Rician-noise based R2* Estimation for Severe Hepatic Iron Overload: Simulation, Phantom, and Early Clinical Experience

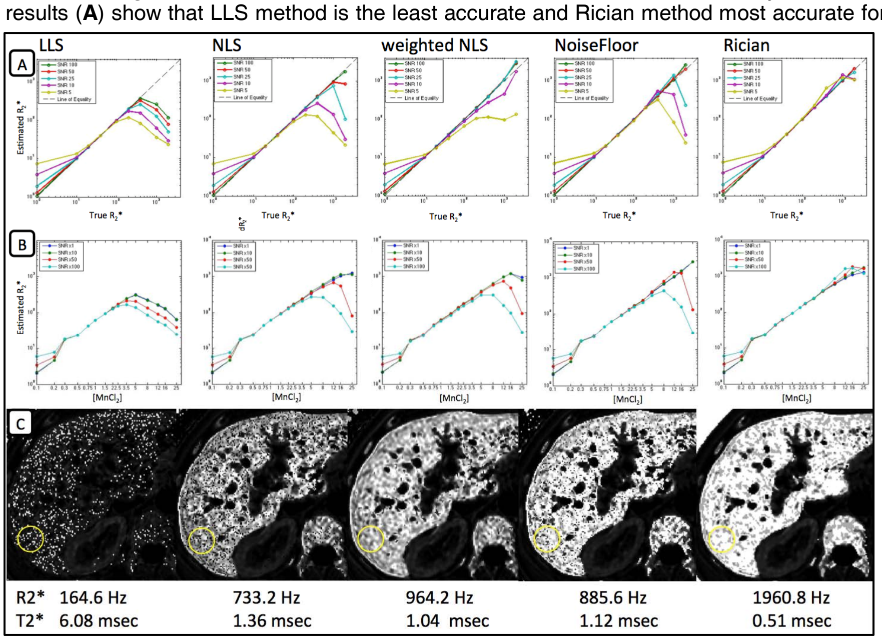
Takeshi Yokoo[1,2], Qing Yuan[1], Julien Senegas[3], Andrea Wiethoff[2,4], and Ivan M Pedrosa[1,2]

[1]*Radiology, UT Southwestern Medical Center, Dallas, TX, United States,* [2]*Advanced Imaging Research Center, UT Southwestern Medical Center, Dallas, TX, United States,* [3]*Philips Research Laboratories, Hamburg, Germany,* [4]*Philips Research North America, Briarcliff Manor, NY, United States*

BACKGROUND/PURPOSE: Hepatic iron overload is a common form of chronic liver disease. It develops in patients with primary hemochromatosis due to genetic mutations or secondary hemochromatosis due to iron-loading anemias, multiple transfusions, and chronic renal failure. If untreated, iron overload in the liver may lead to progressive fibrosis, end-stage liver disease, and hepatocellular carcinoma. The gold standard for the assessment of hepatic iron overload is liver biopsy, from which liver iron concentration (LIC) is biochemically measured. However, biopsy-LIC measurement is impractical for routine clinical use in these patients with hematologic disorders because it is invasive, painful, expensive, and may have sampling variability. Magnetic resonance (MR) imaging is increasingly recognized as a noninvasive alternative to biopsy-LIC. Iron in the liver causes rapid decay of the transverse magnetization in a dose-dependent manner. On spin-echo (SE) sequences, the transverse decay rate is R2, and on gradient-recalled-echo (GRE) sequences R2*, both in Hz. By acquiring magnitude images at progressively longer echo-times (TEs) and fitting to an exponential decay function, R2 and R2* can be calculated pixel-by-pixel to reconstruct R2 and R2* maps. While a SE-based R2 method is now commercially available (FerriScan®, Resonance Health, Australia) and FDA-approved in US, GRE-based R2* methods are not yet FDA-approved or commercially available. GRE R2* methods may be more practical for clinical use due to faster imaging speed and larger spatial coverage. However, several levels of barriers remain. There is lack of consensus on (a) R2* model and estimation algorithms, (b) imaging protocol, and (c) the calibration curve to relate R2* value to biopsy-LIC. For wide acceptance of R2* methods, the standardization of the R2* model and estimation algorithm is first necessary; only then imaging protocol can be optimized, and a single universal calibration curve may be adopted across different sites. Patients with severe iron overload are in greatest need for effective therapy and frequent monitoring of the treatment response. However R2* estimation in these patients can be particularly challenging, as the signal intensity rapidly decays to zero and the noise predominates most of the acquired echoes. The noise in magnitude images is Rician and standard R2* fitting methods based on Gaussian noise assumption may be inappropriate and inaccurate. Several approaches have been proposed to model the noise and improve accuracy, including those based on Rician distribution. The purpose of this study is to compare existing R2* methods in a series of simulation and phantom experiments and in patients with severe iron overload. The following fitting methods were evaluated: (i) Linear Least Squares (LLS) that ignores noise, (ii) Nonlinear Least Squares (NLS) that assumes Gaussian noise, (iii) weighted NLS with SNR-based penalty, (iv) Noise Floor method which models noise as a constant positive offset fitted as a free parameter, and (v) Rician-noise based method [1].

MATERIALS/METHODS: In the simulation study using MATLAB (Mathworks, Natick, MA), mono-exponentially decaying complex signal was synthesized using clinically relevant R2* values (25, 50, 100, 200, 400, 1000, and 2000 Hz). Complex Gaussian noise was added at SNR 100, 50, 20, 10, and 5. The signal-plus-noise complex data were rectified by taking |.| and sampled at 1 msec interval from 1-12 msec. Methods i-v were applied to the 12-echo data to estimate R2*. This was repeated 10^4 times *ala* Monte Carlo for each R2* and SNR values. In the phantom study, the R2* phantoms were constructed in 5 ml glass vials by doping saline solution with $MnCl_2$ at different concentrations (0-25 mM) [2]. These were submerged in water bath and imaged in coronal plane using 12-echo 3D spoiled GRE sequence at 3T (Achieva, Philips Healthcare, Best, Netherlands) with $TE_1/\Delta TE$ 1.5/1.2 msec using XL-Torso 16-channel XL-Torso phased array coil, but without parallel imaging. Background noise was estimated from the expected Rician distribution of the background water, and based on the noise distribution parameters, additional Rician noise was added to generate signal-plus-noise data at SNR x1, 10, 50, and 100. Methods i-v were applied to calculate R2* maps using MATLAB, and average value in each vials were calculated by selecting a slice through the middle of the vials and drawing regions of interest (ROIs). In nine human subjects with known or at risk for liver iron overload, R2* quantification liver MRI was performed at 1.5T Philips Achieva (4-channel SENSE Body coil) using otherwise same imaging protocol as in the phantom study, except for axial imaging plane, $TE_1/\Delta TE$ 0.92/1.01 msec, and SENSE parallel imaging with acceleration factor 2. Methods i-iv were applied to the source magnitude images on MATLAB to reconstruct the R2* maps. Method v was implemented in the Philips reconstruction SW, in which the estimation of the Rician noise parameters accounted for the multi-coil combinations performed in SENSE [1,3].

RESULTS/DISCUSSION: Estimated R2* (methods i-v) in the simulation and phantom studies are plotted for different SNR (**Figure A,B**). Estimated and true R2* should agree in the simulation data. Estimated R2* should increase linearly with increasing $MnCl_2$ concentration in the phantom data. Simulation results (**A**) show that LLS method is the least accurate and Rician method most accurate for the large R2* at all SNR levels. Phantom results (**B**) show that Rician method is the only one that maintains a consistent, linear dose-response at all SNR levels. The R2* maps (methods i-v) of a 45 year-old female with aplastic anemia (**C**) who also had Ferriscan MRI for clinical care. Ferriscan LIC was >43 mg Fe/g dry weight, compatible with severe iron overload. The Rician R2* map was the most spatially homogeneous, likely due to its robustness for large R2* as seen in the simulated and phantom data. LLS is the most heterogeneous with random distribution of extreme pixel values due to spurious R2* estimates. R2* maps of NLS, weighted NLS and Noise Floor methods were less heterogeneous. The R2* maps of other patients with known severe iron overload showed similar pattern (data not shown). Presence of fat can confound R2* estimation, but was not considered in this study. In summary, a Rician-noise based method is clinically feasible and may be necessary to accurately estimate R2* from multiecho magnitude images in patients with severe iron overload.



REFERENCES: [1] Bos, et el. Proc. Intl. Soc. Mag. Reson. Med. 17, 2009 #4526. [2] St Pierre, et al. Blood, 2005. 105(2): p. 855-61. [3] Senegas, et al. Proc. Ntl. Soc. Mag. Reson. Med. 15, 2007 #1782