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Balanced Steady-State Free Precession (bSSFP) from an effective field perspective: Application to the detection of chemical exchange (bSSFPX)

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ABSTRACT

Chemical exchange saturation transfer (CEST) is a novel contrast mechanism and it is gaining increasing popularity as many promising applications have been proposed and investigated. Fast and quantitative CEST imaging techniques are further needed in order to increase the applicability of CEST for clinical use as well as to derive quantitative physiological and biological information. Steady-state methods for fast CEST imaging have been reported recently. Here, we observe that an extreme case of these methods is a balanced steady-state free precession (bSSFP) sequence. The bSSFP in itself is sensitive to the exchange processes; hence, no additional saturation or preparation is needed for CEST-like data acquisition. The bSSFP experiment can be regarded as observation during saturation, without separate saturation and acquisition modules as used in standard CEST and similar experiments. One of the differences from standard CEST methods is that the bSSFP spectrum is an XY-spectrum not a Z-spectrum. As the first proof-of-principle step, we have implemented the steady-state bSSFP sequence for chemical exchange detection (bSSFPX) and verified its feasibility in phantom studies. These studies have shown that bSSFPX can achieve exchange-mediated contrast comparable to the standard CEST experiment. Therefore, the bSSFPX method has a potential for fast and quantitative CEST data acquisition.

1. Introduction

Chemical exchange saturation transfer (CEST) as a new contrast mechanism in MRI is gaining popularity [1,2]. It employs selective saturation of protons in a specific chemical group which transfers to water via chemical exchange to (i) indirectly visualize the low concentration metabolites which are not observable in conventional MR scans and (ii) indicate quantitative environmental parameters such as pH. Many promising preclinical and clinical applications have been investigated using CEST imaging techniques including but not limited to: brain tumor imaging [3–6], brain ischemia [7], prostate cancer [8], breast cancer [9,10], kidney pH measurement [11] and cartilage quality assessment [12,13].

However, a successful translation of CEST into clinical applications is hampered in part by its time-consuming acquisition. Typically, the CEST pulse sequence utilizes a long saturation pulse followed by data acquisition. To correct for the artifacts due to B_0 inhomogeneity, and/or to acquire information about multiple exchanging sites, CEST often employs a series of off-resonance saturation pulses to acquire the so-called Z-spectrum. Moreover, exchange rate quantification methods that lead to metabolite distribution maps or pH measurements require several repetitions of the entire experiment with different saturation time or power [14]. Hence, the already time-consuming whole Z-spectrum acquisition becomes even more time-consuming for exchange rate quantification and 3D CEST imaging. Therefore, seeking faster alternative ways for CEST data acquisition is highly desired.

Recently, steady-state methods for fast CEST imaging were reported, where the long saturation irradiation was split into short parts with intermittent acquisition [15,16]. In steady-state methods, the data acquired first (with shorter saturation time) fills the outer portion of the k-space and the data acquired later (with longer saturation time) fills the center of the k-space. By doing so, the acquisition time is shortened. The extreme case of this approach would be a train of RF pulses with intervals for data acquisition. We observe that this is, in essence, a balanced

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steady-state free precession (bSSFP or FISP) sequence: a train of RF pulses interleaved with balanced gradients for image acquisition.

At the core of our work is the realization that the bSSFP sequence in *itself* is sensitive to the exchange processes, hence no additional saturation, preparation or separate detection pulses are needed to create the CEST effect. Here, the bSSFP spectral profile is collected at multiple frequency offsets. The analysis of the resulting profile provides information about the exchanging moieties, similar to CEST or off-resonance $T_{1\rho}$ experiments. This method, using bSSFP sequence for chemical exchange detection shall be dubbed here bSSFPX (bSSFP for eXchange detection). bSSFPX provides a new way for CEST data acquisition: the acquisition is performed *during* the saturation. Thus, it may speed up the CEST experiment. Also, the bSSFPX method should allow acquisition while the system approaches the steady-state, thus providing the data for QUEST-like quantification [14] in a "single-shot". Notably, in this method we are observing the XY-component of the magnetization and not the Z-component, as is standard in Z-spectroscopy.

Properties of equally spaced pulses have been investigated since the 1960s [17]. Specifically, theory and experiments performed in solid-state NMR had shown that the train of equally spaced pulses creates an effective lock field, similar in its action to the continuous-wave (CW) lock [18–20]. Two cases were thoroughly investigated: with same phase [19] and with 180° phase advance between the pulses [18]. It has been shown that this pulsed spin lock affects the dipolar interaction in the way similar to the application of the CW irradiation.

Since the introduction by Carr in 1958 [21], the basic principles and theory of the steady-state signals (FISP or SSFP) generated by the repetitive pulses, has been explored in numerous publications, including the iconic work by Freeman et al. [22]. Since the introduction of FISP or SSFP imaging combined with balanced gradients (TrueFISP or bSSFP), numerous studies investigated the sequence properties [23–35]. To name a few examples, bSSFP was combined with inversion recovery to continuously acquire data for T_1 quantification [26]. The sequence has been used for fast T_2 mapping (DESPOT2 [28]). The multicomponent T_1 and T_2 relaxation in bSSFP has been investigated (mcDESPOT [29]). Miller et al. investigated asymmetries observed in bSSFP [36]. Bieri and Scheffler have investigated properties of bSSFP to modulate magnetization transfer effects [37]. However, to the best of our knowledge, this is the first time that the *spin-locking* and *off-resonance saturation-transfer* properties of the imaging sequence are investigated, thus explicitly realizing and exploring the analogous nature of bSSFP and CEST/$T_{1\rho}$ experiments.

In this paper, we are implementing the bSSFPX method in the steady-state. We are demonstrating the ability of bSSFPX to create CEST-like effects by theoretical derivation, simulation and phantom study. We are comparing the results of a bSSFPX experiment with that of the standard pulsed CEST experiment. The comparison demonstrates that the bSSFPX method provides contrast comparable to the standard method. Thus, bSSFPX is a highly promising approach to achieve fast and quantitative CEST imaging.

2. Theory

Here, we present the description of the magnetization dynamics under the influence of the train of RF pulses using effective field formalism, thus bridging bSSFP with CEST/$T_{1\rho}$. First, the detailed derivation will be given assuming no exchange. Second, the approximation of the exchange contribution will be discussed. The more accurate and quantitative description of exchange influence will be presented in a subsequent publication.

The pulse sequence for 2D steady-state bSSFPX (ss-bSSFPX) imaging is shown in Fig. 1: a large number of prep-echoes followed by a single imaging acquisition. The prep-echoes are to ensure that the observed magnetization is in the steady-state. The basic repetitive nth unit of this sequence is $[\alpha_{\phi_0+(n-1)\Delta\phi} - TR]$, where α is the flip angle, ϕ_0 is the phase of the first RF and $\Delta\phi$ is the phase advance between two consecutive RF pulses. In a typical bSSFP experiment, $\Delta\phi = 0$ or π. Since the sequence consists of a number of the repeating basic units, the phase advance can be treated as the frequency offset by an amount $\Delta\phi/(2\pi TR)$ [38]. In the bSSFP, all the gradients are balanced over one TR. In other words, the net gradient over one TR is 0. Hence, the influence of gradients can be ignored and the evolution of magnetization at the echo times or the end of each unit is governed solely by RF [27]. For simplicity and without loss of generality, the following derivations assume $\phi_0 = 0$ which makes the basic unit of the bSSFP sequence $[\alpha_{(n-1)\Delta\phi} - TR]$.

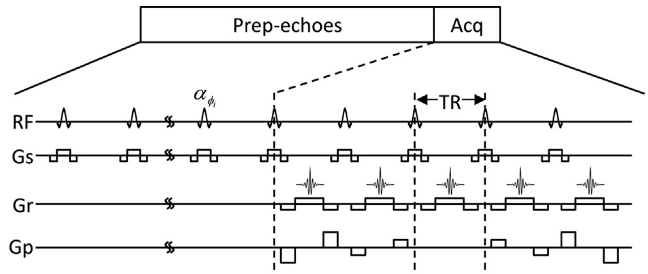

Fig. 1. The schematic for the 2D steady-state bSSFPX pulse sequence. Prep-echoes: preparation echoes needed to reach the steady-state. Acq: acquisition.

The signals acquired by a bSSFP sequence are from M_{xy}. Therefore, the bSSFPX method is observing and analyzing an XY-spectrum for the CEST effect.

2.1. Effective field

First, consider the simplest case in which only one pool is present and $TR \ll T_1$ & T_2 and the influence of relaxation can be ignored. In the absence of relaxation, the propagation of magnetization over one cycle is given by:

$$M_{n+1} = R_z(\theta)R_x(\alpha)M_n = R_{\vec{e}}(\Phi)M_n = e^{H_{eff}TR}M_n \tag{1}$$

where M_{n+1} and M_n are the magnetization vectors at the end of $n+1$ and n cycle. $R_z(\theta)$ and $R_x(\alpha)$ are the standard z- and x-rotation matrices respectively. $\theta = 2\pi\Delta_w TR - \Delta\phi$ is the precession angle, where Δ_w is the off-resonance [30,38]. The propagation of the magnetization is given by two consecutive rotations and thus, in accordance with Euler theorem, can be represented by a single rotation. The composite rotation is described by the directionality vector $\vec{e}$ and the rotation angle Φ [30]. To be specific, $\vec{e}$ represents the axis of rotation about which M_n rotates by the angle Φ. Using Euler parameters, the directionality vector and the rotation angle are:

$$\vec{e} = \begin{bmatrix} e_1 \\ e_2 \\ e_3 \end{bmatrix} = \vec{u}\sin(\Phi/2), \quad e_0 = \cos(\Phi/2) \text{ with } \begin{matrix} e_0 = \cos(\alpha/2)\cos(\theta/2) \\ e_1 = \sin(\alpha/2)\cos(\theta/2) \\ e_2 = \sin(\alpha/2)\sin(\theta/2) \\ e_3 = \cos(\alpha/2)\sin(\theta/2) \end{matrix} \tag{2}$$

where $\vec{u} = (u_1, u_2, u_3)^T$ is the unit vector in the same direction as $\vec{e}$, hence: $u_1 = e_1/\sqrt{1-e_0^2}$, $u_2 = e_2/\sqrt{1-e_0^2}$ and $u_3 = e_3/\sqrt{1-e_0^2}$. In addition, using Eq. (2), the angle Θ between the effective field and the z-axis can be found:

$$\cos(\Theta) = \frac{e_3}{\sqrt{1-e_0^2}} = \frac{\cos(\alpha/2)\sin(\theta/2)}{\sqrt{1-\cos^2(\alpha/2)\cos^2(\theta/2)}} \tag{3}$$