Thanks to Jens Frahm and his team, MRI examinations can be completed in a relatively short time.

A live link to the root of the disease

It is thanks to magnetic resonance imaging MRI – and not least **Jens Frahm** – that doctors are better able to diagnose diseases among patients than they could 30 years ago. The research conducted by the Director of the non-profit making company Biomedizinische NMR Forschungs GmbH at the **Max Planck Institute for Biophysical Chemistry** in Goettingen has succeeded in significantly improving the images made of the body. In the interim, the team from Goettingen has even been able to push MRI from photography to filming.

TEXT **ROLAND WENGENMAYR**

If you ever find yourself lying in the tube of a MRI system, you can be thankful that the examination only takes a few minutes and not several hours, even though one part of the body is scanned from a large number of different perspectives. This is the result of the work contributed by scientists from the Max Planck Institute for Biophysical Chemistry to the development of MRI during the 1980s. The first generation of these devices, which can look inside the human body without using harmful radiation, took several minutes to take just one picture. Not only that, the person needed to lie still for the whole time to ensure that the images were sharp enough.

In principle, this could be compared to the initial stages of photography, when people had to hold still for long periods of time to prevent the pictures from becoming blurred. However, photographic technology improved at an incredibly fast rate, and eventually led to the creation of films. A comparable development towards moving images is now occurring in MRI. And for around forty years, Jens Frahm and his colleagues have helped make major improvements in this respect.

One key discovery made by the researchers in Goettingen was the FLASH technology, which from 1985 onwards drastically reduced the measurement time required for a single image. In so doing, they helped MRI make its big breakthrough. Today, there are over 60,000 devices in use, with 100 million examinations made every year. Thanks to their contribution, the technology is now able to record images of the inside of the body within a relatively short period of time, even in three dimensions, and in addition provide insights into metabolic processes in the

Photo: Frank Vinken

Sarah Willis, a horn player in the Berlin Philharmonic Orchestra, is one of the musicians whose tongue movements are being analyzed using real-time MRI. During the tests, a radiofrequency antenna circumscribes Willis' head while she lies in the MRI device and blows into a horn made of a non-magnetic alloy via a tube. During the entire procedure, she is monitored by researchers who evaluate the data on a computer (from left to right).

tissue with the aid of the chemical information from the MRI signals. This means that brain diseases can be better understood, for example.

A LIVELY INTEREST IN HUMAN STORIES

For several years, researchers have been working to create magnetic resonance images of moving organs. The Goettingen real-time MRI technology now makes it possible to obtain live videos from inside the body. Beating hearts, swallowing and speaking can now be monitored, as well as tongue movements while playing brass instruments. These are just some examples from Frahm's research. The physicist combines a warm-hearted interest in human stories with a fascination for the medical technology to which he has dedicated his life's work as a researcher.

MRI as it is now used in clinical practice is still not a particularly fast way of obtaining images from inside the body. On the other hand, it has the great advantage that it does not expose the body to harmful radiation. Since biologic tissue contains a large amount of water, the MRI method offers another advantage: it works with signals from the water, or more precisely, from the nuclei of hydrogen atoms. This makes it possible to differentiate between tissue such as bones, muscles and organs due to their different water content. By contrast, with X-ray technology, it took a long time before the method was able to show not just bones, but also soft tissue, although often only with the aid of contrast agents. Even so, the first medical imaging technology was such an important step forward that Wilhelm Conrad Röntgen was awarded the first Nobel Prize for Physics in 1901 for discovering the radiation that was named after him. Even at that time, therefore, basic research helped provide completely new opportunities for conducting medical examinations, and this is what Jens Frahm aims to achieve with his research into MRI.

In theory, the Director of the Biomedizinische NMR Forschungs GmbH at the Max Planck Institute for Biophysical Chemistry has already reached an age when professors retire. "I'm already into the extension period," he jokes. The Max Planck Society has made sure that Frahm can continue his work for the next three years.

In so doing, it is helping a researcher who was accepted into the "Hall of Fame of German Research" in 2016, and who has received one award after another, such as the European Inventor Award for Research in 2018. It is also thanks to Frahm that the Max Planck Society was granted the most lucrative patent in its history. However, before the license revenues from

Photos: sarah-willis.com

this patent began to roll in, there was a bitter dispute over the patented FLASH technology used. Frahm fought this legal battle to the bitter end with a will of iron – something you wouldn't think was compatible with his affable, friendly nature.

YEARS OF PATENT DISPUTES

In the mid-1980s, the researchers in Goettingen under Jens Frahm succeeded in accelerating examinations with the MRI devices one hundred-fold thanks to the FLASH procedure. Obviously, all the medical technology companies wanted to use this idea, and big names such as General Electric, Philips and Siemens immediately jumped onto the bandwagon. However, the companies initially refused to recognize the patent owned by the Goettingen scientists and to pay the license fees due to the Max Planck Society. In fact, the Max Planck Society only made moderate demands. "We wanted just one percent of the total turnover," explains Bernhard Hertel, who at that time worked at Garching Instrumente, the predecessor of today's Max-Planck-Innovation GmbH. "Then the major disputes began."

For seven years, Hertel, who is now 79, worked with Frahm to prepare court cases against the device manufacturers. General Electric proved the most obstinate opponent. Hertel flew to the U.S. dozens of times to pursue the legal fight against the medical technology company from Wisconsin. He decided not to use an interpreter, since "that would only have led to unnecessary delays in the proceedings." However, his strategy was not entirely risk-free, since just one careless remark would have caused the Max Planck Society to lose the protective rights to the patent claims. This is exactly what the opposing side hoped would happen, and they arranged for extremely precise minutes to be taken of the negotiations. In some cases, this yielded some strange results, according to Hertel. In the official minutes of the proceedings, it is stated that a dog was barking in the courtroom, and that it was made to stop with a loud "Shut!" by its owner, Frahm's attorney.

The opposing side certainly left no stone unturned. They employed dozens of attorneys, submitted falsified documents and even paid money for the services of a Nobel Prize winner in chemistry, who was presented as a scientific expert. However, he was not very familiar with the imaging variants of the nuclear magnetic resonance technology that were the subject of the dispute.

It was only in 1992, when the European patent was granted in full and when Hertel succeeded in negotiating a license agreement with Siemens, that General Electric finally admitted defeat. A figure of 0.7 percent of the total turnover was agreed, with a down payment of USD 20 million. Licenses were also issued to Toshiba, Hitachi, Philips and other medical technology companies. Ultimately, therefore, the Max Planck Society won the day. The fight was worth the effort: while the legal proceedings through to the final judgment in 1993 may have cost three million Deutschmarks, the license fees for the FLASH patent owned by the Max Planck Society brought in a total of EUR 155 million. To these were added other patents from Frahm's research, which also led to revenues of several million euros.

To understand why FLASH marked such a breakthrough, the basic principle of MRI needs to be taken into account. The signals come directly from the nuclei of the hydrogen atoms, which are present in different concentrations for different types of tissue. The hydrogen nucleus consists of a single proton, which behaves like a tiny magnet in a magnetic field. An MRI device has a strong magnetic field of this type. The magnet that generates this field is usually the large tube into which you are pushed. The magnetic field aligns the protons in the body like small compass needles. A radiofrequency antenna, which is placed on the upper body for examinations of the chest area, for example, is responsible for the measurement itself. The antenna sends a brief radiofrequency pulse into the

Photo: sarah-willis.com

body, which excites the protons out of their equilibrium position.

Where does the information about the tissue properties come from? After the excitation of the protons, they gradually return to their equilibrium state, like compass needles turning northwards. While doing so, they emit the energy absorbed from the radio pulse, and this signal is recorded by the radiofrequency antenna, which is now switched to receiving mode. Put simply, the key information is contained in the frequency and duration of the water proton signal, which is influenced by the local tissue surrounding it.

SHARP, CLEAR IMAGES ONE HUNDRED TIMES FASTER

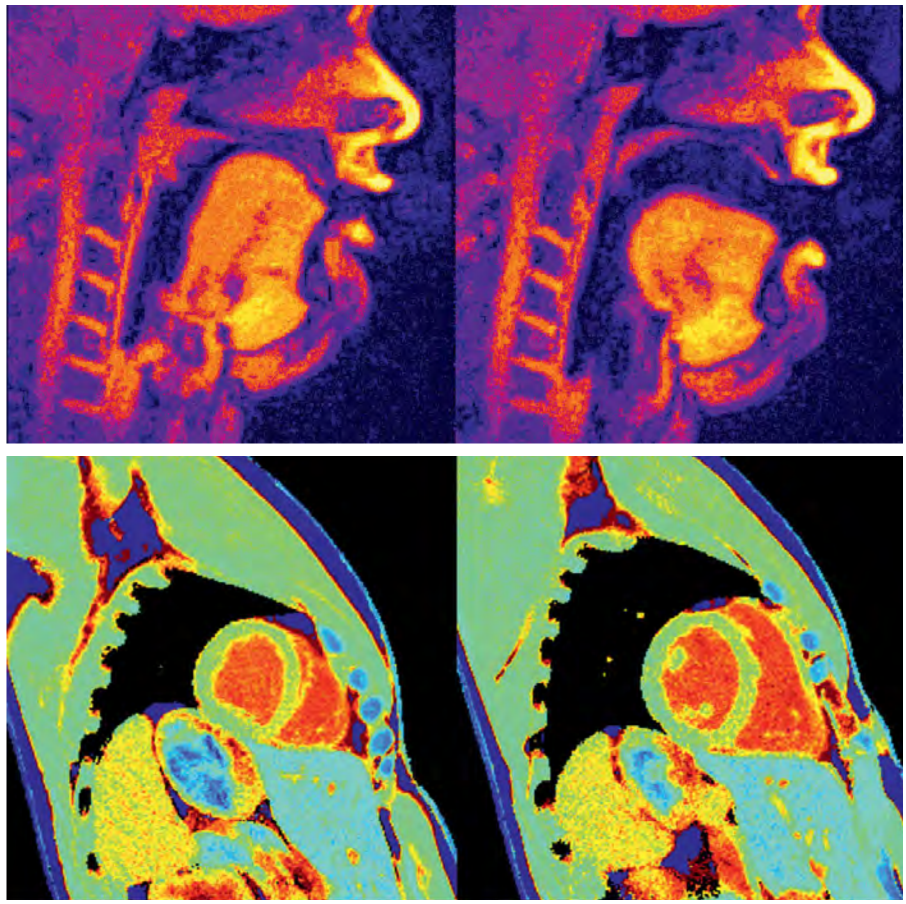
During the initial stages of its development, MRI needed a large number of individual measurements in order to build up a single image, with each measurement requiring two radio pulses. In addition, long waiting times were necessary between the measurements, since all protons were excited in order to produce useful images. Therefore, a long time was needed for them to return to their initial position.

The researchers in Goettingen then succeeded in conducting a measurement with just one radio pulse. Moreover, the FLASH technology excites only a small portion of the protons for each individual measurement by just a low-energy radio pulse. This makes it possible to take the next measurement immediately afterwards. As a result, FLASH technology records clear, sharp images in one-hundredth of the time originally needed to make a recording.

Since then, the researchers in Goettingen have even made sufficient progress with their technology to enable MRI to make the leap from a static image to film recordings. Short sequences made up of individual images have already become an established feature in the clinical field, albeit only with periodic processes such as the beating of the heart. Until now, films of this type were created subsequently from a series of measurements that can take several minutes. When examining the heart, the individual MRI data is synchronized with an electrocardiogram (ECG) recorded at the same time. With this trick, the computer can then correctly assign the images to the right phase of the heartbeat in the video that is retrospectively created. Since MRI and the ECG can interfere with each other, this recording method is subject to error. In addition, patients also have to be wired up with ECG electrodes – and they commonly have to hold their breath to ensure that the images are sharp.

In the real-time MRI technology, i.e. FLASH II developed by Frahm's team, this lengthy process and the discomfort involved are a thing of the past. The new technology delivers serial images or MRI movies from the body in real time, live and directly, without an ECG. The patients can breathe freely, since the system records live videos from inside the body with 30 or 50 images per second and in extreme cases even with 100 images per second.

The bottleneck on the way to achieving real-time MRI was the enormous mathematical effort required to calculate the images. A computer has to convert the MRI measurements into a high-resolution video in real time, in



Studies of singing and quantitative tissue maps: with FLASH II technology, MRI can be used to monitor the tongue movements of a singer, for example, and in so doing to diagnose speech defects (upper half). However, it is also a useful method for differentiating between different types of tissue. The almost round wall of the left heart chamber is light green, while the blood in the chamber is shown in red. The skeletal muscles are shown in green, while the liver is green-blue and the fat tissue is blue.

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other words, almost without any delay. If it fully recalculates each image, the process takes far too long. That's why the technology developed in Goettingen generates the images from only a very small dataset, which then can also be recorded far more quickly. For example, if only 5 percent of the original data needs to be acquired, the measurement becomes 20 times faster.

The procedure used to reduce the data is a distant relative of a technology used for rapid video transmissions. Here, algorithms analyze those areas from the image in a series that have changed in comparison with the previous image. Only these changes are transferred, leading to significant savings in data quantity. The researchers in Goettingen are pursuing a similar strategy. In simple terms, the computer uses the information from the preceding images that hasn't changed, and only calculates the areas of the image that have changed in order to create the new image.

With this trick, Frahm's team succeeded in shortening both the acquisition and computing time. Yet despite this, these MRI video images are sharp and accurate. Two former doctoral researchers, Martin Uecker (now a professor at the University Medical Center Goettingen) and Shuo Zhang (now an employee at Philips in Aachen) played a key role in enabling this new development.

Frahm's team demonstrated just how well the FLASH II technology works with live recordings of a beating heart. With this method, the researchers have found a way around one problem that arises with the standard ECG-synchronized heart MRI procedure that has been used to date. Contrary to requirements when the ECG and MRI are synchronized, the heart does not beat entirely evenly. "If it were to do so, this would result in mechanical problems, and it would never hold out for an entire lifetime," Frahm explains. "Naturally, in all cases of arrhythmia, the old technique has gone wrong," Frahm says. "And these are precisely the patients who need to be examined."

MUSICIANS CAN IMPROVE THEIR PLAYING TECHNIQUE WITH FLASH II

That's why clinics are becoming increasingly interested in the real-time MRI technology from Goettingen. However, the manufacturers of the MRI devices are still not ready to start production, since every new technology must be clinically tested and certified. Even so, Jens Frahm and his staff members, in cooperation with the University Medical Center Goettingen, have already used the FLASH II technology to help their first patients. They include people with swallowing difficulties, or professional brass players who can no longer play properly due to embouchure dystonia, for example, leading to tongue problems due to a lack of muscular control.

It was more or less a coincidence that the researchers discovered that FLASH II can also help these musicians. For one project, Frahm's team recorded the playing technique of professional horn players so that the MRI videos of their tongue movements could be used for educational purposes. "It emerged that even top-notch musicians don't always do the same thing," Frahm explains. "That's because we humans have no sensors in the rear part of our tongue, which would otherwise enable us to control its precise position." However, when the musicians themselves don't exactly know what their tongue is doing, this naturally has an impact on their teaching. It is hoped that the films recorded in Goettingen can now be studied to help teach players the right technique.

During the course of the project, the researcher came across a horn player from California who had speech problems and who also was no longer able to play correctly. In the MRI video, it emerged that while playing, the musician positioned his tongue in a completely different way to other horn players. He was only able to change this after Frahm's group projected back his own live recordings in real time, while playing in the MRI tube. On the basis of this experience, Frahm's team began investigating how useful the visual feedback might be when treating patients with speech deficiencies and brass players with dystonia.

The opportunity of using basic research to help people in a direct and practical way has motivated Jens Frahm for four decades. Now he firmly intends to get real-time MRI up and running in clinics. "I want to see this through to the end!", he says. Enabling doctors to see what is going wrong in the body, live. ◂

GLOSSARY

Magnetic resonance imaging: The technology uses the nuclear spin of hydrogen atoms. The nuclear spin is a quantum mechanical property and virtually turns the atoms into tiny rod magnets. How they behave in an external magnetic field depends on their chemical environment. The imaging technique makes it possible to differentiate between individual types of tissue, since they contain different amounts of water.