

# Magnetic Resonance in Medicine HIGHLIGHTS

## Q&As

with Authors  
of Editor's Picks

## Kawin Setsompop

The quest for speed

Profile of  
ISMRM President

## Jim Pipe

## Erwin Hahn

AN INTERVIEW BY  
DAVID FEINBERG

ISMRM



WILEY

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## CONTENTS

### COVER STORY

#### 2 ERWIN HAHN

The transformative genius of Erwin Hahn

INTERVIEW BY DAVID A. FEINBERG, COVER PHOTO BY JOSEPH HOLMES

### RESEARCHER PROFILE

#### 10 ISMRM PRESIDENT JIM PIPE

On ISMRM's role in revolutionizing healthcare

INTERVIEW BY ERIKA RAVEN AND NIKOLA STIKOV

#### 13 KAWIN SETSOMPOP

To SMS and beyond: Kawin Setsompop on the quest for speed

INTERVIEW BY ERIKA RAVEN AND NIKOLA STIKOV

---

### Q&A | EDITOR'S PICKS

#### 16 BO ZHAO AND ZHI-PEI LIANG

MR Relaxometry will benefit from combining low-rank and sparsity constraints

INTERVIEW BY KAROLINA URBAN AND NIKOLA STIKOV

#### 18 YI WANG AND DAVID PITT

QSM: A breakthrough method to assess iron in white matter MS lesions

INTERVIEW BY LUKE XIE, RYAN TOPFER AND NIKOLA STIKOV

#### 20 MAXIMILIAN HAEBERLIN AND KLAAS PRUESSMANN

Make the gradients sing! Real-time motion correction using gradient tones and an NMR probe array

INTERVIEW BY RYAN TOPFER AND NIKOLA STIKOV

#### 22 ANUJ SHARMA AND WILL GRISSOM

Spokes – not just for wagon wheels! RF pulse design for SMS

INTERVIEW BY ERIKA RAVEN AND NIKOLA STIKOV

#### 24 JUSSI TOIVONEN AND IVAN JAMBOR

Simpler is better: A comparison of diffusion models in prostate cancer

INTERVIEW BY OLIVIER COMTOIS, BENJAMIN DE LEENER, AND NIKOLA STIKOV

#### 26 ISABELL STEINSEIFER AND AREND HEERSCHAP

Spectroscopy in the clinic: Improvements towards prostate cancer characterization

INTERVIEW BY HONG SHANG AND NIKOLA STIKOV

#### 28 NICHOLAS ZWART AND JAMES PIPE

Graphical Programming Interface: The glue for your MRI algorithms

INTERVIEW BY ERIKA RAVEN AND NIKOLA STIKOV

#### 30 BENJAMIN ZAHNEISEN AND BENEDIKT POSER

The Hawaiian life, MR style: On surfing, good weather, and simultaneous multi-slice imaging

INTERVIEW BY SAMANTHA BY AND NIKOLA STIKOV

#### 32 MICHAEL HERBST AND THOMAS ERNST

Correcting for motion on the fly for better diffusion imaging

INTERVIEW BY BENJAMIN DE LEENER AND NIKOLA STIKOV

#### 34 TIJL VAN DER VELDEN AND DENNIS KLOMP

Bilateral breast 31P spectroscopy: A killer app for 7 T

INTERVIEW BY JESSICA MCKAY AND NIKOLA STIKOV

#### 36 HYE-YOUNG HEO AND JINYUAN ZHOU

Improving APT signal quantification one egg at a time

INTERVIEW BY MATHIEU BOUDREAU AND NIKOLA STIKOV

#### 38 GWENDOLYN VAN STEENKISTE AND JAN SIJBERS

Super-resolution and Eureka! moments in diffusion imaging

INTERVIEW BY KAROLINA URBAN AND NIKOLA STIKOV

#### 40 JONATHAN POLIMENI AND LAWRENCE WALD

Go ahead, Breathe: Using FLEET for motion and respiration compensation

INTERVIEW BY SAMANTHA BY AND NIKOLA STIKOV

#### 42 LI FENG AND RICARDO OTAZO

The golden angle and its applications in motion correction

INTERVIEW BY HONG SHANG AND NIKOLA STIKOV

#### 44 DARIYA MALYARENKO AND THOMAS CHENEVERT

Just add ice – Simple water phantoms for detecting multi-site ADC bias

INTERVIEW BY JESSICA MCKAY AND NIKOLA STIKOV

#### 46 ALEXANDER RAAIJMAKERS AND CORNELIS "NICO" VAN DEN BERG

We need antennas - not coils! Body imaging at high field with the fractionated dipole antenna

INTERVIEW BY RYAN TOPFER AND NIKOLA STIKOV

#### 48 GIULIA GINAMI AND DAVIDE PICCINI

No reference? No problem! Self-navigation for irregular breathing patterns

INTERVIEW BY XIN MIAO AND NIKOLA STIKOV

#### 50 STEPHEN PATRICK AND KEVIN BRINDLE

Editing genes for live cell-tracking using MRI

INTERVIEW BY ERIKA RAVEN AND NIKOLA STIKOV

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# Welcome to Magnetic Resonance in Medicine Highlights

**T**oday, when unlimited information is seemingly available on our mobile devices, *Magnetic Resonance in Medicine* continues to be a highly trusted, peer-reviewed publication offering the latest scientific discoveries and methodology in our field. For our journal to continue to thrive, however, we not only must compete for the increasingly divided attention of our current readership, but also reach out beyond our traditional base.

Hence *Magnetic Resonance in Medicine Highlights* was born at discussions held at the 2015 ISMRM Annual Meeting in Toronto. Its audience is the entire MR community, and beyond. Because *Magnetic Resonance in Medicine* publishes papers describing highly-specialized technical developments, its articles can be inaccessible to non-specialists. Our goal is to extract the most important messages, blend them with some of the author's personality, and present the result in an easily-accessible format. The reception has been overwhelmingly positive, judging by the number of page visits and mentions on social media (Facebook, Twitter and YouTube), and by the enthusiastic feedback we have received from readers.

Highlights is a volunteer effort, under the leadership of the journal's Deputy Editor for Scientific Outreach, **Nikola Stikov**, and our Highlights Editor, **Erika Raven**. Each interview of an author of an "editor's pick" has been led by a trainee, under the supervision of Prof. Stikov. The entire list of Highlights contributors is posted on the webpage.

The ISMRM has been tremendously supportive of Highlights, and in particular, John Celio provides valuable support for the webpage. We also thank our publisher Wiley for linking to its content, and composing and printing this special, hardcopy supplement.

Highlights could not be a success without the featured authors, who have enthusiastically contributed their time, both for the Q&A sessions and for production of the audio slides to post on YouTube. So far, 100% of the authors who have been invited have agreed to contribute to Highlights. This perfect response rate is fantastic, but hardly unexpected, given the vibrant and engaged Community of the ISMRM and our journal.

For this special print supplement of *Magnetic Resonance in Medicine Highlights*, we are proud to feature a cover story featuring Erwin Hahn, one of the true pioneers of MR whose contributions to our Community can hardly be overstated. We also feature profiles of the President of the ISMRM, Jim Pipe, and one of its rising stars, Kawin Setsompop. Finally, we present a number of Q&As with authors of editor's picks dating back to August 2015, which offers a glimpse into the exciting work published in our journal during the last year.

I hope you enjoy this first print offering of *Magnetic Resonance in Medicine Highlights*!

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# The transformative genius of Erwin Hahn

INTERVIEW BY **David A. Feinberg** COVER PHOTO BY **Joseph Holmes** JOSEPHHOLMES.COM



Last summer I had the pleasure of meeting Berkeley professor emeritus, Dr. Erwin L. Hahn. His former (and final) graduate student, Larry Wald, was able to connect us in his hometown of Berkeley, CA. Over a hearty breakfast, Prof. Hahn had accepted my hopeful invitation to give the plenary talk at the upcoming ISMRM workshop on simultaneous multi-slice imaging. At one point, he asked me what I worked on in MRI and I replied “pulse sequence physics.” He then asked again, “Well, what do you do?” Only later did I realize the naiveté of my initial response.

In the days leading up to the workshop I spent many afternoons in his house, helping Prof. Hahn find and organize his slides for the plenary talk. It was there that I first saw in a slide (Fig. 1) his 1949 experiment to measure  $T_1$  by incrementally changing the timing between two RF pulses. I came to the realization that this was the very first pulse sequence! Erwin Hahn invented pulse sequences! Of course, I knew he discovered the spin echo, but I thought pulse sequences somehow came from the spectroscopy era, like babies from storks.

Pulse sequences are a specific time-dependent series of radio-frequency pulses and magnetic fields that produce MR signals, and are used to create essentially all imaging methods of MRI. Erwin Hahn is well-known for the discovery of the spin echo, but a fact often ignored by the MR community is that he was also the first to perform pulsed NMR (the first Free Induction Decay (FID)) and

Erwin Hahn's 2015 lecture at ISMRM Workshop:  
<http://www.ismr.org/workshops/MultiSlice15/>

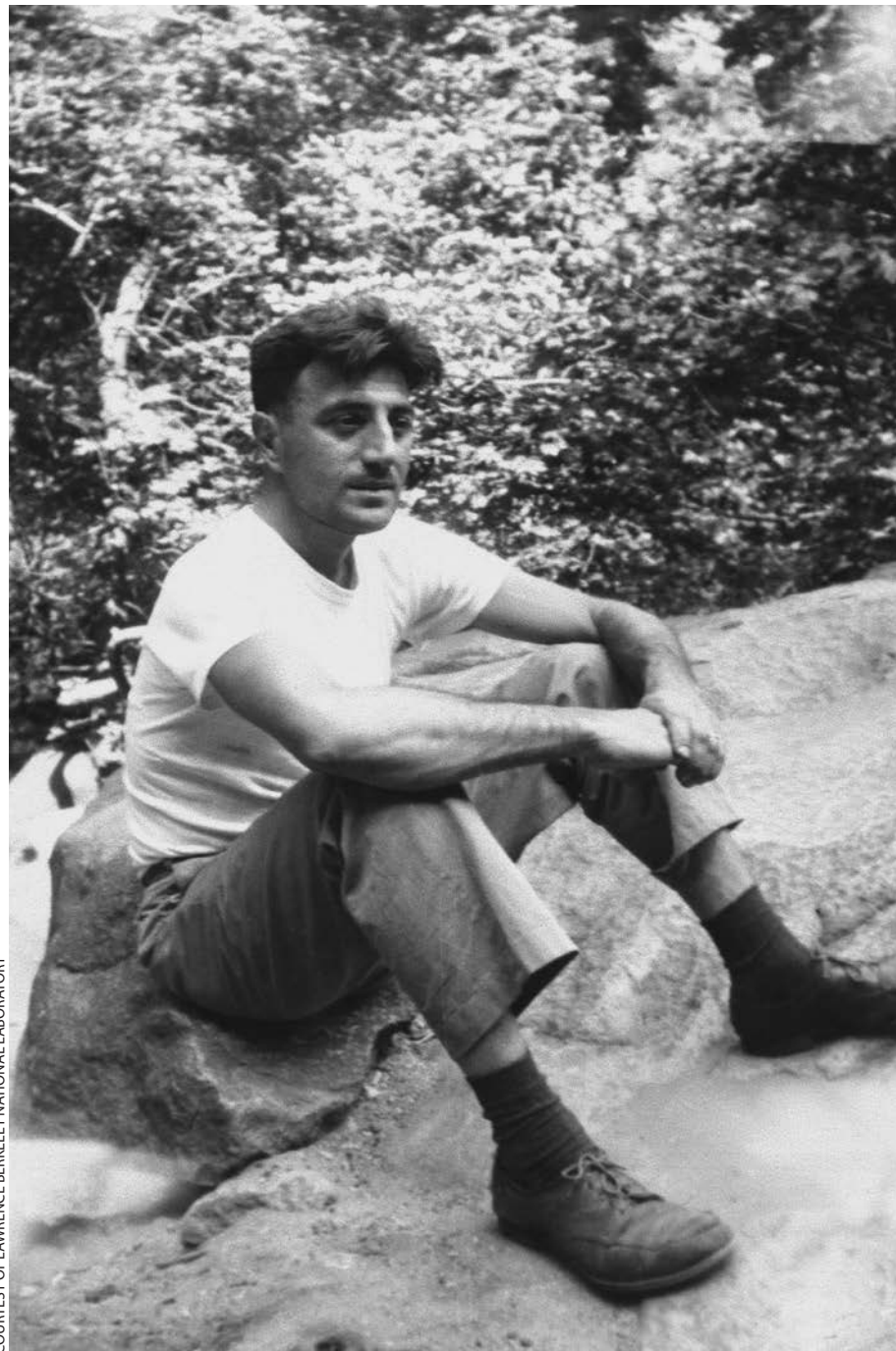
to describe the gradient echo. The FID was published in a brief Physical Review paper in 1949 (Phys. Rev. 76, 145), but was quickly overshadowed by the spin echo paper. The gradient echo was described in a 1960 paper on the MR detection of sea water motion, published in the Journal of Geophysical Research, and it is here that he also described bipolar gradient pulses to encode velocity phase shifts. Yet this and many of his contributions, no less his invention of the pulse sequence, seem to be obscured by history, lying in the shadow of the spin-echo.

Prior to Hahn's research, magnetic resonance was performed by varying the main magnetic field  $H_0$  (now termed  $B_0$ ). This was done either by changing the field in a steady state search method as performed by Purcell's group at Harvard, or by sweeping the  $H_0$  field through the resonance condition as performed by Bloch's group at Stanford. Both of these techniques were performed in the presence of a continuously applied RF field,  $H_1$  (now termed  $B_1$ ), and henceforth called continuous wave (CW) techniques. Hahn's transformative change was to perform magnetic resonance using a constant static  $B_0$  field without sweeping or varying this field, and applying a pulsed  $B_1$  at the Larmor resonance frequency, as now performed by modern day MRI.

It has been thrilling to talk with Erwin Hahn and to learn about what is essentially the creation of modern magnetic resonance. The following interview is an attempt to shine a light on his invention of the pulse sequence, as well as the design of his magnetic resonance instrument.

**DF:** After the war you were in a high energy physics group?

**EH:** When I came back from the war, I was working under Donald Kerst who invented the Betatron which was used to study gamma rays, and later used for medical purposes. And I was unhappy with it because I was just building power supplies, and not learning anything new. Then a theoretical physicist named James Bartlett pointed out papers [by Bloch and Purcell]. And I said to Bartlett, "Can I do that?" And he said, "Go ahead." And the head of the department got wind of it and sent me to Harvard to study the apparatus by Purcell, Pound and Bloembergen. I visited for a week and they were very good to me. And I set it up. At first I used a commercial radio, it was very crude, and had a narrow



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Young Erwin Hahn sitting on Lambert Dome rock in Yosemite Park, from Erwin Hahn's scrapbook.

bandwidth. Then I started using radar equipment that I knew about, to get higher bandwidth so I could achieve better resolution. And I looked at the Bloch equations and saw I could pulse  $H_1$  or the  $H_0$  magnetic field, and I didn't know why they wanted to pulse the  $H_0$  magnetic field. The principle was there, so I pulsed the  $H_1$ .

**DF:** You were a radar instructor during the war?

**EH:** In radar they use X band [8-12 GHz] and they would beat two microwave frequencies together, to get an intermediate frequency of 30 MHz, like in radio, only it's wideband, unlike the radio, and could excite a larger number of nuclei. We had experience with that, so we set it up. Then we used a multivibrator to make square waves and synchronize.

**DF:** What motivated you to use the multivibrator pulse counter?





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Felix Bloch shaking hands with Erwin Hahn.

**EH:** It's called a Higginbotham counter. It came from Los Alamos, and they possibly pulsed it for bomb systems. Some details of the atomic bomb research came out quite early after the war. I think information was informally available through gossip, and some was published shortly after the war was over, in a little magazine, a little booklet that was very valuable. And I got help from a lot of people in terms of information, and together with a good technician we set up the instrument (Fig. 2, 3). I put it in because I saw it could make things much easier. This was after my thesis, when I rebuilt my apparatus. I was a post doc when I did it. I started it before I got my degree, it was in the back of my mind that it could be done, but I had to finish my topic, which was on Rabi flops.

**DF:** The multivibrator is interesting given its convenience for pulse sequence timing.

**EH:** Well, I wanted to measure relaxation

times and how they changed with time during a [chemical] reaction. In order to do that, I wanted to measure intervals of the decay curves. I wanted to measure the abscissa of growth or decay of  $T_1$  or  $T_2$ , not to see the whole thing, but to see pieces. So after my thesis I stayed on and I developed the capability of applying RF pulses, namely leaving a gap between the pulses, whereas Bloch left the RF on all the time. Everybody did. However with the multivibrator system I could do the experiment by turning it on and governing where it would cross the sine wave, and know what the distance was in time, and therefore I could build up a superposition of signals on the Land camera [instant camera, precursor to the Polaroid, used to image the oscilloscopes' output], by many repetitions of the experiment (Fig. 4).

**DF:** But what was your intention for doing this?

**EH:** Well at that time, I was changing the time between the pulses to get a very accurate measure of abscissa. I wanted to measure chemical reactions, by looking at  $T_1$  and  $T_2$  of the reactants as the reaction proceeded. I was a chemistry major in undergraduate school. That's what interested me and I knew about rate equations and also about tuned circuits as I had done tuned circuitry in the navy. So I combined all these things.

**DF:** I'm interested in your instrument compared to Purcell lab's instrument.

**EH:** They didn't have RF pulses, nobody else was pulsing, not the way I was pulsing.

No, well radar has pulses, the closest thing, and pulses have been used in submarines, in battleships and what not. But for this it was a different application. Radar was my business, because I taught it during the war. But anyone could have done it.

**DF:** I know Torrey was doing similar work,

but did he have the ability to change the timing?

**EH:** No, well Torrey turned on a step function of magnetic field and he would tune onto resonance. And then as soon as he tuned on, he got a decay. He was measuring Rabi flops like I was, unknowingly. He would turn  $H_0$  on for a certain interval and then turn off the  $H_0$  field at certain intervals.

**DF:** He wasn't using two pulses?

**EH:** No, he was changing the application of the  $H_0$  field on resonance. In other words, it would precess as long as the field was on, but as soon as he shut the field off he got nothing moving off resonance. So he could not get an echo or FID being way off resonance. All he did was turn the DC field on and off.

**DF:** Did you know of his work?

**EH:** No, I didn't know anything about it. In my PhD thesis I talked about nutations, called Rabi flop oscillations, but Torrey did the same experiment, he beat me to the punch by publishing it first. Although my thesis was Rabi flops, Charlie Slichter misinterpreted it. He kept telling people that I discovered echoes as a graduate student, but I discovered echoes afterwards. In my 1949 paper, I talked only of the FID and said I would talk about the echo next.

**DF:** Your 1949 paper was the first description of a pulse sequence?

**EH:** That's right.

**DF:** A colleague asked me to ask you what made you most excited in your work?

**EH:** When I discovered the echo.

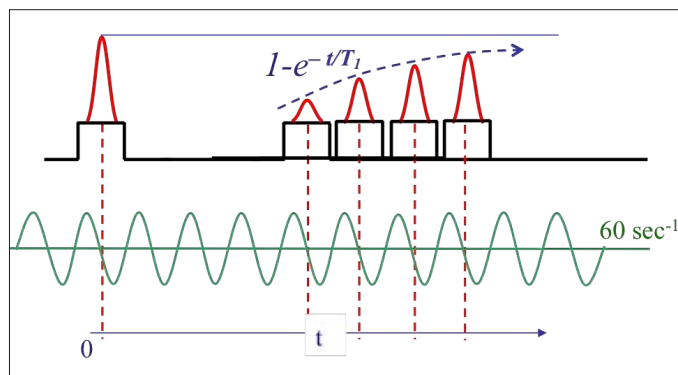
**DF:** At what point did you feel you really had something?

**EH:** When I found out that so many variables were dependent on the echo and exposed. I saw beats, I saw not only exponential decay but other effects, diffusion, chemical shift, cross-coupling, J-coupling. I got a couple of these effects right away. I was exhilarated.

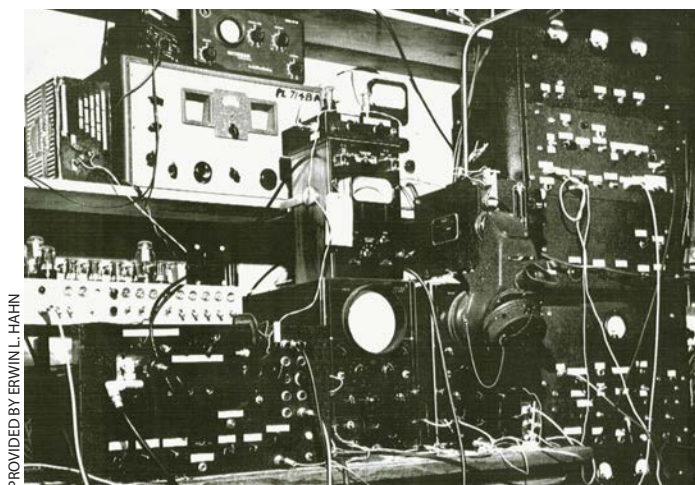
**DF:** Was it all in a day or a night or a week?

**EH:** A week. I happened to narrow the RF pulse and by accident I got this thing and I said hey, what is going on? What's that thing on the right, and I said there is something wrong with the apparatus! I kicked it and it went away. I narrowed the pulse more, I got a bigger echo! That's when I realized I had something. The first thing I saw was an echo, and then an FID for the first time. The FID didn't show up first, the echo showed up first. Then I applied the pulse again at a known time (Fig. 5, top). At an equal time later I saw a spin echo crossing the zero line at an equal number of cycles of the bias field  $\Delta\omega$  (3 Gauss at 60 cycle). The spin echo occurred at exactly the same point where the field is that of the magnet. Then on either side is like a Bloch sweep - down to up and up to down.

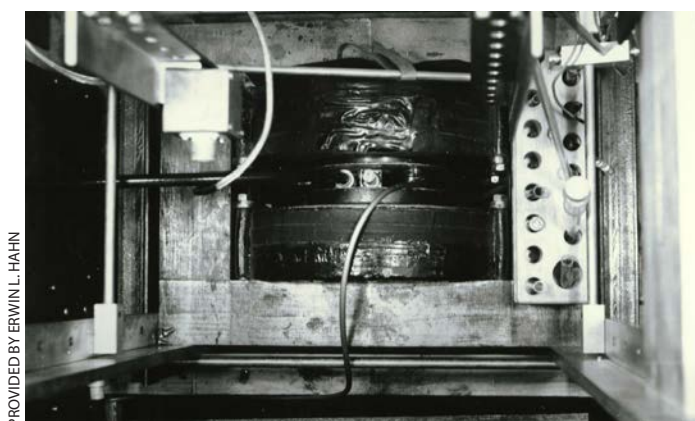
I realized that an FID was being produced, but  $\Delta\omega$  was taking it off-resonance. I shut off the sweeping bias field and it was beautiful (Fig.4). I didn't need it. I just kept the DC field stable by regulating the current of  $H_0$  better. The bias field was turned off after the discovery of the spin echo (Fig. 5 bottom). I didn't need it if the  $H_0$  was stable enough. I also realized the RF pulses needed more power. I had to adjust both the current of the main field and adjust the  $H_1$ . Actually I was doing radical variations of at least four parameters. I maximized everything. I was pio-



**Figure 1.** The first pulse sequence. To measure  $T_1$ , the multivibrator incrementally changed time between the first  $H_1$  pulse and second  $H_1$  pulse shown at different time delays (Hahn, Phys. Rev. 76, 145 (1949)). Adaptation of Bloch adiabatic fast passage provided by Erwin L. Hahn.



**Figure 2.** The apparatus on which the spin echo was discovered. Left center: Higginbotham multivibrator pulse generator and timer. Lower center: Land camera.



**Figure 3.** The magnet that Hahn "swiped" from a cyclotron and used for his magnetic resonance apparatus.





Young Erwin Hahn with his children, from Erwin Hahn's scrapbook.

neering the use of the sweep to go through resonance, but I found it by moving the  $\Delta\omega$  to the zero crossing, when the bias field is zero and I could turn off the bias field as the  $H_0$  was on resonance.

**DF:** How did things go after you first saw the echo?

**EH:** Actually, the echo went away for a week. All my parameters were off. I had it for one day. I thought perhaps the multivibrator was

misfiring. A glitch. And then it came back and I stopped fiddling and I started varying parameters - change B and then change A parameter, etc, and I found I could start to optimize this funny signal. I turned off the oscillating bias field when I tuned the system to the Larmor resonance frequency. This helped stabilize things. It was a high current Varian magnet and difficult to control with low current. I breathed a sigh of relief

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6

*I just varied as many parameters as I could and fought instabilities and incompetencies of circuit designs, and kept careful record to get through a jungle of blindness.*

—Erwin Hahn

9

because I was on the verge of giving up and would have missed the whole discovery, and it would have been easy to miss. I thought at first it could be a rogue wave, but I went to the Bloch equations and found the significance, that varying the amplitude of  $H_0$  or  $H_1$  does the same thing mathematically. I once made a narcissistic remark, I said, “Why didn’t these guys do it first, they’re supposed to be the experts.” I just varied as many parameters as I could and fought instabilities and incompetencies of circuit designs, and kept careful record to get through a jungle of blindness.

**DF:** Did you go around and talk to people about it?

**EH:** Yes. Arnold Nordsieck was a professor at Illinois, and he was on my thesis committee. He was a theoretical physicist, and magnetic resonance had just come along, so I showed him the work. Two days later, while he was working on a lathe, he looked at it, and said that’s interesting, and went back to his lathe. He wasn’t interested. He was building an analog computer. He was so busy with his amp.

**DF:** Early days in MRI must have been exciting?

**EH:** It was Lauterbur who was getting all the recognition. But it was Mansfield who was bringing up the rear. Lauterbur stuck with the back projection and I remember when he was lecturing in Washington from the stage, turning and looking at me, “And Hahn, you don’t need to use pulses.” Then up came Mansfield, with the echo-planar imag-



ing with phase and frequency encoding. In fact I must say I heard that Mansfield put me up for the [Nobel] Prize several times, but not Lauterbur.

**DF:** How about the gradient echo?

**EH:** I described it, and Bob Pound suggested I publish it. People got hold of it and expanded it. Anyway, that's how it went.

**DF:** (referring to Hahn, J. Geophysical Res. 65, 776 (1960)) It's interesting how you completely described changing the current direction in the gradient coil, and the signal would be maximum when the two gradient pulse time durations were the same.

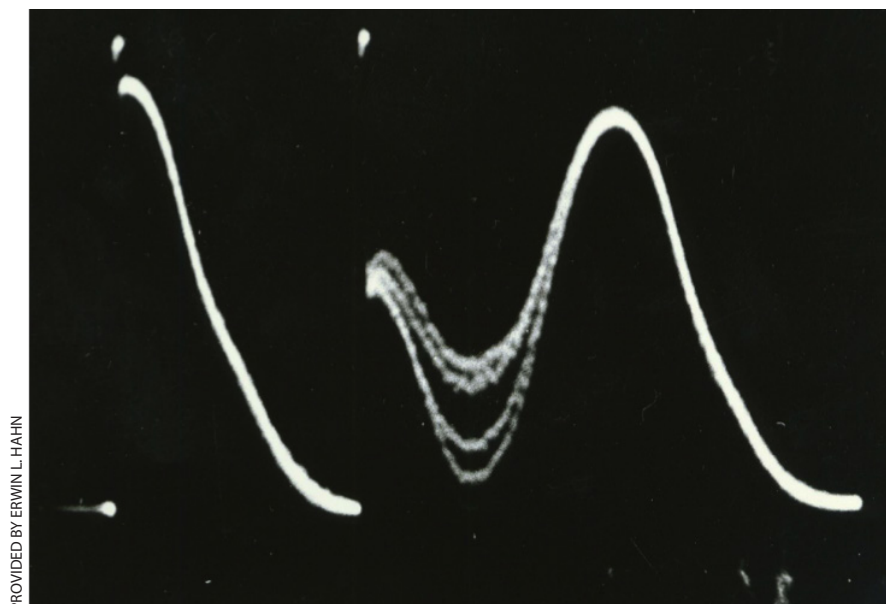
**EH:** That's right, it's a forward backward race all over again. It's refocused in the sense that it keeps going in the same direction but you change the phase, and it's all generally the same thing. Just because you twist something it's a new invention? I think one begets the other; it's in the same kind. I didn't pay much attention to it as I realized it was obvious. It's obvious! I called it the Bloch method because he swept through.

Now the difference between Purcell and Bloch is that Purcell looked at absorption, they looked at a meter and they looked at the Q of the coil. Bloch looked at the signal dynamically. Purcell used the standard optical way of looking at photon absorption, but Bloch's method turned out to be equivalent. There really was a big fight going on. In the beginning the two camps said - what are we doing here? You are doing something different. They finally came to an agreement that they were doing the same thing.

**DF:** How did other work affect your thinking?

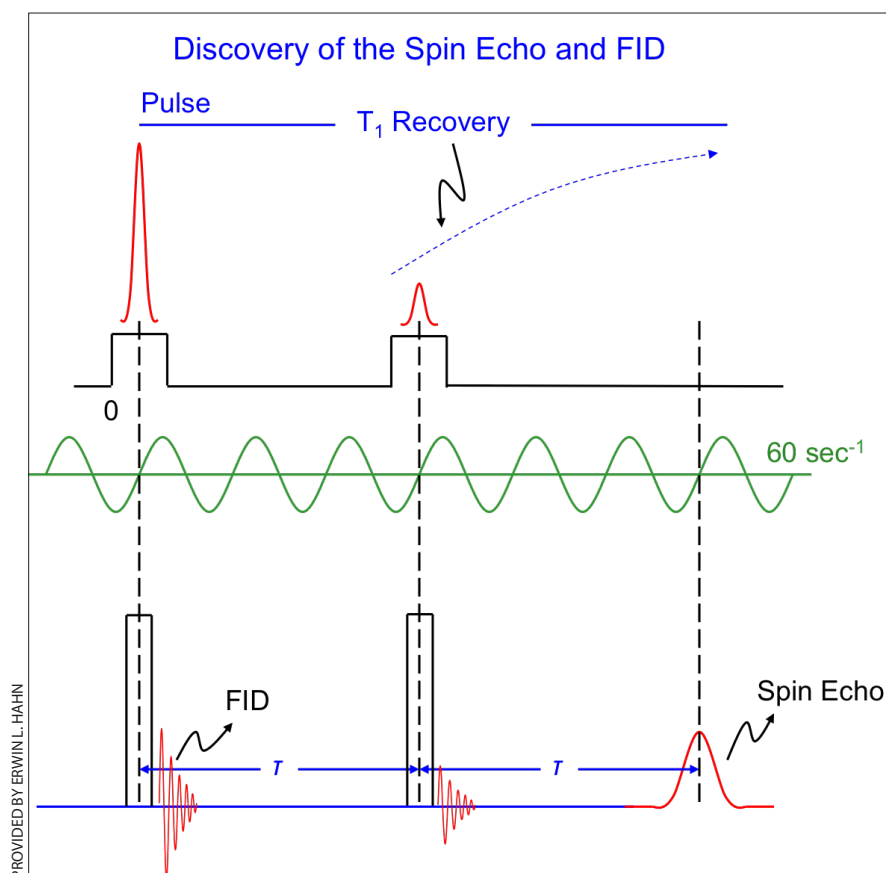
**EH:** Rabi sensed there was a resonance, as I remember once Ramsey, his graduate student, said in an informal talk. Bloembergen noted that Julian Schwinger (who got the Nobel prize together with Feynman) did the quantum mechanics theory that explained what a step function did, verifying Bloch's dynamical equations. It was Schwinger's equation that I recalled when I first used pulses. I got an important hint on his equation from Bloembergen's thesis, it was a great stimulus to me. Please quote me on this. Bloembergen won the Nobel prize later, really for the laser instead, but I've acknowledged him several times.

**DF:** You combined your knowledge of pulses in radar with magnetic resonance, and



PROVIDED BY ERWIN L. HAHN

**Figure 4. Spin echo and FID signals.** The second RF pulse was not phase-correlated with the first RF pulse causing beating in the second FID (seen as 4 different height curved traces in repeated exposures super-positioned on the Land camera). The spin echo (far right) is unchanged.



PROVIDED BY ERWIN L. HAHN

**Figure 5. Top: Pulse sequence used to discover the Spin Echo. Bottom: Optimized pulse sequence.** Tuning to Larmor resonance allowed for turning off the sweeping bias field. The higher  $H_1$  pulse power produced stronger spin echo and FID signals.



Erwin Hahn making a point.

JOSEPH HOLMES





Chamber group musicians with violinist Erwin Hahn (second left), physicist Eugene Cummins (far right) and others.

you did this before spectroscopy and before MRI. MRI is inherently an application of pulse sequences, and it could not exist without echoes. That's because of your inventions, not because of spectroscopy.

**EH:** Spectroscopists spent a lot of time publicizing what they did, and publishing on it over the years, and I didn't. This didn't put me in the limelight. It put them in the limelight. That's what happened.

**DF:** But that doesn't matter because your contributions to MRI are the introduction of echoes and pulse sequences. One can't change history, I only want to remind and educate MRI scientists of your work.

**EH:** Well that's very fine, that's lovely, but it's too late.

**DF:** It's not too late for people to know where the fundamental innovations came from.

**EH:** No well that's fine.

**DF:** Each year, MRI continues to become more vital to medicine and science, so it is important to know where the transformative

work creating the entire field of MR came from. It seems to many people to be a great injustice that Erwin Hahn has not received, or at least shared the Nobel Prize in the many times it has been given for discoveries in magnetic resonance. Peter Mansfield wrote in the Epilogue of his 2013 autobiography, "I can say categorically that without Erwin Hahn's contribution to the principles of spin echoes, there would be no MRI today... his contributions were and remain the cornerstone to the whole concept and implementation of MRI as it is used, not only in the ultra-high speed imaging of the type with which I have been personally connected, but also with the many general aspects of MRI as they have evolved and as they currently exist today."

Last year Richard Ernst wrote to me in an email, "For me it is clear that an ISMRM medal for Erwin is too small a prize for him. Surely, He deserves the Nobel Prize!! And I have tried it more than 10 times without success so far. May be this or next year!" ■

David Feinberg works in the field of MRI pulse sequences for fast imaging, velocity and diffusion measurements. He led the optimization phase in the Human Connectome Project creating pulse sequence and gradient hardware advances for diffusion and fMRI. Several pulse sequences he innovated are now in general use; inner volume (zoomed) imaging, partial Fourier imaging, Twice refocused SE diffusion, gradient and spin echo (GRASE) and EPI variants including fly-back EPI, multiplexed EPI, and different simultaneous multi-slice techniques. At the start of his career, he published the earliest MR images of blood velocity in human vasculature, and of CSF velocity and brain motion. He was the first chair of the ISMRM Study Group on Quantitative Flow and Motion that standardized velocity phase imaging. He is the primary inventor of ASL 3D GRASE, which is becoming popular for clinical applications. His current research as principle investigator of a BRAIN Initiative project is to design a very high resolution MRI scanner for human neurosciences. He is a Fellow of ISMRM, president of Advanced MRI Technologies, and a professor at U.C. Berkeley.

# On ISMRM's role in revolutionizing healthcare

INTERVIEW BY **Erika Raven** AND **Nikola Stikov**

Jim Pipe is the director of neuroimaging research at the Barrow Neurological Institute, as well as current President of the ISMRM. Jim has a long history with the society, starting with his first meeting as a graduate student in 1990. He hasn't missed a meeting since, and has recently been focused on promoting prescient MR healthcare initiatives. In our interview with Jim, we started down memory lane, and then turned to the future of MRI, MRM, and ISMRM.

**The current team. Standing (left to right) is Nick Zwart, Ryan Robison, Jim Pipe, Zhiqiang Li. Sitting (left to right) is Ashley Anderson, Dinghui Wang, and Melvyn Ooi.**

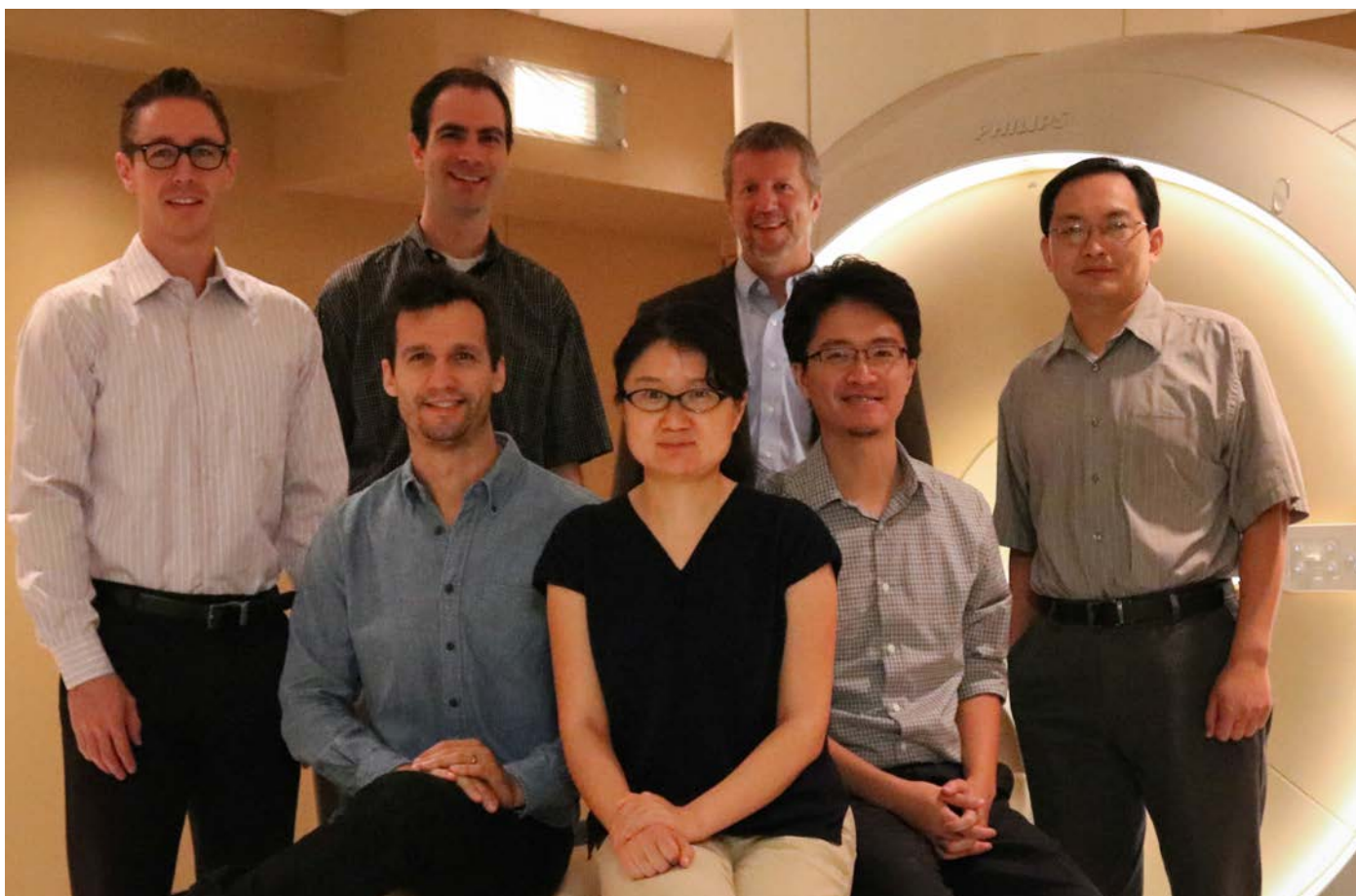
**MRMH: What were your early ISMRM meetings like? Did you recognize many faces?**

**Jim:** In the beginning I was not part of a big group, so I would spend a lot of lunches eating by myself. You're always just amazed when you go as a student or as a young person that the field is so much broader and larger than you're used to. It's pretty overwhelming how much stuff is at the meeting, and I can identify and empathize with

first-timers who don't know anybody yet. But each year you meet new people, then you see them again the following year, and it slowly kind of snowballs.

**MRMH: Do you have any notable memories from past meetings on new technology?**

**Jim:** There are probably a lot of examples of that. But one I remember is when Dan Sodickson had his first paper on SMASH. It was a poster, and every time I went







A young Jim Pipe in San Francisco at SMRM circa 1991.

by that poster it was crowded with people talking about it. I think for Dan, having that as a poster and presenting it all week long – it turned into a huge event, much better actually than had it been assigned as a talk. And it was a focal point of a lot of intense discussion, and really kind of got a lot of people interested in this whole concept that we now call parallel imaging.

I also remember functional MRI when it was just a few posters, right? And now it's a huge section at the meeting. You see these parts of our field that just blossom and then break off, into other groups, like HBM for example. And you just keep thinking that at some point the productivity of MR has to flatten out, but it doesn't, at least to my eye.

**MRMH: Do you remember your first ISMRM presentation?**

**Jim:** I think that the first or second time I gave a talk I was up for the young investigator award. I don't know what a typical word per minute speech rate is, but I was at least double that. I was so nervous. I remember getting off stage and not remembering a thing about my talk.

**MRMH: How has ISMRM changed over the years?**

**Jim:** I think we're getting more mature as a society. We're continuing to expand our international reach, and this is a challenge at times, like with setting conference calls that work for people across every time zone. Also, our central office has grown tremendously in the last several years. I am so impressed at their output - mostly things members never see - and also at the level of professionalism they exhibit. That is something behind the scenes that I have had the pleasure of seeing grow. On the other hand, the society at its core is a bunch of really nice and really bright people who are friendly and have fun working together. So that hasn't changed at all.

**MRMH: Can you pinpoint an event that has had a major impact on the society?**

**Jim:** Moving electronically has had a very big impact. When you submitted to MRM back when I joined the society, everything was on paper and you had to make 5 hard copies of your work, and the pictures were physical photographs. So you had to make 5 copies, cut them out, then use a glue stick to attach photographs to fig-

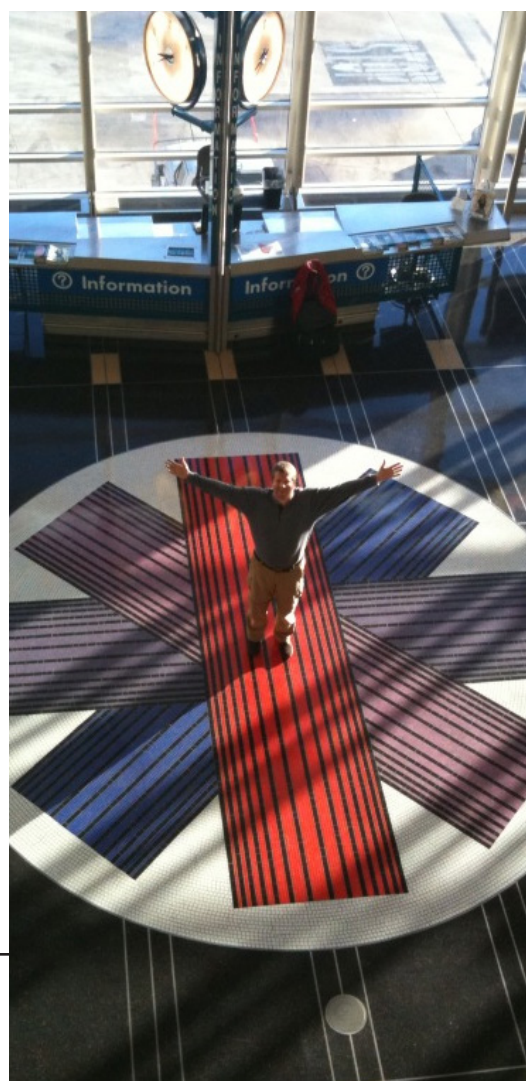
ure pages. The very first day I joined Tom Chenevert's lab as a student I spent half the day attaching all these photographs. The glue smell from that first day is still very vivid to me.

**MRMH: This is a perfect segue to MRM specifically. What does the "Blue Journal" mean to you?**

**Jim:** It is the journal that drives MR technology, and it makes a great team together with JMRI, which has a greater focus on clinical application and downstream development. For the things I do in particular, if you want to have an impact, if you want to have this community read your work and understand it, and I'm talking here on the more technical side – it is the Science or Nature of MR development. Let me just look at my last 20 articles. 1, 2, 3, 4, [continues] ... 17 of my last 20 articles I've published in MRM. It's nearly always my first choice.

**MRMH: Thinking to the future, how do you expect MRM and ISMRM will continue to grow? Are there any initiatives that you are particularly invested in?**

**Jim:** Pushing the boundaries of MR in all the different facets is really important and it's how we expand, but there is one core thing that I would like the society to address, and that's the cost of health care and how that is affecting the many global societies which benefit from



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Our goal is to take what is now roughly a 30 minute brain exam and make it a 5 minute brain exam without any reductions in quality and giving the clinician the same amount of information.

–Jim Pipe

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Jim Pipe standing on PROPELLER k-space.

Enjoying scenic vistas  
with wife Teri at the  
Grand Canyon.



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*You just keep  
thinking that  
at some point  
the productivity  
of MR has to  
flatten out, but  
it doesn't, at  
least to my eye.*

—Jim Pipe

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our work. This ties into the MR Value Initiative that I have promoted this year. MRI is often brought up as an example of costly high tech, but much of what I read is opinion based. If you look for data, there's not a lot there, so I feel like we need to be a part of that discussion. We are the society that should be a part of that discussion, and also we are the society that can bring data and science to this discussion and have it be less opinion and be more evidence-based and fact-based.

**MRMH: Does MR value mean different things to different countries?**

**Jim:** Yea, so there are really four costs to total cost of ownership. There's the scanner, the maintenance, the staffing, and then everything else – including power. In countries like India power is a big deal so I agree that one solution isn't going to fit everybody. But I think there are a lot of opportunities here. For example, I think a lot of the countries where scanner cost has always been a big issue have developed very high efficiencies. I think they have a lot they could teach countries like the US on how to make things more cost effective. It's a very diverse and unique set of solutions that I think everyone is going to have to find for themselves.

**MRMH: How do you prioritize trends in MR with the work that you're doing?**

**Jim:** I would say that historically a lot of my work has been on PROPELLER and motion correction, but that's kind of died down for us. The work going forward is tied to the MR Value Initiative. It's how to make exams fast and efficient. So we're doing a lot of work on spiral MR, focusing on making clinically robust protocols and improving the speed of the exam without changing the quality of the image. Our goal is to take what is now roughly a 30 minute brain exam and make it a 5 minute brain exam without any reductions in quality and giving the clinician the same

amount of information. I work with great people on this and we have a real sense of purpose and excitement about where we're going with this.

**MRMH: Since you started with the society early in your career, do you have any tips for young investigators or PhD students that are just starting in the MR community?**

**Jim:** Take the time to meet people at these meetings and workshops.

**MRMH: So don't sit at lunch by yourself?**

**Jim:** Don't do what I did, right, try to say hi to people. It doesn't work with everybody, certainly, but go to senior members, and just introduce yourself. One of my strongest pieces of advice I give my students is to be nice. Find ways to offer criticism nicely. That doesn't mean you have to back down from what you believe in, but it gets you so much farther because you build your reputation early on. Try to be someone that you would want to hang out with.

**MRMH: Who does Jim want to hang out with outside the lab? How do you fill that little time that is left?**

**Jim:** My wife and I have two kids that are out east, and at home now it's just us and two dogs. We spend a lot of time hiking and exploring the beautiful Southeast. In fact next month, we're going to have our 10TH hike at the Grand Canyon. That's one of our favorite trips of the year. We hike down to the river and back in a day.

**MRMH: Any parting thoughts for our readers?**

**Jim:** Our society is really special. I know I'm not objective, but I hope people appreciate that to have so many bright people who are by and large so very friendly and cooperative, it's really rare. Not every society is as well run and gets along as well as ours does. I think it's a very special thing that way. We are truly international. And we are this mix of physicians and scientists and vendors, academics and clinicians. It's just so unique. ■



# To SMS and beyond: Kawin Setsompop on the quest for speed

INTERVIEW BY **Erika Raven** AND **Nikola Stikov**

Kawin Setsompop is assistant professor of radiology at Harvard Medical School and author of the most cited Magn Reson Med paper for 2012, entitled Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. He is also the guest editor of the recent Magn Reson Med virtual issue on simultaneous multi-slice (SMS) imaging and co-chair of the ISMRM workshop on SMS that was held in Asilomar this summer. We sat down with Kawin to discuss his contributions to SMS imaging, his vision for the future of MRI, and his life outside of the laboratory.

Kawin Setsompop



**MRMH:** Tell us a little bit about your background and what got you interested in MRI?

**Kawin:** I started off doing engineering as an undergrad at Oxford. I didn't really know what I wanted to do after that, but I had a general sense that I wanted to do something related to healthcare or health science. I went to MIT for grad school, where my PhD adviser, Dr. Elfar Adalsteinsson, was very passionate about MRI acquisition research. He was a great mentor for me, and let us really experiment with different ideas, which was fun. I also liked the interdisciplinary nature of MRI research where you interact with physicists, software and hardware engineers, as well as neuroscientists and clinicians.

**MRMH:** Your work on SMS has been widely cited and used in laboratories and clinics around the world. Could you tell us about the origin of SMS and explain the concept to the uninitiated?

**Kawin:** Conventional 2-D MRI acquires one imaging slice at a time, encodes that, and then moves on to the next slice and so forth to acquire the whole volume. Simultaneous multi slice, as the name suggests, tries to acquire and encode multiple slices simultaneously. This allows you to get imaging faster as well as improve SNR efficiency. People developed various methods in the 80s and 90s to do this, but the method that has really taken off is based on parallel imaging simultaneous multi slice that was first developed by David Larkman at Imperial College in London in the early 2000s. Our lab and various others have built and refined these techniques, and in the last few years we've been able to acquire up to 10 slices or more simultaneously. One of the main challenges in developing SMS has to do with getting good

Jon Polimeni, Stephen Cauley, and Kawin Setsompop testing wifi after the 2015 ISMRM meeting in Milan, Italy.



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The last four or five years have seen tremendous advances in creating robust algorithms for parallel imaging reconstruction.

—Kawin Setsompop

Stephen Cauley and Kawin Setsompop dining al fresco in Boston, Massachusetts.



training data to train parallel imaging algorithms. The last four or five years have seen tremendous advances in creating robust algorithms for parallel imaging reconstruction, and we have been very successful in adapting these for EPI-based acquisitions used in fMRI and diffusion. We are now working on adapting our acquisitions and algorithms to structural and perfusion imaging, and the next big challenge will be to apply our methods on clinical brain and body applications.

**MRMH:** How easy is it for a new site to start using the technique?

**Kawin:** As with any new method, it is important to know the limitations of the technique. For example, if you have an eight-channel coil you should not try to acquire eight slices simultaneously, you are better off settling on two to three. Otherwise, the method is pretty straightforward and there are quite a few robust sequences that are available from various sites, such as our lab and the Minnesota group. As we speak, the MR vendors are working on developing product sequences

based on our joint efforts.

**MRMH:** Where has SMS seen most widespread usage so far?

**Kawin:** SMS for fMRI and diffusion has been an integral part of the Human Connectome project, and over a thousand subjects have already been scanned. We are also starting to see SMS used in clinical diffusion scans. Q-ball imaging with high angular sampling can now be accomplished in 2 to 3 minutes, making it particularly attractive for sites that want to go beyond conventional DTI acquisitions.

**MRMH:** The ISMRM workshop on Simultaneous Multi-Slice imaging was held this summer in Asilomar, California. How did it go and what were the notable highlights?

**Kawin:** This was the first workshop of its kind, and it was an unqualified success. There were over 100 participants, mainly researchers who are doing development, but also a significant number of people interested in fMRI and diffusion applications, as well as clinical imaging. The workshop is a culmination of the efforts of a few established labs that have worked on these methods over the last 5 to 10 years, but it is also nice to see new labs that are starting to get interested and contributing to the growth of the field. Asilomar was a great venue and the natural setting provided a space where people could run into each other frequently and discuss science. There was also a great hands-on workshop organized by Steen Moeller, Felix Breuer, Rita Nunes and myself, where we shared our Matlab code and encouraged people to take that home with them and develop it further. Another personal highlight was the talk by Erwin Hahn, one of the pioneers of MRI research, who also happened to be the adviser of my postdoctoral adviser, Larry Wald. He provided the glue for the workshop, recounting the history while also providing a unique perspective of the field.

**MRMH:** Who is Kawin when not doing MRI?



**Kawin:** It's hard for me to think of an answer to that because I've been working so much the last few years that MRI is really an integral part of my life. I have a background where I travel a lot. I grew up in Thailand and then I went to boarding school in New Zealand and then I did my undergrad in England and now I've moved to Boston, and this job allows me to continue traveling and experience different cultures. And being Thai I really like Thai food, as well as other types of cuisine. I like to taste different foods and I like to cook a lot.

**MRMH:** It sounds like you're a foodie... Part MRI, part foodie?

**Kawin:** Yeah!

**MRMH:** Now that you mentioned Thailand, it is probably a good time to say a little bit about your outreach work there.

**Kawin:** In 2011 I participated in an ISMRM outreach program in Macedonia, and it felt really good to be part of an initiative that brings together scientists, MDs and researchers from developing countries that do not regularly attend the annual ISMRM meetings. That is when I decided to organize something similar in Thailand. In Thailand, we have excellent equipment and a lot of medical tourism, but there's not a lot of MRI research going on yet. I really want to bridge this gap, so I organized a workshop where we managed to get people excited about MR research. For example, Larry Wald has these cute little 0.2 T Tabletop MRI scanners, and we are sending one to Thailand so they can experiment with the hardware and software without using precious clinical scan time. I look forward to organizing another outreach seminar there.

**MRMH:** What is your vision for MRI and what do you see happening in the next 10 years? Where do you see the field going and what excites you the most?

**Kawin:** There is always this bounce back and forth between hardware and software development. Now that we have multiple channel receivers, multiple channel transmit, we're starting to see a lot of development in terms of strong gradients as well as local B0 shimming that would allow us to do non-linear encoding. I foresee a closer interaction between hardware and acquisition and reconstruction software that results in more channels, more sensors, and more non-linear reconstructions. I am also excited by the prospect of using these novel acquisitions to explore new contrast mechanisms and characterize tissue microstructure. In particular, I think the brain is a really exciting research problem because of its complex structure, and I hope that as we gain temporal and spatial sensitivity we will get closer to figuring out its mystery.

**MRMH:** Where do you see yourself in 10 years?

**Kawin:** Hopefully in 10 years I will still be as excited to wake up in the morning and work on MRI. I am a nerd at heart and I really like working with people, tinkering with the ideas on a daily basis and coming up with cool stuff. I also hope to use my experience to mentor the next generation of scientists, getting them really excited about MRI research and pushing their new ideas forward. Finally, I am hopeful that by that time I will be able to look back and see some of this technology have an impact on health care and health science, because that is the most important thing in the end. ■

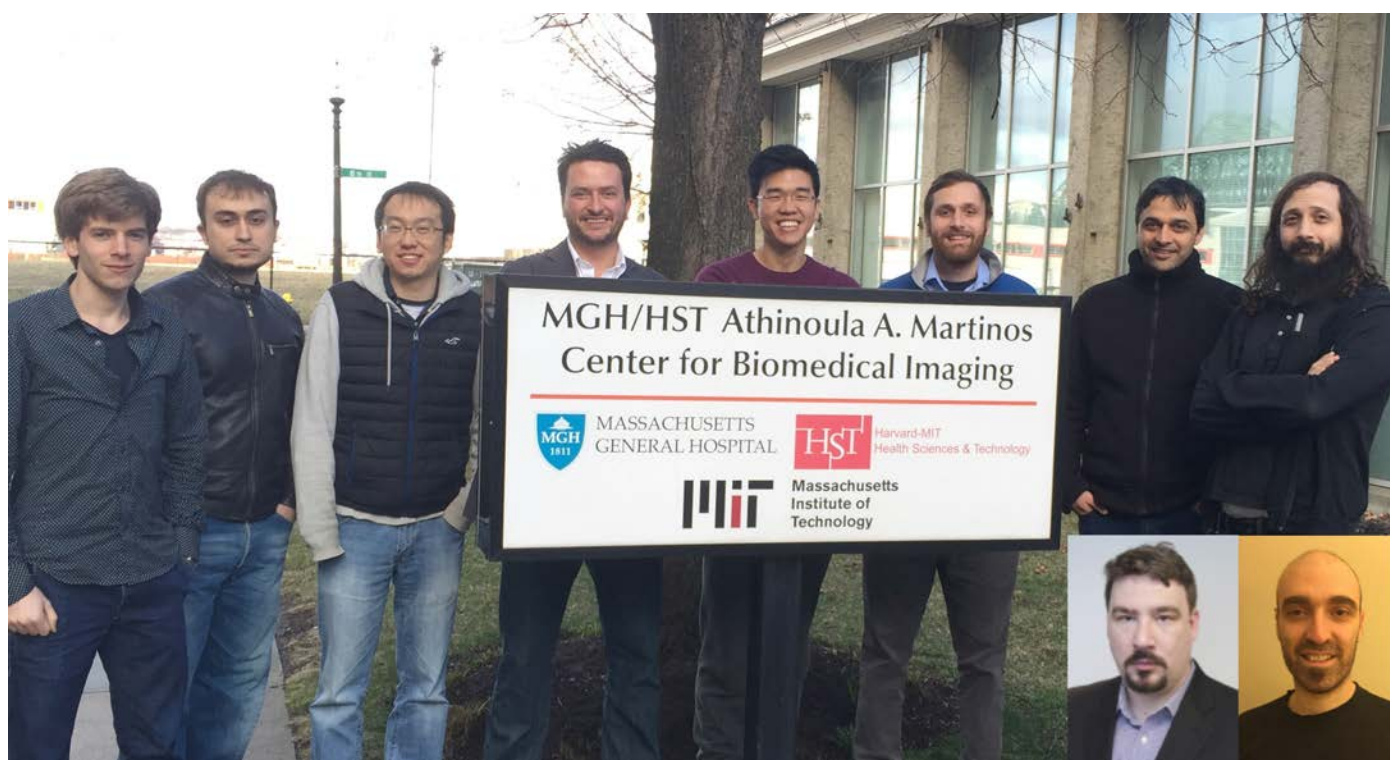
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*Hopefully in 10 years I will still be as excited to wake up in the morning and work on MRI.*

–Kawin Setsompop

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**SMS working group of labmates, collaborators and Siemens engineers. Left to Right is Daniel Polak, Berkin Bilgic, Haifeng Wang, Keith Heberlein, Kawin Setsompop, Stephen Cauley, Himanshu Bhat, Jon Polimeni. Inset, Thomas Witzel, Borjan Gagoski.**



# MR Relaxometry will benefit from combining low-rank and sparsity constraints

INTERVIEW BY **Karolina Urban** AND **Nikola Stikov**

## EDITOR'S PICK FOR AUGUST

Dr. Bo Zhao is a recent graduate from the University of Illinois at Urbana-Champaign where he earned his PhD in electrical and computer engineering. Dr. Zhao is currently a research fellow at the MGH/HST Martinos Center for Biomedical Imaging at Harvard Medical School. His paper entitled "Accelerated parameter mapping with low-rank and sparsity constraints" was an Editor's pick for the month of August. We contacted Bo and senior author Dr. Zhi-Pei Liang to discuss their research and the details of the featured paper.



**MRMH:** Can you tell us in plain language the main points of your paper?

**Bo:** The paper reports a model-based approach for accelerated MR parameter mapping. The model integrates two mathematical constraints known in signal processing as sparsity and low rank structure. As you may know, sparsity constraint is a key element of the popular compressed sensing theory, which enables recovery of signals from sub-Nyquist measurements; complementary to the sparsity constraint, the low-rank constraint provides another mathematical structure to achieve sub-Nyquist sampling. Dr. Liang's group has been working on low-rank model-based imaging for many years. The key novelty of this paper lies in utilizing both sparsity and low-rank constraints to design data acquisition and image reconstruction for accelerated MR parameter mapping with sparse sampling. .

**Zhi-Pei:** A major challenge in parameter mapping is long data acquisition times. Conventional parameter mapping acquires several images with slightly different acquisition parameters, so there is a lot of redundant information collected. Bo's approach reduces the redundancy in data acquisition, hence the acceleration.

**MRMH:** How does your method compare against existing fast relaxometry techniques?

**Bo:** Our method could be used to speed up any MRI application where parameter mapping is used for tissue characterization. In particular, it provides a novel modeling framework to parsimoniously represent MR re-

**Bo Zhao**

Zhao B, Wenmiao L, Hitchens TK, Lam F, Ho C, Liang ZP. Accelerated MR parameter mapping with low-rank and sparsity constraints. *Magn Reson Med* 2015;74:489-498. DOI: 10.1002/mrm.25421  
<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25421/full>



laxometry data. Within this framework, a whole bunch of approaches can be explored, such as simultaneous multi-slice parameter mapping, 3D imaging, and MR Fingerprinting.

**Zhi-Pei:** All those techniques for accelerated parameter mapping are very much complementary at this stage. For example, the famous and powerful MR Fingerprinting technique Bo mentioned uses stronger prior information about tissue parameter distribution to enable ultrafast parameter mapping, but it doesn't preclude the use of sparsity and low-rank constraints for further speed enhancement. Such an integration would be particularly useful for 3D parameter mapping, although computational time could be a concern.

**MRMH:** Dr. Zhao, how did you get into MRI?

**Bo:** After I joined the University of Illinois for my Ph.D. studies, I had a chance to take Dr. Liang's class on MRI. I found that MRI is a fascinating imaging modality, not only because of its tremendous power and potential, but also because of its strong connection to physics and engineering, especially signal processing. So, I decided to pursue my Ph.D. thesis research in this area.

**MRMH:** How about you Dr. Liang, what is your MRI origins story?

**Zhi-Pei:** It was pure luck for me. When I was a graduate student at Case Western Reserve University, I attended a public lecture by Dr. Paul Lauterbur, during a ceremony honoring him for his pioneering work on MRI. I immediately fell in love with the field. After my graduation, I joined the University of Illinois, where I had the privilege of working with Dr. Lauterbur for another 17 years before he passed away in 2007.

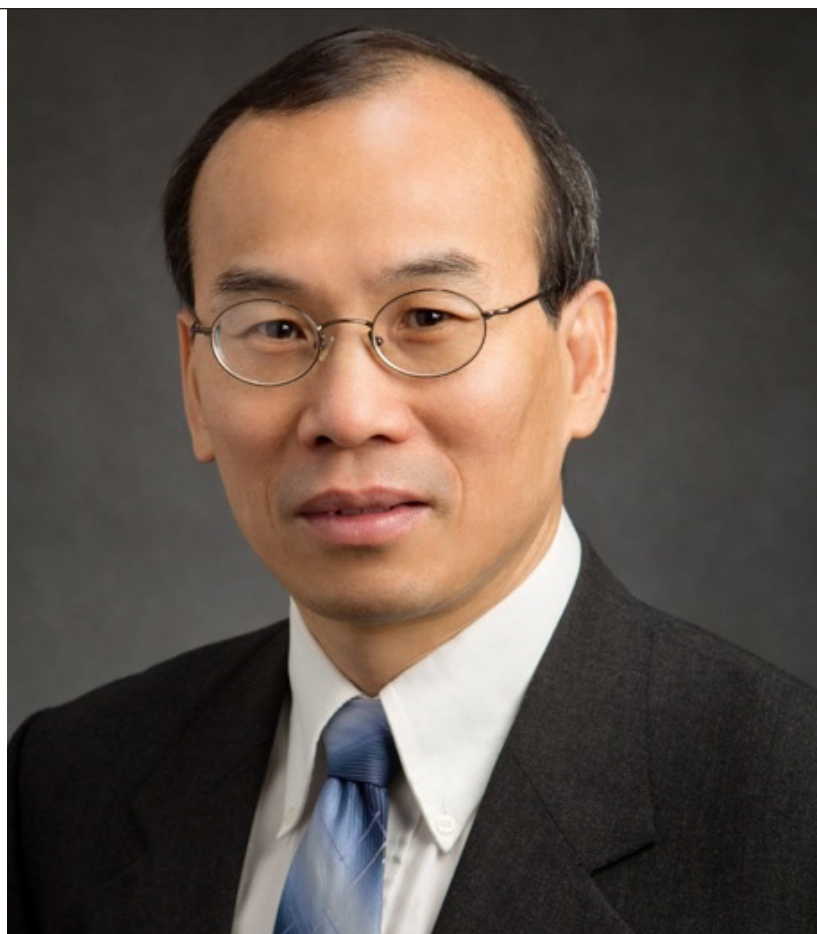
**MRMH:** What do you do outside the lab?

**Bo:** Urbana is a quiet campus, which really lets you focus on your research. Boston, on the other hand, is a fascinating city, with lots of sports, museums... Since I moved there, I have managed to spend some time to explore the city over the weekends.

**Zhi-Pei:** Bo gave you a hint already; Urbana is in the middle of a cornfield, so what can you do other than manipulating spins? (Laughs) As a father and husband, I enjoy spending as much time as I could with my family. And being Chinese, I also like playing table tennis. I walk about 1.5 miles every early morning, which is fun, especially so in the snowy winters here!

**MRMH:** You mentioned your Chinese heritage, are you involved in MRI outreach efforts there?

**Zhi-Pei:** As much as I can, but given my limited ability and charm, I haven't received any call from the ISMRM office about it yet. [Laughs] I did help set up the Paul Lauterbur Research Center for Biomedical Imaging under the Chinese Academy of Sciences. That Institute has really exploded over the last 6-7 years. I expect great work to come out of those talented young people in the coming years.



**MRMH:** What are your plans for the future and where do you see the field of quantitative MRI going?

**Bo:** I think a key challenge in quantitative MRI is to relate the measured MR parameters to true tissue biophysical properties or microstructure. To establish such a correlation, we need to further improve our understanding and modeling of the underlying physical and physiological processes. We also need to improve our technology to better compensate for imperfections from hardware and pulse sequences. Regarding my future plans, I would like to pursue an academic career to push the boundary of MRI technology, especially for quantitative neuroimaging.

**Zhi-Pei:** Bo is very, very talented, and I am sure he will have a successful career in academia. Talking about quantitative imaging, one exciting area is accelerated high-resolution spectroscopic imaging, which would give us important physiological information of tissues beyond  $T_1$  and  $T_2$  values without using exogenous molecular reporters.

**MRMH:** What advice would you give to young MRI researchers?

**Bo:** Get good training in physics and signal processing!

**Zhi-Pei:** Aim high, dream big. God gives us 3 things at a fundamental level: mass, charge, and spin. There is still a lot of exciting work that can be done in using spins to unravel the mystery of biology and revolutionize healthcare. Go "spin"! ■

**Zhi-Pei Liang**

“  
Bo's approach  
reduces the  
redundancy  
in data  
acquisition,  
hence the  
acceleration.

—Zhi-Pei Liang

”

# QSM: A breakthrough method to assess iron in white matter MS lesions

INTERVIEW BY Luke Xie, Ryan Topfer AND Nikola Stikov

## EDITOR'S PICK FOR AUGUST

A new paper on quantitative susceptibility mapping (QSM) in multiple sclerosis is one of our Editor's picks for the August issue of Magn Reson Med. Junior author Cynthia Wisnieff was not available due to her busy medical school schedule, so we asked the paper's senior authors, Dr. Yi Wang and Dr. David Pitt to discuss their exciting work with us.

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So now by  
detecting iron,  
we can have  
a window for  
examining  
inflammatory  
activity.”

—David Pitt

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

**Yi:** QSM offers a method to localize and quantify the underlying source of magnetic susceptibility changes, such as iron in MS lesions, by deconvolving the phase from gradient echo (GRE) data. The breakthrough in this difficult (ill-posed) deconvolution has been made possible using Bayesian inference with anatomic knowledge such as from structural images. For QSM applications in MS, we looked at pathology to determine the QSM specificity to iron, which is associated with inflammation. We compared the iron maps obtained from QSM with immunohistochemistry of post-mortem MS brains. Using QSM we found: 1) bright rims near the lesion periphery reflect iron, 2) lesion volume extended beyond the T<sub>2</sub> weighted imaging volume reflects iron, and 3) lesions with positive QSM volume reflect iron.

**MRMH:** What role does iron play in MS?

**David:** Earlier studies have looked at iron accumulation in deep nuclei, including the basal ganglia—they found a good correlation between disability and the amount of iron in the deep nuclei. But these studies were all carried out with T<sub>2</sub>\* imaging. More recent studies using QSM have found that iron can accumulate in white matter lesions, which opened up a whole new field of investigation. It turned out that this iron was present mostly in inflammatory cells: macrophages and microglia. Iron uptake then makes these cells pro-inflammatory, which means that they are more damaging to the tissue. So now by detecting iron, we can have a window for examining inflammatory activity. Previously, we could detect

new lesions only when they were gadolinium-enhancing, i.e. for 3-4 weeks until the blood brain barrier closes again and the enhancement is lost. Now, with QSM, inflammation is visible for much longer, although, it is a different type of inflammation. We can now get an idea of whether low-grade inflammation is present for any given lesion.

**MRMH:** How long is a standard QSM protocol and what are its main challenges?

**Yi:** It takes 5-7 minutes. More importantly, QSM can



Yi Wang

Wisnieff C, Ramanan S, Olesik J, Gauthier S, Wang Y, Pitt D. Quantitative susceptibility mapping (QSM) of white matter multiple sclerosis lesions: Interpreting positive susceptibility and the presence of iron. *Magn Reson Med* 2015;74:564-570. DOI: 10.1002/mrm.25240

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25420/full>





The team at Cornell, including lead author Cynthia Wisnieff (center).

be easily implemented on any site, since it's just a 3D multi-echo GRE sequence. The key thing is that you have to save the complex data. And thus QSM is really a post-processing technique, so it doesn't add any cost in terms of data acquisition. However, the QSM processing is not trivial. The raw phase is wrapped and is difficult to interpret. It needs to be unwrapped and the background phase needs to be removed in present QSM.

**MRMH:** How do you plan to follow up on this work?



David Pitt

**Yi:** We are actively translating our findings into the clinics. For example, we have found in MS patients that the lesion susceptibility value measured from QSM increases significantly as a lesion changes from Gd enhancing to non-enhancing. This data indicates that QSM can accurately discriminate between enhancing and non-enhancing lesions in multiple sclerosis without Gd injection. Therefore, QSM could be an alternative or complement to existing gadolinium enhancement techniques. We are also continuously developing the QSM technique for MS applications. For example, we are now looking into combining QSM with another myelin specific biomarker, such as myelin water fraction, to enable better discrimination between iron and myelin.

**David:** Looking at long-term inflammatory effects with QSM is very exciting. With this tool, we can now ask what multiple sclerosis drugs can do to inflammation in existing lesions. So far, drug studies have only looked at whether drugs can prevent the formation of new lesions. Currently, we are performing in-vitro studies and in-vivo QSM studies to see how long it takes for the iron-positive lesions to change into low-iron lesions, what we believe indicates a reduction in lesional inflammation. Something else that is on the horizon is the iron content in normal appearing white matter in chronic disease. It turns out that in long-standing MS, the iron is slowly lost from oligodendrocytes in myelinated white matter. This iron loss is not well understood but it is very possible that it affects function of oligodendrocytes and compromises myelin integrity in normal appearing white matter, thereby contributing to progressive MS. QSM can become a tool to monitor this loss of iron, and to assess progression in MS. This would be very exciting.

**MRMH:** Thank you for your time! We look forward to hearing more about your work in the upcoming issues of Magnetic Resonance in Medicine! ■

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QSM is really a post-processing technique, so it doesn't add any cost in terms of data acquisition.

—Yi Wang

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# Make the gradients sing! Real-time motion correction using gradient tones and an NMR probe array

INTERVIEW BY **Ryan Topfer** AND **Nikola Stikov**

## EDITOR'S PICK FOR SEPTEMBER

Among the editor's picks for September is a paper from Klaas Pruessmann's group at ETH Zürich introducing a new method for simultaneous motion correction and field monitoring. We spoke with Klaas and leading author Max Haeberlin about their unique technique to "make the gradients sing".

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We were asking  
ourselves, if  
we have these  
probes, how  
might we  
identify position  
based on  
gradient action?”

—Klaas Pruessmann

**MRMH:** Max, your recent MRM paper was selected as an Editor's Pick for the month of September. Could you tell us about the main aims of this project?

**Max:** The context is really clear cut: Rigid-body motion correction for brain MRI. We're taking up on previous work that used NMR markers but which, in our mind, used a sub-optimal timing strategy – one alternating between image encoding and probe tracking. In our approach, we're trying to remove this fundamental disadvantage by separating the probe tracking and image encoding in the frequency as opposed to the time domain.

**MRMH:** Why  $^{19}\text{F}$  probes in particular?

**Klaas:** Tritium-enriched water would suit better, only it's illegal...

**Max:** [Laughs] As opposed to proton? Certainly to decouple the imaging and field probe signals. And why fluorine? It's probably the most sensitive liquid state nucleus that you could use, but the most important thing is it's different from the nucleus used for imaging.

**MRMH:** So you would need a dual RF system to be able to implement your method at the moment?

**Max:** At the moment, no. At time of publication, yes, that's the way we implemented it. In our lab now we're already working with external spectrometers that do the signal processing for the motion correction. So that's not a fundamental, but more of an engineering issue.

**Klaas:** In the paper, only a clinical spectrometer was used. We think it's fairly simple to integrate because the RF infrastructure is the same and the requirements of the spectrometer are the same – just another few channels, but channels aren't in short supply nowadays.

**MRMH:** Any other challenges to deal with?

**Klaas:** Well the elephant in the room is rigid-body re-

lationship of the sensors and the skull. The residual motion of the marker relative to the brain, due to skin mobility, remains an open issue. If we want to handle 1 cm of motion, that is fine, but submillimeter motion is still difficult to correct.

**MRMH:** Is there anything that surprised you during your study?

**Max:** We didn't start off with individual frequency tones to localize the probes. Initially we thought we'd do it somewhat differently, relying on more readily available wideband signals and no single frequency tones, so that was certainly an insight.

**Klaas:** I must admit I was surprised how nicely all the specs ended up in a good range. For this to work, you need to be sensitive enough with a given nucleus and probes of a given size. You have some degree of sensitivity, which translates into some spatial determination error, and this ended up being some tens of microns, which was exactly what we needed. In principle it could've been two orders of magnitude off, so I was pleasantly surprised. It was almost as though someone, a higher entity, had made sure that this would succeed!

**MRMH:** So the universe conspired to make it work! How did you end up with this insight of single tones?

**Klaas:** It was quite a few moons ago! Every summer we hold a group retreat, which is a full week of the whole group being in a remote place – working, eating, cooking, drinking, and playing soccer. It was a retreat in Italy quite a few years ago. We were asking ourselves, if we have these probes, how might we identify position based on gradient action? And David Brunner, one of the co-authors, he said “Make them sing! Make the gradients sing!” As it is with David sometimes, all his ideas are good, but you don't always immediately know what he's saying. [Laughs] So he explained it, and it was really his spontaneous intuition, which came from his background in sideband modulation – where you have a resonance line, and a  $B_0$  field, and by adding a subfield, at a frequency of 1 MHz perhaps,

Haeberlin M, Kasper L, Barmet C, Brunner DO, Dietrich BE, Gross S, Wilm BJ, Kozerke S, Pruessmann KP. Real-time motion correction using gradient tones and head-mounted NMR field probes. *Magn Reson Med* 2015;74:647-660. DOI: 10.1002/mrm.25432

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25432/abstract>





Max Haeberlin with head-mounted field probe.

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*We modulate the field that the probes see, and this generates a protected sideband from which we can read the position.*

—Klaas Pruessmann

”

the resonance line will split up into the original line and two ghosts 1 MHz away. One could argue that's what we're doing here: We modulate the field that the probes see, and this generates a protected sideband from which we can read the position. And in a moment this all happened in David's mind... under the influence of Italian wine.

**MRMH:** Max, you recently finished your PhD, can you tell us about your career path, past and future?

**Max:** My background is in electrical engineering. I got involved in MRI during my Master's and then started with Klaas as a PhD student. I graduated a year ago and I decided not to pursue an academic career, but it's not

clear at the moment where my life will take me...

**MRMH:** Klaas, what about your vision for the future? Trends in MR, advances that you foresee and you would be excited to work on?

**Klaas:** I see a lot of mileage out of more sensing and more deployment of IT fueled by sensor inputs. Is this a good scan, should it be interrupted? Can we steer against deviations? You don't want to be concerned with head movement, slight heating, or a train driving by. I think the answer is a sensor input to an IT system that makes smart decisions, such as readjusting the geometry of the sequence. If we can leverage IT more, we can definitely boost MR. ■

# Spokes – Not just for wagon wheels! RF pulse design for SMS

INTERVIEW BY Erika Raven AND Nikola Stikov

## EDITOR'S PICK FOR SEPTEMBER

The simultaneous multi-slice imaging momentum continues with a recent paper by Sharma and colleagues on RF pulse design for SMS, which is our Editor's pick for the month of September. We caught up with authors Anuj Sharma and Will Grissom after the SMS workshop held in Asilomar, California.



**MRMH:** What were your impressions from the workshop?

**Anuj:** One of the surprising things that I saw was the number of SMS applications. There were presentations on abdominal imaging, body imaging in the liver and knee, pediatric, and cardiac imaging. We are using SMS as a hammer and hitting everything to see what works.

**Will:** I wasn't able to attend in person, so I had to give my talk over the internet. Just a big looming head on the screen, did you see me, Anuj?

**Anuj:** Yea, I saw your head.

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

**Anuj:** One of the major challenges at high field is the transmit RF inhomogeneity. Spoke RF pulses have already addressed this in single-slice imaging, and we adapted the design to multi-band and created pulses that give greater B1 uniformity and lower peak RF.

**Will:** Spokes always excite the same slice pattern, but in between each slice selective excitation that makes up the spokes pulse you have a gradient blip. Each blip leaves some phase variation across a slice such that you can create a beneficial interference pattern. Then you build up a pulse from multiples of these.

**MRMH:** One very lay question, what is a spoke and why is it called that?

**Anuj:** A spoke is a trajectory in excitation k-space. The more points in k-space we want to visit, the more spokes we need. As you add more and more spokes your inhomogeneity goes down so your flip angle becomes more uniform throughout the slice. The excitation k-space trajectory is shared between the slices, so the k-space trajectory is commonly optimized across the slices. The RF pulse deposits for each slice

Anuj Sharma in Asilomar, California, for the SMS workshop.

Sharma A, Bammer R, Stenger VA, Grissom WA. Low peak power multiband spokes pulses for B1+inhomogeneity-compensated simultaneous multislice excitation in high field MRI. *Magn Reson Med* 2015;74:747-755. DOI: 10.1002/mrm.25455

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25455/abstract>



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*Should this be a button for any sequence, like SENSE or GRAPPA is, or should this be application specific, like for diffusion MRI.*

–Anuj Sharma

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are also optimized, and that is where the independent shimming or independently designed spoke pulse comes into the picture.

**Will:** One last thing, spokes suggests a radial configuration of lines which is a bit of a misnomer, but the terminology was proposed early on and it stuck.

**MRMH:** If you could rename the spoke, what would it be?

**Will:** There have been several names, but rungs probably.

**MRMH:** In your paper you only mention two parallel transmit channels, how scalable would this be if you had more channels?

**Anuj:** Multiband spokes can lead to better flip angle homogeneity even with a single channel system. As you add on parallel transmit channels, you reap more benefits such as needing fewer spokes but the calibration and system setup gets more complicated.

**Will:** Yea, you need more spokes with fewer RF channels, that's for sure. And if you have more channels, then you can reduce the number of spokes, which is good for improving the spectral bandwidth. RF spokes have been a good research topic, but I'd like to see them evolve to the next thing. One of the reasons they're still not quite used is that the trajectory doesn't have broad enough spectral bandwidth. This is one of the goals of the ISMRM RF Pulse Design Challenge: to design single slice tailored pulses, like spokes, but that are more time efficient. So we want somebody to come up with the next great trajectory basically.

**MRMH:** Applications are really only the last sentence of your paper. Here is your chance to continue that thought.

**Anuj:** In general, all applications that use multislice imaging acquisitions at high field or ultra high field could benefit from our pulses. The question now is should this be a button for any sequence, like SENSE or GRAPPA is, or should this be application specific, like for diffusion MRI.

**Will:** Perhaps 3T abdomen is another good example. It is not considered very high field anymore, but there are large inhomogeneities there.

**MRMH:** Anuj, how did you pick the next step in your



career, leaving academia to work for Toshiba?

**Anuj:** Well, I wanted to keep an open door for a career in academia, but also work in industry to bring my discoveries closer to people. It was a logical progression.

**Will:** He is so good, he could really go anywhere

**MRMH:** Will, with unlimited resources, where would you invest your money and your time?

**Will:** I tend to be a bit scatterbrained and I like to work on millions of different projects sort of simultaneously. I am really interested in working on purpose dedicated systems, for example developing different encoding methods or RF coils for a dedicated mammography system. If you only need to hit that one body part you can really size down the system and improve patient comfort and reduce cost. I've really enjoyed working on ways of completely rethinking how the scanners are set up for smaller level or direct applications. We are also building table-top scanners for educational purposes. My student Chris Hasselwander is working on an entire pulse sequence and image reconstruction library for low-cost software-defined radios that can go online for download using open source software.

**MRMH:** What do you think of open science?

**Will:** I love open science. We get more citations, and people don't have to implement techniques from scratch. It is a win-win for everybody. ■

Will Grissom and his son sharing a laugh, and a cupcake.

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*Multiband spokes can lead to better flip angle homogeneity even with a single channel system.*

–Anuj Sharma

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# Simpler is better: A comparison of diffusion models in prostate cancer

INTERVIEW BY Olivier Comtois, Benjamin De Leener, AND Nikola Stikov

## EDITOR'S PICK FOR OCTOBER

Both of our October Editor's picks are on prostate imaging, and the first one comes from the University of Turku in Finland. Jussi Toivonen recently published a paper on diffusion imaging of prostate, and we invited him and senior author Ivan Jambor to tell us about their work.

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*The models can be applied to any cancer and we would like to apply these methods to other cancer types such as glioma.*  
”

—Ivan Jambor

**MRMH:** Thank you for accepting our invitation, can you please tell us a bit about yourselves and your background?

**Jussi:** I have a Master's degree in Computer Science that I obtained in 2007 and I am now a PhD student at the University of Turku. I worked as a programmer for five years, then decided to go back to academia to pursue a

PhD degree.

**Ivan:** I am a research fellow at the University of Turku and currently in the transitional phase of being a PhD student to being a supervisor of PhD students. Jussi is one of my first PhD students. My main research interests are DWI and various spin locking methods.

**MRMH:** Your work is on using diffusion imaging to



Jussi Toivonen and Ivan Jambor in the lab.

Toivonen J, Merisaari H, Pesola M, Taimen P, Boström PJ, Pahikkala T, Aronen HJ, Jambor I. Mathematical models for diffusion-weighted imaging of prostate cancer using b values up to 2000 s/mm<sup>2</sup>: Correlation with Gleason score and repeatability of region of interest analysis. *Magn Reson Med* 2015;74:1116-1124. DOI: 10.1002/mrm.25482

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25482/abstract>





characterize prostate cancer. Could you please summarize your paper?

**Jussi:** We scanned 50 patients twice with diffusion magnetic resonance performed using b values in the range of 0 to 2000 s/mm<sup>2</sup>. Rectangular ROIs were placed on trace images in cancer and healthy tissue. Then, we fitted four different diffusion models, tested their performance in prostate cancer detection and characterization, and evaluated the repeatability of the fitted parameters.

**Ivan:** There are two main aspects of the paper: modeling and clinical application. On the modeling end, the question is how good the diffusion model is for representing the MRI signal. On the clinical end, can clinicians use this, meaning how good the model is for cancer detection and characterization? We found that these more complex models fit the signal better by having more free parameters, but did not outperform the simpler monoexponential model in terms of cancer detection and characterization.

**MRMH:** So were you surprised, in a way, that simpler is better?

**Ivan:** More disappointed than surprised really, because the theory and the fitting work so well. But I am sure that clinicians are happy. Of course, this is just one step towards better prostate cancer DWI signal characterization obtained using high b values.

**MRMH:** Why did you choose prostate cancer and could we apply these methods to different types of cancer?

**Ivan:** The reason we are investigating prostate cancer

is because it is a very common cancer with wide range of cancer aggressions. Thus, it's not anymore about detecting prostate cancer but more about differentiating cancers which need active treatment from those which are better to be left on active surveillance. But of course, the models can be applied to any cancer and we would like to apply these methods to other cancer types such as glioma.

**MRMH:** How easy is it to use your software? In particular, for clinicians to use it?

**Jussi:** At the moment it would be a bit challenging since we are modifying the code quite a bit and the documentation is lagging behind. But ultimately we would like to produce simple instructions in order for other people to reproduce what we have done. The software is freely available, but I am still working on its documentation for easier use.

**MRMH:** Where do you want to take this? Can we use your method to characterize tissue microstructure?

**Jussi:** Physiological interpretation of the signal is a challenge. Some research groups are doing experiments on high-field MRI but it is far from clinical applications.

**Ivan:** Our group is pushing towards semi-automatic quantification in order to take away this burden from the clinicians. We are also trying to move away from ROI fitting to voxel-wise fitting.

**MRMH:** Thank you for your time, we look forward to hearing more from you in the coming years!

**Ivan:** This is a very nice initiative. It helps open up the science, especially a complicated field like MR physics. ■

Members of the group  
at the University of  
Turku in Finland.

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*The question  
is how good  
the diffusion  
model is for  
representing the  
MRI signal.*

–Ivan Jambor

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# Spectroscopy in the clinic: Improvements towards prostate cancer characterization

INTERVIEW BY Hong Shang AND Nikola Stikov

## EDITOR'S PICK FOR OCTOBER

Following last week's feature on diffusion imaging for prostate cancer characterization, this week we focus on prostate spectroscopy and a recent paper by researchers at the Radboud University Medical Center in the Netherlands, entitled 'Improved Volume Selective <sup>1</sup>H MR Spectroscopic Imaging of the Prostate with Gradient Offset Independent Adiabaticity Pulses at 3 Tesla'. We spoke to lead author Isabell Steinseifer and her mentor Arend Heerschap.

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The good news is that with the new sequence and shorter echo times we have a higher SNR, so we can also do spectroscopy without the endorectal coil.

–Arend Heerschap

**MRMH:** Can you please tell us a bit about yourself and how you got interested in MR?

**Isabell:** I studied physics, and afterwards I decided to do something related to medical applications. So I came to Radboud University Medical Center, did my PhD here, and I have just started my training to become a clinical physicist in Radiotherapy.

**Arend:** I got a PhD at the University of Nijmegen, then moved to Philips to be involved in the development of in vivo MR. After about 5 years, I returned back to academia, and built a translational research group, with prostate MR spectroscopy as a main focus.

**MRMH:** Can you talk a little bit about the context, why are you interested in developing prostate MR spectroscopy and whether it is currently used in the clinic?

**Isabell:** We have been doing prostate spectroscopy in our group for a long time. Prostate MRSI is challenging, in particular because the prostate is small and surrounded by a lipid pool. So we developed a semi-LASER sequence with GOIA pulses, to minimize lipid contamination, and to provide more stable spectra with higher SNR. At this moment MRSI is mostly used in academic studies. Some centers are using it clinically for assessing tumor aggressiveness, and also for evaluating the effects of treatment of prostate cancer.

**Arend:** Prostate cancer is a very important clinical problem. MR can be important for diagnosis, but also for aggressiveness assessment, and evaluation during treatment. Over the years, we have seen the development of multi-parametric MRI, including T2 MR, diffusion

MR, MR Spectroscopy, and dynamic contrast MR. Currently they come together in the so-called PI-RADS classification.

**MRMH:** Pirates? What are pirates?

**Arend:** Not pirates, but PI-RADS, it stands for Prostate Imaging Reporting and Data System. It is a classification that radiologists use to identify the localization, and stage/grade of prostate cancer. It is important because it makes consensus diagnosis. A first version of PI-RADS included all four of the approaches listed above. Currently MR Spectroscopy and dynamic contrast are a little bit in the background. That is one of the reasons we work so hard. If you go to MR spectroscopy, you deal with much lower SNR compared to common MRI, so it is a big challenge to get a really good method in the clinic. Yet, there is ample evidence that MRS gives valuable complementary information to T<sub>2</sub> and diffusion, so it is well worth the effort.

**MRMH:** What was the biggest challenge for this project?

**Isabell:** In this project, the most challenging part was implementing the GOIA-WURST pulses, because of the gradient modulation on top of RF modulation, which is quite difficult. But this allows us to go to low RF amplitudes, so it is worth the effort.

**MRMH:** MRI is dense with acronyms, but spectroscopy is the worst offender. Putting an artist (GOIA) next to a sausage (WURST) sure is memorable, but do you plan to come up with a new acronym for this sequence?

**Arend:** Indeed, MR is stuck with acronyms. People usually give a new acronym even if it is a small modification. We actually went the other way, we used other people's acronyms, so for now we don't have our own.

**MRMH:** What would it take to implement this at a different site?

**Isabell:** In the meantime our sequence has become available as a work in progress package for Siemens

Steinseifer IK, van Asten JJA, Weiland E, Scheenen TWJ, Maas MC, Heerschap A. Improved volume selective <sup>1</sup>H MR spectroscopic imaging of the prostate with gradient offset independent adiabaticity pulses at 3 Tesla. Magn Reson Med 2015;74:915-924. DOI: 10.1002/mrm.25476

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25476/abstract>





scanners. Going to other vendors should be possible, the important sequence parameters are described in the article. Also, we need to make sure that we are compatible with sites that do not use an endorectal coil.

**MRMH:** But using an endorectal coil cuts down the scan time, right?

**Arend:** The whole field is now moving toward removing endorectal coils. So it is important for us to demonstrate that we can run this sequence without an endorectal coil. The good news is that with the new sequence and shorter echo times we have a higher SNR, so we can also do spectroscopy without the endorectal coil.

**MRMH:** Patients will be happy to hear that. Where do

you see this project going in the future?

**Arend:** We are planning clinical trials with other sites (e.g. Trondheim in Norway), using this new sequence without an endorectal coil, to demonstrate its clinical value. Our mission is to put the sequence in the clinic, so it has to be very fast. We have the ambition to shorten the spectroscopy exam to within about 7 minutes. Another challenge is post-processing. The radiologist does not want to go to a separate console to get rid of artifacts, so our ultimate ambition is to incorporate the post-processing so it all happens at the push of a button.

**MRMH:** We wish you success in your future endeavors! ■

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*The most challenging part was implementing the GOIA-WURST pulses because of the gradient modulation on top of RF modulation. This allows us to go to low RF amplitudes, so it is worth the effort.*

–Isabell Steinseifer

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# Graphical Programming Interface: the glue for your MRI algorithms

INTERVIEW BY Erika Raven AND Nikola Stikov

## EDITOR'S PICK FOR NOVEMBER

This month's pick highlights a software development package, Graphical Programming Interface or GPI. The lead developer, Nick Zwart, and senior author and current ISMRM president, Jim Pipe, discuss the design of GPI, its functionality, and their future development goals. They also shared several nice pictures, including a selfie.

“  
A lot of people  
have said it  
feels like a video  
game.”

—Nicholas Zwart

**MRMH:** Can you give a brief summary of GPI?

**Nick:** GPI creates a graphical flow chart of a complex algorithm. What that means is you can interact with algorithm processing at different stages of your data pipeline. As you make changes to certain areas, those updates will be managed by GPI and processed in a timely manner. That allows you to rapidly prototype new algorithms by reconfiguring the different nodes you've recreated, almost like a puzzle. A lot of people have said it feels like a video game.

**Jim:** We use it for a ton of stuff. If you want to post-process images, or set up something for a physician who's not a programmer, you can set it up so it's very easy for them to read in files and draw an ROI, and they can get the answer they want. We also use it for education, because all the data gets processed visually. If you want to brainstorm an idea, having these visual blocks and putting them all together is really nice.

**MRMH:** Who is your target audience and are you doing anything to reach out to them?

**Nick:** Our target audience is really ourselves.

**MRMH:** That is very in-house.

**Nick:** Every lab develops their own software, and we're no different in that respect. We are trying to be very efficient at getting our research publicized and finishing it.

**Jim:** Outside the lab, we started by sharing with the Barrow Institute, and the Philips community. And we recently opened this up to the ISMRM and the wider MR community. From our point of view the way you can visualize data doesn't have to be restricted to MR even. There are different levels.

**Nick:** We've also done classes. These courses were to teach Phillips folks who are interested in engaging in the Philips development tools for MR research.

**MRMH:** Classes you hosted were for Philips users and



Nick Zwart

**GPI is sponsored by Philips. Are you also trying to expand across platform?**

**Nick:** We are open source. The project is hosted on GitHub, and that's linked from the website. There is nothing specific about this reconstruction pipeline to MR actually and that should give some indication that it is certainly not specific to the Philips platform. As long as you can get your data into it, you can start processing the data. We do support many different scientific file formats and we are definitely open to collaboration. In terms of our own development we are interested in streamlining our own lab efficiency.

**MRMH:** Have you noticed increases in lab efficiency since you started using GPI?

**Nick:** [laughs] I'm really good at working with GPI.

**Jim:** We've always used this kind of thing and I do feel like it makes us really efficient, because of code sharing. Nick has a really cool diagram in which each GPI node

Zwart NR, Pipe JG. Graphical programming interface: A development environment for MRI methods. *Magn Reson Med* 2015;74:1449-1460. DOI:10.1002/mrm.25528

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25528/abstract>





Jim Pipe with moose at the 2015 ISMRM meeting in Toronto.

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*There is nothing specific about this reconstruction pipeline to MR actually and that should give some indication that it is certainly not specific to the Philips platform.*

—Jim Pipe

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Putting faces to nodes.

get assigned the face of its primary developer, and from it you can see that we all use each others work and there is continuity there. So I don't know what metric of efficiency you could use there, but clearly the work doesn't get duplicated. I think that's really good.

**MRMH:** How big is the developer team and how easy is it to join?

**Nick:** I'll break it down by software components. The framework is developed by two to three people. And the framework is what glues the node code together. It's the canvas that you place nodes on. The node code extends the functionality. I think we probably have about 15 developers.

**Jim:** And the website gets about 300 hits a month now. We know it's downloaded, but it's unknown how many developers there actually are now that it's open to everyone.

**MRMH:** What would be your ultimate vision for GPI?

**Nick:** I think because we're working on MR reconstructions, it would be nice if this ran on the scanner. And if you could run your reconstructions on the fly, to at least be able to probe the data and see what's coming off the scanner, that might help with pulse sequence design. I also see it as a teaching tool. I don't think those are ultimate visions, though. Ultimately, Google says, "Hey, we want this!"

**Jim:** From my perspective, using GPI I think is intuitive. When we're developing algorithms, I think we're learning what is going on. If you can see what happens, if you have some kind of an algorithm, you can look at data at different parts, that is education. In my mind, that's really a big part of why GPI is so nice. The educational part of it ties really nicely to development.

**MRMH:** And you can also see where things break, and learn from that?

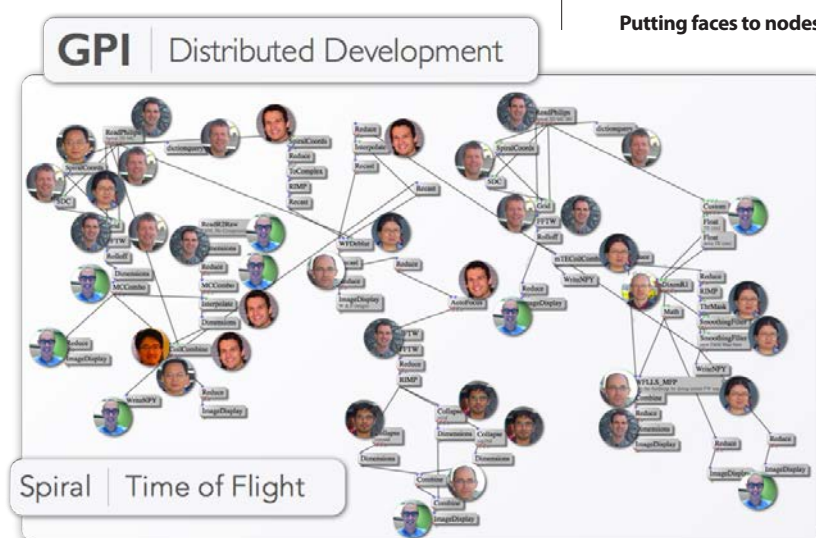
**Jim:** Yea, we get a lot of experience there.

**MRMH:** Nick, what is your plan for the future? Do you plan to stay in academia?

**Nick:** One of the things that is cool about this lab is we are in a hybrid space. We're part academia, and we are part of a healthcare system, but we're also able to function in a sort of industrial capacity. My plans are pretty much to stay in this space as long as possible.

**MRMH:** Any final comments?

**Jim:** Nick has created a really excellent tool! I think many people will find it helpful, and hopefully a few will contribute to the project. ■



# The Hawaiian life, MR style: On surfing, good weather, and simultaneous multi-slice imaging

INTERVIEW BY **Samantha By** AND **Nikola Stikov**

## EDITOR'S PICK FOR NOVEMBER

Among the editor's picks for the month of November is a paper entitled 'SENSE and SMS Imaging' by Drs. Benjamin Zahneisen and Benedikt Poser. Benjamin is currently a researcher at the Lucas Center at Stanford and Benedikt is an assistant professor in MR Methods at the Faculty of Psychology and Neuroscience at Maastricht University in the Netherlands. Benjamin and Benedikt first met during their postdoc in Hawaii, where somehow in between surfing and enjoying the nice weather, they found time for some cool science.



**Benni Zahneisen**

Zahneisen B, Ernst T, Poser BA. SENSE and simultaneous multislice imaging. *Magn Reson Med* 2015;74:1356-1362. DOI:10.1002/mrm.25519

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25519/full>

### **MRMH:** How did you both end up in Hawaii?

**Benjamin:** Sort of by coincidence. I started doing work in MRI in Würzburg, Germany for my Master's, and then continued with my PhD at the University of Freiburg with Jürgen Hennig. Then I went to Hawaii for my postdoc. There is actually a pretty cool connection here: Jürgen Hennig's very first (I think) PhD student, Thomas Ernst, is the head of MR Physics in Hawaii, and I was one of Hennig's last!

**Benedikt:** For me, complete coincidence as well. I studied physics with business management on the side. I considered going into Economics then Aerospace Engineering, but in the end I somehow started doing a PhD in MR Physics with Prof. David Norris at the Donders Institute in the Netherlands. Soon after, I started working as a postdoc at the Hahn Institute in Essen, reinventing some wheels to make fMRI work on our 7T... In 2010 I was looking for a postdoc abroad. Somewhere nicer and warmer, with water, and a good place for starting a family. I ended up with some funding to go to Hawaii to learn about parallel transmission with Andy Stenger.

### **MRMH:** How did you start getting involved in SMS imaging?

**Benjamin:** Benedikt was into multi-band. I was not. [laughs] He dragged me into it.

**Benedikt:** Actually, this started as a bit of a distraction from what I was meant to be doing there, parallel transmission. But everyone was so hyped up about this multi-band stuff so I got sidetracked into it. One night, I quite randomly thought: 'How about we put different frequencies into these different transmitters in the parallel transmit array, so that different elements excite different slices?' Surprise, surprise, they could be reconstructed apart. That's basically how the SMS work in Hawaii started and then Andy got excited about it and we started toying around with other "much simpler" things that don't involve pTX, like the multi-band





Benedikt Poser, Andy Stenger, and Benni Zahneisen enjoying MR in paradise.

spirals, some RF pulses, etc.

**MRMH:** Can you give a brief summary of your work?

**Benjamin:** The main idea we were trying to get across is that we don't have to use all of these fancy reconstruction concepts, like slice GRAPPA, for SMS. Simple, straightforward SENSE works. People have done this before, but somehow, it got lost that it's possible to use the SENSE based reconstruction for multi-band.

**Benedikt:** Exactly. We wanted to remind the community that there is a conceptually easier way to reconstruct SMS; not better, but more intuitive. There was nothing new. David Larkman used SENSE in his landmark paper, Felix Breuer added SMS-CAIPIRINHA in 2005 but since then people went to more complex reconstructions. We actually started with the more complicated non-cartesian schemes we needed for the spirals, and simplified things back to the Cartesian case.

**MRMH:** How did the idea come about?

**Benjamin:** Honestly, just through play. We had many lunches and came up with some nice nuggets of wisdom.

**Benedikt:** The key person in all we did is Andy Stenger. He always comes up with these often half-baked and sometimes crazy ideas that stimulate new adventures! We just toyed around. And we had all the time in the world! No administrative responsibilities, no teaching, easy scanner access to just try things out. So we tried many things, learned a lot, hit many dead ends that no one mentions, but sometimes we found a nugget, as Benni just put it. We surfed, had fun and could concentrate on some nice science. Kind of paradise.

**MRMH:** Would you say that your approach is simpler?

**Benjamin:** There is no objective answer, it is really a

matter of perspective. In a way SENSE and GRAPPA are just different ways of looking at the same thing. It's all a matter of what you like and what you don't like.

**Benedikt:** I agree. I don't know what we were thinking at the time, but I think after using the more complicated SENSE reconstructions to deal with non-cartesian multi-band, it kind of came naturally to try straightforward SENSE for straightforward cartesian reconstruction.

**MRMH:** Any advantage of using one or the other?

**Benjamin:** Not really. In its essence, I think what people appreciated about this paper was not the novelty, but the educational aspect.

**Benedikt:** Yes I agree. It makes it intuitive, and illustrates nicely the analogy between SMS and standard 3D imaging. But objectively, I see no real reason to prefer one over the other. Perhaps SENSE reconstruction could be highly parallelizable on GPU hardware or even on FPGA cards, which would be lightning fast. I think that would be trickier with the k-space based approaches due to their horrendous memory requirement.

**MRMH:** What do you miss about your time in Hawaii?

**Benjamin:** Definitely the weather and surfing. Oh, and free scan time!

**Benedikt:** Absolutely. Doing science without the time pressure that comes with distracting responsibilities. [laughs] Actually, I am going back there next week to spend the winter!

**MRMH:** Well, it looks like you will be there just as we will be interviewing Thomas Ernst for next month's Editor's pick.

**Benedikt:** I will wave to you from the background with my surfboard. ■

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*We wanted to remind the community that there is a conceptually easier way to reconstruct SMS.*

–Benedikt Poser

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# Correcting for motion on the fly for better diffusion imaging

INTERVIEW BY Benjamin De Leener AND Nikola Stikov

## EDITOR'S PICK FOR DECEMBER

For a second week in a row, we report on exciting new work from Hawaii. This time we spoke with Michael Herbst and Thomas Ernst about the importance of motion correction. As they say: the patients that need a scan the most are usually those that move the most.



**MRMH:** Can you tell us about yourself and your background?

**Michael:** My academic training was in Electrical Engineering. I'm originally from Germany, where I did a PhD in the group of Jürgen Hennig. After my PhD, I received a stipend for a two-year postdoc position with Thomas Ernst's group. I've been here for a year and a half.

**MRMH:** It seems that there is a dedicated airbridge from Hennig's group to Hawaii. Thomas, you seem to have started this bridge?

**Thomas:** Yes. I also did a PhD with Hennig a long time ago. After that, I did a postdoc in Pasadena, some research at Caltech for a while and then became faculty at UCLA. I've been at the University of Hawaii for 10 years or so. Most of my early work was on proton spectroscopy, but over the past 5-7 years I've worked on motion correction, using an external tracking system for head movements. That's where a lot of this work originated from.

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

**Michael:** Our goal was to apply prospective motion correction to high-resolution diffusion-weighted imaging. We used an approach called MUSE for image reconstruction. This method combines the coil sensitivity with the phase error resulting from diffusion weighting. From that, we were able to reconstruct artifact-free images.

**MRMH:** What does 'prospective' mean?

**Michael:** Prospective embodies a concept where a camera is placed in the scanner bore to track the patient movements in real-time (about 50 frames per second). The movements of the subject captured by the camera are then fed back to the scanner and the images are corrected on the fly. So 'prospective' actually means 'real-time'.

**Michael Herbst**

Herbst M, Zahneisen B, Knowles B, Zaitsev M, Ernst T. Prospective motion correction of segmented diffusion weighted EPI. *Magn Reson Med* 2015;74:1675-1681. DOI: 10.1002/mrm.25547

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25547/abstract>



**MRMH:** How easily can this technique be applied by other groups?

**Michael:** It is relatively easy to apply in the current setting. The software is consistently effective and very accurate. If you want to apply it to a new sequence, it will need a bit of programming work. The sequence source code is required for modification, but starting there, it could be done easily.

**Thomas:** At this point, the camera and the tracking system are available and installed in approximately a dozen sites worldwide. It is quite easy to install and to use the tracking system on a new machine. The only limitation being, that sequences are currently available for Siemens systems only.

**MRMH:** Your paper talks about head motion. Can your developments be applied to other body structures?

**Michael:** At this time we are focusing on 'rigid-body' motions. We applied it mainly to the brain, but we do have one other paper where we discussed this application on the knee, which can be considered as a relatively 'rigid-body'.

**MRMH:** What is the idea for the long run? Do you plan to make a product from all that?

**Michael:** It is a little bit unclear at the moment since most of the codes in the library are based on Siemens code, which is proprietary information. With that we could not give out the codes ourselves. In the long run, we would like Siemens, or other manufacturers, to sell our software as a package. The only thing that has already been commercialized is the camera and the tracking system.

**MRMH:** Of the twelve sites in which the system is installed, are there any clinical sites?

**Michael:** We don't have FDA approval for the system. It is purely used for research at this time.

**MRMH:** Where would you like to take this work in the near future?

**Michael:** Concerning the scientific aspect of prospective motion correction, I think we are pretty much done. We need to work with manufacturers to see how they plan to invest and commercialize this application.

**Thomas:** We see more and more high-resolution acquisitions of structural and diffusion MRI, up to 0.3 mm isotropic, and it is very difficult for anyone to hold still during a 10-min scan to allow for nice images at that resolution. So it is extremely important to continue to develop motion correction approaches for these applications, especially because it is the patients who move the most that need the scan the most. My vision for the future is to make this system available to clinics where upon the purchase of a scanner system, buyers can just check an option to purchase this prospective motion correction as an additional package.

**MRMH:** It seems that a lot of excellent work comes from Hawaii. How do you do it?



**Michael:** Even though Hawaii is pretty far away, the MR community is very well-connected and it is easy to stay in contact with other researchers and experts around the world.

**Thomas:** People are happy to do a post-doc here because it gives them a chance to stay in Hawaii for a few years. We receive many visiting researchers and there are many opportunities to do good work and to keep the momentum going. ■

**Thomas Ernst**

# Bilateral breast 31P spectroscopy: A killer app for 7 T

INTERVIEW BY Jessica McKay AND Nikola Stikov

## EDITOR'S PICK FOR DECEMBER

Tijl and Dennis are scientists at Utrecht University and their paper on bilateral breast imaging and phosphorous spectroscopy is our Editor's Pick for the month of December. The paper presents a unique bilateral coil array that allows them to acquire both 31P spectroscopic imaging and 1H high-resolution imaging in a single session. Their novel design included quadrature transmit coils and used a floating loop to achieve decoupling at the resonant frequencies of both phosphorous and hydrogen. We discussed their path in MRI research and the features and significance of this work.

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Early in the  
treatment you  
could decide  
whether or not  
you should  
continue with  
the chemo.

–Tijl van der Velden

”

**MRMH:** Can you tell us a little bit about your background and how you got into MRI?

**Tijl:** I started out with a bachelor's in computer science and continued in the biomedical sciences. For my research, I first worked on a project involving the imaging of the carotid artery, also at 7T. Somehow I ended up in work that led to this article. So it was a bit of a curvy path. I am 3 years into my PhD, and expect to finish in about one year.

**Dennis:** You could say I am a hobbyist. I worked on a

team in Nijmegen where I actually learned all of the metabolic imaging features. Before that I worked with Philips in MR engineering. I really believe in metabolic imaging – that it can be helpful for many treatment decisions – but needs SNR. So, I moved from Nijmegen and searched for a location where they actually had some high fields, and ended up in Utrecht.

**MRMH:** Are you currently at a hospital? What is the level of integration between your group and the clinical infrastructure?



Tijl van der Velden holding the bilateral coil array.

van der Velden TA, Italiaander M, van der Kemp WJM, Raaijmakers AJE, Schmitz AMT, Luijten PR, Boer VO, Klomp DWJ. Radiofrequency configuration to facilitate bilateral breast 31P MR spectroscopic imaging and high-resolution MRI at 7 Tesla. *Magn Reson Med* 2015;74:1803-1810. DOI: 10.1002/mrm.25573

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25573/abstract>



**Dennis:** We are in the radiology department of the hospital. We have a quite large research group, which we call the Center of Image Science, with about 150 PhDs and post-docs that all work with MR within the institute and are completely embedded within the university hospital.

**MRMH:** What is the motivation for this work?

**Tijl:** In particular we want to take a look at the response to chemotherapy. Some preclinical data show that phosphorus spectroscopy could already differentiate respondents from non-respondents to chemotherapy after one session of chemo. Early in the treatment you could decide whether or not you should continue with the chemo. Look at the burden of chemotherapy for the patient and the costs of the treatment. I think phosphorus spectroscopy can really make a difference, especially combining it with proton imaging and the main clinical workhorse – dynamic contrast enhanced series.

**Dennis:** With that workhorse, you look mainly at morphology, which starts to alter halfway through treatment, or even at the end of the treatment. Metabolism could be a much faster change, and therefore you could change the treatment in the early phase. Having hydrogen MRI in place, while being able to image both breasts at once, conventional clinical decision-making can be combined with research, which makes life easier both for the radiologist and for the patient.

**MRMH:** Tell us a little bit about the commercialization. Is this coil available now?

**Dennis:** We have a little spin-off company called MR Coils. The whole idea for that is that it's easy for us to ship those hardware components to other research sites. If you do this through the hospital it is very complicated... too many lawyers involved. We have shipped a few of those to other sites and we are continuing to improve on the design.

**MRMH:** Would it be possible to scale your work to 3T?

**Tijl:** Moving to 3T for phosphorus is difficult because of the loss in SNR you have...

**MRMH:** So, in a way you could advertise this as a killer app for 7T.

**Dennis:** You can quote that - it is a good one! Even at 7T we still lack sensitivity. We always want more because our voxels are still quite large, so we still can only include substantial tumor sizes. And particularly deeper in the body, it will be challenging.

**MRMH:** Would you be interested in going to even higher fields?

**Dennis:** Of course! As research moves on we see, from from the University of Minnesota actually, that at 10.5 Tesla the SNR increase is beyond linear. I think that is



Dennis Klomp and a small, winged friend.

the driving force to go to even higher fields in the near future. But first let's find some funding!

**MRMH:** What was the main design challenge?

**Tijl:** The phosphorous frequency was hard to decouple between the left and the right sides.

**MRMH:** Why is it so important to decouple the coils?

**Tijl:** We basically have two coils, one for the left breast and one for the right. We want to avoid, say, cross talk between the coils, so that one coil will not influence the other. The way that the coils influence each other is different between the phosphorous frequency and the proton frequency.

**Dennis:** The coupling between proton and phosphorous is different even though the setups are identical because of the dielectric patterns in the human body. There are a couple of parameters: the size of the loop, the location of the loop, and the frequency of that loop. Those are the three variables you can play with. We did make sure the decouple-loop was not exactly on resonance because if it were, then you would get very high current, and you can even have the local field change.

**MRMH:** What else keeps you busy these days?

**Tijl:** We are working on gradient coils, also for breast. It is very early work still, but it is a fun project to work on.

**Dennis:** At 7T the challenges more than double, so we are investing in the gradient inserts for more gradient power and faster readout trains to utilize the performance of diffusion MRI at higher fields. ■

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Conventional  
clinical decision-  
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combined with  
research, which  
makes life easier  
both for the  
radiologist and  
for the patient.

–Dennis Klomp

# Improving APT signal quantification one egg at a time

INTERVIEW BY Mathieu Boudreau AND Nikola Stikov

## EDITOR'S PICK FOR JANUARY

The first Editor's Pick of 2016 is from Hye-Young Heo and Jinyuan Zhou, researchers at John Hopkins University. Their paper presents a new method, Extrapolated semi-solid Magnetization transfer Reference (EMR), which quantitatively measures two subsets of Chemical Exchange Saturation Transfer (CEST): Amide Proton Transfer (APT) and Nuclear Overhauser Enhancement (NOE). They tested the EMR method in an animal glioma tumor model, and were able to distinguish between active tumor regions, necrotic regions, and healthy tissue. They also pointed out that their quantitative measure of APT was not confounded by NOE effects. We recently spoke with Hye-Young and Jinyuan about their project, what led them to APT imaging, and what advice they have for newcomers.

“The idea behind the EMR method is very simple, but there is a lot of complex mathematics in the paper.”

—Hye-Young Heo

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

**Hye-Young:** My background is in biomedical engineering, and I did proton exchange-based MRI, T1 rho imaging, for my PhD at the University of Iowa from 2008 to 2013. I joined Dr. Zhou's group in fall 2013, where I have worked on another proton exchange-based MRI method, CEST imaging.

**Jinyuan:** I'm an associate professor of Radiology at John

Hopkins University, and my background is in MR physics. I got my PhD degree from the Wuhan Institute of Physics at the Chinese Academy of Science in 1996, where I did solid-state NMR. We started doing CEST MRI here around the year 2000.

**MRMH:** When did you move to the US?

**Jinyuan:** 1997... it's been almost 18 years [chuckles].

**MRMH:** What sparked your interest in chemical exchange and magnetization transfer imaging?



Hye-Young Heo

Heo HY, Zhang Y, Lee DH, Hong X, Zhou J. Quantitative assessment of amide proton transfer (APT) and nuclear overhauser enhancement (NOE) imaging with extrapolated semi-solid magnetization transfer reference (EMR) signals: Application to a rat glioma model at 4.7 tesla. *Magn Reson Med* 2016;75:137-149. DOI: 10.1002/mrm.25581

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25581/abstract>



**Hye-Young:** APT imaging, a subset of CEST, is a very interesting topic. It's an important molecular MRI technique which can detect very low concentrations of amide protons. Clinical applications include tumor detection, treatment assessment, and stroke imaging.

**Jinyuan:** When I first arrived here, I was a post-doc under the supervision of Dr. Peter van Zijl. Peter has many new ideas and always pushed us to try new things. We started with CEST, which was new at the time, and then that led me to APT. Most MRI techniques are water-based, while APT is protein-based. We don't have to inject any contrast agents; we just use the endogenous proteins in our body.

**MRMH:** Could you please give us a quick overview of your paper?

**Hye-Young:** In general, CEST is confounded by the water direct saturation effect and other magnetization transfer effects. So, in MTR asymmetry quantifications, the CEST signal is confounded by the Nuclear Overhauser Effect (upfield from the water). In this study (together with another paper, DOI: 10.1002/mrm.25795), we introduced a new method called Extrapolated Semi-Solid Magnetization Transfer Reference (EMR), to quantify the pure APT signal by isolating it from confounding factors.

**Jinyuan:** Usually, using MTR asymmetry, the obtained APT-weighted intensity values range between 2% and 3%. One thing we found with EMR is that the pure APT effect is very large. It can be more than 10% in tumor. It's very big! Another discovery was that the dominant APT-weighted contrast between tumors and normal tissue is APT, not NOE.

**MRMH:** For those of us unfamiliar with cancer biology, could you please explain why you observed different exchange phenomena between healthy tissue and tumor (center vs. rim)?

**Hye-Young:** We scanned the animal tumor model, human glioblastoma-bearing rats, 45 days post-implantation. At this time, the tumor center had begun necrosis, so there were less mobile APT-detectable proteins there. However, the tumor rim is always very active; there are a lot of mobile proteins compared to normal tissue and the tumor center.

**MRMH:** What advice can you offer to a graduate student who has read your paper and wants to implement EMR in her/his project?

**Hye-Young:** The idea behind the EMR method is very simple, but there is a lot of complex mathematics in the paper. I would recommend to do Bloch equation-based simulations first, to examine how the CEST signal changes with RF power, T1 and T2 relaxation times, and other experimental settings.

**Jinyuan:** I think it's very important that you spend time to optimize your sequence. In my experience, egg white makes a very good/cheap phantom for APT, because it has many natural proteins. Water is not a good phan-



tom for APT. And you should first make sure that your z-spectrum is very smooth, not noisy.

**MRMH:** Do you lose the APT effect if you cook the egg?

**Jinyuan:** [laughs] Yes, if the egg is cooked, you can see the APT effect reduces almost to 0.

**MRMH:** What other topics currently excite you?

**Hye-Young:** Recently, I'm very interested in fast CEST imaging, using parallel MRI, k-t acceleration, and compressed sensing techniques because the CEST imaging has a relatively long acquisition time due to acquiring multiple RF saturation frequencies. I think fast CEST imaging is great for the evaluation of acute stroke patients and pediatric patients.

**Jinyuan:** I'm currently particularly interested in radiogenomics. People are doing radiogenomics to find the correlation between MR features and genes (e.g. gadolinium enhancement, FLAIR hyperintensity). I think that APT-weighted MRI features might be more associated with the genome, because APT is protein-based.

**MRMH:** Thank you and good luck with your future work! ■

**Jinyuan Zhou on the beautiful Hopkins campus.**

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*I think it's very important that you spend time to optimize your sequence.*

—Jinyuan Zhou

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# Super-resolution and Eureka! moments in diffusion imaging

INTERVIEW BY **Karolina Urban** AND **Nikola Stikov**

## EDITOR'S PICK FOR JANUARY

Gwendolyn Van Steenkiste is currently a doctoral student at the University of Antwerp in Belgium, working on super-resolution reconstruction (SRR). Gwendolyn's paper entitled "Super-resolution reconstruction of diffusion parameters from diffusion-weighted images with different slice orientations," was selected as Editor's Pick for the month of January. We contacted Gwendolyn and her supervisor, Dr. Jan Sijbers to discuss the details of the paper.



**Gwendolyn Van Steenkiste**

Van Steenkiste G, Jeurissen B, Veraart J, den Dekker AJ, Parizel PM, Poot DHJ, Sijbers J. Super-resolution reconstruction of diffusion parameters from diffusion-weighted images with different slice orientations. *Magn Reson Med* 2016;75:181-195. DOI: 10.1002/mrm.25597

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25597/abstract>

**MRMH:** Gwendolyn, how did you get interested in MRI?

**Gwendolyn:** I have a strong clinical influence from my family who are dentists, doctors and pharmacists. So when I finished studying engineering in applied physics as an undergraduate, I became very interested in MRI, which has clinical impact but is still physics based.

**MRMH:** Can you tell us in plain language the main points of your paper?

**Gwendolyn:** Whenever you want to increase the spatial resolution of an image, there is either an increase in acquisition time or a decrease in signal to noise ratio (SNR). Our paper showed that it is possible to use the same acquisition time and achieve greater spatial resolution. Additionally we showed that the diffusion model can be incorporated into the super resolution reconstruction process, thus limiting the propagation of errors in the pipeline. Specifically with our approach, you can have greater parameter selection, while sampling Q space more optimally and incorporating the motion correction.

**Jan:** As Gwendolyn said, this method allows for higher resolution and greater freedom with the acquisition parameters. We achieve this by acquiring a set of low-resolution diffusion images with high SNR, and incorporating well-chosen orientations. By optimizing the scanning parameters, you can break the traditional trade-off between acquisition time, SNR, and spatial resolution.

**MRMH:** Are the voxels you acquire isotropic?

**Gwendolyn:** No, the idea is that you acquire images with high in-plane, but low through-plane resolution. The thick slices are acquired at different angles, so that if you project in k-space you create a circle in 2D, or a cylinder in 3D. From this you can reconstruct higher resolution images.

**MRMH:** In short can you describe the signal-generating model?

**Gwendolyn:** The signal-generating model explains what happens in the scanner. First we model the mo-





tion (patient movement and table vibration), then we incorporate the geometry (slice orientation), and also the voxel size (downsampling). This is all modeled by an affine transformation, and it is followed by filtering that accounts for the incomplete k-space coverage and the imperfect slice selection.

**Jan:** The signal-generating model is very important in forward modeling. It allows to forecast how low resolution images (acquired at a specific orientation) would look like, given an estimate of the high-resolution DTI image. This simulated low resolution image can then be compared to actually measured low resolution images. The difference measures how close your assumed high-resolution DTI image is to the true (unknown) high resolution DTI image.

**MRMH:** What are the benefits of using the SRR method? How do you see this translating into future research?

**Gwendolyn:** Well, SRR could be an alternative to the strong gradients of the Connectom scanners. In regular clinical research, it will result in shorter acquisition times, which will in turn produce images with fewer motion artifacts. As for research on SRR, there is still lots to do, on improving the modeling, but also on applying to different modalities, such as T1 mapping and perfusion.

**Jan:** Our ultimate goal is for SRR to optimize each single k-space point for the best parameter maps in a range of protocols (diffusion, T1 mapping, perfusion).

**MRMH:** What has been the biggest challenge of this project?

**Gwendolyn:** Our protocol is very different from what MR operators usually use, so you need to have good

communication if you want somebody else to acquire your data. Basically you need to convince them to let go of what they know and stick with the weird slice orientations and the unconventional acquisition strategy. As we progress, with the more complex diffusion models, I think the difficulty will lie in the computational complexity of the fitting.

**MRMH:** What was your eureka moment?

**Gwendolyn:** When I finally got the acquisition set up on point and I visually saw an enhancement in the spatial resolution of the estimated DTI parameters. Another moment was when I was simulating motion in my diffusion data and realized that including a variety in the q-space sampling resulted in a better estimation of the diffusion parameters!

**MRMH:** Jan, what is life like at the University of Antwerp?

**Jan:** The University is comprised of three campuses, and our campus is located outside the city. It primarily hosts life sciences, it is green, has top research infrastructure, and the food is great.

**MRMH:** What comes next for you?

**Gwendolyn:** I am in my final year of my PhD, and am hoping to continue with MRI research focusing on super resolution methods. I would like to go abroad to explore different opportunities and viewpoints.

**Jan:** Indeed, going abroad during or after your PhD is for sure an enriching experience. Within the Vision Lab, we will continue exploring new avenues in the area of quantitative magnetic resonance imaging and hope that our collaboration with Gwendolyn will last for many years. ■

Jan Sijbers

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The diffusion  
model can be  
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the super resolution  
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propagation of  
errors in the  
pipeline.”

—Gwendolyn Van  
Steenkiste

# Go Ahead, Breathe: Using FLEET for motion and respiration compensation

INTERVIEW BY **Samantha By** AND **Nikola Stikov**

## EDITOR'S PICK FOR FEBRUARY

One of the editor's picks for the month of February is a paper entitled "Reducing Sensitivity Losses Due to Respiration and Motion in Accelerated Echo Planar Imaging by Reordering the Autocalibration Data Acquisition" by Drs. Jonathan R. Polimeni and Lawrence L. Wald. Currently, both are faculty members at the Athinoula A. Martinos Center for Biomedical Imaging at Harvard Medical School and Massachusetts General Hospital. We recently contacted them to talk about their method, which uses fast low-angle excitation echo-planar technique (FLEET) to reorder the auto-calibration signal (ACS) acquisition to compensate for motion and respiratory effects.

“Once parallel imaging started kicking off, a lot of users at the Martinos Center would notice “eyeball artifacts” in their EPI data.

—Jonathan Polimeni

**MRMH:** Jon, how did you get interested in MRI?

**Jon:** My background is actually in neuroscience, but I got involved with MRI because I thought we were limited in our measurements that we had at the time to really answer the questions that we wanted to ask. So I wanted to learn more about MRI, and I joined Larry's group.

**Larry:** Jon, when did you join us?

**Jon:** 2007.

**Larry:** Really?

**MRMH:** Time flies...[laughs]. How about you, Larry?

**Larry:** I studied condensed matter physics and was fortunate enough to be in the lab of Erwin Hahn at Berkeley doing NMR. When I graduated and got my PhD, I thought medical imaging was more interesting, and with this knowledge in MR, it was kind of a logical transition to MRI.

**MRMH:** So, how did your current project get started?

**Jon:** Once parallel imaging started kicking off, a lot of users at the Martinos Center would notice “eyeball artifacts” in their EPI data. Once we implemented a fixation task during the training data, these were removed. At 7T, we would sort of give the volunteers a pep talk and tell them not to move during the beginning of each run.

**Larry:** We started noticing all of these problems that we couldn't explain – discontinuous SNR between slices, the temporal SNR (tSNR) of GRAPPA wasn't as good as expected. But then early on we noticed it would be a big mistake to let the subject scratch their nose during the training data. So we forced everyone to switch off the stimuli during the ACS, so that the subject was resting. Just com-



**Jon Polimeni**

mon sense, but then all of these problems started solving themselves. When we had a subject hold his breath, all the problems vanished and we could point to respiration.

**MRMH:** Eureka! So, that's how you really pinpointed that motion and respiration were an issue. What made you think about reordering the slices?

**Jon:** Ironically, though parallel imaging techniques were being pushed to enable single-shot EPI, on the Siemens platform, when an acceleration factor above 2 is applied, the calibration data is segmented multi-shot EPI. So every run was still subject to motion—but only at the very beginning when the ACS data were acquired.

Polimeni JR, Bhat H, Witzel T, Benner T, Feiweier T, Inati SJ, Renvall VR, Heberlein K, Wald LL. Reducing sensitivity losses due to respiration and motion in accelerated echo planar imaging by reordering the autocalibration data acquisition. *Magn Reson Med* 2016;75:665-679. DOI: 10.1002/mrm.25628

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25628/abstract>





Larry Wald and Jon Polimeni captured mid-thought during the Q&A.

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*The user never notices, but suddenly you're more robust to motion and respiration, with an average 25% increase in tSNR. There's no downside that we can see. That's a rare thing in MRI!*

—Lawrence Wald

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Larry Wald and Jon Polimeni traversing snowy climes,

We saw a striking discontinuous tSNR across slices for GRAPPA-accelerated acquisitions with  $R=3$  or higher. At  $R=2$ , however, the calibration data was still acquired with single-shot EPI and the discontinuous tSNR was no longer present. We had to minimize the time interval between segments.

**Larry:** With the conventional method, the multi-shot EPI acquisition corrupts your data. If you have a 4 second TR, you have 4 seconds in between your shots, which is plenty of time for you to be in a totally different respiratory state. Our solution was to cut that time down and reorder the slices one after the other for each segment.

**MRMH:** You present a lot of data in the paper – could you break it down for us in terms of what you saw in the phantom versus in vivo data?

**Jon:** With phantoms, image SNR and tSNR should be the same measure. As we reduced the flip angle to acquire FLEET data, we saw that reduced SNR in the ACS data had a regularization effect: it could improve the SNR in the reconstructed images. Even in the phantom, which hopefully isn't doing much breathing, we could improve the image SNR by virtue of the fact that the reduced flip angle in the FLEET acquisition was adding a little bit of noise, which gives the kernel a few more degrees of freedom to estimate an accurate fit.

**Larry:** Then we added motion to the phantoms and noticed that with conventional ACS data, there were a lot of errors, but FLEET effectively froze motion by acquiring the data for one slice more quickly. With the conventional method, the first shot of slice 1 is acquired, you go through all the slices, and then take the second shot of slice 1 – now that's a TR apart. To me that's the beauty of the whole method. We didn't really change much of the acquisition. We simply reordered the loop structure of the ACS between the shots and the slices. The user never notices, but suddenly you're more robust to motion and respiration, with an average 25%

increase in tSNR. There's no downside that we can see. That's a rare thing in MRI!

**MRMH:** What about the in vivo data?

**Larry:** This really let us show the impact of respiration on the ACS data. Our FLEET method had the same effect as a breath hold, showing that the method was effective in reducing the noise caused by respiration.

**MRMH:** Are there any artifacts due to cardiac cycle?

**Jon:** That's a good question...but more difficult to prove! The breath hold test, however, was able to resolve most of the artifacts we were seeing in terms of SNR, so this showed respiration was the dominant factor.

**Larry:** Yeah, we can't really have a volunteer turn on and off their cardiac cycle [laughs].

**MRMH:** What are some applications you have in mind?

**Jon:** The Maastricht group is actually using it on their ASL data for perfusion. Diffusion and fMRI are also good applications. Some of our colleagues have been asking about body imaging, which you can imagine is going to be more problematic than the brain.

**Larry:** Certainly any EPI application should automatically have it – we don't really see any negative, so why not give it a try? ■



# The golden angle and its applications in motion correction

INTERVIEW BY Hong Shang AND Nikola Stikov

## EDITOR'S PICK FOR FEBRUARY

Dr. Li Feng and Dr. Ricardo Otazo are researchers at the New York University School of Medicine, whose paper on golden angle radial MRI with compressed sensing and parallel imaging is one of our Editor's picks for the month of February. Li recently finished his doctorate at NYU, whereas Ricardo arrived in New York from the University of New Mexico, where he completed his PhD in 2007. They are both in love with what New York has to offer, academically as well as socially. We met over Skype to discuss XD-GRASP, a free-breathing MR imaging framework that combines the acceleration capability of compressed sensing and the self-navigation properties of radial imaging to reconstruct dynamic motion-resolved multidimensional data.

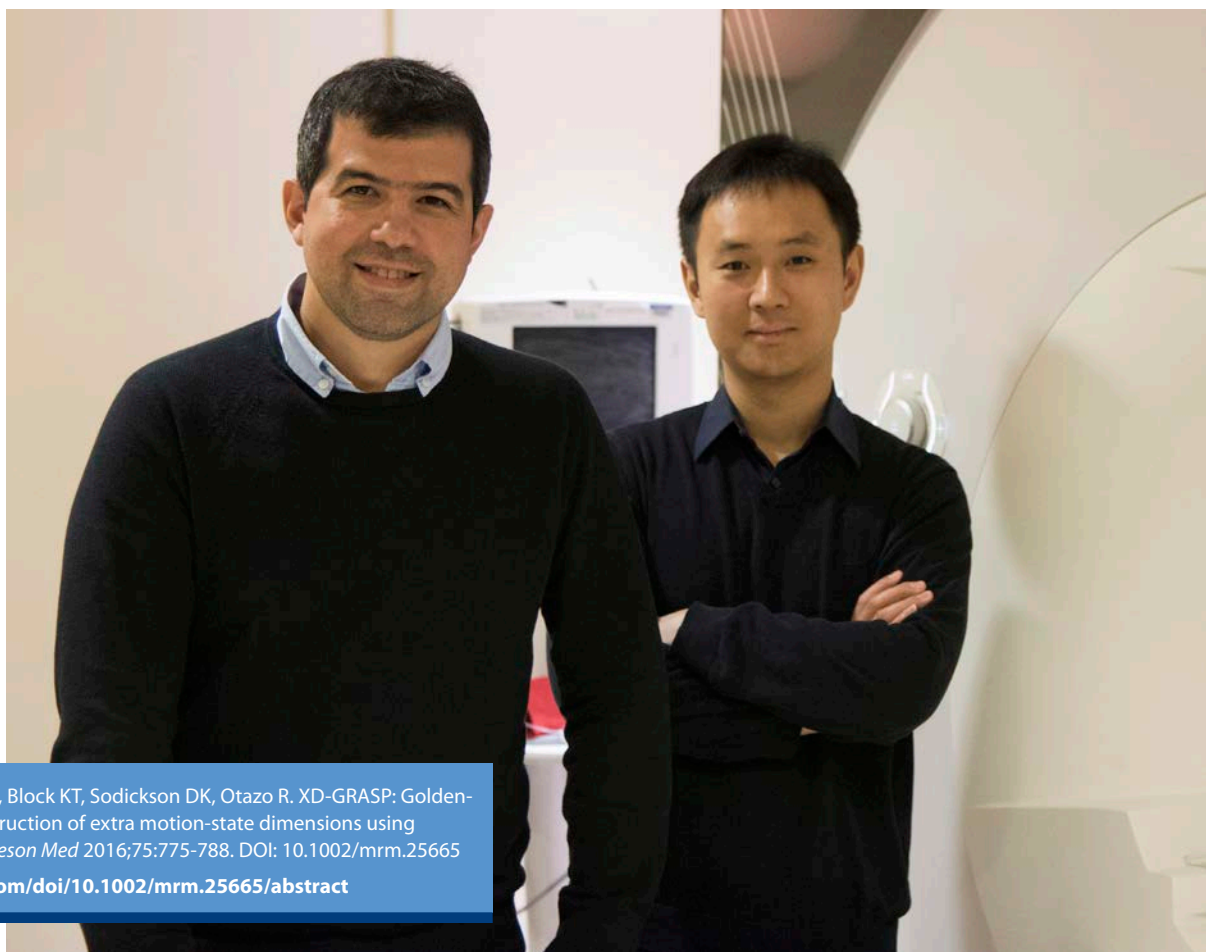
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*In the end, we are not just solving a motion correction problem. We also try to get as much information out of motion as possible, and use it to reconstruct an image.*

—Ricardo Otazo

**MRMH:** Why did you choose to work on this specific project?

**Li:** Since the beginning of my PhD, I have been working with Ricardo and Dr. Dan Sodickson at NYU on compressed sensing (CS) MRI. We started with Cartesian sampling, but we found it had some limitations in terms of incoherence, so we moved towards radial sampling.

We found the golden angle radial sampling very interesting because it enables continuous data sampling without the need to predefine temporal frames. Later we also found that the self-navigation property of radial sampling can be further incorporated into the compressed sensing framework to reconstruct motion-resolved dynamic images.



Ricardo Otazo and Li Feng

Feng L, Axel L, Chandarana H, Block KT, Sodickson DK, Otazo R. XD-GRASP: Golden-angle radial MRI with reconstruction of extra motion-state dimensions using compressed sensing. *Magn Reson Med* 2016;75:775-788. DOI: 10.1002/mrm.25665  
<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25665/abstract>



**MRMH: What is golden angle radial sampling, and why is it important?**

**Li:** The golden angle comes from dividing 180 degrees by the golden ratio 1.618. In golden angle radial sampling, the sampled spokes carry equal amount of information and they never repeat each other. Meanwhile, they always add complementary information by filling the largest gap left by previously sampled spokes in k-space. Therefore, it is well suited for continuous k-space updates.

**Ricardo:** It is important because you can do continuous data acquisition, providing approximately uniform coverage of k-space. This is a perfect sampling scheme for uncorrelated samples along the temporal dimension. That is how we get temporal incoherence for compressed sensing.

**MRMH: What would you say is the biggest advantage and the biggest challenge of your approach?**

**Li:** Our free-breathing imaging framework does not require any assumptions on the motion model. This is a big advantage for moving towards our ultimate goal of rapid and continuous acquisition for easy and flexible MRI workflow.

**Ricardo:** The biggest challenge is image quality assessment, not only for this method but for other compressed sensing reconstruction algorithms in general. Currently we show radiologists the reconstructed images, and ask them to assign a grade. It would be nice if we can have an automatic method that can tell us how well we are doing, in particular for lesion detectability.

**MRMH: Is a periodic signal a requirement for compressed sensing in this framework?**

**Li:** It is a requirement. However, respiratory and cardiac motion are major sources of artifacts in clinical imaging. As both motions are periodic, they are well suited to our framework. However, there is no requirement on the motion pattern, and the change of breathing cycle or cardiac cycle won't matter for our method as long as there are occasional peaks and valleys.

**Ricardo:** If the motion is exactly periodic, that is great. In that case it is very easy to do compressed sensing, because the signal will be really sparse in the temporal Fourier transform domain. In the case of DCE imaging, it is a non-periodic process, but we can still use our approach to reconstruct an extra respiratory dimension. In the end, we are not just solving a motion correction problem. We also try to get as much information out of motion as possible, and use it to reconstruct an image.

**MRMH: So how do you handle both types of motion, cardiac and respiratory?**

**Li:** Cardiac and respiratory motion occur simultaneously at two different frequencies. After the data acquisition, we are trying to sort the data into two separate dimensions according to this frequency difference. Given they are both periodic, we can just scan for 10 to 20 seconds and then sort the acquisitions to get enough



data for each dimension.

**Ricardo:** The sampling frequency depends on the clinical need. For dynamic contrast enhanced imaging of liver, we can just reconstruct several contrast enhancement phases that are needed for clinical diagnosis. In the case where we need finer sampling of the respiratory cycle, such as evaluation of the lung function, we can reconstruct the images with a higher temporal resolution. But that does not mean we need to image faster. We can take advantage of the fact that respiratory motion is periodic, and just image for a longer period of time and synchronize the acquired data.

**MRMH: Is the computation time acceptable?**

**Li:** That depends on the patience of the radiologists. Radiologists at NYU are fine with half an hour or even one hour long reconstruction time. The current reconstruction takes 30 to 50 minutes for the 3D DCE-liver studies.

**Ricardo:** We are regularly using this technique at our site for oncological imaging studies, but more powerful computers can reduce the computation time significantly. With cloud computing, like the Amazon web service, we tested our algorithm on 10,000 cores with 255 GB of memory, and got the reconstruction down to 5 seconds.

**MRMH: Any parting thoughts for our readers?**

**Li:** We would like to share our technique. That is why we put all our source code and example datasets online (<http://cai2r.net/resources/software>) so people can download it and try it out. ■

**Ricardo Otazo  
and Li Feng in  
downtown NYC.**

“  
*We would like  
to share our  
technique. That  
is why we put all  
our source code  
and example  
datasets online.*

—Li Feng

”

# Just add ice – Simple water phantoms for detecting multi-site ADC bias

INTERVIEW BY Jessica McKay AND Nikola Stikov

## EDITOR'S PICK FOR MARCH

The March Editor's Pick features Dr. Dariya Malyarenko and Dr. Tom Chenevert, from the University of Michigan. With a background in solid-state NMR and signal processing for biomarker discovery from cancer proteomics data, Dariya started in MRI as an NIH T32 trainee four years ago. Tom began his work in MRI 25 years ago at the University of Michigan. In their paper they perform a multicenter study to thoroughly characterize the sources of technical bias in quantitative diffusion weighted imaging (DWI), and identify gradient non-linearity as a major contributor.

“  
The oncology  
imaging world is  
looking at ADC  
measurements  
as one of the  
most promising  
approaches to  
measure the  
tissue cellularity.

–Thomas Chenevert

**MRMH:** Let's start with the basics. Can you give us a brief overview of DWI? What is an ADC value?

**Dariya:** Diffusion weighted imaging (DWI) is a commonly used technique that applies additional gradient pulses to encode the mobile spins of water. It is known that the presence of dense cell structures affects the mobility, so we can indirectly monitor the cellularity of the tissue. The apparent diffusion coefficient (ADC) is an isotropic characteristic of the tissue measured by DWI

that is very useful for oncology clinical trials.

**Tom:** ADC is recognized as a very promising biomarker, sort of a self-normalizing measurement that does not depend strongly on the field strength or on the system specifications. The oncology imaging world is looking at ADC measurements as one of the most promising approaches to measure the tissue cellularity. The mathematics to get to a number is quite straightforward; it is inherently a ratio and it is quite objective.



Tom Chenevert and  
Dariya Malyarenko.

Malyarenko DI, Newitt D, Wilmes LJ, Tudorica A, Helmer KG, Arlinghaus LR, Jacobs MA, Jajamovich G, Taouli B, Yankeelov TE, Huang W, Chenevert TL. Demonstration of nonlinearity bias in the measurement of the apparent diffusion coefficient in multicenter trials. *Magn Reson Med* 2016;75:1312-1323. DOI: 10.1002/mrm.25754

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25754/abstract>





Prepping the ice water phantom.

**MRMH:** What was the main motivation for this work?

**Tom:** In diffusion measurements there are a lot of different sources of variability, which limit the power of our clinical trials. There is biological variability, such as tumor heterogeneity in oncology, and then there is the variability in the acquisition technique and the way we process data. All of these things contribute to the overall uncertainty of our measurements. What we are trying to do is to reduce the technical variability in our clinical trials and thereby yield a stronger scientific impact.

**MRMH:** Can you explain the approach you took to understand the bias in ADC measurements?

**Tom:** It is sort of a long story. We came up with this ice-water phantom through a contract supported by the NCI (National Cancer Institute) to devise a phantom for multicenter trials. Ice water has an exact diffusion coefficient, so we had really good precision, but we detected these spatially dependent results. We were not sure what the relative strength of the various contributors was, like shim, eddy currents, and sequence parameters. So the process that we describe was really to tease out these various influences across different vendors and systems. We saw good agreement at the isocenter of the magnet, but moving off-center we saw disagreement, which prompted us to look at the various contributors. Our collaborations within the NCI Quantitative Imaging Network (QIN) provided a fairly broad system landscape to assess these contributors on clinically utilized MRI scanners.

**Darya:** Because we are using a phantom with a single ADC value, the amount of bias in the ADC map provides us directly with the measurement of bias in the diffusion gradients: the general offset of the gradient strengths, the asymmetry of the applied gradients, and the non-linearity, which has a quadratic relationship with the gradient strength.

**MRMH:** How do you maintain the phantom?

**Tom:** We don't. You put it in ice water before scanning and let it come to equilibrium. Once the measurement is done, you dump out the water, put it on the shelf, and wait for the next day that you want to use it. There are multiple ice-water phantoms being devised. In fact, we are working with Michael Boss and Katy Keenan at NIST (National Institute for Standards and Technology) and the QIBA (Quantitative Imaging Biomarker Alliance) to devise another ice-water phantom that has multiple diffusion properties.

**MRMH:** Were you surprised by any of the results?

**Darya:** Yes, actually, we were surprised by how similar the patterns for different systems were. We didn't know a priori how much the gradient non-linearity would contribute, but it was a major source. One interesting point was that the bulk characteristics of the scanner, like bore length and diameter, were very predictive of how much non-linearity we would see.

**Tom:** In fact, that is important; the gradient non-linearity, which we believe is the main source of this spatial bias, is determined on the assembly line for that scanner. It is predictable and therefore correctable. We should be able to impart a practical solution without having to do calibrations on individual subjects. We have to prove that it is static over time, but we expect this based on first principles.

**MRMH:** If a researcher at another site wanted to make these corrections, how might they go about doing so?

**Darya:** There are a couple of approaches. The best and easiest, which we are trying to promote, is for the manufacturer to implement the correction because they have the system-specific information on their gradient design. We are trying to communicate this problem to the manufacturers and form collaborations to fix it. Meanwhile, researchers can use phantom measurements just one time to empirically characterize their system and form these fixed, three-dimensional corrector maps. In our next work with the QIN collaborators we are going to demonstrate how these system-specific maps are applied retrospectively.

**Tom:** We are finding the vendors very cooperative, and we have started an academic-industrial partnership between the University of Michigan, UCSF, and Johns Hopkins University, as the academics, and Philips, General Electric, and Siemens, as the industrials. Together, we are teaming up to investigate and try to implement an online correction. So, while we love our ice-phantom, we really do think that the best way to do this is to use prospective knowledge of the system. In the meantime, we recommend people just make their own phantoms. The one we used was just a 12-inch column of water wedged inside of a bottle that you fill up with ice water.

**MRMH:** Thank you very much; we hope you enjoyed this as much as we did.

**Tom:** I like the MRM outreach concept. It is good to be able to give a short, digestible summary, and it gives us something to show to our grandkids. ■

“  
the gradient  
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believe is the  
main source of  
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scanner. It is  
predictable  
and therefore  
correctable.”

—Thomas Chenevert

# We need antennas - not coils! Body imaging at high field with the fractionated dipole antenna

INTERVIEW BY **Ryan Topfer** AND **Nikola Stikov**

## EDITOR'S PICK FOR MARCH

Among the Editor's picks for March is a paper entitled "The Fractionated Dipole Antenna: A New Antenna for Body Imaging at 7 Tesla". Co-authors Alexander Raaijmakers and Nico van den Berg have cast their coils aside and adopted antennas, with segmented legs and implanted inductors.

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The antenna  
work goes back  
a couple of years  
when we started  
to realize that  
it's antennas  
and not coils  
that you  
need for body  
imaging at 7 T.

—Alexander Raaijmakers

**MRMH:** How did each of you come to work with MRI?

**Nico:** I started in applied physics, and about a year into my PhD, while I was studying hyperthermia, I got sick one week, so I grabbed the Haacke book – the big, green bible of MRI – I took it home and fell in love with MRI! With MRI you can image electromagnetic distributions in the human body non-invasively, which we'd been seeking to do to validate our models in hyperthermia, so I managed to convince my supervisor that it would be a good idea for me to continue studying MRI on the side. After that it was more and more MRI up until the end of my PhD. And then the 7 T came along, and now I'm a MRI physicist... Still love the topic!

**Alexander:** My training was also in applied physics, combining radiotherapy with MRI. After that, it was Nico who approached me, asking if I would like to do something with RF in high field MRI, because body imaging is so challenging and, at that point, the 7 T system at Utrecht had only recently been installed.

**MRMH:** So what were the main ideas behind this latest work?

**Alexander:** The antenna work goes back a couple of years when we started to realize that it's antennas and not coils that you need for body imaging at 7 T. Actually this was a remarkable point at the ISMRM annual meeting in 2010 in Stockholm. Apart from some people that were resisting it quite fiercely, the work was well received. I think people realized that with higher frequencies (shorter wavelengths) you may need something other than coils - you may need antennas. That's where it started, but with a totally different design: it was a ceramic brick with a dipole atop of it. This current paper is the sequel to that – the logical next step, where

we realized we don't need the ceramic spacer, particularly when we segment the dipole and put inductors in between – we get lower SAR levels and it all fits!

**MRMH:** Coil vs. antenna – what's the difference?

**Alexander:** The coil is basically what you'd use if you want to boost something close to you. An antenna does the opposite: like a broadcasting radio, you want to emit something at a distance.

With the higher frequency at 7 T, we enter a sort of transition zone where we can no longer rely on coils because coils only boost things nearby – which is fine if your target is nearby, but “nearby” is actually relative to the wavelength of your signal. As your wavelength gets shorter, what used to be nearby now becomes faraway.

**Nico:** A coil is sometimes also called a near-field antenna. As you go up in field strength, this near-field region shrinks and the deeply-situated body structures move outside it. So you can make a coil to boost your field in the near-field, but, in body imaging, that's no longer your target region.

**MRMH:** So what prompted you to get rid of ceramic bricks from your initial design?

**Alexander:** First of all, they were heavy: it wasn't practical to have these dielectric bricks, each of them weighing a kilo. (So there would be 4 kg laying on the chest of a person when doing cardiac imaging.)

We also thought we needed the spacer to reduce the wavelength locally so that there would be no near-field inside tissue (so, no enhanced electric fields, no exceptionally high SAR levels). But this turned out not to be true because if you make the antenna long enough, the tissue itself acts to dampen the currents, so the conservative E-fields don't show up and all you're left with are the induced electric fields, which do add SAR, but you'll always have those, even with loop-coils.

**Nico:** That was one of the main surprises we found. An electric dipole is often seen as an electric field source that's bringing the problem of tissue heating. The fact that you put these dipoles directly on the body – that

Raaijmakers AJE, Italiaander M, Voogt IJ, Luijten PR, Hoogduin JM, Klomp DWJ, van den Berg CAT. The fractionated dipole antenna: A new antenna for body imaging at 7 Tesla. *Magn Reson Med* 2016;75:1366-1374. DOI: 10.1002/mrm.25596

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25596/abstract>





interplay with the antenna on the body, that actually dampens your currents and induces much lower E-fields than we anticipated. That for us was the big surprise, and I think it's a major factor in the success of this new type of antenna.

**MRMH:** What was the inspiration to segment the dipoles and add inductors in between the segments?

**Alexander:** Actually, it was when I was walking around at the ISMRM meeting in Melbourne (2012), when I realized maybe I could use a dipole antenna, cut it into pieces, and then add lumped elements between them (capacitors or inductors) and see what happens – maybe then I could manipulate the behavior and still have low SAR levels without a ceramic spacer. That's what I tried immediately when I got home and it really worked well! Only after that did I realize if I don't segment my dipole, even without inductors, I still have much lower SAR levels than with the ceramic. So that realization actually came later, although in the paper it was presented first.

**MRMH:** Would there be an advantage of using your antennas at clinical field strengths, or is this just a

high field thing?

**Alexander:** Actually we're already doing it! This is work we've done together with King's College in London, and it will be presented at this year's annual ISMRM meeting in Singapore.

The advantage of the dipole antennas is not so obvious at 3 T – loop-coils have more signal at depth, but they have tremendously more signal at the surface. The dipole antenna has a much shallower profile. It also drops off, but much less steeply – so that's what gives us a relatively homogeneous field distribution that you actually wouldn't expect using a local transmit array.

**Nico:** There's been a lot of work over the last 10 years on coil designs for transmit arrays at 7 T: people have come up with a lot of original solutions, and they've come to have a deeper understanding of RF signal propagation in the body. It's nice to see the expertise and the technology are now being transferred to 3 T, which is clinically more relevant of course. It's nice that 7 T, where there's a lot of activity going on, is acting like a sort of testing ground and a forerunner in some of the technologies. ■

**Cornelis "Nico" van den Berg, Alexander Raaijmakers, and Alex's daughter in Utrecht, Netherlands.**

# No reference? No problem! Self-navigation for irregular breathing patterns

INTERVIEW BY **Xin Miao** AND **Nikola Stikov**

## EDITOR'S PICK FOR APRIL

Giulia Ginami is currently a PhD student at the Cardiovascular Magnetic Resonance (CVMR) group, based in the Radiology Department of the University Hospital of Lausanne (CHUV). Her paper, selected as the Editor's Pick for April, is entitled "An Iterative Approach to Respiratory Self-Navigated Whole-Heart Coronary MRA Significantly Improves Image Quality in a Preliminary Patients Study." This paper proposes a respiratory motion compensation algorithm that is independent of a specific reference position for motion correction. We recently invited Giulia and senior author Dr. Davide Piccini, to talk about their paper.



Matthias Stuber, Giulia Ginami, and Davide Piccini.

Ginami G, Bonanno G, Schwitter J, Stuber M, Piccini D. An iterative approach to respiratory self-navigated whole-heart coronary MRA significantly improves image quality in a preliminary patient study. *Magn Reson Med* 2016;75:1594-1604. DOI: 10.1002/mrm.25761

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25761/abstract>

**MRMH:** You are two Italians in Switzerland. Why did you decide to work in Lausanne?

**Giulia:** My bachelor's thesis was done in Padova (Italy) and already focused on MRI. I then came to Lausanne for my master's thesis, under the supervision of Davide and of Gabriele Bonanno, which focused on respiratory self-navigation. I liked the topic and the group so much I decided to stay for my PhD.

**Davide:** Like Giulia, I also did my university studies in Padova. My first contact with MRI was as an intern at Siemens Corporate Research in Princeton, New Jersey, where I worked on post-processing techniques for cardiac MRI. After that, I worked for 3 years on my PhD with Siemens MRI at the University of Erlangen (Germany). During that time Prof. Matthias Stuber visited us from Lausanne and we started to collaborate on motion correction topics for coronary MRI. Later, I became a Siemens employee in Lausanne, where I continue to collaborate very closely with Prof. Stuber's group.

**MRMH:** Now that we know how you got here, can you tell us about the background of this paper on self-navigation?

**Giulia:** Typically, it takes a long time to acquire a high-resolution 3D coronary MRA dataset in free-breathing. Respiratory motion compensation is a major challenge. Unlike the commonly used diaphragm navigation, self-navigation allows you to extract the structure of interest (the heart) and derive the motion information from the imaging data itself. In this way, reliable motion correction can be performed and 100% scan efficiency is achieved with no need for data rejection.

**Davide:** It isn't easy to prescribe the navigator. It is also nearly impossible to predict the scan time, when you rely on an acceptance-rejection algorithm to suppress respiratory motion artifacts. In comparison, self-navigation promises to be more precise and practical in a



clinical environment, because it allows for motion correction, and has a pre-defined scan duration.

**MRMH:** How did this particular study come about?

**Giulia:** The self-navigation signal used in our studies is a 1D superior-inferior (SI) projection of the 3D volume. Our 3D radial acquisition scheme, based on a golden-angle / phyllotaxis arrangement of the readouts, allows us to acquire such projections with each heartbeat. Conventionally, as in many similar approaches, we take one of the projections as reference, and cross-correlate it with the other projections to track the relative displacement of the heart. We did a preliminary study on healthy volunteers to see if and how different reference respiratory positions impact the final reconstructed images. We found that image quality was significantly better if end-expiration was chosen as a reference. Then, we expanded this study to patients, who usually have more irregular breathing patterns over the duration of the scan, making it hard to determine a preferred reference position a priori. Therefore, we decided to develop a robust algorithm for the patient population that does not require a specific reference position.

**Davide:** The algorithm proposed in this paper considers the whole matrix of SI projections along time and iteratively shifts them along the SI direction to maximize an objective cost function that quantifies the global “degree of alignment” or, more specifically, a global cross-correlation measure. The iterative process is therefore intrinsically guided by the most frequent respiratory phase with no a-priori input needed, which is why it might be more robust in a patient population.

**MRMH:** Can you comment on the reasons for choosing the most frequent respiratory position as reference, and for sticking to a 1D motion model?

**Giulia:** If the motion were purely a 1D translation, the choice of a reference position would not matter. However, in practice, the respiratory motion of the heart has more complicated motion patterns, like rotation and affine transformations. So the shape of the blood pool you see in the 1D projection could vary among the different respiratory positions. If the most frequent respiratory position is chosen as a reference, you maximize the similarity between the reference and the majority of projections. If you choose a less frequent position, the confidence of the cross-correlation algorithm would decrease since the similarity between the reference and other profiles is less pronounced.

**Davide:** The self-navigation technique based on 1D projection has been fully integrated into our routine acquisition, with motion correction and reconstruction happening in real time at the scanner, already three years ago. We saw that in more than one thousand patients that the 1D SI projection was able to capture and correct for the biggest displacement. Along with the intrinsic motion-robustness of the radial acquisition, we are



able to achieve diagnostic quality in most cases. Moreover, the iterative algorithm described in this paper can be extended to more complex 2D or 3D motion models by redefining the cost function.

**MRMH:** What do you want to do next?

**Davide:** We're incorporating the XD-GRASP algorithm into our work. This is a collaborative effort with NYU and it represents a paradigm shift in coronary MRI. Thanks to our golden-angle based 3D radial trajectory, instead of correcting for the respiratory motion, images at different respiratory phases can be reconstructed with a sparse sampling scheme and reconstructed with a compressed sensing algorithm where the regularization happens along the respiratory dimension.

**Giulia:** Another direction we are taking is towards imaging of coronary endothelial dysfunction and “positive remodeling” of the coronary vessel wall. Instead of just looking at stenosis, we can detect coronary artery disease at a much earlier stage by assessing the presence of endothelial dysfunction and outward growth of the vessel wall. For those applications, we're also using a radial sampling scheme and a k-t sparse SENSE algorithm to perform acquisitions at higher spatiotemporal resolution. ■

**Matthias Stuber, Giulia Ginami, and Davide Piccini** jumping for joy after a successful experiment.

“  
We decided to develop a robust algorithm that does not require a specific reference position.”

—Giulia Ginami

# Editing genes for live cell-tracking using MRI

INTERVIEW BY Erika Raven AND Nikola Stikov

## EDITOR'S PICK FOR APRIL

For the month of April, we interviewed Dr. Stephen Patrick and Prof. Kevin Brindle on their paper, "Development of Timd2 as a reporter gene for MRI". Using genetic manipulation of cells, they highlight both benefits and technical limitations for this exciting frontier in live cell-tracking using MRI.

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With Timd2,  
which is a  
cell-surface  
receptor, we  
could produce  
either positive  
or negative  
contrast  
depending on  
what substrate  
it imports inside  
the cell.

—Stephen Patrick

**MRMH:** A bit of background – what has led you to combine both MR and biochemistry in your work?

**Stephen:** I came to work in MR when I joined Kevin's lab as a PhD. student. My undergraduate degree was in cell biology, so I was interested in the cell side of things, especially stem cells. It was great to be able to combine imaging with cell studies during my PhD. specifically developing new methods to track cells using gene reporters. Biochemistry is very relevant to MR because there are a lot of different biochemical phenomena that you can measure with different types of MR, which makes it interesting for me.

**Kevin:** I actually got into the field by accident. I wanted to work in protein NMR and the guy I went to work for, Iain Campbell – and this is back in 1977, had decided at that point in time that protein NMR was done. So, we started doing proton NMR on cells. My first paper was on the effect of susceptibility effects in deoxygenated red cell suspensions, which came to be highly cited because of the BOLD effect.

I got sort of hooked by this, but because I trained as a biochemist, I've always been very focused on biochemical applications of the technology and how it can be translated to the clinic.

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

**Stephen:** The aim of the project originally was to image gene expression using MRI. We did this by making the cell express a receptor on its surface that can bind to tiny magnetic particles. So the idea is you can control the expression of the receptor genetically, and then you can image the effect of the expression of the receptor by the ability of the cell to take up iron oxide particles. These iron oxide particles are conveniently stored inside a protein casing called ferritin that's found naturally inside the cell.



Stephen Patrick

**Kevin:** This reporter gene [Timd2] is only one of several that we've published. The advantage of using a gene reporter is the cell's got to be viable in order to show reporter expression and by using a tissue specific promoter you can also not only track where the cell is, but if that cell differentiates. The downside is sensitivity. In cells with super-paramagnetic iron oxide nanoparticles [SPIO], for example, you can see single cells as you get an amplification effect around the cell, but there are different challenges with this technique. Nevertheless, we feel that reporters are a better way to do this.

**MRMH:** What was the motivation for selecting Timd2?

**Stephen:** With Timd2, which is a cell-surface receptor, we could produce either positive or negative contrast depending on what substrate it imports inside the cell. The substrate in this case is ferritin, which is a hollow protein, and we filled it with either iron or manganese to generate T<sub>2</sub> or T<sub>1</sub> contrast changes, respectively.

**Kevin:** An important point to make of course, if you have endogenous expression of the receptor, then clear-

Patrick PS, Rodrigues TB, Kettunen MI, Lyons SK, Neves AA, Brindle KM. Development of Timd2 as a reporter gene for MRI. *Magn Reson Med* 2016;75:1697-1707. DOI: 10.1002/mrm.25750

<http://onlinelibrary.wiley.com/doi/10.1002/mrm.25750/epdf>





ly you would label those cells as well, so you really want to use a receptor that is not widely expressed.

**MRMH: What are the in vitro versus in vivo limitations for these experiments?**

**Stephen:** The main in vivo limitation is probably being able to deliver the ferritin substrate to the cells. Whereas this wasn't a problem in vitro, we could simply add it directly to the cell culture dish, in vivo it's cleared by the liver and kidneys, and it only stays in the blood for a certain amount of time. You've also got the problem of ferritin getting out of the vasculature and into the tissue. So it's probably a problem with ferritin delivery, which is the main in vivo limitation.

**Kevin:** It gives great contrast in vitro as you can see. Ferritin is a macromolecule so delivering the contrast in vivo is much more of a problem. Which is why we've started to also focus on smaller contrast media, like the gadolinium-based chelates. These are relatively small and if you want to introduce an exogenous agent, you want it to be small so you get good tissue penetration and also fast clearance as well. Otherwise you don't get contrast.

**MRMH: What are the potential applications for MR reporter genes?**

**Stephen:** One of the potential applications would be tracking therapeutic cells that were going to be used for some kind of cell therapy. Possibly for neurodegenerative or degenerative conditions, if you transplant something like stem cells you want to know several things – if they've gone to the location of interest, if they stay there or migrate, or even if they differentiate. To be able to tell these things noninvasively you're probably going to need some kind of imaging technique and it probably

would be best suited to a reporter gene approach.

**Kevin:** The great thing about gene reporters is you know the cell is viable, and you can in principle get very specific information if you use a tissue specific reporter as well. With Timd2 for preclinical it's fine, I think it would be a real challenge to take this particular reporter into the clinic, but we are working on other reporters that would have more potential in that respect. ■



**The University of Cambridge.**



*The great thing about gene reporters is you know the cell is viable, and you can in principle get very specific information if you use a tissue specific reporter as well.*

–Kevin Brindle



**Kevin Brindle**

## CONTRIBUTORS

### Nikola Stikov

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



### Erika Raven

*Magnetic Resonance in Medicine  
Highlights Editor*

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



### Mathieu Boudreau

TWITTER: @\_mattboud

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



### Samantha By

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



### John Celio

*ISMRM IT & Web Coordinator*

TWITTER: @ISMRM

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



### Benjamin De Leener

TWITTER: @BenDeLeener

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





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## Jessica McKay

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



## Hong Shang

Hong is currently a PhD student at the joint Bioengineering program at UC Berkeley and UCSF. His research is focused on developing pulse sequence and hardware for Hyperpolarized Carbon-13 metabolic imaging. He also enjoys scientific outreach, organizing events and playing sports.



## Karolina Urban

Twitter: @UrbanKarolina

Karolina is currently a PhD student at the University of Toronto in rehabilitation science and collaborative program in neuroscience. Her research is focused on using various neuroimaging techniques as MRI and fNIRS to better understand functional and structural changes following paediatric mild traumatic brain injury. Karolina in her extra time enjoys writing blogs, scientific outreach and continually learning something new!



## Luke Xie

Twitter: @lukenxie

Luke is a researcher at the University of Utah. He earned his PhD at Duke University where he also completed postdoctoral training. His work is focused on developing MRI tools for the renal system.



## Xin Miao

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



## Ryan Topfer

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



## Manh-Tung Vuong

Twitter: @vuongmanhtung

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



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