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Local classification of microvascular function based on contrast-enhanced ultrasound data: a feasibility study

M. Doury[1*], A. Dizeux[1], G. Barrois[1], D. Le Guillou-Buffello[1], A. Coron[1], L. Bridal[1], A. De Cesare[1], F. Frouin[1,2]

[1] Sorbonne Universités, UPMC Univ Paris 06, Inserm, CNRS, Laboratoire d'Imagerie Biomédicale, Paris, France.
[2] Inserm, CEA, Université Paris Sud, CNRS, Laboratoire IMIV, CEA-I2BM-SHFJ, Orsay, France.
[*] Corresponding author, maxime.doury@lib.upmc.fr

Abstract *- **Dynamic contrast-enhanced ultrasound can detect microvascular flow changes during tumor development and antiangiogenic therapy. However, the standard method for microvascular flow estimation in tumors is global and can lead to bias in flow estimations in heterogeneous tumors. A new method to segment tumors according to their vascularization was investigated. In addition, parameter normalization with respect to a highly vascularized region of reference was proposed to overcome inter-exam variability in parameters. Results demonstrate the potential to locally classify tumoral tissue using parameters that describes the arrival of an ultrasound contrast agent in the tumor.***

Index Terms *- **Image Processing, Ultrasound, Contrast, Microvascularization, Tumor.***

I. INTRODUCTION

Ultrasound (US) is a real-time, non-invasive, and cost-effective imaging modality, making it a key tool for cancer diagnosis, and treatment monitoring. In particular, it gives access to structural information, using B-Mode, as well as functional information, using dynamic contrast-enhanced US (DCE-US).

DCE-US techniques have demonstrated their potential for early detection of microvascular flow changes during tumor development and antiangiogenic therapy. The current standard technique to evaluate microvascular flow in tumors consists of delineating the entire tumor to estimate the global flow throughout the cross-sectional area of the tumor in the imaging plane. This method masks important information on the spatial distribution of the microvascular flow throughout the tumor and can lead to underestimation of tumor "viability", e.g. in the case of a highly vascularized corona surrounding a necrotic core.

A new method is investigated to more reliably segment DCE-US data into regions with high concentrations of microvessels and/or strong flow rates from more functionalized regions. In this work we also demonstrate that inter-exam physiological variability in a mouse can influence measurements, and propose a normalization technique to provide more robust comparisons of the tumor vascularization during its development.

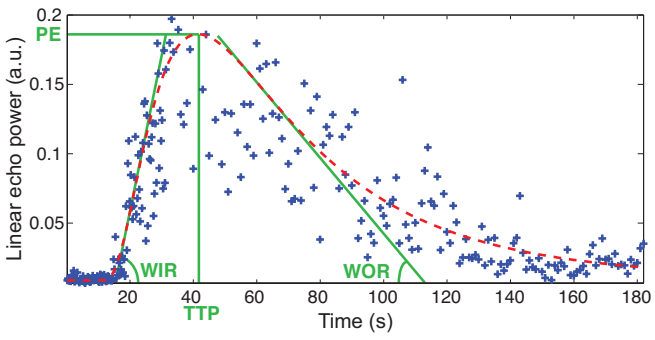

Figure 1: Example of median-filtered echo-power data (blue crosses), the fitted lognormal model (dashed red line), and some of the associated perfusion parameters (i.e. TTP, PE, WIR, WOR).

II. MATERIALS AND METHODS

Data analysis was performed on 17 B-Mode and DCE-US sequences acquired using a 15L8W transducer and a Sequoia 512 US system (Acuson, Siemens, Mountain View, USA) in an ectopic murine model for Lewis Lung Carcinoma [1]. Contrast imaging was performed after controlled injection of a 50 μL bolus of SonoVue (Bracco Suisse SA, Geneva, Switzerland) contrast agent. Imaging was repeated at regular time points at the level of the largest cross-section of each tumor to follow development from days 3 to 15 after tumor implantation. DCE-US imaging was performed with fixed mechanical index (0.1), dynamic range (80 dB), and TGC settings. Motion was negligible for the selected sequences.

A spatially median-filtered echo-power vs. time curve was obtained for each 3×3 analysis block, i.e. 324×324 μm, in each $2D + t$ data sequence. A lognormal parametric flow model was fitted to the resulting curve using a multiplicative noise model [2]. Conventional perfusion parameters were then derived yielding six perfusion parametric maps: time to peak (TTP), mean transit time (MTT), area under the curve (AUC), peak enhancement (PE), wash-in rate (WIR), and wash-out rate (WOR). Selected perfusion parameters can be visualized in Fig. 1 and 2.

Regions of analysis were manually selected on the B-Mode

image: 1) to outline the tumor and 2) to select a highly vascularized tissue outside the region of the tumor. Analysis blocks in parameter maps were classified into three classes, using a standard, unsupervised algorithm: K-Means clustering [3] using $\mathcal{L}^1$ distance.

Classification was performed twice for each longitudinal set of parameter maps, with and without $\mathcal{N}^+$ normalization, where $\mathcal{N}^+$ is the normalization with respect to the median value of the parameter in the highly vascularized reference region: $\mathcal{P}^* = \mathcal{P}/\mathcal{P}_0$, where $\mathcal{P}$ and $\mathcal{P}^*$ are respectively the unnormalized and normalized parameter values, and $\mathcal{P}_0$ the median value of $\mathcal{P}$ in the reference region.

III. RESULTS

Median and quartiles parameter values within the highly vascularized region are shown in Table 1. The quantiles operators were used to limit the effect of aberrant values. Some parameters, e.g. AUC and MTT, globally vary between exams, reflecting physiological changes.

Fig. 2 shows some parametric maps for one mouse at day 11 and 15. The tumor and highly vascularized reference regions are also displayed in this figure. The superficial and central zone of the tumor presents lower values of AUC, than the more peripheral zones of the tumor, while presenting higher values of MTT.

Days	AUC (a.u.)	MTT (s)
D3	111 [82.0 – 177]	22.3 [21.3 – 23.5]
D5	284 [242 – 344]	26.1 [22.9 – 29.3]
D9	279 [191 – 383]	22.2 [20.5 – 23.6]
D11	196 [169 – 232]	20.0 [17.2 – 26.8]
D15	287 [227 – 328]	22.3 [21.0 – 23.8]

Table 1: Median and quartiles parameters values (AUC and MTT) inside a highly vascularized reference region of a mouse.

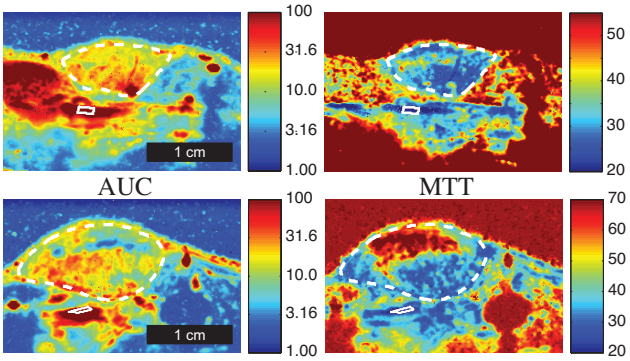

Figure 2: Unnormalized parametric maps (AUC, MTT) of an ectopic tumor implanted in a mouse. Images were acquired 11 (top row) and 15 days (bottom row) after implantation. White curves represent the manually selected tumoral (dashed line) and highly vascularized (plain line) regions.

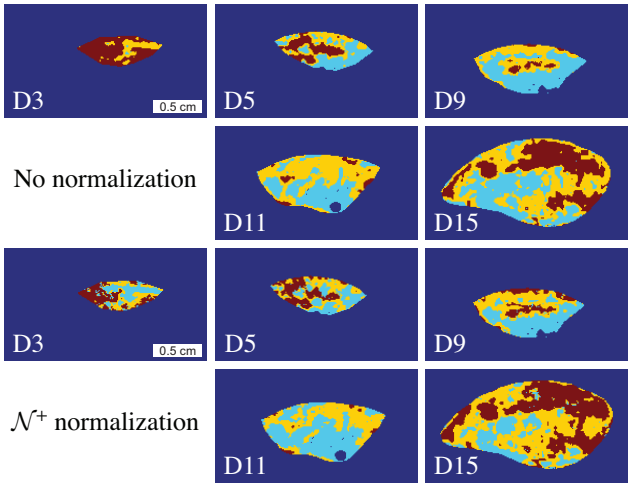

Figure 3: Classification results for one mouse, with and without applying $\mathcal{N}^+$ normalization. Blue, yellow and red classes represent high, intermediate, and low values of AUC, respectively.

Fig. 3 presents classification results of parameter $\log(\text{AUC})$ and $\log(\text{AUC}^*)$. Analysis of these results reveals an increased homogeneity of the classification regions when $\mathcal{N}^+$ normalization is applied. This especially shows at D3 and D11, days for which AUC is the lowest.

IV. DISCUSSION-CONCLUSION

The AUC is directly linked to the amount of contrast agent flowing through the region of analysis. The use of $\mathcal{N}^+$ normalization on AUC led to more continuous classification regions and may potentially reduce inter-exam variability of assessments. MTT is a parameter reflecting a kinetic feature of blood flow in the analysis region. Appropriate normalization will be considered in a future work. Visual analysis of parametric maps reveals partial correlation between maps within the tumor. A finer selection of parameters used for classification could improve system performances. K-Means being an unsupervised classification method, a supervised algorithm that uses immunohistochemistry-stained slides as ground truth data could make classification more robust and accurate.
This feasibility study showed the potential to locally classify zones of the tumor with respect to parameters describing the relative concentrations and arrival times of ultrasound contrast agent. With appropriate validation based on reference measurements of tumor vascular density and microvascular architecture, such classification may provide more robust evaluation of the functional flow in tumors.

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