Session: **Imaging Acquisition and Reconstruction**
Talk Title: **Pulse Sequence Modules II: Tagging, Labelling, Diffusion Sensitization and Magnetization Transfer**

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HIGHLIGHTS:

• Introduction to the principles of myocardial tagging, arterial spin labelling, diffusion imaging and magnetization transfer imaging.
• Description of the pulse sequence modules required to achieve these image contrasts.
• Summary of the different flavours of each method, and the tricks required to minimize confounding artifacts.

TARGET AUDIENCE: MR physicists, plus technologists and physicians with an interest in understanding MR physics

OUTCOME/OBJECTIVES:

• Appreciation of the range of pulse sequences available for cardiac tagging, black-blood imaging, arterial spin labelling, diffusion imaging and magnetization transfer imaging.
• Understanding of the different approaches that can be used for each method, and the best ways to minimize confounding artifacts.

INTRODUCTION:

The impact of magnetic resonance imaging lies in its versatility and ability to report image contrast that arises from a large range of phenomena. Tissue contrast can be imparted either by the readout pulse sequence that is used, or by the preparation module that is deployed either before the readout, or during the readout. This lecture will cover a number of pulse sequence preparation modules and will describe their implementation.

TAGGING:

The ability to track the motion of myocardial tissue is important in assessing cardiac dysfunction, and enables a quantitative measurement of tissue properties such as strain and tissue deformation. Zerhouni described the use of a comb of short RF pulses in the presence of a field gradient in order to saturate the signal from specific repeating positions along the direction of the field gradient [1]. This principle was extended to two dimensions by Axel and Dougherty [2] to create the method of Spatial Modulation of Magnetization (SPAMM). Typically the cardiac tagging is applied early in the cardiac cycle, gated by the QRS complex detected using ECG pads. The rapid SPAMM preparation is deployed and then the imposed ‘grid’ can be read out at a later time, until the perturbed magnetization starts to recover and lose its contrast later in the cardiac cycle. This means that cardiac tagging is best suited to assessing the systolic phase of the cardiac cycle, but may also be used to study diastole.

Typically, spoiled gradient echo sequences are used for the readout portion, although SSFP sequences have also been used due to their lessened impact on the ‘decay’ of the tagging contrast. Also, use of higher field strengths will benefit, due to the prolonged tissue T1 and hence tagging duration.

LABELING:

A variety of preparation modules exist with the intention of labelling blood. In some cases these preparation modules have the intention of crushing the blood signal (for example those used for dark-blood vessel wall assessment). In other cases the preparation modules intend to selectively excite the blood signal, for use in perfusion mapping or angiography. This latter class of labelling approaches is that of ‘arterial spin labelling’.

Black-Blood Vessel Wall Imaging

The mainstay of dark-blood preparation modules is the double inversion-recovery (DIR) method [3, 4]. In this method the entire region (blood and tissue) is inverted with a non-selective 180º inversion pulse, and the slice or slices of interest are immediately uninverted with a selective 180º pulse. A TI inversion-recovery gap is then left before a readout sequence is deployed that is timed to occur at the T1-null of the blood. In this way the blood signal in the slice(s) of interest should be zero; however, the static tissue should be fully relaxed. The DIR method offers high CNR between the tissue and the lumen space, but is not always effective in cases of slow or complex flow, and is not well suited to more than a handful of slices.

Two more recently proposed dark-blood preparation modules are the techniques of Motion-Sensitive Driven Equilibrium (MSDE, [5]) and Delays Alternating with Nutation for Tailored Excitation (DANTE [6]). The MSDE preparation seeks to crush the flowing blood spins by using diffusion-like field gradients, whilst aiming to return the static magnetization back to the longitudinal axis. MSDE preparation has excellent lumen suppression capabilities, but incurs some inherent T2-weighted signal loss of the static (vessel wall) signal. The DANTE preparation uses a train of low flip angle RF pulses in conjunction with embedded gradient pulses to create a high-order transverse phase spoiling that in turn nulls the longitudinal magnetization. All these methods can be used in conjunction with readout sequences with various contrast weightings in order to facilitate the characterization of vessel wall plaque. Ideally it is necessary to acquire combinations of T1-weighted images, and also proton density or T2-weighted images.

Arterial Spin Labelling

The technique of arterial spin labelling (ASL) was first described by Detre and colleagues in 1992 [7], and relies on the subtraction of two images, one that is prepared with the blood in a fully relaxed state (the ‘control’ image) and one that is prepared with the blood in an inverted (or saturated) state (the ‘tagged’ or ‘labelled’ image). The difference between these two images is proportional to the amount of blood that has arrived in the voxel between the time of the labelling and the time of the readout.

There are a number of ways in which the ASL preparation can be effected in practice. The earliest form described by Detre involved continuous labelling of the arterial blood (CASL) using a long (continuous or as near continuous as the hardware will allow) RF pulse in the presence of a field gradient. The motion of arterial blood through the labelling ‘plane’ leads to a flow-driven adiabatic inversion of the moving spins, which then travel to the tissue region of interest (relaxing as they go, thus limiting the ultimate lifetime of the ‘tag’). The control pulse for a CASL preparation, as well as not perturbing the blood spins, needs to mirror the effects of magnetization transfer, so that those effects cancel along with the static tissue signal and do not lead to a confound. In early publications the control pulse consisted of a ‘label’ placed distally above the slice of interest by the same distance as the proximal ‘tagging’ pulse. However, this approach limits CASL acquisition to a single-slice readout, since MT effects are only cancelled when the proximal and distal distances match. However, an alternative control pulse approach was proposed by Alsop [8] that enables multi-slice CASL data to be collected.

Another class of ASL preparations are the pulsed-ASL (PASL) approaches. In these preparations a volume of tissue is inverted using a short 180º pulse that labels the proximal arterial blood, and this is contrasted with a control pulse that does not label the blood. The first such description was the EPI Signal Targeting by Alternating RF (EPISTAR) preparation [9], in which a proximal slab was inverted and contrasted with an image in which no inversion pulse was used (in both cases the preparation was preceded by a saturation pulse in the location of the imaging slice to minimize effects from an imperfect inversion profile). The EPISTAR sequence was sufficiently insensitive to MT effects that no RF was used for

the control pulse, but accurate quantification was problematic for this reason. The later method of Flow Alternating Inversion Recovery (FAIR) allowed a better degree of perfusion quantification [10]. The FAIR method contrasts a global (or large slab) inversion pulse with a slice selective inversion (both centred on the slice(s) of interest). In the case of the global inversion pulse, blood outside the slice of interest is inverted and begins to move into it. In the case of the slice-selective inversion pulse, non-inverted blood moves into the slice to provide contrast. In both cases the static tissue in the slice of interest is inverted and therefore cancels as it has the same magnetization recovery history.

The most widely used PASL methods are those based on the PICORE preparation [11], in which a proximal inversion slab is used for labelling, and an off-resonance MT-matched RF pulse is used for control. The PICORE variants of QUIPSS, QUIPSS II, and Q2TIPS further refine the principle and allow differing degrees of perfusion quantification and slice coverage.

An increasingly prominent ASL method, however, is yet another approach known as pseudo-continuous ASL (pCASL). Rather than using CASL's lengthy high duty-cycle hard pulses the pCASL approach uses trains of low flip angle selective pulses to induce a flow-driven adiabatic inversion [12]. The theory behind pCASL is derived from SSFP sequences, in which off-resonance-dependent magnetization profiles result from a train of RF pulses. In this case an appropriately shaped M_z transition is arranged to occur about the centre frequency, and the position of the centre frequency of the selective pulses is located at the desired 'labelling' plane. Blood flowing through this plane will then experience the imposed M_z transition and will be inverted as it passes through it. The beauty of the pCASL approach is that a perfectly MT-matched control pulse can be applied simply by phase cycling the RF pulses to shift the transition band outside the 'tuned' labelling position.

A final major class of ASL preparation is the velocity-selective (VS-ASL) approach [13]. This preparation seeks to label the magnetization on the basis of its velocity profile, rather than its spatial position. If this can be done at velocities that are sufficiently low (ideally spins decelerating into the capillary bed) then it should be possible to minimize the need to include an arterial arrival delay between the labelling preparation and the imaging readout. If successful VS-ASL can be achieved then it may allow discrimination between absent flow, and flow that is simply delayed in its arrival to the tissue bed (and hence blood that is losing its T1-time-constant label) either due to slow flow or due to circuitous flow.

Vessel-Encoded ASL

Returning to pseudo-continuous ASL, a further feature of this approach is its easy extension to encode the labelling from different feeding vessels. This is possible by adding transverse field gradients between the RF pulses in the pCASL pulse train such that the phase accumulation between successive RF pulses can be adjusted at different spatial locations within the labelling plane to be in either a control state (net phase accumulation 180º between pulses) or a tag state (net phase accumulation 0º between pulses). The locations of the 'tag' and 'control' locations can then be moved around at will, and the perfusion territories [14] or vascular branches [15] from the feeding vessels can be decoded in post processing. By adding the concept of a variable delay time between labelling and readout it is possible to achieve full vessel-selective quantification via a fit to some form of kinetic model [16], yielding both absolute perfusion as well as arterial transit delay (also known as bolus arrival time). Although other CASL and PASL approaches have also been used to achieve selective vessel encoding, the pCASL approach seems to be the most robust and SNR efficient approach.

DIFFUSION SENSITIZATION:

MRI has been used to measure the self-diffusion of water or other substances for many decades. Borrowing from the early work of Stejskal and Tanner [17], who showed how a pair of gradient pulses could be used to measure the diffusion coefficient of a sample, LeBihan was the first to incorporate diffusion measurement into an imaging experiment in the 1980s

[18]. The essential experiment has remained unchanged, in that a large gradient pulse is applied that causes phase accrual to occur in the excited spins, that is then reversed using a second balanced gradient pulse. In the absence of diffusion the full signal (albeit T2-weighted) is recovered. However, in the presence of diffusion there is additional phase misalignment and hence signal cancellation caused by random movement of the spins in the direction of the field gradients. By careful control of the strength of the diffusion encoding gradients a quantitative measure of the diffusion coefficient can be achieved via the equation $S(b) = S_0 \exp(-bD)$ where b is a measure of the diffusion gradient strength and D is the apparent diffusion coefficient.

Diffusion Tensor Imaging

A further extension to diffusion imaging, also pioneered by LeBihan, is the ability of diffusion images to encode diffusion along different physical directions. By measuring a minimum of 6 different directions (e.g., *x*, *y*, *z*, *xy*, *xz* and *yz*) it is possible to characterise the diffusion tensor associated with each voxel [19]. This allows the principal diffusion direction to be determined and hence allows tractography to be accomplished. In order to help differentiate higher order fibre bundles (such as crossing fibres) it is necessary to extend the acquisition to more diffusion directions and even to multiple diffusion *b* values [20].

Readout Trains

The most common diffusion readout sequence that is used is the single-shot EPI sequence, since it offers great robustness to phase errors associated with small motions during the diffusion encoding process. However, single-shot EPI sequences are sensitive to eddy current effects that can differ between different diffusion encoding directions. This has led to the need to develop correction strategies to deal with the resulting subtle mis-registrations between the different directions [21, 22]. An additional tactic to minimize eddy current problems is to use diffusion gradient patterns that are inherently eddy-current compensated [23].

If higher spatial resolutions are desired than are possible with single-shot EPI then multi-shot methods must be used. These require ‘navigator’ information to report on and facilitate correction of any phase errors arising from subject motion. An example of such a sequence is the readout-segmented EPI sequence [24], in which segments of k-space are built up over several TR periods, and a navigator acquisition is acquired alongside every segment. A very different form of diffusion readout is achieved using the SSFP pulse sequence, in which diffusion weighting is built up over a series of TR times. Although harder to quantify, this type of sequence can achieve high *b*-factors with high spatial resolution, and has been used to good effect in post-mortem brain imaging [25].

MAGNETIZATION TRANSFER:

Magnetization transfer contrast (MTC) was first described by Wolff and Balaban in 1989 [26] and involves the exchange of magnetization from slow moving macromolecular spins to fast-moving free water spins. This is accomplished by partially saturating the macromolecular spins using off-resonance RF pulses. Because the macromolecular spins have a broad NMR spectrum they will be affected by off-resonance saturation, which would not normally directly affect the free water pool. However, because there is close contact between the free water pool and the macromolecular pool the saturated macromolecular magnetization will transfer its influence into the free water pool and will result in a lower free water signal. Hence, MTC weighted images can report on the macromolecular content of a voxel, and have applications in the assessment of tissue integrity (e.g., in the assessment of white matter integrity in multiple sclerosis). Most MTC-weighted experiments make use of a simple long off-resonance preparation pulse to reduce the signal from voxels containing a significant fraction of macromolecules. To achieve quantitative MTC measurement, it is necessary to perform a more rigorously controlled preparation in which the B1 strength is carefully calibrated and mapped.

Another common use of MTC weighting is in magnetic resonance angiography, where there is benefit in suppressing the signal from white matter in a time-of-flight angiogram. The goal of TOF-MRA is to induce strong contrast between the moving blood spins and the stationary tissue spins. This contrast is mostly achieved by running a thin-slice acquisition with a short TR (to saturate the static tissue spins whilst allowing high signal from the inflowing and fully relaxed blood). The use of an MTC pre-pulse further reduces the signal from the tissue spins. It is finally worth noting that the more recent method of chemical exchange saturation transfer (CEST) contrast, also first described by Balaban's lab [27], is closely related to MTC and also relies on off-resonance excitation and magnetization exchange, this time between more mobile solute species and water spins. CEST has various potential applications ranging from stroke, to cancer to musculoskeletal MRI.

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