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## Chemical exchange saturation transfer imaging and spectroscopy

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

#### 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 (<sup>1</sup>H), exchange spectroscopy has been applied to other NMR nuclei such as phosphorus (<sup>31</sup>P), fluorine (<sup>19</sup>F), and carbon (13C). 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<sup>7</sup> 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)

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