The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific
and Cultural Organization

International Atomic
Energy Agency

SMR.1670 - 32

INTRODUCTION TO MICROFLUIDICS

8 - 26 August 2005

Chip-based NMR

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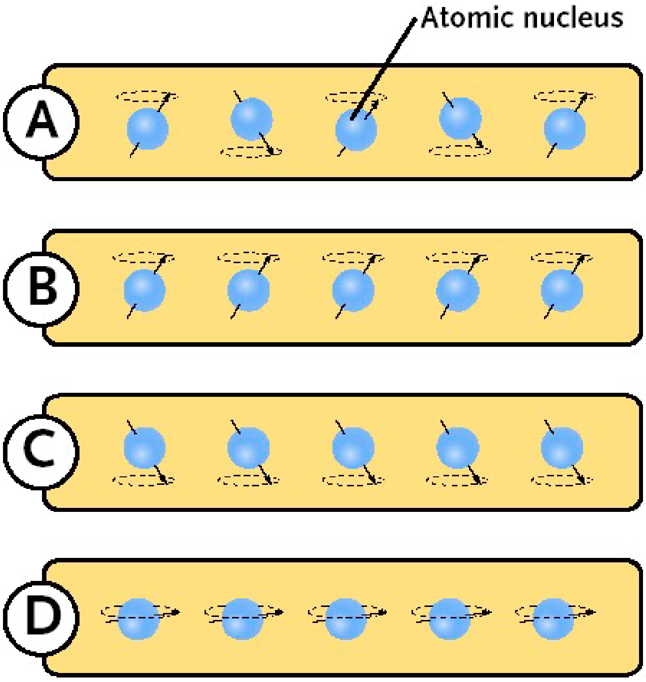
Chip-based NMR

Han Gardeniers
MESA+ Institute for Nanotechnology
University of Twente

Summer School in Microfluidics
ICTP, Trieste, Italy

NMR: how does it work?



NMR = Nuclear Magnetic Resonance

Without a magnetic field
spins are randomly oriented (A)

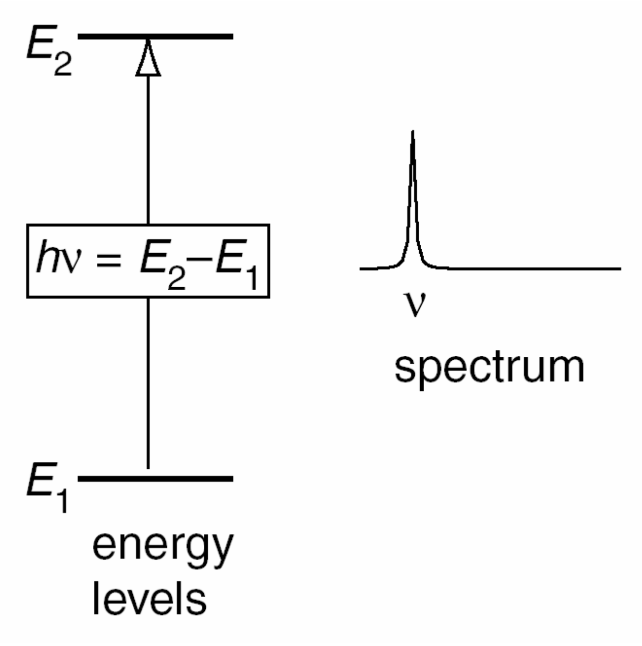
In a magnetic field spins align
parallel (B) or anti-parallel (C)

A matching r.f. signal will switch
the spins from state B to C

When r.f. is turned off, the spins
relax to low-energy state B in a
precession process

Energy level description

Switching between spin-up and spin-down requires/delivers energy



$$\nu_{0,1} = -\frac{1}{2\pi}\gamma_1(1+\delta_1)B_0$$

ν = Larmor frequency
γ = gyromagnetic ratio
δ1=shielding factor / chemical shift

Hydrogen (proton) NMR

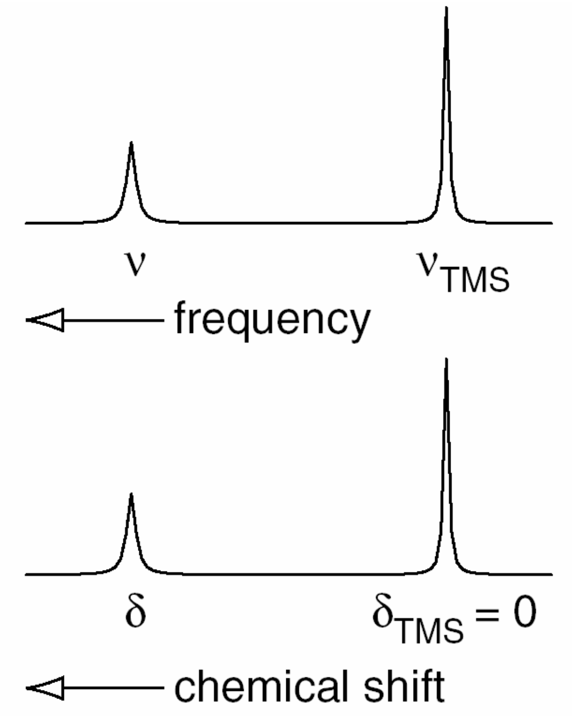
To take a specific example, for protons $\gamma = +2.67 \times 10^8$ rad s^{-1} T^{-1}, so in a magnetic field of 4.7 T the Larmor frequency of a spin with chemical shift zero is

$$\begin{aligned}\nu_0 &= -\frac{1}{2\pi}\gamma(1+\delta)B_0\\ &= -\frac{1}{2\pi} \times 2.67 \times 10^8 \times 4.7 = -200 \times 10^6 \text{ Hz.}\end{aligned}$$

In other words, the Larmor frequency is −200 MHz.

Atom	Frequency/Tesla
^{1}H	42.58 MHz/T
^{13}C	10.71 MHz/T
^{31}P	17.12 MHz/T

Chemical shift



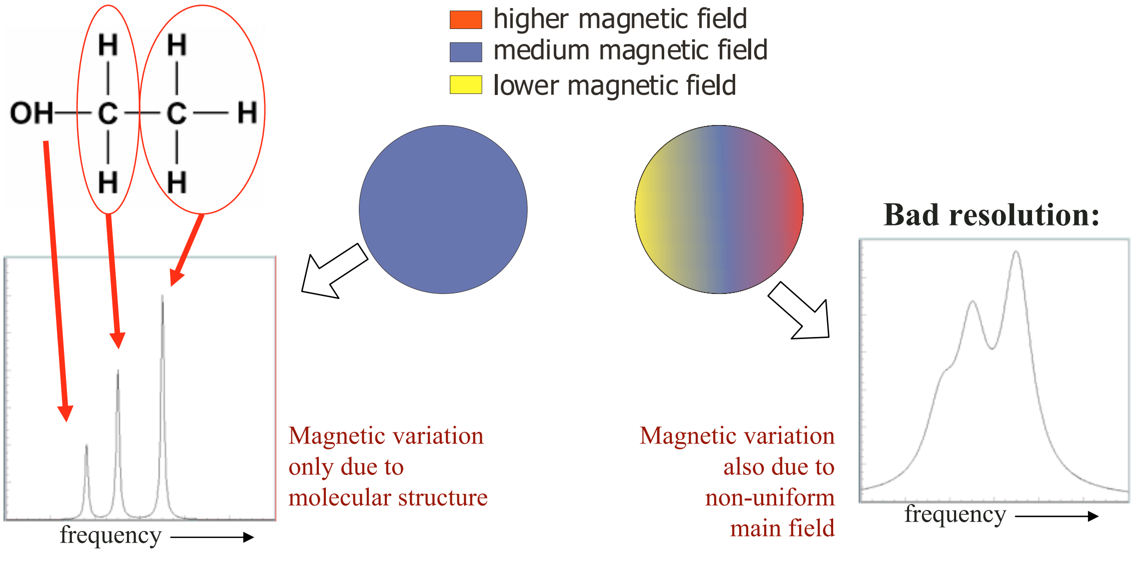
$$\delta_{\mathrm{ppm}} = 10^6 \times \frac{\nu - \nu_{\mathrm{TMS}}}{\nu_{\mathrm{TMS}}}$$

TMS=TetraMethylSilane, $Si(CH_3)_4$

NMR resolution

Electron clouds around atoms shield them from the main magnetic field. This changes the rotation frequency of the atoms. The amount of shielding depends on the atomic environment in the molecule.

Example: ethanol



🟧 higher magnetic field
🟦 medium magnetic field
🟨 lower magnetic field

Bad resolution:

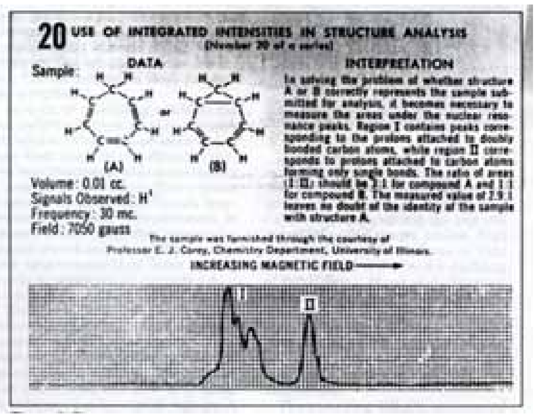
Magnetic variation
only due to
molecular structure

Magnetic variation
also due to
non-uniform
main field

Short NMR history

High frequency microwave tube used for radar in WOII were now put to work for NMR.

1945/6	First NMR measurement (Purcell et al. and Bloch et al.)
1949	W.D. Knight observes NMR chemical shifts
1952	First commercial NMR spectrometer (30 MHz Varian)
1962	Introduction of superconductive magnets
late 1960s	Introduction of Fourier Transformed NMR
1972	First MRI image (Lauterbur)



20 USE OF INTEGRATED INTENSITIES IN STRUCTURE ANALYSIS
(Number 20 of a series)

DATA

Sample:

(A) or (B)

Volume: 0.01 cc.
Signals Observed: H^1
Frequency: 30 mc.
Field: 7050 gauss

INTERPRETATION

In solving the problem of whether structure A or B correctly represents the sample submitted for analysis, it becomes necessary to measure the areas under the nuclear resonance peaks. Region I contains peaks corresponding to the protons attached to doubly bonded carbon atoms, while region II corresponds to protons attached to carbon atoms forming only single bonds. The ratio of areas (I:II) should be 3:1 for compound A and 1:1 for compound B. The measured value of 2.9:1 leaves no doubt of the identity of the sample with structure A.

The sample was furnished through the courtesy of Professor E. J. Corey, Chemistry Department, University of Illinois.

INCREASING MAGNETIC FIELD ⟶

1953 The first problem solved by NMR spectroscopy by E.J.Corey, then of the University of Illinois.

http://www.beyonddiscovery.org/ & http://www.wooster.edu/chemistry/is/brubaker/nmr/nmr_landmark.html

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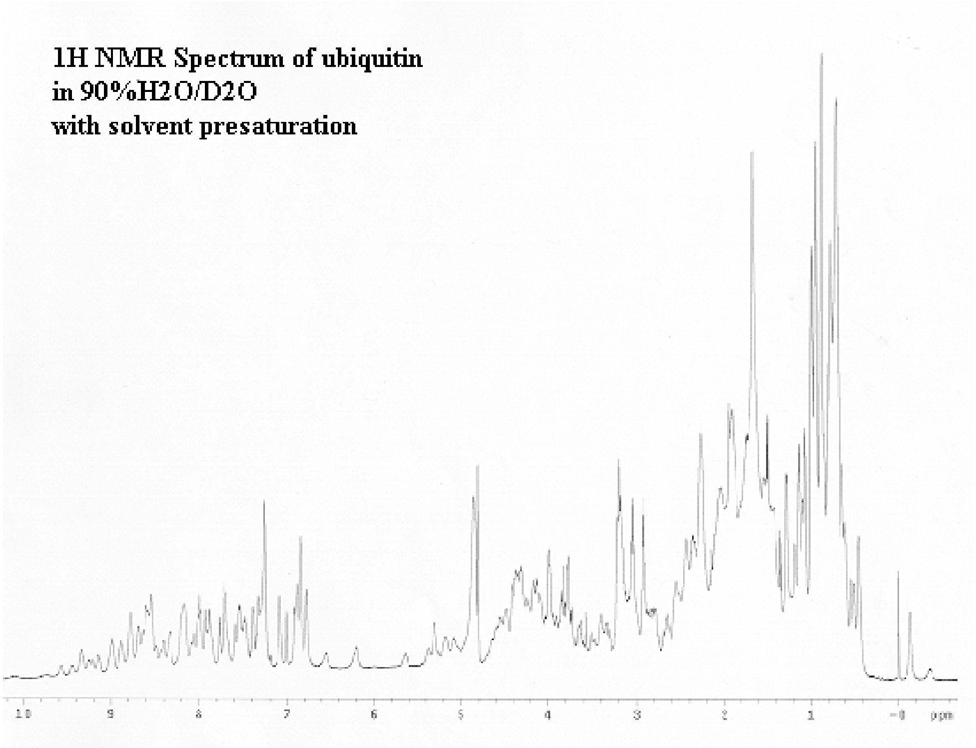
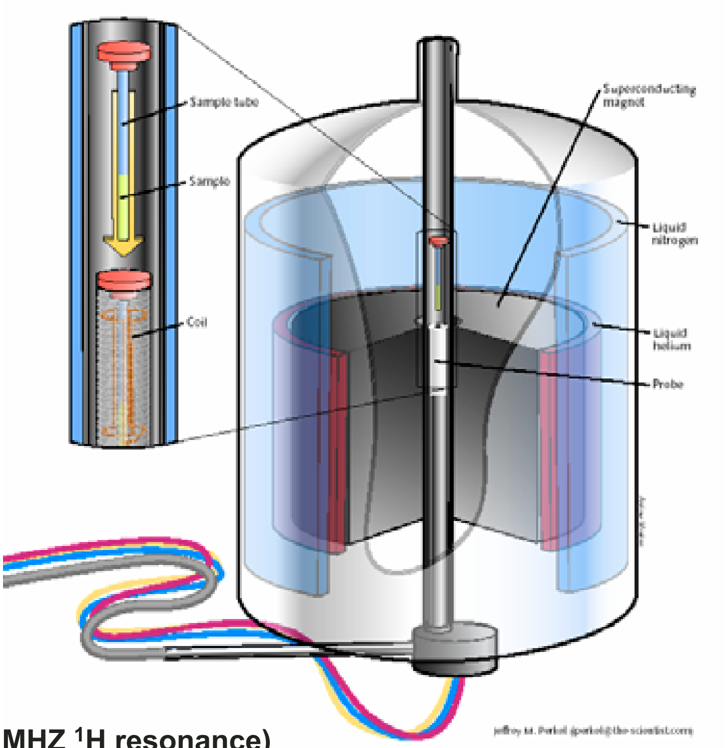
Protein structures from NMR



NMR equipment



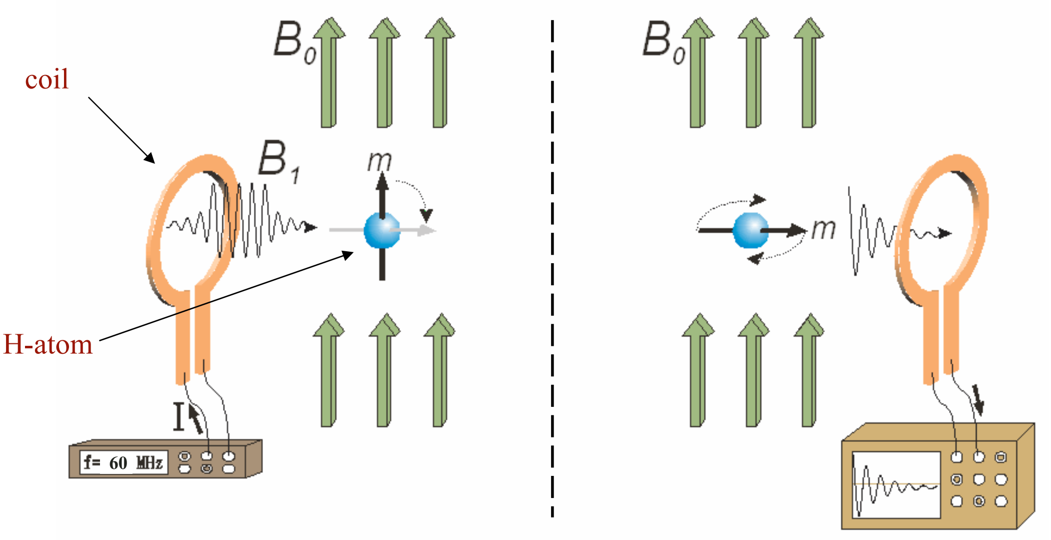
State of the art NMR: 21.1 Tesla (or 900 MHZ ^{1}H resonance)

Jeffrey M. Perkel (jperkel@the-scientist.com)

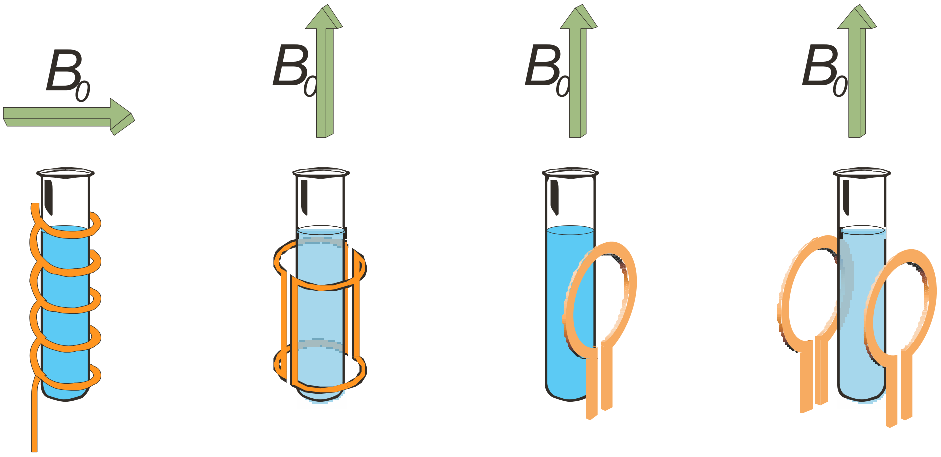
Prepared with assistance by Varian Inc. (www.varianinc.com) of Palo Alto, Calif.

Pulsed NMR measurement

Excitation **Detection**

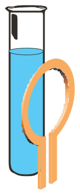


NMR coils

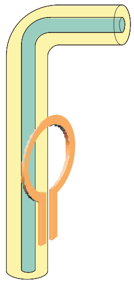


Solenoidal **Saddle** **Planar** **Helmholtz**

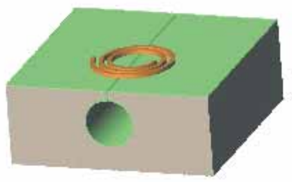
NMR sample containers



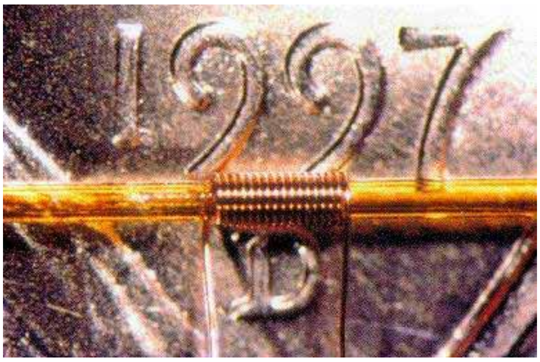
Test tube



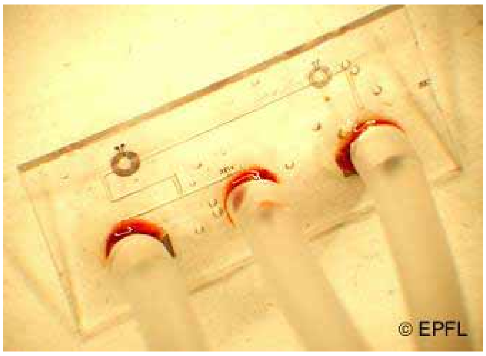
Capillary



Chip



Solenoidal NMR microcoil
around capillary
http://www.protasis.com/



NMR chip with integrated coils and
microfluidic channels
C.Massin e.a. EPFL Lausanne, CH

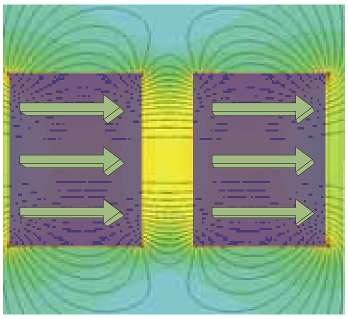
NMR resolution with microchannels

Non-uniform magnetic B_0 field due to:

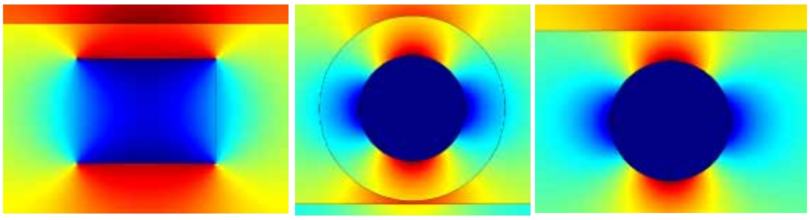
1. **Position in NMR magnet**

2. **Chip geometry**

Position inside the magnet is important:

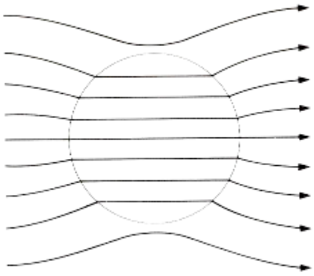


square channel — capillary — round channel



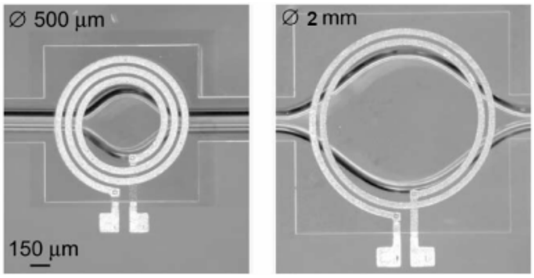
Average magnetic B_0 field non-uniformity (simulation):

square channel	capillary	round channel
15 ppm	0.19 ppm	0.082 ppm



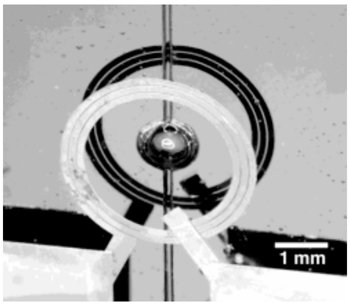
H.Wensink, University of Twente, unpublished, 2002

NMR resolution with microcoils



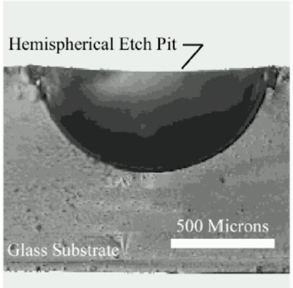
resolution ≈ 0.106 ppm — **resolution ≈ 0.066 ppm**

C.Massin, J.Magn.Res. 164, 2003, 242



resolution ≈ 0.024 ppm

The sample chamber is nearly a perfect sphere which ensures a uniform B_0 field.



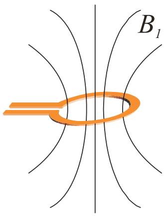
J.H. Walton, Anal Chem 75, 2003, 5030

Planar coil design

The sensitivity of the coil is directly related to magnetic field B_1 created with a unit current:

$$sensitivity \propto B_1 = \mu_0 \mu_r \frac{I}{2r_1}$$

B_1 = magnetic field generated by the coil
I = unit current
$\mu_0\mu_r$ = magnetic permeability
r_1 = coil radius



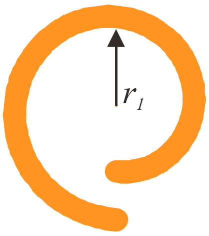
Noise originates from resistive (Johnson) noise of the coil:

$$noise \propto \sqrt{R} = \sqrt{\rho \frac{2\pi r_1}{A}}$$

R = coil resistance
ρ = resistivity
A = coil area
r_1 = coil radius

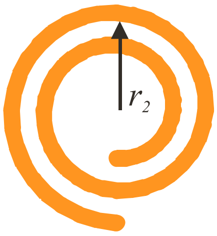
The coil should be as small as possible, while still enclosing the sample (high filling factor)

Planar coil design



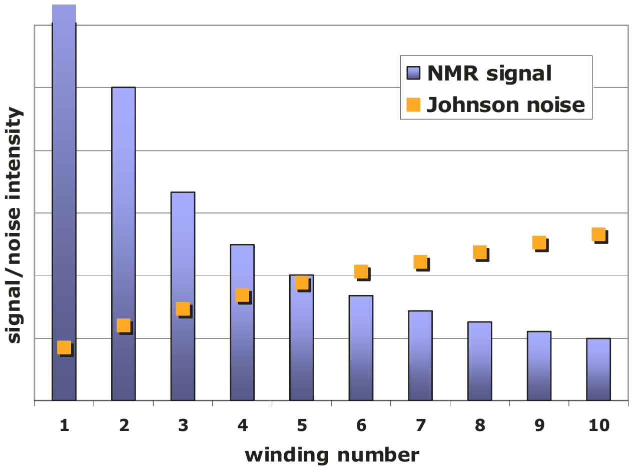
$$sensitivity \propto \frac{1}{r_1}$$

$$noise \propto \sqrt{r_1}$$



$$sensitivity \propto \frac{1}{r_1} + \frac{1}{r_2}$$

$$noise \propto \sqrt{r_1} + \sqrt{r_2}$$



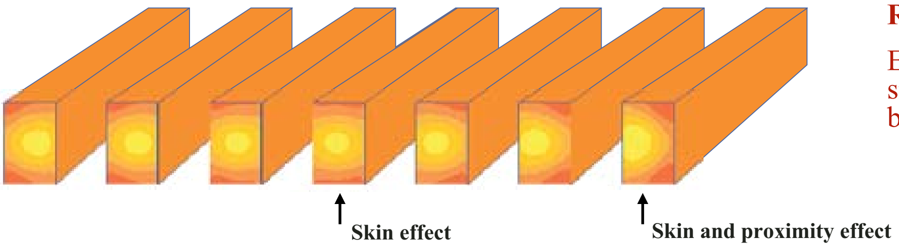
Every additional winding gives more signal, and more noise. At some point, the extra noise is more than the extra signal and no more windings should be added.

Planar coil design

Skin effect:
The tendency of alternating currents to increasingly flow nearer the surface of a conductor as frequency increases

Proximity effect:
The redistribution of current in a conductor brought about by the proximity of another current carrying conductor.

Current distribution:



Result:

Effective wire area becomes smaller, hence the resistance becomes larger.

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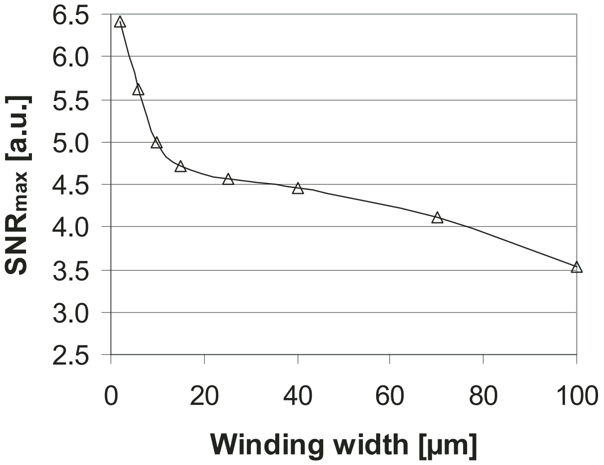
The Netherlands

Planar coil design: signal to noise

Finite element simulations results:

- The resistance of the coils should be optimized for a high SNR
- A smaller winding width is better
- So the best SNR is limited by fabrication techniques



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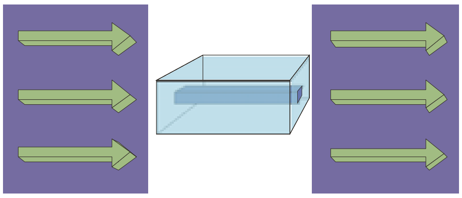
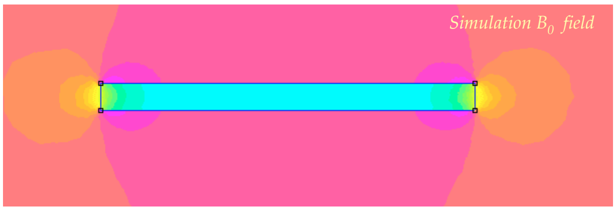
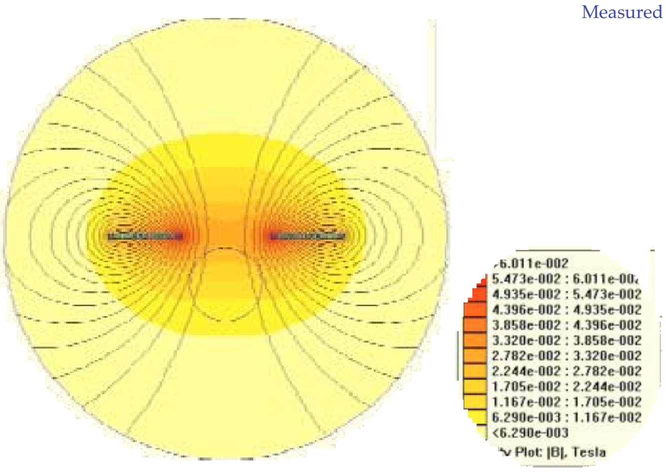
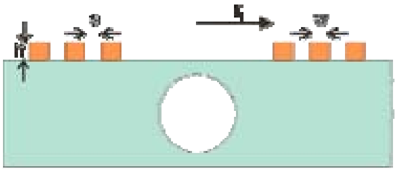
Micro coil and chip design





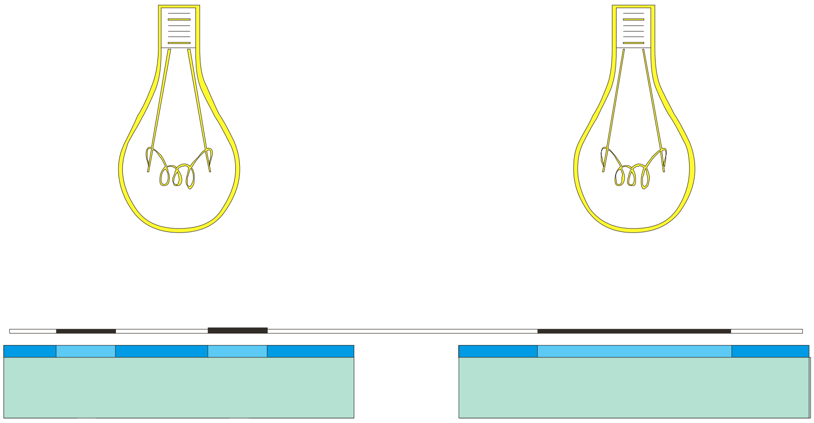
Measured spectral resolution: **0.02 ppm** (1.2 Hertz)





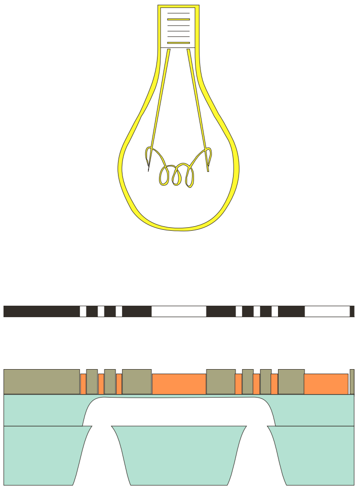
H. Wensink, University of Twente

Microcoil chip fabrication (1)



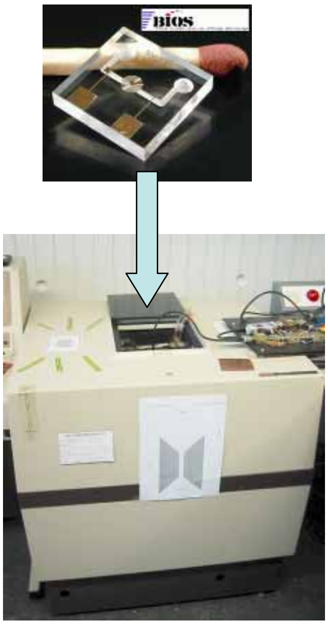
1. **Lithography**
2. **Powder blasting**
3. **Direct bonding**
4. **Thinning down**
5. **Lithography**
6. **Electroplating**

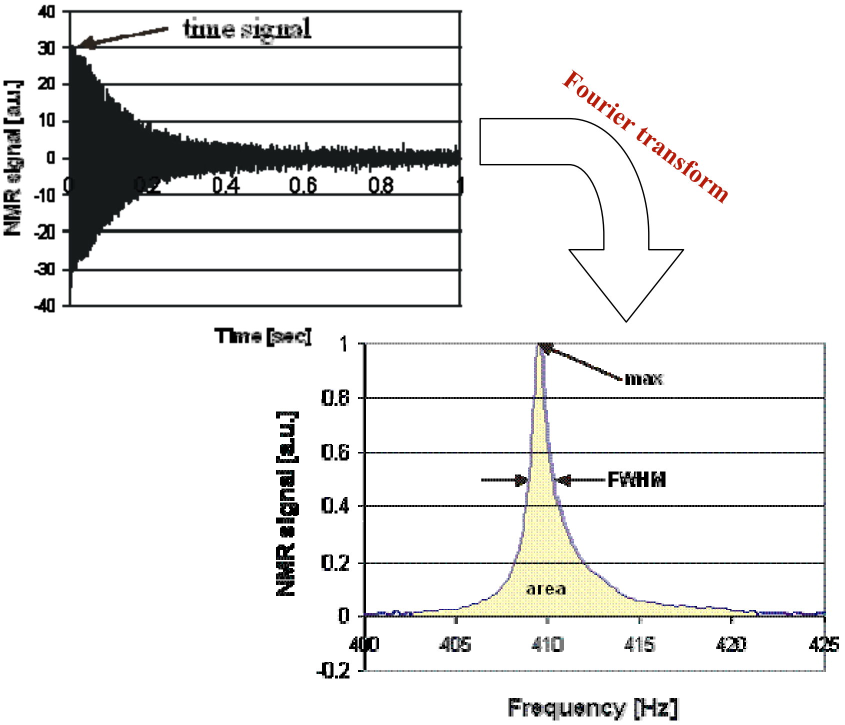
Microcoil chip fabrication (2)



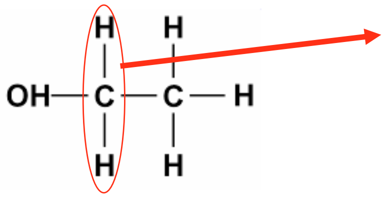
1. Lithography
2. Powder blasting
3. Direct bonding
4. Thinning down
5. Lithography
6. Electroplating

Water ^{1}H-NMR at 60 MHz in microcoil chip





NMR of ethanol in microcoil chip

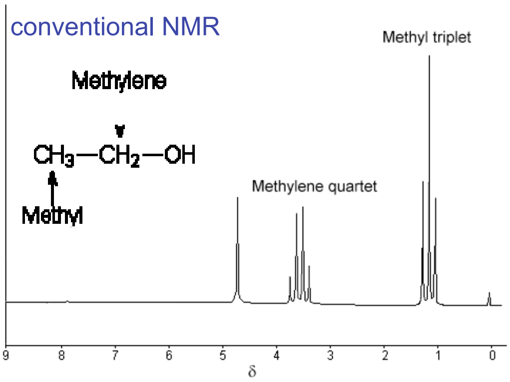


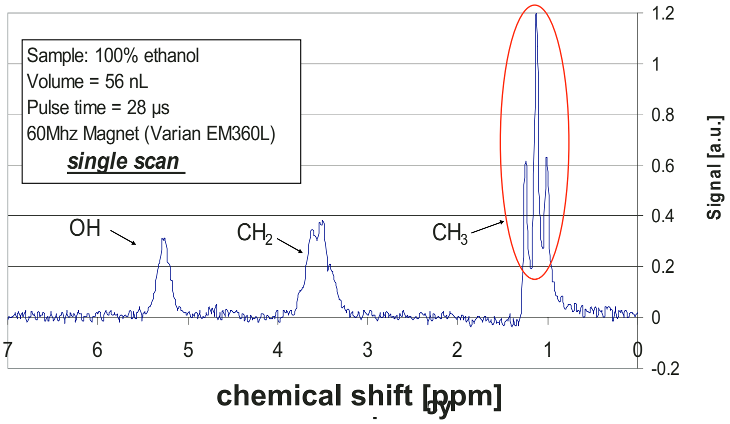
Hydrogen spin:

1. **up & up**
2. **down & down**
3. **up & down**
4. **down & up**

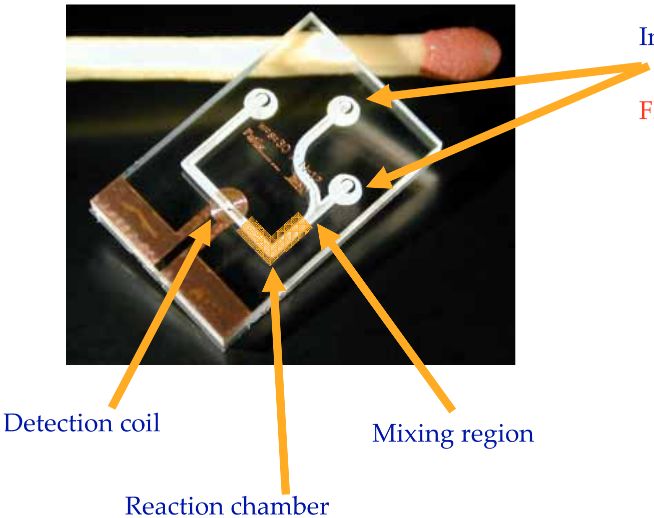
are the same

spin-spin coupling





Chip for reaction monitoring



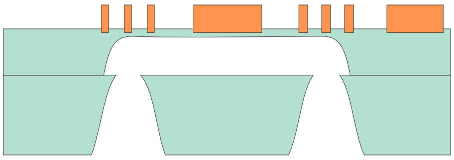
Inlets, connected to syringe pump

Flow rate determines reaction time

Detection coil

Mixing region

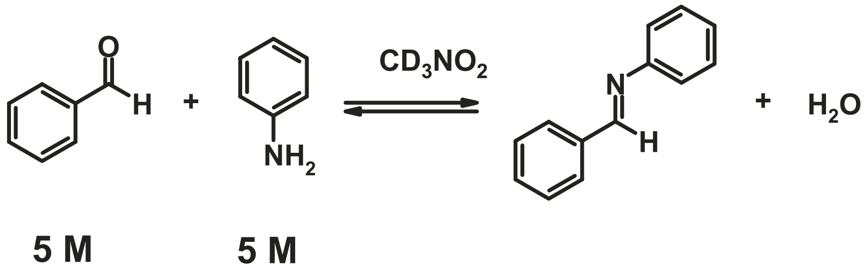
Reaction chamber

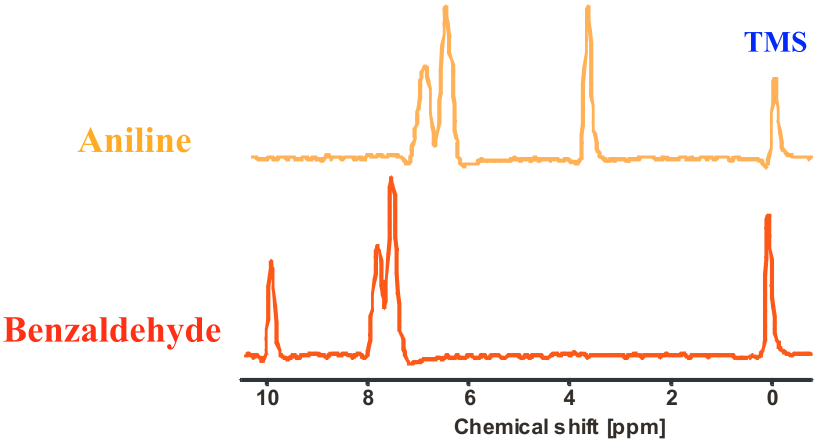


Reaction chamber volume: 570 nl
Detection volume: 56 nl
Minimum time from mixer to coil: 0.9 sec

H. Wensink e.a., submitted to Lab Chip

Example reaction: imine formation

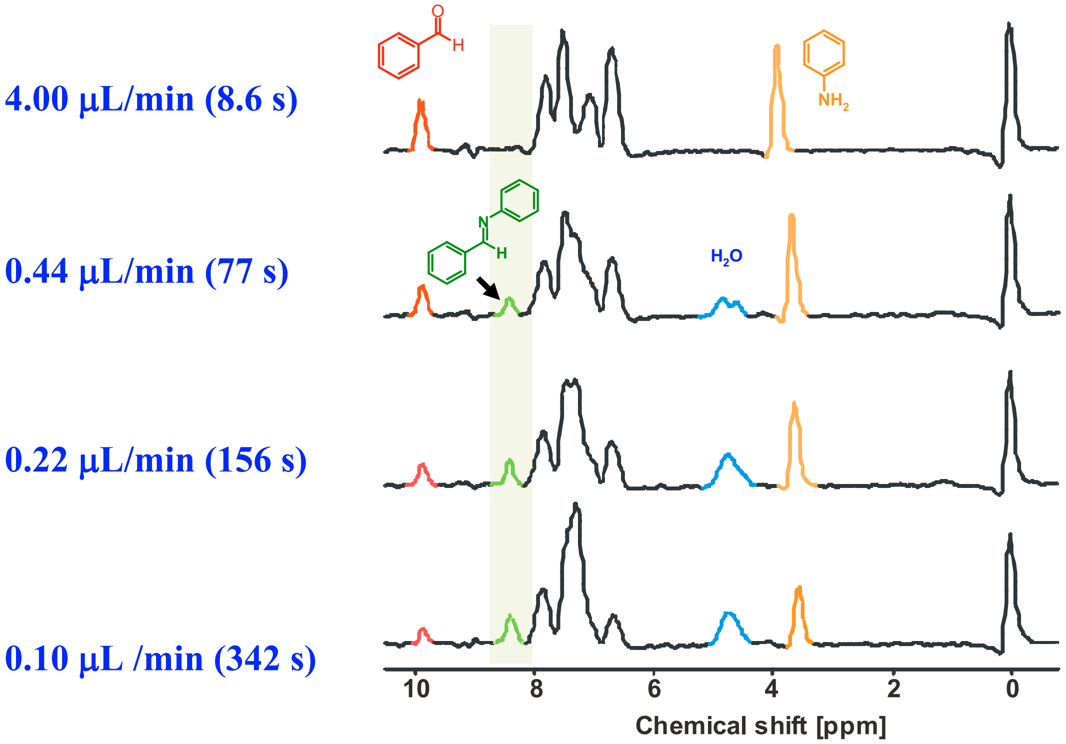




H. Wensink e.a., submitted to Lab Chip

University of Twente
The Netherlands

Reaction monitoring



H. Wensink e.a., submitted to Lab Chip

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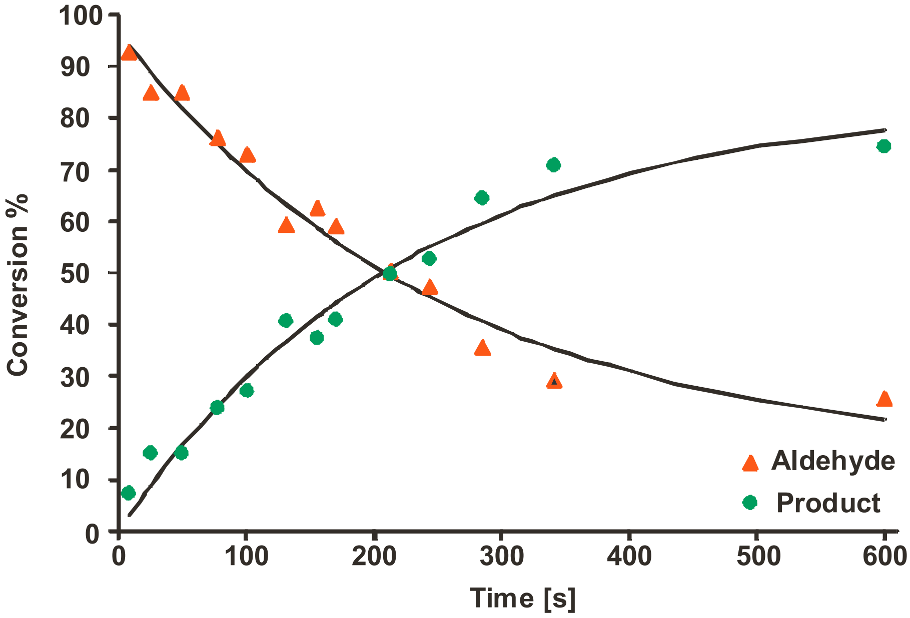
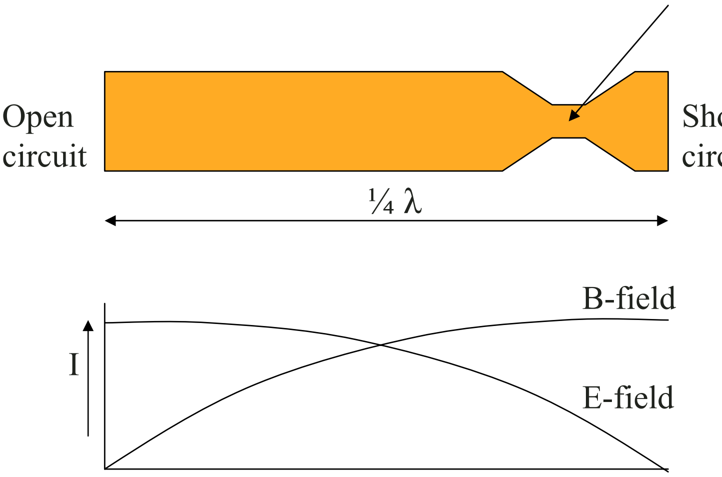
The Netherlands

Conversion

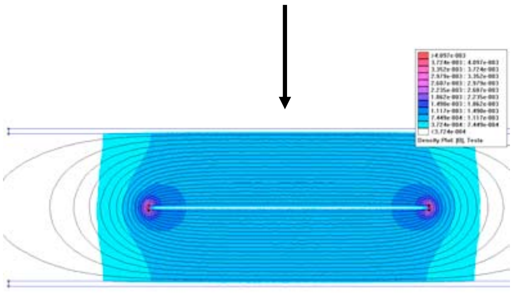


H. Wensink e.a., submitted to Lab Chip

New concept: Transmission line

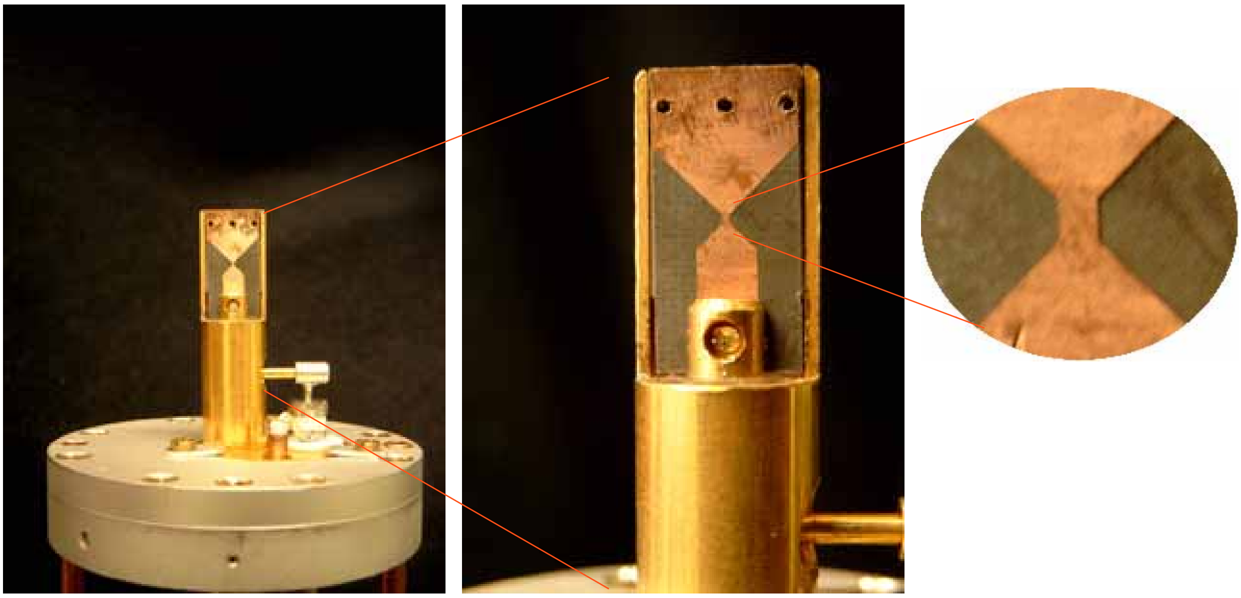


Magnetic field confined by shielding



van Bentum e.a. Analyst, 129, 793-803 (2004)
van Bentum e.a. Radboud University Nijmegen, NL, unpublished

Stripline on PCB



J.van Bentum e.a. Radboud University Nijmegen, NL, unpublished

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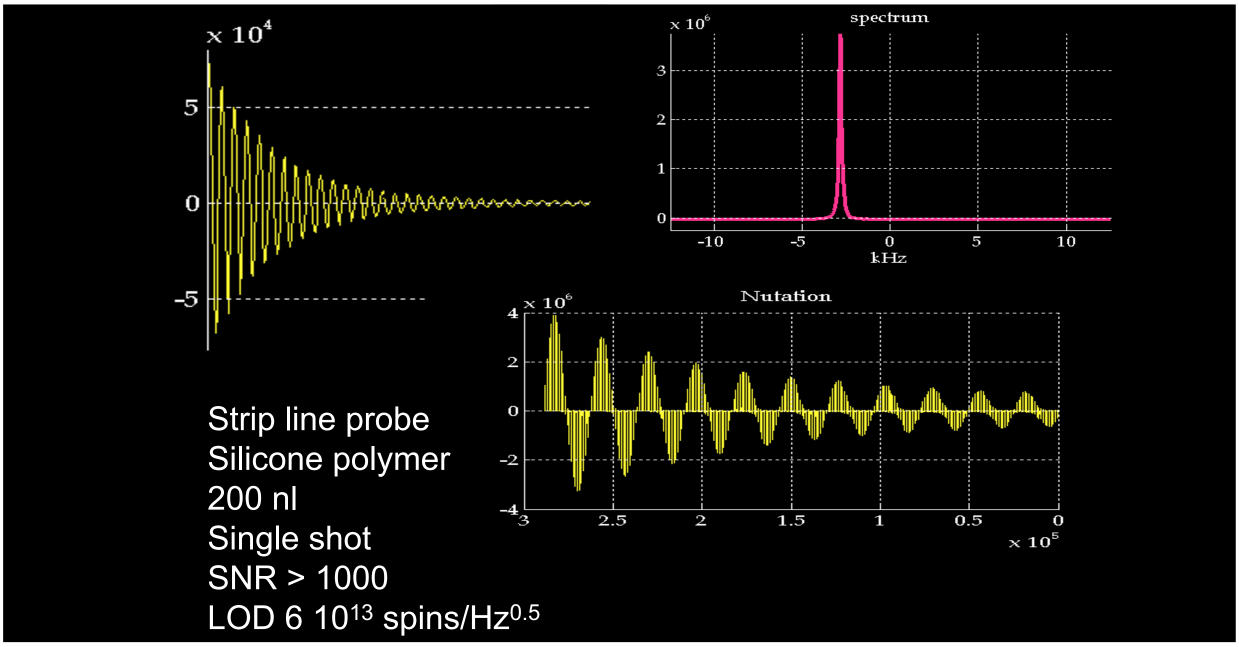
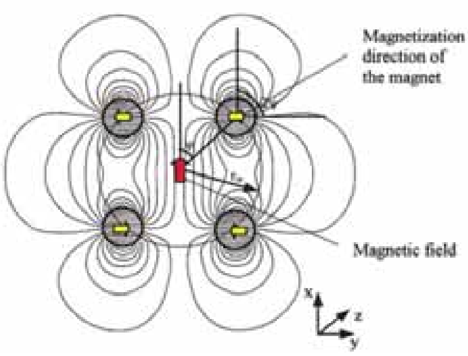
First results

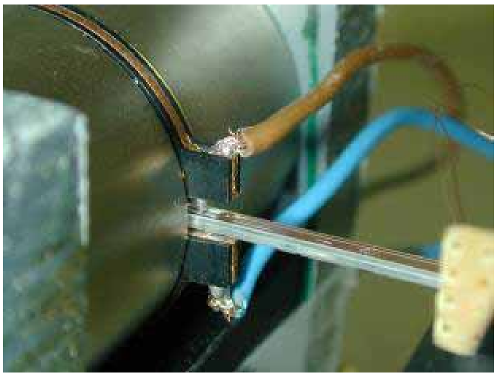


Strip line probe
Silicone polymer
200 nl
Single shot
SNR > 1000
LOD 6 10^{13} spins/$Hz^{0.5}$

J.van Bentum e.a. Radboud University Nijmegen, NL, unpublished

Portable NMR ?



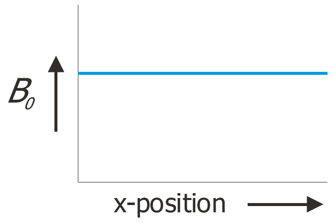


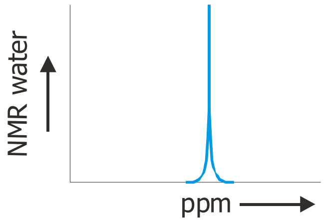
J.Bart & H. Wensink, Univ. Twente, 2003

0.6 Tesla mini-magnet; Moresi e.a. Conc. Magn. Res. B Magn.Res. Eng. 19, 35-43 (2003)

Magnetic Resonance Imaging (MRI)

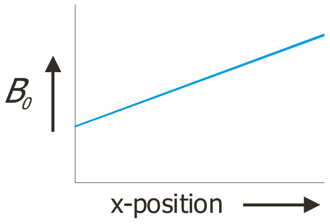
NMR:

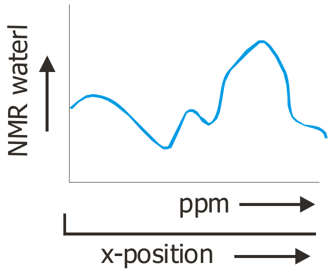




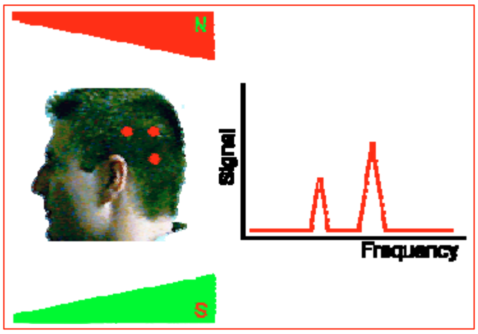
Chemical information

MRI:



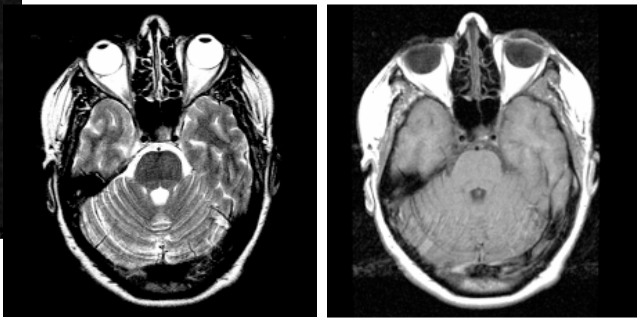


Position information



Magnetic Resonance Imaging (MRI)

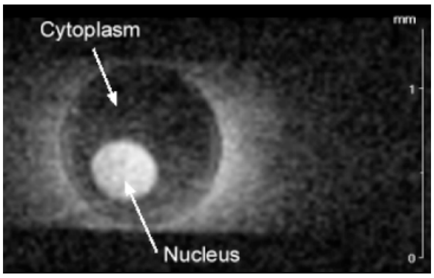
Total head image showing blood flow



Slice of the head, with different acquisition parameters

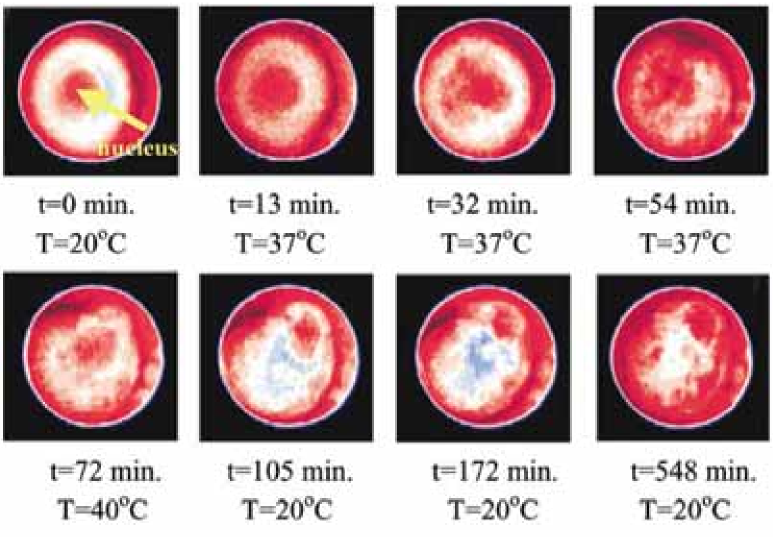
J.P.Hornak, http://www.cis.rit.edu/htbooks/mri/

Small-scale MRI



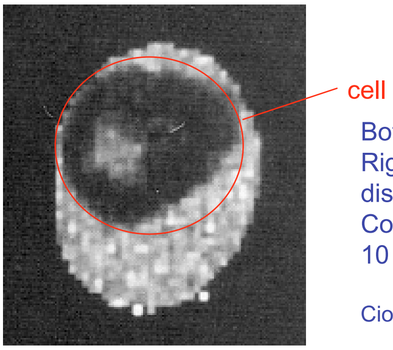
MRI of oocyte with microcoil on microchannel; resolution: 16 µm x 23 µm x 100 µm

Massin e.a. Proc. Transducers 2003, p.967-970



t=0 min. T=20°C | t=13 min. T=37°C | t=32 min. T=37°C | t=54 min. T=37°C

t=72 min. T=40°C | t=105 min. T=20°C | t=172 min. T=20°C | t=548 min. T=20°C



Bottom left: Different diffusion coefficients inside a cell
Right: proton MR images of the time-resolved evolution of water distribution in Xenopus laevis oocyte undergoing extended heat stress. Collected at 11.7 T using probe containing a 1 mm ID solenoid RF coil. 10 µm x 20 µm x 200 µm voxel resolution every 8.5 min.

Ciobanu e.a., Prog. Nucl. Magn. Res. Spec. 42, 69-93, 2003