PATENTS: FROM RESEARCH TO BUSINESS

CASE STUDY: FLASH MRI

In the early 1980s, magnetic resonance imaging was a stressful procedure for patients, requiring them to remain motionless in a narrow tube for long periods of time. Then Jens Frahm and his team at the Max Planck Institute for Biophysical Chemistry in Göttingen invented FLASH, a new and revolutionary MRI method which speeded up image acquisition time by a factor of 100. In order to commercialise the patent for FLASH, a long and fierce litigation battle had to be fought, which ultimately resulted in a significant licence fee income for the Max Planck Society.

In 2010, Frahm and his colleagues developed FLASH 2, which has shortened acquisition times even further. The technology moves MRI from images to films and enables real-time MRI videos of dynamic processes such as the beating heart. The commercialisation of FLASH 2 is based on a unique two-stage licensing scheme.

HOW IT ALL BEGAN

Starting points

The invention of the principle of imaging using nuclear magnetic resonance (NMR) signals by Paul C. Lauterbur at the State University of New York in Stony Brook/Long Island in 1973 sparked a radical change in the world of medical imaging, offering as it did the possibility to capture cross-sectional images of the body without exposing it to harmful radiation.

In the early 1980s, however, when commercial manufacturers of medical equipment began to produce the first MRI scanners, the examination was a stressful experience for patients, who had to remain motionless in a narrow tube for several minutes at a time. This was generally felt to be an insurmountable obstacle, the expectation being that MRI scanning would never be as fast as X-ray computed tomography (CT).

The potential of MRI was, however, recognised at the world-famous Max Planck Institute for Biophysical Chemistry in Göttingen, where a biomedical NMR group headed by Jens Frahm was set up in 1982 to develop scientific and medical applications of the technology. Frahm and his team focussed on the problem of reducing data acquisition times, since this was the main factor keeping MRI from being used on a large scale.

After years of research, Frahm’s team discovered a ground-breaking new technology for speeding up the process by at least two orders of magnitude. With Fast Low Angle Shot (FLASH) MRI, the acquisition time for individual images was reduced from several minutes to a few seconds.

TECHNICAL BACKGROUND

What is MRI?

Magnetic resonance imaging is based on the fact that the human body is largely composed of water molecules, each containing two hydrogen atoms. Their charged nuclei, called protons, have a spin which generates a magnetic moment.

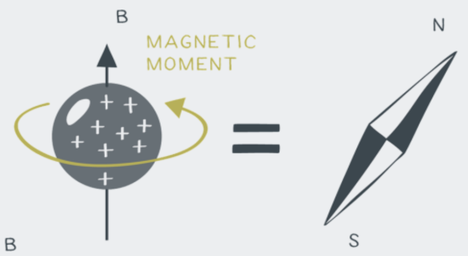

Figure 1: Spin and magnetic moment of a proton*

Inside an MRI scanner, the protons are exposed to a strong and uniform magnetic field which aligns their magnetic moments with the direction of this field. The ensemble of all magnetic moments leads to ***a*** *macroscopic magnetisation which marks the equilibrium state of the proton spins.*

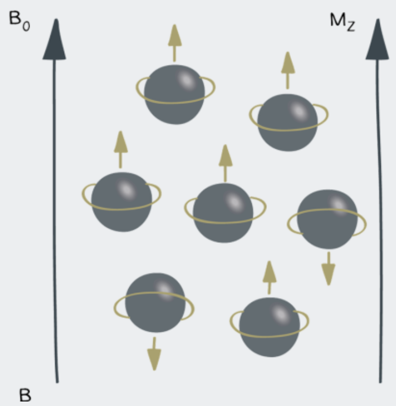

Figure 2: Equilibrium state of proton spins*

The application of a radiofrequency excitation pulse then flips a number of proton spins which – from the perspective of classical physics – results in a rotation of the macroscopic magnetisation by a pre-determined angle ("flip angle") away from the direction of the field. The flip angle depends on the amplitude and duration of the pulse. The excited magnetisation precesses around the direction of the static magnetic field and induces a voltage ("NMR signal") in the receiver coils of the MRI scanner.

This time-domain signal is transformed into frequency space, where it leads to a single frequency representative of the water protons in the body and the strength of the applied magnetic field. Paul Lauterbur discovered that this frequency dependence of the signal can be used to generate an image if a magnetic field gradient is applied during data acquisition. Because the frequency linearly depends on field strength, a signal recorded in the presence of a magnetic field which varies along one spatial dimension automatically results in a frequency distribution which emerges as a one-dimensional signal projection of the object under investigation. In order to measure enough data for an image, such spatially encoded experiments have to be repeated many times, with different magnetic field gradients.

This need for multiple repetitive experiments is the first problem determining the long MRI acquisition times.

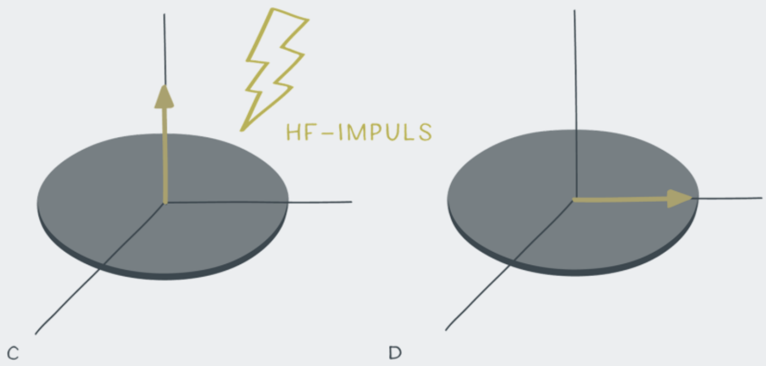

Figure 3: Spin and magnetic moment of a proton*

The second problem is due to the fact that, after each excitation, the excited magnetisation has to return to its equilibrium state. This relaxation process is characterised by two tissue-dependent relaxation times which are responsible for the contrast in the resulting image. Most importantly, however, the proton relaxation time which determines the exponential recovery of the equilibrium magnetisation is of the order of one second. It therefore causes a long waiting period of several seconds before a subsequent experiment with a different spatial encoding can be performed with sufficient signal strength. For example, 256 repetitive experiments with a two-second repetition time result in a measuring time of 512 seconds - almost nine minutes - for one image.

Problems prior to the invention of FLASH

In the conventional MRI technology in use prior to FLASH, the flip angle for excitation was set at 90 degrees in order to maximise the MRI signal picked up by the receiver coils of the MRI scanner. However, as this flip angle excites the entire available equilibrium magnetisation, the delay between two consecutive experiments has to be long enough to allow the macroscopic magnetisation to return to its equilibrium state. This delay is in the order of several seconds. Otherwise a saturation effect will occur such that no useful signal can be acquired anymore during repetitive excitations. Hence, conventional MRI technology prior to FLASH was unsuitable for rapid data acquisition.

It should also be noted that the most promising conventional MRI methods used a second pulse with a flip angle of 180 degrees. This pair of pulses rephased the excited magnetisation in a so-called spin echo signal, which was generally accepted as advantageous for MRI as it was not affected by inhomogeneities of the static magnetic field. Spin-echo images were therefore free from artefacts such as local geometric distortions or signal losses.

The advantages of FLASH

Frahm and his team achieved a huge acceleration in image acquisition times using excitation pulses with flip angles of much less than 90 degrees, in most cases between 5 and 15 degrees. Accordingly, the new method was called "Fast Low Angle Shot" (FLASH) MRI. In order to fully benefit from this trick, Frahm's team also had to abandon the conventional MRI technology. This meant eliminating the established spin-echo technology, because acceleration by low flip angle excitation only works if no following pulse further manipulates the proton spins. The FLASH technology therefore acquires the MRI signal in the form of a so-called gradient echo which may be generated by reversal of a magnetic field gradient after a single low flip angle pulse.

In essence, the combination of two "bad" choices as considered in 1985 state-of-the-art MRI vastly reduced the required delay between successive excitations and resulted in an image acquisition speed-up by two orders of magnitude. At the same time, the strength of the resulting gradient-echo MRI signal during repetitive excitations was only slightly reduced by the lower flip angle because it benefits from continuous signal recovery by relaxation.

PATENTING FLASH

While Frahm and his team were eager to share their FLASH technology with the academic world by submitting papers to scientific journals and conferences, they were also aware of the commercial value of their invention and the need to obtain patent protection for it.

QUESTIONS

- What should you take into account if you want to file a patent application for your invention and disclose it in a scientific publication?
- Bearing in mind the details of the case, where would you have filed the patent application for the FLASH technology?

On the day of the invention, which was made on the morning of Friday, 8 February 1985, Frahm contacted Munich-based Garching Innovation (now Max-Planck-Innovation GmbH), the IP company responsible for advising the Max Planck institutes on patent-related matters, who sent a patent attorney to visit Frahm's team on the following Monday. A patent application was drafted on the train back to Munich and, on Tuesday, 12 February, just four days after the invention was made, the first FLASH patent application was filed at the German Patent Office in Munich. As a result, any scientific report submitted after this date would not be considered as disclosing the invention, nor would it be novelty-destroying prior art for the FLASH patent application.

The German Patent Office was chosen because of the team's familiarity with the German patent system and the desire to secure the invention as quickly as possible. Within a year, further patent applications were filed at the European Patent Office and in the United States, Israel and Japan, all claiming priority from the German application, to get protection for FLASH in the home countries of the major MRI manufacturers (Siemens, Philips, Toshiba and General Electric) and their main markets.

The long road to commercialisation

At a worldwide MRI conference in London in August 1985, a presentation on FLASH was attended by representatives from all the medical MRI manufacturers. A few months later, the first medical MRI systems using FLASH technology appeared on the market. The FLASH patent was granted in the United States in November 1987 and by the European Patent Office in November 1989. Not long afterwards, Garching Innovation sent letters to all potential infringing parties to offer them licences for the FLASH patent in Europe and the United States.

QUESTIONS

- What means of attacking the FLASH patent did the infringing parties have if they wanted to avoid paying licence fees?
- Did any time limits apply to these actions?

In 1990, General Electric, Siemens and Philips opposed the FLASH patent before the European Patent Office and requested its revocation. At the same time, Philips started a nullification action against the US FLASH patent, followed by General Electric in 1992. The legal battle which ensued lasted until 1997, when the FLASH patent was maintained in all jurisdictions. The patent and litigation costs for the Max Plank Society totalled EUR 1.5m. However, by the end of 1997, almost all medical NMR manufacturers had acquired licences for FLASH, making it the Society's most valuable patent, bringing in more than EUR 150m before it finally expired in 2006.

Frahm and his co-inventors were heavily involved in the litigation procedure. They assessed documents, prepared written statements and attended oral proceedings to give expert advice. Frahm even had to postpone his habilitation until it was all over. However, it was definitely worth the effort, considering that inventors at the Max Planck institutes are entitled to 30% of any income from licences.

Lessons learned

The success of FLASH had a tremendous impact on both Garching Innovation and the Max Planck Institute for Biophysical Chemistry in Göttingen, leading to changes in practice at the Max Planck Society and in the industry:

- investment of licence revenues in further research
- establishment of an early invention notification culture
- change in perception of the Max Planck Society by industry

For example, 36.6% of the licensing income was awarded to the Max Planck Institute in Göttingen. The money was used to set up Biomedizinische NMR Forschungs GmbH as a non-profit organisation supporting Frahm's MRI research and to invest in new buildings and state-of-the-art MRI infrastructure.

Within the Max Planck Society, the success of FLASH raised researchers' awareness of the importance of patenting commercially promising inventions. Furthermore, in order to avoid the risk of accidental disclosure before filing, an early invention notification culture was established under which inventions are generally notified to the IP experts six weeks before public disclosure.

The long and ultimately successful litigation surrounding FLASH also changed the way the Max Planck Society is perceived in industry. Previously, companies did not expect a public research facility to defend its intellectual property rights, so they either used their power to negotiate low licence fees or intentionally infringed patents. After the FLASH litigation cases, the Max Planck Society was recognised as a strong patent licencing partner capable of vigorously defending its rights. This put Garching Innovation in a stronger position for patent licence negotiations.

MAKING MRI EVEN FASTER: FLASH 2

Within the newly founded Biomedical NMR company, Frahm and his team continued with their MRI research, but struggled for many years to achieve any further image acceleration. Then, in 2010, they succeeded in developing a new high-speed MRI method, “FLASH 2”, which reduces the acquisition time for a single image down to as little as 20 milliseconds or one-fiftieth of a second. This technology makes it possible to record live videos of moving organs and other physiological processes at a rate of 50 frames per second with high image quality. Major diagnostic applications of FLASH 2 include real-time MRI studies of the beating heart, the flow of blood or cerebrospinal fluid, joint movements and articulation and swallowing processes, as well as minimally invasive surgery.

The original FLASH technology significantly reduced MRI acquisition times and enabled continuous imaging, though still at a temporal resolution of about one second. It was therefore not yet fast enough for true real-time imaging of moving objects. Instead, it relied on a synchronisation of the MRI data acquisition with the electrocardiogram and some retrospective sorting of data from different heartbeats to generate a single synthetic “cardiac cycle”.

Frahm and his team overcame this problem by developing a new MRI technology which enabled the desired real-time imaging. FLASH 2 extends the FLASH principle by the use of extreme (e.g. 20-fold) data undersampling and a novel type of image reconstruction. Undersampling is the acquisition of a few spatially encoded data for each image and directly achieves a corresponding acceleration or reduction in measuring time. Serial image reconstructions are then defined as iterative solutions to a nonlinear inverse problem where the ill-conditioned numerical problem for the actual frame is effectively constrained by temporal regularisation to a preceding frame. In other words, FLASH 2 takes advantage of the similarity of successive frames in an MRI film at high temporal resolution. Technically, FLASH 2 also exploits a low flip angle gradient-echo technology for rapid continuous imaging, but uses a different spatial encoding scheme, wherein the data for a single MRI frame is sampled using radial “spokes” rather than rectilinear (parallel) lines.

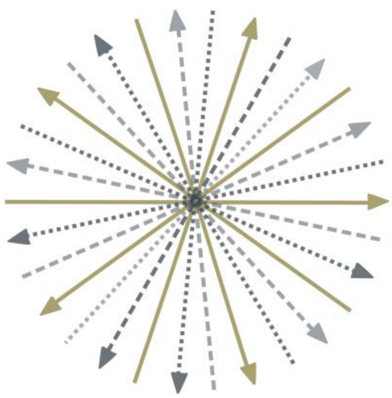

Figure 1: Radial sampling co-ordinate system with 15 spokes

Secondly, in order to further reduce imaging time, an undersampling approach is used in which for a single frame only a small and equally distributed subset of spokes is sampled.

For the following frames, the undersampled radial spokes are turned by a given angle such that a temporally interleaved spoke arrangement is achieved.

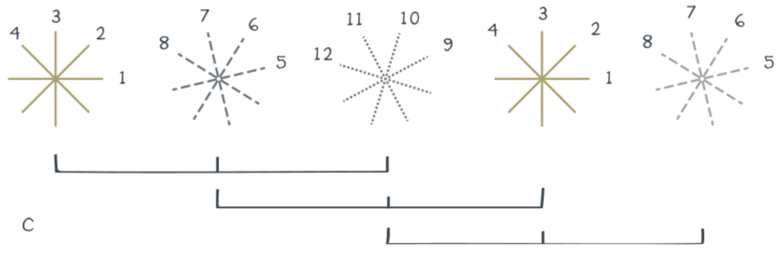

Figure 2: Undersampled temporally interleaved spoke arrangement

According to FLASH 2, each frame is reconstructed from its undersampled radial MRI data using a regularised nonlinear inversion algorithm. Despite a high computational demand, the algorithm allows for real-time image reconstruction when using a high degree of parallelisation and a dedicated computer with graphical processing units. This computer may be connected to an existing MRI system in order to bypass the conventional image reconstruction method.

Taken together, the faster speed of FLASH 2 is the result of the use of extremely undersampled radial acquisition schemes in conjunction with advanced numerical mathematics to solve the reconstruction problem. When implemented on multiple graphical processing units, FLASH 2 allows for true real-time MRI: acquisition, reconstruction and display of serial frames in real time.

Due to the high commercial potential of FLASH 2, the Max Planck Society filed two PCT patent applications and entered the national phases before the European Patent Office and the United States, Japan and Chinese Patent Offices. The advantage of using the PCT route is that applicants can defer patent prosecution and translation costs until the commercial value of the invention becomes clear. The FLASH 2 applications were all granted and can therefore be licensed to interested parties.

QUESTION
What do you think Max Planck Society’s business model will be this time?

Commercialising FLASH 2

In many respects, the possibility to obtain real-time MRI recordings rather than still images came as a shock to the radiology community. Over the previous 25 years, while MRI diagnostics had been refined, they had not really changed, and a whole generation of radiologists and clinicians had either accepted that it was not possible to use MRI to study joint movements or swallowing processes, or had learned to use means such as synchronisation to the electrocardiogram to carry out cardiac or flow MRI examinations. In other words, once real-time MRI had been invented, its clinical translation into routine medical applications asked for a change of paradigm. To achieve this goal requires vision, courage and extensive clinical trials. The benefits to be expected are manifold: patients will no longer need to hold their breath as they do for many of the current examinations or they will undergo a more comfortable MRI examination instead of a stressful non-MRI procedure (e.g. reflux diagnostics). Clinicians may develop new or simplified diagnostic procedures (e.g. providing access to patients with swallowing disorders or cardiac arrhythmias). Economic advantages are also expected thanks to shorter examination times (e.g. when using comprehensive real-time cardiac MRI protocols).

The strategy for commercialising FLASH 2 therefore focuses on making the product known to radiologists and clinicians, creating the medical need for it and finding interested partners among medical MRI manufacturers. To this end, a two-stage commercialisation procedure is used, comprising a first, intermediate commercialisation stage with mostly university-based radiological and clinical partners, followed by a final commercialisation stage with MRI manufacturers.

In the intermediate commercialisation stage, renowned medical research facilities may acquire low-cost licences for FLASH 2 for patient-oriented research in various fields of diagnostic imaging. It is expected that this research will result in peer-review contributions at conferences and in scientific journals. These publications are expected to broaden and change the current practice and in doing so to demonstrate the enhanced diagnostic potential of FLASH 2, which in turn will define clinical need, radiological demand and commercial interest. Furthermore, these research activities are expected to provide valuable feedback to Frahm and his team which will enable them to further optimise FLASH 2. At present, FLASH 2 can be implemented on Siemens MRI scanners with an additional graphical processing computer under the support of Frahm and his team.

In the second commercialisation phase, FLASH 2 will be licenced to MRI manufacturers using a number of potential licencing models. The most commercially promising model is the royalty-based licence scheme, under which manufacturers pay a fixed amount of money per product sold. For FLASH, this licencing scheme proved to be very lucrative. Another licencing model used by Max-Planck-Innovation GmbH (MPI) (formerly Garching Innovation) is based on milestone payments (following an initial down-payment), whereby payments are triggered at significant stages of success in the project for which the licence is granted (e.g. market introduction, sale of the first 100 products, and so on).

Generally speaking, licence agreements with MPI stipulate whether the Max Planck Society or the licensee is responsible for litigation. A clear definition of who is to bear the costs in any litigation proceedings is essential, particularly in view of the very high cost of litigation in the US. If the Society declines to start litigation, as the patent owner it (and MPI) is party to the proceedings but does not have to bear any of the costs.

SUMMARY

The FLASH case study clearly shows just how important - and how easy - it is to file patent applications for inventions prior to their first public disclosure. Research facilities should encourage scientists to notify their intellectual property departments as soon as possible after an invention has been made, and before they publish anything about it. The case study also demonstrates that patent owners need to be prepared to go to court to defend their intellectual property rights and that this may involve a significant outlay in terms of both time and money.

* *Images based on:* Weishaupt, D., Köchli, V. D., Marincek, B. (2014): Wie funktioniert MRI? Eine Einführung in Physik und Funktionsweise der Magnetresonanzbildgebung. Berlin Heidelberg: Springer.