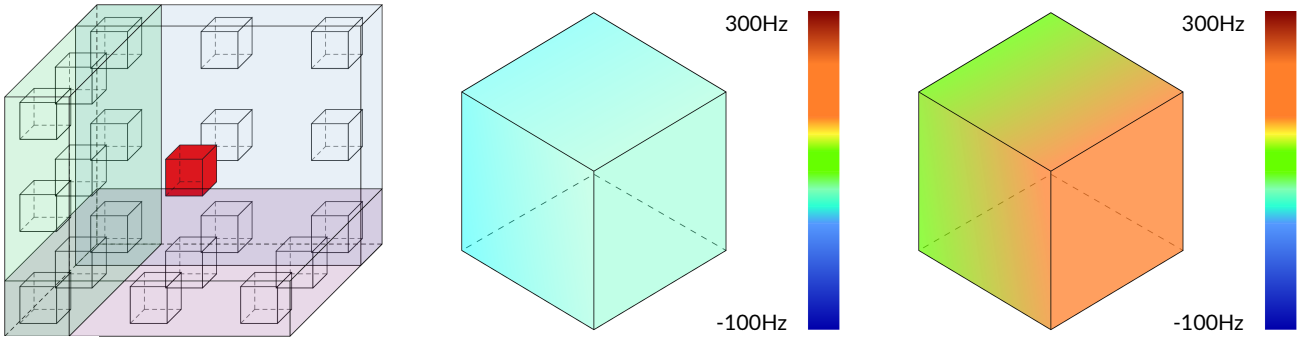


(a) Intravoxel localization **(b)** Intravoxel spatial distribution of B_0 **(c)** Spatial distribution of intravoxel magnetic susceptibility effects

FIGURE 1 Voxels are often treated as singularities, meaning the entire volume is considered to be single point like the red box in the center. Accounting for these intravoxel distributions leads to more accurate and more realistic simulations. (a) highlights the spatial nature of voxels and (b) shows the intravoxel B_0 inhomogeneity.

Until this knowledge gap is filled in, this work uses pre-generated basis functions from Osprey[36] that were resampled to match the simulated basis functions from MARSS.

2.1.3 | Amplitude Modulation

Metabolite quantities produced during spectral fitting are of an arbitrary scale. Comparing these quantities with a standard reference puts them into context. In vivo proton scans generally use an internal reference metabolite for relative quantification. Creatine is the default metabolite because its concentration is relatively stable. As a result, concentrations maps are generally reported as ratios with respect to creatine and all amplitude values in this model are defined *wrt* creatine as the default. For this framework, physiological values were derived from work by Das *et al.*[18,34]. These ranges were then expanded to include values observed in clinical scans from a private glioma dataset. In keeping in line with the LCModel, the expected concentrations ranges represent the scaling factors needed for spectral fitting instead of the ratios of peak integrals or peak heights.

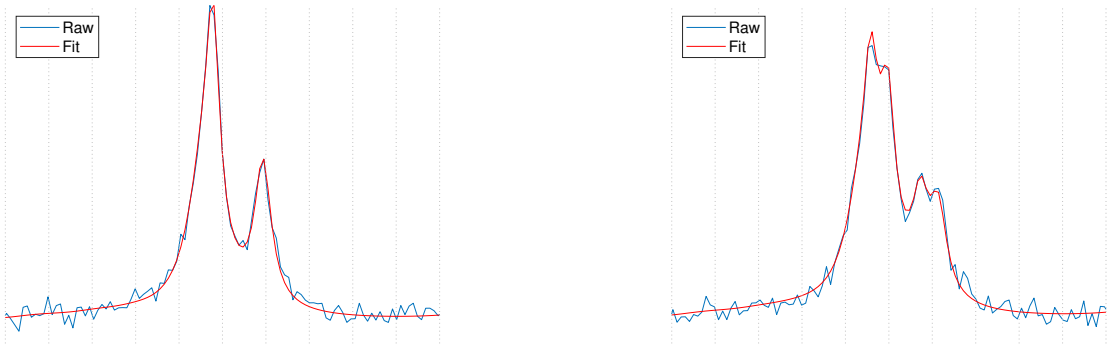
2.1.4 | Lineshape Profiles

In spectral fitting, the Voigt lineshape profile is the most commonly used as it most closely matches clinical data. It is a combination of a Lorentzian and a Gaussian and is used various fitting packages, such as LCModel[37], TARQUIN[38], jMRUI[27], and Osprey[36]. Each peak is characterized by an individual Lorentzian value while a single Gaussian value is applied to the metabolites, while a second value can be applied to the macromolecules and lipids. Standard practice from the aforementioned software packages assigns a single Lorentzian value to each metabolite, instead of each moiety. However, experimental results from Wyss et al.[?] can be selected which characterized T2 relaxation values at the moiety-level for various brain metabolites at 3T in three different regions in the brain. As more metabolites are characterized, new information can be added to the model. For completeness, it is also possible to specify either a purely Lorentzian or a purely Gaussian lineshape.

2.1.5 | B_0 Inhomogeneities

Lower and higher order shimming procedures homogenize the magnetic field in the target volume to different degrees. However, certain regions of the brain, such as the prefrontal cortex or deep brain structures like the thalamus or basal ganglia, are more difficult to shim and therefore suffer from large magnetic susceptibility effects, resulting in significant lineshape distortions. Fig. 1b shows the normal, subtle B_0 changes across the volume of a spectroscopy voxel while Fig. 1c illustrates these high susceptibility effects. In such cases, spectra from these regions exhibit significant lineshape distortions which cannot be adequately characterized using idealized lineshape profiles. Fig. 2 shows the result of high susceptibility effects on lineshapes.

Small B_0 inhomoegeneities are, in general, sufficiently modeled by the Gaussian term of the Voigt lineshape. However, to simulate more severe distortions, a B_0 field volume needs to be modeled and applied to the basis functions. In general, this approach mirrors Li *et al.*[39], but the B_0 field map is simulated rather than acquired. As with MARSS, Li *et al.*suggests using multiple points in each direction instead of a single value per voxel. The exact number of points used in each direction is described by the size of the spectroscopy voxel divided by the size of an anatomical imaging voxel. The default values assume sizes of 10cm^3 and 0.5cm^3 respectively, which results in 20^3 simulation points. However, both cuboidal and rectangular shapes can be modeled. The B_0 field is defined by four variables, all of which are mean offsets: $\pm dx$, $\pm dy$, $\pm dz$, and μ. dx, dy, and dz describe half of the change in B_0 in their respective direction from the voxel's center and μ is the mean of the entire voxel.



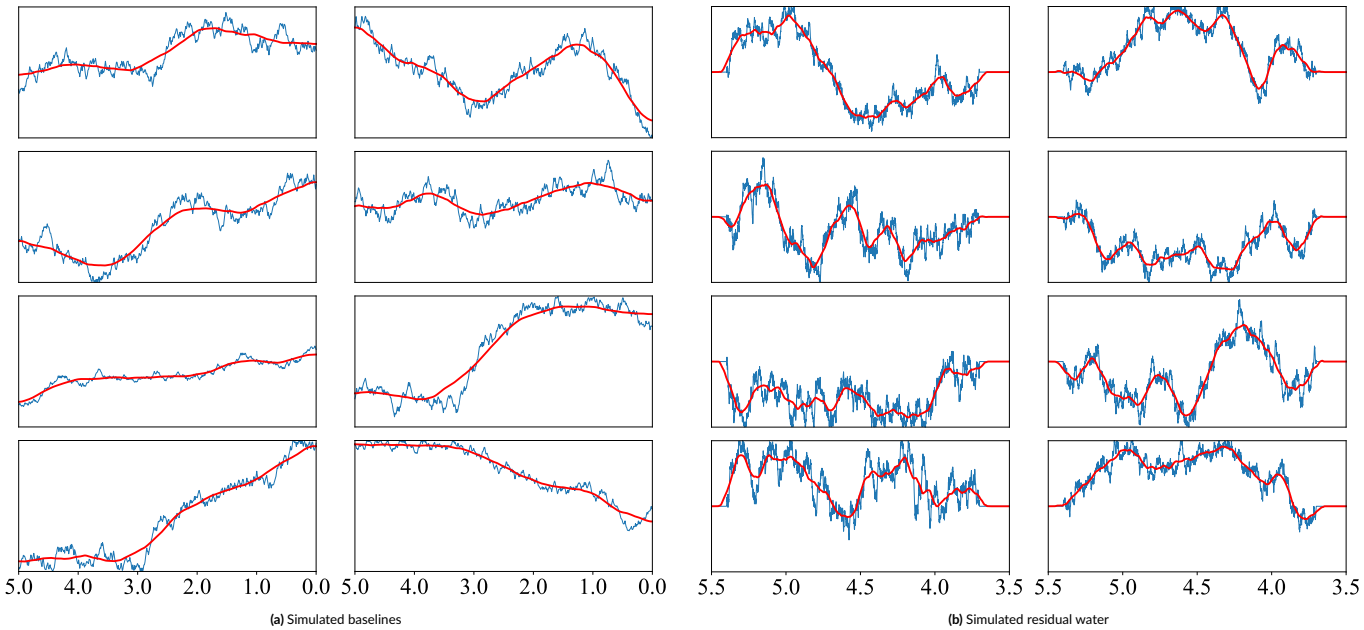
(a) Spectral peaks without B0 inhomogeneities

(b) Spectral peaks with B0 inhomogeneities modeling high susceptibility effects

FIGURE 2 Two samples showing the effects that can be modeled using the 3D $B0$ field simulator. In 2a, the spectral peaks have a Voigt lineshape defined by Lorentzian and Gaussian values. These broaden the peaks and lower their amplitude. In 2b, the lineshape is still Voigtian, but the Gaussian term was replaced by the 3D $B0$ field simulator. Large heterogeneity parameters were selected to highlight the effects. Here it can be seen that the line width is affected, but so are the line shapes. Both peaks have a lower spectral resolution and appear to be splitting.

2.1.6 | Baseline and Residual Water

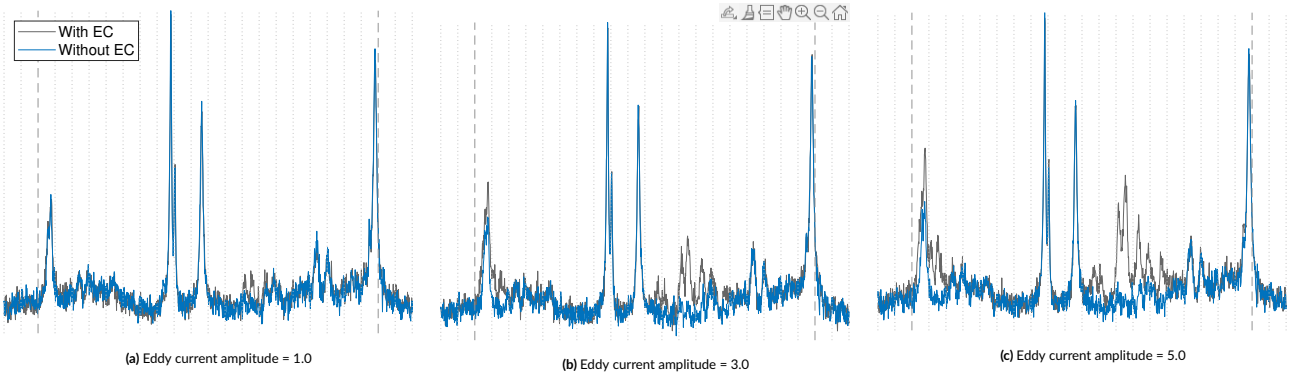
Currently, the underlying physical phenomena that induce spectral baseline offsets are poorly understood. In fact, there is no physics-based model for simulating these offsets. Similarly, the residual water region is also poorly characterized. Therefore, a naive random model can be used in conjunction with clinically observed constraints to approximate what is observed in vivo. This work proposes a smoothed, pseudo-random, bounded walk generator for both the broad spectral baseline and the more irregular residual water region. The approach is elaborated on in Algorithm 1. Customizable profiles were developed for each artifact to more closely approximate what is expected in vivo. Immense variety of outputs can be achieved by randomly sampling the parameters from distributions instead of fixing them to set values. Once simulated, they are resampled to match the ppm range of acquired data and the order of magnitude is matched to the spectra. The hilbert transform is then used to generate the corresponding complex component before being added to the FID. As shown in Fig.3, this generator produces very different outputs depending on the specified configurations. Fig.3a shows very broad, smooth lines while Fig.3b shows highly irregular lines that closely resemble residual water regions. All outputs are then scaled to modulate the impact on the final spectra.



(a) Simulated baselines

(b) Simulated residual water

FIGURE 3 Simulated spectral baseline and residual water using the pseudo-random bounded walk generator. The blue lines are the raw simulations. The red lines are the smoothed versions that are then returned and applied to the simulated spectra.



(a) Eddy current amplitude = 1.0 **(b)** Eddy current amplitude = 3.0 **(c)** Eddy current amplitude = 5.0

FIGURE 4 These 3 samples show the effect of eddy currents on MRS spectra to various degrees. The strength of the eddy currents increases from 4a to 4c. If the time constant, tc, is set too long, the eddy current artifact will appear as a global frequency shift. In these examples, it can be seen that only some frequencies are affected.

the work by[?] which characterized the temperature-induced frequency shift of brain metabolite moieties with temperature sensitivity. As more metabolites are characterized for their temperature- and pH-sensitivities, this information can be added to simulate more realistic spectra.

2.1.10 | Eddy Currents

Eddy currents are common artifacts in MRI acquisitions that are induced by changes in the magnetic field, typically caused by the imaging gradients and present as time-dependent resonant frequency shifts. Correction techniques, such as the Klose[40], tend to be non-parameterized, making it difficult to model the exact effect of each approach. Near et al. in FID-A[24], however, provide a parameterized equation for simulating first-order eddy currents. These artifacts are applied as a function of amplitude, A, time constant, tc, and time, t. The time constant must be short enough that it occurs entirely within the recorded echo, otherwise it will appear as a simple, global frequency shift. The effects of eddy currents can be seen in Fig. 4.

2.1.11 | Multi-Coil Transients

A transient copy is made for each coil in the simulated scenario. These transients will experience additional artifacts including zero-order phase and frequency drifts, scaling due to coil sensitivity, and decreased SNR values. To allow for maximum variation in the simulations, each parameter can be sampled from distributions and is discussed below.

Noise

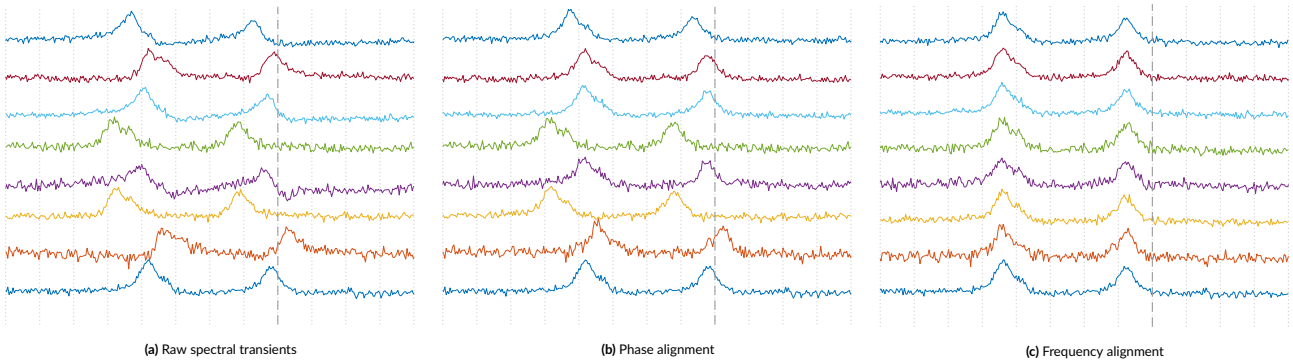
Multi-coil acquisitions lead to an SNR improvement of the final spectrum by a factor of the square root of the number of non-zero weighted transients. To vary the SNR among the transients, this model scales the target linear SNR according to the number of coils and then samples scaling factors from a narrow normal distribution to maintain the mean target SNR.

Frequency Drift and Phase Drift

Frequency drifts and phase drifts are phenomena observed in multi-coil acquisitions in which each coil transient has an independent offset. Transients' lower SNRs make it harder to correct accurately. Therefore, drifts are typically minimized between the transients, called alignment. Proper alignment will preserve the underlying spectral features once the transients are combined. These offsets and alignments are shown in Fig. 5.

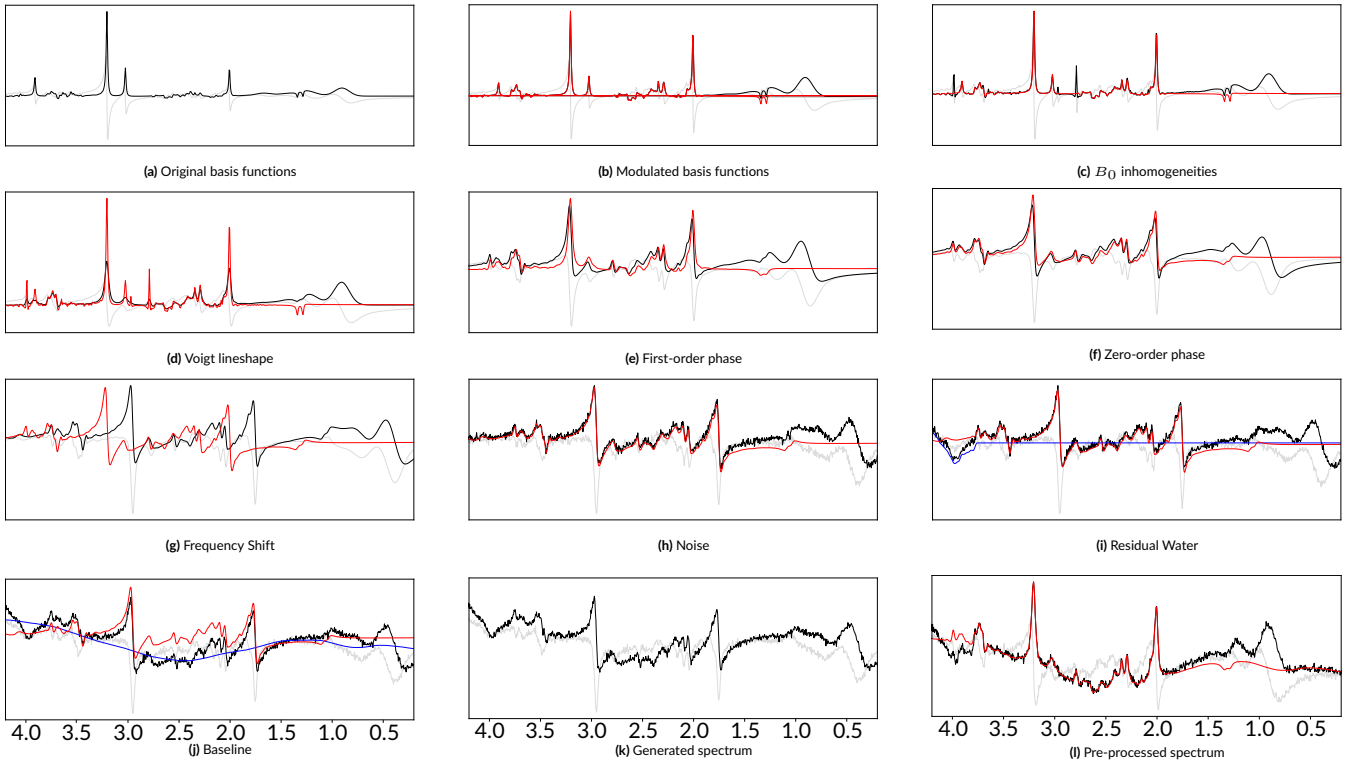
Coil Sensitivity

A variety of coil combination techniques can be used to successfully combine multi-coil spectra. While these techniques differ in how they calculate the weights, all of them use weights to scale the transients before averaging. Assigning context, such as water peak height or coil sensitivity maps, to these weights when planning the simulations can help define the necessary parameter ranges and distributions to be in line with a given clinical protocol.



(a) Raw spectral transients **(b)** Phase alignment **(c)** Frequency alignment

FIGURE 5 Simulated 8 coil transients for a 3T GE PRESS sequence with TE=30ms. (a) shows transients with various SNRs and coil sensitivities along with zero-order phase and frequency offsets. (b) shows the transients after phase alignment. (c) shows the transients after frequency alignment. After (c), the transients could be averaged together and the coil-combined spectrum can then be fitted.



(a) Original basis functions **(b)** Modulated basis functions **(c)** B_0 inhomogeneities

(d) Voigt lineshape **(e)** First-order phase **(f)** Zero-order phase

(g) Frequency Shift **(h)** Noise **(i)** Residual Water

(j) Baseline **(k)** Generated spectrum **(l)** Pre-processed spectrum

FIGURE 6 Step-by-step progression through the physics model. The real and imaginary components are in black and grey, respectively. The red line includes only the metabolites and the offsets from the preceeding steps. 6k is the final spectrum with all artifacts applied. 6l is the pre-processed spectrum with the phase and frequency shifts removed.

2.1.12 | Final Steps

The desired use case will determine if a FID or a spectrum is necessary. If a FID is required, the simulation is finished and the data will be exported. If a spectrum is required, the Fourier transform will recover the spectrum at which point it can be cropped and resampled to a desired ppm range and spectral length. The default interpolation technique in this framework is a cubic Hermite modified Akima interpolator with momentum.