Tailoring Linear Response Equilibrium Spectroscopy of Cholesterol Esters

R. F. Fischer[1], S. Kozerke[1], C. Baltes[1], M. Rudin[1], and P. Boesiger[1]
[1]Institute for Biomedical Engineering, University and ETH Zurich, Zurich, Switzerland

Introduction: Atherosclerosis is an inflammatory disease of arteries accompanied by the deposition of characteristic plaques in the arterial wall rich in cholesterol esters. Plaques with a high content of inflammatory cells and a large lipid core covered by a thin fibrous cap seem to be more prone to rupture and may therefore cause thrombotic events [1]. Magnetic resonance ^{1}H-spectroscopy of cholesterol esters [2] holds potential for classifying the vulnerability of plaques in-vivo if sufficient spatial resolution can be obtained.
Linear Response Equilibrium (LRE) is a time and energy efficient balanced gradient pulse sequence which allows collecting spectra at high spatial resolution. A regular band of short hard pulses drives the nuclear spin system into a steady-state with only discrete frequencies being excited. To resolve spectroscopic information, the steady-state signal is sampled at different time points during its periodic evolution [3, 4]. The purpose of this study was to tailor the LRE sequence for in-vivo cholesterol ester detection in a controlled model system. We present approaches to overcome sequence intrinsic limitations such as aliasing of side bands due to repetition time constraints on human MR systems. Also, an additional water suppression module is introduced into the LRE sequence not disturbing the steady-state.

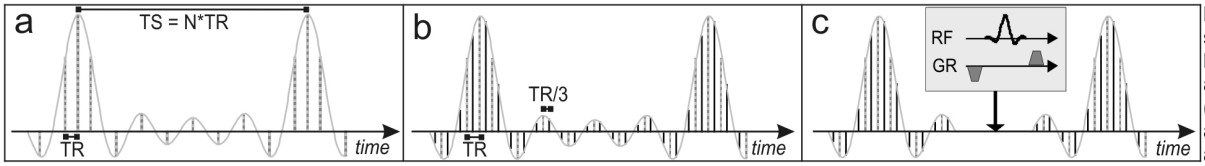

Fig. 1: Schematic view of pulse sequences: (a) conventional LRE; (b) excitation with additional pulses each TR (black solid bars); (c) low flip angle pulses being replaced by a long frequency selective water suppression pulse (inlet).

Methods and Materials: 1) *Pulse sequence*: The LRE sequence (Fig. 1a) periodically excites frequencies separated by a whole number multiple of 1/TR with identical strength resulting in a regular pattern of passbands and stopbands. In case of signals occurring within higher order passbands, aliasing into the central frequency range of interest contaminates the spectrum. In order to suppress alias signal without lowering the width of the central passband, the 1/TR periodicity of the excitation has to be modified by breaking the symmetry of the pulse sequence. For this purpose each time interval TR between neighbouring pulses is subdivided into a ratio of 1:2 by adding a non-selective pulse. These additional pulses form a second chain of regular stimuli separated by TR exciting a second steady-state (Fig. 1b). In the low flip angle approximation regime the resulting signal is the superposition of both steady-states. The phase difference between the pulses of the two shifted bands can be chosen such that destructive interference cancels out every third passband resulting in a three-fold increased suppression band width compared to the original design and a suppression ratio of approximately 1:20 according to simulations. To increase the suppression ratio further, the LRE sequence was modified to accommodate a dedicated water suppression module while blanking a coherent series of small flip angles in the LRE excitation function that has an envelope with periodicity TS = N*TR ($N \in \mathbf{N}$) (Fig. 1c). The water suppression module, consisting of a frequency selective water suppression pulse and spoiler gradients, was played every other TS.
2) *Experiments*: All experiments were conducted on a whole-body Philips 3T Achieva MRI system (Philips Healthcare, Best, the Netherlands).
To visualize the spectral excitation pattern of the LRE sequences a transverse section through a phantom bottle ($CuSO_4$ standard solution) was recorded applying a constant gradient in the imaging plane resulting in a continuous band of resonance frequencies. A plastic sphere filled with cholesterol linoleate (purity > 95%, TCL Europe) was used as a model for the lipid core of an atherosclerotic plaque. The cholesterol ester was melted (T > 42°C) and kept in a water bath at temperatures above 37°C during measurements in order to prevent phase transition from normal liquid to liquid crystalline state. In all LRE scans, passbands of 1.2ppm (153Hz) were excited. The excited bands consisted of 25 discrete peaks each resulting in a spectral resolution of 0.05ppm. LRE acquisitions were performed either by reading out passband and stopband or by reading out the passband only, thereby accelerating the acquisition two-fold in time. Spatial resolution was 1.34x1.34x3.0mm^3 covering a field of view of 85x85x12mm^3. Measurement times were 48s, 25s and 96s for the non-accelerated, the accelerated and the scans with additional water suppression module, respectively. The centre frequency of the excitation was set between the methyl (0.8ppm) and methylene (1.3ppm) resonances. The water line at 4.7ppm was suppressed in the middle of a stopband (Fig. 3). For additional water suppression a 8ms 130deg pulse (BW: 637Hz) was used. As reference, a single voxel PRESS spectrum was acquired.

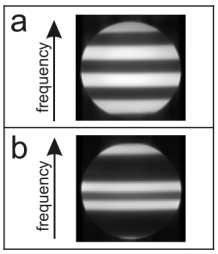

Fig. 2: Frequency specific excitation profile visualized with MRI by applying a constant gradient in plane. a: conventional LRE with equally sized stopbands and passbands. b: LRE according to the scheme shown in Fig. 1b.

Results: Figure 2a and b show the measured spectrally excitation pattern of the conventional LRE sequence and the modified version thereof with additional hard pulses in each TR segment according to the schemes in Figure 1a and b, respectively. The three-fold increased stopband width is well confirmed in the experiments with suppression ratios of 1:9.2 measured. With the additional water suppression module, water signal was further suppressed resulting in residual water signal of approximately two times the averaged noise level. Accordingly, the suppression ratio amounted to approximately 1:47.
Figure 3 shows the single voxel PRESS spectrum of the cholesterol linoleate phantom with resonances for methyl and methylene groups as well as for protons attached to C=C double bonds. Figure 4a shows the LRE spectrum of an exemplary voxel in the phantom acquired with the excitation pattern shown in Fig. 1a. The peaks of methyl (I) and methylene (II) can be identified. A third peak (III) appears due to aliasing of the (CH=CH)-peak (5.3ppm) into the central passband. Accelerated measurements by reading out passbands only show residual signals from stopbands (Fig. 4b). The LRE modifications proposed herein result in a clean spectrum of the methyl and methylene resonances without contamination signals (Fig. 4c).

Discussion and Conclusion: Measured LRE spectra of cholesterol linoleate were in good accordance with reference data. Reading out suppressed bands prevents stopbands to fold into the spectrum at the expense of longer measurement time. The sequence intrinsic aliasing of higher order passbands could be overcome by introducing a dual steady state and frequency selective water suppression into the periodic excitation scheme. Based on the results of this phantom study, the tailored LRE approach is regarded a potential method for acquiring high spatial resolution spectra of cholesterol esters in-vivo in short measurement times.

References: [1] A.P. Choudhury et al., Nature Reviews 3: 913 (2004); [2] Ruberg et al., Journal of Lipid Research 47: 310 (2006); [3] KW Eberhardt, et al., JMR 178:142 (2006); [4] KW Eberhardt, et al., Proc. Intl. Soc. Mag. Reson. Med. 14 (2006)

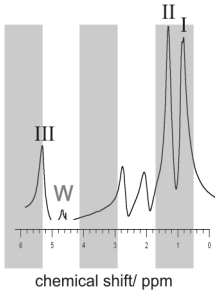

Fig. 3: Single voxel PRESS spectrum: Methyl (I); Methylene (II); CH=CH (III); residual water (W). Gray bars mark bands excited by the LRE sequence.

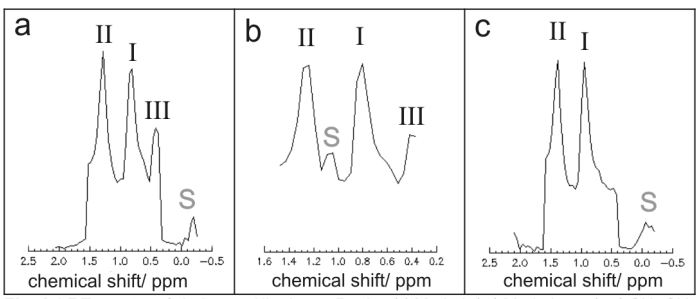

Fig. 4: LRE spectra of cholesterol linoleate. Peaks: (I) Methyl; (II) Methylene; (III) CH=CH; (S) residual signal from stopbands. a: full readout with conventional LRE. Peak (III) aliases into the spectrum. b: readout of passbands only as suggested in [3]. Signal from stopbands (S) folds into spectrum. c: acquisition with additional water suppression. Peak (III) no longer aliases into the spectrum.