Magnetic Resonance in Medicine

HIGHLIGHTS

Penny Gowland

Visualizing the body in action

Daniel Sodickson

Connecting MR in a changing world

Editor's Picks

Al Macovski

An interview by Graham Wright

ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

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March 2017–April 2018

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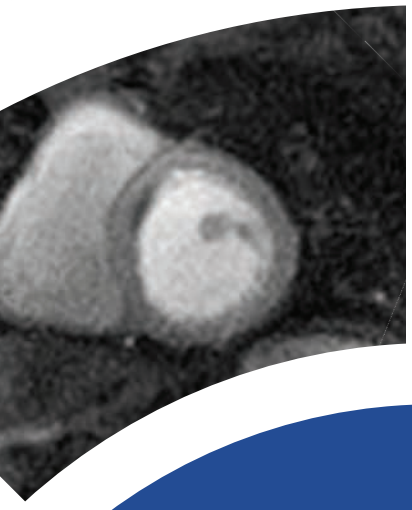
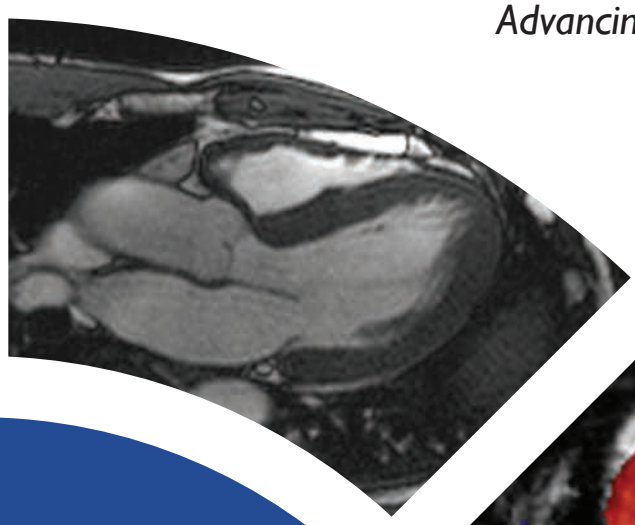
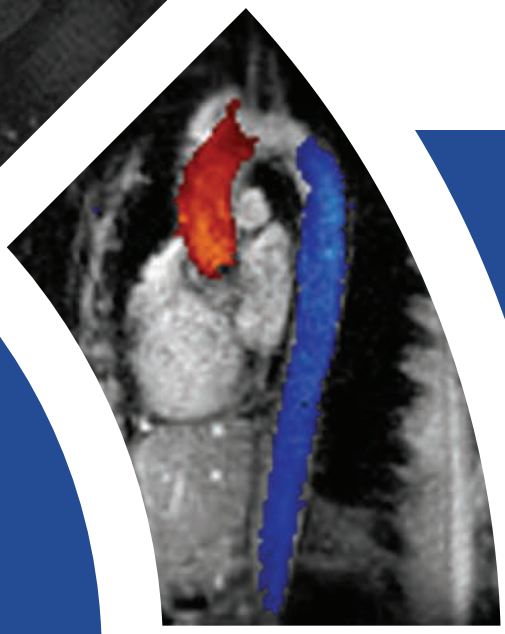


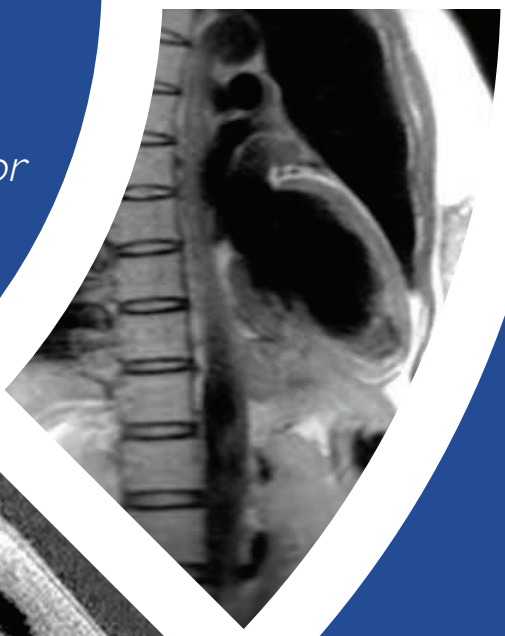


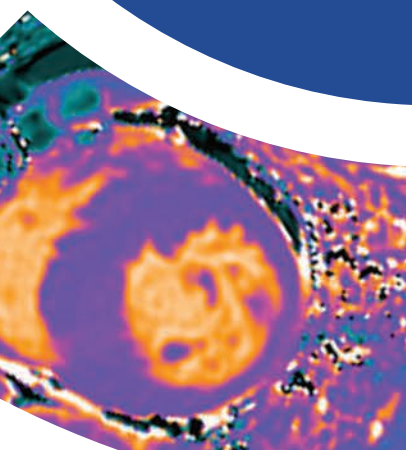


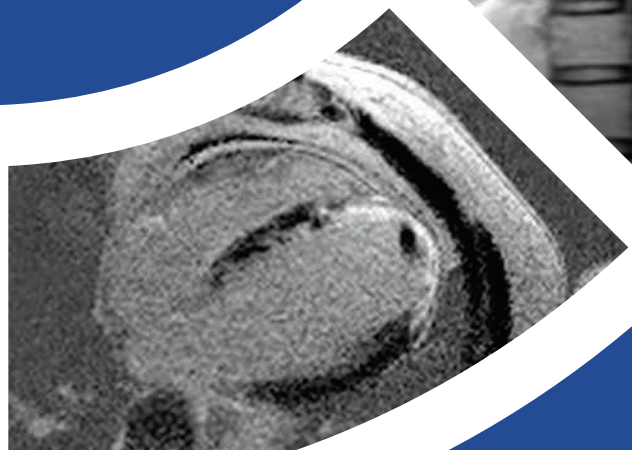
Autonomous MRI

Real-time expert assistant

HeartVista's smart self-driving MRI system uses state-of-the-art machine learning to automate the entire MRI scan.
The company's founders are proud to honor our mentor Professor Albert Macovski.







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FOREWORD

Welcome to *Magnetic Resonance in Medicine Highlights*

This is our third annual print edition of *Magnetic Resonance in Medicine Highlights*. This year's magazine is bursting with content, and we are very proud of both the depth and the breadth of topics presented in these pages.

Our cover story features Al Macovski, whose fascinating backstory as a pioneer in the development of color television led him to a long and profoundly impactful academic career, which resulted in the foundation of the Magnetic Resonance Systems Research Lab at Stanford University. We also include interviews of the current ISMRM President, Daniel Sodickson, last year's Mansfield Lecturer, Penny Gowland, and 26 Q&As with prominent researchers from across our community.

Highlights is entirely a volunteer effort, and has continued to thrive thanks to the journal's Deputy Editor for Scientific Outreach, Nikola Stikov, and our Highlights Editors, Erika Raven and Atef Badji. Each member of the diverse team of junior contributors has jumped into their interviews with vim, bringing a unique perspective to the Editor's Picks covered in this issue. We also thank the authors of the Editor's Pick articles for contributing their time and sharing their stories.

We hope the Highlights initiative will continue for many years to come, and we invite you to get in touch with Nikola or me if you'd like to become part of the team. As articulated in the Al Macovski interview, "In the end, it's all about the people."

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

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Al Macovski in London for a sabbatical at Hammersmith Hospital in 1982.

Albert Macovski – Inventor, Mentor, Mensch

INTERVIEW BY **GRAHAM WRIGHT**

Al Macovski has been an engineering professor specializing in signals and systems for medical imaging for almost 50 years, with a primary focus on MRI over the past 35 years. He established the Magnetic Resonance Systems Research Lab (MRSRL) at Stanford in the early 80s, arguably one of the most prolific and influential labs in MR image acquisition, reconstruction, and analysis. He is an incredible inventor (with more than 200 patents including major contributions to the development of color television, dual energy x-ray, and ultrasound phased arrays, as well as MRI) and academic (directly supervising more than 60 doctoral students), but above all, he is, to borrow one of his many Yiddish phrases, a mensch.

I had the great privilege of doing my graduate training with Al in the mid-80s along with an incredibly talented group of colleagues. When asked by ISMRM to help interview Al for Highlights, I saw it as a chance to try to convey to the broader MR community who may not have had the chance to work with Al some of his magic. In the process, my respect for him grew deeper as many stories unfold-

Al Macovski and Graham Wright, interviewer and former student, at Stanford University.

ed over the course of a wide-ranging 90-minute conversation. For the sake of practicality, Nikola Stikov and I have tried to hone down this story to a manageable article length, focusing on the parts most relevant to Al's work in MRI. But that story needs context if one is to get a glimpse of Al's true genius, so let me begin by providing a summary of our discussion of his journey from being a kid in the Bronx to a Stanford Electrical Engineering professor, with excerpts of Al's comments from that part of the interview.

Graham Wright (GW): To start, can you give us some perspective on your early interest in technology development?

Al Macovski (AM): I was into ham radio as a young kid, 12 or 13. We lived in a one-bedroom apartment with three generations. My grandmother slept in the kitchen on a cot and my folks slept in a bedroom, and my brother and I slept in the living room. So with a little corner I built the little ham radio station.

GW: Where did you go for college?

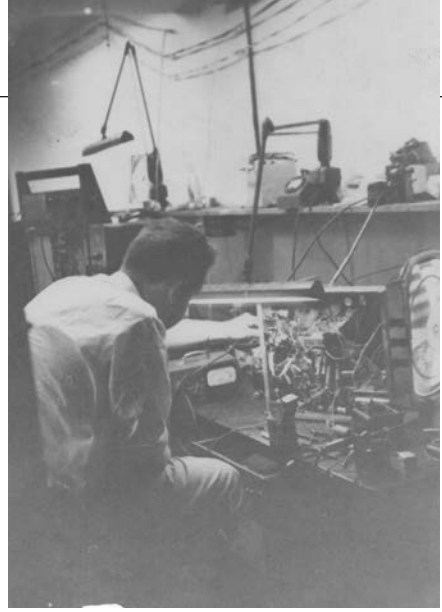
AM: We didn't have any money and the situation at our apartment was terrible with all the crowding, so I wanted to see if there was somewhere I could go to college for free other than City College of New York (CCNY). I thought of West Point, because they had an engineering school, so I wrote to the governor. The trouble is he said you can't go until you're 17 and I got out of high school at 16. So, I went to CCNY and that's where I spent four years. They had a new curriculum, by people like Jacob Millman, where you studied amplifiers and oscillators. That's what I did, despite being initially streamed in the "old" curriculum focused on power engineering.

GW: You finished college in 1949 at age 20 and started searching for your first job. Where did you look?

AM: There was only really one big post-war industry in the US – television. RCA Laboratories was giving a competitive exam and I did fairly well on it. In fact, they were a little bit concerned as to whether or not I was cheating, but after some grilling they were convinced. So, I got the job for the magnificent salary of $215 a month. Shortly after I started there, they gave me an award for my work in synchronization.

GW: What motivated you to head out of RCA Labs and spend more time back in school?

AM: All the work I did was basically circuitry, plus work in systems. But the systems part was so fascinating and I realized that I really didn't have enough of a background in systems – linear systems and the like – so I started going to Brooklyn Polytechnic Institute in the evening after work. And then in '57, I joined the Polytechnic Institute of Brooklyn as an assistant professor. My wife Addie and I had two kids at the time so there was no way I could just do the teaching. So, one day a week, I continued to work at RCA, making just as much as the teaching.



Working at RCA Labs on color television.

GW: But eventually, you ended up heading west for further studies, while continuing to go to work.

AM: I knew if I was going to stay in academia, I would have to have a doctorate. I decided to go to Stanford on the Honors Co-op Program for the doctorate, but at the same time still needed to support a family. So, I interviewed at three places in the Bay Area for outside work. I went to Stanford Research Institute (SRI) and we did a lot of imaging projects – facsimile and some work on TV, and then along the way I worked on

Al Macovski with wife Addie, daughter Nancy, and son Michael — in Massapequa, Long Island 1956.

two important projects. One was ultrasonic imaging, which started me in the medical area. Also, there was this one-tube camera. The big problem with color TV was the registration of the three cameras. I found a way to encode all the information so they were automatically registered, and it not only made the performance better, but allowed you to build a cheap system for camcorders. That was very successful and I got the IEEE Zworykin Award for that.

Developing an interest in medical imaging

As Al noted, it was around the late 1960s that he got interested in medical imaging. He applied for and received an NIH Fellowship, which he used to spend time in the Radiology department of UC San Francisco while completing his PhD on holographic television. It was during this fellowship that he came up with the idea of combining x-ray images acquired with different peak energies to improve conspicuity. Upon completion of his PhD, after looking around at a few universities he settled on an adjunct faculty role at Stanford, supported by Electrical Engineering and Radiology – one of the first multidisciplinary positions shared between the Schools of Engineering and Medicine. In 1972, he convinced them to convert this to a full professorship, focused initially on developing some of his early ideas in dual-energy x-ray and ultrasound. At the time, ultrasound image acquisition was very slow, requiring manual scanning of the ultrasound beam across the volume of interest. Al started to think about phased arrays as a way of addressing this problem.

AM: One of the problems with ultrasound arrays is, on receive, you can focus but on transmit, you can't. I did some work on a circular array which was weighted with a Bessel function on transmit and in one dimension, you have diffraction-limited resolution; without that you don't. You would then receive with dynamic focus and transmit with diffraction-limited resolution with the Bessel weighting.

GW: This is now the early 70s and you're establishing yourself as a medical imaging researcher in x-ray, ultrasound, and CT, but then MRI starts to show up at some of the conferences – what was your impression of MRI when you first heard about it?

AM: The discouraging part was how long it took to acquire images, which we later found out wasn't fundamental. But at the time, we were waiting for the relaxation time and for each excitation. And Lauterbur at the time did projection reconstruction. But it was fascinating – the idea that there was no ionizing radiation.

Career

1950:	BEE, City College of New York
1950-57:	RCA Labs
1953:	MEE, Brooklyn Polytechnic
1957-60:	Faculty, Brooklyn Polytechnic
1960-71:	SRI
1968:	PhD, Stanford University
1971-72:	Research Fellow, UCSF
1972- :	Faculty, Stanford University

Distinctions

- Fellow, IEEE
- National Academy of Medicine
- National Academy of Engineering
- IEEE Zworykin Award
- Gold Medal, ISMRM
- Fellow, Optical Society of America
- Fellow, American Heart Association

GW: At some point you must have caught the excitement because you took a sabbatical to explore the field. What inspired you take that sabbatical?

AM: I had heard that EMI based in London had built an MRI machine and Godfrey Hounsfield was all excited about it. Then everybody else jumped in with better machines, and EMI decided to stick to the music business. They owned the Beatles. Hounsfield was very discouraged.

EMI had built a machine with a resistive magnet and they donated it to the medical physics group at Hammersmith Hospital. And they gave Hounsfield one day a week to go there and play on his own, so I worked with him on those days. I was looking at a lot of the literature and got interested in the sensitive point imaging method.

GW: You're referring to some of Waldo Hinshaw's work?

AM: They had these oscillating gradients, and there was one neutral point in space – where the field was static. They would integrate the signals over time, so the contributions at other locations with time-varying phase would yield net zero signal, isolating the contribution from the neutral point. The thing that occurred to me was that if you take any other spatial point and multiply the signal by the resulting oscillating phase at that point over time, you just get the contribution from that point, effectively decoding it. So, if you apply oscillating gradients you have information about every point.

The nature of the waveforms determined what the impulse response was. And if you had different kinds of waveforms you could determine your impulse response. What I should have done is gone and taken the Fourier transform of the impulse response and then it would have been k-space.

GW: This is captured in your 1985 paper on volumetric NMR with time-varying gradients. Effectively, you came up with a conjugate phase reconstruction approach which had the same effect as a Fourier transform in some circumstances, just as the k-space formalism was emerging. In the same paper, you talk about oscillating gradients in three dimensions to acquire volumetric data and acquiring data in one spatial and one spectral dimension, effectively spectroscopic imaging with time-varying gradients, ideas worked out in more detail by some of your future graduate students.

A second area that you were playing with at the time was angiography and trying to image blood vessels – I think this came out of your x-ray days. Coronary angiography was a major focus of your research.

AM: Yeah, I remember someone said it couldn't be done because of the moving spins. But people had shown that if you have a moving spin in the presence of a gradient, it be-

comes phase shifted. The idea of having phase shift so that static tissue would be cancelled out was attractive.

GW: That was effectively phase-contrast MR before phase contrast existed.

AM: And then the general idea of exciting magnetization in one area and looking at it in another area and then the reverse of that – saturating the magnetization in one area and then when new spins wash in, they contribute relatively more signal than surrounding tissue.

GW: The latter describes the basis of time-of-flight angiography, where static spins in a slice are suppressed by repeated excitations, while signal from blood washing into the area has 'seen' fewer excitations and hence is less saturated. The former is effectively arterial spin labeling, where blood is tagged in an upstream slab and, after a delay that allows those spins to wash in to the region of interest, is excited in a way that isolates the previously tagged blood. That was all in your 1982 IEEE paper.

AM: I forgot! Yeah, I have to look at my papers!

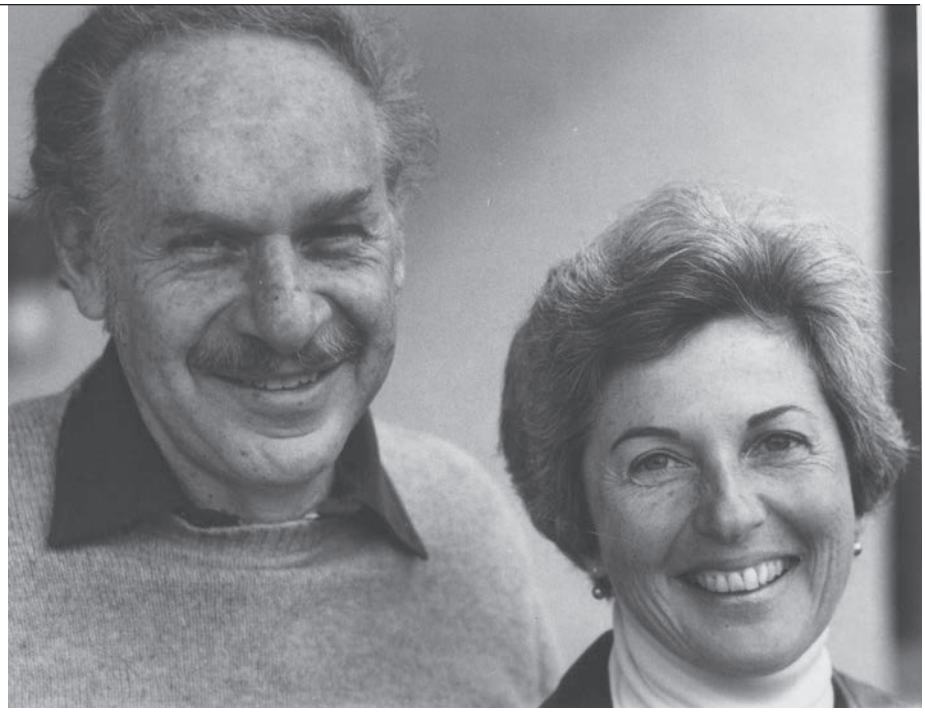
GW: You're an inventor. You wrote patents on a lot of these ideas. What motivated you to write these patents?

AM: Because of my work in RCA Laboratories – they were an extremely patent-conscious operation. And there was a sensitivity to this. The patent staff would come around and look at your notebooks and say "why aren't you applying for a patent for this or that?" And that consciousness remained with me. My feeling is that engineers should write their own patent applications because they know the language. While I was on a fellowship at UC San Francisco, I spent a week at the practicing law institute. They have a course, I think John Pauly also took it. You attend a class for a week, and then you take an exam, which entitles you to write your own patents and write for other people too.

Setting up the MRSRL

GW: Not only did you come up with some great ideas, you created a lab which has been incredibly productive over the years. We're now talking about the early 80s. And to do MR, you need an MR system. Can you reflect on how you managed to set up an MR system in the department of electrical engineering (EE)?

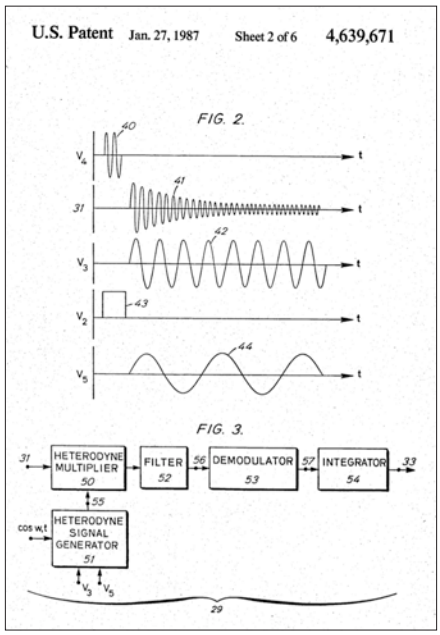
AM: Addie encouraged me to write a letter to GE and they looked at that very favorably



Al and Addie Macovski in the 1980s.

which was great. And then the engineering school said they would give us a quarter of a million dollars to build the laboratory. And then Dwight [Nishimura] and I had some fun and games to find a place for the laboratory.

GW: And so you managed to get an MRI system put in EE. That must've been one of the first MRI systems outside of a radiology department in the USA.



Acquisition and processing of signals with oscillating gradients for 3D imaging (Simultaneous NMR Imaging System, US Patent 4,639,671, 1987).

AM: I think so. I think it was one of the earliest non-clinical MRIs.

GW: Image reconstruction became a big theme in the lab. I remember one area for instance, homodyne reconstruction, and it seemed to harken back to your TV days.

AM: Yeah. Whenever you have low SNR signals, you could decode them synchronously with homodyne detection. And that actually was done in TV too, for dealing with weak signal. So that was a direct analogy to what I had learned in the communications world.

GW: Very early on, I think you were motivated with the paper on the volumetric MR to get the maximum amount of SNR you could per unit imaging time, so you wanted to essentially make the limit to MR acquisition be SNR. But I look at how things have evolved, especially in the reconstruction world, and it seems like even out of your own lab, your 'progeny', they're acquiring less and less data and getting better and better SNRs so it seems like we're violating the Nyquist theorem.

AM: Well, I guess the only thing I can say about that is: you're not asking to make a general image which would have any information in it. First of all, you're dealing with images with finite support. That's a very strong factor. And of course, I myself was never involved in that level of sophistication. But we did do some stuff. I remember in the early days, the strong signal at low frequencies was a technical problem. These signals would saturate some of the electronics and

so we decided, why don't we acquire images without the low frequencies and then, iteratively, just use the finite support to recreate the low frequencies using the known acquired data. I know what they're doing now is much more sophisticated than that, but the general idea that you can leave out information remains the same.

GW: This became a general approach in undersampled reconstruction. Now, people are taking advantage of prior information with compressed sensing and the like, and that seems to be going even further now. An interesting challenge in this whole game is how do you make sure that you're not imposing too much structure on these undersampled systems?

AM: Yeah, you know a lot of those concerns were also raised in the early days of TV. First of all, they did single sideband, which is fine unless there's very strong modulation. And so, for the low frequencies, they were double sideband and only the high frequencies were single sideband.

GW: And it sounds like the low frequency preservation also has parallels in MR. You make sure you get the center of k-space fully sampled, you get the blurry image and then again, you fill in the high frequencies in ways that allow the eye to integrate out the artifacts to make it look like noise. I think that the biggest challenge to industry adoption of these undersampled reconstructions is trusting the data because again, we're imposing a lot of prior information. We also have to make sure that we're not introducing artifacts that look like disease or that hide disease. Essentially, it's a lossy compression.

AM: Right. And getting the clinicians to trust the images is critical.

Broader development of the field

GW: You've been involved in MRI since the early days of the field and a major driver of the broader development in the field has been the academic societies: the International Society for Magnetic Resonance in Medicine (ISMRM) and its predecessor societies SMRM and SMRI. I think you were in the middle of some of the stronger debates at the early meetings.

AM: Oh, you mean on optimal field strength! I don't know how I came out of that alive. I was moderating. Then I ended up hiding. Leon Kaufman thought that 0.3 Tesla was all you needed. Beyond that, you were limited by extraneous noise that had nothing to do with fundamental Johnson noise, and Paul Bottomley said that with a simple equation you could show – the higher the field strength the better the SNR. Leon Kaufman said it didn't

1.5T research scanner in electrical engineering.

work that way.

GW: But somehow, you got out of the debate; the society kept on going, continuing to build. From the beginning, it was really targeted as a multidisciplinary society; it reflects your early academic career of trying to bridge the gap between engineering and medicine. How did you establish your own collaborations [with clinicians] and get the medical perspective on how to develop your ideas?

AM: You had to demonstrate some kind of success. Maybe that was done early on with the EMI machine where clinicians actually saw information coming out of a scientific endeavor that they weren't able to see before and so they started to have some trust in the engineering community. I think that trust slowly built up – although they always were cautious, which they should be, and they are to this day, that you're going to go too far and lose out on some important information.

GW: So it was important to anchor the technical developments with a clinical application.

AM: Yes.

GW: You were recognized in '97 with ISMRM's top honor, the gold medal. Can you reflect on that?

AM: It was very exciting. What was going on that same year was the early work in functional MRI. So that was really the excitement of that time.

GW: And then a few years later, your last major meeting was 2009. You gave a plenary lecture.

AM: Yeah, Honolulu. I forget the title – something like, "A Great Past and a Wonderful Future" (https://onlinelibrary.wiley.com/doi/full/10.1002/jmri.21962), that there were these two avenues of research. One was the chemistry of nuclear magnetic resonance and the other was the imaging that had developed with CT. And so, for example, when Lauterbur did his first reconstruction, he did it in the normal CT fashion because that was all there was, and it all developed. So, it was the meeting of these two armies. And just to be funny, I said that imaging people really don't understand nuclear magnetic resonance. It's a new phenomenon. I said one way they could think about magnetization was water draining, swirling, and refilling in a toilet and that got a lot of laughs.

GW: I think I remember that analogy. In fact, I think you described the idea of T_1 and T_2 with the filling and flushing of the toilet.

Al Macovski and Addie Macovski, his wife of 68 years.

AM: Right...

GW: And you tried to create a steady state at some point.

AM: Just hit the lever right to hit steady state.

GW: The teacher in you came out, trying to get people really thinking about it. I heard afterwards that many people were thinking about MR every time they went to the toilet.

Looking back and looking forward

GW: In many ways, your time in this field has been the golden age of medical imaging. It's been described as one of the major advances in medicine over the last 50 years. You got into it to make a societal impact, which it has done in a huge way. If you were to advise somebody now – would you still recommend them to get into the medical imaging field?

AM: Yeah. I think it's great.

GW: What more is there to do?

AM: Well, when there is a big contribution in physics, it tends to overrun into instrumentation. For instance, if you did have truly warm superconductors, you could make some very interesting MRI machines at low cost and better deploy them in the field. The other thing is just looking at what Bill Gates does – to try to get all kinds of scientific developments out into the developing world. The goal of an MRI machine that you could distribute widely in African nations, I think, is very respected. Perhaps you could build an MRI machine where you would mimic CT scanning – you would move the patient through and you'd have a fixed gradient and have a fairly small machine.

GW: And you see these huge opportunities still in making MRI more accessible?

AM: Lower costs. Even television went that way with these big screens, things that were extremely expensive – I'm amazed how they could bring the cost down. Of course, that's a different world of mass production. I don't think MRI will get to that, but I think you could do clever things that would result in a very low-cost machine. ■

***Graham A. Wright, PhD** is the Director of the Schulich Heart Research Program at Sunnybrook Health Sciences Centre, a senior scientist at Sunnybrook Research Institute, and a professor in the Department of Medical Biophysics at the University of Toronto. Dr. Wright was appointed the Canada Research Chair in Imaging for Cardiovascular Therapeutics in 2010 and is a Fellow of the International Society of Magnetic Resonance in Medicine (ISMRM). He has also served as President of the International MR Angiography Club, Chair of the Interventional Study Group of the ISMRM and Chair of the Science Committee of the Society for Cardiovascular Magnetic Resonance. Together with trainees and collaborators, he has published over 175 peer-reviewed papers and 460 conference abstracts, which have garnered numerous awards and resulted in more*

In the end, it's all about the people

In the second part of the interview, we had a chance to delve more into the personal interactions arising during Al's career. For this, Al's wife, Addie, and one of his early students, Dwight Nishimura, joined the conversation.

AM: Of course, the best part of the experience at CCNY was meeting Addie when I was halfway through. That changed everything.

GW: It inspired you?

AM: Yes, very much.

GW: When did you get married?

AM: We got married in August of 1950. So this summer is 68 years.

GW: How has Addie influenced the way you've approached your career?

AM: Well, I started getting much better grades when we started going together. That's for sure. Got all A's which I didn't do before. And we both came from immigrant families that were in poor circumstances, so we always looked at our life as an adventure in which we supported each other. Addie hadn't had very much education at the time we got married, but subsequently, when we came out to California, she went to Foothill and got a degree. And then went to San Jose State and got a bachelor's degree, then went to Santa Clara and got a master's degree [in Marriage and Family Therapy]. She was the world's best therapist, which her patients will attest to.

GW: Did Addie's experience as a therapist transfer into any of your dealings with students? I imagine being a mentor requires similar strategies.

AM: Yeah. People would get discouraged. I would encourage them and suggest some different lines that they could pursue and that usually worked out.

GW: Did Addie give you advice on anything in particular?

AM: Every once in a while, somebody would come to me with their romance problems. I wasn't good at that.

GW: You and Addie have endowed a chair at Stanford.

AM: Yeah, we got these patent royalties. I figured it was really the result of a whole crew of people, and so we wanted to give back on that level.

GW: You named the chair the Addie and Al Macovski Professorship, and you wanted to focus it on bioengineering, particularly medical imaging. So together you endowed this professorship.

AM: Yes. We both felt very strongly about it, and that the motivations for the research should not be purely monetary. There, on some level, are always some monetary aspects but maybe somebody decides to study some very rare disease, which a commercial company wouldn't think of investigating.

> *[Addie and I] both came from immigrant families that were in poor circumstances, so we always looked at our life as an adventure in which we supported each other.*
>
> –Al Macovski

GW: And academia is probably an optimal environment to encourage those kinds of breakthroughs.

AM: Yes, that's true.

GW: You've had over 60 Ph.D. students, so you are obviously very inspired by teaching and working with students. Maybe you can speak to why you chose to go that route versus continuing in industry?

AM: When I was at RCA Labs, I had all the resources I could possibly need. If I had an idea, I could have a technician build it up immediately and try it. In industry, you have lots of resources but you don't have any choice as to what you work on. In academia, you have very little resources. Everybody's their own technician. But you're free to work in any area you want, so that was very appealing to me. And if you could get an idea in medical imaging, nobody would say you can't work on that, whereas in industry, they will tell you that's not a money maker for us.

I think what was also attractive to a lot of great students, like you, was the idea that it was medical, that it was for humanity. So much of electrical engineering research at that time was Defense Department stuff. I think it was a filter that got some very unique people who wanted to apply their scientific knowledge toward some good cause. Of course, they were all very bright.

GW: The lab itself was an incredibly fun place to be, and MRSRL seemed like a unique environment. I'm just trying to get a sense of what was the secret sauce. What was your goal in setting it up?

AM: I knew there was a lot left to be done. And given the resources of having our own machine and the right motivation, I was very excited about the idea that if you let these guys loose, that they were going to remake the world.

GW: So how would you describe your management style?

AM: Well as I often say, getting out of people's way. If you start out with a little seed of an idea, and they take over from there, then you meet with them and you modify it if they're stuck; maybe you should try this or maybe you should try that. Usually great things come out of it.

GW: It seemed like you set really hard problems in the lab. For instance, noninvasive coronary imaging has essentially been a 20-year problem.

AM: Yeah… or more. But I think that a lot of the students stood on their own and I was more of a kibitzer. They really did it on their own. Wonderful stuff.

GW: It seems that the lab was really encouraged to bounce ideas amongst each other. How do you encourage that?

AM: I don't know.

GW: *[Laughs]* Just lucky?

AM: The harmony among students was just beautiful to watch. Sometimes we ran into this stuff which was just grunt work like installing the magnet. It didn't take any scientific knowledge. Once we had a flood. People

rolled up their sleeves and just jumped right in. It was amazing to watch the dedication that they had. They weren't going to get a thesis out of mopping water.

Dwight Nishimura (DN): But I think part of your secret sauce, Al, was you planted very firm seeds in people's minds. Planted ideas, but you made them feel like it was their idea. And they went off and went very far with these ideas.

AM: Well probably because what I had suggested was vague and they were able to apply specifics.

GW: You gave them the opportunity to imprint their own ideas onto it. It's so important that students take ownership of their ideas. But there's a priming step to that. It's seeding that idea, and then recognizing their contribution to building on that idea. Making sure that the students are recognized for their contributions is something that I think you were a master at.

AM: I tried.

DN: You said you don't know the answer to the question about why it worked. I think for me, and for other students, you set an example. We all wanted to be like you. So we wanted to be that creative type of person that can make an impact.

GW: I think one of the things you also managed, by example, was to create a place without ego. I think everybody recognized that nobody was going to be smarter than you. So, we had these incredibly smart people, but they didn't want to overplay their own importance.

Addie Macovski: Underlying it all is the humanity. It comes through with your trust in the students and in yourself. Within yourself, you were able to give that to the students.

DN: My wife Ann [Shimakawa] thinks the advisor sets the tone and has a huge impact on how people behave in the lab. And that certain personalities, if they had a different adviser, they would have been a real terror. But you moderated them, not because you told them, but because they observed you.

AM: Yeah, the atmosphere. Thank you.

GW: It's been a great discussion. Is there anything that you want to add?

AM: Well, I feel I was given an opportunity to meet some great people doing some extremely interesting work. I consider it a privilege to be able to work with such bright people. It really made my life. It inspired me. ■

Some of Macovski's academic descendants, from his 75th birthday celebration at Stanford University. *Photo by Julie DiCarlo*

Penny Gowland: **Visualizing the body in action**

INTERVIEW BY **WALTER BLOCK**

In the conversation below Dr. Penny Gowland of the University of Nottingham discusses her career path, from her burgeoning interest in MRI in the mid 1980s, to her pivotal contributions in quantitative MRI, and her most recent contributions in body imaging. Penny had an interesting vantage point in MRI, as she was hired by Sir Peter Mansfield, who inspired her and others to develop the field of real-time body imaging.

Last year, her work was recognized by the ISMRM when she was asked to present the Mansfield Lecture at the annual meeting in Hawaii. In the conversation below, she called for the field to move beyond qualitative measures to connect MRI with underlying biology, calls which are being echoed more and more throughout our field. But the conversation often turned to her gratitude for the generous mentoring provided by Sir Peter Mansfield and the supportive environment he and others created at Nottingham.

Penny Gowland

Wally: How did you get involved in MRI?

Penny: I did my degree in physics and astronomy, and in between A levels and university studies I spent a stopgap year nursing. While I was finishing university, I thought I wanted to study medical physics and so I did a Masters of Science program in medical physics at the University College of London. This was back in 1985; an instructor showed this amazing image of a spine from MRI, but said it would never catch on because the scan took a half hour. But then we had another lecture taught by Paul Tofts, who still works in MR in Brighton. He taught me about relaxation time measurements and clinical imaging at the time, and that was it. I was caught! It was that picture of the spine that captured my attention.

Wally: What did Dr. Mansfield see in you as you came to the end of your PhD studies?

Penny: I honestly have no idea. I wrote to his lab and I was invited for an interview on the same day that Prime Minister Thatcher visited the lab! I came from the Institute of Cancer Research in London where they had the first 1.5T imaging system in the UK that looked similar to today's scanners. At Nottingham everything was made of string and tape and to some extent remains that way. We had to bring patients into what was basically a garage in the back of a building and it took a bit of Tender Loving Care to do that. I had a feeling he thought my nursing experience might come in handy! Mind you it took a bit of Tender Loving Care to keep the scanners going too, but honestly I have no idea why he hired me.

Wally: What do you want the MR community to know about the environment that Peter Mansfield created at Nottingham?

With Elena Kleban on the MRI console at the Sir Peter Mansfield Imaging Centre.

I knew Dr. Mansfield for 28 years. We saw him on the 13th of January, 2017 at the rededication of the centre named after him, 25 years after its original opening. He came and really enjoyed himself during a lovely day, staying with us for 9 hours. He died 3 weeks later.

It is only when someone dies that you realize what you've lost. I went to Nottingham to work with Peter Mansfield. I knew it was a good lab, but I didn't quite understand the power of the lab until I got there. When he retired, he was so generous in the way he handed over a significant part of his research to myself and a colleague, Richard Bowtell. He just gave it to us, and he never interfered ever again. He could've interfered and we could never have developed our own research areas but he was just there for advice if we wanted it.

The concept of imaging the body in action was something that was very close to him. We called it snapshot imaging at the time. He really had an insight into the power of EPI, high speed imaging for looking at dynamic processes in the body. At a time when MRI and CT were very much static imaging techniques he had a vision for how MRI could be used to study the functions of the body. But he gave us the room to take his vision and build our own careers. I want others to be aware of his generosity.

Wally: What was the lab like back at the start of your career? Was it aware of the history and future impact that it was likely creating?

Penny: Very friendly and very exciting. We were in an experiential physics environment with a scanner that we could do anything with (as long as it was based on EPI!) Obviously many people created that environment, particularly Paul Glover and Richard Bowtell who were already there well before me, but I think one of the reasons we've kind of kept going at Nottingham is that we aren't weighed down by our history, and maybe again that resulted from Mansfield leaving us to it; we just keep on moving forward from where we were.

It is funny for me, preparing the Mansfield lecture by going back and reading the history of fMRI and how central EPI became to fMRI. We lived through it, we worked on it, it was the ultimate use of EPI in dynamic imaging and we knew everything that was going on across the world. But we didn't really notice that history was being made at the time. I strongly believe that the way to work and live is to look after today. Tomorrow and yesterday don't matter.

Wally: Can you comment on the challenges that the field is facing and your vision for quantitative MRI in the future?

Penny: Peter was very interested in MRI serving as a basic physiological measurement, a scientific tool beyond being a clinical diagnostic tool. I am a physicist, so I like to measure things precisely and accurately. Beyond the brain, there are so many areas of the body that need repeatable, reproducible, quantitative measures. For example, I'm looking at the relationship between histology and MRI signal in the liver, specifically in the information MRI signals provide on fibrosis and finding MRI markers for glycosaminoglycans and collagen. I think that's probably the next frontier, actually understanding how relaxation time mechanisms link histology to MRI data. Now it's time to do that.

I have focused a lot on the use of MRI to develop understanding of physiology, which was exciting. But I think now we also need to drive it back towards clinical utility. Much of what we present at the ISMRM is often too difficult or slow to insert into everyday patient care. This is what I am looking to do now in my career.

I think the other problem with quantitative measurements is that physicists like me sometimes overcomplicate things. We need to work out what we need to measure and not just measure everything.

Wally: But you have had quite a lot of success in your collaborations in asking the right questions. Can

> *I strongly believe that the way to work and live is to look after today. Tomorrow and yesterday don't matter.*
>
> –Penny Gowland

Current and previous members of the Sir Peter Mansfield Imaging Centre after Penny's Mansfield Lecture at ISMRM 2017.

you expand on how you look at developing the right questions?

Penny: The collaborator is absolutely crucial and so the reason I worked in these areas is because I have really good collaborators. For example, our work on the gastrointestinal system is led by an extremely insightful clinician, Robert Spiller, who has a passion to understand functional bowel disorders. At the moment, we're looking at colonic motility. The common thinking is that constipation is caused by a reduction in contractions but it's just being realized that it can alternatively be caused by disorder in the contractions. There is no real way to see what is happening without perturbing the system, except with MRI. Robert understood that and encouraged us to develop the methods needed to assess it.

Wally: The ISMRM leadership has been discussing a lot about our need to communicate outside the ISMRM, with scientists, physicians, patients, and the community at large. You are teaching a course in communicating science at Nottingham now. How do you see the importance of communicating science today and the opportunities for ISMRM in this area?

Penny: Within my role as a teacher in physics in Nottingham, I do a lot of outreach in the local community and also run a module where undergraduate physics students go into schools and teach. Communicating science is extremely important, and it's more important today than it was even a year or two years ago. It's essential to make people understand the power of rational approaches to problems.

MRI is producing some fantastic information about what everybody is interested in, namely their own bodies. As Peter [Mansfield] realized decades ago, the ability to visualize the body in action is something which fascinates people. And so ISMRM has a particular opportunity to communicate science in general because of its links between physics and medicine.

Wally: How has being a woman, often in labs where the numbers are dominated by men, affected your career?

Penny: You know honestly I don't feel it has affected me at all. When I came to Nottingham I was the only woman in the group but I just never really noticed it and no one else seemed to either. I had done a degree in physics; there weren't many women in the class, it was normal to me. Some of my happiest memories as a young adult came from being totally integrated into the group. We obviously have a lot more women now and that's a good thing. It makes the subject more representative, which matters because the questions women and men ask can sometime be different. I have two children who are now young adults. My husband is a physicist, and he works in London, so our life was complicated. Looking back, Peter Morris, Richard Bowtell and other colleagues were really supportive all the way through when my children were growing up. But at the time I never felt like I was being 'supported'; it was just accepted as normal. ■

Penny's husband Paul Marsden and daughters Joanna and Katie.

Connecting MR in a changing world

INTERVIEW BY **AKSHAY CHAUDHARI**

The MRM Highlights team was at the Center for Biomedical Imaging at New York University and got a chance to sit down with ISMRM President, Dan Sodickson. We had a great conversation with Dan ranging from his beginnings with MRI research all the way to the recent strategic initiatives of the ISMRM.

Dan in the radiofrequency engineering lab at NYU.

MRMH: Turning back the page a few years, could you tell us how you got started with MRI research in the first place?

Dan: My beginnings in MR were anywhere but in imaging. I had a background in physics, and my graduate work involved developing methods for molecular structure determination, which had absolutely no direct medical application whatsoever. However, when I found myself in medical school (a story of serendipity for another time), I did a month-long preceptorship rotation – a structured shadowing program – in the lab of cardiac imager Dr. Warren Manning. Warren sat me down and said that, as a focus for my time with him, I could look into anything that interested me about cardiac MRI. I started exploring, and soon got stuck on why one couldn't image faster in cardiac MRI, since cardiac motion was clearly a challenge, and since it is generally considered bad form to stop the heart if we want to image it. Because I knew absolutely nothing about imaging, I started asking what it was that set the fundamental limits of imaging speed, and over the course of the month I stumbled on the idea of sampling multiple lines of k-space at once. I came across an article about RF coil arrays, and it occurred to me, after some casual doodling, that if we had a bunch of coils with distinct sensitivity profiles, then we could generate a signal modulation that resembled the spin modulation produced by a magnetic field gradient. I wrote up a brief research proposal, handed it to Warren, and asked him on the spot if he could take me on as a postdoc. To my surprise, he did! I am eternally grateful for the opportunity Warren gave me to explore a new idea and a new field. So that was my entry into imaging. My ignorance clearly gave me an advantage. I didn't know which questions were too stupid to ask, and the question about imaging speed was one of the most fortunate stupid questions I have ever dared to ask. Which is why I tell my students not to listen to me too carefully, but, rather, to take advantage of their ignorance.

Dan taking advantage of his ignorance, at his grandfather's service station.

I tell my students not to listen to me too carefully, but, rather, to take advantage of their ignorance.

–Daniel Sodickson

MRMH: Here you are alluding to the simultaneous acquisition of spatial harmonics (SMASH) method. How was that initially received?

Dan: I think that two categories of early responses were captured nicely in two opposing reviews I got for the first MRM paper I submitted, introducing SMASH. One reviewer said, more or less, that the idea was crazy and would never work. The other said that he/she had done the same thing ten years ago. So I was tempted to respond simply by asking the two of them to talk to one another.

There were, however, other more encouraging responses. For example, Mark Griswold, who was working at the time with Bob Edelman and whom I had met in my first few months at Beth Israel Deaconess Medical Center, immediately saw the potential of SMASH, and we started working together. Bob himself was an enthusiastic supporter. Peter Jakob was also working at Beth Israel, and he soon became a third musketeer and eventual architect, with Mark and me, of AUTO-SMASH.

The ISMRM meeting in Vancouver (1997), where we had a couple of posters and a talk on SMASH, was very gratifying, though the lead-in to the meeting was definitely a learning experience. Mark's abstract, on an early application of SMASH, was selected for a talk. My abstract introducing the technique was relegated to a poster (and was unceremoniously rejected from the Young Investigator Award competition – a lesson in humility and persistence that I also try to share with students). Mark kindly encouraged me to give the talk in his place, which I did, with the support of the Beth Israel team along with copious quantities of antacids to combat nerves. From that point on, the game was afoot. There was a crowd around the SMASH poster for the remainder of the conference. I remember a particularly pointed discussion with Pete Roemer – the guru of coil arrays, and an author of the paper that had sparked my early doodles – who said that the idea was solid, but the SNR calculations were wrong. This was a direct motivation for one of our next papers, on SNR in SMASH.

So there was a lot of enthusiasm to work with, but still a fair amount of resistance remained. My first experiences presenting SMASH to colleagues in industry were particularly heavy on the skepticism: I remember lots of crossed arms and dour faces at first. Then competition started to appear, and the ensuing back and forth started to win over the skeptics. Klaas Pruessmann and Markus Weiger had spent time at the SMASH poster in Vancouver, and they came up with the rudiments of SENSE on a canoe trip following the meeting. Over the next few years, there followed a kind of tennis match, with advocates of the two techniques battling it out over which one was better. Everybody was watching to see who would come out on top, and, in retrospect, this was probably the best thing that could have happened to generate interest. From then on, a whole slew of brilliant people, both in academia and in industry, entered the fray, and parallel imaging was off to the races.

MRMH: Speaking of ISMRM annual meetings, how large was the meeting in Vancouver?

Dan: That's like asking a child how big his childhood room was. For me it felt big. There were thousands of people – but nowhere near the approximately 7000 attendees our meeting attracts today.

MRMH: Do you think that the level of intimate discussions has decreased with an increasing attendance at the ISMRM annual meeting?

Dan: The fact that we have grown so much larger is certainly in evidence at the meetings. The poster hall used to feel manageable. Time was, one could stroll among the posters and get an immediate sense of the scope of changes in the field. Now there are so many sessions at once, and so many posters, that I do think some of the early sense of intimacy has been lost. In the Annual Meeting Program Committee (AMPC), we are trying to restore some aspects of the smaller-meeting feel, with initiatives such as program chair Karla Miller's brilliantly-conceived and highly successful Secret Sessions. Even though it is harder nowadays to take the full measure of the meeting, the old face-to-face magic still happens in hallways and meeting rooms and exhibition-hall alleyways around the convention center.

MRMH: How does this connect to some of the overarching issues that the ISMRM may be facing?

Dan: In some ways, scope and pace are indeed dominant concerns, not only in our field, but in the world at large. I feel that the issues facing our society and our field are more dramatic, more exciting, and more existential than they have ever been. We are living in a rapidly changing world. This is something that is certainly clear to our young investigators, but has also struck any number of senior members. The world is changing so fast, in fact, that, if we don't choose our way forward well, we run the risk of losing much of our energy and our relevance. We in the ISMRM are arguably at the height of our powers – look at all the high-impact innovations we have introduced, and look at all the fields we have influenced. But, at the same time, consider the insanely fast rise of AI nowadays, not to mention the advent of modular electronics, cheap sensors, and modern software

platforms. Consider also the industrial landscape. Tech companies are moving into healthcare, and our traditional industry partners are reinventing themselves day by day. There are also dramatic economic forces driving change, including relentless downward pressures on reimbursement rates for imaging studies, and seismic shifts from fee-for-service to value-based medicine.

So how do we deal with these disruptive forces? We have undertaken a strategic planning process in the ISMRM this year, and here are four imperatives that are central to our new strategic plan (now available for review and comment by the membership at large): 1) Manage disruptive forces; 2) Marshal disruptive innovation; 3) Connect with the fields around us; and 4) Tell our story. These imperatives reflect some of our longstanding core values of innovation and connection. In order to increase the value of MR in a changing world, however, we must, increasingly, look outwards as well as inwards. Given the maturity of our field and the robustness of our interactions with one another, we risk forgetting that there are forces outside of MR, and forces outside of radiology or even biomedical imaging as a whole, which will shape how we are viewed and valued in times to come. Many people, including top-notch scientists in various disciplines, still think of us more or less as knob twiddlers who minister to the big machines that no-one wants their doctor to send them to. You may be surprised how many otherwise well-informed investigators don't really know that we can help to answer fundamental scientific questions, as opposed to merely generating pretty, macroscopic pictures. And then there is the general public. Part of the reason there is such pressure to cut reimbursements for medical imaging is because the public does not have nearly as deep an appreciation of the value of imaging, not to mention the value of MR in particular, as we pride ourselves on having. Therefore, it is increasingly essential that we get our story out: "This is who we are, this is what we do, this is the power we bring to healthcare and basic discovery, these are the patients whose lives we save." In a world increasingly flooded with information, we need to be sure that we are not the only ones who know the things we think we know.

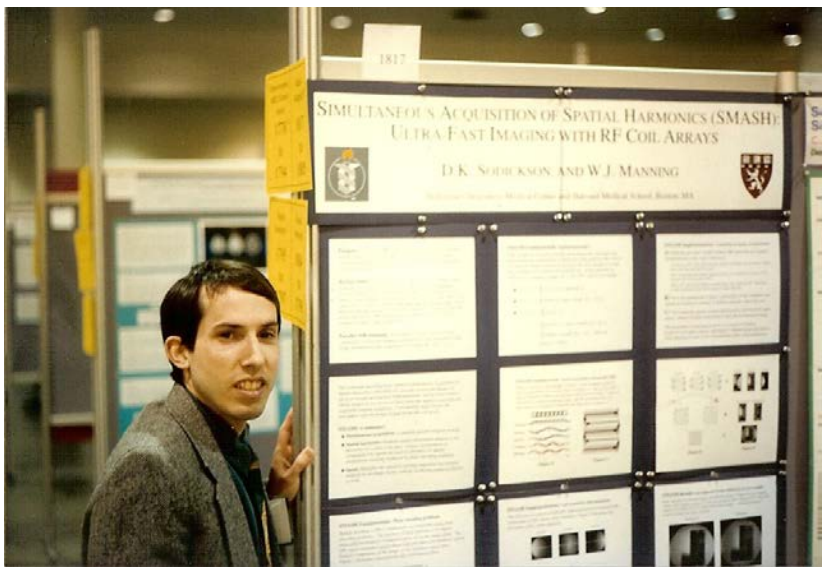
MRMH: What is an effective vehicle to get our story told?

Dan: We are looking to our membership to do what they do best, which is to be creative. When I talk to young scientists, each one of them may have 15 ideas, some of which I cannot even begin to understand, for ways to get our story out, using social media and other nimble platforms. If you think about it, most of our communications as a society to date have been inward-facing, directed towards our membership. We don't really have well-defined structures to broadcast information outwards to the world around us. MR Pulse is one nice example of the kind of thing we could and should be doing more of. And there are so many other things we can try. We can start inviting press to our meetings. We can prepare lay summaries of some of the key articles that appear in our journals. We can invite ambassadors from other fields to attend our meetings, and then sit down with them and ask them to tell us what they saw, or didn't see. We can invite our members to go to meetings in other fields, and to report back. Human interest stories are also important – stories in which we can show our value: "Here is a patient whose doctors didn't know what was wrong, and here is how MR helped to solve the mystery." That is the sort of thing people in public relations do all the time. I am not suggesting that we all become PR professionals, or that we start caring more about image than about imaging science. I am instead suggesting that we give more attention to precisely how we add value to the human experience, so that we can have the most impact as that experience evolves.

MRMH: You mentioned the word "value" a number of times just now. How does this connect to the ongoing ISMRM initiative on High-Value MR?

Dan: Value is, in many ways, the ultimate metric of success for our endeavors. As scientists and as clinicians, we all want to do something of value. The ISMRM Value Initiative, launched by past president Jim Pipe and championed by numerous thought leaders in our society, aims to focus us on proving as well as improving the value of MR. We are a society of inventive thinkers, and we love to come up with the next pulse sequence or the next coil design. But do we think hard enough about what the real impact of that sequence or that coil will be in daily practice? Do we take enough care to identify key clinical questions, and to devise new types of scans – whether they be fast, targeted exams of limited scope, or more expansive studies with previously inaccessible information – that address those questions head-on? And do we take the time to document the comparative effectiveness of our innovations in addressing real clinical or research questions?

> *In order to increase the value of MR in a changing world [...] we must, increasingly, look outwards as well as inwards*
>
> –Daniel Sodickson



Dan by his SMASH poster at the 1997 ISMRM Annual Meeting in Vancouver.

Images are just imperfectly-rendered representations of raw acquired data, and those data can be changed to meet our needs.

–Daniel Sodickson

MRMH: Once we have promising results, how can we really drive changes to clinical practice?

Dan: A combination of appropriate partnerships and appropriate focus is called for here. When it comes to clinical translation, it is common knowledge that change is hard, and it is easy to be daunted by all the well-known obstacles to getting a new technique into routine clinical practice: workflow considerations, regulatory constraints, conservative thinking, you name it. These obstacles are all real. But history has also shown that, when there is clear value in a new medical test or methodology, clinicians are not slow in adopting it. An incremental improvement in lesion visibility is nice, but it may not be enough to change longstanding clinical practices. Answering an important clinical question definitively, on the other hand – that will bring early adopters in droves.

At the same time, it is important to remember that a sequence which can generate all the pretty new images in the world will face an uphill battle for adoption if its introduction complicates clinical workflow. In healthcare, the value proposition is always an equation in which benefits are balanced not only against economic costs but also against opportunity costs. In order to manage all this, you need a well-designed method, the right enabling platforms, and the right partners. Indeed, one thing people sometimes overlook is the importance of developing imaging methods together with the stakeholders who will use them. If you, as an MR developer, try to optimize a pulse sequence all by yourself, and then toss it over the wall to clinical colleagues, those colleagues may find pitfalls that send you right back to the drawing board, and your iteration cycle may be measured in years. But if you have clinical colleagues working side-by-side with you as you develop your method, then they can catch key problems before you invest time in fine tuning, and your iteration cycle can be condensed to days or even hours. This is why our ISMRM model of connecting clinicians with basic scientists is so powerful. When the two are embedded together, the chances of translational success are amplified dramatically. Add in some industry scientists who can navigate the landscape of commercially available scanners, and you're really cooking with gas. This is also why the ISMRM gains so much from connections with industrial partners, such as our longstanding ISMRM corporate members.

Dan with family: Sarah, Hannah, and Noah

MRMH: On the subject of fast iteration times, advances in AI seem to be radically changing how we perform research. What is ISMRM's take on these emerging technologies?

Dan: The speed at which AI is taking hold is absolutely mind-boggling. I did some searches on the ISMRM website for abstracts relating to machine learning, deep learning, and neural nets. In just one year, between 2016 and 2017, the number of abstracts with these keywords increased by an order of magnitude. Whether or not we'll see another full order of magnitude this year remains to be seen – we have a finite attendance at our annual meeting, after all – but it is already clear that we will see dramatic increases from last year. When it comes to rapid adoption of powerful new tools like AI, the ISMRM has no need to push our membership; they are right there at the forefront. But we have taken a couple of measures to try to nurture this enthusiasm and creativity. For example, the ISMRM recently put together, in record time, a late-breaking workshop on machine learning, and, sure enough, the workshop was filled to capacity in no time. We're already planning a follow-up machine learning workshop for this fall. Our idea going forward is to pre-schedule slots for high-profile workshops like this, with topics to be determined at a later time, so that we can be nimble in adapting to late-breaking developments, and not lose currency while we work through logistics.

Moving back to how we tackle AI as a scientific and clinical community, I think that, even as we embrace the new pace, we also must be mindful about our choices. I have seen some of the special teams now being formed in the big tech companies, and it will be hard to outrace them when it comes to sheer person- and programming-power. These teams are full of creative and motivated data scientists who have grown up on modern software platforms. Even the most accomplished of these data scientists, however, tend to share some of the same underlying assumptions: namely, that data is king, that our images are our data, and that the information content of those images is more or less fixed. We ISMRMers, on the other hand, know that images are completely fungible. Images are just imperfectly-rendered representations of raw acquired data, and those data can be changed to meet our needs. This is what we do in MR

Dan with colleagues in Radiology research at NYU School of Medicine.

research – we do it all the time. What does this mean for AI? It means that we have the capacity to adapt our data to AI, rather than just tailoring AI techniques to read our images. We can change our acquisitions, and even our scanners, not merely to optimize image quality, but rather to enhance the quality of information gleaned by neural nets. And that is not all. We are also the people who take imaging information and try to identify its biological context. So, at the end of the day, we have some diverse and truly critical domain expertise that can add value to the AI enterprise. We are the ones who can bring physics, biology, and medicine to AI.

Another way of saying this is that, while it behooves us to join the fray and try out new AI techniques as quickly as we are able, we should also be careful to take best advantage of our ignorance (to return to the beginning of our conversation today). Many of us have the distinction, at least for a little while, of being newcomers to data science. So we can question assumptions, and we can think of things that others might know too much to think of. For example, we can look under the hood of the neural nets that everyone seems to assume to be black boxes, and see what we can learn as physicists, biologists, or clinicians. We can look, for example, at the weights that neural nets converge to, and see what patterns they bring to mind, what transforms they remind us of, what biomedical information they highlight. We can, in other words, treat AI not just as a physician's assistant, or even a physician's replacement, but as a discovery tool. Who knows what we may discover in the process?

MRMH: Do you think there is a need for a specialized journal based on AI methodologies?

Dan: Various bodies in the Society – our publications committee, our editors, our board of trustees, etc – are currently looking into our portfolio of Society journals. First of all, it must be said that our current journals have both time-tested and ongoing value. They have more than just impact factor - they have long-lasting impact. Manuscripts in MRM and JMRI tend to be cited for a long time after they are published, and this is something of which we are exceedingly proud. At the same time, we are looking into whether we would benefit from a third society journal. It is a little too early to decide if we want a machine-learning focused journal in particular – the RSNA, for example, has just launched such a journal – but this and other possible models are on the table and under active consideration. I would welcome thoughts on this front from the membership. I don't want us to take a 'me too' approach just because other societies have developed new journals. Scientists should be wary of hype at any time, and this time in particular is marked by so much buzz and creative ferment that we will need to apply the best of our high standards to separate the good ideas from the chaff and the churn. At the end of the day, we are tool-builders and tool-users, and AI represents a suite of powerful new tools that are newly at our disposal. I believe that the role of the ISMRM should be to enable the innovators in our midst to access these tools as effectively as possible, and to do the greatest possible good with them.

MRMH: Switching from the broad horizon to the relatively near future, and trying to get some parting thoughts - is there something specific that you are looking forward to at this year's ISMRM annual meeting?

Dan: Our Annual Meeting Program Chair Karla Miller has done a remarkable job in preparing the Paris meeting, together with the hard-working members of the AMPC and with our remarkable central office. I am looking forward to year two of secret sessions, and to the newly introduced member-initiated symposia. Keep an eye out for our new President's Lecture on Wednesday, which will kick off a day-long (and, I hope, ongoing) focus on diversity, inclusion, and unconscious bias in our Society. You will find any number of reflections of our new strategic plan at the meeting, including evidence of and responses to disruption, as well as attempts to foster connections within and beyond the traditional scope of MR. And one other plug: Do not miss the closing party this year. The venue for the party is at a bit of a remove from the convention center, but it is worth the trip. Once you go inside, you'll find yourself somewhere truly unique – like nowhere the ISMRM has ever been before. It will, I suppose, be a little like imaging itself: you have to see it to believe it! ■

> *We can, in other words, treat AI not just as a physician's assistant, or even a physician's replacement, but as a discovery tool.*
>
> –Daniel Sodickson

Don't hold your breath, let UTE do the work!

INTERVIEW BY **NIKOLA STIKOV**

EDITOR'S PICK FOR MARCH

This month we are featuring a collaboration between the Cincinnati Children's Hospital Medical Center, the Washington University in St. Louis and the University of Wisconsin - Madison. Nara Higano, Andrew Hahn, Jason Woods and colleagues used a converted orthopedic MRI scanner to measure tidal volume (the difference between lung volume in the inspired and expired state) in neonates. As you can imagine, we are talking small volumes here (on the order of tens of milliliters), and achieving this with 3D radial ultrashort echo-time (UTE) MRI is no small engineering feat that owes a great deal to some of the early MR projection reconstruction techniques.

> *People have used breath-hold imaging for the lungs, but if you want free-breathing images you need center-out acquisitions.*
>
> –Andrew Hahn

MRMH: First of all, can you tell us how you got into MRI?

Nara: I am a physics PhD candidate, and I knew that I wanted to do something applied, which brought me to work with Jason on lung imaging. Working on a neonatal project on lung imaging is extremely rewarding, highly translatable, and it is exactly what I was looking for coming from a technical background.

Andrew: I actually worked with Sean Fain (joint last author of this work) as an undergrad in the early 2000s. Then I graduated from UW with an engineering degree, did some consulting with the Medical College Wisconsin, and started thinking about going back to school. That is when I applied to the biophysics graduate program, Sean took me back, and from there I let the current take me. I am currently a postdoc here.

Jason: I had a very tortuous path toward MRI. I went to grad school in physics, because I wanted to do astrophysics. But then I got bored with it, and I realized I liked quantum mechanics. That led me to atomic physics, spins, that led to some NMR, and then to MRI.

MRMH: What is UTE and why is it good for lung imaging?

Nara: Conventional lung imaging uses Cartesian k-space acquisitions. The crucial part of UTE is that it is a center-out radial k-space acquisition, so this enables us to use very short echo-times. This is advantageous in the lung, because the lung has many air-tissue interfaces and varying local magnetic fields, which lead to very short T_2^* values. So UTE is crucial for lung MRI to image parenchymal tissue before the signal disappears.

Andrew: People have used breath-hold imaging for the lungs, but if you want free-breathing images you need center-out acquisitions. Radial UTE is pretty robust to motion, so that is another benefit from this approach.

Andrew Hahn

Jason: We all say echo-time, but of course this is a misnomer, because there is no echo, this is really FID imaging. In a larger context, this renaissance of radial scanning and UTE is historically neat, because that's how MRI began, as a projection reconstruction technique, and now we are getting back to it.

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

Nara: We focused on neonatal imaging, which is extremely difficult because we are working with very

Higano, N. S., Hahn, A. D., Tkach, J. A., Cao, X., Walkup, L. L., Thomen, R. P., Merhar, S. L., Kingma, P. S., Fain, S. B. and Woods, J. C. Retrospective respiratory self-gating and removal of bulk motion in pulmonary UTE MRI of neonates and adults. *Magn Reson Med.* 2017;77: 1284–1295. doi:10.1002/mrm.26212
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26212/full

Nara Higano and Jason Woods stand by the NICU magnet.

tiny people here. Their lung size is approximately 5cm in any dimension, and their tidal volumes are on the order of a 100ml, so there are many physical challenges. Further, you cannot instruct a neonate to sit still or hold their breath. In addition to retrospective bulk motion removal, we wanted to use retrospective respiratory gating to get functional information from those images.

Andrew: The main thrust of the paper is the development of a robust methodology for free-breathing pulmonary MRI in the most difficult population to image. This translates to other difficult populations where breath-holds are hard, in a sense to do the most we can with a very barebones approach.

Jason: The patients who will benefit the most from our work are actually the sickest patients, the ones that cannot be moved easily outside the neonatal ICU. Our approach doesn't compromise the clinical care, and allows a tomographic look in the lung, which isn't possible even via CT, as the patients are so delicate.

MRMH: Your results agree well in terms of respiratory rate, but it seems like you are underestimating the tidal volume. Can you comment on the discrepancies?

Nara: There is a fine balance between how tightly we can bin, and how we can maintain image quality. That led to some of the underestimations of the neonatal tidal volume. Direct measurements of neonatal tidal volume via infant pulmonary function tests require anaesthesia, are only conducted in large research institutions, and are not without risk to the patient. So our methods might represent the safest functional measurements available in this population.

Andrew: It is hard to get really accurate measurements of these parameters from children, as you cannot directly measure their tidal volume using spirometers, so you have to use physiologically predicted values from the literature for comparison. Trying to measure these small tidal volumes from the self-navigated data required quite a bit of fine-tuning.

MRMH: Where do you see this going, in terms of technical or clinical advances?

Nara: We will continue to use this bulk-motion removal, as we cannot tell a baby to sit still during an MRI. We can also look at other organs besides lung parenchyma, such as airways and airway collapse, so there is potential for clinical translation here.

Andrew: The exciting thing is looking at differences in morphology and function across the array of tidal volumes. We could be getting some SNR back from compressed-sensing techniques, but also look at quantitative measures, such as measuring T_2^* and T_1 across the respiratory cycle.

Jason: I spent most of my career doing adult research, but the last few years have been almost exclusively dedicated to pediatrics. I realize that we often develop techniques in adults, and then push them to pediatrics. But in this particular case, we are developing a new technique in neonates that can then be extended to adults.

MRMH: Is there something that we didn't touch on and you would like the readers to know about?

Jason: I would add that the way that this science has come together is emblematic of how modern science is conducted. We all have a physics background, so we published in MRM, but this work was only made possible by a very good collaboration between our institution and University of Wisconsin, and neonatologists and pulmonologists who were open to learning a new technique. I am very proud of the way the team has come together to produce new and innovative work. ■

> *Working on a neonatal project on lung imaging is extremely rewarding, highly translatable, and it is exactly what I was looking for coming from a technical background.*
>
> –Nara Higano

The QUEST for new MR fingerprinting approaches

INTERVIEW BY **AKSHAY CHAUDHARI**

EDITOR'S PICK FOR MARCH

Today we sat down with Yun Jiang and Mark Griswold from Case Western Reserve University to chat a little about their Magnetic Resonance in Medicine manuscript, entitled, "MR fingerprinting using the quick echo splitting NMR imaging technique." In this manuscript, the authors describe using a novel method to quantify relaxation properties of tissues with considerably lower radio frequency power deposition. While somewhat circuitous, our conversation led us through some of the history of this work, through some of the specifics of the paper, and through the visions for quantitative MRI in the future. Maybe next time when you run into Mark, you may want to ask him if there are now showers in his lab space!

> *One of the largest motivations behind developing this method was to be able to image patients who have metal implants.*
>
> –Yun Jiang

MRMH: Could you describe how you got interested in MRI and what motivated you to start working on MR fingerprinting (MRF)?

Yun: I became interested in MRI in general because it is such a comprehensive subject which covers software, computer science, and hardware. When I first joined Mark's group, I wasn't too aware about MRF, but I started working on a fingerprinting project around the same time as Dan Ma's fingerprinting paper got published.

Mark: I actually got into MR completely by chance! When I was in college and signing up for courses, all the classes that I wanted were filled up. I ended up registering for a medical imaging class mostly because the gym that I was in was hot and I wanted to go home! After that, I had been interested in quantifying relaxation parameters to investigate pathologies using steady-state sequences. However, these methods were too slow and sensitive to other parameters, and ultimately, not very clinically translatable. We almost gave up on the project on three separate occasions and it was that frustration, anger, and disappointment, which led to today's MR fingerprinting ideas.

MRMH: From this paper, how is the QUEST method different than previous MRF experiments?

Mark: The idea behind QUEST came from Renate Jerecic who had worked on the sequence during her graduate studies as a potential replacement for EPI. Renate heard me give a talk and mentioned that we should use QUEST with MRF. I immediately said yes and came home and told Yun about it!

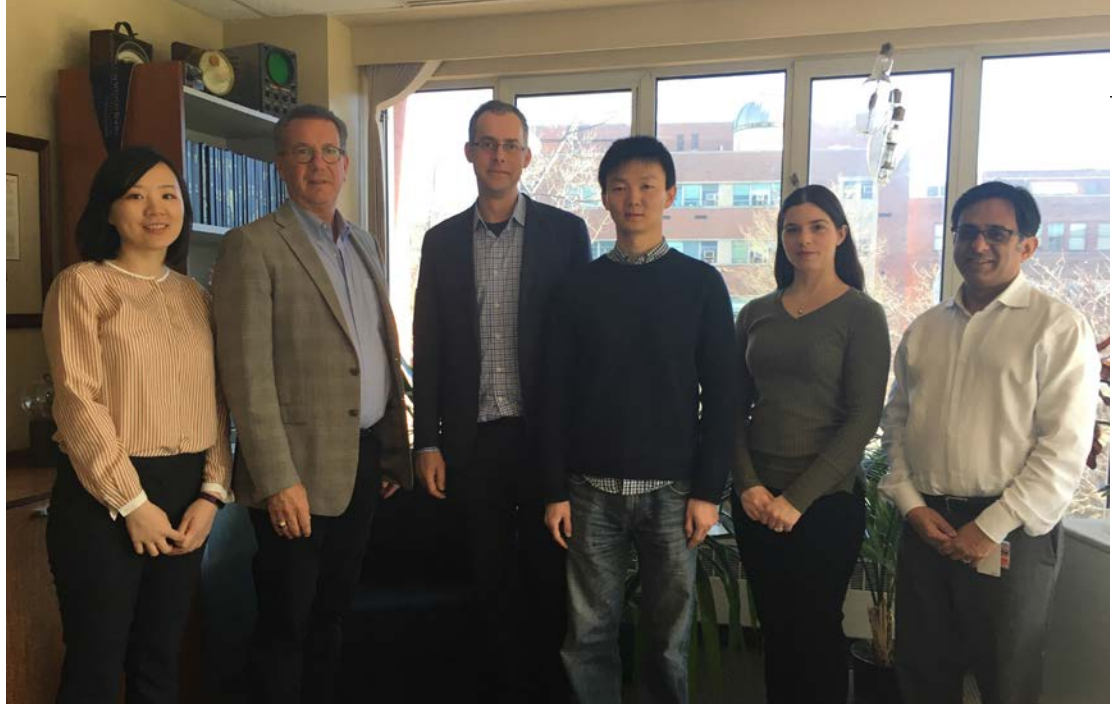
Yun: Mark's conversation with Renate was back in August 2012 which is when I started looking into the literature that existed for QUEST. The beauty behind QUEST is that by altering the RF gaps in a steady-state sequence, every coherence path is separated into echoes that can be sampled independently. Modifying the RF spacing can resolve the different higher-order coherence pathways occurring in the pulse sequence.

Yun Jiang at Deer Creek State Park in Ohio right before he jumped in the lake.

MRMH: What was the primary motivation toward developing the QUEST variation for MRF?

Yun: One of the largest motivations behind developing this method was to be able to image patients who have metal implants. With such patients, there are a limited

Jiang, Y., Ma, D., Jerecic, R., Duerk, J., Seiberlich, N., Gulani, V. and Griswold, M. A. MR fingerprinting using the quick echo splitting NMR imaging technique. *Magn Reson Med.* 2017;77: 979–988. doi:10.1002/mrm.26173
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26173/full



From left to right: Dan Ma, Jeffrey Duerk, Mark Griswold, Yun Jiang, Nicole Seiberlich, and Vikas Gulani.

number of sequences that can be used for clinical scans due to specific absorption rate (SAR) constraints which can lead to heating of the metallic implants.

Mark: In this paper we reported a SAR factor which was a hundred times lower than the FDA limit. This would let us use this sequence in a multitude of patients with implants and almost not have to worry about any RF-induced heating.

MRMH: For patients with such implants, what is the current standard of care? Are there certain sequences that can or cannot be run?

Yun: For the patient population with metallic implants, scanning at 3T is not recommended and only recently is it permissible to image with a head only transmit coil. With the given SAR constraints, it is not possible to run almost any conventional sequence so patients are sometimes imaged with a low flip-angle spoiled gradient echo sequence (FLASH, SPGR, T_1-FFE, etc).

MRMH: Now that this method allows one to scan patients, what are some clinical challenges you might face?

Yun: The biggest challenge in clinical translation of quantitative methods will relate to repeatability of the measurements. The relaxation rates can vary across multiple scans, across scanners, and even times of the day. Establishing a robust method that can deconvolve the physiological changes and scanning-related changes to ensure repeatability of the measurements will be important going forward.

Mark: This ultimately goes towards the idea that the more repeatable our measurements can be, the more sensitive we can be towards disease and treatment responses. Right now, we are under 5% variation which helps us see differences between healthy and diseased physiological states.

MRMH: Given that there is potential to generate robust quantitative measurements with MRI, how do these measurements fit into the clinical workflow?

Yun: For clinicians who have been trained on analyzing contrast-weighted images, it can be quite different to analyze quantitative measurements. However, in our experience, given some time and practice, clinicians can start reading the quantitative images similar to the morphological images.

Mark: When it comes to changes to the clinical workflow, one has to be able to offer something that is new that you cannot do any other way. Otherwise, our clinicians should not be wasting their time on it. For example, in the case of prostate cancer, the availability of the T_1, T_2, and diffusion measurements can help in making diagnoses of cancer and these measurements can help drive clinical decisions whether to biopsy or not. Overall, these measurements can provide value to change clinical practice. ■

Yun Jiang at the Wave in Arizona after a heavy snow.

> *When it comes to changes to the clinical workflow, one has to be able to offer something that is new that you cannot do any other way.*
>
> –Mark Griswold

Don't fight the motion! XD-GRASP for coronary MR angiography

INTERVIEW BY **AGÂH KARAKUZU**

EDITOR'S PICK FOR APRIL

In this April's Editor's pick, pieces from previous Highlights features are coming together. About a year ago Dr. Davide Piccini foreshadowed their collaborative study with NYU to incorporate XD-GRASP into their work on free-breathing motion correction. Seems like it was a productive year for Davide, as he not only delivered on his research promise, but also became a father. The Highlights team extends their sincerest congratulations to the Piccini family! We spoke to Davide and senior author, Prof. Matthias Stuber from the University of Lausanne, about their recent paper on four-dimensional respiratory motion-resolved coronary MR angiography.

Compared to acquisitions that take forever, using patient-specific motion models, this is a paradigm shift. Moving forward, we can try to resolve not only respiratory, but also cardiac motion.

–Davide Piccini

MRMH: Davide, we heard how you got into MRI last time we spoke. Perhaps you can now tell us how fatherhood is treating you?

Davide: At the moment, the lack of sleep does not help the scientific output [*laughs*]. Fortunately I got a couple of weeks of paternity leave, and I extended that and took a personal vacation to spend time with my daughter. I have also been working on a fetal cardiac imaging project recently, and seeing echoes of my own daughter provided additional motivation for that project.

MRMH: Matthias, how did you get into MRI research?

Matthias: I studied electrical engineering at ETH in Zurich. I am lucky ETH had an institute of biomedical engineering, where I took some classes and fell in love with MRI. So I really wanted do a PhD in this field and kept nagging Prof. Peter Bösiger. I was a pest, so he thought it would be easier if he hired me, which he did. Little did I know that it would lead me to a fulfilling professional carrier, where I got to work with leading research labs and companies. It has been a great, great ride!

MRMH: We are curious to know the story behind this fruitful collaboration with NYU. How did it start?

Davide: It was very informal in the beginning. I met Li Feng at SCMR in 2014, where he gave a talk on XD-GRASP. As soon as I saw it, I said this could be done right away for 3D, exploiting the golden angle arrangement of our radial phyllotaxis trajectory! I approached him afterwards, and asked if I could send him a couple of datasets. He agreed, and the first results were very good. Then we kept talking at subsequent conferences, we became friends, then I met Ricardo Otazo and Daniel Sodickson, and we took it from there.

Davide Piccini with his daughter.

Matthias: It helped that I was working with Dan Sodickson in the same office back in my days at Harvard. I have known Dan since 1997, so this connection was very easily made and became successful quickly. Then, there was another critical component. We hired Jérôme Yerly in our lab, who brought with him a lot of knowledge about compressed sensing. He implemented our own compressed sensing engine here in Lausanne, which we are now using every day.

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

Davide: This paper describes how you can acquire a 3D volume over time using a segmented 3D phyllo-

Piccini, D., Feng, L., Bonanno, G., Coppo, S., Yerly, J., Lim, R. P., Schwitter, J., Sodickson, D. K., Otazo, R. and Stuber, M. Four-dimensional respiratory motion-resolved whole heart coronary MR angiography. *Magn Reson Med.* 2017;77: 1473–1484. doi: 10.1002/mrm.26221

http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26221/full

From left to right: Davide Piccini, Matthias Stuber, and Jérôme Yerly.

taxis (golden angle) radial acquisition, which covers the entire k-space uniformly and induces very low amounts of eddy currents. Thanks to the golden angle displacement of the trajectory, the sampled segments allow for pseudo-uniform coverage of k-space even when reordered retrospectively, while the reconstruction artifacts remain incoherent. Looking at the center of k-space for certain projections, we extracted a respiratory signal with which we can bin the 3D radial data in as many respiratory bins as we want. From our experience four bins are enough for regular breathing. Then we end up with a respiratory state for which we have one quarter of the data that we actually need, so we use the XD-GRASP implementation to increase the image quality. We have several 3D volumes of different respiratory states. Each respiratory state differs from the next in small details. This can be used for the regularization process of the compressed sensing algorithm.

MRMH: Why is XD-GRASP a good fit for coronary MRA?

Davide: The whole concept behind XD-GRASP, resolving the motion instead of correcting for it, is a really good fit because it takes away the burden of trying to tweak your acquisition or your reconstruction to the specific problem. Coronary MRA has always been dealing with finding the best period of stillness, or trying to acquire more data and take care of the correction later by approximating to a motion model. However, each subject is different, so this concept of resolving the respiratory motion takes away the burden of figuring out what the motion is in the first place.

Matthias: The concept of the golden angle enables us to pull out any combination of profiles to generate discrete motion states in the respiratory dimension, and XD-GRASP produces beautiful motion-resolved reconstructed images. I have squandered my youth trying to improve motion correction for cardiac MRI. And some 20 years later, this beautiful technique comes along. I think we enter a new era here. There are many more things that we will be able to do with the exact same technology in the future.

MRMH: Such an ease of use! Can we consider this technique as a sigh of relief for coronary MRA?

Davide: The concept of enabling continuous data acquisition is possibly a sigh of relief not only for coronary MRI, but also for many other applications. Compared to acquisitions that take forever, using patient-specific motion models, this is a paradigm shift. Moving forward, we can try to resolve not only respiratory, but also cardiac motion. This is a project that was started by Simone Coppo here in Lausanne, again in collaboration with Li Feng at NYU.

Matthias: Today, most of the centers use navigators for which multicenter experience exists. However, this is neither the case for self-navigation, nor for our new 4D approach. While we are far away from providing a perfect solution just yet, the latter provides both a totally new and exciting paradigm, and new research opportunities for young scientists.

MRMH: Are you planning to make this project open source?

Matthias: As a first step, we want to make this open source within our own group. Right now it is in the hands of Jérôme Yerly, but there is so much enthusiasm in the team, everybody wants a piece of it for different projects. Once we have covered our basis and prove the concept, we really plan to push this out to the public domain, where everybody can take advantage of it. ■

> *I have squandered my youth trying to improve motion correction for cardiac MRI. And some 20 years later, this beautiful technique comes along. I think we enter a new era here.*
>
> –Matthias Stuber

On the hunt to assess renal function using hyperpolarized ^{13}C urea

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR APRIL

This month we sat down with Lotte Bertelsen, Christoffer Laustsen, and our youngest (and cutest!) contributor, Lotte's 8-month-old daughter Ellie. From their respective homes in Denmark, Lotte and Chirstoffer discussed the April Editor's Pick, "Diabetes induced renal urea transport alterations assessed with 3D hyperpolarized ^{13}C, ^{15}N-Urea." In this work, they use MRI to assess renal function in diabetic and normal rats by measuring a hyperpolarized ^{13}C urea gradient across the kidney.

Left, Chrisoffer Laustsen; Right, Lotte Bertelsen with daughter Ellie who sat in on the interview.

MRMH: Lotte, how old is Ellie?

Lotte: Ellie is 8 months old, and I have two older girls at the ages of 8 and 10. It's a full house! Hopefully they'll stay out in the living room for the rest of the interview.

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

Lotte: I'm a post-doc. I finished my PhD in 2014 at The MR Research Centre at Aarhus University, where I've been for nearly 10 years now. My main interest has always been cells, so I started out in immunology and was able to work with tracing cells where I'm using MR as my imaging modality.

Christoffer: I had a pretty typical way into science. I did a little solid state and biomolecular NMR, then moved into dynamic nuclear polarization and MRI. Now I am an associate professor at the same center, and I spend a lot of time with my family when I'm not working.

MRMH: What was your motivation for this work?

Lotte: This was a project where Christoffer and I could combine our forces on hyperpolarization in an animal model that we knew quite well.

Christoffer: We have done a lot of work in relation to diabetic kidney disease in this STZ Type I diabetic rat model. With a similar technique, we demonstrated that there was no alteration in the renal function of a diabetic rat over a shorter time span. Here we wanted to investigate whether or not we would see a change in the kidneys with a longer duration of diabetes using the high resolution that we've achieved previously.

MRMH: What do you mean by longer duration?

Christoffer: In previous work, at 2 weeks of disease we saw no change in the hyperpolarized urea signal pool between the diabetic and normal kidney. However, when using hyperpolarized pyruvate, we saw a dramatic increase in the lactate pool size indicating early renal changes. This led us to try a longer duration timeframe, with measurements using hyperpolarized urea 4 weeks after the induction of diabetes.

MRMH: The physiology is interesting. How do hyperpolarized urea images indicate renal function?

Christoffer: The kidney uses a lot of oxygen to pump fluid to create a gradient that drives the cleaning of the blood. Urea is one osmolyte that follows this gradient. The steepness of this gradient is what we are interested in, because it is believed to indicate the degree of urea reabsorption. A diabetic kidney goes into overdrive and uses too much oxygen, which creates a pseudo-hypoxic situation, even though you have sufficient oxygen. Eventually the kidney does not have enough energy to sustain that gradient.

MRMH: You derive the gradient from the intensity of the image, right? Is it unitless?

Christoffer: Right, one of the drawbacks of hyperpolarization is that the signal doesn't necessarily reflect a

Bertelsen, L. B., Nielsen, P. M., Qi, H., Nørlinger, T. S., Zhang, X., Stødkilde-Jørgensen, H. and Laustsen, C. Diabetes induced renal urea transport alterations assessed with 3D hyperpolarized 13C,15N-Urea. *Magn Reson Med.* 2017;77: 1650–1655. doi: 10.1002/mrm.26256

http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26256/full

Lotte and Christoffer's research group at Aarhus University.

quantitative number. It is dependent upon the polarization level, so we normalize to the signal in the cortex. To ensure comparison across studies, the amount and the timing of the injected tracer needs to be controlled.

MRMH: What advantage does the use of hyperpolarized urea have compared to the conventional measures?

Lotte: Urea is a natural product found in the human body, and the hyperpolarization produces a stronger MR signal. Compared to conventional MR, the hyperpolarized biomarker is especially advantageous for patients or animals with renal insufficiencies because you don't need a contrast agent that may cause severe side effects when accumulated in the diseased kidney.

MRMH: You used a diabetic rat model, but could you use hyperpolarized ^{13}C in other situations where you might have kidney failure?

Christoffer: Yeah! We believe that it is a general biomarker for kidney function. We have demonstrated that in a model of acute kidney injury where you completely abolish the kidney function of one kidney. We have also translated this to a porcine model because the pig's kidney has closer renal physiology to a human.

MRMH: Where do you want to go next?

Ellie: [*babbling and cooing*]

MRMH: Sounds like Ellie has some exciting ideas!

Lotte: Basically exactly what we are doing - going into larger animals and eventually to patients. We intend to move to pancreas cancer patients by the end of this year.

Christoffer: But we will start with hyperpolarized pyruvate instead of urea.

MRMH: I'm missing something; what is the difference between urea and pyruvate?

Lotte: Urea is an end product in the time frame what we are looking at. Pyruvate, on the other hand, is a molecule involved in several metabolic pathways, that will be metabolized to either lactate or CO_2 and bicarbonate depending on the oxygen availability in the given tissue.

Christoffer: It's a completely different thing. With urea you see perfusion and the hemodynamic response, but pyruvate gives you uptake and what it is being converted to.

MRMH: What will it take to translate to humans?

Lotte: It has been challenging to get the right approvals and to ensure that the pyruvate fulfills the requirements of a sterile produced agent.

Christoffer: We also need further comparisons with other biomarkers, especially those that are more accessible. For now it looks very promising – I certainly hope that other scientists will work more on this. We are eagerly anticipating whether they will show some of the first human data with hyperpolarized urea at UCSF. I'm hoping to see some very exciting stuff from them!

MRMH: One last detail… why do you specify that you are using ^{13}C and ^{15}N? Why not ^{14}N?

Christoffer: There is some debate, but the general thought is that ^{14}N is quadrupolar, which relaxes very fast, at low fields at least. At high fields it might not matter too much, but we don't really know. We don't think that we get any benefit from the ^{15}N at 9.4 tesla, but during the transfer from the hyperpolarizer to the magnet, ^{14}N would decay very rapidly.

MRMH: Thanks you guys! I have to say that I love this Highlights feature. It was spontaneous, and we have Ellie to thank for that. It's also different, and I really learned a lot. ■

> *The hyperpolarized biomarker is especially advantageous for patients or animals with renal insufficiencies because you don't need a contrast agent.*
>
> –Lotte Bertelsen

Exploring the echo time dependence of quantitative susceptibility mapping across brain regions

INTERVIEW BY **PINAR ÖZBAY**

EDITOR'S PICK FOR MAY

Among the Editor's picks for May comes a paper from the Center for Advanced Imaging at the University of Queensland, Australia. In their work, entitled, "Echo time-dependent quantitative susceptibility mapping contains information on tissue properties," Surabhi Sood and Viktor Vegh used a 3-compartment model to explore the echo time dependence of quantitative susceptibility mapping (QSM) and how this trend is varying in different regions of the brain. We conducted this Skype interview on a Tuesday evening Eastern time, while Viktor Vegh and Surabhi Sood were having their Wednesday morning coffee.

> *People have observed echo-time dependence in white matter in terms of frequency shifts, but it was interesting we saw it in general across the brain.*
>
> –Viktor Vegh

Surabhi Sood

Viktor Vegh

MRMH: How did you get into the field of MRI?

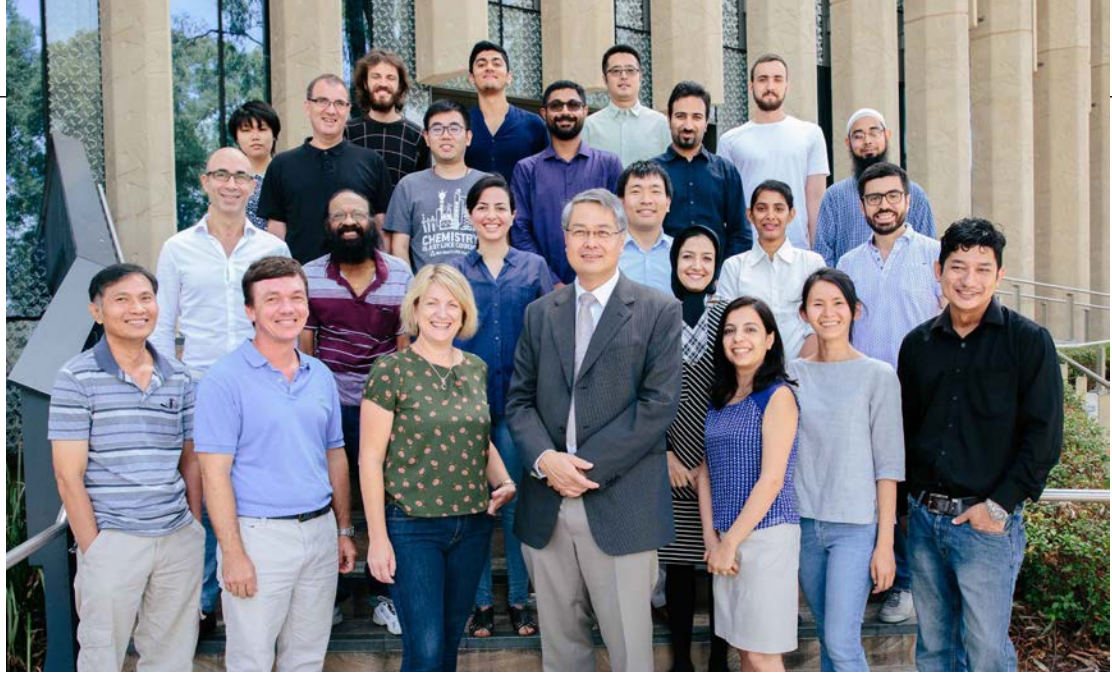
Surabhi: When I decided to do my MSc, I was browsing through websites, and ran across the Center for Advanced Imaging. Then I had a word with Viktor and found his suggestions very interesting. That's how I started my MSc and continued with a PhD.

Viktor: Well, my path was not that simple. I did my PhD in applied mathematics in microwave heating. After my PhD I lectured at another university, then I decided to do a postdoc, and looking around my neighborhood I found the Center for Magnetic Resonance, led by David Doddrell. One colleague advised me to give everything up and try this, so I did and started with MR instrumentation.

MRMH: Could you give us some information on QSM, and temporal QSM in particular?

Surabhi: QSM is a post-processing technique which resolves tissue magnetic susceptibility. It is used in neurodegenerative diseases to study iron distribution. With

Sood, S., Urriola, J., Reutens, D., O'Brien, K., Bollmann, S., Barth, M. and Vegh, V. Echo time-dependent quantitative susceptibility mapping contains information on tissue properties. *Magn Reson Med.* 2017;77: 1946–1958. doi:10.1002/mrm.26281
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26281/full



Surabhi Sood (front row, third from the right) and Viktor Vegh (front row, second from the left) with colleagues from the Center for Advanced Imaging in Queensland.

our paper, we introduced temporal QSM, because we observed echo-time dependent changes in susceptibility curves that were specific to different regions.

Viktor: It is not really QSM in the usual sense. QSM should be quantitative, and you would think the results should not depend on how you make the measurement. People have observed echo-time dependence in white matter in terms of frequency shifts, but it was interesting we saw it in general across the brain. We probably should not call it QSM. We are trying to come up with a new name, something like 'apparent susceptibility'.

MRMH: People would like that, because even in traditional QSM there is a big debate if it is really quantitative or not. Could you briefly summarize your work?

Surabhi: Our main aim was to study susceptibility trends in grey and white matter, and to see how the trend varies between regions. The results were diverse, there were some similar compartments in grey matter structures, and others in white matter.

Viktor: We initially wanted to do something completely different and simple. We recognized that increasing TE will increase noise, and with short TE acquisitions we might not have enough phase evolution. We wanted to write a paper about what echo time is best for QSM.

MRMH: So it was more like an optimization you wanted to do?

Viktor: That's right, but then we started finding temporal trends in the susceptibility curves and they were different in each brain region.

MRMH: Can we say that the modeling part of the paper was added afterwards?

Surabhi: Yes, initially we thought there would be a plateau over the echo time, but then we noticed it is completely different for all brain regions, and thought compartmentalization would be a good idea to analyze those trends.

MRMH: It was also my feeling that there were two big points in the paper, and they were merging together. So how did you come up with the model?

Viktor: We basically started using the frequency-shift model commonly used for white matter, and we adapted it to susceptibility imaging. For white matter there is a good justification for 3 compartments and it seems to be accepted by the community, but in grey matter this is not clear yet and we are still working on it.

MRMH: You used the STI Suite toolbox for your pipeline, what was your experience like?

Surabhi: We processed data from each channel individually, and combined them at the end. Viktor has a paper where you can leave out the noisy channels, and reduce the noise in the final maps. For the phase data, we used iHARPERELLA from STI Suite to unwrap and remove the background fields, and iLSQR to calculate susceptibility maps.

Viktor: Our experience was really good with the toolbox, we also used it for a mice study in another project.

MRMH: Do you have any ideas to improve the model?

Viktor: We would like to know if there is a direct link between tissue properties and the model. In white matter, they say there is a specific compartment for myelin, but in fact the signal is not formed in that way, it is formed in the presence of a distribution of fields, which may be local to the voxel, but not local at the microscopic level. The models are compartmentalizing microscopic components, but we are not sure that is the right thing to do. Maybe we should compartmentalize the field effects and interpret those, so there is room for improvement.

MRMH: Do you see QSM in clinics in 5 years? Any advice to the QSM community?

Surabhi: We need to standardize the pipeline first. If at any step noise is introduced, we need to cut it down to make this work efficiently.

Viktor: Studying brain with QSM has become very accepted. For us it is more about trying to identify compartments and produce spatially resolved maps across the brain. If we can do that, we can apply this approach to myelin and so on. That is actually our 3 year goal, hopefully we'll do even better in 5 years . ■

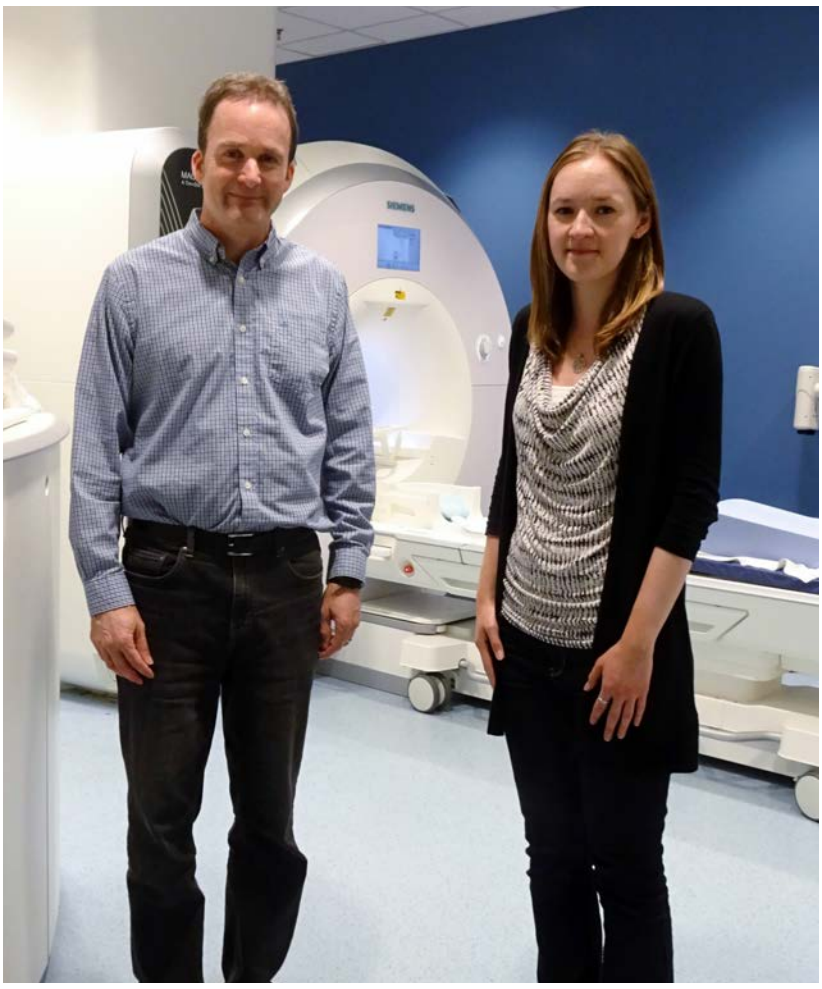
> *Initially we thought there would be a plateau over the echo time, but then we noticed it is completely different for all brain regions.*
>
> –Surabhi Sood

Accuracy and sensitivity of simultaneous T_2/B_1 mapping

INTERVIEW BY **ATEF BADJI** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR MAY

Among the Editor's picks for May comes a paper from the department of physics at the University of Alberta in Edmonton, Canada. In their work entitled, "Transverse relaxation and flip angle mapping: Evaluation of simultaneous and independent methods using multiple spin echoes", Kelly McPhee and Alan Wilman evaluated transverse relaxation (T_2) and flip angle maps derived from Bloch simulations and Extended Phase Graphs (EPG). We conducted this interview with Kelly on a beautiful Sunday afternoon at the Honolulu convention center during the annual ISMRM meeting.



Alan Wilman and Kelly McPhee

McPhee, K. C. and Wilman, A. H. Transverse relaxation and flip angle mapping: Evaluation of simultaneous and independent methods using multiple spin echoes. *Magn Reson Med.* 2017;77: 2057–2065. doi:10.1002/mrm.26285
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26285/full

MRMH: How did you come to work in MRI?

Kelly: I participated in University of British Columbia's (UBC) Co-op program during my undergrad, during which I joined the BC Children's hospital working with Dr. Bruce Bjornson on a fMRI research project. I then met Alan (senior author of this paper) through connections I made at that time and he was also the second reader on my undergraduate thesis. He offered me a position to do my Master's in his lab, but I wanted to stay in Vancouver. Two years later, I contacted him again and joined his lab to do my PhD.

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

Kelly: We are exploring the accuracy and sensitivity of simultaneous T_2/B_1 mapping methods via two different models for fitting multi-echo spin echo experiments, namely Bloch simulations and Extended Phase Graphs (EPG). The main difference between the two is that the Bloch simulation approach calculates the slice profile exactly, whereas the EPG approach approximates it. We used simulations, phantom, and human brain experiments to determine findings. We found that EPG and Bloch approaches provided similar T_2 results in most cases, though they are systematically different. The Bloch approach, and EPG with SLR slice profiles provided the best T_2 values. However, when T_2 and B_1 are simultaneously fit, EPG fitting provides highly inaccurate B_1, although T_2 is adequate. This is due to the slice profile approximation used by EPG. We also found that providing an accurate B_1 map to the EPG algorithm leads to further inaccuracies in T_2, thus a B_1 map should not be provided to the EPG approach. In contrast, the Bloch approach is effective either as a simultaneous fit, or with provided B_1 map. The Bloch approach is much less susceptible to noise when an accurate B_1 map is provided, and we recommend using a separately measured B_1 map when it is available. However, if the provided B_1 map is inaccu-

rate, errors will be introduced.

MRMH: For B_1 mapping you used FSE, which is inherently T_2 weighted. There are other B_1 mapping techniques (AFI, EPI-SE) that might be better candidates. What is the benefit of simultaneous T_2/B_1 fitting?

Kelly: There are a number of B_1 mapping methods that all produce reasonable results. A double angle method with fast spin echo was easy to implement, and we added a correction for slice profile. The benefit of simultaneously fitting B_1 and T_2 is that in data sets that lack a B_1 map, accurate fitting can still be performed. For example, this is very common in retrospective data, where a B_1 map was not acquired.

MRMH: What should people do to get a good T_2 map that is not affected by B_1?

Kelly: If your B_1 value is correct, you can input it into a Bloch based simulation method, but if you don't have a B_1 map, or if you are not sure if there is a bias in your B_1 map, you can do a simultaneous fitting approach. If using the EPG model, simultaneous fitting of T_2 and B_1 should be performed. In terms of code access, Marc Lebel released basic fitting code for the EPG method described in his 2010 MRM paper in a 2012 ISMRM abstract (p2558). I have not released code for the Bloch based method yet, but I would like to release it at some point, when I have the time to make it user friendly.

MRMH: How do you see this being relevant to basic/clinical researchers ?

Kelly: T_2 is a fundamental tissue property that varies in disease states. If we can measure it precisely, we can begin to uncover subtle variations in the individual or in group studies. The first step in this process is to be as precise as possible with minimal error, by measuring T_2 correctly by accounting for stimulated and indirect echoes. If you are trying, for example, to examine changes in a group of patients over time by comparing their T_2 maps, but your scan parameters are different across patients and scanners, then, if only exponential fitting is used, you will end up with biases that could make it impossible to compare these datasets. However, if you use any of these methods correctly and consistently, the EPG method or the Bloch based method, you will have better results.

MRMH: What would you like to do next?

Kelly: Regarding T_2 mapping, I think that if you properly model your sequence, you can unravel all the biases from your slice profile, flip angle, etc, and remove them to get your actual T_2 map. I am also developing a method for T_1 mapping, which I am presenting at this year's ISMRM meeting (E-poster 3712). Certainly, my goal is to make quantitative MRI reproducible so we can combine results across scanners for multicenter studies. ■

Kelly McPhee during a trip to Jasper, Alberta.

Getting T_1 out of cortical bone the ultrashort way

INTERVIEW BY **BLAKE DEWEY**

EDITOR'S PICK FOR JUNE

I recently had the pleasure of chatting with Drs. Jun Chen and Jiang Du about their recent MRM manuscript entitled, "Measurement of Bound and Pore Water T_1 Relaxation Times in Cortical Bone Using Three-Dimensional Ultrashort Echo Time Cones Sequences." We came together over three distinct time zones, stretching from Peking, China, via San Diego, California, and finally to me right outside of Washington, D.C., where thanks to a strong internet connection we discussed the ups and downs of ultrashort echo time (UTE) imaging. UTE is a method for direct imaging of tissues that have short transverse relaxation times by shortening the delay between excitation and readout. For example, in this paper, the echo time for UTE imaging was only 8 μs, compared to a traditional gradient echo readout, that would have a minimum of 2-5 ms, depending on the sequence. Jun and Jiang, along with their colleagues in the U.S. and China, have been working to apply UTE sequences to explore the T_1 properties of cortical bone and give clinically relevant information on components of the cortical bone structures not easily investigated with conventional radiological techniques.

> *UTE has ultrashort echo time, so this sequence can detect the bone structure better than normal sequences because bone has very short T_2*
>
> –Jun Chen

MRMH: Jun, how did you get started working in MR research?

Jun: I started working in the field of MR in 2007 when I began my PhD studies. Back then our lab focused on mental health disorders such as schizophrenia and major depression. As a noninvasive method, MRI, especially fMRI can detect patients' brain activation. This "abnormal" brain activation may be a potential endophenotype which can be used as a classification standard to homogenize patients with various presentations. From then on, I have been focusing on MR imaging and sequence development.

MRMH: And then how did you start this long-distance collaboration that we are highlighting?

Jun: After I got my PhD degree, I started working in the department of orthopedics in Peking Union Medical College Hospital, where we were looking for ways to evaluate the properties of bone. Dr. Du is well known in this field and one of my colleagues once worked in his lab as a visiting scholar. That is how I established contact with Dr. Du and began our collaboration. To further study UTE sequences, I moved to San Diego and worked in Dr. Du's lab as a post-doc for two years.

MRMH: Jiang, what brought you to MR research?

Jiang: My background is in physics, actually nuclear physics, and then I switched to magnetic materials, so it is related to MRI to some degree. Then I went to UW Madison for Medical Physics and started in MRI for my PhD. My first project was actually in MR angiography. Then I joined the UCSD team, I was one of the first recruits of Prof. Graeme Bydder for his UTE program.

Jun Chen and daughter striking a pose.

MRMH: It seems like a long road to get here, but also very applicable to the current work that you do. Let's

Chen, J., Chang, E. Y., Carl, M., Ma, Y., Shao, H., Chen, B., Wu, Z. and Du, J. Measurement of bound and pore water T_1 relaxation times in cortical bone using three-dimensional ultrashort echo time cones sequences. *Magn Reson Med.* 2017;77: 2136–2145. doi: 10.1002/mrm.26292

http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26292/full

From left to right: Shujuan Fan, Yinghua Zhao, Xin Cheng, Lori Hamill, Jiang Du, Saeed Jerban, Rose Luo, Aaron Zhu, Amin Nazaran, Xing Lv, and Yanjun Ma.

move on to the research at hand. Jiang, how could you provide some background on this work?

Jiang: With this technique, we are trying to quantify bone water, specifically the T_1 relaxation times. Previously, people have used UTE to image bone and we have demonstrated, probably several years ago, that UTE sequences can detect both pore water and bound water on clinical MR scanners. Since then people have become very interested in quantifying the absolute volume of bound water, which is a biomarker for the collagen matrix, and pore water, which provides information about cortical porosity. To try to quantify bound and pore water accurately, we need accurate T_1 information of both water components.

MRMH: What strengths does this sequence have? Does it have a specific clinical impact that you are looking for?

Jun: UTE has ultrashort echo time, so this sequence can detect the bone structure better than normal sequences because bone has very short T_2. It can also separate free water from bound water. It is relatively fast and can be used in the clinic. It also tells us more about the bone function, instead of just the structure.

Jiang: A strength of the technique is the ability to measure T_1's of both pore water and bound water. Those measurements can be clinically useful. For example, pore water T_1 may be related to cortical porosity. Bigger pores leads to a longer pore water T_1. Bound water, on the other hand, may be related to the organic matrix, so for the first time we can clinically evaluate the organic matrix part of cortical bone. The current gold standard, DEXA (Dual-Energy X-ray Absorptiometry), can only access the mineral component which takes about 40% of bone by volume. This means that with DEXA, 60% of the information is ignored because of technical limitations. With UTE , we get back the missing information about cortical porosity (pore water) and the organic matrix (bound water), therefore UTE may allow for more accurate evaluation of bone quantity and quality.

MRMH: You mentioned osteoporosis in your manuscript as a clinical target. Is this the main patient population that you will be investigating?

Jiang: Osteoporosis is one application. Not only that, we can apply this to any bone disease: Paget's disease, osteomalacia, and even fractures. We can use this technique for diagnosis and treatment monitoring of any of these diseases.

MRMH: What was the largest difficulty in implementing this method?

Jiang: Eddy currents are one major limitation for all non-Cartesian based techniques that are not commonly used on clinical MR scanners. Each scanner may have different sensitivity to eddy currents, so we need to calibrate the gradient system accurately and make UTE imaging more reliable. I think this is by far the biggest challenge when it comes to clinical application.

Jun: In China, almost all MRI machines are in hospitals and the users are mostly clinicians. When we want to implement the UTE sequence, we need the engineer's help. There are not enough engineers to help everyone. Also, if we want to use the sequence we have to buy the license to use the sequence and that can be expensive.

MRMH: What is the next step for this research? What is on the horizon?

Jun: When we use this technique in volunteers, the measurement is not always stable, so we need to optimize the imaging parameters. Second, we need to reduce the imaging time. This is very important in the clinic, as the patient cannot stay still for a long time.

Jiang: One day, it would be great to have dedicated bone imagers. It could be on the desktop, be low cost and could be used for imaging of bone in fingers or wrists. This could include a whole package, not just T_1s of bound and pore water, but T_2s, bound and pore water concentrations, collagen backbone protons including their fractions and exchange rates with water (via UTE magnetization transfer and signal modeling), and bone minerals (via UTE quantitative susceptibility mapping or UTE-QSM). ■

> *"Each scanner may have different sensitivity to eddy currents, so we need to calibrate the gradient system accurately and make UTE imaging more reliable."*
>
> –Jiang Du

The science of water exchange and the art of choosing acronyms

INTERVIEW BY **THIJS DHOLLANDER**

EDITOR'S PICK FOR JUNE

We sat down across time zones again (Australia in the morning, US east coast late afternoon), this time with Hua Li and Junzhong Xu, first and last author of their recent paper, "Impact of transcytolemmal water exchange on estimates of tissue microstructural properties derived from diffusion MRI." Apart from discussing the paper, we couldn't resist touching on the topic of social media in research these days, as well as the challenges and peer pressure involved with designing good acronyms for novel methods.

Farewell party for Hua Li at Junzhong Xu's home. From left to right: Junzhong Xu, Zhongliang Zu, Hua Li, Jingping Xie, and Xiaoyu Jiang. The baby is Hua's daughter Skylar.

MRMH: Hua, can you tell us a bit more about how you ended up working on (diffusion) MRI research?

Hua: My undergraduate studies were on quantum computing using NMR. It's very fancy - the goal is to build a quantum supercomputer. But when I started my graduate studies, I decided to do something more practical; something that's more valuable or useful today. That's when I switched to MRI for my PhD. I'm pretty interested in different MRI methods and contrast mechanisms: diffusion, relaxation, magnetization transfer… diffusion is just one part of it.

MRMH: Junzhong, what about your background? How did it lead you to diffusion MRI?

Junzhong: I'm a physicist, my background is actually computational physics. I used to do computational nano-optics; that's very different (from MRI). But in the second year of my PhD studies, I decided to change my major. At that time Dr. John Gore (who became my PhD mentor later) was looking for someone who could do diffusion MRI simulations, so I joined his group. That's how I started with my research in MRI and it's been many years since then!

MRMH: Junzhong, when I read the paper, something in the contact information caught my eye - I saw your Twitter handle in there! That's definitely still not a common sight. Do you think social media is starting to play a more important role for researchers?

Junzhong: Absolutely! Frankly speaking, I don't use Twitter a lot. But I do like to use it, for example on my phone when I have some time, it's actually quite fun! In the past, you'd just read finished papers in scientific journals from researchers you may or may not know. Nowadays, you can follow them and get a lot more information; some researchers share ideas they start to think about - and not only about science, but also about their opinions on the world. Twitter, for instance, also has a limit on the number of characters you can publish; so you must be very precise. Nowadays, everybody is very busy, so you want to deliver your message with a limited number of words. I also end up reading a lot of papers recommended on Twitter outside the field of MRI, in journals I wouldn't usually read, which is very interesting!

MRMH: On to the contents of the paper! The title is already very specific - can you explain to us what "transcytolemmal water exchange" (a topic central to the paper) is exactly?

Junzhong: We borrowed this term from the field of dynamic contrast enhanced MRI, where it has been used for more than 10 years now. It mainly indicates the water exchange between the intra- and extra-cellular space. This turns out to be a very important concept for diffusion MRI specifically. For instance, you have to consider very differ-

Li, H., Jiang, X., Xie, J., Gore, J. C. and Xu, J. Impact of transcytolemmal water exchange on estimates of tissue microstructural properties derived from diffusion MRI. *Magn Reson Med.* 2017;77: 2239–2249. doi: 10.1002/mrm.26309
http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26309/full

ent diffusion and relaxation properties in the intra- and extra-cellular spaces, and taking into account the water exchange between both makes the models very complicated. Nowadays, with higher gradient strengths people can probe higher b-values; so it's quite normal now to develop multi-compartment diffusion models… but including the water exchange is still a big challenge. Many diffusion models simply assume no water exchange. This does yield reasonable results, but the question is still - how accurate are these results actually? That's the motivation to study this important topic in our studies.

MRMH: The paper compares several methods, one of which is IMPULSED, a method from your group. Can you briefly give us a bit of background on this method?

Hua: IMPULSED, or Imaging Microstructural Parameters Using Limited Spectrally Edited Diffusion, combines both pulsed gradient spin-echo (PGSE) and oscillating gradient spin-echo (OGSE) measurements. Previously, quantitative diffusion methods were all PGSE based, i.e. based on pulsed gradients which have longer diffusion times. OGSE, using oscillating gradients, can provide shorter diffusion times. Combining both in the IMPULSED method, we use a broader range of diffusion times (both long and short). At long diffusion times, the measurements are more sensitive to restricted diffusion. At shorter diffusion times, the measurements are sensitive to the intrinsic diffusion coefficient. So, using a broader range of diffusion times, we can be sensitive to both tissue properties. Especially for smaller restriction sizes, IMPULSED will be more sensitive.

MRMH: Junzhong, how did you end up choosing that acronym?

Junzhong: Originally, I wanted to choose a cool name… but it turns out I'm not very good at this. I came up with a few names, but realised it's actually quite hard! There's quite a few cool acronyms in the field of MRI: SENSE, PROPELLER, GRAPPA, … but "IMPULSED" was the best I could do. At some point, I even Googled "how to make good acronyms?" Websites exist where you can enter some keywords, and they will suggest some acronyms. I tried for more than an hour, but found out it wasn't very helpful at all! Suddenly, IMPULSED came to mind - it sounded alright, I just had to put the words in the correct order.

MRMH: An acronym like this does make it more easy to remember!

Junzhong: Exactly. Names like OGSE, combined OGSE and PGSE… these things are hard to remember. But some peers said it was much easier to remember acronyms. Some people, on the other hand, hate that there are so many acronyms out there. It's so hard to follow nowadays. I totally understand this.

MRMH: So, the paper investigates the impact of the water exchange on the IMPULSED method, compared to some other methods; but also the impact on different microstructural parameters. Which parameters end up being most susceptible to the effects of water exchange?

Junzhong: The water exchange influences the (intra-cellular) volume fraction significantly, but it has (strikingly!) much less influence on the estimation of cell sizes. Using the IMPULSED method, especially due to inclusion of much shorter diffusion times, the influence of water exchange on the intra-cellular diffusivity is also lower. This work was actually inspired by our previous in-vivo investigations. We measured cell size and cellularity in vivo, and validated the results in a model of pathology (mouse xenografts). Surprisingly, the cell sizes were quite accurate, but the estimated cell density was significantly biased. We then hypothesised that the water exchange was the source of bias, because water exchange is much faster in these tumors. Then we performed this study and it turns out our hypothesis was true.

MRMH: Any specific tips you could give to our readers who may be interested in implementing the IMPULSED method in practice?

Junzhong: On a human scanner, it's well known that OGSE is hard to implement, but we were still able to do it. We found that we may not get a diffusion time that short, but it's still possible to get the diffusion time down to 10 ms with a b-value of about 1000 s/mm^2 (e.g. as in DTI) and for 5 ms the b-value can only get to around 250 s/mm^2. The sensitivity to different length scales depends on the diffusion time you can achieve. For a cell size around 15-20 microns, getting the diffusion time down to 10 ms can significantly enhance the sensitivity. That's why we were able to successfully apply IMPULSED in human breast cancer. The sensitivity is so good we can scan for about 5 minutes and get the total parametric volume of mean cell size and apparent intra-cellular volume fraction of whole tumors. PGSE-only methods would be less sensitive to those cells sizes, so you'd need a longer acquisition time. But the challenge is that IMPULSED is a combination of two very different measurements, PGSE and OGSE. They are susceptible to different things. OGSE is for instance relatively less sensitive to background susceptibility and flow effects. You should at least make sure you get the expected (and identical) ADC values in free water for either OGSE and PGSE!

Hua: But I'd say, let's go for it and implement IMPULSED on human scanners, and see what we can get!

Junzhong: Indeed, unless you can show great potential for applications in the clinic, the scanner vendors won't be interested. But the gradient coil is still a challenge on human scanners; it's typically still limited to 80 mT/m. The shortest diffusion time with a decent b-value will then only be 10 ms. The sensitivity is then mostly valuable for e.g. the sizes of cancer cells. But neuroimaging is still a very different story... ■

> *Using a broader range of diffusion times, we can be sensitive to both tissue properties.*
>
> –Hua Li

A novel QSM algorithm for mapping large susceptibility ranges in the head

INTERVIEW BY **PINAR ÖZBAY**

EDITOR'S PICK FOR JULY

It is our pleasure to present one of the Editor's picks for July, "Preconditioned total field inversion (TFI) method for quantitative susceptibility mapping," from Cornell University. In this work Zhe Liu, Pascal Spincemaille, and colleagues proposed an algorithm which allows mapping of tissue magnetic susceptibility in regions with large dynamic susceptibility ranges, such as cavities, bones, and hemorrhages in the head. There are two main steps in QSM algorithms: the removal of background fields to calculate the local field, and solving the local field-to-susceptibility problem. The latter is an ill-posed problem by nature, hence this step is mainly referred to as the 'inverse problem' in the QSM literature. Their method calculates susceptibility maps via 'total field inversion', which generalizes those two steps as one optimization problem, and further employs preconditioning to achieve fast convergence.

> *Susceptibility imaging got started by treating susceptibility as an artifact, and trying to find the source of that artifact.*
>
> –Pascal Spincemaille

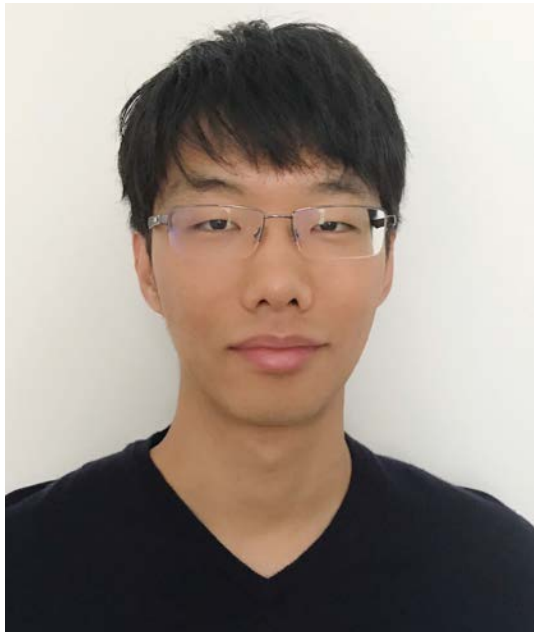
MRMH: Could you tell us about your backgrounds, and you got into the field of MRI?

Zhe: My undergraduate major was in automatic control, which is a combination of computer science and electrical engineering. In my senior year, I started working on motion correction in MRI in CBIR research center at Tsinghua University. I found MRI very interesting, because I could use the knowledge I acquired from signal processing and optimization courses.

Pascal: I am a physicist from Belgium, and I used to work on theoretical physics. Then I decided to look for something more practical and thought I would do MRI for a while, travel around the world, and get back to Belgium - but I never got back. I am really happy I ended up in MRI, which is a broad field that makes a difference in people's lives.

MRMH: This will be the third QSM-related paper in MRM Highlights, and each time we ask the authors to briefly introduce QSM. What is exciting about QSM?

Zhe: For me QSM is interesting in understanding the nature of the inverse problem. It has two major advantages which make it widely useful. First, in comparison to other phase-contrast methods like susceptibility-weighted imaging (SWI), it has less blooming artifacts, and is more accurate for identifying areas which are rich in iron or calcium, such as hemorrhage and MS lesions. The second advantage is it reflects the tissue magnetic properties independently of imaging parameters, so it is ideal for quantification, such as measuring oxygen consumption levels.



Zhe Liu

Pascal: Susceptibility imaging got started by treating susceptibility as an artifact, and trying to find the source of that artifact. That's an interesting problem from a mathematical, physical, as well clinical point of view. In order to do QSM, we had to learn a lot about optimization algorithms, and treat those solvers less as a black box. On the side of the applications, there are two important ones that are implemented at Cornell, one of which is preoperative planning for deep brain stimulation. Namely, one day, a surgeon we collaborate with walked into the scanner control room and saw the subthalamic nucleus (STN) on a QSM image that hap-

Liu, Z., Kee, Y., Zhou, D., Wang, Y. and Spincemaille, P. Preconditioned total field inversion (TFI) method for quantitative susceptibility mapping. *Magn Reson Med.* 2017;78: 303–315. doi: 10.1002/mrm.26331
http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26331/full

The Cornell MRI Research Lab, from left to right: Yi Wang, Alexey Dimov, Pascal Spincemaille, Junghun Cho, Youngwook Kee, Thanh Nguyen, Kofi Deh, Ramin Jafari, Liangdong Zhou, Zhe Liu, and Yan Wen.

pened to be displayed on the viewer. He thought it was the ideal image for deciding on electrode placement, because he could see the STN very well due to high iron content. The other application comes from the MS research group at Cornell. As QSM could be used to determine the MS lesion stage, they are looking into using it as Gd replacement for follow-ups.

MRMH: Could you describe the proposed method in your work, that is, preconditioned total field inversion?

Pascal: QSM turns the images you acquired with MRI into a susceptibility map. The physics tells you that the field inhomogeneity is generated by the convolution of the susceptibility distribution with the unit dipole kernel. And the field you calculate from the complex data has a background and a local component. So, when you first remove the background field, you are left with the local field, which should be generated only by the tissue inside the brain (that's your hope). Once you have the local field, it is easier to do the second step, which is deconvolution (solving the inverse problem). The contrast you expect to see is on the order of 0.1 to 0.3 ppm. If you don't do enough iterations, it appears not to work, but it eventually converges, and if you have a smaller dynamic susceptibility range, your algorithm would run faster. So, what we thought is, why don't we solve those two in one step?

Zhe: The problem with the two steps is that the error of the first step (background field removal) might propagate and cause artifacts in the second step (inverse problem). Because these two steps can be explained by the same physical model we tried to fuse them in one equation, and we observed that we can even use the same iterative solver (conjugate gradient). The only thing is we need more iterations to reach a solution given the large dynamic range of susceptibility, as mentioned by Pascal. In this work, we think of ways to accelerate the speed of the TFI. And for that, we use a preconditioner, which reflects contrast with strong external sources and weak tissue sources, and utilizes additional information such as R_2* to extract the hemorrhage site.

MRMH: Could you give us a summary of your results?

Zhe: Our results show that in healthy subjects we can improve the homogeneity of QSM compared to local field inversion techniques. Compared to the other TFI methods which are based on Laplacian operation, we could preserve the cortical structure of the brain. In the end, we showed that it is possible to do QSM using preconditioned TFI in the whole head and to measure susceptibility in skull. In the patients with hemorrhage, we are able to reduce the artifacts around the hemorrhage.

Pascal: For brain, QSM techniques are well-developed, as the brain only has susceptibility contrast, no fat and other interferences. Outside of the brain (as for liver or cardiac QSM), we need to do water-fat separation first. In those cases, we then almost always use preconditioned TFI, and we believe that's the next frontier for making QSM work in the body.

MRMH: Do you see QSM as a 'push button' method in the scanners soon?

Zhe: It is currently a fully automated process at Cornell and sites, with a dedicated server for QSM reconstruction. The entire process (scanner -> QSM server -> reconstructed maps -> scanner) takes 5-7 minutes, so the results are always ready by the end of the scan session.

Pascal: Other research sites that are interested in using this method can contact us, and we will help them install the system on their sites. Matlab QSM code from our lab is also available, and we are working on incorporating TFI into it. Below is our MATLAB code (http://weill.cornell.edu/mri/pages/qsm.html) and the automated and compiled mode is available upon request. ■

> *Our results show that in healthy subjects we can improve the homogeneity of QSM compared to local field inversion techniques.*
>
> –Zhe Liu

A spin-lock approach for glucose enhanced MRI: from medical physics to patient examination

INTERVIEW BY **BRIAN CHUNG**

EDITOR'S PICK FOR JULY

This week we ventured across continents to speak with Drs. Patrick Schünke and Moritz Zaiss, two primary authors of a recent paper from the German Cancer Research Center (DKFZ) in Heidelberg, Germany entitled, "Adiabatically prepared spin-lock approach for $T_{1\rho}$-based dynamic glucose enhanced MRI at ultrahigh fields." For this paper, the authors developed an NMR method for imaging glucose using an ultra-high field MR scanner and a spin-lock approach to gain sensitivity to chemical exchange. At ultra-high field strengths, distinct artifacts appear predominantly resulting from RF field inhomogeneities. Thus, adiabatic pulses were implemented to enable the application of spin-lock MRI at fields such as 7T. This adiabatic spin-lock approach is explained, its feasibility for application *in vivo* at 7T is verified, the technique's sensitivity to glucose is investigated, and a first proof of concept of spin-lock based glucose imaging for the detection of cancer in humans is presented.

> *I like the idea of keeping the softness of the method by only using natural sugar as a contrast agent.*
>
> –Moritz Zaiss

Patrick Schuenke

Moritz Zaiss

MRMH: Patrick, as Moritz was asked in a previous Q&A, can you speak briefly about your background and how it brought you to MR?

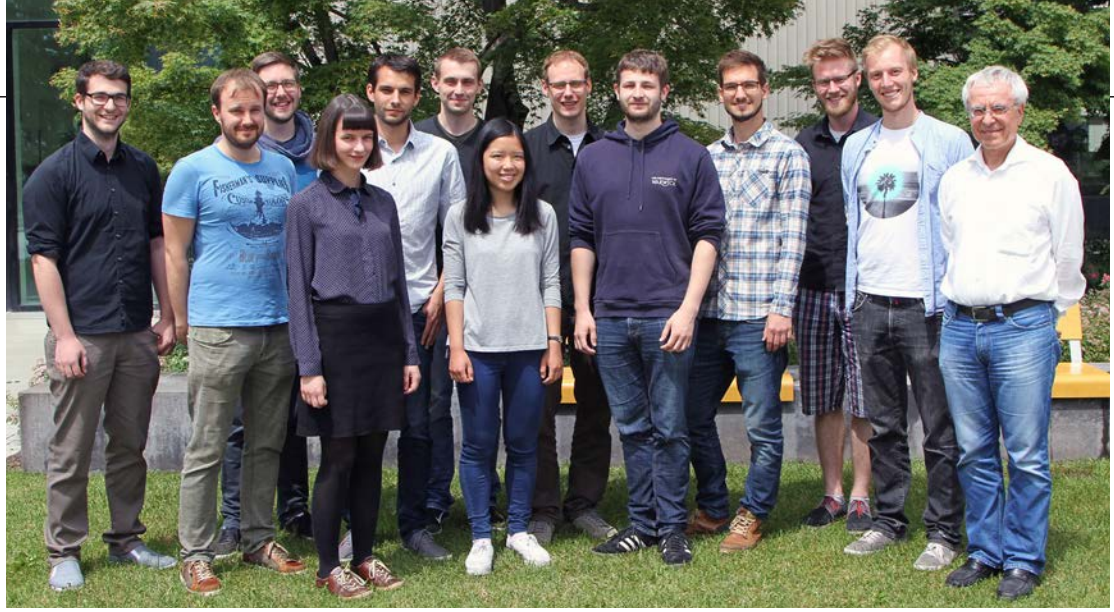
Patrick: I wrote my bachelor's thesis in medical physics about X-ray detectors and started my master's thesis about MR afterwards. After a few months, Moritz convinced me to switch from my project at the time to study the CEST effects of glucose, and that's what I've been doing for about 5 years now.

Moritz: I started right after my undergrad with CEST imaging and B_0 correction. When Patrick joined the group, I asked if he wanted to try glucose imaging with MRI instead of PET.

MRMH: I know other researchers are curious to learn more about a parameter they may be unfamiliar with - $T_{1\rho}$. How would you define it? And what makes it useful?

Schuenke, P., Koehler, C., Korzowski, A., Windschuh, J., Bachert, P., Ladd, M. E., Mundiyanapurath, S., Paech, D., Bickelhaupt, S., Bonekamp, D., Schlemmer, H.-P., Radbruch, A. and Zaiss, M. Adiabatically prepared spin-lock approach for $T_{1\rho}$-based dynamic glucose enhanced MRI at ultrahigh fields. *Magn Reson Med.* 2017;78: 215–225. doi:10.1002/mrm.26370

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26370/abstract



NMR spectroscopy and CEST imaging group at the German Cancer Research Center, Division of Medical Physics in Radiology, Heidelberg, Germany.

Patrick: $T_{1\rho}$ is the longitudinal relaxation time in the rotating frame. A more precise notation would maybe be the longitudinal relaxation time in the presence of an external RF field. Very simply, it's a tunable, slowed-down T_2 relaxation method. The benefit of its use is the sensitivity we gain to relatively slow motional processes, such as the chemical exchange between water and glucose.

Moritz: $T_{1\rho}$ and $T_{2\rho}$ are the generalizations of T_1 and T_2 in the presence of RF irradiation. In the rotating frame of an irradiation pulse (where the ρ comes from), the behavior is very similar to the FID experiment: you have a new transverse magnetization that oscillates and decays with $T_{2\rho}$, and longitudinal magnetization that recovers with $T_{1\rho}$. The only thing that is different is the new tilted coordinate system, and that $T_{1\rho}$ and $T_{2\rho}$ are mixed variables depending on T_1 and T_2, but also exchange terms.

MRMH: And how would you explain spin-lock?

Patrick: In a spin-lock experiment, you first excite the water magnetization into the transverse plane, and then you apply an additional RF field in the same direction as the magnetization to "lock" it. This is known as the spin-lock state during which the magnetization relaxes with $T_{1\rho}$. After a certain relaxation time, the water magnetization is flipped back to the z-axis, and you can read out the prepared signal using a conventional MR sequence, resulting in a glucose weighted signal.

Moritz: The big issue at ultra-high fields is the need to have a perfect 90 degree pulse. This is very difficult when you have RF inhomogeneities of up to 50%, so we tried to use adiabatic pulses for the flipping of the magnetization in the spin-lock experiment. It's a simple approach - a high powered hyperbolic secant pulse tilts magnetization onto the transverse plane, then a conventional rectangular locking pulse is applied, and afterwards we adiabatically flip the magnetization back to the z-axis again.

MRMH: There is only one piece missing! What part of your experiment sensitizes your measurement to glucose?

Patrick: The inverse of the $T_{1\rho}$ relaxation time (the $R_{1\rho}$ relaxation rate) depends linearly on the glucose concentration because of the additional contribution to the relaxation rate due to the chemical exchange between water protons and glucose hydroxyl protons. Therefore, we obtain an indirect detection of the glucose signal by measuring the relaxation affected water signal.

MRMH: Is there a personal contribution or achievement from this work you are particularly proud of or excited for?

Patrick: The basic idea behind glucose imaging for cancer detection is quite old, as it's known for decades that tumors have higher glucose uptake than normal cells. Peter van Zijl's group showed the first glucose images in humans using the CEST technique, and we were the first to prove the feasibility of glucose enhanced imaging in humans using the spin-lock technique.

Moritz: The first Eureka moments were the first patients we measured. In healthy volunteers not much uptake is expected, so we didn't know if our experiment would work until we measured the first brain tumor patients. The very first patient examination and evaluation was especially exciting.

MRMH: On that note, what motivates you to push the scientific boundaries of medical imaging?

Patrick: What I like most about medical imaging is that it is (essentially) basic research, for example studying the spin dynamics during adiabatic pulses or spin-lock experiments, but then you can apply your methods directly to patients and see the results. That's a great feeling and probably a unique feature of medical physics. And the biggest motivation for me is of course the hope that our technique finds its way into the clinical routine at some point in the future.

Moritz: Well, MRI is such a nice method being intrinsically noninvasive. I like the idea of keeping the softness of the method by only using natural sugar as a contrast agent.

MRMH: Finally, what types of cross-collaborative research efforts would you most like to see increased?

Moritz: I think new perspectives for extracting valuable information from raw data could be extremely helpful. I would love to see more radiologists who like to program in MATLAB to quickly test their own new hypotheses. ■

> *The benefit of its use is the sensitivity we gain to relatively slow motional processes, such as the chemical exchange between water and glucose.*
>
> –Patrick Schuenke

NOE the ropes: how to quantify a new -1.6 ppm signal

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR AUGUST

The August 2017 Editor's Pick is from Xiao-Yong Zhang and Zhongliang Zu, researchers at Vanderbilt University in Nashville. Their paper presents a newly discovered Nuclear Overhauser Effect (NOE) signal at -1.6 ppm from water. They measured this signal in normal rat brains at 9.4 T, and found that it changed significantly in a rodent tumor model. Using reconstituted phospholipids and cultured cell experiments, they hypothesize that this signal may originate from membrane choline phospholipids. We recently spoke with Xiao-Yong and Zhongliang Zu about their work.

Xiao-Yong Zhang

Zhongliang Zu

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

Xiao-Yong: My background is in medical imaging. When I was doing my PhD in China, my research focused on MRI techniques. I then came to Emory University and Vanderbilt University for my post-doc, where I focused my research on MRI at the molecular level to detect brain diseases.

Zhongliang: I got my PhD in medical physics at Peking University in China, and then came to Vanderbilt University for my postdoc, where I'm currently an assistant professor. My research focus is on MRI sequence development of chemical exchange saturation transfer (CEST), magnetization transfer (MT), and spin-locking techniques, and their applications in tumors, stroke, and other neurological diseases.

MRMH: Before we dive into the paper, could you explain briefly the MT and NOE mechanisms?

Xiao-Yong: Magnetization transfer (MT) is a physical process by which macromolecules and their closely associated water molecules cross-relax with protons in free water. And the Nuclear Overhauser Effect (NOE) is a nuclear spin-transfer phenomenon by a space-dependent dipolar coupling effect within molecules.

MRMH: Can you give us an overview of your paper?

Zhongliang: In this paper, we introduced how to quantify a newly discovered NOE signal at -1.6 ppm from water. Because it's very close to the water peak, and thus is significantly influenced by direct water saturation effects, it's not easy to directly observe on the CEST Z-spectrum. We used a quantification method to isolate this signal from other non-specific factors. We found that the amplitude, offset, and linewidth of this signal changed in some brain regions of healthy rats. We also explored the potential applications of this signal in a rat brain tumor model, finding that this signal changed significantly in tumors. Lastly, we used reconstituted phospholipids and cultured cell lines to study the possible molecular origin and contrast mechanism of this signal, and found that it could originate from membrane choline phospholipids and may be a new biomarker for diagnosing tumors.

Xiao-Yong: In my opinion, the origin of this signal is very important for us to know. The experiment on reconstituted phospholipids was just a preliminary study. For the next step, I think we should perform further studies on the origin of this signal. If we know the origin of this signal, it may open a lot of applications. It's very interesting.

Zhang, X.-Y., Wang, F., Jin, T., Xu, J., Xie, J., Gochberg, D. F., Gore, J. C. and Zu, Z. MR imaging of a novel NOE-mediated magnetization transfer with water in rat brain at 9.4 T. *Magn Reson Med.* 2017;78: 588–597. doi:10.1002/mrm.26396
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26396/full

a) Zhongliang at the aircraft carrier USS Intrepid in New York; b) Xiao-Yong at Vanderbilt University Institute of Imaging Science; c) Zhongliang travelling; d) Xiao-Yong at a lab party; e) Zhongliang on the beach in Hawaii; f) Xiao-Yong on campus

MRMH: What were some of the technical challenges encountered during this work?

Xiao-Yong: One of the big challenges for this work was developing the quantification method, because this -1.6 ppm NOE signal is very broad and susceptible to direct saturation. It's not as obvious as the typical -3.5 NOE signal, and they overlap. We tried several methods to quantify this signal. Finally, we used a fitting method to get our results.

MRMH: Your quantification method corrects for T_1 and B_0. How sensitive is the signal to B_1?

Zhongliang: Correcting for B_1 is a problem for the CEST community. For people working on clinical scanners, especially on 7T human scanners, where there is significant B_1 inhomogeneity, they measure several Z-spectra with a series of powers, use a linear fit of the signal, and then correct for B_1 effects. This may be applicable to our own method. But currently, we just performed the study on animal scanners, where B_1 is not as much of a problem. If we further investigate our method on clinical scanners, we may try those correction techniques.

MRMH: You mention in your paper that you noticed the -1.6 ppm NOE signal in other published work, but the authors didn't report it. Do you see the need to revisit any other study that didn't consider this effect?

Zhongliang: Yes, definitely! I think the earliest paper where you can see the signal is one by Craig Jones at John Hopkins in 2013. In that paper, they studied NOE on humans at 7T. There's a figure in this paper where you can see a signal around -1.6 ppm. This signal can be found in healthy tissue, but not in tumors, which is in agreement with our study. They did not discuss this signal. There's another paper by Kimberly Desmond in Toronto, from 2014. She showed that in mice the fitted error at -1 to -2 ppm is much bigger than at other offsets, which might mean there is something here.

MRMH: What you do enjoy doing when you're not in the lab?

Xiao-Yong: In my spare time, I enjoy playing ping-pong and Weiqi (Go).

Zhongliang: During off-lab hours, I like to play some computer games, like Civilization and Ages of Empires [laughs]. Also, I'm in Tennessee, Nashville, which is a very beautiful place. I like to go to forests, and drive to nearby rural places. ■

> *Because it's very close to the water peak, and thus is significantly influenced by direct water saturation effects, it's not easy to directly observe on the CEST Z-spectrum.*
>
> –Zhongliang Zu

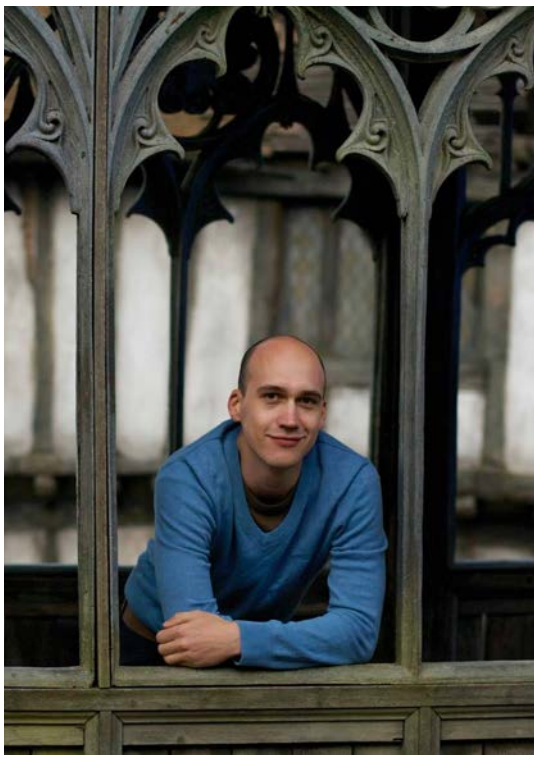
High fields and short scans in spectroscopic imaging

INTERVIEW BY **BLAKE DEWEY**

EDITOR'S PICK FOR AUGUST

This week we gathered across multiple continents (as I feel we always do!) to discuss the ins and outs of spectroscopic imaging with Bernhard Strasser and Wolfgang Bogner, two authors of "(2+1) D-CAIPIRINHA accelerated MR spectroscopic imaging of the brain at 7T", one of the MRM Editor's Picks for August 2017. In this paper, Bernhard and his colleagues propose a new method of acceleration for magnetic resonance spectroscopic imaging (MRSI) that combines 2D CAIPIRINHA with simultaneous multi-slice (SMS) to accelerate imaging in all three spatial dimensions.

> *Unfortunately MRSI is not often used clinically, but I think this would be a big benefit of our method, as we were even able to use it in a clinical study.*
>
> –Bernhard Strasser



Bernhard Strasser

MRMH: Let's begin with a bit of background. How did you become interested in the field of MRI/MRSI?

Bernhard: I just started about 6 or 7 years ago. I began being interested in fMRI and how the brain works and what happens when we are afraid or when we see something pleasant. It turned out that I found MRI spectroscopy to be even more interesting.

Wolfgang: My background is in physics and after my Master's thesis I became bored of radiation prediction, but wanted to stay in the life sciences. I found MR interesting when I came across it in my studies and started my PhD in the field. I have pretty much worked with brain spectroscopy from the beginning.

MRMH: Now moving on to the paper, can you give a brief summary of this work?

Bernhard: What we did in this paper was to create a new method using parallel imaging to accelerate the acquisition of MRSI in all three of the spatial dimensions. We do 2D CAIPIRINHA in-plane and then because we have multiple slices, we do simultaneous multi-slice (SMS) in the slice direction. We then compare this to more common parallel imaging methods, 2D GRAPPA and 2D CAIPIRINHA.

MRMH: Does this require more intricate measurement of sensitivities or can we use a standard method for calculating the required weights?

Bernhard: We can use a standard GRAPPA technique. The only difference is we collect an imaging sequence, a gradient echo sequence, to gather the calibration data. We don't do this with the spectroscopy data, because it would take too much time.

Wolfgang: Our pre-scan also does not include water suppression which gives us many times more signal to use for calculation of GRAPPA or CAIPIRINHA weights. They are pretty much noiseless. These can be then directly applied to the spectroscopic acquisitions.

MRMH: What would you say is the biggest strength of this method?

Bernhard: I would say that the ability to accelerate in all 3 dimensions. That way we are exploiting the sensitivities in each direction and that is very beneficial. Also, the way we acquire the calibration data, but this is just one puzzle piece of our whole methodology. In general, I would say that we can measure, within a reasonable

Strasser, B., Považan, M., Hangel, G., Hingerl, L., Chmelik, M., Gruber, S., Trattnig, S. and Bogner, W. (2 + 1)D-CAIPIRINHA accelerated MR spectroscopic imaging of the brain at 7T. *Magn Reson Med.* 2017;78: 429–440. doi:10.1002/mrm.26386
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26386/full

measurement time, very high resolution MRSI data with very high SNR and I think there is a lot of information that can be extracted from this data. Unfortunately MRSI is not often used clinically, but I think this would be a big benefit of our method, as we were even able to use it in a clinical study.

MRMH: Tell me more about this clinical study.

Wolfgang: We can show multiple cases of MS patients, where we have five, six, or seven different chemical compounds in metabolic maps with a matrix size of 100 x 100, or slightly above. This has not been possible before. In some cases, where we have very small lesions, on the order of 3 mm, we can suddenly see metabolic changes with that resolution. For example, we can observe myo-inositol or NAA in lesions that are only about 2-3 mm large.

MRMH: What would you say the biggest weakness of this method is?

Bernhard: The most difficult part is determining the best patterns, the 2D CAIPIRINHA patterns plus the FOV shift from the SMS. Initially, I thought it is very straightforward, you just test all of the possible patterns, but the problem is there are so many possible patterns, that takes quite some effort. Also, whenever you change, for example, the scanner or the coil, you would need to find the best patterns again.

MRMH: Do you optimize the patterns on each subject or do you do it on each coil and attempt to position the patient similarly?

Bernhard: The latter. It shouldn't change too much from patient to patient as long as the brains or the heads are not so different. What is important is how the sensitivity map looks, this influences the patterns, because of the aliasing that we achieve with the (2+1)D CAIPIRINHA.

MRMH: What is the next step for this research?

Bernhard: I am working on accelerating MRSI acquisition even more, using spectral-spatial encoding, where spatial and spectral information is encoded at the same time using spirals or EPSI. This will help us get bigger coverage in the z-direction to cover even more of the brain.

Wolfgang: Although Bernhard has recently moved from Vienna to Boston, we are still working together, with some of the same common goals. We basically want to have 3D whole brain coverage for spectroscopic imaging and have it in clinical use. MS is where our clinical collaborations have worked very well and we already have 70 scans performed. These clinical scans are only done with the methods that are described in this paper because we know that these sequences are robust. In parallel, we are developing spectral-spatial encoding techniques and only when this runs with 3D and is really robust with scanner reconstruction, will we be able to use this in clinical studies.

MRMH: Thank you so much for speaking with us today. Is there anything else you would like to add?

Wolfgang: We are always looking for collaborators that are willing to try out our methods. We also have a reconstruction pipeline that we are eager to share, if anyone is interested. Thanks so much. ■

Bernhard Strasser (left) and Wolfgang Bogner (right) enjoying an Imperial Stout beer.

> *In some cases, where we have very small lesions, on the order of 3 mm, we can suddenly see metabolic changes with that resolution.*
>
> –Wolfgang Bogner

Quantifying oxygen consumption in the brain: is ^{17}O the way to go?

INTERVIEW BY **ATEF BADJI** AND **NIKOLA STIKOV**

EDITOR'S PICK FOR SEPTEMBER

This September brings us an Editor's pick from Freiburg, where Dmitry Kurzhunov and his colleagues used Oxygen-17 (^{17}O) to quantify the cerebral metabolic rate of oxygen consumption ($CMRO_2$) on a 3T clinical MRI system. While positron emission tomography (PET) remains the gold standard for measuring $CMRO_2$, Dmitry and senior author Michael Bock give us several reasons why ^{17}O might be the way to go.

> *We also want to compare ^{17}O MRI with proton MRI as we don't need additional equipment and the scans are quite fast.*
>
> –Dmitry Kurzhunov

MRMH: How did you become interested in MRI?

Dmitry: I grew up surrounded by physics because my father had been working in academia as a physicist for many years. I also started studying physics in Russia, at Kazan Federal University, and worked on electron paramagnetic resonance (EPR) for my undergraduate thesis. Then I got a German scholarship and came to Berlin for my Master's to work on EPR of proteins. During that time, I got to know the big brothers of EPR, namely nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI). I was fascinated by this new technology so I decided to move to Freiburg and do my PhD in MRI.

Michael: I also studied physics in Braunschweig and Heidelberg, Germany, and in 1990 I joined the Max Planck Institute for nuclear physics. I worked on nuclear physics, electron beams, and particle beams, which was extremely interesting but also very hard. It often took ten people to run these experiments, and they could still fail because one vacuum valve was open. After I finished my diploma, in 1995 I started my PhD at the German Cancer Research Center in Heidelberg, which had its own MR center. From that moment, I only worked in MR because I think that it is one of the most interesting technologies out there to diagnose diseases. In 2011, Jürgen Hennig made me an offer I couldn't refuse, and since then I have worked at the University Medical Center in Freiburg.

MRMH: Can you please give a short summary of your paper?

Dmitry: This paper is a first, but essential step for Oxygen-17 MRI at clinical field strengths. The idea is to perform a direct assessment of oxygen metabolism, which is altered in brain tumor regions and neurodegenerative diseases. This abnormality can be quantified with the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Our goal was to investigate the identifiability of $CMRO_2$ in a pharmacokinetic model that fits the $H_2{}^{17}O$ signal dynamics after inhalation of isotope-enriched ^{17}O gas. For this, the method of profile likelihood analysis was used, with which we investigated the minimal amount

Dmitry Kurzhunov in Toronto for ISMRM in 2015.

Kurzhunov, D., Borowiak, R., Hass, H., Wagner, P., Krafft, A. J., Timmer, J. and Bock, M. Quantification of oxygen metabolic rates in human brain with dynamic ^{17}O MRI: Profile likelihood analysis. *Magn Reson Med.* 2017;78: 1157–1167. doi: 10.1002/mrm.26476
http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26476/full

of required prior knowledge about the other model parameters. It was shown that one parameter assumption was sufficient for reliable $CMRO_2$ quantification. Moreover, an advanced $CMRO_2$ quantification model was proposed that accounts for pulsed delivery of ^{17}O gas.

Michael: People have been using ^{17}O MRI in the past at higher field strengths such as 7T, but it is currently not available in the clinical setting. We want to use ^{17}O as a clinical tracer, which means we have to make this technology available at 3T.

MRMH: What is ^{17}O and why is it useful?

Dmitry: ^{17}O is the only MR detectable stable oxygen isotope with a non-zero nuclear spin. It can be used as an MR tracer to assess metabolic processes that involve oxygen. The major problem is its very low natural abundance (0.037%), which means that we need to acquire MR data for a longer time and the spatial resolution is rather low.

Michael: Currently, the only established method for direct oxygen quantification is PET with the oxygen isotope ^{15}O. However, it is rarely used due to the short isotope half-life of 2 minutes, whereas the MR isotope ^{17}O is stable, so that we do not have any time restrictions. Another advantage of ^{17}O over other MR contrast agents is that ^{17}O is truly an intracellular tracer. It is transported via the blood, it then enters the cells where it is metabolized to water. Only then it becomes MR observable, because the relaxation times of ^{17}O bound to hemoglobin are very short and we cannot observe it there. Therefore, the signal increase that we see after inhalation of ^{17}O gas must have come through a process of metabolization. Another advantage of ^{17}O is that even if the natural abundance is low, we have unlimited access to it in the atmosphere. We don't lose any. We inhale it and give it back again through the respiration process, whereas when we exhale a light isotope such as ^{3}He, it goes into the stratosphere and we lose it. ^{17}O only needs to be enriched, but that is very costly.

MRMH: What is the price?

Dmitry: One liter of 70% isotope-enriched gas would cost a couple of thousand dollars. For each experiment we used 2.5-2.7 liters of this gas. We would like to thank NUKEM Isotopes Imaging for their generous support of our ^{17}O MRI project. We also implemented a rebreathing system, so that we can restore and reuse rare and costly ^{17}O gas.

MRMH: How does dynamic ^{17}O MRI compare with other approaches for characterizing the oxygen metabolism (BOLD, PET)?

Michael: ^{17}O is a direct molecular marker, as it determines the MR signal of oxygen in the cells, whereas proton MRI techniques such as BOLD are looking more indirectly at the susceptibility effects caused by oxygen (e.g., in hemoglobin). These could be two complementary measures. However, the gold standard is PET because its sensitivity is much higher. In fact, we are always comparing our healthy volunteer data to PET data from the literature.

Michael Bock, Robert Borowiak, and Dmitry Kurzhunov doing a ^{17}O MRI experiment at University Medical Center in Freiburg.

Dmitry: We also want to compare ^{17}O MRI with proton MRI as we don't need additional equipment and the scans are quite fast. It could be interesting to compare the differences between grey and white matter, especially for brain tumor patients. Hopefully, ^{17}O MRI and 1H MRI will provide complementary information.

MRMH: What is the biggest challenge for your method and what are your next steps to overcome it?

Dmitry: The biggest challenge is the low SNR due to the low natural abundance of the ^{17}O isotope. To compete with PET, we need to improve everything from hardware and experimental setup to image acquisition and reconstruction. To overcome this challenge, we showed in our recent NeuroImage paper that SNR can be improved using prior information from the co-registered 1H MR data in an iterative reconstruction procedure. We showed a principal feasibility of pixel-wise $CMRO_2$ quantification with ^{17}O MRI in a clinical 3T MRI system.

Michael: A second option would be to acquire data at ultrahigh fields, but this is not done in a clinical environment. If 7T becomes clinically available, this will bring us one step closer to measuring oxygen consumption in the cells of patients affected by brain tumors, stroke or neurodegenerative disease. However, for this technology to flourish at the moment, we need to try to implement it in clinical environments. ■

> *^{17}O is a direct molecular marker, as it determines the MR signal of oxygen in the cells.*
>
> –Michael Bock

Getting rid of nuisance variables using autocalibrated wave-CAIPI

INTERVIEW BY **NIKOLA STIKOV**

EDITOR'S PICK FOR SEPTEMBER

The Martinos center in Boston recently brought us wave-CAIPI, an accelerated 3D imaging technique that uses helixes in k-space to encode information and speed up MRI acquisition. However, differences in the calibration of the gradient systems made it difficult to generalize the wave-CAIPI technique and deploy it on any clinical scanner. This is where the Editor's Pick for September comes in; Stephen Cauley and his colleagues proposed a joint optimization approach to estimate k-space trajectory discrepancies simultaneously with the underlying image. We asked Steve and senior author Larry Wald to tell us the story of autocalibrated wave-CAIPI.

> *… even though it is a complex optimization problem, you can understand physically what it's doing, what information is being leveraged, and I think that's a good thing to keep a grip on.*
>
> –Lawrence Wald

MRMH: Steve, how did you end up in MRI?

Steve: My background is in computer aided design, so I had been working at Intel solving a lot of large scale math and optimization problems. As my wife was transitioning here for her medical residency, a friend of mine told me to talk to a professor at MIT, Jacob White. When Prof. White heard about my background, he said I should go talk to Larry Wald.

Larry: And now Steve has developed a reputation as somebody you go to when your reconstruction is not working [*laughs*].

MRMH: Larry, in our last Q&A we heard about your career beginnings. Your PhD advisor, Prof. Erwin Hahn, is sadly no longer with us. Can you tell us what it was like to learn MR physics from him?

Larry: I was actually his last graduate student. He was winding down at that time, so I was the last one through the door and I was very happy to have had that opportunity. He was a very physical guy. For him to invent something meant you really had to understand the whole picture of what was going on. He rallied against black boxes and not understanding what's inside them. I remember one time when we were in the lab, just unpacking a new digital oscilloscope, and he said 'unless you make it yourself, you don't understand it', and then he went into a story about how when he was a post-doc with Felix Bloch, the first thing Bloch made every student do was build their own oscilloscope.

MRMH: Do you think the field has moved beyond that kind of low-level approach?

Larry: On one hand, things have moved beyond that. On the other, I find myself applying Hahn's philosophy to this day. Even with this paper, one of the things I like about it is, even though it is a complex optimization problem, you can understand physically what it's doing, what information is being leveraged, and I think that's a good thing to keep a grip on.

Stephen Cauley

MRMH: On to the paper. Can you explain briefly what is wave-CAIPI?

Cauley, S. F., Setsompop, K., Bilgic, B., Bhat, H., Gagoski, B. and Wald, L. L. Autocalibrated wave-CAIPI rec onstruction; Joint optimization of k-space trajectory and parallel imaging reconstruction. *Magn Reson Med.* 2017;78: 1093–1099. doi: 10.1002/mrm.26499
http://onlinelibrary.wiley.com/wol1/doi/10.1002/mrm.26499/full

The team that brought you autocallibrated wave-CAIPI: Stephen Cauley (top right), Lawrence Wald (second right), Kawin Setsompop (middle), Himanshu Bhat (second left), Berkin Bilgic (top left) and Borjan Gagoski (back).

Steve: Highly accelerated techniques, such as CAIPIRINHA, use a sampling strategy where you attempt to shift aliasing voxels farther away from each other to take advantage of parallel imaging array coils. Wave-CAIPI builds upon that by adding an extra dimension to the blurring along the readout direction. By playing sinusoidal gradients along the y and z-directions we get efficient spreading along the x-direction, and that enables us to push the acceleration past what you see with standard parallel imaging.

Larry: From a coil point of view, it was always thought that when you have a 3D distribution of receive coils, you can undersample in the two phase-encode directions, but you don't really need to undersample in the readout direction. CAIPIRINHA opened our eyes to the idea that the sampling pattern does change the aliasing pattern, so variations in the readout direction are also useful.

MRMH: As long as you can control them...

Steve: It came down to our ability to get the gradients to do what you want them to do. In the presence of gradient trajectory errors, the artifacts will appear almost everywhere. But we found this nice middle ground, where we keep the benefits of a CAIPI reconstruction, but we pose the problem as a joint convex optimization, where the image reconstruction is coupled with the gradient trajectory constraints.

Larry: Steve really saved us on this technique, because we had been working on wave-CAIPI, it was working well, but we had tested it on only one scanner with just a few coils. And then we gave it to several colleagues to use, and they tilted the volume, and played it on their scanners, and it didn't work so well. And we figured out the reason was that there were differences in the gradient calibration across systems, different resolutions, and all this could break the reconstruction. So we were faced with a dilemma: should we go to the manufacturers and ask them to improve their gradient calibration systems, or do we try to fix it?

Steve: Now we are at a point where we can apply this to several different contrasts, such as susceptibility weighted imaging, MP-RAGE, and many other volumetric sequences. We have refined the technique to the point that this autocalibration only takes several seconds. We have tried it across different strengths of scanners, different coils, sequences, and different parts of the world, and we conclude that it generalizes well.

MRMH: Can you tell us a bit about the team behind the paper?

Steve: To work on a project like this takes many different people and many different backgrounds. It all started with Kawin and Larry writing something down on a napkin...

Larry: But it takes a lot of time to go from napkin to showing the world that this works. These problems are uncovered constantly, even beyond the testing stage. The commercial manufacturers know this painfully well. It is one thing to make things work on one system, another to generalize it. So Kawin (Setsompop) and Berkin (Bilgic) were the ones that uncovered the problems and defined them. Himanshu (Bhat) and Borjan (Gagoski) helped with the coding and testing the fixes.

Steve: People are always walking into each other's offices, helping each other when they are stuck.

MRMH: Where would you like to take this work next?

Steve: The first thing right now is motion correction. We are extending this idea of model reduction to jointly estimate gradient trajectories, as well as patient motion.

Larry: There's always going to be some nuisance variables that are unknown. In the case of this paper it was trajectory errors, but in general the biggest nuisance variable you can think of is patient motion, so this is really high on our plate. Unfortunately, the list of nuisance variables is long.

MRMH: I really like this notion of 'nuisance variables', is it standard terminology?

Larry: No, my wife and I have this private joke. We had racoons living under our chimney, so we had to call the 'nuisance mammal' division of the city to remove them. So referring to these unwanted visitors as nuisance mammals always amused me, and that's where the term 'nuisance variables' came up in my mind.

MRMH: Cool! Please get in touch when you cross the next nuisance variable off your list! ■

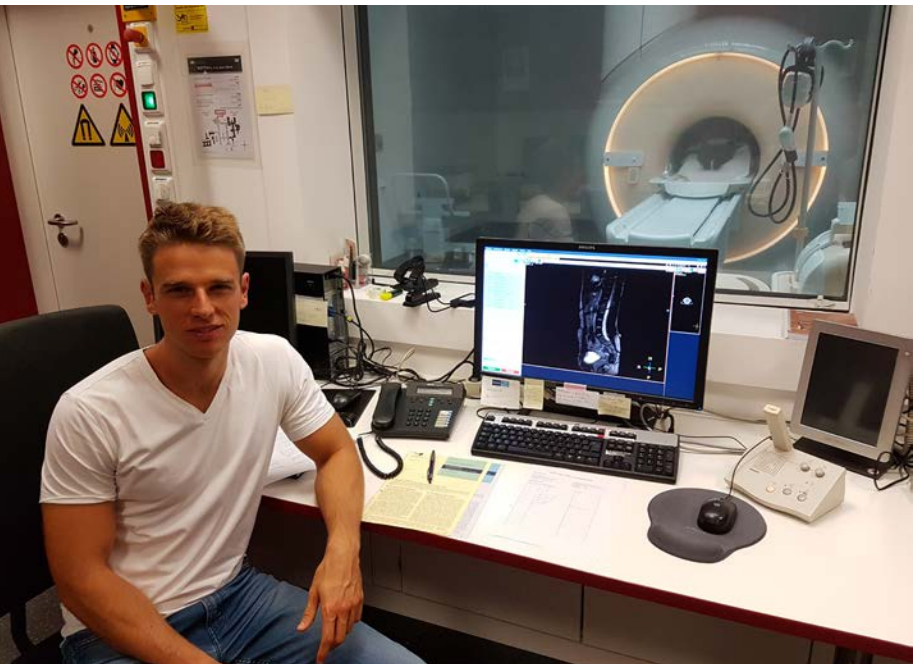
> *To work on a project like this takes many different people and many different backgrounds. It all started with Kawin and Larry writing something down on a napkin...*
>
> –Stephen Cauley

Come for the baguetting, stay for the ADC quantification of bone marrow water

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR OCTOBER

This month we talked to Michael Dieckmeyer and Dimitrios (Dimitris) Karampinos about their work to measure apparent diffusion coefficient (ADC) values in bone marrow. Michael has a very diverse education that includes a master's degree in mathematics, and he is currently completing his final year of medical school. His mentor Dimitris leads a multidisciplinary research team in Munich that focuses on the development of quantitative MRI, targeting musculoskeletal diseases and metabolic diseases like obesity and diabetes. In this paper, they use modeling to overcome some of the challenges of ADC quantification in the presence of fat. By including the proton density fat fraction (PDFF) and the T_2 of water, they can reduce the bias in the ADC measurements that is introduced by residual fat.



Michael Dieckmeyer

MRMH: How did you get involved in this project?

Michael: During my third year of medical school I became interested in a doctoral thesis, so I got in contact with Dimitris. The project sounded great to me because it had this quantitative approach that most of the projects in medical school lack. It was a big plus that I could connect this quantitative aspect with patients/in vivo experiments, so I could use both my mathematical and medical skills.

MRMH: Cool. I'm always impressed by the people who can wear both hats.

Dimitris: We have an entire program focused on quantitative imaging biomarkers using MR techniques in a variety of tissues. The starting point for Michael's work comes from our interest in developing biomarkers for assessing bone health and, more generally, in the quantitative MRI of tissues in the presence of fat. In the big picture, we are interested in looking both at the properties of the adipocytes themselves and also the properties of water in tissues that contain fat.

MRMH: Why should we care about measuring diffusion in bone marrow?

Michael: Diffusion reflects the tissue microstructure and can differentiate between malignant and non-malignant vertebral fractures. In general, diffusion is an interesting biomarker that is better characterized in the brain, so I think it could be beneficial to extend this approach to other body regions.

Dimitris: From a basic biology and physiology perspective, the bone marrow adipocytes are quite special. Their role is not well understood, but it has implications in bone health and metabolic diseases. The Society of Bone Marrow Adiposity was formed just this year to figure out how to study bone marrow structure and function. They are always in need of new non-invasive imaging techniques. In MR this is a niche area where there isn't a lot of activity, but there is a great interest outside.

MRMH: In your paper you discuss fractures. What's the difference between a malignant and a non-malignant fracture?

Dieckmeyer, M., Ruschke, S., Eggers, H., Kooijman, H., Rummeny, E. J., Kirschke, J. S., Baum, T. and Karampinos, D. C. ADC quantification of the vertebral bone marrow water component: Removing the confounding effect of residual fat. *Magn Reson Med.* 2017;78: 1432–1441. doi:10.1002/mrm.26550

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26550/full

Stefan Ruschke (left), Michael Dieckmeyer (middle), and Dimitris Karampinos (right) following the baguetting meme in preparation for the ISMRM 2018 meeting in Paris.

Michael: In a malignant fracture the bone marrow gets infiltrated by cancer cells that destroy the structure of the bone causing the bone to fracture without any strong trauma. In a normal fracture there's usually a traumatic event that causes a healthy bone to crack.

Dimitris: In the bigger picture we are interested in developing quantitative MRI techniques for a range of tissues in the body that contain fat, which makes quantitation more challenging. So, this is a general toolset that is important and can be translated to other tissues.

MRMH: I think some of the brain folks might be wondering, "What's the big problem with fat?" Why can't you just do better fat suppression?

Michael: Fat is a large molecule that has a lot more protons and chemical bonds. Therefore, it has 8 or 9 peaks that have different resonance frequencies, and 2 or 3 of those are very close to the water peak, so fat suppression techniques that are spectrally selective don't suppress these peaks without affecting the water peak. When these two components get mixed up there is a huge bias in the ADC because the water molecules are diffusing at a much higher rate than the fat molecules.

MRMH: What acquisitions are required to account for the presence of fat?

Michael: Basically you need the proton density fat fraction, so you use water-fat imaging. Nowadays these sequences are quite fast; the one we use adds about one minute to the protocol. Secondly you need the T_2 of the water component, which adds about 1.5 minutes to the protocol.

MRMH: How do you know when it's safe to make assumptions in order to simplify your model?

Michael: That's a question that we thought a lot about through this process. It helps to have a tool that can validate your model results and give you confidence that you are on the right path, especially in those moments when you're thinking, "This doesn't work!"

MRMH: What did you use to validate your model?

Michael: We used a diffusion weighed STEAM sequence. The MRS has a spectral resolution high enough to separate the water peak from the neighboring fat peaks, which represent the residual fat in the imaging. You can get a water ADC that is not biased by the overlapping fat peaks.

Dimitris: In quantitative MR we often build phantoms; here we are dealing with such a complex issue because of the diffusion properties and the variation of fatty acid composition that we use another MR technique to validate. Using another MR technique is not always desirable but it is in our case quite powerful. For the broader dissemination of any MR technique, using a technology outside of MR as validation would be highly desirable.

MRMH: Why don't you change all of your parameters simultaneously and model them together?

Michael: That is an interesting question that at least one of the reviewers pointed out in the review process, which made us look into that a bit more. It could save time, but our simulations showed that to get a reliable fit with the additional unknowns you would need such high b-values that you would face SNR issues and need longer scan times to overcome hardware limits. So we figured that it wasn't very practical to do.

Dimitris: That was one point that we didn't explicitly think about, and the review process helped us realize the potential advantage of what we did without knowing it in advance. The review process was not easy on this paper, but it really helped improve it a lot.

MRMH: That is encouraging to hear for some of us! ■

> *Diffusion reflects the tissue microstructure and can differentiate between malignant and non-malignant vertebral fractures.*
>
> –Michael Dieckmeyer

Pre-emphasis by inversion: make the presence of eddy-currents a thing of the past

INTERVIEW BY **RYAN TOPFER**

EDITOR'S PICK FOR OCTOBER

A Highlights Halloween special: For those less than BOLD researchers who remain frightful of Nyquist ghosts, fear not! Johanna and Klaas herein reveal their trick for treating shim and gradient coil-induced field distortions with full cross-term pre-emphasis and, more generally, some tricks of the trade – "How to Make It" in the world of MR engineering research.

Johanna Vannesjo

Klaas Pruessmann

MRMH: Could you tell us how this project came about?

Johanna: Klaas' group had developed these magnetic field sensors with which we could measure field fluctuations with high spatial precision and temporal resolution. At the same time, there was also the desire to use higher order shims to dynamically correct for these fluctuations. But when we began looking at the dynamic behavior of the shim channels we saw some pretty wild field responses!

We observed several extremely strong cross-term responses, mostly from eddy currents. We realized we would need to improve the field responses and – having the characterization of the shim responses from the field sensors – it was then possible to determine the correction one would need to perform on the input waveforms (i.e. the pre-emphasis) to get the desired field responses, without the distortions.

MRMH: Is the cross-term shim coupling just a peculiarity of the Philips system you used?

Johanna: It's really the heatshield of the cryostat that carries the long-living eddy currents responsible for most of the distortion. To the degree that the shim fields and the cylindrical shape of the heatshield will be similar across platforms, and so long as these shim fields couple into the cryostat, I would expect to see similar cross-term behavior across systems.

Klaas: I would second everything Johanna said. The coupling will depend on whether the shims are shielded actively, but it would change the situation if the shims were farther away from the cryostat. With the Yale matrix shim systems, for instance, they see fewer issues with eddy currents simply because the shims are farther away from conductive structures.

MRMH: You used the famous Skope field camera to characterize the shim impulse response functions. Do you need this or are there alternatives?

Johanna: There are alternative ways of measuring the field, but they're generally much slower. With the field camera you have the advantage of being able to do measurements in a single shot.

Klaas: The camera is definitely convenient. You sweep through the frequency band of interest – say, 0 to 30 kHz, like we did here for the gradients – and ten seconds later you have the full, temporally-resolved field response measurements for all sixteen terms of the shim basis. The frequency sweep sounds cool, too – like old Pink Floyd records! Also, we do see thermal changes occurring within seconds, for example, the mechanical resonances of the gradient coils tend to shift as the epoxy softens.

Johanna: Once you start getting interested in these short-term changes, you really need a Skope kind of approach to measure the system responses quickly.

MRMH: We talked about using the field camera to

Vannesjo, S. J., Duerst, Y., Vionnet, L., Dietrich, B. E., Pavan, M., Gross, S., Barmet, C. and Pruessmann, K. P. Gradient and shim pre-emphasis by inversion of a linear time-invariant system model. *Magn Reson Med.* 2017;78: 1607–1622. doi:10.1002/mrm.26531
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26531/full

Klaas Pruessmann's group during a retreat in France.

correct for these sorts of deviations on the fly last time we spoke, when we interviewed Klaas and Max Haeberlin. In the current paper, real-time feedback correction is discussed as a potential alternative to your feedforward pre-emphasis approach. (Incidentally, feedback stabilization is the subject of another one of your papers, with Yolanda Duerst!) But are these correction schemes really alternatives, or are they complementary?

Johanna: The feedback correction will address some of the same deviations as the feedforward correction but it's limited by the delay of the feedback loop. With the combination, you get the best of both: a high bandwidth correction from the feedforward, while the feedback corrects for slower, unpredictable system responses.

Klaas: Indeed, the last implementation Yolanda did before finishing her PhD boils down to feedback control with pre-emphasis included in the actuation. I think that in addressing errors, feedforward control is one layer, feedback control is another, and retrospective data correction is the third – and that should be in the calculation as well. There's always going to be some residual error (which, when large, will tend to yield bad inverse problems in the retrospective correction) but the less that remains, the better we can handle it retrospectively.

MRMH: There has been a great series of complementary papers coming out of the lab at ETH Zurich and, judging by the overlap between coauthors, there seems to be a lot of folks working on these projects together. Klaas, do you have any pro-tips for how to run a research lab effectively?

Klaas: That's a very serious question! No doubt, collaboration is desirable, not only because it's good for the people doing the work, but it's also essential for the work in our area because, as is probably evident, no single person could ever think of doing all this alone. Between building, installing, maintaining all the hardware; then there's the reconstruction and sequence coding as well… The only way of staying afloat in MR technology in 2017 is to have a pretty sizeable and well-coordinated effort. Also, it certainly helps to have base funding that doesn't fluctuate, so you can take on projects that may need ten years to see through (and that may fail after five). Another part of the recipe is not to get too frustrated when it doesn't work out.

Johanna: That was one of the things I highly appreciated being in Klaas' group. While everyone had a subject area over which they had ownership, in the sense that they were driving a particular project, there were enough people working in similar areas that you had this give-and-take, both in terms of ideas (daily exchanges about what you're working on and how to move forward) and in terms of the practical stuff.

Klaas: And when people are at their peak, they leave! So that's another thing to master: people coming and going. And maintaining the flux of the research as well... But this is part of the difficulty! You're asking me about tricks, but I don't have any, full stop.

MRMH: None you're willing to share publicly anyway: They're trade secrets.

Klaas: I'll keep that thought in the back of my mind. Maybe next time I'll have a better answer to the "trick" question. ■

> *With the combination, you get the best of both: a high bandwidth correction from the feedforward, while the feedback corrects for slower, unpredictable system responses.*
>
> –Johanna Vannesjo

One step closer to accurately mapping conductivity in brain tissue

INTERVIEW BY **MARIA EUGENIA CALIGIURI**

EDITOR'S PICK FOR NOVEMBER

Kathleen Ropella received her bachelor's degree in Biomedical Engineering at Marquette University, and her master's degree at the University of Michigan, where she will defend her PhD thesis this semester (busy times ahead!). Douglas Noll did his PhD in Electrical Engineering with Al Macovski at Stanford, after being introduced by his intramural basketball pals, Dwight Nishimura, Steve Conolly, and Craig Meyer. In 1991, he started his first faculty position at the University of Pittsburgh, working on functional MRI with the first 3T magnet GE ever made. Doug later transitioned to be a professor of biomedical engineering at the University of Michigan - so he's been in the field of MRI for about 30 years now! Their paper, "A regularized, model-based approach to phase-based conductivity mapping using MRI," was focused on two things: first, achieving accurate measurements of conductivity - which describes the ability of a tissue to conduct electric current - at tissue boundaries; and second, the possibility of using non-quadratic regularizers, thanks to advances in compressed sensing.

MRMH: Can you briefly explain what is regularized, model-based conductivity mapping?

Kathleen: This is our inverse-problem approach to mapping conductivity in vivo. We've asked ourselves, "Is the inverse of an inverse problem a forward problem?"… but that's another story! It's a matter of iteratively calculating the model-based phase profile on the MRI scanner, and subsequently adding regularization to improve SNR in the results.

Doug: We are always trying to understand physiology better. There are many MR and vascular parameters (T_1, T_2, diffusion, perfusion), and conductivity represents yet another window into tissues, another way to probe what is going on.

MRMH: Which clinical applications do you think would take the most advantage from your approach?

Kathleen: Conductivity is drastically elevated in malignant tumors, so there's plenty of open research questions about how it might correlate with other tumor-induced abnormalities. It would be interesting to see, in future studies, how conductivity would change after treatment, and perhaps use this information for managing treatment choices and patient care.

Doug: We are also hoping conductivity mapping might prove useful in domains we haven't tried yet, so we are still looking for the killer app. Oncology seems to be the most promising one, but time will tell whether conductivity mapping is unique enough compared to other physiological measurements (e.g., use of contrast agents, mean transit time, pharmacokinetic parameters).

MRMH: Conductivity mapping is also a crucial factor when it comes to MRI safety - toward what advances do you think your method could lead us?

Kathleen: A common aim that end-diagnostics and MR safety share is the need for accurate high-resolution conductivity maps. Hopefully, our method will improve calculation and prediction of the Specific Absorption Rate (SAR) and of temperature increases.

Doug: SAR calculations are done with very generic models, e.g., with assumptions based on body weight. There are more precise models where you take the images and perform image segmentation and classification assigning textbook values, and we think this is the next

Kathleen Ropella

Douglas Noll

Ropella, K. M. and Noll, D. C. A regularized, model-based approach to phase-based conductivity mapping using MRI. *Magn Reson Med.* 2017;78: 2011–2021. doi:10.1002/mrm.26590

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26590/full

The functional MRI laboratory team at the University of Michigan.

level of greater accuracy by measuring conductivity directly.

MRMH: Should we be looking at SAR outside the brain? How would you suggest that SAR measurements are done moving forward?

Doug: We work with the brain primarily for convenience in validation, and we discussed with a neurosurgeon about the potential applications in targeting the Glioblastoma Multiforme (GBM). But ultimately, we want to predict SAR over the entire body, since we are using a body transmitter.

Kathleen: The more accuracy you get when it comes to SAR measurements, the more freedom you give to MR pulse designers in terms of safety margins.

MRMH: What was the biggest surprise you encountered while carrying on your work?

Kathleen: That it started working in vivo [laughs]. Also, the use of regularizers helped us get a good trade-off between SNR and resolution. We didn't really expect such improvements in SNR.

MRMH: You validated your method in numerical simulations, a phantom, and human subjects - that's a lot of work! How did you handle it, and which was the hardest part?

Kathleen: I found the electromagnetic simulations challenging, particularly finding the appropriate tools and implementing them.

Doug: Simulations are important because we don't know the ground truth otherwise.

Kathleen: And, in turn, lack of a gold standard for conductivity in the brain introduced challenges with the validation on human subjects.

MRMH: How did you solve this issue?

Kathleen: We reported the measures, and considered it to be positive that there wasn't a consistent bias between our estimates and those obtained with what we consider a conventional method.

Doug: I'm not sure how much faith we have in the textbook values. It is actually very difficult to measure conductivity in non-homogeneous tissues.

MRMH: What are your next steps?

Kathleen: Adding a non-negativity constraint to handle those large zero-valued regions around the ventricles and at compartment boundaries. This problem arises because you try to smoothly connect two parabolas, but there is an apparent inflection in the curvature. It would be sort of an informative constraint for the values in those regions.

We are also looking at conductivity as a tensor, rather than a constant, investigating how it changes as an object moves within the magnetic field. That's certainly more challenging!

Doug: Mapping conductivity is hard, mapping conductivity tensors is going to be even harder, but it's still interesting since it is clear that in striated tissues of the body the conductivity will be directional. However, all current models used in SAR prediction in MRI ignore directionality.

MRMH: Do you expect the conductivity tensor anisotropy to have any relationship with the diffusion-tensor diffusivity of water?

Doug: We expect them to be related: "how", exactly, is not clear yet.

Kathleen: Based on some preliminary results, we think that anisotropy of the conductivity tensor would be on a larger scale than that of the diffusion tensor.

Doug: Anisotropy measurements in water diffusion are on a micron scale, while conductivity tensors seem to be on a larger, possibly millimetric scale - or at least that is what we are able to measure with our instrumentation. ■

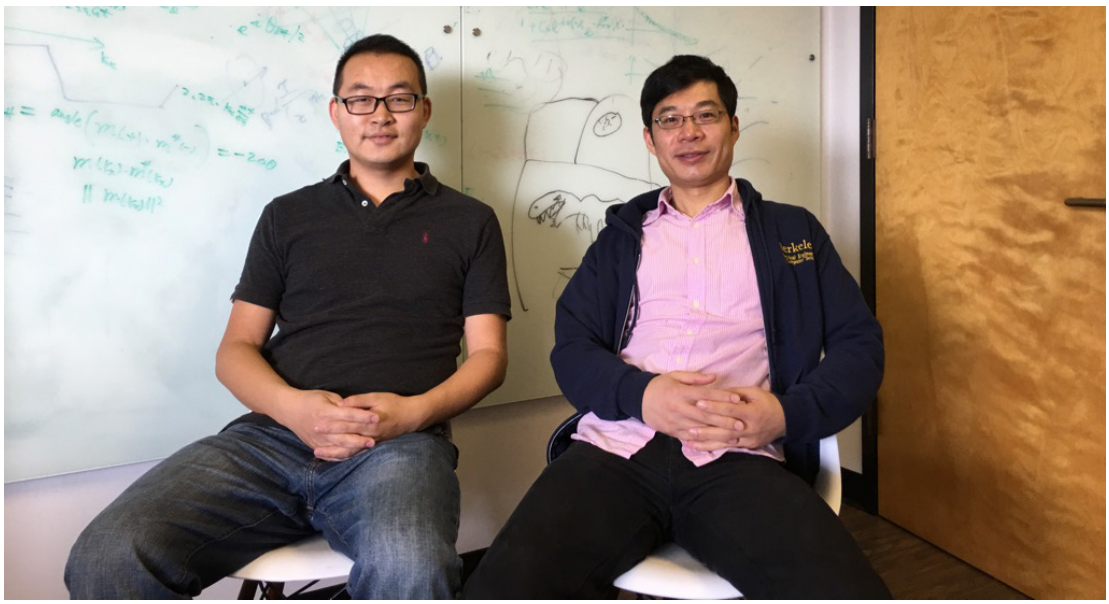
> *It would be interesting to see, in future studies, how conductivity would change after treatment, and perhaps use this information for managing treatment choices and patient care.*
>
> –Kathleen Ropella

What can QSM tell us about the human knee?

INTERVIEW BY **ZAHRA HOSSEINI** AND **PHILLIP WARD**

EDITOR'S PICK FOR NOVEMBER

Recently, we had the pleasure to sit down and have a chat with Dr. Hongjiang Wei and Dr. Chunlei Liu about their manuscript "Investigating magnetic susceptibility of human knee joint at 7 tesla."



Hongjiang Wei (left) and Chunlei Liu (right) at the Department of Electrical Engineering and Computer Sciences, University of California, Berkeley.

> *QSM gives a pretty unique anatomical contrast between the different knee tissues.*
>
> –Chunlei Liu

Hongjiang completed his bachelor's degree in Electrical Engineering in China, then started work in MRI seven years ago for his PhD in France. He was interested in using cardiac diffusion tensor imaging to study myocardial fiber architecture. Towards the end of his PhD, he found that, "quantitative susceptibility mapping was even more interesting." Hongjiang contacted Chunlei after the completion of his PhD in 2014, and was offered a postdoc in Chunlei's lab at Duke University.

Chunlei initially planned to get a PhD in solid state physics, but his main interest has always been how to use physics to study the brain, "I study these fundamental laws of physics, but then I realize there are so many things we cannot fully understand using only these laws… and subjects like biology become intellectually fascinating." Chunlei recently decided to continue with his brain exploration at UC Berkeley, after having spent seven years as a professor at Duke.

How it all began

The conversation took a technical turn right away, when we asked the authors about their chosen technique, quantitative susceptibility mapping (or QSM). Hongjiang explained that, "quantitative susceptibility mapping is an approach to, as the name implies, extract a map of the underlying tissue susceptibility on a pixel-by-pixel basis. QSM computes the magnetic susceptibility from the phase signal of gradient-recalled echoes with the assumption that phase shift is mainly due to susceptibility-induced field inhomogeneity." In simple terms, it is a map that demonstrates how tissues interact with the magnetic field of the MRI scanner.

Wei, H., Dibb, R., Decker, K., Wang, N., Zhang, Y., Zong, X., Lin, W., Nissman, D. B. and Liu, C. Investigating magnetic susceptibility of human knee joint at 7 tesla. Magn Reson Med. 2017;78: 1933–1943. doi:10.1002/mrm.26596
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26596/full

Yuyao Zhang (left) and Hongjiang Wei (right) at the Brain Imaging and Analysis Center (BIAC) at Duke University.

Chunlei has been at the forefront of QSM development, applying this technique to brain, heart, and even kidney. Recently, the knee captured his interest, "It is like everything we do; once you have a hammer, you think everything is a nail." It was the white matter anisotropy in the brain that led Chunlei and colleagues to look at other tissues that would potentially have a similar effect, such as the knee, "QSM gives a pretty unique anatomical contrast between the different knee tissues; for example, the nerve is pretty diamagnetic with respect to the surrounding tissue." With previous studies showing distinct diffusion patterns in cartilage, they were curious to see if they could observe substructures in the knee using QSM.

The major advancement of this work

Hongjiang went on to describe the unique anatomical contrast in the knee joint based solely on tissue susceptibility differences: "Through the developments of this work we have a sensitive way of differentiating a healthy knee from a diseased knee. When validated through clinical studies, this can be a very useful tool for diagnosis." Furthermore, he observed QSM differences for cartilage layers in vivo, which were then validated using simulation studies and ex-vivo experiments. This is particularly relevant as a clinical application, because, "the multi-layer structure revealed by different magnetic susceptibility is missing in patients with cartilage degeneration compared with that of healthy subjects, indicating microstructure alterations or changes in the constituents of the cartilage."

The QSM technique is already translatable into the clinic, "[in terms of clinical usage] I think there are some advantages with this technique; it relies on a simple GRE sequence, which most people use, and most scanners have. It doesn't add to the scan time, which is mainly the issue in the hospital. They can save the raw data, including phase, and produce these QSM images that will be very useful for the clinicians and radiologists."

The double edged-sword: orientation

Susceptibility mapping is orientation-dependent – in knee, for example, this relates to how bundles of collagen fibers are arranged relative to the main magnetic field (B_0). We asked how fiber orientation would affect the interpretation of these models. Hongjiang explained, "We use the susceptibility anisotropy combined with the susceptibility tensor model to quantify the orientation information of the collagen fiber, and we can get very nice 3D fiber tracts of the cartilage. That means we may use the orientation dependence and quantify the orientation information of the collagen fiber to assess the health of the joint. However, rotating the knee at different angles with respect to B_0 is the major challenge."

But as Chunlei added, it can be a double-edged sword, "In one sense, because of the anisotropy we can generate this orientation-dependent susceptibility contrast, which Hongjiang referred to. On the other hand, if the position of the knee is changed between two scans the susceptibility values could be different, because of that same orientation dependence. To fully quantify this, we need to perform susceptibility tensor mapping (much like the ex-vivo experiments in the manuscript), which is not possible on a live person. But because of the anatomical position of the knee, B_0 is likely parallel to the knee joint. So that change should not be a big concern, as long as you position the knee relatively parallel to B_0."

To support this, Hongjiang shared a second paper, published in the same issue of MRM, on their histological validation studies using atomic force microscopy.

QSM compared to other imaging approaches

We asked our authors to comment on how QSM may be similar or different to other approaches that enable visualization of structures in the knee.

"DTI is not very good at getting the orientation information of collagen, because the structures are small, on a scale where the water diffusion is just not sensitive to it. $T_{1\rho}$ is a measure of proteoglycan and the hydration of the collagen, but based on our simulations and calculations, susceptibility is looking more directly at the collagen itself. T_2 tends to be more of a measurement of collagen in the cartilage, whereas susceptibility, as our results show, gives us more information about the microstructure of the collagen fiber. One major benefit compared to DTI and even $T_{1\rho}$ and T_2 mapping is that the 3D GRE acquisition is quite short for this application."

Taking the next steps

Hongjiang is already taking the next steps, with an ISMRM research exchange fellowship award. He is collaborating with Ruijin hospital in Shanghai to investigate QSM for the knee in aging, as well as in diseases such as osteoarthritis.

A final thought from Chunlei on the future of this work, "The question is whether this can be clinically useful. That is not clearly proven; we do not have that evidence or data to support that QSM will have added clinical values for diagnosis or will help treatments; that is why Hongjiang is taking to work with clinicians and to look at what clinical value this technique actually provides." ■

> *"Through the developments of this work we have a sensitive way of differentiating a healthy knee from a diseased knee. When validated through clinical studies, this can be a very useful tool for diagnosis."*
>
> –Hongjiang Wei

Carbon-13 NMR spectroscopy: a promising tool to study brain metabolism

INTERVIEW BY **ATEF BADJI**

EDITOR'S PICK FOR DECEMBER

Sergey Cheshkov received his bachelor's d egree in physics in Bulgaria and his PhD in physics at the University of Texas at Austin. He is currently an assistant professor in the Advanced Imaging Research Center at the University of Texas Southwestern Medical Center. Craig Malloy is a clinical cardiologist and the medical director of the same center. In their paper, they used carbon-13 NMR spectroscopy to investigate non-invasive biomarkers for brain energy metabolism and neurotransmitter production. As you can imagine, we had many questions for them.

> *We know very well that high field will give us better sensitivity and better spectral dispersion, so we decided to use that for this project.*
>
> –Sergey Cheshkov

Sergey Cheshkov

Dean Sherry and Craig Malloy

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

Sergey: In this paper, we wanted to propose a noninvasive method to study brain metabolism and glucose oxidation in the living human brain by utilizing carbon-13 NMR spectroscopy. Current tools used to study brain metabolism have real limitations. For instance, positron emission tomography (PET) scans are more or less the standard for glucose metabolism but have limitations such as ionizing radiation which make them unsuitable for many types of exams. More importantly, PET can't follow the fate of glucose through glycolysis or oxidation in the TCA cycle. There is lots of important previous work infusing carbon-13 labeled molecules into humans with detection by NMR, but these kinetic studies require long infusion periods in the magnet, which is not easily practical for real patients. We wanted to investigate the information that we can get from a relatively simple, steady-state exam. We have a terrific 7T magnet here, and we know very well that high field will give us better sensitivity and better spectral dispersion, so we decided to use that for this project.

Craig: We have a great deal of textbook knowledge about what we think is going on in brain metabolism, but almost all of it based on animal research. How this information fits together in a real human being is highly controversial, and it is even more challenging to study brain metabolism in patients. As Sergey mentioned, the problem with a radioactive tracer is that the physics prevents detection of individual metabolic pathways. The

Cheshkov, S., Dimitrov, I. E., Jakkamsetti, V., Good, L., Kelly, D., Rajasekaran, K., DeBerardinis, R. J., Pascual, J. M., Sherry, A. D. and Malloy, C. R. Oxidation of [U-13C] glucose in the human brain at 7 T under steady state conditions. *Magn Reson Med.* 2017;78: 2065–2071. doi:10.1002/mrm.26603
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26603/full

From left to right: Ivan Dimitrov, Ralph DeBerardinis, Juan Pascual, Craig Malloy, Sergey Cheshkov and Dean Sherry at UT Southwestern.

key advantage of carbon-13 NMR spectroscopy is to investigate the individual metabolic pathways in a person. For example, your brain has to continuously replenish the neurotransmitters (i.e., glutamate, GABA), but what is the rate of this synthesis? It's controversial. Yet, this is a very basic physiological feature of the brain that is difficult to investigate by current technology.

MRMH: You use anaplerosis in your paper as a proxy for metabolic function. What is anaplerosis? Why is it so important to quantify it?

Sergey: When we are talking about the TCA cycle, anaplerosis is the replenishment of intermediate molecules (i.e., malate, citrate, etc.) within the pathway. For instance, in a normal functioning brain, neurotransmitters are released into the synaptic cleft, then mostly recovered afterwards. But the process is not perfect, which means that some of the neurotransmitters are lost. Because of that, the brain must continuously replenish these to function optimally. The replenishment process could be different in pathology. We know from other studies, including Craig's previous work on glioblastoma, that in tumors anaplerosis is ramped up tremendously. That brings us back to the point of markers, which can be extracted from this method.

Craig: The word anaplerosis refers to the capacity of tissues to replenish molecules needed for function or growth. The brain has to restore the neurotransmitters to maintain their concentration via various pathways, which are difficult to dissect in humans. We think that anaplerosis has something to do with brain pathology and clinical disorders. Thus, the advantage of our work is to provide a reasonably simple way to measure it, relative to turnover of the TCA cycle. It's not flux information, but it is a biomarker of anaplerosis.

MRMH: Which clinical applications do you think would benefit the most from your work?

Sergey: After we did this study in normal subjects and we looked at the carbon spectra, it is interesting that we didn't see lactate in healthy subjects. There is a lot of literature about traumatic brain injury (TBI), and a lot of arguments about the role of lactate in those injuries. Is this a harmful by-product? Is it fuel for neurons as long as neurons are still functioning and becomes harmful when they are not? So, my first thinking on clinical application was for mild TBI. For now the approach is not localized, so I think the cases that could benefit the most are those that do not inherently require high spatial resolution.

MRMH: To address the poor sensitivity to ^{13}C, you use the high static field of 7T. You also mentioned another option to increase SNR would be to combine ^{1}H decoupling with Nuclear Overhauser Enhancement (NOE). Could you comment on that?

Sergey: In this particular study, we were looking at the carbonyl region of the spectrum so our carbons of interest were non-protonated. If you were to also apply the ^{1}H decoupling, you would still benefit, but to a much lesser degree than normally observed for carbon spectroscopy with directly-bonded protons. However, you would be able to remove those longer range couplings and increase a little bit of the signal to noise.

Recent work by Jun Shen's group at the NIH implemented a low power NOE and decoupling and observed increases in SNR. We started doing similar experiments in our center with up to 50% increase in SNR in phantoms, which is very promising.

Craig: The reason why we picked on the carbonyls (non-protonated carbons) is because they are convenient to measure in the absence of NOE, but unfortunately, we are throwing away an enormous amount of information from all the aliphatic (protonated) carbons. If we can do proton decoupling safely in a human at 7 tesla, the information content will be vastly greater. For this, we need the help of physicists to make sure that we have safe, convenient, broadband proton decoupling at 7T.

MRMH: Moving forward, where would you like to take this work next?

Sergey: The biggest limitation of this work is the spatial resolution issue. We have several related projects going on currently aimed to develop carbon phased arrays and multinuclear, multi-channel infrastructure, which could give us an additional gain in SNR. Then, we will test if our method is clinically applicable.

Craig: Even if I am interested in detection of glutamate, glutamine, bicarbonate, absence of lactate, etc., it is impossible to imagine clinical applications with zero spatial resolution. If we want to translate this to a real clinical impact, we need better spatial resolution. The coils that we are using are sub-optimal, so this is our highest priority. ■

> *The key advantage of carbon-13 NMR spectroscopy is to investigate the individual metabolic pathways in a person.*
>
> –Craig Malloy

Echo-planar MREIT: fast imaging of electrical tissue properties towards mapping neural activity

INTERVIEW BY **JIAEN LIU**

EDITOR'S PICK FOR JANUARY

In their paper entitled, "Multi-shot echo-planar MREIT for fast imaging of conductivity, current density, and electric field distributions," Drs. Munish Chauhan and Rosalind Sadleir propose an accelerated technique to image electrical conductivity based on MRI. Their goal is not only to image conductivity of biological tissues, but more ambitiously to map neural activity using this fast technique. Let's hear their story behind the paper.

Rosalind Sadleir

MRMH: Can you please introduce yourselves and tell us how you got started in MRI?

Munish: I finished my PhD at Kyung Hee University, South Korea. My field of interest has been MR-based electrical properties imaging. More specifically, I worked on magnetic resonance electrical impedance tomography (MREIT). With this technique, we injected current into the object and used MRI to map out the electrical current density and electrical property distribution. Here at Arizona State University, I continue using this technique in my research.

Rosalind: I came from a background in electrical impedance tomography (EIT), which is a method of using sets of electrodes placed on the boundary of an object to determine the internal electrical properties. In EIT, it is almost impossible to determine the absolute conductivity and the inverse problem is very ill-posed. MREIT is a much more stable problem. It opens up the possibility to measure absolute conductivity and to follow dynamic changes caused by neural activity deep inside the brain.

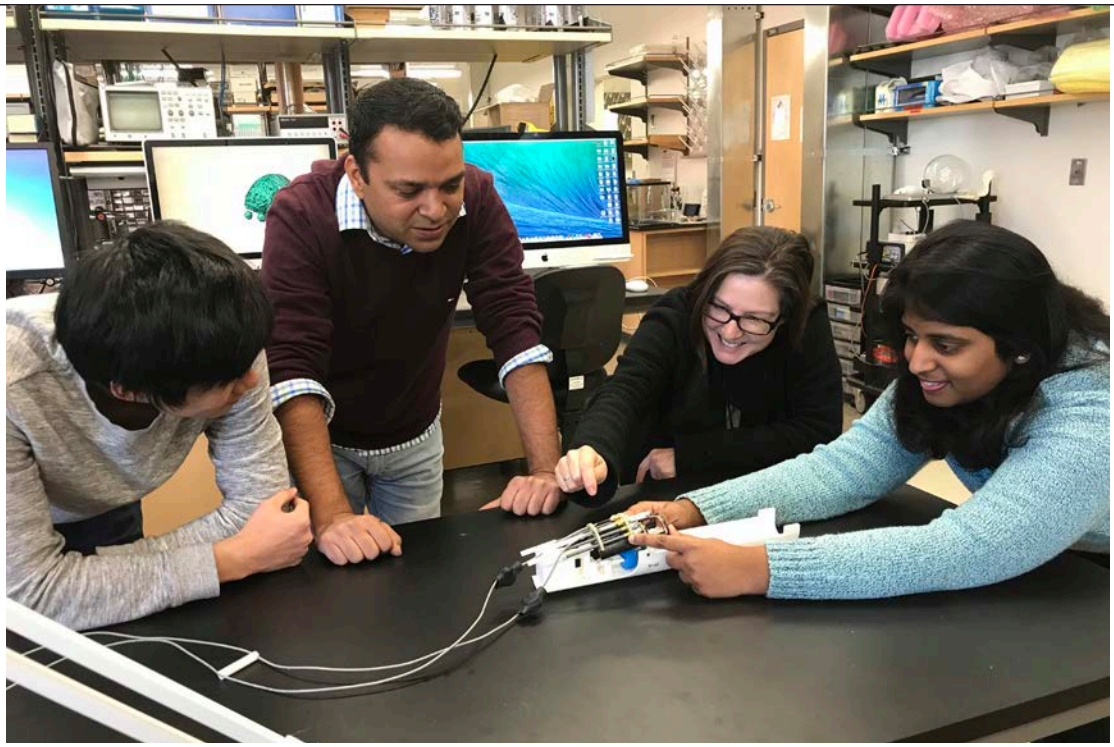
MRMH: What is conductivity of biological tissue and why is it important?

Munish: Conductivity of biological tissue at the frequencies we typically use for MREIT (around 10 Hz) reflects ionic content and mobility and membrane properties. So, we are also able to see effects of conductivity anisotropy. Conductivity of complex tissue tends to increase as a function of frequency. Overall, imaging these properties in conjunction with MR relaxation properties may provide more sensitive MRI-based diagnoses.

Rosalind: Conductivity of biological tissues varies over many orders of magnitude, which is quite an interesting thing. At low frequencies, it's related to ionic mobility and also membrane density, while at high frequencies it is more related just to the ionic properties. You see a large range in conductivity values over different tissues at a single frequency and also in a single tissue as you change frequency. So it's really a key indicator of biological and physiological state. For example, conductivity of cancerous tissue is observed to be quite high.

Munish Chauhan

Chauhan, M., Vidya Shankar, R., Ashok Kumar, N., Kodibagkar, V. D. and Sadleir, R. Multishot echo-planar MREIT for fast imaging of conductivity, current density, and electric field distributions. *Magn Reson Med.* 2018;79: 71–82. doi:10.1002/mrm.26638
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26638/full



From left to right: Fanrui Fu, Munish Chauhan, Rosalind Sadleir and Neeta Ashok Kumar looking at a newly designed rat coil and bed intended for use with a Bruker 7T MRI scanner.

It could be an interesting diagnostic measure in many situations.

MRMH: It is interesting to see that you are switching to functional neuroimaging based on the conductivity. Could you tell us more about the key findings and potential impact of this paper?

Munish: One motivation of the paper is to see if it's possible to accelerate the traditional spin-echo-based MREIT using an EPI sequence and achieve a reasonable SNR. Our paper shows that compared to the "gold-standard" spin-echo sequence, even with the two-shot EPI, we can still get satisfactory images of current density and conductivity. This could allow us to cover the whole brain within the time limit of the traditional spin-echo approach. With this technique, we are running human experiments to map the current path of the Transcranial Direct Current Stimulation (TDCS).

Rosalind: Another motivation to go fast is that we may be able to see the conductivity changes related to neural activity. It's quite a neat contrast. When a neuron undergoes a spike, its membrane changes its conductance because ion channels open and close. When you have a trickle of electrical current flowing through a region of active tissue, the apparent conductivity of all the cells will increase and current gets drawn into that region. With MREIT, we should be able to detect the apparent conductance change of that active tissue. This is quite a subtle effect, but it may have some advantages over existing methods for detecting neural activity using MR.

MRMH: Is this a hypothesis or has it been proven experimentally?

Rosalind: We have published our results that showed the existence of such a contrast just a few months ago (Sadleir et al., Neuroimage, 2017, 161:104-119). This was done using in vitro measurements on Aplysia ganglia tissue and a spin echo sequence with long imaging time. We found significant effect of neural current on the measurement. We would like to repeat this experiment with animals in vivo to include all possible confounds. Currently, we are working out the method in this paper to have both a reliable sequence and analysis method.

MRMH: What is the next step?

Munish: As I mentioned, we are working towards human experiments with the whole brain coverage using this technique, and applying it to TDCS studies. In addition, we will try to include the anisotropy of the conductivity in white matter in our reconstruction algorithm. This is a significant effect in the frequency range we deal with. We get the anisotropy information from the MR diffusion tensor image.

Rosalind: Right. As suggested by Tuch's 2001 paper (Tuch et al., PNAS, 2001, 98:11697-11701), conductivity and diffusion tensors share principle eigenvalues and their relationship should be a scaling factor. On the other hand, once we have a whole brain coverage, we might be able to answer the interesting question about the variation of the conductivity within brain tissues in contrast to the conventional wisdom that it just depends on the general tissue types, for example, the white versus gray matter.

MRMH: Beyond our questions, do you have any additional comments?

Rosalind: People are doing some very interesting work on very low field MRI. The Larmor frequency corresponding to a low field is close to the frequency of the neural current. It might be a very interesting way to measure neural activity by combining conductivity imaging and low-field MRI. ■

> *Overall, imaging these properties in conjunction with MR relaxation properties may provide more sensitive MRI-based diagnoses.*
>
> –Munish Chauhan

Cracking the 1 mm barrier in diffusion MRI

INTERVIEW BY **TANGUY DUVAL**

EDITOR'S PICK FOR JANUARY

Kawin Setsompop and Larry Wald are old friends of Highlights, and their work has been prominently featured in our last two magazines. For this paper, they complement their simultaneous multi-slice (SMS) acquisitions with an additional 3D RF-encoding for each 3 mm slice (or thin slab), in order to push the resolution of diffusion imaging to 600 µm isotropic in the brain. This technique nicely solves the issue of phase corruption in multi-shot MRI acquisitions.

Kawin Setsompop

Lawrence Wald

MRMH: Could you please give us a brief background on how you came up with the gSlider method?

Kawin: Doing volumetric encoding with diffusion is hard due to phase corruption from shot to shot. SMS (i.e., Simultaneous Multi-Slice) has been very successful over the years, but when you go to thinner and thinner slices, there is not as much volumetric encoding per shot. So for gSlider, we wanted to do more volumetric encoding while at the same time taking advantage of the good parallel imaging that we have. The idea was to do 3D volumetric encoding *within* each thin slab.

Setsompop, K., Fan, Q., Stockmann, J., Bilgic, B., Huang, S., Cauley, S. F., Nummenmaa, A., Wang, F., Rathi, Y., Witzel, T. and Wald, L. L. High-resolution in vivo diffusion imaging of the human brain with generalized slice dithered enhanced resolution: Simultaneous multislice (gSlider-SMS). *Magn Reson Med.* 2018;79: 141–151. doi:10.1002/mrm.26653
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26653/full

Larry: 3D encoding is always a great goal because it is so efficient, effectively averaging, and high-resolution diffusion really needs this full SNR efficiency. We've been trying for a long time to do 3D diffusion imaging but there have been a number of barriers, notably motion artifacts and phase corruption. You have to walk on a pretty fine line because of the phase corruption, and 3D imaging does not work so well unless you have full 3D navigators, which are quite time-consuming. So SMS was kind of the start, it offers this 3D efficiency but with 2D acquisition, it is just unfortunate that this method is limited to 2-4 fold accelerations for diffusion imaging due to g-factor penalty problems. So in my mind, gSlider is about solving these problems associated with applying a multi-shot method to diffusion.

MRMH: What was the benefit of the CONNECTOM scanner?

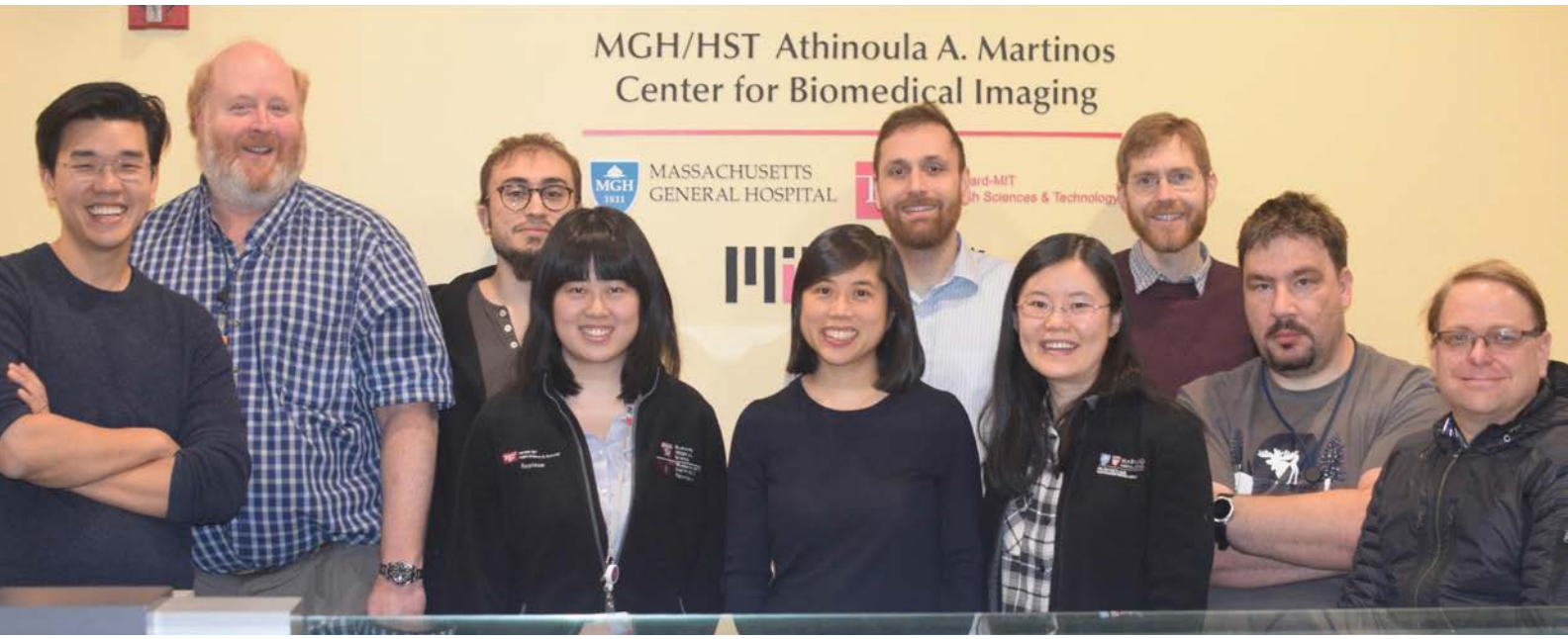
Larry: The benefit of the CONNECTOM for this low b-value sequence is moderate. The main reason was mostly because our PRISMA is so busy, that you don't get much time to develop sequences!

Kawin: We are willing to translate this to a standard PRISMA or to the SKYRA 3T scanner with a standard 32-channel coil. We are making good progress on that - if you scan at 800 µm isotropic, you get the scan time down to about half an hour and that starts to get useful for the people in the neuroscience community. We hope to get that out in a few months from now and then release it.

MRMH: Do you need any particular hardware?

Kawin: I would not use anything below a 32-channel coil at 3T for SNR reasons. I would also not try at 7T yet because we haven't been playing around too much with the RF encoding and the way it interacts with the B_1 inhomogeneities that are quite large at 7T. So you know… people are very welcome to try, but I cannot guarantee it will work!

MRMH: How can we check that the reconstruction is doing well? Can the gSlider introduce any potential



From left to right: Kawin Setsompop, Larry Wald, Berkin Bilgic, Fuyixue Wang, Susie Huang, Stephen Cauley, Qiuyan Fan, Jason Stockmann, Thomas Witzel and Aapo Numenmaa.

bias, notably for quantitative diffusion methods?

Kawin: The SMS and in-plane GRAPPA reconstructions are done in real time on the scanner and you should check if the images look nice directly on the console. In particular, you can check if there is lot of motion at this time. The gSlider reconstruction is done offline in MATLAB at the moment. It is based on a linear reconstruction model so we are not using any parallel information at this point, and the nice thing here is that we are doing real value diffusion which removes the background phase before recombining these data. So, we don't have a magnitude bias, at least from what I can tell!

Larry: There are three types of things going on: the SMS, the in-plane GRAPPA, which is pretty modest, and the gSlider. In order to assess that the sequence is running well, you first need to look for residual aliasing artifacts from the SMS and then GRAPPA-looking artifacts for the in-plane GRAPPA. The kind of new thing in this sequence is this Hadamard-like encoding across the thin slabs. Here I would compare the thick 4-5 mm thick slab, and the sub-0.6 mm slices, and check that you resolve more fine structures. I'm not really even sure what a through-slice encoding artefact would look like – I have a feeling it is just blurriness.

MRMH: What are the applications of this sequence that you foresee?

Kawin: We have collaborations with other people to see how the data you are getting at 600 µm can provide you more information about the brain and some of this work concerns tractography. In particular, it has been shown that tiny fiber pathways that were not visible in the past are making more volume than these large-scale bundles that are connecting the white matter and that people have been studying for the past two decades. Looking at these new fibers opens a new research area, which is very exciting.

Larry: In the diffusion methods, there is a trade-off between high k-space or high q-space methods. Where you want the high b-value, we use the CONNECTOM scanner for that. In these regions you usually want a high angular resolution because you want to resolve multiple fiber crossing in these complex white matter areas where everything is crossing. But in other regions, you want high spatial resolution. For instance, the regions where the fibers enter into the cortex; the cortex itself is a big target for us. We have been highly interested in studying anisotropy in the cortex. For instance, can you use that to determine cortical regions? Is there a laminar difference in anisotropy because layer 4 is going this way, layer 1 and 2 are tangential and everything else is radial? What is the curvature of these fibers? So there are a lot of structures where gSlider can be used for architectonics.

Another thing, that is not even related to that, is the study of brainstem structures. You have these little nuclei, that are like a constellation of literally hundreds of nuclei, and it turns out that diffusion is one of the best ways to see them because of the gray/white contrast but also because these nuclei are partially defined by the bundles that are running around them. We found in our 7T brain stem work that diffusion is one of the most useful contrasts to look at brain stem anatomy, and you need submillimeter resolution to see that, and you probably don't need super high b-values.

Kawin: MRI is a camera and, as we get sharper and sharper images, we are starting to see things that we haven't been able to see before, so we are of course very excited about these types of applications. ■

> *MRI is a camera and, as we get sharper and sharper images, we are starting to see things that we haven't been able to see before.*
>
> –Kawin Setsompop

Beyond "X,Y,Z": Thinking outside the rectilinear box with an 84-channel gradient coil

INTERVIEW BY **RYAN TOPFER**

EDITOR'S PICK FOR FEBRUARY

Having spent over a decade developing MR hardware, the Zaitsev group in Freiburg has tried their hand at "basically everything but the magnet itself." Lacking the Big Budget of industry, they favor a different approach to innovation: creating "strange things" with the "means at hand." Sebastian and Maxim here discuss one of the fruits of this design philosophy: their 84-channel gradient system.

> *People are comfortable with Fourier transforms, and everybody likes to think of the standard gradients as being linear – but they're not!*
>
> –Maxim Zaitsev

MRMH: Could you tell us how this project came about?

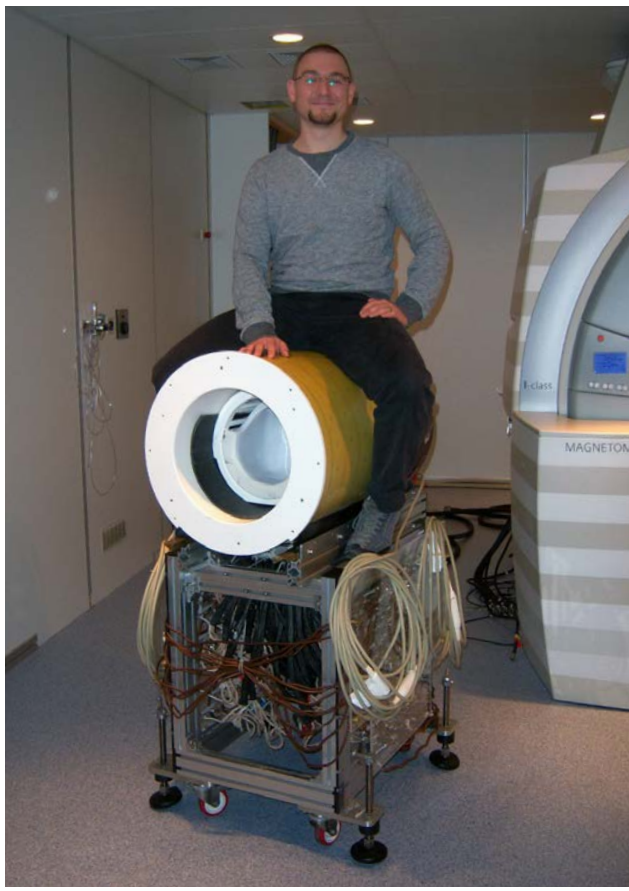
Sebastian: The parallel imaging technique with localized gradients (PatLoc) was developed in a previous project. This was based on nonlinear encoding fields and it demonstrated that many things you can do with RF (not everything, but a lot) are also possible in the gradient domain. In the meantime, Christoph Juchem published his multi-coil approach. So, the idea came about to build a gradient system that would basically generate any kind of encoding field we could possibly wish for a big playground to test new methods and to try out new things.

MRMH: Let's get the obvious question out of the way: Why an 84-channel gradient coil? The standard "x,y,z" gradients aren't enough?

Sebastian: Our aim is really to think in new ways about system architecture, especially the gradient coils – when you begin thinking about them in a different way, new possibilities open up. As for the specific design choices, such as the number of channels, many were based on an analysis by our co-author Feng Jia. The length was chosen to match the dimensions of a whole-body gradient system; however, were we to build it again we would probably make it a bit shorter.

Maxim: Currently, the 84 elements of the coil are arranged in 12 radial segments and 7 rings, and I think we could probably do with 5 rings instead of 7. But in the interest of time you can't simulate everything from beginning to end; you have to make some educated guesses, build what seems reasonable, and move on with the realisation!

Sebastian: Like always in science, you've got to start somewhere. And once you've cast the coil in epoxy you have to live with what you've created!



Sebastian Littin

Perhaps it's often the case when developing technologies that you have to overdo something before later returning to a reduced form. If you look, for example, at parallel transmit, this started out using many channels, but what's now standard on 3T Siemens scanners is a dual-channel parallel transmit option. I would guess that's

Littin, S., Jia, F., Layton, K. J., Kroboth, S., Yu, H., Hennig, J. and Zaitsev, M. Development and implementation of an 84-channel matrix gradient coil. Magn Reson Med. 2018;79: 1181–1191. doi:10.1002/mrm.26700
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26700/full

probably not something people would have expected ten years back. So you may have to go beyond and then bring things back in a somewhat reduced form.

Maxim: Beyond that which seems to be reasonable! We're trying to shake the established concepts. People are comfortable with Fourier transforms, and everybody likes to think of the standard gradients as being linear – but they're not! Put a larger object into the scanner and switch off the built-in distortion correction – you'll see just how nonlinear the so-called linear gradients are! Sometimes rather than trying to get rid of every imperfection, you might be better off accepting some – and even trying to use them. It's a "standard" innovation approach in MRI: you observe an artifact and try to think of how to make it useful, how to turn it into a new method, a new contrast, or a new encoding principle in our case.

MRMH: Was the original design created anticipating that you'd only be using 12 amplifiers to drive the 84 coils?

Sebastian: Originally it was conceived as having independent channels. To be honest, 12 high-current amplifiers were all we could afford in the grant! But the aim was really to have many degrees of freedom, and by having a reasonably low inductance per element, we can interconnect elements to form clustered channels, each driven by an individual amplifier. There's an IEEE paper from our co-author Stefan Kroboth on how to optimally combine the channels to reduce the number of amplifiers needed.

MRMH: Practically speaking, redefining a cluster means rearranging a bunch of cabling?

Sebastian: Sounds simple but it's actually a lot of work! You have 84 x 2 = 168 screw terminals that have to withstand 150 A at 350 V, so you have to be a bit careful to interconnect them. It takes about half a day to set up a new cluster, so it's time consuming, but for the experiments we've been doing so far, the clustering approach has been working quite well.

Maxim: We've also built and tested an electronic switch. Then there was an unfortunate incident where we lost it in a cloud of stinky smoke… One has to be prepared for such events when dealing with hardware development. So, for now everything is fairly manual and limited by the financial side of things; but our vision is that one day we will converge to a lower number of channels, which can then be powered by some lower number of amplifiers, with individual elements electronically switched on/off as needed for a specific application.

MRMH: What else have you done since publication?

Sebastian: At last year's ISMRM I presented this idea to use the matrix gradient coil for novel ways of doing simultaneous multi-slice: e.g. normally, to separate signals from multiple slices that are shifted along the phase-encoding direction; but if we instead apply a field that doesn't have a gradient anymore but just a different constant offset for each of the slices, by playing this out during read-out, you can shift the signals into their own frequency bands. That's just one example of something new, which was impossible before, now becoming possible by this coil. We're also thinking about implementing curved slice acquisition – something which has already been demonstrated on a PatLoc coil by a former colleague Hans Weber – but, with the matrix coil at hand, new degrees of freedom are waiting to be explored.

Maxim: We also had some ideas to do dynamic shimming within the slice. We published a paper already using it with the PatLoc coil, so we could certainly use it with the new matrix coil but, again, more amplifiers would be an advantage there…

Sebastian: And more man power!

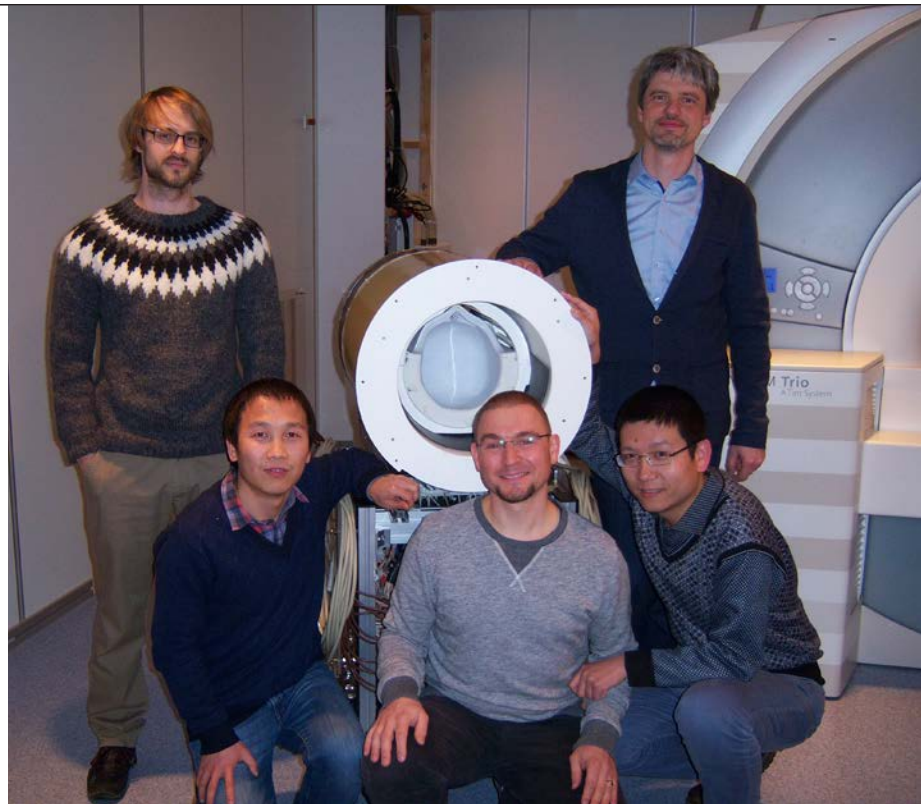
Maxim: Yeah, we have a long list of to-dos for that coil but we're currently four people on the project and we have like ten ideas we could follow.

MRMH: We could use this Highlights feature as a recruitment announcement.

Maxim: Sounds like a great idea! We have other exciting projects coming up around gradient and shim design: one is the optimized shimming coil with Klaus Scheffler in Tübingen; another is to build a local gradient coil for mammography, specifically for diffusion-weighting in the female breast. We're aiming at very high gradient strengths, well above half-a-Tesla per metre. We also have interesting industry collaborations coming up, related to gradients and system design.

Sebastian: If a day only had 48 hours…

Maxim: We would still have much to do! ■



From left to right: Stefan Kroboth, Huijun Yu, Sebastian Littin, Feng Jia and Maxim Zaitsev at their 3T research scanner in Freiburg, Germany.

> *Like always in science, you've got to start somewhere. And once you've cast the coil in epoxy you have to live with what you've created!*
>
> –Sebastian Littin

Getting the time just right with 'Brains on Beads'

INTERVIEW BY **ELENA KLEBAN**

EDITOR'S PICK FOR MARCH

For this month, we discuss the importance of timescale in NMR experiments with Donghan "Mo" Yang, Joseph "Joe" Ackerman, and Joel Garbow. Their work examines the pre-exchange lifetime using 'brains on beads' - a delicate in vitro system of neuronal cells grown on polymer beads. In addition to this marvel, we also consider the accuracy of Joe's premonition regarding MRI.

MRMH: What was your path to MRI?

Mo: I went to graduate school at Washington University in Saint Louis and each of the chemistry department faculty gave an introductory talk about their research. I went to Joe's talk and was fascinated. What he said was basically all about water. Although it's common stuff in a living system, it's also probably the best way in which we can study that living system. And then I was dragged into this topic and came and joined Joe's lab.

Joe: While I was getting my graduate degree at Colorado State University, Paul Lauterbur came by and gave a talk about some new experiments he called zeugmatography. He showed the first images of a mouse, but those images were simply abysmal. It looked like someone took a cheap cloth bag full of black ink and threw it against a white wall! And I remember that after the presentation, a bunch of the junior graduate students gathered around me as the senior guy and asked me, "What do you think about this field, is it gonna go anywhere?" And I said, "Trust me, this is going nowhere!" And then, after a postdoc at Oxford, I came to Washington University, took my first job, and I've been here ever since. I've been here for 40 years. So - this field, which was kind of going nowhere, I'm still involved with it.

Joel: I went to graduate school at the University of California, Berkeley, and worked with Alex Pines. Then I came to St Louis for a postdoctoral fellowship with Jake Schaefer, which turned into 17 years working at Monsanto doing solid-state NMR work. And 18 years ago, I moved from doing really hard-core NMR spectroscopy in non-living systems to doing *in vivo* imaging. It was a nice mid-life transition. It still is a lot of fun.

MRMH: What is the intracellular water pre-exchange time and how did you measure it?

Mo: In a general sense, you can say it's the average residence time of water in the intra-cellular space. We engineered an *in vitro* model system composed of neuronal cells attached to polymer beads, perfused by flowing media, which operates in the MR slow-exchange regime. For this system, we found two distinct relaxation components. The slowly relaxing component was assigned to the intra-cellular water, whose apparent relaxation is modulated by water exchange from intra- to extra-cellular space. So, by specifically measuring the intra-cellular water longitudinal relaxation rate constant, we can derive this pre-exchange lifetime or τ_i. [to Joe] Was that right?

Joe: Yeah you got it! Big picture would be that MR timescales tend to be pretty long, typically on the order of milliseconds to seconds. There is a lot of modelling going on to understand the MR signature of water in tissue but, of course, tissue is way too complex to model exactly. So, one has to simplify this complicated system and many folks talk about intra-cellular and extra-cel-

Mo taking a rest post-run in Forest Park, just outside the Medical School at Washington University, St. Louis.

Co-author and long-time collaborator, Jeffrey Neil.

Yang, D. M., Huettner, J. E., Bretthorst, G. L., Neil, J. J., Garbow, J. R. and Ackerman, J. J.H. (2017), Intracellular water preexchange lifetime in neurons and astrocytes. *Magn Reson Med*. doi:10.1002/mrm.26781
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26781/full

Members of the Biomedical Magnetic Resonance Laboratory at Washington University, St. Louis. Left to right: James Huettner, Larry Bretthorst, Joel Garbow, and Joseph Ackerman.

lular as two compartments in tissue. And if your measurement is on a timescale that is long relative to this exchange timescale, then in fact you only have one average compartment.

So, this begs the question: What is the exchange timescale? We set out years ago to solve this problem. We did it first using HeLa cells (an immortal cell line derived from cancer cells). These are great because they are so robust - anyone can grow them.

Joel: Even a physical chemist!

Joe: And because we were really interested in the brain, Mo developed 'brains on beads' – neuronal cells growing on beads.

MRMH: How long do these 'brains on beads' live?

Mo: The experimental time span is about two hours, and when I did the viability test at the end, the majority of cells were still alive.

Joe: These neuronal cells are very delicate, unlike the HeLa cells. HeLa cells are like cement trucks; they go through walls and can live anywhere. Neuronal cells are extremely difficult to work with, and Mo spent a lot of time adopting his perfusion system and doing the experiment in a time-efficient manner.

MRMH: Could turbulent flow be a problem for the extracellular signal?

Joe: If there was some turbulence, it actually might have created better conditions for this experiment. We used a very thin slice selection (~100 μm) so the gradients were very strong, and turbulence in this instance would look like extremely fast diffusion. That would result in a tremendous suppression of these turbulent spins – the extra-cellular spins whose signal we want to eliminate.

MRMH: What is your recipe for a successful diffusion or relaxometry experiment?

Mo: There are many sophisticated diffusion models or relaxometry models that take into account τ_i. In that case, our number just provides a direct reference. But in more common situations, people probably just assume that they are in the slow-exchange regime. In our system, the measured τ_i is about one-half to one second for intra-cellular water. When you're doing the experiment in the brain, the characteristic exchange time you need to consider is that of the extra-cellular water; given the ~ 1:4 extra- vs. intra-cellular volume ratio, this exchange time is probably ~0.2 seconds. In that case, if you wish to employ a two-compartment model, you need to keep your experimental time scale much shorter; we would argue, to be conservative, at least 10x shorter, i.e., ≤ 20 milliseconds.

Joe: I think the important part is we've set the timescale for this exchange phenomenon. And now we're going to let the modellers figure it out. Some are going to be really happy and some are not going to be happy.

Joel: You don't necessarily have to be in one limit or the other. As long as you understand the potential impact of this exchange, you can create a model that has the exchange parameter in it. What you cannot do is to ignore the contribution of exchange.

MRMH: And finally, any fun stories from this experiment?

Mo: I have to confess that when I started the rather exhaustive systematic evaluation on the perfusion system with and without cells, I ordered too many micro-beads and those are expensive and are probably still stored in the drawer in our 12T room!

MRMH: So there is the possibility of more 'Brains on Beads' in the future. Thanks for your time! ■

> *There is a lot of modelling going on to understand the MR signature of water in tissue but, of course, tissue is way too complex to model exactly.*
>
> –Joel Garbow

Are you up for a challenge? Results from the first QSM reconstruction challenge

INTERVIEW BY **PINAR ÖZBAY**

EDITOR'S PICK FOR MARCH

The quantitative susceptibility mapping (QSM) reconstruction challenge was an open competition designed to systematically compare and quantitatively assess the many available QSM algorithms. As described by the organizers in a recent publication, the challenge was first announced during the 2016 ISMRM meeting in Singapore. The results of the challenge were presented at the 4th International Workshop on MRI Phase Contrast and Quantitative Susceptibility Mapping, held in September 2016 at the Medical University of Graz, Austria. The authors mention that the initial goal was to test the ability of various QSM algorithms to faithfully recover the underlying susceptibility distribution from a healthy volunteer's phase data. As a side-goal, they also wanted to provide a common reference dataset to help benchmark not only existing QSM algorithms, but also methods that would be developed in the future.

We set up a teleconference with Drs. Langkammer, Bilgic and Schweser, as the main organizers of the challenge, and are proud to present the largest crowd (n=5) participating in an MRM Highlights interview so far! We had an exciting discussion about the challenge itself and also the future of the field, while connecting Maryland (Pinar), Massachusetts (Berkin), New York (Ferdinand), Austria (Christian), and Wales (Erika).

> *We were surprised and very happy with the high participation from the QSM community.*
>
> –Christian Langkammer

MRMH: Could you share with us the story behind the work and how the idea got started?

Ferdinand: I remember vivid discussions about visual quality versus quantitative accuracy and standardization already at the first and second QSM workshops held in 2011 and 2013 in Jena (Germany) and Ithaca (New York). Over the years, the validation idea gained more traction. A few years ago, a point was reached at which a pretty high number of different QSM algorithms had been proposed but it was completely unclear how these algorithms should be compared to one another.

Berkin: The trigger for starting the challenge came from Markus Barth who responded to a call for suggestions of pressing topics to be discussed at the 2015 ISMRM Electro-Magnetic Tissue Properties (EMTP) study group meeting in Toronto. Markus pretty much outlined the general idea of the challenge.

Christian: Later, three of us thought to join our forces and planned it further during a fruitful discussion at a bar [*laughs*]. After a year of work, we announced the details of the challenge at the 2016 EMTP study group meeting in Singapore, with the goal to present the results later in the year at the 4th QSM Workshop in Graz.

Ferdinand Schweser, Pinar Özbay, Christian Langkammer, and Berkin Bilgic (above) await you in Paris!

MRMH: Could you give us a summary of the challenge design and analyses?

Berkin: We provided a comprehensive 3T dataset including GRE data from 12 head-orientations, T_1-weighted

Langkammer, C. , Schweser, F. , Shmueli, K. , Kames, C. , Li, X. , Guo, L. , Milovic, C. , Kim, J. , Wei, H. , Bredies, K. , Buch, S. , Guo, Y. , Liu, Z. , Meineke, J. , Rauscher, A. , Marques, J. P. and Bilgic, B. (2018), Quantitative susceptibility mapping: Report from the 2016 reconstruction challenge. *Magn. Reson. Med.* 2018;79: 1661-1673. doi:10.1002/mrm.26830

https://onlinelibrary.wiley.com/doi/full/10.1002/mrm.26830

With the participants of the 4th QSM workshop at the Medical University of Graz, Austria.

structural images, background-field removed phase, COSMOS (calculation of susceptibility using multiple orientation sampling) and the full susceptibility tensor (ST). Furthermore, two QSM algorithms and their evaluation scripts were provided as Matlab scripts for benchmarking. We decided to provide only a single-orientation phase data from this multi-orientation scan, which was representative of any real world acquisition we would routinely perform, including noise and flow artifacts, rather than a contrived and ideal numerical phantom simulation.

Ferdinand: Another critical step of the design was the decision on the ground truth susceptibility data for evaluation. In comparison to the single-orientation methods, multiple-orientation approaches do not depend on the regularization or algorithm parameters, while at the same time overcoming the ill-posed inverse problem by sampling at different angles with respect to the magnetic field. Hence, we thought multi-angle data would be more suitable for a ground truth, although we were well aware that there is actually no real ground truth.

Christian: The participants calculated their QSM maps from the single orientation data and compared them against the STI data using the following metrics: root mean squared error (RMSE), structure similarity index (SSIM), high-frequency error norm (HFEN), and the absolute error in selected white and grey matter regions. While RMSE would serve as a global error metric, with SSIM we aimed to promote images that appear visually similar to the reference data. HFEN was included to penalize over-regularized, smooth susceptibility maps by emphasizing the fidelity of high-frequency edge structures. And lastly, absolute error in ROIs was used to measure the quantitative accuracy of the reconstruction methods.

MRMH: Who were the winning teams? And what do you think made the winning algorithms better than the others?

Christian: We were surprised and very happy with the high participation from the QSM community. We received a total of 27 submissions from 13 groups. One winner was selected for each of the 4 categories: Christian Kames (UBC, Vancouver, RMSE category), Li Guo (Southern Medical University, Guangzhou, tied for first place in ROI accuracy), Zhe Liu (Cornell, New York, also in ROI accuracy), and Xu Li (Johns Hopkins, Baltimore, winner of both the HFEN and SSIM categories).

Berkin: A common thread between some of the winners was keeping the acquired data in the well-conditioned frequency region intact, while compensating for the ill-conditioned frequency content using compressed sensing (CS)-like algorithms. Some have also utilized structural information from the magnitude image to provide prior information.

Ferdinand: We observed two main approaches among the winners, with MEDI-like (Morphology Enabled Dipole Inversion, based on L1-minimization) algorithms, which gave higher quantitative accuracy (ROI metric), and CS-like approaches, which scored better in other error categories such as structural similarity and high-frequency error norm. We believe that the choice of the QSM algorithm would depend highly on the area of the application.

MRMH: Where do you see the field in 5 years? Do you see QSM as a 'push button' method in the scanners?

Christian: Absolutely! This research field has evolved in the last 15-20 years and today we can produce susceptibility maps with next to no apparent artifacts. With highly accelerated GRE sequences allowing up to 0.5mm isotropic resolution, QSM has a big potential to become a clinical tool available at the scanners, as SWI made it 10 years ago.

Ferdinand: Just as a remark, there will also be a member-initiated symposium led by Jose Marques at this year's ISMRM in Paris, which will bring together industry representatives at a round table to discuss a commercial implementation.

Berkin: As a last remark referring to the future of the field, we foresee that machine learning will play an important role in the solution of this difficult reconstruction problem, and we look forward to seeing the first batch of such solutions at the upcoming ISMRM meeting in Paris. However, which will be the best algorithm to implement on a scanner as a black-box tool? We think a Challenge 2.0 will be very important to guide this process. ■

> *We were well aware that there is actually no real ground truth.*
>
> –Ferdinand Schweser

Bringing knee segmentation techniques into the third dimension using deep learning and deformable models

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR APRIL

This month's Editor's Pick is from Fang Liu and Richard Kijowski, researchers at the University of Wisconsin-Madison. Their paper presents a novel approach of automatically segmenting knee joint structures, combining the power of recently developed deep learning techniques with a 3D deformable model approach. We recently spoke with Fang and Rick about their current and upcoming projects.

Fang Liu

MRMH: Please tell us a little bit about yourselves.

Fang: I did my undergrad in China in biomedical engineering. I then moved to London, Ontario, in Canada, where I did my master's at Western University, studying dynamic contrast enhancing MRI techniques for breast imaging. After that, I moved to Wisconsin for my PhD in the medical physics department. My research was primarily focused on musculoskeletal (MSK) imaging using rapid quantitative and morphological MR methods for assessing cartilage, meniscus and bone in MSK diseases like osteoarthritis. Recently, I started quite a few deep learning projects for MR image acquisition, reconstruction, and analysis, so nowadays I also call myself a deep learning and artificial intelligence researcher.

Rick: I am a MSK radiologist here at University of Wisconsin-Madison. I have been here since completing my fellowship in 2003. My main area of research is the use of MRI to investigate all types of MSK diseases, with a specific focus on speeding up quantitative and morphologic MRI of cartilage and other joint structures involved in osteoarthritis.

MRMH: Could you give us a brief overview of the work you did in this paper?

Fang: The idea here is that we adapted a very interesting deep learning technique, called convolutional encoder-decoder (CED) network, which is a type of highly efficient semantic segmentation convolutional neural network (CNN), to extract 3D knee joint image segmentations in an extremely efficient manner. One challenge we faced was how to fine-tune the results from CNNs in 3D MR image space, because the CNN technique is using 2D images, slice by slice. We proposed using a 3D surface-mesh-based modelling technique, the 3D simplex deformable model, to regularize the spatial 3D information from the output of the CED. A nice thing about combining these two techniques is that both methods are highly efficient, providing us with an accurate and time-efficient knee joint segmentation tool.

Rick: I think it is also really important to give credit to what has been done before and to give previous researchers their due. Researchers have developed various semi-automated and fully-automated methods for knee joint segmentation over the past 10 years, since the demand has been so high. There are some really good semi-automated and fully-automated methods out there, which are commercially available and have been used in large clinical studies. They do have a few drawbacks however. They work great, but can be time

Liu, F., Zhou, Z., Jang, H., Samsonov, A., Zhao, G. and Kijowski, R. Deep convolutional neural network and 3D deformable approach for tissue segmentation in musculoskeletal magnetic resonance imaging. *Magn Reson Med.* 2018;79: 2379–2391. doi:10.1002/mrm.26841

http://onlinelibrary.wiley.com/doi/10.1002/mrm.26841/full

consuming and have high computational costs. So, the work we presented here is an alternative deep learning method, which can perform rapid segmentation of not only cartilage and bone but all MSK tissues within the knee joint, which we demonstrated in another recently published MRM paper from our group.

MRMH: How does this work fit in your broader research goals?

Rick: This work basically serves as step one in our broad design to use deep learning as a diagnostic and predictive tool for medical image analysis. It seems reasonable that the first step in detecting a disease is to segment out the tissues where the disease is located. For example, to detect cartilage lesions, we feel that it is best to first segment the cartilage, and then use a second classification system in order to predict the likelihood that the segmented tissue is normal or abnormal. Our overall goal is to apply deep learning technology in clinical practice to improve diagnosis of MSK diseases.

MRMH: Do you have any advice for researchers that may want to do similar work?

Fang: I think that there are at least three essential components to consider before starting deep learning projects. You need to understand the fundamental concepts of deep learning (convolutional layers, pooling process, normalization layers), choose the tools you feel comfortable starting with (such as TensorFlow, Theano, or PyTorch), and, most importantly, identify a research problem that has strong clinical value and you think might fit well into the deep learning scope. Those are all really important to consider when starting a deep learning project for medical imaging applications. Also, it might be helpful to have a group of researchers with a combination of clinical and technical backgrounds to brainstorm ideas and thoughts.

MRMH: Are you considering making your code publicly available?

Fang: We are actually working on a code package. We're hoping to upload our code somewhere online very soon, maybe on GitHub or Sourceforge, to help the MR research community.

MRMH: Is there anything in particular you enjoy doing when you're not in the lab in Wisconsin?

Rick: In the fall, the biggest things in Wisconsin is definitely the football team, the beer, and the bratwursts. ■

Richard Kijowski (left) with Fang Liu (right)

> *This work basically serves as step one in our broad design to use deep learning as a diagnostic and predictive tool for medical image analysis.*
>
> –Richard Kijowski

The Wisconsin Institute for Medical Research, as dreamt up by Google's DeepDream.

Cycling through brain metabolites at 9.4T

INTERVIEW BY **MARK MIKKELSEN**

EDITOR'S PICK FOR APRIL

This month we speak with Ioannis-Angelos Giapitzakis and Anke Henning about their recent work on using metabolite-cycled MR spectroscopy to simultaneously acquire metabolite and unsuppressed water spectra at ultra-high field. They talk about some of the technical challenges they faced in their study and where they see the field of MRS moving forward next.

Anke Henning

Ioannis-Angelos Giapitzakis

MRMH: Could you please tell us a bit about your background and how you got into MR research?

Ioannis: I did my diploma studies in physics at the National Technical University of Athens but I was always fascinated about the application of physics in medicine. This was my main motivation for doing my bachelor's thesis in DTI. Then I continued my studies at Imperial College London, where I did my master's degree in the combination of DTI and fMRI. In the end, I wanted to do more MR physics so I decided to get into MR spectroscopy. It was a great opportunity for me to join Anke's group when she offered me a PhD position at Max Planck Institute in Tübingen, since we have this unique whole body 9.4T MRI scanner.

Anke: I did my studies in physics in Eastern Germany. Then I got the opportunity to go abroad for an internship in Brazil, and it was in MRI. That was my first encounter with MRI and I was fascinated. After my physics degree I looked around for PhD positions and started with structural biology at ETH Zürich (specifically in NMR spectroscopy). I then changed labs during my PhD to join Peter Bösiger's group (also at ETH Zürich) to do MRI. I also learned about MRS from Kurt Wüthrich and Richard Ernst while I was there.

MRMH: So you worked with not one, but two Nobel Laureates.

Anke: Yeah [*laughs*].

MRMH: On to the paper. Could you explain what is meant by metabolite cycling?

Ioannis: Metabolite cycling allows us to simultaneously detect water and metabolite signals. It was first described by Dreher and Leibfritz in their 2005 MRM article. What we do is use an asymmetric adiabatic inversion pulse incorporated in the standard localization schemes. In one acquisition, we invert the metabolite signals downfield of water; in a second acquisition we invert the upfield metabolite signals. When we add these two acquisitions together we obtain a water spectrum, and when we subtract the two we get just a metabolite spectrum free from gradient modulation sidebands. We can then use the water peak for eddy current correction and frequency and phase alignment. Metabolite cycling can also be used to perform functional MRS studies where we simultaneous detect changes in the metabolite and water signals.

Anke: Very few people are aware of the original paper describing metabolite cycling. It was picked up by one or two groups (such as the group in Bern and ours), and now recently the Oxford group has implemented it for MRSI. The first paper was overlooked because the topic focused on exchange spectroscopy measurements, which is very, very specific. Not everyone was interested, but the technique was hidden in it.

MRMH: Was it challenging to make the custom-built RF head coil you used for this study?

Ioannis: We had an experienced RF coil engineer, Nikolai Avdievich, to help us. The main idea was to reduce the chemical shift displacement error by having high-bandwidth, short-duration pulses. This requires high B_1 values. Before, we had an 8-channel coil, but to focus our efforts on the occipital lobe we wanted to implement hardware B_1 shimming techniques. And by playing with just the phase using different cable lengths and the power distribution, we could achieve high B1 values in the occipital lobe. Despite the difficulties, together with Nikolai's great contribution in designing the coil we found this nice solution.

Anke: On another note, we have to build every single coil for 9.4T ourselves because there are no commercially available head coils. We also had to spend two-and-a-half years to convince the IRB committee that these coils are safe – we even put together a 90-page standard operating procedure document for this. Unfortunately, 9.4T is not "push-button".

Giapitzakis, I.-A., Shao, T., Avdievich, N., Mekle, R., Kreis, R. and Henning, A. Metabolite-cycled STEAM and semi-LASER localization for MR spectroscopy of the human brain at 9.4T. *Magn Reson Med.* 2018;79: 1841–1850. doi:10.1002/mrm.26873
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26873/full

The lab on a snowy retreat in Overjoch, Germany.

MRMH: Does your lab have ideas for moving forward with this metabolite cycling technique?

Ioannis: We have actually already used it for functional MRS, and the first results were really promising because we see a nice correlation between the BOLD effect on the water peak and metabolite changes. There are still some things left to improve, and Anke's group continues to work in this direction. We have also applied it to characterize the chemical exchange of the downfield metabolites with water.

Anke: The metabolite cycling technique has become the workhorse for any studies we do now at 9.4T because of the nice feature of being able to use the water signal for retrospective phase and frequency alignment. Prospective approaches that could do this would be more hardware-intense and much harder to implement. We also use it in several clinical studies, including in depression and tumors. In terms of specialized applications, we continue to characterize the downfield part of the spectrum in order to understand the CEST contrast. So, basically what we are doing is the "inverse" version of CEST.

MRMH: Finally, your paper shows how technically challenging MRS can be, especially when conducting experiments at ultra-high field. Do you think this is one reason why MRS is not as popular as maybe other techniques in the wider field of MR?

Ioannis: In order to develop MRS techniques you need a solid understanding of MR physics and sometimes you even need an understanding of spin dynamics. The other reason is that in MRS we care about low-concentration metabolites, and not usually about the high-intensity water peak. That is challenging because we have to fulfill more technical criteria in order to optimally detect these weak signals in the brain. I think what is also challenging is the post-processing – there are some really nice techniques but we still have to improve them.

Anke: My view is that the vendor implementations are not capturing the state-of-the-art. What the vendors are implementing is 20 years old, and it is not standardized. The vendors need to invest more in MRS. It is used clinically, but in specialized centers that have MR physicists that can overcome the challenges. There is a lot of discussion in the MRS community on how to make the implementations standard. Also, as long as it sticks to single-voxel spectroscopy, radiologists are maybe not familiar with reading spectra, as it requires a lot of knowledge of physiology, so they struggle interpreting it. The community hopes that once we move from single-voxel spectroscopy to real spectroscopic imaging we will overcome this hurdle. ■

Ioannis Giapitzakis and Magnetic Resonance in Medicine Editor-in-Chief, Matt Bernstein, at the 2014 ISMRM meeting in Milano.

> *The metabolite cycling technique has become the workhorse for any studies we do now at 9.4T because of the nice feature of being able to use the water signal for retrospective phase and frequency alignment.*
>
> –Anke Henning

Nikola Stikov

***Magnetic Resonance in Medicine* Deputy Editor for Science Outreach**

Prior to joining the faculty of École Polytechnique (University of Montréal), Nikola completed his post-doctoral training at the Montréal Neurological Institute, and his BS, MS, and PhD 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* Highlights Editor**

Erika is a post-doc at CUBRIC in Cardiff, Wales, after recently completing her PhD with the Advanced MRI group at NIH. Her research has taken her across the pond in the ongoing search to find the best methods to track adolescent brain development. Erika enjoys scientific outreach through social media, reaching stage 4 sleep, and the Eurovision Song Contest.

Atef Badji

***Magnetic Resonance in Medicine* Highlights Editor**

Atef is currently working toward her PhD in Neuroscience at the University of Montréal. Her research focus is on the quantitative evaluation of pathological states of the brain using MRI. Among her specific goals are the understanding of the white matter changes in the elderly, as well as the understanding of the natural course of multiple sclerosis. In her free time, Atef enjoys writing, eating chocolate, and watching Big Bang Theory with her husband.

Mathieu Boudreau

Mathieu is a research fellow at the Montreal Heart Institute, after having completing his PhD at McGill University. His current research interests are in developing open-source software for quantitative MRI techniques and other related image processing tools. In his free time, Mathieu enjoys cooking, hiking, and making grad students feel anxious about not having a proper backup of their computers.

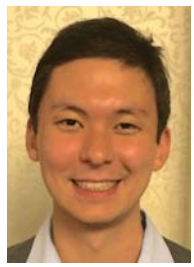
Maria Eugenia Caligiuri

Maria Eugenia is a post-doc at the Neuroscience Research Center of Magna Graecia University in Catanzaro, Italy, where she also completed her PhD and part of her post-doc working at the Institute of Molecular Bioimaging and Physiology of the National Research Council. Her work focuses on advanced methods for multimodal MRI fusion and on their application in the field of neurological disorders and healthy brain aging. In her free time, Maria Eugenia enjoys listening to music, binge-watching TV series with her husband, and being a crazy cat lady.

Akshay Chaudhari

Akshay is a PhD candidate at Stanford University. 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!

Brian Chung



Brian is a PhD student at UC San Francisco researching Hyperpolarized Carbon-13 metabolic brain imaging. He obtained his MSEE from Stanford and enjoys international travel, card games, and patent law for start-ups.

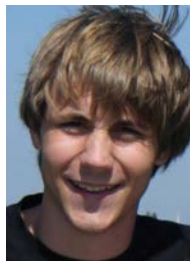
Blake Dewey

Blake is a PhD 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.

Thijs Dhollander

Thijs is a post-doc at the Florey Institute of Neuroscience and Mental Health in Melbourne. He obtained his PhD 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.

Tanguy Duval

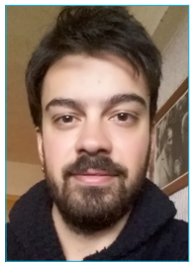


Tanguy graduated from Centrale Lyon in France in 2013. He received his PhD at Polytechnique Montréal trying to make g-ratio imaging more credible. In his free time, Tanguy likes playing rugby, drinking wine, playing soccer, drinking beer, playing basketball, drinking coffee, reading, and eating frog legs.

Zahra Hosseini

Zahra Hosseini is a PhD candidate at Robarts Research Institute in London, Canada (the less exciting London). For her PhD studies, she has explored new processing approaches for multi-channel MR image data with a focus on multi-echo GRE phase images. She has immensely enjoyed meeting people in the ISMRM community through the annual meetings and hopes to continue working with the wonderful set of individuals that help communicate the advances in research in this field.

Agâh Karakuzu



Agah is a PhD student in Biomedical Engineering with NeuroPoly Lab at Polytechnique Montréal. His research is centered on developing a reproducible quantitative MRI platform, with a particular focus on neurocardiology. He is an open science enthusiast and plays an active role as a science communication contributor for several platforms including MR Pulse and OHBM blog. He enjoys graphic design, skiing and exploring specialty coffee.

Elena Kleban

Elena joined CUBRIC at Cardiff University as a research associate in December 2017 after submitting her PhD thesis to the University of Nottingham. She is looking forward to going deeper into matter, if grey or white, and learning more about the origin of the local complex signal in presence of multiple compartments. Elena is curious about many things, and enjoys problem solving, particularly in bouldering and escape rooms.

Jiaen Liu

Jiaen is a post-doc at the National Institutes of Health in the U.S. Before that, he obtained his PhD in Biomedical Engineering at the University of Minnesota. He is currently working on motion correction, image reconstruction and sequence design. He likes to run, play basketball and cook (especially grill!) in his spare time.

Jessica McKay

Jessica is a PhD 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.

Mark Mikkelsen

Mark is a post-doctoral researcher in the Department of Radiology and Radiological Science at the Johns Hopkins University. He did his PhD in spectral-edited MR spectroscopy methodology at Cardiff University. He is currently working on advancing MRS methods for optimally detecting and quantifying brain metabolites such as GABA in vivo, and additionally researches the neurochemical correlates of tactile dysfunction in various neurodevelopmental disorders. Mark likes to spend his free time doing photography and creative writing and is a diehard metalhead.

Pinar Özbay

Pinar joined Advanced MRI group at the National Institutes of Health in January 2017, right after obtaining her PhD at ETH Zurich. She has worked on novel contrast mechanisms for brain imaging, particularly quantitative susceptibility mapping for structural and functional MRI at high field systems. Currently she is trying to understand resting state fMRI signal changes in white matter during long scan times. She enjoys baking, working out and pilates, discovering new coffee spots in DC, and moreover, in her free time, she is practicing conversion between °C and °F.

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 PhD (Polytechnique Montréal) sometime in the next couple years.

Phillip Ward

Phillip is a post-doc at Monash Biomedical Imaging. His primary focus is healthy ageing. He develops MRI and PET techniques to investigate vascular and neural function in the context of dementia and depression. Phillip enjoys cooking, reading, and a broad range of sports.

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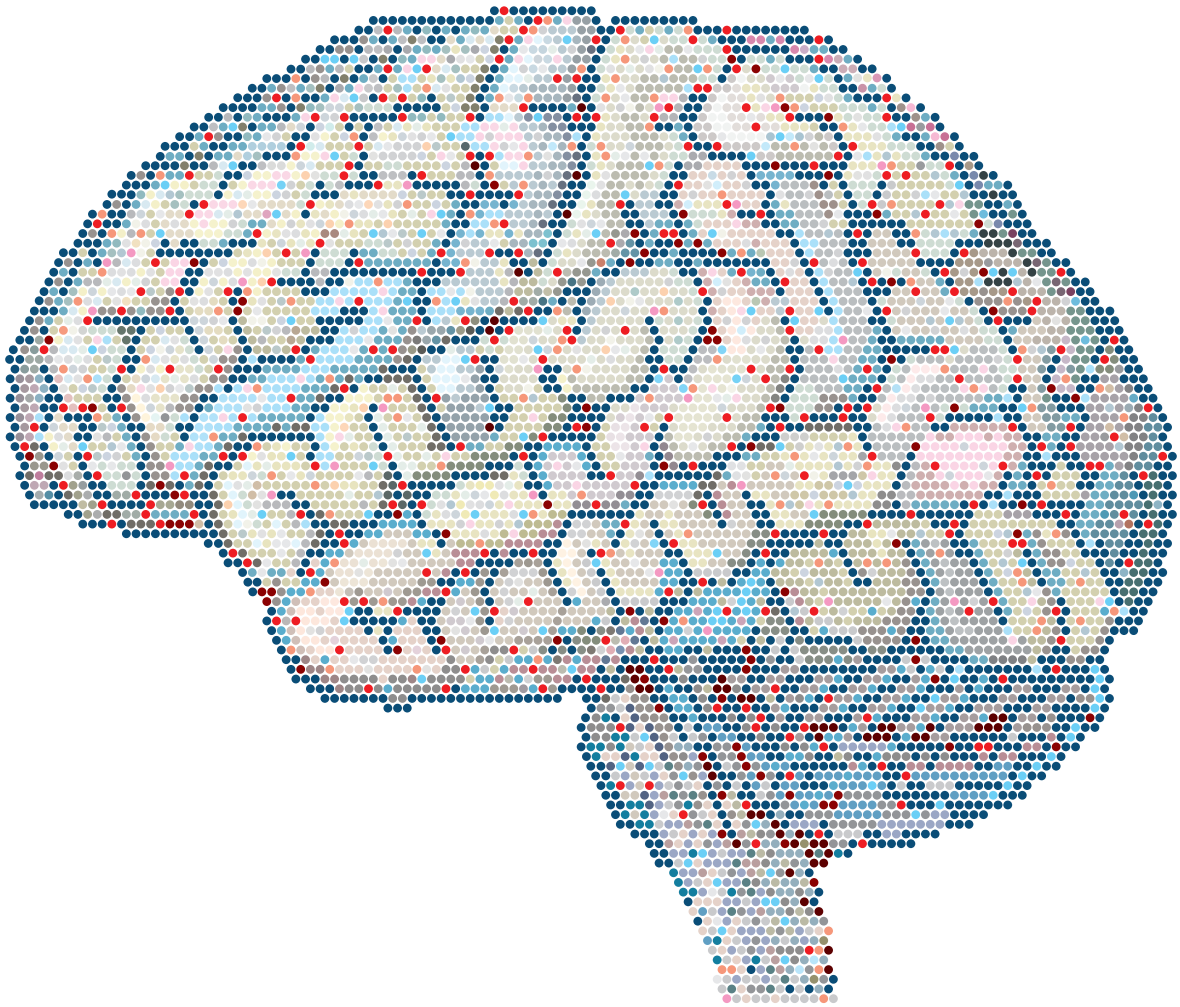

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