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Chemical exchange saturation transfer imaging and spectroscopy

Jinyuan Zhou [a,b,*], Peter C.M. van Zijl [a,b]

[a] *Division of MR Research, Department of Radiology, Johns Hopkins University School of Medicine, 217 Traylor Building, 720 Rutland Avenue, Baltimore, MD 21205-2109, USA*

[b] *F.M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205-1832, USA*

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Contents

* Corresponding author. Address: Division of MR Research, Department of Radiology, Johns Hopkins University School of Medicine, 217 Traylor Building, 720 Rutland Avenue, Baltimore, MD 21205-2109, USA. Tel.: +1 410 955 7491; fax: +1 410 614 1948.
E-mail address: jzhou@mri.jhu.edu (J. Zhou).

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Nomenclature

2D	two-dimensional
APT	amide proton transfer
APTR	amide proton transfer ratio
BOLD	blood-oxygen-level-dependent
CEST	chemical exchange dependent saturation transfer
cs	complete saturation
CSF	cerebrospinal fluid
CW	continuous wave
DIACEST	diamagnetic chemical exchange dependent saturation transfer
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate acid
DOTMA	$\alpha,\alpha',\alpha'',\alpha'''$-tetramethyl-1,4,7,10-tetraacetic acid
DTMA	1,4,7,10-tetraazacyclododecane tetrakis(methylacetamide)
EPI	echo planar imaging
FSE	fast spin echo
IEPA	2-imidazol-1-yl-3-ethoxycarbonyl-propionate
LIPOCEST	CEST system using liposomes
LRP	lysine rich protein
LW	line width
MAC	middle cerebral artery
MACO	middle cerebral artery occlusion
MT	magnetization transfer
MTR	magnetization transfer ratio
PAA	polyallylamine
PARACEST	paramagnetic chemical exchange dependent saturation transfer
PBS	phosphate buffer solution
PCA	perchloric acid
PEI	polyethylenimine
PLE	poly-L-glutamate
PLL	poly-L-lysine
Poly(rU)	polyuridilic acid
PTE	proton transfer enhancement
PTR	proton transfer ratio
RF	radiofrequency
s	solute exchangeable proton or solute-bound water proton pool
SNR	signal-to-noise ratio
SPD-5	generation-5 starburst PAMAM dendrimers
ss	steady-state
TR	repetition time
w	bulk water proton pool
WEX	water exchange

1. Introduction

The study of chemical exchange processes is one of the oldest and still most vigorously investigated topics in NMR spectroscopy. The effects of chemical exchange on the NMR spectrum were reported as early as 1951 [1,2] and investigated intensively during the early days of NMR [3–10]. In a landmark paper published in 1963, Forsen and Hoffman [8] studied moderately rapid chemical reactions by means of nuclear magnetic double resonance. Especially since the advent of two-dimensional (2D) NMR [11,12], numerous important advancements have occurred [13–16]. In addition to protons (^{1}H), exchange spectroscopy has been applied to other NMR nuclei such as phosphorus (^{31}P), fluorine (^{19}F), and carbon (^{13}C). Over the past half century, much valuable information on chemical reactions and exchange processes has been obtained by NMR spectroscopy studies. In the last six years, there has been a surge in NMR exchange applications because of the realization that saturation transfer experiments can be designed that allow a large sensitivity enhancement. The first to demonstrate that exchange between labile protons of low-concentration solutes and water protons provides a sensitivity enhancement scheme were Balaban et al. [17–19], who dubbed this new MRI contrast mechanism chemical exchange dependent saturation transfer (CEST) [19]. After this initial work on small solutes, van Zijl and colleagues [20,21] showed that enormous increases in sensitivity could be obtained for macromolecules with a large number of exchanging sites of similar chemical shift. Enhancements as large as 500,000 were demonstrated for amide protons on cationic polymers [20], such as poly-L-lysine (PLL) and dendrimers, while a record enhancement of 10^{7} or more was reported for the imino protons of polyuridilic acid (poly(rU)) [21]. At the same time, Zhang et al. [22,23] and Aime et al. [24] reported several paramagnetic CEST (PARACEST) agents that made the approach more flexible by significantly enlarging the frequency range for the exchanging sites. By analogy to this nomenclature, we will call the other compounds diamagnetic CEST (DIACEST) agents. In 2003, Zhou et al. [25,26] showed that endogenous mobile proteins and peptides at very low concentration in biological tissue could also be detected via the water signal. In this so-called amide proton transfer (APT)