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GLINT

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D7.2 Estimate of the coefficients of variation, signal- and contrast-to-noise in volunteers

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CI	Classified, as referred to in Commission Decision 2001/844/EC	

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1 Version log

Version	Date	Released by	Nature of Change
V1.0	7/12/2016	F. Torrealdea	First version
V1.1	8/12/2016	M. Kim	Format changes, adding acronyms
V2.0	20/12/2016	M. Kim	Reviewer comments implemented, completion

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2 Definition and acronyms

Acronyms	Definitions
CEST	Chemical exchange saturation transfer
glucoCEST	Glucose Chemical exchange saturation transfer
RF	Radio frequency
SNR	Signal to noise ratio
MTR	Magnetisation transfer ratio
GCE	Glucose CEST enhancement
CNR	Contrast to noise ratio
mM	millimolar

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3 Introduction

3.1 Background and the need

GlucoCEST relies on the measurement inherently low signal levels. In the translation of the glucoCEST technique into the clinic, the lower field strengths of human MRI scanners compared to preclinical systems yields in smaller chemical shift between water and labile protons. As a consequence of the reduced chemical shift, spillover (direct saturation) effects are also more pronounced, and the power needed for effective glucose labelling considerably reduces the net MR signal with the consequent loss in valuable SNR. Optimization of the MR protocol is crucial for the successful detection of glucoCEST signal at 3T.

3.2 Objectives

1. To estimate the expected glucoCEST signal measurable following an IV glucose infusion experiment in which tissue glucose concentration increases 10 mM from baseline.

2. Estimate the signal variability in human volunteers.

3. Based on these estimates, design a MRI protocol to optimise the detection of glucoCEST signal.

3.3 Position of D7.2 in the project

For the translation of glucoCEST to the clinic it is important to simulate a hypothetical glucoCEST experiment at 3 Tesla magnetic field in order to estimate the levels of measurable signal and be able to make informed decisions on the optimisation of MR sequences.

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4 Methodology and Approach

1) Using a multi-pool model Bloch McConnel equations, a theoretical glucoCEST experiment was modelled, in which glucose concentration increases from a baseline of 5 mM to 15 mM. Different levels of Gaussian distributed raw noise were introduced in the simulation in order to estimate the effects of error in the real measurements. Model parameters were set to values fitting in vivo and phantom data with pH values set at 7.2. Two different tissue types, grey and white matter, were considered in the simulations of which values of T1, T2 and M0b (size of the MT pool) were taken from Stanisz et al. [1]

2) To verify computer simulated results phantom data were acquired. Samples were prepared with increasing glucose concentration, 3% agar, titrated to pH 7.2 and doped with Gadolinium to match the relaxation times in brain tissue.

3) CEST data from a volunteer was acquired to evaluate the variability of the MTR asymmetry signal over time. This measurement was used as estimate of signal variability in a real experiment scenario.

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5 Activities carried out and results

For a hypothetical glucoCEST experiment in which glucose concentration in tissues increases by 10 mM, it was estimated that around 30 CEST repetitions would be needed in order to detect glucoCEST signal with 95% confidence interval in a clinical 3T scanner. These figures were estimated assuming a variability (as the standard deviation) in the CEST measurements to be twice the expected GCE signal. These values were justified based on 1) the mean GCE obtained from phantoms at different glucose concentrations and 2) the variability of the signal measured in healthy volunteers.

A set of the phantom data used for these estimations is shown in figure 1. These experiments showed an average of 3% GCE for 10 mM glucose increase. The experimental results match well the predictions of the computer simulation model (Figure 2).

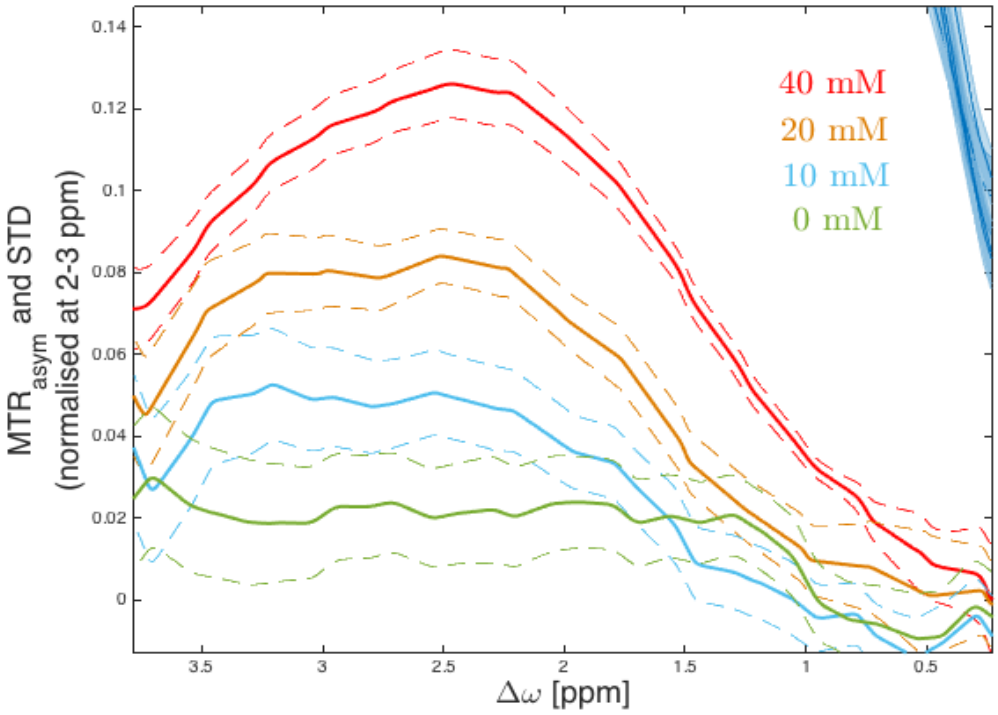

Figure 1: *Phantom experiment (0, 10, 20 and 40 mM glucose solutions in 3% Agar and 0.07mM Gd providing tissue like T1 and T2 at pH 7.1) showing maximum MTR asymmetry at* $\Delta\omega \approx 2.4ppm$ *with* $B1 = 2.3\mu T$ *in 3T Philips Achieva system. Data shows a ~3% GCE per 10 mM glucose increase.*

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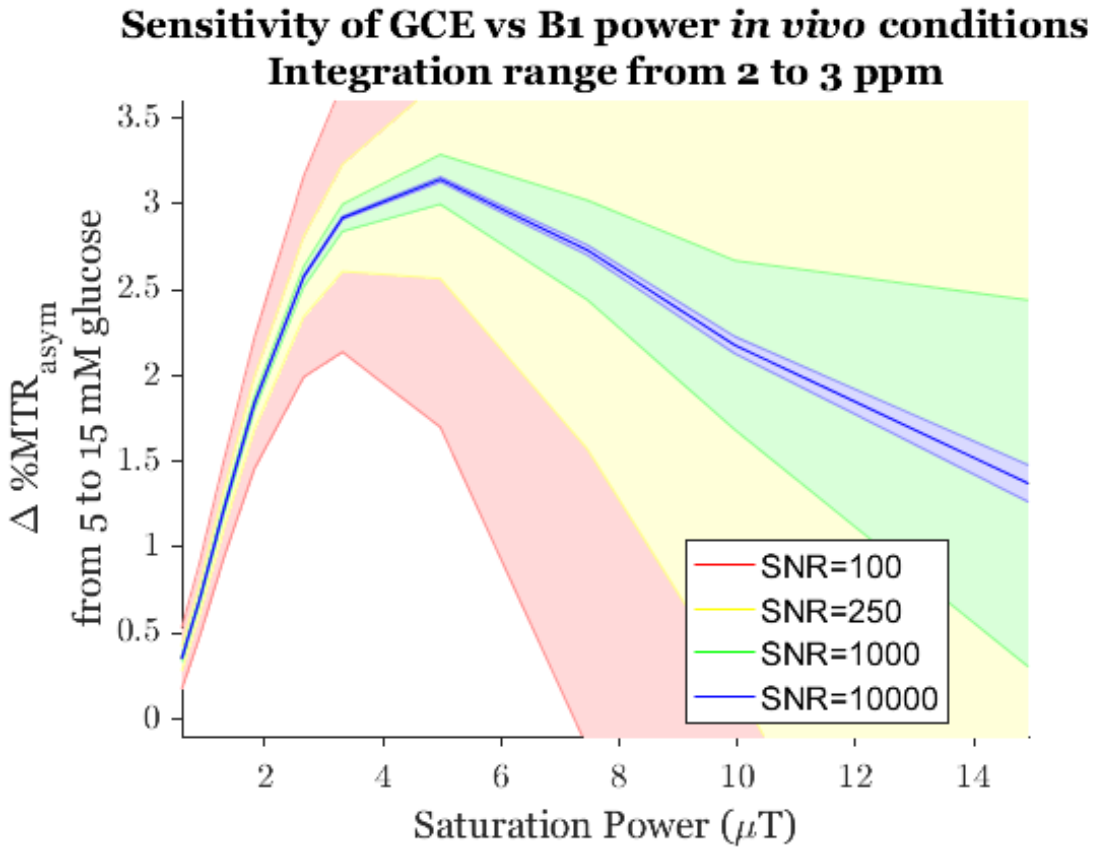

Figure 1 *Predicted in vivo GCE signal at different B1 power and integration range 2-3 ppm. The blue line represents the value of the GCE in an ideal noise free situation. Shaded colors represent spread of the standard error of the mean.*

The standard deviation from the mean CEST signal between scans of the same volunteer over time was measured to be 3.1% between 2 and 3 ppm, the most sensitive range for glucose detection at 3T. (Figure 3).

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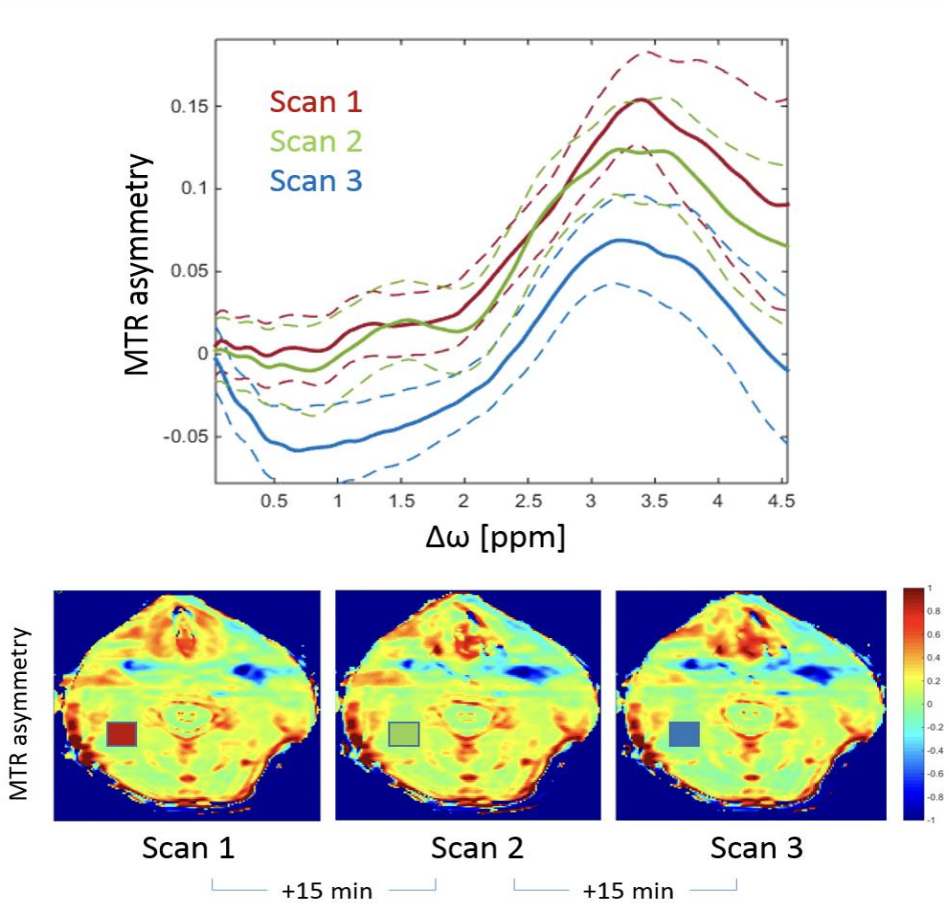

Figure 3: *Reproducibility of the MTR asymmetry in the neck of a healthy volunteer scanned every 15 minutes. Mean and STD of the CEST profile over the selected voxel show signal variability (STD) contained below twice the expected GCE signal in the range between 2 and 3 ppm.*

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6 Conclusions

Suggested approach for clinical glucoCEST

Due to the time constraints in the clinical environment and the low SNR expected in the glucoCEST measurements, it is sensible to target the acquisition on just the offset frequencies most sensitive for the detection of glucose. Sampling a small portion of the offset frequencies instead of the whole Z-spectrum allows more time to repeat acquisitions in order to gain CNR.

Similar as in fMRI, the low CNR in the glucoCEST data can be dealt by averaging multiple acquisitions. Using this approach an example of an optimised glucoCEST protocol is presented in figure 4.

The *CEST block* represents CEST measurements at 2.25, 2.5 and 2.75 ppm off-sets, which provide maximum MTR asymmetry based on phantom data and simulations at 3T. Saturation power should be set at $\sim 2.6\mu T$ for the duration of around one second, to provide optimum contrast from glucose. Frequent B0 maps are also advisable in order to correct for potential field drifts during the glucoCEST experiment.

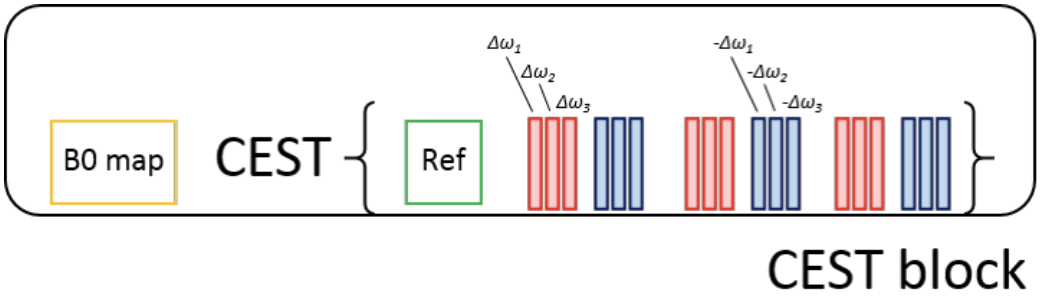

Figure 4: *Diagram of a suggested fast acquisition protocol for glucoCEST experiments. Three pairs of offset frequencies (positive and negative) are sampled centred around 2.6 ppm to allow for B0 corrections. Reference and B0 field maps are also acquired regularly to control for potential field drifts.*

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7 Bibliography / References

[1] Greg J. Stanisz, Ewa E. Odrobina, Joseph Pun, Michael Escaravage, Simon J. Graham, Michael J. Bronskill, and R. Mark Henkelman. "T1, T2 relaxation and magnetization transfer in tissue at 3T". In: Magnetic Resonance in Medicine 54.3 (Sept. 2005), pp. 507–512. ISSN: 0740-3194, 1522-2594. DOI: 10.1002/mrm.20605 (cit. on p. 109).

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