An Improved Magnetization Saturation Transfer Approach---$T_{1,nom}$ for Rapidly Measuring and Quantifying CK Activity in the Rat Brain

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Introduction: The chemical exchange reactions (PCr→ATP→Pi) catalyzed by the creatine kinase (CK) and ATPase enzymes play key roles in maintaining brain function. In vivo $^{31}$P-MRS combined with magnetization saturation transfer (ST) approach provides a unique tool for assessing the reaction rate constants ($k_f$ and metabolic fluxes. The accurate $k_f$ quantification usually requires a very long repetition time ($tr$) for approaching a steady-state saturation condition, however, it suffers from low detection sensitivity and limited utility for biomedical application. This problem could be partially overcome by shortening $tr$, allowing more signal averages. However, it makes $k_f$ quantification complicated due to so-called saturation effect caused by short $tr$ (but not $k_i$). Therefore, it is crucial to develop different approaches able to rapidly measuring and quantifying CK and ATPase enzyme activities in vivo. Several methods have been proposed [1-2]. In this work, we present an improved magnetization ST approach---$T_{1,nom}$ by correcting the partial saturation effect with short $tr$. This approach was tested in the rat brain.

Method and Experiment: Magnetization saturation transfer method illustrated in Fig. 1 has been popularly used to measure chemical exchange fluxes of reactions among PCr, ATP and Pi. In the case of a frequency-selective RF pulse train with a long saturation time ($tr_{sat}$) for completely saturating the $\gamma$-ATP resonance and the magnetization of PCr or Pi reaches a steady-state, the unidirectional forward chemical exchange constant ($k_f$) can be deduced by Eq.1 [3, 4], in which $M^r$ and $M^s$ are magnetization of PCr or Pi at thermal equilibrium without saturation and steady-state with saturation, respectively. $T_{1,i}$ is the intrinsic relaxation time of PCr or Pi. This method is well known as the steady-state magnetization saturation transfer. For the convenience, we rewrite Eq. 1 as Eq. 2. But it is worth to reminding that Eq. 1 only holds under full relaxation condition. In order to improve SNR, a short $tr$ is desired. Generally the magnetizations in the presence ($M_s$) and absence of saturation ($M_i$), as well as their ratio are the function of many given experimental parameters and it was indicated by Eq. 3.

$$k_f = \frac{M^r - M^s}{M^r} \times \frac{1}{T_{1,i}}$$

In Eq. 3, chemical exchange conditions of CK and ATPase reactions are applied. Therefore, the reverse chemical exchange constants of CK and ATPase are explicitly dependent on the forward chemical exchange constants, and not shown in the equation. $T_{1,i}$ and $T_{1,s}$ values of three chemically coupled spins (PCr, $\gamma$-ATP and Pi) have been measured in a previous study [5]. Therein, we can simulate the magnetizations ratios of $M_i$ and $M_s$ as function of chemical exchange rate constants and repetition times using the modified Bloch-McConell equations [3] and known parameters in Eq. 3. The purpose is to obtain $k_f$ with any specific $tr$ and flip angle ($\beta$). All the in vivo $^{31}$P experiments were conducted at 9.4T animal scanner located at the University of Minnesota. A dual RF surface-coil probe consisting of a butterfly-shape $^1$H surface coil and an elliptical-shape $^{31}$P surface coil was used for acquiring anatomy images, $B_0$-shimming and in vivo $^{31}$P spectra. The pulse sequence was illustrated in Fig.1. A BISTRO saturation pulse train scheme and an adiabatic pulse, BIR4 with 45° flip angle (BIR4-45), were used to saturate $\gamma$-ATP resonance and to read out $^{31}$P signal, respectively. To test the performance of adiabatic pulse, a phantom of inorganic phosphate solution ($[Pi]=0.1M$, pH=7.0) was prepared. Five male Sprague-Dawley rats anesthetized with 2% isoflurane were used to acquire in vivo $^{31}$P-MRS with two different repetition times (1 and 3s) and 256 signal averages. The femoral arteries of rats were catherized for blood sampling and physiology monitoring. All surgical procedures were approved by the Institutional Animal Care and Use Committee of the University of Minnesota.

Results and Discussions: An accurate flip angle is critical for $k_f$ quantification. We have tested the performance of BIR4-45 pulse and results were demonstrated in Fig. 2, showing an excellent pulse behavior. The simulated magnetization ratios of $M_i$ and $M_s$ with varied $tr$ were shown in Fig. 3. Obviously when $tr \geq 4T_{1,i}$ (such as $tr=10$ or 30 s, or near full relaxation condition), the ratio of $M_i/M_s$ is a linear function of $k_f$ and the relation approach Eq. 2 with the slope of $T_{1,s}$. Thus, $k_f$ can be deduced as long as $T_{1,s}$ is available. This conventional strategy has been applied to determine the $k_f$ values in the rat brain at 9.4T [5]. For instance, from the previously measured $T_{1,s}$ of PCr (i.e. the slope of the green line in Fig. 3) and the magnetization ratio (the circle in Fig. 3), $k_f$ of CK was deduced as 0.24 s$^{-1}$[5]. When $tr$ is short, however, the ratio of $M_i/M_s$ will be governed not only by $k_f$ and $T_{1,s}$ but also by the repetition time, flip angle and saturation time. In the rat brain with the same animal preparation as the previous study [5], the ratios of $M_i/M_s$, measured with two different $tr$ values (1 and 3 s) in the present study show a good agreement with the predicted values indicated in Fig. 3. In principle, $k_f$ can be estimated from simulations with any arbitrary parameter setup. However, it is more interesting that a simple, linear function following Eq. 4 is still satisfied at a wide range of $tr$. Eq. 4 is very similar to Eq. 1 except that $T_{1,nom}$ is the nominal $T_{1,i}$ indicated by Eq. 5 with a correction factor. The $T_{1,nom}$ value and Eq. 4 can be applied to determine $k_f$ using two spectra (for measuring the $M_i/M_s$ ratio) acquired with desired $tr$ and $\beta$.

$$T_{1,nom} = k_f T_{1,nom} + a$$

In conclusion, $T_{1,nom}$ approach should provide a simple quantification algorithm to rapidly measure chemical exchange fluxes in vivo.


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