CEST exchange rate fitting agreement in non-steady state multi-B_1 multi-concentration buffered solutions

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INTRODUCTION:

Accurate determination of analyte exchange rate is necessary for quantitative CEST (qCEST) and optimizing saturation schemes for sensitivity and specificity, as determined experimentally in VDMP[1]. Existing fitting methods largely depend on steady state (SS) solutions of the Bloch equations for multiple B_1, which do not disentangle CEST proton pool size from transverse dephasing through exchange or relaxation[1]. Non-SS (NSS) measurements address some of these challenges by constraining the CEST effect by exchange rate, but NSS solutions rely on assumptions that do not translate well to fast-exchanging analytes such as in APT or hydroxylCEST[2]. Here, we present experimental data on the agreement between exchange rate fitting of ammonium chloride (NH_4Cl) for SS and NSS experiments with and without potassium hydrogen phthalate (KHP) buffer, using single- and multi-concentration fitting at multiple B_1.

METHODS:

NH_4Cl solutions (5mM to 1M) were prepared through serial dilution in either 275mM KHP or deionized water, both doped with 200μM Gadavist to reduce T_1 for shorter experimental protocols. Samples were loaded into 750μL culture tubes and sealed with Teflon tape. Imaging was performed on a 300MHz Bruker Ascend vertical bore at 0.47 mm in-plane resolution, 1 mm slice thickness. Temperature was maintained within ±0.1ºC using a water bath and fibre optic temperature probe. An inversion recovery T_1 map, WASSR B_0 map, and a multi-flip angle (FA) high FA B_1 map were acquired for Z-spectrum correction. Saturation durations were 200, 585, 1710, or 5000 ms, with saturation B_1 at 0.3, 0.6, or 1.2μT, covering NSS to SS saturation conditions for TR = 5100 ms. The Z-spectrum was sampled at 0.1 ppm intervals across -4 to 4 ppm. ROIs were drawn conservatively to reduce partial volume effects in Aedes, and ROI-mean spectra were fit in MATLAB 2023a using either a NSS discrete time step solver or a SS fit with single- or multi-concentration fits. Initial fit parameters were closest order of magnitude from literature values to mitigate stalling. Markov chain Monte Carlo (MCMC) sampling of the fitting space was used to ensure a minimum was found.

RESULTS:

Fitting Method\Parameter	R_{ex} (Hz)	$T_{2,C1}$ (ms)
Buffered NSS MC ST Fitting	175 ± 9	13 ± 1
Buffered NSS ST Fitting	190 ± 60	16 ± 4
Buffered SS MC ST Fitting	178 ± 7	15 ± 2
Buffered SS ST Fitting	192 ± 33	15 ± 5
Unbuffered MC NSS ST Fitting	129 ± 11	11 ± 1
Unbuffered NSS ST Fitting	53 ± 4	43 ± 4
Unbuffered SS ST Fitting	52 ± 3	32 ± 2
Lit. Unbuffered SS ST Fitting [3]	53 ± 5	13 ± 1
Lit. Buffered SS ST Fitting [4]	160 ± 7	40 ± 2

Table 1. Comparison of Z-spectrum fitting parameters for exchange rate, R_{ex}, and T_2 of the solute pool C1 (NH_4Cl) by experiment type and fitting method. MC indicates a multi-concentration fit, SS indicates a steady state fit on SS data, and NSS indicates a NSS fit across all saturation durations. Literature values for both citrate-buffered and unbuffered NH_4Cl solutions are provided for comparison

DISCUSSION:

The presence and identity of buffer affected R_{ex} most. To quantify solute R_{ex} for clinical translation of qCEST, buffers that accurately emulate physiological conditions will be necessary. Multi-concentration fitting substantially reduced fitting uncertainty, providing greater precision in R_{ex} determination. SS and NSS experiments and corresponding fitting show agreement, with SS fitting of SS experimental data providing higher precision. Buffered MC SS and unbuffered MC SS fitted R_{ex} agree with their respective literature values.

CONCLUSION:

Accurate determination of CEST R_{ex} was most precise when using an MCMC MC SS fitting. Future characterization of R_{ex} for CEST solute quantification and clinical translation of qCEST will require determination of buffers that accurately emulate physiological conditions in the compartments in which clinical CEST measurements will be made.

REFERENCES:

1. Jones K, *et al.* JMRI 2018;47:11-27.
2. Sun P, Magn Reson Med 2021;86(2):765-776.
3. Chan R, *et al.* Magn Reson Med 2019;82(5):1684-1699.
4. Desmond K, *et al.* Magn Reson Med 2012;67(4);979-990.