A new concept for improved quantitative analysis of reversible transverse relaxation in tissues with variable microscopic field distribution

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Purpose: The intravoxel distribution of the magnetic field strongly influences signal dephasing after RF excitation and the resulting signal decay in gradient echo–based MRI. In this work, several different field distribution models were applied and tested for analysis of microscopic field characteristics within pixels.

Theory: A flexible model for improved pixel-wise characterization of the underlying field distribution is introduced. The proposed symmetric alpha-stable (SαS) distribution covers Lorentzian, Gaussian, and intermediate field distributions in a continuous way using a two-parametric (width and shape) function.

Methods: The new model was applied on human brain, potatoes (homogeneous isotropic tissue), and stems of pineapple (anisotropic fibrous tissue). Effects of microscopic structure and background gradients on the shape and the widths of the microscopic field distribution were analyzed using gradient echo sampling of the spin echo and multigradient-echo sequences. Effects of non-Lorentzian shapes of microscopic field distributions on the results of common $T_2^*$ measurements with mono-exponential fitting of signal values were tested.

Results: Many pixels of the examined objects showed field characteristics in between Lorentzian and Gaussian shapes. Microscopic field inhomogeneities caused by microscopic susceptibility effects and background gradients sometimes led to rather Gaussian than Lorentzian field distribution. In cases with nearly Gaussian field distribution, mono-exponential fitting of the signal decay resulted in different $T_2^*$ values, depending on the sampling points.

Conclusions: Using the concept of more flexible distributions for characterization of microscopic susceptibility effects in tissue provides better fitting of data and nearly sampling point–independent results than common $T_2^*$ measurements with mono-exponential fitting.

KEYWORDS
GESSE, magnetic field distribution, $T_2^*$-weighted imaging, transverse relaxation
1 | INTRODUCTION

In most tissues, signal yield as a function of TE in gradient-echo (GRE) imaging sequences is clearly different from spin-echo (SE) type imaging sequences. The SE sequences compensate for frequency dispersion effects in the recorded signal by using a refocusing pulse, centered in the TE interval. Therefore, SE sequences show signal dependence on the TE, which is primarily determined by transverse relaxation, an irreversible process according to the transition of the spin system to the equilibrium state. For single compounds, signal decay as a function of time $t$ can be described by a mono-exponential law \( \exp \left(-t/T_2\right) \).

In contrast, GRE sequences often show clearly faster and irregular signal decay as a function of TE, due to frequency dispersion effects. Marked frequency dispersion of signal components contributing to a pixel are present in tissue areas with significant content of water and fat. Chemical shift effects (eg, 220-Hz frequency difference between water and major lipid signal components at 1.5 T) occur even for relatively short TE and can be used for in-phase and opposed-phase imaging.\(^1\)

Another important factor leading to frequency dispersion of signal components contributing to a pixel is static magnetic field inhomogeneity in tissues, existing independently from switched gradient fields for spatial encoding. In principle, the field distribution inside the volume (typically a few cubic millimeters) forming the recorded signal for the corresponding pixel in the final MR image has to be considered here. Reasons for magnetic field inhomogeneities in tissue consist of macroscopic and microscopic effects: Macroscopic effects arise from extended magnetic material (eg, body parts or implants) inside the bore of the MRI leading to steady field gradients in tissue. Thus, depending on the pixel size, Larmor frequencies of water (and other chemical compounds) might vary from one edge of the pixel to the other, and respective signal contributions show a spectral distribution of frequencies. Microscopic magnetic field inhomogeneities are caused by susceptibility variations of tissue components.\(^2\) All solid tissues and even blood are spatially structured with components of different susceptibility, and therefore never show an ideal homogeneous magnetic field.\(^3,4\)

Because Larmor frequency of signals are linearly correlated to the static magnetic field strength, the magnetic field distribution in a distinct volume of tissue primarily determines the frequency spectrum of signal contribution out of this volume. Effects of field inhomogeneities and chemical-shift effects acting on the frequency dispersion in tissue are visualized in Figure 1.

In GRE examinations of tissues providing solely water signals (or in examinations with sufficient fat-signal suppression), signal decay can be seen as a combined result of “true” transverse relaxation and signal dephasing effects due to magnetic field inhomogeneities. The observed signal decay in GRE sequences is often referred to as $T_2^*$ relaxation.\(^5\) This implies the assumption that the signal decay in GRE sequences can also be described by an exponential function \( \exp \left(-t/T_2^*\right) \), which then can be decomposed into two parts:

\[
\exp \left(-t/T_2^*\right) = \exp \left(-t/T_2\right) \cdot \exp \left(-t/T_2'\right)
\]

with $1/T_2^* = 1/T_2 + 1/T_2'$, where \( \exp \left(-t/T_2'\right) \) characterizes the dephasing by magnetic field inhomogeneities.

Quantitative assessment of $T_2^*$ values is often used for characterization of iron deposition in tissue, as iron is known to act as a strong microscopic magnetic field disturber.\(^6-8\)

Water signal decay of tissues often looks nearly mono-exponential when using multi-echo GRE sequences with relatively long minimal TE values (several milliseconds). At the beginning of clinical tissue characterization by GRE in the 1980s and 1990s, very short TE values were not feasible. The “exponential” fitting of GRE signals and calculation of $T_2$ values were therefore considered a suitable model, which has been kept more or less unquestioned up until now.

Early works by Yablonskiy and others published after the introduction of gradient-recalled imaging in the late 1980s and 1990s already dealt with effects of microscopic susceptibility distributions and background gradients and variable types of signal decay curves.\(^9-12\) More recent works by Mulkern et al have shown clear deviations of the susceptibility-related signal decay from mono-exponential characteristics in brain\(^13\) and prostate tissue.\(^14\) It was demonstrated that those tissues often show a more Gaussian frequency distribution inside areas contributing to single pixels, reflecting a nearly Gaussian microscopic field distribution. The typical nearly Gaussian lineshape characteristics of signals in volume-selective spectra recorded in vivo support this assumption.\(^15,16\)

On the other hand, the assumption of a mono-exponential signal decay corresponds to an underlying pure Lorentzian frequency distribution.

Special multi-echo techniques as gradient-echo sampling of the FID and echo (GESFIDE)\(^17\) or gradient-echo sampling of the spin echo (GESSE)\(^18\) provide a simultaneous measurement of true $T_2$ and frequency dispersion–dependent dephasing, with one single sequence combining simultaneous readouts of spin echoes and gradient echoes. Those sequences allow detailed assessment of the signal yield for a wide range of signal-dephasing conditions, including fully rephased magnetization. This is particularly helpful for an assessment of the intravoxel frequency distribution.

This work aims to introduce and test a new concept with an improved characterization of the underlying intravoxel frequency distribution $\Phi$ for each pixel. The new concept assumes $\Phi$ to be symmetrical and to be approximate to a more general set of distributions: Lorentzian and Gaussian shapes and transitional shapes in between are possible, instead of...
Lorentzian shapes only. This generalized distribution is characterized by a parameter \( \sigma \) for the width of the frequency distribution and a shape parameter \( \alpha \). It should be mentioned that this new approach is dedicated to imaging of tissues without considerable fat content (or imaging with efficient fat signal suppression), as fat components lead to clearly asymmetrical frequency distributions that are not covered by the approach presented here.

### 2 | THEORY

Both GRE and GESSE sequences allow us to follow the evolution of the transverse magnetization \( M \) inside voxels (according to pixels) of a recorded slice along variable dephasing times \( \tau \). Figure 2 shows the timing of both sequence types and the ranges of \( \tau \) accessible by these sequences. Using GRE states with lacking or very short \( \tau \) cannot be measured, as the shortest \( \tau \) corresponds to the nonzero minimal TE of the sequence (Figure 2A). Furthermore, it is hard to differentiate effects of “true” transverse relaxation and signal dephasing effects caused by Larmor frequency dispersion inside the voxels. In contrast, the GESSE sequence allows measurements with arbitrary dephasing states before and after complete rephasing of all frequency components in an SE experiment. With this feature, GESSE enables comprehensive assessment of effects of the Larmor frequency distribution in each pixel and separation of true \( T_2 \) effects.

In the following, \( \Phi \) denotes the frequency distribution inside the voxel of tissue under consideration. In case all frequency components show identical \( T_2 \) (as approximately given for most tissue types containing only water and no fat), the development of the transverse magnetization \( M \) can be expressed by

\[
M(\tau) = M_0 \exp \left( -\frac{\tau}{T_2} \right) \int \Phi(\omega) \exp \left( i\omega \tau \right) d\omega = M_0 \exp \left( -\frac{\tau}{T_2} \right) \Phi(\tau),
\]

where \( M_0 \) is the total transverse magnetization for \( \tau = 0 \); \( \Phi \) is the characteristic function of the frequency distribution \( \Phi \); and \( \omega \) is the angular frequency. The characteristic function \( \Phi \) is the inverse Fourier transform of the frequency distribution \( \Phi \). It
should be mentioned that there is a one-to-one correspondence between the characteristic function $\varphi$ and the frequency distribution $\Phi$.

For a GESSE sequence, it is convenient to rewrite the development of the transverse magnetization $M$ as

$$M(\tau) = M_0 \exp \left( -\frac{TE}{T_2} \right) \exp \left( -\frac{\tau}{T_2} \right) \varphi(\tau), \quad (3)$$

where $\tau = 0$ corresponds to the TE of SE (see Figure 2).

As $\Phi$ is a real function, it follows that $-\varphi(\tau) = \varphi(-\tau)$, where $-\varphi(\tau)$ denotes the complex conjugate of $\varphi(\tau)$ and $M$ can be decomposed into two parts:

$$M_{\text{odd}}(\tau) = \sqrt{M(\tau)/M(-\tau)} = \exp \left( -\tau/T_2 \right) \cdot \exp(i \cdot \arg(\varphi)(\tau)) \quad (4)$$

and

$$M_{\text{even}}(\tau) = \sqrt{M(\tau) \cdot M(-\tau)} = M_0 \exp \left( -TE/T_2 \right) \cdot |\varphi|(\tau). \quad (5)$$

The magnitude $|M_{\text{odd}}(\tau)| = \exp(-\tau/T_2)$ of $M_{\text{odd}}(\tau)$ can then be used to determine $T_2$. As $M = M_{\text{odd}} \cdot M_{\text{even}}$, it also holds that

$$M_{\text{even}}(\tau) = M(\tau) \cdot \exp \left( \tau/T_2 \right) \cdot \exp(-i \cdot \arg(\varphi)(\tau)) \quad (6)$$

and

$$|M_{\text{even}}(\tau)| = |M(\tau)| \cdot \exp \left( \tau/T_2 \right). \quad (7)$$

The value of $M_{\text{even}}$ only depends on the magnitude of $\varphi$, regardless of irrelevant constants (see Equation 5), which means that $M_{\text{even}}$ can be used to determine the magnitude of the characteristic function $\varphi$.

The value of $M_{\text{even}}$ can also be calculated with aid of Equation 6, if $T_2$ values were determined previously as described. This method has the advantage that not only GESSE with symmetrical readout (Figure 2B) but also the GESSE with asymmetrical readout (Figure 2C), which provides more SNR in comparison to the symmetric GESSE due to a smaller TE of the SE, can be used for the calculation of $M_{\text{even}}$.

### TABLE 1 Types of frequency distributions $\Phi$, their underlying frequency distribution functions (if known), and characteristic functions, useful as models for the Larmor frequency distribution within a volume

| Type of frequency distribution | FDF $\Phi(\omega)$ | CF $\varphi(\tau)^a$ |
|-------------------------------|------------------|-------------------|
| Lorentzian                    | $\frac{1}{\pi \sigma} \cdot \left( 1 + \left( \frac{\omega \tau}{\sigma} \right)^2 \right)^{-1}$ | $\exp(-\sigma |\tau|)$ |
| Gaussian                      | $\frac{1}{\sqrt{2\pi} \sigma} \cdot \exp \left( -\frac{1}{2} \left( \frac{\omega \tau}{\sigma} \right)^2 \right)$ | $\exp \left( -\frac{1}{2} \sigma^2 \tau^2 \right)$ |
| Symmetric alpha-stable        | $b$              | $\exp(-2^{1-a} |\sigma| \tau^a)$ |

Note: $\mu$ is the location parameter denoting the mean Larmor frequency within the volume; $\sigma$ is the width parameter, which is a measure of the width of the distribution; and $\alpha$ is a shape parameter with $1 \leq \alpha \leq 2$. The symmetric alpha-stable (SαS) distribution is identical to the Lorentz distribution for $\alpha = 1$ and to the Gaussian distribution for $\alpha = 2$.

Abbreviations: CF, characteristic function; FDF, frequency distribution function.

*aThe common phase factor $\exp(i\mu \tau)$ is omitted.

*bNo analytical form is known, except for certain values of the shape parameter $\alpha$. 

FIGURE 2 Radiofrequency and readout gradient (GR) schemes of a multi-echo gradient-echo (GRE) sequence (A), a gradient-echo sampling of the spin echo (GESSE) sequence with symmetrical readout (B), and a GESSE sequence with asymmetrical readout (C). The accessible range of signal dephasing characterized by the “dephasing” time $\tau$ is highlighted by a gray bar. For complete rephasing of frequency components, value $\tau$ equals zero at this point. This is only possible for the GESSE sequences, allowing analysis of the characteristic function $\varphi$ around the origin.
As mentioned previously, it was recently reported that the microscopic frequency distribution in biological tissue is sometimes found to be more similar to Gaussian than to Lorentzian shape. Based on this finding, one may ask whether there is a tendency to just one of these two distributions for each pixel, or whether a more generalized model allowing further distributions in between Gaussian and Lorentzian shape would be preferable. To examine this issue, it is beneficial to unify the different models (Lorentzian vs Gaussian distribution) in a new more general approach: For further analysis, three distribution types were considered: namely, the Lorentzian distribution, the Gaussian distribution, and the so-called “symmetric alpha-stable” distribution. The symmetric alpha-stable (SaS) distribution has an additional degree of freedom: It is characterized by the mean value $\mu$, a width parameter $\sigma$ (a measure of the width of distribution), and a shape parameter $\alpha$. Particularly this distribution turns into the Gaussian distribution or the Lorentzian distribution for special values of the shape parameter $\alpha$ (see Table 1).

3 | METHODS

3.1 | Magnetic resonance imaging measurements

All MRI measurements of human subjects and biological phantoms (potatoes and pineapples) were performed on a 3T whole-body MR scanner (Magnetom Prisma Fit, Siemens Healthineers, Erlangen, Germany). For GRE imaging, a commercial 2D multi-echo spoiled GRE sequence with monopolar readout was used with TR = 100 ms, minimum TE = 2.5 ms, echo spacing = 2.85 ms, number of echoes = 12 and flip angle = 25°, and phase images of multiple echoes were calculated for calculation of $B_0$-field maps. Two different variants of GESSE sequences were used (Figure 2B,C): In GESSE type 1 (Figure 2B), the SE was centered in the train of gradient echoes for symmetrical readouts with respect to the SE (resulting in an equal number of negative and positive $\tau$ values). In the second variant, GESSE type 2 (Figure 2C), the time of the SE was used for the first echo (with $\tau = 0$ ms), and all further gradient echoes were read out afterward with positive $\tau$ values, as formerly described by Ordidge et al. The GESSE type 1 was used to evaluate $T_2$ as described in the Theory section (see Equation 4). Derived $T_2$ values were used to remove $T_2$ effects from the data acquired with the GESSE type2 with minimum TE = 6.79 ms and number of echoes = 31, to obtain $|\varphi|$ (see Equations 5-7). Common parameters of both GESSE sequences were TR = 2000 ms and echo spacing = 2.69 ms, and common parameters of all sequences were pixel size = 1 mm, slice thickness = 5 mm, bandwidth/pixel = 740 Hz, and one average.

3.2 | Gradient-echo and GESSE imaging of human brain in vivo

Five healthy male volunteers (mean age 38 years ± 12 years) were scanned using a 32-channel head coil of the manufacturer. The study was approved by the local ethics committee, and the volunteers gave written, informed consent prior to the examination. Automatic global shimming of the head was performed before starting the imaging protocol. As a first step, multiple axial images of the brain were recorded using a $T_1$-weighted turbo SE sequence and a fluid-attenuated inversion-recovery sequence, respectively. Based on the resulting stack of images, two different slice positions were selected for further imaging with multi-echo GRE and GESSE sequences: One slice position (with relatively homogeneous distribution of the magnetic field) was selected in the central area of the cerebrum above the lateral ventricles, and the other slice (with a more inhomogeneous field due to nearby bone structures and air cavities) was chosen close to the skull base. The GESSE type 1 images were acquired with a minimal TE of 22.56 ms and 15 echoes.

3.3 | Statistical assessment

The new two-parameter model was statistically compared with its special-case Lorentzian ($\alpha = 1$) and Gaussian ($\alpha = 2$) distribution by means of Akaike’s information criterion (AIC). The corrected AIC ($AIC_c$) was used, which is defined as $AIC_c = AIC + \frac{2k(k+1)}{n-k-1}$ as the sample size was relatively small. The common AIC was calculated by the same expression $AIC = \left(\frac{\text{SSE}}{\sigma^2}\right) + 2k$ as in Bourne et al., where SSE is the sum of squared errors returned by the fit algorithm; $\sigma^2$ is the variance of noise as estimated previously; and $k$ is the model parameter, in which $k = 2$ for the Gaussian and Lorentzian distribution ($M_0$ and $\sigma$) and $k = 3$ for the SaS distribution ($M_0$, $\sigma$, and $\alpha$). Maps of the differences of $\text{AIC}_{c,S}$, $\Delta_l = \text{AIC}_{c,L} - \text{AIC}_{c,SaS}$ and $\Delta_G = \text{AIC}_{c,G} - \text{AIC}_{c,SaS}$ were calculated pixel-by-pixel to get a ranking between the Lorentzian model and the SaS model, and between the Gaussian model and the SaS model, respectively. The values of $\text{AIC}_{c,L}$, $\text{AIC}_{c,G}$, and $\text{AIC}_{c,SaS}$ denote the $\text{AIC}_{c}$ for the Lorentzian, Gaussian, and SaS models, respectively.

3.4 | Gradient-echo and GESSE imaging of potatoes and pineapples for assessment of effects arising from microscopic structure and background gradients

Potatoes show a relatively homogeneous macroscopic structure and were found to be useful as tissue-like phantoms for studies on reversible and irreversible relaxation
using clinical MR scanners.\textsuperscript{13} Because potatoes do not include strongly ordered anisotropic structures (eg, fibers or canals), they are considered to have an isotropic microstructure. A nearly ellipsoidal potato was positioned in the center of the transmit/receive extremity coil of the manufacturer, with its maximum extension along the \( B_0 \) field. The GESSE images with transverse orientation were recorded at the position with maximum cross-sectional area of the potato. In a first measurement, GESSE imaging was performed after shimming (with relatively homogeneous \( B_0 \) field inside the potato). In a second measurement with unchanged imaging parameters, a background gradient in \( z \)-direction with an amplitude of 0.05 mT/m was applied. Signal decay and field distribution were assessed pixelwise for both measurements.

To visualize the effect of the additional background gradient, a 3D-GRE sequence with \( TR = 100 \) ms, \( TE_1 = 2.5 \) ms, \( TE_2 = 40.0 \) ms, and 11 slices was applied for both measurements with and without background gradient, respectively, and magnitude and phase images were acquired to be able to calculate \( G_z \)-field maps. The position of the central slice of the 3D GRE was identical to the position of the slice of the 2D multi-echo GRE sequence. To calculate the \( G_z \) value for each pixel in the central slice, the two \( B_0 \) values, \( B_{0,1} \) and \( B_{0,2} \) of the corresponding neighbored pixels in the adjacent slices along the \( B_0 \) axis, were used with \( G_z = (B_{0,2} - B_{0,1}) / 2\Delta z \), where \( \Delta z \) is the slice thickness. The GESSE type 1 images of the potatoes were acquired with minimal TEs of 44.09 ms and 31 echoes.

A pineapple with its anisotropic microstructure in the stem (due to parallel fibers oriented along the axis of the fruit) was examined with the same GESSE sequence as used for the potato, but a coronal instead of a transverse slice was chosen at the maximal cross section. Anisotropic effects on the signal decay were studied in several measurements, with the stem oriented along or perpendicular to the static magnetic fields \( B_0 \). The GESSE type 1 images of the pineapple were acquired with minimal TE of 17.19 ms and 11 echoes.

3.5 | Postprocessing

Images were analyzed offline on a PC using home-made routines written in MATLAB (The MathWorks, Natick, MA). Noise correction was applied as specified in Gudbjartsson and Patz\textsuperscript{21} in which the variance of noise was estimated as described in Sijbers et al.\textsuperscript{22} To avoid artificial values in the calculated maps in regions outside the object under measurement, signal was set to zero. The \( T_2 \) values determined by GESSE type 1 measurements were used for pixelwise fitting of measured signal intensities using the GESSE type 2 sequences according to

\[
|M| (\tau) = M_0 \exp\left(-\frac{TE}{T_2}\right) \cdot \exp\left(-\frac{\tau}{T_2}\right) \cdot |\phi| (\tau),
\]

to calculate maps of the width parameter \( \sigma \) and the shape parameter \( \alpha \) for the \( S_\sigma S \) distribution. The same images were used to calculate maps of the width parameter \( \sigma \) assuming a Gaussian and the Lorentzian distribution for comparison.

4 | RESULTS

4.1 | Microscopic and macroscopic magnetic field distribution in human brain

Most areas of human brain allowed reliable assessment of the magnetic field distribution in each pixel. Figure 3 shows a transverse slice of brain recorded above the lateral ventricles after global shimming. The width parameter \( \sigma \) (indicating the width of the frequency distribution) varies only slightly in a range from about 15 Hz in central white matter to 25 Hz for gray matter in the cortex, whereas the shape parameter \( \alpha \) indicates nearly Lorentzian shape of the field distribution with values \( \alpha \) ranging from 1.0 (primarily white matter) to 1.4 (primarily gray matter) in brain tissue (colored green and yellow in Figure 3B). Only areas adjacent to the skull and the cerebral falx contain pixels with values \( \alpha \) close to 2, indicating a nearly Gaussian field distribution (red in Figure 3B).

Exemplary signal decay curves (measured by GESSE and corrected for true \( T_2 \) effects) of three pixels (with positions indicated in Figure 3B) are depicted in Figure 3D-F. For \( \alpha = 1.18 \) (pixel 2) and \( \alpha = 1.33 \) (pixel 3), measured signal strengths were slightly but systematically deviating from a mono-exponential decay.

The situation in areas with marked distortions of the magnetic field inside the brain in areas close to the skull base is depicted in Figure 4. Especially brain regions situated near structures with strong susceptibility effects as paranasal sinuses or the petrous bone had clearly broader field distributions with \( \sigma \) values up to approximately 400 Hz. At the same time, shape parameter \( \alpha \) of pixels in those regions was found to be close to 2, indicating nearly Gaussian field distribution. Signal decays of pixels with intermediate field distribution (eg, pixel 2 and especially 3 in Figure 4E,F) were clearly deviating from mono-exponential behavior.

In Figure 5, the results of the statistical assessment using AIC parameters \( \Delta G \) and \( \Delta L \) are shown for the same transverse slices as depicted in Figures 3 and 4, respectively. Consistently positive values in the maps of Figure 5 indicate that the \( S_\sigma S \) distribution generally fits data better than pure Gaussian or Lorentzian distributions. The larger the AIC parameter \( \Delta G \) or \( \Delta L \), the less suitable are the purely Gaussian or Lorentzian models, respectively, in comparison to the \( S_\sigma S \) model. On the other hand, the \( \Delta G \) values or the \( \Delta L \) values are
rather small in regions where the fit quality of $S\alpha S$ distribution and Gaussian distribution or Lorentzian distribution are comparable, respectively.

### 4.2 Microscopic and macroscopic magnetic field distribution in a potato without and with macroscopic background gradient

Oval-shaped potatoes without tears (example in Figure 6) provided a quite smooth field distribution in the pixels representing the central areas of the tuber. After shimming, the width parameter $\sigma$ amounted to approximately 40 Hz in these areas, and the shape parameter $\alpha$ amounted to approximately 1.1. Areas under the skin of the potato showed clearly increased width with partly more than doubled $\sigma$ and higher shape parameters $\alpha$ (in some areas close to 2.0, indicating Gaussian field distribution). A $B_0$ map recorded from the same slice (Figure 6D) and a field gradient map in $z$-direction (Figure 6E) revealed a quite homogeneous $B_0$ field in the central parts of the potato, but distinct underlying macroscopic field gradients close to the surface.

The potato was examined once more after an intentional modification of the electric current in the $z$-gradient coil, leading to a superimposed gradient field in $z$-direction. The influence of this background gradient on the macroscopic field is clearly visible in Figure 7.

This additional background gradient led to an increased width parameter $\sigma$ in extended regions of the tuber (mean value is now approximately 50 Hz instead of 40 Hz for the homogeneous macroscopic field in Figure 6). Furthermore, the shape parameter $\alpha$ is shifted from approximately 1.1 to approximately 1.4 in many pixels. This measurement indicates, first, that field distribution in the potato is not fully Lorentzian even for a homogeneous macroscopic field, and, second, that the shape parameter $\alpha$ gets higher and the field distribution tends to transform more into Gaussian shape in the presence of a linear background gradient.

Measured signal decay from a small subvolume of the potato is depicted in Figures 6C and 7C. Obviously, the signal decay is nearly mono-exponential for the measurement...
FIGURE 4  Pixel-wise-calculated width parameters $\sigma$ (A) and shape parameters $\alpha$ (B) using the $S_{\alpha}$S distribution as underlying model for the frequency distribution $\Phi$ in a transverse slice of the brain slightly above the basis of the skull, with marked macroscopic field inhomogeneities. C, Anatomical image of this slice. D-F, The $T_2$-corrected signal decays $M_{\text{even}}$ (see Equation 7) assessed by the asymmetrical GESSE readout of three different pixels indicated by black circles in the $\alpha$ map of (B). The corresponding fits according to the $S_{\alpha}$S, the Gaussian, and the Lorentzian distributions are indicated by a dotted green line, a dashed blue line, and solid red line, respectively. Pixels with $\alpha$ values up to 2 occur in areas with strong field inhomogeneities.

FIGURE 5  Differences of Akaike’s information criterion (AIC), $\Delta_G$ (A,B) and $\Delta_L$ (C,D), of the same slices as shown in Figure 3A,C and Figure 4B,D, respectively. No negative values are apparent in any map, which indicates that the $S_{\alpha}$S distribution generally fits data better than pure Gaussian or pure Lorentzian distributions. Large AIC parameters $\Delta_G$ or $\Delta_L$ indicate clearly stronger deviations of measured values from fitting curves using the Gaussian or Lorentzian model compared with the $S_{\alpha}$S model. Small $\Delta_G$ or $\Delta_L$ indicate that the fitting quality of the $S_{\alpha}$S distribution and the compared pure Gaussian or pure Lorentzian distributions are similar.
without background gradient (with $\alpha = 1.13$, Figure 6C), whereas clear deviations from a mono-exponential decay and faster signal decline occur in presence of the macroscopic background gradient (with $\alpha = 1.59$; Figure 7C).

### 4.3 Microscopic and macroscopic magnetic field distribution in a pineapple stem parallel and perpendicular to the main magnetic field

The pineapple stem was used as a model for anisotropic microscopic structure. When the pineapple stem was oriented along the static $B_0$ field (Figure 8A), a microscopic field distribution with $\sigma$ values ranging from 60 Hz to 130 Hz was found in extended areas of the stem (Figure 8A). Transitional areas from the stem to the pulp of the pineapple showed increased $\sigma$ of approximately 180 Hz. In all areas of the stem, the shape parameter $\alpha$ ranged from 1.0 to 1.1 for parallel orientation with respect to the outer magnetic field (Figure 8B). Tilting the orientation of the pineapple stem axis to perpendicular to the static magnetic field also changed the microscopic field distribution: Especially outer areas of the stem got clearly more inhomogeneous compared with parallel orientation. Figure 8C indicates regions with elevated width parameter $\sigma > 100$ Hz. Under these conditions with stronger microscopic field inhomogeneity, the shape parameter $\alpha$ was partly changed as well, particularly near both ends of the stem, but not in lateral areas near the transition to the pulp. Those increased $\alpha$ values indicated a shift toward more Gaussian field characteristics for subregions at both ends of the stem, together with an increased width of the distribution (Figure 8D).

### 5 DISCUSSION

Our experiments in different types of biological tissue confirmed previous reports on Larmor frequency distributions in small volumes (according to original volumes of pixels in MRI), which often show clear deviations from Lorentzian shape. As a result, signal decay cannot be well approximated by mono-exponential functions, even in cases in which only water-signal contributions are present (ie, in tissue areas without other chemical shift components).

Since the 1990s, Yablonskiy et al have developed theoretical models of the MR signal behavior in the presence of magnetic susceptibility inclusions in biological tissues leading to
static microscopic magnetic field inhomogeneities. This theoretical work is based primarily on specific spatial arrangements of field disturbers (with specific susceptibilities, with spherical or cylindrical geometry, with different degrees of order and orientation to the external magnetic field, with or without consideration of diffusion effects). The GRE signal intensities for several distinct geometrical arrangements have been reported to show a nearly quadratic decay for short TEs and nearly linear behavior at longer TEs. The characteristic TE of transition between both schemes depends on the tissue model selected. In a subsequent study, this model was applied to MR experiments in a phantom study. For real tissue, the characteristics of microscopic magnetic field disturbances are expected to be more complex, unknown, and varying from pixel to pixel, so that the signal decay is not expected to follow exactly a simple mathematical function with very few free parameters. Our simple two-parametric model matches neither the mathematical model of Yablonskiy nor the more complex conditions in real tissue. However, the aim of our work was to introduce a new descriptive model for postprocessing of multiple-echo GRE or GESSE imaging of biological tissue with reasonable fitting of measured signal decays and clear advantages when compared with common models using mono-exponential or Gaussian fitting.

Our findings also correlate well to a more recent report of Mulkern et al. who stated that assuming a Gaussian frequency distribution is often more adequate for fitting signals of brain than a Lorentzian shape. They also stated that Gaussian fitting is especially useful for measurements at higher magnetic fields, as in our study, susceptibility-related broadening of the frequency distribution often outweighs true T2-related effects (because T2 and natural linewidth are nearly independent of B0).

Our results further suggest that common microscopic field distributions are often neither Lorentzian nor Gaussian, but intermediate. For this reason, it appears appropriate to introduce a more flexible approach for characterization of field distributions: The proposed so-called “symmetric alpha-stable” (SaS) distribution is parameterized by a width parameter \( \sigma \) and a shape parameter \( \alpha \), containing pure Lorentzian shape for \( \alpha = 1 \) and pure Gaussian shape for \( \alpha = 2 \).

The shape parameter \( \alpha \) of the characteristic function \( \varphi \) of the SaS distribution could be generalized to values \( 0 < \alpha < 1 \)
or $\alpha > 2$ in the fitting procedure. However, in this work the shape parameter was restricted to $1 \leq \alpha \leq 2$, as only values in this range were found by the fitting procedure in all tissue areas with reasonable SNR. Therefore, a limitation to this interval was considered sufficient and without loss of generality.

The $S_\alpha S$ distributions are special cases of a more general family of distributions called alpha-stable distributions with an additional parameter $-1 < \beta < 1$ and $\beta = 0$ describing symmetry. Alpha-stable distributions were originally introduced by Lévy and further developed by Mandelbrot. Further information on $S_\alpha S$ distributions can be found in Refs 28-30.

There has been a long discussion about lineshapes (Lorentzian, Gaussian, Voigt [convolution of a Gaussian and a Lorentzian], or pseudo-Voigt [linear combination of Lorentzian and Gaussian]) in localized $^1$H spectra and their consideration for correct approximation and quantification. Voigt or pseudo Voigt lineshapes are comparable to our approach, as Gaussian and Lorentzian lineshapes are combined to extended models. Both pure Gaussian and pure Lorentzian lineshapes are included as special cases. However, the advantage of our model is that it is easier and more intuitive to handle and interpret. The Fourier transform of the distribution or characteristic function is expressed by the simple function $\varphi(t) = \exp(-2^{1-\alpha} |t|^\alpha)$. The dependence of the shape parameter $\alpha$ is as simple as possible, and the width parameter $\sigma$ is identical to the scale parameter describing the width or dispersion of the distribution. For the two special cases of a Lorentzian distribution ($\alpha = 1$) or Gaussian distribution ($\alpha = 2$), the scale parameter is identical to the reversible relaxation rate $R_2^*$ or the SD. For the Voigt or pseudo-Voigt lineshapes, the product or the sum of a mono-exponential function and a Gaussian function would correspond to the “characteristic function,” which is not so easy to interpret. The fact that no analytical form of the $S_\alpha S$ distribution is known is not really disadvantageous, as we only use the characteristic function of the distribution and not the distribution itself.

Residues of fits with the generalized $S_\alpha S$ distribution were found to be distinctly smaller than residues of fits with pure Lorentzian or pure Gaussian distribution. Maps of values $\alpha$ derived from pixelwise fitting of the field distribution, based on GESSE imaging, lead to new and interesting insights about influencing factors on the characteristics of microscopic field distribution:

5.1 Macroscopic background field gradients

It was expected and detected in the studies that increasing steady background gradients of the static magnetic field (macroscopic field effects) leads to larger width of the frequency distribution. In addition, a clear increase of the shape parameter $\alpha$ was found in areas with background gradient as well, indicating that a background gradient turns the microscopic field distributions toward more Gaussian characteristics when compared to a situation without background gradient. This finding can be derived from a comparison between brain tissue in homogeneous central areas in the brain (Figure 3) and areas situated close to the skull base (Figure 4). The same effect was found in measurements of a potato without and with additional background field gradient generated by a linear gradient coil (Figures 6 vs 7). After switching on the additional background gradient, increased width parameters $\sigma$ and shape parameters $\alpha$ occurred in most areas.

Macroscopic field inhomogeneities can affect the characterization of biological tissue by means of susceptibility mapping. Assuming a rectangular slice profile and a linear background gradient in slice direction, the corresponding field distribution can be approximated by a rectangular function. The characteristic function of the macroscopic field distribution is then a sinc function. However, slice profiles are often not perfectly rectangular and may lead to a correction function, which may look rather like a Gaussian than a sinc function, and the assumption of a macroscopic field distribution described by a uniform distribution may be too simple for the in vivo case. Furthermore, field distribution in a voxel depends not only on field gradients in this voxel, but...
also on the neighboring voxels (due to Gibbs ringing). Various methods have been proposed during the last decades to correct for these signal decay distortions under the assumption of a linear background gradient. However, correction of background gradient effects, which usually need 3D data acquisition, recording of phase images, as well as suitable algorithms, was beyond the scope of this work.

5.2 Microscopic susceptibility effects

Presence of microscopic field inhomogeneities caused by microscopic susceptibility effects, as found in the areas under the potato peel, also led to higher σ and α values. It is not proven by the presented experiments, but possible that the geometrical arrangement of paramagnetic/diamagnetic sources of susceptibility effects might influence the shape of the frequency distribution. This assumption is supported by the finding that areas in the potato with homogeneous macroscopic magnetic field (extended central area of the potato in Figure 6) reveals higher shape parameters α than homogeneous white-matter regions (Figure 3).

Anisotropic microscopic susceptibility effects might occur in fibrous or tubular structures (as in the pineapple stem). Here, anisotropic susceptibility distributions lead to orientation-dependent microscopic field distributions. Interestingly, both width and shape parameters show distinct changes when the orientation of the structure is tilted in the outer magnetic field. However, changes of α and σ were not well correlated for all subregions: For example, when the axis of the pineapple stem was turned from parallel to perpendicular to B₀, the σ values clearly increased at both ends of the stem and in areas close to the pulp. On the other hand, the field distributions remained nearly Lorentzian (α ≈ 1) in stem areas under the pulp, but a clear shift toward Gaussian shape (α ≈ 2) was found at both ends of the stem.

5.3 Effects of irreversible relaxation (T₂)

The proposed SαS model was used to characterize the microscopic field distribution on the basis of GESSE data, which allows separation of reversible and irreversible relaxation effects. Thus, an accurate determination of the form and shape parameter of the underlying frequency distribution Φ can be performed. For an application of this approach on multi-echo GRE data, it is important to take the (exponential) influence of true (irreversible) relaxation into account. This can be done by separate T₂ measurements and correction of the measured signal decay.

It should be mentioned that the assumption of monoexponential decay for the irreversible T₂ effects does not take into account tissue with multiple, especially short, T₂ components, as, for example, myelin-associated water in white matter with a T₂ of approximately 5-10 ms as proposed by MacKay et al or Yipping et al. Such components may affect modeling data acquired with the asymmetric GESSE sequence directly after the SE is recorded with short TE. Measuring T₂ values by the symmetric GESSE sequence in a different TE range than evaluating the field distribution by aid of the asymmetric GESSE sequence (with T₂ compensation using T₂ values from the first measurement) can cause a bias, especially in white matter of the brain.

5.4 Problems with T₂* mapping using mono-exponential fitting of the signal decline in the presence of non-Lorentzian microscopic field distribution

Experiments with the GESSE sequence in human brain, potatoes, and pineapples revealed non-Lorentzian microscopic field distributions and pixels with shape parameters α > 1, especially in subregions with marked background field gradients, but also in some areas with a homogeneous macroscopic background field (eg, in the extended central area of the potato; see Figure 6). It is well known and described in the Theory section that the Larmor frequency dispersion within a pixel leads to dephasing and determines (in addition to T₂) the decline of the signal measurable by GRE imaging, according to the Fourier transform of the frequency distribution. Thus, pixels with non-Lorentzian field distribution show clear deviations from mono-exponential decline in multi-echo GRE sequences (examples shown in Figures 3F, 4E,F, and 7C).

When using a mono-exponential function for fitting the measured signal intensities with their non-exponential decline, resulting time constants (often considered to be precise T₂* values) become dependent on the chosen sampling time points (TE values). Figure 9 provides results of derived T₂* values for specific microscopic field distributions with width parameter σ = 100 Hz and shape parameter α = 2. In this example, the choice of supporting points for fitting leads to striking variation in resulting T₂* values. This quite realistic example shows that T₂* measurement of tissue (eg, for assessment of iron content) does not necessarily result in reliable absolute values. Results can only be compared for a given set of supporting points (or TE values used for measurements). It is especially remarkable that the fitted mono-exponential curve in Figure 9 for the longer minimal TE₁ = 10.76 ms matches the data points quite well. This might explain why mono-exponential fitting was introduced in the early times of GRE imaging, and further on applied for decades. With the availability of measurements with shorter TE (eg, using ultrashort TE approaches or modern GRE sequences), discrepancies from the nonexponential decline became more and more evident. The presented SαS distribution appears to
described in the Methods section for a simulated signal decay supporting points for the mono-exponential fitting procedure as inclusion of supporting points with short TE the nonexponential decline only becomes apparent for fitting with matches the data points quite well, and pronounced discrepancy from the first supporting point is TE1 = 2.69 ms or TE1 = 10.76 ms, the resulting T2 value changes from T2 = 9.97 ±0.20 ms to T2 = 6.46 ± 0.29 ms. It is remarkable that the fitted curve for TE0 = 10.76 ms matches the data points quite well, and pronounced discrepancy from the nonexponential decline only becomes apparent for fitting with inclusion of supporting points with short TE be a suitable tool for mapping of susceptibility effects using a broad range of TE values (including very short ones). On the other hand, it remains important to be aware that derived T2 values can be further influenced by unwanted macroscopic background gradients, and in this case may also depend on the chosen pixel dimensions.

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**REFERENCES**

1. Outwater EK, Blasbalg R, Siegelman ES, Vala M. Detection of lipid in abdominal tissues with opposed-phase gradient-echo images at 1.5T: Techniques and diagnostic importance. *Radiographics*. 1998;18:1465-1480.

2. Schenck JF. The role of magnetic susceptibility in magnetic resonance imaging: MRI magnetic compatibility of the first and second kinds. *Med Phys*. 1996;23:815-850.

3. Hopkins JA, Wehrli FW. Magnetic susceptibility measurement of insoluble solids by NMR: Magnetic susceptibility of bone. *Magn Reson Med*. 1997;37:494-500.

4. Jain V, Abdulmalik O, Propert KJ, Wehrli FW. Investigating the magnetic susceptibility properties of fresh human blood for non-invasive oxygen saturation quantification. *Magn Reson Med*. 2012;68:863-867.

5. Chavhan GB, Babyn PS, Thomas B, Shroff MM, Haacke EM. Principles, techniques, and applications of T2*-based MR imaging and its special applications. *Radiographics*. 2009;29:1433-1449.

6. Hernando D, Levin YS, Sirlin CB, Reeder SB. Quantification of liver iron with MRI: State of the art and remaining challenges. *J Magn Reson Imaging*. 2014;40:1003-1021.

7. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J*. 2001;22:2171-2179.

8. Ordidge RJ, Gorell JM, Deniau JC, Knight RA, Helpert JA. Assessment of relative brain iron concentrations using T2-weighted and T2*-weighted MRI at 3 Tesla. *Magn Reson Med*. 1994;32:335-341.

9. Yablonskiy DA, Haacke EM. Theory of NMR signal behavior in magnetically inhomogeneous tissues: The static dephasing regime. *Magn Reson Med*. 1994;32:749-763.

10. Yablonskiy DA. Quantitation of intrinsic magnetic susceptibility-related effects in a tissue matrix. Phantom study. *Magn Reson Med*. 1998;39:417-428.

11. Lüdeke KM, Röschmann P, Tischler R. Susceptibility artefacts in NMR imaging. *Magn Reson Imaging*. 1985;3:329-343.

12. Frahm J, Merboldt KD, Hänicke W. Direct FLASH MR imaging of magnetic field inhomogeneities by gradient compensation. *Magn Reson Med*. 1988;6:474-480.

13. Mulkern RV, Balasubramanian M, Mitsouras D. On the Lorentzian versus Gaussian character of time domain spin echo signals from the brain as sampled by means of gradient-echoes: Implications for quantitative transverse relaxation studies. *Magn Reson Med*. 2015;74:51-62.

14. Ciris P, Balasubramanian M, Seethamraju R, et al. Characterization of gradient echo signal decays in healthy and cancerous prostate at 3T improves with a Gaussian augmentation of the mono-exponential (GAME) model. *NMR Biomed*. 2016;29:999-1009.

15. Marshall I, Higinbotham J, Bruce S, Freise A. Use of Voigt lineshape for quantification of in vivo 1H spectra. *Magn Reson Med*. 1997;37:651-657.

16. Marshall I, Bruce SD, Higinbotham J, et al. Choice of spectroscopic lineshape model affects metabolite peak areas and area ratios. *Magn Reson Med*. 2000;44:646-649.

17. Jingfei Ma J, Wehrli FW. Method for image-based measurement of the reversible and irreversible contribution to the transverse-relaxation rate. *J Magn Reson B*. 1996;111:61-69.

18. Yablonskiy DA, Haacke EM. An MRI method for measuring T2 in the presence of static and RF magnetic field inhomogeneities. *Magn Reson Med*. 1997;37:872-876.

19. Burnham KP, Anderson DR. *Model Selection and Multimodel Inference. A Practical Information-Theoretic Approach*, 2nd edition. New York: Springer-Verlag; 2002.
20. Bourne RM, Panagiotaki E, Bongers A, Sved P, Watson G, Alexander DC. Information theoretic ranking of four models of diffusion attenuation in fresh and fixed prostate tissue ex vivo. *Magn Reson Med*. 2014;72:1418-1426.

21. Gudbjartsson H, Patz S. The Rician distribution of noisy MRI data. *Magn Reson Med*. 1995;34:910-914.

22. Sijbers J, den Dekker AJ, Raman E, Van Dyck D. Parameter estimation from magnitude MR images. *Int J Imag Syst Technol*. 1999;10:109-114.

23. Lévy P. *Calcul des Probabilités*. Paris: Gauthier-Villars et Cie; 1925.

24. Mandelbrot B. The Pareto-Lévy law and the distribution of income. *Int Econ Rev*. 1960;1:79-106.

25. Mandelbrot B. Stable Pareto random functions and the multiplicative variation of income. *Econometrica*. 1961;29:517-543.

26. Mandelbrot B. The variation of certain speculative prices. *J Bus*. 1963;36:394-419.

27. Mandelbrot B. New methods in statistical economics. *J Polit Econ*. 1963;71:421-440.

28. Zolotarev VM. *One-Dimensional Stable Distributions* (Translations of Mathematical Monographs, Vol. 65). Providence, Rhode Island: American Mathematical Society; 1986.

29. Nolan JP. *Stable Distributions: Models for Heavy-tailed Data*. New York: Springer; 2016.

30. Du YP, Chu R, Hwang D, et al. Fast multislice mapping of the myelin water fraction using multicomartment analysis of $T_2^*$ decay at 3T: A preliminary postmortem study. *Magn Reson Med*. 2007;58:865-870.

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