# SELFCALIBRATED DCE MRI USING MULTI SCALE ADAPTIVE NORMALIZED AVERAGING (MANA)

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**Introduction**

In conventional analysis of Dynamic Contrast-Enhanced (DCE) Magnetic Resonance Imaging (MRI) time series, constant sensitivity of the MR-scanner during the experiment usually is assumed. However, patient movement and possible other effects related to hardware and pulse sequence optimizations may affect the sensitivity during the time series. In order to correct intensity inhomogeneity in fat-water MRI using Dixon imaging, and to provide reference scaling in DCE MRI time series, the Multi Scale Adaptive Normalized Averaging (MANA) method has been proposed [1]. MANA estimates a correcting multiplicative bias field based on the observation that pure fat voxels should have the same intensity, independent of their position in the volume. Voxels are classified as pure fat voxels if the intensity ratio of the signals fat/(fat + water) > 0.90. One important assumption of MANA is that the contrast agent does not affect the fat image. The raw bias correction field will be sparse and very localized, since these pure fat voxels are relatively uncommon and unevenly spread in the volume. MANA estimates a dense correction field by using weighted averages on multiple scales, where local signal certainties are used as weights. In this way details are preserved where the pure fat voxel density are high, while giving smooth estimates in sparse regions. In this work, we validate the correctness of MANA compared to conventional scaling assuming constant sensitivity, as implemented in the 1.5T MR-scanner (Achieva, Philips Medical Systems, Best, the Netherlands) used for data acquisition. MANA is also considered as a possible reference scaling method for DCE MRI time series.

**Dataset and method**

Patients were injected with a liver specific contrast agent (0.025 mmol/kg Gd-EOB-DTPA), and DCE MRI time series were acquired using symmetrically sampled 2-point Dixon imaging (TE 2.3 and 4.6 ms, TR 6.6 ms, α=10°, breath hold ≈ 20s) using a phased-array body coil. An initial non-enhanced acquisition was also performed. The purpose of this dataset is to study the hepatocyte-specific contrast agent uptake over time. Here, we use the water volumes to extract data $d$ from 36 patients acquired at 6 different time points in 7 different liver ROIs, placed in homogenous liver parenchyma by an experienced radiologist. Formally we have $d(p,x,y,z,t)$ where $p$ is the patient index, $x,y,z$ are the volume coordinates and $t$ is the time index. We reduce the data set by representing each ROI with its average; we get $d(p,r,t)$ instead, where r is the ROI index. The time points used are {*native, venous phase (vp), 3 min, 10 min, 20 min, 30 min*}. In summation, for every patient we have a time series, or curve, in every liver ROI. We want to statistically validate that 1), the shapes of these curves do not significantly change between the default scanner correction method (denoted $X$) and MANA (denoted $Y$), and 2), the dispersion of the ROI-values should be equal or less for $Y$ compared to $X$ as we believe that homogenous liver parenchyma most likely should have equal signal intensity throughout the liver. Specifically, we want to show that 1): $E_{p,r}[d_X(p,r,t)-d_Y(p,r,t)]=0$ and 2):$\mathrm{var}[v_X] > \mathrm{var}[v_Y]$, where $v_X$ and $v_Y$ are vectors with all the data for $X$ and $Y$ respectively, normalized so the ROI-median always is 1 for every $p$ and $t$. Since $d_X(p,r,t)$ and $d_Y(p,r,t)$ are multivariate, dependent and have non-normal distributions, we must choose our statistics with care. For test 1 we use $D=\log(d_X(p,r,t))-\log(d_Y(p,r,t))$ and use the Hotelling's T2-test [2] for evaluating the hypothesis H0: $E_{p,r}[D]=0$. We test the normality of $D$ using the Doornik-Hansen omnibus multivariate normality test [3,4]. For test 2, we need a test for homogeneity of variance for paired data, i.e. H0: $\sigma_X/\sigma_Y = 1$ against H1: $\sigma_X/\sigma_Y > 1$. The Pitman-Morgan test [5,6] is often used for this purpose but is sensitive for non-normal distributions. We use instead a modified nonparametric version proposed by McCulloch [7], which uses the Spearman correlation instead of the Pearson correlation. We use α=0.01 as the significance level for all tests. An initial scale normalization (multiplication with a scalar constant) was performed on the data so that $d_X(p,r,t)$ and $d_Y(p,r,t)$ have the same median.

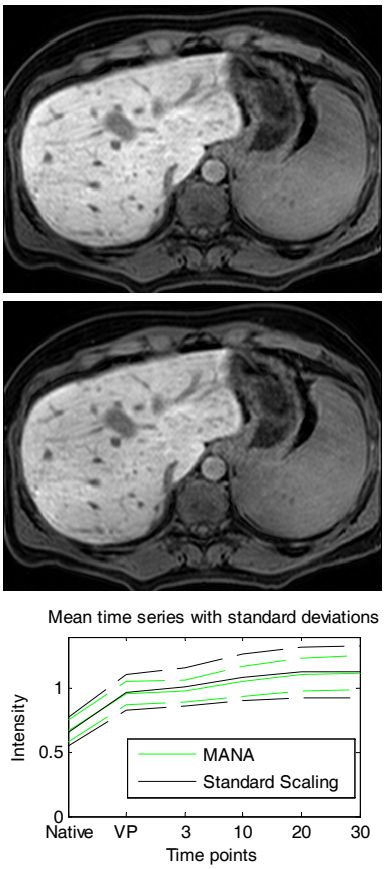


**Fig. 1 Top:** Liver using standard scaling, **Middle:** Liver using MANA. Note the more homogenous liver intensities, **Bottom:** Mean time series with standard deviations

**Results and discussion**

The relative difference norm $|E_{p,r}[d_X-d_Y]|/|sqrt(E_{p,r}[d_X]E_{p,r}[d_Y])|$≈2.1%, indicating a very small mean difference between $X$ and $Y$. The Doornik-Hansen test shows (p=0.49) that $D$ has a multivariate normal distribution. The following multivariate Hotelling T2-test shows, however, that we can reject ($p=4.8\times10^{-7}$) that $X$ and $Y$ are equal. Univariate t-tests for each time point show that $X$ and $Y$ are equal however, so the covariance within the data is important. In addition, preliminary experiments show this difference also exists between the corresponding fat histograms.

The McCulloch test shows ($p=2.3\times10^{-3}$) that the variance of the ROIs is less for MANA. This means that the intensities are more consistent over the liver voxels for MANA.

**Conclusions and future work**

The tests validate MANA as the differences to conventional scaling are very small. In addition, the tests show that MANA results in more consistent intensities over the liver. This decreased variance in water image intensities is particularly positive, considering that the MANA method only uses information from the fat image surrounding the liver. These results are very promising since they show that MANA successfully can recreate scaling information directly from the data. This implies that MANA can be used as a possible reference DCE MRI scaling method, potentially giving more robust and consistent results for time series analysis. However, the small remaining differences are statistically significant and will be the subject for future work.

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