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Short Paper

Recent Advances in MRI and Ultrasound Perfusion Imaging

R. Jiřík[1]

[1] Institute of Scientific Instruments of the Czech Academy of Sciences, Czech Rep.

Abstract

Perfusion imaging is an important diagnostic tool used mostly in oncology, neurology and cardiology, to assess the perfusion status of the tissue on a capillary level, e.g. assessment of angiogenesis, ischemic regions and inflammation. This contribution is a review of recent advances in dynamic contrast-enhanced magnetic-resonance and ultrasound imaging.

Categories and Subject Descriptors (according to ACM CCS): I.4.m [Image Processing and Computer Vision]: Miscellaneous—

1. Introduction

In dynamic contrast-enhanced magnetic-resonance and ultrasound imaging (DCE-MRI and DCE-US), contrast-agent concentration time curves of tissue regions of interest (ROIs) are derived from acquired image sequences for each tissue region of interest. These tissue curves are then approximated by a pharmacokinetic model parametrized by perfusion parameters, such as blood flow, blood volume, vessel permeability-surface area product, and extravascular-extracellular space volume. Depending on the choice of the tissue ROI, the perfusion parameters are estimated for larger homogeneous tissue ROIs or pixel-by-pixel, resulting in perfusion-parameter maps. Although the DCE-MRI and DCE-US methods are known for several decades, they are still mostly considered as experimental research-state methods due to their limited reliability. This contribution is focused on recent advances in DCE-MRI and DCE-US.

2. DCE-MRI

2.1. Pharmacokinetic Model

In DCE-MRI, the pharmacokinetic model of a tissue concentration curve is a convolution of the arterial input function (AIF) and the impulse residue function (IRF). AIF is the contrast agent concentration in the arterial input of the tissue ROI. IRF is a fraction of the contrast agent remaining in the analyzed tissue ROI at time t after an instantaneous contrast-agent bolus application into the tissue ROI (i.e. the Dirac delta function as the AIF).

The most widely used IRF models are the Tofts and extended Tofts models [SB12]. The estimated perfusion parameters included in these models are the forward transfer constant between blood plasma and the extravascular extracellular (interstitial) space, K^{trans}, the rate constant of the efflux from the extravascular extracellular space to blood, k_{ep}, and v_e (and blood plasma flow, v_p, in the case of the extended Tofts model).

To estimate a more complete perfusion-parameter set, including blood plasma flow, F_p, and vessel permeability-surface area product, PS, advanced IRF models [SB12] need to be applied, such as the two-compartment exchange model (2CXM) [BKL*04], the tissue homogeneity model (TH) [JW66], the adiabatic approximation to the tissue homogeneity model (ATH) [SLL98], the distributed-capillary adiabatic tissue homogeneity model (DCATH) [KZD*01], or the Gamma Capillary Transit Time (GCTT) model [Sch12].

However, the parameter estimation of these advanced IRF models requires a high signal-to-noise ratio (SNR) in order not to be ill-conditioned. Furthermore, application of these models assumes a high temporal resolution of the acquisition to capture the vascular-distribution phase of the bolus. These are the main reasons why most quantitative DCE-MRI studies are based on the Tofts or extended Tofts models.

Selection of an appropriate IRF model for a given tissue remains an open question. Assuming a sufficient SNR and temporal resolution (sampling interval of at least 1–2 s), one of the above mentioned advanced IRF models can be chosen. The main difference between these models is the assumption about the spatial distribution of vessels within the tissue ROI.

The 2CXM models the intravascular space as a compartment, i.e. a homogeneous well-mixed space. This assumption is approximately valid for a chaotic spatial arrangement of capillaries, arterioles, venules and larger vascular-tree components. The TH and ATH IRF models assume a ”plug flow” of blood. The red blood cells are typically larger than a capillary diameter and are deformed when passing through capillaries, hence act as ”plugs”, forcing the blood plasma between the red blood cells flow at the same velocity. This model is suitable for parallel vessels of the same length within the ROI. Both intravascular-space models are fairly simplistic. The DCATH and GCTT models introduce a statistical distribution of the lengths of the ”parallel” plug-flow capillaries, formulated in terms

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of capillary transit times. This leads to more general models, at the expense of an additional perfusion parameter to be estimated, being the parameter specifying the width of the capillary-transit-time distribution.

Several studies have been proposed for comparison of the IRF models. One approach is based on data simulated using the multiple path, multiple tracer, indicator dilution 4 region (MMID4) model (National Simulation Resources, University of Washington, http://physiome.org/jsim/models/webmodel/NSR/MMID4/) [Buc02, ZK14]. In [Buc02], the Tofts, extended Tofts and ATH models were compared, with the ATH model. In [ZK14], the extended Tofts and ATH models were compared with their variants accounting for water exchange. In both studies, the ATH model (and its water-exchange extension) provided more accurate estimation of perfusion parameters. In [NKB*09], the comparison of the Tofts, extended Tofts and ATH models on real data (lung cancer patients) was based on the Akaike's information criterion (a measure of a relative quality of statistical models considering their complexity and the goodness of fit) [Aka74]. The best description of the lung tumor data was obtained using the ATH model. Similarly, the Tofts and extended Tofts models have been compared to the 2CXM [DWD*10] on cervix carcinoma patients, based on consistency of the estimated perfusion parameters with known assumptions and on the F test for nested regression models. The 2CXM model proved to be the model of preference.

The 2CXM and ATH models have been compared on mouse masseter muscle, based on the goodness of fit, consistency of perfusion-parameter estimates with assumed treatment effects and based on the quality of subject-specific AIFs estimated using blind deconvolution [TPR*15]. The ATH model gave more reliable results.

The GCTT model [Sch12] might be a good alternative to the 2CXM and ATH models, as it is a generalized model that unifies both models (and also the Tofts and extended Tofts models) within a single formalism, at the cost of an additional perfusion parameter. In high-SNR scenarios, this additional parameter can be used to provide information on realism of the 2CXM and ATH models.

2.2. AIF Estimation

One of the main challenges in DCE-MRI is measurement/estimation of the AIF. It can be obtained using the recorded image sequence from the region within an artery feeding the analyzed tissue [PSL*09]. However, such AIF measurements are corrupted by flow artifacts, partial-volume, T2* and dispersion effects (an AIF from a big artery is different from the local AIF because dispersion leads to a broader local AIF). This makes the approach unreliable, especially in small-animal experiments. Another approach is to use literature-based AIF [LHL*12]. However, this does not take the inter-subject variability of the vascular tree into account and requires the same acquisition technique to be applied as in the underlying publication.

Blind deconvolution provides examination-specific AIF estimates directly from the measured tissue concentration curves, together with their perfusion parameters. It requires imposing of strong prior knowledge (positivity of the contrast-agent concentration curves, nonincreasing IRF or realistic models of the IRF and AIF) and a suitable initial estimation scheme.

Single- [TJR*12, TPR*15] and multi-channel [RDB02, SFD10] deconvolution algorithms have been published. The number of channels stands for the number of tissue ROI signals processed simultaneously. Multi-channel algorithms rely on the assumption that the AIF is the same for all processed ROIs. This assumption, if true, might be regarded as an additional prior information or as a source of errors if the tissue ROI signals differ in the dispersion term of the local ROI-specific AIFs.

The IRF models used in blind deconvolution have been mostly based on the Tofts [RDB02] and extended Tofts [FSD09, SFD10] models. More advanced pharmacokinetic models used for blind deconvolution include the 2CXM [JSK*14], ATH [TJR*12, TPR*15, JSD*14, JSM*14], DCATH [KJB*15] and the GCTT [JSK*15] models.

In blind deconvolution, the AIF can be formulated as nonparametric [RDB02, KJO*11, TJR*12, TPR*15] or as a parametric AIF [FSD09, SFD10, JSK*15, KJB*15, JSD*14, JSM*14]. A correct AIF model can be an important prior information. Clinical applications of blind deconvolution have been based on Parker's AIF model (sum of two Gaussian functions and a sigmoid multiplied by an exponential function) [KJB*15], Fluckiger's AIF model (Parker's model with the Gaussian functions replaced by gamma-variate functions) [FSD09], and its modifications [SFD10]. The gamma-variate AIF model has been also used for preclinical DCE-MRI [JSK*15]. An AIF model formulated as a sum of three gamma variate functions dedicated to small-animal DCE-MRI studies has been proposed in [JSD*14, JSM*14].

Additional information might be necessary for a reliable blind-deconvolution AIF estimation. In addition, the blind-deconvolution approach needs to be validated on more studies to be well accepted as a method of choice.

3. DCE-US

3.1. Quantitative Perfusion Analysis

DCE-US has been mostly based on semi-quantitative perfusion analysis. The challenge of absolute quantification of perfusion parameters has not been addressed by many research groups.

In burst-replenishment acquisition, the contrast agent is administered as an infusion and its replenishment within the imaging plane is recorded following a sequence of high-energy ultrasound pulses destroying the contrast agent within the imaging plane. For this technique, only relative perfusion parameters are estimated from approximation of the tissue intensity curves by a monoexponential model $A(1-exp(-\beta t))$. The values A, β and $A\beta$ are proportional to blood volume, blood velocity and blood flow, respectively. To the author's knowledge, the only aatempt to estimate absolute perfusion parameters using the burst-replenishment method was proposed in [VIR*05], where the missing scaling factor necessary for absolute quantification was derived from image intensity in the ventricle.

In bolus-tracking acquisition techniques, the contrast agent

is administered as a bolus. For this acquisition technique, deconvolution-based absolute perfusion-parameter quantification has been recently attempted in a few publications [GTL*12, GPCT*12, MJH*15, MJM*13]. It is based on the same convolutional model as in DCE-MRI (and in DCE-CT, PET, SPECT). The methods have been validated on phantoms [GTL*12, GPCT*12, MJH*15], tumor-bearing mice [GTL*12, GPCT*12] and pig's heart [MJM*13].

The bolus&burst technique [JNT*12, JNG*13] is a combination of burst-replenishment and bolus-tracking. The contrast agent is administered as a bolus and the high-energy pulses are applied at a defined time point in the wash-out phase. Absolute perfusion-parameter quantification is done by deconvolution. It is based on the same convolutional model as in DCE-MRI extended also to the replenishment phase. The method has been validated on Crohn's disease patients [JNT*12, JNG*13, NJM*13] and tumor-bearing mice [JSM*14].

3.2. Pharmacokinetic Model

The deconvolution-based techniques have been proposed for IRF formulated in several ways. Nonparametric IRF was used in [GTL*12, GPCT*12]. Phantom-based comparison of the nonparametric and the single-compartment (i.e. monoexponential) IRF formulations has been presented in [MJH*15], resulting in a comparable accuracy. The bolus&burst methods have been used, so far, only with a single-compartment IRF model [JNT*12, JNG*13, NJM*13, JSM*14].

The tissue concentration curves of the replenishment phase measured in burst-replenishment techniques can be formulated as a time integral of the IRF [JNT*12, JNG*13]. From this point of view, the models used in burst-replenishment can also be categorized based the used IRF model. The basic single-compartment model proposed originally for the burst-replenishment technique [WJF*98] has been later modified to a more realistic S-shape of the replenishment tissue concentration curve. This led to more complex models accounting for the transmit-receive ultrasound beam shape in the elevation direction and for the fact that vessels have multiple flow velocity values and directions [AFZR06]. A lognormal distribution of vascular transit times within the tissue ROI was used, based on assumptions made in [KBH03]. This resembles the approach proposed in DCE-MRI where Gaussian and truncaated Gaussian distributions were suggested in the DCATH model [KZD*01] and gamma distribution of vascular transit times in the GCTT model [Sch12].

3.3. AIF Estimation

As in DCE-MRI, AIF estimation is a challenge also in deconvolution-based DCE-US techniques. Deriving the AIF from an arterial ROI in the measured image sequence is a problematic task due to attenuation of the contrast agent in the artery, movement artifacts, low spatial resolution, speckles and blood-velocity dependence of the backscattered signal.

Blind-deconvolution AIF estimation in DCE-US has been used so far only for the bolus&burst acquisition [JNT*12, JNG*13]. Nonparametric AIF was used in [JNG*13]. Parametric AIF models were formulated as a sum of two lognormal functions [JNG*13] and a sum of three gamma variate functions [JSM*14]. These models have been compared in [MJSK15]. Both models approximated measured AIFs well, suggesting that they are both realistic. On simulated data, the dual lognormal AIF model gave better results. A more complete evaluation has been performed in [MJD*16], where these AIF models were compared together with eight more AIF models. The goodness of fit was assessed on measured AIFs. The AIF models still need to be compared with respect to the reliability of the blind deconvolution procedure.

In blind-deconvolution AIF estimation, a scaling factor needs to be found to enable absolute quantification of blood flow and volume. It is derived from the area under the curve of an arterial tissue concentration curve [JNT*12, JNG*13]. This is the main drawback of the method since this factor is distorted by attenuation due to the contrast agent, movement artifacts and flow artifacts related to the dependency of the backscattered signal on blood velocity.

4. Conclusion

Absolute quantification of perfusion parameters using MRI and ultrasonography is a viable methodology with an advantage of non-ionizing radiation. In general, there has been a steady increase in image quality in both modalities, enabling use of more complex pharmacokinetic models, parametrized by more perfusion parameters. DCE-MRI has had a longer history in absolute perfusion-parameter quantification and has a higher potential to reach a sufficient reliability to be used in clinical practice. DCE-US has been mostly focused on estimation of semi-quantitative perfusion parameters while their absolute quantification has been attempted only recently. The main problem in DCE-US remains attenuation of the contrast agent and an accurate AIF scaling.

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