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An extended phase graph-based framework for DANTE-SPACE simulations including physiological, temporal, and spatial variations

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Abstract
Purpose: The delay alternating with nutation for tailored excitation (DANTE)–sampling perfection with application-optimized contrasts (SPACE) sequence facilitates 3D intracranial vessel wall imaging with simultaneous suppression of blood and CSF. However, the achieved image contrast depends closely on the selected sequence parameters, and the clinical use of the sequence is limited in vivo by observed signal variations in the vessel wall, CSF, and blood. This paper introduces a comprehensive DANTE-SPACE simulation framework, with the aim of providing a better understanding of the underlying contrast mechanisms and facilitating improved parameter selection and contrast optimization.

Methods: An extended phase graph formalism was developed for efficient spin ensemble simulation of the DANTE-SPACE sequence. Physiological processes such as pulsatile flow velocity variation, varying flow directions, intravoxel velocity variation, diffusion, and $B_1^+$ effects were included in the framework to represent the mechanisms behind the achieved signal levels accurately.

Results: Intravoxel velocity variation improved temporal stability and robustness against small velocity changes. Time-varying pulsatile velocity variation affected CSF simulations, introducing periods of near-zero velocity and partial rephasing. Inclusion of diffusion effects was found to substantially reduce the CSF signal. Blood flow trajectory variations had minor effects, but $B_1^+$ differences along the trajectory reduced DANTE efficiency in low-$B_1^+$ areas. Introducing low-velocity pulsatility of both CSF and vessel wall helped explain the in vivo observed signal heterogeneity in both tissue types.

Conclusion: The presented simulation framework facilitates a more comprehensive optimization of DANTE-SPACE sequence parameters. Furthermore, the simulation framework helps to explain observed contrasts in acquired data.

Keywords
DANTE-SPACE, extended phase graph, MRI, vessel wall imaging
1 | INTRODUCTION

The delay alternating with nutation for tailored excitation (DANTE)-sampling perfection with application-optimized contrasts (SPACE) sequence facilitates 3D intracranial vessel wall imaging by simultaneously suppressing the blood inside the vessel and the surrounding CSF. DANTE-SPACE consists of a DANTE\textsuperscript{1,2} module for suppressing moving spins followed by a variable-flip-angle turbo-spin-echo SPACE readout.\textsuperscript{3} It has been used at both 3 T\textsuperscript{2,4–15} and 7 T\textsuperscript{16–19} and with SPACE parameter configurations resulting in T\textsubscript{1}-weighted,\textsuperscript{4–11,15,19} T\textsubscript{2}-weighted,\textsuperscript{2,13,16–18} and proton density-weighted\textsuperscript{2,10,12,15} contrasts. Across different implementations, many different protocol settings have been used, such as DANTE pulse trains ranging from 64 pulses\textsuperscript{2} to 300 pulses\textsuperscript{2,14–16} and DANTE flip angles ranging from 8\textdegree\textsuperscript{5,6,8,15} to 14\textdegree\textsuperscript{19}. The choice of these parameters directly affects the resulting blood, CSF, and vessel wall (VW) signals. Various authors have used DANTE calculations,\textsuperscript{1,12} Bloch simulations,\textsuperscript{2,4,8,13–16,19} or direct comparison of acquisitions using multiple parameter combinations\textsuperscript{15} to select parameters aiming to achieve the highest contrast between the vessel wall, blood, and CSF.

The validity and accuracy of such approaches rely on design approximations and assumptions. Li et al.\textsuperscript{1} derived a T\textsubscript{1}-decay model to approximate signal decay in moving spins during playout of the DANTE preparation. This approach is both intuitive and computationally efficient. However, it assumes complete velocity-independent spoiling of the transverse magnetization for moving spins. This can be inaccurate for pulsating or slowly moving spins. Furthermore, this model only accounts for the effects of DANTE without considering the effects of readout pulses and multiple repetitions. More accurate models can be achieved using Bloch simulations (either including\textsuperscript{4,8} or excluding\textsuperscript{14–16} readout effects), which directly account for flow effects in the simulations. This requires tissue-specific flow properties as input parameters. For this, CSF is often assumed to be either static\textsuperscript{5} or moving substantially faster (\(\geq 2\) cm/s\textsuperscript{14–16}) than the values found in the literature for the CSF near the circle of Willis (e.g., 0.37 cm/s in the third ventricle\textsuperscript{20} and up to 0.85 cm/s in the cerebral aqueduct\textsuperscript{21}). Furthermore, other processes affecting measured signal levels, such as intravoxel velocity variation and pulsatile flow velocity variation, are generally also not modeled in those simulations. At 7 T, another possibly non-negligible factor is the effect of transmit field variation on the obtained MRI signals and contrasts. Although this can be expected to have a limited effect near the circle of Willis (located in the central region of high B\textsubscript{1}\textsuperscript{+} efficiency at 7 T when using a transmit head coil), it can affect the magnetization of blood spins, which can travel from low-B\textsubscript{1}\textsuperscript{+} areas in the neck into higher-B\textsubscript{1}\textsuperscript{+} areas near the circle of Willis during a single DANTE-SPACE module.

This paper introduces a comprehensive DANTE-SPACE simulation framework to account for all these effects. By including physiological processes, such as pulsatile flow velocity variation, varying flow directions, intravoxel velocity variation, and diffusion, as well as B\textsubscript{1}\textsuperscript{+} effects, this framework attempts an accurate representation of the mechanisms behind the achieved signal levels (VW, CSF, and blood). This in turn can be used for accurate optimization of sequence parameters and to obtain a further understanding of DANTE-SPACE contrast mechanisms.

2 | METHODS

This section will describe the methods used for setting up the general simulation framework and the hardware used for computing the simulation results presented in this paper. A brief description of the way each additional modification was implemented is included with the respective results in the Results section.

All simulation code was implemented in MatLab R2019a (MathWorks, Natick, MA). Extended phase graph (EPG) simulations\textsuperscript{22,23} were used to efficiently simulate the magnetization evolution of ensembles of spin isochromats. This provides a more accurate representation of the signal behavior in an acquired voxel than Bloch simulations of single isochromats while being much more computationally efficient than averaging the results from hundreds of individual Bloch simulations to approximate spin ensemble behavior. Code from the MRSignalSeqs toolbox (github.com/mribri999/MRSignalsSeqs; retrieved July 2020) was used to propagate EPG states through periods of relaxation, gradient waveforms, RF pulse rotation, and diffusion. An additional tool was developed to simulate flow effects.\textsuperscript{3} Simulations were performed using an Intel (Intel, Santa Clara, CA) Xeon CPU E5-2680v4 running at 2.40 GHz with 14 cores and 28 logical processors.

All simulation results in this paper were obtained assuming typical relaxation properties and B\textsubscript{1}\textsuperscript{+} field effects corresponding to 7 T. T\textsubscript{1} and T\textsubscript{2} relaxation times at 7 T for vessel wall tissue were based on carotid artery measurements presented by Koning et al.\textsuperscript{24} For blood and CSF relaxation times, the same values as used by Viessmann et al.\textsuperscript{16} (based on various original sources\textsuperscript{25–27}) were used. The resulting values were:

- VW: T\textsubscript{1} = 1628 ms, T\textsubscript{2} = 46 ms
- Blood: T\textsubscript{1} = 2290 ms, T\textsubscript{2} = 100 ms
- CSF: T\textsubscript{1} = 4019 ms, T\textsubscript{2} = 311 ms
The contrast between tissue types was calculated from the amplitude of the point spread function of the transverse magnetization during the SPACE readout for the various tissue types after correcting for differences in proton density (PD\textsubscript{VW} = 0.72 × PD\textsubscript{CSF} = 0.72 × PD\textsubscript{blood}).

### RESULTS

#### 3.1 Basic DANTE-SPACE simulations

All DANTE-SPACE simulations in this section were performed using the T\textsubscript{2}-weighted 7 T protocol proposed by Viessmann et al.\textsuperscript{16} This protocol consists of 300 DANTE pulses of 10\textdegree, followed by a SPACE readout consisting of 73 refocusing pulses with an equivalent TE of 165 ms and an overall TR of 2.62 s.

#### 3.1.1 DANTE preparation module

EPG DANTE simulations were validated by comparing them to the results of Bloch equation ensemble simulations. The Bloch equation simulations themselves were first validated by comparing single isochromat simulation results to the Bloch simulation results presented by Li et al.\textsuperscript{1} (Figure S1A).

For Bloch equation ensemble simulations, the average results of 1000 Bloch equation simulations over a distance corresponding to unit phase accumulation along the gradient direction were used. Figure S1B,C shows the results of such Bloch equation ensemble simulations and the corresponding EPG simulation results, indicating good agreement. The computation time, however, of the EPG results is two orders of magnitude shorter (0.4 s vs. 57.5 s), which confirms that EPG simulations can provide accurate isochromat ensemble simulations with high computational efficiency.

#### 3.1.2 SPACE readout module

To validate the SPACE-readout simulation using the EPG framework, the simulated transverse magnetization evolution in stationary vessel walls was cross-checked against the previously described target SPACE magnetization function.\textsuperscript{3,16} Figure S2 shows that the prescribed signal evolution used to design the SPACE flip angle train agrees well with the simulated SPACE signal predicted by the EPG simulations. However, when including DANTE preparation, the change in the magnetization state before the SPACE readout module reduces the level of agreement with the prescribed magnetization evolution. This reduces the resulting signal intensity by 29%, and slightly increases the width of the point spread function of the vessel walls (by 6%).

#### 3.1.3 Inclusion of vessel wall, CSF, and blood compartments

The simulation results for the combination of the EPG DANTE- and SPACE-modules are shown in Figure 1 for VW, CSF, and blood. The results show only the most basic simulations of the different tissue types, only assuming their respective relaxation times and (constant) average velocities (from literature; see Refs. 20,28).

![Figure 1](https://example.com/figure1.png)

**Figure 1** DANTE-SPACE simulations of the VW, CSF, and blood, assuming constant flow velocities (0 cm/s for VW, 0.37 cm/s for CSF, and 24 cm/s for blood) and excluding the effects of intravoxel velocity variation, diffusion, pulsatility, flow trajectories, and B\textsubscript{i} variations. Note that a different y-axis range is shown for VW (A) than for CSF and blood (B–C). DANTE, delay alternating with nutation for tailored excitation; SPACE, sampling perfection with application-optimized contrasts; VW, vessel wall.
The results in Figure 1 are shown during the second TR period for the VW and CSF simulations but during the first TR period for the blood. This reflects the fact that although blood flows rapidly in from the upstream arteries (resulting in “fresh” blood spins without magnetization history arriving in the readout volume in each TR), the VW and CSF remain in the same scan region throughout an acquisition. For the VW and CSF simulations, the second TR was chosen because it was found to provide good convergence of the resulting signal within a reasonable simulation time (see Figure S3). For the VW, the signal reduces by 24% from the first to the second TR period, after which it changes by less than 0.01% over the next five repetitions. For CSF, the simulated signal reduces by 25% from the first to the second TR period and then fluctuates by no more than 11% (while continuously increasing the simulation time). Based on this argument, all simulation results presented in this work are based on two repetitions for VW and CSF but only a single repetition for blood.

3.2 Incorporation of physiological and physical effects

Next, we introduce various additions to the simulations on a per-phenomenon basis. Subsections 3.2.1 to 3.2.5 describe all components of the simulation framework in turn, including the effects of each individual component on the resulting simulations. After all individual additions have been introduced, section 3.2.6 shows the effect when all variations are included simultaneously.

3.2.1 Effects of intravoxel velocity variation

As is visible in Figure 1B,C, where moving spins were simulated with a specific velocity, simulations using a single velocity result in unstable predictions of transverse magnetization. However, in reality the measured MR signal in a typical voxel is generated by the transverse magnetization of spins moving with slightly varying velocities around a certain average value. To model this intravoxel velocity variation effect in the simulations, each individual simulation was repeated 100 times using different velocity values described by a normal distribution with $\sigma = 10\%$ around the nominal velocity. This distribution and the resulting change in the magnetization evolution when accounting for a range of velocities is shown in Figure 2. The simulations with this more realistic velocity distribution demonstrate higher temporal stability of the magnetization evolution of both blood and CSF, resulting (especially for blood) in lower transverse magnetization magnitude.
during the SPACE readout and therefore reduced signal levels.

3.2.2 Effects of pulsatile motion

Pulsatile velocity variations over time were added to the simulations to represent fluid dynamics and pulsatile oscillations. Figure 3 shows the flow velocity variations that were modeled and the resulting changes in simulated signal for CSF and blood. Temporal velocity variations due to pulsatile CSF (Figure 3A) were added based on literature-sourced time-varying CSF flow measurements at the third ventricle (with an average flow velocity of 0.37 cm/s\(^2\)). The temporal variation in blood flow velocity (Figure 3D) was modeled on the cardiac pulsatility of blood in the internal carotid arteries.\(^2\) Both pulsation profiles assume a heart rate of 60 beats per min. Because cardiac gating is typically not used for DANTE-SPACE acquisitions, a different random starting point was used for the pulsatile profiles in each of the 100 simulations.

Because the velocity of the blood remains relatively high throughout the cardiac cycle (with a minimum velocity of around 16.5 cm/s), the simulated magnetization of blood remains similar with and without the inclusion of pulsatility in the simulations. In contrast, CSF pulsation results in periods of both positive and negative velocity. This introduces two effects that change the signal attenuation efficiency during DANTE (which were not included in earlier versions of this simulation framework\(^17,18\): periods of near-zero velocity reduce the signal attenuation during DANTE, and partial rephasing can occur when the oscillations change direction. This results in a visible change in magnetization evolution when accounting for CSF pulsatility.

3.2.3 Effects of diffusion

In addition to spins moving due to flow and pulsation, the effects of diffusion were included for CSF and blood using a diffusion coefficient of \(3 \times 10^{-3} \text{ mm}^2/\text{s}\), corresponding to free water diffusion at body temperature. The resulting changes to the simulations are shown in Figure 4. For CSF, the inclusion of diffusion reduces the longitudinal magnetization of the CSF at the end of the DANTE-preparation, resulting in a 54% reduction in the measured signal during SPACE.

3.2.4 Effects of flow trajectory

When modeling the direction of blood flow, a typical flow trajectory was incorporated into the simulations to introduce time-varying flow directions relative to the DANTE-gradient vector direction. This flow trajectory was

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**Figure 3** Pulsatile velocity variations of (A–C) CSF and (D–F) blood, and the resulting changes in the simulated magnetization evolution for both tissue types.
determined from the bright-blood MPRAGE data as shown in Figure 5A. Blood was assumed to flow along this trajectory at the mean flow velocity used in simulations (24 cm/s), resulting in time-dependent variations in the flow direction as the blood moves along the vessel path. At each timepoint in the simulations, the resulting angle $\beta_{\text{blood}}$ between the flow direction and the gradient vector was used to modify the effective blood flow velocity along the gradient via multiplication by $\cos(\beta)$. For simplicity, only orientations within the coronal plane were assumed.

For CSF, directions of motion (on the relevant timescales) are known to vary throughout the brain. The average of simulations using a distribution of flow directions can be used to account for this, at the cost of increased computation times. Therefore, to simplify the simulations while accounting for this variation, the angle $\beta_{\text{CSF}}$ between the CSF flow direction and the gradient vector was fixed as the average angle between a given vector (i.e., the DANTE-gradient vector) and all other possible vector directions (i.e., the possible CSF motion vectors) on a unit semisphere:

$$<\beta_{\text{CSF}}> = \frac{1}{V_{SS}} \int_{SS} \beta dV = 57.3^\circ.$$  \hspace{1cm} (1)

### 3.2.5 Incorporation of $B_1^+$ variations along the blood flow trajectory

$B_1^+$ variations in different parts of the vasculature were included in the model based on measured $B_1^+$ maps. For this, data from a previously presented database of 7T multi-channel $B_1^+$ flip angle maps in both the head and the neck were used. The blood flow trajectory in Figure 5A was used to extract the $B_1^+$ values along the vessel trajectories from the $B_1^+$ maps, as shown in Figure 6A. For CSF and VW, a constant $B_1^+$ offset can be added to simulations, for example, to model the effects of different parallel transmission RF shims on the achieved CSF suppression.

The measured $B_1^+$ values were used in the simulations as a scaling factor between the nominal flip angle and the effective applied flip angle. In the neck, with typically very low $B_1^+$ at 7 T, this effectively reduces the applied flip angles at the start of the DANTE trajectory. This reduces the suppression due to DANTE, which results in a slight increase in the (measured) transverse magnetization during the SPACE readout.

### 3.2.6 Combined variations

The previous sections discussed how intravoxel velocity variation, pulsatile motion, diffusion, flow trajectories, and $B_1^+$ variation were implemented in the EPG simulations, while showing the isolated effect of each individual addition. Figure 7 demonstrates the effect of simultaneously including all these model enhancements. For the examples shown here (using the DANTE-SPACE protocol parameters as proposed by Viessmann et al. and circular polarization-mode $B_1^+$ maps), the combined model enhancements result in a 57% reduction in CSF signal and a 27% reduction in blood signal versus the case in which only the basic simulation from section 3.1 is performed.
Like all CSF and blood simulation results presented here, the results in Figure 7 are shown using a small y-axis range to clearly visualize the changes in the transverse magnetization during the SPACE readout. Figure S4 presents the results in Figure 7 using the full y-axis (ranging from 0 to \( M_0 \)) to also indicate the changes in the evolution of the longitudinal magnetization during the DANTE-preparation. This confirms that in the complete simulation model, the longitudinal magnetization of the blood during DANTE decreases more slowly due to the reduced efficiency of the DANTE-preparation in areas with low \( B_1^+ \).

### 3.3 Sensitivity to simulation parameter values

The proposed simulation model uses various tissue-specific properties to distinguish the different
tissue types. This includes $T_1$ and $T_2$ relaxation times, mean velocities of flow or pulsation, flow directions, the amount of intravoxel velocity variation, and diffusion coefficients. For VW, CSF, and blood, each of these values was carefully chosen with the aim of accurately representing the resulting signal behavior. To assess the extent to which the simulations depend on the exact choice of tissue parameters, and to ascertain that the results are robust to small changes in the selected values (e.g., due to measurement uncertainty), this section compares simulations using variations in these tissue properties.

### 3.3.1 $T_1$ and $T_2$ relaxation times

As described in section 2 (Methods), the $T_1$ and $T_2$ values for VW, CSF, and blood were based on various measurement results from the literature. Each of the resulting values has a certain amount of measurement uncertainty (up to 28%). Therefore, Figure 8 compares the results of simulations for all three tissue types where the $T_1$ and $T_2$ values are varied between the selected value ±30%. This indicates that the results are largely independent of the $T_1$ of blood and the $T_2$ of both CSF and blood. The $T_2$ dependence of the vessel wall signal is consistent with the $T_2$-weighted SPACE readout used in the simulations (which is calculated based on vessel wall relaxation times). Despite this $T_2$-weighting, Figure 8 also shows some $T_1$-dependence of the VW and CSF signals. This is mainly a result of the DANTE-preparation, during which a higher $T_1$ results in increased suppression of the longitudinal magnetization as well as reduced longitudinal magnetization recovery during the TR delay. Because of its higher $T_1$ and increased DANTE sensitivity, this $T_1$ dependence is more pronounced in CSF. However, the resulting CSF signal remains much smaller than the VW signal for all simulated $T_1$ values.

### 3.3.2 Flow properties

Figure 9 shows the effect of different average flow parameter values on the simulated CSF and blood signal. Figure 9A,B show that higher flow velocities result in increased signal attenuation, as expected when using DANTE. However, the velocity at which the signal converges differs between tissue types due to the different relaxation properties and, in particular for blood, the $B_1^+$ effects and flow directions. For example, the required velocity to reach a signal of less than 0.02 $M_0$ is around 0.2 cm/s for CSF and 1.6 cm/s for blood. This velocity threshold is the highest for blood because of the velocity responses of both DANTE and SPACE. During DANTE, the lower $B_1^+$ in the neck means that higher velocities are required for DANTE to be effective. During the SPACE readout, the flow direction of blood is nearly perpendicular to the readout gradient direction. As a result, higher velocities are required to obtain the inherent black-blood SPACE contrast (even without DANTE). Because the typical flow velocity of blood remains substantially higher than the required velocity to achieve black-blood contrast, this should not be a
FIGURE 8 Simulation results when using different $T_1$ and $T_2$ relaxation times. Results are shown for each tissue type for the standard values $\pm 30\%$ (x-axes). Different y-axes are used for the different tissue types, all of which are scaled from 0 to twice the simulated signal using the standard ($T_1/T_2$) values. Dashed lines indicate the standard $T_1/T_2$ values and their corresponding simulated signal.

FIGURE 9 The effect of the selected flow parameter values on the simulated signal levels of CSF and blood. Results are shown for different (A) mean CSF velocities, (B) mean blood flow velocities, (C) the SD of velocity distributions, and (D) CSF pulsation directions versus the DANTE gradient direction. Dashed lines indicate the values generally used in the simulation model.

limitation in practice. For CSF, the average absolute velocity of $0.37 \text{ cm/s}$ is closer to the critical velocity required to achieve sufficient signal suppression; thus, increases in CSF signal level can be expected with slight changes in the average velocity or flow direction.

The effects of varying the SD in the velocity distribution or the direction of CSF pulsation versus the DANTE gradient direction are shown in Figure 9C,D. Figure 9C indicates that although intravoxel velocity variation substantially affects the simulated signal of blood, the exact choice of (non-zero) value for $\sigma$ does not have a large effect on the resulting averaged signal.

The direction of CSF pulsation (Figure 9D), defined as the angle between the pulsation direction and the DANTE gradient vector, results in substantially reduced CSF suppression for near $90^\circ$ angles. A $90^\circ$ angle corresponds to having no effective velocity along the gradient direction, therefore agreeing with the simulation for $v_{\text{CSF}} = 0 \text{ cm/s}$ shown in Figure 9A.

3.4 Accounting for vessel wall motion

Thus far, fully stationary vessel walls have been assumed. However, previously presented in vivo acquisitions...
showed signal variations in the vessel wall, which can be explained using the presented simulation model by including a very slow pulsation of vessel wall tissue (as shown in Figure S5). This is shown in Figure 10 for various mean blood pulsation velocities when using two previously proposed DANTE implementations. Here, VW pulsation was assumed to follow the same pattern as CSF (Figure 3A) because it includes periods of both positive and negative velocity.

To estimate the average velocity of this vessel wall pulsatility such that it can be used in subsequent simulations, we compared in vivo acquisitions in five healthy volunteers to the VW simulations assuming various mean velocities shown in Figure 10. These preliminary data were acquired on a Siemens (Erlangen, Germany) Magnetom 7T scanner under an approved institutional development ethics protocol using a 1 channel transmit/32 channel receive head coil from five healthy volunteers, using three different T2-weighted DANTE-SPACE protocols:

1. The protocol presented by Viessmann et al., which uses 300 DANTE pulses of 10°,
2. The same protocol but using 200 DANTE pulses of 9°, and
3. The same SPACE protocol but without DANTE preparation.

Using these data, the average VW velocity was estimated such that the resulting signal intensities from simulations agreed with observed (experimental) vessel wall signal changes in hand-drawn VW masks. To quantitatively compare in vivo measurements and simulations, both scan data and simulations were expressed relative to the values for stationary VW signal intensity without DANTE preparation. For simulations, this was calculated by expressing the simulated VW signal (S\text{sim}) as a percentage of the signal from a simulation for stationary VW without DANTE (S\text{NoDante}):

\[
S\text{sim}(\%) = \frac{S\text{sim}(M_0)}{S\text{NoDante}(M_0)} \times 100\%.
\] (2)

For in vivo acquisitions, the 80th percentile of the measured signal intensity values in VW voxels in acquisitions without DANTE (S\text{NoDante,80\%}) was used as a benchmark for the signal level for stationary VW tissue. From that value, the relative value in each voxel (and for any protocol) was calculated as

\[
S\text{scan}(\%) = \frac{S\text{scan}(SNR)}{S\text{NoDante,80\%}(SNR)} \times 100\%.
\] (3)

The resulting signal distributions were then compared to estimate the average velocity of vessel wall pulsation, which can be used to account for contrast variations due to vessel wall pulsation in simulation-based optimizations.

Figure 10 indicates that for both protocol 1 and protocol 2, each simulated signal value corresponds to a single (nondegenerate) mean vessel wall velocity. This means that if in vivo vessel wall signal intensity values are also expressed relative to the signal intensity in non-DANTE acquisitions (using Equation 3), it is possible to directly correlate these relative values with the corresponding average velocity in simulations. Based on the preliminary volunteer data acquired using 300 DANTE pulses of 10° (protocol 1), this suggests an average vessel wall velocity of 0.051 ± 0.021 cm/s. The corresponding results based on data acquired from the same volunteers using 200 DANTE pulses of 9° (protocol 2) suggest an average VW velocity of 0.057 ± 0.026 cm/s, in good agreement with the results using protocol 1. The underlying voxel-wise relative signal and corresponding simulated velocity distributions for both protocols are shown in Figures S6 and S7.

4 | DISCUSSION

This work presents an EPG-based DANTE-SPACE simulation framework. By including various physiological and spatial variations to enhance the model, it aims to accurately reproduce the contrast mechanisms for the case of in vivo acquisitions. This helps explain the mechanisms behind various observed contrasts in acquired data and
provides further understanding on how the sequence can be modified to achieve improved contrasts.

## 4.1 Initial validation

The performance of the basic simulation framework design was validated by first separately comparing the performance of the DANTE- and the SPACE-modules relative to literature results, which found good agreement for both. For VW tissue, the addition of DANTE preparation introduces a magnetization decrease in the middle of the SPACE readout. This reduces the VW signal level (as expected when using DANTE\textsuperscript{1,16}) but also results in a slight reduction in the VW sharpness. To retain the desired sharpness, future work could account for the magnetization history effects due to DANTE in the calculation of the SPACE variable flip angles.

## 4.2 Accounting for more realistic physiology in the simulations

Accounting for a more realistic physiology affects the simulation results in multiple ways, thereby improving their accuracy. Simulations that account for velocity distributions (Figure 2) increase the temporal stability of the magnetization evolution of moving tissue, resulting in a reduced simulated signal and improved robustness against small changes in the selected mean velocity. Without this intravoxel velocity variation, the magnetization over time shows rapidly fluctuating transverse magnetization, similar to what Li et al.\textsuperscript{1} showed in DANTE simulations at different specific velocity values.

The introduction of more realistic time-varying pulsatile velocity variation mainly affects the simulations of CSF, which is assumed to oscillate around a central location. This introduces periods of near-zero absolute velocity (which reduce the signal attenuation during DANTE), as well as partial rephasing when the oscillations change direction. In addition to those changes due to pulsation, the inclusion of diffusion reduces the longitudinal magnetization of the CSF at the end of the DANTE preparation, thereby substantially reducing the resulting CSF signal during SPACE.

The addition of a typical blood flow trajectory only introduces minor changes to the resulting blood signal because the effective blood flow velocity along the DANTE gradient direction remains sufficiently high despite the different flow directions. However, the differences in $B_1^+$ along the flow trajectory substantially reduce the efficiency of DANTE in low-$B_1^+$ areas. In quadrature mode at 7T, this increases the measured transverse magnetization during the SPACE readout (Figure 6).

When combined, these simulation enhancements result in a 57% reduction in CSF signal and a 27% reduction in blood signal (for the T\textsubscript{2}-weighted 7 T protocol used by Viessmann et al.\textsuperscript{16}) relative to simulations that do not include these enhancements.

## 4.3 Simulations with different tissue properties

The simulations using various T\textsubscript{1} and T\textsubscript{2} relaxation times (Figure 8) indicate that the (simulated) DANTE-SPACE signal levels are robust to small variations in T\textsubscript{1} or T\textsubscript{2}. However, Figure 8 also shows that the DANTE preparation introduces some T\textsubscript{1}-weighting. Therefore, when proposing modified protocols, it is important to include simulations for relevant pathologies to ensure that the contrast between healthy and diseased vessel wall tissue remains consistent. For reference, estimates of the T\textsubscript{1} and T\textsubscript{2} relaxation times and the corresponding DANTE-SPACE signal simulations of vessel wall pathology at 7 T can be found in Figure S8.

Figures 9 and 10 indicate that for VW and CSF, the respective “critical” pulsation velocities (where the resulting signal rapidly decreases) are close to their expected velocities. Therefore, small variations in the CSF velocity (Figure 9A) and direction (Figure 9D) can result in substantial reductions in CSF suppression, whereas slow pulsation of the vessel wall also reduces the VW signal. Both of those simulation results are consistent with previous in vivo observations for T\textsubscript{2}-weighted DANTE-SPACE, which showed heterogeneous signal levels in both the VW and the CSF.

## 4.4 Vessel wall motion

Figure 10 indicated that very slow VW motion could result in variable VW signal, which could explain the observed in vivo VW signal heterogeneity. This hypothesis was further examined by comparing VW simulations across a range of simulated velocities to the corresponding in vivo signal distributions using two different DANTE protocols. This indicates an average VW velocity of $0.051 \pm 0.021$ cm/s based on data with 300 DANTE pulses of 10° (protocol 1) and $0.057 \pm 0.026$ cm/s based on data with 200 DANTE pulses of 9° (protocol 2). These values are slightly different, whereas the underlying vessel dynamics should be the same. This could be explained by the simplifying assumption that all signal difference in the VW is a result.
of the VW pulsation, which does not account for signal variation due to partial volume effects, sensitivity effects, and different directions of motion relative to the DANTE gradients. Despite this, the resulting values are very similar, and the average value of 0.054 cm/s can be used as an approximate mean velocity of pulsating vessel wall.

When assuming the VW pulsation to follow the same pattern as CSF, this average velocity of 0.054 cm/s corresponds to a maximum displacement of around 200 μm. This result is consistent with displacement simulations in non-stenotic external iliac arteries, which have a similar wall thickness to the middle cerebral artery. This again indicates that the value of 0.054 cm/s provides an adequate approximation. However, there should be noted that other contrast mechanisms such as $B^*_0$ variations and diffusion can also have limited effects on DANTE-SPACE contrasts (Figure S5), which were not accounted for in this estimate. Future work could aim to measure intracranial vessel wall pulsation to improve this estimate. Furthermore, our vessel wall pulsation velocity estimate is based on data from healthy volunteers. A lower VW velocity might be expected in clinical populations due to reduced vessel wall flexibility resulting from pathology and aging, thereby reducing the motion-induced VW signal attenuation. The resulting increased blood flow velocity would improve the robustness of the blood suppression, whereas possible reductions in CSF velocity might reduce the efficiency of the CSF suppression (Figure 9A,B).

In simulations using the protocol by Viessmann et al., VW moving at 0.054 cm/s is predicted to reduce the resulting VW signal by 46%, leading to a reduction in VW/CSF contrast of 51% relative to simulations that assume static vessel walls. When using simulations to optimize a protocol for achieved contrasts, this introduces a significant new constraint that was not accounted for in previously presented DANTE-SPACE simulation models.

In the work presented here, vessel walls were assumed to pulsate using the same time-varying pattern as CSF (Figure 3A). This pattern was selected because it results in a net-zero displacement during each full cardiac cycle, which is expected for both CSF and VW but not for blood. However, it might be possible to represent the VW pulsation more accurately using other profiles.

4.5 Computational considerations

Currently, a single simulation with the computational hardware used in this work takes about 0.16 s for static VW (2 TRs without velocity variation), 9.6 s for pulsating VW (2 TRs with velocity variation), 3.6 s for blood (1 TR with velocity variation), and 7.9 s for CSF (2 TRs with velocity variation). The computation times of individual simulations could be substantially reduced by parallelizing the individual simulations at each velocity. However, in this work the simulations for different datapoints in parameter sweeps were parallelized instead (with each parallel CPU computing a few full simulations rather than parts of all simulations) to achieve a similar net acceleration.

5 CONCLUSION

An EPG-based DANTE-SPACE simulation framework is presented that includes physiological and spatial variations to accurately reproduce in vivo contrast mechanisms. This helps explain observed contrasts in acquired data, such as the VW signal heterogeneity, which can be explained by simulations as being due to slowly pulsating vessel walls. Finally, this simulation framework facilitates a more comprehensive optimization of the DANTE-SPACE sequence parameters, for which it will be used at 3 T and at 7 T in future work.

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CONFLICT OF INTEREST

P.J. is the Editor-in-Chief of Magnetic Resonance in Medicine. In line with Committee on Publication Ethics guidelines, he recused himself from all involvement in the review process of this paper, which was handled by an Associate Editor. He and the other authors have no access to the identity of the reviewers.

DATA AVAILABILITY STATEMENT

In support of Magnetic Resonance in Medicine’s reproducible research goal, the MatLab (MathWorks) code for the simulation framework is openly available online at git.fmrib.ox.ac.uk/ndcn0873/dantescape_epg. The
main simulation tool is epg_dantespace.m. The script example.m shows examples of how to run the simulations after initializing both the desired sequence parameters (set_dantespace_parameters.m) and the tissue properties (set_tissue_parameters.m). Finally, a single script that can be used to reproduce all figures in this paper is included (simulations_paper.m), as well as the required underlying data ($B_1^+$ map and vessel trajectory) and other tools. The simulations require the MatLab Image Processing, Statistics and Machine Learning, Curve Fitting, and Parallel Computing toolboxes.

**REFERENCES**


SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

FIGURE S1. Comparison of DANTE simulations using Bloch equations and EPG. The results are shown for (A) Bloch isochromat simulations, (B) Bloch ensemble simulations, and (C) EPG simulations. $T_{\text{sim}}$ indicates the computation time of the simulation results shown in each figure.

FIGURE S2. Comparison of the transverse magnetization during the SPACE readout. (A) shows the prescribed vessel wall signal evolution (black line) for which the SPACE flip angle train (blue circles) is calculated. The black arrow indicates the equivalent echo time of the acquisitions. (B) shows the resulting EPG simulation for SPACE acquisitions (without DANTE), while (C) shows the EPG simulation for DANTE-SPACE acquisitions. Note that the x-axis in (C) starts near the end of the DANTE preparation.

FIGURE S3. Simulation results after increasing numbers of TRs. Results are shown for (A) the convergence of the simulated signal and (B) the corresponding duration of a single simulation for both (stationary) vessel wall tissue and CSF.

FIGURE S4. The combined effect of intravoxel velocity variation, pulsatile motion, diffusion, flow trajectories, and $B_1^+$ variation on DANTE-SPACE simulations of CSF (A, B) and blood (C, D), shown for the full y-axis range.

FIGURE S5. Comparison of the signal levels (top row) and signal ratio (bottom row) for $T_2$-weighted DANTE-SPACE protocols using 300 DANTE pulses of 10° (“Protocol 1”) and 200 DANTE pulses of 9° (“Protocol 2”), as described in Section 3.4 of the main manuscript. Results are shown for different levels of simulated $B_1^+$, diffusion, and vessel wall pulsation velocity, indicating that vessel wall pulsation can explain substantial signal differences between Protocols 1 and 2.

FIGURE S6. Distribution of (A) vessel wall signal levels in 5 healthy volunteers in acquisitions using 300 DANTE pulses of 10° (Protocol 1), and (B) the corresponding velocity values in simulations. Values in (A) are expressed relative to the 80th percentile of the vessel wall signal in acquisitions without DANTE preparation (using Equation 3 in the main manuscript).

FIGURE S7. Distribution of (A) vessel wall signal levels in 5 healthy volunteers in acquisitions using 200 DANTE pulses of 9° (Protocol 2), and (B) the corresponding velocity values in simulations. Values in (A) are expressed relative to the 80th percentile of the vessel wall signal in acquisitions without DANTE preparation (using Equation 3 in the main manuscript). The orange curve in (B) shows the Rician fit based on the data in Supporting Information Figure S5 for comparison.

FIGURE S8. Comparison of DANTE-SPACE simulations in healthy vessel wall and various plaque components ((B) lipid cores, (C) fibrous cap tissue, and (D) intra-plaque hemorrhages). The sources of the $T_1$ and $T_2$ used for these simulations are described below. The values in red indicate the simulated signal levels in pathology compared to healthy vessel wall tissue.

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