An analytical approach towards pulsed-SL/CEST quantification
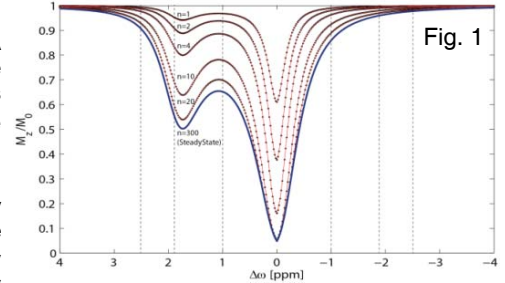
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Introduction: Frequency-dependent spinlock (SL) experiments are able to detect the exchange process between proton pools of different chemical environments. Knowledge about this process can be exploited to image *in vivo* levels of metabolites or pH distributions [1,2,3]. Continuous wave (cw) experiments can be described in terms of analytical expressions [4,5] and therefore yield a straight-forward quantification method. However, due to SAR constraints in clinical MR scanners, pulsed sequences are required that suffer from the lack of direct transferability to the cw-type experiments. Several approaches have tried to relate pulsed and cw sequences by introducing effective parameters [6,7]. This study gives an analytical theory of transient and steady-state Z-spectra obtained by pulsed saturation based on the eigenspace approach for the cw case [8].

Fig. 1

Theory: We consider two pools of protons resonating at different resonance frequencies (pool A and pool B) that are in chemical-exchange with each other. The pools are characterized by their relaxation rates R_{1m} and R_{2m}, their exchange rates k_m, their specific Larmor frequencies $\delta_m (m = A, B)$ and the fraction of their thermal magnetizations $f = \frac{M_{0B}}{M_{0A}}$. It is common to call the water pool A, and to set its Larmor frequency δ_A to 0.

The pulsed-SL experiment is described by a sequence of delay-pulse modules with delay time t_d, pulse width t_p and duty-cycle DC. We assume monoexponential decay towards the cw-steady state with relaxation rate $R_{1\rho} = R_{eff} + R_{ex}$ where R_{eff} is the effective decay rate resulting from the tilted frame of reference and R_{ex} the exchange-dependent part also contributing to the total decay rate. During the pause, as a first approximation, only R_1 relaxation is considered neglecting any magnetization transfer. A recursive formula can be derived relating the n-th pause-pulse-module to its predecessor. Using the sum formula for the geometric series we obtain the explicit formula for the z-component of the magnetization $(z := (M_0 - M_z)/M_0)$ after a pulse train with n delay-pulse modules: $z^n = \alpha \frac{1-\beta^n}{1-\beta} + \beta^n z(t = 0)$ (eq. 1) with constants α and $\beta < 1$. Introducing the steady-state-solution Z_{pulsed}^{SS} for the pulsed experiment and rearranging eq. 1 the dynamics is described by the exponential law

$$Z_n = (1 - Z_{SS}^{pulsed}) e^{-R_{1\rho}^{pulsed} t_{sat}} + Z_{SS}^{pulsed}. \text{ (eq. 2)}$$

By introducing the total saturation time t_{sat} given by $t_{sat} = n(t_p + t_d)$ and the new effective relaxation rate $R_{1\rho}^{pulsed} := DC * R_{1\rho} + (1 - DC) * R_1$ we acknowledge the strong similarity to the cw-SL. Using additional assumptions about the state of pool B after each RF pulse we could derive a correction term ξ, that extends the validity of eq. 2 towards a regime of slower exchange:


Fig. 2

$$Z_n = (1 - Z_{SS}^{pulsed}) e^{-(R_{1\rho}^{pulsed} + \frac{\ln \xi}{t_p + t_d}) t_{sat}} + Z_{SS}^{pulsed}. \text{ (eq. 3)}$$

Determining the effective relaxation rate $R_{1\rho}^{pulsed}$ in the pulsed SL-experiment by varying the saturation time close to the resonance of pool B ($\Delta\omega = \delta_b$) and subtracting by the corresponding value symmetric to the water resonance ($\Delta\omega = -\delta_b$), where R_{ex} is assumed to be negligible, yields $R_{1\rho,on-res}^{pulsed} - R_{1\rho,off-res}^{pulsed} = R_{ex} * DC$. This term can be approximated [6] by $R_{ex} \approx \frac{f k_b \omega_1^2}{\omega_1^2 + k_b(k_b + R_{2B})}$ (approx. 1) or by $R_{ex} \approx k_a$ if $\omega_1 \gg k_{BA}$ (linear approx.).

Materials & Methods: Calculations of z-spectra were performed by fully numerical simulation of the six coupled Bloch-McConnell-equations using typical concentrations and relaxation rates for a creatine phantom. The SL-pulse train was realised by subsequent simulation of RF irradiation with constant B_1 for $t_p = t_d = 100$ ms. The additional flipping of the magnetization into the effective frame was simulated by instantaneous rotation. Simulations were performed using the following parameters: $R_{1A} = R_{1B} = 0.3$ Hz; $R_{2A} = R_{2B} = 3$ Hz; $t_p = t_d = 100$ ms; $f = 0.01$; $B_0 = 3$ T; $B_1 = 0.5$ µT; $\delta_B = 1.8$ ppm. As a model solution, creatine monohydrate (126 mM) in PBS-buffer including 0.5% agarose and sodium acid was used. Measurements were performed on a 3T clinical scanner.

Results & Discussion: Fig. 1 shows simulated pulsed-SL spectra for several pulse train lengths and the steady state solution of the system. With full knowledge about the steady state, the transient spectra are well described by the exponential law. Applying a trust-region-fitting algorithm gives the exponent for each of the offset values from which - assuming full knowledge about the correction term ξ and the pulse train parameters – the maximum (Fig. 2) and the general shape of R_{ex} can be estimated correctly. Fig. 3 shows experimentally determined values for $R_{1\rho}^{pulsed}$ of a creatine solution as a function of the frequency offset. The values are ROI averaged and fit the analytical expression. By an asymmetry analysis the term R_{ex} was isolated and a value $k_{AB} = 0.25$ Hz derived with the linear approximation, which matches to the value determined by WEX-spectroscopy $k_{AB} = 0.26$ Hz [10].

Fig. 3
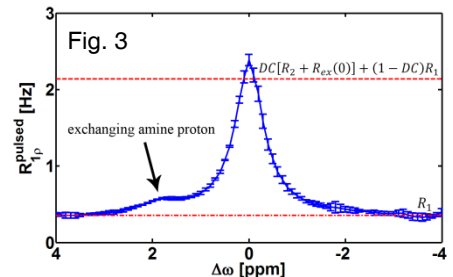
Conclusion: We gave an analytical expression which predicts the Z-spectra of pulsed CEST as function of the pulse train parameters DC, t_p, t_d, n and B_1 instead of an effective B_1. Simulations show that the proposed analytical theory allows determination of the chemical-exchange-dependent relaxation rate for clinically feasible saturation schemes (pulsed-SL sequences, 3T) from which parameters characterizing the exchange process can be derived; even a direct quantification of $k_a = f k_b$ for slow exchange rates is possible. Due to the high degree of similarity between chemical-exchange-dependent saturation transfer (CEST) and SL this theory can be transferred directly to pulsed-CEST experiments and can further be utilized to optimize pulsed-SL/CEST sequences for chemical-exchange imaging contrast and quantification.

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