An optimized T1nom Approach for Super Fast Measuring Enzyme Kinetics in vivo using Saturation Transfer Technique

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Introduction Magnetization saturation transfer (ST) is a most commonly used technique in ^{31}P MRS to non-invasively measure the enzyme kinetics of phosphoryl-exchange reactions such as the creatine kinase (CK) and ATPase reactions. Despite of the simple algorithm for quantification of unidirectional kinetic constant, the lengthy acquisition time of conventional ST approach precludes the applications for *in vivo* enzyme kinetics imaging where large scan numbers are employed for spatial encoding such as 3D chemical shift imaging (CSI). We have previously proposed a "$d_{1,opt}$" approach for ST that significantly reduces the total acquisition time [1], however, moderately long TR is still required and thus unsatisfied with the demand of 3D-CSI. Here, an *optimized* "T_1^{nom}" approach is presented which features with arbitrary TR, flip angle and same simple quantification algorithm, thus making it suitable for imaging enzyme kinetics *in vivo*.

Theory The T_1^{nom} approach is elucidated with an example of three-site model for chemical exchanges of high-energy phosphates (PCr↔ATPγ↔Pi). For conventional approach, the unidirectional forward rate constants (k_f) for PCr→ATPγ or Pi→ATPγ reactions can be directly determined with two spectra with (M_{ss}) or without (M_0) adequate saturation of ATPγ resonance according to Eqn (1) if intrinsic T_1 (T_1^{int}) of PCr or Pi is known. Accurate measurements of M_0 and M_{ss} require long TR (>3 T_1^{mix}) and saturation time (>3T_1^{app}) [2, 3]. Alternatively, the T_1^{nom} approach employs arbitrarily short TR and flip angle to acquire the two spectra, and thus two steady-state magnetizations (M_c and M_s) will be obtained instead of M_0 and M_{ss} in Eqn (1). By simulating the modified Bloch-McConeell equations we found that Eqn (2) generally holds for wide ranges of TR and flip angle. The extra saturation factor from TR and flip angle mainly affects the slope of the linear relation between k_f and the ratio of M_c/M_s, while α is always close to 1. This slop is named as T_1^{nom} (nominal T_1) and can be easily determined from simulation with the known information of TR, flip angle and intrinsic T_1 values. T_1^{nom} is less than but approaches to T_1^{int} as TR increases or flip angle decreases.

$$k_f = \Big/ \frac{M_0 - M_{ss}}{M_{ss}} \Big/ T_1^{int} \Leftrightarrow \frac{M_0}{M_{ss}} \approx 1 + k_f T_1^{int} \quad (1)$$

$$k_f \approx \frac{M_c - \alpha M_s}{M_s} \Big/ T_1^{nom} \Leftrightarrow \frac{M_c}{M_s} \approx \alpha + k_f T_1^{nom} \quad (2)$$

$$K_{flip} = \left(\frac{\delta k_f}{k_f}\right)_{flip} \Big/ \left(\frac{\delta flip}{flip}\right) \approx \frac{\partial T_1^{nom}}{\partial flip} \frac{flip}{T_1^{nom}} \quad (3)$$

$$\left(\frac{\delta k_f}{k_f}\right)_{SNR} = \frac{\sigma}{\sqrt{t}} \frac{M_c/M_s}{M_c/M_s - \alpha} \frac{\sqrt{TR}}{M_c} \sqrt{1+\left(M_c/M_s\right)^2} \quad (4)$$

Optimization The optimization of T_1^{nom} approach is based on human brain data from references [2, 3] to serve as a general guideline for finding the range of TR and flip angle pairs that can provide the most accurate k_f measurement within a given acquisition time. Three types of errors that would influence the accuracy of final k_f measurement are considered for the optimization. I. Deviation of Eqn (2) from linearity. For most practical TR/flip angle ranges, type I error is quite small (Fig 1). Here a type I error level ≤ 1% is chosen as a criterion for the optimization (Fig 2, green lines). II. Error from flip angle variation. Flip angle inaccuracy is commonly observed with surface coil or at ultra-high magnetic field. Here we introduce the ratio of relative k_f measurement error to relative flip angle error (K_{flip}) to characterize this type of error. Following analysis we show that K_{flip} can be expressed by Eqn (3). Optimization based on Eqn (3) favors smaller flip angle or longer TR. This is consistent with the initial simulation results showing that Eqn (2) approaches to Eqn (1) as flip angle decreases or TR increases. Here we arbitrarily choose $|K_{flip}|$=0.5 as an acceptable criterion to guild optimization (Fig 2, blue lines). III. Error propagation from M_c and M_s measurements with finite SNR. Measurements of M_c and M_s from spectra are subject to errors depending on the spectral SNR. Their influence on the accuracy of k_f is governed by error propagation theory as shown in Eqn (4). Here σ and t stand for the intrinsic spectrometer noise level and total acquisition time respectively, and both are independent of TR and flip angle. Optimization based on Eqn (4) leads to unique solutions of TR and flip angle pair which also depends on the k_f value. Alternatively, by defining a confident range of k_f for a specific study (e.g., k_f= 0.15~0.6 s^{-1} and 0.09~0.36 s^{-1} for human brain CK and ATPase reactions, respectively), we can achieve a minimum of relative k_f error due to finite SNR within the k_f range. Then by setting a tolerance level (i.e., the ratio of actual k_f error to the minimal achievable value) we can find a range of TR/flip angle pairs. Here a tolerance level of 1.2 is chosen as a demonstration to guild optimization (Fig 2, brown lines). By taking into consideration of all three criterion, an optimized range of TR/flip angle pair for T_1^{nom} approach can be obtained (Fig 2, shaded areas).

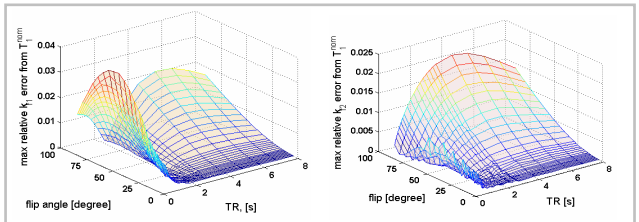

Fig 1. Plot of simulated type I error for CK (left) and ATPase (right) reactions.

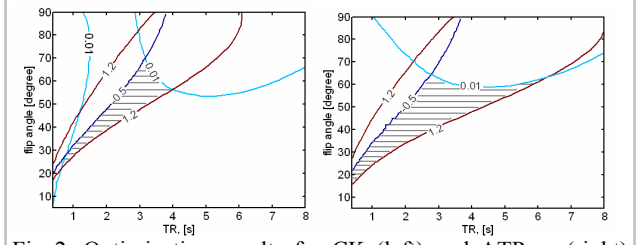

Fig 2. Optimization results for CK (left) and ATPase (right) reactions. The shaded areas represent the TR/flip angle range that satisfies criteria of all three types of errors.

Discussions An important assumption for T_1^{nom} approach is the prior knowledge of T_1^{int} value, which is also required in Eqn (1) for conventional approach. T_1^{int} is commonly accepted as a constant independent from workload or energetic status as suggested by a number of studies. Therefore, reliable T_1^{int} values can be retrieved from literature research or a pilot study of a few subjects. Nevertheless, care should be taken since T_1^{int} values could vary with different magnet field strength or under extreme pathological conditions. The only extra information required by T_1^{nom} approach is the estimation of pool size ratio (PCr/ATPγ or Pi/ATPγ), which is also subject to fluctuation especially for intervention or stimulation studies. This issue can be partly reconsolidated by the relative insensitivity of T_1^{nom} approach upon pool size ratios. Simulation showed that for TR and flip angle within the shaded area (CK reaction), a fluctuation of pool size ratio will result in an extra, small k_f error with 8 folds reduction in amplitude (e.g., a 20% change of PCr/ATPγ will results in a k_f error less than 2.5%). Furthermore, in case of large change of pool size ratio, corrections can be made by comparing the peak ratios of the control spectrum (no saturation) with those in condition of normal pools size ratio. Simulation showed that the correction by control spectra would confine the estimation error of pool size ratios within 5%, which in turn will lead to a negligible k_f error of <1%. The T_1^{nom} approach has been applied to human brain 3D-CSI data for quantifying k_f which will be reported separately. Finally, this approach should be readily applied to other organs (e.g., heart) beyond the brain.

References: [1] Xiong Q, *et al.*, *AJP*, 2009. [2] Du F, *et al.*, MRM, 2007. [3] Lei H, *et al.*, PNAS, 2003.

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