Off-resonance irradiation power to optimize the CEST sensitivity versus the exchange rate-specificity

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Target Audience: Researchers interested in chemical exchange saturation transfer (CEST) imaging.

Purpose: The CEST technique has shown great potential in the field of MR molecular imaging [1], where off-resonance RF irradiation pulse level (B_1) should be chosen to optimize the specificity and/or sensitivity of the chemical exchange (CE) contrast. When targeted labile proton has high specificity in the Larmor frequency (such as in PARACEST studies), B_1 can be adjusted to maximize the CE sensitivity (i.e., CE-based image contrast). To this end, Sun et al. have derived empirical analytical solutions describing CE contrast in the slow-exchange regime and optimized the CE contrast based on these solutions [2]. But when several types of labile protons with similar Larmor frequencies but vastly different k values are present (such as endogenous amide, guanidine and amine protons *in vivo*), B_1 can also be adjusted to selectively enhance the CE contrast from a specific type of labile proton (i.e., k-tuning). In this work, we derived simplified analytical solutions for B_1 optimization of both k-specificity and CE sensitivity in the slow-exchange regime using a theoretical two-site exchange model with asymmetric population approximation [3], and compared the results with simulations of the Bloch-McConnell Equations.

Methods: *Theoretical Model*: During off-resonance irradiation, the water magnetization relaxes to a steady state with rate constant $R_{1\rho}$ ($=1/T_{1\rho}$), the spin-lattice relaxation rate in the rotating frame [4]. From a two-site exchange model with asymmetric population approximation, $R_{1\rho}$ can be expressed as [3]

$$R_{1\rho} = R_1\cos^2\theta + (R_2 + R_{ex})\sin^2\theta, \quad \text{where} \quad R_{ex} \approx p\cdot k\cdot\delta^2\cdot\left[(\delta-\Omega)^2+\omega_1^2+k^2\right]^{-1}, \tag{1}$$

and Ω is the offset of the irradiation frequency from water, $\omega_1 = \gamma\cdot B_1$, $\theta = \arctan(\omega_1/\Omega)$, p is the relative concentration of labile protons (assuming $p \ll 1$), δ is the chemical shift difference between the labile proton and water, and R_1 and R_2 are the intrinsic longitudinal and transverse relaxation rates of water, respectively (excluding CE effects). In the slow exchange regime where $k/\delta \ll 1$, the CE effect is maximal for MTR_{asym} ($=[S(-\delta)-S(\delta)]/S_0$) with is very long irradiation duration [4]. Assuming negligible CE effect at $\Omega = -\delta$, *i.e*, $R_{ex}(\Omega = -\delta) \approx 0$, the steady state MTR_{asym} can be expressed as

$$MTR_{asym} \approx \frac{1}{1+\frac{R_2}{R_1}\tan^2\theta} - \frac{1}{1+\frac{R_2+R_{ex}(\delta)}{R_1}\tan^2\theta} = \frac{1}{\left(1+\frac{R_2\omega_1^2}{R_1\delta^2}\right)\cdot\left[1+\frac{(R_2+R_{ex})\cdot\omega_1^2}{R_1\delta^2}\right]}\cdot\frac{R_{ex}\omega_1^2}{R_1\delta^2} \approx \frac{p\cdot k\cdot T_1}{p\cdot k\cdot T_1+\left(1+\frac{k^2}{\omega_1^2}\right)\cdot\left(1+\frac{R_2\omega_1^2}{R_1\delta^2}\right)^2} \tag{2}$$

In Eq. (2), the term $(1+k^2/\omega_1^2)$ represents the reciprocal of the saturation efficiency, which approaches a maximum value of one when $\omega_1 \gg k$, and the term $[1+R_2\omega_1^2/(R_1\delta)^2]^2$ represents the direct water saturation effect, which increases with water R_2 and ω_1. From Eq. (2), a condition of $\partial MTR_{asym}/\partial k = 0$ gives

$$k_{tune} = \omega_1, \tag{3}$$

indicating that choice of ω_1 tunes the CE contrast to a specific exchange rate (k_{tune}) independent of other parameters such as R_1 and R_2. From $\partial MTR_{asym}/\partial\omega_1 = 0$ we can also get a normalized optimal ω_1 which maximizes the CE sensitivity:

$$\frac{\omega_{1,optimal}}{\delta} \approx \sqrt{\sqrt{\frac{R_1}{2R_2}}\cdot\frac{k}{\delta} - \frac{k^2}{4\delta^2} + \frac{k^3}{16\delta^3}\cdot\sqrt{\frac{R_2}{2R_1}}} \tag{4}$$

which depends on R_1 and R_2, as well as the ratio of k/δ.

Simulations of Bloch-McConnell Equations: MTR_{asym} was simulated by Bloch-McConnell Equations, assuming two-pool exchange and $\delta = 5000$ rad/s, $R_1 = 0.5$ s^{-1}, $p = 0.0005$, and an irradiation duration of 10 s. To evaluate the effect of k-tuning, MTR_{asym} as a function of k was simulated for fixed ω_1 (400 rad/s) at R_2 values of 1, 5, and 20 s^{-1}, and for fixed R_2 values of either 1 or 20 s^{-1} at ω_1 values of 80, 200, 400, 1000 and 3000 rad/s. To evaluate the effect of CE-sensitivity optimization, MTR_{asym} as a function of ω_1 was simulated for $k = 400$ s^{-1} with R_2 values of 1, 5, and 20 s^{-1}, and the results were compared with analytical solutions from Eq. (2). The accuracy of Eq. (4) was tested by simulating MTR_{asym} for R_2 values of 1, 5 and 20 s^{-1}. MTR_{asym} was also simulated for k between 5 and 1500 s^{-1} and ω_1 between 50 and 2000 rad/s, and results for the optimal ω_1 for maximal MTR_{asym} were compared with analytical solutions from Eq. (4).

Results and Discussion: With ω_1 fixed at 400 rad/s, simulations show $k_{tune} = 400$ s^{-1} (MTR_{asym} peak), which is independent of R_2 values and consistent with results of Eq. (3) (Fig. A). As ω_1 is varied, k_{tune} changes accordingly, and MTR_{asym} (CE contrast) is highly sensitive to R_2 values (Fig. B versus Fig. C). Importantly, it should be noted that for labile protons with the same (or similar) Larmor frequency but different k values, a trade-off between k-specificity and optimal CE contrast may be required (*i.e.*, selecting ω_1 for optimal k-tuning may not give maximal MTR_{asym}). For example, consider two labile protons (X and Y) with exchange rates $k_X = 80$ s^{-1} and $k_Y = 200$ s^{-1}, respectively. A pulse with $\omega_1 = 80$ rad/s tunes to labile proton X, but MTR_{asym} is even higher for X with $\omega_1 = 200$ rad/s (Figs. B and C) which tunes to labile proton Y. Thus, this latter condition yields higher CE contrast, but lower specificity for labile proton X. Fig. D shows that for $k = 400$ s^{-1}, MTR_{asym} initially increases with ω_1, then reaches a peak and decreases at higher ω_1 values. The optimal ω_1 for $k = 400$ s^{-1} decreases with an increase in R_2 values, and MTR_{asym} simulations are well described by Eq. (2). Simulations also show $\omega_{1,optimal}$ increasing with k, and a good match to the solution from Eq. (4) for $k/\delta < 0.4$ (Fig. E). In the slow regime, this relationship along with estimates from Eq. (4) when R_1 and R_2 values are known allows estimation of k, an important target of CE studies. [5]

Conclusion: Approximate analytical solutions for MTR_{asym} have been derived from a theoretical model in the slow exchange regime, which agree well with simulations of the Bloch-McConnell Equations. These results should help guide the selection of B_1 for k-specificity and CE-sensitivity optimization in CEST studies.

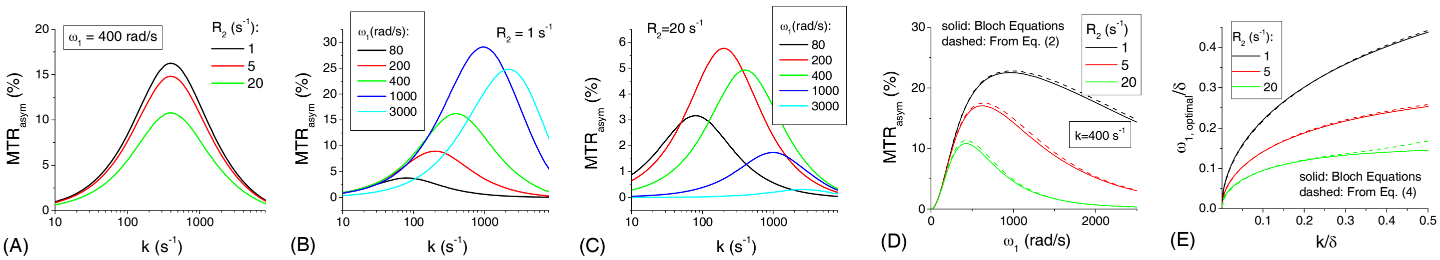

Figure: Simulation of Bloch-McConnell Equations shows that for $\omega_1 = 400$ rad/s, MTR_{asym} peak at $k_{tune} = 400$ s^{-1}, independent of R_2 values (**A**). There is a clear k_{tune} dependence on ω_1 (**B** and **C**) but MTR_{asym} varies with R_2. (**D**). Close agreement is seen for MTR_{asym} as a function of ω_1 for $k = 400$ s^{-1} calculated from Bloch-McConnell Equations vs. Eq. (2). (**E**). There is also a good match for $\omega_{1,optimal}$ as a function of k value for maximal MTR_{asym} calculated from Bloch-McConnell Equations vs. Eq. (4).

References: [1]. Ward and Balaban, JMR 143:79 (2000). [2]. Sun PZ et al., JMR 175:193 (2005). [3]. Trott and Palmer JMR 154:157 (2002). [4]. Jin, T et al., NeuroImage 59:1218 (2012). [5]. Sun PZ et al., JMR 202:155 (2010).