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Exchange-mediated contrast in CEST and spin-lock imaging

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ABSTRACT

Purpose: Magnetic resonance images of biological media based on chemical exchange saturation transfer (CEST) show contrast that depends on chemical exchange between water and other protons. In addition, spin–lattice relaxation rates in the rotating frame ($R_{1\rho}$) are also affected by exchange, especially at high fields, and can be exploited to provide novel, exchange-dependent contrast. Here, we evaluate and compare the factors that modulate the exchange contrast for these methods using simulations and experiments on simple, biologically relevant samples.
Methods: Simulations and experimental measurements at 9.4 T of rotating frame relaxation rate dispersion and CEST contrast were performed on solutions of macromolecules containing amide and hydroxyl exchanging protons.
Results: The simulations and experimental measurements confirm that both CEST and $R_{1\rho}$ measurements depend on similar exchange parameters, but they manifest themselves differently in their effects on contrast. CEST contrast may be larger in the slow and intermediate exchange regimes for protons with large resonant frequency offsets (e.g. >2 ppm). Spin-locking techniques can produce larger contrast enhancement when resonant frequency offsets are small (<2 ppm) and exchange is in the intermediate-to-fast regime. The image contrasts scale differently with field strength, exchange rate and concentration.
Conclusion: CEST and $R_{1\rho}$ measurements provide different and somewhat complementary information about exchange in tissues. Whereas CEST can depict exchange of protons with specific chemical shifts, appropriate $R_{1\rho}$-dependent acquisitions can be employed to selectively portray protons of specific exchange rates.

1. Introduction

There is continuing interest in developing and exploiting novel contrast mechanisms in proton magnetic resonance imaging (MRI) to characterize tissues. Proton exchange between water and exchangeable protons in other molecules provides one such mechanism that reports the presence of specific chemical components within a mixture. Methods such as chemical exchange saturation transfer (CEST) depend explicitly on exchange between water and protons with specific chemical shifts, but other approaches may also be affected by exchange on appropriate time scales, especially at high magnetic fields. In particular, exchange between sites of different chemical shifts contributes directly to both transverse relaxation rates (R_2) and spin–lattice relaxation rates in the rotating frame ($R_{1\rho}$). Here we compare and contrast the sensitivity and selectivity for producing contrast based on exchange processes of CEST with a novel approach based on measurements of $R_{1\rho}$.

The dynamics of exchange with amide and hydroxyl sites in particular have been extensively exploited to generate contrast in CEST imaging [1,2]. To interpret CEST data, protons are considered to comprise at least two pools, the solvent water and the exchangeable protons in the solute, as shown in Fig. 1. Each pool is characterized by its own relaxation times and chemical shift, but they communicate via chemical exchange at specific rates. Where the exchanging species is largely derived from a singular tissue constituent, such as glycogen (glycoCEST) or gycosaminoglycans (gagCEST), the endogenous CEST contrast potentially reports on the concentrations of specific molecules in tissues [3,4]. In addition, exogenous agents such as paramagnetic chelates have been developed to shift proton resonance frequencies to increase exchange effects (paraCEST) [5,6], while common x-ray contrast agents which contain exchanging amide and hydroxyl groups have also been shown to produce significant CEST effects [7,8] and therefore are also potential MRI contrast agents. However, in practice, CEST signal changes may be contaminated by non-specific magnetization transfer and nuclear Overhauser effects, and are sensitive to the effects of direct

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saturation as well as field inhomogeneities. In addition, the derivation of explicit information on exchange rates or molecular concentration requires the acquisition of multiple images and fitting the data to a model.

Measurements of $R_{1\rho}$ using spin-locking sequences are also sensitive to exchange effects at high fields but are less affected by some of the above considerations and are differently influenced by other factors, including the field strength and exchange rates. Here, we present simulations and experimental data to illustrate the influences of factors that affect signals in both CEST and spin-lock imaging and to quantify how specific parameters such as exchange rate and field strength modify contrast. The sensitivities of CEST and spin-locking (SL) techniques to chemical exchange effects in specific experimental regimes are predicted theoretically and measured experimentally and used to quantify contrast in polypeptide and sugar systems of biologic interest.

CEST methods include radiofrequency (RF) saturation of an exchanging species, which is then transferred to water, reducing its longitudinal magnetization. This change does not, in the ideal case of perfectly selective RF saturation, explicitly depend on the chemical shift of the irradiated protons. In practice, RF saturation is applied at a series of frequencies (offset $\delta\omega$ relative to the water peak), and the acquired images yield a "z-spectrum" of the signal intensity at each voxel in which peaks correspond to specific exchanging species. However, the RF pulses may also alter the water signal by direct saturation or non-specific magnetization transfer [9] with other broad resonances. One strategy to correct for these effects is to acquire images at the opposite frequency offset(s) for metabolites of interest. The difference in the normalized signals from opposite sides of the water peak is the magnetization transfer ratio asymmetry (MTR_{asym}):

$$MTR_{asym} = \frac{S(\omega_0 - \delta\omega) - S(\omega_0 + \delta\omega)}{S_0} \quad [1]$$

where $S(\omega)$ is the signal when the RF pulse is at frequency ω, S_0 is the signal without RF saturation, and ω_0 is the resonance frequency of water.

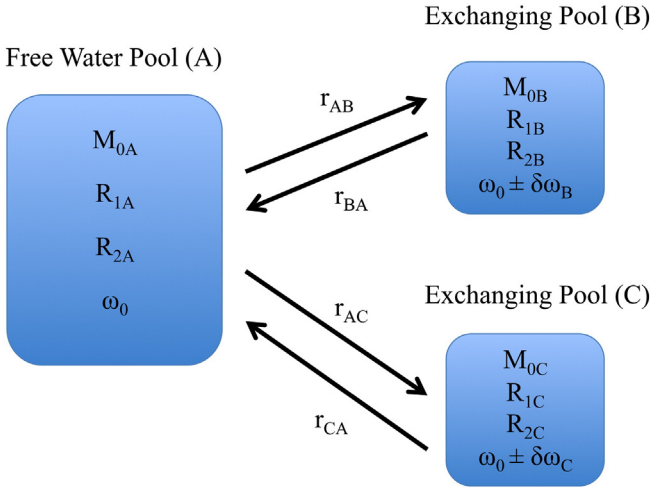

Fig. 1. Model of chemical exchange between a large pool of free water protons (A) and smaller pools of exchangeable protons B and C. The rate r_{AB} represents the exchange rate from free water to the exchangeable proton site, and r_{BA} is the reverse rate. The relaxation rates R_1 and R_2 and resonant frequency offsets $\delta\omega$ are the assumed independent parameters for each site and are distinguished by an appropriate subscript. The total magnetization $M_{0A} + M_{0B} + M_{0C} = 1$. There is negligible presumed communication between pools B and C, and a two-pool model is obtained by simply removing pool C.

Spin-locking techniques may also generate exchange-dependent contrast and can be implemented for imaging experiments [10,11]. Typically, a 90-degree adiabatic half-passage (AHP) pulse nutates longitudinal magnetization to the transverse plane, followed by a spin-locking pulse (B_1) on resonance for some duration. Another 90-degree reverse half-passage (RHP) pulse returns magnetization to the longitudinal axis, residual transverse magnetization is spoiled, and an imaging sequence may then acquire $R_{1\rho}$-weighted images. Relaxation rates in the rotating frame are sensitive to molecular interactions on the time scale defined by the locking field amplitude, B_1, about which magnetization would precess at frequency $\omega_1 = \gamma B_1$ [12,13]. Variations in $R_{1\rho}$ with locking field strength ($R_{1\rho}$ dispersion) can provide quantitative information on the relevant parameters that describe chemical and diffusive exchange [14–16]. In tissues, values of $R_{1\rho}$ are affected by slow molecular motions which modulate dipole–dipole interactions, but at high fields the increased separation of resonance frequencies between water and other chemical species gives rise to large contributions from chemical exchange whose magnitudes depend on the locking field amplitude and exchange rate.

CEST and SL techniques are both sensitive to chemical exchange effects, but have different constraints and sensitivities. Two important parameters are the chemical shift resonant frequency difference ($\delta\omega$) and the rate of proton exchange between the metabolite and free water (r_{BA}) [3,17]. As in conventional spectroscopy, exchange regimes in CEST can be divided into slow, intermediate, and fast exchange relative to the chemical shift between water and the exchanging species. In high-resolution spectroscopy, the chemical shift of an exchanging species must be greater than the exchange rate ($\delta\omega/r_{BA} > 1$) in order for individual peaks to be well resolved. As r_{BA} increases into the intermediate ($\delta\omega/r_{BA} \cong 1$) and fast ($\delta\omega/r_{BA} \ll 1$) exchange regimes, line broadening reduces the ability to resolve individual resonances. At moderate saturation power levels, CEST contrast exhibits similar exchange regimes and constraints due to the spectral blurring effects of the applied irradiation field. Faster exchange requires larger saturating field strengths in order to achieve solute saturation, and creates correspondingly larger blurring of z-spectra. However, if saturation requirements are reduced, the conventional exchange rate constraints can be stretched, allowing, for example, CEST peaks to be resolved when conventional spectroscopy peaks are blurred [1]. Nonetheless, CEST peaks are easiest to resolve in the slow exchange regime.

By contrast, fast exchange can be advantageous for affecting $R_{1\rho}$ values. Chemical exchange between sites of different chemical shift causes spin dephasing, which increases the difference between longitudinal (R_1) and transverse (R_2) relaxation rates, and thereby the dispersion of $R_{1\rho}$ with locking field, to a degree that increases with chemical shift and exchange frequencies. The values of $R_{1\rho}$ observed for different media (and therefore potential image contrast) may be selectively modulated by adjusting the amplitude of spin-locking pulses to reduce the contributions to relaxation of a specific range of exchange rates, up to the point where the rates become so large that the necessary locking field becomes impractical. In practice these rates can be much higher than those detectable by CEST.

Here we study the exchange in solutions of biologically relevant macromolecules (polypeptides and sugars) in order to better understand the factors that modulate exchange-based image contrast for CEST and $R_{1\rho}$ imaging, and examine the limits of each technique. We show, using theory, simulations and experimental measurements, how CEST contrast and a novel metric based on $R_{1\rho}$ dispersion may be used to emphasize the presence of protons characterized either by chemical shifts or by specific exchange rates.