NMR – Past, Present and Future

Physics, Nobel prizes and the emergence of the technique that is now solving problems in process chemistry, biomedicine and pharmaceutical development, as well as food and environmental safety.

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A recent poll of methods utilised by pharma discovery scientists searching for the next new blockbuster drug highlights the dominance of Nuclear Magnetic Resonance (NMR) spectroscopy in fragment-based lead generation (1). In addition, workers investigating food fraud, used NMR to identify imitation cheese and ice cream – products in which the milk fat and/or milk protein had been replaced with cheaper, non-milk components, such as soy, starch or vegetable oil (2).

Almost 60 years ago, when Dr Günter Laukien (the father of the current Bruker CEO) published his important paper 'High-frequency Nuclear Magnetic Spectroscopy' in the 1958 Encyclopaedia of Physics (3) and he, along with other pioneers were building their first instruments, these modern applications of NMR would have been way beyond their imagination.

This article looks back at the work of the technique's creators, and reflects on key developments that have propelled NMR to its position today – as the go-to technique for scientists looking for an information-rich and non-destructive analytical tool to reveal the structure, identity, concentration and behaviour of molecules in solid or liquid samples.

In the Beginning

NMR is indivisible from the early development of the two key companies that went on to establish the field – Bruker and Varian. Günther Laukien studied physics at Tübingen before moving to the Institute for Experimental Physics in Stuttgart in 1952. Dedicating himself to NMR, he conducted post-doctoral studies in NMR Spectroscopy and in 1958 published his pioneering paper on high-frequency nuclear magnetic resonance. This described the theoretical aspects of what was known at the time, while also covering the practical considerations of constructing experimental systems. In 1960, he was appointed Professor for Experimental Physics in Karlsruhe.

Varian was established in 1948, within the Stanford Industrial Park by scientists from Stanford University. One of the early goals of the company was to commercialise the co-discovery of nuclear magnetic resonance spectroscopy by Felix Bloch in 1946. Subsequently, Edward M. Purcell and Felix Bloch were honored with the Nobel Prize for Physics in 1952 for this work.

At around the same time that Laukien was studying, Varian had begun building the first commercial high-resolution spectrometers. They were based on continuous-wave sweep methods and on electromagnets, and designed for use in analytical chemistry. Laukien recognised the power in this technique but saw the need for an impulse spectrometer, something not yet available commercially. He set out to fill this need by establishing his own company, and Bruker Physik was founded in 1960.

The intense competition between these two companies drove many of the early developments and innovations in NMR. See the timeline graphic below for a summary of some key milestones.

From Expert to Everyday

After around 30 years of development, NMR was a maturing technique, and was widely applied; there was hardly a paper in organic chemistry that did not report NMR data.

Moving on to look now at the developments from those initial systems, three key areas can be identified that lead to the systems today: larger magnets to improve sensitivity; improved probe technology and new designs to enhance performance; and a rapid increase in computer power to enable software to be developed that simplifies data processing and opens up the technique to non-experts. The timeline graphic highlights below, highlights some key milestones in this 'second-wave' of development. Interestingly, several of the pioneers and early adopters of NMR have published personal accounts and reviews of the development of the technique through the decades from 1980 to 2010, providing a wealth of fascinating insight (4, 5 and 6).

1937
Nuclear spin first measured in by Isidor Isaac Rabi in lithium isotopes and protons.

1943
Nobel Prize for Physics awarded to Rabi for this work.

1946
Discovery of Nuclear Magnetic Resonance spectroscopy by Edward M. Purcell and Felix Bloch.

1948
Varian established in USA.

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1956
Nobel Prize for Physics awarded jointly to Edward M. Purcell and Felix Bloch for their 1946 discovery.

1960-1965
Prof. Günther Laukien founded Bruker and the development of its first NMR spectrometers began with the production of laboratory magnets and power supplies.

Establishment of Spectrospin AG, a company owned by Bruker.

First NMR, KIS (Kern Induktions Spektrometer (nuclear induction spectrometer)), operated at 25 MHz using a permanent magnet.

KIS 2 introduced for high-resolution spectroscopy (90 MHz).

1964-1966
Ground-breaking research on the use of Fourier Transform algorithm by Ernst and Anderson published.

FT-NMR first described.

1967
Culmination of Bruker / Spectrospin developments – the introduction of rst fully transistorised NMR instrument, the Bruker HFX 90.

1968
TFirst HFX 90 for the United States (Yale Univ.) being loaded onto a Boeing 707.

Pushing the Boundaries – What's Hot?

The reach of NMR continues outside its legacy applications, for example, among the presentations and posters given at the Small Molecule NMR Conference (SMASH) in September 2016 were these highlights:

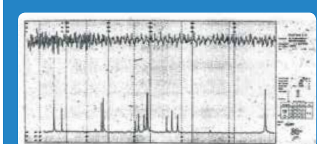
- Practical Applications of Non Uniform Sampling (NUS) for 2D-NMR in the Pharmaceutical Industry
- Determination of the configuration of Small Molecules from Residual Dipolar Couplings
- NMR Spectroscopy for the Characterization of Monoclonal Antibodies
- Putting NMR on the Table – Low Fields and Benchtop NMR

In addition, journals are full of papers proposing – or reviewing – the potential contribution of NMR in a series of important new areas. Many represent a significant change in the application of NMR spectroscopy: in metabolomics, for example, by collecting large amounts of spectra and gathering underlying data on metabolites, statistical analysis can reveal markers for a certain disorder or disease. Once a model has been established, the measurement of a single sample allows the classification of that sample as normal are abnormal – and even allows a diagnosis as to the nature of a disease. This takes NMR and places it in the hands of clinical scientists. They can ask: is this what I expected? And answer questions with 'yes' or 'no'.

In the area of biopharma, researchers are now using NMR for the characterization of the structure of monoclonal antibodies (mAbs). Another application of NMR in scale-up or production of biologics is the monitoring of the composition of growth media. Recognizing the depletion of certain nutrients or the accumulation of potentially toxic metabolites can significantly improve yield as well as the efficiency of the fermentation.

1969

The world's first commercial FT-NMR spectrometer system introduced by Bruker.



Carbon FT NMR spectrum presented by Dr. Tony Keller in 1969 at the Pacic Conference on Chemistry and Spectroscopy in Anaheim.

1970-1975

The work on FT-NMR by Ernst and Anderson in 1966 required minicomputers to generate tapes that could be then be processed on larger computers. The advent of smaller, cheaper, and faster computers in the early 1970's made FT-NMR all but ubiquitous.

1980s

T2D NMR development comprised a huge step in the collection and analysis of data. Structure analysis of small and large molecules became possible and proved very useful in molecular biology and chemistry.

These systems provided a tool that an everyday chemist could use.

1990s

Higher dimensional spectroscopy (3D) developed. This was made possible by rapid developments in computer technology. The Fourier transformation of three and even higher dimensional NMR data can now be performed in a matter of seconds.

Cryogenic probes first developed – signicant reduction in noise from random thermal motion and this, together with tuned electronics delivers around a 5-fold enhancement in signal to noise compared to an equivalent room temperature probe.

In 1991, Richard Ernst was honoured with the Nobel Prize for Chemistry for his contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy – work that begun with his Fourier Transform research in the mid-60s.

2000s

Developments in cryogenic probes further improve performance, ease of use and system automation.

With automation of data analysis, NMR moves to the interpretation of the spectra being the important end result, rather than the spectra itself.

2010s

Bruker introduces world's first commercially available solid-state dynamic nuclear polarization-enhanced NMR system (DNP-NMR). Microwave irradiation is used to transfer polarization from unpaired electron spins to nuclear spins. As a result, polarization enhancement yields a factor up to 200 gain in sensitivity for solid-state NMR

Varian acquired by Agilent in 2010. Agilent exit from NMR business in 2014.

The use of Fluorine in the pharmaceutical industry has dramatically increased over the past few years. Today, five of the top ten selling small molecule drugs contain fluorine. F19 NMR offers unique method in drug discovery, but also in the characterization and quantification of fluorine containing molecules. This has driven the launch of several cryoprobes that are capable of observing this nucleus with very high sensitivity.

The list of new applications seems to go on and on, with recent work in structural biology, natural products, polymer science, petrochemicals, and materials science all being presented and discussed widely.

Conclusion

More than 70 years ago, a talented scientist first measured nuclear magnetic spin, work that resulted in the award of a Nobel Prize in 1943. Over the period from the mid 1950s through to 2010, a small group of companies spurred each other on to develop the technology, instruments and applications of NMR and the scientists that used the systems in their laboratories were extremely innovative in the way that they were applied. Initially Bruker and Varian competed, but Bruker emerged as the dominant player and continues this work today, building the applications base and developing new tools together with its customers and collaborators. It can be seen that NMR has become an essential tool in many industries, and the innovation continues as it expands into new methods and new application areas.

Further reading on all aspects of magnetic resonance can be found at: https://www.bruker.com/products/mr.html

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