Olea Imagein

The Bayesian saga

Olea MEDICAL

#1 - March 2016 - ECR Edition

CONTENTS

NEWS

Olea Medical® launches Olea Innovators

Olea Medical® announces the launch of the first edition of Olea Innovators contest, international call for projects for applicants who wish to successfully develop an innovative technology in MRI.

EDITO


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Fayçal Djeridane, CEO
Olea Medical®

I am extremely proud to introduce Olea Imagein. This journal was born from our wish to bring into light years of innovation in medical imaging. As most of you know, Olea Medical® was created in 2008 with a clear mission: Improved diagnosis for life™. This is our *motto* and it has driven our actions for the last seven years. Today Olea Medical® is part of Toshiba Medical Systems Corporation and as such, we are extremely happy to extend our contribution to healthcare worldwide, with innovative, robust and efficient vendor-neutral solutions.

Olea Imagein is the mirror of our ambition to innovate at the highest level. It represents our mission and it also reflects the standpoints of our partners, collaborators and worldwide renowned advisors.

Our team has been widely acknowledged for their successful integration of Bayesian Mathematics in image post-processing for daily clinical practice. Although many have tried to apply Bayesian Mathematics to imaging in the past, none has succeeded to optimize such complex methods for clinical routine. It is now well known and largely accepted that Bayesian Mathematics are more accurate and resulting solutions are more robust. But, how about the clinical impact of accuracy and robustness? Is this all just for the sake of accuracy? Or do such complex methods have a real impact in clinical practice? Can they change the post-processing paradigm?

We do believe the Bayesian method is a major game changer in medical imaging and so do the experts who contributed to this issue.

So we dedicated this issue to the applicability of Bayesian methods in image post-processing with the hope that you will find here the answers to such questions.

Enjoy your reading!

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Olea Medical® is a subsidiary
of Toshiba Medical Systems Corporation

Printer: Création Communication
Impression (CCI) – 9 avenue Paul Heroult
13015 Marseille – France

Director: Anca Mitulescu

Editor-in-Chief: Sarah Quenet

Content Manager: Marie Dobbels

Graphics: Christophe Rebesco

Selling price: free of charge

Date of legal deposit: March 2016

Publication date: March 2nd, 2016

ISSN Number: application
under examination

Olea Medical® is a French *société anonyme* governed by an executive board and a supervisory board with a share capital of € 2,040,526.

Registered office:
93 avenue des Sorbiers - ZI Athélia IV
13600 La Ciotat, France

The Bayesian method:

a widely applicable algorithm in medical imaging

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Timothé BOUTELIER, PhD
Research & Innovation Director at Olea Medical®
Timothé Boutelier holds an engineering degree in Physics and a PhD in Astrophysics.

He has been working at Olea Medical® for the past six years and his first project was to develop the Bayesian perfusion algorithm. Timothé Boutelier always emphasizes the importance of the Bayesian method and encourages his collaborators to apply it whenever it's possible.

Olea Imagein: Could you simply explain what the Bayesian method is?

Timothé Boutelier: The Bayesian method is a probabilistic method based on Bayes theorem published in the 18th century. It allows to combine experimental data and *a priori* information about the parameters of a model and to infer probability distribution for these parameters.

Thanks to this probabilistic approach, the estimated parameters are more robust while considering the noise issue than any alternative approach. This is paramount in medical context where the physicians have to balance between the acquisition time and the precision of the estimation.

OI: How did the Bayesian method come into Olea Sphere®?

T.B: Historically, Olea Medical® has been working on acute stroke diagnosis using Perfusion Weighted Imaging (PWI). To extract perfusion parameters from dynamic sequences, Singular Value Decomposition (SVD) based methods were used in clinical practice. However, those methods suffer from known defects such as noise sensitivity, under-estimated blood flow and unreliable estimations like negative Mean Transit Time[1] (MTT).

This is the reason why we decided to implement the Bayesian framework to tackle those issues and improve the reproducibility and reliability of PWI.The method was then validated by Pr Sasaki and Pr Kudo, members of the Stroke Imaging Research (STIR) roadmap committee[2,3].

Bayes, Thomas
(1702-1761)

is an English clergy man and mathematician who first exposed his theory of probability in 1764 (posthum)

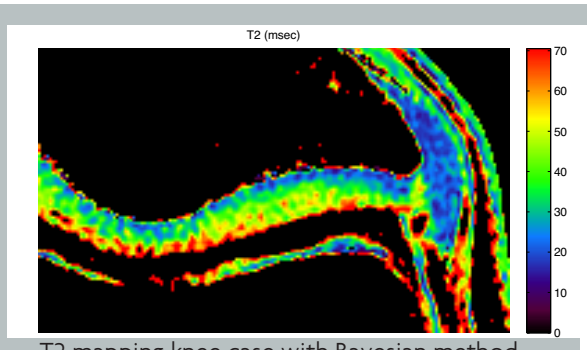
OI: How did this method extend to other applications?

T.B: Bayesian framework can be applied in any context where parameters estimation is required and noise level is a limitation. Hence, we implemented it for relaxometry applications, multi-b Diffusion Weighted Imaging (DWI) and segmentation.

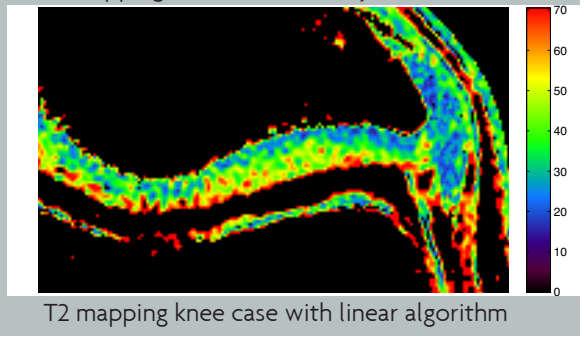
OI: Could you tell us more about the multi-b Bayesian application?

T.B: Multi-b Diffusion Weighted Imaging (DWI) is a very powerful technique to access microscopic tissue properties by probing water diffusion. To do so, advanced modelling of the diffusion signal is required to disentangle contributions coming from Intravoxel Incoherent Motion (IVIM) effect, pure diffusion, and non Gaussian effects (Kurtosis) in the signal.

However, it has been reported that common approaches (linear fitting, non linear optimization, etc.) are prone to artifacts, sensible to initialization, and are usually very slow.



T2 mapping knee case with Bayesian method

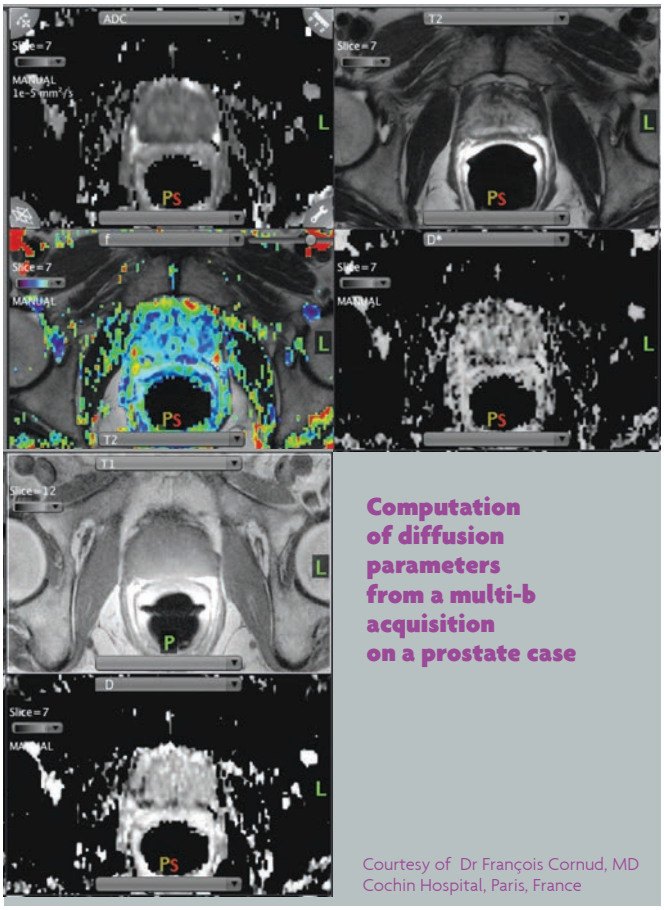


T2 mapping knee case with linear algorithm

Courtesy of Laveran Hospital, Marseille, France

Bayesian methods greatly help to improve the reliability of the estimation and the robustness to noise. We validated our approach internally using digital phantoms.

The high precision of our algorithms allows using the parameters' maps in advanced applications as well, such as computed assisted diagnosis (CAD) to detect breast lesions. Moreover, the time computation is not an issue anymore thanks to our algorithm optimization.



Computation of diffusion parameters from a multi-b acquisition on a prostate case

Courtesy of Dr François Cornud, MD
Cochin Hospital, Paris, France

OI: In the future, do you think this method could address other clinical challenges?

T.B: As mentioned earlier, the Bayesian method can be applied to many topics such as segmentation, machine learning, and in the short term, we decided to apply it to functional MRI, and computed MRI.

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Perfusion: to be or not to be?

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Adam J. Davis received his medical degree from Perelman School of Medicine at the University of Pennsylvania.

He specialized in Neuroradiology and his areas of expertise are cerebrovascular disorder, stroke, arteriovenous malformation and brain aneurysm.

Olea Imagein: Can you quickly explain to our readers perfusion imaging and the dramatic shifts over the past years?

Adam Davis, MD: Perfusion techniques, as you know, are decades old and there were papers published in the nineteen eighties about how to do perfusion imaging. People realized that you can measure the concentration of contrast, graph that out and then use mathematical techniques to tell you more information about that flow of contrast.

It's all dependent on the idea that contrast flow mimics the circulation. So, in the nineteen eighties and even nineties, people were looking at the concentration curves in the parenchymal and vascular voxels and were using the best available Mathematics and computer hardware and software that they had to look at these concentration-time curves. The most obvious and easiest way of understanding these concentration curves was simply to look at the slope of the curves and the area under the curves. That will give you information about the blood flow and the blood volume; they were simple and easy to measure but were unfortunately inaccurate.

> "If results are variable from patient to patient because of your technique, then it's not helping anyone."

When we say inaccurate, there are always different degrees of inaccuracy. Overall the idea of perfusion and what people were doing worked very grossly: you could see if there is a lot of blood flow or little blood flow. A more sophisticated analysis was beyond our field at that time.

And it's really the most sophisticated analysis, giving greatest certainty of perfusion, which is most important as it provides you with reproducibility. If results are variable from patient to patient because of your technique, then it's not helping anyone. That was pretty much the consequence of slope of the curve, area under the curve analysis throughout the nineteen nineties and the early new millennium.Then people started applying more sophisticated algorithms, to these same concentration curves; some of them were deconvolution based methods. That was really a huge change on how to look at perfusion. What the deconvolution algorithms did was to take the measurement of the blood flow within the vasculature into the organ, the concentration in the organ parenchyma itself and solve those two equations simultaneously to give you a third equation which transcended the type of analysis that we had been using previously. This was now information that was theoretical. It had a physiologic correlate but the actual curve itself wasn't something that occurred in nature.

In some ways, that is good because it removes a lot of the artifacts and errors from what you are doing. It simplifies things, and cuts to the chase. But in some ways, it's bad because now it's so esoteric that people have trouble understanding it. That's the way things started to evolve about ten to fifteen years ago.

My experience with perfusion imaging began in the late nineteen nineties, and I have been using it since. Like many people, I wasn't thinking about what was going on in the black box.

When people started looking at the numbers, they realized that they may not have been very accurate. There were problems first of all with the actual data, the signal to noise. If you have a high signal to noise, it gives you a robust, worthwhile result. The way you are measuring the vascular contrast concentration, the volume averaging of your data, how you administer the contrast, the injection rate, the type of contrast, they were all affecting the results. All of these things came together when they started looking at the data more rigorously. They realized that the perfusion results people were getting, were extremely variable, not reproducible: that created a crisis in the stroke imaging world.

People were saying perfusion imaging is not worthwhile and we should abandon it. That was just about the time when I started becoming even more involved in perfusion imaging. So, I walked in when everybody started walking out. I came to realize that certainly the problems lied within our technique, our mathematical method and we could probably do better. I felt like we were moving away from something that worked just because it wasn't working perfectly. Instead of improving it, people were abandoning it.

I continued to advocate perfusion imaging, even though I knew it was not completely accurate. It still provided you with a lot of information which I would argue in favour of when doctors discussed the merits of stroke imaging. Clinical stroke evaluation is discussed at meetings and in the literature, and it always seems to be perfect in those venues but real patients and real practice are of course different.

Sometimes, patients present to the hospital and we believe they have a stroke, but it turns out that they have had a seizure, which is very different. We think they have a hemispheric event but it is an internal capsule event. Sometimes, it is only a Transcient Ischemic Attack (TIA) but we are unsure of that at the earliest evaluation. I argued that perfusion imaging could provide us with important information in all of these circumstances.

> “It was really the next evolution of perfusion. Perfusion was simple, automated and user-friendly.”

So, even though it was not accurate, there was still merit to it but the critics were right, we couldn't really point out the infarct and penumbra. I felt that it was always a problem with our methods and it didn't seem right to me that we couldn't be more precise about this. At the same time, authors such as Campbell and Bivard were publishing data saying that the indices we were looking at were incorrect and if you want to look at the blood flow to the brain, it is really important to look at the blood flow to the brain. I know it sounds silly but, up until then, it had everything to do with the blood volume. It was true that blood volume was a marker for infarction, but it was a marker for ischemia that was extremely advanced, related to territory that was in the most extreme stages of infarction. But there are territories that are also likely to infarct with normal blood volume, but the blood flow is abnormal. What about these conditions?

It's a long explanation why people wanted to have blood volume instead of blood flow; more time than we have in this brief discussion. It has to do with the arteries, reacting to the decrease of blood flow by dilating and then ultimately no longer being able to compensate and then collapsing. But it has never been proven in animal models that this was the way infarction worked. That was the time when articles from clinical research centers were coming out saying that we were doing it wrong. That's about the same time when Olea Medical® arrived in the picture and in my practice.

O.I: How are our solutions embedded in your daily routine?

A.D: We started using Olea Sphere® in 2012. The institution I work at was very involved in the initial research regarding perfusion imaging for brain tumors and authored many of the articles on cerebral blood volume as a marker for tumor aggressiveness, particularly for primary gliomas.

The software we were using was built by a PhD researcher, Glynn Johnson. It provided the data for the earliest research into perfusion for tumors and worked at an academic investigative level but not on a workflow level for a busy practice. That's when we investigated which companies were providing advanced perfusion imaging analysis, and that's when Olea Medical® came into our world.

At first, we were interested solely in tumor perfusion evaluated by MRI, which was dynamic susceptibility contrast (DSC) technique. Olea Sphere® software provided a whole new experience for us, because instead of being a laborious workflow, it became an all-automated workflow. There were color maps, automated arterial concentration curves, easy-to-use regions of interest with comparative relative blood volume results and they could be easily pushed to and stored on PACS, and most importantly, it was robust. If you did the same patient twice, you received the same result twice. We started to use it to do more clinical research as well; it was really the next evolution of perfusion. Perfusion was simple, automated and user-friendly.

> “The big breakthrough was that the Bayesian could be done quickly.”

At that time, we thought to move on to stroke imaging. It was just so difficult to do it because it was so variable and the literature was so negative, that a lot of doctors didn't want to support it. After we started using the CT perfusion software for stroke, things changed. Part of it was just the automation, but part of it was the better way of

measuring Arterial Input Function (AIF) which was a huge difference. I think this is one thing that is lost in the history of perfusion: everyone was focusing on the better algorithm, a more time-insensitive deconvolution, Bayesian etc., which of course is extremely important, but the AIF algorithm that works faster and takes into account all the voxels in the brain, giving you a more local (closer to the parenchyma) value for AIF has a huge impact.

> “Sometimes it’s not the theory, sometimes it’s just the execution.”

O.I: What has the Bayesian method brought to your daily routine?

How does it affect your decision making?

A.D: The final chapter, for now, was really when the Bayesian method was introduced, because we noticed not necessarily a world of difference between the Bayesian and the usual time insensitive deconvolution, but a shade of difference that was very significant - it really gave us confidence. It was important because results could now be a little more individualized to the patient. We could be more confident and make decisions on a voxel per voxel basis if necessary and no longer confined to decisions on a large territorial basis. The big breakthrough, of course, was that the Bayesian could be done quickly. We had Bayesian Mathematics forever, it’s just nobody could wait twenty five minutes for it to be computed.

So, the fact that this algorithm optimized the Mathematics was a huge difference. Sometimes, it’s not the theory, sometimes it’s just the execution. So that brings us to the current moment. Even though the story is not over and there are still a lot of debates out there, it’s becoming obvious case by case, day by day, that perfusion imaging is really becoming an essential part of understanding stroke. This all became much more important in the last one year. Previously, we had treatments for stroke, such as IV TPA, which were somewhat effective although on a three months outcome basis, compared to thrombectomy which was demonstrated in all the recent trials, to definitely outperform conventional therapy in terms of patient outcome.

So, the question then becomes more refined in how we manage our patients and that’s the current debate: do we treat everyone who is symptomatic from vascular occlusion with thrombectomy or do we investigate every patient for a more individualized therapy? Can we go beyond the commonly accepted time guidelines?

I deeply believe you should treat each and every patient individually and you should really understand your patient’s status – what is infarcted and what is recoverable, what is their risk from treatment and what is their potential benefit, and then, apply what you know from both your experience and from the trials to come to a decision; not just blindly apply a population trial result to your individual patient, without thinking about it. That’s how I look at the situation now. Trials can be tricky. After MR RESCUE, no one wanted to do thrombectomy but it just didn’t make sense. I argued at the 2014 ECR that we should keep treating patients with thrombectomy whom we thought would benefit. Now, the pendulum has swung all the way in the opposite direction and some people believe that absolutely every one should be treated. The truth, of course, lies somewhere in between. We need to be thoughtful and use imaging to guide our decisions.

Currently, we use Bayesian methods for stroke evaluation, to determine both infarct and penumbra size and location. We currently use a combination of parameters, particularly cerebral blood flow and arterial tissue delay, the Bayesian equivalent of Tmax. I am still not satisfied that we have gone as far as we can with our perfusion methods and continue to work on our techniques and analysis.

We currently use the Singular Value Decomposition (SVD) method for brain tumor perfusion analysis. The main parameter we look at, is the Cerebral Blood Volume (CBV) and it has always been the more robust parameter. Recently, there have been other thoughts about tumor hemodynamic parameters and that is what we are actively investigating: is it really the CBV we should be looking at or does the CBF provide other important information? Should we be looking at the permeability characteristics? Others have already investigated some of these areas. MRI investigators were using Arterial Spin Labelling (ASL) for brain tumors and demonstrated that it correlates with brain tumor histology and aggressiveness. But ASL is a blood flow measure and not a blood volume measure. This is the new evolution. We will see where it takes us.

Bayesian approach for perfusion imaging: what are we talking about?

DSC (Dynamic Susceptibility Contrast) sequence is performed after the injection of intravenous contrast agent to non-invasively assess tissue and vascular perfusion characteristics. This technique is considered as a highly accurate perfusion measurement, providing important diagnostic information on pathological conditions.

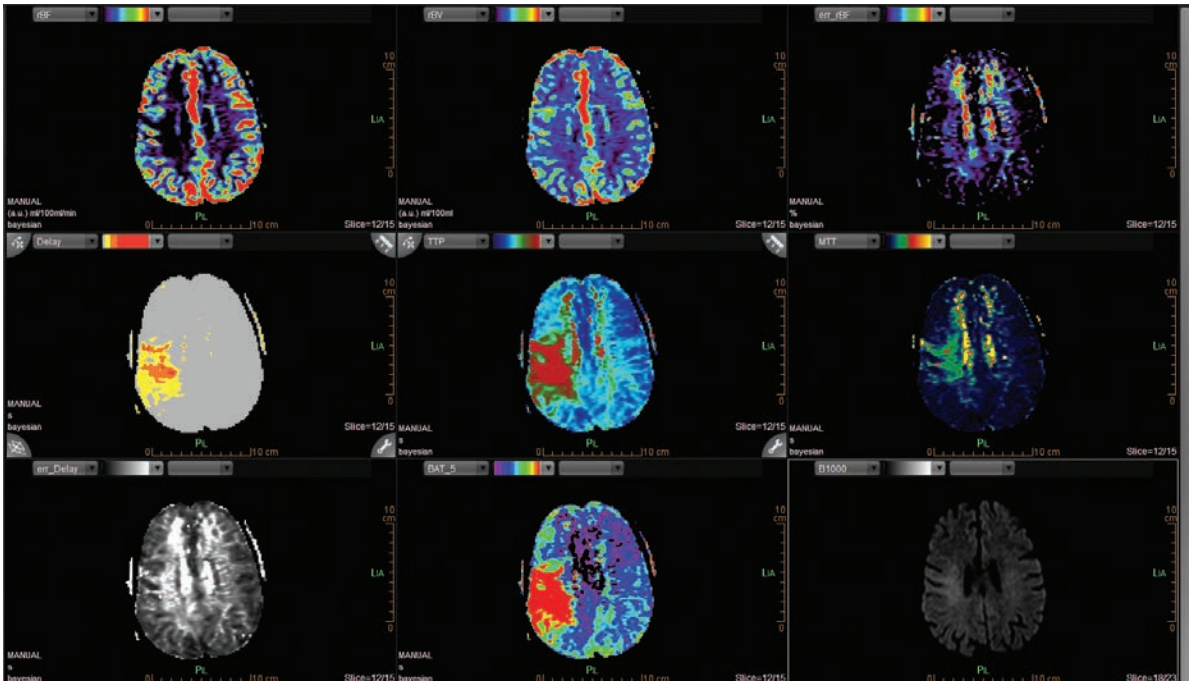
Then, the acquired data are post-processed to obtain perfusion maps with different parameters, such as BV (Blood Volume), BF (Blood Flow), MTT (Mean Transit Time), TTP (Time To Peak), Delay, BAT5 (Bolus Arrival Time 5%).

The Bayesian method used to compute those parameters is a rigorous probabilistic estimation of hemodynamic parameters fully adaptive and delay-insensitive.

A key advantage over SVD approach: accurate estimation of the hemodynamic parameters

The Bayesian post-processing method is a rigorous and recently described probabilistic estimation of hemodynamic parameters given the standard perfusion model. This method has already been validated using simulations on sophisticated MR digital phantoms and, from a quantitative point of view, outperforms SVD-based deconvolution methods.

This approach leads to a better estimation of hemodynamic parameters such as CBF, CBV or MTT evaluation.



Large panel of computed maps with the Bayesian approach

Courtesy of Prof. François Nicoli, MD, PhD

Computed maps with the Bayesian method:

- **rBF:** Relative Blood Flow
- **Delay:** Delay map
- **MTT:** Mean Transit Time
- **TTP:** Time To Peak
- **rBV:** Relative Blood Volume
- **BAT5:** Bolus Arrival Time 5%
- **Sigma:** noise level in the concentration time curve
- **err_rBF:** relative error when estimating the blood flow
- **err_Delay:** absolute error of delay

True arterial-tissue delay assessment

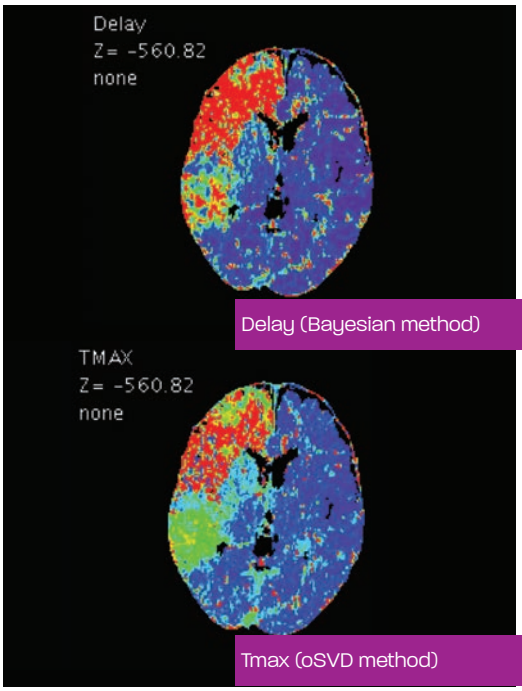
The use of a Bayesian analysis also permits calculation of true delay map.

Just like Tmax for SVD-based methods, the arterial-tissue delay is defined as the time discrepancy between the arrival of the bolus in the tissue concentration-time function and the AIF (Arterial Input Function).

However, the SVD Tmax always overestimates the true delay. is strongly dependent on true MTT even if it should not.

Conversely, the Delay map is a pure arterial-tissue delay estimate, regardless of the MTT.

As a consequence, the Bayesian algorithm provides very accurate and pure estimates of the true delay in any case.



Delay (Bayesian method)

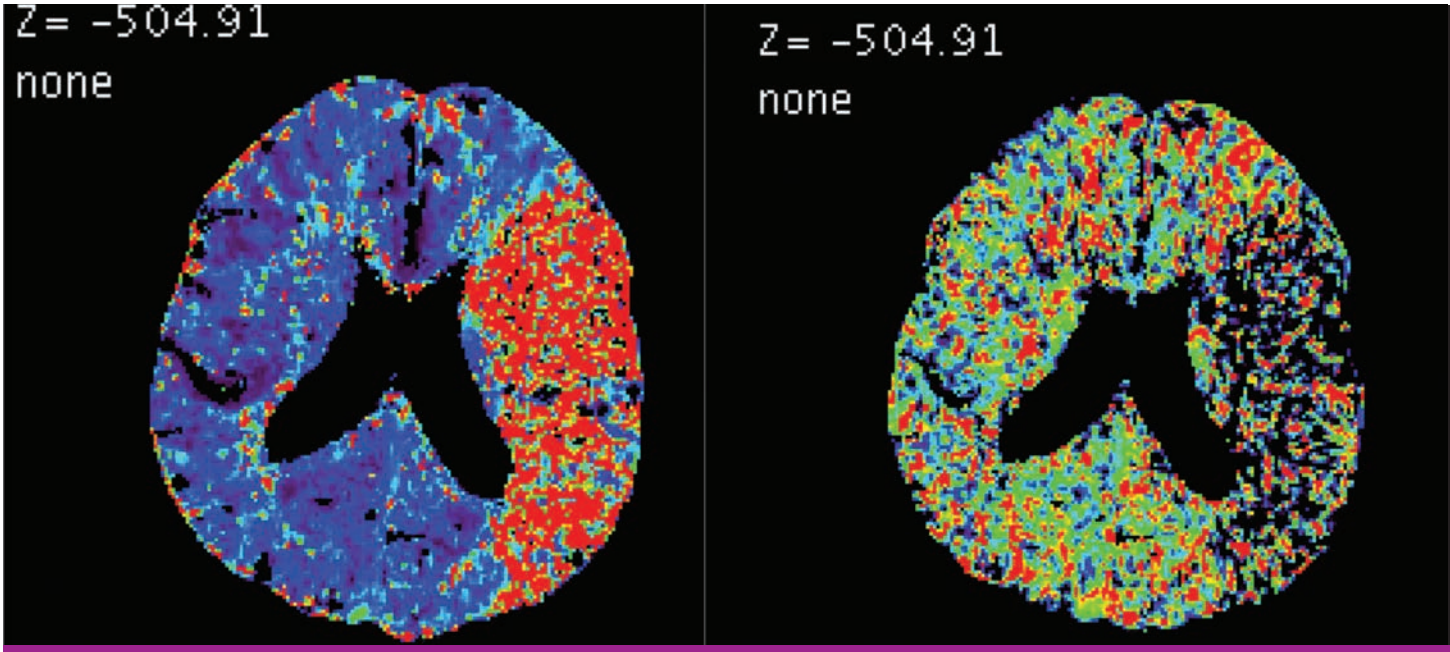
Tmax (oSVD method)

Courtesy of Prof. François Nicoli, MD, PhD

A more robust approach compared with SVD

The Bayesian method is more accurate and more robust against noise and truncation than oSVD, particularly in low SNR (Signal to Noise Ratio) acquisition.

For instance, CTP (CT Perfusion) SNR are too low to reliably estimate MTT with SVD in acute stroke hypoperfused areas.



Acute stroke patient (CTP) with left MCA (Middle Cerebral Artery) occlusion. An increased MTT is expected on the lesion side.
A positive correlation for the Bayesien MTT (on the left) is noticed contrary to the oSVD MTT (on the right) with a negative correlation (negative values).

Courtesy of Prof. François Nicoli, MD, PhD

The Bayesian saga for a good Sunday read

Perfusion imaging, performed after the administration of intravenous contrast agent to access tissular and vascular perfusion characteristics is a widely used technique for quantification of cerebral perfusion; it is applied, for example, for initial evaluation of acute ischemic stroke patients, including prediction of tissue at risk and patient outcome[1,2]; or for assessing other diseases such as hemodynamic ische-mia[3] , subarachnoid hemorrhage[4], and brain tumors [5,6]. Accurate perfusion measurements, accessed through perfusion maps obtained by post-processing CT and MR raw data, provide important diagnostic information on pathological conditions. Although perfusion imaging appears as a promising tool, since one of its advantages is its quantitative nature, it was called into question especially for stroke evaluation.

According to Wintermark et al.[7], perfusion imaging has been incorporated into acute stroke imaging algorithms at some institutions, however, its clinical utility has not been proven and there is no consensus on the optimal perfusion parameter that is most predictive of tissue viability and outcome. In addition, it has been reported that the results of CT perfusion imaging analysis vary substantially due to differences in scan parameters, such as tube voltage[8,9], tube current[9], and temporal resolution[10].

Variations have also been reported in post-processing steps, such as the definition of Arterial Input Function (AIF) and venous output function[11], determination of bolus timing[12], and deconvolution algorithms[13,14].

All this has led to the situation highlighted by Kudo et al.[15], who have demonstrated that for the same patient, when using five different post-processing software, five different clinical interpretations are possible, potentially leading to five different diagnoses. The authors have shown that the abnormal area and relative values of CT perfusion imaging were significantly different among commercially available software. These variations among software should be minimized and therefore, the post-processing should be standardized to improve the reliability of CT perfusion imaging analyses and reading.

In clinical practice, the utility of perfusion imaging is based on two assumptions: the first is that surrogate markers like contrast agent imitate circulation and that is a fairly safe assumption to make; the second assumption is that imaging data is converted into meaningful physiologic correlates by mathematical models and algorithms processed on dedicated software is not a safe assumption to make. Indeed, four problems led to this current situation: inappropriate models used to interpret perfusion data; inconsistent MR/CT acquisition protocols between scanners, doctors and institutions; inaccurate post-processing technique used; and more particularly, there is confusion and misinterpretation regarding relevant brain perfusion indices for determining infarction and penumbra in the academic and clinical practice[16].

In this context, where the clinical application of perfusion imaging was suffering from inaccuracies and inconsistencies in modeling, software and acquisition technique, new robust and reliable models and algorithms needed to be proposed in order to standardize, at least, the post-processing techniques. Ideally, these methods would be independent of clinical protocols and acquisition techniques. Improvement in hemodynamical parameters estimation is paramount for improving diagnosis to the benefit of patients. Therefore, the Bayesian-based deconvolution method has been developed. The aim of this paper is to give an overview of the standard post-processing perfusion techniques to better understand the need for improvement; to finally focus on the new Bayesian-based deconvolution method and to explain its advantages and usefulness in clinical practice.

Perfusion Basics

Basically, perfusion imaging aims to recover parameters related to the passage of blood in the functional part of a tissue (the parenchyma). The amount of perfusion is related to the functionality of the parenchyma and its grade of activity. The perfusion can be characterized in vivo using one of Perfusion Weighted Imaging (PWI) techniques such as Dynamic Susceptibility Contrast MRI (DSC-MRI) or by CT perfusion (CTP) where a bolus of contrast agent (CA) is injected in the subject's vascular system. In each voxel, a signal related to the concentration is acquired on a time sampling grid to derive the correspondent tissue concentration time curve C(t).

The differential equation of the conservation of the mass of the measured C(t) in a voxel can be expressed as follow:

$$dC(t)/dt=BF[C_a(t)-C_v(t)]$$

Equation 1

where BF is the blood flow, C_a (t) is the arterial input concentration to the voxel (also known as the Arterial Input Function - AIF) and C_v (t) is the venous output concentration of the voxel (also known as the Venous Output Function - VOF).

Under the assumption that the system is linear and time invariant, there exists a unique impulse response function h(t) of the blood transit time in the voxel such as: $C_v(t)= C_a(t)\otimes h(t)$, where $\otimes$ stands for the convolution product.

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Therefore, the equation (Equation 1) can be solved with the initial condition C(0)=0 and leads to the indicator-dilution theory formulation for perfusion modeling[17] as follow:

$$C(t)=BF \times C_a(t) \otimes R(t)$$

Equation 2

where R(t) is the residue function - the fraction of contrast agent that remains in the voxel at a time t after its arrival. R(t) is unknown and must be recovered from the observed C_a (t) and C(t) by means of deconvolution.

Thus, the equation (Equation 2) shows that the perfusion modeling is based on a single state equation with three unknowns: the local AIF, the residue function R(t) and the Blood Flow (BF). The current state of the art is to measure the global AIF once and to consider that the arrival of the contrast agent within tissue can be delayed. The predominant techniques for estimating BF are based on deconvolving the AIF with the C(t) using the Singular Value Decomposition (SVD) technique to estimate the impulse response (defined as R(t) multiplied by BF), where its maximum value is BF [18, 19].

Due to the commutative property of the convolution product, the delay τ of the AIF can be introduced in the residue function. The standard perfusion model taking into account the delay can be written as:

$$C(t)=BF \times C_a(t) \otimes R(t-\tau)$$

Equation 3

This delay τ (called Tmax when estimated from SVD methods) is measured as the time to maximum of the residue function (Figure 1).

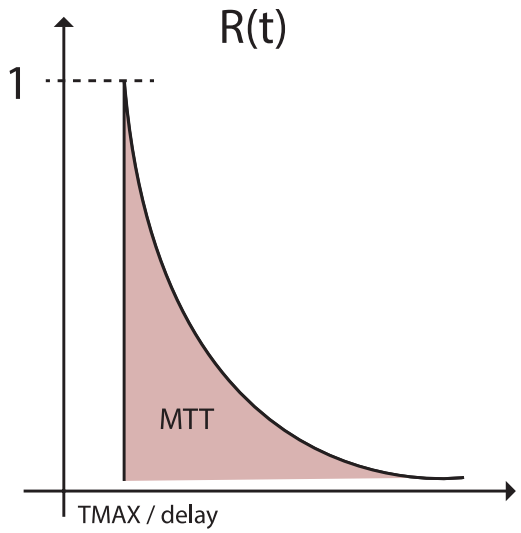

Figure 1: residual function over time

Therefore, the high accuracy and the quality in estimating the reconstructed R(t) directly affects the estimation of the perfusion parameters such as the Blood Flow (BF), the Blood Volume (BV), the Mean Transit Time (MTT) and the Time to Maximum of the residue function (Tmax).

The equations (Equation 2) and (Equation 3) of the standard perfusion modeling can be solved using model-independent, non-parametric deconvolution methods using standard deconvolution methods based on a family of fast-truncated Singular Value Decomposition (e.g. sSVD, cSVD, oSVD) methods[18,19].

However, when the AIF is supposed to be given, dozens of model-independent, non-parametric deconvolution methods have been proposed in the literature. Parameters estimates are found to be extremely variable from one method to the other and prone to error[19,20]. This highlights some defects in the standard perfusion model, the deconvolution methods, and the global AIF approach.

In fact, the original goal of quantitative bolus tracking PWI—the macro/micro-vascular separation—is no longer reachable.

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Moreover, model-independent estimates of R(t) are often inconsistent with the standard perfusion model. For instance, SVD-based R(t) estimators strongly violate the constraints of monotonicity, positivity, and unity at the origin. Another problem encountered in PWI analysis is the estimation of delay between the measured AIF and the observed concentration time curve. Consequently, hemodynamic parameters estimated with the SVD method suffer from some well-known systematic biases and defects such as underestimation of high BF when the AIF lags the concentration time curve[21]; and overestimation of low MTT[18], overestimation of low BF and underestimation of high MTT, or Tmax becomes highly dependent on MTT[22]. Therefore, Tmax cannot be a relevant estimate for true delay.

Regarding the model-dependent approach, parametric or semiparametric models for R(t) and, sometimes, AIF models were introduced. This reduces the underlying blind deconvolution problem to a classical parameter estimation that can be solved using Bayesian methods[23]. However, the model-dependent approach requires to specify the underlying model for R(t) which is unknown. Furthermore, slight misspecification in R(t) model can yield dramatic errors in the parameters estimates, even if it produces a descent fit to the data.More recent works proposed Bayesian model-independent approaches for parameter estimation[24,25]. These methods show the ability of Bayesian framework to solve the perfusion model. In particular, Schmid[25] showed that taking into account spatial information is paramount in improving the methods. However, with these methods, the solution cannot be computed analytically, therefore MCMC (Markov Chain Monte Carlo) algorithms are used. In addition, none of the methods proposed by Schmid et al. allows to oversample the residue function to reduce numerical errors. Finally, these methods do not take into account the delay, nor a circular convolution scheme, leading to a likely strong delay dependency in the parameter estimation. In fact, the authors did not study the delay effect on their estimates. That is the reason why an improvement of this method was performed and a new fully adaptative and delay-insensitive Bayesian-based deconvolution method (BDM) was developed by Boutelier et al. in order to provide a rigorous and logically minimalist solution to the hemodynamic parameters estimation problems under the standard perfusion model[26]. The authors proposed and developed the methodology of the named new deconvolution method and highlighted the ability of the Bayesian Probability Theory (BPT) to reliably estimate CT and MR perfusion parameters when SNR is low and/or the signal is moderately truncated. In addition, the authors improved the post-processing time, so this new method can be used in clinical practice and provides accurate parametric maps in real time.

Bayesian-based perfusion model validation

This new Bayesian-based deconvolution method as proposed by Boutelier et al. was validated on CT and MR phantoms, and was compared to the oSVD algorithm, since it has been demonstrated that the oSVD - robust and accurate method without tracer-delay effect in terms of linearity and fewer errors at

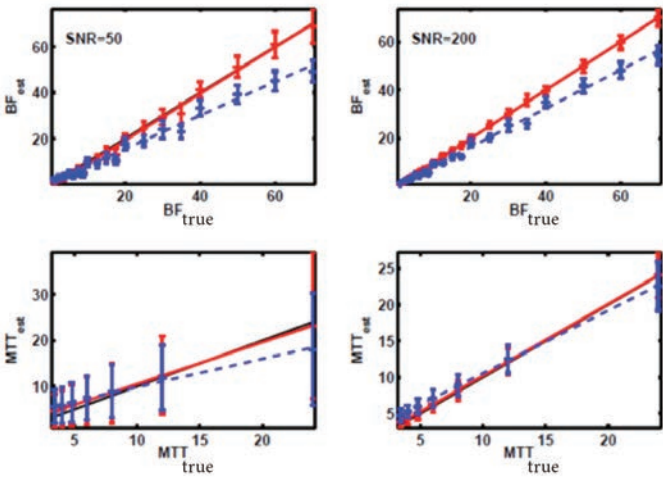

Figure 2: true *vs* estimated MTT and BF parameters validated on MR phantom data. Blue: oSVD / Red: BDM
Originally published in IEEE[26]

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low signal to noise ratio (SNR) - performs better than any other existing SVD-based deconvolution method[20]. For the MR simulated data, the validation study showed underestimation of high BF and MTT values calculated with the oSVD, for low and high SNR. MTT estimated values with the oSVD are overestimated for low values, whereas BF and MTT estimated values using BDM are perfectly correlated with and close to the true values, even for low SNR (Figure 2). In CT simulated data, when SNR or BV decreases, the quality of estimation was shown to be degraded much faster with the oSVD than with the BDM. The BDM outperforms oSVD on MTT and BF estimation, especially at low SNR. In other words, overestimation of low BF and underestimation of high BF are much higher in the case of oSVD compared to the BDM. Furthermore, MTT estimates of oSVD are negatively correlated with true values, which, physiologically speaking is absurd, while the BDM provides reliable positively correlated estimates (Figure 3).

Finally, this paper showed that BDM-Delay is strongly correlated with the true delay as the SNR increases, especially for MR phantom data (Figures 4-5).

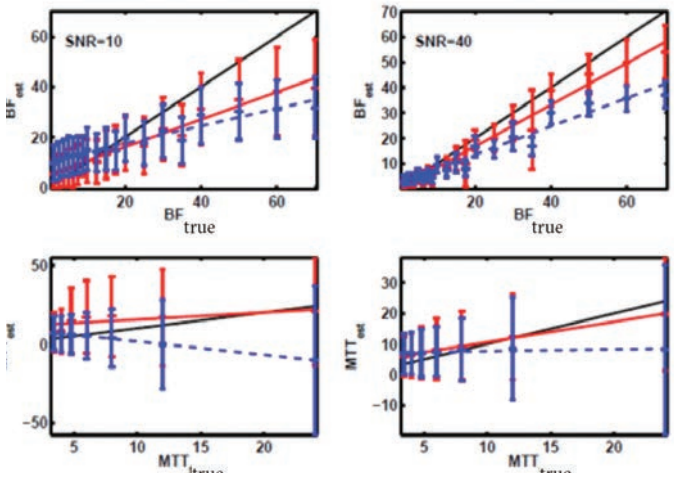

Figure 3: true *vs* estimated MTT and BF parameters validated on CT phantom data. Blue: oSVD / Red: BDM
Originally published in IEEE[26]

BDM-Delay is independent from MTT and only slightly from SNR. By contrast, oSVD-Tmax is poorly correlated with true delay (Figures 4-5), highly biased by MTT, BV and even SNR, and has extremely large standard deviations. The error bars are huge, i.e. up to 8 times the real delay amplitude in the CT digital phantom.

SNR = 50 SNR = 200

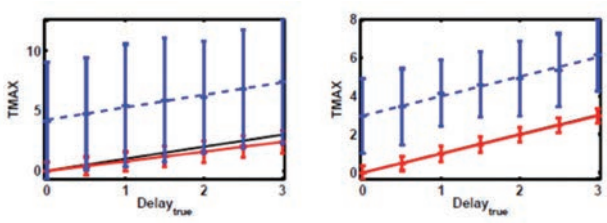

Figure 4: true delay *vs* estimated Tmax parameter validated on MR phantom data.
Blue: oSVD / Red: BDM
Originally published in IEEE[26]

SNR = 10 SNR = 40

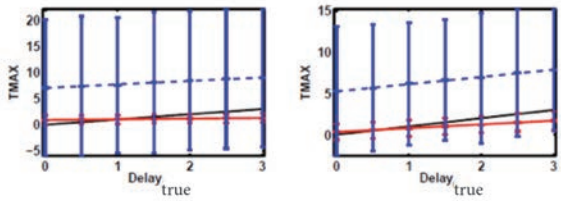

Figure 5: true delay *vs* estimated Tmax Parameter validated on CT phantom data.
Blue: oSVD / Red: BDM
Originally published in IEEE[26]

In addition, one can note that in CT, the higher the SNR, the more oSVD-Tmax seems to be correlated with true MTT than the MTT estimate itself. In the light of the above, oSVD-Tmax cannot be considered as a reliable estimator of the delay and these facts can explain some inconsistencies in the use of oSVD-Tmax to determine the penumbra, i.e. the volume of tissue at risk of necrosis in acute stroke[27,28]. Such drawbacks are strictly related to the complicated dependency of oSVD-Tmax on multiple parameters such as MTT and the noise level.

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Furthermore, the authors noted that even if oSVD-Tmax was a pure delay estimator, it could not be used as a marker of the penumbra. In fact, it is not because blood supply is delayed or not that the tissue will eventually infarct or not. It would rather detect collateral circulation that typically induces increased delays but arbitrary iso- or hypo-perfusion. Hence, a pure delay estimator is expected to be a marker of the vascular territory impacted by the arterial occlusion in ischemic stroke, not of the penumbra.So the authors advocated that if oSVD-Tmax is used to delineate the penumbra with satisfactory results, it is due to its dependency on the tissular parameter MTT. Nonetheless, it remains complicated to calibrate and it could advantageously be replaced, for instance, by the more robust MTT estimate provided by the Bayesian-based deconvolution method. The authors concluded that the estimated BDM-Delay could be more likely to be used for delineating the arterial occlusion territory and collateral circulation. The newly presented Bayesian-based deconvolution method has been validated on digital phantoms, animals' models and human subjects for different clinical purposes, through independent studies. In Sasaki et al. paper[29], the aim of the study was to investigate whether quantitative values generated by the Bayesian-based deconvolution algorithm[26], applied to CT perfusion data, are more accurate than those generated using optimized delay-insensitive singular value decomposition deconvolution algorithms.

The authors compared the accuracy of these algorithms by using a previously tested and validated digital phantom. This work confirmed that the BDM provided CBF, CBV, and MTT maps that were strongly correlated with and close to the true values.

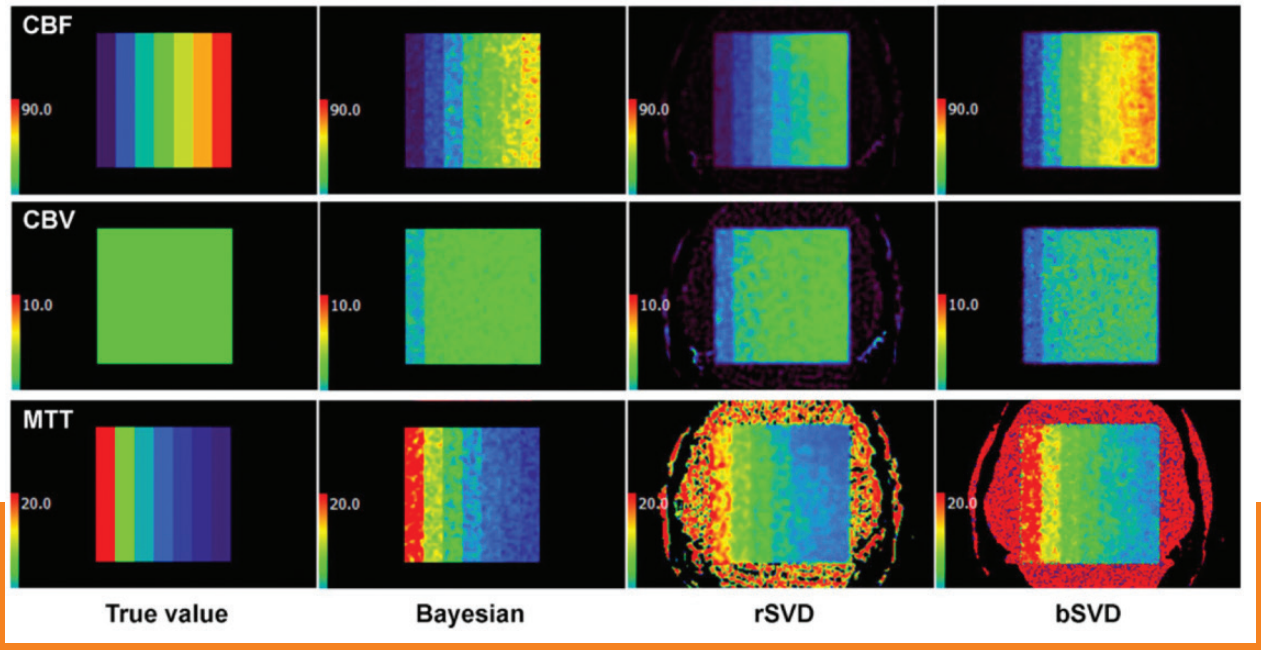

Figure 6: perfusion maps generated with a digital phantom using different deconvolution algorithms. Color maps of CBF, CBV, MTT generated with the Bayesian-based deconvolution method (BDM), reformulated singular value decomposition (rSVD) algorithm, and block-circulant singular value decomposition (bSVD) algorithm appear to be roughly comparable to the true values, although an improvement with the BDM can be seen. No distinct gradation in the vertical direction is found in any of the algorithms, indicating insensitivity to the tracer delay.
Originally published in Neuradiology [29]

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More specifically, the BDM-MTT map was estimated with better agreement than those produced using the delay-insensitive SVD algorithms (Figure 6).

In the light of these findings, it is reasonable to consider that the accuracy of this method has been indisputably assessed from a theoretical point of view. However, although documenting mathematical accuracy is a very good start, the impact of such gain in accuracy in clinical practice had yet to be investigated. Kudo and his team[30] tested the performance of the Bayesian-based deconvolution method (BDM)[26] for the prediction of final infarction in a primate model (monkey) with permanent unilateral occlusion of the middle cerebral artery (MCA), in comparison with the oSVD deconvolution method.

Their study showed that the volumes thresholded using all perfusion maps (BF, BV, TTP and MTT) calculated with the BDM had higher correlation coefficients with the final infarct volume defined by diffusion-weighted imaging (DWI) or by specimen volumes, than those calculated with the oSVD method. The improvement was more relevant for the BF and MTT maps, where the thresholds of MTT > 1.8 s and BF < 0.26 a.u and MTT > 1.6 s and BF < 0.33 a.u, provided final infarct volumes very close to specimen and DWI volumes respectively.

The authors concluded that the final infarct volume can be more reliably estimated using the Bayesian-based deconvolution method than with the oSVD method (Figure 7).

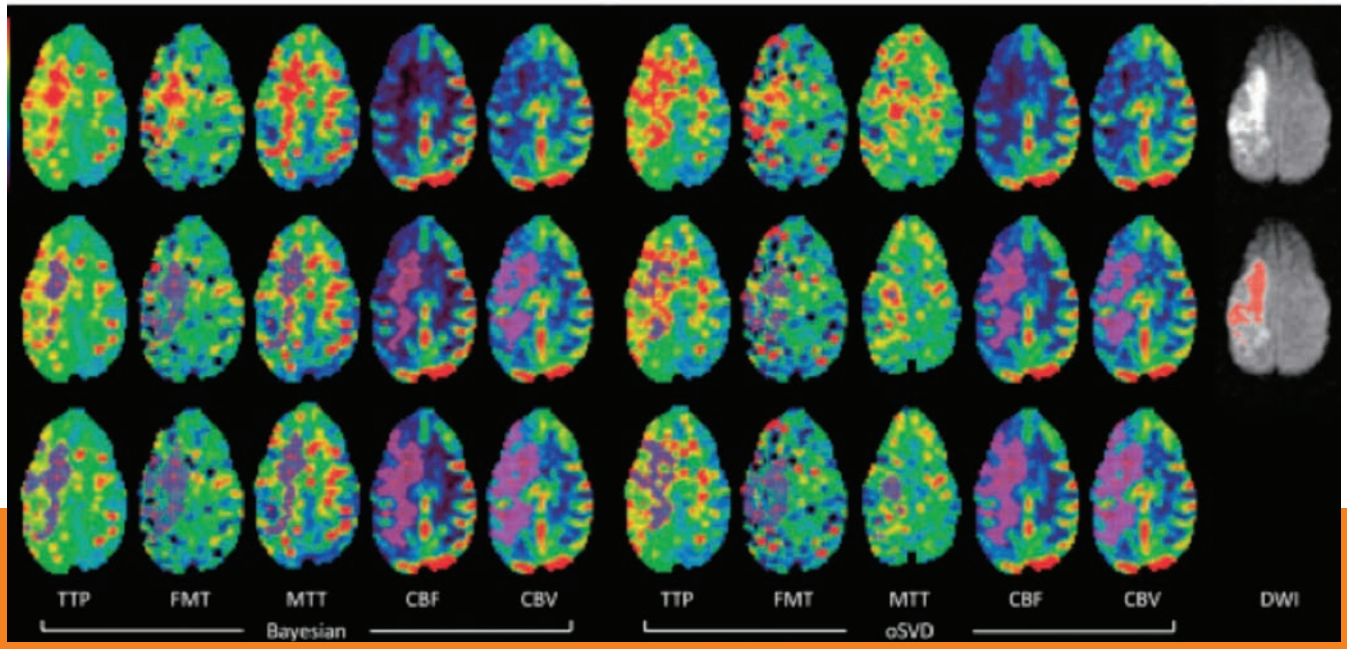

Figure 7: perfusion maps from Bayesian-based deconvolution method and oSVD algorithms. Various perfusion maps and DWI map are shown in the top row. The area of the final infarct is shown in purple (time to peak [TTP], first moment of transit [FMT], and mean transit time [MTT] maps) or pink (cerebral blood flow [CBF] and cerebral blood volume [CBV]) at the best threshold, which was determined with the final infarct of the specimen volume (middle row) and DWI volume (bottom row). The volumes of the final infarct differ among maps and algorithms. In this particular subject, perfusion abnormalities in the FMT, MTT, and CBF of the Bayesian-based deconvolution methods correspond well to the high signal area of DWI.
Originally published in Magn Reson Med Sci [30]

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In addition, Nicoli et al.[31], further tested if MRI-derived indices from DWI and perfusion maps, such as the arterial tissue delay (ATD) calculated using the Bayesian-based deconvolution method[26], alone or in combination - could predict M1 middle cerebral artery (MCA-M1) recanalization after endovascular thrombectomy. The study showed that the Bayesian Delay maps and DWI maps provide a non-invasive assessment for the degree of collateral flow and predict the rate of full recanalization of MCA-M1 occlusions. It was demonstrated that the combination of baseline DWI lesion volume and VolATD6 (the volume of tissue with severely prolonged ATD › 6 s) is highly reproducible and closely correlated with the angiographic collateral grade (Figure 8).

Quantitative values of CBF, CBV and MTT in Bayesian processed data were comparable in the half-dose and full-dose groups (0.1 mmol/kg) and the differences observed were not statistically significant. Conversely, cSVD derived half-dose perfusion values were significantly different from those of the full-dose group both in GM and WM.

In conclusion, the Bayesian-based deconvolution method is a unique, fully adaptive delay-invariant algorithm providing minimum variance Bayes estimators. Voxel-wise signal-to-noise ratios (SNR), realistic intervals and their odds are available for all parameters. The Bayesian-based deconvolution method delivers natural, real-time, quasi-exact Bayes estimators.

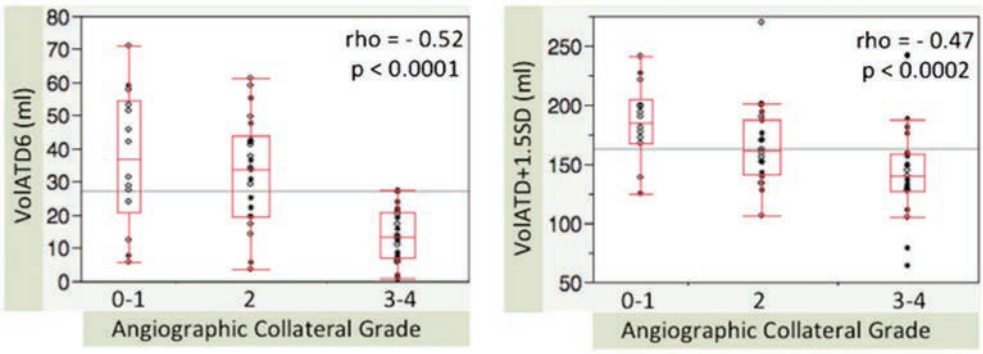

Figure 8: correlations between Bayesian parameters (the volume of tissue with ATD›6s -VolATD6), diffusion lesion volume (the volume of tissue with ADC‹600x10-6 mm2/s - VolDWI) and the angiographic collateral grading (0–1 vs 2 vs 3–4) in patients with acute MCA-M1 occlusion. VolATD6 and VolDWI have the highest correlation with the angiographic collateral Originally published in Neuroradiology[31]

More recently, in Nael et al.[32] study, the authors aimed to establish the feasibility of reduced-contrast-dose brain DSC perfusion by using a Bayesian-based deconvolution method[26] and to compare the results with the commonly used block-circulant singular value decomposition (cSVD) technique. This study demonstrated, as expected, that the SNR was significantly lower in the half-dose group with 32% and 40% reduction in gray mater (GM) and white mater (WM), respectively. In the half-dose group (0.05 mmol/kg), the image-quality scores were significantly higher in Bayesian-derived CBV and MTT maps in comparison with cSVD-derived maps.

Thereby, this method provides more precise hemodynamic maps (parameters) and it has been established that they may, ultimately, significantly impact clinical practice and patient assessment. This method is CE marked and FDA cleared within the Olea Sphere® software (Olea Medical®, La Ciotat), and it is nowadays used in clinical settings. The validation of this method in digital phantoms, primate specimens and on clinical data in humans documented its accuracy, robustness and reliablility opening the path to a more extensive clinical application of this method in the future.

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Bayesian perfusion for contrast dose reduction

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Kambiz Nael is a board-certified radiologist with specialty certification in Neuroradiology.

Kambiz Nael did his Radiology residency at David Geffen School of Medicine at UCLA in Los Angeles, followed by a fellowship in diagnostic Neuroradiology at UCLA.

Later, he worked at University of Arizona as an Assistant Professor of medical imaging, where he was the Director of Neuroradiology MRI and stroke imaging, before joining Mount Sinai in July 2015.

Kambiz Nael's clinical and research interests include advanced imaging, quantitative Neuroimaging, and multiparametric imaging approaches in the diagnosis of a variety of cerebrovascular disorders and brain and spinal neoplasms.

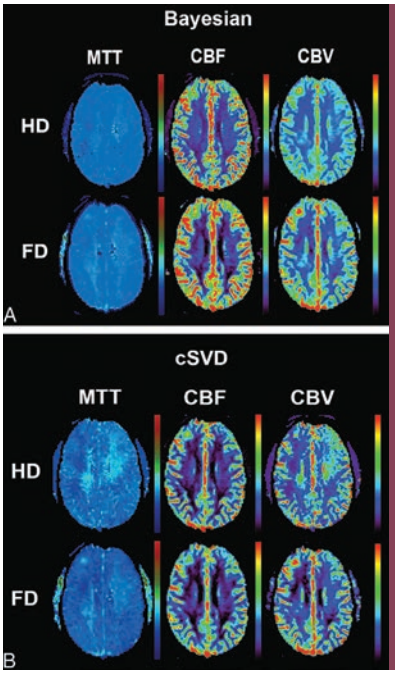
Olea Imagein: When did you first hear about the Bayesian perfusion method?

Kambiz Nael, MD: I heard about Bayesian back in 2013 when it was in a beta version. I started using it for my research when I was at the University of Arizona.

OI: Do you use it in clinical routine or only in research? For MRI or CT?

K.N: I have been using it for clinical practice in MRI post processing. I haven't used it for CT but that is something that we are looking into.

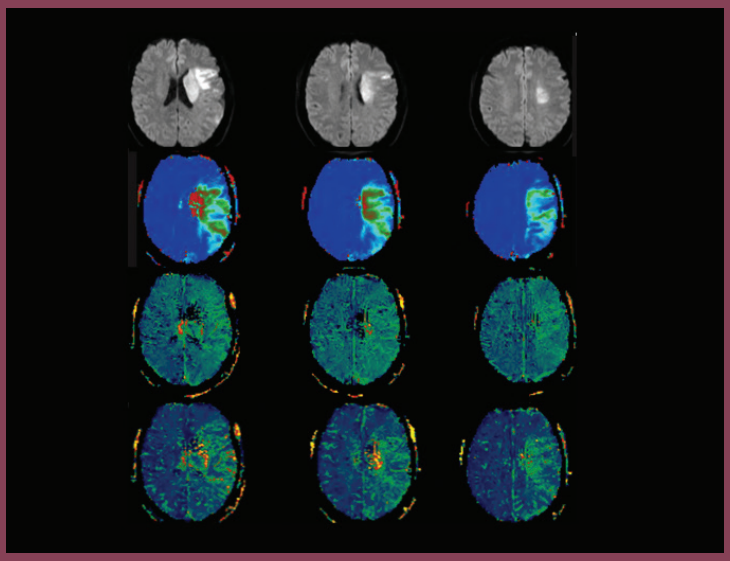
For MR, I have been using it as part of my research and for a few applications in my clinical practice. I use Bayesian mainly in contrast-enhanced MRI protocols that require more than one injection.



Coregistered and aligned MTT, CBF and CBV maps from Full Dose (FD) (0.1 mmol/kg)and Half Dose (HD) (0.05 mmol/kg) DSC perfusion imaging are shown in this 40-year-old man who presented with headache.

While the image quality of perfusion maps in FD scans is comparable between Bayesian and cSVD, note the heterogeneity and regional errors seen in cSVD-derived MTT and CBV maps in HD scans.

Originally published in AJNR[1]



Originally published in ASNR[2]

Patient with left middle cerebral artery infarction.

DWI (1st row) shows acute infarction.

MR perfusion was performed after injection of 0.05 mmol/kg of Gd.

TTP (2nd row) shows large delayed perfusion involving left MCA territory.

cSVD-MTT (3rd row) and Bayesian-MTT (4th row) are shown. Perfusion deficit is difficult to apprehend on cSVD-MTT maps due to significant background noise.

Despite using low contrast dose (0.05 mmol/kg), the delineation of perfusion deficit is more apparent on Bayesian-derived maps, as it is a more robust technique in processing of images in low SNR environment.

O.I: In your opinion, what are the main advantages of this method in clinical practice?

K.N: The main advantage of Bayesian in my practice so far has been the ability to reduce contrast (gadolinium) dose. Since Bayesian processing is inherently less sensitive to noise, I use it to avoid unnecessary contrast dose.

> “I use Bayesian to avoid unnecessary contrast dose.”

O.I: Can you tell us more about the dose reduction?

K.N: I have used the Bayesian method on patients with brain tumour to perform both DSC and DCE perfusion using a standardized contrast dose as describe in our work, published in AJNR last year. Also I am using Bayesian in patients with acute stroke to perform CE-MRA and DSC perfusion in the same session without the need to double the contrast dose.

O.I: Does this technique slow down your clinical workflow?

K.N: I used to have it on my Mac and it was relatively slow. It would take two to three minutes to process. I have the new version of Olea Sphere® 3.0 on a PC workstation and it takes less than a minute to process.

We do have offline processing installed but I like to process my clinical cases on my own, because I like to do quality checks. We do get offline maps for routine practice.

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Bayesian offline:
For a smooth clinical routine

Lawrence N. Tanenbaum, MD
Vice President and Medical Director East region - Director of CT, MR and Advanced Imaging at Radnet, USA
Lawrence N. Tanenbaum is a neuroradiologist by fellowship training.

Associate professor of Radiology, he was Director of MRI, CT and outpatient/advanced imaging development at Icahn School of Medicine at Mount Sinai, in New York, since 2008. Prior to 2008, Lawrence N. Tanebaum spent over twenty years in the private practice of Radiology at the JFK Medical Center/New Jersey Neuroscience Institute as the Director of MRI, CT and Neuroradiology.

Olea Imagein: You have trusted Olea Medical® from the early days. What drove you to this young team?

Lawrence Tanenbaum: What attracted me to the Olea Medical® team, right from the beginning, was their passion for excellence, and strong desire to be at the cutting-edge of every advanced visualization technology. I was also drawn by their passion for being accurate and quantitative, in facilitating the diagnosis and treatment of stroke. They rapidly expanded from that hallmark strength to deliver the highest standard of capability and accuracy in many areas of advanced visualization, beyond neurologic diseases including physiologic breast, prostate, and liver imaging.

Being involved with a company like this, is exciting and being a collaborator, very rewarding. The Olea team is young, vibrant, aggressive and agile, qualities uncommon in an industry dominated by larger manufacturers. Much like steering an ocean liner, things with the large imaging OEM's move slowly. At Olea Medical®, if a need is identified, and the solution is valid then they go from project to product at a brisk pace.

O.I: This is the first issue of Olea Imagein. Obviously, we chose to focus on the Bayesian method. Would you say this mathematical method literally made a difference in Neuro imaging?

L.T: I am fascinated by the Bayes method and the entire concept behind the Bayesian approach of data analysis. Initially deployed to decode encrypted messages in war, it is adept at extracting critical data from sparse information such as a radiation or contrast dose challenged perfusion exam. With the speed delivered by the exclusive Olea Medical® algorithms, Bayesian approaches facilitate virtually any type of data analysis.

O.I: How about the offline feature? Is it really useful? How did it change your practice?

L.T: Fully automatic, offline processing capability with no need for operator interaction is enormously impactful. If trained, personnel are required to process a CT perfusion exam. I am never fully comfortable with my ability to deliver. I am always concerned that the wrong person is on call or a technologist has not performed the exam for a while and has lost familiarity with processing. Automatic means I can rest assured knowing that no matter when a patient presents, from Bastille Day through Christmas morning, I will have the in-house capabilities to get the information out to the enterprise. As we know, time is of the essence when it comes to stroke imaging, even with the wider therapeutic windows we are seeing today. Offline processing delivers the data in brief minutes. Before the treating team can aggregate and discuss therapeutic options, the perfusion maps are distributed throughout the enterprise. Reliable delivery of valid information is enormously powerful and the stroke team really does appreciate getting what they need consistently.

> “It allows us to focus only on delivering care.”

We don’t see that many acute stroke cases per year. On the other hand, I may scan three or four patients with brain tumor cases in a given day. Here, the workflow load requirements can be daunting. We typically perform a perfusion exam, with DSC (Dynamic Susceptibility Contrast), and a permeability exam with DCE (Dynamic Contrast Enhancement). Lots of individual steps between networking data to and from the workstation to processing all the individual parametric maps, many steps, in none of which I really need to be involved. To open the case on PACS, see all the routine images and then have to go back to the workstation to process the data, the workflow is just prohibitive. In our shop, the images are automatically networked to the Olea Sphere® server and automatically processed through the offline workflow. When I open the PACS, I can look at my structural images, and already have my processed perfusion and permeability images. I would say eight times out of ten, I don’t need to do any further interaction with the workstation.

I move right on to interpretation. Should I need a detailed analysis or quantitative measures, I know exactly what I am after when I go to the Olea Sphere® workstation. The difference in my efficiency can be as much as twenty minutes per case. Offline workflow is one of the most important features that Olea Sphere® offers, it is a differentiator and it has enormous impact on workflow as well as the quality of care I can provide.

O.I: How long have you been using the Bayesian computation method and the offline processing in your hospital?

L.T: We have been using the Bayesian processing and offline processing for quite some time. I suspect we were among the first adopters because I realized, as the director of CT and MRI, that workflow is a critical factor in terms of our ability to deliver care in an efficient way. Whether it is acute stroke, triage and diagnosis or just getting me through the many complex exams we do every day, automation has an enormous impact. I said “please, make this workflow work for us because we think it will change our lives”, and whether it comes to affecting on acute stroke patients, triage and diagnosis, it has an enormous impact.

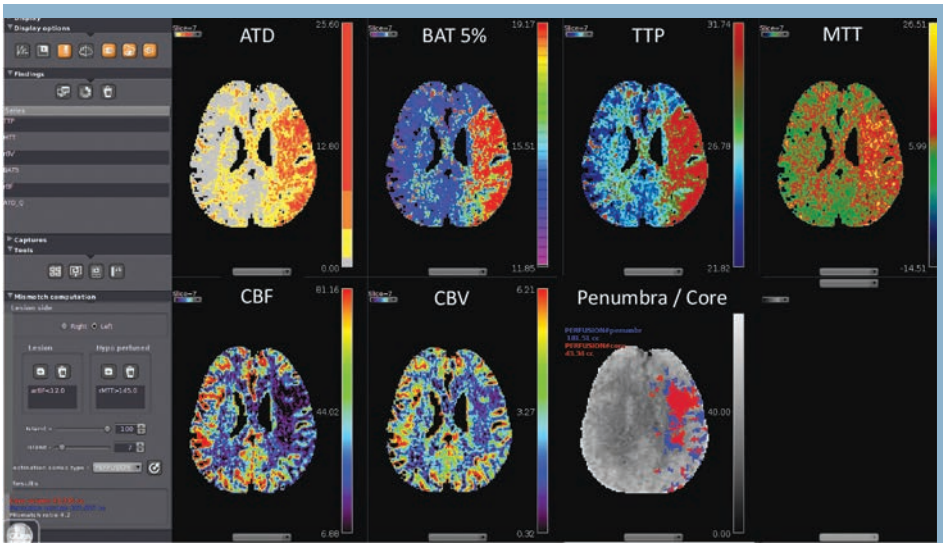
Left MCA occlusion using CT perfusion

How-to session

Prof. François Nicoli, MD, PhD

The case report below enables to better understand the added value of the Bayesian method in stroke imaging.

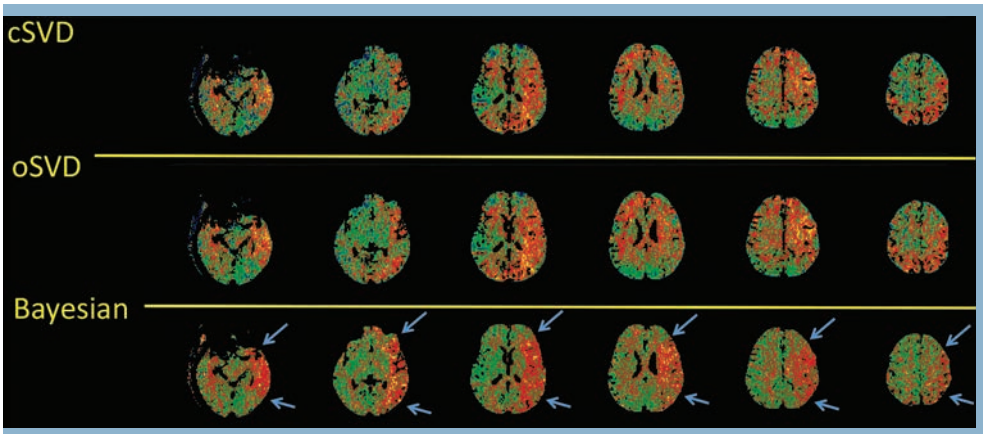
BAYESIAN CT POST-PROCESSING



Example of Bayesian processing for CT perfusion images.

We notice a stroke located in M3 cortical MCA territory. A high quality distinction between white and grey brain matter on all the Bayesian maps can be observed.

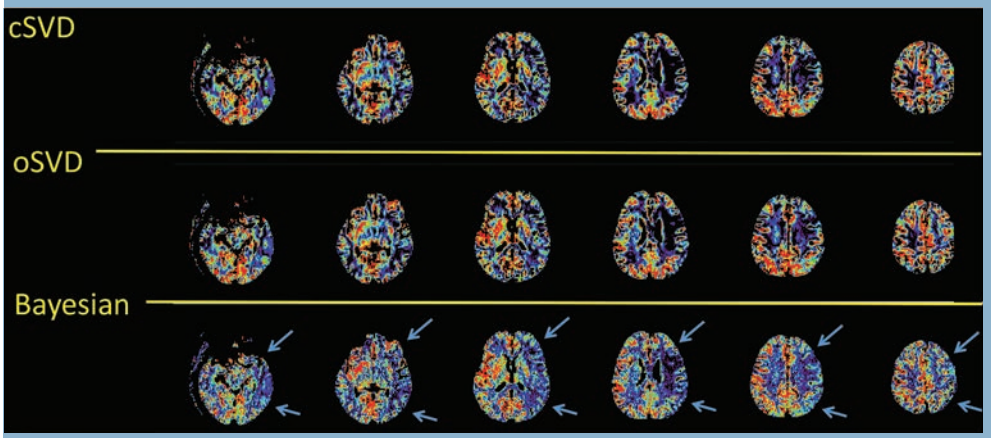
CT POST-PROCESSING



True theoretical borders of the MCA territory

MTT maps (acute MCA M1 occlusion)
The distinction between grey and white matter and ischemic lesion is not clear on MTT maps with cSVD and oSVD deconvolution methods. There are remaining artifacts that could lead to an overestimation of ischemic area.

The Bayesian processing solves this problem and perfectly delimits the stroke on the MTT map (blue pointers).



True theoretical borders of the MCA territory

CBF maps (acute MCA M1 occlusion)
Bayesian processing offers more consistent CBF maps and a clear emphasise on a decrease in cortical CBF in the whole left MCA territory (blue pointers) whereas it seems mainly preserved in the right MCA territory with cSVD and oSVD methods.

Early and late MR diffusion follow-up of a stroke

How-to session

Adam J. Davis, MD

The following case report explains the usefulness of the Bayesian method in CT stroke imaging

Patient history:

A 58 year-old female patient with transient right-sided weakness saw her condition improve. She then presented a sudden onset right hemiparesis and aphasia. Upon arrival at the ER, a CT perfusion was performed in emergency, evidencing sylvian superficial ischemia on left M3. Diffusion MR was also performed after eight hours and at day four.

Imaging findings and discussion:

The Bayesian method is an approach using a probabilistic estimation of hemodynamic parameters, used in perfusion imaging[1]. A quantitative analysis using digital phantoms was performed and demonstrated that the Bayesian estimation algorithm lead perfusion maps (such as CBF, CBV and MTT) to strongly correlate with the true values[2].

Another study showed that the Bayesian method clearly outperformed oscillating singular value decomposition (oSVD) in terms of goodness-of-fit, linearity, statistical and systematic errors on all perfusion parameters, especially at low Signal to Noise Ratio[3] (SNR). Indeed, low SNR and short acquisition time usually introduce strong bias in MTT estimation when using SVD methods.

Furthermore, short acquisition time can deeply affect stroke assessment in clinical routine as MTT becomes less reliable. Most often, CT perfusion SNR is too low to accurately estimate MTT-based penumbra when using oSVD in acute stroke. Therefore, the Bayesian method is more appropriate and robust against noise and truncation, in comparison to oSVD[4].

Figures 1-3 show the comparison of the perfusion parameter CBF (Cerebral Blood Flow) computed with either

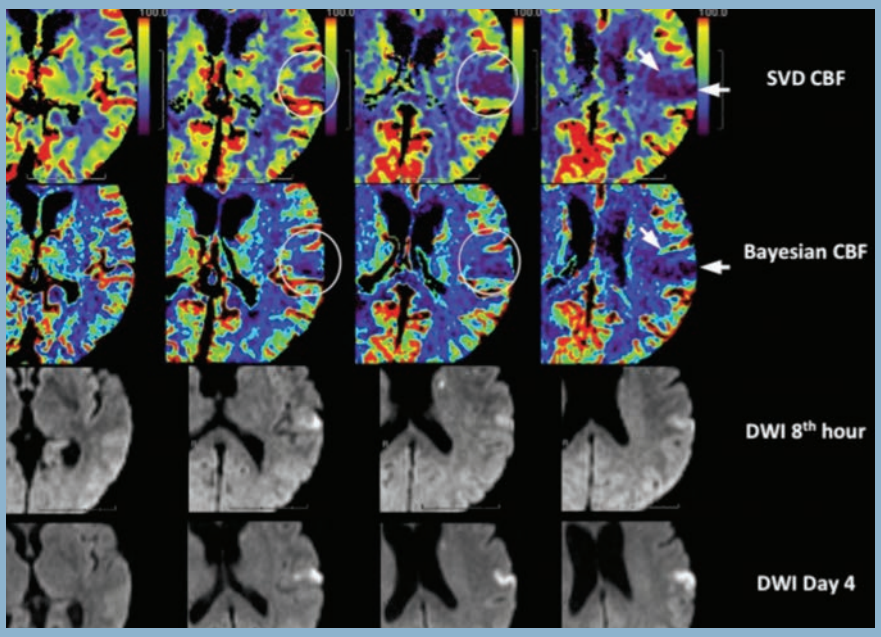


Figure 1: comparison of CBF computed using the Bayesian method from Olea Medical® with SVD and lesion follow-up using diffusion MR at eight hours and after four days.

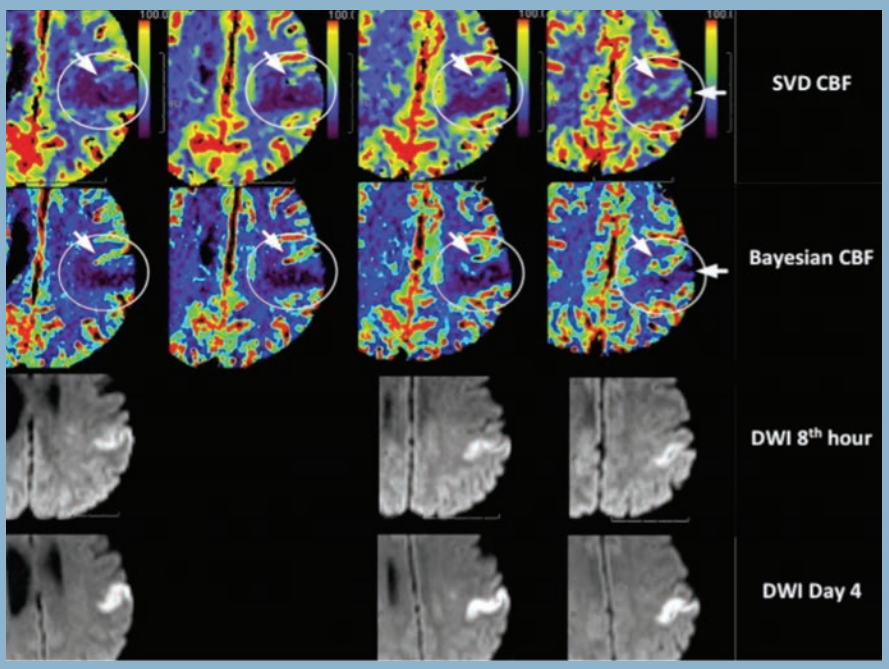


Figure 2: comparison of CBF computed using the Bayesian method from Olea Medical® with SVD and lesion follow-up using diffusion MR at eight hours and after four days.

standard deconvolution method (SVD) or the Bayesian method, developed by Olea Medical®, at different slice levels, along with DWI follow-up.

The area where the CBF is drastically decreasing appears to be a lot more restricted in the Bayesian processing of CTP data. This volume, (circled on Figure 1) where the CBF is clearly dropping, correlates with the limited lesion volume that one can see in DWI MR, whereas the non-Bayesian processing suggests a wider lesion volume.

According to numerical simulations, the Bayesian processing provides a better estimation of the CBF, whereas deconvolution methods underestimate it.

This case is demonstrative of the cortical CBF underestimation in the penumbra when using SVD deconvolution methods. Hence, the observation of the hypoperfused zone in a wider area, while Bayesian processing defines an area where CBF is significantly reduced, much smaller than the deconvolution method and more in agreement with the lesion volume defined by MR early and late diffusion (white arrows in Figure 2 and Figure 3).

This CT perfusion case strongly correlates with the literature observations. Moreover, the fact that the lesion was assessed using diffusion MR imaging after eight hours and four days, shows once more the relevance of the Bayesian estimation method.

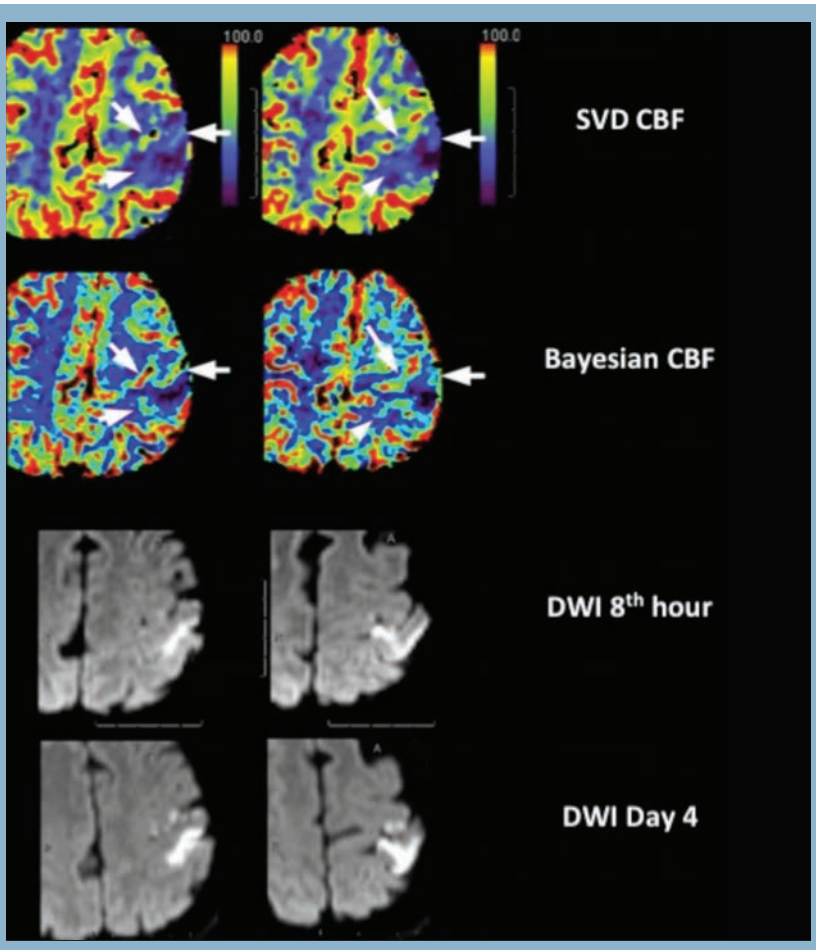


Figure 3: comparison of the CBF computed using the Bayesian method from Olea Medical® with SVD and lesion follow-up using diffusion MR at eight hours and after four days.

Conclusion:

By comparison with deconvolution methods, the Bayesian approach offers a much better definition of the abnormally perfused areas. This new delimitation of the penumbra in acute stroke imaging is confirmed by diffusion weighted MR imaging.

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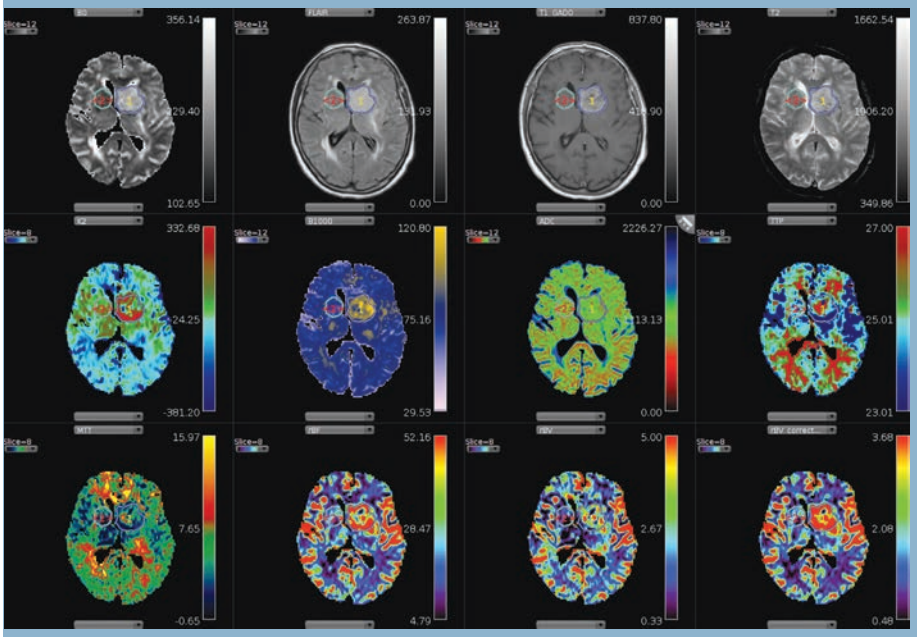
2. Makoto Sasaki, K.K., Timothé Boutelier, Fabrice Pautot, Soren Christensen, Ikuko Uwano, Jonathan Goodwin, Satomi Higuchi, Kenji Ito, Fumio Yamashita, Assessment of the Accuracy of a Bayesian Estimation Algorithm for Perfusion CT by using a Digital Phantom. Diagnostic Neuroradiology, 2013: p. 1237-7.
3. Timothé Boutelier, K.K., Fabrice Pautot, Makoto Sasaki, Bayesian Hemodynamic Parameter Estimation by bolus Tracking Perfusion Weighted Imaging. Part 1: Theory and Preliminary Results. IEEE Transactions on Medical Imaging.
4. Fabrice Pautot, K.K., Timothé Boutelier, Makoto Sasaki. SNR and Acquisition Duration Explain Erroneous Mean Treansit Time in Acute Stroke CT Perfusion Imaging. in ISC. 2012. New Orleans.

Basal ganglia Glioblastoma at 1.5T

Prof. François Nicoli, MD, PhD

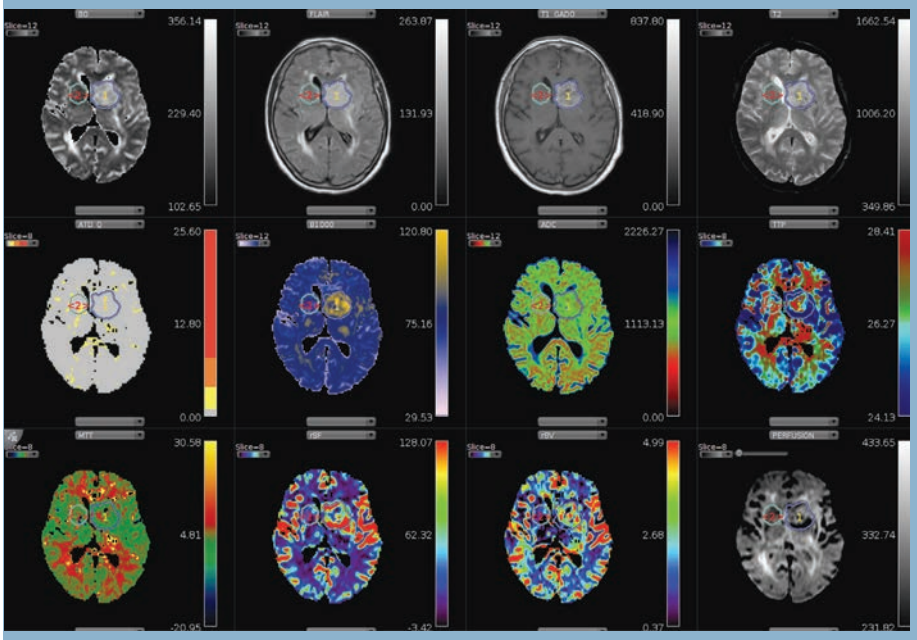
The case report below enables to better understand the added value of the Bayesian method in brain tumor imaging.



Series	1	<2>
ADC	1061.69 [1.16]	913.59
B1000	97.32 [1.37]	71.18
rBF	53.67 [2.54]	21.17
rBV	2.83 [2.47]	1.15
MTT	3.48 [1.17]	2.98
rBV_corrected	4.3 [2.73]	1.58

Hemodynamic parameters computed with the oSVD method

The CBF (Cerebral Blood Flow) ratio, compared to the controlateral side, is 2.54.



Series	1	<2>
B0	248.21 [1.55]	159.91
ADC	1061.69 [1.16]	913.59
B1000	97.32 [1.37]	71.18
ATD_Q	0.08 [0.18]	0.45
rBF	127.89 [4.6]	27.79
rBV	2.79 [2.35]	1.19

Hemodynamic parameters computed with the Bayesian method

The CBF (Cerebral Blood Flow) ratio, compared to the controlateral side, is 4.6.

In this basal ganglia Glioblastoma case, the relative CBF is considerably underestimated using deconvolution methods by comparison with the Bayesian method.

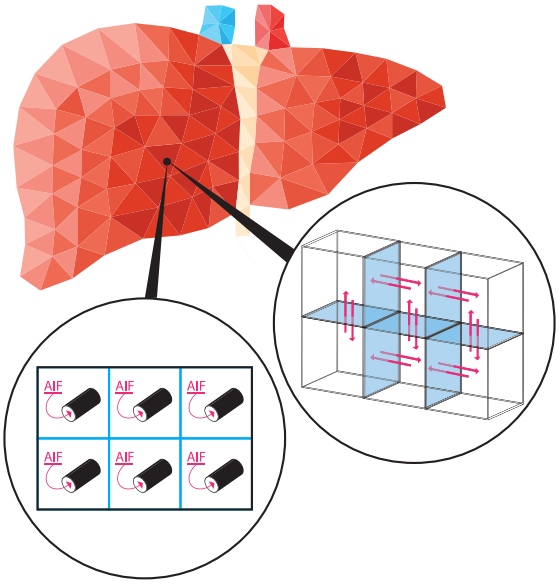
Think outside the voxel

Perfusion Weighted Imaging (PWI) relies on the injection of an intravascular contrast agent that perfuses through an organ of interest. Dynamic acquisitions in Magnetic Resonance imaging (MRI) or Computed Tomography (CT) enable the measurement of the temporal evolution of contrast agent concentration in each voxel of an organ. Proper modelling of the concentration time curve yields hemodynamic parameters.

So far, all attempts to model the perfusion process are based on the indicator-dilution theory developed by Zierler and Meier in the early 50's. Those models simplify a voxel as a system with one input[1], Arterial Input Function (AIF) and one output, Venous Output Function (VOF). The ability of the perfusion models to derive quantitative parameters makes PWI a promising technique, widely used in a clinical context. However, PWI is facing standardization issues, because only pseudo-absolute values can be derived, and estimations are model-dependent. Hence, there are still some debates about its clinical utility for various applications, and about the perfusion value, supposed to predict the outcome of a tissue. The main reason is that some fundamental limitations exist in current models, which are all based on the same framework of the indicator-dilution theory, proposed more than sixty years ago.

Until now, voxels have been considered as elementary tubes which are all fed by the same AIF, that do not see each other nor communicate. As a consequence, all the attempts to model the perfusion phenomena are doomed to ignore completely the circulation of fluids between voxels through body tissue. The absence of interaction between voxels in the current models has been the starting point of our reflexion that led us to develop a new framework to model perfusion. Before going further, it is also worth remembering what the definition of a flux is, which is a simple and perfectly defined concept in physics and Mathematics. Quoting James Clerk Maxwell, "in the case of fluxes, we have to take the integral, over a surface, of the flux through every element of the surface"[2]. Hence, a flux (or a flow) is defined throughout a particular surface. Therefore, one can wonder through which face of a voxel the blood flow is being computed? The answer to this question is in fact very simple, and we will see that it will serve as a new paradigm for perfusion modelling, leading to a new theory for in vivo tomographic tracer kinetics.

Indeed, a voxel is an open system, interacting and exchanging blood with its six neighbours through its six faces. Therefore, six directional flows must be defined for every voxel, instead of only one as it is assumed with the current standard perfusion model. From this obvious observation, we applied fluid dynamic theory to derive the equations that describe the circulation of blood and contrast agent throughout a whole organ divided into voxels. Within this paradigm, voxels receive input from their neighbours, rather than from a global AIF.



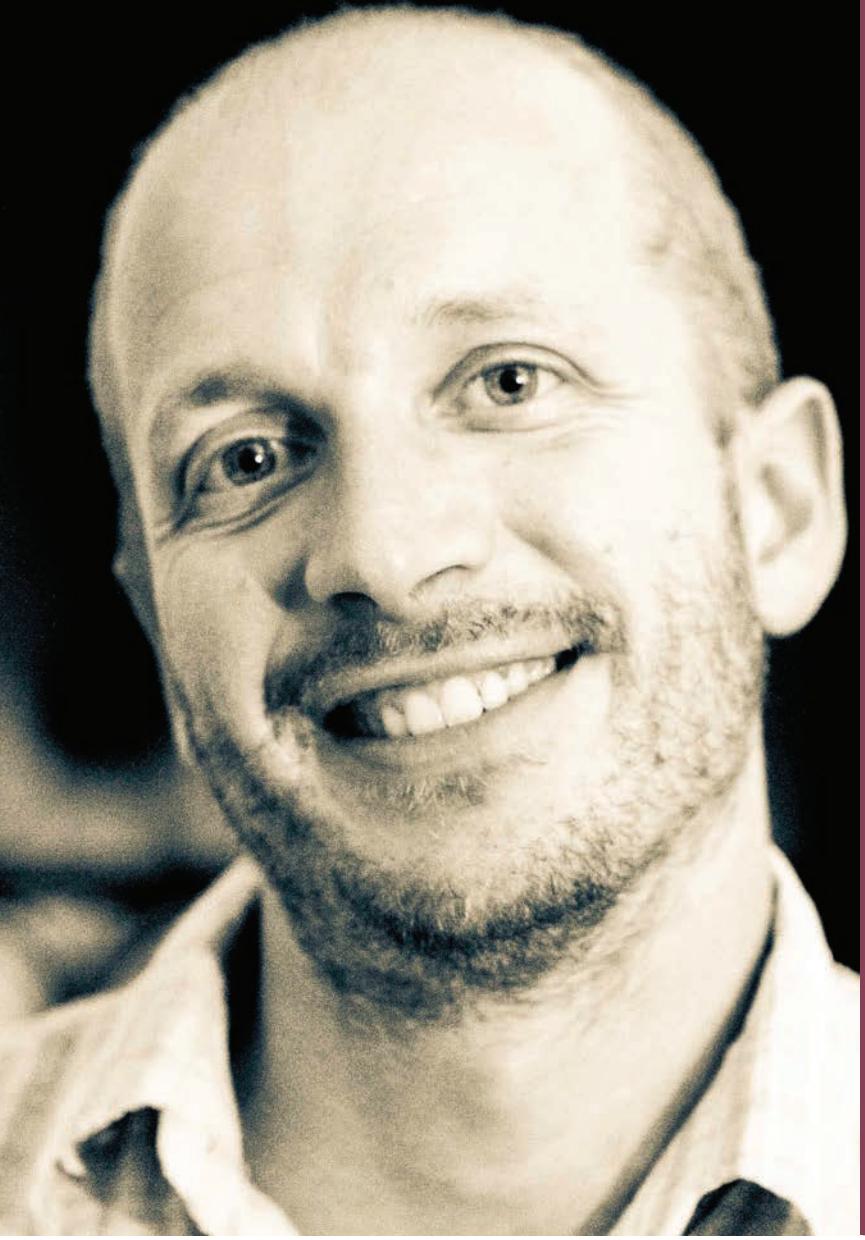
Until now, voxels have been considered independent and fed by the same AIF. Our new paradigm proposes a different model: each voxel would receive input from their neighbours rather than from a global AIF.

Whilst actual models are 0D approaches (a voxel is considered as a point), this is the first attempt to develop a full 4D spatiotemporal analytical model dedicated to perfusion analysis. It may be applied to any imaging technique, involving an endogenous or exogenous kinetic tracer, like ASL, fMRI, PET, etc.

We believe that this approach will eventually supersede the current ones. It will have a deep impact on our understanding of the circulatory system, with potential applications, such as dynamic angio-tractography, detection of aneurism, recirculation, to cite just a few. Therefore, it is just about time we start thinking outside the box... or the voxel.

Timothé BOUTELIER, PhD
Director Research & Innovation, Olea Medical®

1. Liver is an exception: it receives two inputs.
2. Maxwell, James Clerk. Treatise on Electricity and Magnetism. 1892, ISBN 0-486-60636-8.



Computed MRI:
higher flexibility for improved diagnosis

Arthur Varoquaux, MD, PhD
Radiologist at CHU La Timone
Marseille, France

Arthur Varoquaux has a post-doctoral position at CRMBM and is in charge of the head and neck imaging department at AP-HM.

Olea Imagein: Could you please explain what computed MRI is?

Arthur Varoquaux: For the radiologist, the aim is to make a diagnosis and if possible a diagnosis in reasonable time, compatible with a clinical activity. That's what makes us different from researchers.

The researcher has to come to a conclusion on an interrogation, whereas the radiologist needs to come to a conclusion on the diagnosis.

Computed MRI is a technique allowing to recompute images from different ponderations from T1 and T2 relaxometry acquisitions. This technique directly offers the capability to have T1 and T2 weighted images at the same slice, all the voxels being coregistered, as opposed to conventional sequences.

This could be a real breakthrough for specialists that would save a considerable amount of time when they interpret images.

O.I: What are the main advantages of this technique?

A.V: The most significant advantage is mainly the improvement of the diagnosis. Additional studies are necessary to determine whether computed MRI offers a better distinction between normal tissues and pathologic tissues compared with conventional sequences.

During the acquisition of source images, having a high quality contrast between the tissues may be rather uncertain, when setting T1 and T2.

When we acquire images at the scanner, we take an empiric gamble by setting T1 and T2 hoping the contrast between tissues will be optimum.

However, we can bet that the setting of this parameter is not accurate enough and that, *a posteriori*, it can increase the capability to discriminate and define the pathological tissues, compared with the normal tissues. According to me, this is the main theoretical advantage in Oncology.

O.I: In your opinion, how does the Bayesian method impact the computation of computed images?

A.V: The Bayesian algorithm is a post-processing method of images from a statistical model, allowing the reduction of noise on a generated image.

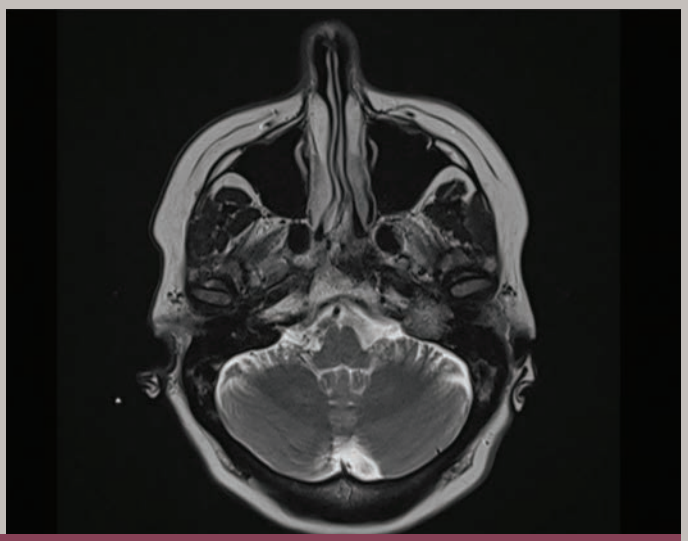
The Bayesian method has a real added value to optimize the acquisitions, time of sequences, and perfusion for example[1]. This is highly useful for the computed MRI since the Bayesian method could help overcoming the drawbacks of computed image processing, such as a loss of overall quality of the final image associated with this technique. Consequently, this process would help to reduce the acquisition time.

This perspective has a positive impact for head & neck radiology since the motion artifacts are numerous in patients, due to the ventilation and the deglutition. So, this technique should be tested and further studies should be made in order to assess its full potential and, eventually, to transfer it to routine clinical practice.

HOW-TO SESSION:
Heterogenity of the left jugular foramen

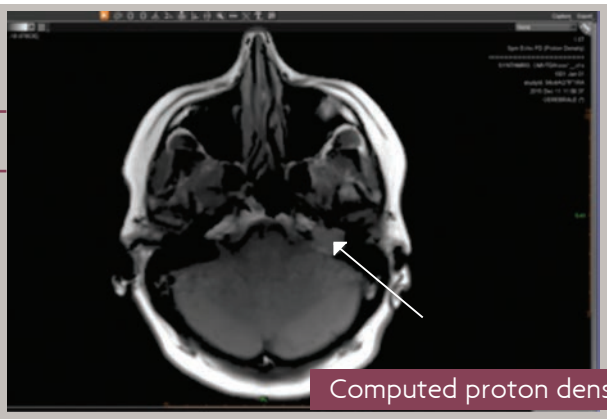
Arthur Varoquaux. MD, PhD, CHU La Timone, Marseille, France

61-year old woman.
Acquisition of T1, T2, diffusion, perfusion and T1 post contrast.

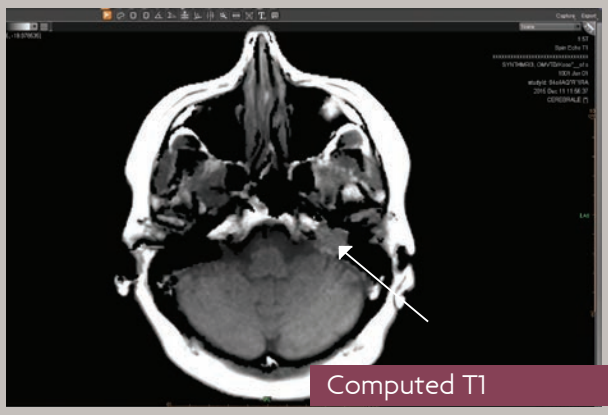


Native T2 shows lesion centred on left jugular foramen involving petrous apex.

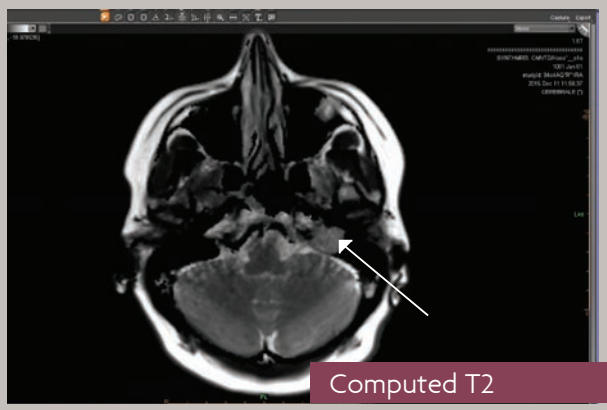
Next to the posterior fossa dura, computed MRI offers the opportunity to raise contrast to noise ratio (SNR) of the lesion, compared to adjacent structures in the most common pulse sequences. This left jugulo paraganglioma was classified FISCH C3. A succinate peak was demonstrated by 1HMR spectroscopy[2]. Final diagnosis of a SDHD related paraganglioma was confirmed with genetic testing.



Computed proton density



Computed T1



Computed T2

References:
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2. Varoquaux A, le Fur Y, Imperiale A, Reyre A, Montava M, Fakhry N, Namer I-J, Moulin G, Pacak K, Guye M, Taïeb D. Magnetic resonance spectroscopy of paragangliomas: new insights into in vivo metabolomics. Endocr Relat Cancer 2015;22:M1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26115958.

The key role of post-processing in cartilage diseases assessment

Garry E. Gold, MD
Professor and Associate Chair for research in the department of Radiology at Stanford University, USA

Garry E. Gold started his career as an electrical engineer and grew up programming the MRI scanners. He conducted research, in addition to his clinical training throughout graduate school and medical school residency and he continued to work at the interface between Engineering and Radiology.

He is interested in methods to detect and characterize early degenerative changes in articular cartilage and other tissues in the joints, with the goal of helping to discover therapies for osteoarthritis.

Garry E. Gold is currently Vice-President for the ISMRM and helds several other societies positions as well as Vice-Chair of the research department of Radiology in Stanford.

Olea Imagein: Do you have connections with scientific communities outside Radiology?

Garry Gold: I have worked with the comity that helped to set the MRI protocol for the osteoarthritis initiative, which included Rheumatology and Orthopedics. I have spoken at the American College of Rheumatology as well as the Osteoarthritis Research Society and at national meetings.

I am a regular attendee and speaker at the Orthopedic Research Society, so, many other societies outside of Radiology, where people need our expertise in MR imaging, as it applies to a musculoskeletal disorder.

O.I: How relevant is the post-processing for cartilage diseases assessment?

G.G: For current clinical cartilage diseases assessment, in reading musculoskeletal MR, we don't typically use post-processing. We are able to see on our conventional images early cartilage damage, such as fibrillation or fissuring and then later damage like partial thickness or full thickness loss. That doesn't require the post-processing tools to detect. But If you want to find the earliest changes in the cartilage and catch the development of the diseases before the tissue has been lost or broken down, you need post-processing. Similarly, if you want to do any quantitation and follow the progression of diseases based on some numerical metrics like thickness in a region, you absolutely need post-processing to do that.

So even the basic quantification we do in the osteoarthritis, where you look at the regional thickness, overtime requires careful post-processing with segmentation and registration. Then, if you go a step beyond that into what I call physiologic imaging of cartilage, you get into techniques such as T2 mapping, T1 rho mapping, and sodium. All of those have very complicated post-processing requirements. But most of these techniques have the highest potential for drug and therapy developments, I believe, because you are detecting the diseases before the tissue is in an irreversible stage.

O.I: Could you please summarize the main aim of T2 and T1 rho mapping?

G.G: If you imagine you are going to treat osteoarthritis, with a focus on the cartilage for the moment, it is hard to believe you could give someone a drug that will magically regrow the cartilage tissue that is there. But what is believable, for me anyway, is that you can give a drug that will activate repair processes in a tissue that is damaged

but still there. We think that the earliest changes in cartilage degeneration involve loss of proteoglycans and glycosaminoglycans and damage to the small fibers of ecologyn network. The loss of proteoglycans can be detected by T1 rho or sodium MRI for example.

The damage can be detected by elevation in T2 relaxation times and T2 map. So, both of those techniques in MR will require post-processing with a large detection of diseases in a very early stage. At that stage, I think that intervention is much more likely to be successful.

We have seen a couple of small studies, there was one paper published in 2005 by Y. Ruth that shows that mild or moderate exercise could actually reverse loss of glycosaminoglycans in the cartilage. There have also been some mostly small abstract studies that have shown some nutritional supplements may have an effect but none of the large studies have demonstrated preventing irreversibility, but we are actually hoping that.

> “We use T2 mapping, T1 rho mapping to track the progression of osteoarthritis.”

The other thing to try, besides drug therapy, is gait retraining, so it turns out you can use optic feedback to teach people to walk differently. This alters the contact stress in different regions of the joints. So, it has some potential to really slow the progression of osteoarthritis and we use T2 mapping, T1 rho mapping to track that.

Another thing people have tried or we have seen recently are shoes with different insoles: the idea is to change the gait.

O.I: What does the Bayesian method bring to T2 and T1 rho mapping?

G.G: One of the interesting things about T2 and T1 rho mapping is, when you study a population, you see significant changes in patients with osteoarthritis compared to normals. But with conventional fitting methods like magnitude exponential decay fittings, there is usually a large degree of variation and a large standard deviation around the fits, particularly the T2 and T1 rho mapping, so in any individual patient, it will be difficult to say what the changes you are seeing mean, because the standard deviations are so large. So anything, such as the Bayesian approach, that improves our ability to fit that data more accurately, is going to help. And I am very excited to try!

O.I: Is cartilage segmentation still a huge challenge for cartilage post-processing?

G.G: That is a huge problem. Right now, it is a big bottle-neck in any research, because the best post-processing method still depends on manual or semi-automated segmentation and it requires training and expertise, it is slow. I want to say that ten years ago in the back of an osteoarthritis magazine, I saw an ad that said “Automated calculated segmentation” and I thought “This is great! Somebody finally solved this!” I looked at the ad and it is basically that you send them the images and they have people segment them for you and send them back to you. That is not what “automated” means. So, by the time we are talking, there is no automated tools for that. People are working on it, and have worked on it for a long time. Automatic segmentation should certainly have better reproducibility than manual or semi-automated and even if it is not strictly as accurate in terms of ground truth accuracy, it would be a huge step forward.

News of the day:
get a good dose of glucosamine
by eating shrimp-shells!

Hyaluronic acid protection of cartilage

Xavier Alomar, MD, Clinica Creu Blanca, Barcelona, Spain

How-to session

Patient history

A 42-year old marathon man, healthy and asymptomatic, who runs a marathon every 15-30 days. The patient underwent a MRI exam of both knees one month before a marathon and another after the injection of hyaluronic acid (4ml high density) in the articular left knee and performed a marathon of 45 km. This preliminary study intends to assess the protective effect of the hyaluronic acid injection in the patellar cartilage during a long and loading effort. The MRI protocol includes axial spin-echo T2 mapping sequence (TE=24.8, 37, 49, 62, 74.4, 90 ms, Slice thickness=3mm, TR= 2000 ms, FOV=14x14, Matrix=320x192).

Post-processing and analysis

MRI manufacturer post-processing was first performed study by study, but it was difficult to assess the value variations in the cartilage, due to signal intensity changes in this area. Post-processing was then performed on a dedicated workstation (OleaSphere®, Olea Medical®, La Ciotat, France) which allows to assess quantitative measurements of T2 map computed using a Bayesian approach and to visualize the T2 maps from two different dates (before and after running). T2 mapping is intended to measure the transverse relaxation from a spin-echo sequence, and T2 parameter being very sensitive to noise and sampling, the Bayesian probability theory is used to estimate this parameter.

Automatic co-registration of both exams was applied based on the femur localization. Since the patella moved between the two exams, a manual adjustment was done to match the cartilage zone.

Subtraction maps were computed to assess value changes for both knees. Quantitative values allow to confirm and quantify post-effort lesion.

Image findings

A dissection of medial patellar cartilage of the left knee is observable, water was trapped in the crack and the T2 maps values increase. The subtraction map shows no significant changes on T2 values in

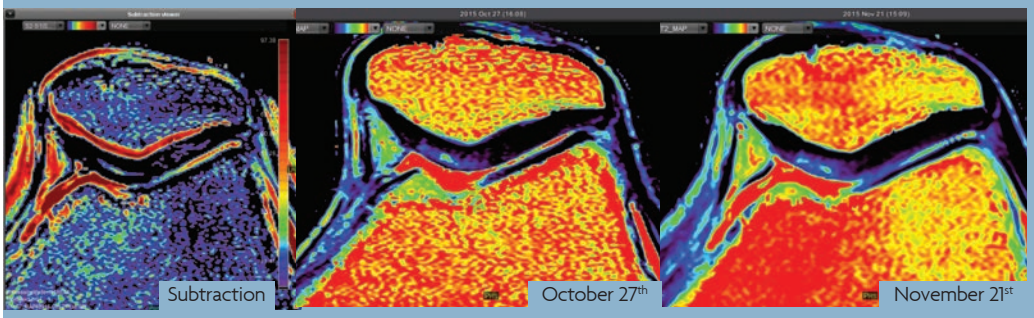

Figure 1: left knee

- October 27th: T2 map before running

- November 21st: T2 map after hyaluronic acid injection and 45 km running

- Left map: subtraction map of these two dates.

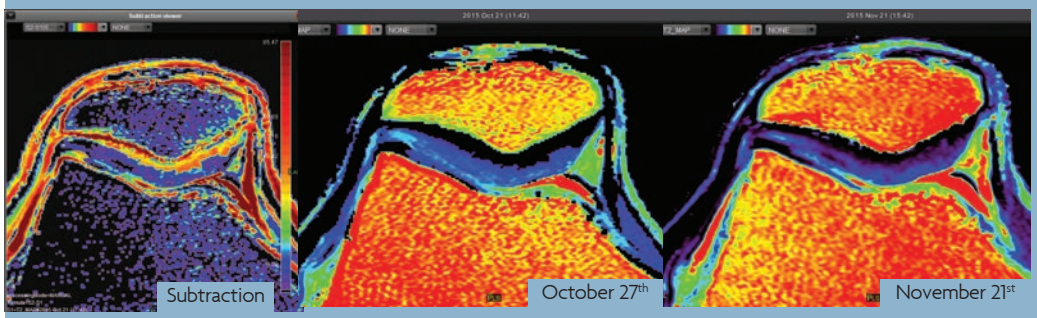

Figure 2: right knee

- October 27th: T2 map before running

- November 21st: T2 map after 45 km running

- Left map: subtraction map of these two dates.

the lateral patellar cartilage and minimal changes in the crack.The right knee did not undergo injection, the subtraction map clearly shows higher T2 values than those of the left knee that suggests an increase water proportion in the matrix.

The comparison of both subtraction maps from T2 maps before and after running confirms the separate analysis done previously. Focal regions of interest (ROIs) containing thirty five pixels (7mm2) were drawn in the central patellar cartilage of the left (ROI1) and right (ROI2) knees and a significant difference was remarkable (ROI1=2.23; ROI2=7.38) (Figure 3).

In addition, free hand ROIs surrounding the cartilage were drawn in the left (ROI3) and right (ROI4) knees and they also show a major increase in values of the subtraction map of the right knee, compared to those of the left knee (ROI3 =1.95; ROI4=5.57) (Figure 4).

Discussion

The cartilage in joint areas helps to absorb the strengths and share the loads supported by the joints. These structures supporting repeated loads for many years can be broken, but their degeneration always comes before. The consistency of these structures changes but without any modification of their morphology or their size.

T2 mapping sequences are commonly used to quantify the grade of the edema and the alteration of connective tissues, part of the cartilages in the human body. Therefore, the degree of chondral degeneration can be measured before its breakage.

In order to assess the efficiency of a treatment intended to repair or protect the articular cartilage, it is essential to undertake a longitudinal study, using images that quantify the chondral damage prior and post-treatment. Measuring the signal variations in the cartilage using ROIs is very complicated. That is why subtracting images from two different exams is very useful to assess the changes in the cartilage composition. Such technique helps to rapidly, simply and objectively quantify the effects of the different chondral therapies. Figures and statistical works allow to demonstrate their efficiency.

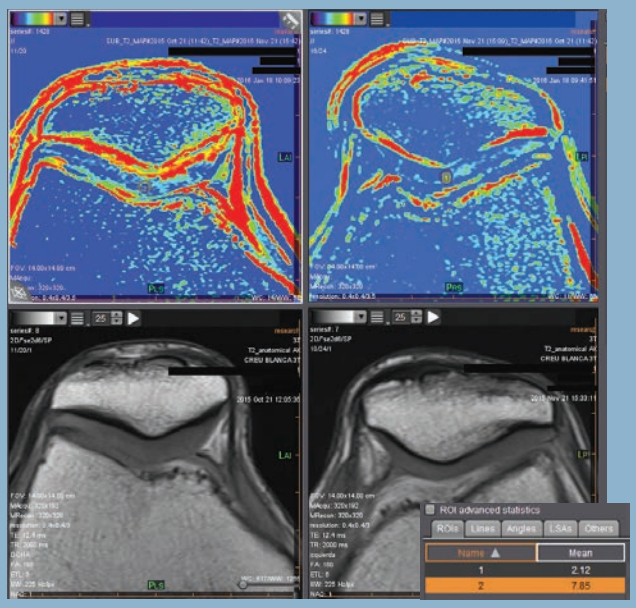

Figure 3: subtraction maps from T2 maps before and after running of right and left knees with focal ROIs in the central patellar cartilage; axial T2 series of right and left knees after running.

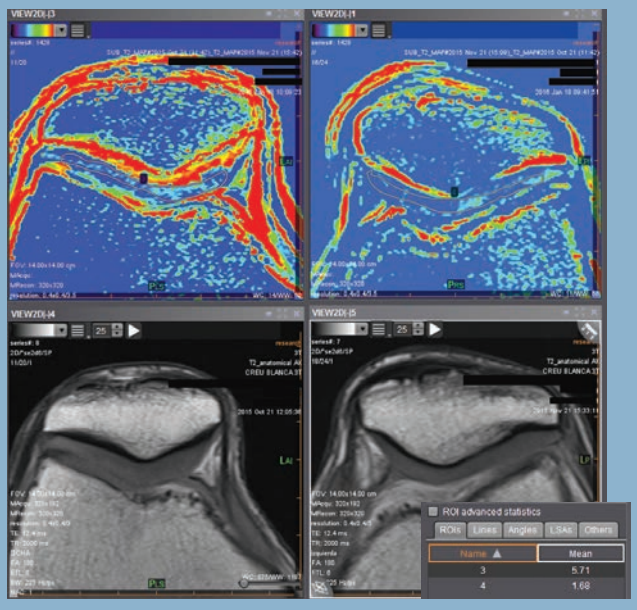

Figure 4: subtraction maps from T2 maps before and after running of right and left knees with free hand ROIs surrounding the cartilage; axial T2 series of right and left knees after running.

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Bruges, Belgium

March 30 - April 1
Société Française de Neuroradiologie (**SFNR**)
Paris, France

April 15-16
Clinical **fMRI & DTI** Course
Basel, Switzerland

April 14-17
75th Annual Meeting of the Japan Radiological Society (**JRS**)
Yokohama, Japan

May 7-13
International Society for Magnetic Resonance in Medicine (**ISMRM**)
Singapore, Republic of Singapore

May 19-21
Swiss Congress of Radiology (**SCR**)
Davos, Switzerland

May 21
Knee imaging: essential guidelines in less than 20 lessons (French language)
Bordeaux, France

May 23-26
American Society of Neuroradiology (**ASNR**)
Washington, USA

June 11
13th Meeting of **Hepato-Biliary Radiology**
Paris, France

June 17
Prostate hands-on-session
managed by François Cornud, MD
(French language)
Cochin Hospital, Paris, France

August 11-14
Eastern Neuroradiological Society 27th Annual Meeting (**ENRS**)
Quebec, Canada

September 7-9
The International Skeletal Tradeshow
Paris, France

September 7-11
American Society of Head & Neck (**ASHNR**)
Washington, USA

September 22-24
European Society of Head & Neck Radiology (**ESHNR**)
Leiden, the Netherlands

October 5-8
Deutschen Gesellschaft für Neuroradiologie (**DGNR**)
Cologne, Germany

October 14-17
Journées Françaises de Radiologie (**JFR**)
Paris, France

October 21
ESMRMB course on
Prostate MR Image Analysis
Cochin Hospital, Paris, France

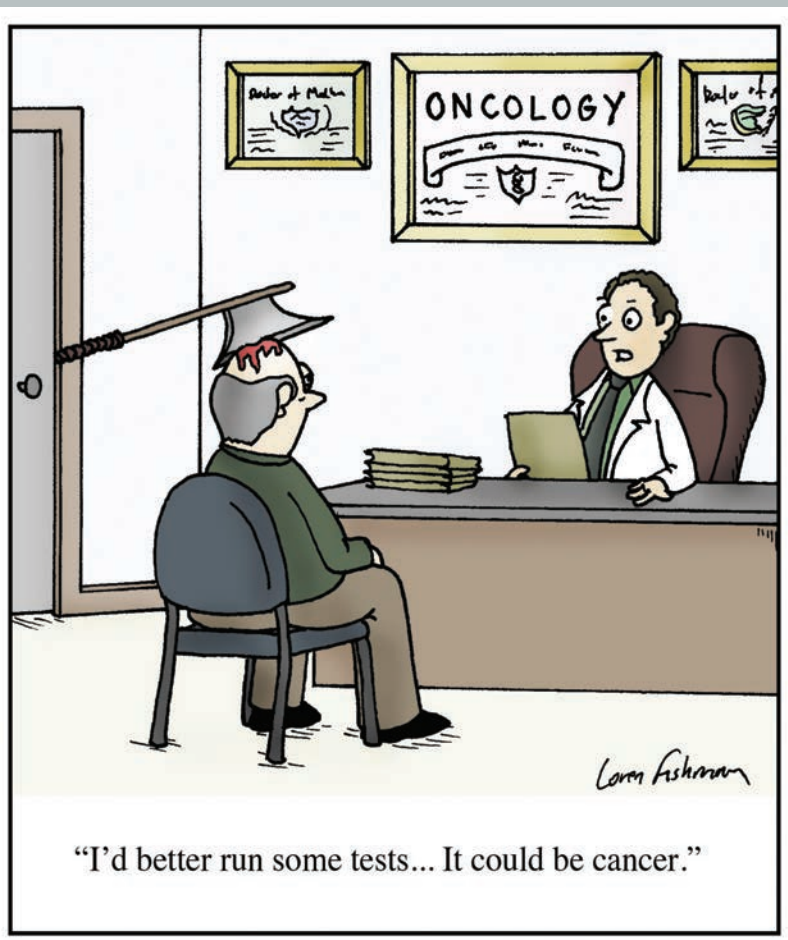
November 27 - December 2
Radiological Society of North America (**RSNA**)
Chicago, USA

December 16
Prostate hands-on-session
managed by François Cornud, MD
(French language)
Paris, France

Word scramble

F	P	Y	A	A	E	L	O	J	V	F	J	Q	Z	V
Z	N	N	K	L	O	V	X	M	F	D	N	R	M	S
N	O	I	T	U	L	O	V	N	O	C	E	D	B	J
Y	G	O	L	O	C	N	O	D	X	K	L	Q	Y	S
D	J	T	J	N	V	Y	X	B	O	R	C	M	F	K
O	P	H	J	X	O	C	N	L	H	S	I	F	V	R
I	A	N	T	E	H	I	I	O	Z	L	E	Z	W	O
S	S	H	O	G	D	N	S	T	L	N	P	L	I	B
Z	A	C	W	I	E	T	D	E	E	W	X	V	J	U
T	Q	N	A	I	S	E	Y	A	B	H	M	Z	Z	S
M	T	X	U	R	J	U	N	L	N	R	T	X	J	T
V	I	W	V	T	H	X	F	I	R	S	W	N	Y	A
W	R	R	H	Q	T	E	K	R	A	W	R	X	Y	W
W	K	E	U	T	I	G	D	Z	E	R	P	R	V	S
E	N	I	L	F	F	O	K	S	M	P	B	R	W	E

- BAYESIAN
- BRAIN
- DECONVOLUTION
- DOSE
- NOISE
- OFFLINE
- OLEA
- ONCOLOGY
- PERFUSION
- ROBUST
- COMPUTED



"I'd better run some tests... It could be cancer."

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