Magnetic Resonance in Medicine

HIGHLIGHTS

Matt Bernstein

Building the MRI community one paper at a time

Pia Maly Sundgren

Opening doors within ISMRM

Editor's Picks

Joanne Ingwall

An interview by Derek Jones

ISMRM ONE COMMUNITY FOR CLINICIANS AND SCIENTISTS

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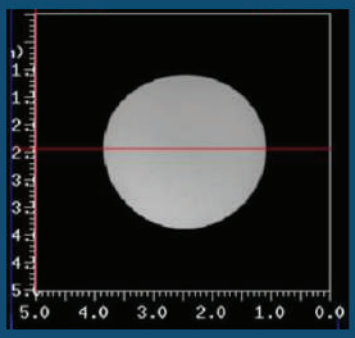
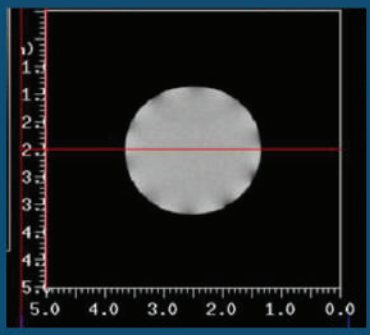
May 2018 - March 2019

Millipede Coils –
Hundred-Element Birdcage Coils

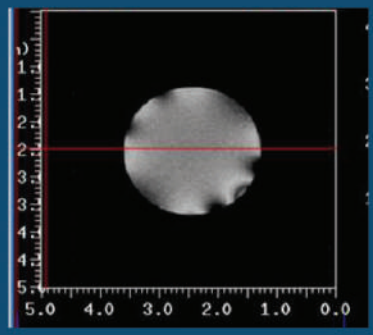
Extraordinary uniform RF profile for all imaging applications



Millipede coil



Birdcage coil



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- Better filling factor – *better SNR*
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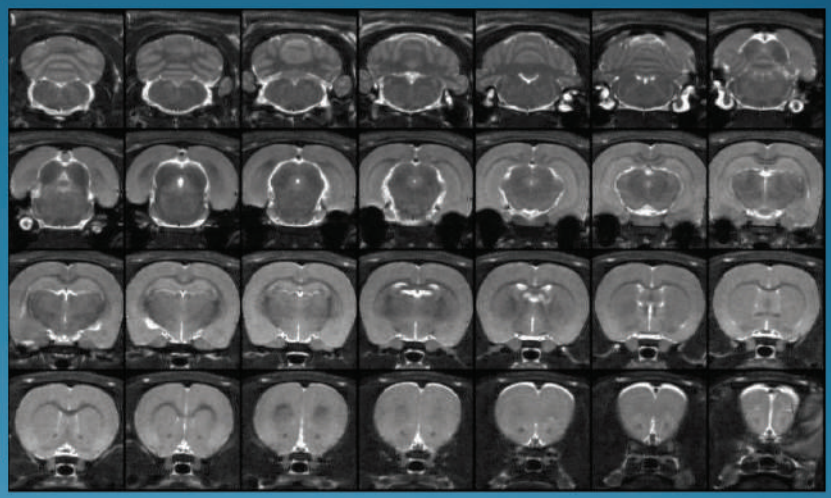

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Excellence breeds excellence!

This is what MRM editor-in-chief Matt Bernstein told us in 2016, upon completion of the first issue of the Magnetic Resonance in Medicine Highlights magazine. That magazine was the culmination of one year of interviews, blogging, and a social media blitz the likes of which the journal had never seen before. Over 50 people contributed to it, many of them trainees who had yet to publish an MRM paper.

As we were relaxing with drinks at the first Highlights party in Singapore, we realized that we had tapped into a unique community of researchers interested in science communication. It wasn't planned, it just kind of happened. It fed off the energy of trainees who wanted to get involved with the society and didn't know of a way in. It fed off the enthusiasm of authors of articles published in the journal, who were surprised that somebody would spend a week obsessing over tiny details in the paper so they could have a conversation about it. Finally, it fed off the curiosity of magnetic resonance professionals, drowning under a pile of 10-page PDFs and looking for an alternative science communication venue where the language is simple, and the writing is peer-reviewed.

Four years later, we are still going strong. Many of the Highlights posts get more page visits than the papers they are highlighting. The Highlights YouTube channel is increasingly becoming the place where a researcher goes to understand the details of a paper published in the journal. Our social media channels are buzzing with activity, and the Highlights after-party is the trendiest place to be. All of this without anybody getting paid for it.

How did we make this grassroots initiative so successful? I don't really know. I don't think we were trying to build a community, but we were rather trying to build something new, and the community got excited by it. By now the Highlights initiative has taken on a life of its own, and every year we listen to feedback from our contributors and try to bring innovation to the world of science communication.

In the pages of this year's magazine the past and the future of the society blend seamlessly. Our cover story honors Joanne Ingwall, the first woman president of the SMRM (the ISMRM predecessor society) and a charter member of the MRM editorial board. The researcher profile of current ISMRM president Pia Sundgren emphasizes the importance of opening doors to young researchers. The mentoring theme is further expanded in the interview with our outgoing editor-in-chief, Matt Bernstein, who has been bringing innovation to the field for over 30 years. The 20 Q&As with authors of editor's picks confirm that the journal is vibrant and diverse, and that the future of MRI is bright.

Matt, thank you for opening the door to Highlights! Erika and Atef, thank you for walking through it with passion and professionalism, bringing in over 200 contributors and thousands of readers over the past four years. All the rest, thank you for sharing, blogging and reading! With Highlights we have made something truly special, and I hope it continues to breed excellence in the years ahead.

Nikola Stikov
Deputy Editor for Scientific Outreach
Magnetic Resonance in Medicine

MAY 2019 / VOLUME FOUR

WILEY

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Joanne Ingwall – Pioneer of cardiac energetics

INTERVIEW BY **DEREK JONES**

Professor Joanne Ingwall pioneered the use of phosphorous magnetic resonance spectroscopy to study cardiac energetics. She played a major role in shaping the ISMRM, introducing initiatives and frameworks that persist to this day, and is a keen advocate of mentoring students, fellows and junior faculty.

On Friday 5th April, during the peak of the 'SuperBloom' in her home town of Borrego-Springs, Southern California, Professor Ingwall kindly agreed to chat, over the internet, about her life in NMR and her role in the society, including the recognition of spectroscopists and her love of conference ribbons.

Joanne Ingwall

Derek K. Jones (DKJ): Professor Joanne Ingwall, welcome to MRM *Highlights*.

Joanne Ingwall (JI): Thank you. I'm delighted to be here.

THE FORMATION AND EARLY DAYS OF SMRM AND ISMRM

DKJ: Many people will be reading this interview at the ISMRM in Montreal, and a good proportion of those will be attending the meeting for their very first time. Before we explore your story, could you cast your mind back to your very first meeting, of what was then called SMRM? What are your recollections of those early days?

JI: Well, I probably attended the first SMRM meeting in Boston in 1982. The group of people that formed the society was based there. Gerry Pohost[1] loves to organize things like this, and spent a lot of energy pushing for it, together with Tom Budinger, Alex Margulis, Paul Lauterbur and Britton Chance. They also invited me and Kate Scott, who was in Florida at the time. Tom Budinger decided that we had to be identifiable as members of the board and had to wear big name badges – horrible things with ribbons coming out. Oh, it was awful. I nearly died.

DKJ: The tradition of board ribbons has continued to the present day!

JI: Really? I think that's awful. I understand the rationale, but it's a bit much, it's like a horse!

DKJ: "Best in Show"?

JI: Exactly! But I also remember being amazed that there were so many people who came out

1 Prof Gerald Pohost was the Founder of the Society of Magnetic Resonance in Medicine in 1982. The other organizers were Paul C Lauterbur, PhD (nobel laureate); Tom Budinger, MD, PhD, University of California, Berkeley; Alex Margulis, MD, University of California, San Francisco, and Britton Chance, PhD, University of Pennsylvania.

of the woodwork, even though the field was exceedingly new, and how many people actually showed up year after year.

I remember the New York meeting best of all, I suppose because it was fun to go to New York. I'll tell you a funny aside. The meeting was held at the New York Hilton; we were their largest client by the time the 89 and 90 meetings came around. When I was president, they sent a car to the airport to get me and my husband. We get in this limousine and we're driving through Central Park, and my husband turns to me and said, "*I don't understand this. I thought limos were only for important people.*" I nearly killed him!

DKJ: So this was SMRM, not ISMRM. Many people reading this interview won't be familiar with the backstory of how SMRM became ISMRM, and that you had quite an influential role in this. From 1982 to 1987, you served on the board of trustees, and as president from 1989 to 1990. In 1992/1993 you served on the committee overseeing the merger of the Society for Magnetic Resonance Imaging (SMRI) and the Society for Magnetic Resonance in Medicine (SMRM). What was the rationale for the merger?

JI: There were several reasons. I think the primary motivation was money. There was significant pressure from the MR manufacturers to avoid setting up for two meetings. Clearly, many people went to both meetings, (not me because I was a spectroscopist) – and so it made sense.

The merger was a difficult task because the two societies had very different models for how to do their business. SMRM did everything in house, and we had staff who had competencies in administration, publishing, and running meetings, while SMRM outsourced everything. Ultimately, the SMRM model was chosen for ISMRM. Moreover, the executive director of SMRM at that time, Jane Tiemann, was chosen to be executive director of ISMRM. I'm very glad that the two societies merged, and that efforts were made to not disenfranchise the pure spectroscopists. Spectroscopists are not only a minority, we are a very, very small minority.

CONTRIBUTIONS AS PRESIDENT

DKJ: We already discussed your role as president. In 1995, you were made fellow of the ISMRM, and in 2001, you received the silver Distinguished Service Award from

Past SMRM presidents: Joanne Ingwall (front) with (from left to right) Paul Laterbur, Tom Budinger, George Radda, Gerald Pohost and Herb Kressel.

At the fish market in Buson, Korea

ISMRM. Only 20 of those have ever been awarded in the history of the society, that must have been a very proud moment?

JI: Yes, the silver medal was wonderful, because it recognised my administrative contributions. When I was president, we were undergoing significant growing pains. We were in the process of becoming larger, more well-known and more established, and we discovered that we had no written policies and procedures for anything. So I spent a great deal of that year flying back and forth to the Berkeley office and creating the policies and procedure manuals that served as the basis for the merged societies. Working closely with Herb Kressel, I also developed the overall administrative structure still used by ISMRM.

The other thing I did was to develop a strong executive committee. There were times for months on end where we would meet every week over phone. It's very important to build consensus. That was also part of the transition from being a "Mom and Pop" organization to a more professional organization.

I also introduced the Young Investigator Award. That's just a no brainer. It really helps the people who are the finalists gain profile, and that helps them with their career development.

DKJ: Well as a runner up in the Young Investigator Award, I can fully agree with you. It was a career booster.

JI: What was the title of your project?

DKJ: *"Smashing Pumpkins and Squashing Peanuts". It was about how noise distorts the profile of diffusion in fibers. Yaniv Assaf, who I'd already become friends with, was also in the final and we sat mutually disappointed, side-by-side, as the prize was given to the more-deserving Florian Wiesinger for his work on parallel imaging. The right person won.*

JI: But all three of you were at least profiled and you made friends, so that's good. The very first winner was Doug Lewandowski, who was immediately recruited to the MGH in Boston.

DKJ: That's an awesome legacy, to have set that wheel in motion!

CARDIAC ENERGETICS

DKJ: So I'd now like to talk about the science. You've been a prolific writer, with over 140 papers focusing primarily on cardiac energetics. For the reader who is unfamiliar with basic physiology, could you just give us a quick summary of the kinds of questions you've been interested in? Perhaps starting with ATP, which, in one of your review articles, you refer to as the "universal currency of energy".

JI: My own passion is indeed the energetics of the heart, or muscle, basically excitable tissues, but the heart is the easiest model to study. Okay, no living organism, no cell can live without the chemical energy derived from ATP. As you say, it's the universal currency of life. That's not my phrase, unfortunately, I wish it were. Very famous biochemists before me called it that. If you were a student of Lehninger at Hopkins, you think Lehninger invented it, and if you were a student of Stryer at Stanford, you'd think he invented it. The concept of there being a single small molecular weight molecule that is responsible for supplying the chemical energy needed for all processes in the cell is around 80 years old. So if one wants to study something important, what could be more important than the basis of life?

DISCOVERING 31P NMR SPECTROSCOPY FOR THE HEART

JI: There are lots of ways of studying ATP. But the only one that's any good is NMR! Before NMR spectroscopy, to get a handle on whether the amount of ATP changed in a tissue or organ you had to prepare and process your sample. Let's imagine an isolated heart hanging from some complicated plumbing that's perfusing it. You'd have to smash it as rapidly as possible with tongs chilled in liquid nitrogen, making wafers as thin as possible. Then you have to give it to a really good technician who has the good hands to grind it up without letting it get warm and then finally perform demanding biochemical assays. We had lots of biochemical assays, but we didn't have a good way to preserve the physiologic state of the sample we were interested in. And few pairs of hands can really prevent some loss of ATP. As I am fond of saying: NMR allows us to respect the integrity of the physiological state of the heart while simultaneously defining molecular events occurring within cells.

So – what's not to like when you discover phosphorus NMR spectroscopy could be used to look at the amount of ATP that was in the heart, how it was being made and used – and all in real time without destroying the tissue?

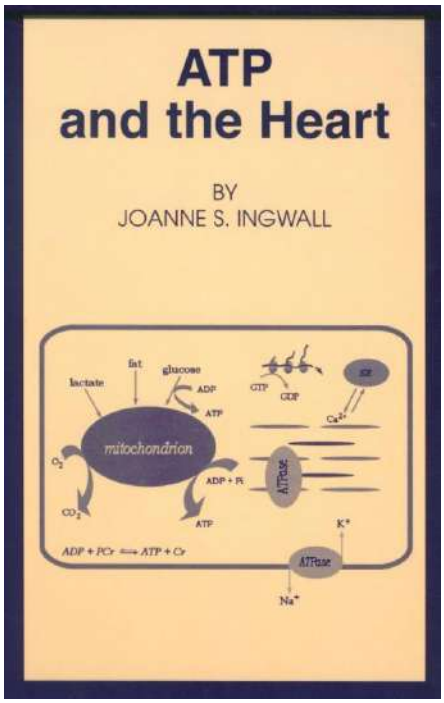
DKJ: I'm fascinated to learn how you and phosphorus spectroscopy became acquainted?

JI: I had just received an award from the American Heart Association and was recruited by the cardiology group at UCSD. I was a very junior faculty member collaborating with the late Marlene De Luca, who was the more senior biochemist. She was part of the Lehninger biochemistry group at Hopkins and her husband, Bill McElroy, became Chancellor at UCSD, so Marlene needed a place to work. Totally by chance, she and I ended up in the same cardiology group at UCSD.

Well, Marlene comes into the lab one day, and says, "*Look at this thing. David Hoult in England has literally just cut up a hunk of muscle and put it in an NMR tube, and you can see ATP and phosphocreatine*". Well, the muscle wasn't contracting and so it was a stable system. It was a brilliant experiment in concept, but trivial to execute. And so we said, "*We've got to do this for the heart*!".

So, we march over to the chemistry department and talk to the NMR spectroscopists that were used to only putting solutions in a narrow bore magnet. They didn't want to have anything to do with physiologic systems. They thought the heart was disgusting. They had a narrow bore system so the only hearts that would go in would be fetal mouse hearts weighing two to three milligrams. But even those were too big to have adequate oxygen diffusion – so it was a bust.

We quickly figured out that we had to understand how to perfuse the heart. People down the hall said, "*Oh, I can make that happen*". Well, by the time they ever got around to trying, my husband and I had moved to Boston, me to the Brigham. People there also said they could do that – they couldn't. So we went to Hershey, Pennsylvania, to visit Bob Neely and Howard Morgan who were venerable cardiac physiologists. They taught us how to perfuse hearts. We came back and started to perfuse rat hearts in the 270 MHz system at MIT. And that's how it all started. Then we got our own system, the first wide bore 360 MHz system in an academic environment, and we shared it with the world and also did our own work.



The cover of Ingwalls's magnum opus, ATP and the Heart. Illustration by Linda Johnson.

So it was fun to do something new, that nobody else had done. Unbeknownst to me, my colleague, Bill Jacobus at Hopkins was trying to do the same thing. And of course, he beat me to publication because I was always pretty bad at writing things.

COMPETITION

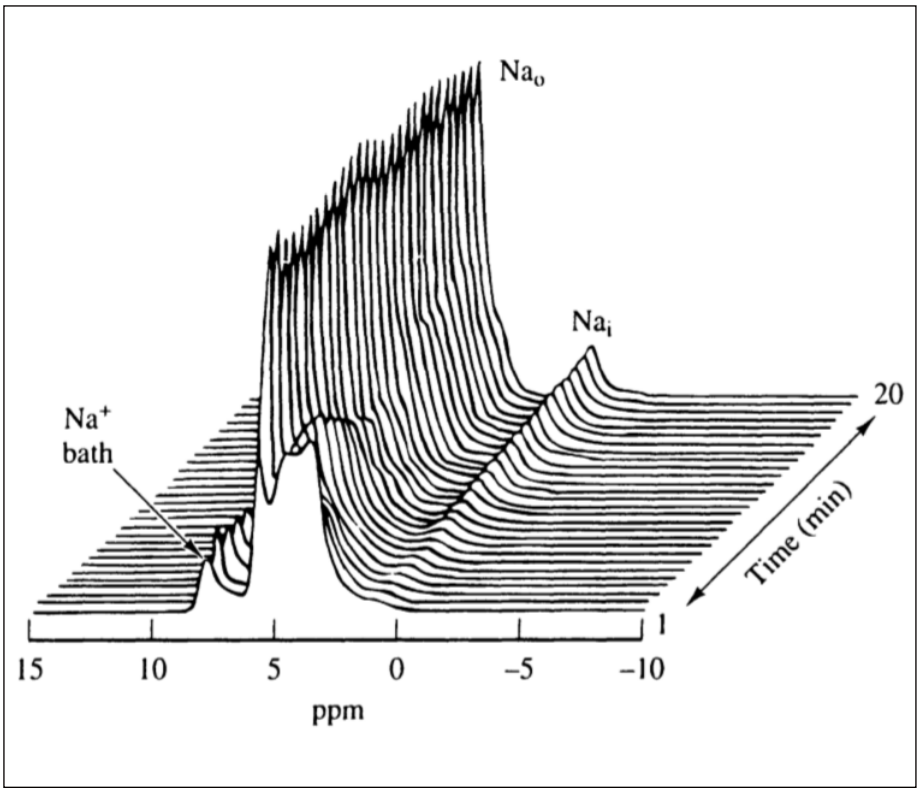
DKJ: That prompts me to ask about competition in the field at the time. Who were your competitors? And was it competitive or collegiate?

JI: Both! In the early days of NMR spectroscopy, there were two or three giants: the George Radda group, the Bob Schulman group, and Britton Chance with Jack Leigh's incredible brilliance with technology.

It wasn't competitive in the sense of who was racing to do the same experiment, because everybody had a different idea of what experiments were important, as we had very different backgrounds. Bill (Jacobus) and I were both trained as biophysical chemists, but we were interested in doing biophysical chemistry in intact tissue. It's a different mindset and a different approach.

DKJ: Was the competition a motivator for you?

JI: No, we were too busy trying to survive. So many people were coming to the lab from all over the world because it was new, including people from Germany, France, Belgium, Italy, and Japan. Senior people too. Charlie Springer, "Mr. Sodium NMR" did a sabbatical in my lab and sent us two of his students. In fact, when I left the lab, it was taken over by one of Charlie's former graduate students, Jim Balschi. Jim did his postdoc with us and was then recruited to a faculty position at Harvard. Jim has only recently retired himself. He is a very fine spectroscopist. No, I don't think the competition was a motivator. I think I was already



Sodium NMR spectra of isolated perfused rat heart.

maxed out supporting my own work, so it was a busy time.

OTHER SCIENTIFIC MILESTONES

DKJ: You referred to the study of ATP and cardiac energetics as your personal passion. But there were other important outputs of the lab that you wanted to talk about….

JI: Yes, from the "NMR Lab for Physiological Chemistry". The first important thing we did, at the Francis Bitter National Magnet Lab at MIT, was to figure out how to gate the NMR experiment to the heartbeat. That was important, because if you perfuse the rat heart, with a substrate that rapidly produces a lot of ATP from mitochondria, (i.e., you give the heart pyruvate), you don't see any fluctuation in ATP or PCR across the beat. But if you deprived the heart of a substrate that it liked, and gave it only glucose, and varied the amount of work the heart did, then you could see enormous changes across the cardiac cycle. This is because it was really a stressed-out heart – like being in the middle of a heart attack.[2] So, that was fun. A lot of people tried to repeat that experiment, some of them more successfully than others. It was repeated using freeze-clamping and standard biochemistry and the results agreed with us. So that was important.

When we first got the 360 MHz, we recruited Jean DeLayre to be the NMR person in the group. He immediately turned the spectrometer into an imaging system and obtained the first non-proton image of a biological sample – the heart!. That's his work. He did it all in a week, and it was published in *Science*.[3] That was pretty cool.

The other really important thing the lab did was working with Charlie Springer on sodium NMR of the heart. I mean, how cool is that? That you can use NMR to track the movement of an ion from outside space to the inside space in real time? *Oh, my God*! I mean, that's so cool!

So those were the watershed projects. The fun thing for me with those experiments was that nobody else had ever done them before us. That's the coolest part, you know? And that's the motivator.

DKJ: So those are the things that went well. But I guess you will also learn a lot from the things that don't go well. What were the biggest technical challenges that you had to overcome?

JI: The biggest was a simple one – and for a chemist this is really tough. We had to be sure that when we assigned a concentration, that it was in fact correct. We spent a lot of time building standard curves as you would do in any kind of chemistry experiment, that would allow us to assign a value to all the intensities of the peaks. That took a lot of time. It sounds straightforward, but it was not. We used a combination of standard curves in the NMR tube and mapping the homogeneity of the field across the NMR tube (because if it is not homogeneous we'd be messed up). We had a really nice magnet, so that was not a problem. And then I set up a whole wet lab to do all the biochemical measurements to support the NMR experiments, not only the amounts of the metabolites, but also had machines that would measure enzyme activities, isozyme distributions of the family of isozymes. So we had to do all of that. That's expensive and time consuming – but it's doable and we did it.

What didn't work? There were reports that you could use F-BAPTA and fluorine NMR to measure intracellular calcium concentrations in a heart. If only! BAPTA had to be given in such high concentration that it killed the heart. BAPTA is a chelating agent that reversibly binds calcium, so you're using a compound that changes the size of the pool that you are trying to measure. From the 'get go', it was ridiculous. Two parts were bad: One it killed the physiology; and two it was bad chemistry.

DKJ: Okay, it sounds like a winner!

JI: We spent a lot of time on that. We also spent a lot of time on bioengineered mice, which turn out to be not as uniform as you would hope. You have to study a lot of mouse hearts to get any kind of believable statistics.

DKJ: It sounds like most of the challenges were around the biochemistry and perturbing normal physiology, but not so much with the NMR?

JI: Well, when Jean DeLayre was in the lab, he was such a phenomenal spectroscopist, he

2 Fossel ET, Morgan HE, Ingwall JS. Measurement of changes in high-energy phosphates in the cardiac cycle using gated 31P nuclear magnetic resonance. Proc Natl Acad Sci U S A. 1980 Jun;77(6):3654-8.

3 DeLayre JL, Ingwall JS, Malloy C, Fossel ET. Gated sodium-23 nuclear magnetic resonance images of an isolated perfused working rat heart. Science. 1981 May 22;212(4497):935-6.

figured out how we could do magnetization transfer experiments. The method had been worked out by Forsén and Hoffman in Sweden in principle. In practice, when you try to apply that to a system as complicated as a heart you have to apply the saturating pulse over a relatively narrow ppm. Otherwise, you would totally mess up the experiment. We had ways of checking it because we would move the saturating pulse 300 ppm, to a region that had no signal. We built in as many checks as we could, but I'm sure the saturating pulses were not perfect. And as a physical chemist, if it's not perfect, it's not great. But it was the best we could do. Measuring the rate of reactions in an intact beating heart…in vivo biochemistry…is nothing but seductive. We had to do it.

ATP AND THE HEART

DKJ: You've highlighted the accomplishments of the lab. In addition to your papers, there's your *magnum opus,* the big book "ATP and the Heart", published by Springer in 2002.

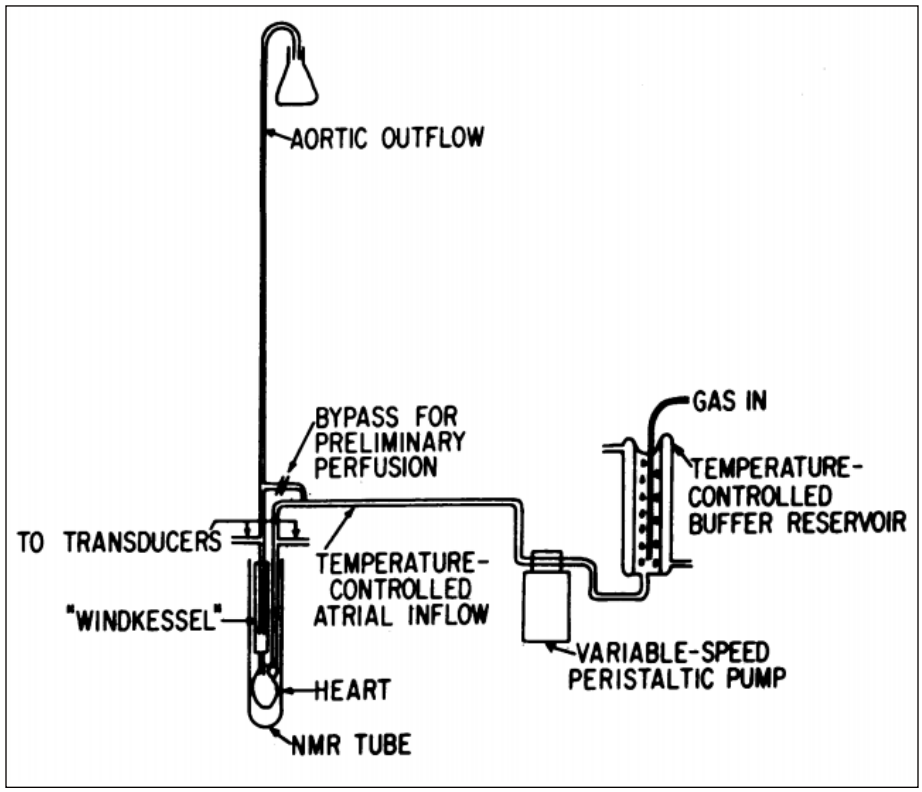
JI: My little book? That took me a year. A little bit of it was written by Jim Balschi, I have to say, and the diagrams were all done by my admin assistant, Linda Johnson, who took care of me for 30 years, and is still my friend.

THE ROUTE INTO SCIENCE

DKJ: I'd like to go back to the early years. What inspired you to follow a career in science? Did you always want to be a scientist growing up?

JI: Yes, the only debate was whether I'd go to medical school first or go to graduate school. I guess I always had an interest in physiology. The neighborhood boys would catch frogs in the pond for me to cut up, much to my mother's horror and my father's delight!

I was a chemistry major in my undergraduate school, in part because the scholarship for studying chemistry was greater than the one for studying biology. I like chemistry, it's the stuff of life, and biochemistry is truly the stuff of life. For graduate studies, I went to the Chemistry Department at Cornell University and obtained a degree in biophysical chemistry in Harold Scheraga's laboratory. Harold is an eminent structural protein chemist. But my project in the lab was not peptide structure, it was to study a blood clotting protein, a side interest of Harold's. I was in the cold room all the time isolating prothrombin from blood. When I got a good enough preparation, I put it in all the biophysical instruments that you could put it in. That was my thesis, and it was the first physical characterization of a blood clotting protein.



The setup for perfusion of isolated rat hearts in the NMR magnet, taken from the 1980 PNAS paper by Fossel, Morgan and Ingwall.

So I already was interested in proteins, but I didn't want to be in the cold room anymore. I then went to UCSF, and spent some time on myosin, which was very messy. At that point, nobody even knew how many subunits there were. I got interested in cells and how they make proteins. Then we moved to UCSD and I started collaborating with Kern Wildenthal who was, at the time, an investigator at Southwestern Medical School (he subsequently became its president). I learned how to culture fetal mouse hearts from him and use them as a model to study biochemistry and physiology of heart diseases and cardiac development. So my interests just evolved. Some people choose what they want to study very early on and never change. I moved around.

DKJ: Your recent focus over the last ten years has been on transgenic animals. One question that often gets asked is about translatability. In your opinion, are the animal models a good model of human physiology, or have there been some surprises when one attempts to translate a finding from a rodent heart to a human heart?

JI: Well, there must be some surprises, but in my experience, we learned things from the transgenic mice well before we could learn from humans. Maybe I was lucky in my choices. The example that I can give you is a collaboration with Kricket and John Seidman, who are well known in the field of familial hypertrophic cardiomyopathy. Kricket was the first in the world to discover that a single amino acid mutation in myosin was associated with a cardiac disease in humans.

Everybody thought that was going to explain heart failure. Well, that didn't happen. But they made a mouse to mimic the disease. We put the hearts in the magnet, studied the energetics and physiology and found that it displayed pure diastolic dysfunction. Systolic function was normal. It took years before they could show that in humans, but they reproduced our mouse experiments.

DKJ: That leads me to ask about clinical adoption of MRS. At the 2014 ISMRM

Joanne Ingwall and her husband Richard paying homage to Grant Wood's painting American Gothic, before heading to search for dinosaur fossils.

meeting in Milan, there was a plenary session with the title Bamboccioni, which is a name for a bachelor who hasn't left the home yet. The allusion was to powerful MR techniques that have yet to leave home, and the challenges to widespread clinical adoption. MR spectroscopy was included in the talk, as it seems to always be just around the corner from being widespread adopted.

My question to you is: "Are we there yet with widespread clinical adoption of spectroscopy?" And I think your facial expression says it all! If not, why not? And what will it take?

JI: You really should ask Carolyn Mountford in Australia. She was one of the women early in MR. So that's how we met and ultimately became friends. When she was at the Brigham and MGH, she spent all her time on molecular imaging. I probably don't know enough to answer your question, but I can tell you my gut feeling. They're not easy experiments to do in humans. They're really hard technically. How do you fix the localization issues? It may be that I don't know whether the localization issues have been solved, or whether they're being solved or whether anybody's even trying harder to make that happen.

It's probably not a money-maker. It may be wonderful in terms of understanding the biochemistry, but I bet the scans take so long that it's financially not a money maker yet, and maybe never will be.

DKJ: So are there other outstanding challenges in spectroscopy or phosphorus spectroscopy? I'm thinking about inspiring the next generation, telling them "If you could crack this, would it make a big difference"?

JI: Mitochondria have now been elevated in terms of popularity, all over the world. And I think in the next five to ten years, using spectroscopy as well as other tools, we will see some major new insights into how mitochondria work and are regulated.

DKJ: So maybe that will be the target for someone's Young Investigator Award in the future!

PROMOTING WOMEN IN SCIENCE

DKJ: I wanted to move away from the science for a moment and explore a couple of other topics. Looking at your CV and the accolades that you've received, one thing is very striking. You were the first female president of SMRM, there were just two women on the original MRM editorial board, and you're the only female recipient of the distinguished silver medal.

But I wondered if you had reflections on changing diversity and promotion of women in science. Was it important to you that you were a rare female scientist in such positions of leadership in the field at the time?

JI: No. I didn't have enough time to worry about that stuff. I had too much to do. There was a period of time, 15-20 years ago, where all the teaching hospitals at Harvard Medical School were creating offices for women's careers. So I'm thinking this is really dumb. They should have

offices for faculty careers – everybody's careers, men and women, PhDs and MDs.

When Herb Kressel moved to the Beth Israel Deaconess Hospital at Harvard, as head of radiology, we wanted to work together. We had already worked side by side, as president and vice-president of SMRM. Herb invited me to come to work with his faculty, all MDs, all radiologists, to see if I could increase the success rate of their grant writing and their rates of promotion. The bizarre experiment of matching a PhD with MDs worked!

I learned that the Beth Israel Deaconess was going to copy the MGH and the Brigham models and create an office for women's careers. I was asked to apply but I said that I would not take such a job unless it was for everyone. So they changed the focus, and I took the job. I think that's a better strategy. It's not just all boats rising, but it's a better strategy for the institution, for the culture of the hospital. Similarly, later on, when the Department of Medicine at the Brigham and Women's Hospital created an office for faculty careers for everyone, I led that.

MENTORING

DKJ: You have won a number of awards for your role in mentorship, including the *John MacArthur Research Service Award* from Brigham and Women's in 1999, and the *A. Clifford Barger Excellence in Mentoring Award* from Harvard in 2000. It seems that mentoring and promoting junior faculty is just as important to you as the science?

JI: Oh yes, absolutely! As soon as I became full professor, which took forever, (it's Harvard for heaven's sakes, I was 50), I was delighted to be able to do a number of faculty development jobs and ended up doing something at all the teaching hospitals, except Children's.

DKJ: So, perhaps this is an unfair question, but which was most important to you, your accomplishments in mentoring or your accomplishments in science?

JI: That's hard to answer, because in some ways, if you have helped, say 200 young people with their careers – those investments probably have a bigger payoff. On the other hand, I don't think I could imagine not doing science. I still do science. I do vertebrate curation for the local State Park; I am past president of the local botany society. My husband and I do several citizen science projects in Massachusetts in the summer: water quality, saving terrapins, tree phenology – but they're all "Mickey Mouse" compared to real science!

Joanne Ingwall with desert poppies.

CAREER ADVICE

DKJ: So to conclude, I'd like to go right back to where we started. You have just talked about helping 200 young faculty starting out, and I started the interview by asking you about your first time at the annual meeting. If you could speak to Joanne Ingwall, who was attending her first meeting in Montreal in May this year, with 40 or 50 years of research ahead of her, what advice would you give to her?

JI: One, don't be afraid to try new things. Two, don't be afraid to ask someone to collaborate. Three, create your own unique contribution. Maybe I am colored too much by what it took to get promoted at Harvard – but it's probably true in most institutions – you're not going to be promoted if you're just doing something well that other people are also doing. You have to create your own unique contribution. And four, get a mentor to help you navigate the political world.

And you can't hide under a bushel. You have to invest in your own career development. I hate to say it this way, but you have to sell your science. You cannot be just somebody that sits in a little lab and doesn't communicate. It isn't enough to write papers, you've got to go to meetings, you really do! It's a rare person who can really be a player in the field, who hates going to meetings.

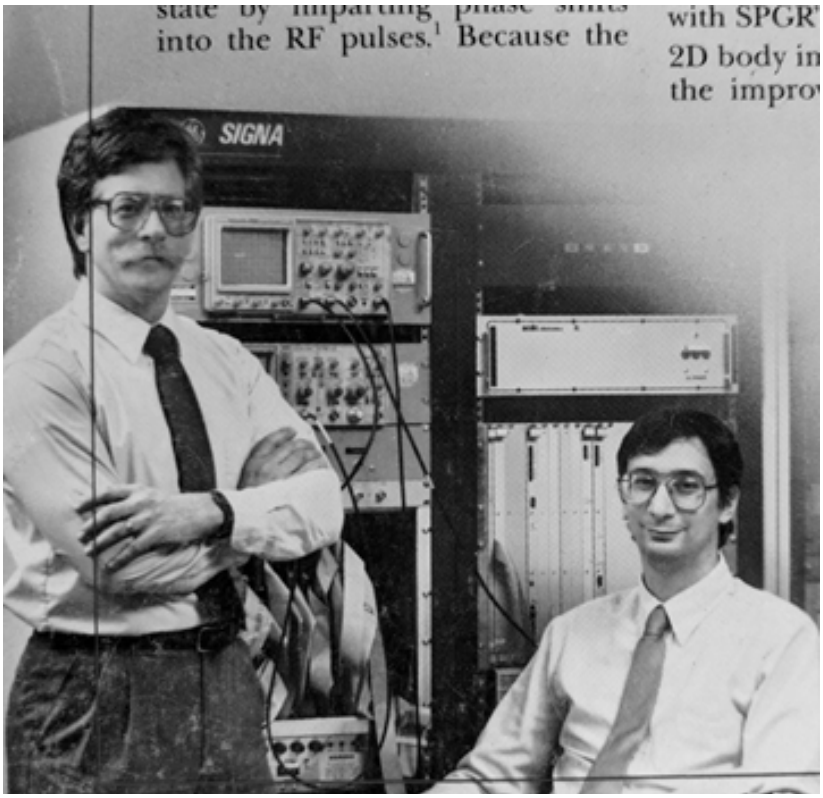
DKJ: Excellent advice! Well Professor Ingwall, it has been a real honour and privilege spending time talking with you today. On behalf of the entire *Highlights team,* I'd like to thank you for your scientific contributions, for your mentoring contributions and for your contributions to the Society. But most of all, thank you for taking the time to talk to *Highlights!*

JI: Well – thank you. It was a pleasure! ■

Building the MRI community one paper at a time

INTERVIEW BY **NIKOLA STIKOV** AND **ERIKA RAVEN**

Matt Bernstein has been shaping the field of MRI for over 30 years, first as a researcher at GE Medical Systems, and then as a clinical medical physicist at Mayo Clinic. During this time, he has authored over 130 research articles, 250 abstracts, as well as two books including the widely-read Handbook of MRI Pulse Sequences that can be found on the desks of most MRI engineers around the world. He has also been issued 35 U.S. patents. Matt spent the last eight years as editor-in-chief of Magnetic Resonance in Medicine, and in 2020 he will be handing over the reins to Peter Jezzard. This interview is an opportunity to recognize the many innovations Matt introduced to the field of MRI, one of which is the Highlights magazine that is now in its fourth year.



Matt with Larry Ploetz in Waukesha, Wisconsin, as featured in a 1990 GE ad highlighting the development of a radiofrequency spoiling technique on a novel digital transceiver.

MRMH: Looking back at the Highlights initiative, what do you think it brought to the journal?

MB: Well, I think it gave the journal an increased sense of community, by profiling the people behind the research and making the journal more accessible on a personal level. I think it's fair to say that Highlights is different from most journals' outreach efforts, and that has a lot to do with the youthful energy associated with it. It's especially fun going to the Highlights after-party that takes place on the last night of the ISMRM conference, because there we're really looking at the future of the society.

MRMH: Before we look to the future, can you give us a flashback of your career path?

MB: I've been doing MR for a while now. I started in 1985, so that's 34 years ago. Before that, in college I was a mathematical physics major at the State University of New York in Binghamton, and then I did a PhD in theoretical nuclear physics at the University of Wisconsin-Madison. When I graduated, I was debating whether to accept a postdoc offer in the same field, and I remember meeting an early-career researcher in theoretical nuclear physics who was excited by the prospect of studying one particular topic for his whole career. And I just said, that's not for me! My idea was more to get a PhD to learn a skill set, and then to be able to apply it to new things. When I was graduating in 1985, there was this new thing coming out, I don't think everyone even called it MRI at the time, and it turned out that the University of Wisconsin had the second commercial 1.5T MR scanner. So I ended up doing a postdoc at Madison in the department of radiology, and then I spent the next 11 years at GE Medical Systems. That was a tremendous education, because when you try to actually make a product and make it work reliably at thousands of sites, you learn it's a lot harder than it looks. The engineers and scientists at the companies really are the unsung heroes of our field. In 1998 I left GE and I've been at Mayo Clinic since then, working as a clinical medical physicist and researcher.

MRMH: How did the MRM editor-in-chief job come about?

MB: I was on the editorial board of MRM in 2010, so I knew that Mike Smith stepped down, but I wasn't seek-

ing the job. But then a previous editor, Felix Wehrli, approached me and asked if I would be interested. So I started thinking about it, and one thing led to another, and here I am.

MRMH: You are in your ninth year as editor-in-chief, and you will be stepping down at the end of 2019, after three terms. What is one thing you will miss, and one thing that you're glad is almost over?

MB: I'm really going to miss the community, the tremendous group of deputy editors, the office staff led by our managing editor Shannon Stepanian, the reviewers, the authors, the executive and production editors at the publisher, and the ISMRM office staff led by Roberta Kravitz. And the Highlights team, of course--sorry if I left anyone out!

Being the MRM editor is probably the best job in the whole MR universe, but it's certainly not the easiest. Papers are constantly coming in, and it's not the type of job where you can just go offline and disappear for a few weeks. So I look forward to disconnecting for a little while, maybe going on a cruise with my family or something. It'll be nice to unplug.

MRMH: Looking back on your tenure, what is your proudest accomplishment?

MB: That's probably not for me to judge, but in terms of objective metrics, my aim was to leave the journal in better shape than when I took it on, and I think the numbers show that.

MRMH: What metrics would you use to illustrate that?

MB: I think the growing number of submissions, as well as the reduced time from when a paper is submitted to when the first decision letter is sent out. And then there is the impact factor, which is the main metric that journals are judged by. Most editors, including me, hate the impact factor! It has such great importance placed on it -- it feels like your entire journal is being judged on a single number, and that's kind of ridiculous. Journals are very complicated, and they have a lot of moving parts. Having said all that, I'd rather hate the impact factor while it's going up, than hate it while it's going down. Luckily for us, the MRM impact factor has been going up.

There's also something called altmetrics, which captures social media and other non-conventional types of citations, and Highlights has really helped boost those. However, it will be up to the academic promotion committees to decide whether they will look beyond the impact factor in any serious way.

Matt addressing the Magnetic Resonance in Medicine editorial Board in Melbourne, Australia at the ISMRM Annual Meeting in 2012, with managing editor Shannon Stepanian.

On an ISMRM Outreach trip in Hangzhou, China in 2013. From left to right: John Detre, Jürgen Hennig, Alex Guimaraes, Derek Jones, Matt, Handbook of MRI Pulse Sequences co-author Xiaohong Joe Zhou, and Katarzyna Macura. Inset: the third Handbook co-author, Kevin F. King.

Top: Visiting the compact 3T magnet under development in 2015 in Niskayuna, New York: Tom Foo, Matt, and John Huston. Bottom: Matt's collaborative compact 3T research group at Mayo Clinic in 2018: Nolan Meyer, Jeff Gunter, Norbert Campeau, Ziying Yin, John Huston, Yunhong Shu, Matt, Erin Gray, Myung-Ho In, Uten Yarach, Daehun Kang, David Jones, Josh Trzasko, and Arvin Arani.

MRMH: What do you think is the most important skill for an editor-in-chief?

MB: Of course, it's helpful to have in-depth knowledge of the topics that your journal covers, but that's becoming increasingly difficult with a journal such as MRM. We cover pretty much everything that's covered by the ISMRM. The society currently has 28 study groups, and I don't think there's anyone who's really an expert in all those 28 fields. So I rely a lot on our deputy editors for their specialized expertise, but still issue the decisions myself for consistency

Over the last eight years I've also tried to immerse myself into the field of scholarly publishing, following blogs such as The Scholarly Kitchen, and getting involved in the program committee of the yearly Editor's Forum organized by editors-in-chief of RSNA journals, Herb Kressel and Jeffrey Klein. Editing is a strange thing, because you do it alone, but it's really a very social activity and it helps to be people-oriented. I've always tried to be an advocate for the authors, because as a researcher myself I know how difficult it is to get research done and to publish it, and how tough rejection is. So if I rejected your paper, I'm sorry!

In terms of strategy, I focused on continuous improvement when leading MRM. I think it comes down to having a vision – mine is an increased sense of community, then benchmarking other journals, recognizing best practices, and then filtering and adapting what would be good based on the strategic goals of the journal. And then implementing it, which takes a lot of energy and perseverance.

MRMH: Thinking about the future of the journal, where would you hope MRM goes next?

MB: With Peter Jezzard taking over, I'm sure the best days of MRM are ahead of us. But it's going to be up to Peter to set the course. Do you remember the movie Jurassic Park where Jeff Goldblum's character says that the dinosaurs had their shot? After I become a former editor on January 1, 2020, I'll be like those dinosaurs. I had my chance, so I won't be telling anybody what to do. But I'll be happy to offer advice, if ever asked.

Having said that, I do hope some trends will continue, such as reproducible research and encouraging authors to share their source code and their data. Another hot topic right now is access to articles, which I have concerns about. Currently MRM is a hybrid open access journal, which allows authors to choose, after it is accepted, whether they want to pay to make their article open access, or leave it behind a paywall. The latter option allows free publication for authors. I've always felt that it's important to keep a firewall between journal revenue and editorial decisions. We also combine that with a relatively liberal policy on pre-printing, which is a type of green open access. I think it's a good model.

There are recent proposals such as Plan S in Europe that mandate authors funded by some agencies publish only in gold open access (all articles in the journal being free to read). I really worry that some new investigators and researchers from emerging economies won't be able to afford the article processing charges if MRM went to gold open access.

MRMH: Open science advocates blame the hybrid model for double-dipping, because the journal charges libraries for subscriptions, but then it also charges authors that want to make their articles open-access.

MB: That's a legitimate concern, which I've discussed with our publisher Wiley. It turns out that if a library takes out a subscription to MRM, they get a rebate based on the number of open access papers we publish. I think that approach can address the double-dipping.

MRMH: You are successful as a researcher, and you've mentored many students and postdocs who are making big contributions to the field. What are you looking forward to now that you'll have some more time for research?

MB: The best part of all my jobs, not only as editor, but also the research and the clinical work, is mentoring young people. The fact that I get to work with young investigators, and pass along some knowledge, is fantastic. The research program I lead is doing really well, and our main focus is a compact 3T scanner that is able to scan heads, extremities and infants. It has a smaller bore size, but it also has very strong gradient performance and is easy to site.

The family at daughter Juliet's 2011 wedding in Seattle: Lee, Sara, Juliet, Rhoda and Matt. Inset: Matt and Rhoda recently celebrating their 35th anniversary in Las Vegas.

In the early 2000s, Siemens offered a commercial head-only 3T scanner, but it never really caught on. A little over 10 years ago, John Schenck at the GE Global Research Center (GRC) asked me if I thought a head-only scanner was a bad idea, or if it was a good idea and was just introduced ahead of its time. I went with the second interpretation, and 10 years later, we're still working on it under an NIH-funded collaboration with GRC. Now we're also working on a compact 7T, which is an NIH-funded collaboration between GRC, UCSF, and Mayo Clinic. The programs have been granted over $20 million in NIH funding, and the compact 3T results are really exciting to me. The compact 3T program has been a fantastic collaboration with my colleagues at Mayo like John Huston, and of course Tom Foo and his team at GE Global Research. For me personally, it has recaptured a feeling I had back in the mid-80s, when MRI was really something new and exciting. Back then, MRI was far from being a commodity business and the pace of innovation was exhilarating. Mayo's compact 7T effort is being led by a former student of mine, Yunhong Shu, who is now a clinical medical physicist colleague at Mayo.

MRMH: Another big contribution to the field is the Handbook of MRI Pulse Sequences, which is one of the most influential MRI books of all time. How did it come about?

MB: Well, that's all about my co-authors, Kevin King and Joe Zhou. We were all at GE Medical Systems back in the 90s working in the Applied Science Lab in Waukesha, Wisconsin. I organized an MRI course for the engineers that we all taught in, so we developed some material. After Joe and I left GE, Joe came up with the great idea for us to write a handbook. The book then took about a year of planning and about three years to write. It was very intense work, but it was also a lot of fun working with Kevin and Joe. One thing that I really like about the Handbook is, it's not a chapter book. Contributed chapter books have their place, but I don't think you can get the same level of consistency that you can with a co-authored book. I think part of the reason why our Handbook has been helpful is because it provides a consistent perspective across many topics.

MRMH: Any chance for a second edition?

MB: We came close a few years ago, but in the end we couldn't find the time. There's always a chance to revisit it in the future, maybe adding some new authors to the mix.

MRMH: Who is Matt outside the lab? Can you tell us about things that keep you busy and happy when you're not doing work?

MB: As I'm getting older, I'm enjoying traveling more, and I am fortunate to have a career that allows that. We all know ISMRM picks fantastic places for the annual meeting! I also like cooking and chess. I've been married to my wife Rhoda Lichy for 35 years and we have three wonderful kids, Juliet, Sara and Lee. Being an editor is all about decisions, and marrying Rhoda was my best one! Both our daughters are married now, so I have two fantastic sons-in-law, Xander Fiss and Chris Cline. Sara and Chris are parents to Oliver, so I'm a grandpa, and that's really the coolest thing.

MRMH: Excellence breeds excellence, as you told us after the first year of Highlights. Guess that applies to more than just work…

MB: Hmm, that's a segue. I don't know where I heard that old saying from, but I think it applies to many aspects of our professional lives. It can be more challenging to go for excellence, but it's more rewarding, whatever we end up achieving. And the Highlights team has achieved so much. My sincere thanks for that! ■

> *Editing is a strange thing, because you do it alone, but it's really a very social activity and it helps to be people-oriented.*
>
> – Matt Bernstein

Opening doors within ISMRM

INTERVIEW BY **ERIKA RAVEN** AND **ATEF BADJI**

Pia Maly Sundgren is this year's ISMRM president leading up to the annual meeting taking place in Montreal. Pia's research has always been patient oriented, with a focus on brain tumor imaging, autoimmune diseases, and pain conditions. Her background as an MD/PhD has shaped her views on research in the clinic, and the importance of the MD perspective within the broader community. After discussing the serious topics that occupy Pia professionally, we took a look at the lighter side of life in Sweden and all break for a "fika".

Pia and her son, Alexander, visiting Windsor Castle in the UK.

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

Pia: Okay, the first part is easy. I was very lucky because the hospital at Lund University where I work was one of the first places to get an MRI scanner in Sweden, and there I learned how to operate the MR scanner myself. Nowadays with all the different machines, it's not that easy anymore, but I still try to keep my MR driving license and my MR safety card.

I had always wanted to do neuroradiology and it became obvious that MR had a unique potential compared to all other techniques at the time. I got interested in more the clinical aspects of MR to study specific diseases and cases to see what MR could add to the diagnosis, and then started going to the ISMRM meetings.

How I became president, I have no clue! I have served ISMRM by being committee member, APMC member and chair of the Neuro Table, served on the Board of Trustee during my years in ISMRM and made a lot of friends and colleagues over the years. I think ISMRM members and colleagues could see me as a reliable, hardworking and happy person and not somebody that was constantly complaining, but actually trying to find solutions to problems. Still - it was a big surprise. Was I happy? Yes, very. Was I honored? Yes, deeply. I am very happy and deeply honored for being elected to the position of ISMRM President.

MRMH: It seems like having a track record of saying that you'll do something and then actually doing it goes a long way and leads to people wanting to work with you!

Pia: Yes, maybe that's why my PhD students like me.

MRMH: During a leadership panel at the Honolulu meeting in 2017, you said if someone opens the door for you - walk through it and do a good job. What is an example from your own walk? And did something inspire you to do this?

Pia: Well, I think I have had several opportunities. However, I remember especially one occasion when I was

quite young, still a resident at the department of Radiology in Malmöe, which is part of Lund University, Professor Torsten Almén gave me the opportunity at the time to go to the United States during my residency and I decided, okay, he opened the door, and I better do something good with this. I went and tried to do a good job so he would be proud when I came back.

MRMH: Last year, there was much discussion about expanding diversity and inclusion initiatives at the ISMRM. What has resulted from these efforts in the short term and for years to come?

Pia: It opened up discussions about how difficult it is for women, in general, to make a career and how they are treated. However, I believe that similar things are happening for the younger generation of men, so they need the same kind of support. We want to make both women and men feel welcome in the ISMRM community, regardless of their ethnic background, sexual preference, skin color or their education level. As we are such broad international society, we have excellent opportunities to meet others, chat, cross the barriers and the boundaries as much as possible. If I am just sitting chatting with my equals or colleagues, what is the point of going to ISMRM?

MRMH: What changes at the leadership level demonstrate the commitment of the society to inclusivity?

Pia: First of all, Elisabeth Morris has been given the task to evaluate decisions made at the leadership level to make sure we are inclusive and diverse in terms of number of participants in a committee. This means participation should be proportional to the numbers of the society in terms of gender and geographic composition. This goes for all committees. The AMPC and Board of Trustees already select members from both within and outside North America. We always have been, and I expect we will be even more diverse in the future. This is also true for the awards committee. We want the best person in the committees and the best awardee regardless of who she or he is, but at least the gender and the geographic balance among the nominees should be reasonably equal.

MRMH: That goes back to opening the doors that you were talking about.

Pia: I think everybody and especially more senior people have an important role to play to promote, support, and suggest new colleagues - basically opening the door. And if you get the chance - you have to walk through it. Certainly, if you do a good job, you will have a chance to continue. If you do not take the chance or do not perform that was up to you, but you have at least been given the chance.

Also, in the way the ISMRM program is put together, we try to minimize having speakers and moderators from the same place in the same session. Sometimes this is difficult, because maybe it's a topic that is very specific and geographically oriented, but we should at least try to

Summer chores reached new heights as Pia painted the family summerhouse in Näsviken, Sweden.

Pia and her husband Pavel toasting at the Amaranther Event in Malmöe, Sweden.

not have everybody coming from the same institution.

MRMH: Your research has been very patient oriented. From your experience what are some challenges with research in the clinical environment?

Pia: With the growing need for clinical studies and examinations, it is a challenge trying to create the time for research on the scanner. I'm lucky as it works very, very well in Lund - where actually you can run a couple of patients, then run a research study and then run patients again, and not just be told that, well, if you want to do research, you can do it after eight o'clock tonight or on Saturday and Sunday.

Getting ready to hit the slopes in Obertauren, Austria.

Pia and Pavel enjoying a sunny spot and cold beer while visiting their second home of Prague.

MRMH: You mentioned that one of your goals as ISMRM president is to increase the number of physician members of the ISMRM community. Why is this so important for you?

Pia: I'm worried about seeing the decreasing number of MDs or even MD/PhDs attending the meetings. I think the environment within the ISMRM where you have this possibility of networking, where you have the possibility to talk to people from different areas - coming together is extremely valuable. And I think the society will gain from having a substantial number of MDs. I mean, I don't want MDs to take over, that's not the point. But if we have a diminishing number, the clinical aspects of things can easily be lost.

For example - something can sound great, but is it clinically valid? Is it clinically valuable? Is it clinically practical? Or is it something that we really need or want? And those discussions you need to have among those who are actually doing the work. One of the things I used to bring up is how people talk so much about fast scanning. But when we boost the throughput, who's going to read the scans, with the lack of radiologists in many countries and the cut backs institutions are facing? The examinations will be waiting to be read for weeks on the other side. So what have we done for the patient then? Two weeks of worry until the study is read and reported to the clinician?

MRMH: Has there been a decrease in the number of MDs as full members?

Pia: There has been a slight decrease over the past couple of years. I really want to push for new MDs to join, not just see the established ones attending our meeting. The MDs have a unique possibility to collaborate with MR physicists, trainees, PhD students, and postdocs, and it is a beautiful opportunity for collaboration and networking.

MRMH: Du är svensk så undrar vi naturligtvis om du tycker att alla ISMRM-medlemmar ska fika mer? (You are Swedish, so we naturally wonder if you think that all ISMRM members should have more coffee?)

Pia: Ya! It's a tradition, very classic. At 9:30AM - try to call any department - everybody is on coffee break. Try to call somebody around three o'clock. Everybody's on coffee break! In my early days, before I started with research, we had a coffee break with the professor twice a day. I had coffee breaks with my senior colleagues. That's how I got to know them and they got to know me as a person. That kind of environment where you actually talk about different things is very beneficial.

MRMH: So should we go for a fika?

Pia: Yes! I think it's time for it. ■

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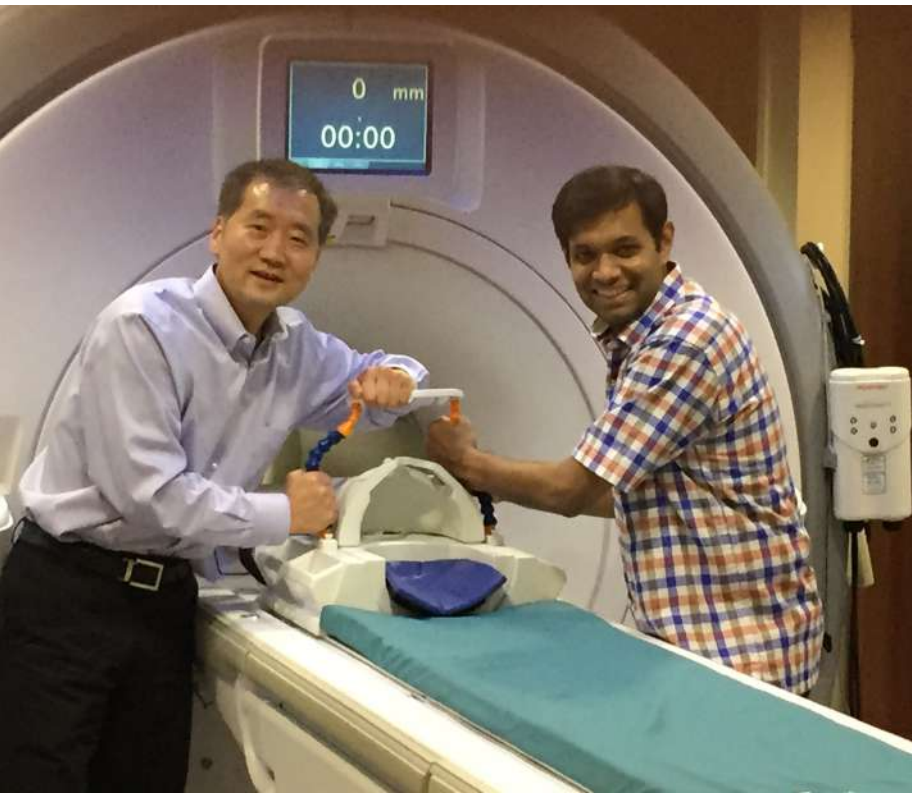
Traversing through k-space with Steer-PROP

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR MAY

This May we got the inside scoop on Steer-PROP from Dr. Girish Srinivasan and Dr. X. Joe Zhou. Steer-PROP is a GRASE-based PROPELLER sequence that traverses k-space in a new way to reduce the echo train length and the demands on the steering blips while maintaining the ability for robust motion correction. Girish provides some helpful audio slides with lots of great details on the evolution of FSE-PROPELLER to the original GRASE-PROPELLER, Turboprop, to to their newest version, Steer-PROP.



Joe and Girish steering k-space together.

MRMH: Thank you guys for joining us!

Joe: Thank you for having us! Reading somebody else's paper is fun but reading our own paper to learn more is even more fun!

MRMH: Can you tell us a little bit about who you guys are and what lead you to this work?

Girish: My undergraduate and masters were in computer science in India, and I had a strong interest in the medical field. I started this Ph.D. program while I was working full-time at Motorola and that's when I connected with Dr. Zhou, who had been working on fast spin-echo (FSE). Of course, Dr. Zhou is one of the earliest researchers on FSE optimization and artifact reduction. FSE-based PROPELLER offers a considerable advantage in motion correction and has been used in routine clinical practice but needs improvement in time efficiency. That's where I came in with my coding background. I started off understanding the sequence, designing and building the sequence, and then taking it to the scanner and evaluating it. Then we added the reconstruction and correction parts.

Joe: I started in MR physics in 1987, so more than three decades ago. The very first sequence that I was working on as a student was a projection reconstruction sequence. Today we call it radial sampling. Back then the spin-warp sequence was only a few years old, or young. Those two ways of traversing k-space really amazed me: one is radial and the other is a rectilinear or Cartesian. So, when Jim Pipe's PROPELLER was published in 1999, I was really intrigued that you could have a sequence that could combine the merits of both. Fortunately, I have Girish in my group and also some other people who are really interested in further improving this wonderful concept.

MRMH: How did Steer-PROP evolve out of GRASE and PROPELLER?

Girish: The initial implementation of PROPELLER was based on an FSE sequence. With each spin echo, you acquire a single line of k-space in Cartesian grid until you get an entire blade in one TR. That's when you apply the rotation and switch to the subsequent blade. That is basic PROPELLER. Then Dr. Pipe introduced a GRASE-based PROPELLER called Turboprop where each spin echo is divided into multiple gradient echoes. So, your blade becomes much wider.

Because PROPELLER inherently samples the center of

Srinivasan, G., Rangwala, N., Joe Zhou, X. Steer-PROP: a GRASE-PROPELLER sequence with interecho steering gradient pulses. *Magn Reson Med.* 2018;79: 2533–2541. DOI: 10.1002/mrm.26898
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26898/full

The UIC Steering team. From left to right: Yi Sui, Girish Srinivasan, Novena Rangwala, Fred Damen, Mike Flannery, Joe Zhou.

k-space over and over again, you can use this redundant information for motion correction. In the Turboprop implementation you have a larger overlap, so you can do an even better job correcting motion artifacts and the time taken to cover all of k-space is shorter compared to standard FSE-PROPELLER. However, the motion correction in the standard FSE-PROPELLER was already pretty good. So the question is "do you really need this additional redundant information or can we use that time towards a better sequence that maintains the merit of PROPELLER?". Steer-PROP was born out of that.

Joe: In Turboprop you have a mixture of gradient echo and spin echo within a blade. As you know, the phase error is a major problem in GRASE because you have to deal with two types of phase errors, one from the spin echoes and the other from the gradient echoes. In Steer-PROP we can separate out those two phase errors. Within the blade, we only deal with the spin-echo phase errors.

MRMH: How did you come up with the name?

Girish: When we were discussing it, we kept talking about the concept of how we would "steer" the blades towards a particular direction, and the name kind of fell out of that.

MRMH: And I see there was a lot of work involved in determining the gradient sizes to "steer" those blades.

Girish: I think that is probably the most time spent. Tons and tons of hours of brainstorming within the lab because the x and y gradients (or blips) used to the corresponding line in the next blade have to be very precise. Otherwise you start losing signal and get streaks and other artifacts.

Joe: Steer-PROP was not the first name that we came up with. We first named it GRASP for a GRASE-based PROPELLER sequence. But later we found out that GRASP was already used for a projection reconstruction sequence. We fully respect the other inventors' work and didn't want to create any confusion. We liked the name PROPELLER because it is not only a name but also associated with an action… you are traversing k-space just like a PROPELLER would. We wanted to follow the footsteps of Jim Pipe; "Steer" is really an action that reflects what we are doing in this sequence. So, when Girish came up with "Steer-PROP", we stuck with it and stopped calling it GRASP.

MRMH: I like that! It's just like the drink theme in the parallel imaging world with GRAPPA and Caipirinha…

Joe: Exactly, we wanted to follow the path of the other great scientists.

MRMH: Can you speed up Steer-PROP even more with in-plane parallel imaging or simultaneous multislice?

Girish: Both should be possible.

MRMH: But what about SAR limits with all of your 180s?

Joe: That's the beauty of GRASE-based sequences. The T_2 and T_2^* are what define the data acquisition window allowed. We can split between spin echoes and gradient echoes to best use that time. If you run into a SAR issue, then you can look into lengthening the gradient echo train while shortening the spin echo train.

MRMH: Girish, considering your interest in the medical field, where do you see this fitting into translation to the clinic?

Girish: Because the PROPELLER family sequences are robust against motion, one of the natural next steps is to take this outside of the brain. Diffusion has great potential in body imaging, and this could provide a way to address body motion.

Joe: To apply this technique to body imaging would really present a huge opportunity. And even for the central nervous system, it can be useful to address some unmet needs. For example, substantia nigra in the brainstem is of great interest in the study of Parkinson's disease. In single-shot EPI for DWI, the whole brainstem is kind of a blob and badly distorted. High resolution and distortion-robust Steer-PROP can make a contribution in that area.

MRMH: Well then, we look forward to seeing what you do with Steer-PROP next! ■

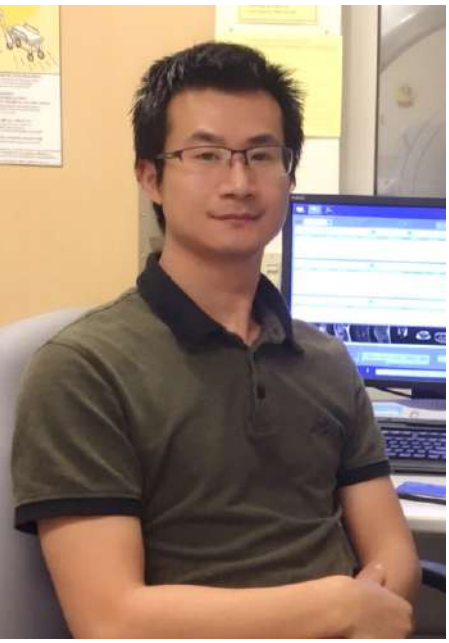
> *The phase error is a major problem in GRASE because you have to deal with two types of phase errors, one from the spin echoes and the other from the gradient echoes.*
>
> –Joe Zhou

Improving UTE contrast and specificity with double inversion recovery

INTERVIEW BY **TANGUY DUVAL**

EDITOR'S PICK FOR MAY

Being well aware of the challenges involved in achieving accurate and specific myelin imaging, I was delighted to have the opportunity to talk to Yajun Ma and Jiang Du about their recent paper on ultra-short echo time (UTE) imaging, a technique able to directly encode the signal from protons with ultra-short T2 values, such as those from myelin macromolecules, but also many others such as cortical bone and tendons. Jiang is no newcomer to our blog, having talked to Highlights last year about his work with UTE sequence development, and we are now keen to hear about the group's recent advances in this area.



Ya-Jun Ma

Jiang Du

MRMH: Could you start by telling us a bit about yourself and your team?

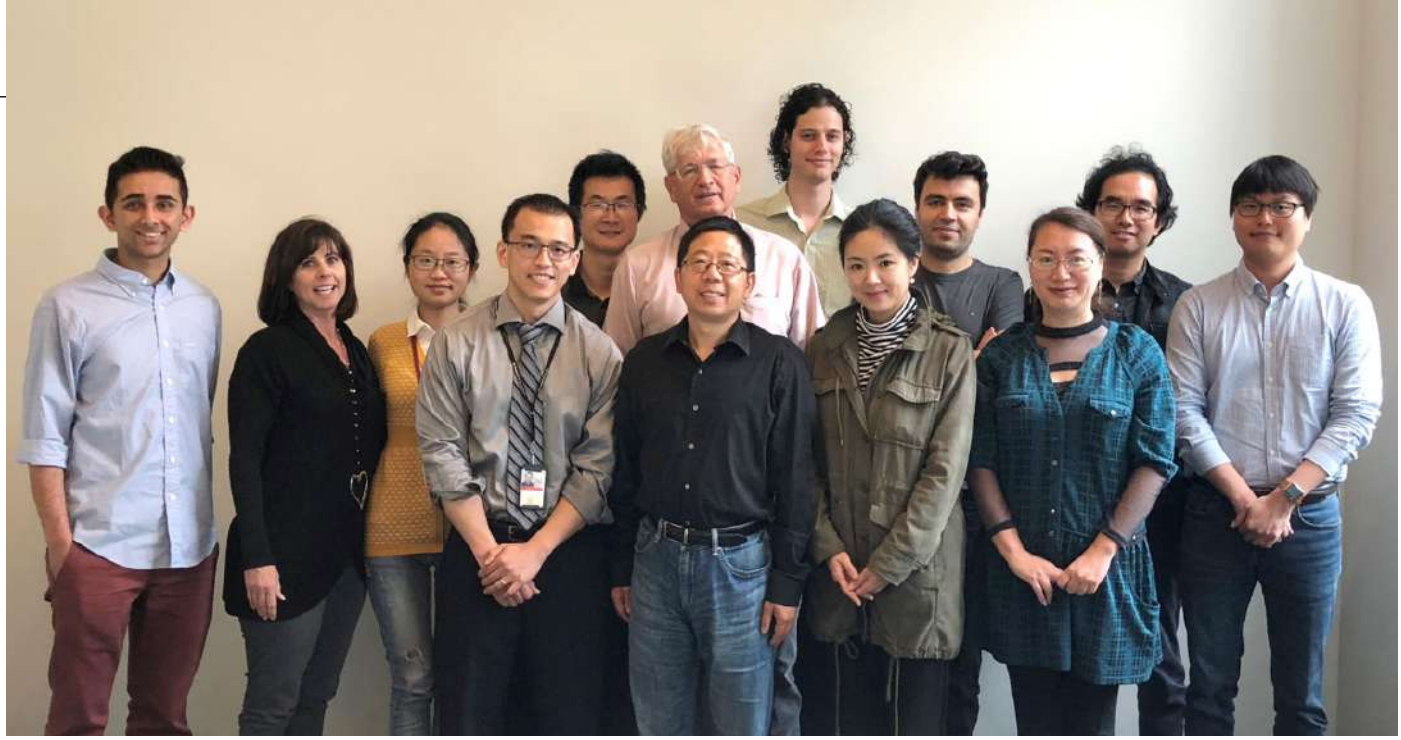
Yajun: After getting my PhD from Beijing University, I joined Dr Du's lab as a post-doc in October 2015. I'm now working on UTE biomarkers for bone and musculoskeletal tissues. Most of my research has been focused on quantitative UTE imaging of cortical bone using double adiabatic inversion recovery UTE (DIR-UTE), accurate T_1 measurement for total water and pore water using the UTE actual flip angle-variable TR (UTE-AFI-VTR) technique, collagen proton imaging using UTE magnetization transfer (UTE-MT), and bone mineral imaging using UTE quantitative susceptibility mapping (UTE-QSM). I have also been working on new techniques for morphological and quantitative imaging of myelin in the brain and spinal cord.

Jiang: I joined UCSD in 2005 as an assistant professor in Prof. Graeme Bydder's team to work on the UTE program. In collaboration with GE, UCSD has been developing UTE biomarkers for close to 15 years. We have six post-docs in the lab, as well as five visiting scholars, three technicians, and two research coordinators. The research we do covers sequence development, modeling of contrast mechanisms, and UTE imaging applications for various tissues and conditions. We study the correlation of various UTE biomarkers (T_1, T_2, $T_1\rho$, MT, and susceptibility mapping) with changes in cartilage, tendons, ligaments, and so on. We also aim to measure myelin directly, and are trying to work out whether the signal really does come from myelin protons. In addition, we study bone biomechanics and are trying, for instance, to correlate various UTE-measured water compartment volumes with bone porosity. As for clinical applications, we want to establish whether re-myelination can be detected using UTE acquisitions. We are currently running an in vivo longitudinal study involving 30 patients with multiple sclerosis. We are also testing re-myelinating drugs using UTE imaging. This work, in collaboration with Novartis, is conducted in rats and mice using 7T and 11.7T Bruker scanners. So, there's lots of stuff going on here!

MRMH: Could you tell us briefly about the history of UTE imaging?

Jiang: UTE imaging started with John Pauly's famous SMRM abstract in 1989. The main problems in those early days were the technique's sensitivity to eddy currents and its poor contrast, so the images weren't that great. As a result, clinical applications were practically non-exis-

Ma, Y., Zhu, Y., Lu, X., Carl, M., Chang, E.Y., Du, J. Short T2 imaging using a 3D double adiabatic inversion recovery prepared ultrashort echo time cones (3D DIR-UTE-Cones) sequence. *Magn Reson Med.* 2018;79: 2555–2563. DOI: 10.1002/mrm.26908
http://onlinelibrary.wiley.com/doi/10.1002/mrm.26908/full



UTE lab. From left to right: Akhil Kasibhatla, Lori Hamill, Lidi Wan, Eric Y Chang, Ya-Jun Ma, Nick Szeverenyi, Jiang Du, Adam Searleman, Wen Chen, Saeed Jerban, Mei Wu, Tan Guo, Hyungseok Jang

tent. Then, in 2003, Prof. Graeme Bydder and colleagues proposed many new contrast mechanisms, especially adiabatic inversion recovery UTE (IR-UTE) where the long T_2 components were suppressed leading to significantly better contrast. Later, Philips incorporated the 3D radial UTE technique into their scanners, while Siemens developed PETRA in their systems. We have been working with GE developing 3D Cones for fast morphological and especially quantitative UTE imaging. All the major MR vendors have developed zero echo time (ZTE) imaging, mainly for morphological purposes. Quantitative ZTE imaging remains to be developed.

MRMH: What do you measure with UTE imaging?

Jiang: By using T1 or MT contrast mechanisms, for instance, we can see short T_2 components much better, and this allows us to derive specific UTE biomarkers. For example, we can quantify all the components of bone: water, collagen protons (using UTE-MT modeling) and minerals (using susceptibility mapping). This is a significant advance over the current standard approaches such as DXA or CT which can only assess the mineral component.

MRMH: On to the paper at hand. Could you tell us about the 3D DIR-UTE-Cones sequence?

Yajun: A typical adiabatic full passage (AFP) pulse is several milliseconds in duration and can only invert the longitudinal magnetization of long T_2 tissues (such as fat and muscle), but not those of short T_2 tissues or tissue components (such as bound water in cortical bone or myelin protons in white matter of the brain). The short T_2 components, although saturated, quickly recover because of their short T_1 values, and a strong contrast can be obtained when data are acquired around the signal nulling point of the long T_2 tissues. The double adiabatic inversion recovery (DIR) preparation allows us to suppress signals from long T_2 components with a large range of T1 values. For example, we can get excellent suppression of signals from both fat (T_1 ~ 350 ms) and muscle (T_1 ~ 1400 ms). The acquisition of multiple spokes per DIR preparation is also employed to significantly improve the sequence time efficiency. Our signal model can be used to get the best inversion times, to minimize the long T_2 signals, and to quantify the short T_2 tissues or tissue components, such as bound water in cortical bone.

Jiang: 3D radial encoding is very time consuming. Cones encoding is much faster. The downside, however, is more blurring, which can affect quantification accuracy. We still seem to be able to do fairly accurate measurements in meniscus, ligaments or tendons, where T_2 components aren't that short. Bone tissue, however, has a shorter T_2 which makes it more challenging; but even with bone, the error in quantification is in the order of ~3% when compared with radial UTE imaging.

MRMH: What challenges do you face in UTE image acquisition?

Yajun: With such short echo times, the eddy currents are particularly strong. This problem is overcome by using short rectangular pulses for excitation, as can be done in 3D imaging. Another challenge is the management of the ADC delay and the gradient trajectories, which are particularly off for regions far from the isocenter. We have to take these problems into account.

Jiang: It's true, partial volume, eddy currents, and scan times were all major problems with 2D-UTE, but 3D UTE imaging has overcome them to an extent. Keeping scan times manageable continues to be a particular challenge especially in 3D IR-UTE imaging: because of the long inversion times, we have to acquire multiple spokes per preparation, and this is particularly complex. Using cones encoding to improve acquisition efficiency provides a partial solution. But we have to propose even more advanced encoding and reconstruction schemes to solve these issues. ■

> *The double adiabatic inversion recovery (DIR) preparation allows us to suppress signals from long T_2 components with a large range of T_1 values.*
>
> – Ya-Jun Ma

Machine learning and the need for MR images acceptable to the human eye

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR JUNE

This first June 2018 Editor's Pick features Kerstin Hammernik and Florian Knoll, researchers at Graz University of Technology in Austria and New York University School of Medicine (NYU), respectively. Their paper presents a novel approach to MR image reconstruction in which a generalized compressed sensing framework, formulated as a variational model, is combined with deep learning. Tested on a musculoskeletal disease patient population, their reconstructions preserved the natural appearance of MR images and worked well with pathologies that were not included in the training dataset. We met them to find out more about this project and the people behind it.

Kerstin Hammernik with co-authors Erich Kobler and Teresa Klatzer (from left to right)

Daniel Sodickson, Kerstin Hammernik, Florian Knoll, and Michael Recht (from left to right) at the 2018 ISMRM-ESMRMB annual meeting in Paris

MRMH: First of all, could you fill us in on your backgrounds?

Kerstin: I did my Bachelor's and Master's degrees in Biomedical Engineering. For my Master's, I focused on image processing, specifically 3D registration and segmentation of dental data and vertebrae using CT images. I'm currently doing a PhD in Computer Science which is supervised by Prof. Thomas Pock. It wasn't until after I started my PhD that I began working with Florian, in the field of medical image reconstruction.

Florian: I actually come from Graz, where Kerstin is currently doing her PhD and I did my Master's and PhD there as well. I became interested in machine learning, the focus of my Master's, some time ago, before it became the hot topic it is today. I then did my PhD in MR imaging. After that, about five years ago, I moved to NYU, where I'm mainly responsible for the development of new methods in data acquisition and reconstruction, and their translation into clinical practice.

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

Kerstin: The main idea was to come up with a generalized compressed sensing framework, formulated as a variational model. Our reconstruction model has a data term, which allows us to fit the collected k-space data and transform the image with an operator into

Hammernik, K., Klatzer, T., Kobler, E., Recht, M.P., Sodickson, D.K., Pock, T., Knoll, F. Learning a variational network for reconstruction of accelerated MRI data. *Magn Reson Med.* 2018;79: 3055–3071. DOI: 10.1002/mrm.26977
https://onlinelibrary.wiley.com/doi/full/10.1002/mrm.26977

Vision, Learning and Optimization group of Thomas Pock in front of the clock tower, the famous landmark of Graz.

k-space, and also a regularization term, which imposes prior knowledge on the image. We then combined the variational models with deep learning to learn the parameters of the regularization term and data term in an unrolled gradient scheme, and applied this combination to reconstruct accelerated MRI data. We did experiments on clinical knee data, and looked at how the network performed for different contrasts, orientations and SNRs. We also performed a reader study to evaluate the difference between the compressed sensing methods we tested and our deep learning approach.

Florian: It perhaps helps to understand what first prompted us to do this work. When talking with clinical radiologists, we always encountered resistance when presenting them with images using our compressed sensing reconstructions: they would complain that the images looked a little unnatural and say they weren't confident making a diagnosis based on them. We discovered, over the course of this research, that handcrafted models (like total variation) overly simplify the image content, resulting in this unnatural cartoonish appearance. Our approach allows us to use much more complex image models that can describe the character of our images better. When the method we presented in this work is used as a regularizer, it results in images that are more acceptable to the human eye.

MRMH: Were you surprised by any of the results of this study?

Kerstin: When things work, you're always surprised! [laughs]

MRMH: Where would you like to see this work going from here?

Kerstin: It would be very interesting to establish whether this really is a feasible method for clinical exams – whether it could be applied to a clinical workflow.

Florian: Clinical validation is obviously really important. There are a lot of unanswered questions, and people are always skeptical when they hear the words machine learning. We need to show, in a reasonably sized patient population, that we can produce images that have complete diagnostic value.

MRMH: Are there any other particularly exciting aspects you'd like to highlight?

Kerstin: This method is a tool of exploration and discovery that may be applied to what we already know from compressed sensing. We have shown with our filter kernels and learned functions that we actually get filters and functions that have already been studied and reported in the literature. The next step is to look at whether the number of parameters can be reduced by imposing some structure on the models, and if so how this can be done. This is an important research direction for me.

Florian: At the moment, we are still considering image reconstruction as a step that is isolated from the data acquisition and the diagnostic pipeline. But later on, once we have established that images can be reconstructed in this way, we can look at whether it is possible to go back and change the way we acquire the data, and whether this can help to improve the diagnostic interpretation of the images and the post-processing as well. Furthermore, with the substantial improvements that are constantly being made in computing power and data science, could some of the traditional constraints on our imaging hardware be relaxed by incorporating novel calibration and correction procedures in the reconstruction procedure? All these are certainly exciting questions and ambitious objectives.

MRMH: What do you enjoy doing when you're off duty?

Kerstin: It's important for me to really switch off and relax in my spare time. I love dancing – styles like salsa, bachata, kizomba and zouk. I also love to be outdoors in the mountains and do ski touring, hiking or mountain biking.

Florian: I mainly do sports stuff too – marathons, and martial arts.

MRMH: Have you run in any of the major marathons?

Florian: Of the big city marathons, I ran New York and Chicago. For my next challenge I am considering doing a trail race. That would make an interesting change! ■

> *This method is a tool of exploration and discovery that may be applied to what we already know from compressed sensing.*
>
> –Kerstin Hammernik

Extracting vascular maps with the intracranial artery feature extraction tool (iCafe)

INTERVIEW BY **GIULIA GINAMI**

EDITOR'S PICK FOR JUNE

The second Editor's Pick for June 2018 is a paper entitled "Development of a quantitative intracranial vascular features extraction tool on 3D MRA using semiautomated open-curve active contour vessel tracing" by Li Chen and Chun Yuan of the University of Washington in Seattle. We caught up with Li and Chun during the ISMRM conference in Paris, where we took a break from the meeting's incredibly packed and stimulating program to talk about their work.

Li Chen and Chun Yuan at Washington Park in Washington, USA.

MRMH: To begin with, could you tell us how you came to work in MRI and in Seattle?

Li: My introduction to this field was an MRI course in Shanghai, which quickly taught me that MRI is not only about equations, but can provide quantitative information that can significantly impact people's lives. The instructor on that course went on to become my mentor, and under her guidance I began focusing on vascular image processing. I then reached out to Chun — the possibility of working with him sounded like a great match! — and indeed my transition from undergraduate to graduate studies went very smoothly. And so, here I am!

Chun: Well, I started working in MRI in 1984, way before Li was even born! My mentor was Prof. Dennis Parker, who was working in the field of vascular imaging. My PhD thesis focused on MR flow. I ended up in Seattle as I wanted to live on the West Coast. California was not an option, and I like to be close to the mountains. The University of Washington has an excellent cardiovascular biology program and is also strong in imaging, and I am therefore very happy to work here.

MRMH: Could you give us a brief summary of your paper?

Li: Our paper describes an intracranial artery feature extraction tool. The intracranial arterial system has a very tortuous geometry with significant individual variations. We set out with the idea of generating, starting from an MRA image, a reconstruction of the arterial tree, in order to then extract morphometry and intensity information for quantifying any physiological or pathophysiological changes that occur.

Chun: The crucial thing to understand here is that information about the vasculature, in terms of its distribution, tortuosity and length, can tell us about the state of the blood flow in the brain at any given time. Indeed, our target isn't just stenosis; our aim is to put together a complete description of the cerebral vasculature, in the hope that we can then see how it changes over time.

MRMH: How does your approach differ from other feature extraction tools?

Li: We believe the features extracted from our tool are comprehensive and accurate. The tool is comprehensive in the sense that it allows us to extract all arteries, even the distal ones with radii of less than one pixel. Furthermore, in addition to tracing the vessels, we can also divide and label them into 24 types, which is more than most previous tools can do. With this comprehensive labelling process, we can extract not only global but also

Chen,L., Mossa.Basha,M., Balu,N., Canton,G., Sun,J., Pimentel,K., Hatsukami,T.S., Hwang,J.N., Yuan,C. Development of a quantitative intracranial vascular features extraction tool on 3D MRA using semiautomated open-curve active contour vessel tracing. *Magn Reson Med.* 2018;79: 3229-3239. DOI: 10.1002/mrm.26961
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.26961

regional vascular features of interest. The accuracy of the tool derives from the fact that the arteries, once automatically traced, can easily be edited by humans, thereby ensuring the quality of the artery reconstruction results.

Chun: I don't think it would be fair to say that our method is only about accuracy, as we are certainly working on different aspects. As I already said, we don't typically focus on stenosis. I would say we aim to obtain an accurate description of the vascular map, and particularly of sub-regional bases. And it's also important to keep things simple. After all, if tools take days to process, this may hinder the broader clinical implementation of these techniques.

MRMH: What can you tell us about the manual editing part of your algorithm? Do you think it could be extended and made fully automated in the future?

Li: At the present stage, human interaction remains crucial in order to obtain an accurate map. It is very hard to design a fully automated yet accurate feature extraction tool. We feel that, for now, the manual editing part actually confers added value on our tool. In the future, however, combining our approach with the machine learning technique may help to reduce the importance of the manual editing part.

Chun: In this era of artificial intelligence, I believe that deep learning algorithms may significantly improve the performances of this feature extraction tool. 3D time-of-flight images are routinely acquired in many centers. The information that we are trying to extract is not yet used clinically, but it is hugely important from a research perspective.

MRMH: There are many applications that would benefit from the vascular feature extraction approach you are proposing. Do you think it could be applied in other human organs, too?

Li: The approach exploits contrast between foreground and background, therefore it could potentially be extended to many applications. We are currently applying it to peripheral arteries. Cardiac or abdominal vasculature are other possible options. I have been asked several times whether it might be applied to retinal images or vessels of mice, which are really fascinating possibilities. But with different applications, the distribution of the vessels and the intensity of the background may change, of course, and therefore optimization steps may be needed.

Chun: Yes, that sums it up perfectly. The key point is the contrast in the particular region. With current approaches, the lumen has to be brighter than the background. However, applying the technique to images with black-blood contrast is a possibility.

MRMH: So, what's next?

Li: We would like to extend the approach to other body parts and other imaging modalities. For now, the tool is built in C++ for Windows, and we are thinking of extending it to other platforms so that it might be adopted more widely. Using cloud computing as well as crowdsourcing may also help in this sense. Another direction is applying iCafe on clinical studies. At the ISMRM meeting in Paris I presented an abstract describing how we used this tool to analyze 163 elderly subjects and found decreased number of branches and increased tortuosity through aging. This is a direction that also looks very promising.

Chun: Li has correctly outlined the future technical developments. Our idea is to keep on generating a quantitative set of parameters that can describe the vasculature at a given time. The resulting data can then be used to shed light on the blood flow conditions, how they interact in brain function, as well as in other tissues, and how they evolve in different diseases and aging processes. Meanwhile, we are planning to build a network of iCafe users with diverse backgrounds and expertise for different research and clinical applications. The feedback from those users will be valuable for iCafe development in the future. ■

Left to right: Zechen Zhou, Chun Yuan, Huijun Chen, Li Chen at Pacific Grove, California, USA.

Li Chen and Chun Yuan hitting the slopes in Whistler, British Columbia, Canada.

Improving MR oximetry to study sickle cell disease

INTERVIEW BY **MARIA EUGENIA CALIGURI**

EDITOR'S PICK FOR JULY

Adam Bush received his Bachelor's Degree in Physics from Loyola Marymount University, and his Master's Degree and PhD, both in Biomedical Engineering, from the University of Southern California, where he worked under the supervision of Prof. John Wood. He is currently a post-doctoral research fellow in Radiology at Stanford University. John Wood trained in Electrical Engineering at UC Davis, received his MD/PhD in Bioengineering from the University of Michigan in 1994, and did a residency and fellowship in Pediatric Cardiology at Yale. When he joined the Children's Hospital in Los Angeles, as Professor of Pediatrics and Radiology, he was given the "keys to the car" to build a pioneering cardiac imaging program. He first crossed paths with Adam in 2009. In the time since then, they have developed a fantastic mentor-mentee relationship, which was evident throughout this conversation. Most recently the two have focused on improving the applicability of T_2 relaxation under spin tagging (TRUST) MRI oximetry FOR patients with sickle cell disease (SCD).

> *While global oxygen delivery in the sickle cell disease brain is fine, at a local level it is impaired.*
>
> –John Wood

Adam Bush in front of the United States Capitol in Washington, DC.

Adam and John following a successful thesis defense.

MRMH: Can you briefly explain what TRUST is?

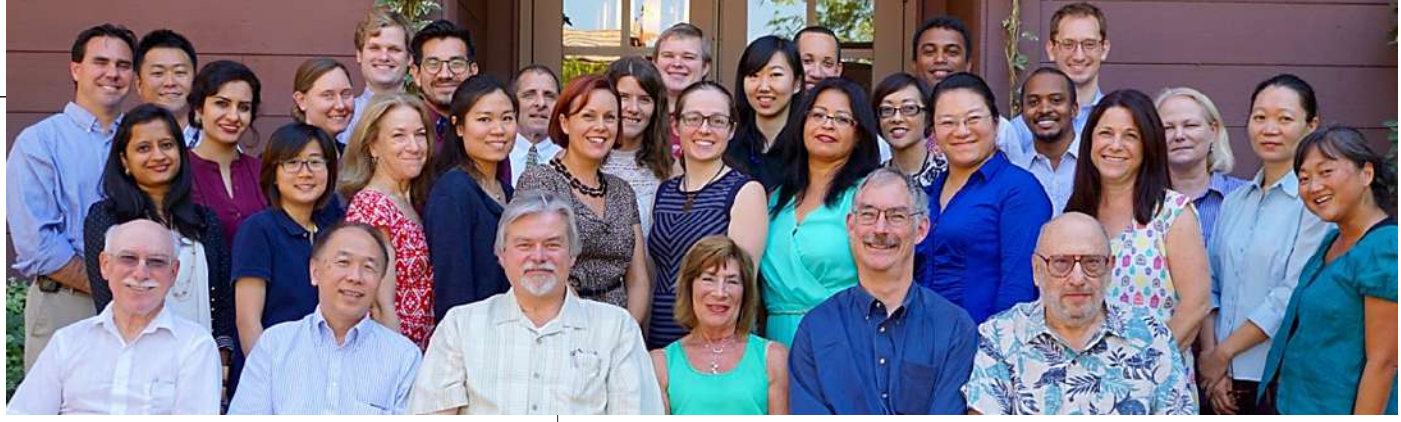
Adam: It is a technique used to measure the T_2 of intravascular blood in large brain vessels. The measurements obtained are converted into oxygenation values using empirical, predetermined calibration curves that relate T_2 values to hematocrit and oxygen saturation.

John: TRUST is an extremely robust, widely validated technique. Its major technological innovation is the use of arterial spin labeling (ASL) tagging to remove partial volume effects in T_2 measurements. We are grateful to Dr Hanzhang Lu, currently at Johns Hopkins University, for sharing his code with the MRI community, as this has opened the way for scientists worldwide to gain experience and insights across different blood diseases.

MRMH: What is SCD, and how might your results impact its clinical management?

Adam: SCD is a common genetic disease in the USA, affecting approximately 100,000 people, particularly of African descent. Having one mutated copy of the SCD gene – a condition called sickle cell trait – provides protection against malaria. However, mutation of both alleles leads to the production of sickle hemoglobin (HbS), which polymerizes into long rigid fibers. This, in turn, can give rise to several complications, the worst being overt stroke, which occurs in about 11% of affected children. We hope that greater understanding of ox-

Bush, A.M., Coates, T.D., Wood, J.C. Diminished cerebral oxygen extraction and metabolic rate in sickle cell disease using T2 relaxation under spin tagging MRI. *Magn Reson Med.* 2018;80: 294-303. DOI:10.1002/mrm.27015
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27015



Members of the Excellence in Hemoglobinopathies Research Team at Children's Hospital Los Angeles.

ygen supply and demand in the SCD brain will help us to identify better biomarkers for increased stroke risk and thus to improve patient outcomes.

John: Blood transfusions and screening have recently lowered the rate of overt stroke in SCD. But there also exists something called silent stroke, which results in small white matter lesions throughout the brain. The prevalence of this form reaches 50% by the age of 30, significantly altering brain tissue integrity. Complications like these made me appreciate the urgency of reaching a better understanding of oxygen supply and demand in SCD, so as to achieve better-tailored, protective therapies.

MRMH: You have evaluated the applicability of TRUST in SCD. What are the limitations of current models when it comes to performing oximetry in sickle blood?

Adam: Let me say, first of all, that our work was made possible only thanks to the excellent previous efforts of scientists like Graham Wright, Bob Hu and Al Macovski. When dealing with SCD, a major limitation of any T_2-based oximetry approach is that the empirical models are derived using bovine blood, which has different T_2 properties compared with human blood. Additionally, the hematocrit range over which calibration curves were defined was limited to healthy values (35-55%), making these curves less applicable to patients with SCD, who are anemic (characterized by a lower hematocrit).

John: We were also concerned about the huge differences between healthy and SCD blood cells in terms of their structure and tendency to aggregate. For this reason, sickle blood has a different magnetic microstructure that could affect the relationship between T_2 and oxygen saturation and hematocrit; we therefore felt it was essential to properly validate calibration in SCD.

MRMH: Were you surprised by your findings?

Adam: Since our initial objective was to reproduce recent literature, in which models using healthy human hemoglobin were compared with models based on bovine blood, we weren't really expecting the surprising results that we got.

John: Previous literature had suggested that oxygen extraction is increased in SCD patients. Paradoxically, we found just the opposite. We know these brains undergo stress, and we know they suffer strokes, so it made sense to take increased oxygen extraction as a marker of brain stress. However, what we found was quite the opposite, and at first I thought Adam was crazy! Moreover, my fundamental premise, that cerebral metabolic rate is conserved in SCD, turned out to be wrong as well! Fortunately we found literature supporting the idea that blood flows too quickly through the SCD brain, precluding adequate exchange of oxygen with tissues. This convinced us that we were not crazy after all, simply observing a mismatch between oxygen supply and demand. In short, while global oxygen delivery in the SCD brain is fine, at a local level it is impaired.

MRMH: Why did you choose phase contrast, as opposed to ASL, to measure cerebral metabolic rate of oxygen?

Adam: First of all, phase contrast MRI is used clinically, and this made integrating it into a research protocol quite straightforward.

John: Also, since phase contrast is completely independent of T_1 and T_2, we didn't expect the technique to produce any disease-specific effects on our measurements. ASL might be less efficient in SCD. The basic problem with phase contrast is making sure you achieve enough resolution to resolve partial volume effects; this is easier in SCD because the vessels are slightly bigger.

MRMH: What were the main challenges you faced?

Adam: When performing experiments involving blood in an MRI scanner, you obviously also have to deal with the related biohazard issues. This can make the process very time consuming, but it was definitely worth the while!

John: I don't think Adam's sleep patterns have recovered yet! [laughs]. He spent hours in the early mornings making sure that the magnet was perfectly sterilized for the next day. Another challenge was related to the need to limit red blood cell rupture, or hemolysis: this narrowed the hematocrit we were able to study, since these cells couldn't tolerate much manipulation. This is a fundamental limitation that could be addressed in future, larger studies.

MRMH: Are there any other shortcomings that you plan to address?

Adam: Recent work has shown that regional oxygen extraction is variable across the brain in SCD, whereas we performed measurements only in the sagittal sinus. In the future, we could address this aspect using multidimensional T_2 MRI oximetry.

John: We are also looking at responses to therapies in SCD, including blood transfusion and hydroxyurea, and their impact on cerebral metabolic rate and oxygen extraction. There is, as yet, no perfect agreement between TRUST and other magnetic-susceptibility-based oximetry techniques, either in SCD or in control subjects, and we would like to try and overcome this through the use of an independent standard. ■

> *First of all, phase contrast MRI is used clinically, and this made integrating it into a research protocol quite straightforward.*
>
> –Adam Bush

Characterizing ultrashort-T_2 components in the brain

INTERVIEW BY **HOLDEN WU**

EDITOR'S PICK FOR AUGUST

For this month's Highlights interview, we were pleased to talk with Tanguy Boucneau and Peder Larson to learn more about their recent paper, *"In vivo characterization of brain ultrashort-T2 components.*

> *There were trade-offs between 3D image quality, shortening the sequence scan time, and not burning the subject.*
>
> –Tanguy Boucneau

MRMH: First of all, could you tell us a little about yourselves and how you came to be doing MRI research at UCSF?

Tanguy: I am a French PhD student about to start my third year. Three years ago I was given the fantastic opportunity of working with Peder at UCSF for a year. I am now back in France where I am still working in MRI, in the area of lung imaging.

Peder: I got into MRI research because my undergraduate advisor at Stanford was Dwight Nishimura. I liked the guy, and also what he was doing. It was very clear to me, even then, that MRI was one of the most interesting things going on. One of my first memories in the field is of Krishna Nayak showing some real-time cardiac imaging and flow. That blew my mind.

MRMH: Could you summarize your paper briefly, and tell us what prompted it?

Peder: The seeds for this particular paper were planted around 2004, during one of my first years in graduate school. The first bigger project I worked on was designing long-T_2 suppression pulses and applying them in the brain. You could see something there and it looked like myelin, but that's as far as I got in grad school. So I always had this idea in the back of my mind, and I wanted to come back to it.

Tanguy: The main goal was to characterize and image the myelin in cerebral white matter. Myelin has a very short T^{2*} value, and can't be seen using traditional MRI pulse sequences. The only way of seeing it is either with long-T^2 suppression pulses, or with very special pulse sequences, such as ultrashort echo time (UTE) MRI.

Tanguy Boucneau

Peder Larson

Boucneau, T., Cao, P., Tang, S., Han, M., Xu, D., Henry, R.G., Larson, P.E.Z. In vivo characterization of brain ultrashort-T2 components. *Magn Reson Med.* 2018;80: 726-735. DOI:10.1002/mrm.27037
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27037

Lab dinner at the 2018 ISMRM meeting in Paris.

For this project we went with UTE, using a high number of TE values (32) ranging from 50 μs to 5 ms. Since there exists a pool of long T_2* components and a smaller pool of short T_2* components with a chemical shift, these data can be fitted using a two-component model. We used the second pool to represent myelin.

Peder: That's a great summary. Previous research seemed to suggest that the ultrashort T_2 or T_2* component was not coming from myelin water, but from protons in the phospholipid membranes. We decided to step back from designing RF pulses, and first learn as much as possible about the MR characteristics of the ultrashort components in the brain, in the hope this might provide a foundation for developing other imaging techniques. Given that we are talking about methylene protons in the phospholipid membranes, it is, in retrospect, obvious that there is a large chemical shift. But demonstrating this was both a big challenge and a big result from the paper.

MRMH: Could you help us put this paper's in v ivo findings into context? How do they relate to previous ex vivo work?

Tanguy: Previous ex vivo experiments showed a chemical shift very close to that of lipids. The first time we saw these oscillations in our signal curves we were very encouraged. The T_2* values we measured in vivo were different from the findings of previous ex vivo studies of tissue extracts, which were in a different state.

Peder: Everything was reasonably consistent between this work and prior work. There were some differences, such as a large drop in T_2* from 500 μs at 3T to 200 μs at 7T, which is at the limit of what is measurable. Some of the *ex vivo* work was done at even higher field strengths, sometimes leading to the conclusion that it would be impractical to pursue this type of measurement in vivo. Our present results are more optimistic.

MRMH: What do you see as the advantages and challenges of UTE myelin imaging at 3T vs 7T?

Tanguy: It was difficult to work on 7T, not only because of short T_2* and B_1 inhomogeneity, but also because of the specific absorption rate (SAR). In UTE we use very short TRs, and therefore repeat RF pulses very often. There were trade-offs between 3D image quality, shortening the sequence scan time, and not burning the subject.

Peder: I'd say that any advantage of 7T, due to the increased polarization, is probably offset by the decreased T_2*, the other technical challenges, and the limited availability of 7T scanners. 3T is now the direction I'm pushing for, primarily due to the longer T_2* and chemical shift considerations.

MRMH: What were the most exciting parts of working on this project?

Tanguy: Tuning the sequence. It was like a game, you tune one parameter to reduce scan time, but that increases SAR. I think in the end we were able to achieve a good balance.

Peder: The final sequence with this random encoding doesn't have any tonality to it. It's like listening to a blender for an hour! So we are really grateful to all of our volunteers.

MRMH: So where do you, and the project, go from here?

Tanguy: Maybe optimizing the pulse sequence. I think we've reached a milestone, we have a good sequence right now. Another possibility is to improve the reconstruction. When I was at UCSF we were not using parallel imaging, but Peng Cao in Peder's group implemented this for the final results.

Peder: And also comparing with other neuroimaging modalities and measures of myelination and brain connectivity. Another important direction would be to study diseases with demyelination.

Tanguy: This was actually my very first project in MRI and it made me want to continue working in MRI research. In my current lab in France I am still using many of the things I learned at UCSF.

Peder: This was a project with a lot of unforeseen obstacles. It provided a good reminder not be afraid to tackle difficult problems, to expect to encounter unforeseen difficulties, and to be persistent. I hope it inspires more people to look into the characterization of myelin. ■

> *Any advantage of 7T, due to the increased polarization, is probably offset by the decreased T_2*, the other technical challenges, and the limited availability of 7T scanners.*
>
> –Peder Larson

Turning image artifacts into coils

INTERVIEW BY **RAMAN SAGGU**

EDITOR'S PICK FOR AUGUST

JVC-GRAPPA creates additional channels by treating data from other echoes/cycles as extra coils. A potential exciting outcome of this method is in single-shot or multi-shot diffusion imaging where the acquisition time could be substantially reduced. We sat down with Kawin Setsompop and Berkin Bilgic from A. A. Martinos Center for Biomedical Imaging, and their collaborators Justin Haldar and Tae Kim from the University of Southern California, to discuss their paper, which is this month's Editor's Pick.

Kawin and his daugther Mae (left), Berkin and his daughter Ada (right).

Bilgic, B., Kim,T.H., Liao, C., Manhard, M.C., Wald, L.L., Haldar, J.P., Setsompop, K. Improving parallel imaging by jointly reconstructing multi-contrast data. *Magn Reson Med.* 2018;80: 619-632. DOI:10.1002/mrm.27076
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27076

MRMH: Kawin, you're no stranger to MRM Highlights. You produced the most cited MRM paper of 2012, on simultaneous multi-slice imaging (SMS), and you've also featured in our magazines with your researcher profile and the g-slider method. We'd like to know something about the background of the other members of this collaboration. Berkin, how did you start doing MR research?

Berkin: Before coming to Martinos I was at MIT doing a Masters in Computer Vision, and then I joined Elfar Adalsteinsson's lab. After finishing my PhD I joined Kawin's lab at Martinos, and now I am an instructor in Radiology there.

Justin: I was an undergraduate student at the University of Illinois. I knew I liked signal processing and that I wanted to go to grad school, but that was about it! It was a great break for me when Zhi-Pei Liang asked if I would like to work on MRI. Of course, it didn't hurt that Paul Lauterbur, a good friend and collaborator of Zhi-Pei, had just won the Nobel Prize. Everything came together and I've been in the field ever since.

MRMH: So did you get to work with Dr Lauterbur?

Justin: Paul had moved out of MRI at that stage, but I saw him around quite a bit. I was there for all the Nobel Prize celebrations but didn't work on the technical aspects with him.

MRMH: How about you, Tae, how did you get started with MRI?

Tae: I did my Bachelor's in Electrical Engineering in South Korea. When I applied for an imaging program I realised that MR reconstruction fits perfectly with my interests. So I ended up coming to USC where I met Justin.

MRMH: Kawin, can you tell us how this collaboration between Martinos and USC came about?

Kawin: A few years back I was reading one of Justin's papers on constrained reconstruction. I was impressed by his work and felt I wanted to collaborate with him. At the ISMRM meeting in Toronto, we went for brunch and started talking about a collaboration.

MRMH: So, networking at breakfast, lunch and dinner at these conferences really pays off...

From left to right: Justin Haldar, Mary Kate Manhard, Larry Wald, Berkin Bilgic, Congyu Liao, Kawin Setsompop, Tae Hyung Kim in Charlestown Navy Yard.

Kawin: [laughs] It's always important to have a face-to-face chat to establish a rapport and see what the other person is working on; most of my collaborations begin this way.

MRMH: How did you come up with the concept that echoes/cycles could act as extra coils, creating more channels in the JVC-GRAPPA method?

Berkin: We began by looking at balanced SSFP and phase cycling. With phase cycling you get this banding artifact that causes intensity variations in the image, both in amplitude and phase, and we thought we could convert these into additional encoding power. This joint-GRAPPA reconstruction worked well, and we began to realize the approach would also work for multi-echo, multi-contrast reconstruction. Subsequently, though, we found a paper about the TIAMO method (https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.22527) and realized that the idea was actually 10 years old.

MRMH: Was it disappointing to realize that somebody else had already had the idea, or did you feel vindicated by this discovery ?

Berkin: Our approach was a bit different - we were looking to go faster, whereas they wanted to compensate for the difficulties encountered at 7 T.

Justin: When Berkin showed me that others had already explored this idea, I felt a little disappointed that there was already a precedent.

MRMH: Did you find that there were technological constraints or challenges associated with the JVC-GRAPPA method?

Berkin: One issue is reconstruction time because in these GRAPPA-like k-space domain techniques, this usually scales with the square of the number of coils, and since we synthetically increase our number of channels, the reconstruction time increases. But I'm not too worried about this because every couple of years computers get faster.

Tae: Memory may be another issue, especially with 3D images, if we use a lot of echoes.

MRMH: Do you see the potential of machine learning for further improving the reconstruction?

Berkin: Generally speaking, we're a bit concerned about this black box application of machine learning, as we see machine learning as complementary to what we do conventionally with physics-based hardware encoding. We try to use it to give us some sort of initial clue to help us approach very difficult non-convex joint reconstruction problems. By using it solely in our initial approach to these problems, we are more resilient against generalization issues.

Tae: Conventional reconstruction techniques such as GRAPPA are also classified as machine learning, but the difference between conventional and modern methods is that today we learn about prediction relationships from another data set as opposed to the same data. This is a potential major pitfall of the machine learning approach. It isn't such a problem in phase detection, but in medical imaging we should be very cautious.

MRMH: How is this body of work going to develop and branch out?

Kawin: Our aim is to do this multi-shot, multi-contrast imaging well using different reconstruction methods, constrained reconstruction and machine learning.

Justin: There are lots of important practical things we can do with these techniques, but the thing is that advanced reconstruction requires you to make a number of assumptions when formulating the problem. What happens if these are not true? What will cause the method to fail, and if so, how? Will you end up inappropriately reconstructing a tumor, or the absence of a tumor? We currently have good empirical evidence that things are robust and working well, but it would be nice to have confirmation of that at a deeper level. Ultimately, what matters is accuracy and seeing in an image what is really there in the subject.

MRMH: This collaboration seems to have gone really well but you are all based in different places. Have you had a chance to celebrate?!

Kawin: We Skype from time to time and meet at ISMRM. Justin has been particularly busy because he just got tenure, but we hope to meet up at some point soon and grab a beer.

MRMH: Definitely more than a beer… champagne?! We could perhaps arrange it for the Highlights party in Montreal!

Kawin: Yes, that would be great! ■

> *We see machine learning as complementary to what we do conventionally with physics-based hardware encoding.*
>
> –Berkin Bilgic

Using CT and deep learning to remove streaking artifacts from undersampled radial MRI

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR SEPTEMBER

The first September 2018 Editor's Pick is from Yoseob Han and Jong Chul Ye, researchers at the Korea Advanced Institute of Science & Technology (KAIST) in Daejeon, Republic of Korea. Their paper presents a deep learning approach that allows streaking artifacts to be removed from undersampled MR images acquired with a radial k-space acquisition pattern. They used a deep learning network pre-trained on a large CT dataset and then used a small MRI dataset to adapt it for their application. They demonstrated that this process (domain adaptation) performed better than other reconstruction techniques (e.g. compressed sensing), and has the added benefit of a much shorter image reconstruction time (post-training). We recently spoke with Yoseob and Jong about their project.

> *We set out to pre-train the deep learning model with a large CT dataset, which has a similar radial acquisition pattern, and then perform domain adaptation.*
>
> –Yoseob Han

Yoseob on vacation at the beach.

Jong in a teahouse.

MRMH: First of all, we'd like to know something about you and your background.

Yoseob: My name is Yoseob Han and I am a PhD candidate at KAIST in Korea. During my Masters I worked on CT reconstruction techniques using compressed sensing, and my current interest is image reconstruction using deep learning, for both CT and MRI applications.

Jong: I am Professor Jong Chul Ye, Yoeseob's PhD advisor. Our research group has been working in the MRI field for nearly 14 years, but we don't only do research in this field – we are interested in image reconstruction problems encountered in various biomedical applications, such as CT, PET, ultrasound and optical techniques. We focused on compressed sensing for many years, and developed some well-known techniques in the MRI field such as the k-t FOCUSS algorithm and ALOHA. However, in the past two years we have turned our attention to deep learning approaches applied in biomedical imaging reconstruction, starting with CT, and then moved on to our present work with MRI.

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

Yoseob: The goal of the proposed method was to use deep

Han, H., Yoo, J., Kim, H.H., Shin, H.J., Sung, K., Ye, J.C. Deep learning with domain adaptation for accelerated projection-reconstruction MR. *Magn Reson Med.* 2018;80: 1189-1205. DOI:10.1002/mrm.27106
https://onlinelibrary.wiley.com/doi/full/10.1002/mrm.27106

BISPL group happy hour (BISPL: Bio-Imaging, Signal Processing and Learning).

learning to remove the streaking artifacts from MR images corrupted as a result of accelerated acquisition performed using a radial k-space pattern. The challenge to overcome was the lack of sufficient MRI data to train the deep learning network adequately. To resolve this issue, we set out to pre-train the deep learning model with a large CT dataset, which has a similar radial acquisition pattern, and then perform domain adaptation by fine tuning the CT-trained model using the limited MRI data available for the particular application. On using this technique, we discovered that our network outperformed some existing compressed sensing methods with much shorter image reconstruction times.

Jong: In fact, the takeaway message from this paper is that it is not the end of the world if you don't have enough data to train a neural network for your application. You simply need to have enough data to train it in another domain with a similar acquisition pattern. And for this purpose, you don't only have to use real data, such as CT images; you can also use simulated data, provided the acquisition trajectory is similar.

MRMH: Could you clarify what you mean by "domain adaptation"?

Yoseob: If a neural network is pre-trained with a specific dataset (in our case, CT), then we say that the network is biased for this domain (referred to as the source domain). Accordingly, our network cannot reconstruct the corrupted MR images well because it has not learned the characteristics of MRI data (that is, of the target domain), and is biased for the source domain (CT). But because the two domains contain similar information, deriving from shared characteristics (e.g. radial acquisition pattern), then we can adapt the source domain to the target domain by fine tuning it with, in this case, MRI data.

Jong: Yoseob himself is actually an example of domain adaptation [laughs], because he started his career learning about CT and deep learning for CT reconstruction, and then I asked him to adapt his knowledge of reconstructing CT images using deep learning to another application: reconstructing accelerated MRI images with radial trajectories. We didn't need to retrain him from scratch [chuckles].

MRMH: What are your main "takeaways" from this study?

Jong: Many people may initially be concerned about not having enough data to apply deep learning approaches in their MR reconstructions. But one take-home message is that if you use domain adaptation or transfer learning techniques, you can still do a decent reconstruction even with limited data, provided you have another well-trained model in another domain.

MRMH: Where do you see this work heading? Have you thought of any exciting ways of using or extending it?

Jong: I think the main challenge with model-based regularization techniques like compressed sensing is their very long reconstruction times, but as we have seen, this is now being overcome by deep learning, an approach that can easily be adapted to learn from big data. And furthermore, even though the training takes a long time, real-time reconstruction is much faster with deep learning, and that's actually all that practitioners are concerned about. So, this is really where the image reconstruction field is heading, and we are proud that this paper may contribute to progress in this direction.

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

Yoseob: I recently went to Seoul with my girlfriend to visit the Han River. It was great, and we ate some very delicious food [laughs].

Jong: Yeah... he's a young guy [laughs]. I myself usually enjoy playing with my kids. Daejon is a science town, and we have a lot of national labs based here. It's a good area to educate children, and I enjoy life here. But if you want to enjoy more fun stuff, like this young guy [laughs], then you can easily get to Seoul, which is just an hour away by train. ■

The pre-trained deep learning networks for this work is available online: (https://github.com/hanyoseob/domain-adaptation-MR).

> *If you use domain adaptation or transfer learning techniques, you can still do a decent reconstruction even with limited data, provided you have another well-trained model in another domain.*
>
> –Jong Chul Ye

You don't always need a laser, sometimes a hammer will do!

INTERVIEW BY **EMILIE MCKINNON**

EDITOR'S PICK FOR SEPTEMBER

The second Editor's Pick for September comes from the Institute of Health and Biomedical Innovation at the Queensland University of Technology (QUT) in Brisbane, Australia. We recently spoke with co-authors Monique Tourell and Konstantin Momot about why and how they used portable NMR to assess breast tissue density.

Monique Tourel

Konstantin Momot

MRMH: First of all, can you tell us a little bit about your journey to MRI?

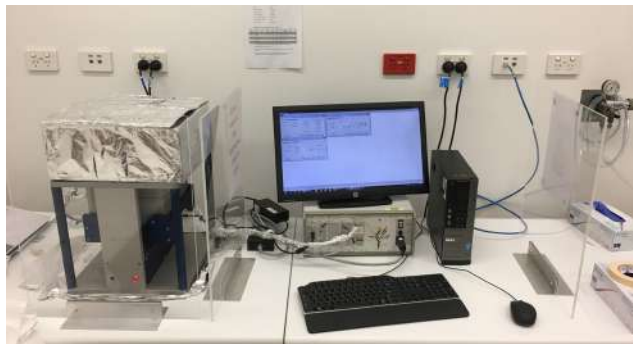
Monique: I did my undergrad studies at QUT (Queensland University of Technology) and did both my honors (a mini-masters) and PhD with Konstantin, using diffusion to study anisotropic structure in collagenous tissues. Then, while my PhD was being conferred, we worked on this paper together. Over the last year, I have been doing more fundamental NMR research at the University of Southampton and now I am back in Brisbane looking for my next project!

Konstantin: I am actually a physical chemist by training. I did my undergraduate studies in Russia, at Novosibirsk University, my PhD in Arizona with inorganic physical chemist Ann Walker, and my first post-doc in North Carolina at UNC with Charles Johnson (the inventor of DOSY-NMR). That was my first serious introduction to diffusion, and my research has since been connected to various aspects of diffusion, although it is actually not part of this paper [laughs]! I have now been in Australia for about 17 years where my work involves using MRI and NMR to deal with problems that have some sort of biomedical relevance.

MRMH: What are the take-home points of your paper?

Monique: Well, the main one is that the Mouse (the portable NMR probe) can be used to distinguish between low- and high-density tissue. We also found that the range of values seen across the patients could be attributed to different compositions in terms of fatty versus non-fatty tissue. Another take-home message is that the different regions could be determined just as well in the large breast slices as in the smaller segmented regions.

Konstantin: Yes, I would agree with that! This was a proof-of-concept paper in the sense that we demonstrated the use of portable NMR to distinguish between high- and low-density breast tissue. This study was done in vitro but it would actually be easy to extend to in vivo settings. In time, this technique could allow us to work not just with small excised portions, but also with large masses of tissue and still see what's going on.



The NMR-Mouse

MRMH: Can you tell us a little bit about the hardware that was used for the experiment?

Konstantin: The first single-sided NMR sensor was made in 1996, I think. Back when it was invented it looked like a computer mouse, and was thus dubbed the "Mouse"! The hardware has undergone massive redevelopments since then, and now it just looks like a sort of rectangle. Basically, it's a portable scanner with a permanent magnet, which you can move up and down to give you the depth profile. It costs only a small fraction of the cost of a full-blown MRI. Portable NMR is more of a sensing than an imaging technique and there is a definite niche in the clinical environment for this sort of instrumentation! After all, you don't always need a laser, sometimes you just need a hammer!

MRMH: Why did you start with T_1 as opposed to T_2 relaxation, or ADC let's say? Do you think these various NMR metrics could complement each other?

Monique: There are probably two reasons. The first is that T_1 is more clinically relevant and is used more for

Tourell, M.C., Ali, T.S., Hugo, H.J., Pyke, C., Yang, S., Lloyd, T., Thompson, E.W., Momot, K.I. T1-based sensing of mammographic density using single-sided portable NMR. *Magn Reson Med.* 2018;80: 1243-1251. DOI: 10.1002/mrm.27098
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27098

imaging breast tissue because of its fat suppression capabilities. It was also just a simpler measurement for us to do straight up. It fits a mono-exponential curve, and so it was nice not to have to worry about issues like the distribution of different relaxation times or tissue orientation.

Konstantin: We have actually tried T_2 and diffusion measurements as well! T_2 brings out the composition differences in a slightly different way, and we expect T_1 and T_2 quantification to prove complementary. As another option, we could potentially ditch the idea of the recovery curve and explore approaches such as MR fingerprinting. Instead of a detailed image you can acquire a "fingerprint" based on the magnetization response of your sample and classify it as high or low density. This is one of the obvious avenues to pursue with portable NMR, especially seeing how successful MR fingerprinting has been in the brain over the last 2-3 years!

MRMH: One practical disadvantage of using NMR is that it would allow only a subset of the tissue to be explored. Do you foresee your technique being used in conjunction with mammography?

Monique: I see it as complementary to other spatially resolved techniques. It allows you to monitor changes in breast tissue more frequently, and then, if you spot something not quite right, you can go ahead and do a more detailed scan in that particular region, using MRI or mammography.

Konstantin: This is still an open question really, but I can see three basic scenarios. One of the problems with mammography is that it is a 2D projection technique being used to try and visualize a 3D structure. In this sense, portable NMR, allowing depth profiling, could be highly complementary. Another possibility is that we could select a number of certain strategic locations on the breast and use those as markers. The third scenario would be to use the technique for longitudinal monitoring of mammographic density, given that portable NMR is harmless and does not involve the use of ionizing radiation. There are certain treatments, such as hormonal treatment with tamoxifen (a breast cancer prevention drug), to which approximately 2/3 of patients respond. The major indicator of who is going to respond is the presence of early changes in mammographic density. From this perspective, longitudinal measurements are very useful clinically. In this setting, the same locations would be scanned each time.

Honor Hugo (left) and Xuan Huang (right) at the Translational Research Institute in Brisbane, Australia.

MRMH: This project seems to be a collaboration between many different specialties: pathologists, surgeons, radiologists and so on. What lessons did you learn from the clinicians that contributed to the successful completion of this project? What were the particular challenges you faced?

Monique: Communication is definitely a massive challenge when you are dealing with that many people! That said, I think clinicians are really good at keeping you focused on the clinical goal and what is actually relevant.

Konstantin: That was one of the lessons I learned as well. And I also came to realize that research involving actual patients takes a long time! We are used to working with *in vitro* samples, where things are easy. If you want to measure something, you just measure it [laughs]! It was a bit of an eye opener to see just how slowly clinical research can progress compared with basic science. Another lesson was that to get clinicians involved you have to show them the carrot. You might say, "This is the research and if it's successful it's going to reduce the non-responder rate of breast cancer treatments by 80%." At that point, their eyes will light up [laughs]. ■

> *Portable NMR is more of a sensing than an imaging technique and there is a definite niche in the clinical environment for this sort of instrumentation!*
>
> –Konstantin Momot

From left to right: Konstantin Momot, Xuan Huang, Honor Hugo, Rik Thompson, Gillian Jagger, Thomas Lloyd.

Get in the mix! Using fast and slow exchange for the detection of metabolites

INTERVIEW BY **ERIKA RAVEN**

EDITOR'S PICK FOR OCTOBER

We met with Lin Chen and Jiadi Xu from the Kennedy Krieger Research Institute at Johns Hopkins University to discuss their paper, "Separating fast and slow exchange transfer and magnetization transfer using off-resonance variable-delay multiple-pulse (VDMP) MRI". First of all, a little about the two authors: Lin obtained his PhD in 2017 from Xiamen University in China, then traveled 'round the world to research quantification methods for chemical exchange saturation transfer (CEST) MRI. Jiadi has a background in solid-state and solution NMR, and works to detect all types of exchangeable protons using MRI and tissue modeling. Their paper attempts to separate and quantify CEST signals based on exchange rates. This is different from a typical CEST experiment that targets a spectral frequency associated with a specific metabolite (e.g. creatine), or filters out "unwanted" contributions, such as those from macromolecules using their unique line-shapes. The VDMP approach can detect all contributions, as long as they exchange, and is not even limited to metabolites.

> *In the current study, we did not try to suppress any contributions, just to separate and quantify them.*
>
> –Jiadi Xu

MRMH: Can you briefly outline your technique?

Lin: Many existing CEST methods are good at detecting clear peaks in Z-spectra. But in the presence of overlapping CEST peaks, they become invalid. The proposed method provides a new dimension for separating and quantifying CEST signals in Z-spectra based on the exchange rates. Here, we divided these into two categories: fast (>1 ksHz) and slow exchange rates. The contributions of fast and slow exchanging components can be obtained by their characteristic VDMP build-up patterns.

Lin Chen

Jiadi Xu

MRMH: Did you have any 'ah-ha!' moments when

Chen, Li., Xu, X., Zeng, H., Chan, K.W.Y., Yadav, N., Cai, S., Schunke, K.J., Faraday, N., Van Zijl P.C.M., Xu, J. Separating fast and slow exchange transfer and magnetization transfer using off-resonance variable delay multiple pulse (VDMP) MRI. *Magn Reson Med.* 2018;80: 1568-1576. DOI: 10.1002/mrm.27111
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27111

developing the technique, or draw inspiration from previous work?

Jiadi: This technique borrows the idea of 'mixing time' from a very important NMR method called NOESY (Nuclear Overhauser Effect Spectroscopy). In NOESY, mixing time reflects changes based on the distance between protons and with this you could finally calculate a structure from it. Actually, that was how Kurt Wüthrich and Richard Ernst got their Nobel prize for research in NMR.

When I began working on CEST, people seemed to just be using the mixing time as a duty cycle, which confused me for a while. Since I come from an NMR background, I could see that the mixing time was very similar to the NOESY study, and could therefore play an important role, beyond just adding to the duty cycle. That was actually the 'ah-ha!' moment when developing the VDMP method. Of course, during its development, I drew considerable inspiration from discussions with my mentor Peter van Zijl, and also my colleague, Nirbhay Yadav.

MRMH: Z-spectra seem like a murky place. Can you break down the sources of magnetization we're dealing with here?

Lin: Z-spectra are the outcomes of CEST experiments. To generate them, a saturation pulse is first applied to saturate the magnetization of the protons present in metabolites. Then, thanks to the action of exchangeable protons, this magnetization will transfer to water and reduce the water signals. This means we can detect changes from water and use this information to quantify the various proteins and metabolites.

Jiadi: The negative part of Z-spectra contains aliphatic protons from both lipids and proteins. The positive part is much more complicated. For example, there are amide protons from the backbone of the amino acids in proteins. Also, some amino acids in proteins, such as arginine, asparagine and serine, have additional exchangeable protons in their side chains. Furthermore, some metabolites contain amine and hydroxyl exchangeable protons. All the exchanging protons are crowded within a narrow range, from -5 to 5 ppm.

MRMH: With so many metabolites in the spectral mix, how do we decide whether to keep or ignore certain signals?

Jiadi: Separating the individual contributions of metabolites is undoubtedly challenging, and it is possible only for certain special compounds, such as creatine and phosphocreatine, which show sharp peaks in Z-spectra. Hence, we try to separate the fast- and slow-exchanging compounds. In the current study, we did not try to suppress any contributions, just to separate and quantify them.

MRMH: What experimental conditions might shift fast and slow exchange?

Jiadi: Fast and slow exchange rates are separable by varying the mixing time of the pulse train. The ratio between them can be controlled through the saturation power of the pulse. If we use weak power, then we mainly see the slow-exchanging protons, such as amide and aliphatic protons. If we use high power, then the fast-exchanging protons will be stronger, but we will see strong magnetization transfer (MT), too, since they also contain slow-exchanging process.

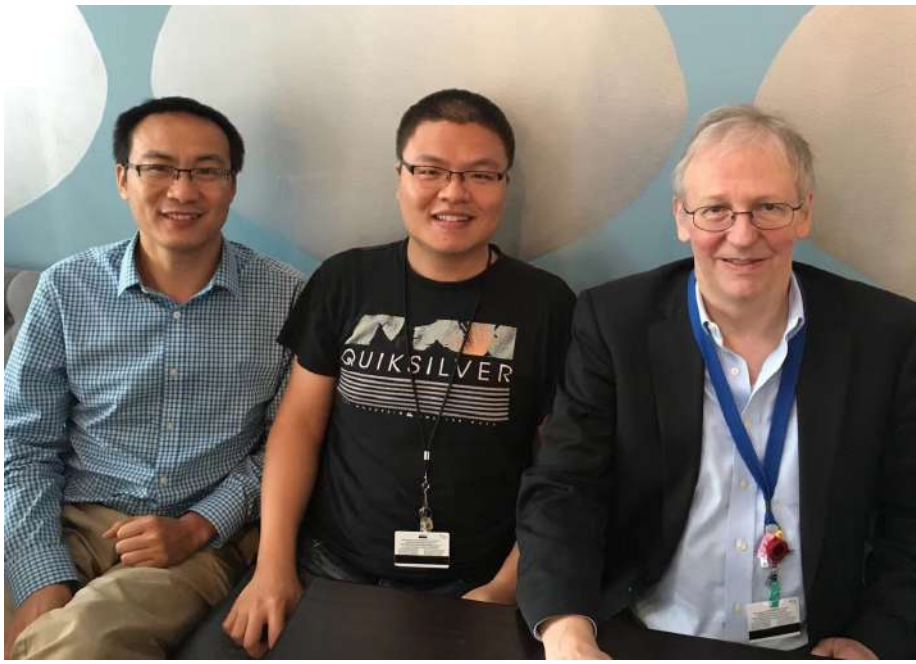
Lin: Besides the experimental parameters, there are other factors, such as the temperature and pH value that will also shift fast and slow exchange.

MRMH: Any caveats for those looking to separate exchange components in their signals?

Jiadi: It is important to bear in mind that this is a transient method and that it uses a build-up of CEST contrast. Hence, you need to keep the pulse number relatively small. Also, the saturation power cannot be too strong, otherwise the build-up will be dominated by MT. Also, direct saturation of water will shorten the build-up process and reduce the build-up signal with strong power.

MRMH: What are the future directions for this technique?

Jiadi: Actually, the method has already been used in many studies. One involved tuning the mixing time to remove MT and get pure amine and aliphatic peaks (https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.25990). Also, the fast-exchange component is sensitive to pH, and can be used for pH mapping. We demonstrated this on a stroke model in collaboration with Nauder Faraday and Kathryn Schunke (http://archive.ismrm.org/2017/0270.html). This technique is not specific to CEST; it works for any exchange process in MRI, such as arterial spin labeling. ■



Jiadi Xu, Lin Chen, and Peter van Zijl

> *This technique is not specific to CEST; it works for any exchange process in MRI, such as arterial spin labeling.*
>
> –Jiadi Xu

Brothers in MR: Gopi and Ranga Deshpande are fighting together to improve resting state connectivity

INTERVIEW BY **TOMMY BOSHKOVSKI**

EDITOR'S PICK FOR OCTOBER

For our second October Editor's Pick, we were pleased to talk with Gopikrishna Deshpande and Ranga Deshpande about their study on the effects of hemodynamic response function (HRF) variability on resting-state fMRI functional connectivity.

Ranga and Gopi Deshpande

> *HRF variability will impact functional connectivity estimates from BOLD data, for a long time nothing was done to shed light on its confounding effect on resting-state functional connectivity.*
>
> –Ranga Deshpande

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

Ranga: I did my undergrad studies in electrical engineering in India and my master's degree in biomedical engineering at the Indian Institute of Science in Bangalore, where I worked on EEG signal processing. I then did a PhD in the MRI Center at Auburn University, where I worked on fMRI connectivity modeling in PTSD. Currently, I am a postdoc at UCLA working on brain imaging of body image and eating disorders.

Gopi: Like Ranga, I am also an alumnus of the Indian Institute of Science in Bangalore. I did my PhD and postdoc in biomedical engineering at Georgia Tech under the supervision of Dr. Xiaoping Hu. Then I came to Auburn University, where I'm an associate professor at the MRI Research Center in the Department of Electrical and Computer Engineering. My research has since been connected to various aspects of fMRI analysis, including the current topic of HRF variability.

MRMH: Can you briefly summarize your paper?

Ranga: fMRI is an indirect measure of brain activity and the HRF is the intermediary between neural activity and its related fMRI BOLD signal. Several years ago it was shown that the HRF is variable across the brain and individuals. Even though it is evident, in principle, that HRF variability will impact functional connectivity estimates from BOLD data, for a long time nothing was done to shed light on its confounding effect on resting-state functional connectivity. This is what prompted us to do this study, in which we looked at the impact of HRF variability on resting-state fMRI functional connectivity in healthy controls.

Rangaprakash, D., Wu, G.R., Marinazzo, D., Hu, X., Deshpande G. Hemodynamic response function (HRF) variability confounds resting-state fMRI functional connectivity. *Magn Reson Med.* 2018;80: 1697-1713. DOI: 10.1002/mrm.27146
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27146

Gopi: Specifically, what we found is that HRF variability induces false connectivities. Generally, we found more false positives with a mean error of about 15% in connectivity values, and clearly if you're interpreting specific connections with such large HRF variability then you're in trouble. We're not saying that the method we use to deconvolve and estimate the HRF is the best there is, but it is definitely a good one and it has been validated. However, regardless of the method used to deconvolve fMRI data, the variability of the HRF between brain regions and across individuals must be accounted for when performing resting-state fMRI analysis and that, basically, is the message of the paper.

MRMH: Why do you think that the impact of HRF variability on resting-state functional connectivity has been largely overlooked?

Ranga: The situation is rather like what was previously seen with head motion, which used to be corrected simply through rigid body transformation. People were basically satisfied with this, and although they still realized, in a qualitative sense, that head motion causes a lot of artifacts in the data, the problem was otherwise ignored until maybe five years ago, when the effects of residual head motion, after rigid body correction, became more widely appreciated. Essentially, we are facing a similar scenario here.

Gopi: Another point is that you need a good blind deconvolution technique in order to estimate the HRF in every voxel. Such techniques have been under development for many years, and it is only recently that we have seen the emergence of valid ones for resting-state fMRI. This is another reason why this issue has been largely overlooked.

Also, people have previously tended to use resting-state fMRI connectivity for more basic applications. But now it is being used in more sophisticated applications, like connectome fingerprinting or in machine learning algorithms to predict disease status. Obviously, in such applications, HRF-induced errors of the magnitude mentioned earlier really matter.

MRMH: You implied that pseudo positive connections have a detrimental impact on fMRI analysis. Can you offer any insight as to why more pseudo positives were detected than pseudo negatives?

Ranga: In our particular setting, pseudo positives are those connections that exist in the original fMRI data, but become weaker in the deconvolved fMRI data. The HRF is quite a smooth function throughout the brain and it is similar in neighboring voxels, which are thus strongly correlated with each other. When we perform deconvolution, this correlation, which is a confounding element, is minimized. On average we observed a reduction in connectivity after deconvolution and that is why we get more pseudo positives.

Gopi: Put another way, there is an HRF-induced correlated component within the connectivity value between two regions, therefore, when its effect is minimized through deconvolution, the average connectivity value is reduced too. That is why we have more pseudo positives than pseudo negatives.

The research team at the Auburn University MRI Research Center.

MRMH: In the paper, you stated that the confounds will be even greater on 3T data. Can you clarify this?

Ranga: What was stated is based on theory, not on actual data, and that is what we are looking at right now. And we cannot say by what magnitude the effect will be larger in 3T data, as there is no data allowing us to do so. However, we know there is a theoretical basis for the effect.

Gopi: In high-field fMRI data, it is well known that there is more contribution from small vessels compared to 3T, and the HRF variability is lower for smaller than larger vessels. Because of that weighting towards smaller vessels, we just hypothesized that the HRF variability should be smaller at 7T. However, nobody has really empirically tested whether the HRF variability is larger at 3T, so hopefully, we will show that in our ongoing study.

MRMH: We noticed that you share the same last name, are you related?

Gopi: Ranga is my younger brother.

MRMH: So, what led two brothers to work together?

Gopi: I'll let Ranga tell the story.

Ranga: [laughs] During my Master's I was working on EEG in epilepsy and I used to have frequent discussions with Gopi about my ideas on the brain and how I should go forward. That's how I was drawn to brain imaging and fMRI, and I was particularly interested in the work that Gopi and Tom Denney were doing at Auburn with 7T scanners. In short, I was attracted by both the place and the research. Actually, it was a nice coincidence.

Gopi: Our father is also a scientist and we always used to talk about science and research. I think that probably just rubbed off on Ranga and inspired him to go the same way, I guess. ■

> *Specifically, what we found is that HRF variability induces false connectivities.*
>
> –Gopi Deshpande

Building a smarter interpolator with AI

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR NOVEMBER

This month MRM met Akshay Chaudhari, Zhongnan Fang and Brian Hargreaves, whose recent paper "Super-resolution musculoskeletal MRI using deep learning" asked "how can we make a thick slice thinner?" Co-first author Zhongnan explains, "In many applications people prioritize the in-plane resolution, and therefore many sequences acquire thick slices. This can complicate matters for radiologists assessing oblique images, or surgeons planning an operation and needing to look at the whole structure, for example. Our project set out to establish whether the latest AI technology can reduce slice thickness without more scanning."

"Where most AI in MRI is used for detection, we are using it for image acquisition."

– Zhongnan Fang

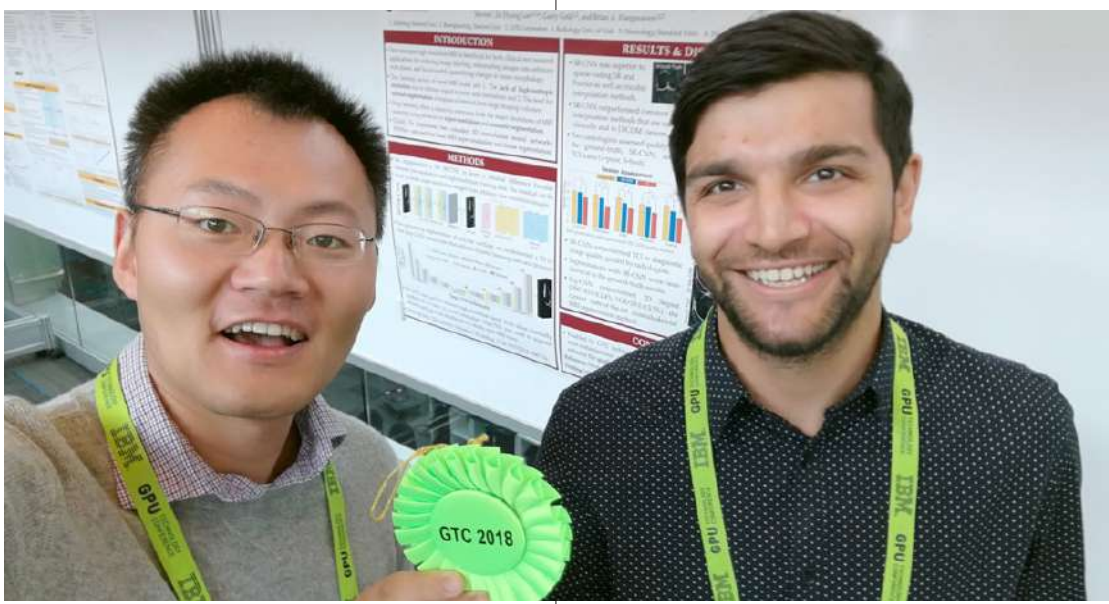
MRMH: Tell me about yourselves. How did you end up developing a deep learning technique for musculoskeletal (MSK) imaging?

Akshay: I am currently a first year postdoc at Stanford, where I also got my PhD in Bioengineering, focusing on fast, quantitative MSK imaging. In the past, we've tried many different methods to obtain a fast, diagnostic, quantitative MR sequence, such as parallel imaging and compressed sensing. All have tended to have limitations. Having already tried some traditional approaches, I was excited by new literature emerging in the field of computer vision and figured, why not give it a shot? They say, "There's no such thing as a free lunch", but this might be the nearest we can get! So, we evaluated it, and luckily it works relatively well!

Zhongnan: I am a senior research scientist at LVIS Corporation. We are a startup out of Palo Alto working on medical image visualization. I also got my PhD at Stanford in Electrical Engineering, working on compressed sensing fMRI with Dr Jin Lee. My goal is to see images better reconstructed with less sampling. This project started at the 2017 ISMRM conference where I met Akshay. We had an idea, why not try this new AI technology with knee imaging and see how it works?

MRMH: Brian, I don't think I've ever heard the story of how you ended up doing MRI.

Brian: I came to Stanford in 1995. I was interested in coming back to graduate school to do something more satisfying than working in my previous consumer product-oriented field. I took Prof. Dwight Nishimura's course and liked the way he taught. He very quickly got me interested in MRI and I've never left! Now we have this project involving high-resolution, quantitative knee imaging. We are looking at it from many angles,



Co-authors Zhongnan and Akshay after winning the best poster award at the GPU Technology Conference in San Jose, California, for work featuring MRI super-resolution.

Chaudhari, A.S., Fang,Z., Kogan, F., Wood, J., Stevens, K.J., Gibbons, E.K., Lee, H.J., Gold, G.E., Hargreaves, B.A. Super-resolution musculoskeletal MRI using deep learning. *Magn Reson Med.* 2018;80: 2139-2154. DOI:10.1002/mrm.27178
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27178

from the acquisition right through to the reconstruction phase.

MRMH: How do you benefit in MSK imaging from going faster and getting quantitative data?

Akshay: There is plenty I could say in reply to that, but essentially MSK imaging has a clinical side and a research side. From the research perspective, we are interested in diseases, like osteoarthritis, which affect many collagen-rich soft-tissues. A lot of promising research suggests that quantitative MR parameters such as T_2, $T_1\rho$, gagCEST, etc., are correlated to the collagen structure and can tell you about the biochemical status of these tissues over time.

Why do we want to faster? Because we can! Clinically, there's this big push towards value-based imaging since the high cost of MRI is a large burden on the healthcare system, and from a research perspective, it allows us to implement many promising new sequences in studies.

Brian: In the context of the osteoarthritis initiative, of course, we are studying a slow degenerative disease that involves numerous different factors. Arguably, the best approach would be to study changing patterns in different groups within a broader population. This is a huge motivation to bring down the cost of research scans. Shorter exams would cost less and offer a widespread test suitable for research purposes. Fighting the clinical cost is harder, for many reasons, so we should leave that discussion for now.

MRMH: Why did you choose to draw your data from this osteoarthritis initiative?

Akshay: Because it has a lot of data sets. With deep learning, you need a lot data, but it isn't easy to know how much is enough, so we started where there are thousands of datasets available. We only worked with ~170 to start with, knowing we could easily access more if needed.

MRMH: "Deep learning" is a big buzzword right now. How does your work compare with other great uses of AI in MRI?

Zhongnan: The similarity is that we are all trying to reduce the cost of MRI. However, where most AI in MRI is used for detection, we are using it for image acquisition, to get better image quality with less sampling.

Brian: I like to think of this work as a smart interpolator that uses multiple dimensions.

MRMH: What about the network? How did you decide what components and parameters to use?

Zhongnan: Our network consists of 20 layers of cascading convolutional layers and ReLu layers. Instead of learning the high-resolution image directly, we actually try to learn the residual between the high-resolution and interpolated images because the network converges faster when learning residuals than the high-resolution image itself.

MRMH: Why do so many neural networks use ReLu layers?

Zhongnan: The ReLu is a rectified linear unit that introduces nonlinearity into the function.

Akshay and Brian enjoying a well-earned beer at Akshay's Bioengineering Ph.D. graduation.

Akshay: It took me a long time to understand the significance of having nonlinearity in the neural network. Let's say the convolutional neural network has 20 layers and we look at the output of each individual one. The first convolution generates features like the edges in the x-direction, etc. In the next layer, the convolution gathers information about how these edges sit relative to one another. As you cascade through different convolutions, you pick up features of different levels. The ReLu is important because it can introduce nonlinearity into your system, allowing the network to learn high-level features. Without the nonlinearity, 20 convolutional layers could be represented using a single convolution.

MRMH: Looking back on this work, what have been your biggest successes and your biggest frustrations?

Zhongnan: I enjoyed working on this project, which was a great collaboration between LVIS and Stanford. We got feedback from many people from different fields and with different expertise. The outcome was positive and we published the paper! Training the network could be frustrating though! Sometimes, even after 3-4 days of training, your image was no better than the linear interpolation. I would have to go back to the source code and debug everything from the beginning. But that was also a fun part: seeing how AI technology can help us get a smarter interpolator.

Akshay: I loved the fact that this project had a very technical component but we also worked closely with clinicians. It was fascinating to be constantly getting feedback helping us to establish what was "good enough". After all, you can keep optimizing these networks forever, but it's important to learn to recognize when to stop.

Brian: I find it really exciting that AI is being led by people who are younger and newer to the field. It's great to have this fresh energy that is pushing the limits and asking some difficult questions. ■

> *You can keep optimizing these networks forever, but it's important to learn to recognize when to stop.*
>
> – Akshay Chaudhari

Using detective skills for rapid quantitative CEST imaging with MR fingerprinting

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR DECEMBER

Our first December 2018 Editor's Pick is from Ouri Cohen and Christian Farrar, researchers at the Martinos Center at the Massachusetts General Hospital (MGH) and Harvard Medical School. Their paper presents an MR fingerprinting approach to quantitative chemical exchange saturation transfer (CEST) imaging. We recently spoke with Ouri and Christian about their project.

Left: Ouri enjoying tropical sea kayaking after the ISMRM annual conference; Right: Chris racing at the Green Mountain Stage Race.

MRMH: First of all, we'd like to know a little about you and your backgrounds.

Ouri: After doing degrees in electrical engineering and physics, I did a PhD in biomedical engineering at Columbia University. I joined the Martinos Center for my postdoc, and this is where Chris and I met. I recently accepted a faculty position at the Memorial Sloan-Kettering Cancer Center in New York City.

Cohen, O., Huang, S., McMahon, M.T., Rosen, M.S., Farrar, C.T. Rapid and quantitative chemical exchange saturation transfer (CEST) imaging with magnetic resonance fingerprinting (MRF). *Magn Reson Med.* 2018; 80: 2449-2463. DOI: 10.1002/mrm.27221

https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27221

Christian: I was a physics undergrad major at the University of Wisconsin, and then came to Boston for grad school at Harvard, where I got my PhD in chemistry. I did a postdoc at MIT, doing high-field dynamic nuclear polarization and electron paramagnetic resonance. I did a second postdoc at MGH doing MRI, and now I'm an assistant professor in the Department of Radiology here at Harvard Medical School and MGH.

MRMH: Could you explain, in simple terms, the concepts of MR fingerprinting and CEST?

Ouri: Everyone knows that a regular fingerprint left at a crime scene can give you a lot of information about a suspect, providing the fingerprint is in your pre-compiled database. Well, the idea behind MR fingerprinting is essentially the same. Basically, by exciting the magnetiza-

tion with varying acquisition parameters, you can induce signal evolutions that are unique for each tissue type; then, by matching the result to a pre-computed database, you can infer information about the underlying tissue.

Christian: And with CEST, you're basically measuring contrasts that depend on the chemical exchange rate. By saturating exchangeable protons that exchange with bulk water, you observe a decrease in your water signal. The contrast is going to depend on the exchange rate, and the proton volume fraction of these exchangeable protons. The exchange rate is very sensitive to pH, while the volume fraction gives you information about protein and metabolite concentrations.

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

Ouri: Traditional CEST pulse sequences are mostly qualitative and have very long scan times. This is the challenge addressed by the paper. Our solution was to integrate an MR fingerprinting paradigm into a CEST acquisition. Unlike traditional MR fingerprinting, where you only vary the flip angle and TR, here the idea was to vary the off-resonance CEST saturation power as well, so as to sensitize the sequence to different exchange rates and concentrations. We found we could reduce the scan time very significantly, to approximately two minutes, as opposed to the 10 minutes or more needed for a traditional CEST sequence. More importantly, we were able to get quantitative CEST maps far more easily than you can when using conventional techniques.

Christian: I've been pretty surprised at how well our technique works. In this paper, we only show data from a normal rat, but we now have data from rat stroke models and mouse brain tumor models too. In the brain tumor models you see a decreased proton volume fraction because you've got a lot of edema diluting your protein concentrations. And in stroke lesions you see decreased exchange rates consistent with decreased pH, and also slightly decreased proton volume fractions. It's great that this technique allows you to get a deeper insight into what's going on in these disease pathologies.

MRMH: How could this technique be further improved in the future?

Ouri: There's a lot we plan on doing to improve it – I feel like we've barely scratched the surface. Just to give an example, the acquisition schedule that we are currently using was selected at random, so it's not going to be optimal. Optimizing the acquisition schedule will almost certainly improve the discrimination between different tissue types, or further reduce the scan time, so that's something that we are definitely going to pursue.

Christian: We also want to get whole-brain coverage by exploiting simultaneous multi-slice (SMS) EPI methods, and exciting multiple slices after each saturation pulse while permuting the order of the slices for the different saturation powers; this might also help us to optimize the tissue discrimination even further.

Ouri: From a clinical perspective, I think all these developments would be very important. Essentially, our work is leading up to having a kind of push-key clinical sequence that people can use in different pathologies to generate these useful maps in a reasonable amount of time.

MRMH: What advice would you give to a new grad student wanting to embark on a similar MR fingerprinting project?

Ouri: I would suggest running lots of simulations. The nice thing about MR fingerprinting is that you can simulate a lot of this stuff before even sitting down at the scanner. If you generate ideas and test them in simulations, you can achieve a very quick development cycle, and hopefully get something really interesting going. So I would say, focus on seeing if your work makes sense in simulations, and keep going until you get to something that's worth trying on the scanner.

Christian: I agree with Ouri that it is very important to run lots of simulations to understand how good your particular acquisition schedule is at discriminating different tissue parameters. I've recently noticed that a lot of people trying to quantify chemical exchange rates are getting values that are all over the place. I think this is largely due to the fact that they don't realize that their fits are not unique. One nice thing about the MR fingerprinting dictionary is that by taking the dot product of the dictionary with itself, you can look at the correlation of the signal trajectories between different tissue parameters and get a sense of how good a particular acquisition schedule is at discriminating between different parameters. ■

> *The nice thing about MR fingerprinting is that you can simulate a lot of this stuff before even sitting down at the scanner.*
>
> –Ouri Cohen

Co-author Matt Rosen in action blowing glass for 3He hyperpolarization experiments.

Quantification of myocardial perfusion using simultaneous PET-MRI

INTERVIEW BY **GIULIA GINAMI**

EDITOR'S PICK FOR DECEMBER

Karl Kunze was recently awarded his PhD from the Technical University of Munich (TUM), and is now working as a cardiac MRI research scientist for Siemens at King's College London. Part of Karl's research, performed during his time at TUM, is summarized in "Myocardial perfusion quantification using simultaneously acquired $^{13}NH_3$-ammonia PET and dynamic contrast-enhanced MRI in patients at rest and stress", which is our latest Editor's Pick article. We met Karl, together with co-author Stephan Nekolla and senior author Markus Schwaiger, to talk about their research.

> *The uniqueness of this platform is that it allows us to compare two distinct technologies in the same patient and under the same physiologic condition.*
>
> –Markus Schwaiger

MRMH: Could you tell us about your backgrounds, and how you all ended up working in MRI and in simultaneous PET-MR?

Karl: I studied physics at TUM, and during my master's degree studies, Prof. Axel Haase supervised me in a project undertaken in collaboration with the Nuclear Medicine Department. The rest is history, as they say! I liked the project, and stayed with Prof. Nekolla and Prof. Schwaiger for my PhD.

Stephan: I was trained by Prof. Haase, too. I am a physicist and I have been working with Markus for almost 25 years on cardiac PET-MR and PET-CT.

Markus: I have trained in cardiology, and this is what drew me to nuclear medicine, which allows non-invasive imaging of cardiac function.

MRMH: Could you tell us a little about how this paper came about? What is the rationale for the study?

Stephan: The interesting thing is that we have been correlating perfusion data from MRI and PET for over 20 years! Back in those days, PET and MRI acquisitions were performed sequentially, whereas today we can acquire data from both modalities simultaneously. This

Karl Kunze

Stephan Nekolla

Kunze, K.P., Nekolla, S.G., Rischpler, C., Zhang, S.H., Hayes, C., Langwieser, N., Ibrahim, T., Laugwitz, K.L., Schwaiger, M. Myocardial perfusion quantification using simultaneously acquired $^{13}NH_3$-Ammonia PET and dynamic contrast-enhanced MRI in patients at rest and stress. Magn Reson Med. 2018;80: 2641-2654. DOI: 10.1002/mrm.27213
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27213

evolution is actually quite a fascinating story!

Markus: Initially, perfusion imaging was performed only using nuclear technologies, but with the advent of MRI it became clear that we had two modalities at our disposal for quantitatively assessing myocardial blood flow. For us, the logical consequence of this realization was to compare them. Subsequently, simultaneous PET-MR became available. In my opinion, the uniqueness of this platform is that it allows us to compare two distinct technologies in the same patient and under the same physiologic condition.

Karl: I actually came on board after the study was conceived. I would say Stephan and Markus have summarized its rationale perfectly.

MRMH: Your study showed differences in rest and stress perfusion ratios between MRI and PET. How can this be explained?

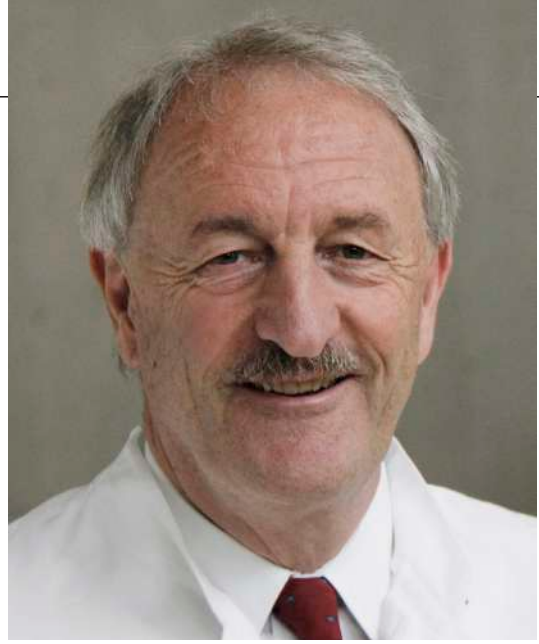
Karl: Our findings echo those of previous studies that compared MRI and PET, albeit not acquired simultaneously. Typically, resting perfusion is reported to be overestimated when using MRI as opposed to PET. One potential reason for this is the particular biodistribution of the contrast agent in MRI, which results in a hematocrit dependency of the final flow that we quantify. In other words, what we are observing is plasma flow, and correction factors are needed in order to make it comparable to blood flow. In this study, we aimed to obtain a better understanding of such systematic differences between the two modalities, which is very important when it comes to defining inter-patient cut-offs and thresholds for diagnosing certain disease patterns.

Stephan: This concept is not new to the nuclear medicine community. For instance, reference values can change between PET and SPECT, where we use different radiotracers.

Markus: First of all, we were happy that all the measurements correlated. This study was challenging to perform as we were trying to measure myocardial blood flow with both MRI and PET simultaneously: Physiology affects the derived measurements in different ways. However, the aim of this study was not to establish the specific thresholds that might allow us to obtain a diagnosis of CAD. Rather, we wanted to show systematic trends and compare different methods of analyzing dynamic MRI results in comparison to PET reference values.

MRMH: Could you comment on the advantages of simultaneous MRI and PET acquisition for the assessment of perfusion in these patients?

Markus: Our intention was to rigorously validate the two modalities in terms of perfusion quantification, and to prove that you can obtain reliable measurements from both. Having established this, it would be sufficient to use one or the other independently. However, PET-MR as a modality goes beyond blood flow measurements, as it allows us to use many different PET tracers and MRI sequences to investigate other tissue characteristics or functions. In short, the possibility of combining many parameters coming from both MRI and PET opens many possibilities for research.



Markus Schwaiger

Karl: I completely agree; MRI perfusion imaging offers a lot of other parameters to look at, such as permeability or vascular volume. This is very interesting from a research perspective and may allow even more extensive cross-use of information than we have seen to date. If one modality is unable to provide certain data, perhaps the other can help.

MRMH: What would you like to do next?

Markus: Ultimately, we would like to be able to replace invasive coronary angiography with multimodal imaging. The problem with PET-MR right now is that it does not visualize the coronaries as well as CT does. If we could include coronary MR angiography into this approach, and ideally coronary plaque imaging with specific tracers, a comprehensive characterization of CAD will be possible. Perfusion data integrated with information on regional coronary anatomy as well as with molecular signals suggesting the presence of unstable plaques are theoretically available with PET-MR. In the long term, this combination represents every cardiologist's dream!

Stephan: Twenty years ago, when we started doing PET perfusion, there was a real sense, in part of the community, that this was already something "you could actually do". But the fact is that, in terms of spatial coverage, what we generate now is the same as what was available back then, and we should really work to improve on this. At the same time, in seeking to develop the technology, we should also remember what it is that PET can uniquely depict, for instance inflammation.

Karl: Building on what Markus and Stephan have said, one of the things I hope this paper conveys is that it's probably not a wise idea just to replicate other modalities; instead, we need to appreciate the differences between them and develop new standalone paradigms for new imaging modalities such as PET-MR. ■

> *It's probably not a wise idea just to replicate other modalities; instead, we need to appreciate the differences between them.*
>
> –Karl Kunze

Flip angle is not the only parameter that varies in VFA T_1 mapping

INTERVIEW BY **AGAH KARAKUZU**

EDITOR'S PICK FOR JANUARY

Welcome to the first Editor's Pick of 2019! We are starting off this year's Q&A series with a reproducibility assessment study by researchers from the University of Zurich. We interviewed Yoojin Lee and Zoltan Nagy about their paper on establishing intra- and inter-vendor reproducibility of T1 relaxation time measurements at 3T, which shines a light onto one of the less prominent features of variable flip angle (VFA) T_1 mapping.

> *MRI scanners are built to aid humans in making diagnoses and in effect the scanners themselves are not required to be quantitative measuring devices.*
>
> –Yoojin Lee

MRMH: Can you tell us a bit about yourselves and how you came to be involved in MRI research?

Yoojin: I studied electrical engineering for my bachelor's, but I have always been interested in how the human body works. So, MRI was the ideal option for me. I saw my current position advertised on the ISMRM website and applied. That's how I started working with Zoltan.

Zoltan: I have a very similar story. I studied physics and math, but I, too, was always interested in the brain. My master's was already in physiology with single-cell patch-clamp recordings of synaptic transmission. I attended a summer program at the Karolinska Institute in Stockholm, and afterwards I switched to a PhD in MRI. It was exciting to go from studying single cells to the entire brain.

MRMH: Can you give us a brief summary of your paper and explain how this work fits in with your broader research goals?

Yoojin: More broadly, our aim is cortical parcellation, especially using diffusion datasets. We extract fingerprints (we call them feature vectors) and use them to distinguish cortical areas. To introduce more information into this feature vector, we decided to acquire quantitative T_1 maps. However, in seeking to establish that the datasets we use are comparable to those of others, we discovered that there was actually quite a big difference - about 10%. The difference could originate from several sources. For example, differences in B1 mapping methods implemented by vendors. We examined many possible sources and detailed them in our paper. We also performed a longitudinal study, where we scanned one subject in two Siemens scanners of the same model, and still found differences of around 1-2% which was higher than the test-retest variability. In addition, an-

Yoojin Lee skiing in the beautiful Swiss Alps.

Zoltan Nagy

Lee, Y., Callaghan, M.F., Acosta-Cabronero, J., Lutti, A., Nagy, Z. Establishing intra- and inter-vendor reproducibility of T_1 relaxation time measurements with 3T MRI. *Magn Reson Med.* 2019;81: 454-465. DOI: 10.1002/mrm.27421
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27421

other subject was scanned on the same Philips scanner before and after a software upgrade. Interestingly, the software upgrade led to a 2-4% differ ence in T_1 values.

MRMH: You did everything in your control to minimize vendor-based differences in data acquisition and used highly conservative ROI masks for the analyses. Yet, even so, inter-vendor variability was notable. Insights? Is there any way to adjust for it?

Yoojin: MRI scanners are built to aid humans in making diagnoses and in effect the scanners themselves are not required to be quantitative measuring devices. We for example expect a thermometer to give us a measurement that is pretty close to the true temperature. But the actual numbers in MR images can be anything as long as a human eye can detect an injury/disease/abnormality. In the actual pixel intensities there are so many sources of variability that it is impossible to match them across different scanners. Such differences make multicenter studies really difficult. I would say that manufacturers should work more on standardizing certain acquisition methods, such as B_1 mapping.

Zoltan: The research community has come a long way toward quantitative imaging, but given that MRI scanners are such complex instruments, we need the involvement of the vendors. This involvement could amount to as little as more convenient access to the scanner calibration and sequence parameters. Better yet, co-supervision of PhD students in an industry and academia setting would be great. Of course the above-mentioned collaborations may not be possible for logistic, IP or financial reasons, so I'll be happy if a quantitative MRI scanner just arrives on the market.

MRMH: If multiple imaging centers around the world were to decide to make their VFA data for T_1 mapping publicly available, what suggestions would you have for them?

Yoojin: Because of the complexity of MRI scanners and the sensitivity of T_1 relaxation time measurements to the design, settings or state of the individual components of a scanner, we would need as much information as possible, especially details about the RF pulse they use, the spoiler gradient moments and the RF phase cycling factor. For example, we know from experience, and mentioned it in our accompanying YouTube video, that in B_1+ mapping with the actual flip angle method, setting the spoiler gradients properly can increase test-retest reproducibility. But really it would be far better if they were to provide the pulse sequence itself.

MRMH: The potential use of relaxation time mapping in clinics is a decades-old debate. What is your take on it?

Zoltan: I don't doubt that quantitative imaging could provide useful biological markers for clinical practice. But even if the methods for quantitative MR imaging were firmly nailed down the results would only be as good as the state of the scanner. At our research sites quality assurance scans are run regularly (weekly or even more often than that). In contrast, some clinics hardly ever do quality assurance scans and, depending on the site, the scanners may be older and hence unable to cope with all the current state-of-the-art methods. In some cases, vendors come in a few times in a year and do their routine adjustments. If something breaks down, you might not know about it for months. As such, "a clinical method" may not mean the same thing at every site. I always say that when we buy a scanner it is rather like a Toyota, mass produced on a conveyor belt. But the thing is, we need Formula 1 performances from it! Research is therefore very much about "pimping" our scanners.

Yoojin: I think it will take some time for relaxation time mapping to be used in clinics. If you want to use it in diagnostics, then the effect size of the specific disease should be significantly higher than the T_1 variability we measured, which was sizable in the multicenter setting. We should solve this issue first, then maybe we can use T_1 maps in clinics.

Zoltan: At the advanced neuroimaging workshop organised by ISMRM in Korea several presentations and the ensuing discussions dealt with reproducibility. We agreed that granting agencies are not very interested in funding reproducibility studies. In my view, if you have $100 million to allocate to research, it would be beneficial for the community as well as the agency to allocate a certain percentage of that allowance to quality assurance and reproducibility research. Otherwise we/they risk wasting resources on efforts that produce false positives or negatives simply because nobody ever bothered or had a chance to check the variance components of the chosen method. Having said this, we cannot deny that there is an increased awareness of the importance of reproducibility. The quantitative imaging biomarkers alliance (QIBA) has been working toward this goal for years, the OHBM Replication Award will be given out for the third time this year in Rome, and the Quantitative MR and Reproducible Research ISMRM study groups were recently formed as well. We are happy to be part of this movement and delighted that our efforts and results were selected as the editor's pick. ■

Antoine Lutti and Zoltan Nagy.

> *When we buy a scanner it is rather like a Toyota, mass produced on a conveyor belt. But the thing is, we need Formula 1 performances from it!*
>
> –Zoltan Nagy

Can MR-based electric impedence tomography measure neural activity?

INTERVIEW BY **JIAEN LIU**

EDITOR'S PICK FOR JANUARY

Rosalind Sadleir and Munish Chauhan are old friends of Highlights. In our previous interview with them we found out about their career paths and their work on multi-shot echo-planar MR-based electrical impedance tomography (MREIT). They recently published a new paper in MRM in which they theoretically investigated the effect size of tissue conductivity changes caused by neural activity and the feasibility of measuring these changes using MREIT.

Rosalind Sadleir

MRMH: Could you briefly introduce the history of brain activity measurement based on electrical impedance changes?

Rosalind: It has been shown that changes in voltage across cell membranes in active brain tissue caused by either intrinsic internal sources or externally administered current can be measured. But one aspect that has been overlooked is the changes in cell membrane conductance that occur around the same time as these membrane voltage changes. Inactive neuronal cell membranes are more isolating to the passage of an external electrical current than the membranes of active cells. This idea, studied through the fast neural electrical impedance tomography (EIT) technique, has been around for almost thirty years. With this technique, very subtle conductivity changes related to brain activity can be monitored using an electrode array. But experimental evidence has shown that it is necessary to remove the skull of the animal, and even use implanted electrodes, in order to measure these changes practically. We took this neuroimaging concept from EIT and adapted it to the field of MRI-based electrical property imaging. Basically, we measure the conductivity changes on the basis of MR signal phase changes, using the so-called MREIT method. This method has the significant advantage of allowing us to measure the signals not only noninvasively but also in the particular tissue we are interested in.

Munish: This idea is an extension of previous neural current density imaging attempts using MRI. People have tried using MRI to directly measure neural currents, which change the B_0 field and therefore MR phase images. But the problem is that the extremely small neural currents only generate magnetic field changes at around the 10^{-12} Tesla level, which is difficult to detect above the noise floor. We use externally injected current to boost the small phase changes caused by changes in membrane conductance. The external current pathways and therefore recovered phase images change because of the slight cell membrane conductance changes occurring with activity. The amplification is related to the external current magnitude.

MRMH: Do your results confirm previous findings in similar fields?

Munish Chauhan at the 2018 ISMRM meeting in Paris.

Sadleir, R.J., Fu, F., Chauhan, M. Functional magnetic resonance electrical impedance tomography(fMREIT) sensitivity analysis using an active bidomain finite-element model of neural tissue. *Magn Reson Med.* 2019;81: 602-614.DOI: 10.1002/mrm.27351
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27351

Rosalind: In the field of neural current MRI, I do not believe there have been any reports of successful *in vivo* experiments, although effects have been observed *in vitro.* Even if it is possible to somehow boost the very small signal above the noise floor, there remains the considerable problem of cancellation of the fields caused by the various electrical dipole orientations within a voxel. The conductance contrast we work with does not have this issue. More brain activity should increase the conductance. We have verified the existence of our contrast in *vitro,* and we are presently preparing *in vivo* work.

MRMH: For the *in vivo* situation, do you anticipate any interference of the external current with the neural activity?

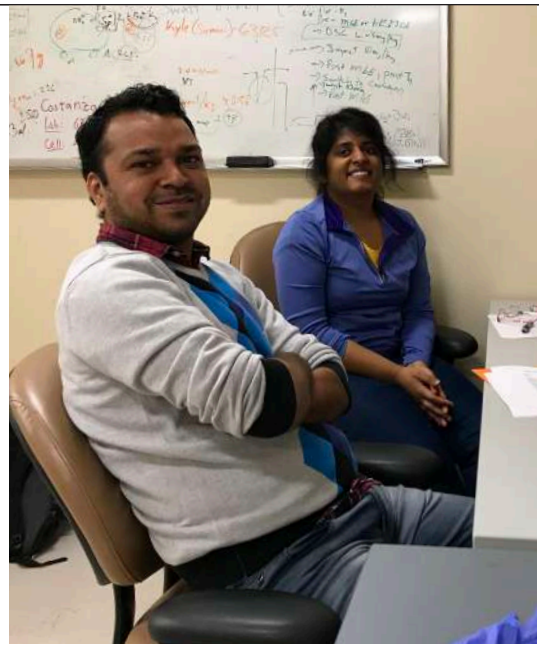
Rosalind: It's very likely that any injected current will change the level of activity. We therefore always assume that when you have intrinsic activity and apply MREIT imaging currents, this will change the activity in some way. Basically, the way to test this technique, as we have done in our studies, is to compare this effect on the activity both with and without other treatment. For example, in our *in vitro* study, we compared spontaneous activities in Aplysia when the animal underwent MREIT both with and without potassium chloride treatment. In that case potassium chloride increased the spontaneous activity level compared with the control medium.

Munish: The technique can also be tested using optical manipulation, on salamander retina cells, for example. In this case, we can synchronize the optical stimulus with the MREIT current, whereas activities from Aplysia are spontaneous. We can concentrate the activity in response to the light just at the time we apply the imaging current.

MRMH: What else can you tell us, broadly, about your lab's work?

Munish: In another project, we image current density distributions in the human brain during transcranial direct current stimulation (TDCS) using MREIT methods. During TDCS, current is applied to the scalp and stimulates the brain. The reason we are interested in observing current distribution during TDCS is that it may help us to better understand the mechanism of its effect on the brain. The beauty of this method is that it also allows us to combine DTI and MREIT data in order to calculate the conductivity tensor of the brain in vivo. In addition, we are working on using the multiband technique in order to accelerate this data acquisition and thus cover more of the brain. We have found that subjects do not usually enjoy having the (MREIT) imaging currents applied for too long inside the scanner.

Rosalind: In the TDCS field, people want to concentrate the current on a particular structure, but have mostly relied on computational models in order to figure out where to place the electrodes. We are seeking to move this field forward by measuring an individual's conductivity distributions in order to better define the electrode positions. In addition, our approach might also benefit a field called EEG-based source imaging, which locates sources in the brain from EEG recordings, but needs correct conductivity distributions for accurate reconstructions.



Munish Chauhan with Neeta Ashok at the Barrow Neurological Institute.

MRMH: What do you see as the possible *in vivo* application of your methods?

Rosalind: In principle, MREIT-based functional imaging could be a useful alternative to BOLD fMRI. It provides a more direct indication of neural activity than BOLD does, and with similar resolution. Also, it could exploit existing fMRI analysis pipelines to analyze statistical differences based on our contrast. However, when working ***in vivo,*** we also need to consider the effect of blood flow changes, which can change the conductivity of tissue. We might exploit the different temporal scales of the two approaches to address this potential problem. For example, we can saturate the BOLD response or observe the conductivity changes before blood flow effects appear. We are also working on boosting the SNR by using either high-field or implanted DBS electrodes in order to obtain larger or phase changes. We may end up using carbon electrodes to get rid of the susceptibility artifacts caused by metal electrodes.

MRMH: What's your advice for people starting to work in this field?

Munish: Our collaborator in Korea published a paper in IEEE (https://ieeexplore.ieee.org/document/7994618) that introduced the principle of MREIT and current density imaging, and they have also established an open source Matlab toolbox. People will need expertise in MRI and electrical engineering to work in this field. But in many ways it's less complicated than the related EIT field, since MRI can provide information on current flow inside the brain. ■

> *It's very likely that any injected current will change the level of activity. We therefore always assume that when you have intrinsic activity and apply MREIT imaging currents, this will change the activity in some way.*
>
> –Rosalind Sadleir

Ultrafast 3D Bloch-Siegert B_1^+ mapping using variational modeling

INTERVIEW BY **MATHIEU BOUDREAU**

EDITOR'S PICK FOR FEBRUARY

This Editor's Pick interview is with Andreas Lesch and Rudolf Stollberger, researchers at Graz University of Technology in Austria. Their paper presenting a variational modeling algorithm for reconstructing B_1^+ maps from highly accelerated Bloch-Siegert data demonstrated that even acceleration factors of up to 100 can produce good quality B_1^+ maps, allowing quantitative maps to be acquired in the space of a single breath-hold. We recently spoke with them to find out more.

Andreas and Rudolf with the city of Graz in the background.

MRMH: Andreas and Rudolf, could you introduce yourselves and tell us a little bit about your backgrounds?

Andreas: I completed my bachelor's degree in biomedical engineering in 2011 here in Graz, and got my master's degree in the same field in 2014. For my master's I focused mainly on medical imaging, and my thesis was on T_1/T_2 mapping using bSSFP with slice profile correction.

Rudolf: I started out in electrical engineering, also doing some courses in biomedical engineering. This was around the time that the first MRI scanners were appearing. I then went to Zurich to study MRI, before coming back to Graz, where I worked in the clinic for about 20 years in the medical physics and radiology department. Now I'm at the Graz University of Technology (Technische Universität Graz), as a professor of medical engineering.

MRMH: Before we get into the details of your work, could you explain the concept of variational modeling?

Andreas: Variational modeling is based on a minimization procedure of a cost function that includes a data fidelity term, where you measure the similarity of your reconstructed image to the measured data, and regularization terms, which model some behaviors of the underlying image.

Rudolf: In principle, you try to find an unknown function that represents the image you are looking for. In variational modeling, we have more flexibility than in traditional fitting since we do not define an explicit function. There are a number of solutions depending on encoding, sampling and the noise of the given problem, and therefore it's necessary to add some properties of the solution, which is done by regularization.

MRMH: Please give us a brief overview of your work.

Andreas: In this paper we described a mathematical formulation that we developed in order to regularize the underlying B_1^+ field, and developed an image reconstruction algorithm to produce B_1^+ maps out of highly undersampled data. Furthermore, we evaluated the influence of different undersampling patterns, how to choose the right regularization parameters, and applications to different anatomical regions.

Rudolf: Basically, we were extending the Bloch-Siegert method to variational modeling.

MRMH: Did any of your results surprise you?

Andreas: We were surprised that our approach worked so well. Even with very low amounts of data, we could still achieve good estimates of the B_1^+ field, which I hadn't expected. I was also surprised that the optimal

Lesh, A., Schloeg, M., Holler, M., Bredies, K., Stollberger, R. Ultrafast 3D Bloch-Siegert B±-mapping using variational modeling. *Magn Reson Med.* 2019;81: 881-892. DOI: 10.1002/mrm.27434
https://onlinelibrary.wiley.com/doi/epdf/10.1002/mrm.27434

strategy was to use the same undersampling patterns for both acquisitions.

Rudolf: In dynamic imaging, it's typical to change the sampling pattern from frame to frame. We assumed this would be the case for this application too, but our results showed that it is not.

Andreas: It could be that our algorithm can reduce artifacts more properly if they appear in the same way in both images.

MRMH: You reported an accelerating factor of up to 100 for this technique and application – do you think this can be improved even further, or are we near the information limit?

Andreas: [laughs] In terms of k-space lines, I don't think much more acceleration would be possible, because we only have a very small amount of data. But we are currently working on combining this method with an EPI readout in order to improve the speed of the measurement without reducing the quantity of information acquired.

Rudolf: We should really discuss whether it is even acceptable to call it an "acceleration" of a factor of 100, given that we found that value for a specific image matrix size. Theoretically, if we acquired a higher resolution image with the same field of view, then we might be able to use a higher acceleration factor to reconstruct the profile of the B_1^+ function. So it may not be reasonable to talk of an acceleration in the same way as we do for other techniques used to reconstruct conventional MR images.

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

Andreas: We are using it in some quantitative MRI projects that I am partially involved in. I also did some work on fat-water separation, another situation in which there is an important background field, the B_0 field.

Rudolf: For me, this is a special topic because my PhD thesis was on B_1^+ mapping [smiles]. It was on the double angle technique; I first presented it in an abstract in 1988, and later on I published it in an MRM paper. Here, the Bloch-Siegert method has one advantage over older, more common techniques, namely that it also produces the absolute value of B_1^+ This is important for certain applications, such as CEST (Chemical Exchange Saturation Transfer) imaging, which we are also exploring at the moment.

MRMH: Why did you choose to make your code open source?

Andreas: Because we wanted to share our results with other researchers, in the hope that they might further develop them or to use them for their own research. Had we kept the code for ourselves, this would only have created more barriers in the usability of the work we presented in the paper.

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

Andreas: For me, it's very important to do activities that relax my brain! I really enjoy hiking and climbing in the mountains. I also like to travel a lot, all round the world.

Rudolf: Well, I grew up in the Austrian mountains, so I'm also an outdoor guy. I like hiking, mountaineering, skiing and biking in the summer. I also like gardening at home, where I grow tomatoes and other Mediterranean plants and herbs. ■

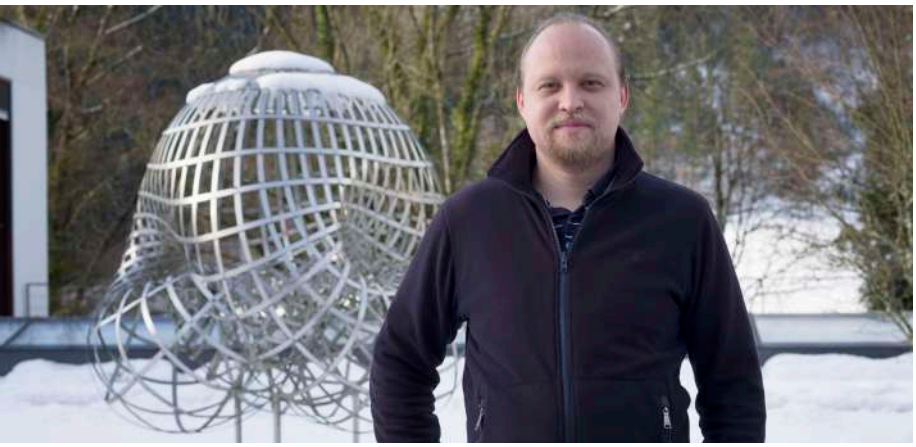
Part of the MR group during a skiing event in early winter.

Deep learning to speed up cardiac imaging

INTERVIEW BY **AGAH KARAKUZU**

EDITOR'S PICK FOR FEBRUARY

MR image reconstruction has become a magnet for deep learning and cardiac imaging is definitely playing a part in this! For our second Editor's Pick of the month, we interviewed Andreas Hauptmann and Vivek Muthurangu about their paper on real-time artifact suppression for accelerating real-time cardiac exams using deep learning. It is worth noting that their method can reconstruct images superior in quality to those obtained with compressed sensing, yet without sacrificing acquisition speed.



Left: Andreas Hauptmann at the Mathematical Research Institute of Oberwolfach in Germany; Right: Vivek Muthurangu

MRMH: Can you tell us a bit about yourselves? What sparked your interest in MRI research?

Vivek: I've been involved in MRI since 2002. I am a clinician, but I also work in MRI physics. From a clinical point of view, my main interest is congenital heart disease both in children and adults, so I am very interested in fast imaging. As you can imagine, overcoming problems like breath holding and motion is really important if you are working with children.

Andreas: I am relatively new to MRI. I got my PhD in applied mathematics from the University of Helsinki. My research dealt with inverse problems and focused in particular on medical imaging. About two years ago I started my postdoc at University College London in the Centre for Medical Image Computing, where our research group was already collaborating with Vivek's group. This led us to discuss how we might combine our expertise, and we came up with the idea of applying deep learning to cardiac imaging.

MRMH: Can you explain your paper in a few sentences? What was the driving motivation for it?

Andreas: When we first discussed the possibility of using deep learning for reconstruction, we realized that we already have a large dataset of magnitude images from the past 10 to 20 years that might serve as the ground truth for a supervised training project. We created retrospectively undersampled data, obtained the corresponding undersampled reconstructions, and trained a network to remove noise and artifacts, basically a sort of denoising network. As the first tests with the simulated data worked out really well, we proceeded to use this trained network on prospectively undersampled data. We were quite happy with the results from this reconstruction, too. For us, it was not necessary to beat compressed sensing (CS) in terms of reconstruction quality, but really to obtain clinically useful reconstructions with a considerable speed-up. As a clinician, image quality is not enough without information quality. I am happy to sacrifice a bit of image quality, as long as the information is the same. Speed is important, though, and that was the real push here.

Hauptmann, A., Arridge, S., Lucka, F., Muthurangu, V., Steeden, J.A. Real-time cardiovascular MR with spatio-temporal artifact suppression using deep learning-proof of concept in congenital heart disease. *Magn Reson Med.* 2019;81: 1143-1156. DOI: 10.1002/mrm.27480

https://onlinelibrary.wiley.com/doi/epdf/10.1002/mrm.27480

Vivek: I would like to talk about clinical motivations. My group is involved in developing non-Cartesian real-time imaging, leveraging various kinds of reconstruction, ranging from parallel imaging to k-t SENSE. More recently we have started using CS and have been getting pretty good image quality. The big problem is reconstruction time, even when the reconstruction is performed on a GPU. For example, a recent spiral SSFP real-time sequence that we developed can take up to 10 seconds per slice to reconstruct, depending on the hardware. That may not sound like a long time, but if you are attempting to complete the whole scan in 10 minutes, reconstruction time becomes an issue. So, we decided to take a different approach by leveraging the large amount of image data that we already have.

MRMH: The model you trained with retrospectively undersampled data worked like a dream in reconstruction during new *in vivo* scans. Did this outcome exceed your expectations?

Andreas: Of course our approach didn't work right from the beginning on the prospective data. The first tests on the scanner gave decent results, but they were far from perfect. The most important aspect in order to get the trained network working for prospective acquisitions was consistency between simulations and the data acquired from the scanner. Once we managed to get the undersampling artifacts in the simulations to resemble, sufficiently closely, those from actual prospective data, the network indeed worked like a dream, and yes, we were really surprised to see how well it worked in the end!

Vivek: Personally, I was extremely surprised to obtain such good results for both retrospective and prospective data. An important aspect of our method is that the synthetic data must be created in such a way that it closely resembles real-time data that is going to be acquired in real life. This requires a little bit of work when you start with retrospectively gated Cartesian Cine MRI data and are trying to create pseudo real-time radial acquisitions. You have to do this properly and if you get it right, the reconstruction works extremely well. Furthermore, this reconstruction outperformed CS in terms of image quality. This is a really important point, as I and my clinician colleagues often find that CS data has an odd, cartoon-like image quality. One of my colleagues calls this the "disneyfication" of cardiac MRI. We don't see that in the machine learning reconstruction.

MRMH: The choice of sampling pattern seems a critical aspect, and continuously rotating tiny golden angle sampling (tGAro)t comes out top in this regard. How are you going to make use of this information in your future studies?

Andreas: Yes, the sampling pattern is really crucial for denoising temporal reconstructions. For the network to perform properly, we need the aliasing artifacts to be noise-like structures in time. That means our network primarily denoises in the temporal dimension, rather than learning how to reproduce structures from the training data. In fact, even if we change the target completely it manages to create good reconstructions without reproducing features learned from the training on hearts only. For our approach to work properly, in future studies, we will really need to use efficient sampling patterns creating artifacts that are incoherent in time.

Vivek: Aliases have to look like noise in our approach. The whole idea is to reformulate reconstruction as a denoising problem. For example, we did some testing with spiral acquisitions and found that the results were not as good as with radial acquisitions. This is because aliases are less incoherent and don't have a noise-like appearance. A lot of work has been done by the CS community to produce these noise-like artifacts with different types of sampling. I think we can build on these findings for machine learning reconstruction, too.

MRMH: Bias in training data is not desirable for diagnostic efficacy. How do you see initiatives such as ISMRM raw data format (ISMRM-RD) clearing the way for consistency?

Vivek: We have run a few tests on the effect of bias in reconstruction. The whole network was trained on images from patients who have two ventricles. We prospectively scanned one patient who had one ventricle, and it still worked beautifully. Initially, bias was something we were worried about, but the way we implemented our machine learning reconstruction seems to overcome this problem. As for ISMRM-RD, I think it is a fantastic resource for machine learning reconstructions. However, for our implementations, we need magnitude data and there needs to be a parallel standard for this type of data.

MRMH: In this ever-changing artificial intelligence (AI) landscape, can you imagine AI-powered reconstructions as end products able to fit clinical reality?

Andreas: Our driving incentive for the study was to see whether our approach was clinically applicable. We have previously encountered some limits with CS reconstructions, especially in terms of reconstruction speed. Given the competitive results of our study, I see a big opportunity here for the clinical end-use of this method and machine learning in general.

Vivek: We shouldn't develop techniques if we can't use them clinically. For these machine learning reconstructions to have clinical uptake, people have to believe in them. This means that you can't just validate new techniques in 40 patients and convince people that they work. You have to demonstrate this in hundreds of patients from multiple sites. People have bigger concerns about machine learning, as it is considered a sort of a black box. I think machine learning is a technique that holds clinical promise, but we need to be transparent in the way it is developed. ■

> *As a clinician, image quality is not enough without information quality.*
>
> –Andreas Hauptmann

Fusing diffusion and functional MRI with HARFI

INTERVIEW BY **TOMMY BOSHKOVSKI**

EDITOR'S PICK FOR MARCH

For our first Editor's Pick for March, we were pleased to talk with Kurt Schilling and Bennett Landman about their new model for high angular resolution functional imaging.

Kurt Schilling

Bennett Landman

MRMH: Can you tell us a bit about yourselves and how you got involved with MRI?

Kurt: After my undergrad studies I became involved in product development in the medical device industry, specifically focusing on implants and instruments for total knee surgeries. I then applied to Vanderbilt and started working on a project with Adam Anderson. From there I became interested in diffusion MRI, particularly in validating diffusion measurements, microstructure modeling, and connectomics.

Bennett: Mine is a similar story. I was working on image processing for smartphones and connected devices and on visual optimization. After that, I got a job in a science startup company which just happened to be working with EEG and MRI. After a couple of years I joined Jerry Prince's lab at Johns Hopkins before going into Vanderbilt Electrical Engineering where John Gore leads the imaging institute. That's where I met Kurt, and it just sort of snowballed from there into this big data connectomics endeavor.

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

Kurt: With HARFI (high angular resolution functional imaging), we presented a new way of analyzing resting-state BOLD contrast. Specifically, instead of looking at the global connectivity in gray matter, which is the conventional approach, we looked at local orientation information in the white matter. The interesting part of this was being able to use our experience in diffusion MRI to do fMRI fiber tracking in the white matter.

Bennett: This came out of a high angular resolution validation grant. We were doing implementation and characterization of basically every HARDI method possible. Zhaohua Ding and John Gore were working on this new idea of a functional correlation tensor (FCT). Then Kurt came along and put everything together. Basically, it's about thinking of fMRI not just as a voxel-by-voxel comparison, but rather as a field of connectivity. If you look at this field of connectivity, there start to emerge biophysical patterns that seem to be more than just noise.

MRMH: How should we interpret the functional connections/fibers?

Kurt: They could possibly be interpreted in terms of microfields due to susceptibility fields that cause correlated noise, which is why we get correlations in certain directions. This could be why we're actually getting these orientations that seem to agree with what we expect from the structure. Alternatively, and this is possibly more exciting, we hope these fibers are actual functional activity because they are slightly different from what we would obtain if we just took the diffusion tensor, which we know is structural information. In short, this method could be a really unique way to bridge the gap between functional and structural.

Bennett: I don't think it's necessarily an either/or situation. It could be this microarchitecture, the structural connectivity, that is shaping the noise, meaning that we're not talking about a Gaussian random field, but rather some sort of overlaid local structural pattern. At the same time, it could also be the resting state of the

Schilling, K.G., Gao, Y., Li, M., Wu, T.L., Blaber, J., Landman, B.A., Anderson, A.W., Ding, Z., Gore, J.C., Functional tractography of white matter by high angular resolution functional-correlation imaging (HARFI). *Magn Reson Med.* 2019; 81: 2011-2024. DOI: 10.1002/mrm.27512

https://onlinelibrary.wiley.com/doi/pdf/10.1002/mrm.27512

Medical-image Analysis and Statistical Interpretation (MASI) Lab.

white matter connectivity. This is a form of connectivity, but it's neither of the two types of connectivity that we've seen before.

MRMH: You did your analysis on resting-state fMRI data. How would you expect the results to differ if you were to do it on task-based fMRI data?

Kurt: We have an ISMRM abstract this year which describes our application of this model to task-based functional data. Our work was based on the hypothesis that the orientation distributions and the resulting tractography would change under different functional loading scenarios. We chose to use a simple task because, from the conventional fMRI analysis approach, we know which brain areas are involved in the processing of that task. We compared the resting-state and the task-based approaches and resolved very large differences in spatial orientation between them, but we're not yet sure how to interpret these differences. The next step would be to actually do tractography on both tasks.

Bennett: This raises another area of interesting math and modeling issues in terms of what we do regarding statistics and how we interpret tasks by confound-related changes. We need to start thinking about how to properly conduct the preprocessing steps that have been used for regular fMRI and task-based connectomics when the underlying structure is a tensor or this tensor correlation field.

MRMH: How do you see HARFI within the bigger picture of fusing two complementary modalities, specifically dMRI and fMRI, to better understand the brain?

Kurt: When we first introduced this technique and looked at the orientation information we got, we were very excited because of the fact that the functional data doesn't have to be bipolar or symmetric. As a result, we got three-way crossings, fanning and bending that diffusion would tell us are ambiguous orientations. We think it can increase the specificity of the fiber tracking process itself by telling us where we might expect a bending as opposed to just some dispersion of fibers. It's a unique method by which diffusion and fMRI can now give us very similar orientations that can be analyzed in a similar way but that may mean something different.

Bennett: I'll agree with that. We don't really understand where exactly HARFI fits between functional connectivity and structural connectivity, as it doesn't really seem to be either. It's some sort of hybrid, and we really need to understand where it fits. That's what makes it exciting and interesting, because there isn't an obvious experiment to do.

MRMH: Besides science, what do you like to do in your spare time?

Kurt: Well, we live in Music City and I love going to country concerts. You can just walk down the street and find live music at Dunkin' Donuts. I also like playing sports and getting involved in the community.

Bennett: I'm on a mission to explore our state parks. We love visiting them with my kids and seeing the parks in all the different seasons. I come from California, which I love. I'm still a Californian, but when you fly into Tennessee, it's green, not golden. There's just life everywhere. ■

> *We don't really understand where exactly HARFI fits between functional connectivity and structural connectivity, as it doesn't really seem to be either.*
>
> – Bennett Landman

Cutting corners with a circular echo-planar sequence for fast volumetric fMRI

INTERVIEW BY **ATEF BADJI**

EDITOR'S PICK FOR MARCH

For our second Editor's Pick for March, we are thrilled to talk to Christoph Rettenmeier and Andrew Stenger about their latest paper entitled "A circular echo planar sequence for fast volumetric fMRI".

Christoph Rettenmeier in front of the MRI scanner at the University of Hawai'i/Queen's Medical Center.

Rettenmeier, C., Maziero, D., Qian, Y., Stenger, V.A. A Circular echo planar sequence for fast volumetric fMRI. *Magn Reson Med.* 2019;81: 1685-1698. DOI: 10.1002/mrm.27522
https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.27522

MRMH: Let's start with a little bit about you and your backgrounds. How did you both become involved in MRI research ?

Christoph: I did my PhD in molecular chemistry at the University of Heidelberg, Germany. We had a well equipped NMR laboratory where I used to spend hours acquiring NMR spectra. I got really interested in learning more about MR research, and that's how I ended up switching fields from chemistry to more engineering-based MRI.

Andy: Mine is a similar story. I did a PhD in physics at Ohio State University where they had the first 8 Tesla MRI scanners. I took a class in MRI, and wrote a paper on BOLD fMRI when the field was in its infancy. After my PhD, I went to the University of Pittsburgh where I met Doug Noll, a prominent MRI researcher, who taught me all about fMRI sequences. I stayed there for almost nine years, before moving to Hawaii about 14 years ago. I have been working in the field of MRI ever since.

MRMH: Before we get into the details of your recent paper, could you explain the concept behind the circular echo planar imaging (CEPI) sequence?

Christoph: The main attribute of this sequence is its reduced trajectory, which is similar to those of standard EPI sequences, but instead of going through the whole square coverage of k-space, you end up getting rid of the edges and thus form a circular shape. We are basically cutting the corners, and this reduces the overall readout length and gives the technique an edge in terms of speed. In addition, we integrated it into a generalized reconstruction framework.

Andy: I think using a generalized framework is, in a way, more important than the actual trajectory that we're able to use. If you just think of it as a spiral trajectory and throw it into this new, non-uniform, fast free transform reconstruction framework, you can use all the tricks that people are already using for model-based reconstruction, including compressed sensing. In our case, we were able to successfully model ghosting, at

MRI Group photo in front of the UH/QMC MRI Research Center. Left to right: Danilo Maziero, Christoph Rettenmeier and Andy Stenger.

least for the Siemens scanner that we were using.

MRMH: What are the pros and cons of using the CEPI sequence as opposed to other sequences for fast fMRI?

Christoph: We already mentioned that CEPI is faster. The flip side, though, it is that we lose a little bit of SNR because we don't have that many sampling points, but I would say that's a minor issue. The other flip side is that the reconstruction is a bit more complex, computationally more demanding, and takes a little bit longer. It's not just a plain fast Fourier transform. But again, this isn't a major issue.

MRMH: Regarding your reconstruction, is it easy to get hold of the necessary reconstruction algorithm?

Christoph: We use the toolbox developed by the Fessler lab at the University of Michigan, which is publicly available.

Andy: I think you could use any of the existing image reconstruction toolboxes, such as the Michigan image reconstruction toolbox (MIRT) for example. The only thing is, you might have to add a small ghost correction term, but that's very simple to do.

MRMH: Where do you see this method gaining traction?

Christoph: We developed it with a view to applying it to fMRI, to see how fast we can make the acquisition. We think it's an interesting tool, and will probably continue to look into its application in the field of fast fMRI. However, as has been mentioned before, provided you have an EPI readout train, you could potentially use CEPI instead to make it a little bit shorter. The real question would be: is it worth it for your particular application? That's what you have to ask yourself, but in principle, it's applicable to all EPI sequences.

MRMH: Can you tell us a bit about the ghost correction approach? What's special about it?

Christoph: We measured the artifact and then corrected it by using a constant and linear term base. We figured that the constant term itself is actually close to zero and can be disregarded with our system. We don't know whether this is true with other systems as well. In our case the approach involved simple subtraction of correction of the linear term. You can add that information prior to the reconstruction by just one line of code.

MRMH: And I guess our last question is what should people do if they want to use this sequence?

Andy: In our case, we inserted the gradients into the system as an external file, so people need a sequence that can do this; if they have that, then we would be more than happy to give them the MATLAB code to generate all the waveforms as well as the reconstruction. However, if they can't insert the gradient as an external file, they could probably program it themselves on the scanner. ■

> *We are basically cutting the corners, and this reduces the overall readout length and gives the technique an edge in terms of speed.*
>
> – Christoph Rettenmeier

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.

Atef Badji

Magnetic Resonance in Medicine Highlights Editor

Atef is an MD, 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.

Erika Raven

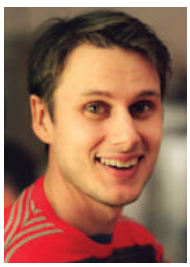
Magnetic Resonance in Medicine Highlights Editor

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.

Tommy Boshkovski

Tommy is a PhD candidate in the NeuroPoly lab at the Institute for Biomedical Engineering at Polytechnique Montréal. His research focuses on introducing quantitative myelin metrics to the study of brain dynamics. Tommy is a contributor to the ISMRM online education program, as well as to the ISMRM blog, MR Pulse. In his spare time, he enjoys watching sci-fi movies and medical TV shows.

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.

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. He is now post-doc at INSERM Toulouse working with a neurosurgeon. In his free time, Tanguy likes playing rugby, drinking wine, and eating frog legs.

Giulia Ginami

Giulia obtained her PhD from the University of Lausanne (Switzerland) in 2016, with a thesis focusing on coronary MR angiography. Subsequently, she moved to London (United Kingdom) where she continued her research experience in cardiac MRI as post-doctoral Research Associate at King's College. Recently, Giulia has joined Siemens where she is currently the Product Marketing Manager for the hybrid MR-PET system. Giulia enjoys running, skiing and tennis - both as a player and as a supporter.

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 the OHBM blog. He enjoys graphic design, skiing and exploring specialty coffee.

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 developing techniques for high resolution breast diffusion weighted imaging (DWI). She also enjoys downhill and water skiing.

Emilie McKinnon

Emilie is an MD-PhD Candidate at the Medical University of South Carolina. She is currently finishing her PhD which focused on the application and development of diffusion MRI techniques at high b-values. In her free time, Emilie plays competitive roller derby for the Lowcountry Highrollers and for the South Carolina state team. In these circles she is better known as Waffle, named after the delicious treat from her home country Belgium.

Raman Saggu

Raman is the preclinical MRI neuroscientist at the German Center for Neurodegenerative Diseases (DZNE) where she established experimental neuroimaging on the 11.7 T/ cryocoil MR system in 2012 and has been working on the system ever since. Raman was awarded her D.Phil. from the University of Oxford and has extensive experience imaging neurodegenerative disease models including cerebral inflammation, stroke, cerebral malaria, vascular dementia, ageing and Alzheimer's Disease. Raman is a professionally-trained classical dancer and enjoys performing. She is engaged with organisations working to highlight women in science and technology.

Holden Wu

Holden is an Assistant Professor in the Department of Radiological Sciences at the University of California Los Angeles. Before joining UCLA, he completed his PhD in Electrical Engineering and postdoctoral training at Stanford University. Holden's current research focuses on developing new quantitative MRI and real-time interventional MRI techniques for cancer and metabolic diseases. In addition to research, Holden enjoys reading history and non-fiction books, listening to music, and learning to play the ukulele!

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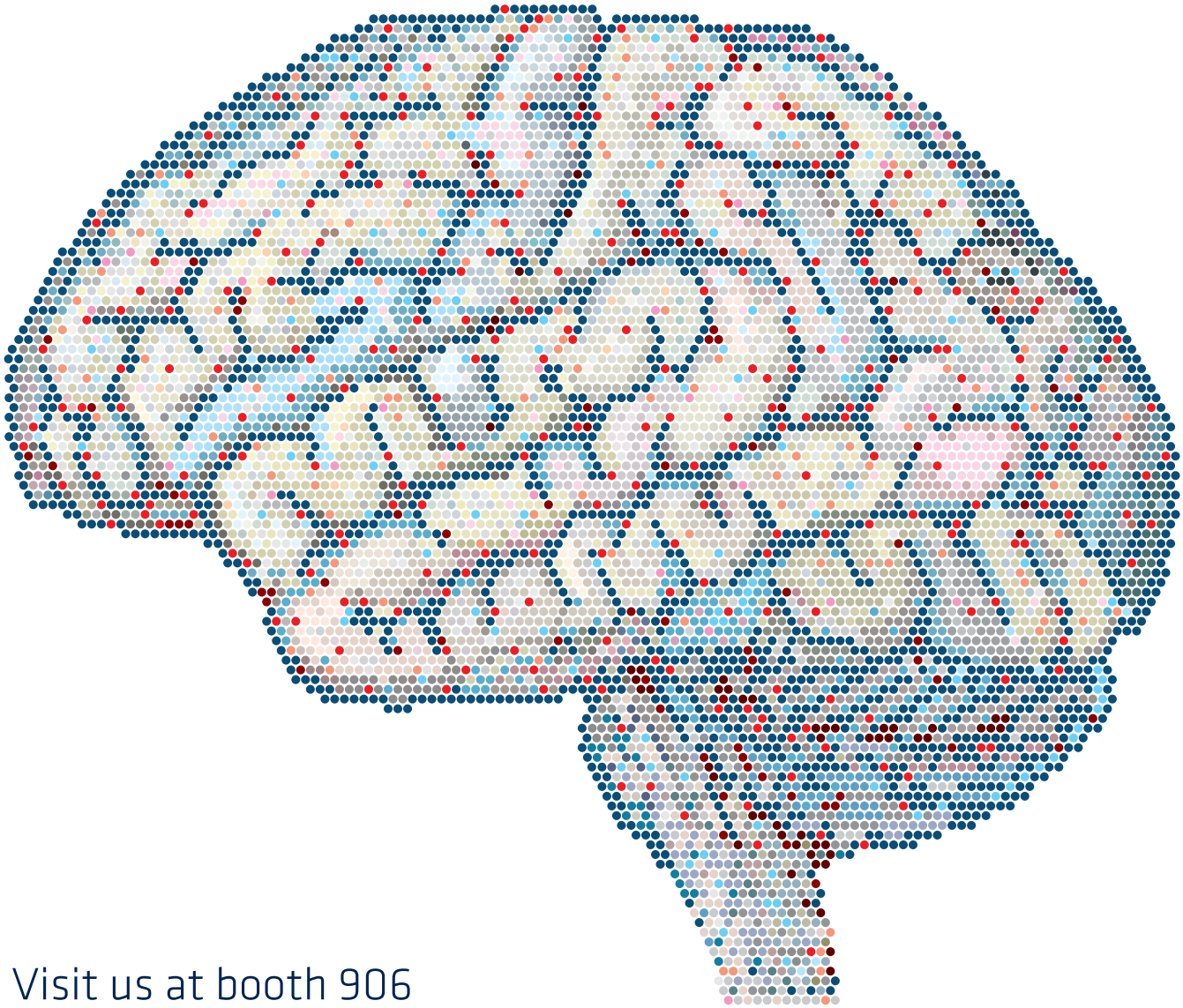

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