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Impact of Recirculation in Dynamic Contrast-Enhanced Ultrasound: A Simulation Study

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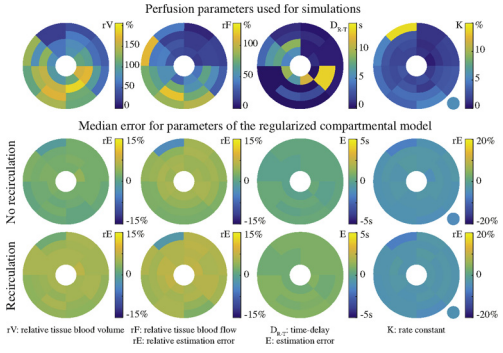
Graphical abstract



Abstract

Objectives: The impact of recirculation on the quantification of perfusion is often neglected. It can however introduce a bias or some variability in the estimation of perfusion parameters and thus hamper comparison between exams.

Methods: Time-intensity curves (TICs) were simulated using a one-compartment model fed by an arterial input function (AIF). A simple model was developed to simulate recirculation in the AIF. Using AIF with and without recirculation, and sets of regional perfusion parameters, TICs corresponding to different tissue regions were simulated by convolution of the AIFs with the transfer function associated to each region. Ten noise levels and 150 simulations for each noise level were then computed. For each simulated study, six quantification methods based on either Log-Normal modeling or a compartmental modeling using a reference tissue were tested. Variations of the conventional Log-Normal model were also investigated, using parameters estimated in the reference tissue for normalization purposes, and fitting only the first phase of the TIC to avoid recirculation.

Results: The impact of recirculation varies according to the quantification method. Restricting parameter estimation to the first samples of the TICs, before recirculation occurs, appears to be the worst strategy. Errors are largely minimized when using a reference tissue to establish relative parameters. The most robust approach is the compartmental modeling based on a reference tissue and applied to multiple regions with a regularization constraint.

Conclusion: This simulation study demonstrates the influence of recirculation on the estimation of perfusion parameters. To reduce the impact of this unavoidable effect, the quantification method based on compartmental modeling and using a reference tissue appears to be the most reliable strategy.

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1. Introduction

With the advent of contrast agents, perfusion imaging has been developed for different medical imaging modalities, including PET, CT, MRI, and more recently ultrasound. Perfusion parameters including regional tissue blood volume and tissue blood flow are functional indices which can help in the diagnosis of some vascular abnormalities, such as ischemia. Vascular modification in tumors is also a key application of perfusion imaging and can be used in order to assess tumor diagnosis or tumor monitoring [1].

A widely used approach to estimate perfusion parameters relies on bolus injections of contrast agent and dynamic recording of frames. However the quantification of signal and the estimation of perfusion parameters through mathematical modeling remains a hard task and has generated a lot of research work [2]. An accurate and robust estimation of perfusion parameters is of course crucial to compare perfusion imaging exams meaningfully. This is primordial in order to allow inter-subject exams or to perform monitoring. Among the different mathematical models that have been proposed in contrast-enhanced ultrasound (CEUS) studies, little attention has been devoted to compartmental modeling, despite its wide use in PET or MRI studies. Indeed, explicit modeling using for instance a Log-Normal function is often recommended to analyze dynamic data [1,3]. Of course different reasons can explain this restricted use of the compartmental approach; among them the difficulty in estimating a correct arterial input function in dynamic ultrasound images can be cited. To get rid of this difficulty which occurs also while using other imaging techniques, some authors in PET imaging and more recently in MRI have proposed to use a reference tissue in order to define relative perfusion parameters [4,5], defined as the ratio between the perfusion parameters in the tissue of interest and the perfusion parameters defined in the reference tissue. Our group has recently shown the practical interest of this approach in a test–retest protocol applied to a murine tumor model [6,7].

As no absolute gold-standard exists for preclinical or clinical studies, simulations can be used to assess the performance of different models and compare them. Of course, as it is quite complex to reproduce *in silico* the complexity of *in vivo*, the extrapolation of simulations to real cases should be done very carefully. However they can be used to focus on one specific trait and to quantify its impact. In the present study, the studied trait was recirculation, since this process is often overlooked when quantifying CEUS exams. This is especially true in small animals, where recirculation occurs quickly and can overlap with the first pass of the bolus of micro-bubbles in tissues, affecting the time-intensity curves (TICs) used for quantification.

For the present study, a one-compartmental model was assumed to be representative of the underlying physiology that is observable at a regional scale. The simulation was based on measurements coming from a preclinical CEUS study involving male mice from the Balb/C line observed 24 days after the implantation of CT-26 colon cancer cells. For this preclinical model, spatial heterogeneity of the vascular network was systematically observed. Indeed, at this time of tumor development, a necrotic core was present. Furthermore regional variations of tumor blood flow, tumor blood volume and contrast arrival time were noticed according to the distance between the different tumor sub-regions and the necrotic core and their relative position to the main feeding arteries. Angular and radial divisions of the non-necrotic tumor area were thus proposed. A number of sub-regions of 32 was chosen as a good compromise in order to get large enough regions to keep the noise low while being able to assess the local heterogeneity of the tumor. The values that were chosen for the parameters in the simulation (tissue blood flow, tissue blood volume, and time-delays) correspond to the values that have been estimated for one specific mouse [7].

In addition to recirculation, the impact of signal to noise ratio was studied. For the modeling approach, two versions of the Log-Normal model (absolute and relative), and two versions of the relative one-compartment model (one based on a single region, one taking advantage from the existence of multiple regions) were considered. In addition, in order to limit the impact of recirculation while estimating perfusion parameters with the Log-Normal model, a simple and popular strategy was tested which consists in using the first samples of TICs, i.e. samples acquired before recirculation occurs [8]. These six perfusion quantification methods were fitted to simulated TICs to study the precision and the accuracy of the estimated perfusion parameters.

2. Theory

2.1. One-compartment vascular model

Consider N vascularized tissue regions T_i, $i = 1, .., N$ in a spatial domain, each region being an homogeneous compartment fed by the same arterial input function (AIF), C_A. This mono-compartmental hypothesis is realistic since the distribution of micro-bubbles is restricted to the vascular space [9]. Each tissue TIC, C_{T_i}, is characterized by a tissue blood volume V_i, and a tissue blood flow F_i. Since introducing a time-delay parameter in this model was shown to improve the quality of fit in tumor tissues [7], a parameter D_i reflecting the transit time of the contrast agent from the feeding artery to the tissue was also considered. The mathematical relationship between the tissue TIC and the TIC in its feeding artery is given by equation (1):

$$C_{T_i} = C_A * h_{F_i,V_i,D_i} \tag{1}$$

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