

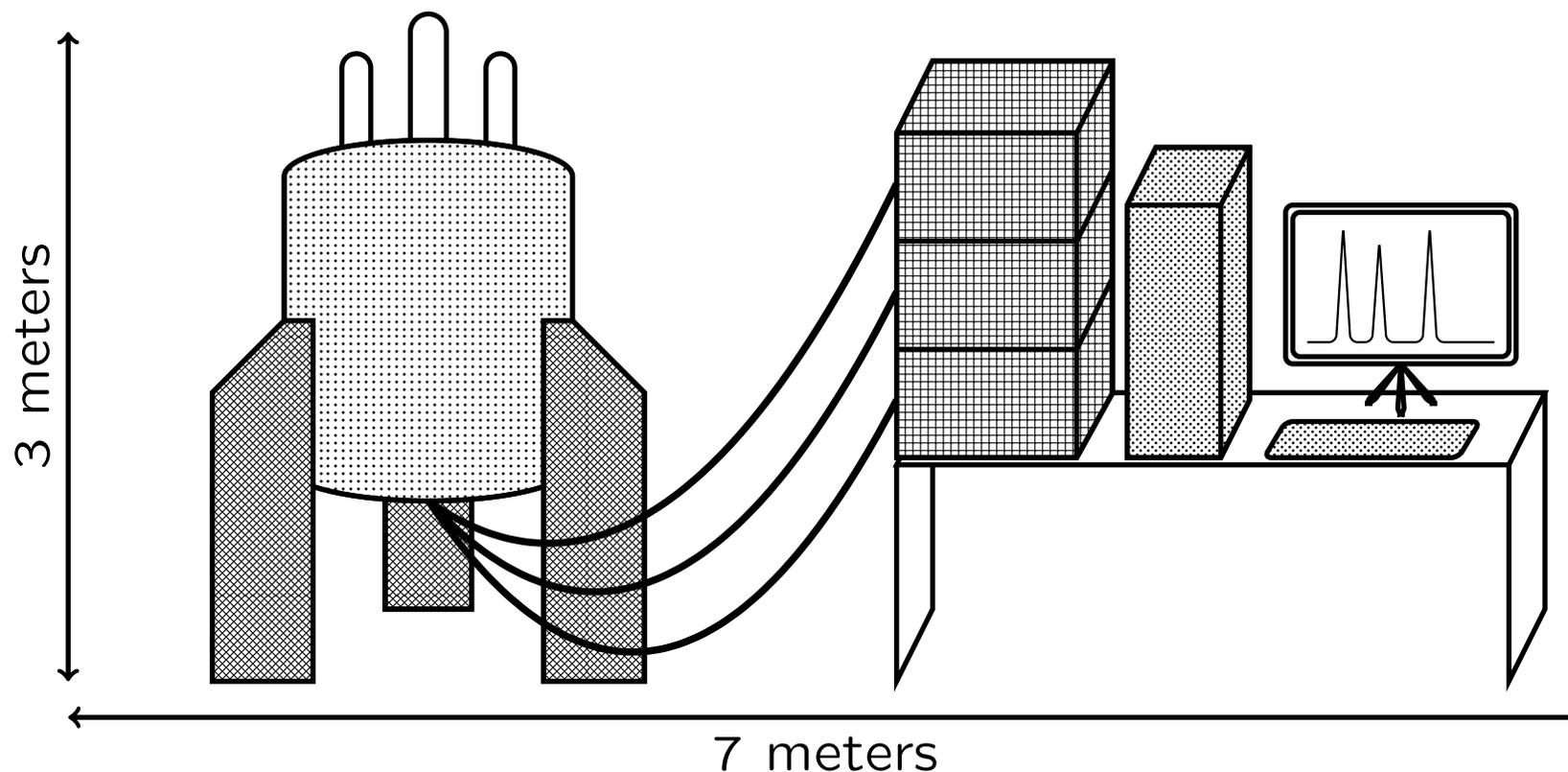
# Enhanced multi-nucLEar Generation, Acquisition, and Numerical Treatment of Nuclear Magnetic Resonance Spectrometer

## Elegant NMR Stick

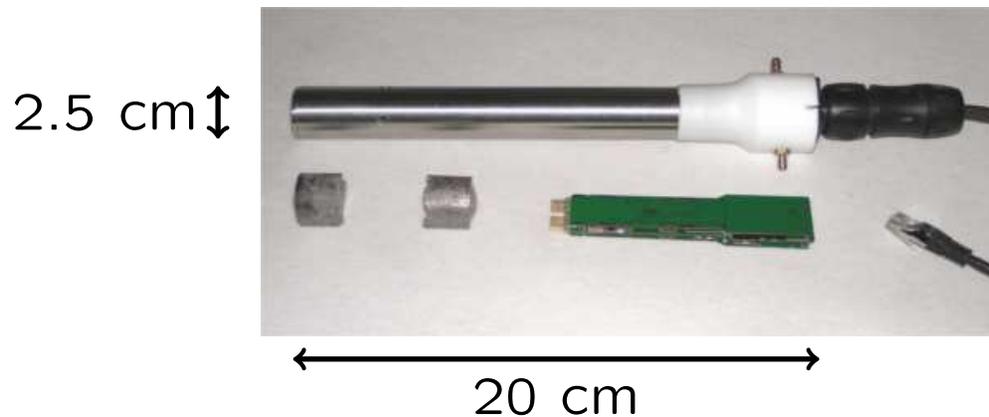
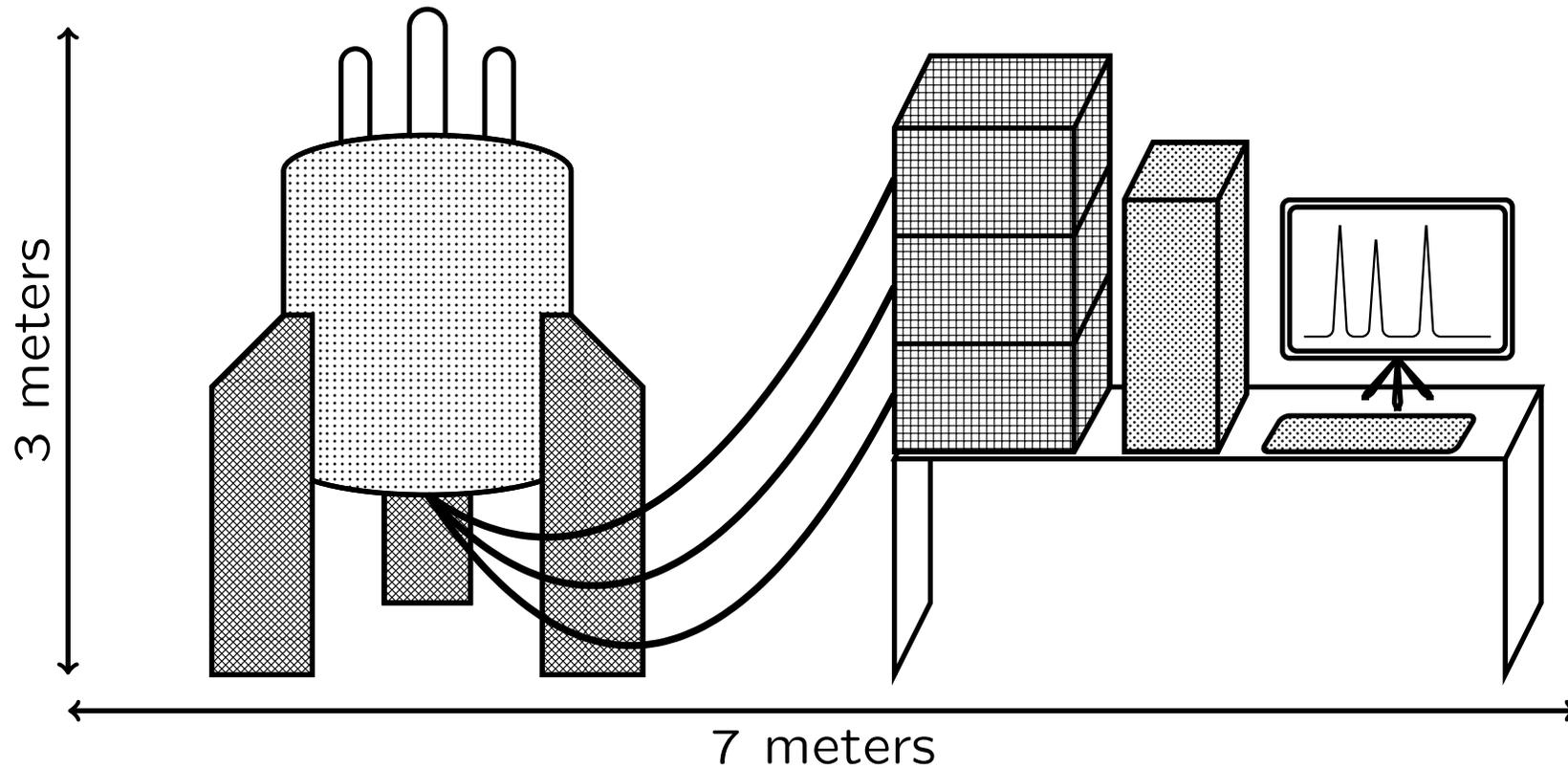


Suitable for nearly all chemical reactions and processes, the Elegant NMR Stick provides real-time, in situ monitoring of key information for an advanced understanding and control of reactions without the need for extractive sampling.

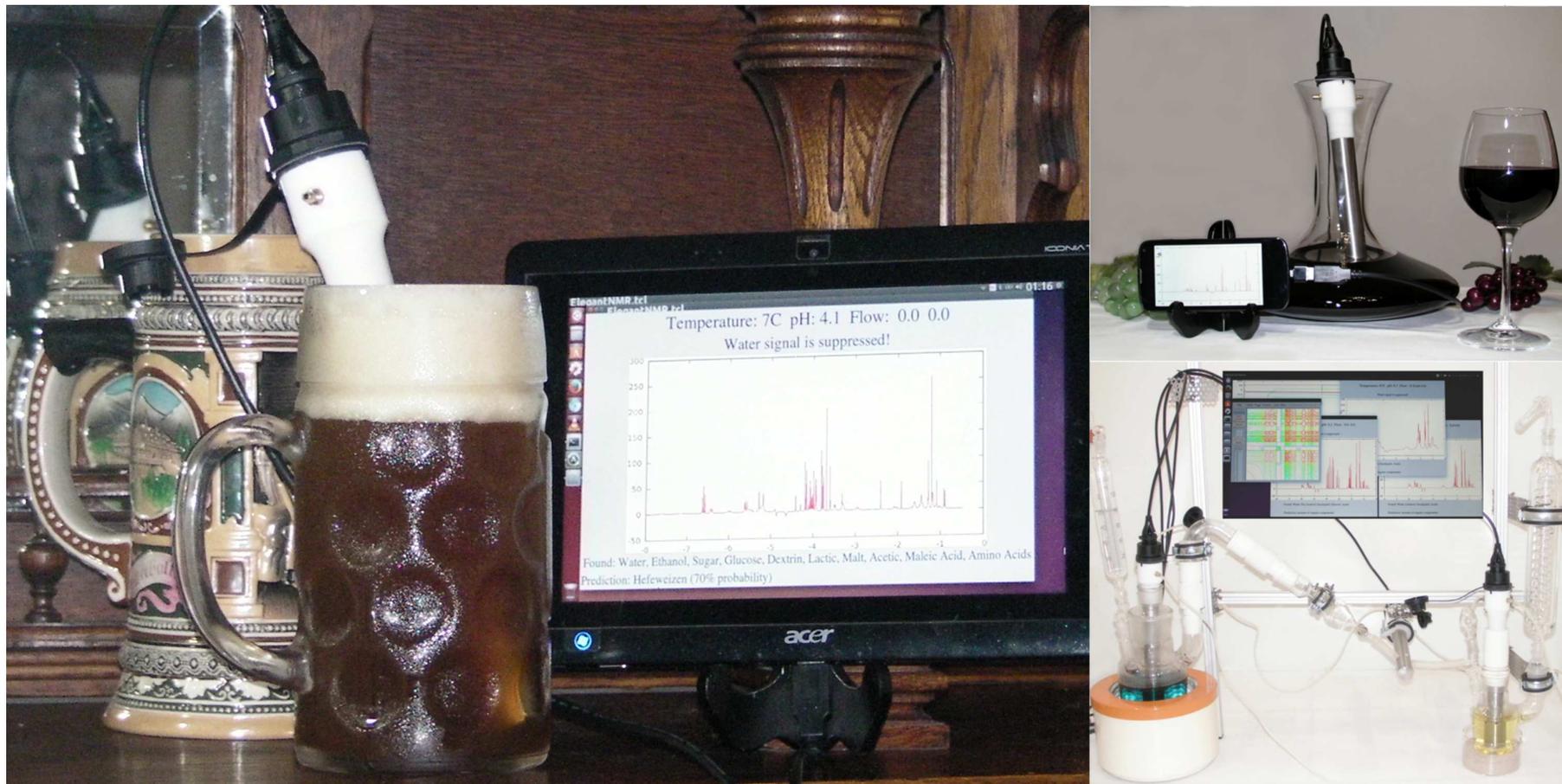
The comprehensive nature of the data makes it especially useful for kinetic analyses. The ELEGANT NMR Stick delivers in-depth reaction information, assisting organic chemists and scientists in their research and development of chemical compounds, synthetic chemical pathways, and chemical processes.



Beginning with its inception over 60 years ago, Nuclear Magnetic Resonance (NMR) technology has been a powerful method for investigating the chemical compositions of matter and even the atomic structure of molecules. Currently, conventional NMR spectrometers are large, expensive, and very complex to operate.



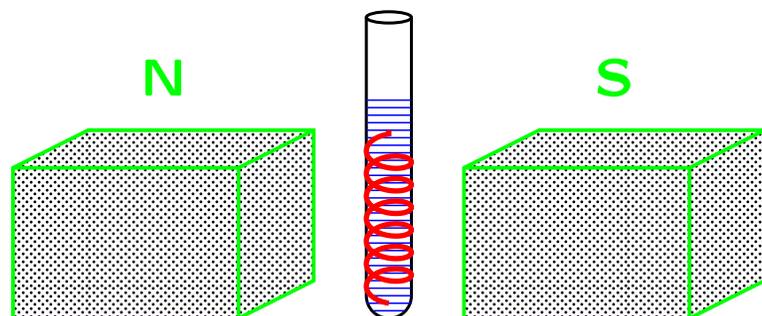
Our innovations in numerical algorithms and hardware design have made it possible to produce an easy-to-use, pocket-sized NMR spectrometer, which we call the Elegant NMR Stick.



Now, NMR technology is available for:

- universities and research institutions: for real-time monitoring of chemical synthesis
- the chemical industry: for real-time, in situ monitoring of chemical processes and reactions
- the oil and gas industry: for real-time droplet size and quality control
- the beer/wine/soft drinks industries: for real-time quality control
- the medical and pharmaceutical industry: for real-time, in situ quality control.

In addition to these uses, many other industrial facilities can profit from the use of a simple, robust, and affordable NMR spectrometer!

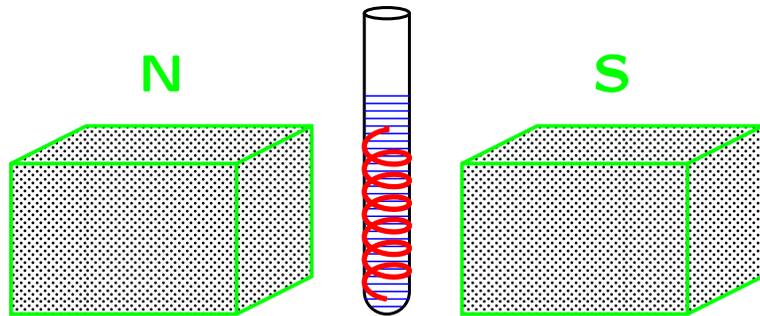


All chemical elements are composed of one or more isotopes. Every isotope is either a zero-spin isotope or a non-zero-spin isotope.

Nuclear magnetic resonance (NMR) is a physical phenomenon in which **non-zero-spin isotopes absorb and re-emit electromagnetic radiation (energy) when placed in an external magnetic field.**

$$Freq \sim B$$

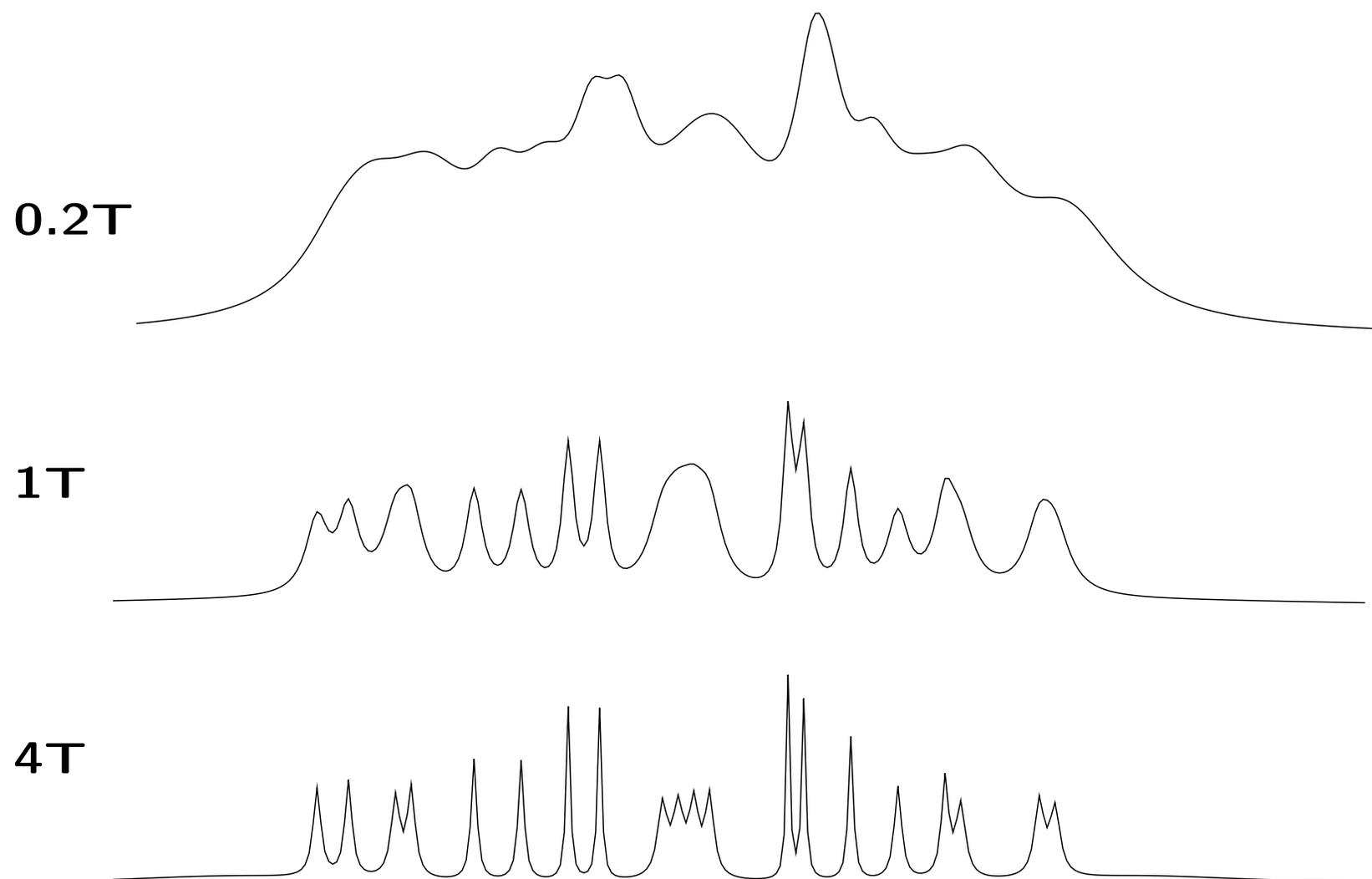
NMR occurs at a specific resonance frequency; this frequency has a linear relationship with the strength of the permanent magnetic field and the magnetic properties of isotopes in the target field. Resonance occurs when the absorbed alternate magnetic field is transmitted orthogonally in the direction of the permanent magnetic field.



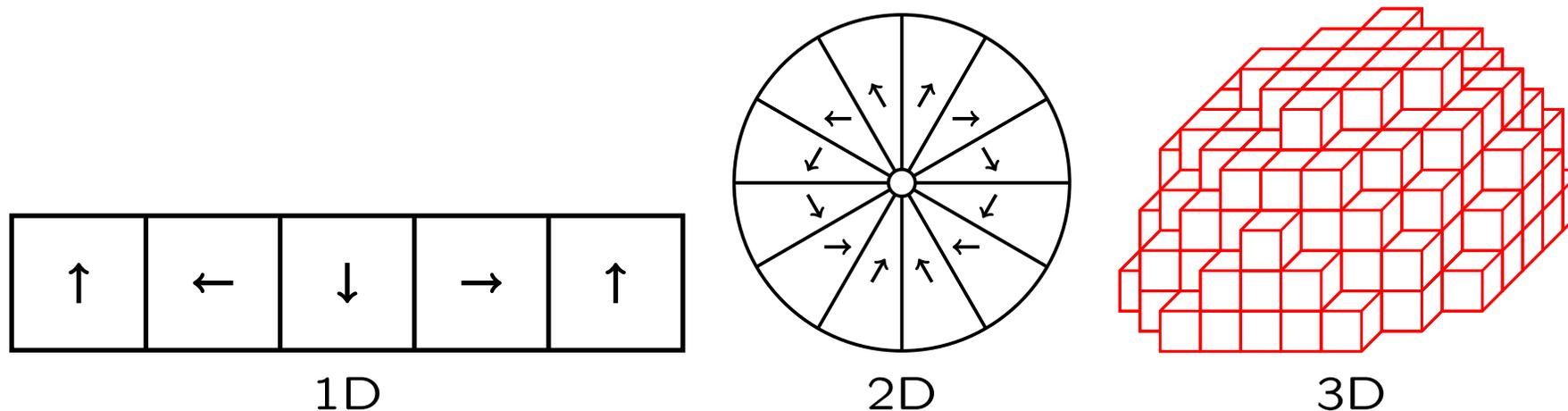
NMR spectrometers and magnetic resonance imaging (MRI) devices generally comprise one or more magnets that produce a strong magnetic field within a test region. These magnets are usually superconducting magnets, thus NMR applications are restricted to laboratory environments. Currently, anisotropic permanent magnets, i.e. having all parts magnetized in one direction, can achieve magnetic fields of only 1.5 T in strength compared to the 23 T of superconductor magnets.

$$\text{SNR} \sim B^2$$

The NMR signal response (i.e. SNR — signal to noise ratio) grows quadratically with regard to the magnetic field strength used in the experiment, which highly constrains the sensitivity and informativity of spectra produced by NMR spectrometers that have permanent magnets. NMR devices with permanent magnets are often referred to as low-field NMR spectrometers.

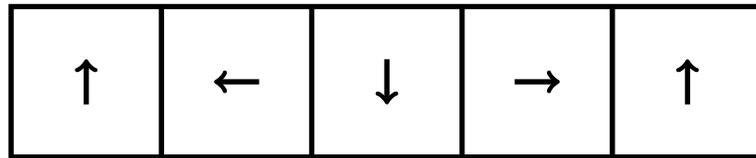


One dimensional  $^1\text{H}$  NMR Spectra of 1,2-dichlorobenzene (o-dcb) under ideal conditions on 0.2T, 1T and 4T. All spectra are scaled to  $[-7.6, -6.8]$ ppm chemical shift range.

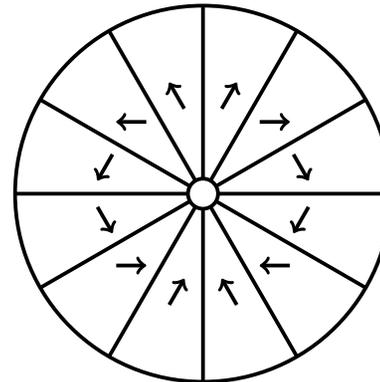


When permanent magnets are combined with several other parts having appropriate magnetization, it is possible to build a focused magnetic field of greater strength than the maximal field achievable with the permanent magnet alone. One well-known combination is the Halbach structure, introduced by Klaus Halbach in 1980, which makes a 5 T magnetic field possible with permanent magnets. This structure is often used in NMR spectrometers; however, it requires joining an enormous number of magnetized pieces. **Doing so may be commercially ineffective, or unreasonably sophisticated when using magnets of small size.**

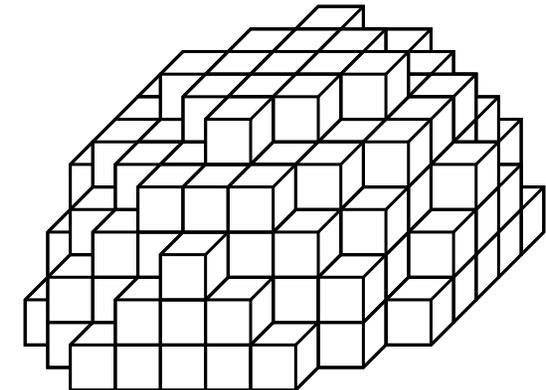
The second problem characteristic of the Halbach structure is the high instability of the generated magnetic field in terms of both time and temperature if the same material is used throughout. Patent US8148988 describes a Halbach system that compensates for this drawback through using several permanent magnets of different materials, albeit it only obtains almost half of the maximally achievable magnetic field strength.



1D  
 $2B$



2D  
 $B \log \left( \frac{R_o}{R_i} \right)$



3D  
 $\frac{4}{3}B \log \left( \frac{R_o}{R_i} \right)$

$B=1.43\text{T(NdFeB)}$ ,  $R_o = 12\text{mm}$ ,  $R_i = 1.5\text{mm}$ ,  $\sim 100\text{ g}$

2.8T

4

3.0T

4.3

4.0T

7.7 (SNR)

$B=1.43\text{T(NdFeB)}$ ,  $R_o = 100\text{mm}$ ,  $R_i = 2\text{mm}$ ,  $\sim 35\text{ kg}$

2.8T

4

5.6T

15

7.5T

27 (SNR)

An important NMR parameters:

$W_{\text{isotope}} = \text{Const}_{\text{isotope}}^{(w)} B$  a carrier frequency of non-zero-spin isotopes

$\text{SNR}_{\text{isotope}} \sim \text{Const}_{\text{isotope}}^{(snr)} B^2$  a signal to noise ratio of a signal response

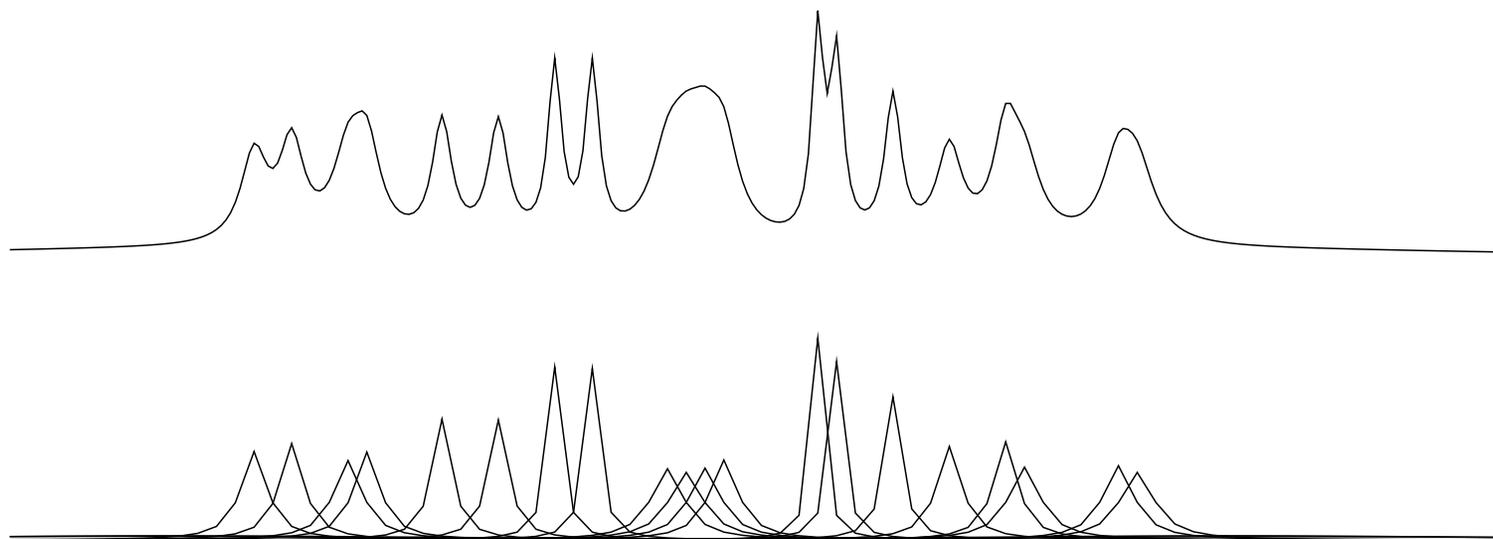
$\text{SW}_{\text{isotope}} \sim \text{Const}_{\text{isotope}}^{(sw)} B$  a spectra width of corresponding non-zero-spin isotope response

$\text{LW}_{\text{isotope}} \sim \text{Const}_{\text{isotope}}^{(lw)}$  an average line width of each peak in the isotope's spectra

$T_{1,\text{isotope}} \sim \text{Const}_{\text{isotope}}^{(t_1)} B$  an average time of signal decay below noise level

Consider 1H NMR, SW=13PPM,  $B = 1.5T$ ,  $B_{\text{Earth}} = 4 \times 10^{-5}$ :

If the magnets are small (of a size appropriate to a portable device), the intensity and direction of the external magnetic field may be adversely affected. *Even turning a 1.5 T NMR spectrometer to an angle about several degrees perpendicular to the Earth's magnetic force lines will ruin any measurements, and the device will have to be recalibrated!*

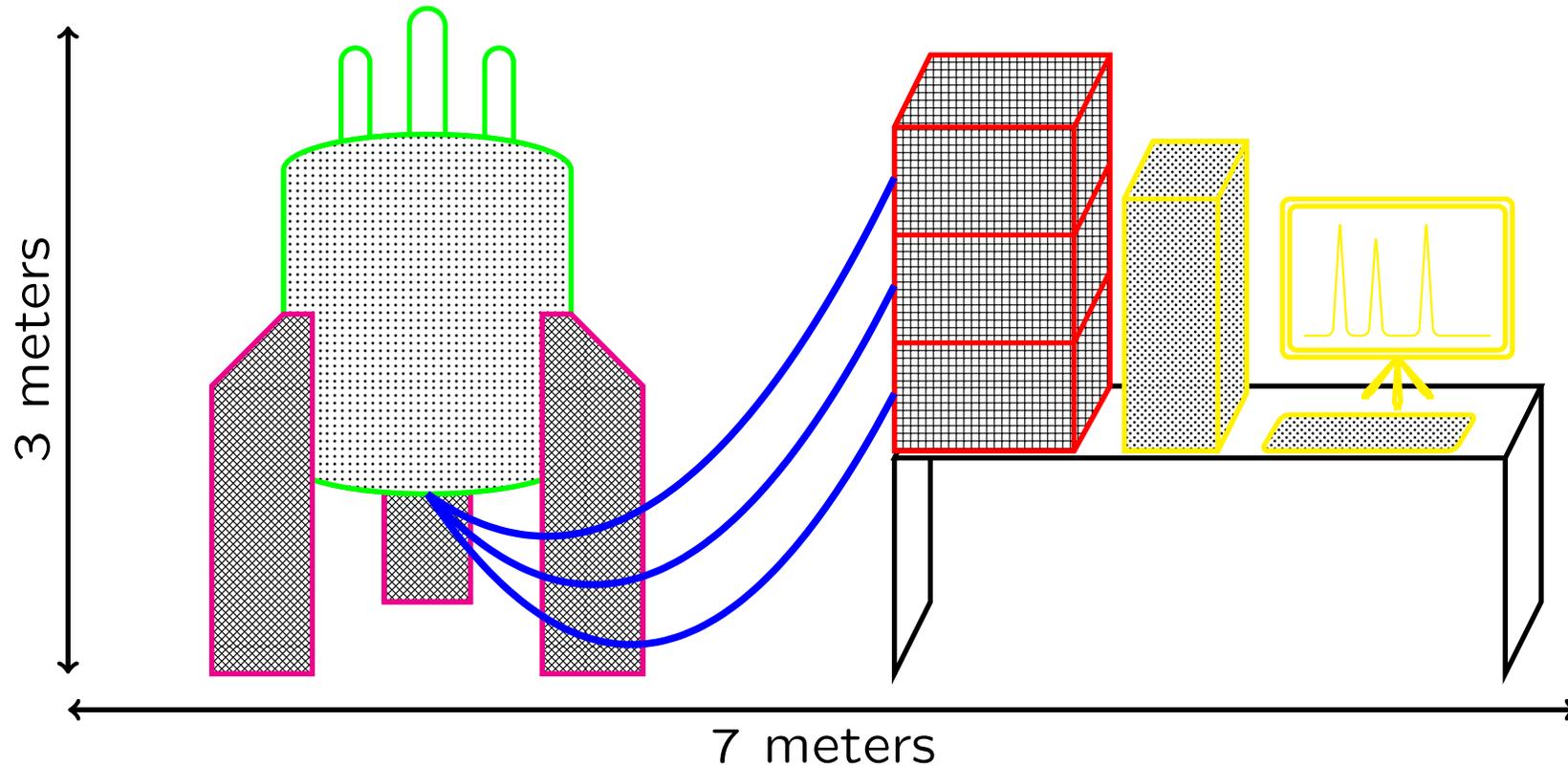


Improvement by HSQC ( $^{35}\text{Cl}$ - $^1\text{H}$ ,  $^{37}\text{Cl}$ - $^1\text{H}$ ,  $^{13}\text{C}$ - $^1\text{H}$ , and four-dimensional  $^{35}\text{Cl}$ - $^{37}\text{Cl}$ - $^{13}\text{C}$ - $^1\text{H}$ ) followed by peak-picking of NMR Spectra of 1,2-dichlorobenzene (o-dcb) under ideal conditions on 1T. All spectra are scaled to  $[-7.6, -6.8]$ ppm chemical shift range.

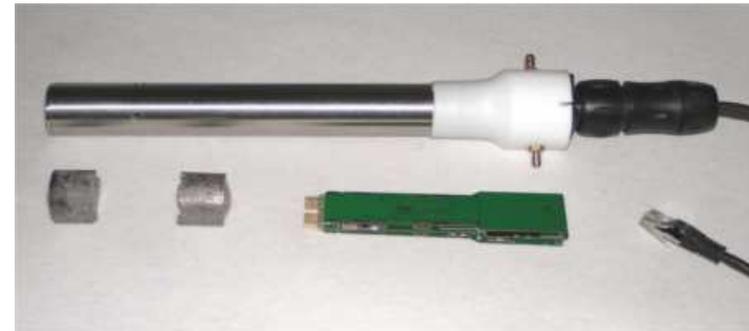
Take care about large measuring time, for example, by using non-uniform sampling:

Jaravine V, Ibragimov I, Orekhov V. Removal of a time barrier for high-resolution multidimensional NMR spectroscopy. *Nature*, **2006**, 3:605–607.

Hiller S., Ibragimov I., Wagner G., Orekhov V. Coupled Decomposition of Four-Dimensional NOESY Spectra. *JACS*, **2009**, 131(36):12970–12978.



Average hardware costs consist on **permanent magnets**: \$50K for 1.4T, \$100K for 2T, or superconductor magnets: \$300K for 5T, \$1M for 12T., **\$10-50K**, ca. \$20K for **stable quartz per channel**, \$1K per **1 meter** for the **NMR cable**, \$20K for **the powerful computer with software**.



Our target price for all-inclusive offer is \$2K

Taken together, prospective inventors of a portable NMR spectrometer for industrial environments must overcome the following problems:

- construct a signal acquisition scheme that is stable despite fluctuations of the permanent magnetic field and/or of the signal generator, or that can work without a signal generator;
- use NMR to detect all (or most) visible, non-zero-spin isotopes that are present in the investigated area;
- construct compact magnets with Halbach or Halbach-like structures that have better magnetic field strengths and are resistant to large temperature range.

Assume a pure spectrum of each  $n$ -th non-zero spin isotope ( $n = 1, \dots, N$ ) of the investigated substance is written as:

$$p_n(t) = \sum_{m=1}^{M_n} A_{nm} e^{i\omega_{nm}t + ib_{nm}} \in \mathbb{C}, \quad A_{nm}, b_{nm} \in \mathbb{R}, \quad \omega_{nm} \in \mathbb{C},$$

$$p_n(t) = r_n(t) e^{i\theta_n(t)}, \quad r_n(t) = |p_n(t)|, \quad r_n(t), \theta_n(t) \in \mathbb{R}$$

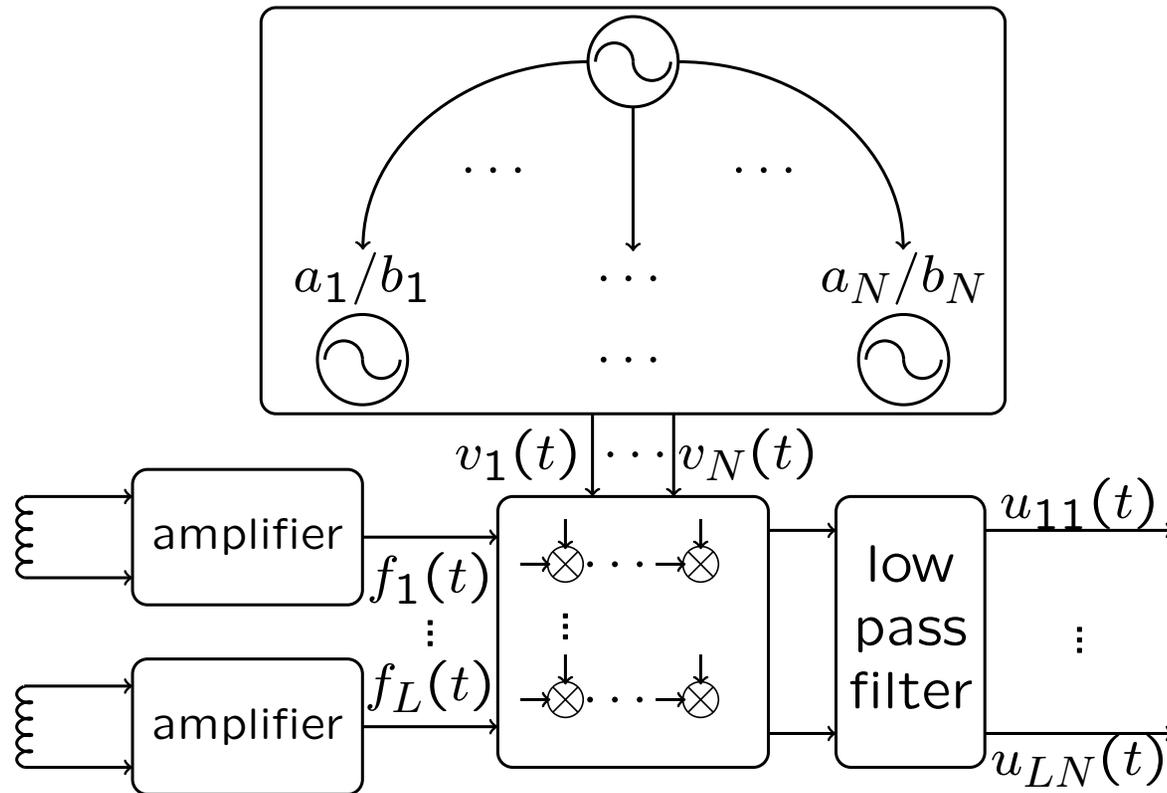
where  $A_{nm}$  are amplitudes,  $b_{nm}$  are phases, and  $\omega_{nm}$  are resonance responses in the  $n$ -th non-zero-spin isotope spectrum. Consider that the input NMR signal is disturbed because an unstable magnetic field and unstable oscillator are used. In this case, this signal can be written as the following form:

$$f(t) = \sum_{n=1}^N \operatorname{Re} \left( e^{iW_n t + iW_n \sigma(t) + i\tilde{\sigma}(t)} p_n(t) \right),$$

where  $\sigma(t)$  refers to the function of the unstable magnetic field, and  $\tilde{\sigma}(t)$  — refers to the function of the unstable oscillator. In this case  $u_n(t)$  reads as:

$$u_n(t) = r_n(t) e^{i\theta_n(t) + iW_n \sigma(t) + i\tilde{\sigma}(t)},$$

so that  $r_n(t)$  can be easily computed as  $r_n(t) = |u_n(t)|$ .



Some important considerations should be taken into account:

- affordable unstable oscillators do have local stability and are stable for a short period of time (several microseconds and less); however, they may be unstable over longer periods (several milliseconds and more);
- in normal laboratory or industrial conditions, a magnetic field does not fluctuate with high deltas, which only occur in an exceptional cases like close proximity to electromotors, electromagnets, high current switchers, etc; said magnetic field can be stable for a short period of time (several microseconds and less), but it may be unstable over longer periods (several milliseconds and more).

This gives the construction,

$$u_{nj}(t) = r_{nj}(t)e^{i\theta_n(t)+iW_n\sigma_j(t)+i\tilde{\sigma}_j(t)},$$

where  $\sigma_j(t)$  refers to functions of the unstable magnetic field and  $\tilde{\sigma}_j(t)$  — to functions of the unstable oscillator for every particular  $j$ -th experiment.

As above,  $r_{nj}(t) = |u_{nj}(t)|$ . Assuming

$$\tilde{u}_{nj}(t) = -i \ln \frac{\mathbf{u}_{nj}(t)}{\mathbf{r}_{nj}(t)},$$

then  $\theta_n(t), n = 1, \dots, N$  are computed according to the minimization of:

$$\min_{\sigma_j(t), \tilde{\sigma}_j(t), \theta_n(t)} \sum_{n=1}^N \sum_{j=1}^J \|\tilde{u}_{nj}(t) - \theta_n(t) - W_n\sigma_j(t) - \tilde{\sigma}_j(t)\|_2^2$$

so that

$$\theta_n(t) = \frac{1}{J} \sum_{j=1}^J \tilde{u}_{nj}(t) - \frac{\varkappa_0(t)(\varkappa_2 W_n - \varkappa_3) + \varkappa_1(t)(\varkappa_2 - N W_n)}{\varkappa_2^2 - \varkappa_3 N},$$

$$\varkappa_0(t) = \frac{1}{J} \sum_{j=1}^J \sum_{n=1}^N \tilde{u}_{nj}(t), \quad \varkappa_1(t) = \frac{1}{J} \sum_{j=1}^J \sum_{n=1}^N \tilde{u}_{nj}(t) W_n, \quad \varkappa_2 = \sum_{n=1}^N W_n, \quad \varkappa_3 = \sum_{n=1}^N W_n^2.$$

In general:

$$\min_{\sigma_j(t), \tilde{\sigma}_j(t), \theta_{nk}(t)} \sum_{k=1}^K \sum_{n=1}^N \sum_{j=1}^J \|\tilde{u}_{njk}(t) - \theta_{nk}(t) - W_n \sigma_j(t) - \tilde{\sigma}_j(t)\|_2^2$$

where

$k$  refers to a coil index,

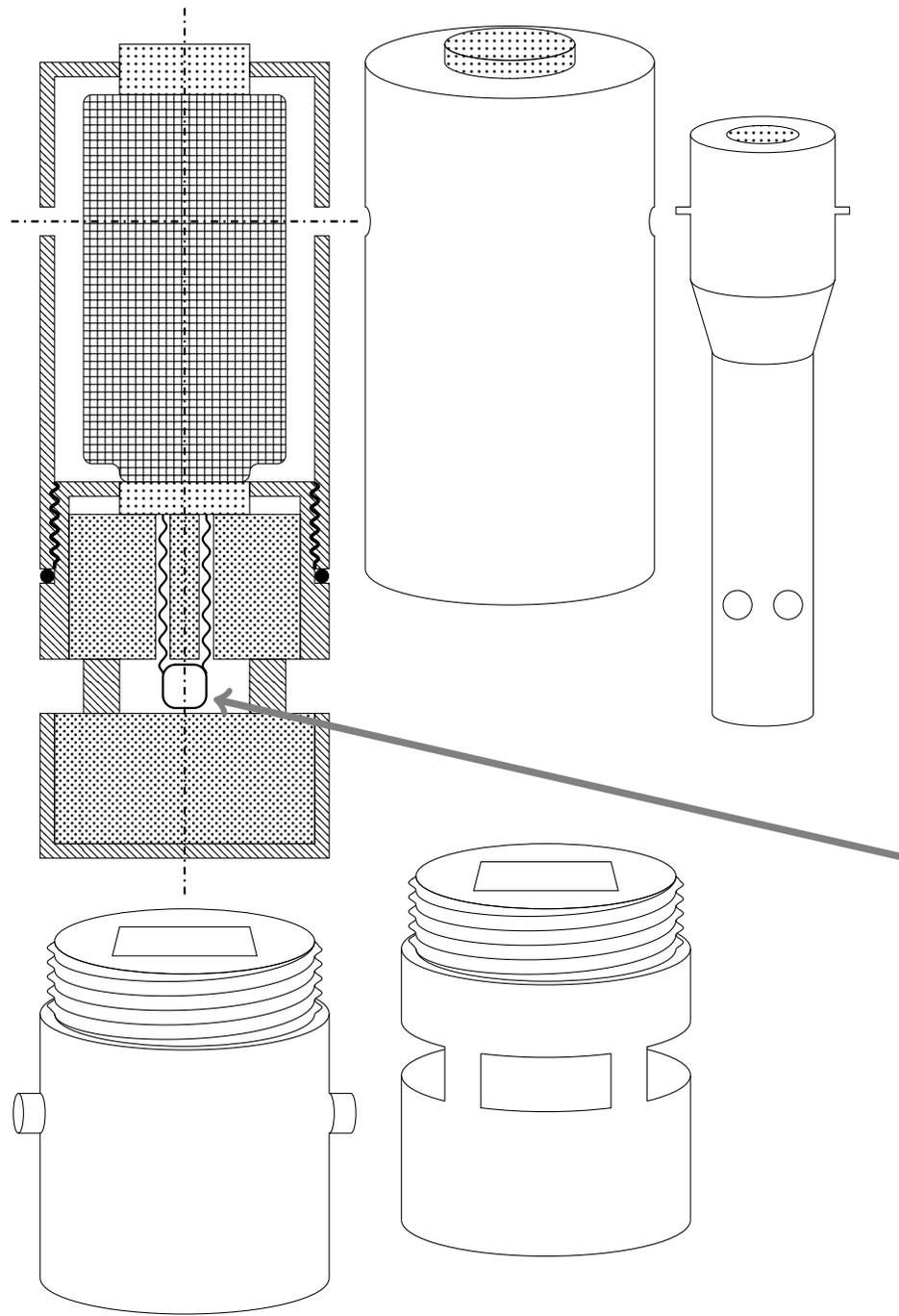
$n$  refers to a isotope index,

$j$  refers to an experiment index.

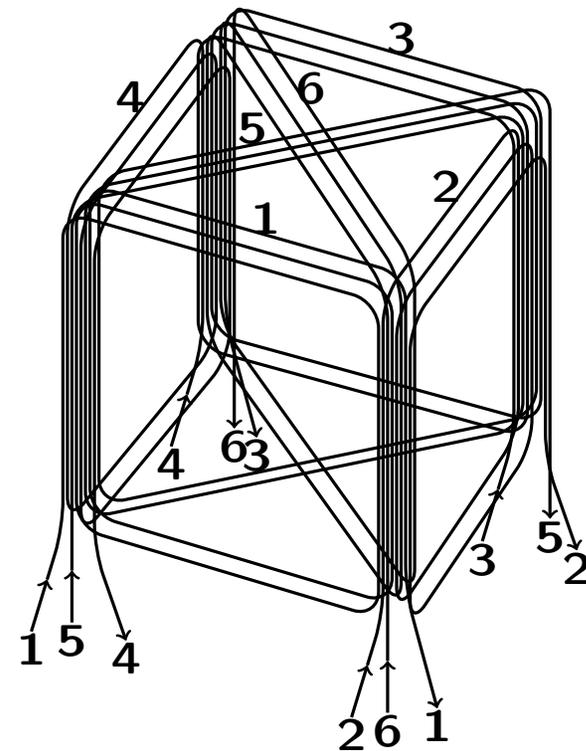
Complicated numerical problem, some good solutions are already known, for example:

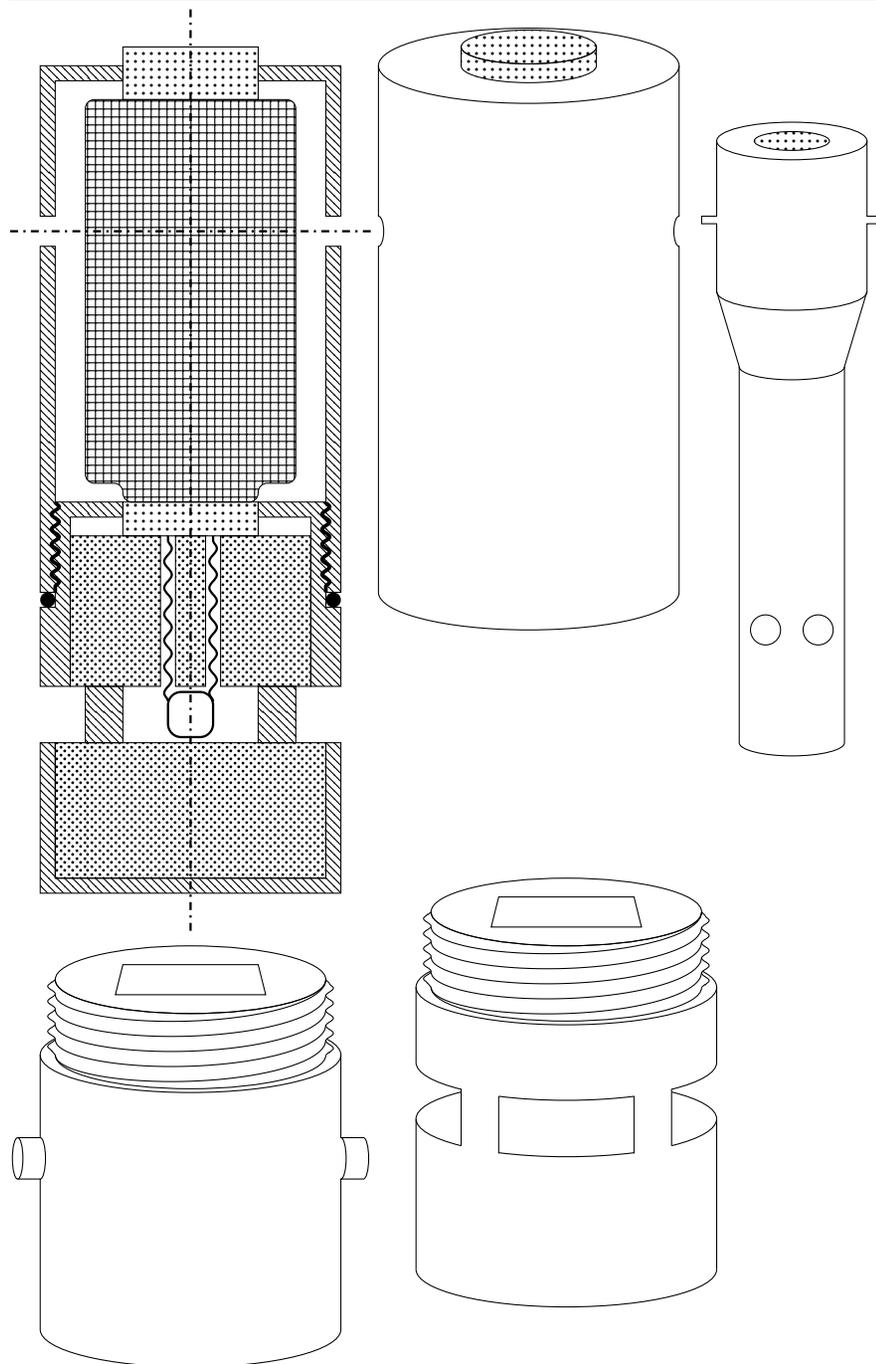
Ibragimov I. Application of the three-way decomposition for matrix compression. *Numer. Lin. Alg. Appl.*, **2002**, 9:551–565.

Hence, we demonstrated that correlated oscillators allow the removal of instability in the magnetic field and/or oscillators. This capability opens a new horizon for the use of small and affordable magnets, magnets with Halbach-like focusing of the magnetic field, and affordable oscillators.



Usage of several receiving coils pointed in different directions, with all axes of these coils situated in the plane that is perpendicular to the permanent magnetic field, opens new horizons for making NMR possible without highly intensive shimming.





### Advantages:

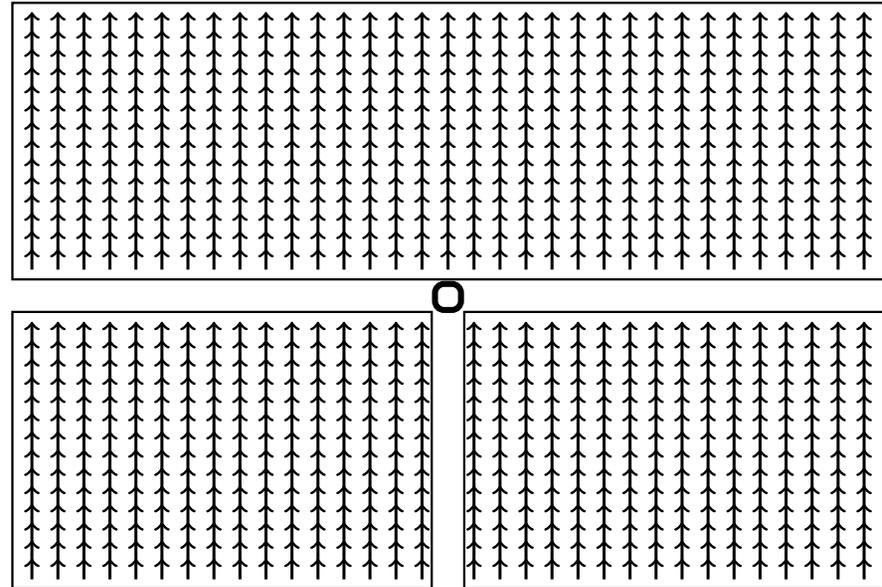
The first and second parts of the in-situ NMR detector are hermetically isolated from each other.

The advantage of coupling small magnets to the electronics relies on the fact that the conductive traces between electronic chips on PCB boards and coils are several times shorter than the wave length of the largest electromagnetic wave traveling on them; this permits disregarding the wave impedance of electromagnetic signals traveling on said traces.

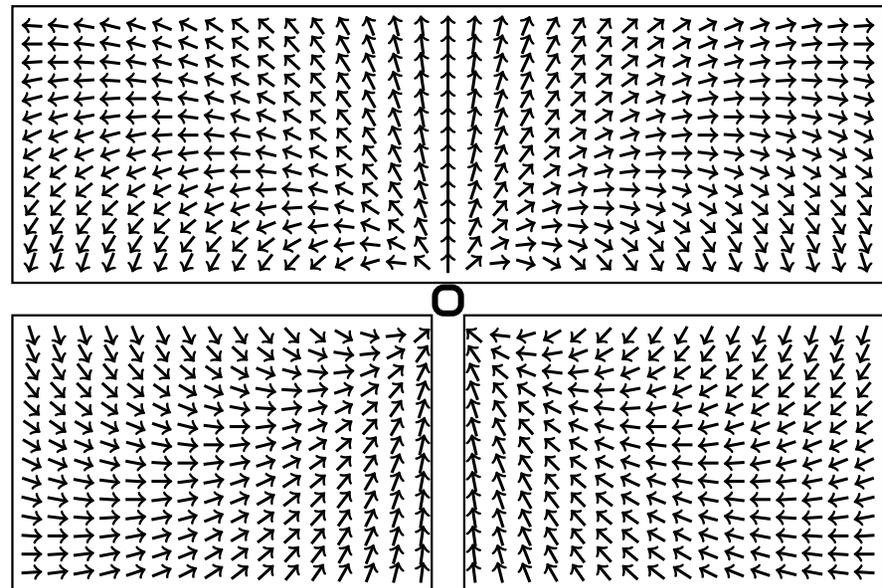
In addition, using a conductive magnetic material for the magnets reduces the electromagnetic interference of signals traveling on said traces because said magnets act as electromagnetic shields.

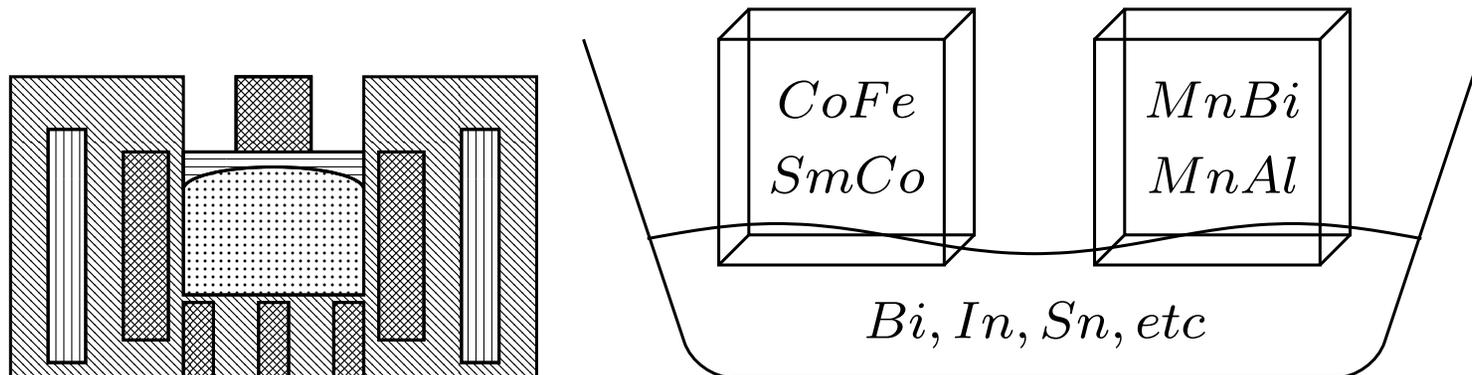
Can work as: temperature, density, flow, pressure and level sensors.

Consider magnets with linear magnetization up to  $B$  magnetic field strength



and compare it with the spherical Halbach of  $\frac{4}{3}B \log\left(\frac{B_o}{B_i}\right)$  magnetic field strength

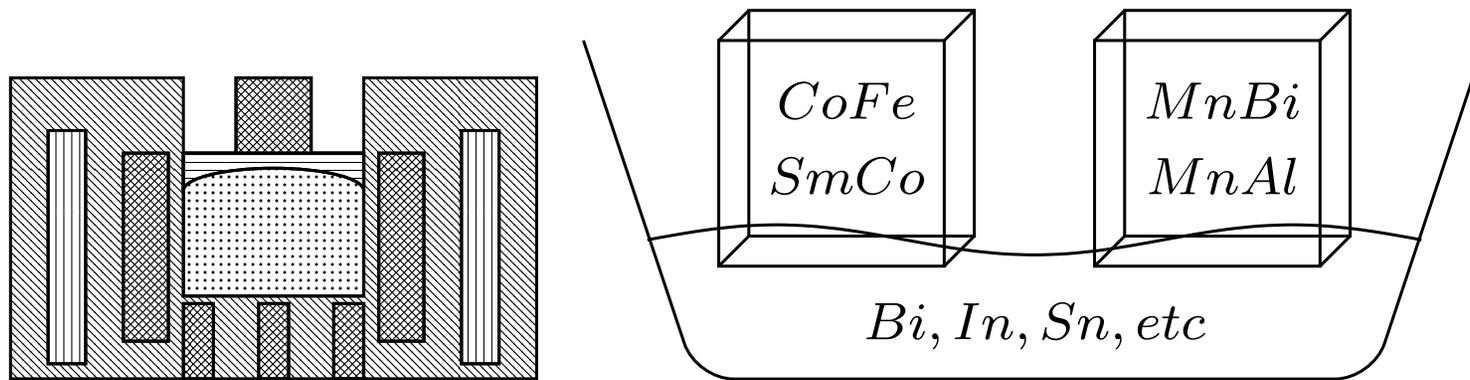




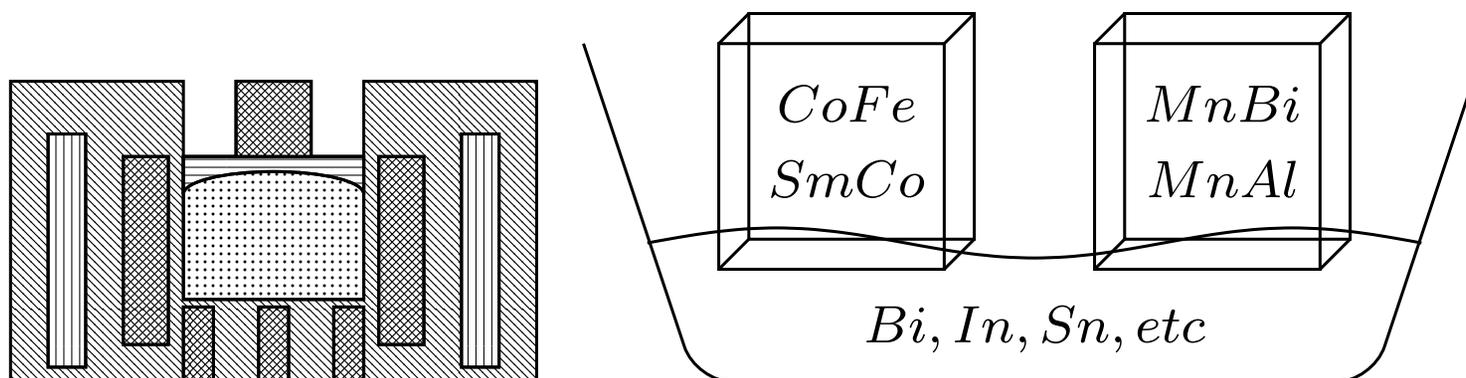
To predict predetermined spatial configuration of a magnet, one needs to use a well-known equation that computes the magnetic field in a point  $Y \in \mathbb{R}^3$  occurring from a magnetic dipole situated at a point  $X \in \mathbb{R}^3$  with its magnetization direction  $\vec{M} \in \mathbb{R}^3$ :

$$B(\vec{M}, X, Y) = \frac{3(Y - X)(Y - X)^T \vec{M} - \vec{M}(Y - X)^T(Y - X)}{\|Y - X\|_2^5}$$

and performs the following algorithm.



1. perform finite element discretization of the complete area where the molded magnet is being pressed,
2. for the spatial distribution of every permanent magnet and/or permanent electromagnet,
3. find the numerically appropriate magnetization direction for every said finite element, checking that discretization in that finite element is fine enough to achieve a smooth and accurate solution,
4. take each finite element and scale the magnetic field in such a way that it is maximally magnetized,
5. compute with a magnetic field from the all finite elements in the measured area.
6. perform steps 3-5 maximizing/optimizing the magnetic field in the desired area; if needed, constrain divergence of the field in that area; and find the best possible configuration of permanent magnets and/or permanent electromagnets.

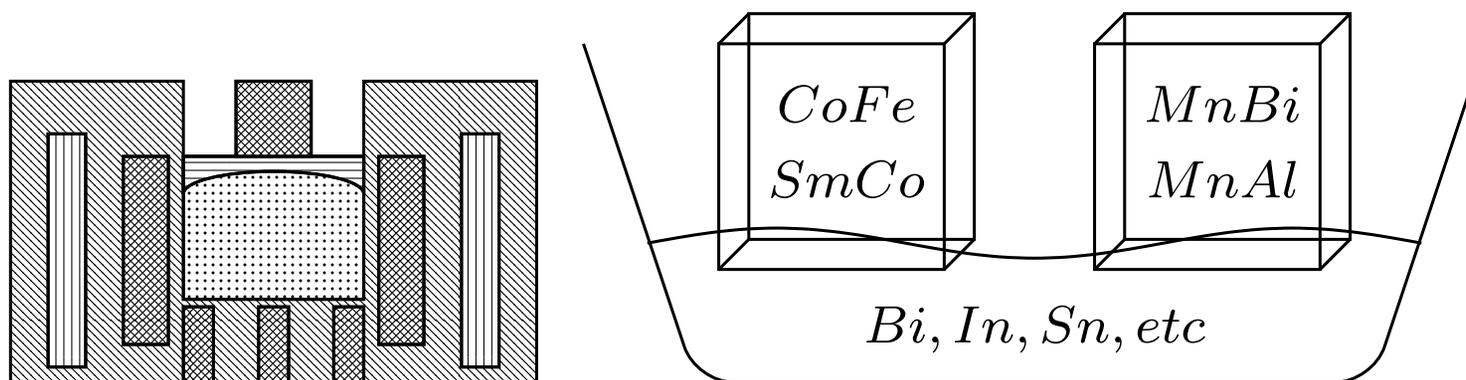


Nowadays, there are many magnetic materials available for magnet construction by either sintered or casted processes;

sintered magnets may contain Nd-Fe-B, Sm-Co, Al-Ni-Co-Fe, Mn-Bi, Mn-Al, and many other alloys, while

casted magnets contain mainly Al-Ni-Co-Fe alloys.

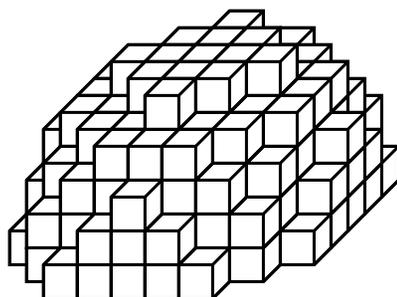
We suggest the substitution of AlNi crystals in Al-Ni-Co-Fe alloys with other magnetic materials that have lower melting temperature and/or less resistance to high pressure. A good candidate would be the well-studied MnBi crystals that, when more Bi is incorporated, can be melted at temperatures as low as 400°C. Any other low-temperature and low-viscosity magnetic material can be also used, for example MnAl alloys.



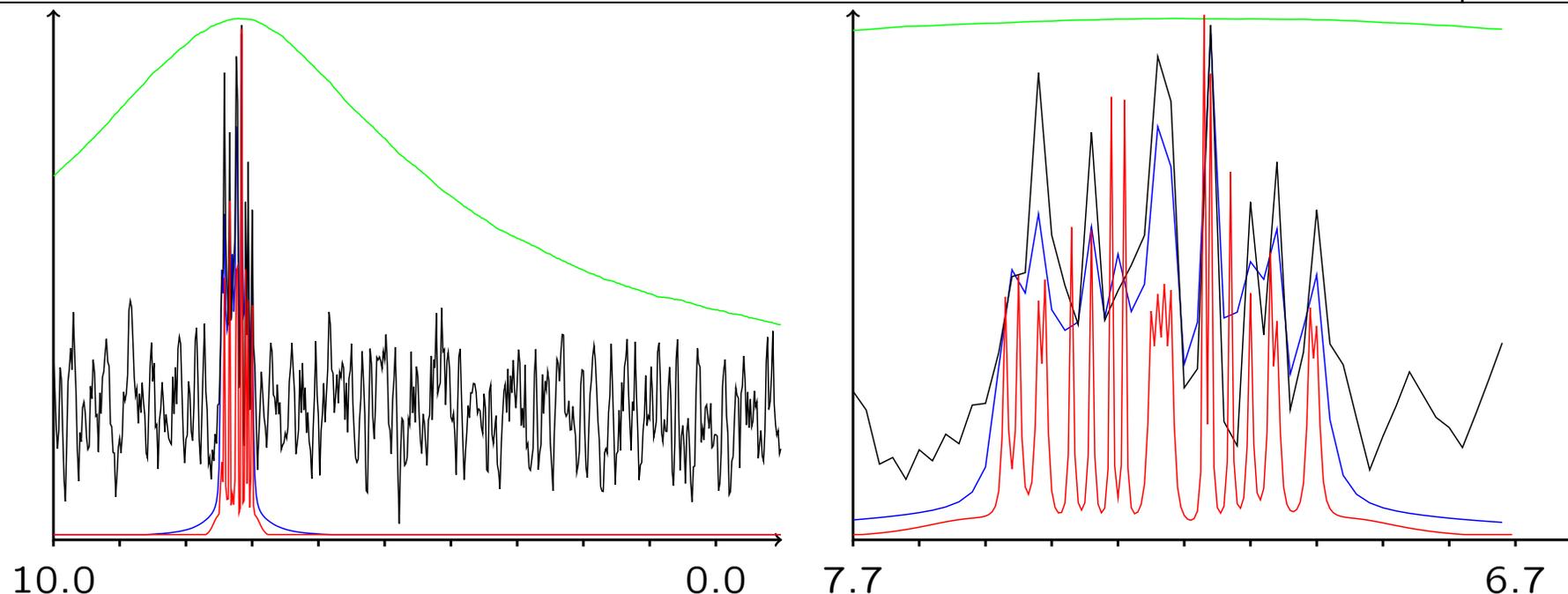
Co, Fe, Mn, Bi, and In at a molar ratio of 1:2:1:1.1:0.27

- can be sintered at low pressure (1000 bar),
- can be casted at low temperature (500°C and below),

and is perfectly suitable for a Halbach-like sintering/casting process (we achieved 4T on ca. 100mm diameter and 1.6T on 24mm diameter).



Hence, crystalline structure of Co-Fe and Mn-Bi alloys (ca. 1-2  $\mu\text{m}$  linear dimensions of said crystals) build a spherical Halbach structure additionally providing high homogeneity of achieved magnetic field.



One dimensional <sup>1</sup>H NMR Spectra of 1,2-dichlorobenzene (o-dcb) with:  
 1.4T magnet with linear magnetisation with 12cm diameter, the correlated oscillator method is not used, highly stable mechanical, temperature and electromagnetic conditions (30 minutes measurement time);  
 the same as the previous one, but with a gentle touch at the spectrometer during acquisition;  
 small magnets with linear magnetization (3cm diameter) with 1.4T, the correlated oscillator method is used, the spectrometer is kept in hand (20 minutes measurement time);  
 correlated oscillator method, casted spherical Halbach-structure with 1.6T, and non-uniform sampling for multidimensional NMR spectra with further projection to one-dimensional spectra are used, the ELEGANT NMR Spectrometer is kept in hand (2 minutes measurement time).

Hence, the ELEGANT NMR Technology incorporates:

- a new processing method for nuclear magnetic resonance spectrum acquisition, which remains stable despite magnetic field fluctuations and resonator stability (patent pending US62674050);
- a new processing method to detect all (or most) visible, non-zero-spin isotopes that are present in the investigated area (patent pending US15990666);
- a new method of constructing predetermined magnets from appropriate magnetic material that allows for focusing the magnetic field in a target region (patent pending US62677010);
- an automatic procedure for well known multidimensional HSQC and NOESY methods over all visible non-zero-spin isotopes with non-uniform sampling accelerations (doi: 10.1038/nmeth900),
- an automatic procedure for spectra recognition over predetermined data base reference using well known least squares method;
- an automatic procedure for spectra decomposition without predetermined references in case if concentration of changes during measurements using multilinear decomposition (doi: 10.1002/nla.297);
- and many useful features, like solvent suppression, droplet size measurements, flow, temperature and density measurements.

The above-mentioned technological components render to affordable, compact and portable in-situ NMR spectrometer that can be dipped in the fluid to be measured and are easily maintained without NMR experience.