Deciphering the diffusion signal in upper abdominal organs

INTERVIEW BY **JESSICA MCKAY**

EDITOR'S PICK FOR MAY

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

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

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

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

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

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

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

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

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

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

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

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http://onlinelibrary.wiley.com/doi/10.1002/mrm.25765/full

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

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

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

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

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

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

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

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

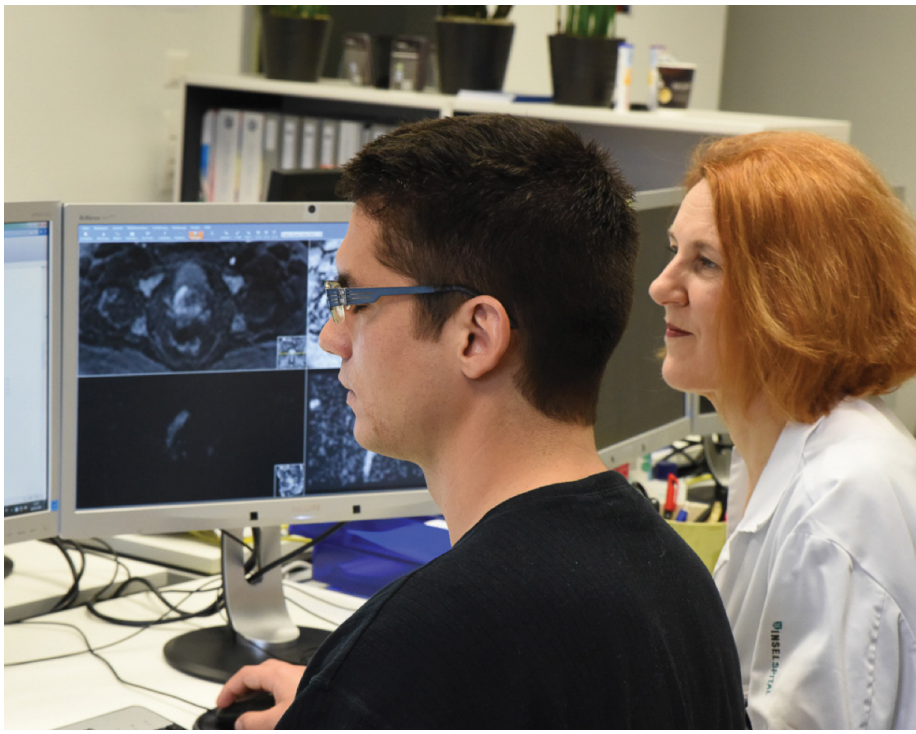
Harriet: I was a little bit more troubled than surprised because there is so much literature. Everybody writes about it and everybody reads about it, but how can we compare? The problem is not only standardization of the technique and image parameters but also how you perform image analysis thereafter.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

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

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

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

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



Sebastiano Barbieri and Harriet Thoeny testing their algorithms.

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

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

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

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

MRMH: The kidney is considered an upper abdominal organ?

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

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

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

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

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