Quantitative pH and Temperature Mapping In Vivo

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INTRODUCTION: The pH and temperature (T) represent two valuable imaging biomarkers for the assessment of many diseases (e.g., cancer, inflammation, stroke and neurodegenerative diseases). In principle, pH and T mapping is feasible by means of endogenous CEST signals, which originate mainly from proteins and metabolites within cells.[1] In fact, the complete information about pH and T is hidden within the measured exchange rate $k_{ex}(pH,T)$. However, state-of-the-art methods do not allow for isolation of the pH and T components of k_{ex}.
The aim of this study was to develop a method that allows for isolation of pH and T in order to enable quantitative pH and T mapping in vivo. We hypothesize that this can be realized at B_0=7T by using (i) extracted $k_{ex,s}$ from endogenous s=amide, amine and guanidino protons ($\Delta\omega_{amide}$=3.5, $\Delta\omega_{amine}$=2.7 and $\Delta\omega_{gua}$=2.0 ppm, respectively) in combination with (ii) a numerical lookup-based approach.

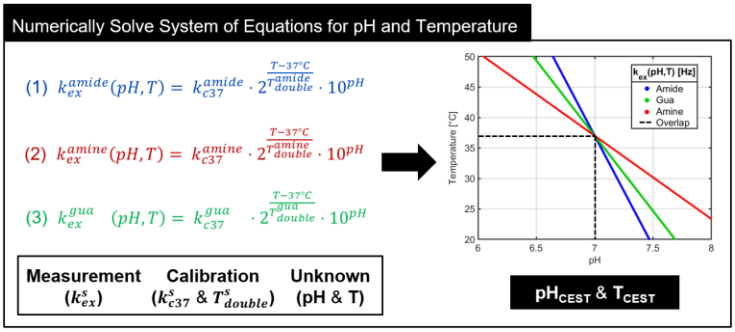

Fig. 1: The system of equations (left) can be numerically solved for pH_{CEST} and T_{CEST} (right) using a lookup-based approach encompassing k_{ex}(pH,T) for s = amide, amine, and guanidino protons (colors). This enables quantitative pH and temperature mapping.

THEORY and METHODS: Recently, we extended our method for quantitative pH mapping in vivo[2-4] by introducing an exponential T dependency of the calibration parameter (k_c), yielding[5]: $k_{ex}(pH,T) = k_c(T) \cdot 10^{pH} = k_{c37} \cdot 2^{\frac{T-37°C}{T_{double}}} \cdot 10^{pH}$ [Eq.1]. Here, k_{c37} represents the value of k_c at T=37°C and T_{double} represents the T increase for which the value of k_c, and thus k_{ex}, doubles. For each proton species s, this theoretical framework enables the complete description and calculation of $k_{ex,s}$(pH,T) lookup tables using only two calibration parameters (i.e., $k_{c37,s}$ and $T_{double,s}$). For any individual proton species s, it is not possible to isolate the pH and T components of the measured $k_{ex,s}$(pH,T). However, (i) Eq.1 holds true for each s, i.e. yielding a system of n_s=3 equations (Fig.1, left), and, more importantly, (ii) the calibrated values of k_{c37} and T_{double} are distinct and characteristic for each s,[5] thus enabling to numerically solve for pH_{CEST} and T_{CEST} (Fig.1, right).
The lower leg muscle of one healthy volunteer was measured (B_0=7T, whole-body MR scanner, Siemens). All examinations were approved by the local ethics committee. Written informed consent was received before examinations. Acquisition of CEST data and calculation of the relaxation-compensated MTR_{Rex}[6] at multiple B_1 [0.3:0.1:0.9 µT] allows for precise extraction of $k_{ex,s}$ ∀s.[2,3] Using literature values[5] of $k_{c37,s}$ and $T_{double,s}$ allows for calculation of quantitative pH and T maps by numerically solving for pH_{CEST} and T_{CEST} in each voxel (Fig.1). CEST data was corrected for B_0 and B_1 inhomogeneities.[7,8]

RESULTS and DISCUSSION: For the measured $k_{ex,s}$ of each proton species s, using Eq.1 enables voxel-wise calculation of distinct pairs of values (pH_s,T_s) that are represented as straight lines (Fig.1) in the parameter space (pH,T). Assuming that all n_s signals within one voxel originate from the same micromolecular environment, it follows that pH and T must be the same for all s. In an ideal measurement of $k_{ex,s}$, the true (pH_{true},T_{true}) are given by the point of intersection. However, in a real CEST experiment, the measured values of $k_{ex,s}$ will be somewhat erroneous. Therefore, a weighted approach can be used to obtain broader sets of (pH_s,T_s), with their overlap yielding an estimated value of pH and T (i.e. pH_{CEST} and T_{CEST}).
The application in vivo to human lower leg muscle showed plausible values of pH_{CEST} = 6.98 ± 0.46 and T_{CEST} = 35.52 ± 1.57 °C (Fig.2), in good agreement with literature[9-11], thus supporting the proposed method and the transferability of in vitro calibrated values (k_{c37} and T_{double})[5] for examinations in vivo. However, the influence of the specific chemical environment and buffer/ion concentration[5,12,13] on k_{ex} needs to be further investigated. In the future, the obtained pH_{CEST} and T_{CEST} can be validated directly in vivo by correlation with ^{31}P MRSI pH data.[9,10]

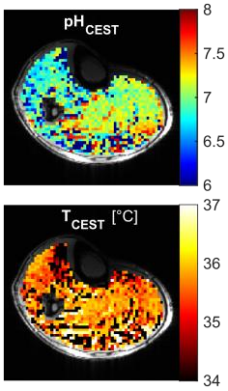

Fig. 2: Application in vivo to human lower leg muscle.

CONCLUSION: We presented a novel method that enables quantitative pH and temperature mapping in vivo. This was accomplished by exploiting the different temperature dependencies (T_{double}) of endogenous amide, amine and guanidino CEST signals to isolate the pH and temperature components of k_{ex}(pH,T), which previously was not possible. Applicability in vivo was demonstrated in the human lower leg muscle showing an average pH_{CEST} and T_{CEST} of approximately 7.0 and 35.5°C.

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