



Une petite histoire de la Résonance Magnétique Nucléaire

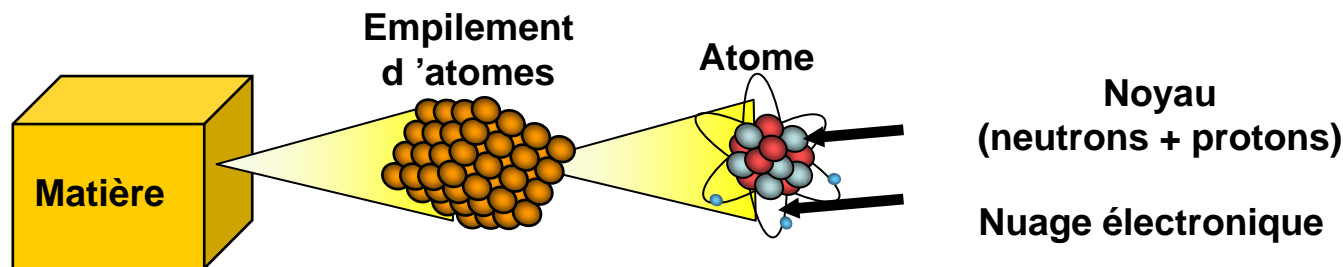
De la physique fondamentale à un outil de biologie

Hervé Desvaux

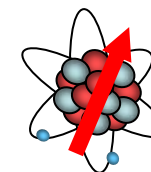
*Laboratoire Structure et Dynamique par Résonance Magnétique
Service de Chimie Moléculaire
CEA/Saclay
F-91191 Gif sur Yvette*



Structure de la matière en 1945



Certains noyaux d'atome ont des propriétés analogues à celles de microscopiques boussoles



- L'amplitude absolue de la boussole dépend de l'isotope
- La projection de sa direction est quantifiée (quelques valeurs possibles seulement)
- Les amplitudes avaient été mesurées par Rabi, Alvarez et Ramsey en 1936 dans des expériences de jets atomiques (précision $\sim 1\%$), puis en 1938 par Gorter
- Connaître cette amplitude permettait d'espérer remonter à une meilleure connaissance de la physique des noyaux

Les (ou plutôt la) découvertes



L'approche spectroscopique : l'absorption



Phys. Rev., **69**, 37 (1946)

Resonance Absorption by Nuclear Magnetic Moments in a Solid

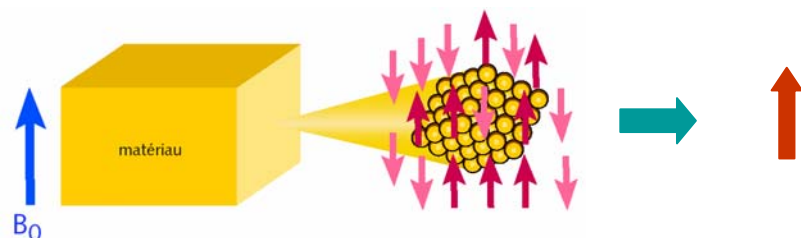
E. M. PURCELL, H. C. TORREY, AND R. V. POUND*
*Radiation Laboratory, Massachusetts Institute of Technology,
Cambridge, Massachusetts*
December 24, 1945

IN the well-known magnetic resonance method for the determination of nuclear magnetic moments by molecular beams,¹ transitions are induced between energy levels which correspond to different orientations of the nuclear spin in a strong, constant, applied magnetic field. We have observed the absorption of radiofrequency energy, due to such transitions, in a solid material (paraffin) containing protons. In this case there are two levels, the separation of which corresponds to a frequency, ν , near 30 megacycles/sec., at the magnetic field strength, H , used in our experiment, according to the relation $h\nu = 2\mu H$. Although the difference in population of the two levels is very slight at room temperature ($h\nu/kT \sim 10^{-5}$), the number of nuclei taking part is so large that a measurable effect is to be expected providing thermal equilibrium can be established. If one assumes that the only local fields of importance are caused by the moments of neighboring nuclei, one can show that the imaginary part of the magnetic permeability, at resonance, should be of the order $h\nu/kT$. The absence from this expression of the nuclear moment and the internuclear distance is explained by the fact that the influence of these factors upon absorption cross section per nucleus and density of nuclei is just cancelled by their influence on the width of the observed resonance.

A crucial question concerns the time required for the establishment of thermal equilibrium between spins and

Les (ou plutôt la) découvertes

L'approche magnétique : l'induction



Détection par ondes continues

- Irradiation à la fréquence constante ω
- Modification du champ magnétique B_0
- Quand $B_0 = \omega/\gamma$: détection de l'induction
 γ caractéristique du noyau

Phys. Rev., **70**, 474 (1946)

Nuclear Induction

F. BLOCH, W. W. HANSEN, AND MARTIN PACKARD
Stanford University, Stanford University, California
January 29, 1946

THE nuclear magnetic moments of a substance in a constant magnetic field would be expected to give rise to a small paramagnetic polarization, provided thermal equilibrium be established, or at least approached. By superposing on the constant field (z direction) an oscillating magnetic field in the x direction, the polarization, originally parallel to the constant field, will be forced to precess about that field with a latitude which decreases as the frequency of the oscillating field approaches the Larmor frequency. For frequencies near this magnetic resonance frequency one can, therefore, expect an oscillating induced voltage in a pick-up coil with axis parallel to the y direction. Simple calculation shows that with reasonable apparatus dimensions the signal power from the pick-up coil will be substantially larger than the thermal noise power in a practicable frequency band.

We have established this new effect using water at room temperature and observing the signal induced in a coil by the rotation of the proton moments. In some of the experiments paramagnetic catalysts were used to accelerate the establishment of thermal equilibrium.

Les (ou plutôt la) découvertes

L'approche magnétique : l'induction

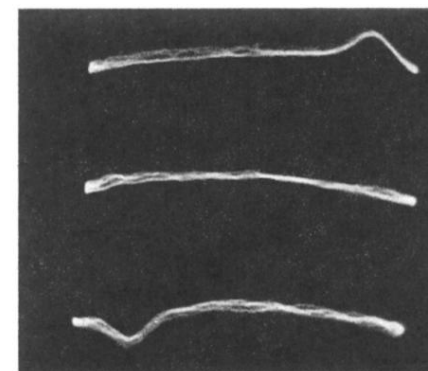
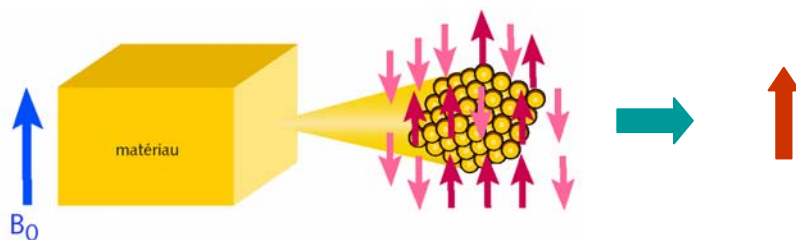


FIG. 8. Photographic record of the proton signal from water. The three traces from top to bottom correspond to the situation *a, b, c* of Fig. 7.

Détection par ondes continues

- Irradiation à la fréquence constante ω
- Modification du champ magnétique B_0
- Quand $B_0 = \omega/\gamma$: détection de l'induction
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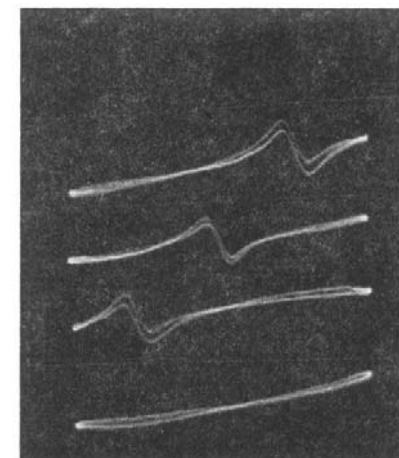


FIG. 12. Photographic record of the proton signal in a concentrated solution of $\text{Fe}(\text{NO}_3)_3$ in water. The four traces from top to bottom are in the text referred to as *a, b, c, d*.

Phys. Rev., **70**, 474 (1946)



RMN par impulsions

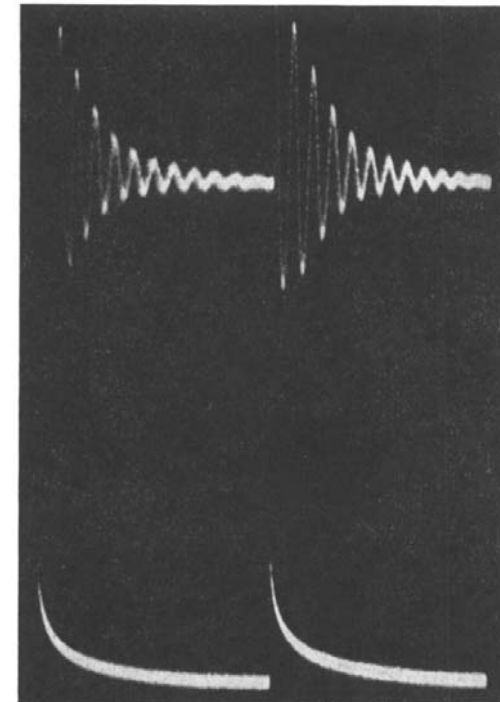
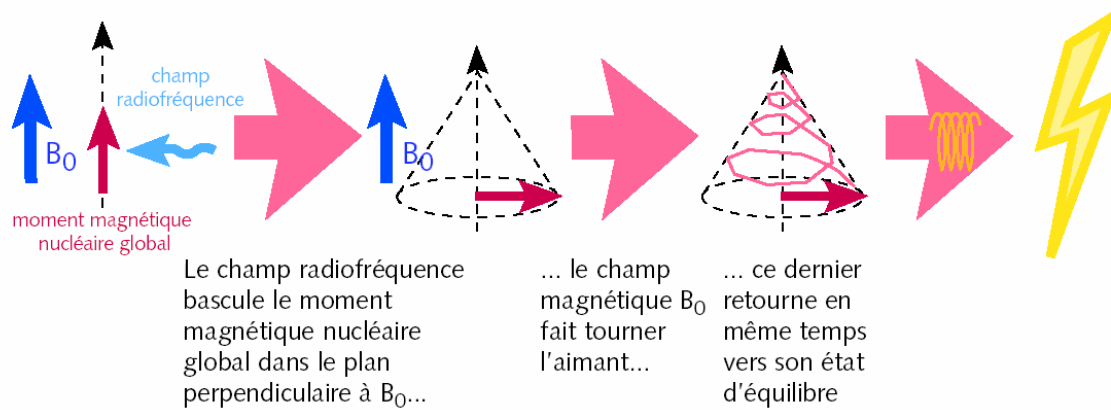


FIG. 2. The top trace indicates a beat note between an external r-f signal generator (near the Larmor frequency, loosely coupled to the inductive coil) and the nuclear signal shown alone (after detection) on the bottom trace. This beat note is identical in principle with the "wigggle effect" (see reference 5) except that H_0 is held constant in this case.

F. Bloch, *Phys. Rev.*, **70**, 460 (1946)

cea Echo de spins

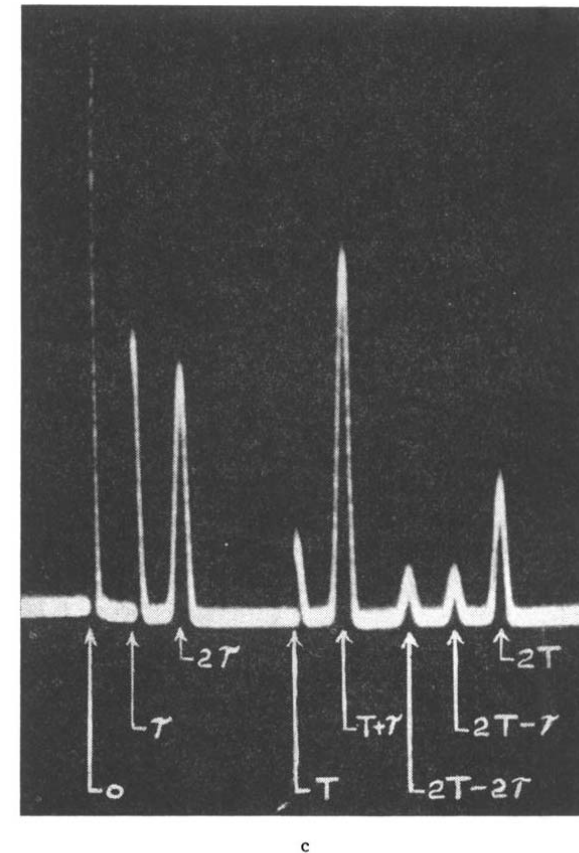
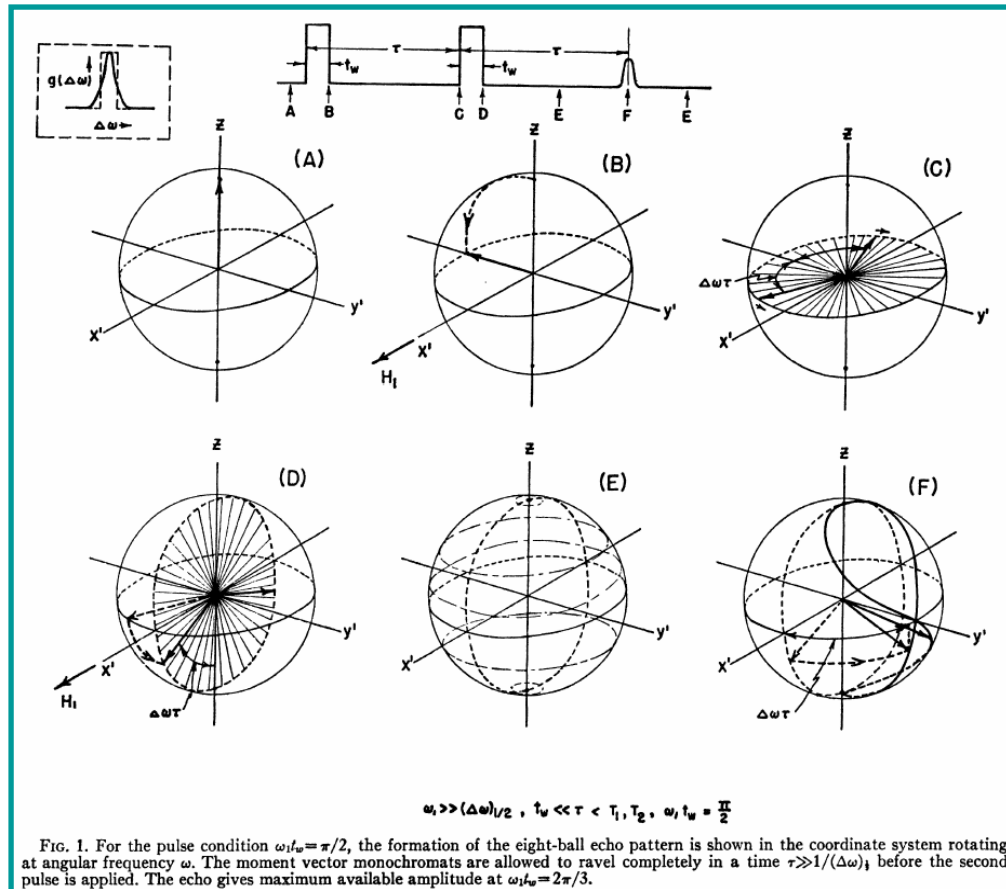
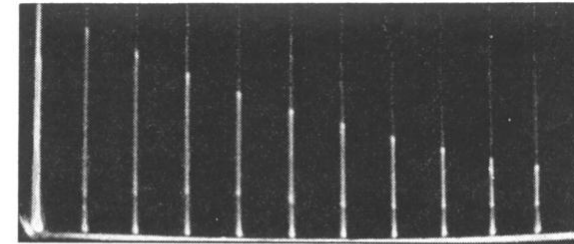
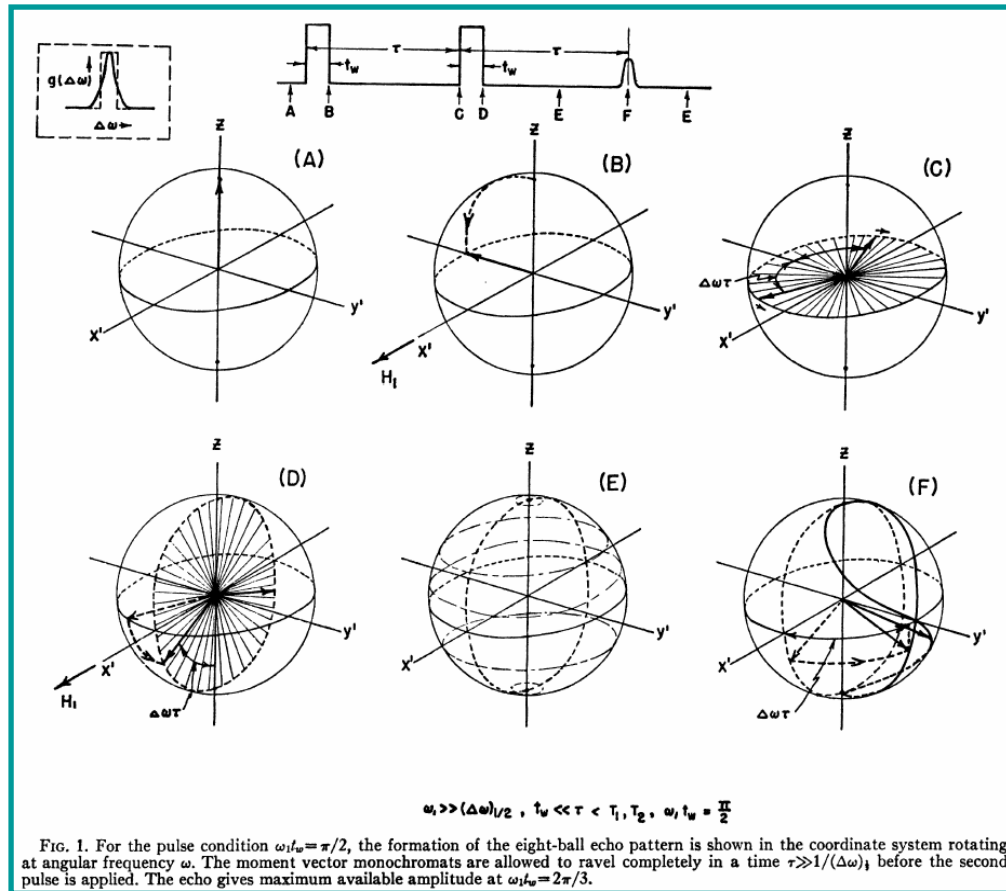


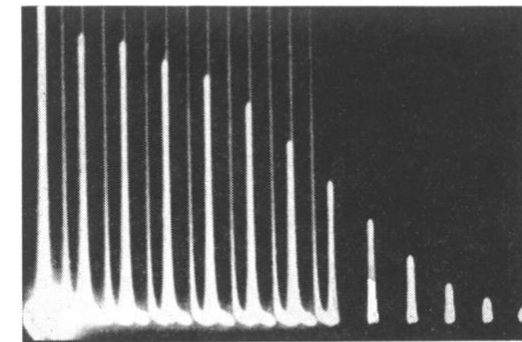
FIG. 5. Proton echo patterns in H_2O resulting from three applied r-f pulses. The pulses are visible in the upper two traces, and have a width $t_w \sim 0.5$ msec. In the upper trace $\tau = 0.008$ sec., $T = 0.067$ sec., and for the second trace $\tau = 0.046$ sec. and $T = 0.054$ sec. The bottom photograph shows a similar pattern for the case $T > 2\tau$ where induction decay signals can be seen following very short invisible r-f pulses. Saturation of a narrow band communications receiver, used in the case of the upper two traces, prevents the observation of these signals, whereas a wide band i.f. amplifier makes this observation possible in the bottom photograph.

E.L. Hahn, *Phys. Rev.*, **80**, 580 (1950)

cea Echo de spins



(a)



(b)

FIG. 7. A typical exponential plot of stimulated echo amplitudes is shown in the top photograph for protons in H₂O. This is obtained in a manner described for Fig. 3, except that T for the third pulse here is increased by 16/60 sec. intervals while τ is fixed at 0.0039 sec. The measured decay of the envelope is 1.89 sec. which serves as a point on the graph in Fig. 8. The apparent break in intensity in each of the stimulated echoes (seen as vertical traces because of the slow sweep speed) is due to a condition where the echo follows so soon after the stimulating pulse that it superimposes upon the voltage recovery of the receiver detector RC filter.

The bottom photograph indicates approximately an $\exp(-kt^3/3)$ decay law for the primary echo envelope in H₂O. The separation between echoes is 1/60 sec.

E.L. Hahn, *Phys. Rev.*, **80**, 580 (1950)



Le déplacement chimique : la découverte

The Dependence of a Nuclear Magnetic Resonance Frequency upon Chemical Compound*

W. G. PROCTOR AND F. C. YU

Department of Physics, Stanford University, Stanford, California

January 18, 1950

IN the course of measurements on N^{14} , mentioned in the previous letter, we made the surprising observation that its frequency of resonance, in liquid samples, depended strongly upon the chemical compound in which it was contained.^{1,2} This effect is strikingly demonstrated by the appearance of two resonances, separated by 1.6 kc in the neighborhood of 3300 kc, corresponding to a field of 10,500 gauss, using a solution of NH_4NO_3 in 2.0-molar $MnSO_4$ as a sample. These resonances presumably arise from the NH_4^+ and NO_3^- complexes, since samples of $NH_4C_2H_3O_2$ and HNO_3 separately give rise to two different resonances whose frequencies approximate those from the above sample. The separation is four times greater than the line widths measured between points of maximum slope.

Dependence of the F^{19} Nuclear Resonance Position on Chemical Compound*

W. C. DICKINSON

Research Laboratory of Electronics, Massachusetts Institute of Technology, Cambridge, Massachusetts

January 9, 1950

MOST unexpectedly, it has been found that for F^{19} the value of the applied magnetic field H_0 for nuclear magnetic resonance at a fixed radiofrequency depends on the chemical compound containing the fluorine nucleus. The assumption has generally been made that the time average of all internal magnetic fields is zero, excluding of course the small diamagnetic field at the nucleus due to the Larmor precession of its atomic electrons in H_0 . Nuclear resonance shifts in metals,¹ interpreted as being due to the conduction electrons, are larger by about an order of magnitude than those reported here.²

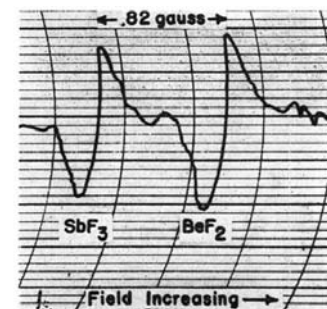


FIG. 2. The nuclear resonances of F^{19} in a single sample containing a half and half mixture of SbF_3 and BeF_2 (saturated aqueous solutions). The applied resonance magnetic field is about 7000 gauss at a radiofrequency of 28.0 megacycles.

Phys. Rev., 77, 716 (1950)

Phys. Rev., 77, 736 (1950)



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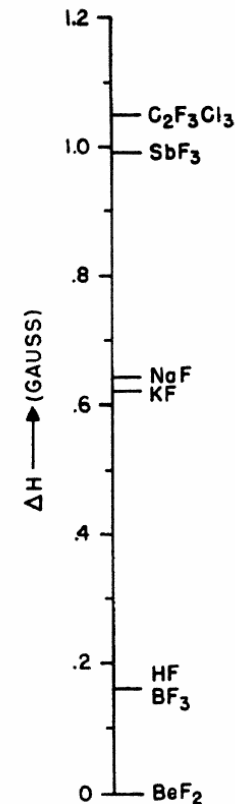


FIG. 1. Dependence of F^{19} nuclear resonance position on chemical compound. $H_0 \approx 7000$ gauss. ΔH represents an aiding field at the nucleus and has arbitrarily been set equal to zero for BeF_2 . All compounds except $C_2F_3Cl_3$ and BF_3 (ether complex) were in aqueous solution.

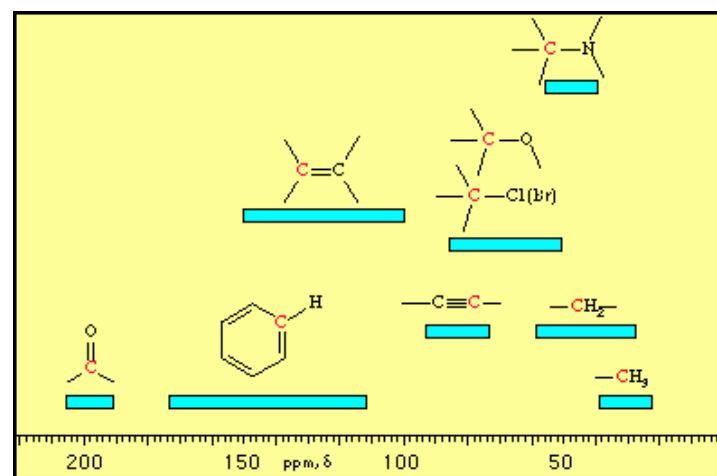
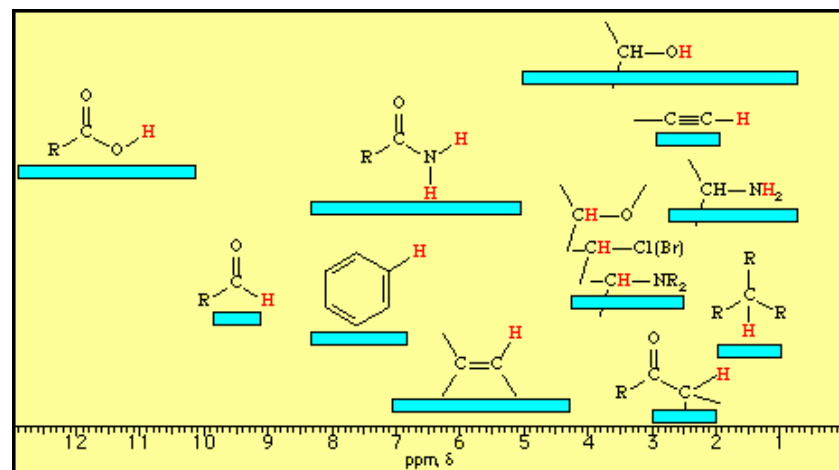
Phys. Rev., **77**, 716 (1950)



Déplacement chimique : fonction chimique

- Explication :
 - Champ magnétique créé par le « mouvement » des électrons
- N.F. Ramsey, *Phys. Rev.*, **78**, 699 (1950)

Le déplacement chimique est donc caractéristique de la fonction chimique

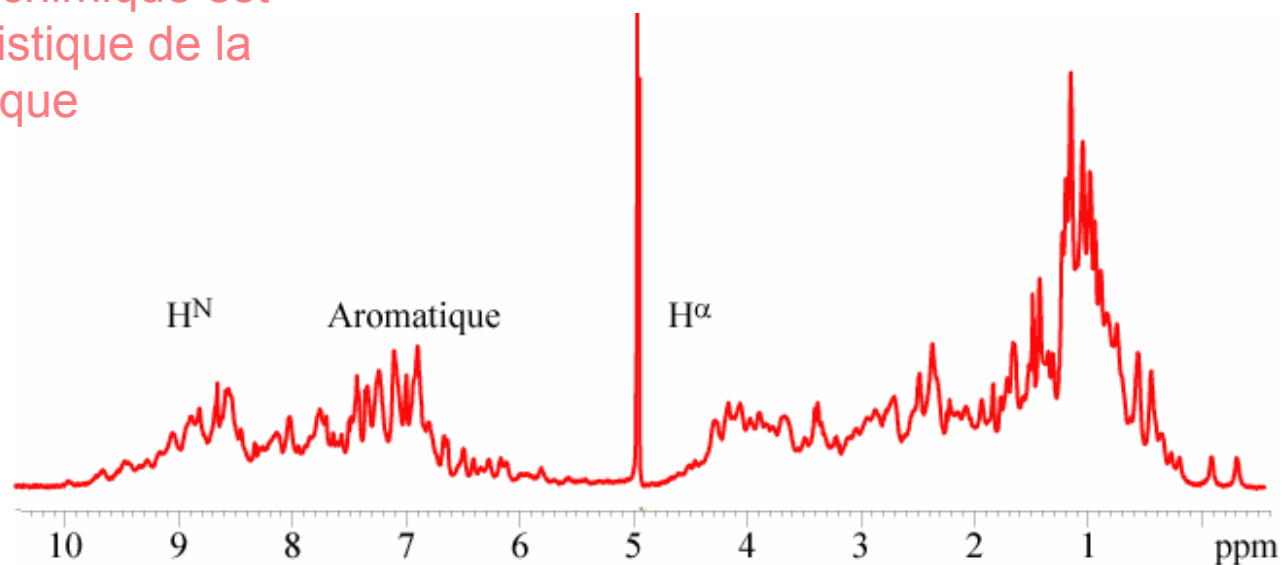




Déplacement chimique : fonction chimique

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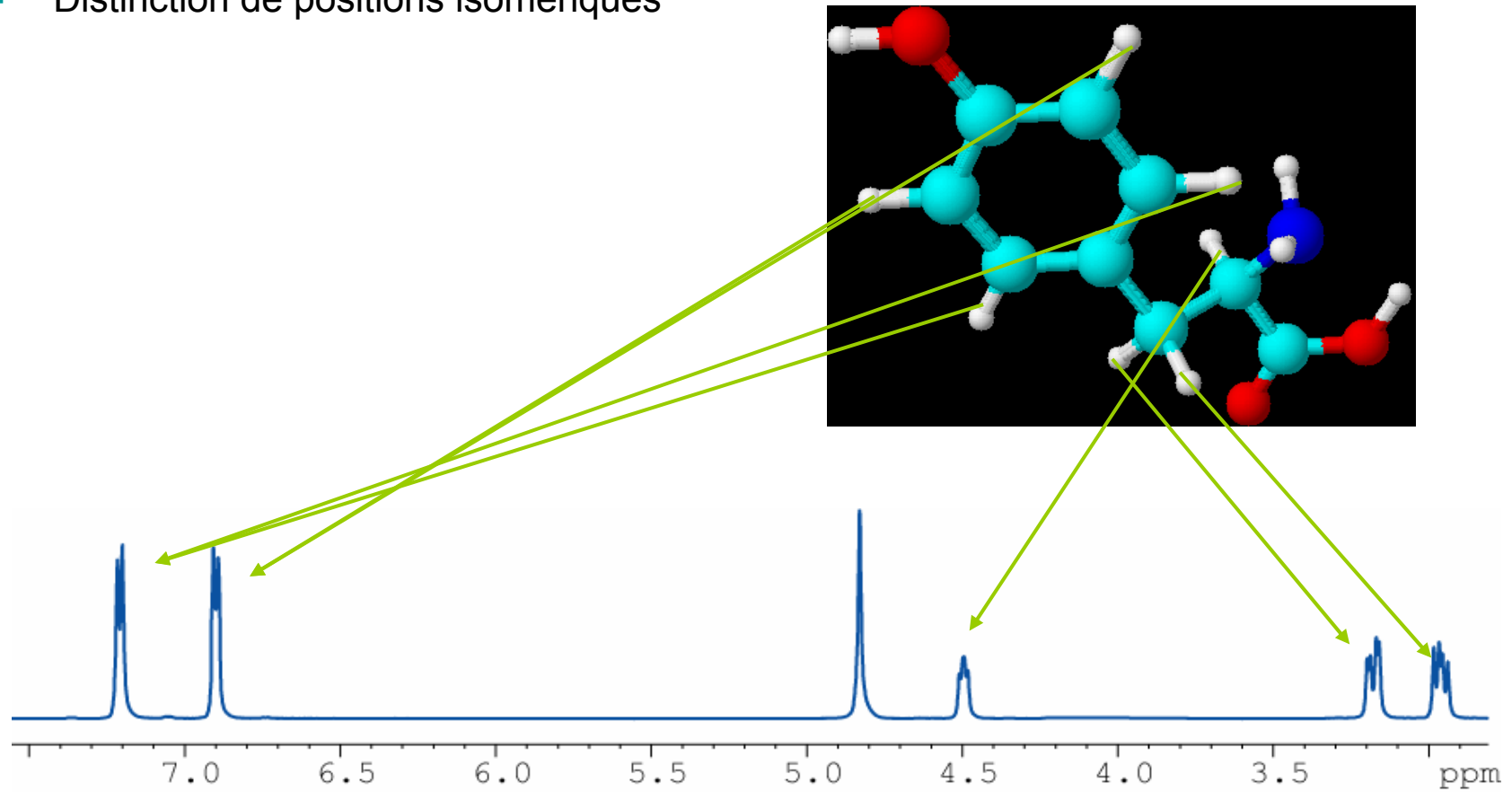
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Déplacement chimique : la structure

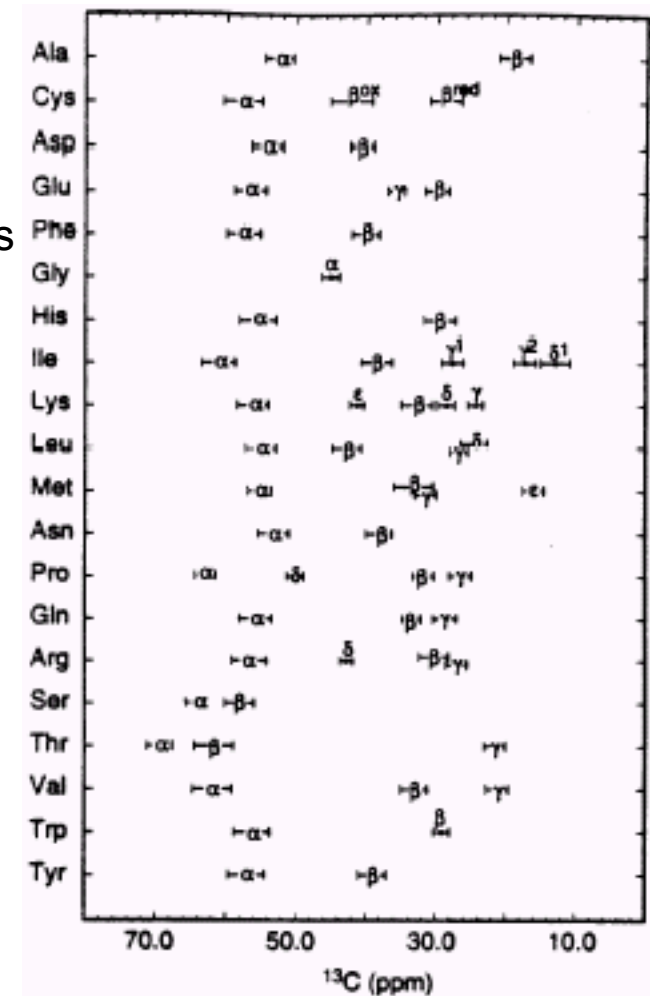
- Distinction de positions isomériques





Déplacement chimique : la structure

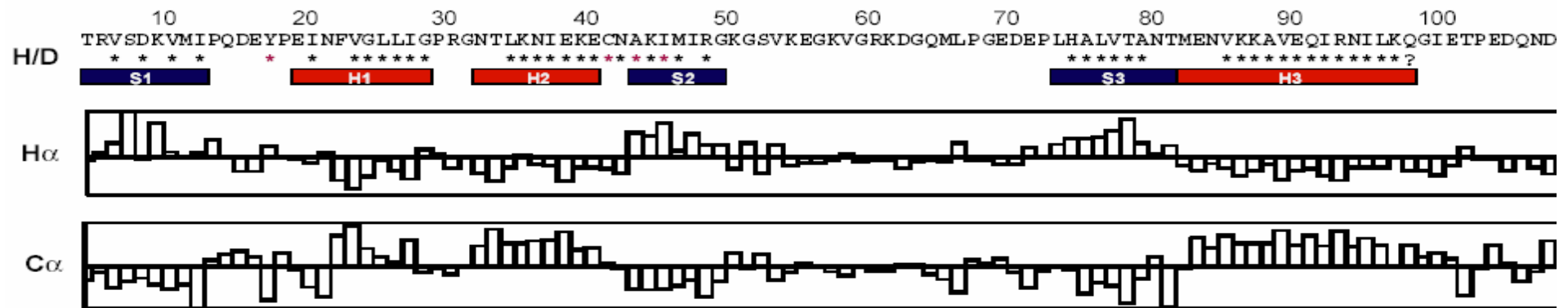
- Distinction de positions isomériques
- Informations précises sur la nature des acides aminés





Déplacement chimique : la structure

- Distinction de positions isomériques
- Informations précises sur la nature des acides aminés
- Information structurale : index de déplacements chimiques





Le couplage scalaire : la découverte

Nuclear Magnetic Resonance Fine Structure in Liquids

H. S. GUTOWSKY AND D. W. MCCALL
Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois*
(Received April 16, 1951)

MULTIPLE nuclear magnetic resonance lines with separations of about 0.3 and 0.7 gauss, respectively, have been observed for F^{19} and P^{31} in several liquid phosphorus halides. The ratio of the P^{31} line splitting to that for F^{19} , in the same compound, equals $\mu(F^{19})/\mu(P^{31})$, indicating that the effect is associated with the local nuclear magnetic-dipole fields in the molecule. In the simpler, rigid-lattice solids, these local fields may split the resonance line into several components separated by as much as 5 to 10 gauss.¹ In liquids, molecular rotation ordinarily produces a zero time average for the local fields and single, narrow lines result.² The appearance of multiple nuclear magnetic resonance

Phys. Rev., **82**, 748 (1951)

Spin Echoes*†

E. L. HAHN‡
Physics Department, University of Illinois, Urbana, Illinois
(Received May 22, 1950)

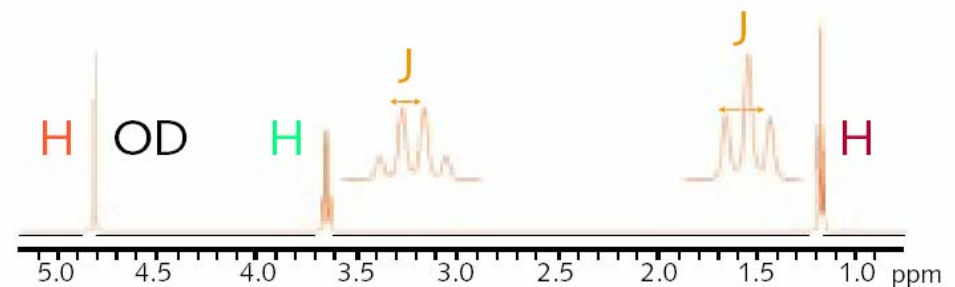
Intense radiofrequency power in the form of pulses is applied to an ensemble of spins in a liquid placed in a large static magnetic field H_0 . The frequency of the pulsed r-f power satisfies the condition for nuclear magnetic resonance, and the pulses last for times which are short compared with the time in which the nutating macroscopic magnetic moment of the entire spin ensemble can decay. After removal of the pulses a non-equilibrium configuration of isochromatic macroscopic moments remains in which the moment vectors precess freely. Each moment vector has a magnitude at a given precession frequency which is determined by the distribution of Larmor frequencies imposed upon the ensemble by inhomogeneities in H_0 . At times determined by pulse sequences applied in the past the constructive interference of these moment vectors gives rise to observable spontaneous nuclear induction signals. The properties and underlying principles of these spin echo signals are discussed with use of the Bloch theory. Relaxation times are measured directly and accurately from the measurement of echo amplitudes. An analysis includes the effect on relaxation measurements of the self-diffusion of liquid molecules which contain resonant nuclei. Preliminary studies are made of several effects associated with spin echoes, including the observed shifts in magnetic resonance frequency of spins due to magnetic shielding of nuclei contained in molecules.

Phys. Rev., **80**, 580 (1950)

Explication:

- Interaction entre noyaux transmise par les électrons de liaison

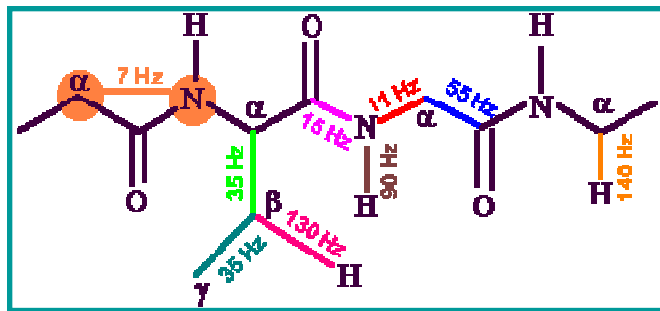
N.F. Ramsey, *Phys. Rev.*, **91**, 303 (1953)



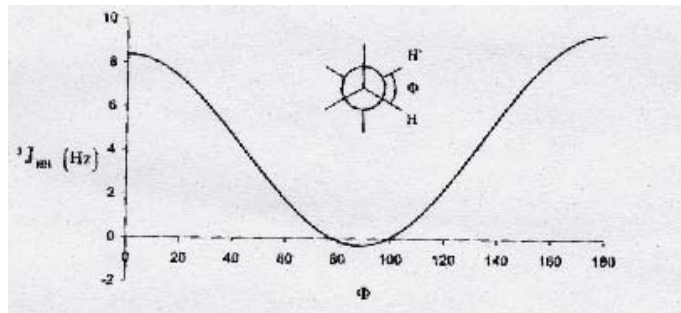


Le couplage scalaire : l'utilisation

Réseau de couplages dans les protéines

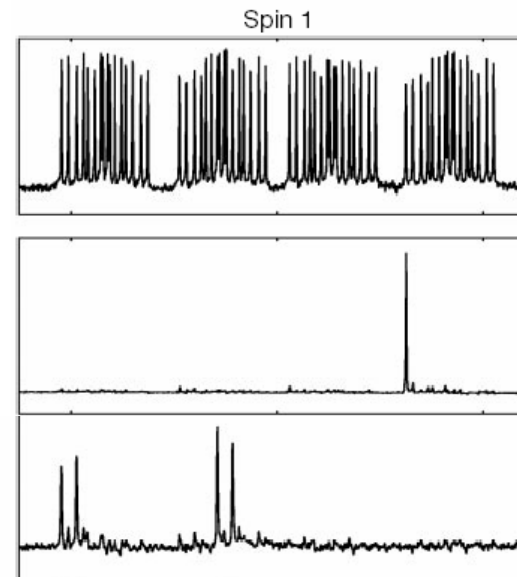
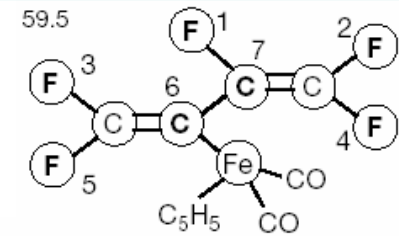


Relation de Karplus



M. Karplus, J. Chem. Phys., **30**, 11 (1959)

Ordinateurs
quantiques



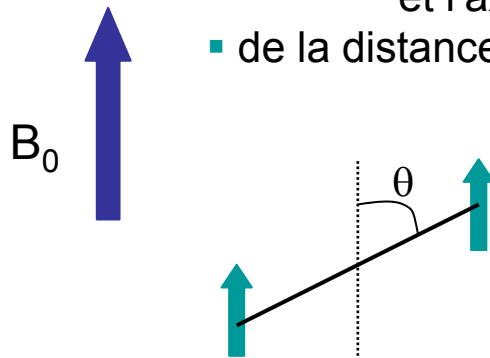
Factorisation de 15 en 3 fois 5!

L.M.K Vandersypen, M. Steffen, G. Brevta, C.S. Yannoni,
M.H. Sherwood, I.L. Chuang, Nature, **414**, 883 (2001)

Le coupage dipolaire et la RMN du solide

L'interaction dipolaire dépend

- de l'angle entre le vecteur internucléaire et l'axe du champ magnétique
- de la distance internucléaire



Conséquences :

- Phase liquide : θ varie \Rightarrow moyenne nulle
- Phase solide : θ fixe \Rightarrow interaction principale \Rightarrow raies très larges et anisotropie

Resonance Absorption by Nuclear Magnetic Moments in a Single Crystal of CaF_2

E. M. PURCELL, N. BLOEMBERGEN, AND R. V. POUND*
Harvard University, Cambridge, Massachusetts
 December 1, 1946

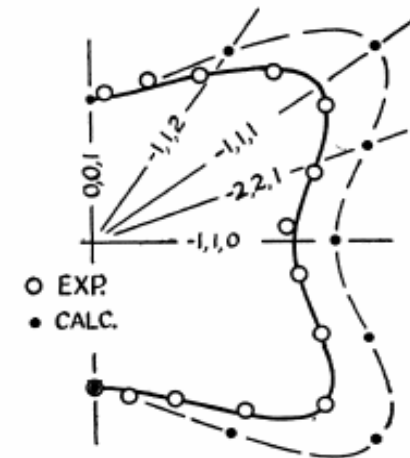


FIG. 1. Polar plot of the dependence of the intensity of magnetic resonance absorption in CaF_2 with the direction of H_0 with respect to the crystal. Absorption is maximum, for example, when H_0 lies along the $(-1, 1, 1)$ direction.

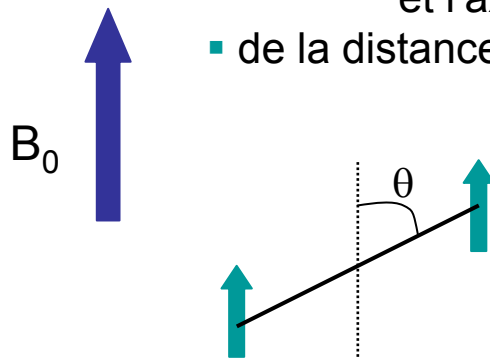
Phys. Rev., **70**, 988 (1946)



Le coupage dipolaire et la RMN du solide

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- de l'angle entre le vecteur internucléaire et l'axe du champ magnétique
- de la distance internucléaire



Conséquences :

- Phase liquide : θ varie \Rightarrow moyenne nulle
- Phase solide : θ fixe \Rightarrow interaction principale
 \Rightarrow raies très larges et anisotropie

Solution :
Faire tourner l'échantillon

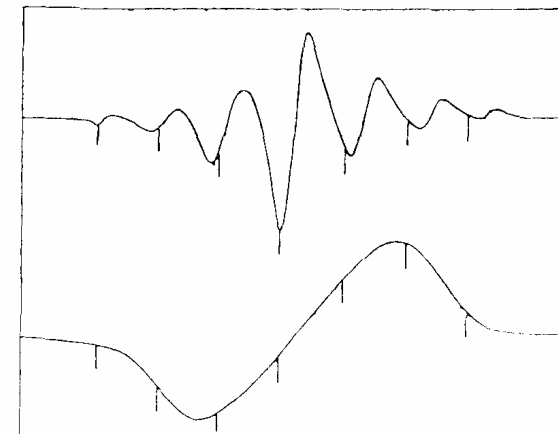
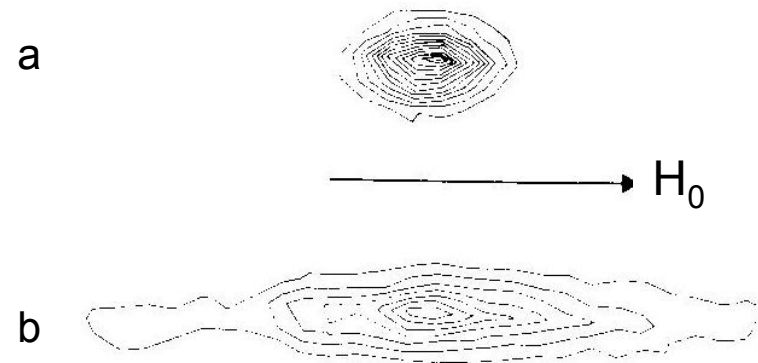


Fig. 2. The upper curve is the derivative spectrum for the crystal rotated at 810 c./s. about an axis making an angle $54^{\circ} 44'$ with the direction of the field. The lower curve is the derivative spectrum for the static crystal. The markers are 790 c./s. apart

E.R. Andrew, A. Bradbury, R.G. Eades, *Nature*, **183**, 1802 (1959)

- RMN dans les métaux
 - Déplacement de Knight
 - Loi de Korringa
 - Effet Overhauseur
- RMN et thermodynamique
 - Température de spin
 - Ordre magnétique nucléaire
- RMN et très basses températures
 - Hélium 3 solide et superfluide
 - Refroidissement jusqu'au 40 μK



Taches bidimensionnelles de diffraction de neutrons sur un monocristal de LiH

a) Noyaux polarisés
b) Après désaimantation adiabatique avec température de spin négative. La forme de la tache prouve la création d'un ordre ferromagnétique avec des domaines en forme de galettes superposées d'aimantation de signes opposés

A. Abragam, M. Goldman, « *Nuclear magnetism : Order and disorder* » (1982)

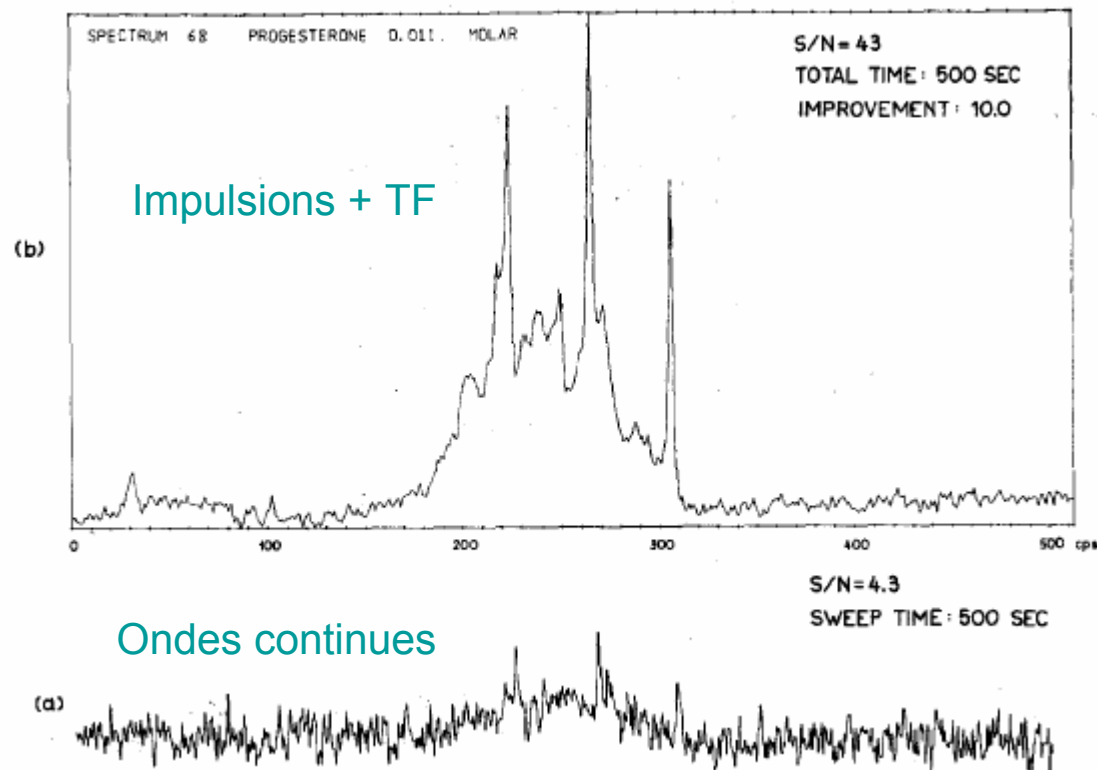


La transformée de Fourier

Application of Fourier Transform Spectroscopy to Magnetic Resonance

R. R. ERNST AND W. A. ANDERSON

Analytical Instrument Division, Varian Associates, Palo Alto, California 94303



Rev. Sci. Instr., **37**, 93 (1966)



La RMN à deux dimensions

The unpublished Baško Polje (1971) lecture notes about two-dimensional NMR spectroscopy

J. Jeener

Faculté des Sciences (CPI-232), Campus Plaine, Université Libre de Bruxelles, B-1050 Brussels, Belgium

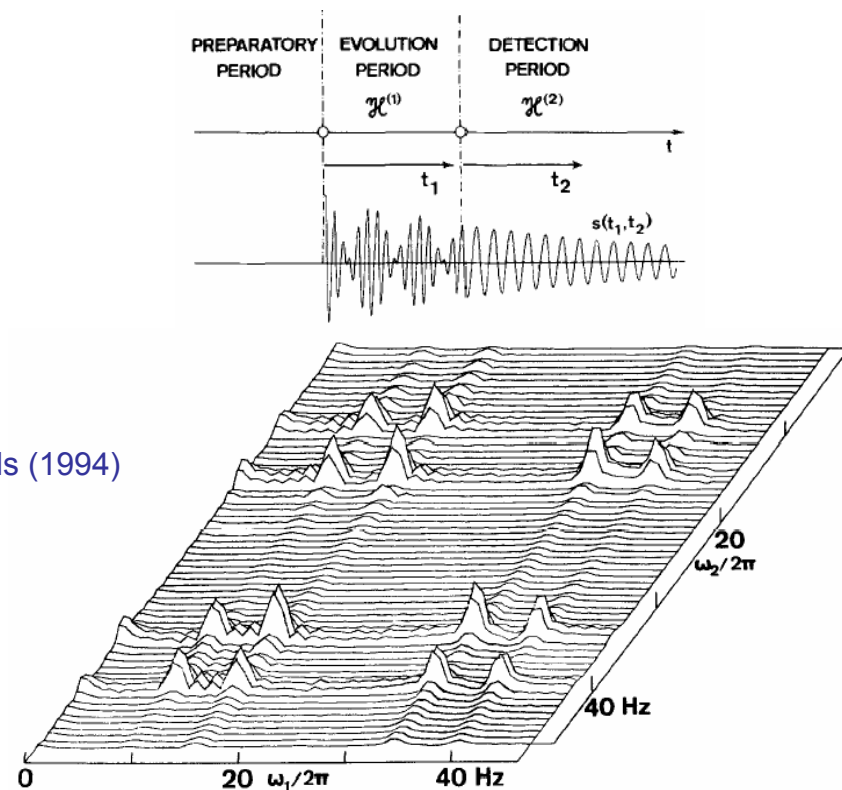
Abstract. — The main part of this paper is a reproduction of (previously unpublished) lecture notes, which were circulated in 1971, and which are often cited as the initiation of two-dimensional NMR spectroscopy. A brief discussion follows, about the way of handling dates and durations in time-dependent quantum mechanics, and about the use of diagrams in NMR pulse spectroscopy in the usual or the superoperator formalisms.

In « *NMR and More* », M. Goldman et M. Porneuf Eds (1994)

Two-dimensional spectroscopy. Application to nuclear magnetic resonance

W. P. Aue, E. Bartholdi, and R. R. Ernst

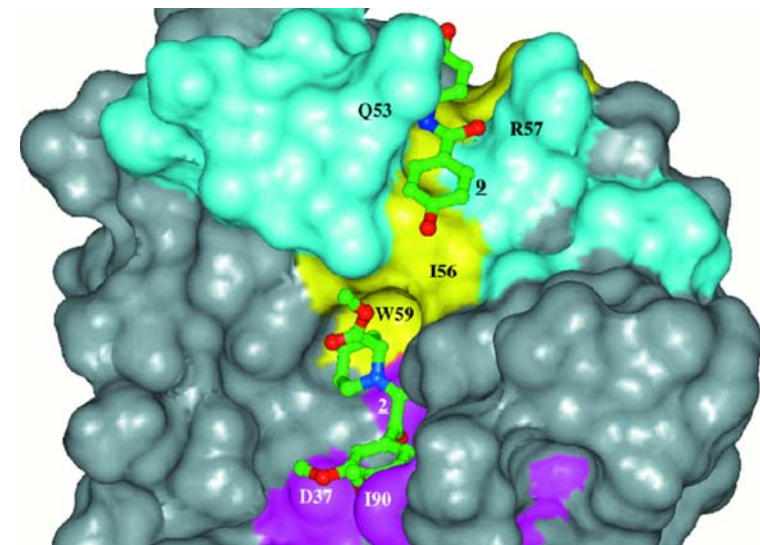
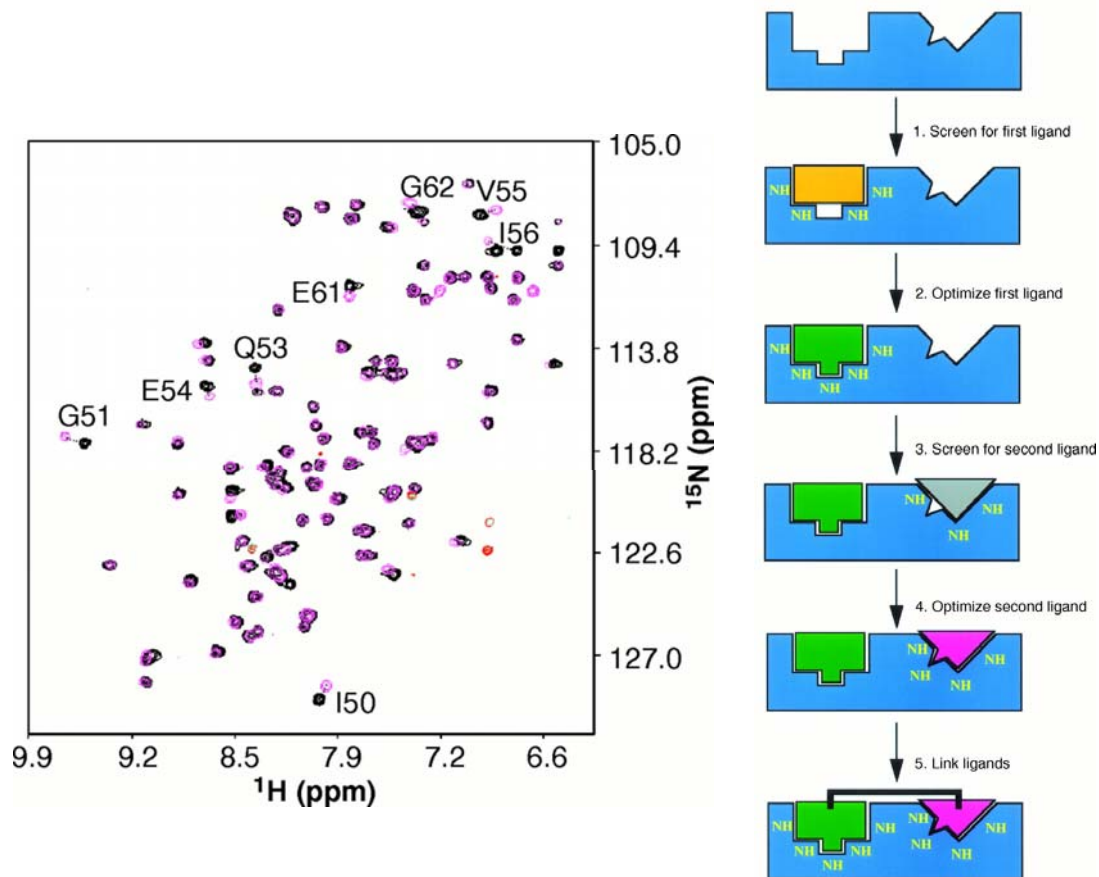
Laboratorium für physikalische Chemie, Eidgenössische Technische Hochschule, 8006 Zürich, Switzerland
(Received 13 November 1975)



J. Chem. Phys., **64**, 2229 (1974)



Relation Structure-activité par RMN



S.B. Shuker, P.J. Hajduk, R.P. Meadows, S.W. Fesik,
Science, **274**, 1531 (1996)



Retour à l'équilibre : La relaxation

- Hypothèse : émission de photons
 - Calcul par les coefficients d'Einstein
 - Spontanée: > age de l'univers
 - Stimulée: ~ qq centaines d'année!
- Contradiction totale avec l'expérience

R10. Spontaneous Emission Probabilities at Radio Frequencies. E. M. PURCELL, *Harvard University*.—For nuclear magnetic moment transitions at radio frequencies the probability of spontaneous emission, computed from

$$A_{\nu} = (8\pi\nu^2/c^2)h\nu(8\pi^2\mu^2/3h^3) \text{ sec.}^{-1},$$

is so small that this process is not effective in bringing a spin system into thermal equilibrium with its surroundings. At 300°K, for $\nu = 10^7 \text{ sec.}^{-1}$, $\mu = 1$ nuclear magneton, the corresponding relaxation time would be 5×10^{22} seconds! However, for a system coupled to a resonant electrical circuit, the factor $8\pi\nu^2/c^2$ no longer gives correctly the number of radiation oscillators per unit volume, in unit frequency range, there being now *one* oscillator in the frequency range ν/Q associated with the circuit. The spontaneous emission probability is thereby increased, and the relaxation time reduced, by a factor $f = 3Q\lambda^3/4\pi^2V$, where V is the volume of the resonator. If a is a dimension characteristic of the circuit so that $V \sim a^3$, and if δ is the skin-depth at frequency ν , $f \sim \lambda^3/a^2\delta$. For a non-resonant circuit $f \sim \lambda^3/a^3$, and for $a < \delta$ it can be shown that $f \sim \lambda^3/a^3$. If small metallic particles, of diameter 10^{-3} cm are mixed with a nuclear-magnetic medium at room temperature, spontaneous emission should establish thermal equilibrium in a time of the order of minutes, for $\nu = 10^7 \text{ sec.}^{-1}$.

Phys. Rev., **69**, 681 (1946)

Retour à l'équilibre : La relaxation

- Hypothèse : émission de photons
Calcul par les coefficients d'Einstein
 - Spontanée: > age de l'univers
 - Stimulée: ~ qq centaines d'année!
- Contradiction totale avec l'expérience

- Bonne explication:
 - Théorie BPP:
Processus non radiatif: fluctuations aléatoires du champ magnétique ressenti par le noyau; fluctuations induits par les mouvements moléculaires

Relaxation Effects in Nuclear Magnetic Resonance Absorption*

N. BLOEMBERGEN,** E. M. PURCELL, AND R. V. POUND,***
Lyman Laboratory of Physics, Harvard University, Cambridge, Massachusetts

Phys. Rev., **73**, 679 (1948)

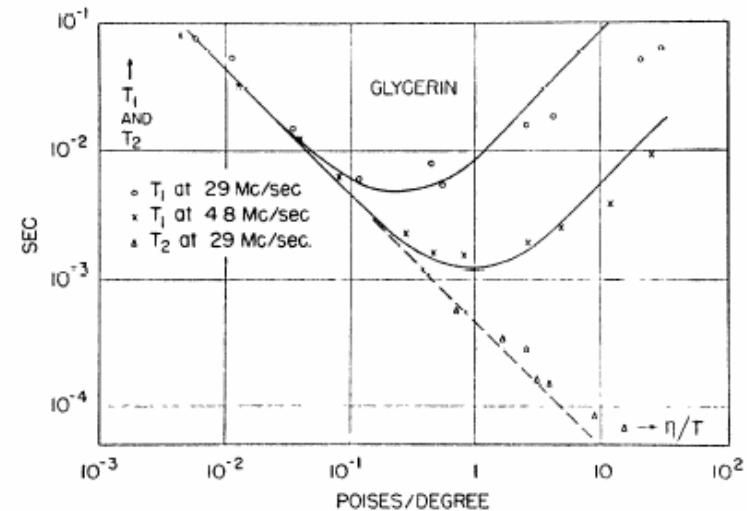


FIG. 13. The relaxation time T_1 and the line-width parameter T_2 , plotted against the ratio of viscosity to absolute temperature, for glycerin.



Retour à l'équilibre : La relaxation

- Hypothèse : émission de photons
Calcul par les coefficients d'Einstein
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- Bonne explication:
 - Théorie BPP:
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Généralisation et extensions :

- Matrice de relaxation

A. Redfield, *IBM J. Res. Develop.*, **1**, 19 (1957)
Adv. Magn. Reson., **1**, 1 (1965)

- Opérateurs

A. Abragam « *Principles of nuclear magnetism* » (1961)

Phys. Rev., **69**, 681 (1946)

La relaxation croisée : les distances

Relaxation Processes in a System of Two Spins*

I. SOLOMON†

Lyman Laboratory, Harvard University, Cambridge, Massachusetts

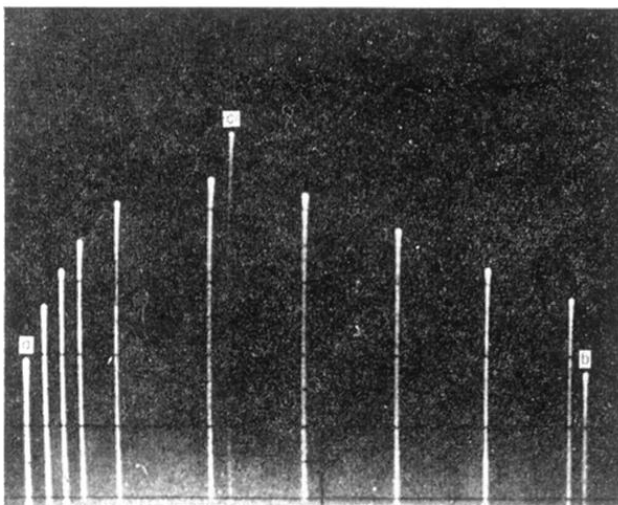


FIG. 5. Amplitude of tails of 90° pulses at fluorine frequency after having applied a 180° pulse at hydrogen frequency in hydrofluoric acid. *a* and *b* represent the amplitude of the tail when no 180° pulse has been applied; *c* represents the amplitude of the tail when the proton resonance has been saturated (steady Overhauser effect).

Irradier un spin modifie le signal d'un autre
Et cela en fonction de la distance entre les deux!

Phys. Rev., **99**, 559 (1955)

Investigation of exchange processes by two-dimensional NMR spectroscopy

J. Jeener

Université Libre de Bruxelles, B-1050 Brussels, Belgium

B. H. Meier, P. Bachmann, and R. R. Ernst

Laboratorium für physikalische Chemie, Eidgenössische Technische Hochschule, CH - 8092 Zürich, Switzerland

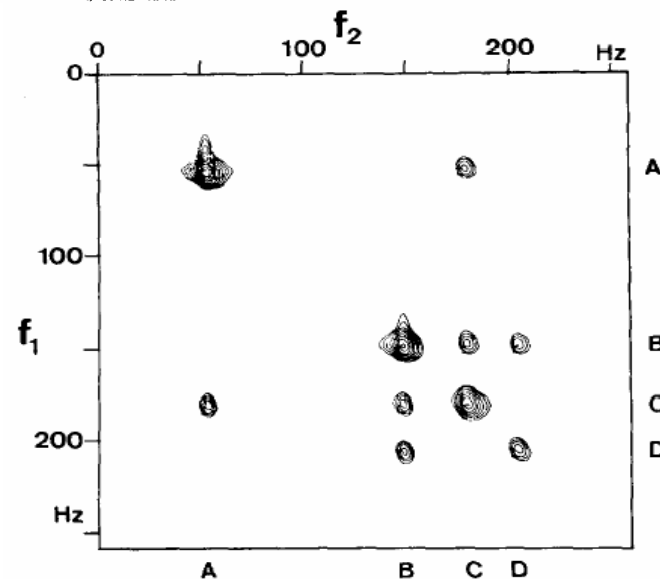


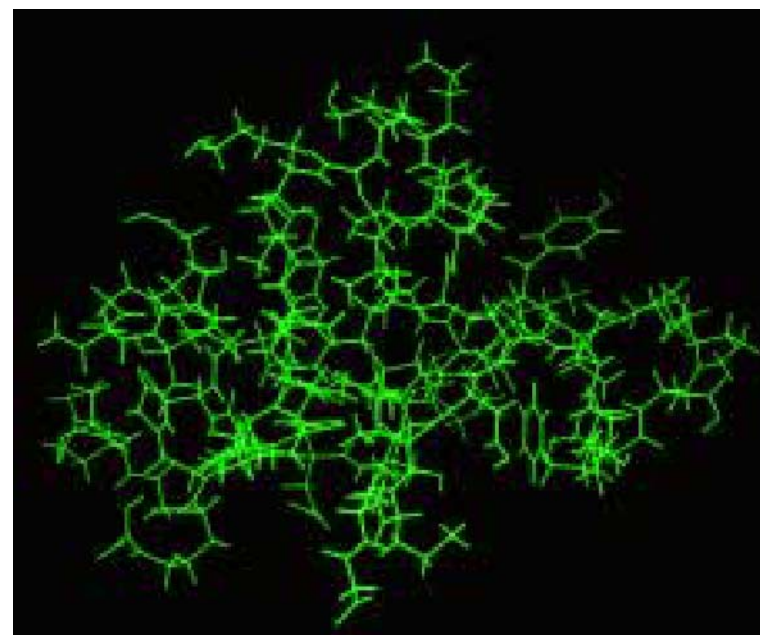
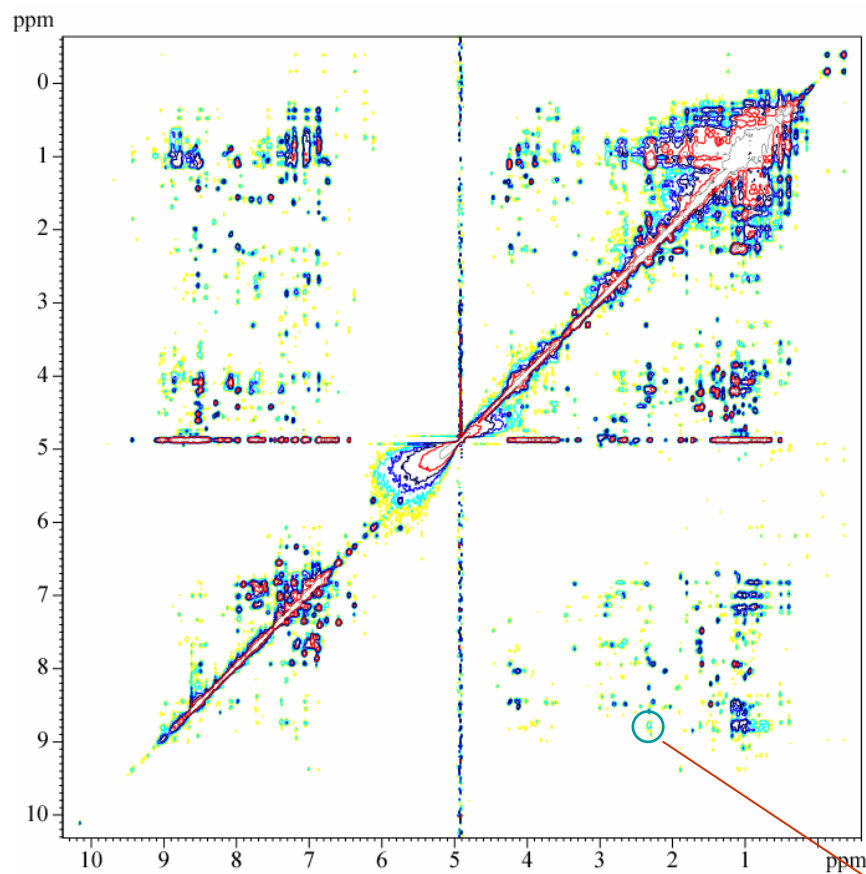
FIG. 2. 2D exchange spectrum of heptamethylbenzenonium ion. A contour plot of the 60 MHz 2D proton resonance spectrum, recorded at 40°C in 9.4 M H_2SO_4 , is shown.

J. Chem. Phys., **71**, 4546 (1979)



La relaxation : la structure

1^{ère} structure par RMN



M.P. Williamson, T.F. Havel, K. Wüthrich,
J. Mol. Biol. **182** 295 (1985)

Spectre NOESY d'une protéine

Intensité = $f(1/r^6)$



La relaxation : la dynamique interne

Backbone Dynamics of Proteins As Studied by ^{15}N Inverse Detected Heteronuclear NMR Spectroscopy: Application to Staphylococcal Nuclease[†]

Lewis E. Kay,[‡] Dennis A. Torchia,[§] and Ad Bax^{*†}

Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, and Bone Research Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20892

Biochemistry, **28**, 8972 (1989)

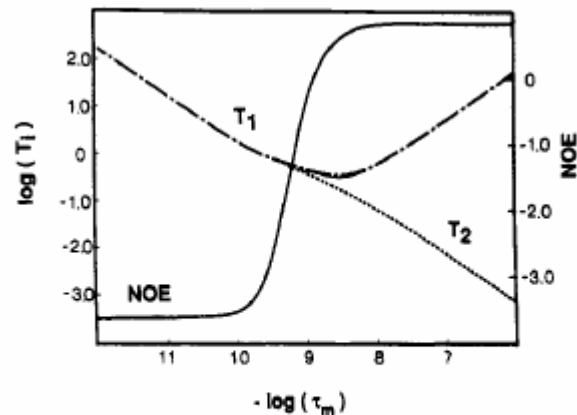


FIGURE 2: Plots of $\log(T_i/i = 1,2)$ and $^1\text{H}-^{15}\text{N}$ NOE vs $\log(\tau_m)$ for ^{15}N relaxed by $^1\text{H}-^{15}\text{N}$ dipolar and CSA interactions at a nitrogen frequency of 50.7 MHz. An N-H bond vector tumbling isotropically with $S^2 = 1.0$ and a bond length of 1.02 Å was assumed. A value of $\sigma_{\parallel} - \sigma_{\perp} = -160$ ppm was used.



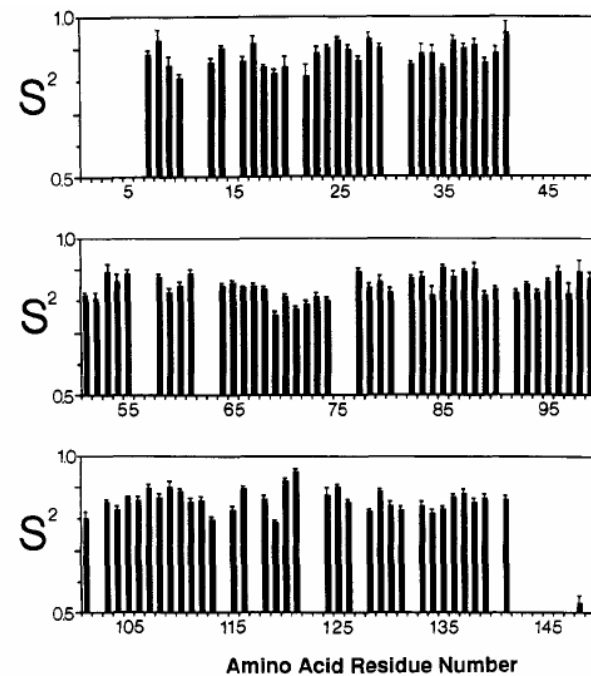
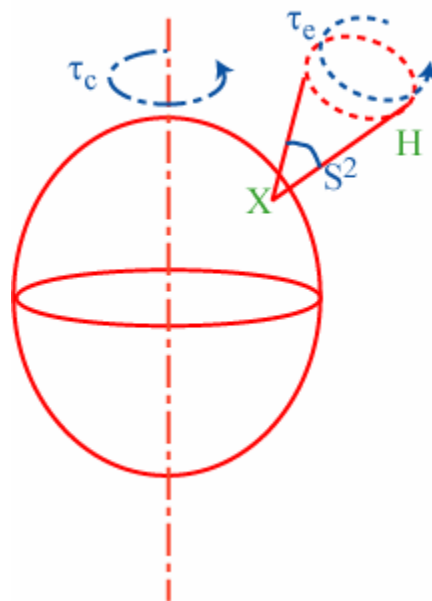
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Biochemistry, **28**, 8972 (1989)





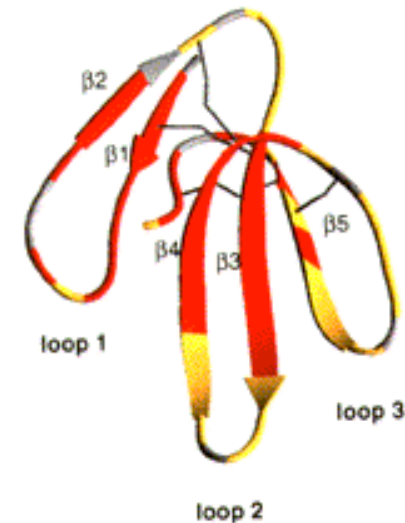
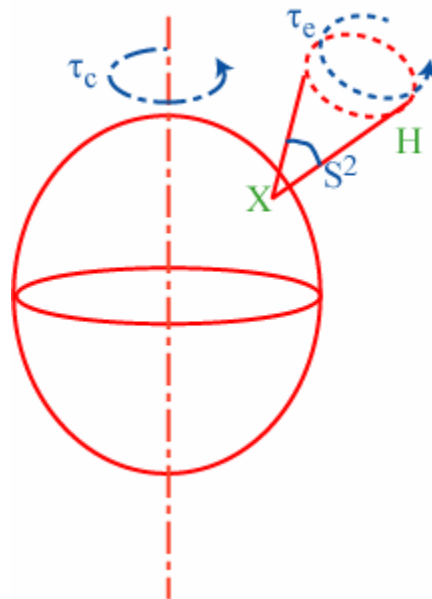
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National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20892

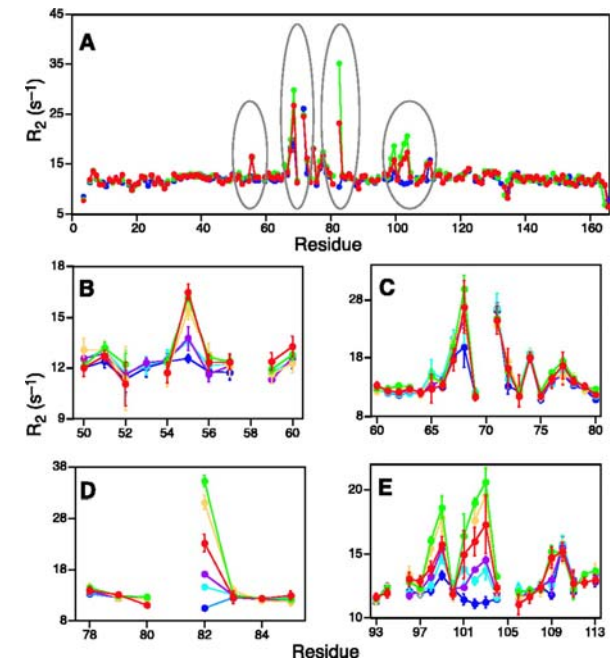
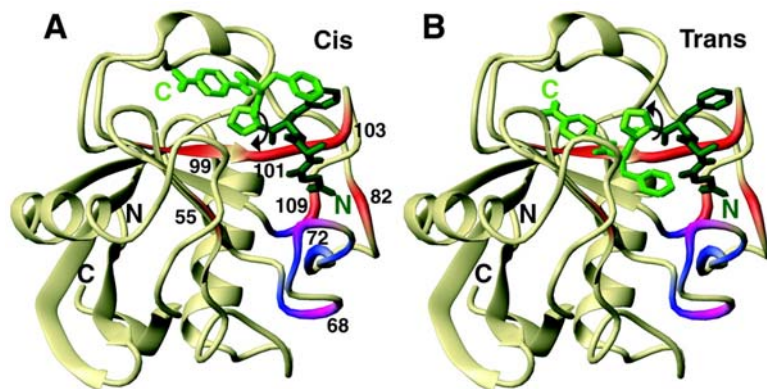
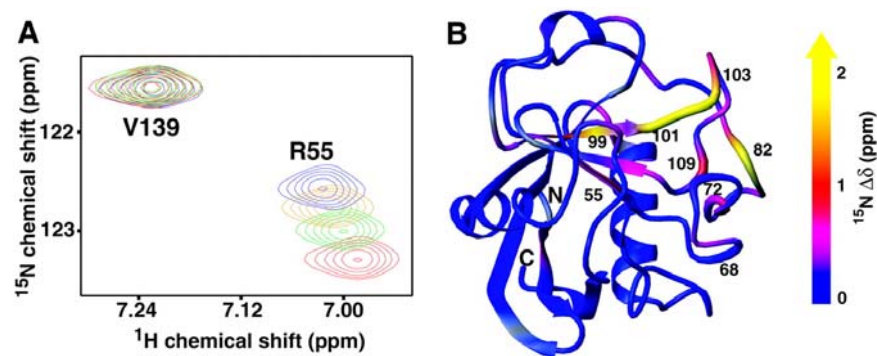
Biochemistry, **28**, 8972 (1989)





La relaxation : les mouvements lents

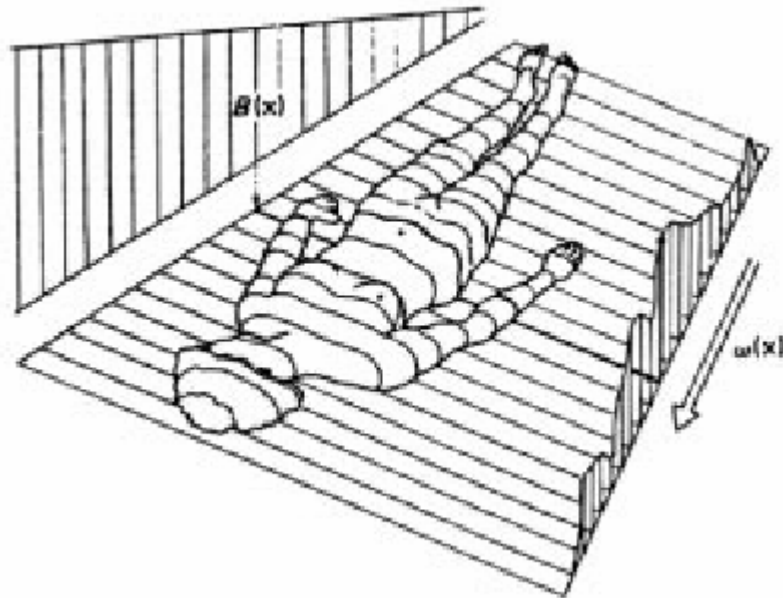
Etude du cycle catalytique de l'enzyme Cyclophiline A en présence ou non de substrat



Bleu, cyan, magenta, vert,
jaune, rouge, concentration croissante

E.Z. Eisenmesser, D.A. Bosco, M. Akke,
D. Kern, *Science*, 295, 1520 (2002)

CEA L'imagerie par résonance magnétique

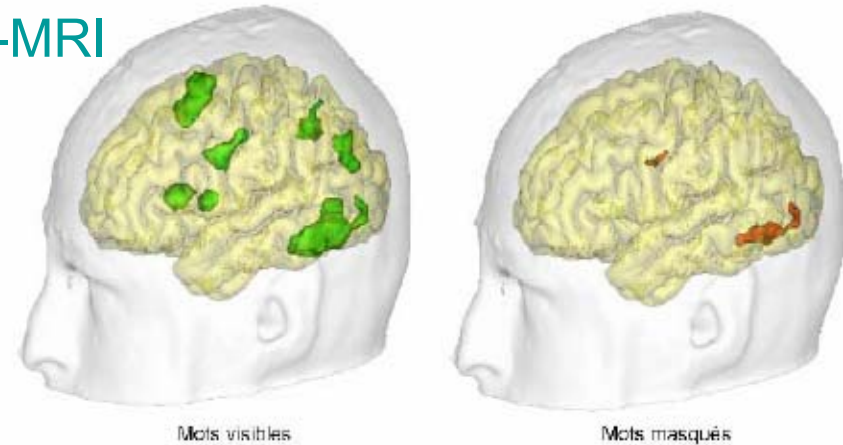


- Fréquence de résonance proportionnelle au champ magnétique appliqué
- Signal proportionnel à la quantité de noyaux (eau)

P.C. Lauterbur, *Nature*. **242**, 170 (1973)

P. Mansfield, *J. Physics C Solid State Phys.* **10**, L55–L58 (1977)

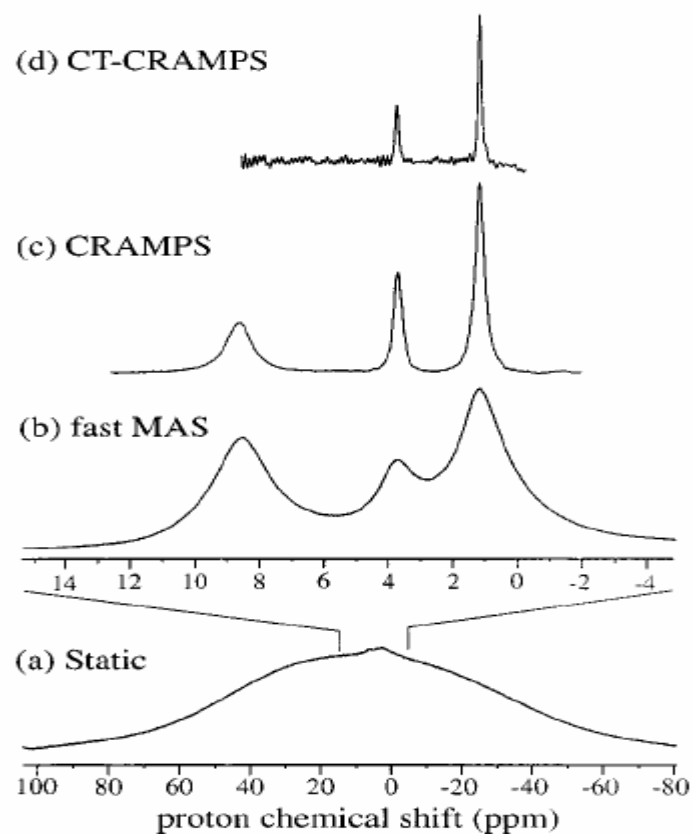
f-MRI



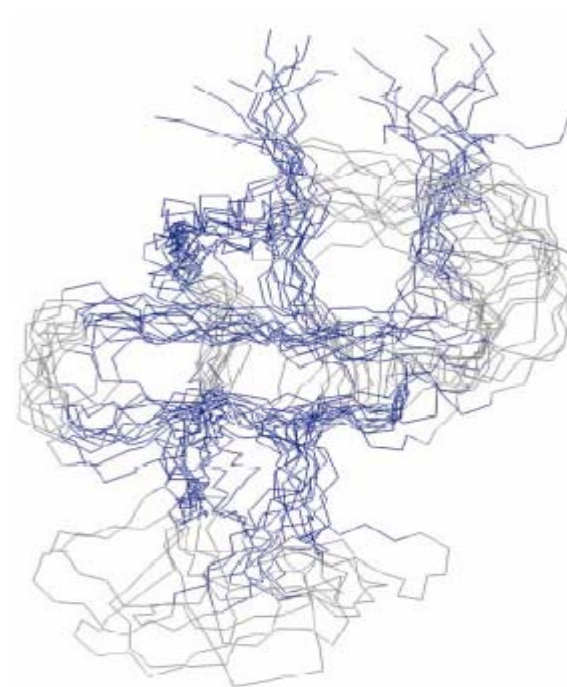
S. Ogawa, D. Tank, R. Menon, J. Ellermann, S.-G. Kim, H. Merkle, K. Ugurbil *Proc. Natl.Acad.Sci.* **89**, 5951 (1991)

Les tendances récentes :

RMN du solide haute résolution



1^{ère} structure



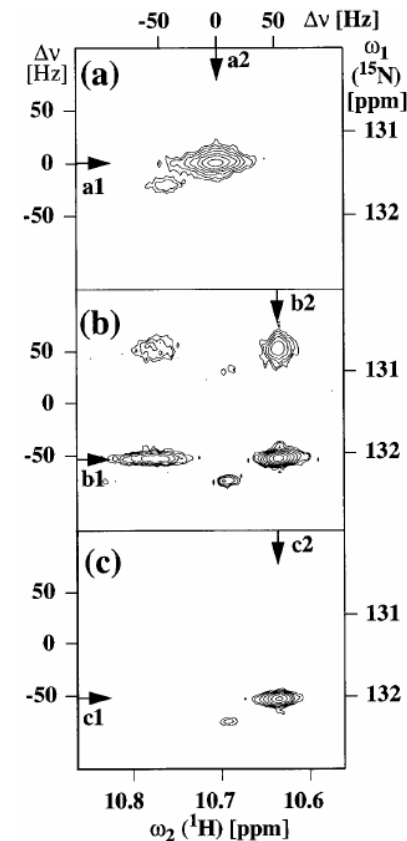
A. Lesage, L. Duma, D. Sakellariou, L. Emsley,
J. Am. Chem. Soc., **123**, 5747 (2001)

F. Castellani, B. van Rossum, A. Diehl, M. Schubert,
K. Rehbein, H. Oschkinat, *Nature*, **420**, 98 (2002)



Les tendances récentes en RMN liquide

- Relaxation et déplacement chimique : vers l'étude de grosses protéines

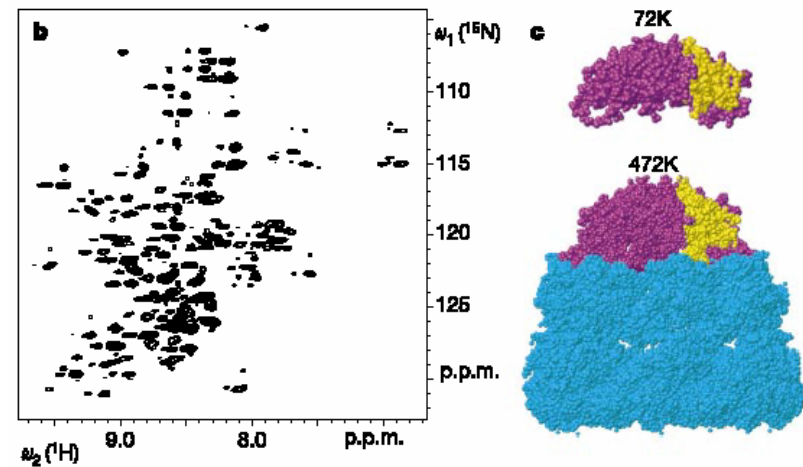


K. Pervushin, R. Riek, G. Wider, K. Wüthrich,
Proc. Natl. Acad. Sci. USA **94**, 12366 (1997).



Les tendances récentes en RMN liquide

- Relaxation et déplacement chimique : vers l'étude de grosses protéines



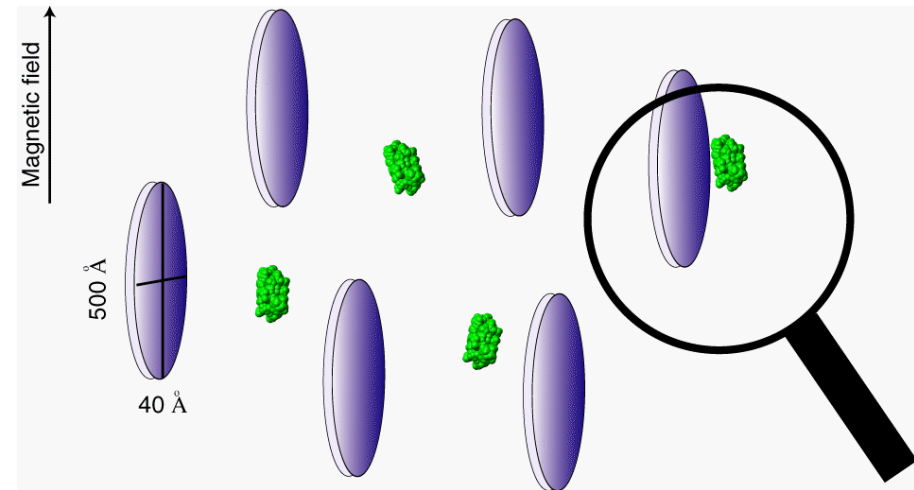
Etude du complexe GroEL-GroES (900kDa)

J. Fiaux, E.B. Bertelsen, A.L. Horwich, K. Wüthrich
Nature, **418**, 207 (2002)



Les tendances récentes en RMN liquide

- Relaxation et déplacement chimique : vers l'étude de grosses protéines
- Cristaux liquides et RMN : vers des informations d'orientation



N. Tjandra, A. Bax, *Science*, **278**, 1111 (1997)

Les tendances récentes en RMN liquide

- Relaxation et déplacement chimique : vers l'étude de grosses protéines
- Cristaux liquides et RMN : vers des informations d'orientation
- RMN liquide et *in vivo*: RMN dans les cellules

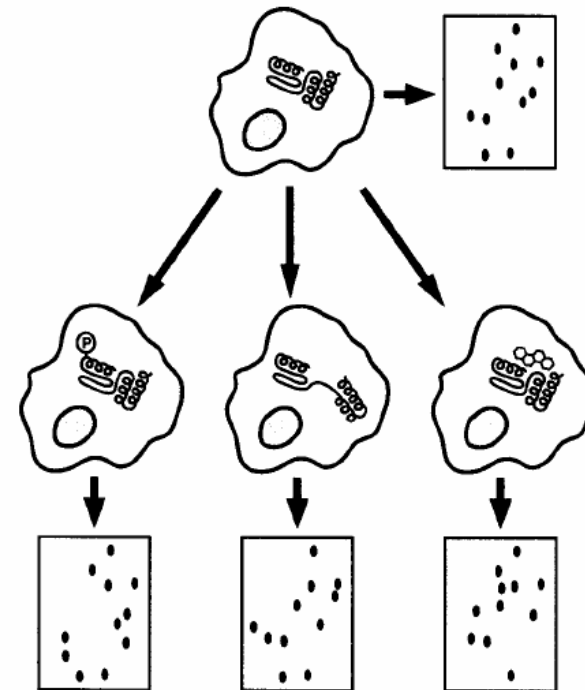


FIGURE 1: Examples of potential applications of in-cell NMR spectroscopy. Posttranslational modifications (left), conformational changes (middle), and binding events (right) can be monitored relative to the unaffected protein (top) through changes in the resonance positions of peaks in NMR spectra. Schematic NMR spectra are shown next to each cell.

Z. Serber, A.T. Keatinge-Clay, R. Ledwidge, A.E. Kelly, S.M. Miller, V. Dötsch *J. Am. Chem. Soc.*, **121**, 2446 (2001).
J.-M. Wieruszkeski, A. Bohin, J.P. Bohin, G. Lippens, *J. Magn. Reson.*, **151**, **118** (2001).



Les tendances récentes en RMN liquide

- Relaxation et déplacement chimique : vers l'étude de grosses protéines
- Cristaux liquides et RMN : vers des informations d'orientation
- RMN liquide et *in vivo*: RMN dans les cellules
- RMN liquide et imagerie: 2D en 1D gain en temps

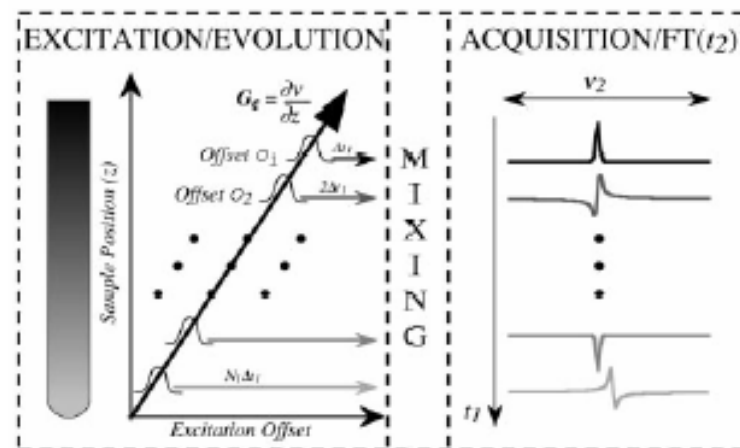


Fig. 2. Potential use of spectral heterogeneities toward the acquisition of multidimensional NMR data within a single scan. Heterogeneities are assumed to arise from the application of an external magnetic field gradient G_z . In combination with frequency-selective pulses, this enables spins throughout the sample to undergo spatially distinct t_1 evolution periods. Once spatially discriminated during the t_2 acquisition, this strategy allows one to collect a complete 2D NMR data set within a single scan.

L. Frydman, T. Scherf, A. Lupulescu,
Proc. Nat. Acad. Sci. USA, **99**, 15858 (2002)



Quels problèmes ?

Signal sur bruit, résolution et polarisation

Signal proportionnel à la polarisation :

$$P = \frac{n_{\alpha} - n_{\beta}}{n_{\alpha} + n_{\beta}} \approx \frac{\gamma h B_0}{2kT}$$

A température ambiante $P \sim 10^{-5}$

Resonance Absorption by Nuclear Magnetic Moments in a Solid

E. M. PURCELL, H. C. TORREY, AND R. V. POUND*
*Radiation Laboratory, Massachusetts Institute of Technology,
Cambridge, Massachusetts*

December 24, 1945

IN the well-known magnetic resonance method for the determination of nuclear magnetic moments by molecular beams,¹ transitions are induced between energy levels which correspond to different orientations of the nuclear spin in a strong, constant, applied magnetic field. We have observed the absorption of radiofrequency energy, due to such transitions, in a *solid* material (paraffin) containing protons. In this case there are two levels, the separation of which corresponds to a frequency, ν , near 30 megacycles/sec., at the magnetic field strength, H , used in our experiment, according to the relation $h\nu = 2\mu H$. Although the difference in population of the two levels is very slight at room temperature ($h\nu/kT \sim 10^{-6}$), the number of nuclei taking part is so large that a measurable effect is to be expected providing thermal equilibrium can be established. If one assumes that the only local fields of importance are caused by the moments of neighboring nuclei, one can show that the imaginary part of the magnetic permeability, at resonance, should be of the order $h\nu/kT$. The absence from this expression of the nuclear moment and the internuclear distance is explained by the fact that the influence of these factors upon absorption cross section per nucleus and density of nuclei is just cancelled by their influence on the width of the observed resonance.

A crucial question concerns the time required for the establishment of thermal equilibrium between spins and

Phys. Rev., **69**, 37 (1946)



Quels problèmes ?

Signal sur bruit, résolution et polarisation

Signal proportionnel à la polarisation :

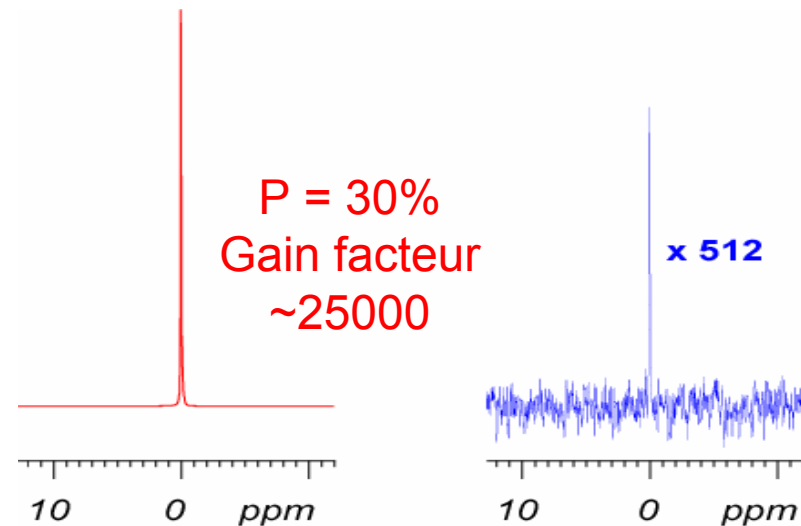
$$P = \frac{n_{\alpha} - n_{\beta}}{n_{\alpha} + n_{\beta}} \approx \frac{\gamma h B_0}{2kT}$$

A température ambiante $P \sim 10^{-5}$

Comme B_0 limité technologiquement à $\sim 25T$

- Transfert de polarisation à partir de systèmes plus polarisés (DNP, pompage optique, parahydrogène)
- Détection optique, mécanique ou par SQUID

Signal de xénon polarisé par laser





Quels problèmes ?

Signal sur bruit, résolution et polarisation

Signal proportionnel à la polarisation :

$$P = \frac{n_{\alpha} - n_{\beta}}{n_{\alpha} + n_{\beta}} \approx \frac{\gamma h B_0}{2kT}$$

A température ambiante $P \sim 10^{-5}$

Comme B_0 limité technologiquement à $\sim 25T$

- Transfert de polarisation à partir de systèmes plus polarisés (DNP, pompage optique, parahydrogène)
- Détection optique, mécanique ou par SQUID

Solution fiable et générale : augmenter B_0



Bravo et mes meilleurs vœux!