Evaluation of paraCEST detection threshold on human stem cells under physiological constraints

Wen Ling1, Francesca Nicholls1, Silvio Aime2, Daniela Delli Castelli3, and Michel Modo1

1Radiology, University of Pittsburgh, Pittsburgh, PA, United States, 2dept of Neuroscience, King’s College London, London, London, United Kingdom, 3Dept of Chemistry, University of Torino, Torino, Torino, Italy

Introduction:
Paramagnetic agent based chemical exchange saturation transfer (paraCEST) is capable of tracking several distinct cell populations, which is critical for non-invasively imaging brain tissue regeneration after stroke1,2,3. Nevertheless, one key question for multi-color paraCEST application remains its detection threshold. To address this, we here aim to improve paraCEST scanning conditions for both Eu-HPDO3A (Eu) and Yb-HPDO3A (Yb) by considering both signal-to-noise ratio (SNR) and phantom temperature, then use such conditions for evaluating the detection threshold of paraCEST ex vivo.

In theory, CEST is normalized contrast that is independent of voxel size, but dependent on concentration. However, normalization should be affected by SNR since bulk magnetization appears in form of SNR, which is proportional to voxel size. When the paraCEST agent is taken up into cells, it is normally localized to endosomes, which affects the imaging characteristics of the agents5. It is therefore essential that cells scanned as phantoms remain viable during the scanning procedure so that conditions will be comparable to in vivo.

Results & Discussion: Increasing the power for scanning decreased SNR and increased CEST effect and sample temperature (Fig. 1A & 1C). A power over 40 uT decreased SNR to below 75 and led to either physiologically borderline temperatures (40°C) or above. To achieve a CEST contrast of at least 5%, a power of over 25 uT is needed (Fig. 1B & 1D). As a consequence, specific absorption rate (SAR) is the limiting factor to further increase the CEST effect and applicable power is constrained between 25 - 40 uT by temperature. These imaging parameters did not affect the acute viability of cells after scanning up to a duration up to 5 hours. However, longer scanning times exhibited a significant reduction in viable cells (Fig. 2). Fig. 3 shows CEST effects as a function of voxel size when the concentration of paraCEST agents varies. As expected, CEST effects are not reduced as voxel size decreases. On the contrary, the amplitude of the CEST effect seems to increase as voxel size decreases This is because the SNR of bulk magnetization acts as denominator in CEST quantification. As SNR decreases, the CEST effect falsely appears to increase. As a result, sufficiently high SNR is necessary for CEST quantification. Fig. 3 also indicates that both Eu and Yb have a detection threshold of 1mM in terms of concentration while the minimum feasible voxel size is about 0.016uL.

Conclusion: A major limiting factor in paraCEST imaging is the SAR, which increases sample temperature potentially above physiologically tolerable levels. Therefore, a long TR time is necessary to dissipate these adverse effects. We have here established scanning conditions that can sustain viable cells for scan duration of up to 5 hours. Using these scanning conditions, the detection threshold for paraCEST agents is ~1 mM in concentration and ~0.016uL in voxel size. Further work may include: 1) the assessment of any more subtle effects of SAR on cell biology; 2) addressing the ramicification in CEST quantification caused by low SNR. One limitation of current work is the lack of theoretical prediction of CEST contrast for individual agents due to the shortage of literature on the physical properties of Eu and Yb. These developments will be essential to quantify paraCEST effect for tracking stem cells in regenerative medicine.

References: