Magnetic Resonance in Medicine

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FOREWORD

Welcome to *Magnetic Resonance in Medicine Highlights*

We are very pleased to offer the second annual print supplement of *Magnetic Resonance in Medicine Highlights*. This year's cover story features an interview with John Tanner, Ph.D., one of the founding pioneers of diffusion imaging. We also present a number of Q&As with prominent *Magnetic Resonance in Medicine* contributors, which offer insights into some of the exciting work published in our journal.

Highlights is a volunteer effort, under the leadership of the journal's Deputy Editor for Scientific Outreach, **Nikola Stikov**, and our *Highlights* Editor, **Erika Raven**. Each interview was led by a trainee, under the supervision of Prof. Stikov.

Like the ISMRM and *Magnetic Resonance in Medicine, Highlights* is truly an international effort. Sometimes due to time differences, the interviews were conducted late in the evening or early in the morning, or even both simultaneously. Despite this, we are all part of a close-knit MR community, and our shared enthusiasm for the field can bridge gaps caused by vast distances or national borders. The accompanying map illustrates the impressive global span of the contributors to this issue.

We hope you enjoy this print issue, and maybe use it to take a moment to reflect on how extraordinary our international community really is.

Matt A. Bernstein
Editor-in-Chief, *Magnetic Resonance in Medicine*

APRIL 2017 / VOLUME TWO

John Tanner, the return to Germelshausen, and the work that nearly never happened

INTERVIEW BY **DEREK JONES** COVER PHOTO BY **TOM ROBERTS**

Toward the end of 2016, I felt honored to be invited by the editors of *Magnetic Resonance in Medicine Highlights* to interview John Tanner, Ph.D. With Ed Stejskal, John Tanner, invented the pulsed-gradient spin echo method, and conducted theoretical and experimental works that pushed the field of diffusion NMR forward, including the first use of the stimulated echo for diffusion NMR, and the use of restricted diffusion NMR to estimate barrier spacing, true diffusion coefficient, and membrane permeability.

John kindly agreed to travel from his home in Idaho to Cardiff, UK, for the interview. Realizing that many people would be keen to hear Dr. Tanner speak, a two-day meeting was organised entitled, "A Spin Thro' The History of Restricted Diffusion MR", (Jan. 31-Feb. 1, 2017) assembling key innovators in the field from the last 50 years. Dr. Tanner was the first speaker of the meeting, after which we chatted about his life and career.

What emerged was a story of a brilliant physical chemist who almost gave up on his research career, facing several challenges along the way, but who made a number of fundamental contributions to our field. It also became clear that until recently, Dr. Tanner was unaware of the huge impact that his work has had on the use of magnetic res-

John Tanner (right) and Derek Jones at the Cardiff University Brain Research Imaging Centre.

John Tanner in Cardiff, UK.

John Tanner at one year of age in Alliance, Ohio.

onance in medicine.

DKJ: Dr John Tanner, it's my pleasure to welcome you to the Cardiff University Brain Research Imaging Centre. Perhaps we can begin by learning about the early life of John Tanner?

JT: I was born in Cleveland, Ohio, in 1930, and subsequently raised in Alliance, Ohio. In my last two years of high school, I went to a small boarding school, where I found I liked chemistry. When I got home, I set up a small lab in my basement, bought a nine-pound bottle of concentrated sulphuric acid through the mail, and made ether and gassed myself on chlorine!

Then I went to Oberlin College, Ohio, majoring in physical chemistry. I had a family interest in German, and German was an important scientific language at the time, so I minored in German.

DKJ: After graduating, you did a master's thesis. What was that in?

JT: We were making precision measurements of specific heats of salt solutions to test the Debye–Hückel theory. I used a delicate, fragile apparatus that was very painstaking to use, but I learned a lot about tools, about complicated soldering, and about precision electrical resistance measurements.

After my thesis professor died, I wrote to two others who had made measurements with the same equipment, suggesting we publish together. They wrote back and said in their lifetime as scientists this was the most exasperating research they'd ever done, one saying *'Those lead wires would break if you just looked at them crosseyed'*.

DKJ: But that experience probably stood you in good stead for your later electronics work. On completion of the Master's, what happened next?

JT: I had accomplished at least one set of measurements, but I got tired, and wondered if this was what research was really like. I was tired of research, and so I volunteered for the draft (U.S. Army). I went to the Army Medical X-ray Technician training school, and was stationed at hospitals in Germany. So I became familiar with every fossa and protuberance of all the bones in the body!

DKJ: So, after you completed your service in medical imaging, unaware that your future work would have a huge impact on imaging the body, what did you do next?

JT: I got admitted to the University of Wisconsin graduate school, and spent two years doing course work. One professor suggested a research project, but I immediately did an experiment to show that his idea wouldn't work! I was a little bit tired of things so I took a job at a research laboratory outside of town. Their major focus was on physical chemistry of the rapid freezing of solutions related to preserving bull semen. I did a number of experiments studying the colligative property of gelatin in solution and interpreting patterns of rapidly freezing salt solutions. The boss was interested, but then decided I had done enough of that.

DKJ: So, what was the route to your Ph.D.?

JT: I'd started taking courses again at the University (while at the nearby private research lab), and decided to continue with a Ph.D. I interviewed all over the department and chose Ed Stejskal to work with. I was interested in diffusion, Ed had a magnet and I knew about the spin echo method of measuring diffusion coefficients. I thought it was a neat method, partly because sample preparation was pretty simple once you had the equipment, and the experiments didn't take very long.

DKJ: So you were familiar with Hahn's paper as a potential method for measuring diffusion, but there was a problem, wasn't there? Inspired by your previous work on gelatin, you wanted to look at samples with very low diffusion coefficients?

JT: Yes, I wanted to study the relation between viscosity and self-diffusion of water in gelatin solutions, which involves viscous solutions with low diffusivity, which in turn would require much stronger gradients with the Hahn method.

While I was building my gradient coils, Ed was thinking about the problems I was going to run into, and had his midnight brain storm that I ought to apply the field gradients in pulses, instead of continuously, to avoid the problem of having the RF pulse not cover the frequency spectrum of the solution as you go to higher and higher field gradients.

DKJ: Yes, you told me that at one a.m., Ed left a note for you before he went home, complete with some finely crafted calligraphy:

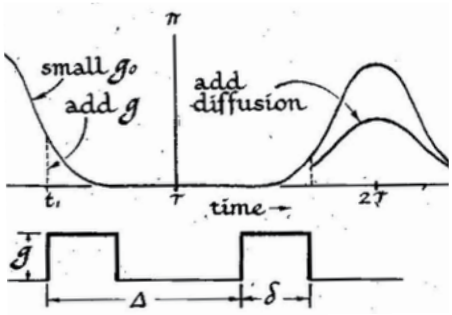


Figure 1. Illustration from the midnight brainstorm by Ed Stejskal.

JT: Yes, and he left a sketch of a transistorized amplifier that we could attach to our pulse generator.

DKJ: So that was the origin of the pulsed-gradient spin echo. But the aim at the time wasn't what we now know as the main application of the sequence. To quote you from your 1965 paper, *'In an attempt to eliminate some of the experimental limitations mentioned above, we have developed a technique in which the field gradient is considerably reduced during the times at which the RF pulses are being applied and also at the time of the appearance of the echo.'*

You were really trying to solve a problem, of how to measure low diffusion coefficients, and you realized that Ed's suggestion would open new possibilities for your research.

JT: Yes, but I didn't realise that our pulsed-gra-

dient method was going to be useful for an even more important purpose until I started designing the amplifier. I started asking myself about timing of the pulses, and thinking about the motion of the spins and what that might have to do with any timing requirements. It was then that I had a key insight. I realised that any diffusion motion would have the same effect regardless of where it happened between the pulses. It didn't really matter how the pulses were spaced, as long as the two were on opposite sides of the 180 RF pulse, and their magnitude was equal. You couldn't say the same thing about motions that happened during application of a steady gradient, or within a gradient pulse. In that case, it would depend on where within the gradient time the motion happened, but by making those pulses narrow compared to their separation, you could have a clean experiment and 'the time during which the diffusion process is being observed is precisely defined'.

DKJ: You've also told me that you were inspired by Don Woessner's work? (Woessner DE. NMR spin-echo self-diffusion measurements on fluids undergoing restricted diffusion. *J Phys Chem.* 1963. 67:1365–1367.)

JT: Well, I thought it was interesting that by varying the diffusion time, you could see the effect of barriers. The question was how would you actually analyse that to get a quantitative estimate of barriers, and I thought 'Well this looks kind of complicated.' (Ed had the same feeling, and had also thought about going into this problem, but decided against it)! But I realized that with precisely defined diffusion times the mathematical analysis should be much simpler.

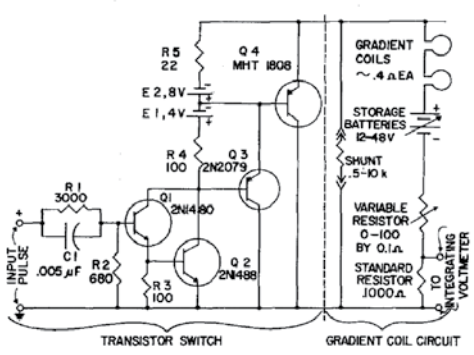


Figure 2. Transistor switch and gradient coil circuit. Resistance values are in ohms. (Tanner JE. Pulsed field gradients for NMR spin-echo diffusion measurements. *Rev Sci Instrum.* 36:1086–1087.)

Family portrait taken in 1980.

DKJ: But back then you couldn't just order a pulsed-gradient amplifier from a catalogue, so you had to make your own amplifier?

JT: Well, Ed had sketched the circuit diagram for a simple two-stage amplifier. Of course, he hadn't included all the little features and resistors needed to make it work right, and so I had to work that out myself. Then after I had done the preliminary experiments testing the theory, I wanted to go to more viscous solutions, so I enlarged the amplifier to four stages and designed that.

DKJ: But with no background in electronics, how did you know how to construct this circuit?

JT: I was self-taught. I read about the properties of various transistors and what you needed to do to make the circuitry work.

DKJ: So you'd made the kit, and you then needed to quantify the effect of the gradients and the timing on the signal.

JT: By that time Ed had worked out the theory of the signal attenuation from the Bloch-Tor-

Former Ph.D. advisor, Edward O. Stejskal, and joint namesake of the Stejskal-Tanner equation.

rey equations. He derived the equation where the log of the echo attenuation is proportional to, amongst other things, three parameters - gradient strength, gradient length, and separation between the gradients. What I did was to test variation of each of those independently on a water sample and showed that no matter what you varied and how you varied it, it still obeyed that relationship.

DKJ: That relationship is what we all now know as the "Stejskal-Tanner equation:"

$$b = \gamma^2 G^2 \delta^2 (\Delta - \frac{\delta}{3})$$

which you had now verified experimentally in fluids.

Did you have any impression of the impact it was going to have, beyond those initial physical chemistry arenas?

JT: Besides the restricted diffusion studies I made, I figured people would want to measure other things using the idea. I thought there would be a lot of systems (some biological, some mineralogical) with barriers of colloidal dimensions that people would find interesting, so there ought to be a number of studies of that sort of thing over the years.

DKJ: That brings me very nicely onto your 1968 paper "Restricted Self-Diffusion of Protons in Colloidal Systems by the Pulsed-Gradient, Spin-Echo Method," where you discuss the benefits of measuring restricted diffusion using the pulsed-gradient. Equation 3 stood out to me. Here you have effectively written down the q-space formalism. Although it wasn't explicitly referred to as a reciprocal Fourier relationship at this point, it's fair to say this was the first time it was written down. It has since turned out to be incredibly important in the medical literature, and was ahead of its time.

JT: I'd have thought this was something pretty obvious. It's just integrals of things that you do in heat flow analysis.

DKJ: That's a nice link into the various systems considered in the paper, borrowing models for the propagator from heat flow literature to look at diffusion in laminar systems. You started off with a mica stack?

JT: Yes, 99 layers of mica spaced by strips of aluminum foil. After designing it so I could accurately observe restricted diffusion, it took me two weeks to build it. I had to smooth off all the wrinkles in the aluminum foil and scrape burrs off the mica, so that it would be very even. Ed used his stereomicroscope to look at it and said he was surprised how regular the spacing was.

DKJ: You then derived what I believe were the first ever examples of analytical models for the diffusion signal in restricted geometries. Many of these have been since carried forward to applications in biological systems. Your next big innovation was looking at anisotropic and restricted diffusion, but with very long diffusion times, without suffering excessive T_2 relaxation.

JT: Yes, using the stimulated echo method, which I'd read about in Hahn's paper. The triple-90 RF pulse method looked attractive

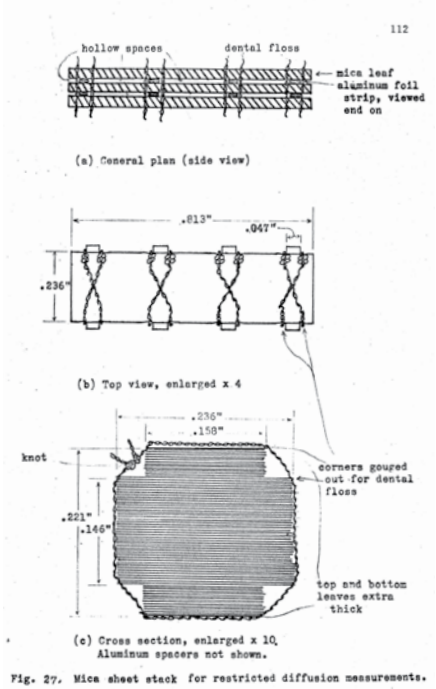


Figure 3. Diagram of mica stack, aluminum foil, and dental floss used for experiments on restricted diffusion.

because you could have a long space where signal decay was only due to T_1 instead of T_2. You paid a penalty at the start with a loss of 50% of the signal, but in cases where the T_1 / T_2 ratio was large enough, it was worth it.

DKJ: Did you encounter any problems with implementation?

JT: The main problems were in the first use of the pulsed-gradient, with all the battery recovery times, and the drift of the analogue pulse-generators. So I had to watch the echo and make sure it happened at the right time.

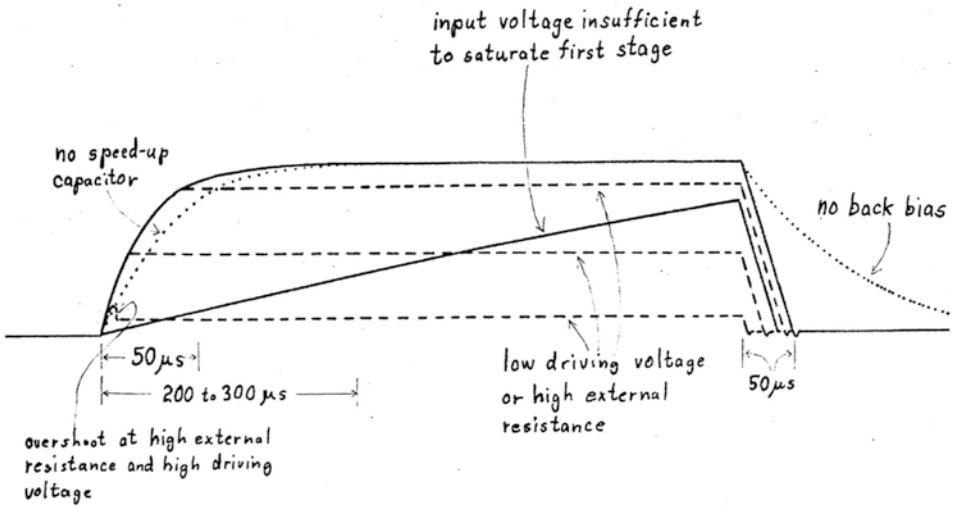


Figure 4. Hand-drawn figure of the gradient pulse design used for diffusion measurements.

There were also problems with eddy currents with tails lasting several milliseconds. I had to resolve this by redesigning the probe.

DKJ: At the time you were doing this work, what were the social pressures on funding for research? And how did they impact your research career?

JT: Well, there was a real love affair with science in general after the Russians had sent up their first Sputnik, and we failed in a couple of subsequent attempts to do the same. People said we needed more trained scientists, so science got heavily funded for a while. But toward the mid-1960's, people began to doubt whether they were getting their money's worth. Things began to change and companies started actually laying off scientists. It was a tough time to do job hunting and that was right when I was on the job market.

DKJ: You found it hard to find a job?

JT: Oh indeed!

DKJ: So where did you end up?

JT: After a few postdoctoral appointments I was employed at the Naval Weapons Support Centre at Crane, Southern Indiana, doing research on pyrotechnics, smoke, illuminating flares, and decoy flares. I may have made some fundamental steps forward there, but I would not be allowed to know whether there was any follow up.

DKJ: Well, what we are allowed to know is that, while there, you wrote another theoretical paper entitled "Transient Diffusion in a System Partitioned by Permeable Barriers."

JT: On the side, I was allowed to apply for funding to do more NMR diffusion work. Some of it was theoretical, and some experimental, where I rented equipment at nearby Indiana University. That was where the frog muscle paper was done.

DKJ: That paper, "Self Diffusion of Water in Frog Muscle", is one of the earliest to apply a whole series of pulse sequence designs to the study of biological systems. The paper shows you using oscillating gradients, pulsed-gradient spin echo and stimulated echo in the same experiment (Figure 5). There's been a resurgence of the use of oscillating gradients to study cell sizes as you heard over the last two days at the conference. But the Naval Weapons Support Centre allowed you to study frog cells. Was there a plan to deploy frogs as weapons?

JT: No. It was just that we were not an official lab, so we had to apply for grants. My boss told us to get whatever money we could for

Backpacking in Glacier National Park during his time as a graduate student.

John Tanner with his grandson.

whatever purpose.

DKJ: What were the key results from the frog muscle paper?

JT: Well the measurements were made perpendicular to the long axis of the muscle, and I showed that generally the diffusion coefficients at shorter diffusion times, where the barriers weren't apparent, were somewhat less than pure water due to the various obstacles along the way, but the obstacles were too close to observe a specific effect, so more like the obstacles of a viscous solution. They were about 20% lower than the diffusion coefficient of free water due to the finely spaced barriers. I was then able to detect barriers separated at larger distances, which apparently were the cell wall boundaries. I was also able to make an estimate of the cell wall permeability using the theoretical work I'd done on permeable barriers. Apparently it was useful, because I got a lot of postcard reprint requests.

DKJ: So was that your last paper in diffusion NMR?

JT: Yes, that one and another paper in *Archives of Biochemistry and Biophysics* on a few more cell samples from various professors. I left for Idaho before I could finish everything.

DKJ: Looking over a relatively compressed research career in diffusion NMR, could you reflect on the piece of work that gave you the biggest 'Eureka!' moment?

JT: I suppose the biggest eureka moment was realising that this pulsed-gradient method was a cleaner experiment with a good definition of the diffusion time (as we later called it), and that the analysis of restricted diffusion would be much simpler and cleaner, so there'd be a lot of things you could do with it. It was then that I totally gave up on the idea of the gelatin solution viscosity problem.

DKJ: Your last diffusion MR paper was in 1983. What has happened since then?

JT: Well after the pyrotechnics work, I moved to Idaho. I was part of a two-year project developing a method for long-term storage of radioactive krypton by compressing it into a zeolite and then sintering that zeolite. But the project ended as we realised that there wasn't much krypton to be disposed of and there was big industrial demand for whatever there was left. My remaining 15 years were in criticality safety, doing mostly Monte Carlo calculations on various operations to avoid unintended criticalities with the highly enriched weapons-grade uranium we were using. That

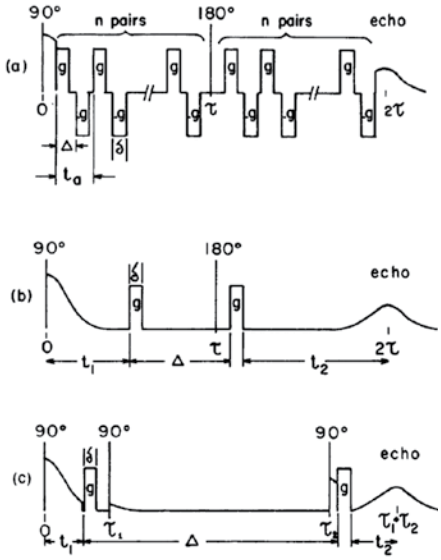


Figure 5. Radio frequency (900, 1800) and field gradient (g,-g) pulse sequences suitable for diffusion measurements at (a) short, (b) intermediate, and (c) long diffusion times, respectively. (Tanner DE. Self diffusion of water in frog muscle. *Journal of Biophysical Society.* 1979. 28:107–116.)

was interesting, I did miss the lab work, but I enjoyed the calculations too.

DKJ: How are you enjoying your retirement?

JT: I've always been interested in gardening. But one of the major things my wife and I have gotten into is advocacy for treatment of the mentally ill. Our younger son was talented in organic chemistry, but developed schizophrenia. We had a rollercoaster of a time ensuring that he received the care he needed. We've since been involved with legislators, forwarding them information from medical journals, and now sit on several statewide committees on this topic.

DKJ: You've been out of the field for quite a while. Last year, the ISMRM awarded you Honorary Membership and you came along to your first ISMRM! Reflecting on this prompted you to tell me a German folk story.

JT: Yes – Germelshausen. Well, I was in an environment that was totally out of magnetic resonance and diffusion, and not much into deep science. Then spending a few days at the ISMRM, I was back in the kind of environment I was in 40-50 years ago before heading back to my old environment. Now suddenly in Cardiff, I'm back into this environment once again. This reminded me of an old German folk tale, about a village, Germelshausen, which existed for just one day every 100

years. At midnight it disappeared, and was pasture again, until the next 100 years.

DKJ: Well you re-entered the diffusion Germelshausen a couple of days ago, and you were our first speaker at our celebration of the history of restricted diffusion MRI. You got to hear your name many times during the meeting. I kept looking across and saw you smiling. I wondered how you felt? This work, that you started off nominally to remove an obstacle to measuring low diffusion coefficients, has since had huge impact, leading to early diagnosis of ischemia, allowing people to navigate and resect tumours – the full gamut. How does it feel?

JT: I hadn't thought of all of that. I was amazed, of course, looking over the program of the ISMRM. In fact, at the ISMRM, one of the guys saw my nametag and said, 'So you're the guy who put us all to work?' It floored me, it really did.

DKJ: Well, I'm incredibly grateful to you for putting me to work, and there's thousands more people around the world who are grateful to you for putting them to work.

JT: Well I did the research for fun. Not to benefit someone. It was just fun.

DKJ: Well John, it's been great fun talking to you. Thank you for the interview and on behalf of the entire diffusion MR community, thank for your seminal contribution to our field. ■

Interview has been lightly edited for clarity. A video of the entire interview can be found at: www.youtube.com/watch?v=ixu6I7eJZEc

Derek Jones

Prof. Jones is Fellow of the International Society for Magnetic Resonance in Medicine (ISMRM) and the Royal Society for Biology (FRSB). He has held various positions within the ISMRM including Programme Chair of the ISMRM Annual Scientific Meeting in Milan, 2014, has twice been Chair of the Diffusion Study Group, and served as Deputy Editor for Magnetic Resonance in Medicine. He has published widely on all aspects of the diffusion MRI pipeline, from data acquisition through to applications, and edited the book 'Diffusion MRI: Theory, Methods and Applications' – to which Dr. Tanner contributed his personal reminiscences together with Ed Stejskal. Prof. Jones is Director of the Cardiff University Brain Research Imaging Centre (CUBRIC) in Wales, UK (http://sites.cardiff.ac.uk/cubric) and his research is supported by the Wellcome Trust, EPSRC, MRC and Wolfson Foundation.

John Tanner, and his wife of 50 years, Martha Tanner, MD.

Extending the global reach of ISMRM

INTERVIEW BY **NIKOLA STIKOV**

Garry Gold is an electrical engineer, a musculoskeletal radiologist, and a professor at the Stanford University School of Medicine. He is also this year's ISMRM president. With so many diverse experiences under his belt, Garry has a unique perspective of the field of MRI, and a broad vision for the future of the society. He shared with us some of his favorite ISMRM moments, as well as his plans to extend the reach of the society.

MRMH: You've been involved with the society for a very long time. When was your first ISMRM meeting?

Garry: So my first SMRM meeting (at the time it was called Society for Magnetic Resonance in Medicine) was in 1994 in San Francisco. The year before that in 1993 was the ISMR meeting in Dallas, and 1995 (Nice) was the first year of the merged society that became ISMRM.

MRMH: And how many of these meetings have you been to since?

Garry: Every single one, I have not missed a meeting yet.

Garry Gold and family on a recent trip to Fallen Leaf Lake in California.

MRMH: Can you tell us a bit about your early days at ISMRM?

Garry: When I first started in MRI it was in the late 1980s, and I was a master's student at Stanford in Electrical Engineering. I started working with John Pauly, looking at ultrashort echo time imaging with half-pulses and projection reconstruction. We initially were applying this to imaging the lung, but as I went along, after I completed my master's degree and went to medical school at Stanford, I became interested in the problem of imaging atherosclerotic plaque, using what later became known as UTE imaging. I worked with John [Pauly], and Al Macovski and Bob Herfkens to apply some of the UTE spectroscopic imaging we were doing at the time to atherosclerotic plaque in cadaver specimens and correlating that with pathology. That was the basis of my initial work with that technique, that we presented in Dallas and published in JMRI. A little later on, starting my residency in radiology I became interested in musculoskeletal imaging. That was in 1994. My first poster at the SMRM meeting in San Francisco was on multislice UTE spectroscopic imaging and it was initially applied to tendons and knee menisci. For the Nice meeting in 1995 I submitted an abstract and a paper, which was necessary for the Young Investigator Award.

MRMH: How has the society evolved since then?

Garry: There is terrific growth in the breadth of the meeting and the type of technology that is available. I would say at that time we mostly focused on hydrogen proton imaging or spectroscopy. Even though there were probably groups working in multi-nuclear or multiple contrast mechanisms, this was before fMRI, and before diffusion was a common contrast mechanism. I remember at that time people talked a lot about magnetization transfer, it was quite new. I would say one the explosive growths I have seen is along the axis of exploiting the flexibility of MRI in terms of multiple

contrast mechanisms to explore tissue.

MRMH: So that brings us to the present day, and you as ISMRM president. How has the recently announced (and contested) immigration ban affected the society?

Garry: It is very sad and disheartening that the recent immigration action has had a negative effect on our meeting. I have had multiple conversations with young scientists whose work has been impacted by the proposed travel ban. Without getting into the politics of the ban, I can only say that I support all scientists and students worldwide in their research, and their efforts to publish and present their work at our meeting. The ISMRM is committed to be the home for the best worldwide science of MR in medicine, regardless of where the researcher is from. We are a global society. We are working with the researchers who are affected by this proposed policy to ensure they have an opportunity to participate in the annual meeting.

MRMH: What is your vision for the society and how do you see it evolving over the next couple of years?

Garry: I will give a two-part answer to that question. One is I strongly believe in the MR value initiative that Jim Pipe has started, and I committed to work with him and Dan [Sodickson] in continuing the initiative. If you think about where we are as a society, MRI is viewed as a very expensive technology. At this point in time it is rarely used as the first line of imaging test in medical care. It is usually used as the second or third test. Despite the power of the technology, because of the cost and the way it is utilized we are in danger of payers and governments saying 'well that would be great, but it is just too expensive'. We need to be able to counter that argument. We need to be able to demonstrate that even if it is expensive it is worth it, because it saves money from going to surgery, which would be even more expensive. Or it prevents somebody from taking the wrong medication. We've done a great job of improving the technology, but we have not done a great job of proving the value. Along those lines there's a lot that we can do to lower the cost, to make MRI a faster, more accessible, and more targeted exam that could be used as the first choice in the clinic.

MRMH: What are the competing modalities?

Garry: X-ray and CT or ultrasound, typically. Let me give you an example. Imagine you went rollerblading and fell down, and hurt your wrist. You would go to the ER and they would take an X-ray. If the X-ray showed a fracture you are done. But most of the time it does not show a fracture, but you still have wrist pain. And we are not sure based on the X-ray whether there is really a fracture or not. You get put in a splint, you get sent away, you come back two weeks later and you get another X-ray. Maybe they can see a fracture at that point, maybe not. In the meantime you've been wearing this splint or cast for two weeks. After two weeks, if the X-ray is negative, and if you are still in pain, you get an MRI. But if instead of an X-ray on your first visit you could have done an MRI scan, one sequence, one T_2-weighted fat-suppressed sequence, could have told us if there was a fracture there or not. We know that power exists, but it is not being used right now because the perception is that the MRI exam is too expensive, too hard to access and takes too long.

MRMH: This is a great initiative moving forward and I assume you would like people to get involved on many levels. How do you see young people contributing, either to the value initiative, or just to the society in general? Do you have any particular activities that get junior researchers and clinicians involved in the society?

Garry: Most of our student members are researchers at a stage where they are either trying to get their MD or their Ph.D., and I think that they can contribute to the value initiative in many ways. There's a need for more rapid scanning protocols and reconstruction methods that allow us to move quickly in the clinic, to quickly get to a diagnosis, or exclude a diagnosis. Techniques such as parallel imaging and simultaneous multi-slice, compressed sensing, have the potential to take MRI from an hour-long or 45-minute long exam to a two-minute exam. That immediately makes it much more accessible for patient care. So on the technological front there is a tremendous amount that can be done. On the reconstruction and processing side there is a need to be able to rapidly reconstruct the data and present it in a way that a physician, even a primary care physician, can easily understand. Christiane Kuhl at last year's annual meeting showed projection imaging of the breast that was acquired in three minutes, and the image could be interpreted in three seconds by a radiologist. This was a perfect example of what we are talking about on the technical side. On the clinical side, for a clinician junior member, there is tremendous opportunity to do research around where is the value, where does MRI fit in the care of the patient, where are the places where MR can have a big impact, and what are the barriers

Garry Gold achieving great heights on a hike in Telluride, Colorado.

> *The overarching goal is to show that we are a global society, and for that we need to be comfortable and accessible and ready to engage in any area of the world.*
>
> –Garry Gold

Garry Gold and his wife, Audrey, on a trip to Philadelphia in 1999.

to it being used in that setting now. Why isn't it that if you hurt your wrist, you don't just get a five-minute MRI scan instead of X-ray, cast, X-ray, wait, pain, maybe MRI six weeks later.

MRMH: So these would be contributions on the research side. What if junior people want to get involved on the strategic side, administration, logistics?

Garry: Absolutely. One of the reasons that the Junior Fellow program was started was to identify future leaders in the field of MR. And the idea behind the junior fellowship is that it is not only an honor, but an opportunity to identify folks who are engaged in MRI, and who can be tapped to help the society. We are trying and we are continuing to come up with new ways to ask for their help. In the society they participate as observers on committees, there is the Trainee Working Advisory Group, and we use their feedback to listen to the membership. One of the things we had heard through that group was that ISMRM can be a bit overwhelming and a bit big on your first visit, so that was the impetus for creating the newbie reception. That's been the past. Going forward, where I think we need to engage the talent of the junior members is really in the explosion of web and social media, interaction, education, and outreach. I joined Facebook because it was the only way to see one of my student's baby pictures. I rarely ever log in. I have never used Twitter. I used Slack for the first time this year. Most of us in the leadership are just not in the same cohort as our students. People are communicating and interacting in entirely different ways and I think we need to engage our students and our trainees and our junior fellows to make sure that what we do as a society is out there in the right way. By out there I mean online, on social media, on twitter, on slack, on instagram, so that new potential students/members and the lay people know who we are.

Group photo of the Magnetic Resonance Systems Research Lab at Stanford University taken in 1998 (Garry Gold in the middle, back row).

There is one more initiative that I think would be worth featuring. My major initiative as president is called 'Engaging Asia'. We are an international global society, but there are areas of the world where we haven't been. We've never held a workshop in China, in South Korea, or India.

MRMH: Except for the outreach programs.

Garry: The outreach programs have been very successful, but outreach is different. Flying five faculty members to speak in a session of an existing meeting is different than trying to logistically plan and execute a workshop, or even a future annual meeting. We all recognize the explosive growth of MRI in Asia, particularly East Asia. We need to be in this part of the world to engage the members here. We need to engage the local communities and show what we can offer in terms of training and experience in using this technology. I feel very strongly we need to move in this direction. With the support of the Board of Trustees we've set aside funds for supporting a series of workshops in East Asia, meaning full ISMRM workshops with a mixture of international speakers, local speakers, and students from all over the world. We might have a workshop on PET/MRI in China. We are also discussing the idea of holding a workshop on liver disease, which is a huge problem in Southeast Asia, including hepatitis and liver cancer. We've engaged the workshop and study group committees, we've formed an ad hoc committee with advisors from the relevant countries, and my goal in the next two years is to hold at least four workshops in East Asia. The overarching goal is to show that we are a global society, and for that we need to be comfortable and accessible and ready to engage in any area of the world. ■

Closing the loop in MR research

INTERVIEW BY **ERIKA RAVEN**

Karla Miller is a professor of biomedical engineering at the Oxford Center for Functional MRI of the Brain (FMRIB, pronounced "fim-rib" for short). She directs the FMRIB Neuroscience Physics group, which specializes in many projects, from pulse sequence development to biophysical tissue modeling. More recently, she's been a key figure of the UK Biobank, a mega-sized data initiative charged with imaging 100,000 adults by 2022. Karla is also this year's ISMRM education chair, and is poised to chair the entire program for the 2018 meeting in Paris. In our interview, Karla makes connections between the many themes in her life, which ultimately are resolved by finding the right balance.

Karla Miller (fourth from left, bottom row) and members of the Neuroscience Physics group at Oxford University.

MRMH: You're one of the few people that feel comfortable straddling the line between ISMRM and OHBM. Do you see a synergy between these two societies, or would you rather they keep running on parallel tracks?

Karla: I think it's incredibly important that people who are developing MRI techniques don't do so in a vacuum. I've benefited tremendously from being at the FMRIB center. Although I'm in a physics group, I rub elbows with people on the analysis and neuroscience side. I think it's important for people who are developing to understand how neuroscientists will want to use them. Cross society outreach is something I am keen to do as part of becoming chair of the ISMRM's annual meeting program committee (AMPC) in about six months.

MRMH: How did you first become involved with ISMRM and what led you to become this year's education chair?

Karla Miller and her husband, Stephen Smith, take in the scene on a trip to Slovenia.

Karla: I first attended the ISMRM in Philadelphia (1999) and I have attended every ISMRM since. One of the first official roles I held was to serve on the AMPC. The AMPC is the hardest working, but also the most exciting, committee to be a part of. Now for this year's ISMRM, I am coordinating the education for Hawaii, and then at the Paris meeting in 2018 I'll be chairing the entire program. I'm incredibly grateful to Dan Sodickson for appointing me, although as the huge task ahead really hits me, I might save my thanks until the meeting is a wrap!

MRMH: You've given many educational seminars. What is it about MRI education that you like?

Karla: I absolutely love teaching. Beyond it being immensely satisfying to help people grasp difficult concepts, I think it's a good experience for the lecturer to think hard about the material. It's an interesting challenge, can I do a better job of teaching this to other people than it was taught to me?

Members of the Magnetic Resonance Systems Research Lab at Stanford University. Left to Right: Bill Overall, Brian Hargreaves, Karla Miller, Krishna Nayak, Julie DiCarlo, Bob Schaeffer.

MRMH: Your work is multifaceted, can you explain your primary research themes and how those came to be?

Karla: My training was very much in pulse sequences and image reconstruction. And so I still have a big chunk of my group working in that area. In the past few years, I've become interested in the idea that we can improve our acquisitions and reconstruction by taking a lead from how people analyze their data. We tend to think of this as a linear process – you try to get the best data you can and then you analyze it. But there are tricks that we can learn based on how people analyze the data that would enable us to improve the acquisition and reconstruction itself.

MRMH: In the exploration of better, faster methods, do you find yourself going outside the lab and initiating collaborations, or do you work with a core group?

Karla: To be honest, the most useful resource that I have in picking up on interesting ideas in the analysis world is that I happen to be married to the chief author of the FSL software toolkit [laughs]. As it turns out, he knows a bit about analysis! And we talk about science a lot at home. Whether that's cool or pathetic is a matter of debate.

MRMH: I would imagine he would be useful! You also study biophysical modeling and *ex vivo* imaging of tissue microstructure. Can you tell us about that?

Karla: We're acquiring microscopy data so we can close the loop between what is the biophysical model, what is the MRI data, and what is the actual measurable microstructure. The key aspect of our experiments are that we have all three things –MRI and microscopy in the same tissue samples, and a proposed model linking them. By actually having a measurement of the underlying microstructure, it guarantees is if you've got your model wrong, you are the absolute first person who is going to know. Not just, "can I take a biophysical model and show that it kind of matches the data", but "can I actually take something that I know reflects the underlying microstructure, make a prediction through some biophysical model, then say - YES - that is exactly the MRI signal that I measured". And it's a really hard thing to do.

MRMH: That sounds like a mission statement!

Karla: Putting this process to work, we've been looking at diffusion based estimates of fiber dispersion. We use microscopy techniques to essentially ask what aspects of the microstructure you need to incorporate to accurately predict what the diffusion signal looks like. It's a project that has a true palpable output, and interestingly it's created a signature that we hadn't expected

to find. We've now demonstrated that this particular effect also exists in the Biobank data - so it's a real effect, which is potentially a signature of something biologically interesting. More importantly, we've managed to have a first go at what it might look like to actually close the loop of biophysical modeling, microscopy, and MRI acquisition.

MRMH: I really like that turn of phrase, closing the loop. And since you mentioned the UK Biobank, I've given myself permission to bombard you with Biobank questions! To start, when did you first become involved?

Karla: What I'm actually doing right now as you're asking me this question is looking in my emails to see when I had my first Biobank email logged. 2008! Email from Paul Mathews, basically asking if we would be interested in getting involved in the Biobank. It's quite a project – scanning 100,000 subjects. And although there is quite a long author list on the paper that we published this year, that doesn't even begin to cover the number of academics involved, let alone the enormous staff that is entirely dedicated to the project. As one colleague said – it's a behemoth. In a good way.

MRMH: What do you think will change from having 10,000 scans to 100,000 scans?

Karla: One of the most exciting aspects of Biobank is that it's an entirely prospective study: it has no particular disease focus, but is playing the numbers. Most of the participants in this huge cohort have yet to show symptoms of major disease, but we'll be able to follow their health records as that changes. So, for example, we expect 2000 new diagnoses of Alzheimer's and 50 new diagnoses of ALS over the next five years from participants who were pre-symptomatic at the time of imaging. The value in Alzheimer's is obvious, but for rare diseases like ALS, that is a needle in a haystack. You just can't find those subjects otherwise. It certainly might provide you with markers for tracking response to therapy or disease progression.

MRMH: What is your opinion on how this data set will be used in the long term?

Karla: There is a lot to be said for exploratory analyses, but one of the big concerns is – how do you control for the fact that there are going to be lots of people asking lots of questions in the same dataset? We suddenly have a new kind of multiple comparisons problem. So, do we ask people to register hypotheses? Do we ask people to do certain types of test-retest? The imaging community has not so far been one to come down heavy handed on this kind of issue in the same way as genetics, for example.

MRMH: It sounds like the translational aspect of this research might become even more important now, such as borrowing techniques from other fields that have already been established and validated for big data sets.

Karla: It's partly techniques and it's partly culture. The same thing with open science – I know it's the right thing to do, but there is part of me that thinks, "Ahh!, it's going to be yet another thing I have to adhere to." But once we have a culture of doing it, everybody looks back and says, "What were we thinking?"

MRMH: A more general question, what brought you to the academic life? Did you have any major influences that led you down this path?

Karla: I got very interested in the brain when I was a kid. My mother had to have pretty drastic brain surgery when I was about 12 or 13. It really struck me; the idea that it might fundamentally change who she was. When I went to university, I started out as a psychology major. I was taking a cognitive psychology class in maybe 1995 when I saw functional MRI in a textbook, totally state-of-the-art . I was so impressed with what it had to offer compared to current methods for studying cognition. I also thought maybe the way I could have an impact was to develop the technology and move towards the engineering side. And so it's kind of nice for me now that I've done the engineering side in anger for about 10 years, and I'm able to shift towards getting back to neuroscience. And for me that's incredibly rewarding.

MRMH: It's like you're closing your own personal loop.

Karla: There's a theme there, isn't there?

MRMH: Now for some words of wisdom. What things did you learn along the way that you feel would be important for people who are just starting out?

Karla: I have to be profound on short notice! Well, going into science with a great deal of passion, and a great love of what you're doing is absolutely critical. Particu-

Karla Miller with former Ph.D. advisor John Pauly at Oxford University.

> *We're acquiring microscopy data so we can close the loop between what is the biophysical model, what is the MRI data, and what is the actual measurable microstructure.*
>
> – Karla Miller

Karla Miller in Tibet, demonstrating her superior jumping skills.

> *Being an expert is the way you earn the opportunity to be an inexpert, that is the fun bit.*
>
> –Karla Miller

Karla Miller adorned with a student's research.

larly if you want to stay in academia, because let's face it, academia is a tough world to get by in. One of the things I did sort of instinctively early on was to look towards people who were a year or two ahead of me, doing the kind of science I wanted to do. If I have to name names, Brian Hargreaves and Bill Overall. They were my role models. I tried to see what it was that they were doing at my stage to get where they were. That sounds simplistic, but honestly, that was what I did. And it's good advice.

MRMH: It has come up repeatedly that you frequently go outside your comfort zone. That's sometimes a scary thing to do. What drives you to change?

Karla: You know how I would sum this up… For me – and I know this is not true for everyone – being an expert is boring. To some degree, the fact that I'm the one "blah blah'ing" in this interview the whole time, from my perspective, it's flattering but not stimulating. It would be far more fascinating for me to be asking you about what you're doing and learning about what you're doing. Being an expert is, for me, it's the way you earn the opportunity to be an inexpert, that is the fun bit. That said, I wouldn't encourage people to just jump from one thing to the next willy nilly, because you'll never become an expert in anything, and that's also not good. You have nothing then to leverage. So you have some safe stuff, and some risky stuff, and you're hopefully pushing your personal envelope the whole time. It's kind of about finding the right balance. ■

ISMRM Challenge on **RF pulse design**

For me it was a way to assess my own skill in RF pulse design.

–Mihir Pendse

INTERVIEWS BY **WILL GRISSOM**

The ISMRM Challenge (http://challenge.ismrm.org) is an open competition series that seeks solutions to critical problems in MRI. As described by organizers in a recent publication, the 2015 Challenge focused on radiofrequency (RF) pulse design, with two specific sub-problems. The first was the design of shorter slice-selective parallel transmission (pTx) pulses for ultra-high field MRI, which are necessary for multislice acquisitions with uniform sensitivity and contrast. Before the Challenge, the best slice-selective pTx pulses required users to sacrifice resolution in the slice dimension as well as spectral bandwidth, in order to gain uniform contrast and signal. The Challenge sought to overcome that tradeoff by encouraging contestants to design the shortest possible slice-selective pTx pulses that excited sharp slices with uniform flip angles in-plane. The second problem was the design of shorter multiband refocusing pulses which are required for spin echo simultaneous multislice (SMS) imaging. Before the Challenge, the maximum achievable multiband factor for important spin echo SMS neuroimaging scans was limited by the high SAR of their refocusing pulses, which must simultaneously refocus a large number of slices. The Challenge sought to overcome that problem by encouraging contestants to design the shortest possible multiband refocusing pulses, subject to peak power and SAR constraints.

The 2015 Challenge began in November 2015, and ended just before the 2016 Annual ISMRM Meeting. A total of 13 teams participated from 10 countries. Team StanfordUHF won the pTx sub-challenge with a new approach to spokes pulse design that yielded 10.6 times shorter pulses than conventional methods. Team rfcontrol won the SMS sub-challenge with a new multiband pulse design algorithm that produced 5.1 times shorter pulses than conventional methods. After the competition ended, Challenge organizer Will Grissom interviewed both of the winning teams about their experience with the Challenge and their winning approaches.

Mihir Pendse (left), of pTx winning team StanfordUHF, and Christoph Aigner (right), of SMS winning team rfcontrol, accepting their awards from ISMRM president Garry Gold at the 2016 Annual Meeting.

Grissom WA, Setsompop K, Hurley SA, Tsao J, Velikina JV, Samsonov AA. Advancing RF pulse design using an open-competition format: Report from the 2015 ISMRM challenge. *Magn Reson Med*. 2016. doi: 10.1002/mrm.26512
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26512/full

Brian Rutt (left) and Mihir Pendse.

Interview with Mihir Pendse of team *StanfordUHF*

Mihir Pendse won the pTx sub-challenge, competing under team name *StanfordUHF*. He is a Ph.D. student in Electrical Engineering at Stanford University who works on parallel transmit RF pulse design for ultra-high field MRI, and is supervised by Professor Brian Rutt.

Will: What motivated you to participate in the Challenge?

Mihir: I think this challenge was a good way to compare different pulse design ideas across institutions in a well-organized manner. For me it was a way to assess my own skill in RF pulse design.

Will: How hard was it to get started?

Mihir: It wasn't hard to get started as the problem description was defined very clearly by the organizers.

Will: Tell us about the design approach you devised, at a high level.

Mihir: The challenge required optimizing the slice profile (or SMS profile), the channel weightings and the spokes locations for in-slice homogeneity. I was able to design the single-slice torso pulses using a straightforward adaptation of my previous minimum-SAR spokes design method (IMPULSE),[1] but the brain SMS designs required me to develop a new approach in which I optimized the subpulse shape for each slice so that the summed power would be minimized, using an optimal control approach adapted from the method of Aigner et al.[2] After that I further adjusted the phase of each slice's subpulse to minimize the peak amplitude of the summed subpulses, and applied time-optimal variable-rate selective excitation (VERSE).[3,4]

Will: Did your approach evolve during the Challenge as you found ways to improve it, or did it stay fixed and you found improvements through manual adjustments?

Mihir: The approach evolved significantly during the course of the challenge especially for the pTx-SMS tasks as I tried to come up with ways to reduce the peak pulse power in a time-optimal manner. One of the ideas I implemented was to reduce the subpulse durations using minimum rather than linear phase pulses, and I found I was still able to keep the phase roll through the slice flat enough when I did that.

Will: What did you learn from the Challenge, at a high level?

Mihir: While I was fairly comfortable with pTx theory before the challenge, I learned a lot about other aspects of RF pulse design including the design of SMS pulses.

Will: If you were an organizer of the Challenge, what would you have done differently?

Mihir: While the challenge was well organized I think there were several limitations in the design specifications:

1. The design tasks were limited to the small tip regime which made the problem considerably simpler. I think the skills of the contestants would have really been tested with more demanding large-tip design tasks.
2. There was no B_0 inhomogeneity incorporated into the pulse design so the B_0 robustness of the pulses was not assessed. One of the limitations of the spokes trajectory is it is not very robust to B_0 inhomogeneity so I think my design may be different if off-resonance was a concern, even though the durations were relatively short. This concern is abated by the fact that most of my designs were very short, through my coronal SMS pulse was about 5 ms long, so B_0 considerations may have changed my solution.
3. SAR information was provided to the contestants only in the form of VOPs. If the SAR matrices were provided directly, that would provide more ability for the contestants to make better use of SAR headroom and perhaps achieve a better pulse.
4. There was no dwell time specification and some of the dwell times that I used were much shorter than what is practical on a scanner. Maybe a lower limit on the dwell time should have been specified.

Will: What's next? Did you come up with new ideas that you will further develop and publish, as a result of your participation in the Challenge?

Mihir: Yes, I am in the process of preparing a manuscript on my IMPULSE pTx design methods that I used and

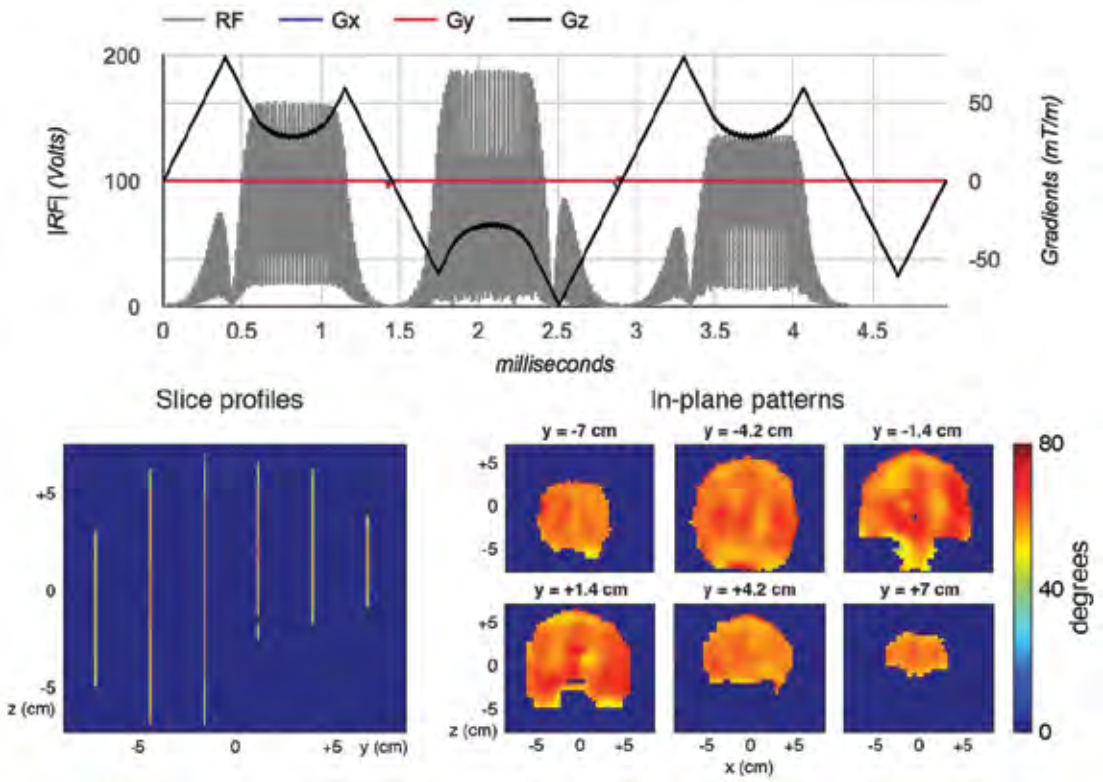


Figure 1. 5-slice, 16-channel pTx coronal brain excitation pulses designed by pTx sub-challenge winner StanfordUHF. (Top) 3-Spoke RF and gradient waveforms. (Bottom) Slice profiles of the winning pulses.

extended for the challenge. This first paper will be focused on conventional sequential multislice excitation and will probably be followed by a second paper describing the extension to SMS. I presented early accounts of IMPULSE with sequential and SMS excitations at the 2015 and 2016 ISMRM meetings, respectively.[1,5]

Will: What do you think was unique about your approach that gave you an edge over other contestants?

Mihir: I think the ability of my IMPULSE method to mitigate local SAR hotspots is superior to existing methods in the literature as it exploits optimization of both spokes locations and channel weightings even though this makes the problem non-convex. The ADMM algorithm used in IMPULSE is particularly efficient and even allows for optimization using SAR matrices directly without VOP compression, although that wasn't relevant for this challenge. I think formulating the pTx optimization as minimizing SAR subject to in-plane inhomogeneity constraints rather than minimizing inhomogeneity subject to absolute SAR constraints (as is more typical in the literature) is also advantageous, because instead of needing to specify the slice selective subpulse shape up front (in order to compute the absolute SAR constraint) the slice selective subpulse can be optimized later (after the RF shims and spokes locations have been found) in order to minimize total pulse duration subject to absolute hardware, SAR, and excitation accuracy constraints.

Interview with Armin Rund and Christoph Aigner of team *rfcontrol*

Team rfcontrol won the SMS sub-challenge, and comprises four team members. Armin Rund is a postdoc in applied mathematics working on optimal control of partial differential equations and multiphysics models. He is supervised by team member and Professor Karl Kunisch at the University of Graz, Austria. Team member Christoph Aigner is a Ph.D. student at the Institute of Medical Engineering working on RF pulse design and its applications in MRI. He is supervised by team member and Professor Rudolf Stollberger at the Graz University of Technology, Austria.

Will: What motivated you to participate in the Challenge?

Christoph: Our main motivation was the chance to put our optimal control methods in competition with other approaches, and to test our algorithms on accepted problems.

Will: How hard was it to get started?

Armin: The phase I example code showed that we needed to do a lot. We needed to develop new algorithms; in particular we had to develop a new algorithm for time-optimal control[6] multiband pulse design to obtain the shortest possible pulses, and we needed a global optimization scheme to overcome the non-convexity of the problems. We had done previous work on time-op-

> *The brain SMS designs required me to develop a new approach in which I optimized the subpulse shape for each slice.*
>
> –Mihir Pendse

Armin Rund and Christoph Aigner.

> *Our main motivation was the chance to put our optimal control methods in competition with other approaches.*
>
> –Christoph Aigner

timal control,[7] which helped us get started. We also had to develop techniques to incorporate the $l\infty$-norm constraints that were enforced in the challenge, whereas in our previous work we had only used quadratic regularization.[2]

Will: Tell us about the design approach you devised, at a high level.

Armin: We came up with a new approach that was built using our existing building-block optimization codes that implement semi-smooth Newton and quasi-Newton methods. As mentioned, we implemented a time-optimal control design, along with a new strategy for globalization based on an auxiliary optimization problem. We implemented $l\infty$-norm constraints on refocusing efficiency error, RF amplitude, and the gradient amplitude and slew rate. We also found that using complex RF modulation did not significantly reduce our pulse durations, so all our designs were real-valued.

Will: Did your approach evolve during the Challenge as you found ways to improve it, or did it stay fixed and you found improvements through manual adjustments?

Christoph: We recognized early on that we should use a time-optimal control approach, but it evolved quite a lot, particularly in phase I as we tested different sub-algorithms. Of course we also made a lot of adjustments to the algorithm parameters along the way. We had to put our code on a diet for phase II, by optimizing and parallelizing our code to cope with the larger number of design problems in phase II. The overall algorithm is structured so that the longer you let it run, the shorter the pulse gets. Early in the challenge we let it run for weeks; by the end of phase II we could get the same answer in a day using our optimized codes.

Will: What did you learn from the Challenge, at a high level?

Armin: Most importantly, we learned interdisciplinary collaboration can lead to ground-breaking research. We successfully combined my basic research in applied math with the challenging application in biomedical engineering that Christoph is working on.

Will: If you were an organizer of the Challenge, what would you have done differently?

Christoph: It would have been nice to have a dedicated scientific or poster session during the ISMRM meeting in Singapore, to give contestants a forum to present and share their ideas and approaches. The whole society could benefit from such an event to connect participants and exchange ideas.

Will: What's next? Did you come up with new ideas that you will further develop and publish, as a result of your participation in the Challenge?

Christoph: Our next step is to publish a paper on our constrained and globalized time-optimal control method, and to present the new techniques we developed for the challenge such as the globalization steps. We may start new collaborations and address more complex questions such as designing more robust inversion pulses or use more complete MR equations such as Bloch-McConnell. We would also like to try initializing our algorithm with existing low-peak power complex-valued solutions.

Will: What do you think was unique about your approach that gave you an edge over other contestants?

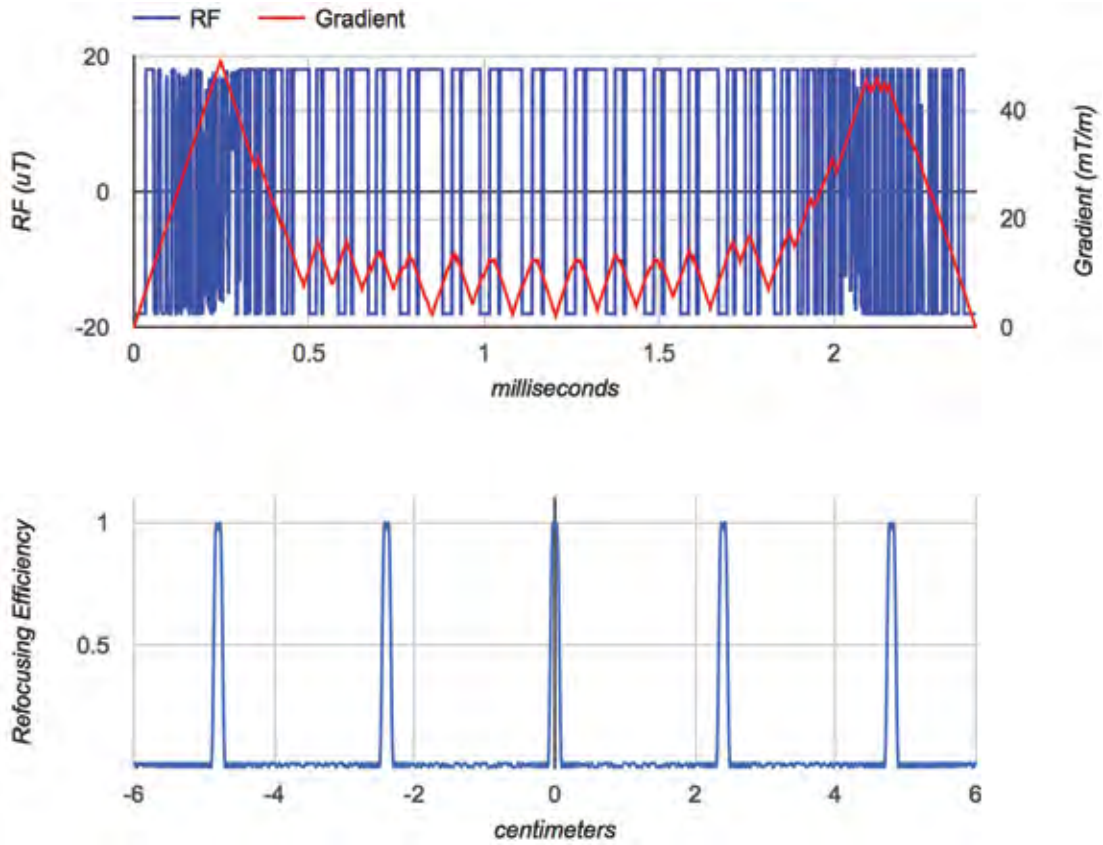
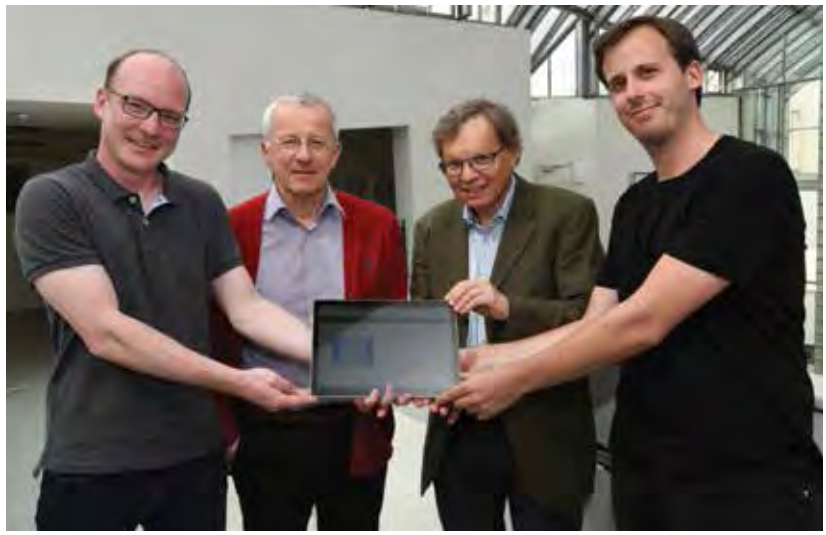


Figure 2. 5-slice SMS refocusing pulse designed by SMS sub-challenge winner rfcontrol. (Top) RF and gradient waveforms. (Bottom) Slice profiles produced by the waveforms.

The whole society could benefit from such an event to connect participants and exchange ideas.

–Christoph Aigner

Armin: The detailed modeling of the problem set as constrained optimal control problem and its accurate solution using iterative mathematical optimization techniques allowed us to reduce the pulse duration maximally by fully exploiting the constraints. The new globalization techniques we developed also helped to improve our scores. ■



Left to right: Armin Rund, Karl Kunisch, Rudolf Stollberger, and Christoph Aigner, with a display of their winning SMS pulses.

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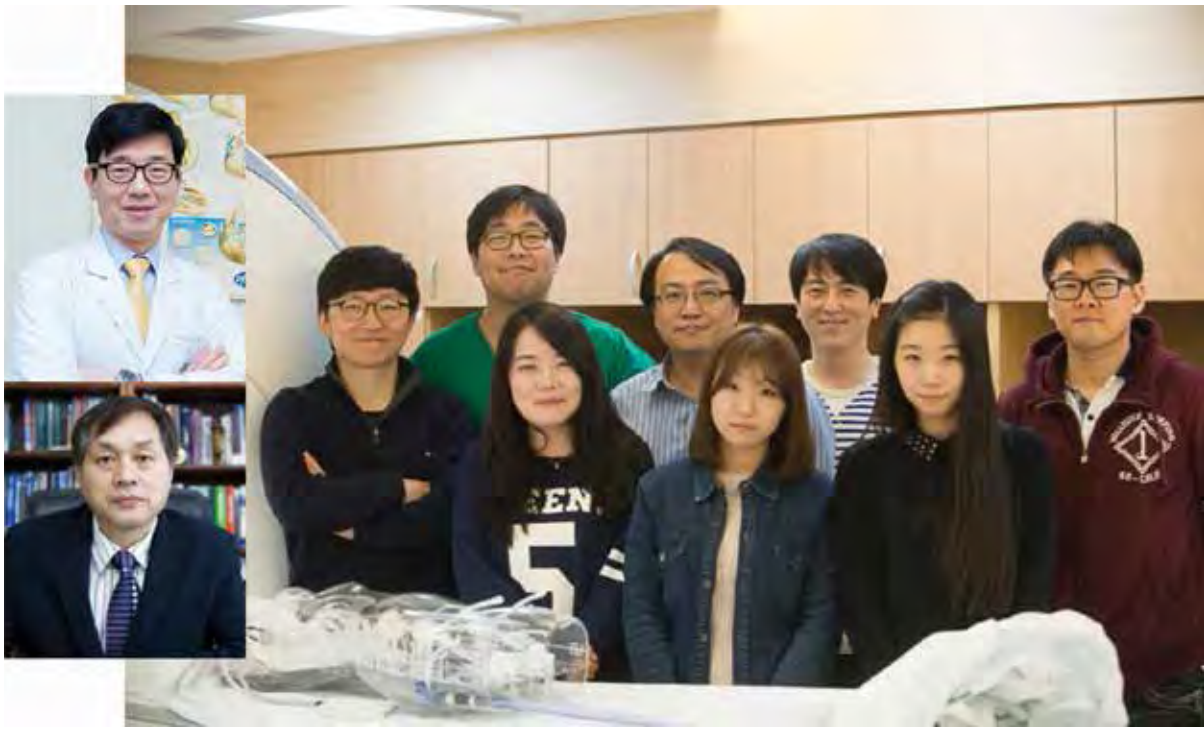
Improvements in velocity estimation for 4D flow MRI

INTERVIEW BY **MARIO MALAVÉ, SRI KOUNDINYAN, DAVID ZENG** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR MAY

Hojin Ha is currently a postdoctoral researcher at Linköping University in Sweden, working on developing 4D phase-contrast MRI (PC-MRI) techniques. His paper entitled "Multi-VENC Acquisition of Four-Dimensional Phase-Contrast MRI to Improve Precision of Velocity Field Measurement" was selected as an Editor's pick for the month of May. The paper demonstrates a technique for improving the velocity signal of 4D PC-MRI, and the use of a 3D printed phantom for modeling the aortic valve. We caught up with Hojin to discuss his work and life in Sweden.

> *Demonstrating accuracy in patients was the most difficult part for us.*
>
> –Hojin Ha



The flow team. Insert: Young-Hak Kim (top), Sang-Joon Lee (bottom). Back row (left to right): Dong-Hyun Yang, Namkug Kim, Guk-Bae Kim, Hojin Ha. Front row (left to right): Ji-hoon Kweon, Eun-mi Yoon, Ji-hyun Ko, Dan-bi Song.

MRMH: Can you tell us a little bit about your background?

Hojin: I studied fluid dynamics during my graduate studies in Mechanical Engineering at Pohang University in Korea. At the end of my Ph.D., I was fascinated with 4D PC-MRI that can measure temporal variation of 3D velocity field noninvasively, so I worked with Dr. Sang Joon Lee and colleagues in Asan medical center (Korea).

MRMH: So this work started as an extracurricular activity?

Hojin: Yes, it was an extra paper for me, and it was the start of my career in the field of PC-MRI. And now I have moved to Sweden for a postdoc to continue working on 4D PC-MRI.

MRMH: Can you give a brief summary of your paper?

Hojin: When I compared the velocity field from 4D PC-MRI with the conventional velocimetry (i.e. particle

Ha H, Kim GB, Kweon J, Kim Y-H, Kim N, Yang DH, Lee SJ. Multi-VENC acquisition of four-dimensional phase-contrast MRI to improve precision of velocity field measurement. *Magn Reson Med*. 2016;75:1909–1919. doi: 10.1002/mrm.25715
http://onlinelibrary.wiley.com/doi/10.1002/mrm.25715/full

image velocimetry), I realized that 4D PC-MRI showed good agreement with PIV for a high velocity flow region. However, it did not provide good results for low velocity flow regions such as recirculation flow in post-stenosis, mostly due to the lack of velocity-to-noise (VNR) ratio. Since then, we aimed to improve precision of 4D PC-MRI technique by using multiple Velocity ENCoding (VENC) for better analysis of flow structures.

The concept of the study is simple. Lower VENC usually resulted in better VNR, however, it may also result in phase aliasing. Therefore, the velocity field obtained for large VENC was combined with that from small VENC, unless velocity data were lost by phase aliasing or phase dispersion. We investigated noise levels of the combined velocity fields by increasing the overlapping number of VENC parameters, and the result showed that VNR at stenosis flow could be increased by two to six times.

MRMH: What are some alternative methods for estimating velocity fields?

Hojin: In the clinic, we have echocardiography and 2D PC-MRI to measure velocity fields. It also has some disadvantages, such as not being able to obtain the whole 3D field of view. Various hemodynamic parameters, such as energy and pressure loss of blood flow and the workload of the heart represent the complex interaction of the flow velocity field and its spatial gradient, which can only be analyzed with 4D PC-MRI. 4D flow research will bring new diagnostic methods based on fluid-dynamics, and that is why 4D PC-MRI is important to us.

MRMH: What are the next steps for improving 4D flow and velocity estimation for MRI?

Hojin: First, the scan time needs to be reduced. When we use conventional Cartesian sequences for measuring cardiac flow it takes 30-40 minutes, which is too long for patients. Major vendors and many researchers are trying to reduce the scan time by using various acceleration techniques.

MRMH: What was the biggest challenge and practical consideration you had to deal with when conducting your project?

Hojin: Developing new reconstruction applications is relatively easy in phantoms, but to employ this in clinical routines is difficult. Demonstrating accuracy in patients was the most difficult part for us, and follow-up studies are needed to show the relationships, accuracy and performance of this kind of technique.

MRMH: Can you tell us about the phantom you used?

Hojin: The model was a canonical form of stenosis, which has been previously studied and models the aortic flow. If you want to investigate the effect of aortic valve types on the aortic flow, you can fabricate various patient-specific phantoms using a 3D printer and perform a test scan.

The phantom, known informally as "Eve," is constructed to mimic a human's circulatory system.

MRMH: What sequence were you using?

Hojin: We used a 4D-Flow product sequence from Siemens, with a second order correction to correct for background noise. The present study was just a proof of concept. When I went to ISMRM, I got a lot of questions about how to optimize the VENCs, so we are currently working on optimization for each scan and patient.

MRMH: Have you tried a different method for combining the data to improve the VNR, such as Kalman filtering?

Hojin: We haven't considered Kalman filtering. We have been asked about Gaussian averaging, and we would like to look into that. When deploying this sequence for patients, I do believe that averaging techniques will be needed for higher VENCs to minimize motion artifacts. Currently, in the published paper the motion artifacts were not severe.

MRMH: What are you working on in Sweden?

Hojin: I work with Tino Ebbers and Peter Deverfeldt in Linköping, Sweden, on 4D PC-MRI, developing a sequence and reconstruction methods to measure turbulence flow in the aorta and turbulence dissipation of energy in patients.

MRMH: How does Sweden compare to Korea in terms of everyday life and the research climate?

Hojin: One of the main differences between Korea and Sweden is the work schedule. They have different working hours and I have more free time for creative thinking.

Mario: Any parting thoughts to the readers?

Hojin: The groundbreaking work in my field, such as 4D flow developmental acceleration techniques, was published in MRM, so I was honored to present my work in the same journal and to participate in this interview. ■

> *I do believe that averaging techniques will be needed for higher VENCs to minimize motion artifacts.*
>
> –Hojin Ha

Deciphering the diffusion signal in upper abdominal organs

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR MAY

We sat down with Dr. Sebastiano Barbieri and Dr. Harriet Thoeny from Inselspital University Hospital in Bern, I to discuss their paper, "Impact of the Calculation Algorithm on Biexponential Fitting of Diffusion-Weighted MRI in Upper Abdominal Organs." Sebastiano, who completed his Ph.D. at Jacobs University and the Fraunhofer Institute for Medical Image Computing in Germany, has a background in math and image processing. Harriet is a radiologist dedicated to urogenital and head and neck radiology with main research interest in functional MRI, and special focus on diffusion-weighted MRI. In their paper, they assess six different algorithms for fitting a biexponential IntraVoxel Incoherent Motion (IVIM) model.

> *Low variability is really important if we want to use IVIM for treatment monitoring.*
>
> – Harriet Thoeny

MRMH: Can you tell us a little bit about how you got here? What was your main motivation as you began this endeavor?

Harriet: I am a clinical radiologist. I did a lot of MR in my daily work for many years, but I started research because there are several questions that are not met by morphological imaging. So, I went to Belgium in 2003 where I started doing diffusion-weighted imaging (DWI) outside the brain with focus on treatment monitoring of a vascular targeting agent in an animal model. I also studied DWI of the kidneys in patients with diffuse parenchymal disease compared to healthy kidneys. We were able to detect changes that preceded morphological changes. I continued applying diffusion-weighted MRI to detect lymph node metastases in normal-sized pelvic lymph nodes for the differentiation of recurrent or residual disease from post-treatment changes in patients with head and neck malignancies, as well as prostate cancer detection and the evaluation of various pathologies in native and transplanted kidneys. Then, luckily, Sebastiano joined me two years ago for this project.

Sebastiano: I think that the processing of medical images is a very interesting challenge. Before I was working mainly on DWI in the brain, then I joined Harriet and started looking at DWI in the pelvis and abdomen. Here in Bern, I started reading about IVIM (intravoxel incoherent motion), and it seemed that basically every paper used different algorithms and processing techniques, so the idea came up to compare how similar the results are.

MRMH: Let's talk about IVIM. Why is the model biexponential and what parameters does it include?

Sebastiano: The IVIM model tries to explain the diffusion-sensitized MRI signal by using two terms. One is the classic diffusion-related term and the other is related to perfusion effects, which may include both bulk perfusion at the micro-capillary level, as well as fluid movement in predefined structures, like the tubules of the kidneys for example. Both terms are modeled as exponential functions and they are summed up and weighted by a term called the perfusion fraction.

Harriet: In one of the most interesting studies we had patients that had calculi (stones) in the ureter and consequent obstruction of the kidneys. When we looked only at the apparent diffusion coefficient (ADC) there was no significant difference between the obstructed and the contralateral normal kidney. We thought, 'How is this possible?' We found out that the diffusion went up, probably due to edema, and the perfusion fraction went down. Both parameters changed but in the opposite direction so that they canceled each other out! That was why the simple, monoexponential ADC did not show any change. Since we could separate perfusion and diffusion in IVIM, we were able to use it in a clinical context.

MRMH: Are there any applications where the simple monoexponential model is sufficient?

Harriet: Yes, for example we just did a study on prostate imaging and did not find that using a more complicated model was helpful.

MRMH: In the paper you compare six different algorithms to fit the IVIM model. Tell us a little bit about the winner.

Sebastiano: The winner was an approach based on Bayesian Probability that models the probability density function of the parameters we want to estimate as the product of the probability for the data and the joint prior probability for the parameters. The prior allows the

Barbieri S, Donati OF, Froehlich JM, Thoeny HC. Impact of the calculation algorithm on biexponential fitting of diffusion-weighted MRI in upper abdominal organs. *Magn Reson Med*. 2016;75:2175–2184. doi: 10.1002/mrm.25765
http://onlinelibrary.wiley.com/doi/10.1002/mrm.25765/full

user to incorporate prior knowledge into the model. On one hand this is a strength of the Bayesian probability model, but it is certainly a source of controversy.

MRMH: Are you satisfied with the Bayesian Probability approach or do you want to further refine it?

Sebastiano: We certainly have further ideas. It is accurate, but it is also very slow! We would like to improve its speed, and it may make sense to use a fast initial algorithm to get a rough initial estimate of the parameters then use this estimate to model the prior for the Bayesian algorithm.

MRMH: How slow is slow? Does the speed limit its use clinically?

Sebastiano: Possibly. To process a whole data set takes a few hours, actually. There are some parameters that one could tune to make it faster, but possibly at the cost of some accuracy.

Harriet: Actually, when we use DWI clinically we usually apply the monoexponential fit calculated by the scanner. In the clinical routine we don't often use quantitative image analysis but qualitative images to see 'is there a lesion… yes, no? Is it probably malignant or not? Is it an abscess or a solid lesion, etc.'

MRMH: Were you surprised that each of the algorithms yielded significantly different results?

Sebastiano: From a mathematical point of view, some variation was expected, but I was actually quite surprised by the magnitude of these differences. The results of some of these different algorithms were barely comparable to one another.

Harriet: I was a little bit more troubled than surprised because there is so much literature. Everybody writes about it and everybody reads about it, but how can we compare? The problem is not only standardization of the technique and image parameters but also how you perform image analysis thereafter. It is also important that this is mentioned in the paper and that the reviewers ask, 'What algorithm did you really use for image analysis?'

MRMH: What level of variability is acceptable for clinical use?

Harriet: Low variability is really important if we want to use IVIM for treatment monitoring. Let's say we have a patient undergoing treatment and a change in our diffusion or perfusion fraction is about 10%. How can I say whether this value is clinically relevant or not? It is important that the variability is as low as possible or at least that we know the variability in order to correctly interpret our findings or compare them to the literature.

Sebastiano: Another point is that when one is conducting a clinical study and your parameters change less across subjects, you will need a smaller number of patients to actually detect a significant difference.

MRMH: But don't you expect inter-subject variability even among healthy subjects?

Sebastiano Barbieri and Harriet Thoeny testing their algorithms.

Harriet: We did a study once on transplanted kidneys, and we had patients with normal renal function to look at inter-individual and intra-individual variability. The perfusion fraction had high variability, but it was still within a reasonable range. A healthy person should have similar parameters, but there could be an age dependence.

MRMH: How much variability did you see between the upper abdominal organs?

Sebastiano: We observed higher variability in the liver, maybe due to cardiac artifacts.

Harriet: Luckily the kidney was quite good, and that is one of our main organs of interest.

MRMH: The kidney is considered an upper abdominal organ?

Harriet: Yes, upper abdominal includes the liver, spleen, kidneys, adrenals, and pancreas. The pelvis includes the bladder, the prostate, the uterus, ovaries, testicles, and penis. The upper abdominal organs are the same for men and women, the lower are not.

MRMH: One more question. You use simulated data to assess the algorithms' accuracy. Is there a gold standard to look at *in vivo* perfusion?

Sebastiano: Some studies are trying to correlate arterial spin labeling or dynamic contrast enhanced MRI with IVIM parameters. They may correlate to some extent, but they cannot be used as a gold standard for IVIM. It may be possible to construct some fancy phantoms.

Harriet: Actually Tom Chenevert is quite famous for his phantoms for diffusion; maybe he could make one for IVIM too? ■

> *From a mathematical point of view, some variation was expected, but I was actually quite surprised by the magnitude of these differences.*
>
> –Sebastiano Barbieri

paraCEST pHrequency: A new paradigm for robustness in pH imaging

INTERVIEW BY **BO ZHU** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR JUNE

For the first Editor's pick of June, Dr. Yunkou Wu and Prof. Dean Sherry from the University of Texas Southwestern Medical Center have developed a novel paraCEST agent seeking to push the envelope of robust pH quantification in-vivo. We spoke with them over Skype to discuss this new technique and its implications for the CEST field, as well as the broader MR community.

> *Our agent allows us to simply follow the frequency of the CEST peak as a function of pH, because the pH calibration curve is independent of the solution system.*
>
> –Yunkou Wu

Yunkou Wu

Dean Sherry

MRMH: What is your background and how did you get involved with MRI research?

Yunkou: I obtained my Ph.D. in Chemistry, with a background in organic synthesis. I started to do research on developing MR contrast agents as a post-doc, but things really picked up when I moved to Dr. Dean Sherry's group at UT Southwestern Medical Center, where I became more familiar with operating MRI scanners and understanding more fundamental MR physics.

Dean: My scientific interests in this area go way back – I was likely doing NMR before either of you were born! I've had a long history of working on lanthanides, studying everything from ligand synthesis, to water coordination numbers, to NMR Dispersion analyses of gadolinium relaxation, to measuring water exchange rates. We had used gadolinium as a "relaxation reagent" to study protein structure before the discovery of MRI by Paul Lauterbur so we immediately recognized the potential of gadolinium as an imaging contrast agent. Paul's discovery really jump-started my interest in the field of MR contrast agent development.

MRMH: What were the motivations for this work, and

Wu Y, Zhang S, Soesbe TC, Yu J, Vinogradov E, Lenkinski RE, Sherry AD . pH imaging of mouse kidneys *in vivo* using a frequency-dependent paraCEST agent. *Magn Reson Med.* 2016;75:2432–2441. doi: 10.1002/mrm.25844

http://onlinelibrary.wiley.com/doi/10.1002/mrm.25844/full

Dean Sherry and Yunkou Wu relaxing with colleagues.

could you give a brief summary of the paper?

Yunkou: We are interested in pH imaging because dysregulation of pH is associated with many diseases, like cancer or renal tubular acidosis, so developing a simple way to image pH *in vivo* is a big component of our MR imaging research.

Dean: When Yunkou came to my lab, he was clever enough to realize that instead of altering the intensity of the paraCEST signal with changes in pH, you might be able to alter the frequency of the signal instead. After he developed this current agent, we then began thinking about the best way to detect it *in vivo* to get a direct readout of pH based upon frequency rather than intensity. That's the fundamental idea behind this latest paper in *Magnetic Resonance in Medicine*.

MRMH: What are some foreseeable advantages of this technique in the context of other pH-sensitive CEST approaches?

Dean: The frequency of many paraCEST signals can be quite large – in this case, the paraCEST signal is around 50 ppm downfield of water. DiaCEST agents, on the other hand, have exchange peaks typically no more than ~5-6 ppm from water so suffer from interference from hundreds of other endogenously exchanging species. This makes it more difficult to separate the CEST signal you wish to detect from all the others.

Yunkou: Also, the conventional way to obtain a pH value from CEST agents is by a ratiometric analysis, where the agents have two chemically distinct exchanging protons exchanging with bulk water at two different frequencies, and you make a ratiometric plot of the pH based on the ratio of CEST intensities at these two frequencies. The problem is that this ends up being very sensitive to solvent or tissue composition, which you would have to correct for with prior knowledge which isn't always available. Our agent allows us to simply follow the frequency of the CEST peak as a function of pH, which we have observed to be a more stable method, because the pH calibration curve is independent of the solution system.

MRMH: How flexible would you consider paraCEST to be as a chemical platform for sensing new biological phenomena?

Dean: The nice thing about paraCEST systems is that they are paramagnetic and sensitive to many physiological and biochemical phenomena such as temperature, oxygen levels, pH, endogenous metal ions, specific metabolites, etc. There are different lanthanides you can use as well, so imagine giving a cocktail of molecules, one reading out pH, one reading out tissue redox, and one reading out calcium ion concentration with each activated at a different, specific frequency. That's the direction we'd like to take.

MRMH: And for this paper, why did you choose to image kidneys?

Dean: One of the difficulties with imaging pH *in vivo* is that there isn't a gold standard. You can use a tumor model and get a pH readout but the question always arises, does this readout truly reflect the correct tissue pH? At least in well-functioning kidney, the pH gradient has been established by others using invasive microelectrodes to map out the pH gradient across the kidney. So if we can do this non-invasively using a paraCEST agent, we would be able to compare our results with the established gold-standard microelectrode measurement.

MRMH: Where do you see this research going into the future?

Yunkou: We would like to use this sensor for tumor imaging, as pH is associated with various aspects of tumor physiology. However, the concentration of CEST agents like ours accumulated in tumors is too low to be detected reliably. We are currently working on ways to improve the sensitivity of these agents, for instance by introducing them into polymers and nanoparticle systems.

Dean: Also, we're gradually learning how to make these agents less sensitive to the presence of hundreds of other exchanging species in tissues, which would dramatically improve sensitivity, perhaps up to 10-fold. That would allow us to keep the agent concentration low and well within acceptable toxicity limitations. ■

> *Imagine giving a cocktail of molecules, one reading out pH, one reading out tissue redox, and one reading out calcium ion concentration with each activated at a different, specific frequency. That's the direction we'd like to take.*
>
> –Dean Sherry

MR fingerprinting: "Hands on" with the team that started it all

INTERVIEW BY **SUMEETH VIJAY JONATHAN** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR JUNE

Magnetic resonance fingerprinting (MRF) was all the rage at the annual ISMRM meeting in Singapore, culminating with the Young Investigator Award (YIA) given to Dan Ma for her work on MRF music. Eric Pierre's paper that we are highlighting in June provides the reconstruction framework that led to the YIA. The *Highlights* team interviewed Eric and senior author, Mark Griswold.

> *The conceptual way you can think about this paper, then, is that we reconstruct the low frequency components of our image first since we have slightly higher sampling in the center.*
>
> –Mark Griswold

MRMH: What is MR fingerprinting?

Mark: Back to the defense questions, I love it!

Eric: In short, MR fingerprinting or MRF is a very efficient parameter mapping technique. Each tissue type generates a signal evolution that is unique to it. This signal evolution acts like a temporal fingerprint. By comparing that fingerprint to a pre-computed database, MRF can then identify all the parameters of interest at once. That's what makes MRF so powerful: it is able to produce, for example, T_1, T_2, and off-resonance maps – all registered perfectly to each other – in a very efficient timeframe.

MRMH: What does a typical MRF pulse sequence and reconstruction look like?

Eric: That's a bit of a tricky question, because there are many ways to produce an MRF sequence. Conventionally, the sequence calls for pseudorandomly varying flip angles and TRs. The object is encoded at each TR, usually with a highly efficient and highly undersampled trajectory like a spiral or an EPI sequence. The key aspect is that you need the k-space coverage to change with each TR. This way, at a pixel level, the aliasing artifacts act like random noise with respect to time. This preserves the overall shape of the temporal fingerprint. What never ceases to amaze is that, while each reconstructed image usually looks like garbage, MRF can cut through all this noise and retrieve the right tissue fingerprint. It's just that powerful!

Mark: From a big picture perspective, we can use almost any sequence that you can dream of. It only has to have two requirements. First, we have to be able to separate different tissue types from one another based on their signal evolutions, meaning that they have to look different in time. Second, in order to make an image, we have to separate different spatial locations. So, any sequence that can meet those criteria – which is an infinite number of combinations – is one that is a potential MRF sequence.

Eric Pierre and Mark Griswold officially dressed.

MRMH: Can you give us a brief summary of your paper and its significance?

Eric: What the paper presents is a very broad, flexible scheme to reconstruct image series acquired with an MRF sequence with improved accuracy of the parameter maps. While conventional reconstruction techniques end up with a guess that is usually right, there may be errors, especially when we try to reduce the length of the acquisition. The reconstruction scheme uses a Projections Onto Convex Sets (POCS) method where we iteratively bounce between denoised image series, and image series that match the data. So, it becomes denoising, reincorporating the data, denoising, until you converge to a solution. The trick we added in our paper is a Gaussian filter that controls the effective resolution of the image series and reduces error as the method converges to a solution. This is what we show in the paper. We are still able to converge to acceptable

Pierre EY, Ma D, Chen Y, Badve C, Griswold MA. Multiscale reconstruction for MR fingerprinting. *Magn Reson Med*. 2016;75:2481–2492. doi: 10.1002/mrm.25776
http://onlinelibrary.wiley.com/doi/10.1002/mrm.25776/full

maps, even with a lot fewer time points than MRF conventionally calls for.

Mark: The errors that come from the noise are coming from spatial undersampling. The conceptual way you can think about this paper, then, is that we reconstruct the low frequency components of our image first since we have slightly higher sampling in the center. We then use that information to reduce the aliased energy at the other pixels. This is what makes the estimate better and converge to the right result.

MRMH: What are the limitations of MRF?

Mark: First, simply implementing a sequence that is fingerprinting capable, where the TR varies continuously, the flip angle, getting that coded up and stable is difficult. The second challenge is actually having a gold standard to compare to. The ISMRM NIST phantom is incredibly important to have because we have an infinite number of sequences to choose from – and each one of them can have different errors – and having an unbiased phantom that is validated by an institution is wildly important. Beyond that, while the dictionaries that we use for the database can be large, they are completely compressible. We have done a lot of work in that area. It can seem like a daunting reconstruction problem, but in reality, I think the code we put in the original Nature paper was way less than 50 lines. It's really not difficult to program up.

MRMH: What's next for MRF?

Eric: With respect to this paper, we are looking for ways to make the reconstruction process more efficient. As it is, the method can take hours, sometimes even days, to produce maps with this process, particularly for MRF sequences with high resolution and lengthy time series. That's the next obvious low hanging fruit for this technique. As far as fingerprinting as a whole, well, there are tons of different optimization problems to tackle, and it's a bit early to say how far it will take us. It's a bit like seeing the first flight of the Wright brothers and asking "so where are you going with this?" In particular, a hot topic for MRF right now is that while we know what a good dictionary looks like, we don't know how to automatically create a pulse sequence that would generate such a dictionary. Finding a method that can reverse engineer the dictionary creation process will be a big problem to solve.

Mark: People are starting to look at making sequences that are sensitive to different things. CEST, spectroscopy, diffusion, partial volume estimations, just diversifying what we can see. The next approach that I saw a lot of at ISMRM are people trying to optimize the sequence, which is difficult because it is a wildly non-linear and non-intuitive problem. Clinically, there is a ton of work happening in the lab. We're using this in the heart, brain, liver, prostate, breast.

MRMH: And on top of it, MRF can also sound beautiful.

"On stage" selfie at Eric Pierre's graduation with Mark Griswold and Jeffrey Duerk.

Eric: This ability to move away from conventional k-space trajectories gives you a degree of freedom. If you want a k-space that can generate music like Dan Ma showed, you can. It's extremely powerful.

Mark: As you can imagine, trajectories like the music-based trajectories are not as efficient as spirals. But, using the method that Eric published, Dan Ma showed that its efficiency per unit time is actually the same as the spiral-based one! So, just by applying this reconstruction method, we went from super efficient spirals – which sound horrible – to beautiful sounding music, and the impact on the results were basically nonexistent. That's kinda cool.

MRMH: Eric, can you tell us about your background?

Eric: I was very lucky to have Mark accept me as his Ph.D. student. After graduating in 2014, I moved to Australia to start a postdoc at the Florey Institute of Neuroscience. That's in "cold" Melbourne, so no surfing for me. I moved a little bit away from the reconstruction world and more into the realm of diffusion and acquisition. Adding more arrows to my quiver.

MRMH: Mark, you just chaired the annual ISMRM meeting. Can you tell us what the experience was like for you?

Mark: It's an amazing honor to be able to put together this meeting. We had a closing party with the staff on Friday night of the meeting, and I talked about the fact that this is my home society. I don't need to go anywhere else. I've been coming to the meeting since 1995. To be able to organize it, to provide that home for the next generation of people, it was just fantastic. We had so much fun in Singapore, I didn't feel like I did that much. My job was to manage the team that does all the stuff. The annual meeting program committee members are just some of the best minds in our field. The amount of work that goes into making this meeting happen is just immense and they did just a phenomenal job. If you remember, we changed the abstract format this year, which meant changing the review process, and generally how we assembled the entire meeting. The fact that they all stuck with this is just amazing. ■

> *What never ceases to amaze is that, while each reconstructed image usually looks like garbage, MRF can cut through all this noise and retrieve the right tissue fingerprint. It's just that powerful.*
>
> –Eric Pierre

One step closer to quantifying microstructure: Overcoming Gibbs ringing in diffusion MRI

INTERVIEW BY **SAMANTHA BY**

EDITOR'S PICK FOR JULY

One of the Editor's picks for the month of July is a paper entitled "Gibbs Ringing in Diffusion MRI." Recently, we talked with Drs. Jelle Veraart, Els Fieremans, and Dmitry Novikov to learn more about how they use regularization functions to mitigate artifacts induced by Gibbs ringing in diffusion MRI.

> *The number of papers in microstructure has doubled every 2.7 years for the past 15 years. Truly exponential!*
>
> –Dmitry Novikov

MRMH: Jelle, how did you get into MRI?

Jelle: I was working on my master's thesis on computer vision for industrial applications. While doing that, I met my Ph.D. supervisor, Jan Sijbers, who convinced me to go into MRI, where I started working on noise and biases in diffusion MRI.

MRMH: And why'd you come to New York?

Jelle: Well, I was hoping to leave the noise in the background and focus on the signal instead. [laughs]

MRMH: How about you, Els and Dmitry?

Els: I was always interested in medicine and mathematics, so I studied engineering and physics, where I got familiar with medical imaging. My interest in MRI was sparked when a sick family member required MR imaging. I got to visit an MRI facility and reading room, and was really impressed by the images of the inside of the brain. It was then that I became fascinated with MRI, so I decided to do a Ph.D. in diffusion MRI.

Dmitry: I was always fascinated by physics and did my Ph.D. in theoretical condensed matter physics at MIT, followed by postdocs at Princeton and Yale. It was through understanding the physics of transport of disordered systems that I got to realize that the problems in MRI are not that different from this wealth of understanding that has been accumulated in theoretical physics for over half a century, but in a different context. So I eventually switched fields, and am now a faculty member at NYU focusing on using diffusion to understand brain microstructure.

MRMH: Let's jump into some of the technical details of the paper. How does Gibbs ringing occur?

Jelle: Basically, a function can be written as a sum of waves with different frequencies. If you have sharp edges, like a sudden step from high to low intensities such as from CSF to the corpus callosum, you need high frequencies to describe this step. In MRI, however, because of scan time and resolution limits, we have to limit ourselves to low frequencies. Therefore, those steps cannot be well approximated, and the ringing occurs from those low frequency waves. That ringing creates over and undershoots in your signal. So, the problem is that pattern depends on the underlying signal, and in diffusion MRI, that signal depends on your b-value.

Jelle Veraart

Dmitry: And the direction.

MRMH: How does this bias your diffusion MRI?

Jelle: When your non diffusion-weighted signal is being underestimated and, at the same time, the associated diffusion weighted signal is being overestimated, such as in the corpus callosum, rather than a decay in signal, you see an uptake. This can lead to negative apparent diffusivities, negative apparent kurtosis values, and basically all of the parameters that you estimate from this

Veraart J, Fieremans E, Jelescu IO, Knoll F, Novikov DS. Gibbs ringing in diffusion MRI. *Magn Reson Med*. 2016;76:301–314. doi: 10.1002/mrm.25866
http://onlinelibrary.wiley.com/doi/10.1002/mrm.25866/full

Dmitry Novikov, Els Fieremans, and Jelle Veraart in New York City.

signal can be biased or just plain unphysical.

Dmitry: More generally, now that the field is working towards quantifying microstructure at a sub-voxel level, a lot of biophysical modeling is involved and any artifacts like Gibbs ringing, can bias any of the microstructural metrics. That was one of the main messages of our paper.

Els: To that end, we got really interested in getting rid of specific artifacts, because usually, the community uses smoothing to get rid of Gibbs ringing. However, we wanted to step away from that and have a more specific, targeted way of removing each specific artifact, including ringing, individually without losing anatomical detail.

MRMH: When did you decide smoothing just wasn't going to cut it and started investigating better ways to tackle this problem?

Jelle: The timeline of Gibbs ringing in diffusion MRI is actually very interesting. In 2002, there was one ISMRM abstract by Gareth Barker and coauthors, but there was no follow-up on that problem. In 2006, Cheng Guan Koay and coauthors started doing constrained fitting, realizing it was still a problem. In 2008, Tobias Block, who is also now at [New York University] NYU, came up with regularization to solve Gibbs ringing in MRI, so since we were so close to each other things started coming together with us. In the meantime, other groups have been working on this problem too. In the last year, there were three papers on Gibbs ringing in diffusion MRI: ours, Daniele Perrone and coauthors using TV regularization, and Elias Kellner and coauthors using an elegant idea of sub-voxel shifts. Three different approaches, but now we can start thinking of the best way to solve this problem.

Dmitry: Maybe the best solution isn't even out there yet, but I think it's really great that people are starting to pay attention to artifacts like this one. This attention to processing details is not accidental, but is rather commensurate with the exponential explosion of interest in diffusion microstructure. The number of papers in microstructure has doubled every 2.7 years for the past 15 years. Truly exponential!

MRMH: So in this paper, you tested a lot of regularization terms. What is the difference between total variation (TV) and total generalized variation (TGV)?

Jelle: In L1 regularization, you need some underlying model that sparsifies your image. With TV you assume your image can be modeled by a piecewise constant function. With TGV, it is a generalization of that, so you basically allow gradients in your image. It's a less patchy, more natural representation of the image.

MRMH: How did these regularization functions reduce Gibbs ringing artifacts in your images?

Jelle: What we see in Gibbs ringing are oscillations, so by forcing it to a piecewise linear function, we can suppress Gibbs. We also suppress other fluctuations, such as noise, but the downside is that we might remove anatomical detail if the wrong regularization parameter is chosen. A fine balance between what's noise, what's Gibbs and what's anatomy, has to be met. Compressed sensing has been using L1 regularization for a while now, but has never really answered the question of how we optimize the regularization parameter. We found that we have to tune the regularization parameter as a function of the noise level; which we recently also learned how to estimate based on random matrix theory methods.

Dmitry: That's also how we avoid over-regularization.

Jelle: It's funny ... I was trying to step away from the noise, but when I started looking at the signal, I was automatically pushed to the noise again! Understanding noise seems to be essential to understand signal.

MRMH: How long does the processing take for full brain coverage? Is this something you think could be implemented on the scanner for on the fly reconstruction?

Jelle: In the current implementation, it's CPU driven, so it would take about 45 minutes. With that said, I don't think this technique is necessarily the endpoint. Rather than taking it to the clinic now, I think we should step back, compare all of the methods, and decide which one needs to be optimized in terms of computational time.

Dmitry: Or come up with something even better! We need to first educate ourselves, then the research community, and then the clinical community.

Els: We are collaborating with the neuroradiologists to evaluate the effect of reducing artifacts and noise. Here at NYU we have a really good connection with clinicians, so we are trying to see how our work is relevant. ■

It's funny... I was trying to step away from the noise, but when I started looking at the signal, I was automatically pushed to the noise again! Understanding noise seems to be essential to understand signal.

–Jelle Veraart

Balanced SSFP-fMRI at 9.4T: BOLD-ly going where no one has gone before

INTERVIEW BY **MARK CHIEW**

EDITOR'S PICK FOR JULY

On the 24th of June, we sat down with Klaus Scheffler and Philipp Ehses to ask them a few questions about their recent MRM paper, "High-Resolution Mapping of Neuronal Activation with Balanced SSFP at 9.4 Tesla." They are based out of the Max Planck Institute for Biological Cybernetics in Tübingen (where Klaus directs the High Field Magnetic Resonance Center), which houses one of the few 9.4 T human MRI systems in the world. We were fortunate enough to have a really fun discussion about their work on SSFP fMRI, the importance of eating breakfast (at ISMRM), and whether or not EPI has passed its "best-before" date.

Klaus Scheffler and Philipp Ehses

Scheffler K, Ehses P. High-resolution mapping of neuronal activation with balanced SSFP at 9.4 tesla. *Magn Reson Med.* 2016;76:163–171. doi: 10.1002/mrm.25890
http://onlinelibrary.wiley.com/doi/10.1002/mrm.25890/full

MRMH: Can you tell us a bit about how you got into MR research?

Philipp: For me it was a bit random. I studied in Würzburg, which was a big MRI site (at least at the time), and I did my diploma thesis in 2005. There I did some NMR spectroscopy, but I had befriended a bunch of MRI guys, so then I moved to imaging and very soon was interested in sequences and sequence design. After that I moved to Tübingen and I was looking for new projects, and at some point Klaus suggested we try bSSFP again, and that's how we ended up here.

Klaus: I very randomly came to MR. I did theoretical physics at Freiburg working on something completely different. Then I moved to another university and I wanted to get involved with chemistry, and my supervisor, he just said, "No, you are a physicist, you have to do MR". And that's how I came into it. We had one of the first MR systems in Basel, but I never chose it actually, it was really by chance.

MRMH: How did you come up with the original idea of using SSFP for fMRI?

Klaus: As far as I remember, this idea came up at the ISMRM in Colorado in 2000. I was sitting for breakfast together with Mark Haacke and Michael Deimling from Siemens, and we discussed the features of the [bSSFP] stop band. We talked about the very high sensitivity to phase in the stop band, and the idea was born to try BOLD imaging. I was at Freiburg with Jürgen Hennig at the time, and I immediately started with these experiments in the stop band at 1.5 T (I think). We did five experiments: three went fine and two didn't work, so that's how it came about.

MRMH: What are some of the unique challenges you face working at 9.4 T?

Philipp: In general things are just magnified at 9.4 T, so we kind of have the same challenges as at 7 T. Things like transmit field inhomogeneities are worse, so certainly these are big problems. Apart from that, a unique

Philipp Ehses hiking the Canyonlands National Park in Utah.

challenge for us is that until recently there was no RF hardware available, so our RF specialists had to build and design RF coils, both receive and transmit, over multiple iterations, basically until we had our system running so we could do these experiments.

MRMH: Do you expect bSSFP imaging to see increased use at ultra-high field compared to conventional gradient/spin-echo EPI methods, and what do you think the primary barriers are to its adoption?

Klaus: I think in the next few years nobody will use EPI anymore [laughs]. No, but seriously we are really currently working on this. The speed of bSSFP is about three to four times slower than EPI, and so it's not as efficient, and that's of course a very important issue if you really want to get this work into functional or clinical studies. What we are trying to do is acquire not just one echo, but three or five echoes and it looks really good, and we are on our way to preparing our next paper. The latest sequences we have now have about 80% of the EPI performance, in terms of speed. Besides the speed, the signal change is less than with gradient echo EPI, which is of course also an issue with spin-echo EPI as well. I don't know, maybe it's three and a half years before EPI is useless… [more laughs].

Philipp: First of all, most people would probably think banding artifacts are the biggest barrier to adoption, but I think that's actually not really the case because the banding artifacts we see right now (at least with the relatively short TRs that we are using) are not that bad, and are usually in areas where you would have very strong distortions or signal dropouts in EPI anyway. So in this case, it's relatively similar to EPI in that some regions are just not measureable. There is also a lack of bSSFP sequences that are really optimized for functional imaging. Right now bSSFP is mostly used in cardiac imaging. It also has to be user friendly. Right now we take great care in getting the field homogeneity just right, because of course this is really important for bSSFP, even more so than for EPI.

MRMH: Before we wrap up, is there anything you'd like to add?

Klaus: Thank you very much for the interview.

Philipp: Thank you! ■

> *The latest sequences we have now have about 80% of the EPI performance, in terms of speed.*
>
> –Klaus Scheffler

Klaus Scheffler making the most of a past ISMRM in Hawaii.

The return of *ex-vivo:* Diffusion anisotropy in fixed and fresh prostate tissue

INTERVIEW BY **BENJAMIN DE LEENER**

EDITOR'S PICK FOR AUGUST

We spoke to Dr. Roger Bourne from the University of Sydney about his recent paper, "Diffusion Anisotropy in Fresh and Fixed Prostate Tissue *Ex Vivo*." Roger says he is an expert in absolutely nothing. We disagree.

> *If you can't do it ex vivo under ideal conditions, then your chances of doing it in vivo are very, very slim.*
>
> –Roger Bourne

MRMH: Can you tell us a bit about your background?

Roger: I completed my Ph.D. in ^{31}P magnetic resonance spectroscopy of yeast at the Department of Microbiology, University of Queensland. For my postdoc, I went to the lab of Peter Mitchell in the UK (he got the Nobel Prize in Chemistry in 1978), where I worked on a sodium pumping electron transport complex. I returned to Sydney to work on phosphate MRI, also a bit on effluent treatment (microbiology), and then finally I came back to MRI and MR spectroscopy.

MRMH: What spurred your interest in diffusion MRI of the prostate?

Roger: We did 16 T microimaging of prostate and saw amazing diffusion contrast of the glandular tissue. Clinically, there have been a few people trying to improve the apparent diffusion coefficient (ADC) measurement in prostate using biexponential model fitting. There isn't much known about what the two biexponential components might be in structural terms. We thought that it might relate to the diffusivity differences between epithelium and stroma. In 2012, we published a paper in MRM where we basically did diffusion imaging at two different scales, a very high-resolution scale and a much lower scale. We correlated the relative amounts of bi-exponential component signals from the low-resolution data with the epithelium and stroma volumes estimated from the high resolution data, and we got a pretty good correlation – more epithelium meant lower ADC.

So we were wondering if the changes seen clinically in ADC in prostate cancer (i.e., ADC decreasing as cancer grade increases) are really due to increasing "cellularity," or due to more low diffusivity epithelium. We showed in the journal *Radiology* a few years ago that there is a much stronger correlation between the amount of epithelium and stroma and the ADC than between "cellularity" metrics and ADC. However, the one big thing we don't know yet is why epithelium has low diffusivity relative to stroma. We have seen the same thing in breast tissue (MRM 2015), and a Japanese group has seen it in esophagus epithelium (MRM 2015).

Roger Bourne at Mount Arapiles in Victoria, Australia.

MRMH: Can you explain what you did in the paper we are highlighting today?

Roger: In this particular paper, we did DWI in the prostate at 9.4 T *ex vivo*. If you do high-resolution DTI

Bourne RM, Bongers A, Chatterjee A, Sved P, Watson G. Diffusion anisotropy in fresh and fixed prostate tissue *ex vivo*. *Magn Reson Med*. 2016;76:626–634. doi: 10.1002/mrm.25908

http://onlinelibrary.wiley.com/doi/10.1002/mrm.25908/full

measurements, you can see a lot of anisotropy in the prostate, but you don't get much coherence in fiber orientation over large regions. Smooth muscle is not random but has little bundles that are coherent in small spaces. Some clinical papers find correlation between cancer and diffusion anisotropy (FA), some don't, and we think the problem is that on a microscopic scale you have high anisotropy, and if you go to a typical clinical voxel size, the anisotropy is averaged out because of the fiber orientation heterogeneity. So we did high resolution DTI measurements on the whole prostate, and then started downsampling the data, creating larger voxels. As we did this, FA went down.

An unexpected finding of this study is how much difference there is between prostates. I suspect the reason we see such differences is because different men have different amounts of fibrous tissue in their prostates. All of this suggests that there is a big variation between prostates, and that FA might not be useful alone. Nevertheless, this information provides some background for modeling diffusion in prostate tissue.

MRMH: So anisotropy might be more useful for higher order diffusion model fitting and cancer characterization?

Roger: Yes, because a significant isotropic background signal is masking the true anisotropy. We actually just published a paper in *NMR in Biomedicine* (after being turned down by MRM) where we compared ten different compartmental models. The best models included both a restricted component and an anisotropic component.

MRMH: What are the biggest challenges for doing *in vivo* imaging compared to *ex vivo*?

Roger: Many, many challenges: lousy SNR, patients that move, perfusion of tissue. *Ex vivo* SNR is in the 100s instead of in the tens, and we can scan for 48 hours if we want to. *Ex vivo* tissue work is neglected, and dismissed as "non-clinical", yet there are too many studies where people just put patients in scanners and try something without knowing the contrast mechanisms. Worst of all, they try brain methods in prostate, but the tissue structures have no similarity, so it is crazy to think that some brain method will work in the prostate. Our approach is to simplify the system we are looking at, get rid of perfusion and movement, and see if we can detect any useful properties. If you can't do it *ex vivo* under ideal conditions, then your chances of doing it *in vivo* are very, very slim.

MRMH: What are your recommendations for the community?

Roger: Put the *ex vivo* work together and start applying it to *in vivo*. We just published a review paper in *Diagnostics* and made some suggestions as to what needs to be done. There are a number of studies about ideal b-values, but what is neglected is the diffusion time. This can vary enormously between scanners. Most scanner software doesn't report the diffusion time and most studies don't either. This could be a significant contribution to the lack of sensitivity and specificity in clinical DWI.

Also, T_2 differences in tissue might affect diffusion modeling and a couple of pilot studies suggest there is microscopic T_2 heterogeneity in the prostate. Another more difficult thing in terms of modeling prostate diffusion is to look at exchange between compartments. We just don't know yet whether that is important.

Finally, how do people assess diagnostic accuracy? There is a weakness in the literature about that. Testing the diagnostic value of "improved" multi-parameter models one parameter at a time is not the way to go. You don't know how the information is distributed across model parameters, so to take one parameter at a time and correlate with pathology is defeating the purpose of multi-parametric modeling. ■

Roger Bourne

SWIM without flow: 3D flow compensation for susceptibility weighted imaging and mapping

INTERVIEW BY **RYAN TOPFER** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR AUGUST

In this *Highlights* Q&A we chat with Dongmei Wu about her technique to reverse phase history through gradient moment nulling, and senior author E. Mark Haacke takes a moment to tell us the history behind "The Green Book."

> *The idea was to do full three-dimensional flow compensation for all the echoes so we could do MR angiography, SWI QSM and T_2* mapping all in one scan.*
>
> –Dongmei Wu

Dongmei Wu

MRMH: To start off, could you give us an idea of what this project was about?

Dongmei: The idea was to do full three-dimensional flow compensation for all the echoes so we could do MR angiography, SWI (susceptibility weighted imaging), QSM [quantitative susceptibility mapping], and T_2* mapping all in one scan. Extracting all of this from a single sequence saves time, which is really important for clinical applications.

MRMH: In the paper, vessel wall imaging is mentioned as a clinical application. Normally this is done with a T_1 -weighted scan or black blood imaging. What's the advantage of using SWI and QSM?

Wu D, Liu S, Buch S, Ye Y, Dai Y, Haacke EM. A fully flow-compensated multiecho susceptibility-weighted imaging sequence : The effects of acceleration and background field on flow compensation. Magn Reson Med. 2016;76:478–489. doi: 10.1002/mrm.25878

http://onlinelibrary.wiley.com/doi/10.1002/mrm.25878/full

Mark: The point in studying vessel wall is to look for vulnerable plaque, and also to look at plaque formation. What Dongmei has demonstrated is that, by using this double echo approach, with the shorter echo, we can see the vessel wall and therefore do a QSM map of these abnormalities. SWI and QSM can differentiate the type of plaque: diamagnetic (calcified) material or paramagnetic blood products. If it turns out to be the latter (i.e., hemorrhagic plaque), especially if it's beginning to infiltrate the edge of the vessel wall, then that's the first indication it could be vulnerable plaque. Black blood imaging can't do that because if the signal from the tissue is dark then you can't see it. If you use a short echo time and you don't lose that signal, then you may see a T_1 enhancement; however, this enhancement may disappear over time. So the beauty of the approach here using SWI-QSM is that you can differentiate this tissue purely from its susceptibility factor. It's a new idea, but I believe it's complementary to what people have done over the last 25 years to study atherosclerosis.

MRMH: So you want the scan to be sensitive to tissue iron content, and susceptibility contrast evolves with echo time, manifesting itself as increased phase contrast. Why bother with the short echo?

Mark: Theoretically, the QSM reconstructions should be echo-time independent, so you should get the same answer whether you use short or long echo. If you find something that's in the second echo but not in the first (assuming it's not a question of SNR) then clearly what's in the second echo is wrong. Though, as you know, life is not always quite that simple.

Dongmei: Even with flow compensation, the residual background field inhomogeneity (from imperfect shimming), when combined with flow, can induce artifactual arterial phase that will produce streaking artifacts in the susceptibility map. So we use information from the first echo to suppress the artery in the second echo. Figure 6 in the paper shows that, without masking out the phase of the arteries before the QSM reconstruction, the arteries appear to have high susceptibility. But, in reality, the arteries have roughly the same susceptibility as the surrounding tissue and should not be visible in the phase images.

Mark: Clinicians, like our longtime collaborator Dr. Karen Tong at Loma Linda University, have been asking for ten years, "Please help us differentiate thrombus from veins!" At the long echoes you see so many veins that this is difficult to do. This need by the clinicians was part of the motivation for Dongmei's project and now we've basically solved the problem. It could be an entirely new dimension for the clinicians to begin using; with the short echo you can visualize high iron content, which enables you to see the thrombus very well, and distinctly from the veins.

It was to our delight and surprise that we found short echo times (7.5 ms) do a very good job of reconstructing QSM in regions of high iron content. They have less artifacts than the long echoes because there's less aliasing to deal with and there's less cancellation effects at the edges of regions of high iron content. The long echoes remain useful for their grey-white matter contrast, and for finding asymmetrically prominent cortical veins and microbleeds (the latter of which is very important for studying dementia, stroke, and traumatic brain injury).

MRMH: Any other surprises during the course of this research? Where is it leading to next?

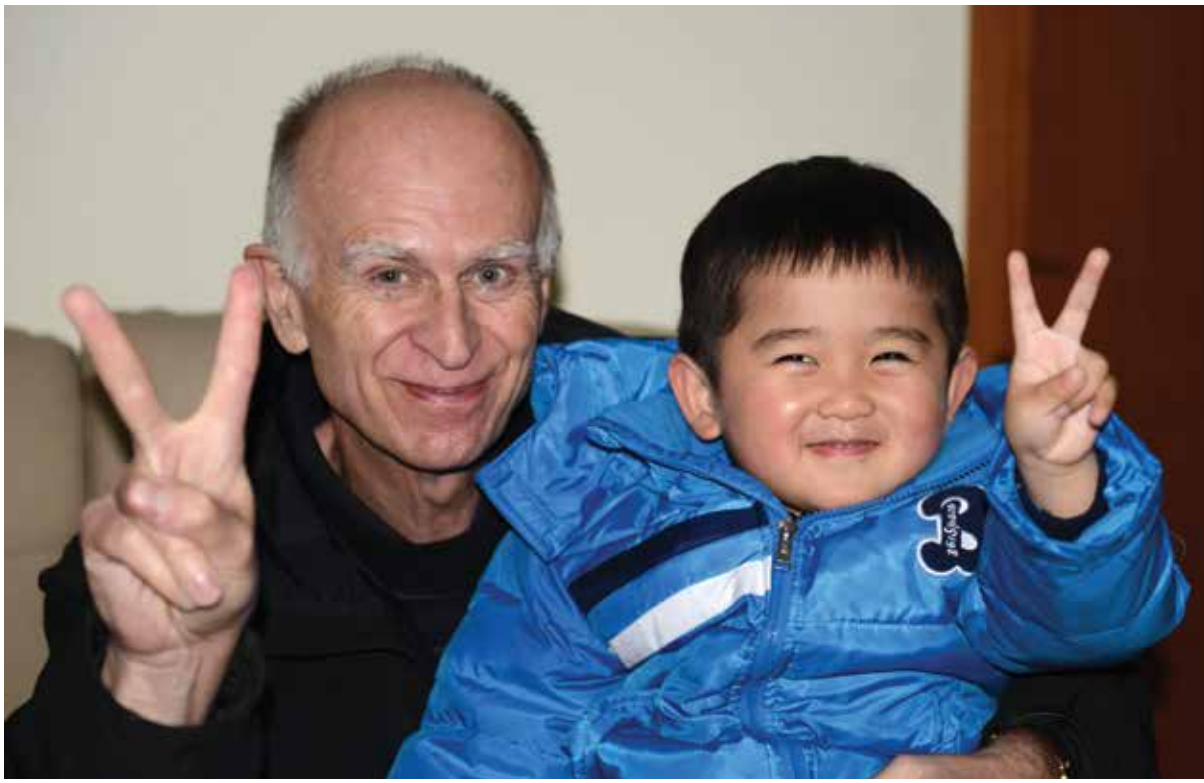
Dongmei: During the design of the flow compensation, the trick was really to have the flow compensation for each echo strictly independent. To do this, we designed the gradient structure to reverse all the earlier gradient moments before applying flow compensation to the later echoes. So the flow compensation for each echo then had a similar form, making it easy to extend to any number of echoes (e.g., in this paper, we used five echoes to do the T_2* map).

Mark Haacke on a visit to East China Normal University in Shanghai.

We're now beginning a project to speed up the SWI scan by using segmented EPI (SEPI). With SEPI SWI, we can use an echo train length of three to seven. Conventional SWI takes about 12 minutes, whereas with SEPI and parallel imaging, whole brain coverage can now be accomplished in one to three minutes depend-

The ability to monitor the presence of microbleeds using this technique may become a very important clinical tool.

–Mark Haacke



Mark Haacke, also known as "yeye," and Dongmei's son discussing future sections for the Green Book.

ing on the desired resolution.

Mark: There's something magical about SEPI SWI. In almost all imaging methods where you speed up data acquisition you will lose SNR. That isn't true for SEPI SWI for reasonable length TR and TE, since you're sampling with the echoes, and there's not very much T_2 decay. This would be tremendous because current imaging times for resolutions ranging from 0.65 x 0.65 x 1.3 mm^3 to 0.65 x 1.3 x 2 mm3 can now be run in one to three minutes as Dongmei alluded to with almost no loss of SNR! It will be up to the clinicians to decide which resolutions and SNR they prefer for a given application.

MRMH: Is there a specific clinical application you're hoping to apply this faster sequence to?

Mark: We wrote a paper a few years ago studying 75 patients with mild cognitive impairment. We showed that patients with four or more microbleeds all converted to progressive dementia during that study. So that becomes a potential biomarker for the presence of cerebral amyloid angiopathy. Realizing this problem – the longer echo time you get, the harder it becomes to flow compensate – the method Dongmei is developing now, ironically, is looking at the opposite effect that we tried to correct for in this paper. She's looking at purposely dephasing all the signal, so there are no remnant artifacts, and getting the black blood type of image that allows for very high resolution, rapid SEPI SWI that could then also be used to detect microbleeds. In that case, the implications are tremendous for dementia, and traumatic brain injury. And very recently a group in Shanghai has shown that if you have three or more microbleeds in stroke, you maybe shouldn't do anti-platelet therapy. So the ability to monitor the presence of microbleeds using this technique may become a very important clinical tool.

MRMH: Dongmei, how did you get into MRI? And how did you come to work with Mark?

Dongmei: I began my MR research career in 2006 when I finished my master's studies and went to Siemens in Shenzhen to work on sequence development and ICE programming. After three years there I returned to Shanghai to work in the physics department at East China Normal University (ECNU), where they have a Siemens Trio. I began working with Dr. Haacke in 2008 when he started collaborating with our department. I officially became his Ph.D. student in 2014, which is when we initiated our research on flow compensation.

Mark: We also knew each other because Dongmei's husband Dai Yongming works in MR. So we actually began collaborating, working on SWI sequence related issues, before she became a student. In 2014, I took on an adjunct position there as a professor in the physics group and I was then able to formally have her as a Ph.D. student, in collaboration with Chen Qun, who's a member of that department and now also the president of the university! It was nice to see an MR person become president of the university – hopefully boding well for the future of MR research at ECNU!

THE GREEN BOOK

MRMH: Mark, how did you get started in MRI? And how did "The Green Book" come about?

Mark: I was at Case Western Reserve University, in Cleveland, doing high energy physics and I left to take a job in Pittsburgh, doing seismic tomography. That was my introduction to imaging. At that point, my wife had started medical school back in Cleveland so I was looking to return. I interviewed with Picker International and ended up starting there, right at the very beginning, just as they were switching from resistive to cryogenic units. I worked there for two years but maintained contact at Case Western with Robert Brown. We decided we would put together a course on imaging, which first involved CT, ultrasound, and MRI all together; however, as the interest in MRI grew and grew, the other topics dropped away. I had taught the course for almost fifteen years before "The Green Book" was first published in 1999.

It was around 1992 that I decided to begin putting a book together, because I was teaching the course every year and that gave us an opportunity to really look at the fundamentals, and also appreciate the students' problem: The thing they liked least about most books was the statement, "It is easy to prove that." So we really thought it was best to have a clear enunciation of the problem and a step-by-step review, with as much insight as possible into where it would go in research applications. Since we were so embedded in the research at that point it became a really wonderful seven-year project for four people (so that first edition was really a 28 man-year project).

The timing was perfect because John Wiley was interested in getting involved in JMRI, and I had known the people there very well. We actually had a totally complete text, done with LaTeX, so the publishers didn't have to do anything! It was a print-ready copy and, up to this point, we've continued to do that. We had a hundred percent control of the format, structure, size of the book, type of images, and this really allowed us to do everything we wanted to do. Maybe in the future they won't do this anymore!

I'll add one more comment, because Dongmei is here. Sometimes, there were some Ph.D. students whose work became an integral part of a given chapter. It might've just been an image representing some new concept, for example. In some cases those images might represent a year's worth of effort – or even four years! Two of the authors of that book, Ramesh Venkatesan and Mike Thompson, were both Ph.D. students at the time, and they both took an extra year of their Ph.D.s to help put this book together. That's part of the magic of this book. The next version might contain a new paragraph in the discussion of flow compensation based on Dongmei's results! So the book continues to evolve thanks, in part, to the wonderful work students do during their research. ■

Haacke EM, Brown RW, Thompson MR, Venkatesan R. *Magnetic Resonance Imaging: Physical Principles and Sequence Design*. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2014:944.

> *We had a hundred percent control of the format, structure, size of the book, type of images, and this really allowed us to do everything we wanted to do.*
>
> –Mark Haacke

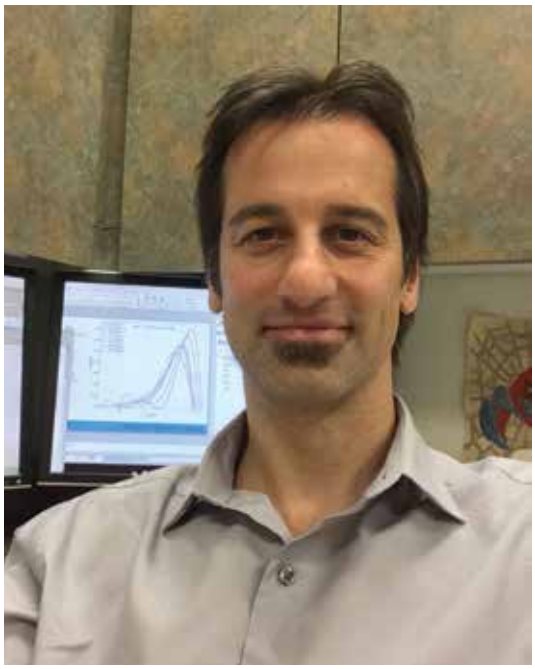
Nothing wrong with these anomalous cartilage relaxometry models!

INTERVIEW BY **AKSHAY CHAUDHARI**

EDITOR'S PICK FOR SEPTEMBER

We virtually sat down with David Reiter and Richard Spencer from the National Institute on Aging at the National Institutes of Health to talk about their recent publication entitled "Anomalous T_2 Relaxation in Normal and Degraded Cartilage." This paper showed that the stretched exponential decay model reflects the microstructural complexity of a cartilage matrix better than the conventional monoexponential decay model. Our conversation with David and Richard took us down a winding path filled with mathematics, modeling, MRI, and clinical translation, all towards, as Richard puts it, making cartilage great again.

> *I joined Richard's group as a post-doctoral scholar and became even more engrossed in the application of quantitative MRI to soft tissue.*
>
> –David Reiter



David Reiter

Richard Spencer

MRMH: How did you come into this particular field?

David: In graduate school, I became interested in the biomechanics of spinal disc injury. I started using MRI to study this and was immediately impressed with the potential for making quantitative measurements of soft tissue. From there on, I joined Richard's group as a post-doctoral scholar and became even more engrossed in the application of quantitative MRI to soft tissue, and was fortunate to stay on as a staff scientist.

Richard: I am a physician and I have been working at the Aging Institute for around 25 years. I have been motivated by the fact that osteoarthritis is the largest source of limited mobility in the elderly population. As such, cartilage as a tissue and osteoarthritis as a process deserve a lot of attention.

MRMH: Given your backgrounds, how did this specific study come along?

David: When I arrived here as a post-doc, Richard and I started looking into different signal models to describe relaxation in cartilage so that we could step away from some of the existing quantitative methods that showed limited specificity to disease progression. We wanted to be able to better quantify extracellular components in the cartilage matrix; this lead to our interest and investi-

Reiter DA, Magin RL, Li W, Trujillo JJ, Pilar Velasco M, Spencer RG. Anomalous T_2 relaxation in normal and degraded cartilage. *Magn Reson Med.* 2016;76:953–962. doi: 10.1002/mrm.25913
http://onlinelibrary.wiley.com/doi/10.1002/mr m.25913/full

gation of anomalous relaxation models. Our idea was to examine some of the plausible signal models and how well they fit the experimental data as an initial approach towards model selection, and to try to determine ideal experiments to do this.

Richard: Years ago, my lab used T_1, T_2, and magnetization transfer as markers of cartilage degradation and as markers for engineered cartilage. But at some point, it seemed that after initial work relating these parameters to cartilage status, they were providing only limited additional insight. So we extended our cartilage program to include non-conventional signal models for transverse relaxation. David's multiexponential work, first published in 2009, really brought this into the mainstream of cartilage magnetic resonance. It was a large step forward because these models allow you to look at different molecular compartments. Then, use of the stretched exponential model for relaxation was suggested by our co-author Richard Magin in the context of fractional-order analysis. We published our first paper incorporating this concept in 2011. The current work we are discussing is a major extension of that, and includes study of degraded cartilage.

MRMH: How do the anomalous models from this study arise?

David: As Rick just mentioned, Richard Magin had developed a fractional-calculus derivation of the Bloch equation for describing anomalous relaxation, which leads to the stretched Mittag-Leffer signal model. The origin of the stretched exponential is a little less straightforward. One way it arises from the Bloch equation is under the assumption that transverse relaxation is not a constant but rather has a power-law relationship with time. Given the evidence in non-NMR systems, there could also be a relationship between the stretched exponential model and diffusion in heterogeneous media, but this hasn't been rigorously proven yet. Based on how well these models fit the experimental data, they are certainly worth further consideration.

MRMH: How do you think such quantitative parameters can change the clinical standard of care, down the line?

David: In osteoarthritis, radiographs tend to detect later changes; this affords limited options for treatment. While MR parameters such as T_2 are very sensitive to cartilage matrix status, they are non-specific, so that even with a T_2 measurement you don't know what's going on in the cartilage. We think these anomalous relaxation models can provide more specific information.

Richard: Right now, there are no effective therapies for osteoarthritis. But to develop a therapy, you have to be able to measure a disorder in a meaningful way. This is just like the fact that developing treatments for high blood pressure requires the ability to measure it. T_2 is sensitive to many factors, which is commonly presented as an advantage, but the fact that it is sensitive to orientation, dehydration, macromolecular composition, motion, etc. makes it a poor marker for understanding pathology. An elevated T_2 is generally "bad", but you don't actually know what's going on in the tissue. So new methods need to be applied to monitor tissue degradation and evaluate therapy.

MRMH: Are there any specific challenges that you face with the anomalous models that you might not face with conventional T_2 relaxometry?

Richard: As is the case with any model, additional parameters will lead to better fits. But we want to make sure that these parameters are physiologically and statistically meaningful. Moreover, with conventional relaxometry, or other pre-defined models, you only have to face the issue of how best to estimate parameters. If you open up the possibility of other models, including multi-exponential, Mittag-Leffler, stretched exponential, and even combinations of these, you also have to figure out what the optimal model is.

MRMH: As a parting thought, do you have any ultimate goals for general musculoskeletal imaging?

David: Musculoskeletal imaging is a large field with many challenging problems, so I'd hate to dilute my answer too much – so I'll just talk about cartilage. We want to develop a method to reliably detect and quantify changes in the extracellular matrix. Degradation of cartilage can progress through multiple steps such as loss of proteoglycan content to fibrillation and loss of tissue. If we can measure the earlier changes, we have made a huge advance because it allows us to start looking at therapeutic interventions for osteoarthritis.

Richard: From a clinical perspective, all of our work has to be for diagnosis, prognosis, or therapy. That is what medicine does. It is not clear that conventional cartilage matrix measurements based on bulk parameters values will lead to any of those three. Ultimately, our clinical goal is to further all three of these arms of clinical medicine by establishing more specific magnetic resonance models for tissue pathology. ■

David Reiter and Richard Spencer at the National Institute on Aging in Baltimore, Maryland.

> *An elevated T_2 is generally bad, but you don't actually know what's going on in the tissue.*
>
> –Richard Spencer

What do jazz legends, mobile phones and MRI safety have in common?

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR SEPTEMBER

The September 2016 Editor's pick is from Manuel Murbach and Niels Kuster, researchers at the Foundation for Research on Information Technologies in Society (IT'IS) in Zurich. Their paper presents a simulation-based approach to evaluate the safety of the radiofrequency field (RF) shimming in magnetic resonance imaging (MRI). Current safety standards typically call for the whole-body averaged specific absorption rate (wbSAR) – a measure of the total RF power absorbed by the human body – to be limited to 4 W/kg, and assume that the thermoregulation capacity of the scanned patient is normal. However, new generations of MRI systems support RF shimming operating modes that may induce local SAR values that might be hazardous for patients with impaired or dysfunctional thermoregulation, increasing the risk of tissue damage after long scanning sessions. Manuel and Niels' simulation study used the Virtual Population (ViP) human models to assess different RF shimming modes in several anatomical regions, and they've established safety recommendations for scanning patients with impaired thermoregulation. We recently spoke with Manuel and Niels about their project.

Manuel Murbach (left) expounding on topics other than MRI safety with Niels Kuster (right) and colleague Parisa Fallahi (center) late into the night at the IT'IS Foundation 2016 annual retreat at a remote winter resort in the Swiss mountains.

Murbach M, Neufeld E, Cabot E, Zastrow E, Córcoles J, Kainz W, Kuster N. Virtual population-based assessment of the impact of 3 Tesla radiofrequency shimming and thermoregulation on safety and B_1+ uniformity. *Magn Reson Med.* 2016;76:986–997. doi: 10.1002/mrm.25986

http://onlinelibrary.wiley.com/doi/10.1002/mrm.25986/full

MRMH: Please tell us about yourselves and the IT'IS Foundation.

Manuel: I did my Ph.D. studies in MRI safety at IT'IS and ETH Zurich, and I am currently working as a project leader there.

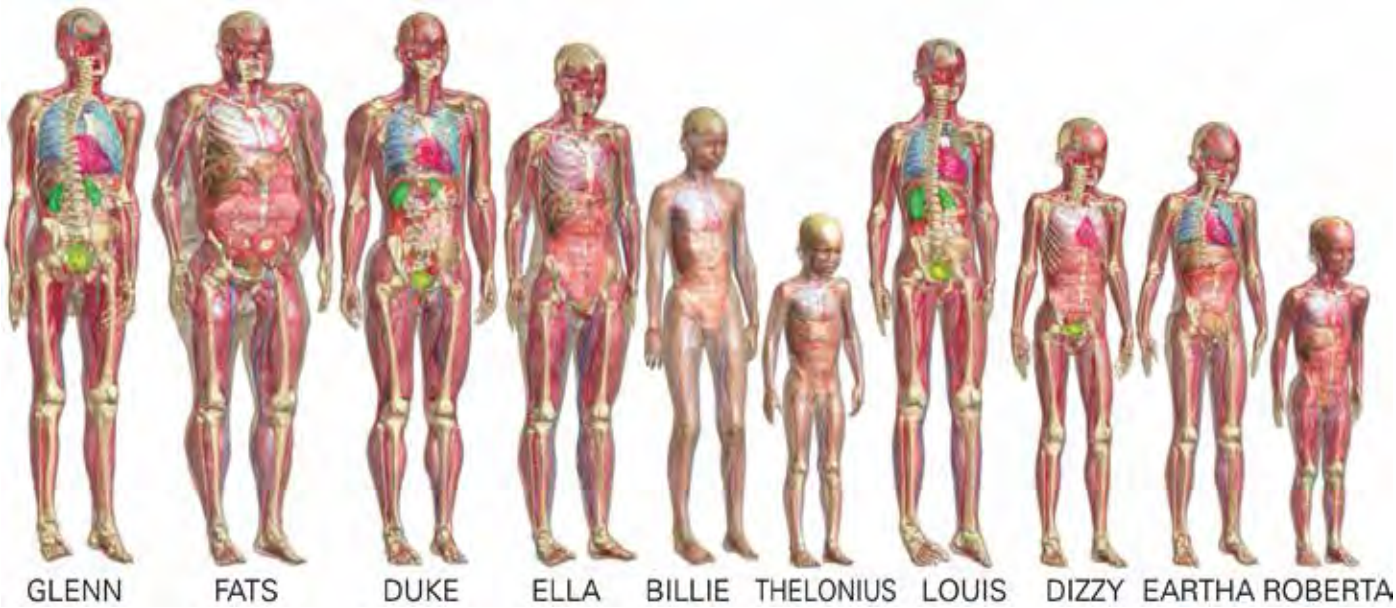
Niels: I'm the founding director of IT'IS, which was established in 1999 with the support of the ETH Zurich. The objective was twofold: to create a flexible institute that can quickly respond to technology-related safety concerns by providing science and engineering solutions to mitigate risks, and to act as a bridge between academia, regulators, industry and the clinics. Our core competencies are electromagnetics and computational life sciences.

MRMH: Can you give us a brief overview of your paper?

Manuel: The overall goal of this paper is to assess the SAR distribution and the related thermal safety of patients who are undergoing MRI scans with simulations. One current issue is that new MRI systems have parallel RF transmit capability, which leads to much more focused RF energy absorption patterns in the body. We wanted to develop a robust simulation method to evaluate thermal safety for MRIs that use parallel transmit to shim the RF field. Our first approach in the paper was to model the local temperature increase that occurs with RF shimming.

MRMH: What do you mean by "RF shimming"?

Manuel: So, in our case, we're shimming the B_1 field, also known as the transmit RF field, which is approximately 128 MHz at 3 T. To improve image quality, many vendors implement RF shimming, which applies a different polarization configuration instead of the standard circular polarization. With RF shimming, you



The Virtual Population (ViP) human models.

can increase the quality of the B_1+ field inside the body, which results in better image quality. However, doing so also changes the RF absorption patterns in the body, which is what we investigate in this paper. Until now, most papers interested in RF safety only use circular polarization.

MRMH: How did you use simulations to investigate the thermal safety of RF shimming in humans?

Manuel: We used the ViP human anatomical models. The models range in size from a little girl to an obese adult, so they have quite different absorption patterns. In addition, we investigated how much RF exposure can be safely tolerated by patients with impaired thermoregulation, such as the elderly and diabetics. These patients have a limited ability to increase the local blood flow when heating occurs, so they tolerate less RF absorption safely.

MRMH: Some of our readers may not be aware of the ViP models. Could you explain what they are, and what their limitations are?

Manuel: These are highly detailed whole-body virtual human models that have been widely used for dosimetric and biomedical computer simulations. In the modeling world, most people know Duke and Ella, who are probably the two most famous models and part of the Virtual Family, but the ViP has grown since then to a broader set of models, the Virtual Population.

MRMH: And they are all named after legendary jazz artists, right?

Manuel: Yes, exactly [laughs].

Niels: We started developing the Virtual Family in 2005 for the mobile phone industry, which at the time was challenged with demonstrating that mobile phone use is safe for all users. The original Virtual Family was then expanded with the child models of the Virtual Classroom and later with obese, elderly, and paediatric models. All models are based on real MRI scans of people, have 1 millimeter slice thickness, and are segmented with semi-automated tools and functionalized with tissue models. Because of resolution limitations, the models don't yet have complete vascular structures or sufficient detail in neural tissues, but we are in the process of adding these features. We want to push this concept into the world of virtual clinical trials.

Manuel: And of course in terms of MRI safety, simulations are indispensable to see what is going on inside the body – you cannot insert probes inside human volunteers.

MRMH: What did you conclude from your study?

Manuel: We concluded that if you use the RF shimming mode, it is possible to end up with a configuration that leads to very high local SAR values. If the patient has impaired thermoregulation, they may not be able to tolerate the first level operating mode due to high local temperature increases. This can be avoided by staying in the normal operating mode or in the circular polarized mode.

Niels: The study also confirms that the safety standards that are used today are insufficient and need to be revised, especially as providers are moving forward with future generations of MRI systems that have multi-port RF shimming capabilities.

MRMH: Did anything surprise you over the course of this study?

Niels: I think the biggest surprise is the discrepancy between the shortcomings of the current safety standard and the incident rate of reported hazards. Since the safety standard is practically never fully exploited with respect to maximum SAR, little happens.

Manuel: Yes, the standard would allow us to apply RF exposure of 4 W/kg constantly for an hour. This would put an extreme RF load on the patient. And although you would be allowed to do that, nobody actually does it because of safety margins and interruptions between the scans. The overall average wbSAR is maybe around 1.5 W/kg, instead of the 4 W/kg that is allowed. But, it's kind of an unholy situation if you have a standard that allows a lot of exposure but no one uses it fully, and then they claim the standard is safe. It's not the standard that's safe, it's the usage pattern that makes it safe. So we should adjust the standard. ■

> *It's not the standard that's safe, it's the usage pattern that makes it safe. So we should adjust the standard.*
>
> –Manuel Murbach

Exploring the reproducibility of spectral quantification

INTERVIEW BY **ADAM ELKHALED**

EDITOR'S PICK FOR OCTOBER

In this edition of *Highlights* Q&A, we were treated to a virtual interview with Dr. Melissa Terpstra and Dr. Gülin Öz, whose work at the University of Minnesota Center for Magnetic Resonance Research (CMRR) has provided unique insight into the reproducibility of spectroscopic data. Our conversation revolved around their investigative efforts to understand how field strength influences consistent neurochemical quantification. By comparing short-echo semi-LASER data from 3 T and 7 T acquisitions, they managed to arrive at some interesting conclusions that bear direct relevance to other studies, and also underscore the necessity of quality assurance for purposes of clinical translation.

Melissa Terpstra and Gülin Öz.

MRMH: How did you become interested in MR spectroscopy?

Melissa: I've always loved spectroscopy, ever since I was young, because I consider rainbows and thin film interference on oil spills to be spectroscopy. During my undergraduate experience, I was naturally drawn to it through physics. I found a common passion with my thesis advisor in using the physics of the nucleus and coupling to perform some challenging and interesting work. When I came to graduate school, the CMRR was a large, dynamic group doing pioneering work in spectroscopy, so I started doing research here.

Terpstra M, Cheong I, Lyu T, Deelchand DK, Emir UE, Bednařík P, Eberly LE, Öz G. Test-retest reproducibility of neurochemical profiles with short-echo, single-voxel MR spectroscopy at 3T and 7T. *Magn Reson Med*. 2016;76:1083–1091. doi: 10.1002/mrm.26022

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26022/full

Gülin: Having majored in both physics and chemistry during undergrad, I was always interested in areas where the two fields intersected. I especially loved the fact that I could draw the chemical structure of an unknown compound in the test tube in my chemistry class just by looking at the NMR spectrum. I moved into biochemistry during my Ph.D. to study protein structure and dynamics. At CMRR I was finally studying chemistry within its intact context, *in vivo*.

MRMH: How would you summarize the work performed in this study?

Melissa: I have typically worked with edited spectroscopy, using molecular coupling in order to uncover tiny resonances. This was an opportunity to understand the extent to which those tiny resonances can be robustly quantified within the entire spectrum, measuring all of the peaks; and also to push the quality control standards of what we're measuring.

Gülin: My overall goal with this work was a field comparison. There have been lots of comparisons for spectroscopy to investigate SNR and resolution advantages at ultra-high field; but, in a clinical study, especially in a treatment trial, what really matters is the test-retest reproducibility of your measurement. We always come across the choice of 3 T versus 7 T, and I wanted to have some guidelines for my own work.

MRMH: What are the advantages of using a semi-LASER spectroscopy sequence over the traditional PRESS sequence, or even STEAM?

Gülin: The main reason for choosing the semi-LASER sequence was to minimize the chemical shift displacement errors you get with PRESS, which are substantial even at 3 T; using broadband adiabatic pulses minimizes this problem. I want to emphasize that whatever sequence is used, whether it is PRESS or semi-LASER, it really needs to be optimized. Not all semi-LASERs are created equally, just like not all STEAMs are created

equally. In our case, we are working with a sequence that's been optimized to obtain clean single shots, so that you don't have to rely on phase-cycling to remove unwanted coherences.

Melissa: In my past work with edited spectroscopy, you needed very long echo times to detect tiny signals, but, as a consequence, all of the overlying resonances were excluded. I personally came to realize the confounding of the data by T_2 when measuring glutathione concentrations in older people. My main interest in STEAM is that it has an ultrashort echo time compared to my past work, and I was willing to pay the penalty of losing half the signal to eliminate this T_2 confound.

Sequence	Axis	Generalized Schema
PRESS	RF gradient	90_x—180_y—180_y x y z
LASER	RF gradient	90_x—180_y—180_y—180_y—180_y—180_y—180_y x x y y z z
semi-LASER	RF gradient	90_x—180_y—180_y—180_y—180_y x y z z y
STEAM	RF gradient	90_x—90_y—90_y x y z

Table 1. Generalized RF pulse and gradient localization schemes for common spectroscopy sequences. Point-RESolved Spectroscopy (PRESS) consists of a slice-selective excitation, followed by two refocusing pulses; each pulse is used to partially localize the signal in 3D. The Localization by Adiabatic SElective Refocusing (LASER) sequence features non-slice-selective excitation to minimize inter-pulse timing; and six adiabatic full passage (AFP) refocusing pulses for localization. Such AFP pulses reduce chemical shift misregistration errors owing to their high bandwidths and provide better spin echo profiles compared to the traditional PRESS sequence. As a variant of the LASER, the semi-LASER sequence retains four AFP refocusing pulses, while employing slice-selective excitation. In the STimulated Echo Acquisition Mode (STEAM) sequence, three consecutive 90-degree slice-selective pulses excite and localize the signal to allow for ultra short echo times.

MRMH: Can you explain some of the challenges that you confronted in trying to compare the reproducibility of spectra at 3 T versus 7 T?

Melissa: One of the biggest ongoing challenges that we face, and really a motivator for this work, was using quality control cut-offs. In the field of spectroscopy, we use Cramer-Rao lower bounds (CRLBs) to inform reliably of quantification of a given resonance, but it is really a judgment call in terms of what number you are going to use, similar to p-values in statistics.

Gülin: I would say the biggest challenge with any field comparison is the associated hardware. No comparison is perfect unless you keep everything other than the field identical, but in our human study that was not an option, as we chose different coils that were available to us at the time. On the other hand, this practical comparison did allow us to look at situations where, for example, we had the same SNR at 3 T and 7 T and could still delineate some of the advantages of 7 T.

The University of Minnesota Center for Magnetic Resonance Research (CMRR) specializes in research at ultrahigh magnetic fields (7 Tesla and above).

MRMH: How did you improve your understanding of CRLBs and their relation to test-retest reproducibility?

Melissa: Cramer-Rao lower bounds are really the mathematical fitting piece of the measurement error, but there are other contributions to that error related to the effects of patient motion and also making sure that you have the proper reference for a signal. Overall, there is a good relationship between CRLBs and coefficients of variance, though there are noteworthy deviations. You cannot rely on just CRLBs, however, you need a test-retest aspect built into the clinical study for reproducibility.

Gülin: We found that CRLBs are not necessarily reflective of the 3 T-7 T relationship when it comes to reproducibility. At 7 T, we could reduce the CRLBs relative to 3 T for almost all metabolites, but the test-retest coefficients of variance were not lower than 3 T for many metabolites. Most studies perform a single retest; we went up to four scanning sessions and determined that one should get at least three measurements for a more accurate determination of coefficients of variance.

MRMH: What are the long-term goals and potential applications for this research?

Gülin: I am interested in applications for clinical trials of neurodegenerative diseases, which require robust outcome measures. We've been putting a lot of effort into cross-platform standardization of the method and making simplifications to the protocol that would overcome the clinical barriers to advanced spectroscopy.

Melissa: Being part of a lifespan human connectome project on aging, this adds to my repertoire of modalities that may help us understand why some people experience cognitive decline, by measuring anti-oxidant changes in the context of other neurochemical changes. In a parallel trajectory, I am also interested in how we fundamentally characterize the quality of our data, alongside the NIH mandating higher standards for reliability. ■

> *Most studies perform a single retest; we went up to four scanning sessions and determined that one should get at least three measurements for a more accurate determination of coefficients of variance.*
>
> –Gülin Öz

Stretching for the high-hanging fruit in MR elastography

INTERVIEW BY **YOGESH MARIAPPAN**

EDITOR'S PICK FOR OCTOBER

As the field of MRI is slowly but surely moving from qualitative to quantitative, and from imaging structures to imaging other properties, the choice of this month's *Highlights* article is apt: the research group led by Ingolf Sack has been at the forefront of both of these aspects with their work on MR elastography (MRE). This is a quantitative imaging technique capable of measuring the mechanical properties of tissues of interest and is available from all the major vendors. The current clinical application is focused on liver where the stiffness (measured in kilopascals) is used for fibrosis assessment. In this article, they have provided recent results from their *in vivo* wideband multi-frequency work on liver and brain.

> *The brain is surprisingly soft at low frequencies.*
> –Ingolf Sack

Ingolf Sack and Florian Dittmann.

MRMH: Tell us about yourselves and your academic journey so far.

Florian: I did my bachelor's and master's degrees in medical informatics, worked in the field of radiation therapy for the German Cancer Research Center in Heidelberg, Germany, and then at Massachusetts General Hospital in Boston. Later I found my true calling and have been doing my doctoral thesis work with the elastography group since 2013. My future plan is to work in industry, but as of now I am not sure where. (Talent HR in industries: are you reading?)

Ingolf: I have always been interested in the physical and chemical aspects of biological tissues. I started as a chemist from which I came to analytical chemistry, to spectrometry, to MR imaging and now finally to MR Elastography. I started working with elastography when it was in its infancy and have seen it grow leaps and bounds for the last 16 years.

MRMH: Could you please provide us a glimpse of your academic institute Charité, especially from the MR research perspective?

Ingolf: Charité is one of the biggest university hospitals in Europe, which provides us the opportunity to have many clinical collaborators constantly pushing us to de-

Dittmann F, Hirsch S, Tzschätzsch H Guo J, Braun J, Sack I. In vivo wideband multifrequency MR elastography of the human brain and liver. *Magn Reson Med.* 2016;76:1116–1126. doi: 10.1002/mrm.26006
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26006/full

velop methods for detecting diseases better and quicker. The hospital itself is spread over three campuses in Berlin with multiple research-dedicated MR scanners. Our group works mainly on basic research, solving equations, but our collaborators provide the motivation and bring our methods to the clinic.

MRMH: Elastography and MR elastography in particular are still considered novel. Could you comment on the application, awareness and acceptance?

Florian: MRE is quite an interesting field, currently being used for the staging of liver fibrosis clinically. And it is being actively investigated for brain and tumor characterization applications. In most of these cases, I believe that it will be beneficial to use the wideband approach elaborated in our article.

Ingolf: Elastography has penetrated deeper in the field of ultrasound, where it is implemented in all commercially available ultrasound systems. Elasticity imaging is not only a diagnostic imaging technique, it is a new approach to study the biophysics of tissues. Once we can better solve the inverse problem (calculating the tissue mechanical properties from the acquired ultrasound/MRI images), I think there will be widespread applications. While MR elastography is also available from all the big vendors, it is currently used only for additional investigation for cases that are suspicious. The clinicians typically have an idea of the tissue mechanical properties from ultrasound, but then turn to MRE for providing high resolution images.

MRMH: Could you please provide a brief overview of the paper?

Florian: Our goal was to develop the MRE method for time-harmonic multi-frequency elastography, specifically using very low frequencies below 25 hertz. We developed a new modeling framework and a fast imaging sequence to achieve this in clinically acceptable scan times. We tested our technique first in gel samples, and then in human brain and liver. We were able to create very high resolution stiffness elastograms using our wideband multi-frequency approach.

Ingolf: Brain is surprisingly soft at low frequencies; so while we did expect to measure low elasticity values, we obtained values almost half of what we had expected. We were initially skeptical of the accuracy of these results. But then we went to literature, and we found our values fit perfectly. In the liver, we have low SNR with long echo times, and at low frequencies elastograms suffer from noise. This is even worse in fibrosis where the stiffness increases. In the brain, it is the other way around, brain gets softer with most brain disease processes. This softness in the brain enables the use of low frequency vibrations and helps our inversion algorithm. Low frequency vibrations are better transmitted in the body. In fact these waves do actually travel through the entire body, so one can do MRE with one actuator without strong attenuation. This is a big advantage with the lower frequencies compared to conventional MRE.

MRMH: So maybe in the future one can get whole body MR elastography under five minutes.

Ingolf: [laughs] Yes, that is the idea, we are not interested in low hanging fruits. Getting the high hanging fruits is the motivation.

MRMH: Could you comment on the safety of these vibrations?

Ingolf: Vibrations coming from the scanner during normal MR Imaging are sometimes higher in amplitude than the low frequency vibrations we apply for MRE. And there are several advantages of low frequency: safety, homogeneous penetration, and the sensitivity to solid-fluid interactions.

MRMH: What is one key concept you would like the community to remember after reading your paper?

Florian: Low frequency MRE is feasible, and is good for the future of MRE research, as other mechanical properties like poroelasticity come into play.

Ingolf: With the low frequency vibrations, the safety is greater and tolerance for the technique is higher. When we tell the patients that we don't touch their head but we do brain MRE, that helps.

MRMH: What do you do when you are not in the lab?

Florian: I like bicycles which I ride every day, I enjoy cooking, and traveling to places that are peaceful and breathtaking.

Ingolf: Florian, you have a life after the lab [laughing]? For me, I spend time with family, kids, and I love my garden.

That wraps up our discussion with Florian and Ingolf. This group is working on a wide range of applications (fibrosis, cancer, diagnostic MRE for tissue culture analysis), organs (liver, brain, breast) and frequencies (from a few hertz to a few kilohertz). Thus, when Ingolf, being an avid gardener, says that they are heading for the high hanging fruit, we cannot wait to find out what's on their menu next. ■

Ingolf Sack harvesting fruits from his bountiful garden; Florian Dittmann exploring a glacier on his travels.

> *Low frequency MRE is feasible, and is good for the future of MRE research.*
>
> –Florian Dittmann

Diffusion kurtosis imaging at lightning speed

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR NOVEMBER

This month's Editor's pick features a project that makes kurtosis imaging more accessible to clinicians and researchers, alike, from a group in Denmark that includes our interviewees: Brian Hansen and Sune Jespersen. Diffusion kurtosis imaging (DKI) increases sensitivity to microstructural changes by extending the diffusion signal expression to account for non-Gaussian effects, but it typically requires time-consuming acquisitions with high diffusion weighting. Brian and Sune's group had previously described a fast protocol, referred to as the 1-3-9 scheme, that includes three diffusion directions at a low b-value to determine the mean diffusivity and nine specific diffusion directions at a higher b-value to calculate mean kurtosis (Hansen et al., MRM 69, 2013). In this work, they extend the protocol to make it more robust to experimental imperfections by acquiring all nine directions at the lower b-value, which they call 1-9-9. They further characterize the optimum b-values and propose a method to correct for imperfect diffusion directions. Keep reading to find out how their acquisition scheme expands the clinical value and feasibility of kurtosis imaging and you may even be inspired to add this ~1-minute scan onto your own protocol.

Brian Hansen and Sune Jespersen.

MRMH: Tell us a little bit about yourselves. What led you into this project?

Brian: I am a physicist, biomedical engineering-type. I have been interested in microstructural imaging for a while, but the experiments are very remote from the clinical applications. This project attempts to lower the data demands of DKI and make microstructural imaging techniques more suited for the clinic.

Hansen B, Lund TE, Sangill R, Stubbe E, Finsterbusch J, Jespersen SN. Experimental considerations for fast kurtosis imaging. *Magn Reson Med.* 2016;76:1455–1468. doi: 10.1002/mrm.26055

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26055/full

Sune: My background is in theoretical physics, and I am interested in how the diffusion signal reports on microstructure and what information is actually contained in the diffusion signal. I have mostly been working with modeling, but kurtosis imaging is a different approach that is more generic. It is very sensitive but not very specific; nevertheless, it may be a valuable biomarker. It is not very widespread in the clinic yet, so we wanted to lower the barrier: both the analysis and the acquisition times. People are less likely to adopt a time-consuming protocol, especially since they are still not sure how kurtosis might be used. If they can just use a one-minute sequence, it is easier to explore its possible uses and to persuade doctors to add it to their exams.

MRMH: How long does your DKI protocol take and how does that compare to a standard DKI acquisition?

Brian: Most people use a two-shell acquisition with ~30 directions for each b-value in 7 to 10 minutes. With our protocol, we can reduce that to about a minute. That might not sound so impressive, but it makes a big difference for clinicians and can be added cheaply to your protocol.

MRMH: Well a factor of 7 to 10 is pretty impressive!

Sune: I think so, too! You can also trade the time gain for SNR. If you are willing to sacrifice those extra 6 minutes, who wants to say 'no thanks' to extra SNR?

MRMH: Kurtosis is something that a lot of us keep hearing about, but many don't really understand what it is.

Brian: The diffusion kurtosis framework contains diffusion tensor imaging (DTI), but it takes non-Gaussian effects into account. By including kurtosis you partially account for the effects of the microstructure on the diffusion and indirectly become more sensitive to the

microstructure.

MRMH: Is DKI more challenging that DTI?

Brian: Not really in principle, but in practice DKI has some additional experimental challenges. It is acquired with the same sequence as DTI, but with higher b-values where you are closer to a low SNR limit.

Sune: The higher gradients also make things like eddy currents more problematic, and you need more directions with those higher gradients. The estimation problem is also harder because you have more parameters to estimate: 22 in DKI vs. 7 for DTI.

Brian: The fitting is a difficult numerical problem and will be influenced by noise. One advantage of our technique is that it doesn't involve fitting. It calculates the mean kurtosis from a weighted sum of log signals, so that removes a whole set of problems related to analysis.

MRMH: Is the computation time limiting?

Brian: Yes, especially in an acute setting, such as a stroke patient. It can take hours to perform the DKI post processing, so most clinicians would say, 'we can't use that for decision making; we could perhaps use it for follow up', which limits the clinical applicability. In our technique, since there is no optimization procedure, the post processing can be done very rapidly. Jurgen Finsterbusch (co-author) implemented an online reconstruction of these parameter maps for Siemens systems. The code is available as a Siemens c2p sequence. That way the clinician has the maps available to him/her immediately.

Sune: Even for cohort studies, a small computation time is convenient. We all know that in research you rarely have to do anything only once because we often make mistakes the first time around. So, two hours for each brain is a bit of a hurdle.

MRMH: Why might a clinician care about the resulting parameter maps?

Sune: It is not a routine clinical tool yet, but many groups have shown that in various diseases DKI contains complementary information to the DTI parameters.

Brian: DKI has increased sensitivity to microstructural changes. For instance in stroke, DKI has been shown to outline the lesion better than the typical DTI-derived measures. It is also possible to detect more subtle changes earlier in the disease progression for earlier diagnosis, which is crucial for many diseases.

MRMH: Are there any body applications?

Brian: There's growing interest for DKI in the body. We recently published a paper on fast DKI of renal fibrosis, where biopsy is often used to monitor disease, but with many complications. It would be great if we could replace those biopsies with a scan.

MRMH: What makes nine the magic number of directions to measure kurtosis?

Brian: When you measure mean diffusivity you can measure along just three orthogonal directions because the mean diffusivity is proportional to the trace of the tensor. Similarly, we define the mean kurtosis proportional to the trace of the kurtosis tensor so that you can use the same trick, but the kurtosis tensor is bigger so three directions are not enough. The directions you need were derived by Sune… by magic. On a more serious note: we provided a detailed derivation that explains the need for these specific directions. It's available, here, as online supplementary materials for the 1-3-9 paper.

Sune: For DKI you need extra directions to remove unwanted cross-terms, and that turns out to be nine: three orthogonal directions and two directions for each cross term.

MRMH: Are the kurtosis tensor and fractional anisotropy (FA) related?

Brian: In general, the FA relates to the diffusion tensor and is not connected to the kurtosis tensor.

Sune: You can actually have a situation where you have zero FA, but you still have an anisotropic diffusion kurtosis tensor. In practice they might tend to follow, but theoretically speaking they are independent.

MRMH: Where might this project go next?

Sune: We are trying to extend this to not only get the mean kurtosis but also to get two other commonly used kurtosis measurements, axial kurtosis and radial kurtosis. We can estimate basically all kurtosis measures in current use with our protocol.

MRMH: How can other researchers in your field apply your conclusions to their own work?

Sune: We are hoping that many more researchers would be interested in applying this technique, especially in the body. When my collaborators do diffusion imaging in the body they often use trace imaging. This work is basically an extension of that approach to kurtosis, and it might help people find out if kurtosis is a useful biomarker or not.

Brian: We'd also like to say that if anybody reading this is interested in applying the fast kurtosis technique we are very happy to help set up the method, test pilot data quality, and provide analysis scripts. Look us up on http://www.cfin.au.dk. ■

View of Aarhus University in Denmark.

> *There is no optimization procedure, the post processing can be done very rapidly.*
>
> –Brian Hansen

Seeing the invisible by hiding Gibbs ringing

INTERVIEW BY **THIJS DHOLLANDER**

EDITOR'S PICK FOR NOVEMBER

Recently, we had a chat with Elias Kellner, Valerij Kiselev and Marco Reisert from the University Medical Center Freiburg about their MRM paper entitled "Gibbs-Ringing Artifact Removal Based on Local Subvoxel-Shifts." A challenge in time zone management, the interview was an early morning event for the MRM *Highlights* editor (Nikola, in Montreal) and a late evening for the interviewer (Thijs, in Melbourne); however, that didn't stop us discussing not only the paper, but also the art of paper writing and valuable lessons for the developers of novel acquisition strategies.

> *Today, writing a paper is more difficult; nobody has time. You should really fight for your readers' attention.*
>
> –Valerij Kiselev

MRMH: Elias, can you explain us how you got into MRI-related research?

Elias: I entered the world of MRI six to seven years ago when I started my master's thesis. I needed a topic and came across Valerij, working here at the University Hospital. We started a project on perfusion MRI, about a new technique to measure the arterial input function. It involved theoretical modelling and sequence programming. After I finished, things were running so well, Valerij asked me to stay. I continued working for four years on this. One year after I started my Ph.D., I entered Marco's office. We started working together and I also started working on diffusion MRI, which led to this work on Gibbs-ringing.

MRMH: Marco, what about you? I know you're very active in diffusion MRI.

Marco: I did my Ph.D. in computer science. I also ran into Valerij coincidentally, looking for some data while I was working a lot with tensors. MRI seemed like a good fit, because DTI is also based on tensors. I have a machine learning background and at the moment we are focusing on how to apply these ideas (we call it Bayesian techniques) to diffusion MRI. In machine learning, you don't have a complete world knowledge. In physics, however, you may have a nice model and you can simulate things. We actually just have a paper accepted in NeuroImage about applying these ideas to microstructure imaging. That is, how to obtain things like axonal volume fraction in a different way than just fitting models, but using probabilities and distributions on the parameters.

MRMH: Valerij, you're the "most senior" one here. How did you get into MRI?

Elias Kellner

Valerij: I completed a Ph.D. in Moscow, about phase transitions in quantum field theory. Later on, I got an Alexander von Humboldt stipend, which gave me the freedom to work for two years in Germany. I used the last half-year looking for something new that would be more applicable. By chance I came to an MRI group led by Stefan Posse in Jülich. People were writing all the time about imaging; but what do the images mean? Back then, fMRI was a major application. But how are things reflected in the (BOLD) signal? I want to find out about things which you don't see directly – it's like trying to see the invisible. Diffusion MRI is the major discipline in this way.

MRMH: On to the paper! Most of us know and recognise Gibbs ringing very well. Why is it still important to try to correct it?

Elias: For clinicians, if they know where an artifact comes from, it's sometimes easier if it stays there. Their brains are very capable of correcting for it. But when, for example, you calculate something based on two dif-

Kellner E, Dhital B, Kiselev VG, Reisert M. Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magn Reson Med.* 2016;76:1574–1581. doi: 10.1002/mrm.26054
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26054/full

ferent contrasts, then the artifact may change in appearance. In dMRI, when we calculate ADC, we mix two contrasts, so the artifact will even get enhanced!

Marco: Our Bayesian method to estimate the dMRI models, for example, is based on a prior distribution of all possible physically reasonable constellations of the parameters. But the signal that you get after Gibbs ringing is not physically reasonable anymore! Next to a ventricle, you may get a negative kurtosis value. This really challenges the Bayesian method in particular – it's not modelled, it's not in the prior distribution. This also goes for other artifacts, ringing is just one of them.

MRMH: In the paper, you first describe the problem and method in one dimension, and only thereafter move on to 2D. Was this a conscious choice to make it more educational?

Elias: The reason is twofold: it's easier to explain in 1D, but the extension to 2D is also not straightforward in this case.

MRMH: Valerij, how important is the educational value of papers these days?

Valerij: Today writing a paper is more difficult; nobody has time: you should really fight for your readers' attention. I like papers that go step by step. On one hand it has educational value, on the other hand you offer the reader the possibility "to start easily", and after that they can decide to read further or not. But at least, they got something already from the paper. Today, we have so much information and complexity that writing really becomes more like an art.

MRMH: What are the core principles or assumptions the method relies upon?

Elias: Ringing occurs because we try to reconstruct a sharp edge from a finite k-space: high frequencies are missing. But because we reconstruct on a grid, we don't need the high frequencies if we sample the edge "in a good way", so that we hit the zero crossings of the sinc point spread function (PSF), which arises from these high frequencies missing.

Valerij: Shortly, if you do a Fourier transform, inevitably you have ringing. But you can move a little bit back and forth to make it invisible when you sample it on a grid. It's still there, but it is invisible for us.

MRMH: [playing devil's advocate]: Why not 'simply' use median filtering, or a total variation regularizer during the reconstruction?

Marco: These methods may make the image look more smooth, and may also remove (some) noise. But we try to keep the image as clean as possible, and also not touch the noise.

Elias: Whereas the filtering strategies cannot differentiate between noise and artefact.

Marco: Exactly. Unlike in filtering, you can apply our method two times, and the result would not change.

MRMH: Can you explain to our readers why you actually want to retain noise?

Marco: Well, we don't know if it's noise, or a feature!

Valerij: So we do it in a clean way – just remove the artifact, nothing else.

Marco: If we destroy the noise, we have no idea about the noise distribution any more, and it may actually become impossible to separate it from the signal. Imagine for example what would happen to the smart denoising methods recently proposed by our colleagues, Jelle Veraart and others, at NYU. (Read more from Veraart et al in the July 2016 *Highlights* interview).

MRMH: Are there limitations to the method, or is it always a no-brainer to apply?

Elias: It won't fully work for partial Fourier acquisitions. The assumption is that you have full, symmetric, k-space data. If zero-filling is needed, the rings have a longer distance and our method cannot remove them. Otherwise, it can be applied safely. It's a very surgical operation; if there's no ringing, it will do nothing.

MRMH: Any (future) hopes for tackling the non-Cartesian acquisitions?

Marco: The PSF of a partial Fourier acquisition is complex. We don't know the distance of the zero crossings… it's very irregular.

Elias: Perhaps if you use projections on convex sets (POCS).

Valerij: Fortunately, Cartesian acquisitions are still the most common.

MRMH: So, any particular messages to the developers of these "fancy" new acquisition strategies?

Elias: If your fancy method introduces complex artifacts, and the benefits are not so high, it doesn't really help you.

Marco: Of course, with simple EPI, everything is nice (if there's no partial Fourier).

Valerij: There is no free lunch! A faster acquisition never comes for free. Every acronym should come with a list of compromises.

MRMH: How can our readers access and use your method?

Elias: There is an open source Matlab implementation and an FSL plugin available online! (www.bitbucket.org/reisert/unring) ■

Valerij Kiselev, Elias Kellner, and Marco Reisert perform a live action simulation of Gibbs ringing.

> *We try to keep the image as clean as possible, and also not touch the noise.*
>
> –Marco Reisert

When sparsity and low-rank meet: ALOHA!

INTERVIEW BY **XIN MIAO**

EDITOR'S PICK FOR DECEMBER

Dongwook Lee is currently a Ph.D. student at the Korea Advanced Institute of Science and Technology (KAIST). He works on advanced image reconstruction techniques for dynamic MRI. His paper, selected as the Editor's pick for December, is entitled "Acceleration of MR Parameter Mapping Using Annihilating Filter-based Low Rank Hankel Matrix (ALOHA)." ALOHA is a novel image reconstruction algorithm with the goal of clear, artifact free images acquired from very fast imaging schemes. For this paper, ALOHA was applied to accelerated MR parameter mapping, but could also be used for dynamic and parallel MRI, and even non-MR applications. We recently invited Dongwook and his supervisor, Dr. Jong Chul Ye, to talk about this paper.

> *We realized that the killer application of ALOHA should be accelerated MRI.*
>
> –Jong Chul Ye

MRMH: Can you tell us a little about your academic background?

Dongwook: I'm a third-year Ph.D. student at KAIST. I also did my bachelor's and master's degrees here.

Jong: I am currently KAIST endowed chair and a professor at the Department of Bio and Brain Engineering. For the past 11 years at KAIST, my research has been focused on compressed sensing (CS) image reconstruction, signal processing, and machine learning for medical imaging applications such as MRI and CT.

MRMH: ALOHA is an interesting name. How did you come up with it?

Jong: Regarding the name "ALOHA", it stands for Annihilating filter-based LOw-rank Hankel matrix Approach. Looking back to when we discovered the algorithm, I asked my student to invent a nice name, so that people could easily remember it. The student brought me several candidates, but as soon as I saw this name, I immediately thought "ALOHA" is perfect because it has all the important terms, and moreover it gives very positive feelings. What a coincidence that the coming ISMRM will be held on ALOHA island!

MRMH: Can you explain the main idea and inspiration behind this paper?

Dongwook: Compressed sensing (CS) tries to reconstruct an image from sub-Nyquist sampling by exploiting the sparsity of the image in certain transform domains. The main idea of ALOHA is converting the CS problem to a weighted k-space interpolation problem. In ALOHA, a structured matrix, called Hankel matrix, is constructed from weighted k-space data. If the MRI images are sparse in a certain transform domain, such as total variation or wavelet, we expect the corresponding Hankel matrix to be rank-deficient. Based on this theory, image reconstruction is formulated as a low-rank matrix completion problem.

Dongwook Lee and Jong Chul Ye.

Jong: The original form of ALOHA occurred through serendipity. My former student, Kyong Hwan Jin, was testing various interpolation approaches for optical microscopy (not MRI). He showed me excellent interpolation results using structured matrix completion. We spent several months to establish the mathematical framework, which gave birth to the theory behind ALOHA. Then we realized that the killer application of ALOHA should be accelerated MRI.

MRMH: Can you explain the dual relationship between sparsity and low-rankness?

Dongwook: This duality comes from basic signal processing: the multiplication in spatial domain corresponds to convolution in Fourier domain. If an image A is sparse in the spatial domain, then we can find an

Lee D, Jin KH, Kim EY, Park SH, Ye JC. Acceleration of MR parameter mapping using annihilating filter-based low rank hankel matrix (ALOHA). *Magn Reson Med.* 2016;76:1848–1864. doi: 10.1002/mrm.26081
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26081/full

annihilating function B to make the product of A and B equal zero. Equivalently, in Fourier domain, we can build a discrete convolution matrix from the Fourier transform of image A. This convolution matrix should have low rank because the multiplication of it with an annihilating filter is zero.

Jong: The images don't have to be sparse in the spatial domain. If they can be sparsified using some transformation, then we can apply an appropriate k-space weighting based upon this transformation. After the weighting, we are able to interpret sparsity in the image domain as low-rankness in the Fourier domain.

MRMH: What's the biggest difference between ALOHA and other low-rank based methods, like kt-SLR and LORAKS?

Jong: SAKE, LORAKS, and ALOHA arrange k-space data into a structured Hankel matrix. These methods all rely on the low-rank property of the Hankel matrix to reconstruct images. SAKE exploits multi-coil correlation, LORAKS exploits finite spatial-support or smooth phase condition, and ALOHA reformulates sparsity in the transform domain as low-rankness in Fourier domain. Before forming the Hankel matrix, ALOHA applies a weighting to k-space data, based on the chosen sparsifying transform. In this way, ALOHA can be applied in more general situations where a suitable sparsifying transform is found. In addition, ALOHA also allows data redundancy in any dimension to be exploited in the same framework. For example, for dynamic imaging applications, ALOHA constructs the Hankel matrix from k-t space data. To integrate parallel imaging, ALOHA stacks multi-channel data side by side.

Dongwook: While kt-SLR also exploits low rank properties, it is different from ALOHA-like methods because its matrices do not have Hankel-like structure. Kt-SLR stacks vectorized dynamic images from all time frames with high temporal correlation to create a low-rank matrix. Note that kt-SLR keeps the original structure of the matrix without lifting to a Hankel-like structure.

MRMH: Can you talk about the advantages of ALOHA compared to existing CS methods?

Dongwook: The most important advantage of ALOHA is accuracy. ALOHA's annihilating filter exploits the edge information, so the edges are reconstructed reliably. Reconstruction error appears as random noise rather than structured noise along the edges in conventional CS. This could be an important advantage in clinical applications.

MRMH: Why is parameter mapping your application of choice for ALOHA?

Dongwook: If you look at any T_1 and T_2 dataset, contrast changes over time but structure is maintained, indicating sparsity in the x-f space. Because of this sparsity, we can construct a rank-deficient Hankel matrix from weighted k-t space measurements.

Jong: Parameter mapping demonstrates advantages of ALOHA over existing methods. We have previously tried global and locally low-rank approaches on parameter mapping. However, above a certain acceleration factor, global and locally low-rank methods leave unresolved aliasing artifacts, which can indicate a need for constraints beyond the low-rankness due to temporal correlation. Therefore, we wanted to further explore the low-rankness resulting from x-f sparsity using ALOHA.

MRMH: I'm sure ALOHA is not limited to parameter mapping. Is there any other application where ALOHA might be helpful?

Dongwook: Yes. Another interesting application of ALOHA is Nyquist ghost correction in EPI, which is the research work of my colleagues, Juyoung Lee and Kyong Hwan Jin. The mismatch between odd and even lines causes Nyquist ghosting artifact in EPI. We have proposed that such artifacts can be corrected by solving a k-space interpolation problem using ALOHA. Specifically, the odd and even lines were separated from the EPI dataset and stacked side by side in the form of a Hankel matrix. Due to the high correlation between the odd and even samples, this Hankel matrix should be rank-deficient. This work was also published in the current issue of MRM.

Jong: We have applied ALOHA for dynamic MRI, parallel MRI as well as MR artifact correction. ALOHA can even be used for non-MR image processing applications such as image inpainting and super resolution microscopy. ■

Jong Chul Ye, Juyoung Lee (Ph.D. student), and Dongwook Lee at Korea Advanced Institute of Science & Technology.

> *ALOHA's annihilating filter exploits the edge information, so the edges are reconstructed reliably.*
>
> –Dongwook Lee

De-noising fMRI with low-frequency oscillations: Not your grandma's pre-processing

INTERVIEW BY **MARK CHIEW**

EDITOR'S PICK FOR DECEMBER

Two days after American Thanksgiving, we had the opportunity to speak with Lia Hocke, Yunjie Tong, and Blaise Frederick about their recent MRM paper "Comparison of Peripheral Near-infrared Spectroscopy Low-frequency Oscillations to Other Denoising Methods in Resting State Functional MRI with Ultrahigh Temporal Resolution." Working out of the McLean Hospital, part of Harvard Medical School, they shared their perspective on the mutual information contained in peripheral NIRS (near infrared spectroscopy) and fMRI signals. They also used the word "photoplethysmograph" correctly in a sentence, and left us with a delightful shout-out to statistical rigor.

> *We believe that the whole body has these low-frequency oscillations which propagate everywhere.*
>
> –Yunjie Tong

MRMH: Tell us a bit about yourselves, and how you got into imaging research.

Lia: I was always interested in how the mind works – in elementary school, when asked about my dream job, I'd always say "psychologist". My bachelor's degree was in psychology, at the University of Maastricht. I continued there with my master in clinical and cognitive neuroscience with Rainer Goebel as my supervisor, and he recommended Blaise's lab, so this is where I got into NIRS imaging and fMRI, and stayed for my Ph.D. in biomedical engineering.

Yunjie: I was in biomedical engineering at Tufts, working with NIRS, and after I graduated in 2008, Blaise offered me a post-doc at the McLean Hospital. Here (I'm still at McLean) we were able to do concurrent NIRS and fMRI, which has been going on for the past 8 years.

Blaise: I went to work for John Gore (at Yale) for a while, and decided that imaging was what I wanted to do. I then went to Tom Budinger's lab at Berkeley, and got my Ph.D. in stochastic NMR. After that, I came here as a post-doc to McLean, and have been here ever since.

MRMH: Can you give us a brief summary of the paper?

Lia: We compare several low frequency fMRI denoising methods, relying on respiratory and cardiac recordings, and one which we developed that uses a different method, NIRS, which measures similar effects as fMRI. What came out was that we see high variance reduction with NIRS low-frequency oscillations (LFOs), which measure information distinct from the respiratory and cardiac models, used as the gold standard comparison.

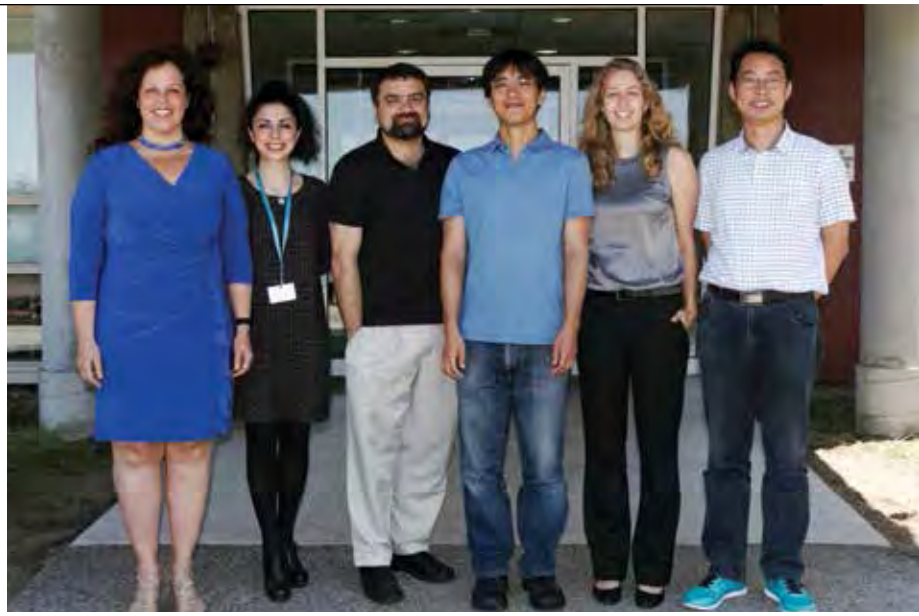
Lia Hocke

Yunjie: The key point of the paper is the LFOs might not be the result of respiration and heart beat effects, and might have their own origin and function. So this paper mainly compares this LFO signal, which we believe is an independent physiological process, with current respiratory and cardiac models to see if they are the same or not.

Blaise: What we're finding now as we're going to multiband sequences and much faster acquisitions, we can ask whether the low frequency effects we attribute to cardiac (and respiratory effects) are caused by aliasing or are fundamental. I think what we've concluded is that

Hocke LM, Tong Y, Lindsey KP, de B Frederick B. Comparison of peripheral near-infrared spectroscopy low-frequency oscillations to other denoising methods in resting state functional MRI with ultrahigh temporal resolution. *Magn Reson Med.* 2016;76:1697–1707. doi: 10.1002/mrm.26038
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26038/full

Senior author, Blaise Frederick.



The Opto-magnetic Group (OMG) at McLean Hospital, a Harvard Medical School Affiliate. From left to right: Kimberley Lindsey, Sinem Erdogan, Blaise de Frederick, Yunjie Tong, Lia Hocke, and Yingwei Li.

it's not being caused by respiratory and cardiac fluctuations – it's its own thing.

MRMH: How exactly are pulse oximetry and NIRS related?

Lia: They're actually not that different – pulse oximeters just cut out the low frequencies we're interested in.

Blaise: Fundamentally, a PPO (photoplethysmograph) is a NIRS spectrometer. For PPO, all you care about is heart rate and blood oxygenation, and to look at those you only want to look at cardiac frequency bands, so you filter out all the low-frequency information. The hardware is identical, and it's the software that's different (if you're looking at the finger).

MRMH: What is the impact of looking at a peripheral NIRS signal, instead of one closer to the head?

Yunjie: We have tried measurements on different locations, and in summary, we believe that the whole body has these low-frequency oscillations, which propagate everywhere, starting from the heart/lung system. As it goes along different paths, it picks up different noise along the way, so we want to find a recording location where the low-frequency oscillations are the most representative of those in the brain. We tried different locations, and to really avoid picking up neuronal activation, so far the earlobe has been the best, so that's what we're going to do next.

Blaise: If you look at vascular architecture, the earlobe is fed by the auricular artery which comes off of the external carotid, after it branches from the internal carotid, so it really is pretty much what is going into the brain.

MRMH: Thanks for doing this. Do you have any last comments, or shout-outs?

Yunjie: I wanted to point out a very interesting point in the paper, in that Lia performed an extensive study on how the correlations can be "incorrect" under certain circumstances. For example, when you low-pass filter your signals, you exaggerate your correlation values. I think that's a critical point of the paper, that when you rely on correlations, you have to be really careful about filtering or processing of your signals.

Lia: I completely agree! One shout-out would be what you just said, don't abuse your p-value and look at your data. Also a shout-out to the first reviewer of our paper, who first let us know that statistical methods don't work in the way we were initially trying to use them.

Blaise: People are just not used to looking at low-pass filtered cross-correlations. The standard methods for determining significance aren't valid. It's not something that I think has been laid out anywhere near as clearly as Lia did in the paper (the problem or her solution). If I had to guess 10 years from now, I would say at least half the citations to this paper will be for that part, and not for the main message. ■

Yunjie Tong

> *Correlations can be incorrect under certain circumstances.*
>
> –Yunjie Tong

Improvements in Amide-CEST-MRI: Just the tip of the iceberg

INTERVIEW BY **BLAKE DEWEY**

EDITOR'S PICK FOR JANUARY

In the early days of 2017, we sat down (virtually, of course) to have a conversation with Moritz Zaiss, Johannes Windschuh and Alexander Radbruch. Our topic was their recent MRM paper, "Downfield-NOE-Suppressed Amide-CEST-MRI at 7 Tesla Provides a Unique Contrast in Human Glioblastoma." Chemical Exchange Saturation Transfer (CEST) imaging is an indirect imaging technique for the protons of certain metabolites, where saturation is applied off-resonance (with respect to water). Saturated protons are allowed to exchange with water protons and then imaged using conventional imaging methods. However, frequency selection is not always enough to specifically target a functional group, such as amide groups, which are common in CEST imaging methods, producing a "mixed" contrast. Moritz, Johannes, and Alexander, together with others in their group, have been slowly removing confounding effects in an attempt to isolate the measurement of amide proton transfer. In this paper, they continue their efforts by removing the downfield Nuclear Overhauser Effect (NOE), resulting in clinically relevant findings and correlation with gadolinium uptake in patients with glioblastoma.

> *Finally, after all the effort to isolate this amide effect and test it, we could apply it in glioblastoma patients*
>
> –Moritz Zaiss

MRMH: Moritz, to break the ice a little bit, how did you get started in MR research?

Moritz: Well, I actually did solid state physics for quite a while, but decided to move to a more applied field, and move from solid state to not-so-solid state, which was the human body and especially the brain.

MRMH: And Johannes, what brought you into MR?

Johannes: Well, my way was more direct. I started with hyperpolarized MRI and Moritz got me over to the CEST side of things and that is where I stayed.

MRMH: Finally Alexander, you come from the clinical side of things, but what got you into MR research?

Alexander: Actually, I got fascinated by the images. I was always very interested in physics and built strong relationships with our great physics d epartment in Heidelberg. That's why I decided to study radiology, and ever since I have been working closely together with the physics guys like Moritz and Johannes.

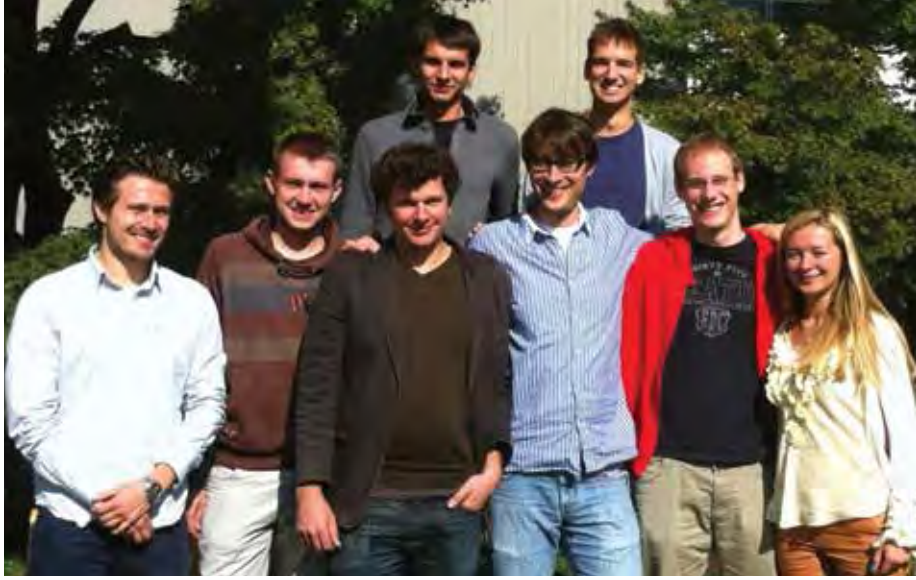
MRMH: That's a great relationship to have. Moving onto your research, can you summarize your method for us?

Moritz: One of the first CEST contrasts detected *in vivo* was amide proton transfer, which we tried to isolate as best as possible in this work. CEST is an indirect measurement via the water pool, which is comparable to estimating the size of an iceberg by using only what is visible above the surface of the water. The apparent height of the visible tip will not only depend on the total shape of the iceberg, but also on the density of the surrounding water, and on the amount of snow on the iceberg. Similarly, the "amide" CEST signal at 3.5 ppm, is in principle affected by water relaxation and concomitant semi-solid MT, and 'some snow' which would be other CEST contributions. The big idea of this work is to separate all of these contributions and isolate the one originally aimed at amide proton transfer. More techni-

Moritz Zaiss

Zaiss M, Windschuh J, Goerke S, Paech D, Meissner J-E, Burth S, Kickingereder P, Wick W, Bendszus M, Schlemmer H-P, Ladd ME, Bachert P, Radbruch A. Downfield-NOE-suppressed amide-CEST-MRI at 7 Tesla provides a unique contrast in human glioblastoma. *Magn Reson Med.* 2017;77:196–208. doi: 10.1002/mrm.26100
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26100/full

Alexander Radbruch



The research group in Heidelberg, Germany.

cally speaking, the peak 3.5 ppm downfield from water seems to originate not only from amide protons, but also from a pool with dipolar-coupled NOE-like behavior, which is not pH dependent. So, we measured the well-known upfield NOE effect and used this to remove the downfield NOE effect and also isolate the pH dependent exchange effect. Then, by correcting for water relaxation, semi-solid MT, and B_1 inhomogeneity influences, we could estimate the total iceberg from the tip of the iceberg. Finally, after all the effort to isolate this amide effect and test it *ex vivo*, we could apply it in glioblastoma patients and what we saw was surprising; the isolated amide contrast showed a very strong correlation to gadolinium uptake not only in the same region – as APT did already before, but really showing very similar structures.

MRMH: What is the strength of this method? How would you convince the Chief of Radiology to use your method?

Alexander: In my experience, it is actually quite easy to convince them to put it into clinical life, if you highlight that we are in desperate need of new sequences. If you look at the criteria for radiological assessment of neurooncology, they say we rely on T_1- or T_2-weighted imaging. If we focus on T_2, we want to know is it invasive tumor or is it only edema? This has major clinical relevance for the patient, as they may be taken to the operating room again, or not, depending on the assessment. We cannot say it is an easy answer with CEST, but it is a new chance to finally have a sequence with *in vivo* access and with the benefit that we don't need contrast agents.

Moritz: I think it is a major strength that without any contrast agent, we see the same regions that are defined on gadolinium-enhanced scans. So, we see something on the metabolic level which corresponds to what we know is an affected region.

MRMH: Now for the hardest question for researchers, what is your method's weakness?

Johannes: We gain so much from the higher field strength at 7 Tesla, but there are always problems. B_1 inhomogeneity is one that we solved with a simple method of measuring at multiple B_1 values, but that increases the measurement time. Measurement time is always of the essence, so this is critical, of course, in the clinic. In addition, we are also dependent on so many points in the Z-spectrum, so this also means even longer measurements.

Moritz: Maybe a last weakness to add is that it is a single slice method and this is a bad thing for clinicians.

MRMH: Is going to multi-slice the next technical step?

Moritz: It's actually in the pipeline. We were able to extend our sequence to 3D, and that can now be used in forthcoming studies.

Johannes: In addition, all of the contrasts have to be evaluated on how to use them. Maybe there are different diseases that are interesting for different contrasts, like NOE.

Alexander: Actually, my task is always to keep my physics friends on track and focus them on what we need in the clinic. I love the potential of 7 T and 9.4 T, but this should also be possible at 3 T.

Moritz: And I argue that you should buy a 7 T, because it is much more fun for the physicists. ■

Johannes Windschuh

> *A major strength is that without any contrast agent, we see the same regions that are defined on gadolinium-enhanced scans.*
>
> –Moritz Zaiss

Everything in its right place: The FID-A spectroscopy software package

INTERVIEW BY **BENJAMIN DE LEENER AND NIKOLA STIKOV**

EDITOR'S PICK FOR JANUARY

In early 2017, the *Highlights* team had our first ever in-person interview with authors of this January's Editor's pick. For this historic event, we met with Gabriel Devenyi and Jamie Near, researchers at the Douglas Mental Health University Institute in Montreal, and authors of the recent MRM article "Advanced Processing and Simulation of MRS Data Using the FID Appliance (FID-A) – An Open Source, MATLAB-Based Toolkit." It was noon on Friday, and we decided to get an early start on the weekend by heading to a most Canadian interview location: a skating rink at Beaver Lake in Montreal. Over beer and bison hamburgers, we discussed spectroscopy, open science, and the musical inspiration behind the acronym FID-A.

> *The main feature is it is designed for raw data, whereas most other tools are for data that have already been averaged.*
>
> –Jamie Near

Gabriel Devenyi and Jamie Near.

MRMH: Tell us a bit about yourself and your background.

Jamie: I am assistant professor at the department of psychiatry at McGill, with an affiliation with the biomedical engineering department as well. My background is in physics and engineering and my research focuses on developing methods for MR spectroscopy (MRS) of the brain, both in humans and in animals. I did my undergrad at Queen's University in engineering physics, my Ph.D. in biophysics at the Robarts institute (University of Western Ontario), and my postdoc at the FMRIB Centre in Oxford.

Gabriel: I am a research computing engineer at the Douglas Institute. I did my undergrad in engineering physics at McMaster University, where I stayed on to do my Ph.D. in semiconductor physics, nanocrystals and electro-optics. I then had a lateral shift into computing as a Software Carpentry volunteer, and that is how I heard about a software opportunity at the Douglas. Now I support both computing and open science work at the Douglas Institute, where I work with Jamie and others to contribute open-source software to the community.

Jamie: Gabriel encourages everyone in our lab to do open science related things.

MRMH: Talking about open science, could you talk a little bit about your research and the FID-A software package?

Jamie: I wrote the actual code of the software during my postdoc at the FMRIB in 2010 or around that time. It was already known that MRS preprocessing could

Simpson R, Devenyi GA, Jezzard P, Hennessy TJ, Near J. Advanced processing and simulation of MRS data using the FID appliance (FID-A) – An open source, MATLAB-based toolkit. *Magn Reson Med.* 2017;77:23–33. doi: 10.1002/mrm.26091
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26091/full

improve our data, but there was no publicly available software to read and process data in [the] original RAW format. So, I wrote my own software using MATLAB to have access to averages, coil channels, and sub-spectra. At the same time, Peter Jezzard and I co-supervised a Master's student, Robin Simpson, and he wrote some nice code for NMR simulation in MATLAB, which is the basis of the simulation part of this toolkit. Even though Robin only worked on it for four months, he made a lasting contribution. I have used that code for many years, but it was only two years ago that Gabriel encouraged me to make this publicly available and open source. Back then I didn't even know what Github was!

MRMH: What are the main functionalities of FID-A?

Jamie: The software itself is composed of three parts: the first part is the processing toolkit, including frequency drift, phase drift correction, removal of motion corrupted averages, filtering, eddy current correction, etc. The main feature is it is designed for raw data, whereas most other tools are for data that have already been averaged. The second part is the simulation toolkit, for doing density matrix simulation for *in vivo* spectroscopy data to predict what the spectra would look like. And then there is the RF pulse toolkit to analyze RF pulse shapes. By the way, the name "FID-A" is actually a tribute to the excellent Radiohead album, Kid A!

MRMH: That's awesome. How many people are using the software now? Do you have statistics about that?

Jamie: About 100 visitors on Github every two weeks currently, which is quite a lot considering the small community.

Gabriel: Since I started working on open-source software, this has been our most downloaded work, and seems like it will be my most cited paper. As an aside, open science projects tend to have higher citation rates, something I've lectured on before at the Douglas.

Jamie Near and Gabriel Devenyi have become adept at coding during the icy Canadian winters.

MRMH: What kind of challenges did you face when releasing FID-A?

Gabriel: The big challenge with releasing open-source software is writing enough documentation for a typical user. As somebody who knows the software well, I have lots of blind spots, meaning I don't know what other people don't know.

MRMH: How do you ensure that the software keeps its accuracy and reproducibility?

Jamie: For simulation, there are good ways of testing accuracy, such as acquiring phantom data and comparing it to your simulations. At some point, we did find discrepancies between GABA simulations and phantom results. The problem was actually with the published chemical shift and coupling values for the GABA spin system, and this led to a paper to update those literature values.

Gabriel: Going forward with the reproducibility, we are looking at implementing continuous integration with Travis and Github. So we are planning unit tests for this code, to make sure it is consistent with previous results. If there are discrepancies we will investigate carefully.

MRMH: Why did you choose MATLAB for an open-science project?

Gabriel: MATLAB is most commonly taught in engineering classes, so it makes sense that an engineer would choose it first. There are also many tools in the neuroscience community that are written in MATLAB, so we can benefit from that. Going forward we want to test compatibility with Octave, the main challenge being the graphical interface. However, if I am writing a software from scratch, I would usually use another language, such as Python.

MRMH: Do you recommend labs to openly release their software and research?

Jamie: Yes, definitely. It's a great way to maximize the wider impact of the code you write, and to improve the replicability of research between sites. I should mention that even this software benefited from scientists sharing and being open about their work. Although they are not co-authors on the paper, this toolkit contains contributions from lots of other people, including as Philipp Ehses, Martyn Klassen, Richard Edden, Ashley Harris, Kimberly Chan, and Saad Jbabdi. Thanks to all of them! ■

***Highlights* team members, (clockwise from left), Benjamin De Leener and Nikola Stikov, chat with Jamie Near and Gabriel Devenyi over a cold drink at Beaver Lake in Montreal, Canada.**

> *The big challenge with releasing open-source software is writing enough documentation for a typical user.*
>
> –Gabriel Devenyi

Paired but not coupled: A dipole completes the loop

INTERVIEW BY **RYAN TOPFER**

EDITOR'S PICK FOR FEBRUARY

Among the Editor's picks for February comes a paper from the Center for Magnetic Resonance Research at the University of Minnesota, where they've paired loops with dipoles for a novel hybrid transceiver. Last year, we featured the work of Alexander Raaijmakers (second author of the current work) on the fractionated dipole antenna design and we published the feature under the headline, "We need antennas – not coils!" To understand this seeming about-face, we confronted Arcan and Greg over Skype about their decision to defy their collaborator's unconventional wisdom.

> *We don't really need antennae or coils, per se. What we need is B_1! And efficient B_1 at that – both with respect to input power and local SAR.*
>
> –Gregory Metzger

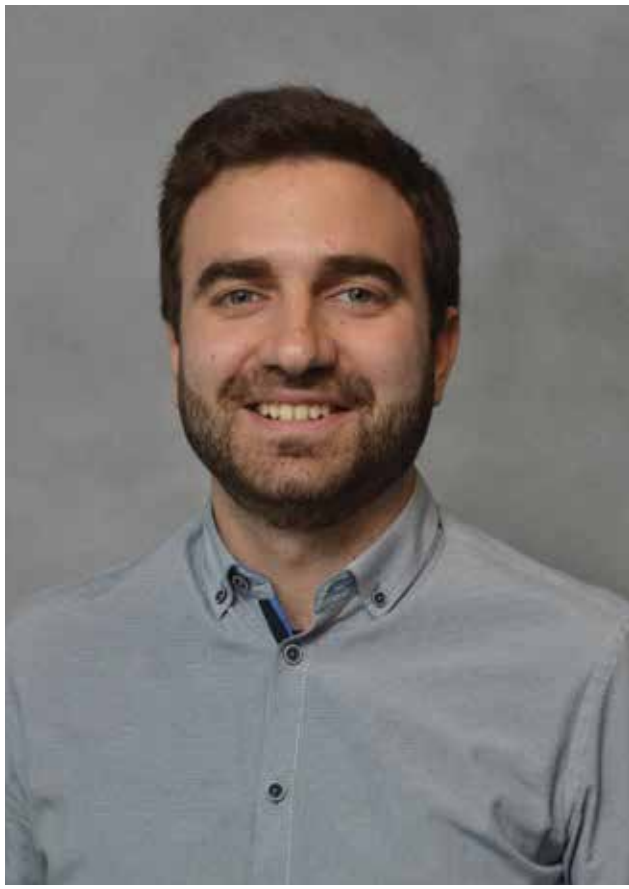
MRMH: So here you are using coils again… What gives?

Greg: We don't really *need* antennae or coils, per se. What we need is B_1! And efficient B_1 at that – both with respect to input power and local SAR.

Arcan: We really liked the performance of the dipoles but fitting more than 10 of them around the body was not practical. We have 16 channels to our transmit system and wanted to make full use of them, but adding more dipoles wasn't optimal.

Greg: The decoupling of the dipoles was achieved by placing them a certain distance apart, so we didn't need active decoupling, but it was clear that if we wanted to get a higher density of elements then we'd have to come up with another strategy. There were a lot of nice characteristics to the dipole – on top of the performance advantages that Alex had shown – which we were interested in pursuing and quantitatively comparing against our previous arrays.

Arcan: Our idea was to add loop coils under the dipoles as transceiver elements since they should be inherently decoupled. So we tried that – eight dipoles, each with a loop underneath – increasing the channel count without increasing the complexity of the design. Antennas perform great, but loops are complementary: close to the surface and in the intermediate region, you get an advantage using loop coils; but in deep regions the dipole antennas tend to perform better. In addition, with the loop-dipole array we no longer have to tune and match, compared to our previous body array designs. We just place the coil on the subject and send them right into the scanner. The new array is also lighter than previous designs, which is good for patient comfort.



Arcan Erturk

I'd like to point out that this isn't the first loop-dipole work. Yigitcan Eryaman did some numerical work with a spine array showing that placing dipoles inside loops could potentially reduce SAR, and Graham Wiggins also experimented with loops and dipoles for a head coil. But here we really have the first implementation of such a transceiver dipole-loop coil, which we're now using for all of our body imaging studies at 7 T.

Ertürk MA, Raaijmakers AJ, Adriany G, Uğurbil K, Metzger GJ. A 16-channel combined loop-dipole transceiver array for 7 Tesla body MRI. *Magn Reson Med.* 2017;77:884–894. doi: 10.1002/mrm.26153
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26153/full

MRMH: Adding the loops doesn't seem to raise SAR. Why not?

Arcan: The highest SAR of the dipole antenna is right beneath the feed-point, which is positioned in the middle of the loop, whereas, for the loop, peak SAR tends to be right beneath the conductor. So they don't coincide. There's some constructive addition at one side of the loop, with destructive interference at the other side – these regions move to the left or to the right depending on the transmit phase difference between the dipole and loop elements. There's an animation available in the supplementary materials section of our paper showing this.

Greg: Again, they're really complementary structures in terms of the SAR distributions as well as their B-field distributions.

Gregory Metzger

MRMH: We've crowd-sourced a question to Jason Stockmann at the Martinos Center who says: "This is a cool idea. My question would be how you get the two coils to work together like this, each with the desired current distribution, while only having one resonance? My intuition is that the loop and dipole would each have their own resonance and would therefore couple and split the resonance. But they seem to have accounted for this, maybe by geometrically decoupling the two."

Arcan: Yeah, it's using geometric decoupling. If you place a dipole exactly in the center of a loop, they're inherently decoupled from each other due to the different current patterns. That's the beauty of using dipoles and loops together. If you move the dipole away from center, you'll see increased coupling.

Greg: Right. But there was still a disconnect between simulation and implementation that needed to be addressed.

Arcan: All this works well when you simulate it, but when you actually go to build it, the cables and feed-points can disturb some of the symmetry. That's why we chose to feed the loop from the bottom as opposed to the side, and to use baluns at the feed-points to minimize the interaction between the cable and the dipole and loops. Also, securing the cables made the design more stable, since if you let them move around freely they can produce coupling.

MRMH: What's the next step?

Arcan: It could be to increase the number of channels. In Utrecht, Alex and his group are working on a similar project but instead of having a single receive loop beneath each dipole, having multiple receive loops stacked along the z dimension.

Greg: We have an abstract at this year's ISMRM (abstract #4902) presenting work on a 32-channel transmit coil which is essentially this design, but with 3 loops – each an independent transceiver – beneath each of the dipoles.

Right now our approach to body coils is essentially "one size fits all" – whether we're looking at prostate, kidneys, heart, or any anatomy in the torso. But coil designs could be tailored for different anatomies, so you might have larger loops, for example, to hit deeper structures, or more elements along each dipole to handle larger fields of view along z.

MRMH: What would it take to get our hands on a loop-dipole array?

Greg: The design isn't too complicated – it could be replicated from the manuscript other than maybe some minor details that we'd be happy to fill anyone in on if they're interested.

Arcan: Anyone with some experience building RF coils could reproduce this, it's fairly straight-forward.

Greg: Especially compared with our previous bread-and-butter body coil, which had a lot of components (Teflon blocks, tunable capacitors, decoupling circuitry between ground planes and the conductors), the loop-dipoles blocks are very easy to deal with. So along with its efficiency in terms of B_1^+ and SAR, this makes it a really useful coil. I don't see anything competing with it yet! Though I still hold out hope that there's something better, so we'll keep innovating and looking out for developments coming out of other groups. ■

> *That's the beauty of using dipoles and loops together. If you move the dipole away from center, you'll see increased coupling.*
>
> –Arcan Erturk

Faster isn't always better: Echo time optimization in MRS

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR FEBRUARY

The February 2017 Editor's pick is from Kimberly Chan and Richard Edden, researchers at John Hopkins University and the F.M. Kirby Center for Functional Brain Imaging in Baltimore. Their paper presents a study aimed at optimizing the echo time for measuring glutathione using J-difference editing. Glutathione is the brain's main antioxidant, and may play an important role in several psychiatric and neurological illnesses, such as schizophrenia, bipolar disorder, and Parkinson's disease. We recently spoke with Kim and Richard about their project.

Kimberly Chan on the big gunpowder trail in Maryland.

Chan KL, Puts NA, Snoussi K, Harris AD, Barker PB, Edden RA. Echo time optimization for J-difference editing of glutathione at 3T. *Magn Reson Med.* 2017;77:498–504. doi: 10.1002/mrm.26122
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26122/full

MRMH: Please introduce yourselves and tell us about your background.

Kim: I'm a third year Ph.D. student at John Hopkins in Biomedical Engineering. I did my bachelor's degree in Bioengineering at Yale. After I graduated, I did diffusion MRI research for a year. My current advisors are Richard Edden and Peter Barker. I work primarily on the development of spectroscopy and spectroscopic imaging methods.

Richard: I studied in Cambridge, and then came to Hopkins to do a post-doc in 2005, doing small molecule pulse sequence design. I left for a bit, and came back in 2009. Our group is mainly focused on developing acquisition tools and data processing tools for edited magnetic resonance spectroscopy (MRS), and disseminating them.

MRMH: Before getting into the details of you paper, could you explain what you mean by J-difference editing?

Richard: The basic problem with proton MRS is that there are a lot of protons in the brain, and the chemical shift separation is not particularly good. What we try and do with J-difference editing is to quantify some of the signals that are less strong and are overlapped in the spectrum. Editing the spectrum amounts to removing information from that spectrum to improve the resolution – throwing out a bunch of signals we are less interested in, and retaining some signals that we are interested in.

Kim: So, in J-difference editing, there are two types of sub-acquisitions: one where an editing pulse is placed on-resonance for your metabolite of interest, and one where it's not. When you apply these editing pulses, it refocuses the J-coupling of your metabolite of interest. When you subtract your off scan (where these editing pulses are not applied) from the on scans, you get a difference spectrum, and that's where the J-difference comes from.

MRMH: Could you briefly explain what you did in this work?

Kim: We wanted to determine the optimal echo-time to measure glutathione with J-difference editing. We looked into this using simulations, phantom experiments, and *in vivo* experiments. We found that the optimal echo time was about 120 ms, taking account of *in vivo* T_2 losses. As a secondary benefit, the longer echo time lets us include higher-bandwidth refocusing pulses, which reduces signal loss from the chemical shift displacement artifact.

Richard: Within the literature, there are conflicting reports of the echo time that is best for glutathione editing. The discussion is complicated by the fact that you get a sinusoidal dependency of the signal from editing, and exponential T_2 decay on top of that, and these two are fighting against each other. A lot of the motivation in this paper was to lay to rest, to some extent, the discussion about what the spin system does, and try to present it as clearly as possible.

MRMH: We noticed that you have an online software package called Gannet. Was Gannet used in this work?

Richard: So, Gannet is a preprocessing and quantification package for edited MRS. Originally, it was targeted just at measuring GABA. Part of the process of broadening our horizons slightly has been looking at things that aren't GABA, which involved trying to develop the software to quantify glutathione. And one of the complications of measuring glutathione is that the echo time influences the shape of the spectrum, and the shape of the spectrum influences how you want to go about modeling it.

MRMH: Speaking of software, we heard that you're a big fan of the FID-A package, which was the topic of our last month's feature.

Richard: I did see that! All of the simulation work that Kim's done in this paper was done using FID-A. And actually, as a result of some of the issues we had with the implementation, we fed back to Jamie some tweaks as to how he should handle some things, which I think have made it into the package. It's been really valuable for us and we use it in all of our papers.

MRMH: Kim, what advice can you give to new graduate students in this field?

Kim: I think the greatest challenge was –

Richard: – sitting next to me. [laughs]

Kim: No no no! I think he made it much easier for me actually. I didn't understand a lot of the terminology. So just learning the basics of that was a challenge. There are a variety of books out there – I read Robin de Graaf's spectroscopy book.

MRMH: What do you enjoy doing in your free time?

Kim: I do a lot of reading in my free time. I'm currently reading Dune.

Richard: I have a young family, and I enjoy spending time with them. I'm also slightly obsessed with birds.

Kim: Slightly?

Richard: Maybe more than slightly obsessed with birds. Whenever I do travelling for work, I try and see what different birds there are there. So, if anyone that reads this is an ISMRM birder and wants to go birding in Hawaii, drop me a line. ■

A Japanese white-eye, photographed by Richard Edden.

Richard Edden in his natural habitat.

Nikola Stikov

Magnetic Resonance in Medicine
Deputy Editor for Science Outreach

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Prior to joining the faculty of École Polytechnique (University of Montreal), Nikola completed his postdoctoral training at the Montreal Neurological Institute, and his B.S., M.S., and Ph.D. degrees at Stanford University. A son of a sports journalist, Nikola has made journalism his hobby by periodically contributing pieces on science and film to newspapers and blogs in his home country, Macedonia. His career and his hobby are finally united in *Magnetic Resonance in Medicine Highlights.*

Erika Raven

Magnetic Resonance in Medicine
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Erika is working towards her Ph.D. in Neuroscience from Georgetown University and the National Institutes of Health. Her current research focus is using novel MRI methods to study white matter microstructure during adolescent development. Erika also enjoys scientific outreach through social media, reaching stage 4 sleep, and IDL programming. In addition to tweets for @mrm_highlights, she is @erikaraven.

Atef Badji

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Atef is a medical graduate from Iuliu Haţieganu University of Medicine and Pharmacy in Romania with a deep interest in neurodegenerative disease and neurocognitive disorders. The desire to help develop treatments through gaining a better understanding of these afflictions motivated her to pursue a career in neuroscience research, and drives her passion day-to-day. She is currently working toward her MSc in Neuroscience at the University of Montréal. In her free time, Atef enjoys writing, eating chocolate, and watching Big Bang Theory with her fiance.

Mathieu Boudreau

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Mathieu is a Ph.D. student in the Biomedical Engineering Department at McGill University. His research interests are quantitative MRI methods of the brain (B_1, T_1 , magnetization transfer) and their applications to multiple sclerosis. In his free time, Mathieu enjoys cooking, juggling, and is a cinephile.

Samantha By

Samantha is currently a Ph.D. student in Biomedical Engineering at Vanderbilt University. Her research is focused on the development of quantitative MRI methods for the spinal cord to study its role in neurodegenerative diseases. In her free time, Samantha enjoys cooking, playing soccer, and traveling.

John Celio

ISMRM IT & Web Coordinator

TWITTER: **@ISMRM**

John is an ISMRM employee and runs the society's website and social media accounts. As a sometime graphic designer, he helped develop the MRM *Highlights* graphics you see on the blog, Facebook, and Twitter. Although not a scientist himself, he did pretty well in high school physics.

Akshay Chaudhari

Akshay is a Ph.D. candidate at Stanford Unviersity. He is interested in pulse sequence design and image reconstruction for performing quantitative musculoskeletal imaging in patients with osteoarthritis. Akshay is an avid cyclist who enjoys racing bikes as well as playing lots of ultimate frisbee!

Mark Chiew

Mark is a post-doc at the FMRIB Centre in the University of Oxford, after having obtained his Ph.D. at the University of Toronto. He currently works on developing novel acquisition and reconstruction techniques for highly accelerated fMRI. Mark enjoys eating noodles, wearing sandals to work, and watching Star Trek.

Blake Dewey

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Blake is a Ph.D. student in Electrical and Computer Engineering at Johns Hopkins University. He works at the F.M. Kirby Center for Functional Brain Imaging, where he works on pulse sequence design and compressed sensing reconstruction. In his free time, Blake enjoys reading and photography.

Benjamin De Leener

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After obtaining a joint master's degree from Polytechnique Montreal and Université Libre de Bruxelles, Benjamin started a Ph.D. in NeuroPoly lab with Julien Cohen-Adad. He is leading the development of the Spinal Cord Toolbox, the first comprehensive software for processing MRI data of the spinal cord. Benjamin is particularly interested in understanding secondary mechanisms of spinal cord injuries and how we would be able to repair the spinal cord following an injury. Benjamin is also interested in the combination of neuroscience and art.

Thijs Dhollander

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Thijs is a postdoc at the Florey Institute of Neuroscience and Mental Health in Melbourne. He obtained his Ph.D. at the University of Leuven in Belgium. He is working on automated data-driven methods to extract and process tissue-specific information from more conventional (clinically feasible) diffusion MR data. Living in Melbourne, he has become a coffee snob and tea addict, and is fascinated by Australian wildlife.

Adam Elkhaled

Adam is a Ph.D. student in the joint Bioengineering program at UC Berkeley and UCSF, whose research focuses on the development and translation of metabolomic biomarkers for brain tumors using *ex vivo* and *in vivo* CPMG-inspired sequences. He is also an avowed motorcycle and mountaineering enthusiast that enjoys exploring new places as part of his external research.

Sumeeth Vijay Jonathan

Sumeeth is an MD/Ph.D. student in Biomedical Engineering at Vanderbilt University. His research is focused on pulse sequence design and image reconstruction techniques for MR-guided focused ultrasound surgery (MRgFUS) and its applications in functional neurosurgery. In his free time, he enjoys exercising, exploring the ever-expanding foodie scene of Nashville, and hanging out with his dog Johnny.

Srivathsan Koundinyan

Srivathsan is a second year Ph.D. student in Electrical Engineering at Stanford University. His research interests are in the development of novel acquisition and reconstruction techniques for abdominal imaging. Outside of research, he enjoys watching and playing sports, and traveling.

Mario Malavé

Mario is a Ph.D. student in Electrical Engineering at Stanford University. His research is focused on trajectory design and reconstruction techniques for cardiac imaging. He also enjoys traveling and salsa dancing.

Yogesh Kannan Mariappan

Yogesh is currently a Senior Technical Specialist at Philips HealthTech in Bengaluru, India. He did his Ph.D. in Biomedical Engineering at Mayo Graduate School and served as an Assistant Professor at the Mayo Clinic College of Medicine in Rochester, Minnesota. His hobbies include reading, tennis, searching for the meaning of life, and lately, changing diapers.

Jessica McKay

Jessica is a Ph.D. student in the Biomedical Engineering Department at the University of Minnesota. She works at the Center for Magnetic Resonance Research where she is investigating techniques to correct ghosts and distortion in breast diffusion weighted imaging (DWI) with spin-echo EPI. She also enjoys downhill and water skiing.

Xin Miao

Xin is currently a Ph.D. student in Biomedical Engineering at the University of Southern California. Her research is focused on novel constrained reconstruction methods for cardiac imaging. In her free time, Xin enjoys traveling and singing in the choir.

Ryan Topfer

Ryan spent his undergrad (geophysics, UAlberta) imaging slate; was reborn, a blank slate, as biomedical engineer, for his MSc (UAlberta); and is slated to complete his Ph.D. (Polytechnique Montréal) sometime in the next couple years.

Manh-Tung Vuong

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After completing a master's degree in Telecommunications Engineering in Italy, Tung changed his career path to a master's project in Biomedical Engineering at the NeuroImaging Research Laboratory (NeuroPoly) of École Polytechnique, Université de Montréal, Canada under the mentorship of Dr. Stikov and Dr. Cohen-Adad. He is working on implementing novel quantitative magnetization transfer imaging techniques, focusing on measuring the fiber g-ratio in demyelinating mouse models.

David Zeng

David is a Ph.D. student in Electrical Engineering at Stanford University. His research is focused on pulse sequence design and reconstruction techniques for cardiac imaging. He also enjoys lifting, film, and travel.

Bo Zhu

Bo is a postdoc at the Massachusetts General Hospital Martinos Center and Harvard University, pursuing development of novel acquisition techniques and contrast mechanisms, much of which is suited for Low Field MR. He obtained his Ph.D. in HST/Biomedical Engineering and bachelor's in Electrical Engineering at MIT. He enjoys reading, traveling, and skiing.

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