Title: An introduction to Dynamic Contrast-Enhanced MRI

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What is DCE-MRI? A historical perspective

Indicator-dilution experiments are a class of physiological measurements where an indicator is injected in the body, and the properties of body fluids are determined by analysing the indicator's concentration as a function of time in a region of interest [Zierler1961, Perl1975, Lassen1979, Jacquez1985]. These methods were first translated into MRI in the mid 1980's, using (currently standard) MRI contrast agents as indicators for the extracellular fluid [Runge1984, Pettigrew1986]. These early studies used T1-weighted sequences to assess the indicator concentration as a function of time after injection. This method is now generally referred to as Dynamic Contrast-Enhanced MRI or DCE-MRI. It was later discovered that the signal changes in normal brain tissue (ie. in the absence of contrast agent leakage) were much stronger when T2*-weighted sequences were used [Villringer1998]. This method is now known as Dynamic Susceptibility Contrast MRI or DSC-MRI [Choyke1989, Rosen1990].

Which parameters can be measured with DCE-MRI?

The target parameters (biomarkers) of any DCE-MRI experiment can be separated into two main groups [Sourbon2012]. The "perfusion" parameters characterize the microvasculature: tissue blood flow (in ml blood per min and per ml tissue), tissue blood volume (in ml blood per ml tissue) and blood mean transit time (in sec). The "permeability" parameters characterize the leakage of indicator into the extravascular space: the permeability-surface area product PS (in 1/min), the interstitial volume (in ml per ml tissue) and the interstitial mean transit time (in min). An especially important physiological parameter is the volume transfer constant (Ktrans), which measures the rate at which indicator is delivered to the extravascular space (in 1/min). Ktrans is not an independent parameter but a combination of perfusion and permeability parameters. However, as the delivery of nutrients is ultimately the main function of the microvascular bed, Ktrans is a more direct measure of tissue function. Some other parameters can be measured which are specific to certain organs, such as the glomerular filtration rate (in the kidney) or the portal-venous fraction of tissue perfusion (in the liver).

When should DCE-MRI be used?

The discovery of Villringer et al [Villringer1988] led in the 1990's to a paradigm where DSC-MRI was considered the method of choice for the measurement of perfusion parameters [Rosen1990, Kuhl1997], and DCE-MRI the method of choice for the measurement of permeability parameters [Tofts1989, Larsson1990, Brix1991]. At the turn of the century it became increasingly clear that absolute quantification with DSC-MRI is more difficult, and the weaker signal enhancement of DCE-MRI in the first pass is only a limitation in the brain. Today, DCE-MRI remains the method of choice

for the measurement of permeability [Tofts1997, Leach 2005], and has replaced DSC-MRI as the method of choice for the measurement of perfusion in all areas except the brain: eg. in the liver [Materne2002, Pandharipande2005], tumours [Brix2004, Kershaw2009], myocardium [Jerosch-Herold 2004], kidney [Vallee2000, Dujardin2005], lungs [Risse2006] or skeletal muscle [Lutz2004].

Acquisition and analysis in DCE-MRI

DCE-MRI is usually performed with a standard dose (0.1 mmol/kg) of a clinical contrast agent (Gd-DTPA) injected at a flow rate of 2-3ml/s [Sourbron2010]. The acquisition is either performed with a 2D spolied gradient-echo sequence with a non-selective preparation pulse, or a 3D spoiled gradient-echo sequence in the steady-state. A critical parameter in the optimisation of a sequence is the temporal resolution. For most accurate quantification, this must be significantly shorter than the typical width of the first-pass in the blood, and also shorter than the mean transit time of blood. As this is in the range of seconds, this requires significant compromises in terms of spatial resolution and/or coverage. Hence for clinical applications where absolute accuracy is less important and/or spatial resolution is more critical, the optimum acquisition may represent a compromise [Ledsam2013]. Alternatively, a separate measurement may be performed to determine the blood concentrations [Risse2006]. It is also common to include T1-mapping before contrast injection to calibrate the dynamic sequence [Kershaw2009].

As in DSC-MRI, the analysis of the data requires the extraction of a reference concentration in arterial blood (the arterial input function or AIF), a signal analysis step to convert measured signals into concentrations, and a tracer-kinetic analysis step to relate the concentrations to the targeted perfusion or permeability parameters. In abdominal organs it may also be necessary to include an image registration step to minimise or remove the breathing or cardiac motion.

Sources of error in DCE-MRI

The accuracy and precision of DCE-MRI is critically dependent on the details of the acquisition and analysis setup. The most significant errors are often caused by inaccurate measurement of the concentration in the AIF [Sourbron2010]. A particular problem is the rapidly flowing blood, which may cause a flow-weighting that corrupts the concentration estimates if not properly mimized by sequence optmisation or accounted for in the signal analysis. In areas like the brain, where the feeding arteries are relatively small, the AIF concentrations may be corrupted by partial volume effects. Also, since the concentrations in the blood are very high, their estimates may be corrupted by signal saturation and/or T2-interference.

Other errors that may arise on the level of signal analysis are discrepancies between actual and nominal flip angle due to B1-effects or slice profiles, errors in the signal model due to imperfect spoiling, or a bi-exponential T1-recovery due to limited water exchange between tissue compartments with different concentrations.

A more fundamental problem arises if (some of) the targeted parameters are essentially unmeasurable. For instance, if the exchange of contrast agent between intra- and extravascular spaces is very fast (high PS), then blood and interstitium are at equal concentrations at all times and their volume fractions are not separately measurable. Any attempt to measure the blood volume under such conditions will produce unreliable results. The problem is that this may not always be obvious a priori since PS is an unknown, and the problem may only exist in part of the organ. For clinical practice it is therefore important to supply an error estimate with any measured parameter, so that unreliable values are not overinterpreted.

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