PARAMAP: an Automated Imaging Analysis Tool for Quantitative CEST Molecular Imaging: Validation *in vitro*

J. Flament[1], B. Marty[1], S. Mériaux[1], J. Valette[1], C. Medina[2], C. Robic[2], M. Port[2], F. Lethimonnier[1], and F. Boumezbeur[1]

[1]NeuroSpin, I2BM, Commissariat à l'Energie Atomique, Gif-sur-Yvette, France, [2]Research Division, Guerbet, Roissy-Charles de Gaulle, France

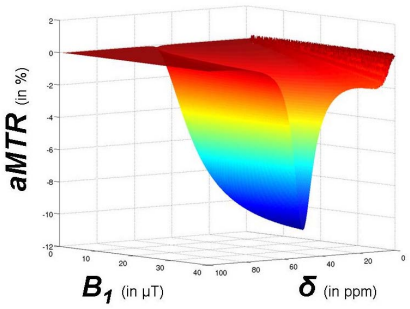

Fig.1. 3D asymmetrical Z-spectrum for [Eu^{3+}]DOTAMGly exhibiting variation of the %CEST effect for different B_1 intensities and saturation offset frequencies.

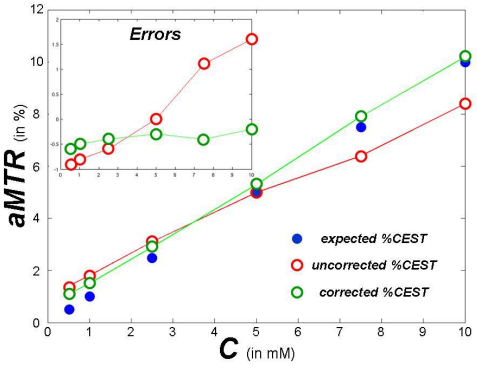

Fig.2. Comparison of %CEST effects within each tube before (open red dots) and after correction for B_0- and B_1-induced errors (open green dots) to the expected %CEST effect (blue dots). The errors are reported in the box at the top-left corner.

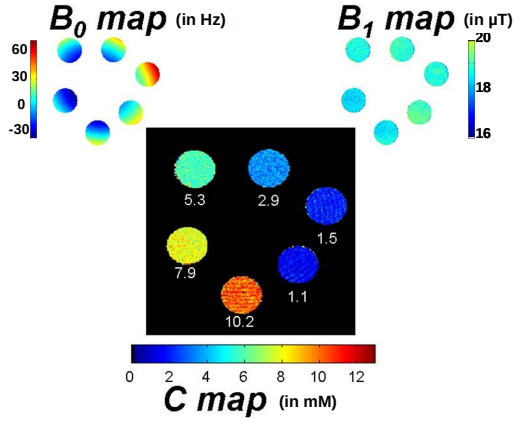

Fig. 3. Color coded quantitative PARACEST concentration (C) map after corrections for B_0 and B_1 inhomogeneities (top left corner and top right corner). The mean concentrations calculated in each tube are given explicitly (in mM).

Introduction

Recently, a new class of paramagnetic contrast agent has been developed for Chemical Exchange Saturation Transfer (PARACEST) magnetic resonance imaging [1-3]. Since visualizing CEST contrast requires two measurements with B_1 saturation applied on-resonance (at +δ, frequency of the shifted bound water) and off-resonance (at -δ), CEST imaging is sensitive to inhomogeneities in both B_0 and B_1 fields. Therefore, in order to generate quantitative CEST maps, it is important to elaborate correction algorithms to get rid of errors induced by B_0 and B_1 fields. In this study, we proposed to use a numerical simulation of the CEST contrast mechanism based on the Bloch equations modified for chemical exchange incorporating B_0 and B_1 dependencies [4]. The efficiency of our analysis tool was verified *in vitro*.

Materials and Methods

MRI acquisition. Experiments were realized on a 7 T small animal MRI scanner (Bruker, Ettlingen, Germany) using a bird-cage 3-cm-diameter ^{1}H coil for acquisition and reception. CEST images were acquired with a RARE sequence (TE/TR=80/5500 ms; turbo factor 32) preceded by a CW saturation pulse being applied at ± 50ppm (T_{sat}=400ms, B_{1sat}~20µT). B_0 and B_1 maps were acquired separately using a GE sequence (TE=5, 7.5, 10, 15ms; TR=300ms, flip angle of 30° and 60°). *In vitro* tests were performed on a 6-tubes phantom each containing [Eu^{3+}]DOTAM-Gly (Guerbet, Roissy, France; concentrations of 0.5, 1, 2.5, 5, 7.5, 10 mM) [3] embedded in a low-gelling point 4% agarose matrix.

Z-spectra Simulation and Image Analysis with PARAMAP. Our image analysis tool designed as PARAMAP is a Matlab (The MathWorks Inc., Natick, MA) based program aiming at correcting the B_0 and B_1 induced errors on the native CEST image ($I_{CEST}=(I_{ON}-I_{OFF})/I_{REF}$). Briefly, PARAMAP simulates for each pixel **r** a series of asymmetric Z-spectra using $B_1(\mathbf{r})$ and $B_0(\mathbf{r})$ values with the concentration C as a variable (aMTR(C,**r**)). The others parameters of the simulation (k_{ex}, δ, T_1 and T_2 of both pools) are extracted from experimental Z-spectra of [Eu^{3+}]DOTAM-Gly (data not shown). The concentration map C(**r**) is then calculated from the minimization of the cost function: $|I_{CEST}(\mathbf{r})-aMTR(C,\mathbf{r})|$.

Results and Discussion

As illustrated by the figure 1, field inhomogeneities manifest themselves strongly on the amplitude of the observed CEST effect for a given concentration. Therefore a 10% error on B_{1sat} leads to a 4% over- or under-estimation. Similarly, a 100Hz frequency error leads to a 1% over- or under-estimation. In our experiment, B_0 et B_1 inhomogeneities were quite modest as illustrated (standard deviations: σ_{B0}=21Hz and σ_{B1}=0.5µT), yet without correction, the calculated %CEST effect (Fig.2, open red dots) is quite different to the %CEST effect expected (blue dots). If not corrected, discrepancies between the known and the estimated concentrations are on average of 0.8mM. The B_0 and B_1 corrections (green line) improve significantly the quantitativity of the established PARACEST concentration map with an averaged over-estimation of 0.3 mM (See Fig.3).

Conclusion

CEST agents are promising new contrast agents for MR molecular imaging since they allow to reach nanomolar sensitivity [5]. Yet, their susceptibility to parameters such as B_0, B_1 is a real issue to achieve truly quantitative CEST imaging. In this study, we validated *in vitro* PARAMAP, a home-made software aimed at correcting not only for B_0 and B_1 field inhomogeneities. Ultimately, quantitative PARACEST concentration maps were obtained within a reasonable margin. To move further toward *in vivo* quantitative CEST imaging, we are actually extending the simulation to a 4-site chemical exchange model similar to the one described by Li et al. [6].

The software will be available at: http://groups.google.com/group/paramap .

Acknowledgments Grant sponsor: Iseult/Inumac French-German Project.

References

1. Ward KM *et al.*, J Magn Reson 2000;143:79
2. Zhang S *et al.*, Acc Chem Res. 2003;36:783
3. Aime S *et al.*, MRM 2002;47:639
4. Woessner DE *et al.*, MRM 2005;53:790
5. Terreno E. *et al.*, CMMI 2008;3:38
6. Li AX *et al.*, MRM 2008;60:1197