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**Improving the quantification of Contrast Enhanced Ultrasound  
using a Bayesian Approach**

Gaia Rizzo, Matteo Tonietto, Marco Castellaro, Bernd Raffeiner, Alessandro Coran, Ugo Fiocco,   
Roberto Stramare and Enrico Grisan

*Abstract*— Contrast Enhanced Ultrasound (CEUS) is a sensitive imaging technique to assess tissue vascularity, that can be useful in the quantification of different perfusion patterns. This can particularly important in the early detection and staging of arthritis. In a recent study we have shown that a Gamma-variate can accurately quantify synovial perfusion and it is flexible enough to describe many heterogeneous patterns. Moreover, we have shown that through a pixel by pixel analysis, the quantitative information gathered characterizes more effectively the perfusion. However, the SNR ratio of the data and the nonlinearity of the model makes the parameter estimation difficult. Using classical non-linear-least-squares (NLLS) approach the number of unreliable estimates (those with an asymptotic coefficient of variation greater than a user-defined threshold) is significant, thus affecting the overall description of the perfusion kinetics and of its heterogeneity.

In this work we propose to solve the parameter estimation at the pixel level within a Bayesian framework using Variational Bayes (VB), and an automatic and data-driven prior initialization.

When evaluating the pixels for which both VB and NLLS provided reliable estimates, we demonstrated that the parameter values provided by the two methods are well correlated (Pearson’s correlation between 0.85 and 0.99). Moreover, the mean number of unreliable pixels drastically reduces from 54% (NLLS) to 26% (VB), without increasing the computational time (0.05 s/pixel for NLLS and 0.07 s/pixel for VB). When considering the efficiency of the algorithms as computational time per reliable estimate, VB outperforms NLLS (0.11 versus 0.25 seconds per reliable estimate respectively).

Description of purpose

Contrast-enhanced Ultrasound (CEUS) is an imaging technique that uses microbubbles as contrast agent to visualize and assess tissue vascularization and perfusion. In particular, CEUS has been widely used in the study of the arthritis disease to non-invasively assess synovial neo-vascularization and local perfusion variations for early detection and grading of the pathology [1–5]. CEUS data are generally quantified at the region of interest (ROI) level, i.e. analyzing the time activity curve (TAC) obtained by averaging all pixel TACs within a specific user-defined region. In a previous work, we have tackled the CEUS quantification problem at the pixel level and we have demonstrated that pixel-wise quantification allows such an effective characterization of different perfusion patterns that they can be then used to discriminate between arthritis subtypes [8]. Moreover, we showed that a physiologically motivated perfusion curve, such as the Gamma-variate model, can accurately quantify synovial perfusion and it is more flexible than a mono-exponential or logarithmic model (generally employed for CEUS kinetic description) to describe many heterogeneous patterns [6]. However, the choice of the pixel-wise estimator of the perfusion kinetic model to perform parametric mapping is crucial to obtain reliable estimates of perfusion parameters at the pixel level. The use of a non-linear estimator, the standard method for ROI-based quantification, leads to a high number of unreliable estimates (between 27% and 80% of pixels) when applied to pixel-level, thus losing an important part of the physiological information in the synovia [6]. A valid alternative for pixel-wise quantification is represented by Bayesian methods, which incorporate prior information on the tissue kinetic and are widely used in other imaging techniques but seldom applied to CEUS data.

In the current work, our aim is to present a more robust and efficient estimation algorithm for the derivation of the pixel-wise estimates of perfusion information. In particular, we applied the Gamma model to CEUS data, but we solved it at pixel level within a Bayesian framework using Variational Bayesian estimator, already applied to MR [7] and positron emission tomography (PET) data [8]. Prior information for the pixels were generated automatically from the image data using the estimates obtained by applying the model to a set of regional time courses solved with a nonlinear estimator in a hierarchical, user-independent, approach [8,9].

# Methods

The model for the vector of CEUS measurements (i.e. the tracer concentration in a pixel over time) is:

where is the model with the parameter vector (which represents all the individual rate constants of the model) and is the measurement error. For the sake of clarity, the dependency from the time has been omitted in the following passages. We assumed the measurement error to be additive, independent and identically distributed with a normal density function with zero mean and unknown variance, i.e. .

The Gamma-variate model equation is:

with the parameters **[]** where is a scaling factor, and determine the bolus shape (raise and washout of the dye from the vascular bed) and is the contrast arrival time. The amplitude of the Gamma-variate function is normalized for , the maximum value of (i.e. the peak value), in order to have varying between 0 and 1. From the gamma-variate estimated microparameters it is possible to derive a set of additional macroparameters, such as the peak value , the time of peak , the raise time and the washout time (computed as the time needed to raise the intensity from the baseline value to half maximum and from the peak value to half maximum respectively), the mean transit time , the blood flow index and the blood volume index , for a total of 11 parameters for each curve.

## Non-Linear Least Squares estimation

The classical parameter estimation is performed by minimizing, for each pixel, the residual function between the parametric model and the corresponding intensity data at each time point :

## Variational Bayes estimation

In the Bayesian framework, we want to estimate the posterior distribution of the parameters given the data and the model , where is the vector of the parameters of a chosen model from a set of measured data . In real applications, the numerical integrations needed for the direct computation of the posterior are usually intractable. Briefly, VB uses an analytical approximation to describe the true posterior, therefore shifting the problem to the minimization of the distance between the approximation and the actual posterior distribution of the parameters, usually measured via the Kullback-Leibler divergence:

where F is the Free Energy which is defined as:

For maximizing F, we applied a mean field approximation of , as previously done in [7,8]: it consists in collecting the vector of parameters into two separate groups, one for the model parameters () and one for the single noise parameter (). Each parameter has its own approximate posterior distribution ( and ), assumed independent (i.e. ), with the unknown variance of the measurement error. We defined the prior distributions as a multivariate Gaussian distribution for the vector of model parameters and a Gamma distribution for the variance scaling factor , and in order to simplify the computations we used prior conjugated with the likelihood, i.e. with the same parametric form of the posterior making the VB update become a process of updating the posterior hyper-parameters.

The data-driven priors were obtained from the parameters estimated on 6 regions of interest within the synovia, identified by functional clustering (k-means partitioning method [10], Euclidean distance, 6 clusters) to detect the main kinetic behaviors of CEUS data as previously presented in [10,11], and setting the variance of the priors as 50% of the mean priors value:

## Dataset

Data from previously reported studies [6] of 115 subjects affected by arthritis were used in the current study. The criteria for subject inclusion and the procedure for CEUS exams are described in detail in [6].

All patients showed signs of inflammatory finger joint involvement: the joint with the highest disease activity was chosen for CEUS examination. All patients gave their informed consent to the examination, to the intravenous administration of the contrast agent and to the participation of the study that was approved by the local institutional ethical committee. Each subject underwent a 2-min CEUS study with a 7-MHz transducer US device (MyLab25, EsaOte) equipped with Contrast tuned Imaging (CnTI; Esaote), according to the procedure described in [12]. Gray-scale US (anatomical B-mode image) were acquired to define the boundaries of the synovial tissue (semi-automatically outlined by the radiologists as in [13]). CEUS images were motion corrected and coregistered to the anatomical image, normalized, and extracted the pixels within the synovial boundaries showing a significant enhancement [6]. We excluded sixteen subjects with no active pixels from the analysis. Our final dataset comprised 99 subjects (53 RA, 21 dpPSA, 9 RA-like PSA, 8 uSPA and 8 CTD).

# RESULTS

For each pixel, the set of parameter describing has been estimated using either the NLLS or VB approach, and the asymptotic coefficient of variation of the estimates has been computed. We set a threshold of 200% as the upper limit to deem any parameter as estimated reliably. The number of pixels estimate that have been discarded based on this threshold are reported on Tab. 1

|  |  |  |
| --- | --- | --- |
| Unreliable estimate % | **NLLS** | **VB** |
| Mean |  |  |
| Std Dev |  |  |
| 25th percentile |  |  |
| 75th percentile |  |  |

Tab. 1 Percentage of unreliable estimate for each patient provided by the two methods

In order to evaluate if the VB and NLLS provide the same estimate on the pixel data where both methods provide reliable estimate we evaluate the correlation between the microparameters **[]** and the derived parameters , , , and . The correlations are reported on Tab. 2. Moreover, the computational time required by the full VB framework (clustering, priors estimation, pixel by pixel parameter estimation) is only slightly higher than NLLS approach (0.07 seconds per pixel versus 0.05 seconds per pixel). However, when considering the amount of estimates that have to be discarded since they are unreliable, by considering the computational time required per reliable estimate, the VB approach halves the time of NLLS (0.11 seconds per reliable estimate versus 0.25 seconds per reliable estimate)

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  | MTT | BFI | BVI |
| r | 0.99 | 0.82 | 0.85 | 0.85 | 0.99 | 0.99 | 0.94 | 0.94 | 0.95 | 0.97 | 0.98 |

Tab. 2 Pearson correlation between the NLLS and the VB parameter estimates

# New or breakthrough work to be presented

# A Bayesian approach has been proposed for the first time on contrast-enhanced ultrasound data, and evaluated against the classical non-linear least squares method. Automatic setting and patient-specific priors are derived from the CEUS data.

# Conclusions

The proposed Bayesian technique for estimating perfusion parameters from contrast-enhanced ultrasound data proved to be reliable with respect to the gold-standard non-linear least squares with respect to the agreement of the estimated parameter. Additionally, it proved to be more robust, providing a larger amount of reliable estimate in the same amount of time required by a NLLS analysis.

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Figure 1 Representative results of parametric mapping obtained with NLLS (left panels) and VB (right panels) on two different patients. The arrows show the region where the NLLS failed the most with respect to VB.

Statement of originality

This study has not been submitted, published, or presented elsewhere.

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1. G.T., M.T., M.C., and E.G. authors are with the Department of Information Engineering, University of Padova, Padova, Italy.

   B.R. and U.F. and R.S. authors are with the Department of Medicine, University of Padova, Padova, Italy

   A.C. is with the IRCCS Veneto Institute of Oncology, Padova, Italy [↑](#footnote-ref-1)