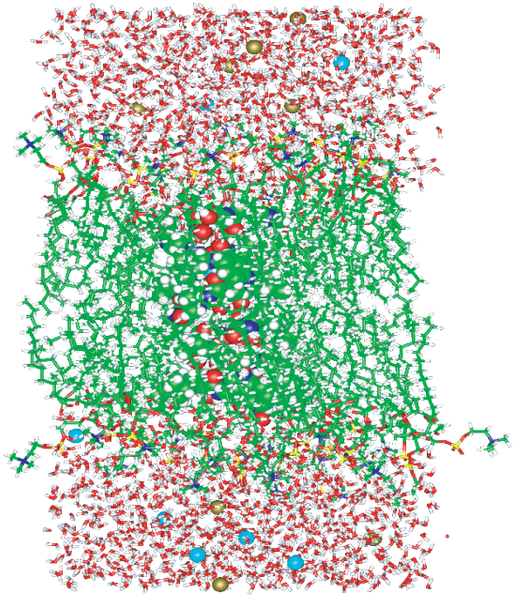


Multi-dimensional NMR: Pairwise Correlations

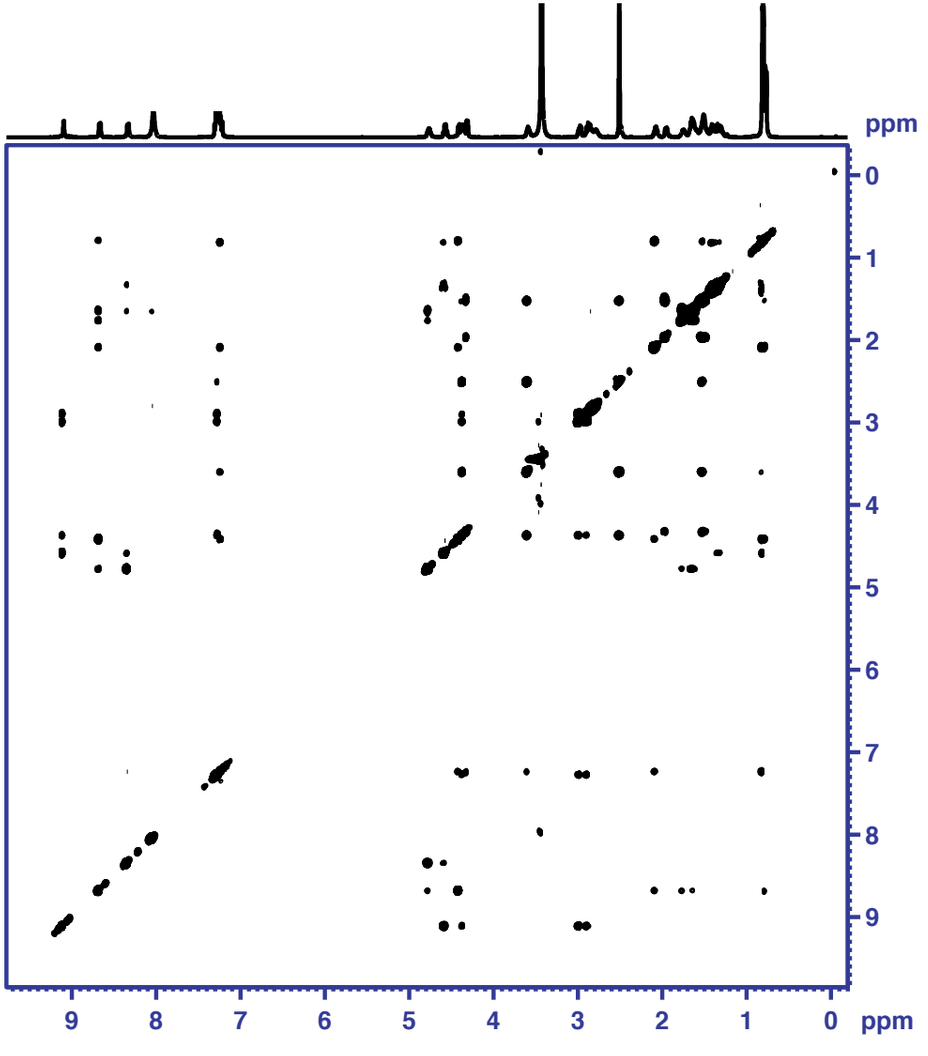
NOESY Spectrum of Gramicidin
The intensity of the cross peaks is related to the inernuclear distance between the two nuclei that are correlated.



Gramicidin A



The whole system

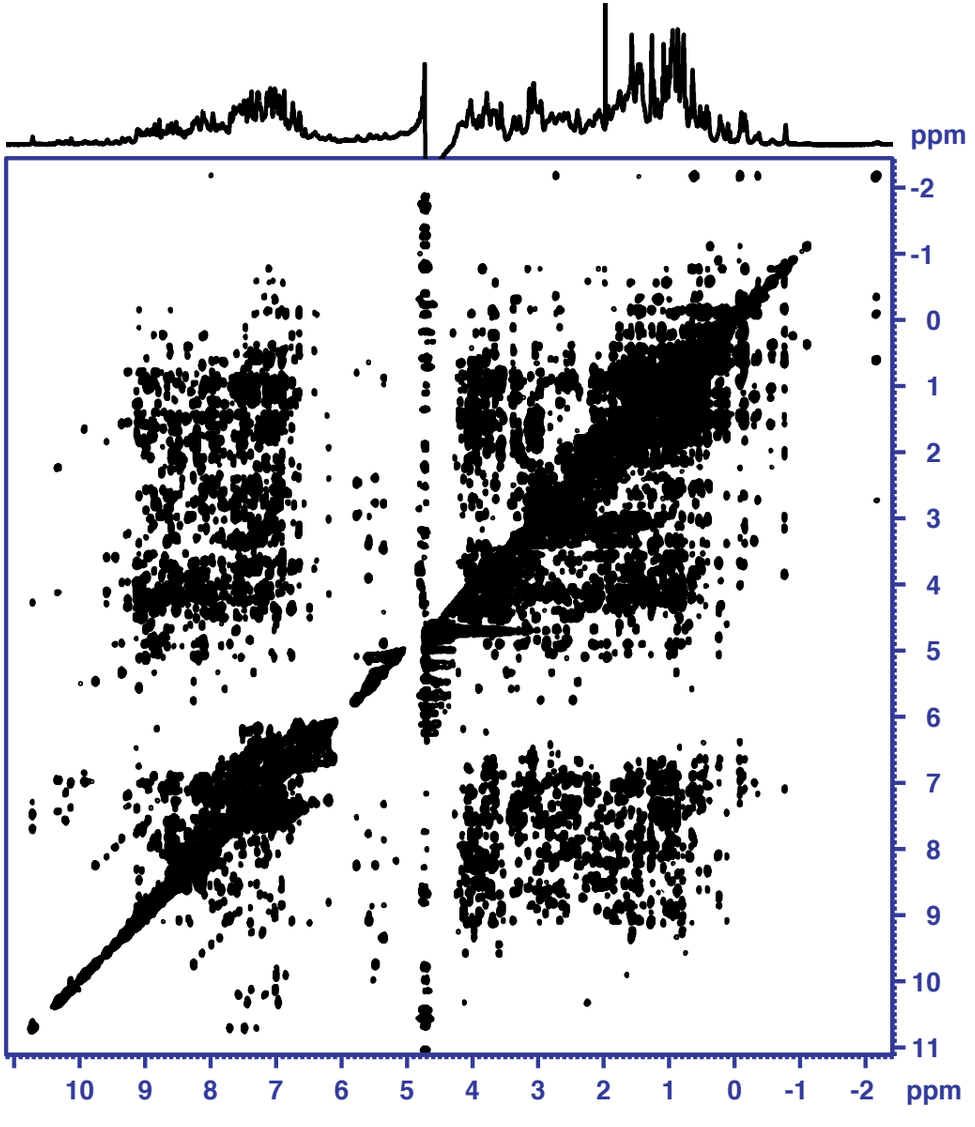


Multi-dimensional NMR: Pairwise Correlations

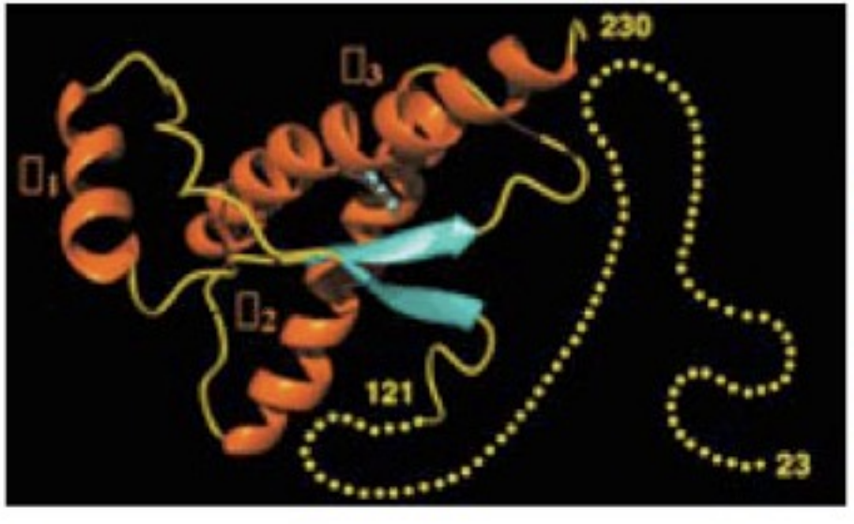
measuring dipolar couplings and

determining atomic-level 3D structure

NOESY Spectrum of Lysozyme
The intensity of the cross peaks is related to the inernuclear distance between the two nuclei that are correlated.



three-dimensional structures of proteins in solution

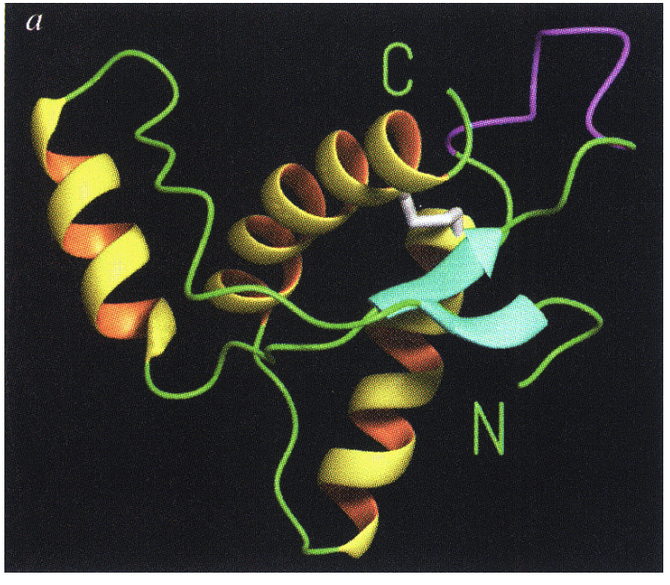


In 1986, using NMR, the group led by Wütrich determined a protein structure in solution for the first time. In 2000 he was the first to determine the structure of a human prion protein. In 2002 he wins the Nobel Prize for Chemistry.

NMR structure of the mouse prion protein domain PrP(121–231)

Roland Riek, Simone Hornemann, Gerhard Wider, Martin Billeter, Rudi Glockshuber & Kurt Wüthrich

Institut für Molekularbiologie und Biophysik, Eidgenössische Technische Hochschule-Hönggerberg, CH-8093 Zürich, Switzerland



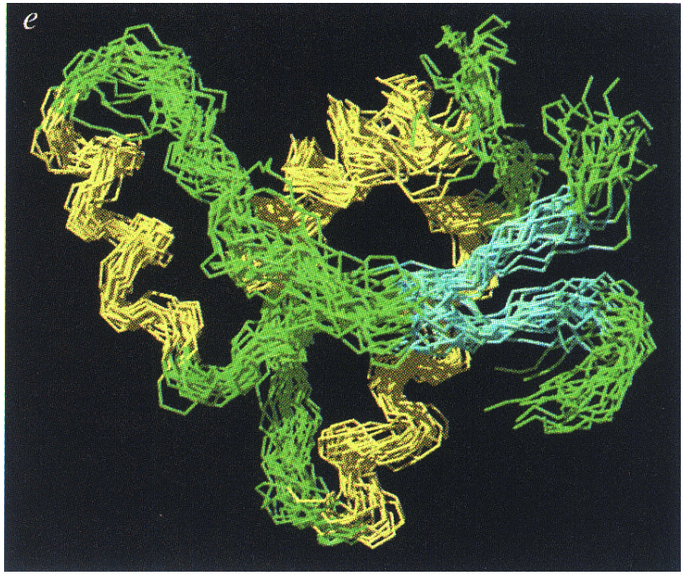
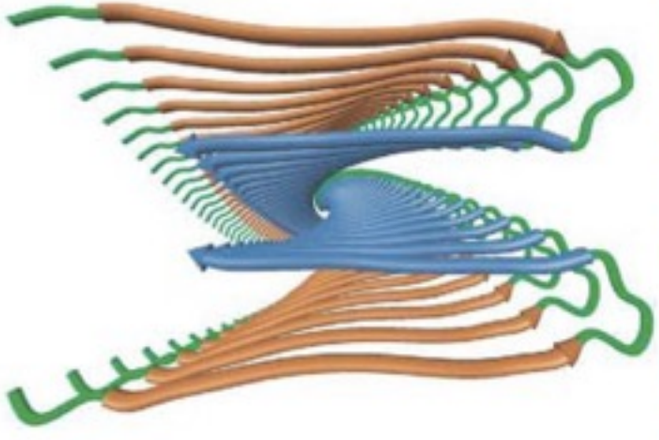


TABLE 1 Parameters characterising the NMR structure determination of PrP(121–231)

Extent of assignments (backbone and side chain ^{1}H, $^{13}C^{\alpha}$, backbone ^{15}N)	93%
Number of distance constraints	1,368
Number of dihedral angle constraints	227
Distance constraint violations >0.1 Å (per conformer)	1.5 ± 1.3
Dihedral angle constraint violations > 2.5° (per conformer)	0.15 ± 0.36
Intra-protein AMBER energy (kcal mol^{-1})	$-5{,}041 \pm 97$
R.m.s.d. to the mean for N, C^{α} and C′ of residues 125–166 and 177–219	1.4 Å
R.m.s.d. to the mean for all heavy atoms of residues 125–166 and 177–219	2.0 Å

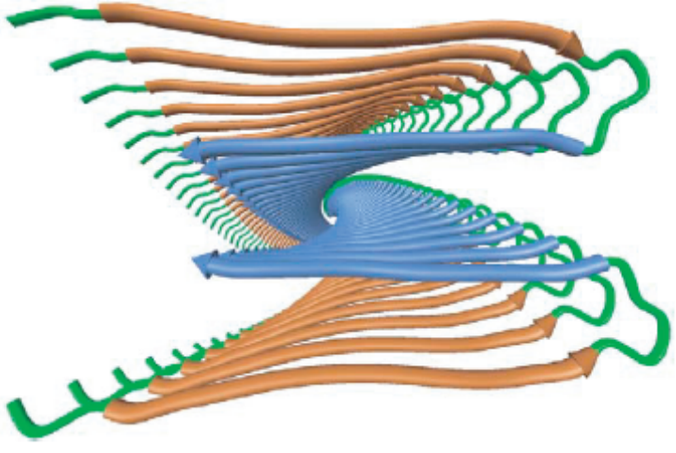
The NMR structure of PrP(121–231) was calculated with the program DIANA[21]. Starting from 100 randomized structures, the 20 conformers with the lowest DIANA target function values were energy minimized in a water shell of 6 Å minimal thickness, using the program OPAL (P. Luginbühl, P. Güntert, M. Billeter and K. Wüthrich, submitted) with the AMBER force field[22].

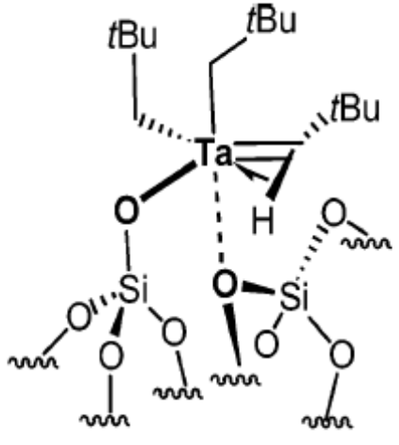
insoluble Alzheimer's proteins determined by MAS NMR



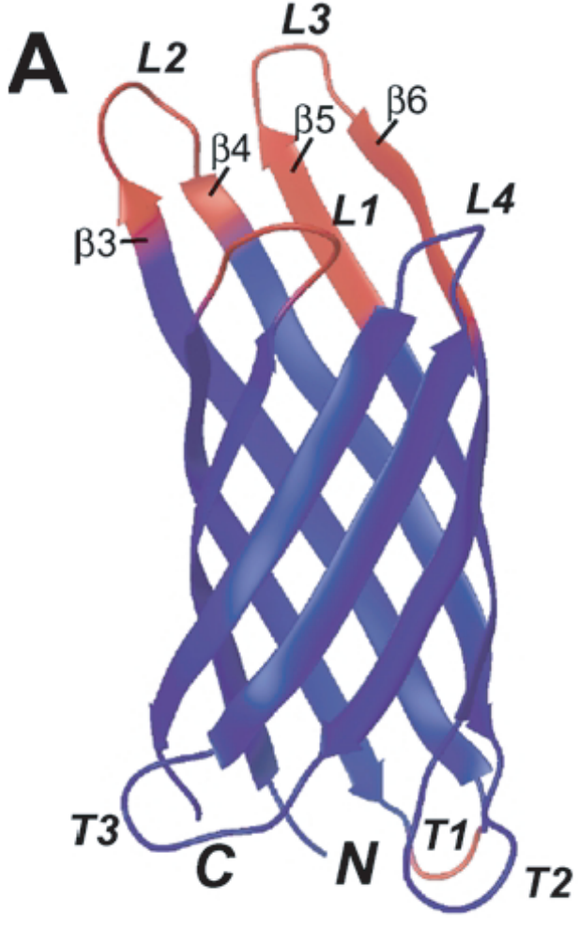
In the 1960s, the work of Andrew, Waugh, Pines, Stejskal and Shaeffer, provides high resolution spectra from solids with magic angle spinning (MAS). From 1994 onwards Griffin (MIT) provides increasingly detailed evidence for functional mechanisms in membrane proteins such as rhodopsin and bacteriorhodopsin, shining light on the primary steps in vision; in 2002 Tycko (NIH) uses NMR techniques to provide the first structure of the plaque forming amyloid proteins responsible for Alzheimer's disease; and in 2006 Oschkinat (Berlin) shows preliminary three-dimensional structures for membrane incorporated proteins obtained from 900 MHz NMR spectra.

NMR: Is this it?

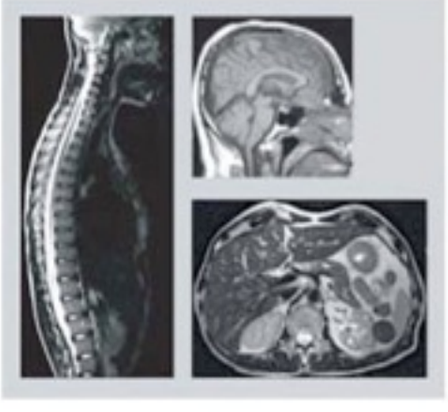




1a'

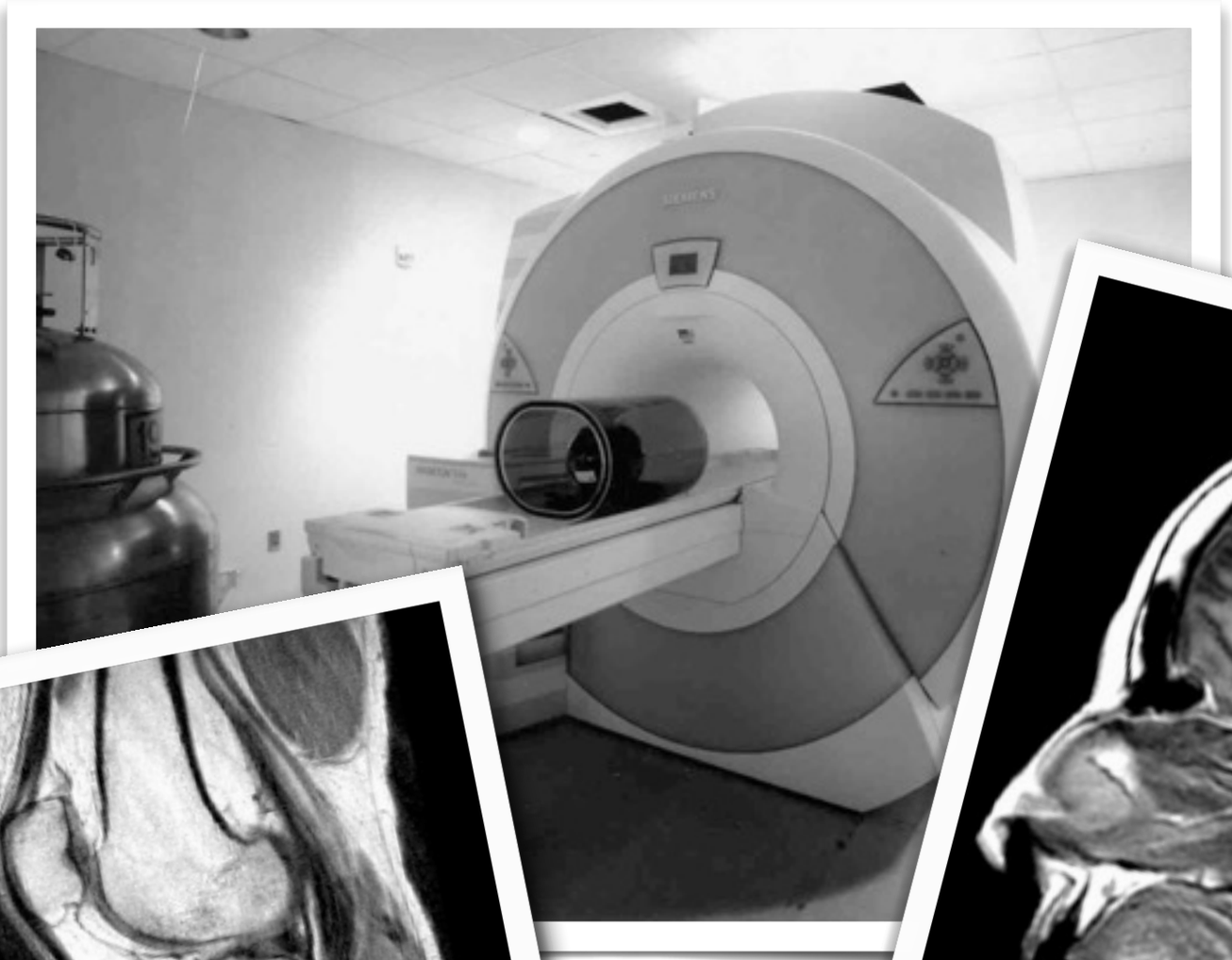


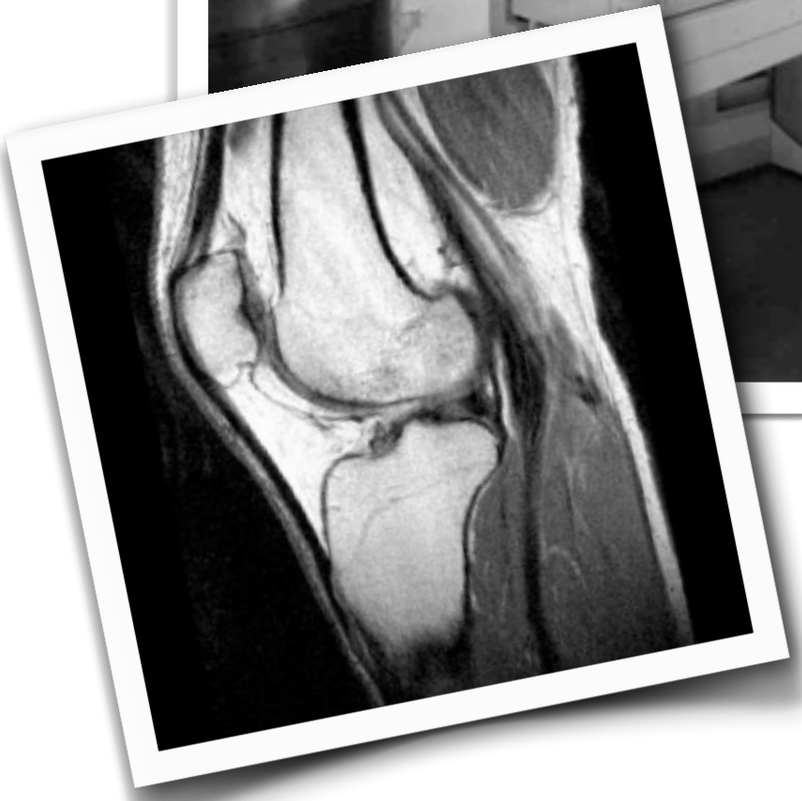
magnetic resonance imaging: a clinical tool for diagnosis.

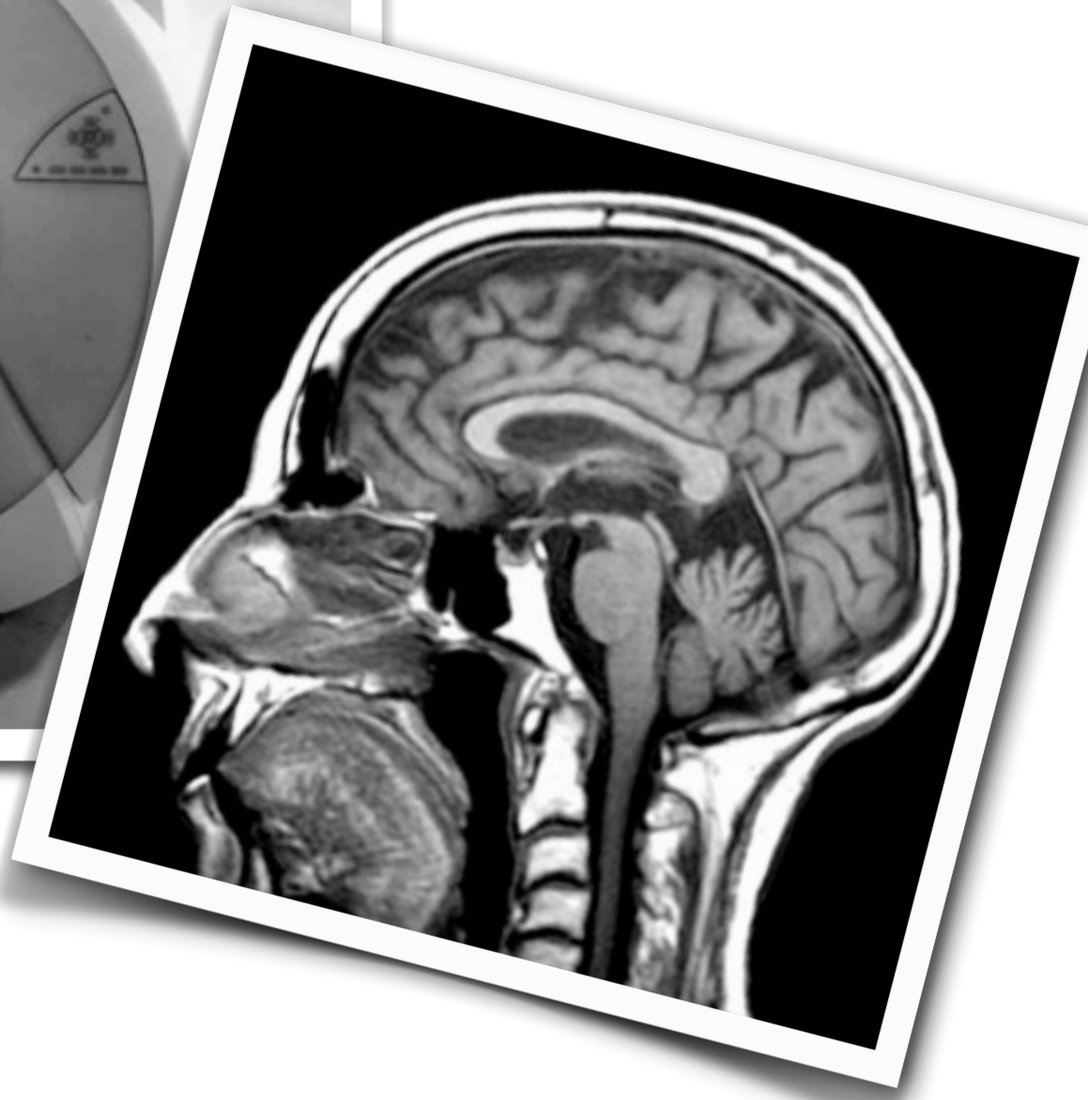


In 1973 Paul Lauterbur uses a high-resolution NMR spectrometer to provide the first Magnetic Resonance Image (MRI). In 2006 this has a become a multi-billion dollar industry, and is the technique of choice for the diagnosis of many common tumors. In 2003 Lauterbur and Mansfield win the Nobel Prize in Medecine.

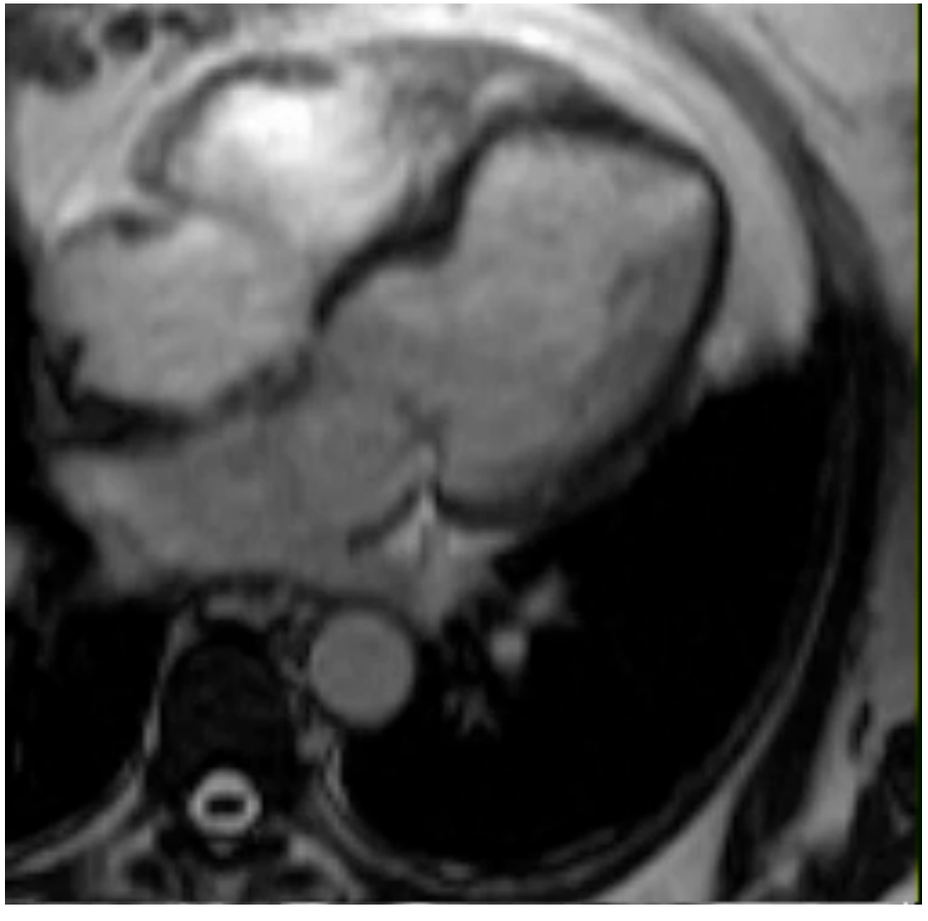
Magnetic Resonance Imaging (MRI)





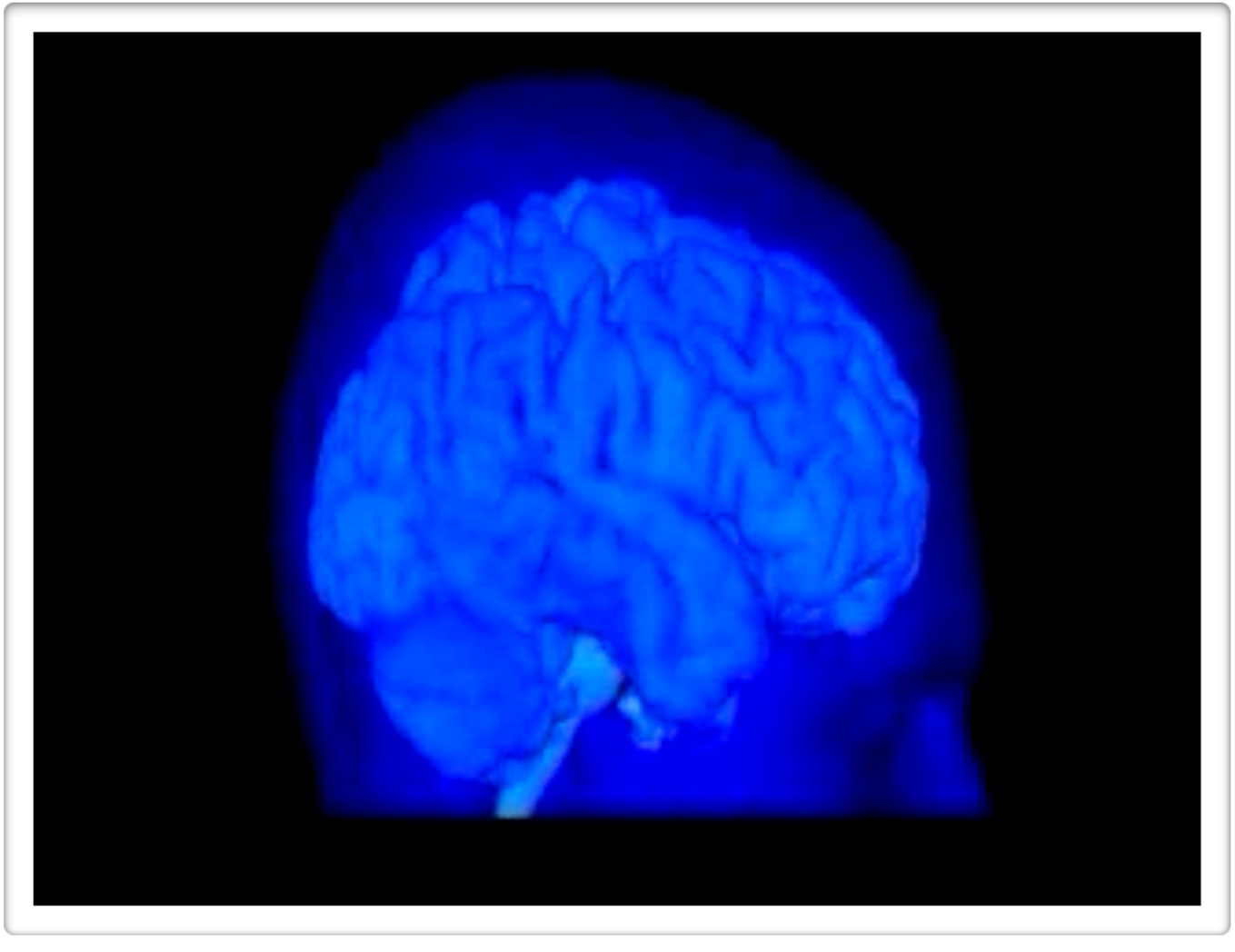


Magnetic Resonance Imaging (MRI)



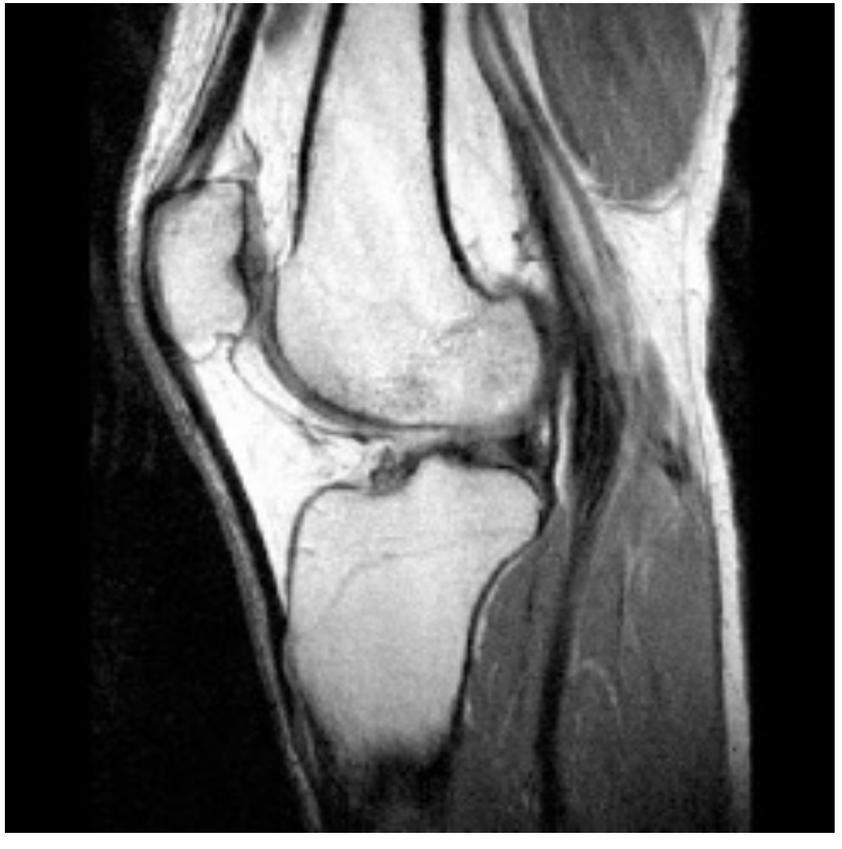
making movies!

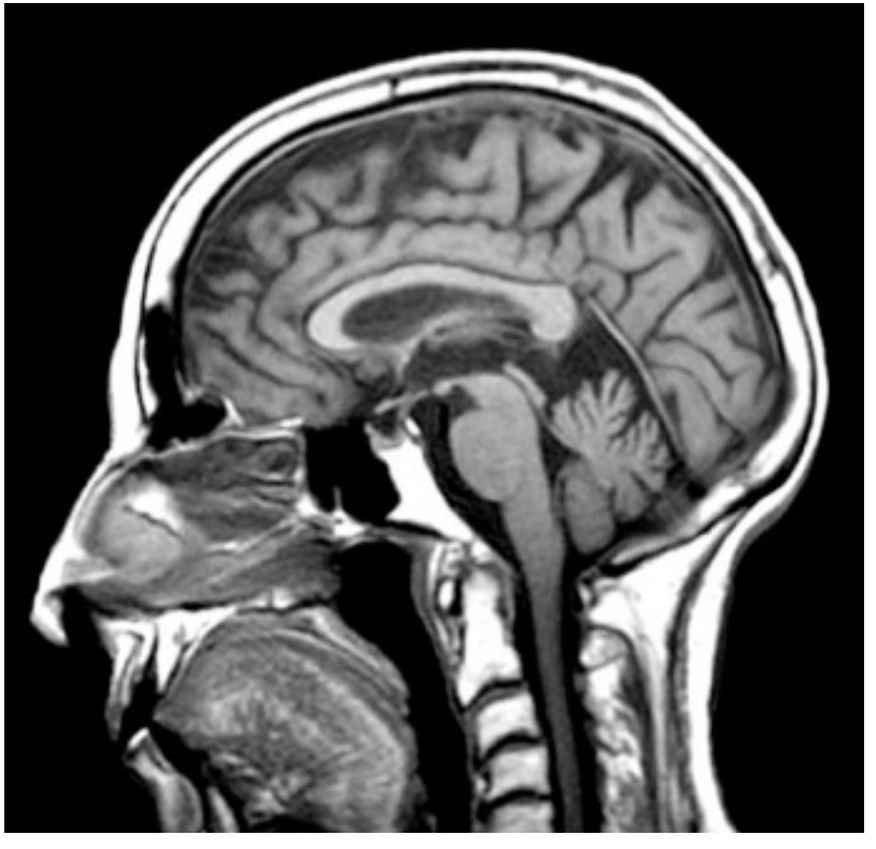
Magnetic Resonance Imaging (MRI)



reading your mind!

Magnetic Resonance Imaging (MRI)





determining meso- and macro-scale 3D structure of objects that are not transparent

Advanced NMR & Imaging

Course content:

Methods for three-dimensional structure determination by NMR, from atomic-level structures to macroscopic imaging

- Advanced fundamental principles of NMR spectroscopy
- Illustrated by applications to chemistry, materials science and medicine, with examples and case studies
- Lectures, group problem sessions, and a practical session.

Advanced NMR & Imaging

Course evaluation:

- The problem sets will be graded by assigned groups (20%)
- Analysis of a research article by group, after the end of the course (20%)
- Written exam (60%)

We Need You!

Please, please be interactive!

- If you don't follow the content, *speak up*! (Don't wait till after the lecture or until the course evaluation to say the lecture was rubbish.)
- Reading your minds is difficult, especially if you don't come to class.
- Come to class, and f*ollow the course, the problems, and the homework in real time*.

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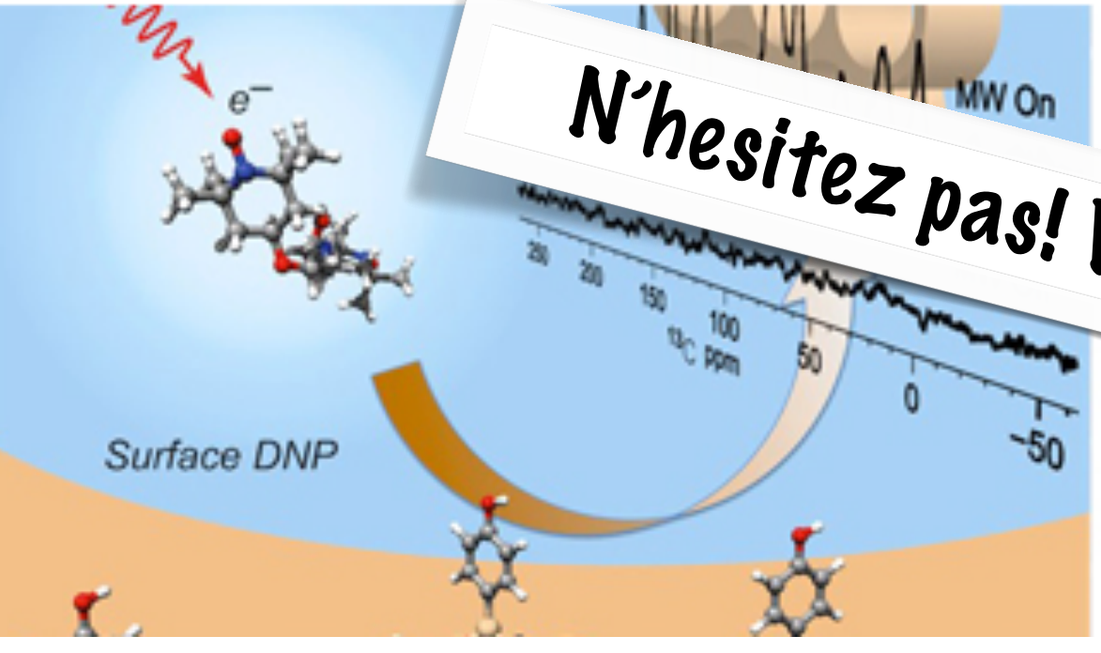

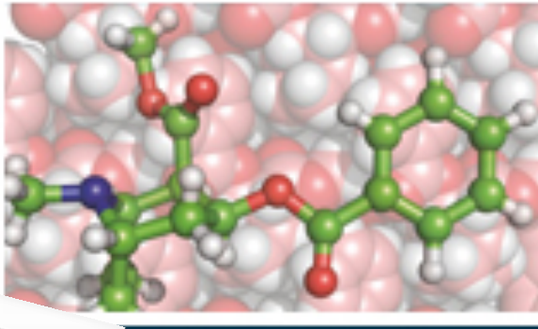

N'hesitez pas! Venez nous voir!

LRM