# Analytical description of WALTZ-PARACEST experiments

**E. Vinogradov[1], H. He[2], A. Lubag[3], J. A. Balschi[2], A. D. Sherry[3,4], and R. E. Lenkinski[1]**

[1]Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States, [2]NMR Laboratory for Physiological Chemistry, Brigham and Woman's Hospital, Harvard Medical School, Boston, MA, United States, [3]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, TX, United States, [4]Department of Chemistry, University of Texas at Dallas, Dallas, TX, United States

## Introduction

Recently, PARACEST[1] agents were introduced, in which complexes of paramagnetic lanthanides are used for CEST imaging[2]. The CEST effect can be switched "on" and "off" using suitable RF irradiation and offer the potentially new platform for generating contrast agents in MR. The standard CEST experiment employs CW saturation placed on the frequency position of the exchanging (usually bound) site[1]. However, achieving the maximal effect for a lanthanide complexes with fast water exchange like $Tm^{3+}$ and $Dy^{3+}$ (1-5 μsec) may require RF deposition that is above FDA guidelines[3]. In addition, the frequency of the bound water peak needs to be known *a priori* but may vary with temperature and thus be unknown *in vivo*. For these reasons, an alternative approach was developed[4] using the RF pulses (WALTZ-16$^*$) placed on the free water resonance (WALTZ-PARACEST). Using this approach, microMolar concentration of the agent were detected *in-vitro* and milliMolar *in-vivo.*

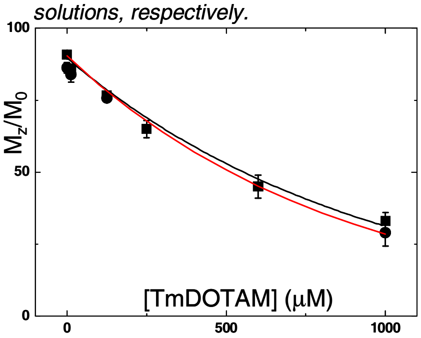
For molecular imaging applications, simple detection of a contrast agent may not be the only requirement. Additional information, such as agent concentration or *in vivo* exchange lifetimes may be required to characterize the agent's response to its surroundings. In particular, for some targeted agents under development, the exchange lifetimes *in vivo* may differ from those measured *in vitro*. Hence, it is important to provide *quantitative* information about the agent behavior *in vivo.* In order to achieve this, an analytical relationship between system parameters such as relaxation and exchange times and sequence parameters such as RF timings and intensities is needed. Such relationships might also provide useful information about the agent concentration and its dynamics. Approximate analytical solutions have been developed for CEST experiments[5,6]. However, paramagnetic agents exhibit different dynamics than diamagnetic agents and the WALTZ-16 RF train is time dependent, making existing approximate solutions inapplicable.

Here we develop an analytical description of the system dynamics of a PARACEST agent under application of a WALTZ-16 pulse train. Analytically predicted effect sizes are compared with experimental observations and exact numerical predictions.

## Theory

A two-pool model is used, consisting of bound and free water. The solution of the Bloch-McConnell equations in the presence of RF is based on two assumptions: (i) the relaxation and exchange times of the bound pool are much faster compared to the same processes in the free pool and the RF pulse duration; hence, the bound pool can be considered in the steady-state; (ii) relaxation and exchange rates of the free pool are smaller than the RF intensity, thereby allowing rejection of some of the cross-terms in the derivation of the solution. This model does not require any assumptions regarding the degree of saturation of the bound pool. Note that assumption (i) is valid for the complexes with Tm and Dy since these lanthanide complexes exhibit very short bound proton relaxation and exchange lifetimes. These assumptions are not applicable for description of DIACEST, APT or MT experiments.

***Figure1.*** *Relative Magnetization ($M_z/M_0$) after an application of WALTZ-16* train at the different concentrations of TmDOTAM. Squares and circles correspond to spectroscopy and imaging results, respectively. Black and red lines correspond to numerical and analytical solutions, respectively.*



## Results

Given the assumptions stated above, the solution of the coupled Bloch-McConnell equations was found for the CW case. This solution was used to build the solution for WALTZ-16 train, which can be viewed as back-to-back CW pieces with alternating phases. The relationship between Z-magnetization at the end of the WALTZ-16$^*$ RF train ($M_z$) and water relaxation times ($T_1$, $T_2$) in the absence of exchange, and exchange lifetime of the free pool ($k_f$) for Tm and Dy compounds is given by:

$M_z/M_0=\exp(-1/2(R_1+R_2+2k_f)t_w)$ (1)

where $R_i=1/T_i$ and $t_w$ is the total length of WALTZ train ($t_w$ = 220 msec here). Figure1 shows the comparison between $M_z/M_0$ obtained using approximate solution (Eq.1), exact numerical solution of two-pool Bloch-McConnell equations and experimental results in phantom solutions. An interesting feature of the expression is that there is no dependence on the RF intensity. This can be expected since the underlying characteristic of WALTZ-16 train is its robustness with respect to $B_0$ and $B_1$ inhomogeneities. Another noteworthy feature is inclusion of *scaled* $R_1$ and $R_2$ values. It points at the analogy of the experiment to $T_{1\rho}$ experiments, in particular off-resonance $T_{1\rho}$ methods in which the direction of the effective RF field is not perpendicular to the Z direction [7]. Based on the Eq.1, the ratio of the observed intensities in the experiments with (I(wCA)) and without (I(woCA)) the contrast agent provides exchange constant of the free pool:

$I(wCA)/I(woCA) = \exp(-k_f t_w)$ (2)

From here, given the stoichiometric requirement, $[H_2O]^*\tau_b = [CA]^*\tau_f$, the agent concentration, [CA] or $\tau_b=1/k_b$ the exchange lifetime of the bound pool can be deduced. Assuming that the minimal observable intensity change is 2%, the minimum observable concentration of the agent with $\tau_b$=2.5μsec is 12.7μM. This number is in agreement with the lowest concentration detected in TmDOTAM, 12.5μM.

Similar assumptions were also applied to derive expression for the relative magnetization obtained when the standard CW saturation methodology is used for the observation of PARACEST effects.

To make the analytical description relevant *in-vivo*, a third pool describing the MT effects must be included in the model. In addition, different acquisition techniques and parameters will influence the measured intensity of the signal and need to be included as well. Work is currently in progress to incorporate these effects and to validate the resulting model *in-vivo.*

## Conclusions

An analytical approximate solution that relates the signal reduction in a PARACEST experiments using WALTZ-16$^*$ with the relaxation and exchange parameters was derived. This expression can potentially assist in the *quantification* of the effects of PARACEST agents *in-vivo,* such as a determination of agent concentration or changes in exchange lifetimes in response to surrounding environment.

**References** **1.**S.Zhang, *et.al.*, *J.Am.Chem.Soc***124,** 4226(2002); **2.** K.Ward, *et.al.*, *Magn.Reson.Med.***44,** 799(2000); **3.** S.Zhang, *et.al., Acc.Chem.Res***36**, 783(2003); **4.** E.Vinogradov, *et.al. J.Magn.Reson.***176**, 54(2005); **5.** J.Zhou, *et.al., Magn.Reson.Med.***51**, 945(2004); **6.** M.T.McMahon, *et.al., Magn.Reson.Med.***55**, 836(2006); **7.** O.Trott, *et.al. , Mol.Phys.***101**, 753(2003).