

## Other Contrast: Polarization Transfer, Chemical Exchange & Magnetization Transfer

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*Target audience:* Physicists with prior experience of working in MR.

*Learning outcomes:* At the end of this session learners will be able to explain the physical origins of CEST and NOE signals, ways to measure and separate them, and ways to use them.

### Highlights

- The different effects contributing to the z-spectrum.
- Methods for detecting and separating these effects
- Evolving applications of these techniques

Until recently, the only way of obtaining chemical information with MR was to use MR Spectroscopy which has low sensitivity and low spatial resolution. However, recently new forms of magnetization transfer MRI have been developed, which can amplify sensitivity to a range of biologically relevant species by cross relaxation, proton exchange or molecular exchange, providing sufficient sensitivity to allow data to be acquired at high spatial resolution within a convenient imaging time. These techniques have the potential to transform MRI into a molecular imaging technique; they can detect endogenous species of interest or a new range of contrast agents that will compliment those used in nuclear medicine.

The basic experiment is a magnetization transfer experiment involving (usually) off resonance saturation which then transfers to the water protons. However the standard MT experiment includes signals from many different sources, and the physicochemistry of the experiment is complex: the 'z-spectrum' (the effect of off-resonance saturation on the water signal on a frequency scale that is referenced to the water frequency), contains contributions from a range of phenomena which will be defined as follows<sup>1</sup>:

Chemical Exchange Saturation Transfer (CEST): proton chemical exchange between water and specific moieties with long T<sub>2</sub>s. These generally resonate down field of water (0-+10 ppm) due to the deshielding associated with the labile protons. Exchange rates are defined as slow, intermediate or fast relative to the water proton T<sub>1</sub>. The term Amide Proton Transfer (APT) is used for to exchange with amides. The chemical exchange of amide protons is base catalyzed so the exchange rate decreases with decreasing pH.

Nuclear Overhauser Effect (NOE): intermolecular cross relaxation (0-5 ppm upfield) between water and mobile aliphatic protons<sup>2-4</sup>. This peaks around -3.5 ppm in the brain, showing a remarkable similarity to the myelin proton spectrum<sup>5</sup> and is likely to relate to mobile lipids. The NOE effect could be exchange relayed via another proton containing species, but recent work has found no in vivo pH dependence suggesting it is likely to be a direct intermolecular relaxation<sup>2</sup>.

Conventional magnetization transfer MT<sub>ss</sub>: transfer of magnetization between water protons and protons in semisolid macromolecules with short T<sub>2</sub>, resonating over a wide frequency range (±100 ppm) (this may be mediated by some less specific NOE and chemical exchange effects). The term Magnetization Transfer (MT) is generally used generally to encompass all these processes. Initially CEST was studied using the asymmetry of the z-spectrum but this is confounded by other features in the z-spectrum.

Increased sensitivity compared to MRS occurs since the saturation of protons in a pool of interest transfers to the water pool, and the water saturation gradually builds up, providing amplification of the signal from the transferring species. The sensitivity of the z-spectrum to different exchanging species depends on the experimental conditions. However since the z-spectrum contains small, overlapping contributions from many species, there is some scepticism about claims to be able to detect specific molecules of interest with endogenous CEST. Significant technical hurdles must be overcome if z-spectrum MRI is to be exploited in clinically useful protocols. The exchange time (which affects the amplitude and frequency of the z-spectra peaks), depends on concentration and the presence of exchange catalysts including pH and phosphates. Fortunately exchange rates and relaxation times can be measured and experiments can be tuned to particular moieties. This is because the observed effects depend on the amplitude and bandwidth of the saturation, and therefore are sensitive to RF and B<sub>0</sub> inhomogeneities.

1. van Zijl, P.C.M., et al., MRM, 2011, 65, 927.

2. Jin, T., et al., MRM, 2012.

3. Narvainen, J., et al., JMR, 2010, 207, 242.

4. van Zijl, P.C.M., et al., MRM, 2003, 49, 440.

5. Wilhelm, M.J., et al., PNAS, 2012, 109, 9605.

