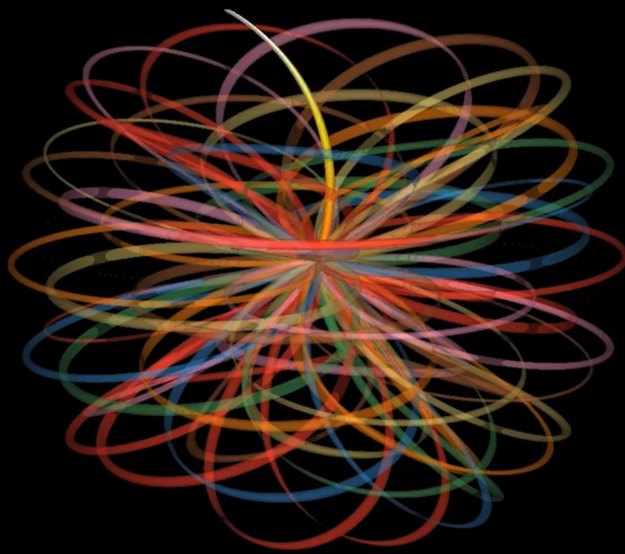

MRI

Novel Magnetic Resonance Imaging (MRI) Sequence Unlocks New Doors in Preclinical Imaging

Innovation with Integrity

The analytical capabilities of magnetic resonance imaging (MRI) can be used in both clinical and preclinical imaging applications to understand structural and functional information with high spatial and temporal resolution.

Professor Uzay Emir, Dr. Stephen Sawiak, and the teams from Purdue University, the University of North Carolina at Chapel Hill (Biomedical Research Imaging Center (BRIC)), and the University of Cambridge collaborated on research that enhances the MRI capabilities using a three-dimensional (3D) dual-echo ultrashort echo time (UTE) sequence with a novel rosette petal trajectory (PETALUTE) for fast, flexible contrast in preclinical imaging.

The PETALUTE story

Prof. Emir's experience of creating his own clinical MRI sequences led him to use a 3D dual-echo rosette k-space trajectory, specifically designed for UTE MRI applications and modify it for his work. This experience formed the basis of PETALUTE. Its advantages are improved signal-to-noise ratio, higher resolution, and significantly reduced imaging times.

The rosette sequence starts in the center of k-space and comes back to the center, generating two echoes, and, when repeated, produces multiple echoes. Prof. Emir explains: "The rosette trajectories are well known for the multiple crossings of the k-space origin which suggests the potential for multiple-echo acquisition. We modified the standard rosette trajectory to spend more time at the k-space center, which has a higher signal-to-noise ratio, and to spend more time at the outer k-space, allowing us to simultaneously achieve higher resolution." This way, a hybrid sequence was developed that utilizes the advantages of other trajectories, such as spiral and radial.

The next step in developing PETALUTE was to explore under-sampling with compressed sensing to go faster. The expectation was that this approach would enable researchers to perform previously unachievable imaging. Dr. Sawiak gives an example: "In non-proton spectroscopic imaging, you must produce new images fast, otherwise it is not possible to obtain the spectral width needed to identify the relevant metabolites. At high field MRI, this becomes more important as you need to go even faster to produce these images."

The first applications of PETALUTE

Dr. Sawiak and Prof. Emir met whilst working on a large Wellcome Trust collaborative grant-funded project (led by Prof. Zoe Kourtzi) at the University of Cambridge looking to improve the measurement of GABA in the brain. This project was where the first application of PETALUTE was explored.

First discovered in the 1950s, GABA is the major inhibitory neurotransmitter that has been shown to be involved in anxiety, epilepsy, memory, neurodegenerative disorders, schizophrenia, sleep, stress, and cardiovascular and neuroendocrine function, for example. In addition, many agents act through GABA mechanisms, including barbiturates, benzodiazepines, ethanol, flavonoids, general anesthetics, and neuroactive steroids.

GABA is challenging to measure due to its low abundance and spectral overlap – its signal is very low and overlaps with other molecules such as glutamate and glutamine. Current methods of detecting GABA involve measuring a single voxel with a large enough area to provide enough signal-to-noise. The acquisition typically takes 10 to 15 minutes to get enough signal from one individual voxel, representing only one part of the brain. With PETALUTE, an image can be acquired with similar information but spatially resolved over a section of the brain where the signal appears in sub-voxels, within the same timeframe (Figure 1). Dr. Sawiak adds: "It allows us to see changes across that section of the brain rather than having to choose one small part of the brain. This is an immediate advantage."

About Professor Uzay Emir

Professor Uzay Emir recently joined the University of North Carolina (UNC) Department of Radiology with a joint appointment in the Department of Biomedical Engineering as an associate professor from Purdue University. He is the Director of MRI physics at the BRIC at the UNC. By training, Prof. Emir is an engineer, and his research focuses on trying to understand the brain using different imaging modalities. During his undergraduate degree, he started to look at biopotential amplifiers with an electroencephalogram (EEG), going as far as developing his own device to see how brain oxygenation is changing. This background continues to drive him to understand brain function and dysfunction in more detail.

He found that current techniques lacked detail and developed his own MRI sequence to explore how oxygenation changes within the brain. Prof. Emir comments: "During my undergraduate studies, I exposed myself to biomedical signals, such as electrocardiographic, and how to non-invasively measure those signals. In my PhD at Bogazici University, Turkey, one method I explored was near-infrared spectroscopy, but it had limitations. I then discovered MRI and functional MRI (fMRI) and started to explore different possibilities of fMRI such as arterial spin labeling. The results were good, but it wasn't giving the full picture."

Prof. Emir then moved to the University of Minnesota to complete his post-doctorate using ultra-high field magnetic resonance spectroscopy, which, together with fMRI, provided more specific information about brain functions, such as neurotransmitters and metabolites that appear in disease conditions. He then led the spectroscopy program as a principal investigator at the Oxford Centre for Functional MRI of the Brain (FMRIB), University of Oxford. He moved to Purdue University before being appointed to his current position at UNC.

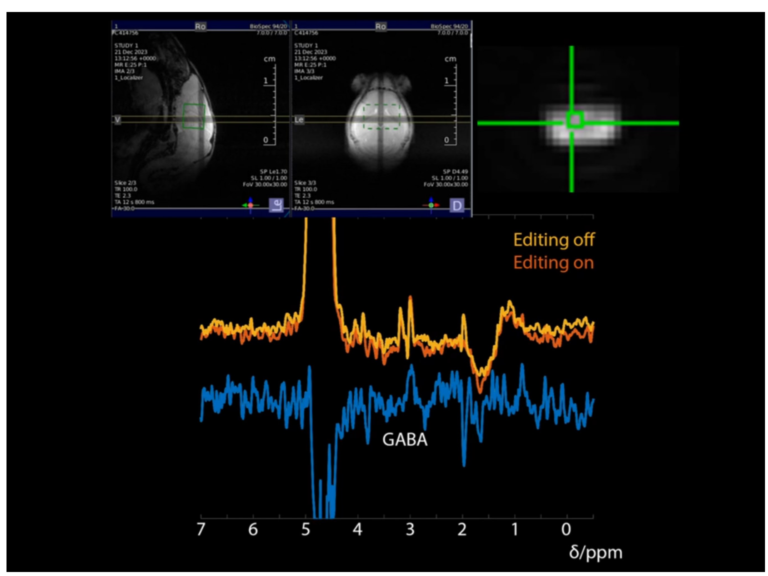

Figure 1: Neurotransmitter imaging with semi-LASER MRSI and MEGA editing on a Bruker BioSpec 94/20 with a 4-channel mouse brain coil. GABA-edited spectra in 8.5 minutes. Image source: University of Cambridge.

A further application of PETALUTE currently being explored in brain imaging is the ability to see myelin sheath signals[i] – signals that usually decay too rapidly to measure. The myelin sheath is a protective membrane that envelops certain nerve cells and is an important research field due to its implications in several disorders and changes in healthy brain development. PETALUTE offers two important advantages, the first being that it is fast enough for the signal to be seen in the first place and the second is it can be more specific about what is happening within the brain (Figure 2).

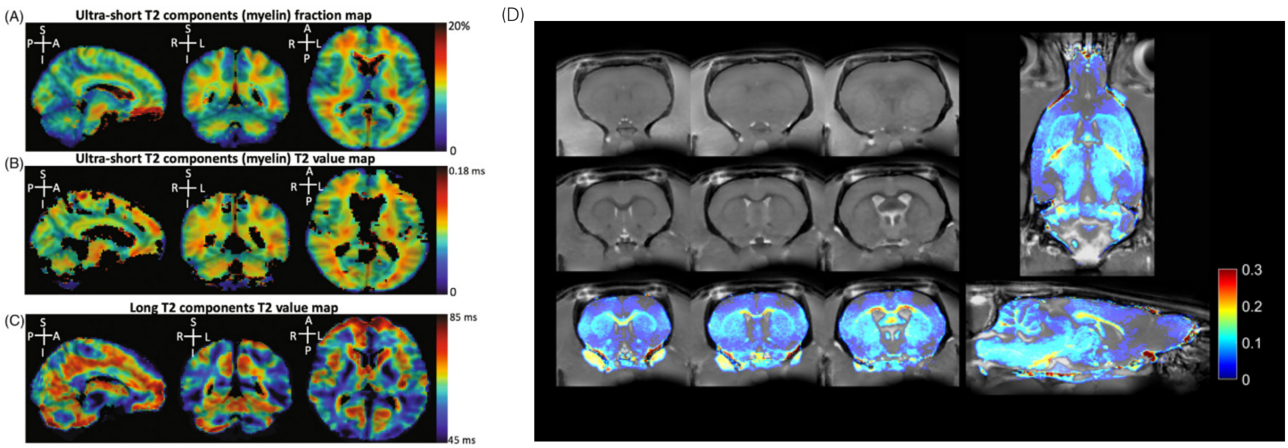

Figure 2: The results of dual-exponential fitting: (Left) the mean ultra-short T2 components (uT2) fraction map (A), the mean uT2 value map (B), the long T2 value map (C). A, anterior; L, left; P, posterior; R, right. The image was taken from a reference i in accordance with Creative Commons Attribution 4.0 International License. (Right) (D) A corresponding acquisition was conducted on a BioSpec 94/20 with and without magnetization transfer preparation. PETALUTE acquisition with a resolution of 150 μm with an acceleration factor of 2.

As for other applications, Dr. Sawiak and Prof. Emir see the potential of PETALUTE in many other fields outside of brain research. Fast decaying imaging signals are quite often a challenge, in applications such as bound membranes or near solids, for example. Prof. Emir and his colleagues conducted research into bone imaging[ii] (Figure 3). He explains the benefits of PETALUTE: "Usually when imaging bones using MRI, you just see the marrow as, with anything solid, the signal has decayed too fast to capture it. With PETALUTE, images are captured in tens or hundreds of microseconds, enabling us to see the fast-decaying components or components we haven't seen before."

Prof. Emir, Dr. Sawiak and other collaborators have also published work applying PETALUTE to phosphorus magnetic resonance spectroscopy imaging (MRSI), where a wide spectral bandwidth is needed.[iii] The research used a novel rosette k-space pattern for UTE ^{31}P 3D MRSI to mitigate long acquisition times and improve signal-to-noise ratio and resolution compared to conventional spectroscopic imaging. The team applied the sequence in both preclinical and clinical imaging, successfully creating phosphorus mapping of the brain.

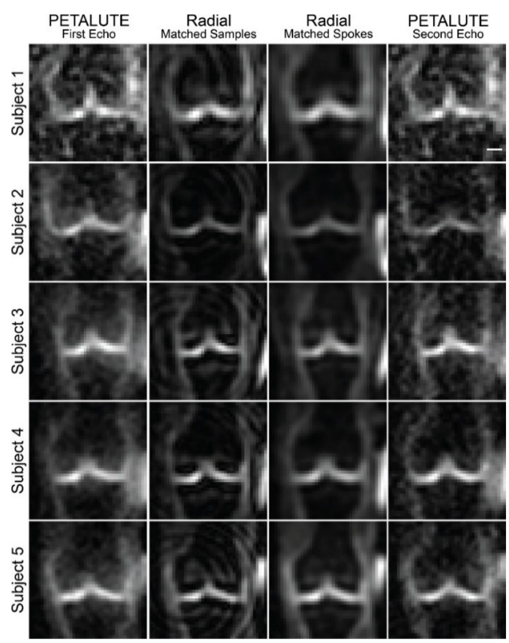

Figure 3: ^{23}Na MRI of the knee was implemented using PETALUTE and DA-Radial UTE. Cuboid cropped volumes were centered on the joint midline and included the distal femur and proximal tibia. Scale bar = 1.5 cm. Image source: reference ii in accordance with Creative Commons Attribution 4.0 International License.

Translating from clinical to preclinical

After working together in the collaborative project from the University of Cambridge, Dr. Sawiak and Prof. Emir decided to continue their work together with Dr. Sawiak beginning to work on an implementation of the sequence in a preclinical environment.

MRI has traditionally been used either solely as a research tool or in the clinic to diagnose patients, with translation between the two not being fully utilized. Dr. Sawiak explains: "In preclinical imaging, you can use techniques and animal models to see exactly what is happening. Measuring the same thing in preclinical and clinical helps validate the clinical technique by being able to go down to the molecular level."

The unique benefit of the PETALUTE sequence is that it was first translated from the clinic into preclinical, and then, following further work, it was translated back into the clinic. Prof. Emir comments: "My work is in the clinical domain. That's where I first started to utilize the rosette sequence and modify it into PETALUTE. Then Dr. Sawiak implemented the sequence on a Bruker preclinical instrument to test and improve it even further, the results of which we duplicated back onto my clinical instrument. We repeated this cycle until we had something robust that really works."

Encouraging collaboration in research

With the benefits of PETALUTE established and Prof. Emir and Dr. Sawiak already exploring other applications, the potential for using the sequence is clear. The next steps for PETALUTE are to share the code far and wide to allow others to find out how the signal performs in their applications. Dr. Sawiak comments: "We've already had a lot of interest from colleagues and other researchers who want to use the code and install it on their imaging instruments to test its capabilities. We're in the process of sharing it with others who are working in several different applications where it could really make a difference."

Prof. Emir adds: "Many of these applications have not yet been fully explored, so the potential to go to higher resolutions and perform the analysis even faster may bring additional benefits. We hope PETALUTE unlocks a lot of doors in both preclinical and clinical imaging."

The development of PETALUTE was a team effort. The sequence can now be shared with the wider research community so scientists can learn from each other's efforts to progress and develop the sequence even further.

The team is also collaborating with other community members on papers that are in preparation, which include single voxel spectroscopic imaging, balanced steady-state free precession (b-SSFP) techniques, and iron oxide measurements in cancer treatment models.

Unlocking future research doors

After winning the Bruker MRI Award in 2024, Prof. Emir and Dr. Sawiak credited it for helping to develop interest in the sequence from the community. Dr. Sawiak says: "Some of our collaborators are people that we knew from our networks, but we were pleased to find that we were contacted by several people after the announcement of the award who wanted to use the code. As the news spreads, we hope more people will get in touch to expand the applications and provide better outcomes."

As for the next steps, Prof. Emir and Dr. Sawiak plan to highlight PETALUTE's applications by presenting their research at industry conferences. Prof. Emir concludes: "Although we've outlined how PETALUTE is useful right now, we believe we are yet to discover some of the key applications of this technique and what doors it will allow us to open. By spreading the word to the imaging community, we hope it will encourage others to apply PETALUTE in their research fields to reveal what has previously been unseen."

About Dr. Stephen Sawiak

Dr. Stephen Sawiak is a senior research associate and fellow of Fitzwilliam College at the University of Cambridge. By education, Dr. Sawiak is a physicist with a PhD in imaging focusing on neuroscience: "During my PhD, I was surprised to see that imaging was not being used to its full potential. There is sometimes a disconnect between the biomedical researchers who have questions and the physicists who have the tools to provide the answers."

To overcome this, his current research focuses on trying to directly address biomedical questions with physics resources and bridging the gap between the two. Specifically, Dr. Sawiak is measuring gamma-aminobutyric acid (GABA), a domain inhibitory neurotransmitter in the brain that is notoriously difficult to see with traditional spectroscopy. His other research interests involve measuring brain changes across adolescence in animal models with applications in neuropsychiatric diseases.

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[ii] Villarreal, C.X., Shen, X., Alhulail, A.A. *et al.* An accelerated PETALUTE MRI sequence for in vivo quantification of sodium content in human articular cartilage at 3T. *Skeletal Radiol* (2024). https://doi.org/10.1007/s00256-024-04774-5.

[iii] Alcicek, S., Craig-Craven, A., Shen, X. *et al.* Multi-site Ultrashort Echo Time 3D Phosphorous MRSI repeatability using novel Rosette Trajectory (PETALUTE). *bioRxiv* (2024). https://doi.org/10.1101/2024.02.07.579294.

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