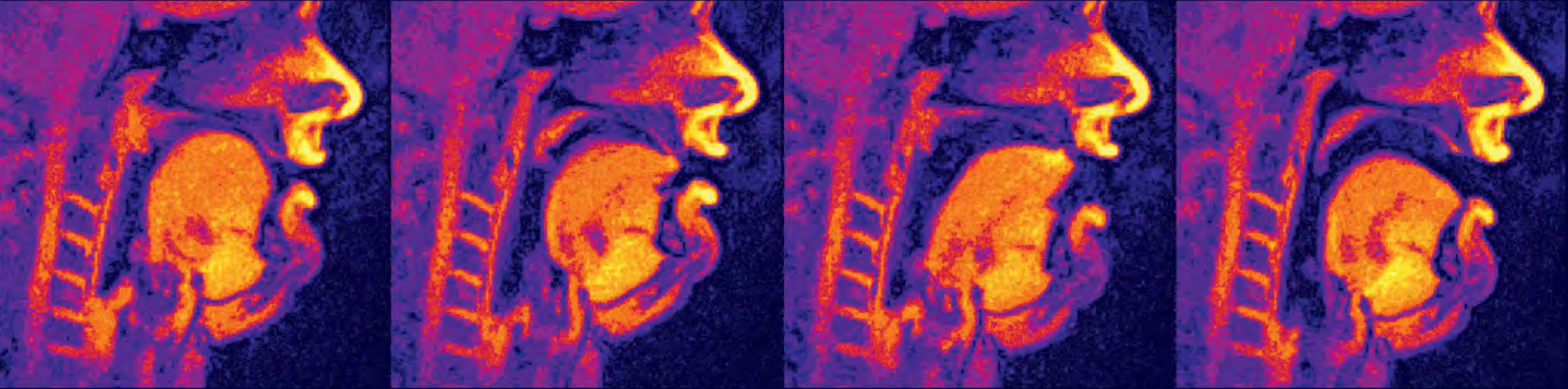
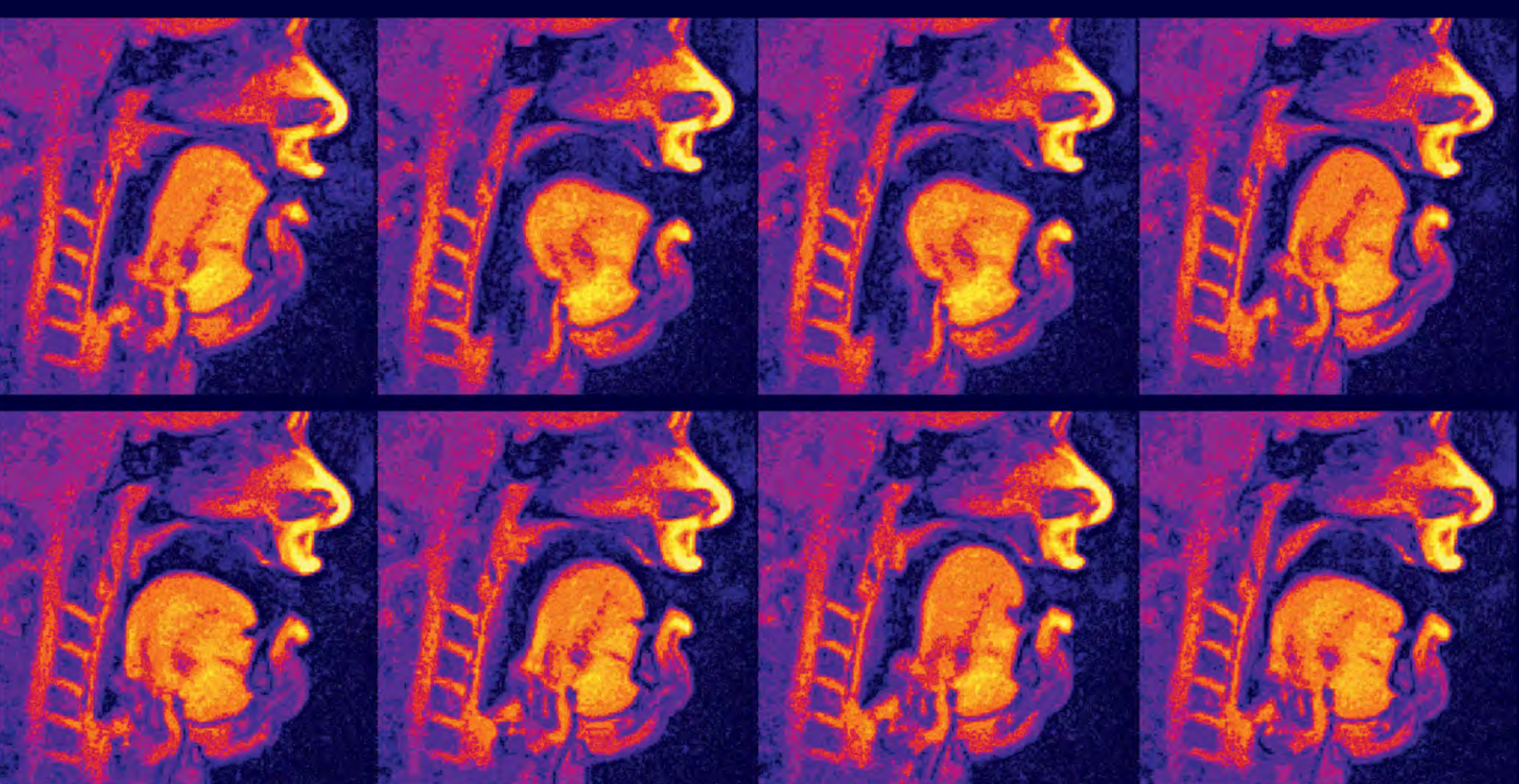


Live View
of the Focus of Disease

Doctors and patients can thank magnetic resonance imaging – and not least **Jens Frahm** – for the fact that many diseases can now be diagnosed far more effectively than they could 30 years ago. The research carried out by the director of the Biomedizinische NMR Forschungs GmbH (non-profit) at the **Max Planck Institute for Biophysical Chemistry** in Göttingen has greatly simplified the process of capturing images of the body's interior. Now the team from Göttingen wants to bring those images to life.



Singing lessons: The FLASH II technique can follow the tongue movements of a singer. It also facilitates the diagnosis of speech disorders.

TEXT **ROLAND WENGENMAYR**

When you're lying in the tunnel of a magnetic resonance imaging (MRI) scanner, you can be thankful that the examination will take only a few minutes rather than hours (despite the images being taken from a multitude of angles and with different contrasts). This improvement was achieved in the 1980s by scientists at the Max Planck Institute for Biophysical Chemistry. The first generation of these devices, which peered inside the human body without the use of harmful radiation, took several minutes to produce a single image. Worse still, to get sharp images, the patient had to lie motionless throughout the procedure.

This period generally calls to mind the early years of photography, when people had to hold very still for a long time to get a sharp image. However, photographic technology advanced rapidly, and eventually gave birth to motion picture films. Today, MRI is following a similar path toward moving images. And Jens Frahm, along with his staff, have been vigorously advancing that development for more than three decades now.

A key discovery by the Göttingen-based researchers was the FLASH technique in 1985, which drastically shortened the time needed to acquire a single image. Only then did MRI really take off, and today there are more than 30,000 scanners in the world that perform 100 million examinations a year. This breakthrough allows today's clinicians to study all body organs within a relatively short time and in three dimensions. Technical variants even use chemical information from the MRI signal to gain insights into metabolic processes in tissues and thus further improve our understanding of brain diseases and other disorders.

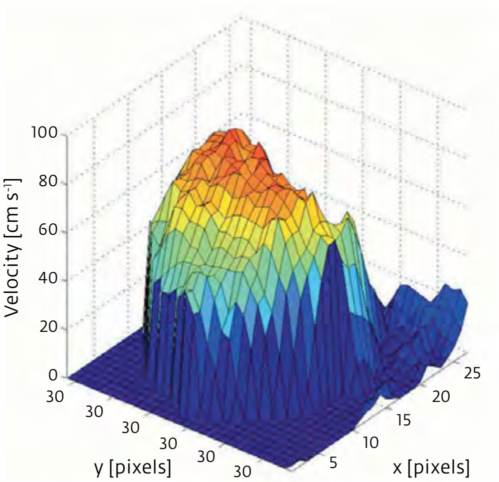
KEEN INTEREST IN THE FATES OF FELLOW HUMANS

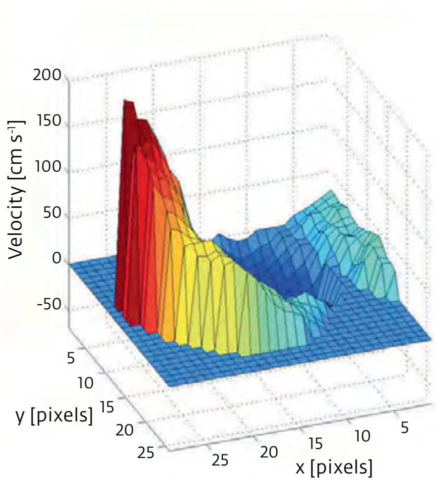
For some years now, the team has been teaching MRI how to move: their real-time image series deliver live videos of the body and its organs as they move. These series can follow the beating heart and swallowing and speaking processes, and even tongue movements while a subject is playing a brass instrument. These are just some aspects of Frahm's research. The physicist combines a warm-hearted interest in the fates of fellow humans with a fascination for medical technology, and he has devoted his entire scientific career to its advancement.

Magnetic resonance imaging in its present clinical form still isn't a really fast imaging method. However, it has the key advantage that it doesn't expose the body to harmful radiation. Because tissues have a high water content, the MRI method works with signals from water, or more precisely, from the nuclei of hydrogen atoms – the protons. This makes it possible to distinguish between various tissues, such as bones, muscles and organs, based on differences in their water content and internal structure. By contrast, it took a protracted period of development before X-rays, the first imaging process in the history of medicine, could show not only bones but also soft tissues – albeit often only with the help of contrast agents. Nevertheless, the first imaging technique was such a major advance that Wilhelm Conrad Röntgen was awarded the Nobel Prize for Physics for his discovery of X-radiation in 1901. Even back then it opened up new avenues of research, and that is precisely what Jens Frahm also hopes to achieve today through his research into magnetic resonance imaging.

Actually, the director of Biomedizinische NMR Forschungs GmbH at the Max Planck Institute for Biophysical Chemistry has already reached the retirement age for professors. "I'm now in the extension phase," he jokes, referring to the fact that the Max Planck Society has enabled him to continue his work for the next three years. >

Photo: Jens Frahm/MPI for Biophysical Chemistry





Above We have Jens Frahm and his colleagues to thank for the fact that MRI scans can now be performed relatively quickly.

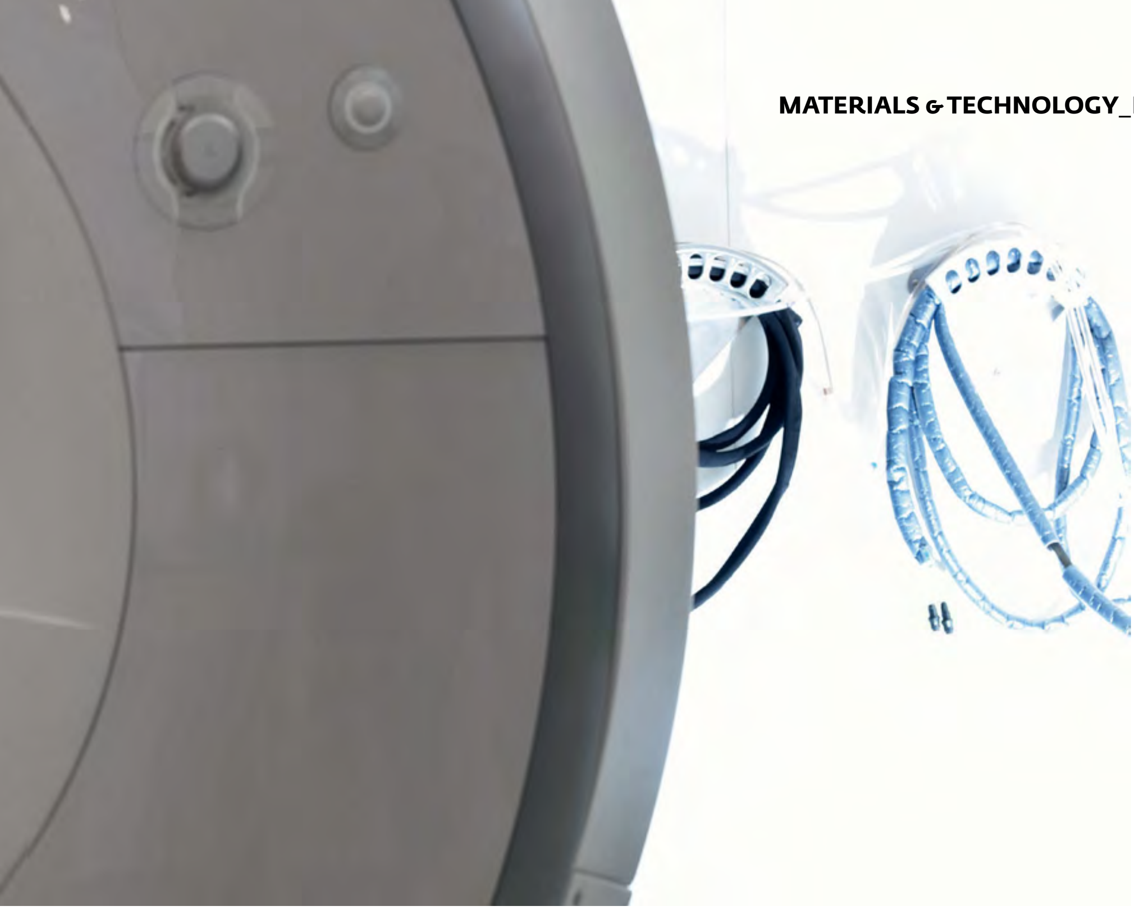
Left Real-time MRI can be used to measure how fast blood is flowing through the aorta. The velocity profile for a cross-section of the aorta (x and y axes) just above the heart shows how well the aortic valve is functioning. With a healthy valve (left), blood flows fastest in the center of the vessel (red). If the valve doesn't open correctly (right), blood flows more slowly or even backwards in the center of the vessel (blue), but at higher speeds along the vessel wall, putting great strain on it.

In doing so, they are lending support to a scientist who was admitted to the "Hall of Fame of German Research" in 2016 and who has garnered numerous awards. Frahm was also instrumental in giving the Max Planck Society the most lucrative patent in its history. But before the licensing fees for the patent began to flow in, there was a bitter patent battle surrounding the FLASH technique, which Frahm fought with steely resolve – something you wouldn't immediately attribute to him from his pleasant and friendly manner.

The discovery of the FLASH technique in the mid-1980s by Jens Frahm's team in Göttingen accelerated examinations with MRI scanners by a factor of one hundred. It was only to be expected that every medical manufacturer wanted to use the method: General Electric, Philips, Siemens and others immediately jumped on the bandwagon. Then the plot thickened: some companies used the technology developed by Frahm's team happily enough, but then refused to recognize the team's patent and pay licensing fees to the Max Planck Society.

Fortunately, Frahm had the support of the patent experts at today's Max Planck Innovation GmbH. The man responsible for the case, Bernhard Hertel, waged a seven-year suit against pirate equipment manufacturers. Frahm had to explain the technical details of the FLASH technique to his own lawyers. "For me as a scientist it was fascinating to watch the whole spectacle," Frahm says with a grin. The opposing parties marshalled dozens of lawyers. "They even worked with forged documents," the physicist says, "and retained a Nobel laureate in chemistry as a scientific expert." But he wasn't familiar with the various types of magnetic resonance technology, and that was central to the matter. In the end,

Photo: Frank Vinken; graphic: Jens Frahm/MPI for Biophysical Chemistry



the Max Planck Society was victorious. By the time the final verdict was issued in 1993, the process had cost three million deutschmarks – but licensing fees from the FLASH patent, on the other hand, have brought the Max Planck Society a total of 155 million euros. To top things off, Frahm's research has produced other patents that have also generated millions of euros.

To understand why FLASH was such a breakthrough, it's important to understand the basic principle of magnetic resonance imaging. The signals are emitted directly from water protons, which are present in tissues in various concentrations. When exposed to a strong magnetic field, protons behave like tiny magnets that are aligned like compass needles. An MRI scanner produces such a field with the help of a wide-bore magnet, which is the tunnel in which the patient is examined. The aligned protons may be excited by a short radiofrequency pulse that causes them to send a radiofrequency signal themselves when gradually returning to their original state of equilibrium. A radiofrequency antenna, which can be placed, for instance, on the upper body to examine the chest, is then responsible for detecting the signals. To put it simply, the key information lies in the signal frequency and the signal duration, known as the relaxation time. Both are influenced by the protons' immediate environment, namely the local properties of the tissue. An MRI scanner uses the frequency to compute an image, and the relaxation time to differentiate tissues of various kinds.

ONE IMAGE FROM MANY INDIVIDUAL MEASUREMENTS

The MRI signal gets strongest when all protons are excited at once – at least that was the credo in the early years of MRI. It is also necessary to build up a single image by taking a large number of measurements. The problem is that protons that are used during a measurement take a relatively long time to return to their home position. This means long waiting periods between the many measurements.

The scientists in Göttingen bypassed this problem with the help of two tricks. The generally established method at the time used two radiofrequency pulses followed by an echo signal. In a first step, FLASH reduced the measurement to just one pulse and thus allowed for a second trick that really speeded things up. The new technique excites only a small portion of the protons and leaves most of them untouched, so that the next measurement can be taken immediately. "According to the state of the art in 1985, we were doing two things wrong," Frahm says wryly. But it is for precisely that reason that FLASH produced images in just a hundredth of the time originally needed.

Since then, the team in Göttingen has even refined its technique to the point that MRI is now on the threshold of being able to make the leap from stills to motion pictures. Although dynamic MRI sequences have been used in clinical practice for some time, they can capture only periodic processes, such as the beating heart. Currently, such films have to be assembled from measurements that can take several minutes to produce. For examinations of the heart, the MRI data is synchronized with a simultaneously recorded electrocardiogram (EKG). This trick enables a computer to correctly assign each image to a corresponding phase of the heartbeat in the finished video. Because MRI and EKG can interfere with each other, the technique is prone

> The bottleneck on the path to real-time MRI was the need for many different measurements to compute a single image.

to errors. Moreover, patients must usually hold their breath to ensure that the image isn't corrupted by respiratory motions.

The real-time MRI technique now developed by Frahm's team dispenses with such time-consuming procedures and discomforts. It delivers live video images of the body's interior – without the need for EKG and with patients breathing freely during the examination. Thanks to the refined form of the FLASH technique, the Göttingen team can acquire live body films at 30, 55 and, in extreme cases, as many as 100 frames per second.

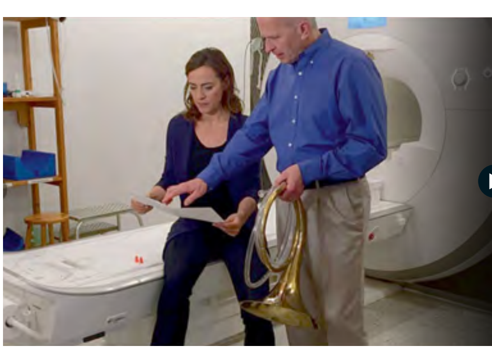
The bottleneck on the path to real-time MRI was the need for many different measurements to compute a single high-quality image. Now there is a simple solution: the new FLASH-based technique creates images from only very few measurements, which moreover can be recorded much faster. The price to be paid is the staggering amount of number crunching needed to compute an image from little data. A computer must convert MRI measurements into a high-resolution video in real-time, meaning without any appreciable delay.

RESEARCHERS USE A TRICK TO SHORTEN THE COMPUTING TIME

The method used for dealing with scant data is distantly related to a technique used for fast video transmissions. Algorithms analyze only those sections of the image in a sequence that have changed from the previous image, and only those changes are transmitted, dramatically reducing the volume of data needed. The scientists in Göttingen are pursuing a similar strategy. The computer keeps any information from the previous images that hasn't changed, and for each frame, computes only those parts of the image that have changed. Using this trick, Frahm's team reduced the amount of data required for each image to just a few percent of what it was. Nevertheless, the MRI video images are sharp and clear. Two doctoral students at the time, Martin Uecker, now a professor at the University Medical Center Göttingen, and Shuo Zhang, who now works at Philips in Singapore, played a key role in the development.

Frahm and two colleagues demonstrated just how well the FLASH II technique works in the basement of the Institute, where an MRI scanner of the type used in hospitals is installed. Dirk Voit, who is also a physicist at the Göttingen-based Institute, guides a doctoral student into the tunnel. We then withdraw to the control room. Voit launches the program with a few mouse clicks. In the shielded room behind the window, the MRI machine springs audibly to life – and then the first images of our subject's torso form on the display.

Photos: sarah-willis.com



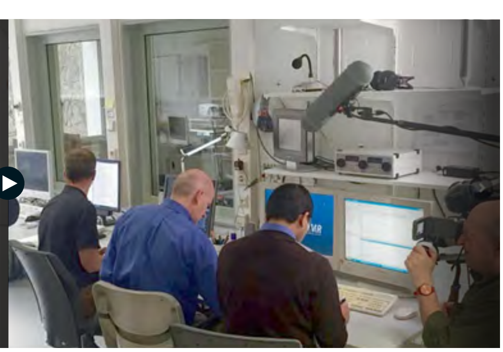
“First, we’ll do cross-sectional images and examine the heart,” Frahm explains, pointing to the display. After making a few adjustments, Frahm is satisfied: “We now have a four-chamber view that cuts right across the long axis of the heart, as it were. Even a layperson can immediately make out the four pumping heart chambers and also the flowing, eddying blood.”

As the live transmission of the beating heart runs, Jens Frahm explains exactly how FLASH II technology represents a huge advance over conventional EKG-synchronized MRI. “Did you know that the heart actually must not beat with a perfectly regular rhythm?” he asks. “If it did, it would lead to mechanical problems, and the heart would never be able to continue working for a lifetime. Each heartbeat is a little shorter or a little longer than the previous one, and that is already at odds with what is required for conventional EKG-synchronized MRI of the heart,” he explains. The heart would have to operate like a machine to march in time with the technical synchronization. “Of course, that’s not the case in patients with cardiac arrhythmias,” Frahm says, “and it is precisely those patients who doctors want to examine.”

Above Jens Frahm’s team is pursuing a number of ideas to further refine MRI, including real-time videos of the body’s interior. Here, the researchers are discussing a suggestion by Zhengguo Tan.

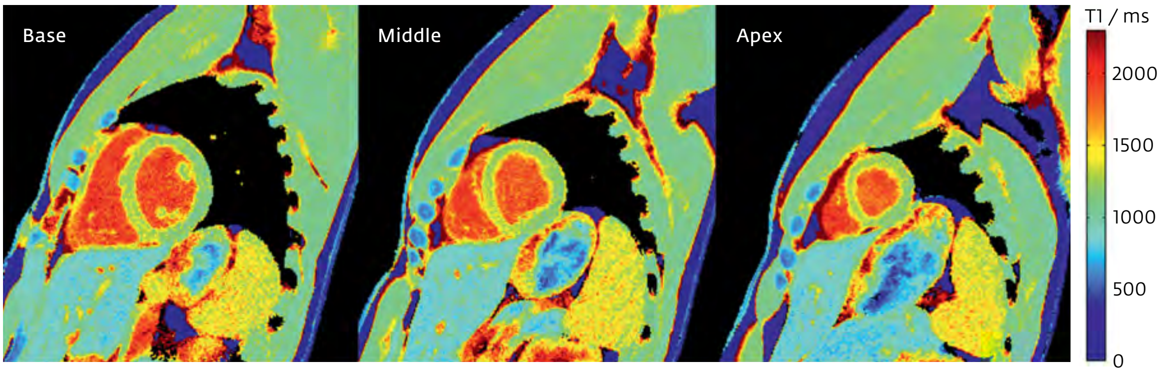
Below Sarah Willis, horn player in the Berlin Philharmonic, is one of the musicians whose tongue movements Peter Iltis (far left image), professor at Gordon College in Massachusetts, is analyzing with real-time MRI. For this purpose, Willis is lying in the MRI scanner while blowing through a tube into a horn made of a nonmagnetic alloy (link to a video of the project: http://sarah-willis.com/episodes/15-music-and-science/).

Photos: Frank Vinken (top); sarah-willis.com (bottom)



A LITTLE PINEAPPLE JUICE AS A CONTRAST MEDIUM

That’s why hospitals are showing increasing interest in the real-time MRI from Göttingen. Manufacturers of MRI scanners, however, are still wary. After all, every new technology requires costly clinical testing and certifications. Nevertheless, Jens Frahm and his colleagues have joined forces with the University Medical Center Göttingen to apply the FLASH II technique to help the first patients, such as patients with swallowing disorders. With a little pineapple juice as a contrast medium, the live videos show what goes wrong when those patients try to swallow or when they suffer from reflux. >



Tissue maps of the chest: How quickly the water protons return to their equilibrium after being excited with a radiofrequency pulse depends on the T_1 relaxation time, which is characteristic for the tissue type. These T_1 maps of the chest show the base, the middle and the apex of the heart in its relaxed state. The almost perfectly round wall of the left cardiac chamber is shown in light green, and the blood in the chamber, in red. Skeletal muscle appears green, the liver blue-green and fatty tissue blue.

Professional players of brass instruments who find they can no longer play properly due to tongue cramps have a similar problem. The scientists discovered somewhat serendipitously that FLASH II can also help them. During a research project, Frahm's team recorded the playing technique of professional brass players to use the MRI videos for training purposes. The team in Göttingen performed MRI scans on several world-class musicians who were asked to play about 30 exercises on a valve-less, nonmagnetic natural horn. They then recorded the sound together with the rapid tongue movements at 55 frames per second.

"We found that not even elite musicians always do the same thing," Frahm says. "That's because we humans get very little if any sensory information about the back part of our tongue to control its precise position." But if musicians don't know exactly what their tongue is doing, it affects their teaching. Studying the video recordings made in Göttingen should now help to identify the ideal playing technique.

During the course of the project, the team also studied a musician from California who had speech problems and who also could no longer play correctly. "Together with the University Medical Center Göttingen, we also investigate cramps that occur during speech or stuttering," Frahm says. The MRI video showed that the placement of the musician's tongue was completely different from that of other horn players. He was, however, unable to simply change it. Frahm's team therefore came up with the idea of showing him his live MRI video stream in real-time as he was playing. "The visual control was so effective," Frahm says, "that it immediately enabled the musician to practice the correct tongue position." This experience led the researchers to an ongoing project. They are studying how suitable visual feedback is for coaching patients with speech disorders, as well as for brass players with tongue cramps.

For decades, Jens Frahm has been driven by the possibility of helping people in a direct and practical manner through basic research. Now he is intent on bringing MRI to life. "I still want to realize that dream!" he says. In the future, this could enable doctors to watch live what has gone wrong in the body. ◂

TO THE POINT

- **The FLASH technique has reduced the time required for MRI scans by a factor of one hundred, which is why this imaging technique is used so widely today.**
- **The FLASH technique excites only a portion of the total MRI signal for each measurement, thus allowing measurements to be taken in rapid succession without any waiting period.**
- **The Göttingen-based researchers came a step closer to real-time MRI by reducing the amount of data required for a single image. Live videos from the body's interior now help, for example, in the diagnosis of cardiovascular diseases, but they can also be used for swallowing or speech disorders and for musicians with tongue cramps.**

GLOSSARY

Magnet resonance imaging: This technique relies on the nuclei of hydrogen atoms (protons), which behave like little magnets in an external magnetic field. MRI detects radiofrequency signals from tissue water protons that are excited by a radiofrequency pulse from the scanner. These signals depend on the location in the MRI scanner and are used to compute an image. The technique can distinguish between various tissue types because they contain differing amounts of water with differing properties.

Photo: Jens Frahm/MPI for Biophysical Chemistry