Basic Research in Industrial Environment Resulted in Wide Range Applications in Society

An Example in Magnetic Resonance

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The field that magnetic resonance covers has been remarkable in developing science and technology and has provided highly useful tools for the society. The high recognition of the field by the society is manifested in the number of Nobel Laureates, 6, recognized for their contribution to the field. Since I have my interests are in one branch of the field, I like to start by mentioning these laureates.

In pursuing ways to measure nuclear magnetic moments with high accuracy, F. Block and E M Purcell found a way of detecting nuclear magnetic resonance using radio frequency excitation of spins, one by RF absorption (Purcell) and the other by nuclear induction (Bloch). Their invention of the methods to observe the resonance phenomena not only provided ways to measure nuclear magnetic moments including of neutron at unprecedented precision, but also opened a new field of magnetic resonance spectroscopy. It is quite worth noting what the Nobel committee pointed out in their introduction of the two laureates during the 1952 award ceremony, as quoted below.
[The methods of Purcell and Bloch …………we can in any object placed between the poles of an electromagnet seek out and examine with radio waves all the various kinds of atom and isotopes present in the object in question, and, *which is the essential point*, this without in any perceptible way affecting the same, its form, crystalline structure, etc. This form of analysis *in situ* is therefore probably not paralleled in any other known methods of analysis. …….]
Yes indeed, the method is not only non-destructive but also non invasive.

After the first publication of NMR in 1946 by Bloch and Hansen, Varian Associates was incorporated in 1948 with Russell Varian's strong foresight of NMR future as a tool for chemical analysis. Russell was an associate of Bloch and Hansen at Stanford. This may be an early bird of academics-initiated entrepreneur efforts around the Stanford Campus...When the magnet was improved to have better field homogeneity, a broad proton peak resolved into some peaks, i.e. the observation of chemical shift that depends on chemical bond. This affirmed the future of NMR as a chemical analysis tool.

Varian then had very high power scientists and engineers to make many innovation and inventions in NMR. One of those was FT-NMR by Anderson and Ernst. The sensitivity of NMR was enhanced and the time domain signal detection became possible.

When a broad NMR peak further resolves, a new field of NMR is opened. Unresolved resonance peaks after chemical shift were further distinguished by the strength of the physical interaction of the spin to its environment. A new axis was added to represent the physical interaction and the new NMR called 2D-NMR was generated. R. R. Ernst was the one who established this 2D NMR and he was awarded 1991 Nobel Prize in chemistry.

When the physical interaction is dependent on the spatial distance and the orientation between the spin and interacting spins nearby, this information in 2D NMR can be used to construct 3d- spatial structure of the substance under examination. Kurt Wuethrich did this application of 2D NMR to protein in solution to develop the new method to construct 3 dimensional spatial structure of protein. Wuethrich received 2002 Nobel Prize in chemistry. The determination of protein structure has become an important part of the research on genetically manipulated protein synthesis. This basic research led to large-scale industrial activities.

When a bottle of water is placed in an NMR spectrometer, a featureless single peak is observable. If the field homogeneity is lowered, the peak becomes broader further. Some parts of water do have different contribution to yield the shape of the water peak. If one imposes a known additional magnetic field to the sample, such as a linear field gradient, the water peak is dispersed along the local field variation. With such a linear field gradient, one can put the spatial information in the resonance signal. That was the way in which P. C. Lauterbur and P. Mansfield invented to visualize the water as image in NMR signal display. The new field of NMR, magnetic resonance imaging (MRI) was born. If any image lacks contrast, however, the image is featureless and useless. In magnetic resonance of water, the magnetic characteristics of water are dependent on its local environment and the image contrast can be introduced by taking a suitable way of acquiring an image to enhance the spatial variation of the characteristics such as the relaxation time. With MRI, the internal structure of human body can be viewed *non-invasively*. Especially for the brain, MRI is the choice of modality to observe the structure in details. A huge industry of the medical device was generated and has contributed to advance medical engineering as we see nowadays. Lauterbur and Mansfield received 2003 Nobel Prize in physiology and medicine.

MRI has been known as the method to measure the structure of the brain. Radiologists read MRI picture and seek abnormality in the image relative to the normal image they are trained to be familiar with. Any structural abnormality indicates some physiological character at the location is different from the normal and may well be the brain function impaired. However, the structural information in the image was not explored to sense the functional aspect of the brain. Functional MRI seeks the functional aspect of the brain in the structure we see in MRI.

"Structure and Function in Biological System" was the guiding key words for the research when I joined Biophysics department in Bell Laboratories. At that time, Kurt Wuethrich was spending his last year in the United States before he returned to Zurich. The biological system in our research interests was protein. I studied hemoglobin measuring paramagnetic NMR peaks that Kurt found in hemoproteins. These peaks depended on the paramagnetic state of the heme iron, and in hemoglobin they were found to show some sensitivity to the functional variation of the protein.

In later years, we switched the biological system to biological cells, cellular organelles and organs and measured cellular metabolism in situ. This MR approach is now known as MRS (MR spectroscopy) and is used in medical research.

With the same key words, we further changed our interests to MRI of the brain, hoping MRI signal carries some factors that may have sensitivity to functional or physiological variation. When we were studying some image contrast, we encountered the case that the contrast depended on the physiological condition of the brain. We found the contrast was dependent on the paramagnetic state of the heme iron of hemoglobin in the blood, namely deoxy-heme with high spin ferrous iron induced strong contrast and with diamagnetic oxy-heme there was no contrast. One of the key observations was in anesthetized mouse that breathing with air and pure oxygen the contrast changed and CO bound heme did not give any contrast in spite of the anoxic condition.

With these observations, the effects of cerebral blood flow (CBF) and oxygen consumption were examined and the contrast was concluded to be blood oxygenation level dependent (BOLD). Since it has been known for a century that at the location of functional activation in the brain the CBF increases, BOLD signal would correspondingly increase as a response to the functional activation.

This was successfully shown in 1992 in the human brain (Univ. of Minnesota with Bell labs, Massachusetts General Hospital, Milwaukee College of Medicine) and the new field of MRI approach was open as fMRI.

FMRI has been shown to detect localized functional activation not only by sensory stimulation but also by higher order brain activity such as language and memory related functions. Since it is a non-invasive method, a normal person can be the subject of the study. The fMRI application has now been widely made in brain research, such as in neuroscience, psychology and medical neurophysiology. There are, however, still some aspects of the methodology to be developed further, especially for the method to be useful for clinical purpose.

A very basic research even in an industrial environment contributed to an emergence of a new field of science and technology. The particular environment was a uniquely well-provided one that allowed basic research endeavor for a long period of time. A basic research, which does not have apparent clear prospect of success in horizon, sometimes may lead to an important development.

As an industrial application of MRI as a non-invasive method to measure structure of matter, a process of drying solgel was presented in time series revealing unexpected phenomena occurred during the drying process. The advantage of non-invasive method was clear.