Image analysis in DCE-MRI

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1. Introduction

Dynamic contrast-enhanced MRI (DCE-MRI) uses a bolus of paramagnetic tracer, injected after the start of a T1-weighted dynamic imaging technique. The data consist of the signal changes S(t) induced by the tracer as a function of the time t. The purpose of the measurement is to extract tissue-characteristic indices from the measured time-curves S(t). Generally speaking, data can be analysed by visual assessment, descriptive parameters, or quantitative parameters [1].

- *A visual assessment* of images at various time-points is the most intuitive approach [2], but it does not produce a quantifiable index, it does not separate perfusion and permeability, and produces no information on the rate of tracer uptake or washout.
- *Descriptive parameters* are indices that characterize the shape and structure of the curves, such as the time to peak enhancement, bolus arrival time, maximum upslope, maximum downslope, area under the curve, or maximum enhancement. Deriving descriptive parameters is straightforward, but the link to physiology is not always clear, and they are only reproducible when an identical measurement protocol is used.
- *A quantitative analysis* aims to directly measure physiological parameters such as tissue blood flow, blood volume, interstitial volume or permeability-surface area. From a measurement perspective, the main complication for a quantification is the need to accurately measure the concentration in the lumen of a major feeding artery. Also, additional post-processing steps are required.

Data analysis of DCE-MRI can be separated into 3 consecutive steps: image preprocessing for segmentation and registration (section 2), MR signal analysis to derive the tracer concentration from the signals (section 3), and tracer-kinetic analysis to derive the required indices from the concentrations (section 4). Only for a fully quantitative analysis are all three steps required.

2. Preprocessing

ROI or voxel

Quantitative or descriptive parameters can be calculated on the level of voxels, or of regions of interest (ROI). For an ROI analysis, a region is outlined manually or by some (semi)automatic segmentation procedure [3], and the signal-time curves of all voxels in the ROI are averaged to produce one single curve. The post-processing protocol is then applied to this curve. For a voxel-based analysis, a curve is extracted for each voxel. The post-processing protocol is applied to each voxel-curve individually, producing an image for each calculated parameter.

The main advantage of a voxel-based analysis is that it produces information on the heterogeneity of perfusion and/or permeability within the organ or tissue [4]. Summary parameters (mean, standard deviation, ...) for a lesion or an anatomical structure can always be derived by defining an ROI on one of the parametric maps. A ROI analysis produces more accurate average values since the CNR of the signal-time curves is improved by the averaging over the ROI.

A hybrid approach is to perform a voxel-based analysis first, define ROIs on the parametric maps, and repeat the analysis on ROI-level. In this case, it may be sufficient to perform a simple and robust analysis on the pixel level, and a complete quantification on the ROI level only.

Motion compensation

The data may be corrupted by organ motion due to breathing (in adominal organs), or by patient motion. As an alternative to motion compensation approaches on the acquisition level (breath hold or gating), or complementary to them, motion correction may be performed on the post-processing level [5]. Technically, the major difficulty in DCE-MRI compared to similar problems in medical imaging is the changing signal intensities during bolus passage. The challenge for a (semi) automatic motion correction technique is to distinguish these changes from those due to motion, and the development of robust techniques remains an active topic of research.

For an ROI based analysis, the most straightforward approach is to redraw or modify the ROI for every individual dynamic. The process is tedious and time-consuming, difficult to automatize, and is not suitable for a pixel analysis. An alternative approach is based on co-registration techniques, which aim to match motion-affected images to a reference image by a rigid or non-rigid deformation of the image. Coregistration is attractive in theory, as it fully removes motion effects and reconstructs the data that would be measured in the absence of motion. However, it is computationally challenging and usually requires expert intervention.

3. DCE-MRI signal analysis

The aim of DCE-MRI signal analysis is to calculate or approximate the longitudinal relaxation rates $R_1(t)$ (= $1/T_1(t)$) from the measured signals S(t), then the concentrations C(t) from $R_1(t)$. We restrict the discussion here to methods that assume fast water exchange between the various tissue compartments. The major difficulty with incorporating the effect of limited water exchange is that it introduces unknown parameters in the model. Corrections have been proposed using approximations and experimental values for the water exchange rates, but recent evidence suggests that the assumption of fast water-exchange is accurate with current measurement sequences [6].

Relaxation rates

The signal equation (1) forms the basis for any method aiming to derive $R_1(t)$ from S(t):

$$S = \Omega \cdot c \cdot M_0 \cdot e^{-T_E/T_2^*} \cdot \sin\alpha \cdot m_z(R_1) \qquad (1)$$

All factors apart from $m_z(R_1)$ are regarded as constant in time: the global calibration constant Ω, the coil sensitivity c, the equilibrium magnetization M_0, the flip angle α, and the exponential T_2^*-weighting. The (normalized) longitudinal magnetization m_z is a function of R_1 and the sequence parameters, but its precise analytical form is dependent on the design of the sequence.

All methods for inverting Eq. (1) assume that T_2^* -weighting is negligible, so that the amplitude of $m_z(R_1)$ in Eq. (1) can be treated as a constant and eliminated by scaling out the baseline signal S_0:

$$R_1 = m_z^{-1}\left\{m_z(R_{10})\frac{S}{S_0}\right\} \qquad (2)$$

Hence an additional measurement of precontrast relaxation rate R_{10} is required. A literature value for T_1 may be used to avoid this (eg. for blood in the AIF), but T_1-values in tissues are variable and may change in pathology. An alternative is to use a reciever/transmit coil with a maximally uniform coil sensitivity, so that the amplitude of $m_z(R_1)$ in Eq. (1) is independent of voxel position. It can then be determined by a reference measurement in a region with a known T_1 [7].

A second potential complication with Eq. (2) is the dependence of m_z on the flip angle, since the exact value may be unknown due to B_1-inhomogeneities or imperfect slice profiles. One possible solution is to insert a second precontrast calibration sequence to measure the flip angle. An alternative solution is to impose the additional assumption that m_z is proportional to R_1:

$$R_1 = R_{10}\frac{S}{S_0} \qquad (3)$$

The linearity assumption is valid at small enough concentrations, and its validity may be improved by sequence optimization. However, it is often violated in blood and highly vascularized tissues, where concentrations may enter the non-linear regime during the first pass.

Concentrations

For standard doses of contrast agent, the change in relaxation rate induced by the tracer is proportional to the concentration C(t). Hence C(t) can be derived directly from $R_1(t)$:

$$C = \frac{R_1 - R_{10}}{r_1} \tag{4}$$

Absolute values can be quantified if the relaxivity r_1 is known. However, if the relaxivity is independent of tissue type, it scales out in a quantitative analysis. In that case the outcome of the measurement is independent of the value chosen for r_1.

For a quantitative analysis, an accurate measurement of the concentration in the blood of an arterial feeder is required (the arterial input function or AIF). If the AIF is measured far from the tissue, the arterial transit causes significant dispersion errors that are difficult to correct [8]. Hence dispersion errors should be minimized by measuring the AIF close to the tissue of interest. If only small arteries are available, partial-volume errors may arise by contributions of vessel wall or surrounding tissue. However, in contrast to dispersion errors, they can be corrected in a straightforward manner by a reference measurement in a large vein or artery.

Since MR tracers are extracellular, the AIF is the concentration in the plasma of the artery. Hence the measured curve for whole blood must be divided by a factor (1 − H), where H is the patients' hematocrit. If the value is not known from laboratory data, a standard value of H = 0.45 is often used.

4. Tracer-kinetic analysis

The second step in a quantitative data analysis is to apply the principles from tracer-kinetic theory to extract the haemodynamic parameters from the concentration-time curves C(t), $C_A(t)$:

$$C(t) = F_P R(t) * C_A(t) \tag{5}$$

Here * is convolution, F_P is the tissue plasma flow, and R(t) is the residue function of the tissue [9]. We distinguish between direct methods, which produce some of the haemodynamic parameters directly from the concentration-time curves, and deconvolution methods, which calculate the full residue function from Eq. (5). The group of deconvolution methods can be classified into model-free, parametric, and model-based methods.

Direct methods

Integration of Eq. (5) and using the central volume theorem [9] produces a useful formula to calculate the extracellular volume:

$$ECV = \frac{\int_0^\infty dt C(t)}{\int_0^\infty dt C_A(t)} \tag{6}$$

A disadvantage of such relations is that concentration-time curves must return to zero within the acquisition window to allow calculation of the areas. Hence such methods are usually accompanied by a preprocessing step that extracts the first pass of the bolus [10]. However, this is difficult to justify in tissue types with rapid tracer uptake, where the first pass is not clearly differentiated.

A direct method for calculating F_P is obtained by considering only the time points shortly after the bolus arrival in the tissue. If the time since arrival is sufficiently short, no tracer has yet left the tisse, so that R = 1 in Eq. (5):

$$C(t) = F_P \int_0^t du C_A(u) \tag{7}$$

F_P can be determined directly from this equation, or from the maximum derivative [7]. The limitation of this approach is that only very few data points can be used.

Model-free deconvolution

Model-free deconvolution methods do not impose any constraints on the form of the residue function or the structure of the tissue. They produce a measurement of the impulse response $F_P R(t)$ directly from the data $C_A(t)$ and C(t). The plasma flow F_P can then be found as the maximum of $F_P R(t)$. The extracellular volume ECV by integration of $F_P R(t)$, and the mean transit time (MTT) from the ratio of ECV to F_P.

The first model-free deconvolution methods proposed in DCE-MRI were based on the Fourier theorem [10], but since a calculation of the Fourier transform involves integration, they suffer from the same limitation as Eq. (6). Most current methods are based on a discretisation of Eq. (5) which rewrites the formula as a matrix equation [11].

$$\mathbf{C} = \Delta t F_P \mathbf{C_A} \mathbf{R} \tag{8}$$

A solution can then be obtained using standard regularization methods for linear ill-posed problems [12].

Parametric deconvolution

Parametric methods do not make any explicit physiological assumptions, but they do assume that the residue function has a known analytical form. The free parameters are then determined by minimizing the difference between both sides of Eq. (5).

One example of a parametrization is the Fermi model, which has been used extensively for analysis of DCE-MRI data in the heart [13]:

$$R(t) = \frac{1+b}{1+be^{at}} \tag{9}$$

Alternative parameterizations proposed are gamma-variate functions or polynomial representations.

Compared to model-free methods, parametric methods may improve the accuracy in plasma flow estimates when the residue function has the required shape – particularly when the data quality is poor. On the other hand, a systematic error may arise when the actual residue function has a different functional structure. Parametric methods usually produce a number of additional parameters apart from blood flow, but these cannot be interpreted due to the lack of an underlying physiological model.

Model-based deconvolution

Tracer-kinetic models provide a well-defined relation between a parametric representation of the residue function and physiological parameters [14]. Model-based approaches therefore offer the possibility to measure additional hemodynamic parameters such as the volume of different tissue compartments, or the exchange rates between them.

Virtually all models proposed in DCE-MRI are one- or two-compartment models [15, 16] or two-space distributed parameter models [17, 18]. Most models are generic, but particular organs may need particular solutions. A typical example is the liver, where tracer enters through arterial and venous inlets [19]. Another example is the kidney, where processes of filtration require a different model architecture than typical tissue types, and where resabsorption leads to interpretation issues in some of the parameters [20].

A typical problem is that multiple models may be appropriate for a given tissue type [21]. For particular applications, prior knowledge and experience may be available to eliminate all but one of the possible models. In general, however, the natural variability in the tissue types of interest may be too large to reduce the number of possible models to one. For an analysis on ROI level, the accuracy of the fit can be evaluated by an expert observer, but this requires expert intervention, introduces a level of subjectivity in the results and is impossible for a pixel-by-pixel analysis. Automated methods for model selection are more practical, the most popular being the F-test and the Akaike criterion [22].

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