

Optimising combined angiographic, structural and perfusion imaging using arterial spin labelling MRI

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Abstract

Visualizing the dynamic blood flow in the brain is crucial for diagnosing and monitoring cerebrovascular diseases. Arterial spin labeling (ASL) MRI offers a non-invasive approach to simultaneously image both dynamic blood flow and tissue perfusion without contrast agents. However, ASL techniques face challenges such as limited spatial/temporal resolution, low signal-to-noise ratio (SNR), and susceptibility to motion artifacts. This thesis focuses on addressing these limitations to enhance the quality and clinical utility of ASL-based combined imaging of blood vessels, brain structure, and tissue perfusion.

Firstly, a novel, efficient two-stage curved cone trajectory is introduced for k-space sampling, improving the spatial resolution and SNR of both angiographic and perfusion images compared to conventional radial trajectories. The trajectory design allows for flexible parameter adjustments and is adaptable to various scanner hardware constraints. To further improve the temporal resolution of dynamic angiography, a subspace reconstruction method incorporating a kinetic model of blood flow is implemented. This approach achieves ultra-high temporal resolution, enabling detailed visualization and accurate quantification of blood flow dynamics. To mitigate motion artifacts, a novel motion correction technique is presented, utilizing subspace-based self-navigation to reconstruct robust navigator images. The proposed method effectively corrects motion artifacts, enabling accurate assessment of blood flow and perfusion even in the presence of subject motion.

This thesis contributes to the advancement of ASL-based imaging techniques by enhancing spatial and temporal resolution, improving SNR, and correcting for motion artifacts. The developed methods have the potential to improve the clinical diagnosis for neurovascular disease.

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List of Abbreviations

ASL	Arterial spin labeling
CASPRIA	Combined angiography, structural and perfusion radial imaging using arterial spin labeling
CASL	Continuous arterial spin labeling
CS	Compressed sensing
CT	Computed tomography
DCE	Dynamic contrast enhanced (MRI).
DFT	Discrete Fourier transform.
DSA	Digital subtraction angiography.
FA	Flip angle.
FFT	Fast Fourier transform.
FISTA	Fast iterative soft thresholding algorithm.
FOV	Field of view.
GR	Golden ratio.
GRAPPA	Generalized autocalibrating partial parallel acquisition.
MIP	Maximum intensity projection.
MR	Magnetic resonance.
MRI	Magnetic resonance imaging.
NMR	Nuclear magnetic resonance.
NRMSE	Normalised root mean square error.
NUFFT	Non-uniform fast Fourier transform.
PASL	Pulsed arterial spin labelling.
pCASL	Pseudo-continuous arterial spin labelling.
PI	Parallel imaging.
PLD	Post labelling delay.

PSF		Point spread function.
RF		Radio frequency.
RMSE		Root mean square error.
SD		Standard deviation.
SENSE		Sensitivity encoding.
SNR		. Signal to noise ratio.
T1, T2, T2*		Tissue dependent time constants that determines magnetic resonance signal decay and recovery rates.
TE		Echo time.
TI		Inversion time.
TOF		Time of flight.
TR		Repetition time.

1

Introduction

Contents

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1.1 Motivation

Visualizing the dynamic process of blood flow along the vascular tree to the tissue facilitates the diagnosis and treatment monitoring of various cerebrovascular diseases. Stroke, for example, is a significant cause of mortality and disability and is caused by a reduction in blood supply, either from blocked/narrowed arteries (ischemia) or bleeding into the brain tissue (hemorrhage)[1] and blood flow imaging helps differentiating between the two for appropriate treatment. Similarly, moyamoya disease, caused by the progressive narrowing of intracranial arteries and leading to downstream tissue ischemia[2], can also be diagnosed through blood flow imaging. The development of neurodegenerative disease like Alzheimer's and Parkinson's is related to changes in blood flow [3]. In addition, high quality blood imaging can enable quantitative evaluation for further analysis. For instance, cerebral blood

flow calculated from dynamic perfusion images can be used for evaluating brain function and neurovascular coupling[4].

Different methods have been developed to acquire brain blood images. X-ray based methods like digital subtraction angiography (DSA)[5] use the injection of a contrast medium into arteries to differentiate intravascular signal from brain tissues. Computed tomography (CT) based methods like CT angiography (CTA)[6] use a contrast agent injected into a vein. Apart from imaging arteries, brain tissue perfusion can also be accurately imaged using positron emission tomography (PET)[7] by injecting radioisotopes (e.g. ^{15}O) as tracers. Radiation-free MR based imaging methods have also been developed. Dynamic susceptibility contrast (DSC)[8] exploits the paramagnetic property of the gadolinium contrast agent injected in subjects to measure various characteristics of brain blood flow.

However, both X-ray and contrast agents can be harmful to health. On the contrary, a recently introduced technique arterial spin labeling (ASL) [9, 10] uses blood magnetization as endogenous tracer and is non-invasive and radiation free. To be more specific, ASL combines RF pulses and gradients to invert the magnetization of inflowing blood. This alters the signal in blood vessels and perfused tissue downstream, allowing blood flow to be visualised and quantified. However, the ASL signal suffers from low SNR due to limited blood volume relative to tissue signal, leading to prolonged scanning time, limited temporal and spatial resolution and sensitivity to motion.

The thesis aim to overcome the major disadvantages of ASL from different perspectives. Firstly, different modalities can be simultaneously reconstructed from the same sequence [11, 12] by grouping different portions of the acquired data. Secondly, the sampling efficiency can be improved to increase SNR and spatial resolution during the given amount of time. Thirdly, exploiting model constraints compensates for the temporal resolution important for quantitative analysis. Finally, the retrospective correction improves the robustness to subjects' movement.

1.2 Structure

The thesis is structured into 7 chapters. Following this chapter, the second chapter introduces some basic concepts of MRI image formation including k-space encoding and image reconstruction. Chapter 3 introduces existing imaging methods for blood flow and structural imaging, including some non-MR based methods. Major components of the imaging methods used in this thesis are described as well.

The first research chapter, 4, describes a novel cone trajectory design, which improves sampling efficiency compared to a previously used radial trajectory. The efficient cone trajectory is parameterized and easy to adjust, laying the foundation for later chapters. Attempts made to introduce water excitation pulses for clearer structural imaging are also included. At the end of the chapter, we showcase examples of high resolution angiography ($0.78mm^3$) and perfusion ($2.34mm^3$) to demonstrate the potential of the developed cone trajectory. This work has been published in *Magnetic Resonance in Medicine*[13].

Based on the cone trajectory in chapter 4, the temporal resolution of dynamic angiography is further improved in chapter 5 by incorporating an angiographic signal model into the reconstruction process. To be more specific, a subspace method is adopted to enforce signal evolution constraints. The temporal resolution of 4D dynamic angiography was pushed to an unprecedented $15ms$, enabling fine visualization of blood flow and accurate quantification. The work in this chapter has been submitted to *Magnetic Resonance in Medicine*, and received minor revision. Its preprint is available online[14].

Chapter 6 aims to improve the motion robustness for our combined imaging sequence. It also uses the cone trajectory developed in chapter 4 and is inspired by chapter 5. Specifically, the subspace method is exploited again for modeling the static tissue signal variations after a single inversion pulse used for background suppression. This allows accurate navigator images to be reconstructed to estimate and correct for motion, overcoming artifacts caused by contrast-mixing. Additionally, a novel split-update method is proposed to reconstruct high quality blood flow images from k-space mismatched data. Further discussion for improving the registration

accuracy is also presented at the end. The work has been submitted to *Imaging Neuroscience*, and its preprint is available online [15].

Finally, the thesis is summarized in chapter 7 where extensions and limitations are discussed. The future works to further improve the blood flow imaging quality and analysis are envisioned at the end.

2

Principles of MRI

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In this chapter, we will start from how the Magnetic Resonance Imaging (MRI) signal is formed and methods to encode spatial information into the MR signal using spatial gradients in the magnetic field. Depending on the pattern of the gradient over time, the space in which data must be sampled to allow an image to be reconstructed, the Fourier or "k-space" domain, can be traversed with different trajectories. The quantitative metrics to evaluate these trajectories are also covered in this chapter. The second part of this chapter covers the reconstruction methods that reverse the process of spatial encoding and recover images from the acquired signal. Reconstruction techniques to accelerate acquisitions, like parallel imaging and regularization approaches, are discussed in detail.

2.1 Data sampling

2.1.1 MR signal generation

Spin is a property for particles, including protons, neutrons and electrons. In MRI as applied to the human body, the signal from water protons is typically measured due to its abundance. While electrons only have one spin value $\frac{1}{2}$, nuclei have different spin values ranging from 0 – 8, with a fixed increment of $\frac{1}{2}$. Only nuclei with non-zero spin values exhibit resonance phenomena when experiencing an external magnetic field. An ensemble of spins act together to generate net magnetisation, and this can be treated in a semi-classical way, which undergoes precession. The net magnetization formed by the ensemble of spins is represented as a 3D vector. The net magnetization tends to align with the external static magnetic field B_0 and precess with a specific frequency called Larmor frequency $\omega = \gamma B$ (γ is gyromagnetic ratio dependent on the nucleus). Conventionally, the axis parallel to the static magnetic field B_0 is defined as longitudinal axis whereas the plane orthogonal to the magnetic field is defined as the transverse plane. When a radiofrequency (RF) pulse is applied also at the Larmor frequency, the net magnetization will tip away from its alignment with the external magnetic field, causing the magnetization to have some component in the transverse plane. According to Faraday’s law of induction, the transverse component creates changing magnetic field and induces the electrical current in the receiver coils. The longitudinal component, however, does not precess and cannot induce current in receiver coils. Therefore, only the transverse component of magnetization generates a measurable signal in receiver coils. Once the RF pulse is switched off, the spins no longer experience external forces and start to return to their equilibrium state. The process of returning to equilibrium is called relaxation. Relaxation occurs in two ways: the relaxation of longitudinal magnetization, T1 relaxation, refers to the recovery of the net magnetization along the direction of the external magnetic field, which involves energy transfer from the spin system to its surrounding environment. The relaxation of transverse magnetization, T2 relaxation, originates from the loss of phase coherence of spins because of spin-spin

interaction, leading to signal decay. Loss of phase coherence can also be induced or accelerated externally by introducing an inhomogeneous magnetic field. $T2^*$ decay describes the combined effects of loss of phase coherence due to spin-spin interactions as well as inhomogeneous external magnetic field.

2.1.2 Image formation

Apart from the static magnetic field B_0 , gradient coils are another important component of the MRI system that provide additional magnetic fields. These additional magnetic fields are also aligned along the z direction but their magnitude varies linearly in space. There are usually 3 gradient coils (x , y , z), each of which creates linear variations in the magnetic field along one axis. Figure 2.1 shows examples of these additional magnetic fields when gradient coils on x and y axes are turned on.

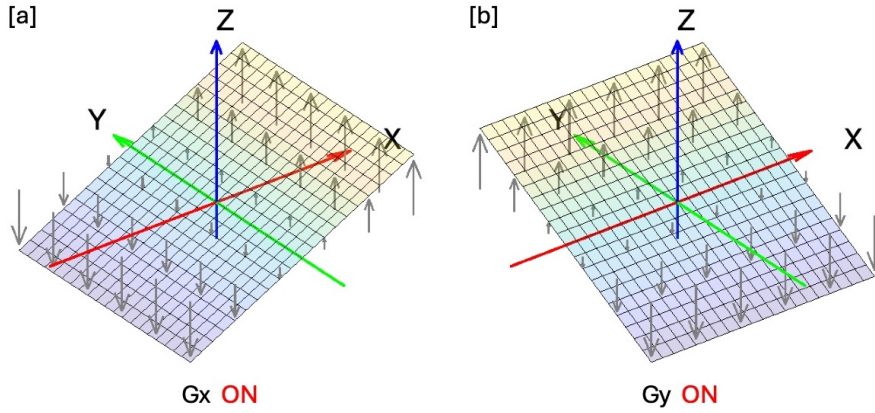


Figure 2.1: Illustration of additional magnetic fields created by the gradient system. [a], a gradient on the x axis is turned on creating a linear variation in the additional magnetic field along the x axis. [b], a gradient on y axis is turned on.

According to Larmor equation $\omega = \gamma B$, spatially varying magnetic fields introduced by the gradient system result in magnetization rotating with different frequencies at different locations. The amount of additional phase (relative radial position in transverse plane) $\Delta\phi$ for magnetization at location $\vec{r}$ accumulated over time T can be calculated from Equation 2.1. G is the gradient vector describing the gradient amplitude on each axis.

$$\Delta\phi(\vec{r}, T) = \gamma \int^T \vec{G}(t) \cdot \vec{r} dt \quad (2.1)$$

Denoting the magnitude of magnetization at spatial location $\vec{r}$ as $\rho(\vec{r})$ and neglecting other factors that affect the measured signal, such as receiver coil characteristics, for now, the total signal received by the receiver coil, $s(t)$, is proportional to the vector sum of the magnetisation across space, which, after demodulation with the central signal frequency, $\omega_0 = \gamma B_0$, in complex notation gives Equation 2.2.

$$s(t) = \iiint \rho(\vec{r}) e^{-i\Delta\phi(\vec{r}, t)} d\vec{r} \quad (2.2)$$

Additionally, slightly reformatting $\int \vec{G}(t) \cdot \vec{r} dt$ to $\vec{r} \cdot \int \vec{G}(t) dt$, we have the definition for spatial frequency, $\vec{k}$, which governs the length scale over which spatial variation in the phase of the magnetisation has been introduced by the gradients, as in Equation 2.3.

$$\vec{k}(t) = \gamma \int \vec{G}(t) dt \quad (2.3)$$

Equation 2.2 could be rewritten as Equation 2.4, which has the exactly same form as the Fourier transform.

$$s(t) = \iiint \rho(\vec{r}) e^{-i\vec{k}(t) \cdot \vec{r}} d\vec{r} \quad (2.4)$$

Therefore, to obtain the target distribution of magnetisation, $\rho(\vec{r})$, to allow an image to be formed, the acquired signal $s(t)$ must be sufficiently sampled within this **k-space** domain, to allow the inverse Fourier transform (or more complex image reconstruction algorithm) to be applied.

2.1.3 K-space sampling

As explained above, an image can be obtained by inverse Fourier transforming the data $s(t)$ acquired in **k-space**. To sample k-space, the most straightforward method is to acquire signals on a equispaced Cartesian grid. We use gradient waveforms

to move around in k-space following Equation 2.3, and after each excitation, all magnetization is aligned and we start from k-space center. The grid spacing of which should satisfy Nyquist sampling theorem as shown in Figure 2.2. However, sampling does not have to be on the grid. For example, it can be done using a non-Cartesian sampling pattern as shown in 2.2. To explain k-space sampling more clearly, it is necessary to explicitly explain the sampling process mathematically.

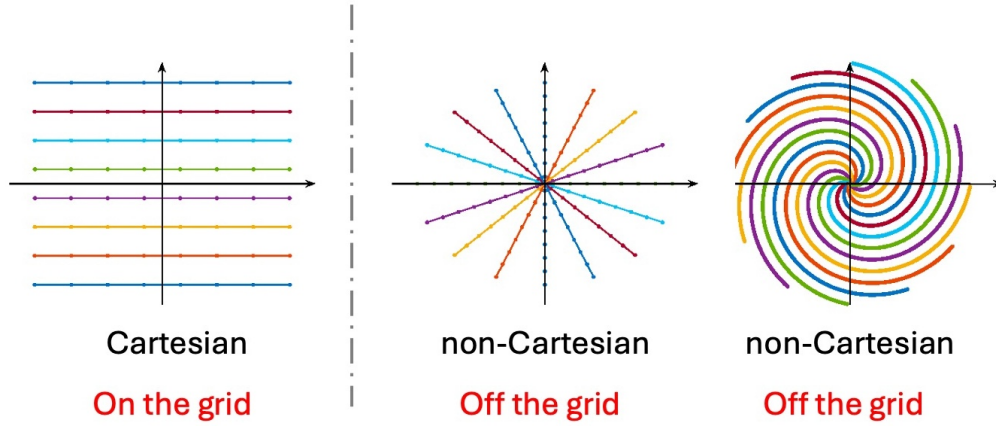


Figure 2.2: Illustration for Cartesian and non-Cartesian radial and spiral sampling pattern in **k-space** (from left to right).

General form for k-space sampling

The relationship between k-space sampling and final image is illustrated in Equation 2.5. $m(x, y)$ represents the ground truth image, while $M(k_x, k_y)$ represents its k-space representation. As the multiplication in k-space is equivalent to the convolution in image space, the effects of sampling in k-space on final images could be investigated using its representation $s(x, y)$ (note it is different from the signal notation above) in image space, which is the point spread function (PSF) we are going to cover next.

$$\begin{array}{c}
 \text{Image equivalence in k-space} \\
 \downarrow \\
 M(k_x, k_y) \cdot S(k_x, k_y) \xrightarrow{\mathcal{F}} m(x, y) * s(x, y) \\
 \begin{array}{ccc}
 \text{Sampling function} & & \text{Image in image space} \\
 \uparrow & & \uparrow
 \end{array}
 \end{array}
 \quad \begin{array}{c}
 \text{Point spread function} \\
 \downarrow \\
 s(x, y)
 \end{array}
 \quad (2.5)$$

Point spread function

Before introducing the concept of the point spread function, we start with the concept of an impulse response function commonly used in engineering. Given a linear time-invariant system, we could evaluate the system by measuring the output response for an input impulse with infinitesimal duration as shown in Figure 2.3a. Extending the concept to imaging, where the image reconstructed from a single point of magnetisation could be used to evaluate the sampling in k-space. For example, Figure 2.3b shows point spread function with loss in sharpness compared to the actual object. Note the reconstruction method will be covered later in Section 2.2.2.

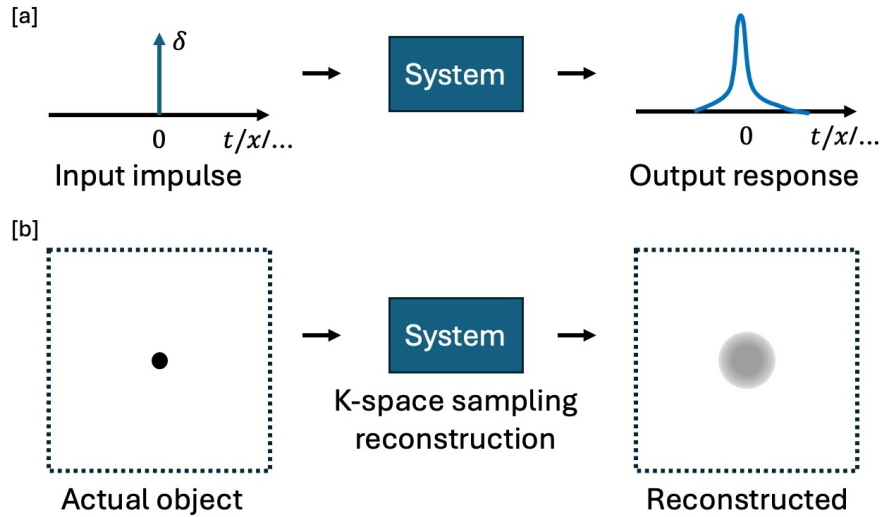


Figure 2.3: Explanation for point spread function used for evaluating k-space sampling trajectories

A more realistic scenario simulating the point spread function is shown in Figure 2.4[a], where the Cartesian sampling was 4 times undersampled along the anterior-posterior direction (also the phase encoding direction), resulting in a PSF being 4 replicates of the original point source. Figure 2.4[b] further demonstrates the reason why PSF is suitable for evaluating the effects of sampling pattern, as convolving the real brain image with PSF will result in the reconstructed image.

PSF would look different with different trajectories. Figure 2.5 demonstrates a PSF of radial trajectory (will be introduced in the next section) differing greatly

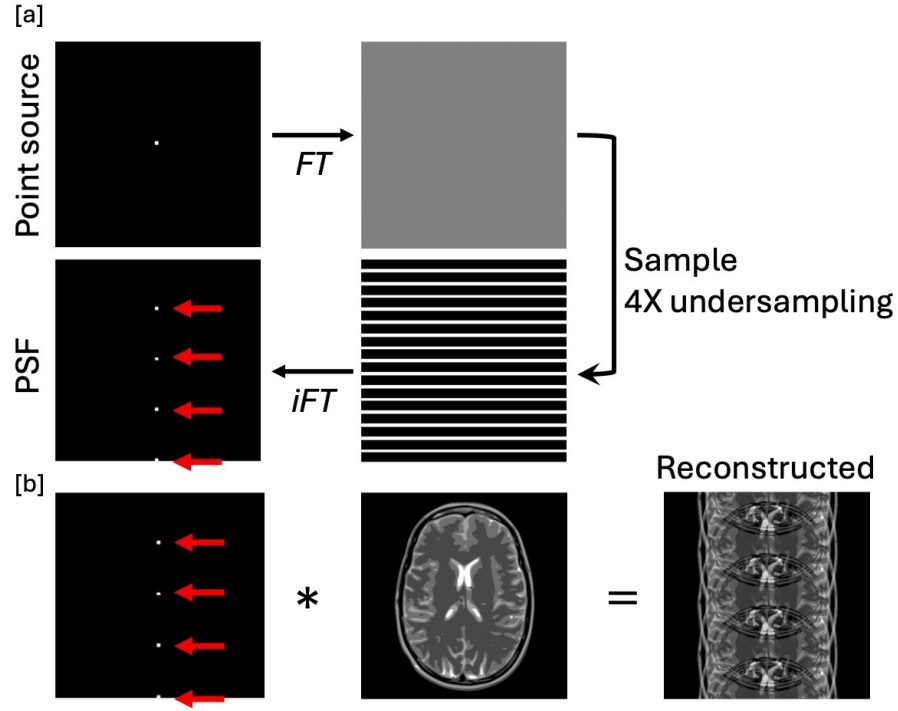


Figure 2.4: [a] The same undersampling pattern as Figure ??, but on a single point source image. The resulting aliased points are the point spread function for this sampling pattern. [b] Convolution between the aliased PSF and original brain image result in an aliased brain image.

from that of Cartesian trajectory. Unlike the reconstructed image in Figure 2.4[b], no notable replicates can be seen in the result acquired by radial trajectory.

SNR efficiency

Another important metric for evaluating the non-Cartesian sampling is SNR efficiency, which measures loss of SNR due to non-uniform sampling in k-space.

For MRI acquisitions, neglecting factors not directly related to k-space sampling, such as relaxation, the theoretical SNR for uniform sampling is proportional to voxel size and the square root of the time spent sampling the signal[16], as shown in Equation 2.6. However, this calculation does not hold for non uniform sampling, because, for example, repeated sampling of one k-space point does not reduce noise variance of the whole image proportionally[17]. Therefore, an additional factor *SNR efficiency* μ is introduced to measure the ratio of SNR of non uniform sampling compared to uniform sampling in Equation 2.7. Based on previous literature[18],

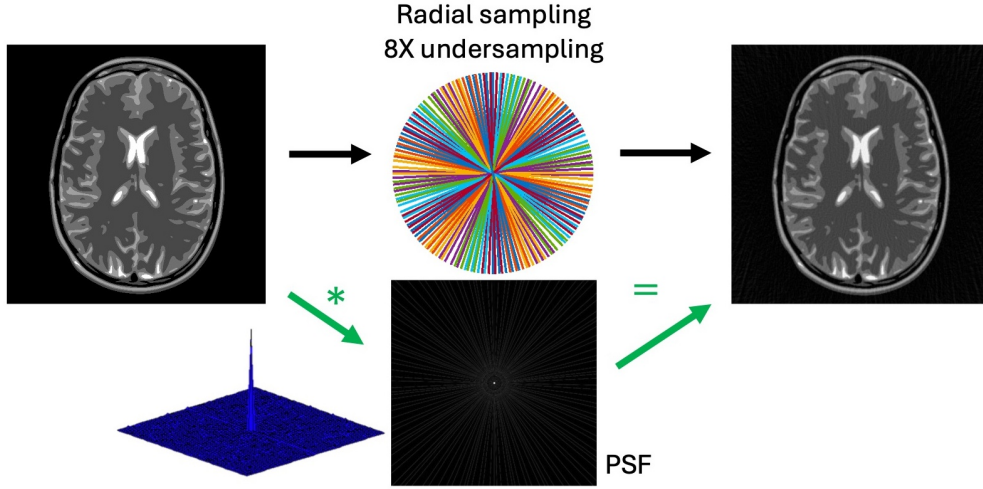


Figure 2.5: The same brain image sampled using a radial trajectory. Despite the number of radial spokes used here being half the number of the phase encoding lines in Figure 2.4, the reconstructed brain image does not have noticeable aliasing.

SNR efficiency could be calculated using Equation 2.8, where $D(k_x, k_y)$ is the local sampling density. $\iint_K D(k_x, k_y) dk_x dk_y$ is the total number of samples and $\iint_K \frac{\sigma_i}{D(k_x, k_y)} dk_x dk_y$ represents the noise reduction ratio due to repeated sampling (the number of repeated sampling is equivalent to local sampling density). As shown in Equation 2.8, (A_k is the total sampled area in k-space, c is a constant, T is the acquisition time, V is the voxel size and σ_i represents noise), the SNR efficiency μ is always smaller than 1, suggesting non-uniform sampling always comes with loss in SNR compared to Cartesian sampling when other conditions are the same. Note that SNR efficiency is different from sampling efficiency which is one of the reasons for choosing non-Cartesian trajectories.

- SNR of uniform sampling density

$$SNR = \underbrace{c}_{\text{constant}} \cdot \sqrt{\overbrace{T}^{\text{Acquisition time}} \cdot \underbrace{V}_{\text{Voxel size}}} \quad (2.6)$$

- SNR of non-uniform sampling density

$$SNR = c \cdot \mu \cdot \sqrt{T} \cdot V \quad (2.7)$$

$$\begin{aligned}
\mu &= \frac{SNR}{c\sqrt{TV}} \\
&= \frac{A_k}{c\sqrt{T}\sigma_i} \\
&= \frac{\iint_K 1 \cdot dk_x dk_y}{\sqrt{\left(\iint_K D(k_x, k_y) dk_x dk_y\right) \left(\iint_K \frac{1}{D(k_x, k_y)} dk_x dk_y\right)}} \leq 1
\end{aligned} \tag{2.8}$$

↑ Local sampling density

Example Non-Cartesian sampling trajectories

In this section, a range of non-Cartesian trajectories that are commonly used are covered.

- **Radial trajectory** The radial trajectory was initially developed by Lauterbur as the first demonstration of imaging using the principles of MR [19]. It is one of most commonly used non-Cartesian trajectories and relatively simple to implement. As shown in Figure 2.6, the gradient shape of a radial trajectory is also a trapezoidal gradient, which is the same as in Cartesian sampling. The gradient waveform represents the "steepness" of the spatial gradient in the magnetic field along each axis at different time.

The full radial trajectory is formed by rotating one basic single shot (the k-space trajectory after one excitation pulse) with different angles to cover 2D (or 3D) k-space. Because the centre of k-space, where the majority of the signal lies, is sampled after every excitation, radial trajectories tend to be robust to signal variations from a number of sources, including motion. Another nice property of radial trajectories is that they can be readily combined with golden angle rotations[20, 21]. The rotation angle in 2D for each basic shot follows a sequence with a fixed increment $\alpha = 111.2^\circ$, which is equal to π/γ_{GR} , where γ_{GR} is the golden ratio. α is sometimes referred to as the "golden angle" in MRI, not to be confused with the definition of the golden angle in geometry, which yields 137.5° . The advantage of the golden angle lies at its computational simplicity and approximately uniform distribution with any number of consecutive shots, as shown in Figure 2.7. Therefore,

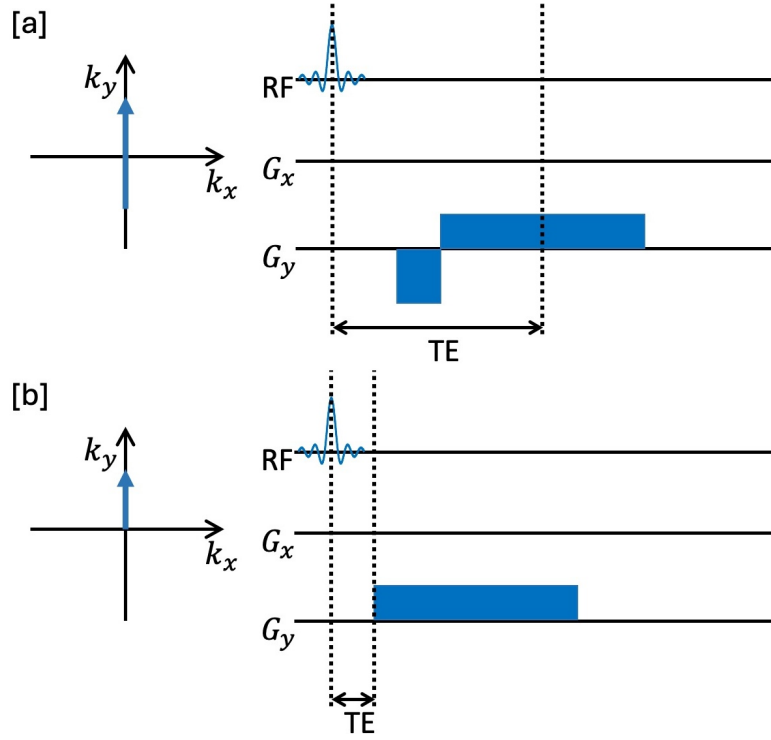


Figure 2.6: Gradient for an end-to-end 2D radial trajectory[a], and a center-out radial trajectory, [b]. The center-out trajectory has a short TE and is suitable for ultra-short echo time imaging.

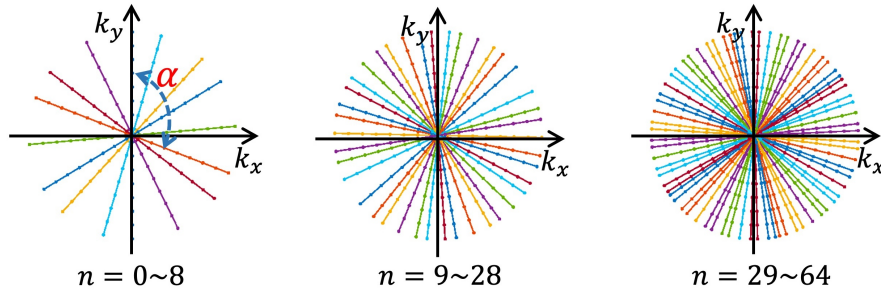


Figure 2.7: Sequence of rotation angles $n \times \alpha$ with fixed golden angle increment. Trajectories binned with arbitrary window result in approximately uniform sampling.

it is particularly suitable for dynamic imaging, since the number of k-space spokes included, and thus the temporal resolution, can be arbitrarily chosen retrospectively.

Another property of the radial trajectory is its robustness to high undersampling factors. According to Nyquist sampling theorem, two neighbouring sampling points should not be further than $\frac{1}{FOV}$ to avoid signal aliasing. However, radial sampling can tolerate violation of Nyquist sampling theorem

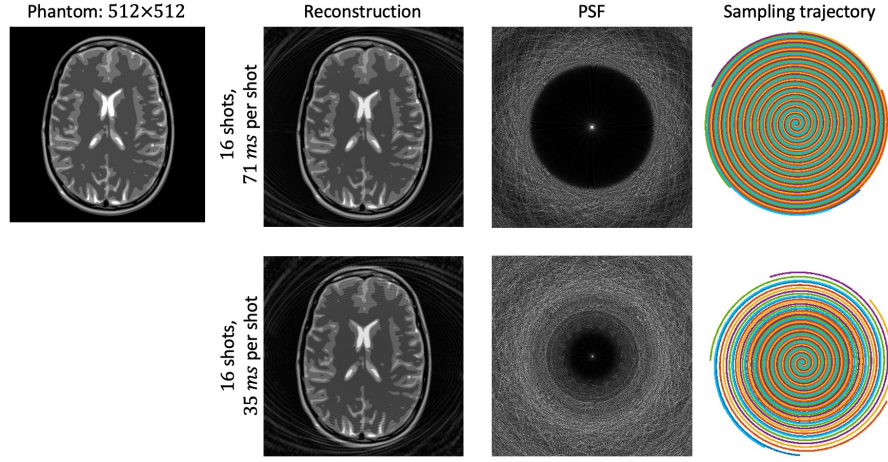


Figure 2.8: Two examples of multi-shot spiral trajectories with corresponding reconstruction results.

at the edge of k-space without introducing significant artifacts. As illustrated in Figure 2.5, results reconstructed from radial sampling can generally recover the original object without much aliasing. That being said, streaking artifacts are typically observed in highly undersampled radial reconstruction.

- **Spiral trajectory** The spiral trajectory[22] is another type of non-Cartesian trajectory as plotted in Figure 2.8. Compared to the radial trajectory, it provides better coverage of k-space for a single shot and more efficient use of gradient power. By careful designing, spiral trajectories can cover k-space approximately uniformly with a single shot or multiple shots. The sampling density of spiral trajectories can also be designed to be variable along the radius[23] to reduce acquisition time without compromising too much image quality. Figure 2.8 demonstrates two cases with same number of shots with different total acquisition time. The full sampling case takes $71ms$ for each shot while the variable density one takes $35ms$ for each shot with slightly more artifacts crossing the brain.
- **3D non-Cartesian trajectories** Both radial and spiral trajectories can be extended to 3D. For example, 3D radial and 3D cones in Figure 2.9. 3D cones [24] is essentially projecting a 2D spiral trajectory onto a conical surface.

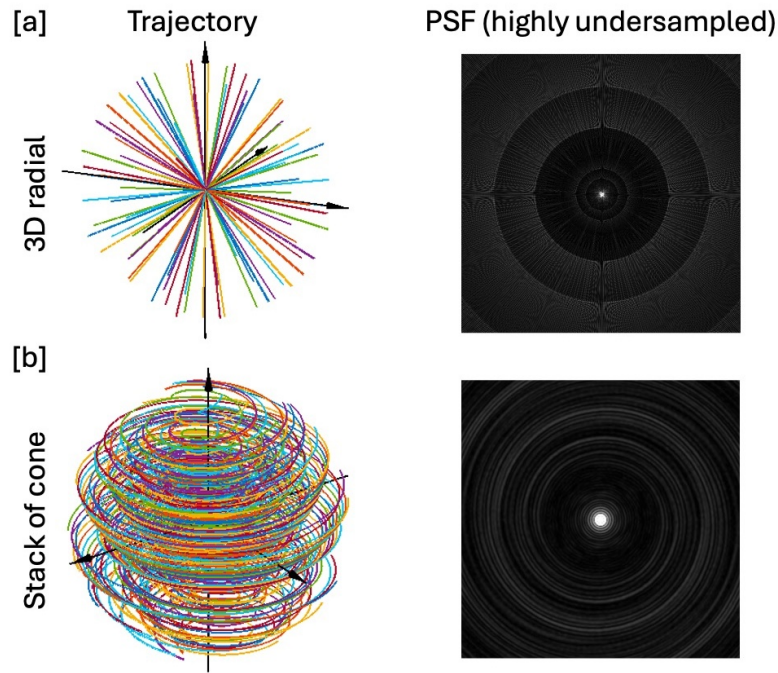


Figure 2.9: Two example 3D non-Cartesian trajectories and their corresponding PSF.

- **Time optimal gradient design** Trajectory design not only includes the curve shape in k-space but also the gradient waveform on 3 axis to traverse the curve. Although analytical methods can be used to design gradient waveform for the aforementioned trajectories, they are limited when encountering more complex shape. An optimization based method[25] was developed to generate time optimal gradient waveforms given an arbitrary desired k-space curve and hardware limitations. For example, a curved cone trajectory in Figure 2.10 can be converted to corresponding gradients on 3 axes.
- **Fully optimized trajectory** Instead of designing empirically, or rigorously to satisfy Nyquist sampling theorem, trajectories can also be optimized based on some criteria like evaluating the uniformity. SPARKLING [26] is one of such examples. The method optimizes the trajectory based on repulsion and attraction cost functions to ensure globally uniform but locally incoherent sampling. An example optimized trajectory is shown in Figure 2.11a. From the PSF in Figure 2.11b, it can be seen the PSF is isotropic with sharp central peak. However, such numerically optimised trajectories generally have the

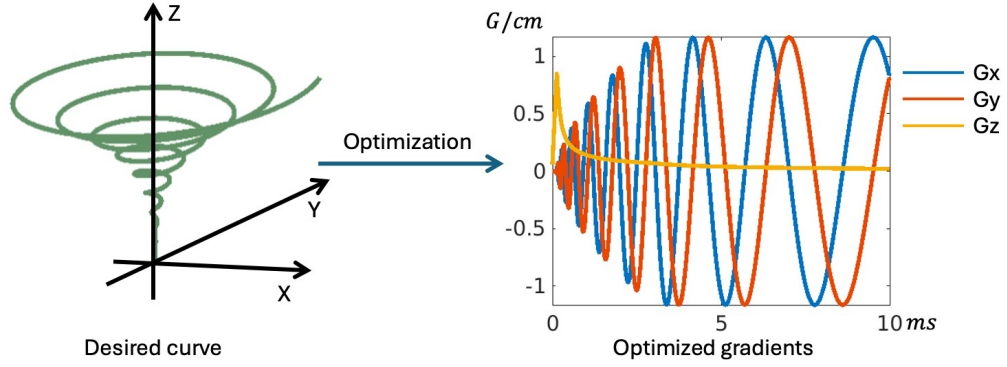


Figure 2.10: A desired curve in k-space can be converted to gradients on 3 axes to traverse that shape with minimum time spent.

disadvantage that the number of shots, spatial resolution and other parameters must be fixed prior to the optimisation, making them less flexible in terms of spatiotemporal resolution than golden ratio-based methods.

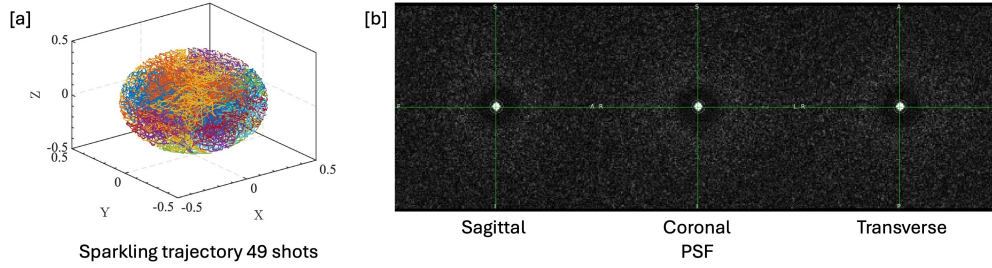


Figure 2.11: [a] SPARKLING trajectory in k-space. [b] Corresponding PSF.

2.2 Image reconstruction

2.2.1 Parallel-imaging reconstruction

Full Nyquist sampling of k-space can sometimes take a prohibitively long time. In this section we explore image reconstruction methods that are designed to reconstruct artefact-free images from undersampled data that can be acquired in a fraction of the time.

SENSitivity Encoding (SENSE)

SENSE[27] is one of the most widely used parallel imaging methods. It uses the additional spatial information provided by multiple receive coils at different

locations to provide additional spatial encoding power so that k-space can be undersampled for faster imaging. Without the spatial information provided by the receive coils, the images reconstructed from the undersampled data would be aliased as shown in Figure ?? . However, if multiple coils have different sensitivities to the magnetisation across the phase encoding direction, the undersampled information can be reconstructed without aliasing. SENSE reconstruction can also be written in a more general form beyond Cartesian sampling[28] as in Equation 2.9. The coil sensitivity maps are usually calculated from multi-coil low-resolution images. Here, P is the sampling mask, F is Fourier transform, C represents the coil sensitivity, x is the reconstruction target and y is the acquired k-space data.

$$\hat{x} = \arg \min_x \|PFCx - y\|_2^2 \quad (2.9)$$

The minimization problem is usually solved iteratively using a method such as the conjugate gradient algorithm (CG)[28]. Compared to direct matrix inversion, CG is memory efficient as it does not require explicit construction of the large PFC matrix.

GeneRalized Autocalibrating Partial Parallel Acquisition (GRAPPA)

Instead of unfolding from images independently reconstructed from separate coils, GRAPPA [29] uses the coil information in k-space before it is transformed to image space. Despite the undersampling, a small number of phase encoding lines around the k-space center are fully sampled, namely the calibration region. A learnable interpolation kernel is defined, which combines information from multiple coils and infers the k-space value for the missing lines. The kernel is trained on the calibration region first before applying it to the whole k-space. Since the kernel shape is fixed, it is not flexible for variable sampling patterns. To address this issue, iTerative Self-consistent Parallel Imaging Reconstruction (SPIRiT) [30] generalized the idea of GRAPPA to arbitrary sampling patterns. Unlike GRAPPA, which only enforces consistency within the calibration region, SPIRiT ensures self-consistency at all k-space points.

Coil compression

With the improvement of MRI hardware, coil arrays have been developed to contain 32-128 channels, which benefit SNR and parallel imaging performance, but also higher computational consumption for reconstruction. As sensitivity maps from different coil elements are highly correlated, this redundancy can be removed using methods like principal components analysis[31]. Therefore, a much smaller number of virtual coils, formed through linear combinations of the physical coils, which have orthogonal sensitivity profiles can be generated and used for reconstruction, reducing computational requirements while preserving rich spatial information.

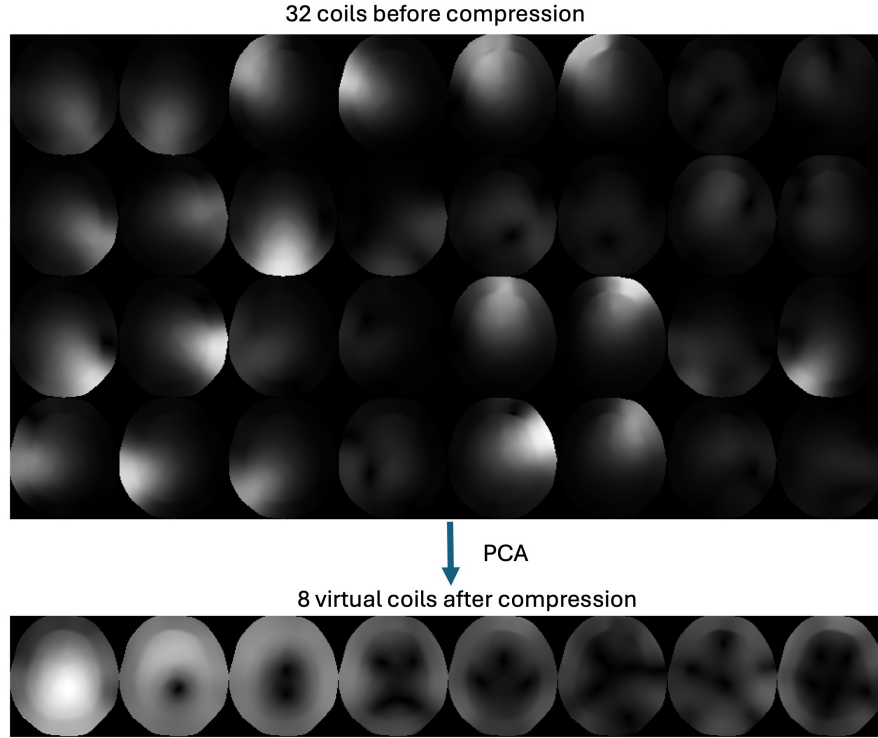


Figure 2.12: Example of 32-channel coil sensitivity maps being compressed to 8 virtual coils using PCA.

2.2.2 Non-Cartesian sampling reconstruction

For data acquired on the regular grid in k-space, the inverse fast Fourier Transform (iFFT) can be used to convert the filled k-space into an image. However, if the data acquired are not positioned on a regular grid, for example the non-Cartesian

sampling trajectories shown in previous sections, data needs to be interpolated to regular grid before using the iFFT. The data interpolation process is called gridding.

Gridding process

An intuitive explanation for the gridding process is demonstrated in Figure 2.13. Taking one data point on this center-out spiral trajectory as an example, the acquired value is multiplied with a kernel covering the surrounding k-space. Depending on the distance to the sampled location, nearby Cartesian grids will be assigned a value based on the acquired data and the applied kernel function. Conventionally, the kernel function is chosen to be isotropic and decays from the center (e.g., a Kaiser Bessel kernel). The gridding algorithm repeats this process for each data point on the trajectory, and sums together the values contributed from different samples on each individual grid point. After the gridding, the iFFT can be performed to reconstruct the image.

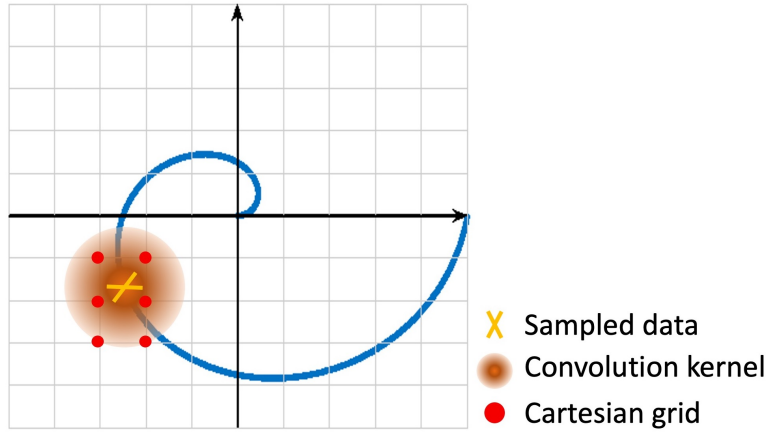


Figure 2.13: Illustration for gridding process.

Let us take a look at the gridding problem from another perspective. In Equation 2.10, the rigorous mathematical representation of gridding is laid out following Jackson et al.[32]. $m(x, y)$ and $M(k_x, k_y)$ are images in image space and k-space respectively, continuous without discretization. $S(k_x, k_y)$ is the sampling trajectory which is a set of dirac delta functions $S(k_x, k_y) = \sum_i \delta(k_x - k_{x_i}, k_y - k_{y_i})$ at different sampling location (k_{x_i}, k_{y_i}) in k-space. Its equivalence in image space is exactly the

point spread function we mentioned in the previous section. $C(k_x, k_y)$ represents the convolution kernel, while $c(x, y)$ is its Fourier transform, also known as the apodization function. As we mentioned in Figure 2.13, the final step is sampling to a Cartesian grid, defined as $U\left(\frac{\Delta k_x}{\alpha}, \frac{\Delta k_y}{\alpha}\right)$. Similar to S , U is also a set of dirac delta functions but positioned on an equispaced grid. The Fourier transformed U is u , and is also another set of dirac delta function with equal spacing, except the spacing becomes αFOV in image space. In other words, the $[m * s \cdot c]$ replicates itself every αFOV in image space. Therefore, the Cartesian grid is usually oversampled in k-space using factor α to avoid aliasing. Given enough oversampling, u could be temporarily ignored in Equation 2.10, as aliasing is not an issue within the FOV anymore. To recover the true object $m(x, y)$ in final image, the gridded data $[m * s \cdot c]$ after deapodization (divided by c in image space) has to approximate $m(x, y)$, implying that $s(x, y)$ (PSF) needs to approximate a delta function as well.

$$\begin{aligned}
 & \left[M(k_x, k_y) \cdot S(k_x, k_y) * C(k_x, k_y) \right] \cdot U\left(\frac{\Delta k_x}{\alpha}, \frac{\Delta k_y}{\alpha}\right) *^{-1} C(k_x, k_y) \\
 & \quad \quad \quad \Updownarrow \\
 & \left[m(x, y) * s(x, y) \cdot c(x, y) \right] * u(\alpha FOV_x, \alpha FOV_y) \div c(x, y)
 \end{aligned} \tag{2.10}$$

Sampling density compensation

However, if following the above mentioned gridding process, one would find grid points in densely sampled regions have abnormally high intensity contributed from the large number of samples nearby. The gridded result does not truthfully reflect the intensity at that spatial frequency. Taking radial sampling as an example, the center of k-space is highly oversampled as shown in Figure 2.14. After transforming to image space using the iFFT, the result is dominated by the low frequency signal at the k-space centre. In the previous section, we mentioned that the point spread function needs to approximate a delta function for high fidelity reconstructions of the true object. However, from the Equation 2.10, we could notice that the actual point spread function after gridding reconstruction is not only dependent on the

sampling trajectory $S(k_x, k_y)$, but also the convolution kernel $C(k_x, k_y)$, as shown in Figure 2.15. Gridded k-space needs to be corrected for sampling density of the original trajectory to avoid over/under-representing certain spatial frequencies.

To be more specific, the weights are multiplied onto each individual sampling point. For convenience, $S(k_x, k_y)$ is combined with pointwise weight to $W(k_x, k_y) = \sum_i W_i \cdot \delta(k_x - k_{x_i}, k_y - k_{y_i})$. And we aim to recover the original signal M after weighted sampling and convolution, as shown in Equation ??, on the sampled points $S(k_x, k_y)$.

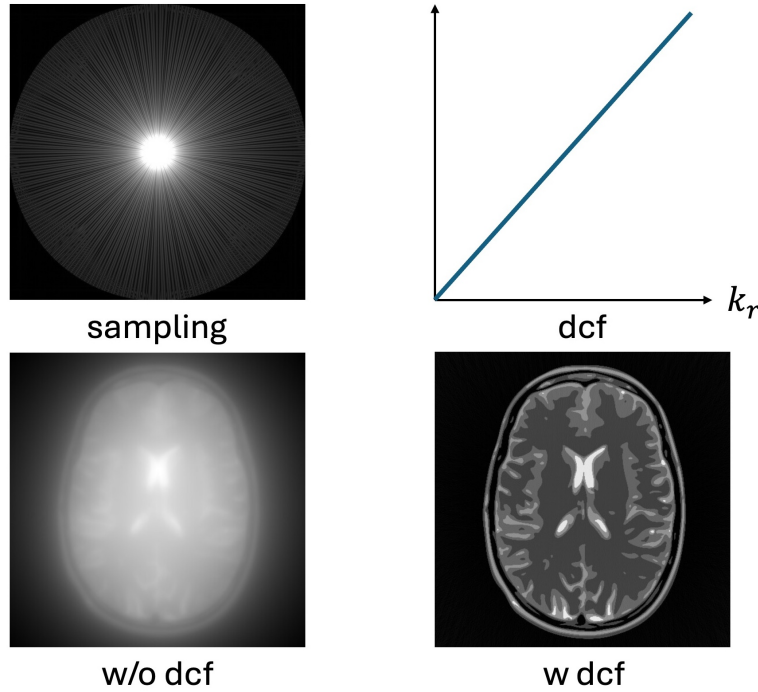


Figure 2.14: Brain image sampled with radial trajectory and reconstructed with and without density compensation.

From Equation 2.10, we could notice that as long as let $w(x, y)$ (weighted $s(x, y)$) be a delta function inside the FOV, the final reconstruction would be the same as $m(x, y)$ inside the FOV. Therefore, for any kernel ψ , Equation 2.11 should satisfy, which naturally leads to Equation 2.12, 2.13. To solve for W in Equation 2.13, we could iteratively converging W using Equation 2.14.

$$w * \psi = \sigma \quad (2.11)$$

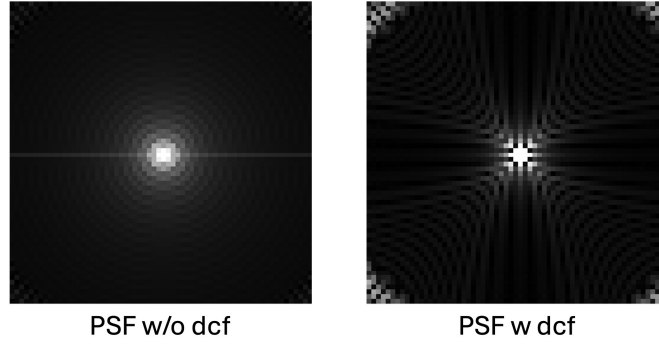


Figure 2.15: Point spread function for radial sampling with and without density compensation.

$$w \times (w * \psi) = w \quad (2.12)$$

$$W * (W \times \Psi) = W \quad (2.13)$$

$$W_{i+1}(k_x, k_y) \approx \frac{W_i(k_x, k_y)}{W_i(k_x, k_y) * C(k_x, k_y)} \quad (2.14)$$

2.2.3 Regularized reconstruction

For highly undersampled data, simply minimizing the l_2 norm between the reconstruction and the acquired data would not be sufficient and is prone to under-sampling artifacts since the problem is underdetermined. Therefore, some form of regularization is needed to improve the condition of such problems[33]. The regularized problem can be written in the form of Equation 2.15. Based on the prior knowledge of specific modalities, different regularization methods have been developed. Here, we are going to describe three regularization approaches: Tikhonov, wavelets and locally low rank.

$$\hat{x} = \arg \min_x \|PFCx - y\|_2^2 + R(x) \quad (2.15)$$

- Tikhonov

One basic regularization term is Tikhonov regularization, where the l_2 -norm of the reconstruction target is added as an additional term to the cost function, as shown in Equation 2.16. This essentially allows us to find the lowest "energy" solution that is consistent with the measured data, preventing excessive noise amplification. α is the regularization weight. It is usually solved with iterative methods like conjugate gradient [28].

$$\hat{x} = \arg \min_x \|PFCx - y\|_2^2 + \alpha \|x\|_2^2 \quad (2.16)$$

- **Wavelets** Most natural images, including MR images, are sparse in the wavelet transformed domain. According to compressed sensing theory[34], such a sparse image can be recovered from undersampled data by incorporating a sparsity regularization (l_1) term on the estimated image in the sparse domain, such as the wavelet coefficients as shown in Equation 2.17, where P is the sampling mask in k-space, F is the Fourier transform and C is the coil sensitivity.

$$\hat{x} = \arg \min_x \|PFCx - y\|_2^2 + \lambda |W(x)|_1 \quad (2.17)$$

- **Locally low rank** For dynamic MRI, different frames are usually spatially and temporally correlated. Therefore, the temporal variation across the whole dataset can be represented by a small number of orthogonal temporal vectors. Low rank regularization is designed to take advantage of such redundancy[35]. Many datasets are particularly low rank when considering small regions of the image at a time, since nearby regions often have similar temporal characteristics, and are therefore "locally low rank".

The general form of low rank regularization imposed on dynamic images can be expressed as Equation 2.18, where R is the patch extraction operator. Initial methods applying low rank regularization on dynamic images explored enforcing a low rank constraint on the whole image[35]. In this case, the patch extraction operator R keeps the input x , and reshapes the estimated image, x , to a $N \times T$ Casorati matrix. However, drastic reduction of matrix rank

on the whole image can cause temporal blurring. Therefore, a locally low rank approach [36] was proposed, where R_i extracts local patches sequentially throughout the image, as shown in Figure 2.16. Patches can also have different sizes as proposed by multi-scale low rank [37], which incorporates different scales of information.

$$\hat{x} = \arg \min_x \|PFCx - y\|_2^2 + \lambda \sum_i |R_i(x)|_* \quad (2.18)$$

In practice, low rank regularization is difficult to optimize. Therefore, minimizing the rank of a matrix is usually approximated by minimizing the l_1 norm of singular values (D in Figure 2.16b).

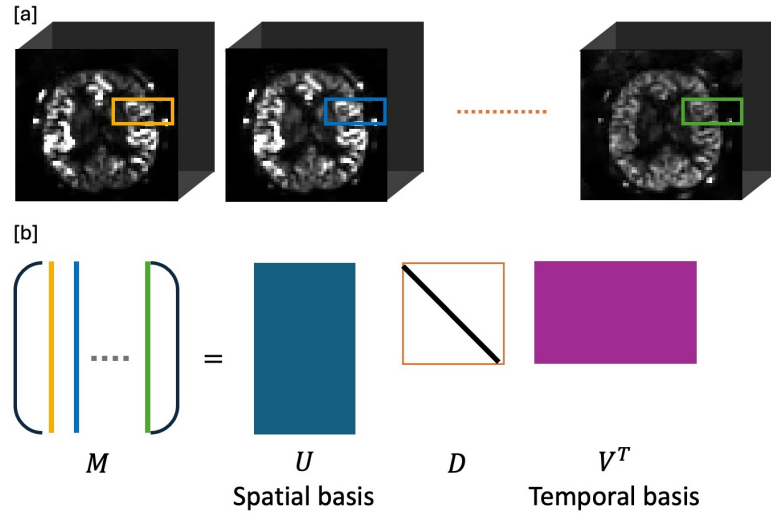


Figure 2.16: [a], Patch extraction R_i process at location i . [b], The extracted patches are flattened and concatenated into a casorati matrix. The rank regularization is applied on the singular value decomposition of the matrix.

- **Subspace constrained reconstruction** Another constraint for reconstructing is subspace. Specifically, the constraint confines the target time series, x , to lie on a subspace spanned by a combination of orthogonal principal components, Φ . The subspace can either be estimated from acquired data itself [38] or from some signal model [39]. As shown in Equation 2.19, the voxel-wise weights for each principal component, α , are to be estimated. The reconstruction problem was converted to the form of Equation 2.20, where

P was the sampling mask, F was the Fourier transform and C was the coil sensitivity.

$$x \cong \Phi\alpha \quad (2.19)$$

$$\hat{\alpha} = \underset{\alpha}{\operatorname{argmin}} \|PFC\Phi\alpha - y\|_2^2 \quad (2.20)$$

As operators F , C were applied on the spatial dimension, independent from the operator Φ on the temporal dimension, the original order of operators could be modified to $P\Phi FC\alpha$. The combined operator $\Phi^H P\Phi$ used in every iteration could be calculated before the start of iterative optimization, so that the whole optimization process could be performed entirely in the subspace domain without expanding to a full time-series[39].

3

Existing blood flow and structural imaging methods

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In this chapter, medical imaging methods, including non-MR methods, developed for acquiring the three modalities involved in our combined imaging sequence, namely angiography, perfusion and structural images, are briefly summarized, showing the context where our ASL-based combined imaging method is placed. The technical

details of arterial spin labeling (ASL) are introduced, followed by a description of each component of the combined imaging ASL sequence, which will be used heavily in the following chapters.

3.1 T1-weighted structural imaging

Magnetization Prepared - RApid Gradient Echo (MP-RAGE)[40] is the dominant sequence for 3D T1-weighted imaging. To be more specific, a non-selective inversion pulse is used to prepare the magnetization. After some dead time, TI (inversion time), a train of single line Cartesian readouts are acquired with constant flip angle to fill 3D k-space. The critical parameters used in the sequence to acquire MP-RAGE images across this whole thesis were listed in Table 3.1. Based on these, the signal magnitude across the echo train can be simulated as in Figure 3.1.

Param names	Value
TI	904ms
TE	3.71ms
Echo spacing	8.8ms
ETL	128
TR	1.9s
Flip angle	8°

Table 3.1: Sequence parameters used for MP-RAGE across whole thesis. Echo train length (ETL) is the number of readouts following one inversion pulse.

As can be seen from this simulation, this set of parameters gives a relatively stable signal across the readout with good contrast based on the T1 of the tissue: tissues with short T1 values have high signal and those with long T1 values have low signal. The use of a single line readout after each excitation pulse makes this method very robust to B_0 inhomogeneity, with minimal distortions and artefacts, making it well suited as an anatomical reference.

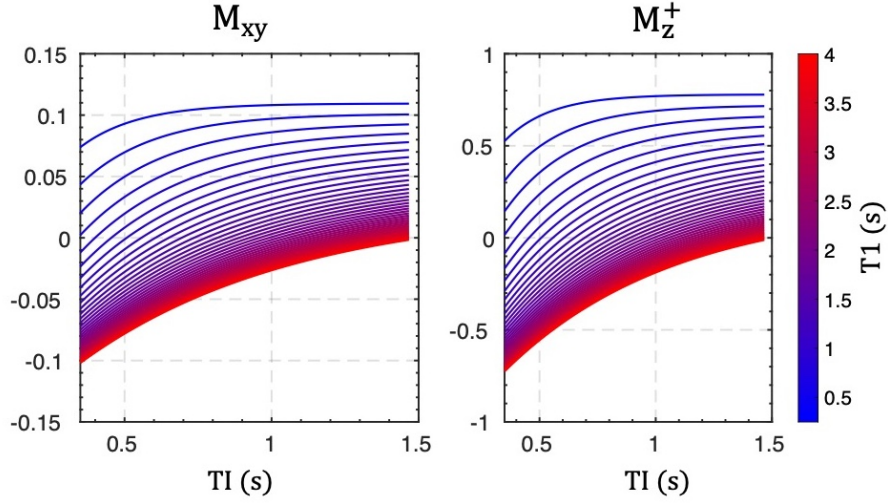


Figure 3.1: Simulation of transverse magnetization M_{xy} and longitudinal magnetization M_z^+ after each excitation pulse during the train of readouts of MP-RAGE with T_1 varying from 250-4000 ms, shown as different coloured lines.

3.2 Angiography

3.2.1 Non-MR angiography

Different methods have been developed to image brain blood vessels in the past 50 years[41]. Among them, Digital Subtraction Angiography (DSA) [5], first introduced in 1982, is capable of 2D real-time imaging. To perform DSA, a contrast medium (Iodine) is injected into the arteries through a catheter inserted from the leg and guided up to the brain. Taking the difference between images after injection and pre-injection produces the clear visualization of the arteries. DSA has very high sensitivity for detecting vascular abnormalities and is treated as the gold standard angiography method. DSA also allows for real-time imaging, which is advantageous for guidance during surgical operations. However, the method is invasive and has high radiation exposure, increasing the risk for patients.

Computed Tomography Angiography (CTA) is another contrast-based imaging method using X-rays, first introduced to clinical applications in the 90s[6, 42]. Compared to DSA, CTA injects the contrast agent through a peripheral vein, greatly reducing the risk of complications. Subjects are also typically exposed to less radiation than with DSA. However, it is less sensitive than DSA for detecting small

aneurysms [43]. Real-time imaging using CTA is also not feasible at the moment.

3.2.2 MR angiography

Methods using MRI to image vessels in the brain have also been developed over the years. Time of flight (TOF) [44] was first introduced in the late 90s. The method applied repetitive RF pulses to the imaging region in the brain to saturate the magnetization of the static tissue. The blood, which is continuously flowing into the imaging region, however, is not saturated, and has high contrast to the low signal intensity of the static tissue. As shown in the example in Figure 3.2, the arteries are much brighter than the brain tissue. TOF has high SNR and is advantageous for high spatial resolution. The disadvantages of TOF include poor SNR with slow flow and limited imaging slab thickness.

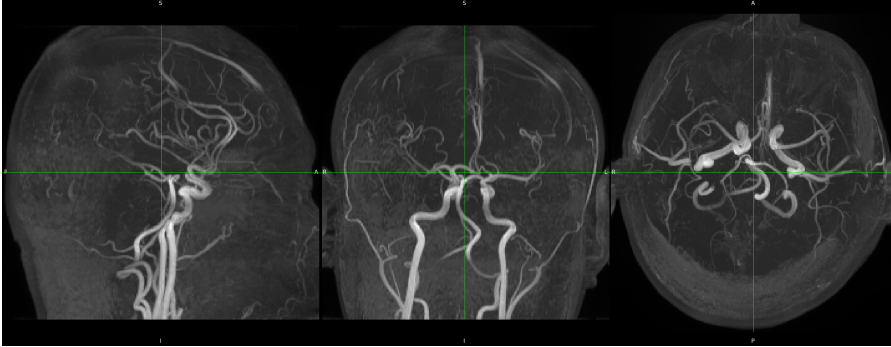


Figure 3.2: Maximum intensity projection (MIP) example of TOF angiography on whole brain at $0.78mm$ isotropic spatial resolution.

Another non-Contrast MRA technique called Phase-Contrast, was first introduced by Moran [45] in the 80s. The method also exploited the difference of moving magnetization in the blood and spatially stationary magnetization in the static tissue. Unlike TOF, where the contrast arises from the difference in the magnitude signal intensity between moving and stationary spins, Phase-Contrast uses the difference in the signal phase. To be more specific, equal-area bipolar gradients are used in this method. For static tissue, the net phase increment after the bipolar gradients should be 0, whereas the phase of blood moving along the direction of the gradients will change according to its velocity. That difference in phase between

data acquired with and without the bipolar gradients constitutes the contrast. In practice, the polarity of the bipolar gradients are toggled to remove background phase accrual from field inhomogeneities. Generally, the method is less popular than TOF MRA as it requires multiple gradient directions and velocity encodings to be sensitive to a wide range of blood velocities and is sensitive to partial volume effects. It also takes longer to acquire than TOF MRA, particularly when it is cardiac gated and multiple temporal frames are to be reconstructed.

3.3 Perfusion imaging

3.3.1 Non-MR perfusion

Positron emission tomography (PET) uses isotopes emitting positrons as a tracer to assess cerebral blood flow (CBF)[7]. These tracers (e.g., $^{15}\text{O}-\text{H}_2\text{O}$, $^{15}\text{O}-\text{CO}_2$)[46] are injected into the subjects' vein and distributes in the brain according to blood flow. The PET scanner detects the γ -rays emitted from the annihilation of the positron produced by the tracer with an electron, and reconstructs an image showing the distribution of the tracer. PET is considered the gold standard for CBF measurement. PET can also be combined with CT or MRI for structural reference. The spatial resolution of PET has seen significant improvement reaching 1mm [47]. However, the PET examination is expensive as it is limited to centers with on-site cyclotrons.

Apart from PET, CT can also be used to image brain perfusion (CTP) by injecting an iodinated contrast agent [48]. Since Iodine (I) has an atomic number of 53, significantly heavier than that of most tissues in the body, it increases the likelihood of photoelectric absorption, so it is used as a tracer with the whole passage through vasculature being imaged, as in DSA. CTP is the most commonly used perfusion method in acute stroke. It is cheap, readily accessible in most hospitals, fast. However, it still has some radiation dose and some might be allergic to contrast agents.

3.3.2 MR perfusion

Dynamic Susceptibility Contrast (DSC)

DSC was developed by Østergaard et al. [8] in the 90s. A gadolinium-based contrast agent is injected into the veins. As it passes through the vasculature, the paramagnetic contrast agent introduces an additional T_2^* decay. By measuring the signal change over time and fitting a complex model, various properties of blood perfusion can be calculated, cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP). The acquisition time is relatively short (2 min).

Dynamic Contrast-Enhanced (DCE)

Similar to DSC, DCE [49] also requires administration of gadolinium based contrast agent. However, instead of observing T_2^* -based signal changes during the contrast agent's first pass through the arteries, DCE uses T1-weighted imaging to be sensitive to the T1 shortening effect of gadolinium. By using repeated imaging, the gradual accumulation of the contrast agent in the interstitial space can be observed. Since the exchange rate depends on the tissue permeability and regional blood flow, DCE is sensitive to diseases such as tumors or infection due to the break down of the blood-brain barrier [50]. The quantification for DCE is similar to DSC.

3.4 Arterial spin labeling (ASL)

ASL is a "non-contrast" MR technique that can be used to image the blood vessels (angiography) and tissue perfusion. Instead of using an injected exogenous contrast agent, it uses 1H in blood water as an endogenous tracer. In ASL, the magnetization of 1H in blood water is saturated or inverted before it enters the imaging region and is then imaged after a delay. An identical image is also acquired where the blood magnetization is not labeled. By taking the difference between two images, the static tissue in the imaging region (which was not labeled) is subtracted out, while the labeled blood signal remains. Several methods have been developed

to invert the magnetization in the in-flowing blood using a combination of RF pulses and gradients.

3.4.1 Pulsed ASL (PASL)

The first PASL sequence was Echo-Planar Imaging-based Signal Targeting by Alternating Radiofrequency pulses (EPISTAR) [51]. As shown in Figure 3.3, EPISTAR images blood by taking the difference between **label** and **control**. For acquisition of the **label** image, a 90° RF pulse is applied over the **imaging slice** followed by a **spoiler** to null the transverse magnetization. A 180° **slab selective inversion pulse** is then applied below the **imaging slice**. The blood flowing into the **imaging slice** therefore carries inverted magnetization. For the **control** image, the in-flowing magnetization of blood is not inverted, creating the difference with the **labeled** blood. However, the labeling **inversion pulse** will induce additional signal loss in the **imaged slice** due to magnetization transfer [52]. To counter this effect, a **slab selective inversion pulse** is applied above the **imaged slice** in the **control** acquisition.

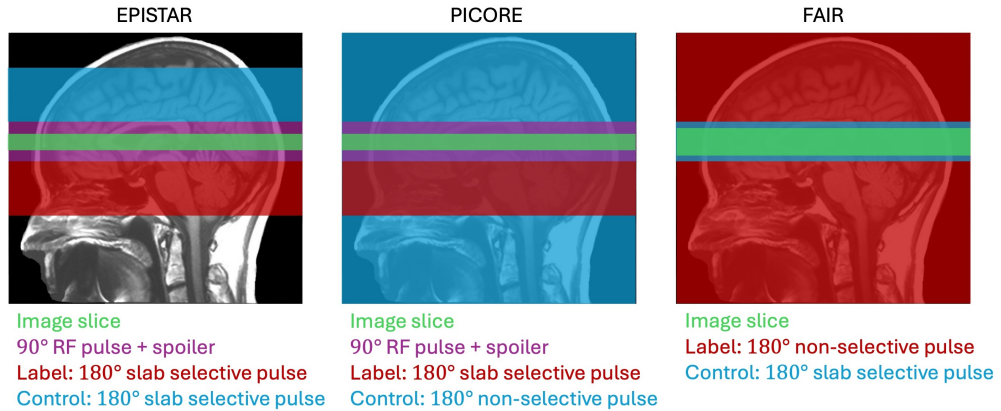


Figure 3.3: Three representative PASL methods.

Proximal Inversion with Control of Off-Resonance Effects (PICORE) [53] has a similar design to (EPISTAR) [51]. The label image acquisition for each method is identical. However, PICORE uses non-selective off-resonance inversion pulse in the control image acquisition. The center frequency for the inversion pulses in both **label** and **control** acquisition are aligned for mitigation of magnetization transfer

effect as well. This has the advantage that blood flowing into the imaging slice from above will have zero signal, whereas it will have negative signal in EPISTAR.

Flow-sensitive Alternating Inversion Recovery (FAIR) [54] is another implementation of PASL. For acquisition of the **label** image, a **non-selective inversion pulse** inverts the magnetization everywhere. In the **control** acquisition, a **slab selective inversion pulse** inverts magnetization within the **imaging region**. The difference image then contains positive signal for blood that enters the imaging slice from either side, which may be useful in distal slices or in cases with complex arterial geometry.

All three methods typically use adiabatic pulses [55] for inversion. One such example is hyperbolic secant pulse shown in Figure 3.4. The mechanisms for adiabatic inversion will be covered in section 3.4.2.

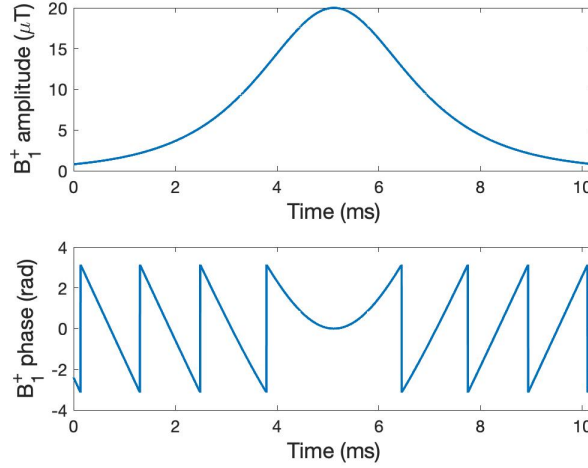


Figure 3.4: Adiabatic inversion using hyperbolic secant pulse.

3.4.2 Continuous ASL (CASL)

The mechanism of CASL is referred to as *flow-induced adiabatic inversion*[56], which is as an extension of *adiabatic inversion*[55] described below.

Adiabatic inversion

Conventionally, the flip angle θ and RF pulses $B_1(t)$ obey the relationship as stated in Equation 3.1. γ is the gyromagnetic ratio.

$$\theta = \gamma \int_0^T B_1(t) dt \quad (3.1)$$

However, this relationship does not hold when the frequency of the RF pulse, ω_{rf} , is different from the precession frequency of the magnetisation, $\omega = \gamma B$. Consider the RF pulse $B_1(t) = A(t)e^{-i\omega_{rf}t}$. The effective field B_{eff} combined by B_0 and B_1 field can be calculated. Additionally, the B_{eff} is calculated in the rotating frame with frequency $\omega_{rf} = \gamma B_1$ as Equation 3.2. In Equation 3.2 $B_{eff\perp}$ is the combined magnetic field in transverse plane and $B_{eff\parallel}$ is the combined magnetic field along longitudinal axis.

$$\begin{aligned} B_{eff\perp} &= A(t) \\ B_{eff\parallel} &= \frac{\omega - \omega_{rf}(t)}{\gamma} \end{aligned} \quad (3.2)$$

The Equation 3.2 can be rewritten as Equation 3.3.

$$\begin{aligned} |B_{eff}| &= \sqrt{A^2(t) + \left(\frac{\omega - \omega_{rf}(t)}{\gamma}\right)^2} \\ \theta_{B_{eff}} &= \arctan\left(\frac{\gamma A(t)}{\omega - \omega_{rf}(t)}\right) \end{aligned} \quad (3.3)$$

According to the *adiabatic passage principle*, the magnetization follows the direction of B_{eff} if it changes slowly, namely the *adiabatic condition*, expressed as Equation 3.4.

$$\left| \frac{d\theta_{B_{eff}}}{dt} \right| \ll \gamma |B_{eff}| \quad (3.4)$$

Flow-induced adiabatic inversion

The principles for adiabatic inversion derived above can be readily translated to flowing spins. As shown in Figure 3.5, the RF pulse, B_1 , now has constant amplitude and on-resonant frequency for a given position along the z-axis. Because of the existence of the constant gradient, G , along the z-axis, B_{eff} varies with z from positive to negative. As the blood flows through the labeling plane with velocity v ,

the magnetization follows the B_{eff} and inverts, as long as the *adiabatic condition* is satisfied. The *adiabatic condition* in the flow-induced case is Equation 3.5

$$\frac{1}{T_2} \ll \frac{Gv}{B_1} \ll \gamma B_1 \quad (3.5)$$

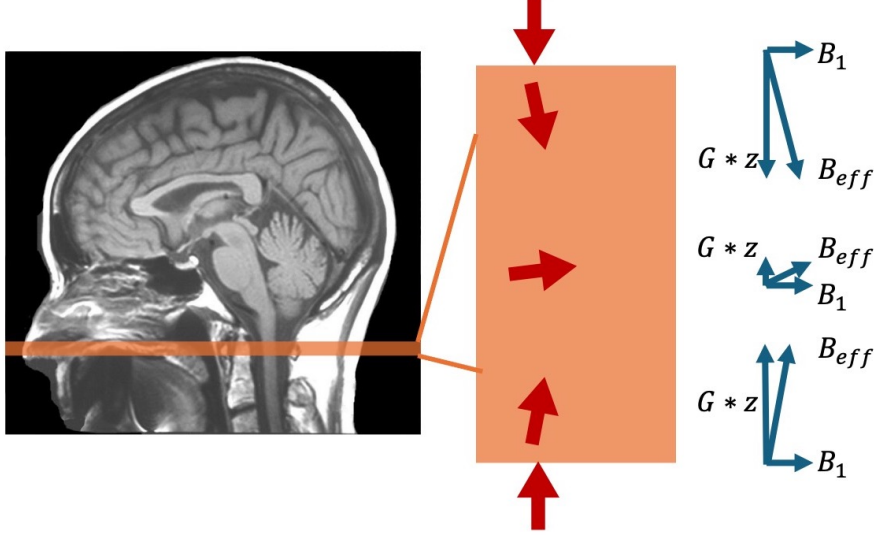


Figure 3.5: Illustration for flow-induced adiabatic inversion. The red arrow represents the blood magnetization flowing through the labeling plane (the orange area). The RF pulse has constant amplitude and same frequency as Larmor frequency. The constant gradient G along z -axis is turned on. The magnetic field along longitudinal axis varies with along z -axis, resulting in the B_{eff} slowly rotates from positive to negative along the longitudinal direction.

The CASL[56] method is not commonly used anymore, because the requirement for a long continuous RF pulse is not consistent with the design of modern scanners which are optimized for short RF pulses, thus, it requires dedicated hardware to run. Strong RF pulses persisting for a long duration also causes high tissue energy deposition.

3.4.3 Pseudo-Continuous ASL (PCASL)

To resolve the hardware incompatibility of CASL[56], PCASL[57] was developed. Here, the continuous RF pulse and gradient of CASL were split into a long train of repetitive, short RF pulses and gradients where the mean RF and gradient amplitude is similar to that in CASL, as shown in Figure 3.6a-b. As the equilibrium

magnetization flows from below the inversion plane, as in Figure 3.5, the magnetization experiences a gradually increasing on-resonant B_1 amplitude, until it reaches a maximum at the center of the labeling plane. As the magnetization travels through the labeling plane, the phase it accumulates in the gaps between consecutive RF pulses will vary based on its location, z , due to the mean gradient. The steady-state effect of the PCASL train on flowing magnetization is determined by the phase shift between RF pulses, ϕ , and flip angle, α , [58] as shown in Equation 3.6. Setting the flip angle, mean gradient and duration between RF pulses appropriately so that the magnetization experiences a $-\pi$ to π phase shift as it flows through the labeling plane, the M_z can be successfully inverted. This inversion process can also be visualized in Figure 3.7, which is the simulation of 3.6. Red and black curves in Figure 3.7 represents two scenarios when $+$ or $-$ is used in Equation 3.6.

The inversion process during the train of RF pulses can also be simulated using numerical bloch simulations. Figure 3.6c simulates the labeling process in Figure 3.6a, whereas Figure 3.6d simulates control sequence in Figure 3.6b. In the control sequence, the phase of RF pulse alternates between 0° and 180° and the magnetization is flipped back and forth correspondingly.

$$M_z = \frac{\pm \sin \alpha \sin \frac{\phi}{2}}{(1 - \cos \alpha)^2 + \sin^2 \alpha \sin^2 \frac{\phi}{2}} \quad (3.6)$$

3.5 Combined angiography and perfusion imaging designs in detail

Combined angiography and perfusion radial imaging using ASL (CAPRIA)[11] is a combined imaging sequence containing multiple repeats. We can use ASL to generate angiograms and perfusion maps. The first shows stenosis/occlusion/vascular malformation, but the second shows the effect of any vascular issue on downstream perfusion. Both are often simultaneously desired, but separate acquisitions are quite lengthy. Naturally, the idea is to use a single ASL preparation and then visualize the blood flow through the arteries and into the tissue. Combined angiography,

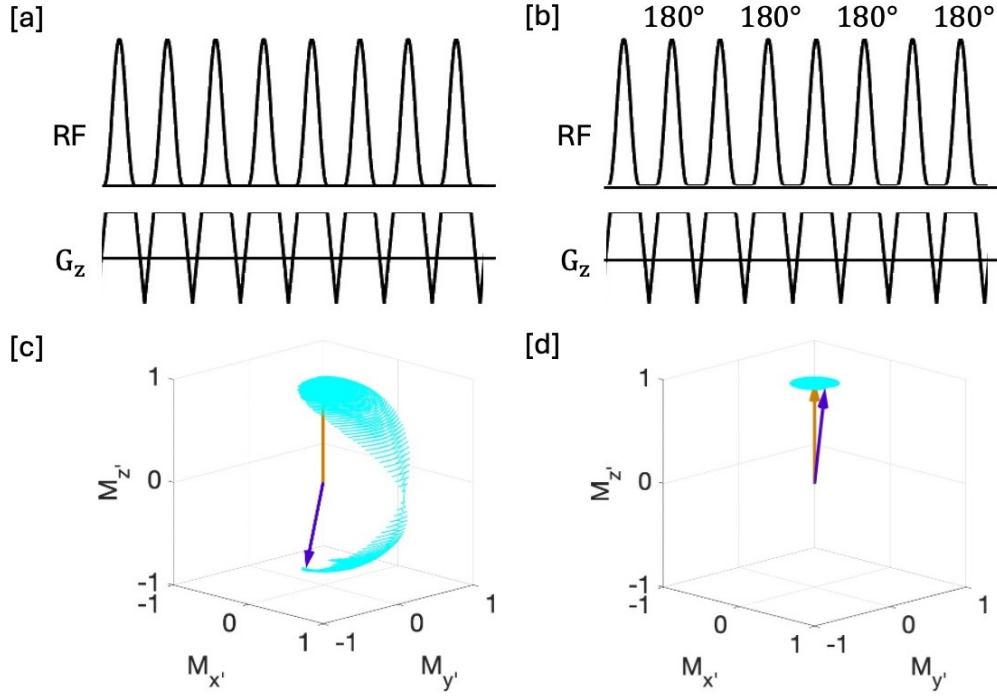


Figure 3.6: Illustration of gradient and RF pulses for PCASL label and control. [a]. Repetitive RF pulses and gradients for label. [b]. Repetitive RF pulses with phase alternating between 0° and 180° . [c]. Bloch simulation for magnetization traversing through the PCASL labeling plane during the label condition. [d]. Bloch simulation for magnetization traversing through the PCASL labeling plane during the control condition[59].

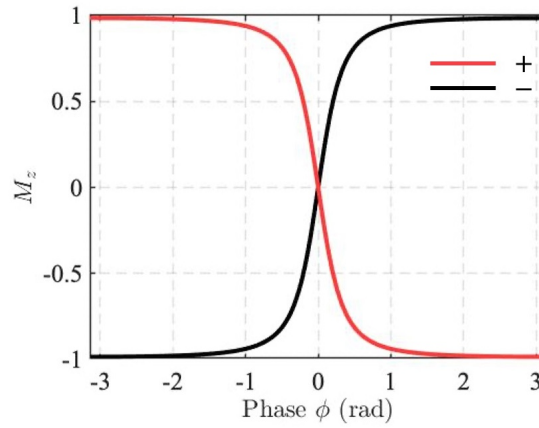


Figure 3.7: M_z as a function of ϕ , Equation 3.6. Depending on the sign in 3.6, the relationship between M_z and ϕ is plotted red and black curves

structural and perfusion radial imaging using ASL (CASPRIA)[60] shares the same sequence as CAPRIA, but further reconstructs structural images by taking the average of ASL label and control data. Note the name CAPRIA and CASPRIA can be used interchangeably in the thesis when referring to the sequence. CASPRIA will be used when structural images are reconstructed.

Each repeat of CAPRIA is composed of four consecutive modules as shown in Figure 3.8. The first module saturates the magnetization in the imaging region. The second module is the PCASL preparation, which alternates between tag or control in different repeats. Then an inversion pulse is applied that aims to suppress background signal in the imaging region during the readout train that follows. Each module will be introduced in detail in the following subsections.



Figure 3.8: Illustration of the CASPRIA sequence, with the spatial locations of each module. The Imaging region and pre-saturation slab cover the whole brain. The single inversion pulse also covers the whole head. The PCASL labeling plane is placed on the neck.

3.5.1 Pre-saturation module

The pre-saturation module followed the design of the water suppression enhanced through T1 effects (WET) module [61, 62]. As shown in Figure 3.9, the module is composed of 4 similar sections. For each, a slice selective excitation pulse is followed by a large spoiler gradient, where the area under the spoiler gradient

on each axis is $2k_{max}$. The 4 flip angles were numerically optimized to minimize the residual water magnetization for a range of T_1 and B_1 values appropriate for 3T ($400 \leq T_1 \leq 4200ms$, $\Delta B_1 \pm 10\%$). Spoiler gradient cycling among the 4 sections is used to avoid stimulated echoes.

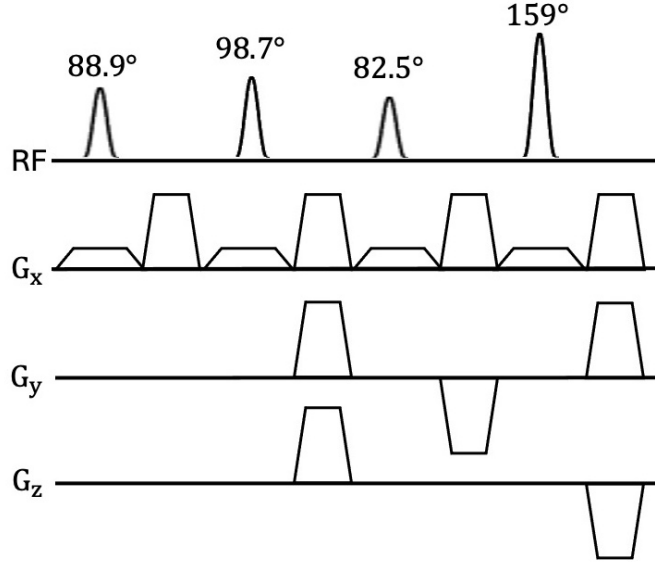


Figure 3.9: Water suppression enhanced through T1 effects (WET) used in CASPRIA sequence. The dephasing gradient has area equivalent to $2 \times k_{max}$.

3.5.2 PCASL

The gradients for the PCASL labeling and control conditions are kept the same, following the balanced PCASL approach [63]. The labeling duration in the CASPRIA sequence is $1.8s$. A Gaussian RF pulse with Hann window was used.

3.5.3 Single inversion pulse

The single inversion pulse was a hyperbolic secant [55] pulse, as shown in Figure 3.4. The single inversion pulse further suppresses the background tissue signal especially towards the end of the CAPRIA sequence to allow better SNR for perfusion signal. Figure 3.11 demonstrates the typical longitudinal magnetization evolution over time in grey matter, white matter and CSF.

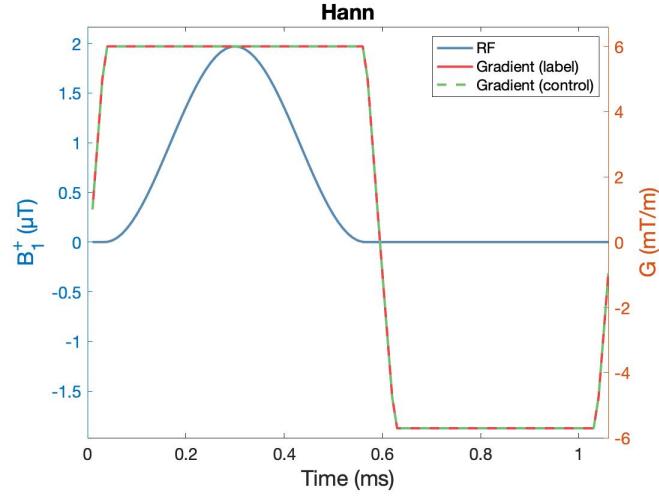


Figure 3.10: RF pulse and gradients used for PCASL.

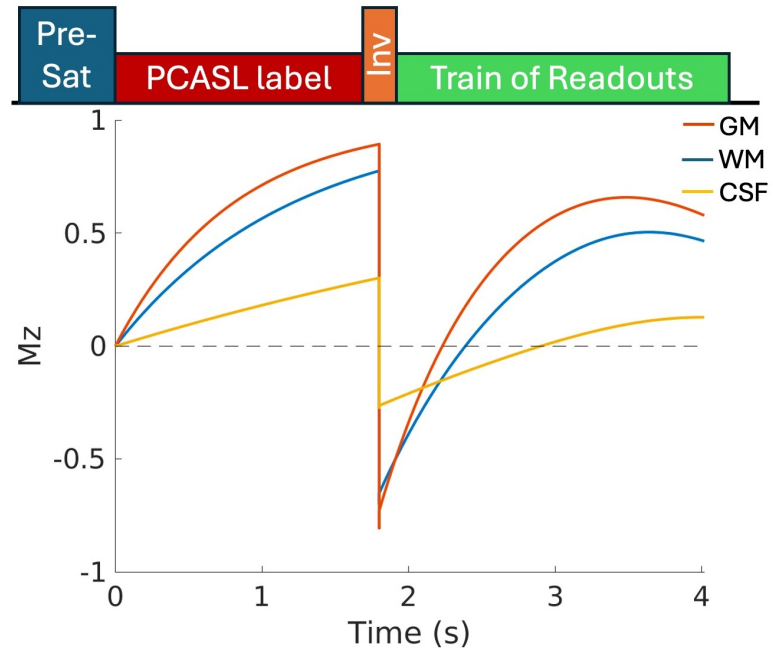


Figure 3.11: The longitudinal magnetization M_z in GM/WM/CSF during one repeat of CAPRIA sequence. The introduction of single inversion pulse suppresses the signal of static tissue in compensation for the signal recovery after pre-saturation.

3.5.4 Train of readouts

- **Excitation** As CASPRIA is a combined imaging sequence, and the perfusion and angiography signals peak in different periods during the train of readouts, a variable flip angle scheme was adopted to jointly maximize these signals at different times. The importance of flip angle selection lies at the contradiction between long train of acquisitions and low SNR of perfusion images. To be more specific, large flip angle can improve the limited SNR of perfusion signal while potentially attenuating the longitudinal magnetization and SNR of subsequent images and vice versa for small flip angles. The variable flip angle optimization followed previous literature [12] to maximize the mean angiographic signal when labeled blood was present and mean perfusion signal after all blood reaches the tissue.
- **Readout** We use GRE readouts in our sequence for full brain 3D acquisition. bSSFP readout, however, suffers from banding artifacts especially in large FOVs (like full brain) at 3T. Echo planar imaging (EPI) readout covering k-space with single long readout is also not suitable as it suffers from distortion and signal dropout [11]. Using a long train of readouts with radial trajectory improves the motion robustness and allows for flexibility in varying temporal and spatial resolution.

Gradient spoiling is standard in GRE readouts but, because radial/cone readouts point in different directions with each readout, a constant spoiler relative to the current projection might create unwanted echo formation due to accidental gradient rewinding. Therefore, for each projection, we rewind the data to k-space center and then spoil it in a consistent direction in the laboratory frame of reference. To be more specific, a rewinder trajectory reaches the k-space center with maximum gradient and slew rate. A constant spoiler gradient points to positive k_x direction and reaches $2k_{max}$ so that magnetization will not be accidentally moved to k-space center in later readout as cone trajectory can only reach k_{max} .

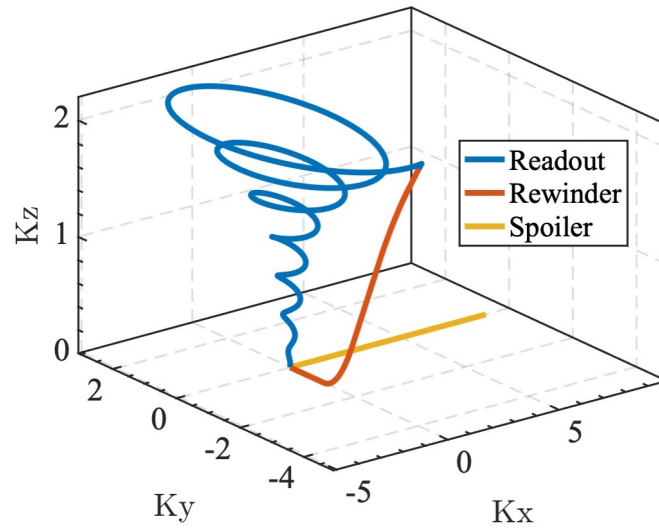


Figure 3.12: The base cone trajectory used in CASPRIA sequence. The rewinder starting from the end of readout cone trajectory and reaches the k-space center. The gradient spoiler stays constant in all readouts and points to positive k_x direction reaching $2k_{max}$ to prevent forming echoes in subsequent readouts.

4

Cone trajectory design for efficient k-space sampling

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4.1 Introduction

4D Combined Angiography and Perfusion using Radial Imaging and ASL (CAPRIA),[11, 12] provides a scheme to simultaneously map the dynamics of blood flow through the arteries and at the level of the brain tissue, enabling both sets of information to be obtained in a time-efficient manner. The sequence is capable of visualizing blood flowing through the arteries and into the tissue continuously in a single acquisition. Combined with golden ratio, images can also be reconstructed with variable spatiotemporal resolution, providing rich information of blood flow. Yet, the resolution and SNR of the images is constrained by the limited sampling efficiency of the radial trajectory used by the sequence, with poorer sampling density in the periphery of k-space and the requirement for many excitation pulses, which attenuate the ASL signal. Improved sampling density at the edges of k-space and increased k-space coverage per excitation are desirable to improve both spatial resolution and SNR. This will enable more accurate diagnosis with improved visualization of small distal vessels and subtle perfusion alterations and motivates our search for a more efficient k-space trajectory for CAPRIA that maintains its flexibility in spatiotemporal resolution.

In addition to radial trajectory, numerous other designs of 3D non-Cartesian trajectories have been proposed over the years. Stack-of-stars[64] and stack-of-spirals [65] were proposed to improve sampling efficiency but were anisotropic between slice and within slice. Stack-of-cones[24] was designed to uniformly cover k-space in a shorter total scan time than an equivalent Cartesian trajectory, while satisfying the Nyquist sampling theorem. Density adapted radial[65], variable density cones[66] and FLORET[67] are some variations of the radial and cone trajectory with improvements in sampling efficiency and uniformity. Other trajectories, such as radial-cones[68] and Seiffert spirals[69], focus on incoherent and relatively uniform sampling, but the Nyquist sampling theorem is no longer strictly enforced. Optimization-based trajectories like SPARKLING[26], PILOT[70] and SNOPY[71] are gaining more attention recently, but the optimal trajectory usually takes a time-consuming process to recalculate for specific scanning parameters.

To improve on 4D CAPRIA, we require a trajectory that: i) can be simultaneously optimized for both angiography and perfusion imaging; ii) samples a large region of k-space with each readout to minimize the number of excitation pulses required, and therefore the attenuation of the ASL signal; iii) has a short echo time to maximize SNR and minimize flow-based dephasing; iv) accommodates dynamic imaging with variable temporal resolution; and v) has different but comparable sampling patterns for each temporal frame that result in incoherent aliasing across time to enable the use of temporal regularization in the reconstruction. Unfortunately, although they have many desirable features, none of the trajectories outlined above satisfy all of these requirements. The anisotropic sampling of stack-of-cones creates difficulty in undersampling different temporal frames with comparable sampling patterns. Radial-cones specifies the direction of each shot with isotropically distributed radial directions, which is not suitable for varying the temporal resolution post-hoc. Additionally, the trajectory formulation does not provide a means of trading off the sampling density in peripheral and central k-space, which are more important for angiography and perfusion imaging, respectively.

In this work, we aimed to improve the spatial resolution and SNR for angiographic and perfusion images acquired with 4D CAPRIA. Taking inspiration from the radial-cones approach[68], we present an efficient and flexible two-stage parametric cone design that can be combined with golden ratio rotations around the k-space center to satisfy the trajectory requirements outlined above. The structural images reconstructed following 4D Combined Angiographic, Structural and Perfusion Radial Imaging using Arterial Spin Labeling (CASPRIA)[60] with severe off-resonance artifacts, for which we incorporated water excitation pulse. We then used numerical simulations and physical phantom scanning to optimize the cone shape parameters. The off-resonance artifacts were also simulated and compared between radial and cone trajectories. We performed in vivo scans with healthy volunteers to demonstrate the superior image quality obtained with our cone trajectory compared to the original radial approach.

4.2 Methods

4.2.1 Pulse Sequence Design

As illustrated in Figure 4.1, the original 4D CAPRIA method[12] consists of a pre-saturation module (to remove spin history effects and reduce static tissue signal), a pseudocontinuous ASL (PCASL)[57] labeling preparation (to label/control blood magnetization as it flows through a defined labeling plane in the neck) and a continuous golden ratio radial readout to image the blood as it traverses the arterial tree (allowing the generation of angiographic images) and exchanges into the tissue (yielding perfusion images). In this implementation, an additional inversion pulse is added to improve the suppression of static tissue signal, reducing physiological noise, as per[60]. The blood signal is isolated from static tissue signal by reconstructing from the subtraction of control and label data in k-space. High spatiotemporal resolution angiograms can be reconstructed using a small temporal window, giving a high undersampling factor ($\sim 50X$ undersampled) that can be tolerated due to the sparse and high SNR nature of the angiographic signal. Lower spatiotemporal resolution perfusion images can be reconstructed from the same raw data using a broader temporal window and only using the samples in a central region of k-space ($\sim 4X$ undersampled), improving the conditioning of the reconstruction for this weaker and less sparse signal. Variable flip angles are used in the train of readouts to reduce the signal attenuation from the initial excitation pulses and boost the perfusion signal at later timepoints.

CAPRIA relies on grouping readouts from multiple repeats for the reconstruction of both sets of images. In this work, we use the golden ratio ordering approach proposed by Song et al.[72, 73], incrementing the golden ratio rotations first across repeats and then across time, to maintain exact golden ratio ordering when grouping readouts across repeats for any temporal resolution. The original 3D radial approach is flexible, approximately isotropic, and motion robust, making it suitable for this application. However, the limited coverage of each radial spoke limits its k-space sampling efficiency.

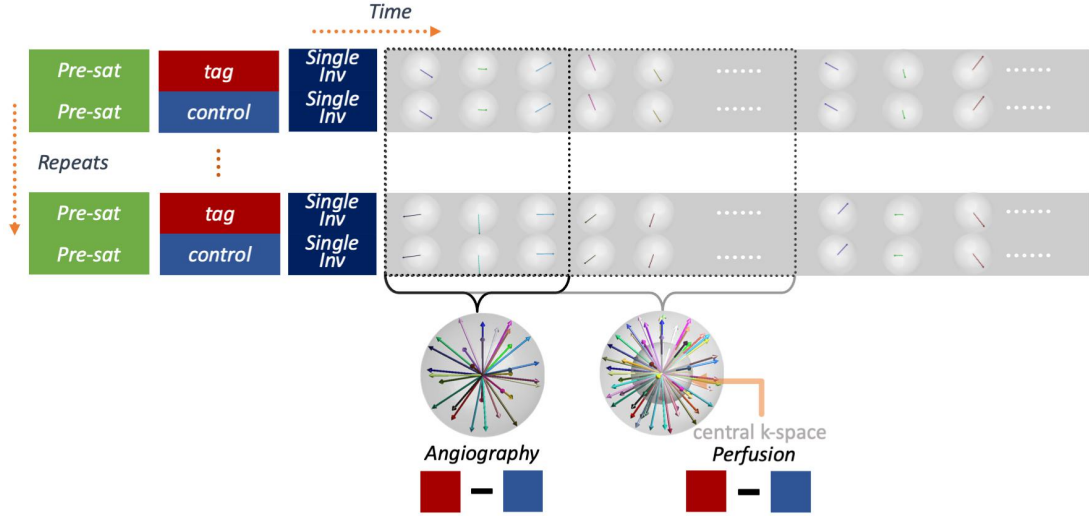


Figure 4.1: Schematic pulse sequence diagram. The preparation period (pre-saturation, pseudo-continuous ASL labeling and a slab-selective inversion pulse) is followed by a continuous golden ratio readout. The radial case is shown here, representing the original 4D CAPRIA approach, but the proposed cones case is similar, with each radial spoke replaced by a cone at the same orientation. Samples across all repeats can be flexibly combined across time with variable temporal resolution, whilst maintaining approximately uniform sampling. Examples for grouping one frame of angiography (high spatiotemporal resolution) and perfusion imaging (low spatiotemporal resolution, using only the central region of k-space) are illustrated using red and blue boxes, respectively.

4.2.2 Base cone trajectory design

Inspired by 3D cones trajectories[24, 66, 68], in this work each CAPRIA radial spoke is replaced by a cone to give a much broader coverage of k-space after each excitation pulse. The excellent sampling efficiency of the cone is integrated with the advantages of a 3D golden ratio radial trajectory, to improve the spatial resolution and SNR while keeping the temporal flexibility for dynamic imaging.

A two-stage parametric design is proposed that jointly considers the sampling density within central and peripheral regions, because: 1) angiographic reconstructions utilize the full k-space data, whereas perfusion reconstructions only use the central region of k-space; and 2) spending more time in central k-space could improve robustness against motion and other sources of signal variation, whereas more samples in peripheral k-space could help improve spatial resolution. This is done by combining a conventional cone shape with a fixed cone angle[24] for the central region of k-space (stage 1) with a cone whose cone angle increases with

the radial distance for the peripheral region of k-space, as in radial-cones[68](stage 2). The overall shapes of two parts for a base cone oriented along the k_z axis are described by Equation 4.1.

$$\vec{k}_\alpha = \begin{cases} \hat{k}_z k_{max} \cos(\theta)\alpha + (\hat{k}_x \cos(A\alpha) + \hat{k}_y \sin(A\alpha)) * m^{n-1} k_{max} \sin(\theta)\alpha, & 0 < \alpha \leq m \\ \hat{k}_z k_{max} \cos(\theta)\alpha + (\hat{k}_x \cos(A\alpha) + \hat{k}_y \sin(A\alpha)) * k_{max} \sin(\theta)\alpha^n, & m < \alpha \leq 1 \end{cases} \quad (4.1)$$

Where $\vec{k}$ represents the trajectory coordinates in 3D k-space; $\hat{k}_x$, $\hat{k}_y$, $\hat{k}_z$ are three orthogonal unit vectors; θ , m , n are three free parameters that enable adjustment for different sampling requirements: θ is the cone angle spanned by the endpoint of the trajectory and the central axis, m is the separation point for the two parts, and n controls the curvature for the cone trajectory (as shown in Figure 4.2c); α describes the relative position along the trajectory; and A is a scaling factor to accommodate an arbitrary trajectory duration and gradient hardware limitations. Example trajectories with various parameter choices are shown in Figure 4.3b,c.

Once θ , m , n and the readout duration have been chosen, the gradient waveforms and k-space samples for a given system performance (maximum gradient amplitude and slew rate) can be solved using a constrained optimization, as in Lustig et al.[25]. In our trajectory, the maximum gradient amplitude and slew rate were limited empirically ($G_max=11.64$ mT / m , $S_max=61.54$ T/ m/s) to reduce peripheral nerve stimulation and minimize the impact of gradient imperfections, while still being sufficient to cover the required k-space trajectory.

4.2.3 Cone rotations

Given a single base cone trajectory (referred to as one shot below), the base shape can be rotated around the k-space center to cover the sphere of k-space to be sampled. As illustrated in Figure 4.2c,d, the central axis is first rotated using the 3D golden ratio [20]. The cone is further rotated around its central axis by an additional random angle. This random rotation provides sufficient incoherency

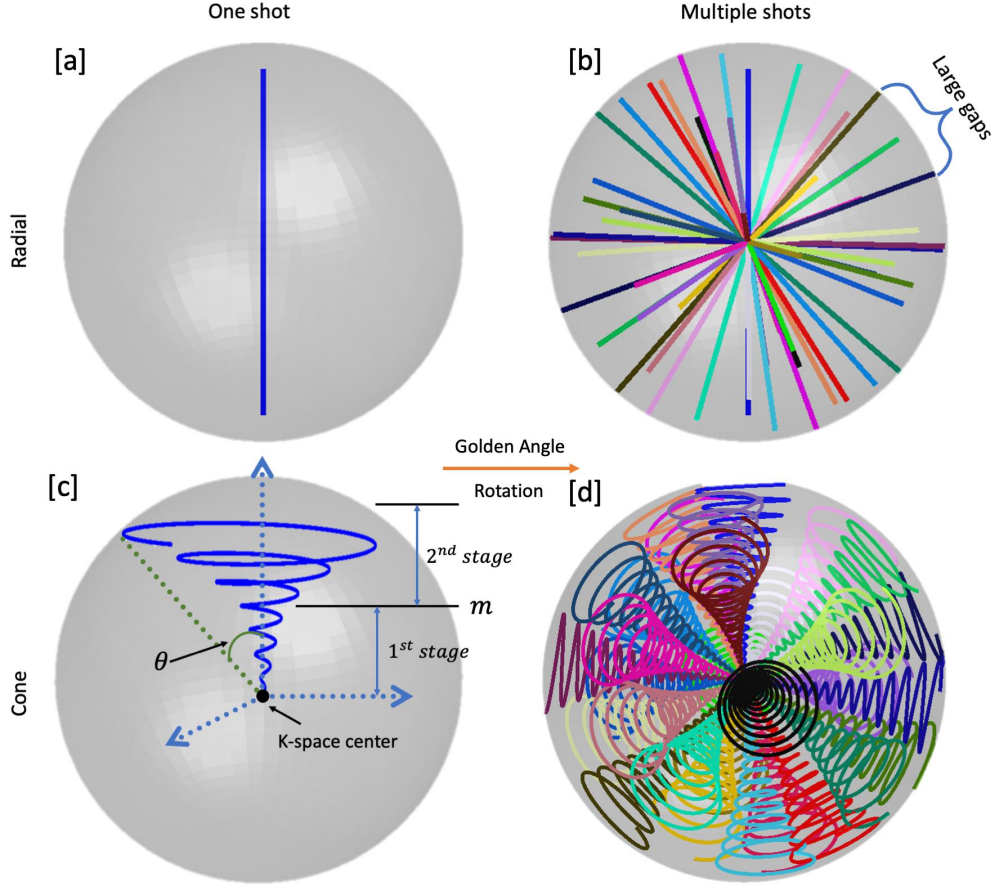


Figure 4.2: Design of the cone trajectory and the rotation scheme. Exemplary single radial spoke used in the original 4D CAPRIA is plotted in [a]. [a] demonstrates 30 radial spokes, each rotated using the 3D golden ratio relative to the previous spoke. Our cone design is detailed in [c], with shape control parameters cone angle θ , two-stage separation m in the plot. [d] is obtained by replacing the radial spokes in [a,b] by the cone trajectory in [c]. The comparison between [b] and [d] emphasizes the advantages of cone trajectory in terms of sampling efficiency and k-space coverage, particularly in the periphery.

and uniformity without loss of flexibility for altering the total number of shots as shown in Figure 4.3d. The golden ratio approach specifies a series of sequential acquisition directions so that any set of readouts with contiguous golden ratio ordering covers k-space approximately uniformly.

4.2.4 Optimization of cone parameters

Unlike numerically optimized approaches, the proposed trajectory has only a few free parameters that need to be optimized. In preliminary experiments it was found that metrics derived from numerical simulations alone could only partially

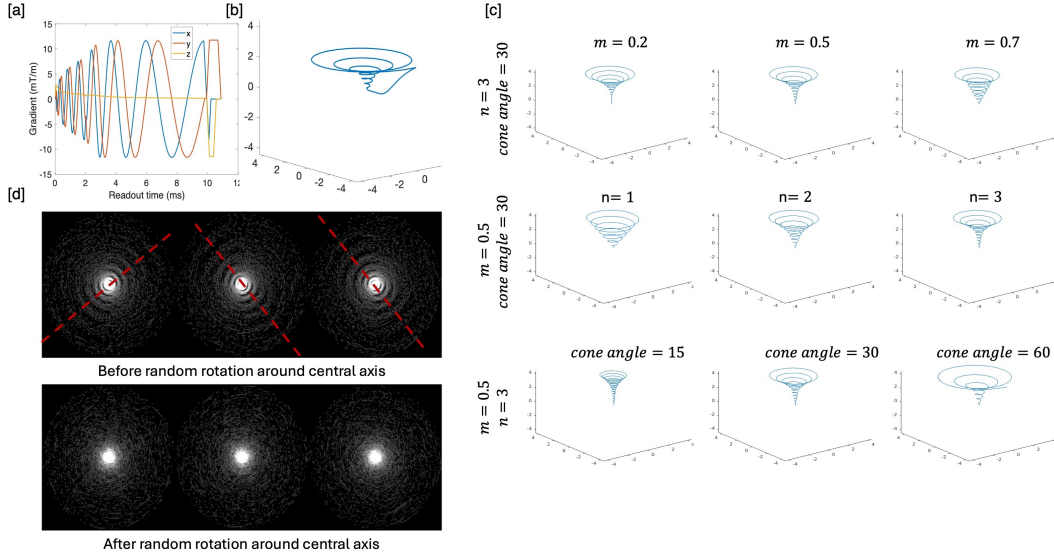


Figure 4.3: [a] Example gradient waveforms. [b] corresponding trajectory in k-space. [c] The effect of varying the free parameters in the proposed cone design on the trajectory shape. Fixed parameters are displayed on the left of each row, then variation in one other parameter is shown: m (top row), n (middle row) and the cone angle, θ (bottom row). [d] The cone trajectory formed some large gaps in k-space as indicated by the diagonal red lines, which can be addressed with random rotations around each of their central axis.

capture the imaging performance in real experiments due to complex interactions between signal attenuation, aliasing patterns, spatial resolution and robustness to real-world off-resonance effects and signal variations. Therefore, the free trajectory parameters were jointly optimized based on the results of numerical simulations and phantom scanning, utilizing the efficiency of numerical simulations and fidelity of physical phantom scans.

First, a wide range of parameters m , n , θ and readout time were simulated and compared. Using these simulations, the candidate parameter values were narrowed down to a smaller set of combinations, which were then further investigated with phantom scans to explore the behavior of the different trajectories under the effects of eddy-currents, off-resonance, and signal variability.

4.2.5 Numerical simulations

For simulation experiments of cone trajectory optimization, we simulated a single acquisition frame for both angiographic and perfusion images. The use of Song

ordering[73] and Golden ratio angle increments[20] mean that subsequent frames would have similar properties once the trajectory for single frame was optimized. A previously acquired high quality angiography image[74] and a simulated perfusion phantom[75] were used as the ground truth for all trajectories. Coil sensitivity was assumed to be uniform in numerical simulation for simplicity, while the effect of inhomogeneous coil sensitivity profiles is included in the phantom scanning below. The reconstructed spatial resolution was 1.13 mm and 3.39 mm isotropic for angiography and perfusion images, respectively. The number of repeats in sequence was fixed to 48 in all experiments, so the total number of shots is dependent on the temporal window of each binned frame. Perfusion images were reconstructed using all shots but only the central region of k -space (up to $\frac{1}{3}k_{\max}$). Angiographic images used the full k -space trajectory, but only half the temporal window (half of the shots). The numerical ground truth of both modalities is shown in Figure 4.4.

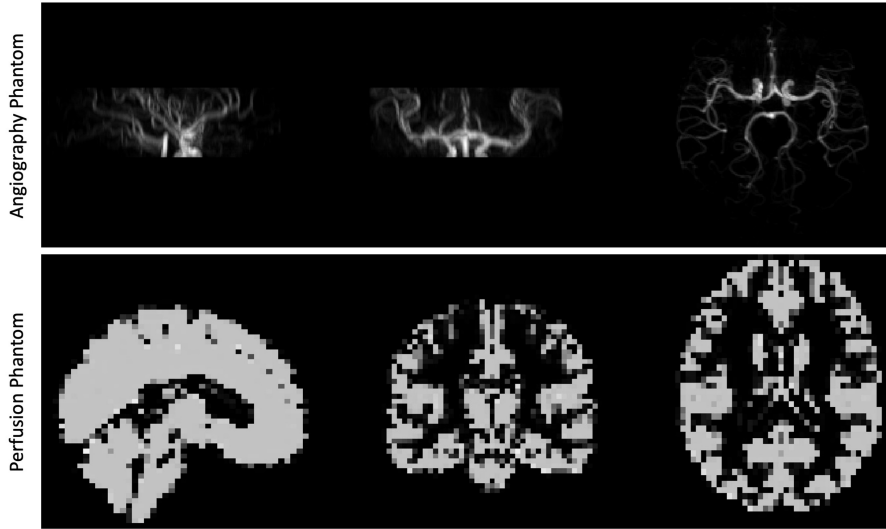


Figure 4.4: Numerical phantoms for angiography (shown as maximum intensity projections, top) and perfusion imaging (example slices in all three planes, bottom) that were used for simulation experiments.

The range of cone parameters used in simulations were as follows:

- The power term n : 1, 2 or 3.
- The separation point m for the two-stage design: 0 (i.e., single stage) or 0.5 (i.e., two-stage, transition of cone shape halfway through the trajectory)

- the cone angle θ : 15°, 30°, 45°, 60° or 75°

As resulting trajectory would not vary greatly with slight change of parameters, discrete values were tested in experiments.

Three metrics were calculated for comparison, each characterizing different aspects of the trajectory in this highly undersampled case:

- Full width half maximum (FWHM): characterizes the spatial resolution by measuring the width of the central peak of the point spread function (PSF)
- Effective SNR: characterizes how the thermal noise in the acquisition is transformed into noise in the output image. The pseudo-replica method[76] was used, such that multiple images were reconstructed from the same k-space data with additional random Gaussian noise. The standard deviation of each pixel from all reconstructed images was taken as the “noise” and the mean value as the *signal*. *SNR* was calculated as the total power of signal divided by the total power of noise within a foreground mask (where the ground truth image had non-zero intensity). Since spatial resolution also affects SNR, this effect was compensated by dividing the calculated “SNR” with the product of the FWHM in three orthogonal planes (approximating the true voxel volume).
- Signal to aliasing power ratio (SAPR). This metric evaluates non-Cartesian artifacts in the background relative to the signal in the foreground. In numerical simulation, the average power of the reconstructed image I within foreground mask M_f (where the ground truth image has non-zero intensity) was divided by that within a background mask M_b (voxels not included in the foreground). N_f , N_b represent the number of voxels within foreground and background masks, respectively.

$$SAPR = \frac{\sum \|I * M_f\|^2 / N_f}{\sum \|I * M_b\|^2 / N_b} \quad (4.2)$$

4.2.6 Experiments: Physical phantom acquisition

Following on from the numerical simulations, in the physical phantom scans m and n were fixed to 0.5 and 3 respectively, and the effect of the cone angle θ and readout time were further investigated within the following ranges:

- The cone angle ϕ : 30° , 45° and 60°
- The readout time: 6.6 ms , 8 ms and 10 ms

A quality assurance phantom (GE DQA Phantom; GE Healthcare) was used to visualize spatial resolution changes and artifacts caused by the interaction of signal variations with different non-Cartesian sampling patterns. Additionally, only a single frame was acquired, reconstructed, and analyzed using the density compensated adjoint NUFFT because the temporal stability of the trajectory ensured by the 3D golden ratio means that subsequent frames would have similar properties. SNR was also calculated in specific regions within the reconstructed images. A foreground mask was first extracted from the radial result by thresholding at 10% of maximum intensity. All voxels not included in the mask were considered as background. The same mask was used to calculate SNR for all trajectories. Note, in physical phantom scanning, we aimed to evaluate the more general performance of different trajectories in a more realistic environment. Hence, we extended the SNR calculation to include the noise-like artifacts due to undersampling.

4.2.7 Experiments: In-vivo scanning protocol

Based on the numerical simulation and phantom experiments, a combination of the 4 parameters (m , n , θ , *readout time*) was selected that resulted in high SNR and spatial resolution and few artifacts (see Results section). These parameters were used for the cone trajectory in vivo with 4D CAPRIA.

To assess the proposed cone trajectory, it was compared with radial trajectories using two different protocols: the first was a protocol optimized in a previous study [12](referred to as optimal radial protocol) while the other matched the

TR and flip angle schedule of the cone protocol (referred to as matched radial protocol), to ensure any differences seen were not attributed solely to the changes in these other parameters. In total, 8 subjects (age range 25-35) were scanned on a 3T Prisma scanner (Siemens Healthineers, Erlangen, Germany) using a 32-channel receive-only head coil under a technical development protocol agreed by local ethics and institutional committees.

A quadratically varying flip angle scheme was separately optimized for the different protocols using the same method as the original 4D CAPRIA sequence[12]. For the optimal radial protocol, the flip angles ranged between $2^\circ - 9^\circ$. For both the matched radial protocol and the cone protocol, the flip angles ranged between $3^\circ - 12^\circ$. The temporal resolution used to reconstruct perfusion and angiographic images was 352.8 ms and 176.4 ms , respectively. Note that the total time for all readouts after each ASL labeling module (2116.8 ms) as well as the total scan time ($6\text{ min } 12\text{ s}$) were kept consistent between different protocols for a fair comparison. The PCASL pulse design was kept same among all three protocols. Details of parameters for balanced PCASL and readouts were listed in Table 4.1.

The FOV for the 8 healthy subjects were 200mm^3 , and the spatial resolution for perfusion and angiographic images were 3.37mm and 1.12mm respectively. To demonstrate the potential of the cone trajectory, an additional protocol with higher spatial resolution was acquired for 1 more subject. The cone parameters were kept the same as those used in "cone protocol". The spatial resolution for perfusion and angiography images were 2.34mm and 0.78mm respectively. As the k_{max} increases with the spatial resolution, the maximum gradient and slew rate were also increased to $G_{max} = 22\text{mT/m}$, $S_{max} = 120\text{T/m/s}$ so that the cone trajectory scales proportionally.

Coil compression[77] was performed, reducing the original 32 channel data to 8 channels for reconstruction. Coil sensitivity maps were estimated from a pseudo-structural image (reconstructed by regridding averaged label and control data from the final 352.8 ms of the readout where the static tissue signal is more consistent)

Parameters \ Protocols		Optimal radial	Matched radial	Cone (Ours)
Label	Labeling duration	1.8s		
	RF pulse type	Gaussian		
	RF flip angle	20°		
	RF pulse duration	500 μ s		
	RF pulse separation	1000 μ s		
	Mean tagging gradient	0.8mT/m		
	Tagging gradient	6mT/m		
Readout	Flip angle	2 – 9°	3 – 12°	3 – 12°
	readout time	6.6ms	10ms	10ms
	TR	9.8ms	14.7ms	14.7ms
	TE	4.56ms	6.26ms	1.35ms
	# of readouts per repeat	216	144	144
	# of repeats	96	96	96
	Acquisition time	6min12s	6min12s	6min12s

Table 4.1: Acquisition parameters for the three different in vivo protocols.

using the adaptive combine method[78]. K-space data were multiplied by a Hann window prior to reconstruction to reduce undersampling artifacts.

A T₁-weighted MPRAGE image with 1.5 mm isotropic resolution was acquired for each subject for analysis (described below).

4.2.8 Image reconstruction

In numerical simulation and phantom scanning, the adjoint NUFFT[79] was used to reconstruct every image for a faithful reflection of the SNR and spatial resolution using different sampling patterns.

For in vivo data, preliminary work showed that subtraction of separately reconstructed label and control images resulted in noisy blood signal, particularly at long PLDs due to the attenuated signal intensity and gradually recovering static tissue which contributes more physiological noise. The use of magnitude subtraction as a post-processing step to isolate the blood signal could also cause difficulties with

inverted static tissue passing through its null point during the readout. Instead, complex k-space subtraction was performed before reconstruction, and a locally low rank (LLR) regularization[36] was used to exploit the spatiotemporal redundancy in the difference data across all frames and the complementary sampling at different time points (Equation 4.3), in a similar manner to previous work[12]:

$$x = \underset{x}{\operatorname{argmin}} \|PFCx - y\|_2 + \lambda \cdot \sum_i \|R_i x\|_* \quad (4.3)$$

Where x is the image to reconstruct, y is the difference data of label and control in k-space, P is the sampling mask, F is the Fourier encoding matrix, C are the coil sensitivity maps, λ is a regularization factor and R_i is the operator extracting each patch (indexed by i) from each frame. The patch size and regularization parameter were chosen empirically: $\lambda = 10^{-1}$ and patch size $5 \times 5 \times 5$. Aligned with CAPRIA[12], angiography was reconstructed from the full k-space data, whereas perfusion was reconstructed from central k-space data with a cut-off frequency at $1/3 k_{max}$. The threshold was empirically chosen to match the typical spatial resolution of perfusion images.

All reconstruction was implemented with MATLAB 2021a (Mathworks, Natick, MA). Running on a 12 core CPU (AMD Opteron(tm) Processor 6328), the reconstruction time for perfusion and angiography images was ~40min and ~6h respectively.

4.2.9 Mean repeatability calculation

For in vivo experiments, a repeatability metric was calculated to report the scan-rescan stability. Specifically, each subject was scanned using the three protocols described above, with each protocol being repeated twice back-to-back to minimize motion or other signal variation between repeated scans. Note that the conventional SNR metric was not evaluated as undersampling artifacts resemble noise after non-linear reconstruction.

To minimize the impact of relative motion between repeated scans, a pseudo-structural image was reconstructed for each scan by taking the mean of label and

control signals, which were then registered to the MPRAGE image using affine registration (FSL's FLIRT[80]). The same linear transformation was then applied to angiography and perfusion images. We then followed the steps described in Okell et al.[12] to calculate scan-rescan repeatability for angiography and perfusion images separately. The results were Fisher transformed prior to performing the multi-way ANOVA on the group level with all 8 subjects to determine whether differences due to trajectory, timepoint or subject were significant.

4.3 Results

4.3.1 Numerical simulations

Quantitative results from the numerical simulations used to optimize the cone trajectory are shown in Figure 4.5. For brevity, only the most important metrics (FWHM and effective SNR) are displayed for angiographic (full k -space, temporal resolution of 176.4 ms) and perfusion (central k -space with radius $1/3\text{ }k_{\text{max}}$, temporal resolution of 352.8 ms) reconstructions, with the rest of the metrics and comparisons shown in Figures 4.6,4.7. In Figure 4.5a-b, our two-stage design ($m = 0.5$) is compared with the single-stage design ($m = 0$), similar to radial cones[68]. Despite some variations across different cone angles θ , the two-stage design ($m = 0.5$) consistently outperformed the single-stage design ($m = 0$) for both angiographic and perfusion reconstructions, in terms of spatial resolution and SNR. Similar results were obtained using readout times of 8 ms and 6.6 ms (see Figures 4.6,4.7).

When varying the parameter (n) that controls the curvature of the cone trajectory (Figure 4.5c-d), both the FWHM and the effective SNR fluctuate across different cone angles, but the trajectory generally performs best when $n = 3$. Both FWHM and effective SNR metrics are optimal at a cone angle of around $30 \sim 60^\circ$ in the case of angiography, with a weaker dependence for perfusion imaging. Note that the small perturbation in these metrics across different parameter choices depends on the complex interactions and overlap between neighboring cones, so there are no simple monotonic relationships here. A combination of $m = 0.5$ and $n = 3$ was

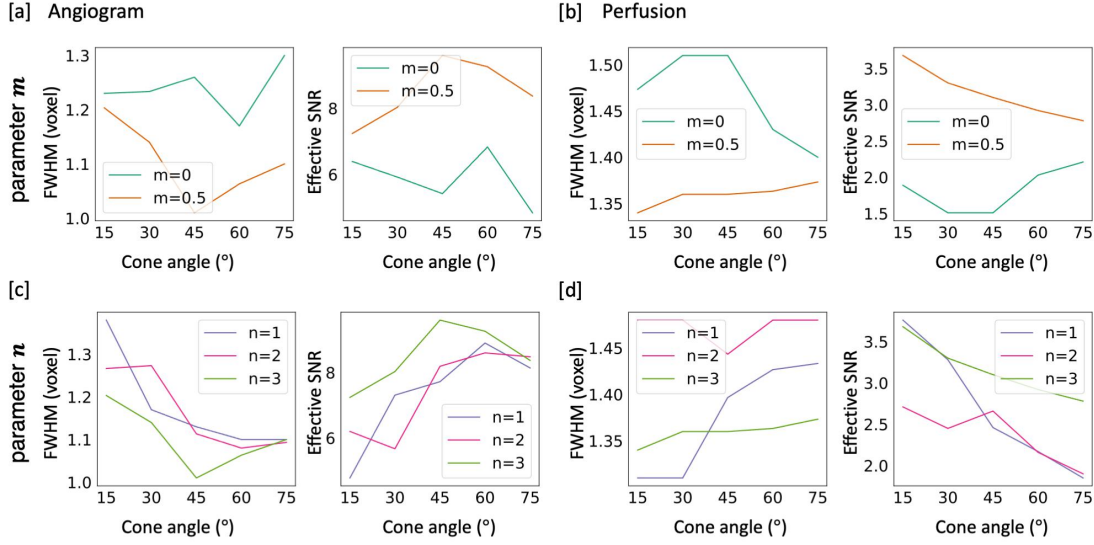


Figure 4.5: Representative numerical simulations for determining m and n in the cone design. In [a, b], readout time was fixed to 10 ms and n was fixed to 3. In [c, d] readout time was fixed to 10 ms and m was fixed to 0.5. [a], Simulation of angiography images to compare different selections of m on a range of cone angles. [b], Simulation of perfusion images using the same set of trajectories as [a]. Note that two-stage option $m=0.5$ surpassed the conventional single stage design ($m=0$) in resolution and SNR for both modalities regardless of cone angles. [c, d] Simulation for the effects of parameter n on angiography and perfusion images respectively, demonstrating that $n=3$ generally results in better spatial resolution and effective SNR. For angiography [a, c], the cone trajectory achieves the best resolution and effective SNR when the cone angle falls within the range $30^\circ \sim 60^\circ$. For perfusion imaging [a], these metrics do not have a strong cone angle dependence (note the y-axis scaling)

chosen based on these numerical simulation results to narrow down the parameter space to be investigated using a physical phantom.

4.3.2 Phantom scanning

Representative results of phantom scanning are shown in Figure 4.8, with the remaining comparisons in Figure 4.9, 4.10. Figure 4.8a shows the comparison between radial and cone trajectories with cone angles of 30° and 60° . Consistent with numerical simulations, the radial images are much blurrier than the cone images, due to the sparser sampling of peripheral k-space. In addition, radial trajectory produced coherent streaking artifacts (indicated with the red arrow). 60° cone trajectory, however, generated images with better discernable thin structures (pointed by the blue arrows) and superior SNR (zoomed in regions) compared

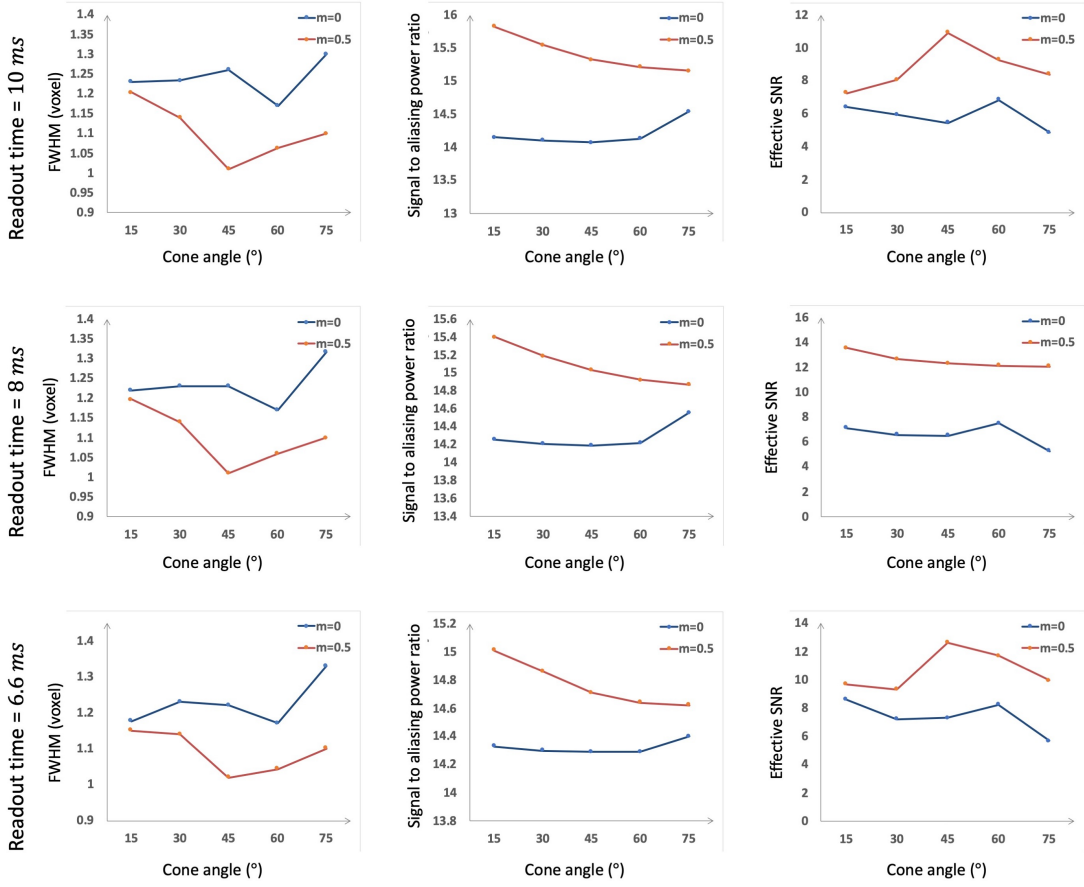


Figure 4.6: Numerical simulations for angiographic imaging, showing variation in PSF FWHM (left), signal to aliasing power ratio (middle) and effective SNR (right) with variable readout times (top to bottom), m values and cone angles. In these simulations, n was fixed at 3.

with 30° cone and radial trajectories.

In Figure 4.8b, the cone angle is fixed to 60° while the readout time is varied. The comb-like structure pointed to by the green arrow further confirms the improved resolution using the proposed cone trajectory. Here, the SNR of cone trajectory with longer readout time surpassed that of shorter readout times, while the best SNR of radial trajectory was mainly attributed to its intrinsic smoothing with the wider point spread function.

Combining the results of the numerical simulation and the physical phantom scanning, using a cone trajectory with a larger cone angle (60°) helps improve spatial resolution and reduce background signal due to aliasing. A longer readout time is also favorable for reducing artifacts and has the additional advantage that

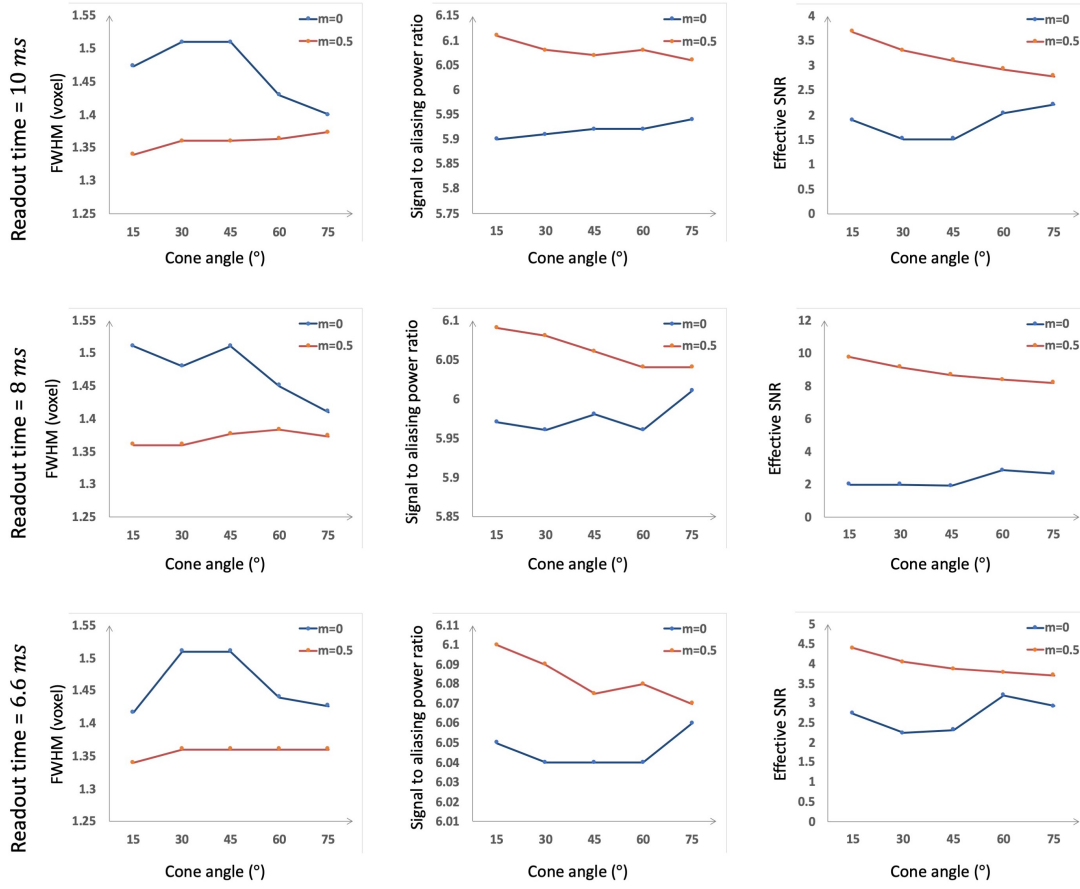


Figure 4.7: Numerical simulations for perfusion imaging, laid out as in Figure 4.6

fewer excitations are required after each ASL preparation, reducing the attenuation of the ASL signal and allowing higher flip angles to be used to further increase the SNR. Two factors prevent us from choosing a very long readout time. Firstly, the undersampling factor could be too high to compensate from longer readout time when the TR is too long, as we need to keep the total readout time after each labeling module fixed. Reducing the number of shots could also increase the anisotropy of the binned k-space coverage. Secondly, off-resonance issues become more prominent with longer readouts. Therefore, in this work, a combination of 10 *ms* readout time with 60° cone angle was chosen for the in-vivo acquisition. The corresponding effective spatial resolution for angiography and perfusion was 1.19 mm and 4.62 mm (nominal spatial resolution multiplied by FWHM of PSF) respectively, although it is likely this is a conservative estimate for in vivo data where the LLR reconstruction used in this study combines information across time in a data-dependent way.

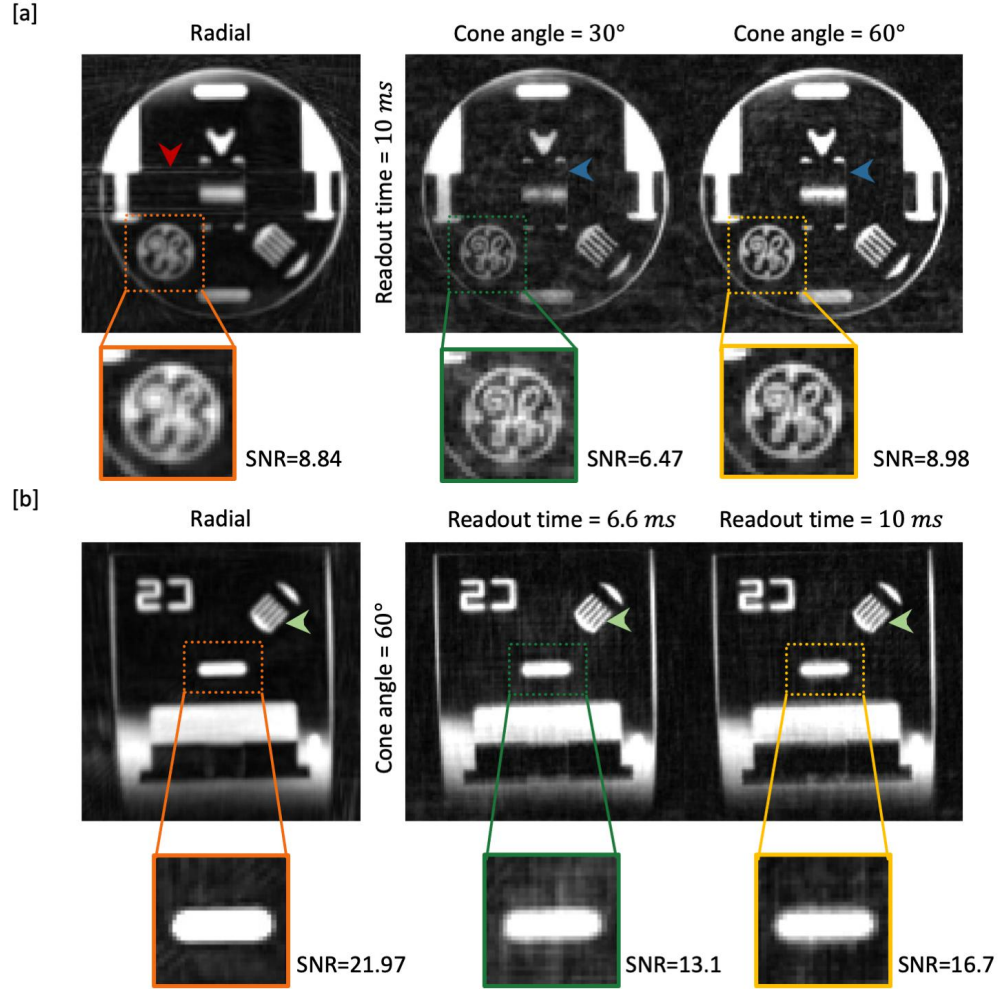


Figure 4.8: Comparison of a physical phantom scanned with different protocols and reconstructed with a density compensated adjoint NUFFT. [a] Here the readout time was fixed to 10 ms while the cone angle was varied between 30° – 60° . Undersampling in the radial trajectory resulted in coherent streaking artefacts (red arrow), whereas in the cone trajectories aliasing was more noise like, but less prominent in the 60° cone design, allowing fine details to be visualized (blue arrows). [b] Here the cone angle was fixed to 60° while the readout time varied between 6.6 ms ~ 10 ms. The improved visualization of thin structures demonstrated the better spatial resolution of both cone protocols compared to radial (green arrows). Among the cone protocols, the lowest level of background artefacts was achieved when the readout time was 10 ms and the cone angle was 60° . More examples are given in Figures 4.9,4.10 The SNR was also reported on the zoomed in patches. A foreground mask was first extracted from the radial result by thresholding at 10% of maximum intensity. All voxels not included in the mask were considered as background. The same mask was used to calculate SNR on all trajectories in [a] and [b] respectively.

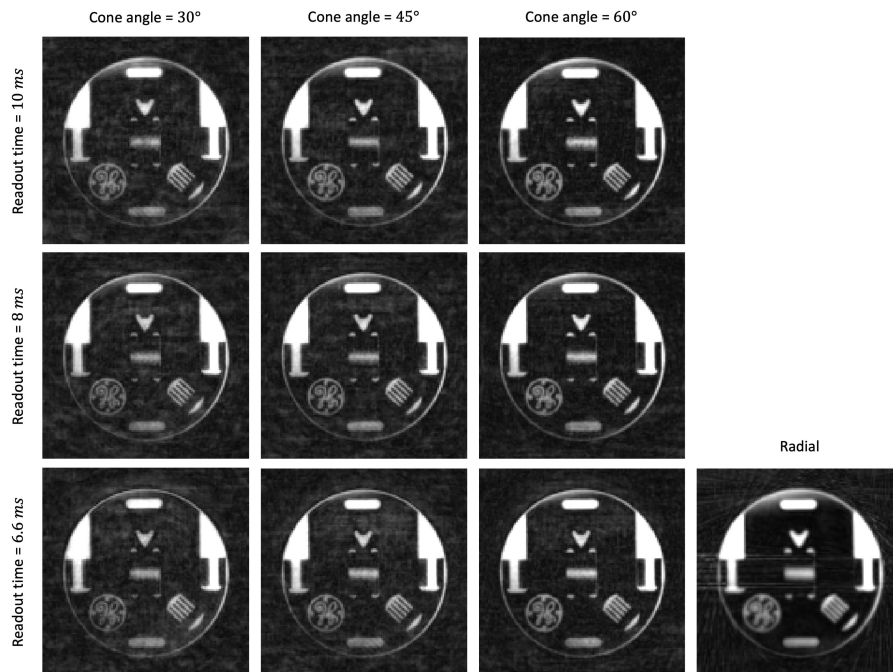


Figure 4.9: Physical phantom comparison, view #1.

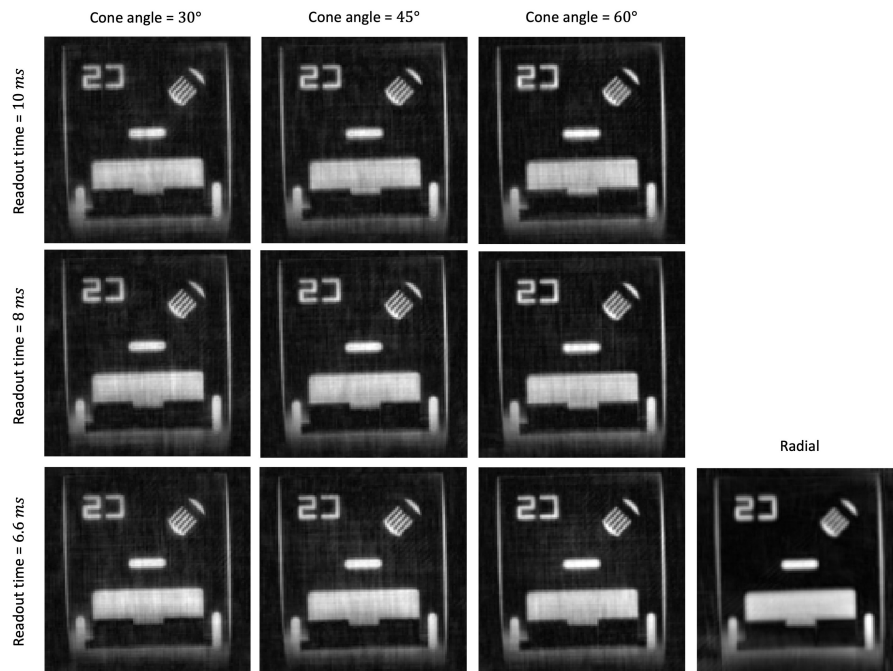


Figure 4.10: Physical phantom comparison, view #2.

4.3.3 In-vivo perfusion results

Figure 4.11 presents a comparison of in vivo perfusion images acquired using radial and cone trajectories in one subject. Figure 4.11a compares the proposed cone protocol (readout time 10 ms , flip angles 3-12°) with the previously optimized radial protocol[12] (readout time 6.6 ms , flip angles 2-9°) as well as a radial protocol with a readout time and flip angle schedule matched to that of the cone protocol (readout time 10 ms , flip angles 3-12°). Qualitatively, the cone trajectory demonstrated considerable improvement in visualizing fine tissue structures, whereas the radial results suffered from blurring that obscured some of these details. In the case of radial trajectory, the matched protocol with a longer TR and fewer spokes tended to yield more pronounced blurriness due to the limited peripheral k -space coverage and more T2* decay.

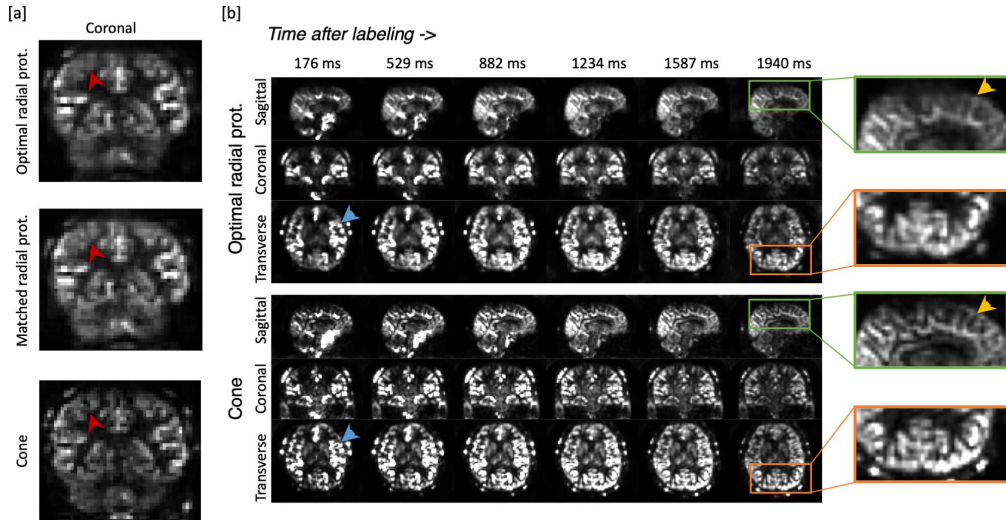


Figure 4.11: Example perfusion images acquired using different trajectories. [a], Coronal slice of an example frame for each of the three protocols, demonstrating the improved spatial resolution achieved with the proposed cone trajectory (red arrowhead). [b], Comparison between the proposed cone trajectory and the better-performing radial trajectory (using *the optimal radial protocol*[12]) showing example sagittal, coronal and transverse slices for all six frames. The displaying window of each frame is rescaled to its maximum intensity for better clarity. Zoomed sections again demonstrate the improved spatial resolution achievable with the cones approach.

Figure 4.11b compares radial and cone data across all the time points in multiple orientations. The initial timepoints showed the clustering of high-intensity signals,

which could be attributed to the presence of labeled blood within vessels. Specifically, vessels marked by the blue arrow exhibited clear contours in the cone trajectory results, whereas the radial counterparts displayed noticeable blurring. The final frame corresponds to a typical Post-Labeling Delay (PLD) used in single timepoint protocols[81], where large vessel signal is generally absent in healthy volunteers. Enlarged regions in the green and orange boxes highlight resolution improvements also in this perfusion-weighted signal using the cone trajectory.

Figure 4.12 shows the comparison between the perfusion images acquired by the cone trajectory design at different spatial resolution. The perfusion images at $2.34mm$ resolution showed much better visibility of tissue structures than the original spatial resolution.

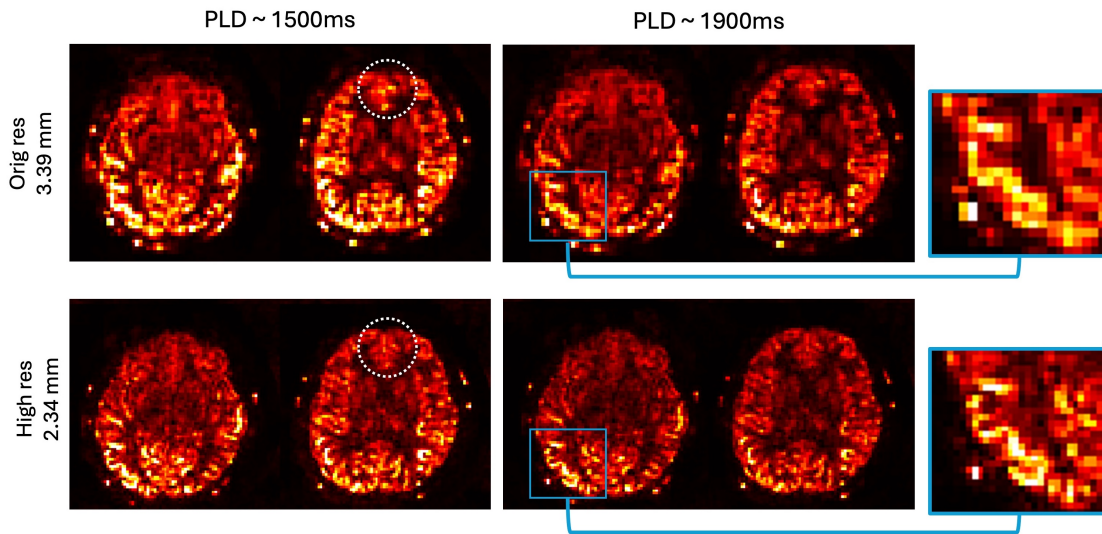


Figure 4.12: Comparison of perfusion images acquired at $2.34mm$ and $3.39mm$. The higher resolution improved the discernibility of the tissue perfusion, as marked out by white circles and blue boxes.

4.3.4 In-vivo angiography results

Figure 4.16 presents a visual comparison of in-vivo angiography results obtained from the same raw datasets as the aforementioned perfusion images, albeit reconstructed at a higher spatial and temporal resolution. Because of the long labeling duration ($1.8s$), the labeled blood has already filled the vasculature before the first readout.

So the dynamic angiogram shown throughout the thesis acquired by CAPRIA all show "out-flow" of blood.

In Figure 4.16a, three illustrative transverse view maximum intensity projections acquired with the three different protocols are presented. Clear vessel delineation was achieved in all cases with clean subtraction of background tissue. However, focusing on the vessels highlighted by the red arrow, the cone protocol provided a much better visualization of the small distal vessels due to its improved spatial resolution resulting from the better coverage of peripheral k-space. Of the two radial protocols, it is evident that the radial trajectory with TR matched to the cone protocol yields marginally blurrier outcomes compared to the radial trajectory with the previously optimized protocol, which is expected due to the smaller number of spokes acquired. Notably, the vessel's sharpness, indicated by the blue arrow, is diminished in the former.

To facilitate clarity, the comparison between the cone trajectory and the optimal radial protocol is presented in Figure 4.16b, showcasing three exemplary frames for each protocol in all three views. The advantage of the cone trajectory lies in the enhanced visualization of distal vessels with sharper contours, consequently improving the diagnostic and vessel-related analysis capabilities. In the orange box, particularly within the region enclosed by the yellow circle, a conspicuous disparity emerges: the radial approach fails to preserve signal intensity within some segments of the proximal arteries, likely attributed to signal dephasing due to B_0 inhomogeneity and/or flow effects. In contrast, the cone trajectory has less signal loss, thanks to its center-out design and substantially shorter echo time.

The full time-series of angiography acquired with three protocols are also provided. Figure 4.13, 4.14 show the baseline upon which Figure 4.15 shows clear improvement in both the richness and sharpness of the vascular tree.

Finally, the angiography images acquired with same cone trajectory design but scaled to higher spatial resolution were shown in Figure 4.17. As demonstrated in the zoomed in red boxes, the vessels clustered in the original $1.13mm$ resolution can be visually separated in the higher $0.78mm$ resolution without notable loss of SNR.

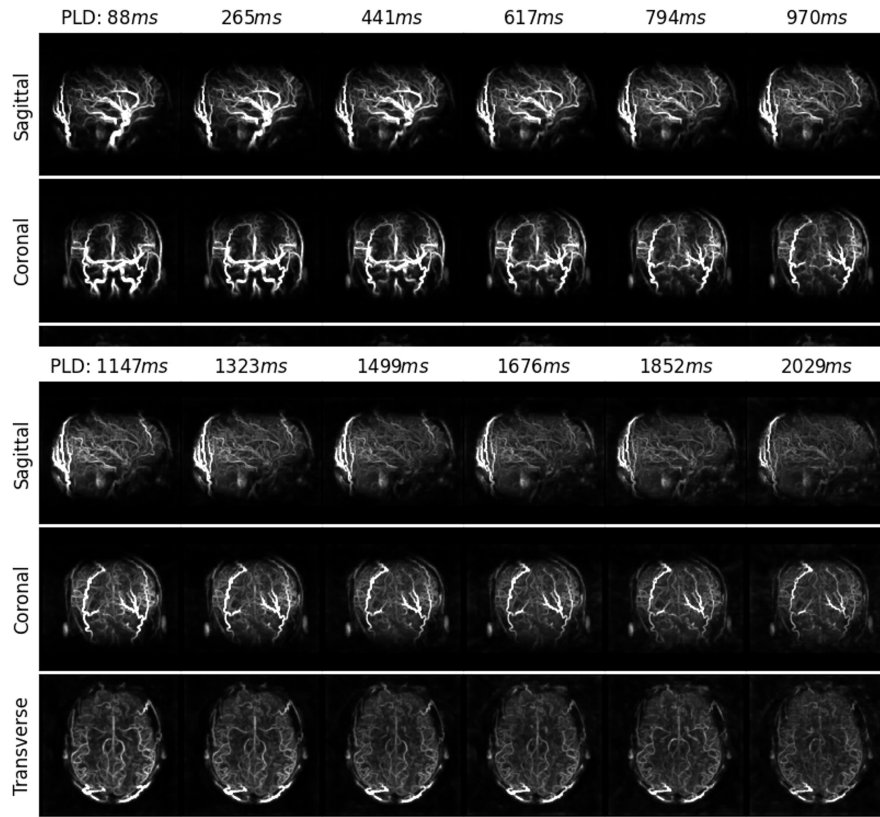


Figure 4.13: All reconstructed angiography frames in one subject acquired with the 4D CAPRIA protocol using a radial trajectory.

4.3.5 Quantitative comparisons

The quantitative repeatability evaluation of the perfusion images is presented in Figure 4.18a. The observed trend in repeatability follows a gradual decline as the post-labeling delay increases, reflecting the signal's natural attenuation after labeling. In agreement with the visual comparisons in Figure 4.11, the cone trajectory was more repeatable than the two radial trajectories. Similar result for the angiographic images is shown in Figure 4.18b. Given the considerably stronger angiography signal compared to perfusion, the absolute values of scan repeatability were inherently higher. In both radial trajectories' results, repeatability declined quickly as frames progressed. In contrast, the cone trajectory maintained a relatively higher repeatability across frames. The consistency further substantiates the robustness and reliability of our proposed cone design. The significance for the cone trajectory improvement was confirmed by multi-way ANOVA test ($p < 0.001$).

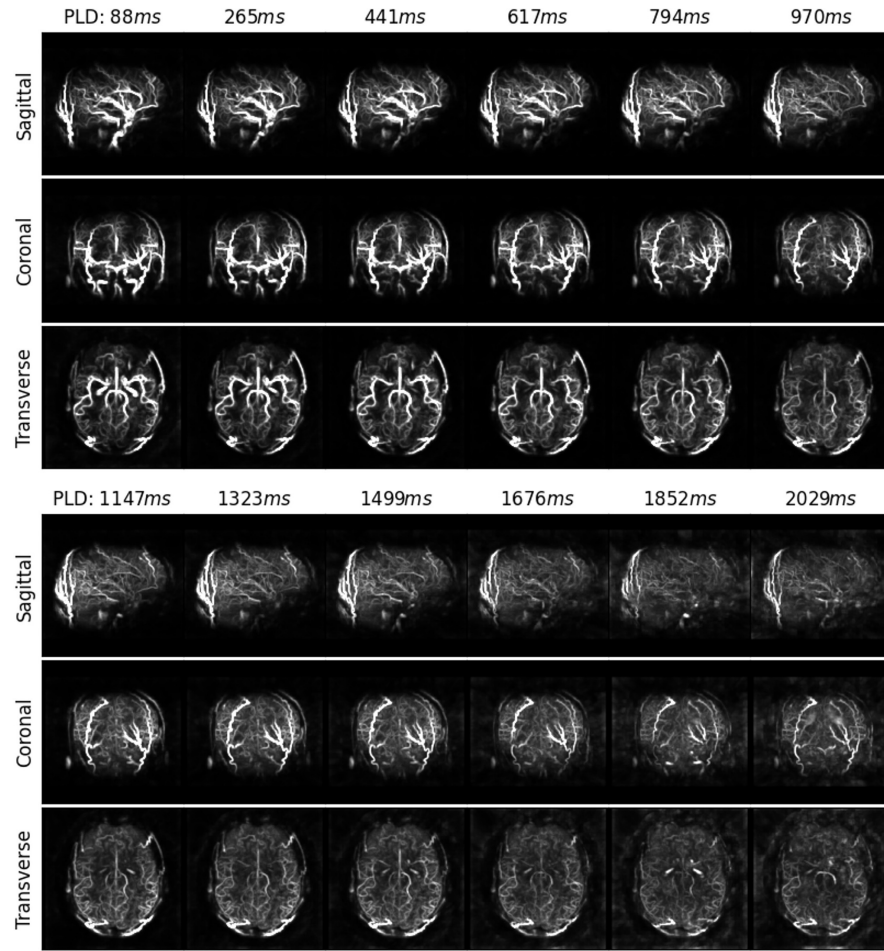


Figure 4.14: All frames of angiography image acquired by radial trajectory (TR matched with cone protocol)

Figure 4.19 demonstrates two examples showcasing how difference in repeatability measurements translates into image quality. In Figure 4.19a, the perfusion images from repeat scanning in the same subject acquired with both cone and optimal radial protocols are compared. The tissue perfusion signal appears more stable in results acquired using the cone protocol compared to the optimal radial results (red arrows). Figure 4.19b shows the angiography results from the same subject acquired with cone and optimal radial protocols as well. Like the perfusion results in Figure 4.19a, the vessel detail has higher similarity between images acquired with cone protocol from two scans, than those acquired with optimal radial protocol. In summary, the cone trajectory outperformed the radial protocol not only quantitatively, but also qualitatively, so these improvements are likely to be important in the context

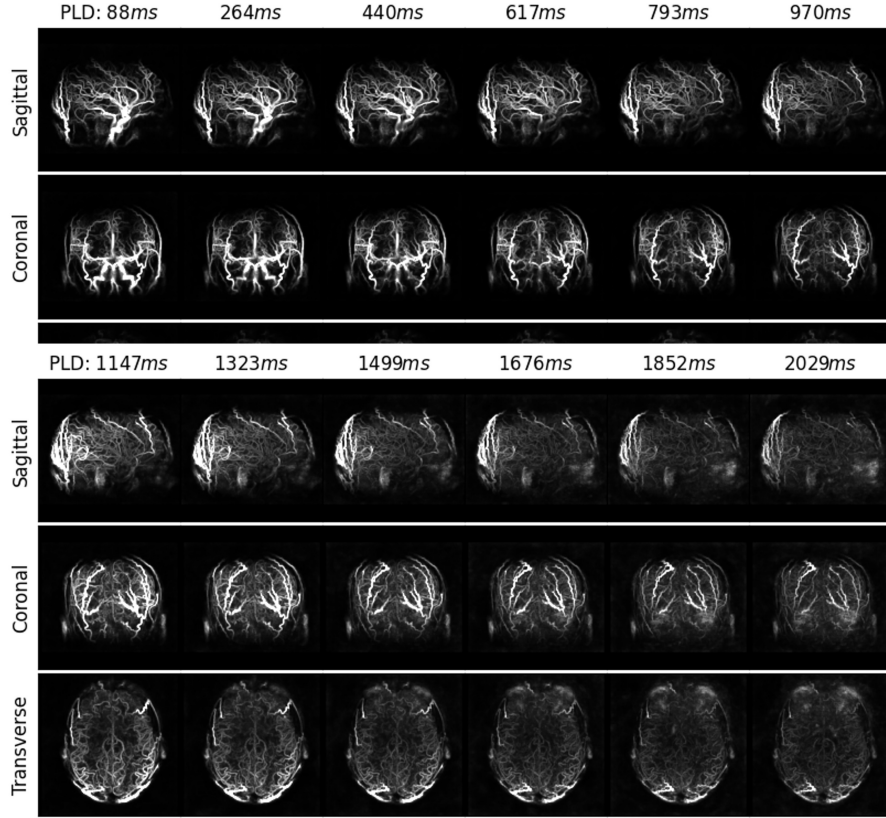


Figure 4.15: All frames of angiography image acquired by the cone trajectory

of qualitative clinical assessment.

4.4 Discussion

In this work, a novel two-stage curved cone trajectory design was proposed and integrated into the 4D CAPRIA sequence to improve the spatial resolution and SNR of both the angiographic and perfusion images. This allowed high quality dynamic 3D maps of blood flow through the vessels and into the tissue bed to be acquired simultaneously in a single short scan (6 mins), providing a comprehensive evaluation of cerebral blood flow. A process using numerical simulations and physical phantom acquisitions for optimizing the cone design parameters suitable for our application was presented. LLR regularization was used within the in vivo reconstruction to take advantage of the incoherent sampling of our trajectory and reduce artifacts and noise. The cone trajectory was compared against the previously optimized 4D CAPRIA radial trajectory on a group of healthy subjects, demonstrating that our

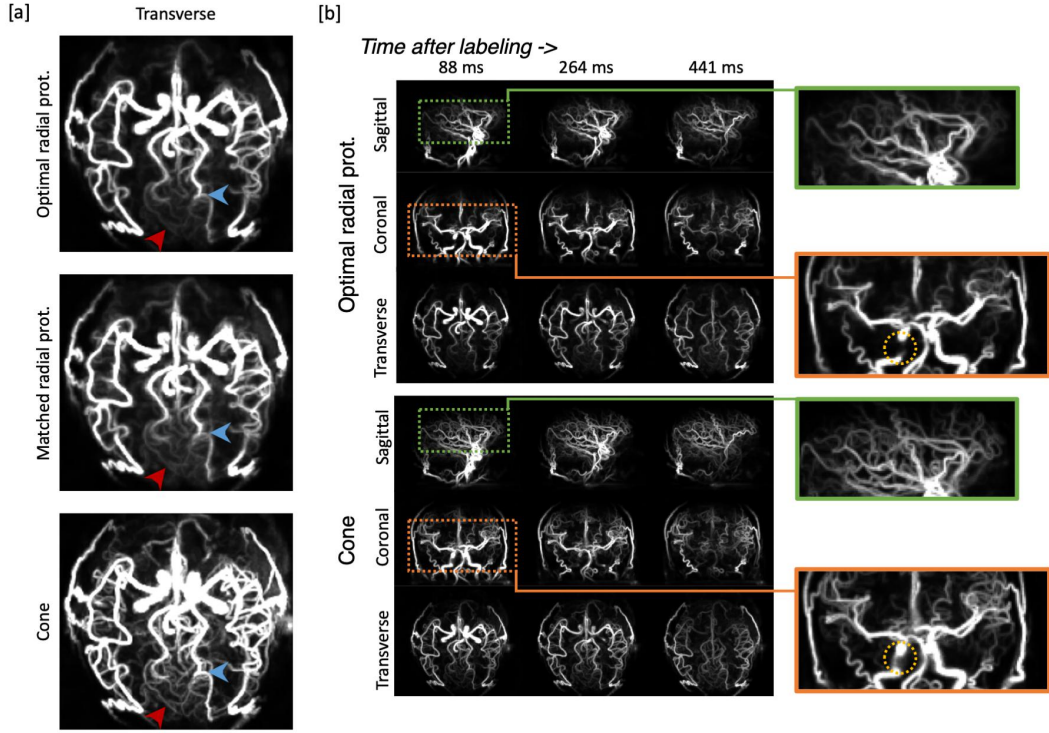


Figure 4.16: Example angiographic images acquired using different trajectories. [a], transverse maximum intensity projection of an example frame in angiographic images reconstructed using the same set of raw data as the perfusion images in Figure 4.11. The improved visualization of small vessels (red and blue arrows) emphasizes the superior resolution of the proposed cone trajectory. [b], Comparison of angiographic images between radial and cone trajectories (Maximum Intensity Projections) in three example frames. Two regions were enlarged for both trajectories respectively. Orange box: The cone trajectory provided better visualization of the proximal arteries, reducing signal dropout due to B_0 inhomogeneity and/or flow effects. Green box: The cone trajectory allowed clearer visualization of small distal vessels than the radial trajectory.

cone design could improve 4D CAPRIA through higher spatial resolution, improved scan-rescan repeatability, and reduced signal loss in proximal arteries.

The most straightforward explanation for the improvement from radial to our cone design is the increased sampling efficiency and better utilization of the gradient system. The radial trajectory features oversampling at the k-space center, but it does not make full use of the degrees of freedom afforded by the gradients. Our proposed cone trajectory design is based on the intuition that traversing more of k-space in each readout by adding twists to the radial spokes will be beneficial both to improving the resulting point spread function by improving sampling in peripheral k-space, as well as more uniform sampling throughout k-space which is

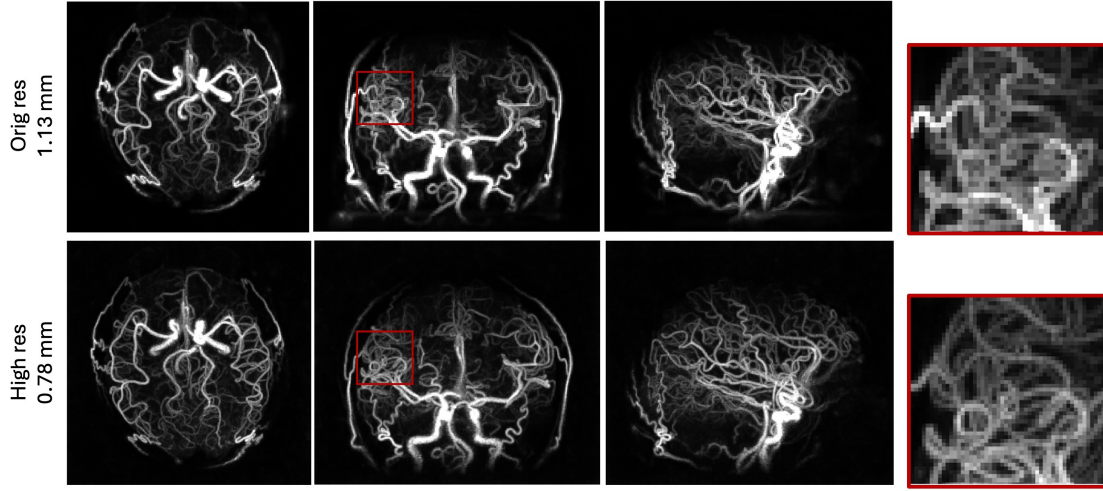


Figure 4.17: Comparison of angiographic acquired at two spatial resolutions: $0.78mm$ and $1.13mm$.

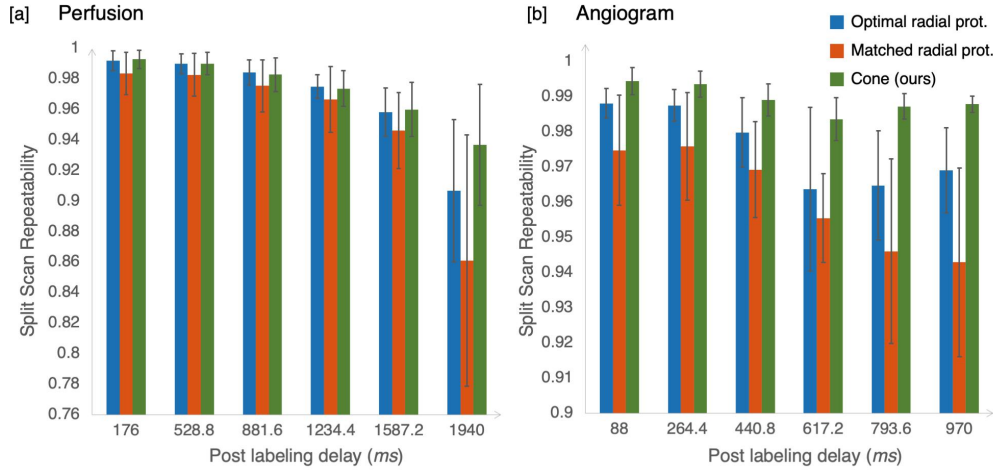


Figure 4.18: A) Comparison of the repeatability of the perfusion images between three protocols: 1) the optimal radial protocol, 2) the matched radial protocol, and 3) our cone trajectory. The mean and standard deviation across subjects are shown here. Overall, the scan repeatability decreased with the PLD due to the signal attenuation. The cone trajectory had the highest overall scan-rescan repeatability of three protocols, particularly at later PLDs, and its performance was the most stable across different subjects ($p < 0.001$ in multi-way ANOVA test). B) Comparison of the repeatability of the angiographic images between the three protocols. Only the first 6 frames out of the 12 reconstructed frames were used for repeatability calculation, as later frames are dominated by perfusion signal and the vessel mask was no longer applicable. Since the angiography signal is much stronger than perfusion, the average scan repeatability is higher than perfusion. However, the cone trajectory still maintains the best and most stable performance across different subjects and frames, and the significance was confirmed by multi-way ANOVA test ($p < 0.001$) as well.

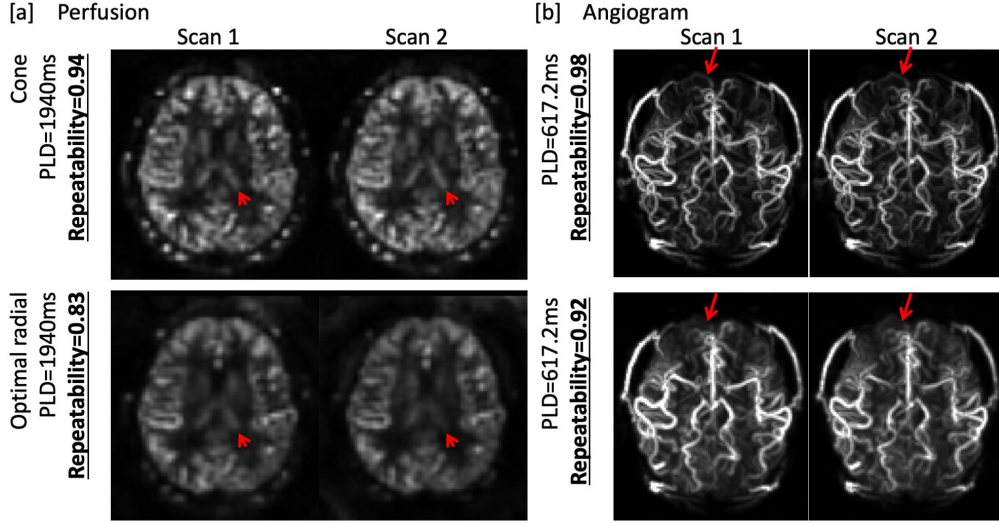


Figure 4.19: Qualitative assessment of improvements in repeatability. [a], Comparison of perfusion images at $PLD=1940$ reconstructed from repeated scans for both cone and optimal radial protocols. [b], Comparison of two scans for angiography images at $PLD = 617.2ms$ acquired with cone and optimal radial protocols. The red arrows highlight regions with improved signal stability when acquired with a cone trajectory.

beneficial for SNR [17]. A large cone angle 60° was also adopted, as we speculate that trajectories with larger cone angles has a larger gradient perpendicular to radius and traverse longer distance at the k -space center compared to those with smaller cone angles and thus more robust to signal variations. It agreed with the observations from the phantom scanning, which, in a given readout time, cone trajectories with larger angles exhibit less aliasing due to signal variations.

Additional flexibility in the design of the trajectory over existing approaches was desired for better adaptation to our combined imaging of two modalities with different spatiotemporal resolution requirements. To be more specific, if only angiography is considered, the time spent at the k -space central region is less important than focusing on traversing quickly to peripheral k -space. Therefore, a two-stage design was introduced, which allowed for different trajectory properties in central and peripheral k -space to better accommodate both modalities. Additional simulated results comparing the proposed two-stage design with existing base cone trajectories are shown in Figure 4.20, demonstrating the smaller FWHM for angiography and higher effective SNR for both angiography and perfusion reconstructions using our

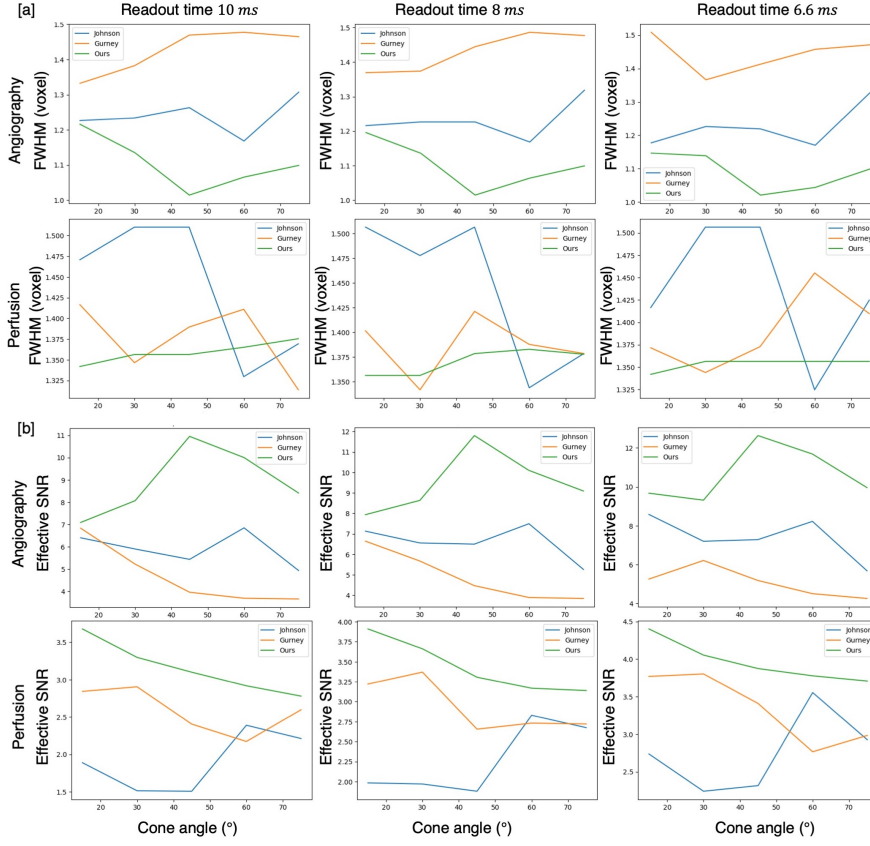


Figure 4.20: Simulated comparison with Gurney's[24] cone and Johnson's[68] cone in both angiogram and perfusion

cone design, compared to Johnson's[68] and Gurney's[24], when combined with the golden ratio rotation approach. Because of the complex interaction between signal variations, off-resonance sensitivity, and non-Cartesian undersampling artifacts, a purely simulation-based optimization would have been unreliable.

Instead, a two-step process combining numerical simulation and physical phantom acquisition was adopted to find suitable parameters for the proposed cone trajectory. To ensure a trajectory versatile to variable spatial and temporal resolution, advanced non-linear reconstruction method was not used in searching for optimal parameters. However, the improvement of PSF and reduction in artifacts observed with vanilla reconstruction would also transfer to more advanced reconstruction method. The optimization not only covered a considerable range of possible values but also reflected realistic scanning conditions faithfully. One exception was the parameter m , which was heuristically chosen by placing the

separation point at the middle of two parts of the cone trajectory. Preliminary experiments varying m found that it interacted with other parameters during the optimization process, therefore m was fixed for two-stage cone trajectory to reduce complexity.

Our design also possesses a range of advantages when compared with other non-Cartesian trajectories developed over the years. Conventionally, non-Cartesian trajectory design focused on the fully sampled case, where rigorous calculation is performed to satisfy the Nyquist sampling theorem, from 2D spiral[82, 83] to 3D cone.[24, 66] Given careful analytical formulations, these trajectories are fast to compute but cannot be easily adapted to a more flexible highly undersampled case, which we required to achieve clinically feasible acquisition time for this application. The approach taken in the original radial-cones[68] trajectory did not require precise adherence to the Nyquist sampling requirements, but the design and optimization were still targeted to achieve approximately full sampling. Our design, however, has a set of free parameters which can be determined through a two-step process to be fine-tuned for specific applications without the requirement for full sampling. Additionally, as our trajectory is generated within the sequence code, the trajectory parameters can be easily adjusted during scanning without manually loading a new trajectory, as with numerically optimized trajectories[26, 70]. In addition, the use of golden ratio rotations means the undersampling factor and temporal resolution can be chosen arbitrarily during reconstruction. For example, Figure 4.21 demonstrates exemplary reconstructions using various temporal resolutions.

Despite the improved sampling efficiency, the additional twists in the cone trajectory design make the acquisition more susceptible to gradient imperfections such as gradient delays. The mismatch between the actual and expected trajectory can introduce errors into the reconstruction. For our trajectory, the slew rate and gradient were limited to reduce the effect of the trajectory mismatch. Furthermore, experiments to assess the potential impact of gradient delays were performed (see Figures 4.22, 4.23 for additional delays on numerical simulation and 4.24, 4.25 on in-vivo data). No notable gradient imperfection related artifacts were observed in

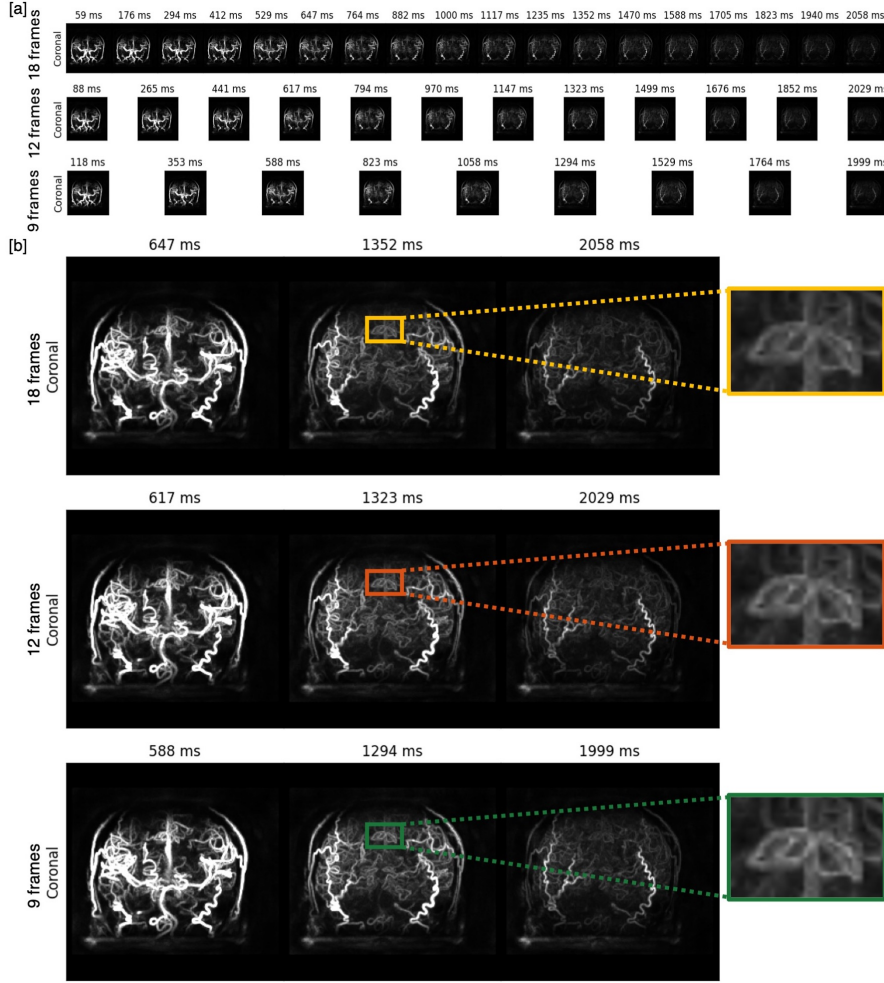


Figure 4.21: [a],CAPRIA sequence using cone trajectory and 3D Golden Angle enables flexible reconstruction of dynamic angiogram with different temporal resolution. [b], there is a slight tradeoff between temporal resolution and spatial resolution. As shown in the zoomed-in boxes, vessels in the 9-frame result are sharper than those in the 18-frame one.

all our experiments. However, use of the gradient impulse function[84, 85] could improve the reconstruction further and allow the full potential of the gradient system to be utilized. Correction for gradient imperfections will be explored in future work if higher gradient amplitudes and slew rates are required for certain applications to improve sampling efficiency.

In-vivo scans in clinical settings often suffer from patient motion. Cone design maintains the ability to use retrospective motion correction while the improved sampling at the central k-space also enables better quality navigator for more accurate registration.

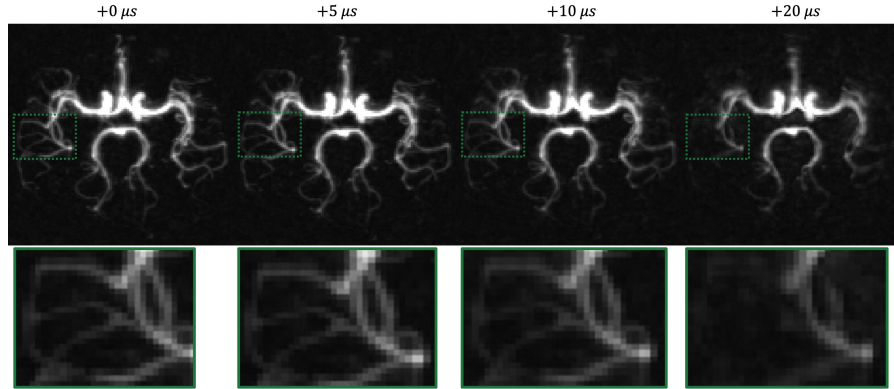


Figure 4.22: Simulation of the angiography phantom with different gradient delay times. According to Addy et al.,[84] gradient delays in modern gradient systems are generally less than 10 μ s. Such delays did not result in major artefacts, although larger gradient delays caused additional blurring and detail loss in angiography.

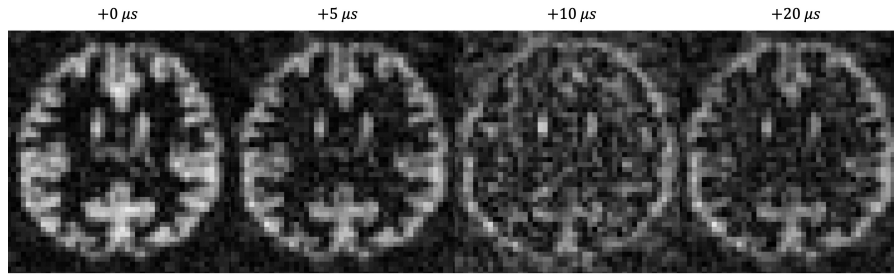


Figure 4.23: Simulation on the perfusion phantom with different gradient delay times. In this case gradient delays also caused signal loss and had greater impact on perfusion images than on angiography.

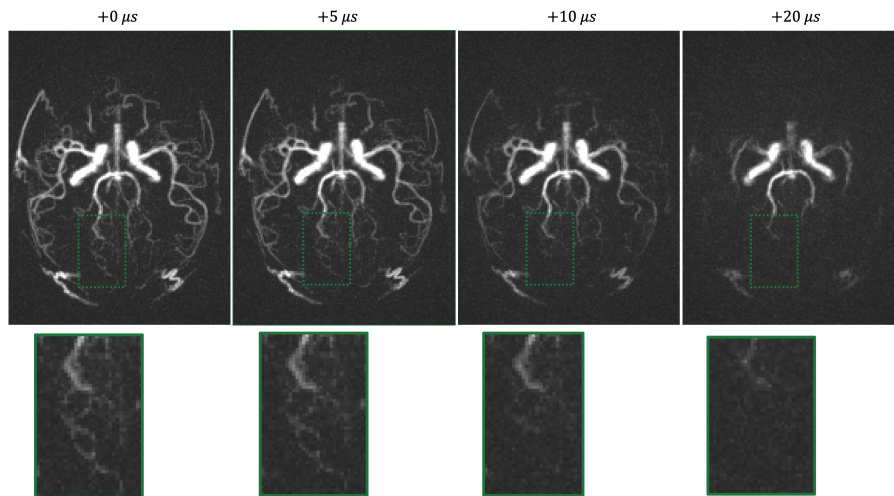


Figure 4.24: Simulation on in-vivo data with retrospectively added gradient delay. Angiography details were lost as the gradient delay increased.

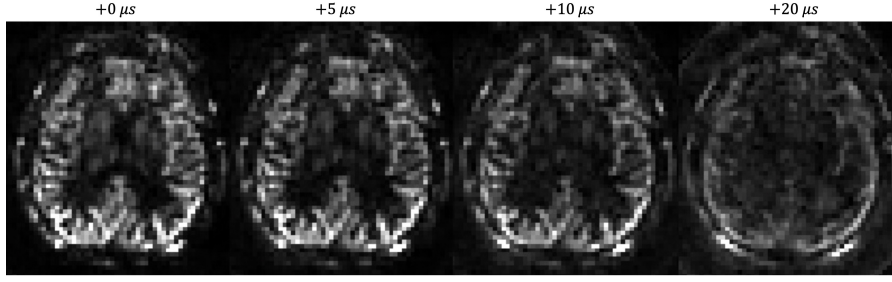


Figure 4.25: Simulation on in-vivo data with retrospectively added gradient delay. Perfusion image quality was strongly impacted at large gradient delays, but the difference was less obvious when gradient delay was $\sim 5\mu s$.

Furthermore, the cone design could also be incorporated into other imaging frameworks (e.g., XD-GRASP[86]) and applied on other parts of the body (e.g., liver). Especially for existing methods that use a radial trajectory, our cone design could readily replace each radial spoke to improve spatial resolution.

In the current implementation, a single inversion pulse was used before the readout which might be suboptimal for background suppression. One possibility would be adding another inversion pulse in the middle of readout train to reduce the recovery of the static tissue at long PLDs. However, the exact implementation in sequence programming as well as the additional side effects for introducing another inversion pulse remain to be investigated.

At present, perfusion quantification using the CAPRIA sequence is non-trivial since the acquisition of an M0 image is not straightforward. Preliminary work suggests we should be able to reconstruct multi-contrast structural images from the sequence by taking the mean of *label* and *control* data and use this to fit for M0[60]. In addition, perfusion models need to be adapted to incorporate the saturation of the bolus from the excitation pulses used. We will continue to refine these approaches to achieve quantitative perfusion imaging with CAPRIA in future work.

In this preliminary investigation, a small group of 8 relatively young healthy subjects were scanned. In the future, a broader comparison within a larger group of older healthy subjects and patients with cerebrovascular disease should be carried out for a more comprehensive validation of the generalizability of our cone design.

We could also perform a thorough comparison with more conventional methods and explore the quantification of blood flow from these images[87, 88].

4.5 Conclusion

In this work, we introduced an innovative 3D cone trajectory design, combined with a golden ratio rotation strategy, to enhance SNR and resolution without prolonging acquisition time. Our design better utilizes the gradient system, covering more k -space than the radial trajectory in a single readout. Notably, its non-Cartesian artifacts exhibit enhanced incoherence and uniformity compared to the radial approach, making it more suitable for LLR reconstruction. Through a comprehensive process involving numerical simulations and physical phantom scans, a combination of the most suitable trajectory parameters was selected. The evaluation on a group of healthy subjects demonstrated that our cone trajectory surpassed the original 4D CAPRIA approach, not only in terms of spatial resolution but also in scanning repeatability for both angiography and perfusion images.

The code for generating the trajectory and aforementioned simulation is openly available on Github (<https://github.com/Michaelsqj/TrajectoryDesign>). The code used for image reconstruction used in the study can be found at (https://github.com/Michaelsqj/cone_recon).

5

Ultra-high temporal resolution 4D angiography using arterial spin labeling with subspace reconstruction

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5.1 Introduction

Dynamic MRA allows the visualization of blood flowing through the vascular tree, which provides much richer information for clinical diagnosis than static (e.g. TOF) angiography[89], and allows for the fitting of physiological models, providing quantitative metrics which could be sensitive to pathology[90]. Numerous methods have been developed recently to reconstruct time-resolved ASL angiograms.

Some methods seek to encode temporal information into the ASL preparation process. Based on a Hadamard encoding scheme, the PCASL[57] pulse train can be separated into blocks which are set to either “label” or “control” mode in a varying pattern across repeats[72, 91], followed by only one readout[92] or a limited number readouts[93, 94]. The time-resolved angiography information can then be reconstructed by “decoding” the resulting encoded images. Alternatively, a long train of temporally resolved readouts can be acquired immediately after each fixed labeling module to generate dynamic images[11, 73, 74]. High undersampling factors for each temporal frame are used to achieve high temporal resolution in short scan times. Advanced reconstruction methods can be adopted to leverage the complementary information available across multiple timepoints to mitigate undersampling artifacts. Song et al.,[95] proposed K-space Weighted Image Contrast (KWIC)[95] with radial sampling to reconstruct 4D dynamic MRA, which combined segmented spokes from different shots at different parts of k-space. KWIC was later adopted in different dynamic MRA sequences[73, 96]. Similarly, the keyhole method has also been exploited for time-resolved MRA[97] reconstruction to combine data with different contrast while reducing artifacts.

Despite sophisticated design for data combination, these methods averaged readouts acquired at different timepoints with different contrast to achieve sufficient k-space sampling. They not only limited the temporal resolution that dynamic MRA could achieve, but also affected the spatiotemporal fidelity of the reconstructed images, since different k-space samples are acquired with the labeled blood at different spatial locations, especially for vessels with fast transiting blood. Inevitably, obtaining dynamic MRA without averaging data across timepoints

would dramatically increase the undersampling factor. To compensate for this, improved priors for the MR signal would need to be incorporated to improve the conditioning of the reconstruction problem.

In this work, we aim to reconstruct ultra-high temporal resolution 4D ASL angiography images. Firstly, a kinetic model[90] describing the angiographic signal during the course of a series of readouts after each ASL preparation was introduced to simulate a set of physiologically plausible signal curves. Secondly, the subspace technique developed by Tamir et al.[39] was adopted to linearly compress this model and convert the poorly conditioned problem of reconstructing each time point into a better conditioned problem of estimating a small number of coefficient maps of these subspace components, greatly reducing the number of unknown variables and computational requirements. Thirdly, as well as conventional 3D radial sampling, the cone trajectory developed in the previous chapter[13] was integrated for efficient sampling of high spatial frequencies. Numerical simulations were performed to examine the spatiotemporal characteristics of our reconstruction and optimize the regularization weight. The in-vivo data was acquired with a combined angiographic and perfusion sequence (CAPRIA)[12] but with only the angiogram reconstructed here. Altogether, high spatial resolution dynamic MRA images with temporal resolution equal to the sequence TR (~ 15 ms) were reconstructed. The physiological parameters estimated from the in-vivo results were cross-validated with the numerical simulation for confirmation of the improvement in physiological modeling accuracy.

5.2 Method

5.2.1 Pulse sequence design

The pulse sequence used in this study was very similar to that used in the previous chapter, but is plotted again in Figure 5.1 for completeness. As before, the sequence is composed of multiple repeats where an identical PCASL preparation is used but different k-space information is acquired. Within each repeat, a PCASL labeling or control module is followed by a single inversion pulse, as used in previous work[60] to help suppress background tissue signal, before a series of readouts are acquired.

The direction of each readout spoke followed the golden ratio[20], the indices of which increased along the repeat dimension first as proposed by Song et al.[73]. Variable flip angles were applied to the train of readouts within each repeat to reduce the signal attenuation from the initial excitation pulses. In this work, two protocols were compared: one with a 3D radial trajectory and another with an in-house designed efficient cone trajectory[13]. The sequence design followed the combined angiographic and perfusion sequence[12] (CAPRIA) although here we only focus on the reconstruction of angiographic images.

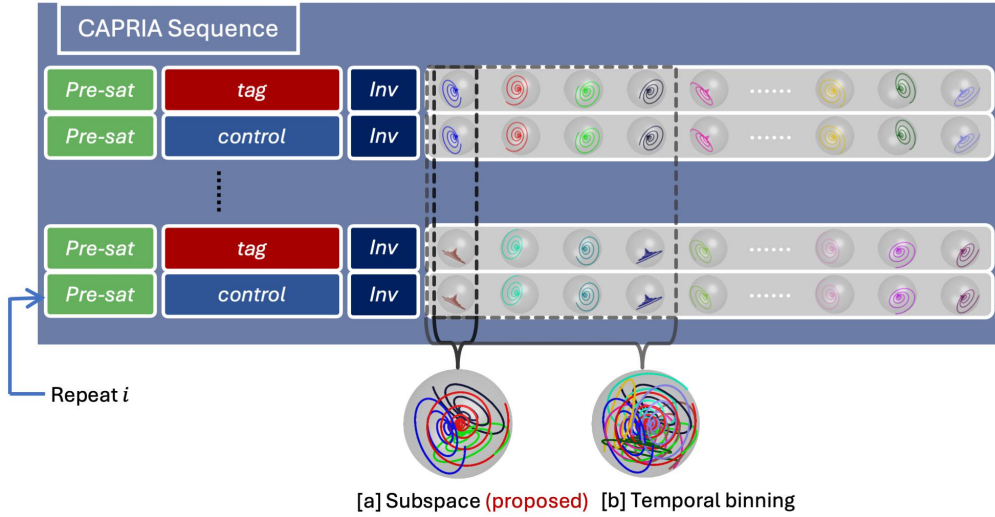


Figure 5.1: Overview of the CAPRIA pulse sequence with two different reconstruction methods: [a], In the proposed subspace method, each temporal frame contains only readouts at a single timepoint. [b] In contrast, in the temporal binning reconstruction scheme, each angiographic frame consists of readouts from several adjacent timepoints. Note that in the radial protocol, each cone trajectory plotted in the figure would be replaced by a radial spoke aligned with its central axis.

To reconstruct a dynamic angiogram from the acquired data, conventionally, readouts from multiple TRs would be grouped to achieve sufficient k-space sampling, as shown in Figure 5.1b, which we term the *temporal binning* method. However, the proposed method, referred to as the *subspace* method in Figure 5.1a, combined spokes within only one TR for each frame, achieving a temporal resolution the same as the TR. Further implementation details are explained below.

5.2.2 Angiographic kinetic model

Given the sequence parameters (i.e., labeling duration, TR, flip angle, etc.), the angiographic signal evolution within each voxel after PCASL labeling was explicitly modeled by Okell et al.[90], with 4 independent parameters: the blood transit time from the labeling plane to the imaging voxel, δt ; the sharpness, s ; and time-to-peak, p , of a gamma variate dispersion kernel, and a scaling factor proportional to blood volume, A . Note s and p don't have units and are two parameters deciding the shape of the dispersion kernel. The model describing the signal variation across time is composed of effects from dispersion, relaxation and attenuation due to RF pulses, which are explained below.

$D(t_d)$: The ideal temporal profile of the blood bolus is a rectangular function with a width equal to the labeling duration. Depending on the dispersion time-to-peak and sharpness, this ideal profile is blurred, which is described by its convolution with a gamma variate kernel, $D(t_d)$, while flowing through the vascular tree on the way to the voxel of interest, as described by Equation 5.1. t_d is the transit time delay due to blood dispersion.

$$D(t_d) = \frac{s}{\Gamma(1 + ps)} e^{-st_d} (st_d)^{ps}, \quad (st_d > 0, ps > -1) \quad (5.1)$$

$T(\delta t, t_d)$: Additionally, the inverted magnetization of blood experiences T_1 recovery as described by $T(\delta t, t_d)$ in Equation 5.2. T_{1b} is the T_1 of arterial blood.

$$T(\delta t, t_d) = \exp\left(-\frac{\delta t + t_d}{T_{1b}}\right) \quad (5.2)$$

$R(t_i)$: The attenuation of the longitudinal magnetization difference signal by the imaging RF pulses is described by $R(t_i)$ in Equation 5.3, making the simplifying assumption for this 3D acquisition that all labeled blood experiences all RF excitation pulses from the start of the readout at time, t_0 , to the current time, t_i . TR is time for one RF pulse to the next in the train of readouts.

$$R(t_i) = \prod_1^n \cos(\alpha_i), \quad (n = \lceil \frac{t_i - t_0}{TR} \rceil) \quad (5.3)$$

$S(t_i)$: Finally, the actual signal amplitude received after the i^{th} excitation pulse depends on the flip angle of that pulse, contributing an additional $\sin(\alpha_i)$ term, as described previously[12]. Combining all these effects, the final signal profile S at each time after labeling t_i and each voxel position is characterized in Equation 5.4.

$$S(t_i) = A \sin(\alpha_i) R(t_i) \int_{t_i - \delta t - \tau}^{t_i - \delta t} D(t_d) T(\delta t, t_d) dt_d \quad (5.4)$$

In Figure 5.2, we showed that the bottom of the imaging region is about 3cm above the labeling plane, which takes blood about 30ms to travel. Further considering the single inversion pulse after the labeling pulse uses 10ms, the blood inverted by the very end of the labeling plane would have 20ms to reach the imaging region by the time the first excitation pulse starts. However, that 20ms only accounts for 1.1% of the total labeling time 1.8s. Furthermore, the blood magnetized at the end would only miss 1 – 2 readouts. Therefore, it's theoretically safe to make the simplified assumption that all labeled blood experienced all excitation pulses.

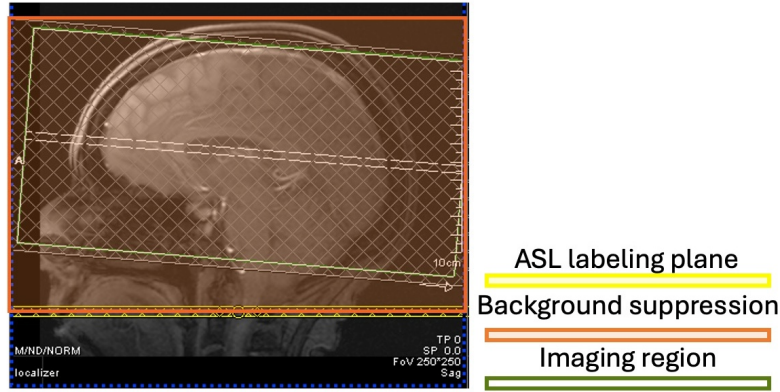


Figure 5.2: The typical choice for labeling, single inversion and imaging region during CAPRIA acquisition.

5.2.3 Subspace generation

The prior knowledge of the signal time series was incorporated into the reconstruction using a subspace method. Specifically, a plausible range of model parameters was chosen as follows: δt : 0.1 ~ 2.0 (second), p : 0.001 ~ 0.5 (second), s : 1 ~ 20 (second^{-1}) (Note the parameter name s is different from second as a unit). To

cover a wide range of temporal variations for blood flow, 40 equispaced samples were drawn for each parameter within the range and combined, forming a dictionary with 40^3 samples in total. The scaling factor A was not included in the dictionary generation process as it would not affect the subspace. As these different signal time courses are strongly correlated with each other, they lie on a low-dimensional manifold embedded in a high-dimensional space. Although the exact manifold is not easy to find, a linear subspace can serve as a sufficient approximation, with straightforward calculation and computational convenience[39]. Principal component analysis (PCA) was applied to the generated dictionary, as shown in Figure 5.3a. The space spanned by a small number of principal components was regarded as the subspace for the signal variation. As plotted in Figure 5.3b, the first few principal components capture slow signal variations, with higher order components containing more rapid oscillatory behavior. Using more principal components can give a better approximation to the signal variation but requires higher computational cost. To determine the number of components required to strike a good balance between computational efficiency and accuracy, the relative error $\sqrt{\frac{\|X - \Phi\Phi^H X\|_F}{\|X\|_F}}$ was calculated on the whole dictionary as shown in Figure 5.3c. X is the generated dictionary and Φ is the subspace. We found that using the first 12 components resulted in 0.961% relative error while keeping the same size of unknown parameters to solve as in reconstructing 12 temporally-binned frames[12, 13]. The NRMSE at each timepoint is also shown in Figure 5.3d. Using 12 principal components achieved greatly reduced oscillatory errors compared to 4 or 8 components. Further increasing the number of components from 12 to 16 did not bring about significant improvements but increased computational requirements. Therefore 12 principal components were chosen for the subspace reconstruction for angiography in this work.

5.2.4 Subspace reconstruction for angiographic images

The target time series, x , can be approximated by the weighted combination of principal components, Φ . As shown in Equation 5.5, the voxel-wise weights for

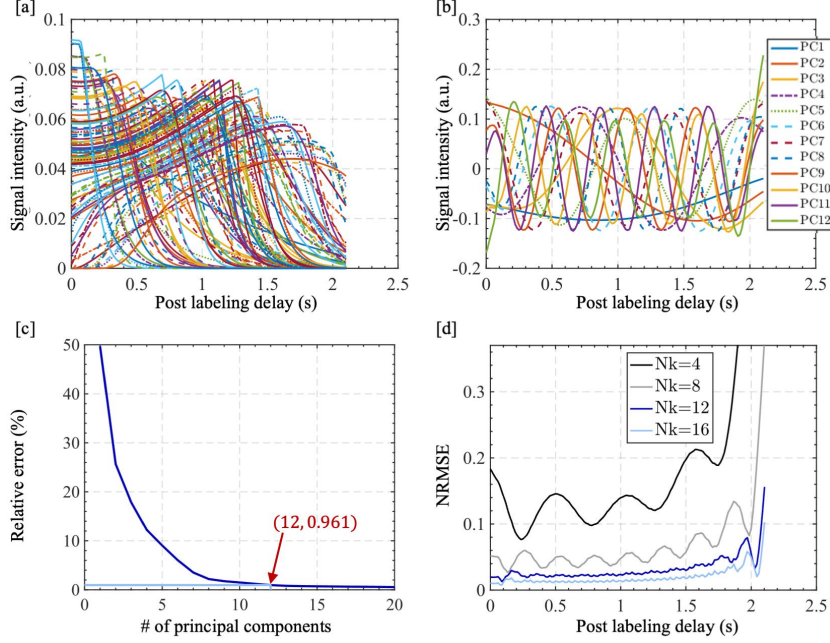


Figure 5.3: Subspace generation for the angiographic time series. a) Simulated dictionary of angiographic time series across different combinations of plausible physiological parameters. b) The first 12 principal components (PC) were extracted using PCA. Curves of PCs with larger indices manifest higher oscillating frequency. c) Relative reconstruction error of the dictionary with different number of principal components used for angiography signal compression. d) NRMSE at each timepoint with a different number (N_k) of principal components.

each principal component, α , are to be estimated. The reconstruction problem was converted to the form of Equation 5.6, where W_i was the i^{th} patch extraction operator, P was the sampling mask, F was the Fourier transform and C was the coil sensitivity. Similar to previous work[39], locally low rank regularization[36] (LLR) was applied across the principal component coefficient maps to reduce noise. λ was the weight adjusting the LLR regularization.

$$x \cong \Phi\alpha \quad (5.5)$$

$$\hat{\alpha} = \underset{\alpha}{argmin} \|PFC\Phi\alpha - y\| + \lambda \sum_i \|W_i(\alpha)\|_* \quad (5.6)$$

As operators F , C were applied on the spatial dimension, independent from the operator Φ on the temporal dimension, the original order of operators could be modified to $P\Phi FC\alpha$. The combined operator $\Phi^H P\Phi$ used in every iteration

could be calculated before the start of iterative optimization, so that the whole optimization process could be performed entirely in the subspace domain without expanding to a full time-series[39]. The technique reduced the computation time of subspace reconstruction to that of the temporal binning reconstruction.

5.2.5 Temporal binning reconstruction method

The proposed subspace reconstruction was compared against the method used to reconstruct 4D dynamic MRA in previous work[12, 13]. As presented in Equation 5.7, the LLR regularization was directly applied to the dynamic image x . Each frame involves grouped k-space data sampled from multiple TRs. Note the meaning of each notation was shared between Equations 5.6 and 5.7.

$$\hat{x} = \underset{x}{\operatorname{argmin}} \|PFCx - y\| + \lambda \sum_i \|W_i(x)\|_* \quad (5.7)$$

5.2.6 Numerical simulation

Before in-vivo acquisition, numerical simulations were performed to examine the spatiotemporal characteristics of the subspace reconstruction results compared to the original temporal binning reconstruction approach. A line with one voxel width crossing the center of every 3D volume and varying across time was created, simulating a time-series of a single vessel. The four parameters of the kinetic model in Equation 5.4 (i.e., δt , p , s , A) were distributed along the line in a linearly varying fashion, simulating increasing transit time and greater dispersion along the length of a vessel. Following the previous literature[90], δt ranged between 0.25 and 1.8s, p ranged between 0.1 and 0.5s, s ranged between 1 and 10s⁻¹, and the scaling parameter A was set to be equal to 1 along the simulated vessel. A 4D time-series with the same spatial resolution (1.1 mm) as in-vivo reconstruction was simulated with these parameters and the kinetic model. The TR, number of readouts and k-space trajectories in the simulation were also kept the same as for the in-vivo acquisition protocols. After transforming the 4D timeseries to k-space with a single coil and uniform sensitivity using the forward NUFFT[79, 98], temporal binning and subspace methods were used to separately reconstruct from

the k-space data. In order to compare the spatial resolution, a point spread function was also calculated along the direction perpendicular to the simulated line. Both the radial trajectory used in Okell et.al.,[12, 60] and the cone trajectory used in Shen et al.[13] were simulated and reconstructed with the two methods. A variational Bayesian method (Fabber[99], part of FSL[100]) was used to infer the four model parameters from the reconstructed images and evaluate the reconstruction quality. Additionally, weights 1e-4, 5e-4, 1e-3, and 1e-2 for the LLR regularization term were tested for subspace reconstruction to inform the in-vivo scenario. The data transformed from the numerical phantom into k-space was scaled in the same way as the in-vivo data (described below) before iterative reconstruction to ensure the derived regularization weight was transferable to in-vivo reconstructions. To align with the optimal design in previous literature[12, 13], the regularization weight of 1e-1 was used for temporal binning reconstruction.

5.2.7 In-vivo acquisition and reconstruction protocols

To evaluate the proposed reconstruction method, a group of 8 subjects were scanned on a 3T Prisma scanner (Siemens Healthineers, Erlangen, Germany) using a 32-channel receive-only head coil under a technical development protocol agreed by local ethics and institutional committees, and they all provided consent.

For each subject, two back-to-back scans with two different protocols were acquired. The two protocols followed the same design as the *cone protocol* and *matched radial protocol* in the previous literature[13]. The variable flip angles varied quadratically across the readout and ranged between $3^\circ - 12^\circ$. The TR for each readout was $14.7ms$, where the readout time was $10ms$. Note that the ASL labeling duration ($1.8s$), the total time for all readouts after each ASL labeling module ($2116.8ms$) as well as the total scan time ($6min12s$) were kept consistent between the two protocols. The FOV was $200 \times 200 \times 125mm$, and the spatial resolution was $1.13mm$ isotropically.

Before reconstruction, the original 32-channel data were compressed to 8 virtual coils[77]. Coil sensitivity map estimation used the adaptive combination method[78].

For the temporal binning reconstruction, we followed previous literature[13] and used $1e-1$ as the LLR regularization weight. For the subspace reconstruction, differences in data scaling between simulated and acquired data were removed by dividing both k-space data sets by their 95th-percentile magnitude value before reconstruction to allow transfer of the finetuned regularization weight from numerical simulation to in vivo data. Based on the numerical simulation, a regularization weight of $5e-4$ was adopted for subspace reconstruction.

Apart from the subspace and temporal binning reconstruction methods mentioned above, two advanced image reconstruction methods were also included for comparison, where the temporal resolution was matched to that of the subspace method. Firstly, we adapted the LLR regularized reconstruction used by temporal binning to achieve the same temporal resolution as the subspace method, termed “LLR-matched” below. Another method “Extreme MRI”[37] which combined multi-scale low rank and stochastic reconstruction was also used for comparison. For both methods, different regularization weights were investigated, the details of which are shown in Figures 5.4 and 5.5.

5.3 Results

5.3.1 Numerical simulations

Simulated results on a single-vessel numerical phantom are shown in Figure 5.6. In the 4D phantom (Figure 5.6a), the blood bolus flows from left to right, with early blood arrival and minimal dispersion on the left and delayed arrival and greater dispersion moving to the right. The signal time-series from three representative locations along the simulated vessel are displayed to compare the reconstruction fidelity between the subspace and temporal binning methods. Where the ground truth signal varies rapidly on the left of the phantom (early arrival and low dispersion), the subspace reconstruction cannot fully represent this rapid signal change and there is a slight discrepancy between the reconstructed signal and the *ground truth*. However, the subspace method still captures the overall signal trend. In contrast, the temporal binning signal curve drops from the beginning and fails

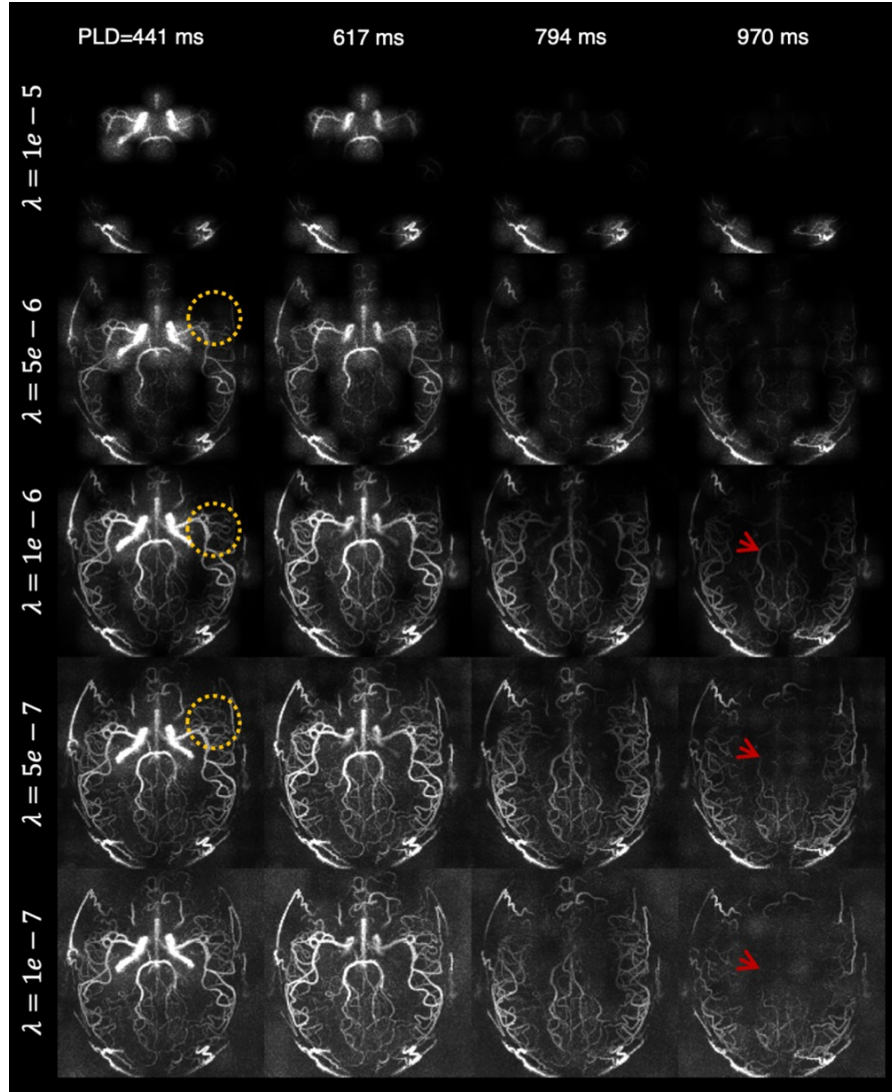


Figure 5.4: Angiograms reconstructed by Extreme MRI with different regularization weights. Low regularization weight kept the fidelity of angiography but lost SNR, whereas high regularization weight overly smoothed the image and lost visibility of thin vessels, as indicated by the yellow circles. Arteries pointed by the red arrows also appeared at late timepoints only at high regularization weight, confirming these were artifacts introduced due to over-regularized on the temporal dimension.

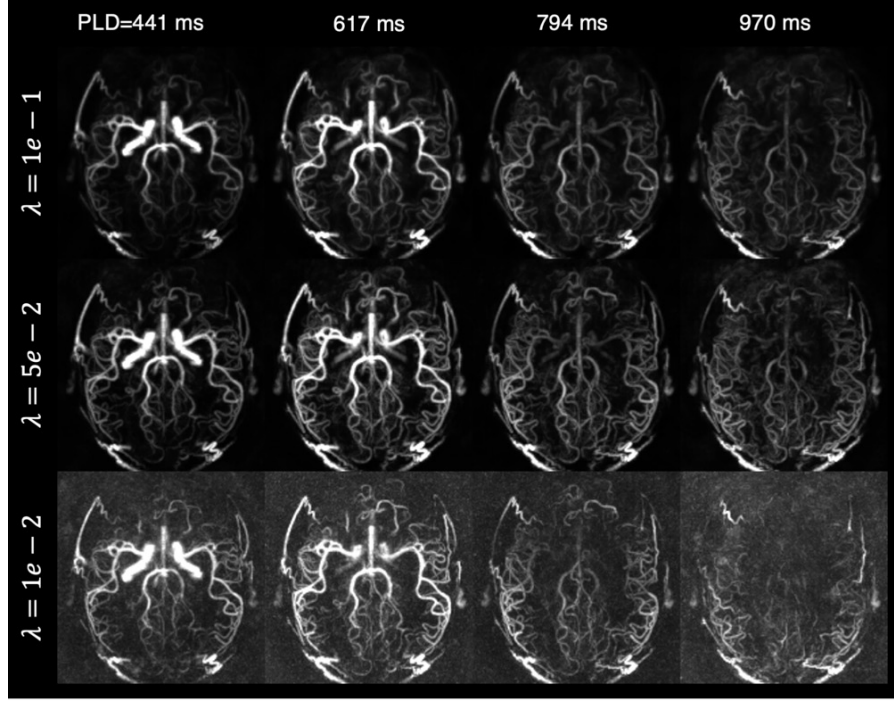


Figure 5.5: Angiography reconstructed by “LLR-matched” with different regularization weights. In a similar way to Extreme MRI, the choice of regularization weight for LLR matched was a compromise between excessive smoothing and noisy images.

to delineate the plateau and sharp transition because of averaging data points across a wide temporal window. Towards the middle and right of the phantom where the signal arrives later and is more dispersed, the subspace method gives a very good approximation to the *ground truth* signal, whereas the temporal binning result still deviates from the “ground truth” before the signal peak. Additionally, in the temporal binning results, when the peak time lies between two reconstructed frames the resulting signal curve shows a plateau rather than a single peak, as shown in Figure 5.6a.

In Figure 5.6b-c, the spatial characteristics of both reconstruction methods as well as both sampling trajectories were examined. Since the phantom was one voxel wide, the point spread function (PSF) on the plane through the volume center and perpendicular to the line was plotted. In Figure 5.6b-c, regardless of the sampling trajectory, the central peak was thinner in the subspace PSF than it was for temporal binning. The sidelobe aliasing was also better suppressed when

using the subspace reconstruction approach compared to the original temporal binning method for both cone and radial trajectories.

Figure 5.7 shows how the improvement in the temporal fidelity of the reconstructed signal with the subspace approach translated into improved angiography parameter estimation. In Figure 5.7a, parameters estimated with the temporal binning method exhibited a discrete and stepwise pattern, unlike the gradual variation in the ground truth image. As shown in the zoomed-in region in Figure 5.7a, one cause of these errors was when the true signal peak was not captured in the temporal binning reconstruction due to the limited temporal resolution. In comparison, the parameters estimated from the subspace approach were smoothly varying and closer to the ground truth. In Figure 5.7b, the relative error of the temporal binning and subspace methods with different regularization weights were plotted. It could be observed that parameters of temporal binning were mostly overestimated and deviated from the ground truth much further than the subspace results. In addition, the most accurate quantification was achieved when the regularization weight was set to $5e-4$ in the subspace reconstruction, which was adopted for subspace reconstructions of the in-vivo data below.

5.3.2 In-vivo angiography results

In-vivo angiograms reconstructed with subspace and temporal binning methods are compared in Figures 5.8 and 5.9. Note that the vasculature was already filled with blood at $PLD=88ms$ because a relatively long (1.8s) labeling duration was used in the protocol.

The notable improvement in spatial fidelity could be observed in images reconstructed from data acquired with a radial trajectory (Figure 5.8). Consistent with the simulated results in Figure 5.6b, the angiograms generated by the subspace method show improved delineation of fine vessels compared to temporal binning. For instance, more vessels could be visualized with better clarity branching off the middle cerebral artery (MCA) in the subspace result compared to the temporal binning result as shown in the enlarged blue box in the figure. The relative signal intensity of

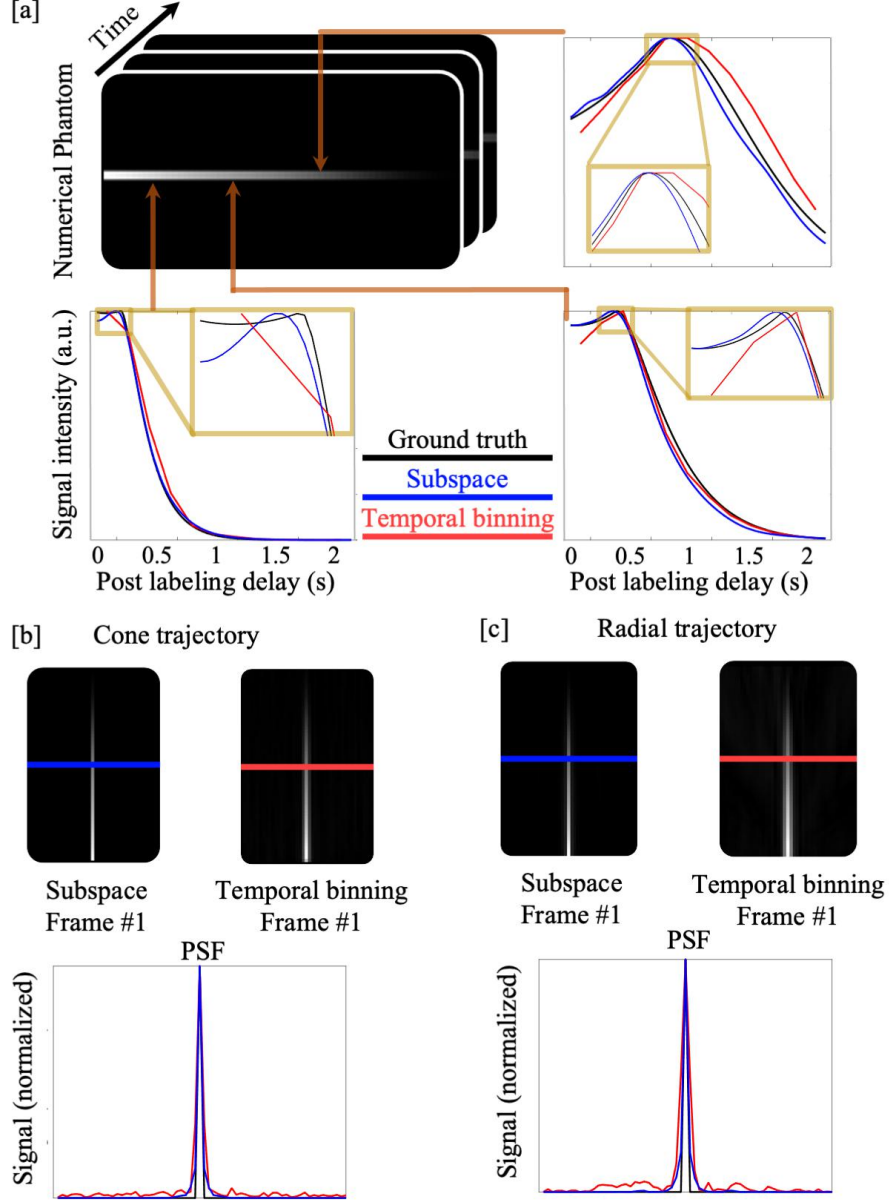


Figure 5.6: Spatiotemporal comparison of simulated results between the subspace and temporal binning reconstruction methods. a) The signal timecourses sampled from three points along the simulated vessel are shown. The curves reconstructed using the subspace method approximated the “ground truth” with better accuracy. b,c) The point spread function from the plane perpendicular to the simulated vessel using both cone (b) and radial (c) trajectories for the two reconstruction methods. Combined with cone and radial trajectories, the subspace method showed a thinner central lobe, lower sidelobe aliasing, and improved delineation of this narrow structure than temporal binning in both cases.

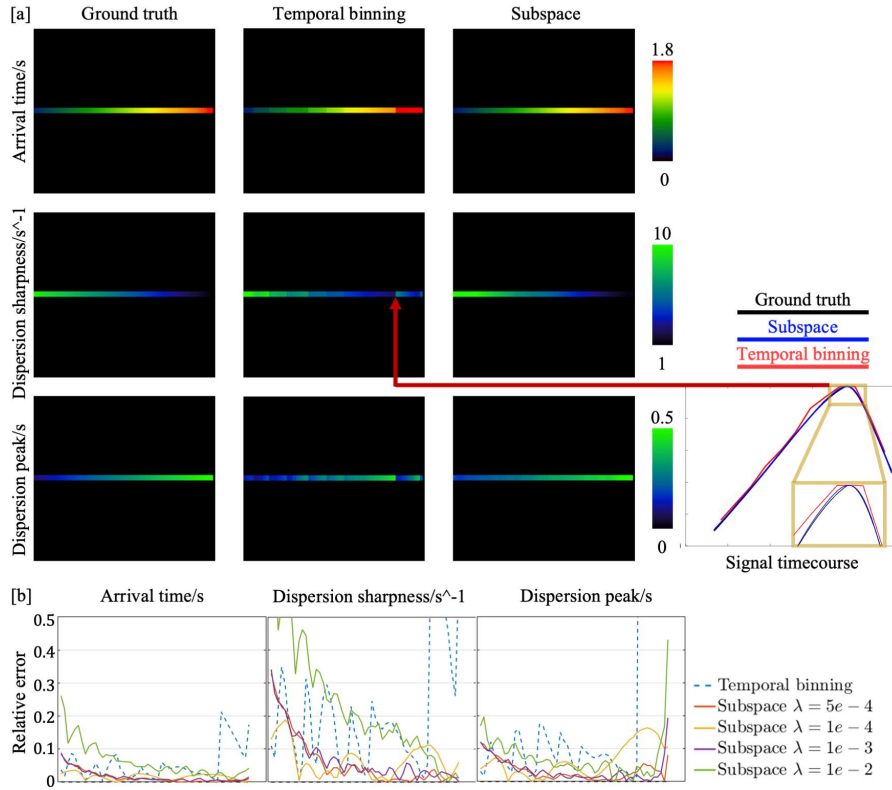


Figure 5.7: Parameter estimation from numerical phantom images reconstructed by subspace and temporal binning methods using the cone trajectory. a) Comparison of estimated dispersion parameters and arrival time between the two methods. b) Relative error of the estimated parameters along the simulated line compared to the ground truth. Parameters estimated from the subspace method with different regularization weights were explored.

vessels compared to background was further investigated with line profiles, where the peak to bottom difference were noticeably larger in subspace data, indicating that vessels were more discernable from the background in the subspace reconstruction.

In Figure 5.9, the data acquired with the cone trajectory was also reconstructed with temporal binning and subspace approaches respectively. Three consecutive frames in temporal binning angiography are shown in the first row. The subspace results have much higher temporal resolution than the temporal binning results. Between every two successive temporal binning frames, 10 more frames were reconstructed using the subspace method, demonstrating much smoother signal variations. Note, only one intermediate frame is shown here in Figure 5.9 for brevity. Regions around the internal carotid artery (ICA) were zoomed in from each frame and the dynamic of blood flow was better depicted temporally in subspace method

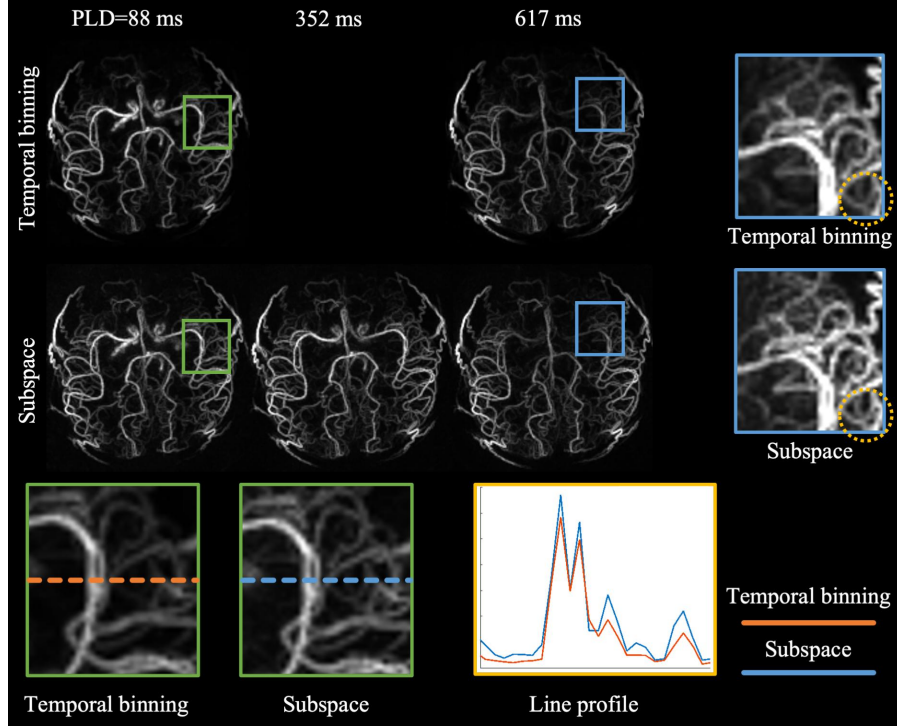


Figure 5.8: Spatial comparison of dynamic MRA acquired with a radial trajectory and reconstructed by subspace and temporal binning methods. Note that the vasculature was already filled with blood at PLD=88ms as a relatively long labeling during (1.8s) was used. The quoted PLD represents the center of the temporal window for each frame. The temporal binning result did not have the image at PLD=352ms due to limited temporal resolution. Regions in the green box were zoomed for comparison of the visibility of thin vessels. Line profiles were sampled within the green box for both reconstruction methods. Regions enclosed in the blue box were also zoomed in to confirm the better visibility of vessels in the subspace results across time. The yellow circle marked an example where thin vessels were hard to distinguish from the background when using temporal binning but became much clearer when using the subspace approach.

than in the temporal binning method. In addition, the spatial fidelity of MRA was also improved in the subspace approach compared to temporal binning as illustrated in the zoomed-in green regions.

5.3.3 Quantitative comparison

The time-resolved MRA in vivo data reconstructed by the two different methods was further analyzed to extract physiological parameter maps (Figure 5.10). In agreement with the simulation results in Figure 5.7a, the in vivo arrival time estimated from temporal binning exhibited stepwise discontinuities along the arteries (Figure 5.10a), while the subspace data gave a more realistic smooth, continuous increase in transit

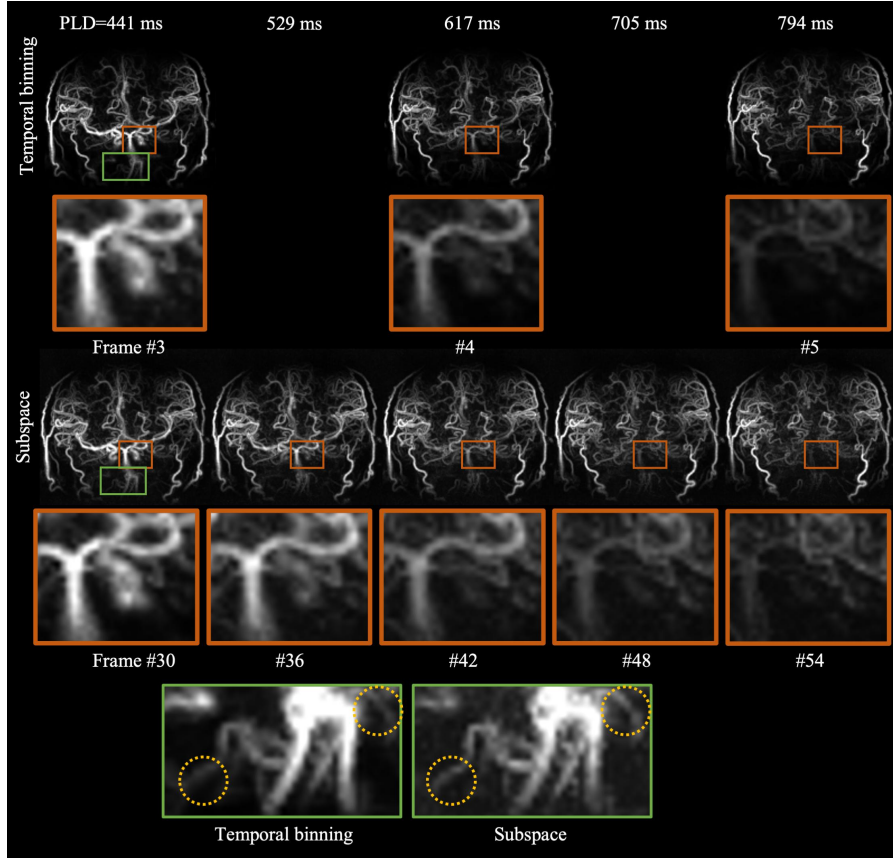


Figure 5.9: Comparison of in vivo dynamic MRA acquired with a cone trajectory and reconstructed by subspace and temporal binning methods at different post labeling delay times. 3 out of 12 frames reconstructed by temporal binning were shown on the top row. Similarly, among the 144 frames in total reconstructed by subspace method, 5 equispaced frames between 441 ms and 794 ms after labeling are also shown. 3 of them matched the timepoints of the consecutive frames #3~5 of temporal binning result. The blood flow dynamics shown in the zoomed-in regions demonstrated superior temporal discernability of subspace method compared to temporal binning. The zoomed-in green box further showed evidence that the subspace method provided better clarity of vessels than temporal binning as highlighted by the yellow circles.

time along the arteries, thanks to its ultra-high temporal resolution. Additionally, although there is no ground truth for this in vivo data, the arrival time appears to be over-estimated with temporal binning when the transit times are close to the length of the readout train (~ 2.1 s). This overestimation was observed in both simulated and in-vivo results, exemplified in the white circle, but was noticeably improved in the subspace results. The blood dispersion parameters also benefited from the improved temporal resolution and fidelity available with the subspace method as shown in Figure 5.10b. For instance, the dispersion sharpness of temporal binning

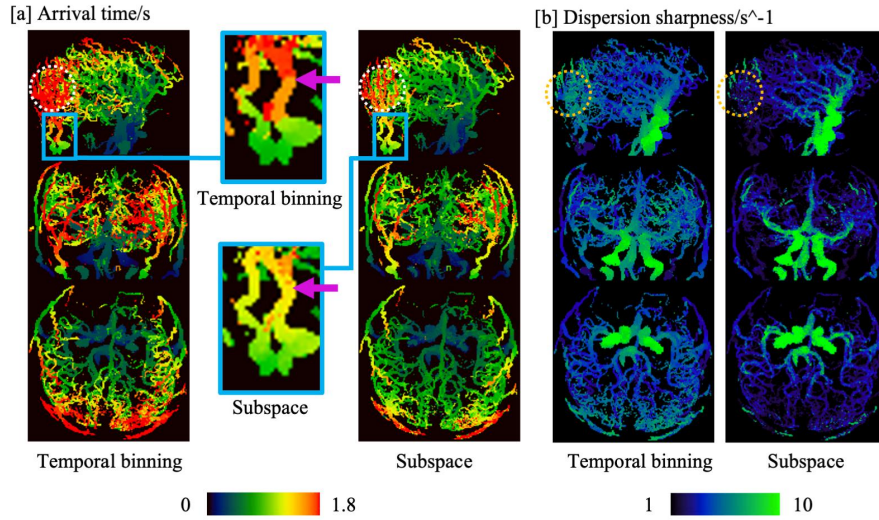


Figure 5.10: Comparison of blood arrival time and dispersion sharpness estimated from temporal binning and subspace results. a) Arrival time in temporal binning MRA was overestimated and discontinuous (highlighted by the purple arrows), whereas that in subspace was smoother and more realistic. b) The dispersion sharpness estimated from temporal binning also demonstrated an increase in very distal vessels, which would not be expected as dispersion should continue to increase along the path of the vessels, whereas this effect was much less apparent in the subspace data. These results are consistent with the numerical phantom simulations shown in Figure 5.7

MRA in the distal arteries was much higher than with the subspace reconstruction, which is inconsistent with previous work[90] and the expectation that dispersion will continue to increase as blood passes down the vascular tree. This observation was also consistent with the simulation results (yellow circle).

Parameter map histograms derived from the temporal binning and subspace reconstruction methods are shown in Figure 5.11, both for a single subject (Figure 5.11a) and for all subjects (Figure 5.11b). In both cases, the arrival time distribution for the temporal binning data showed discrete peaks, unlike the smoother distribution observed with the subspace data, most likely caused by the limited temporal resolution of the temporal binning data. As was observed in Figure 5.10, the dispersion sharpness appeared to be overestimated in temporal binning relative to the subspace approach. Although the dispersion peak was also likely biased in the temporal binning results based on our simulation results, the direction of deviation varied (Figure 5.7a).

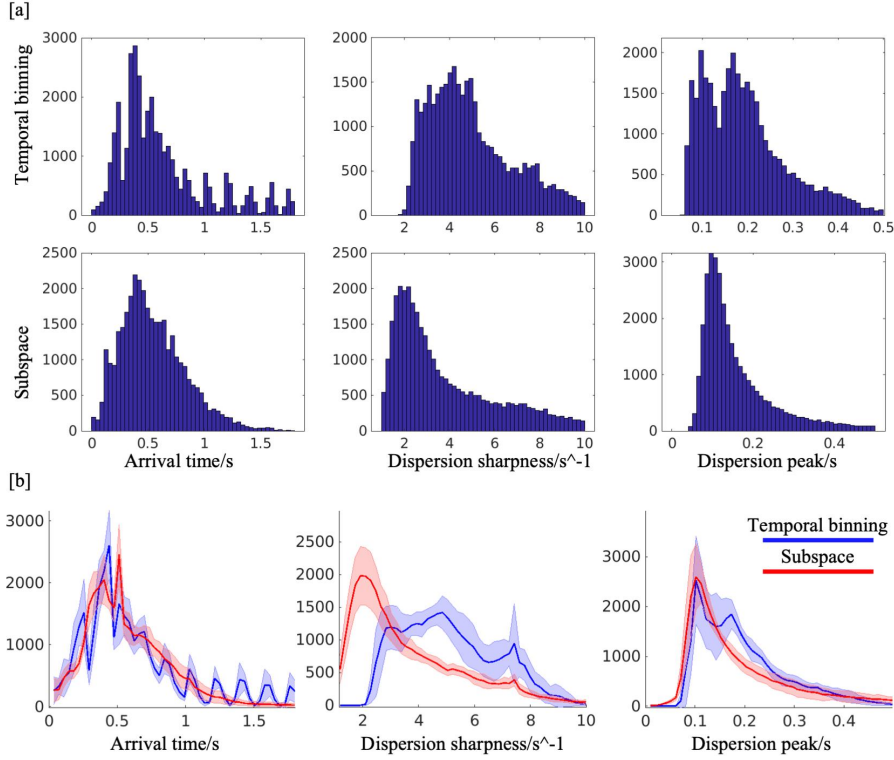


Figure 5.11: a) Histogram of three angiography parameters estimated from one subject. b) The distribution of these parameters on the group level. The average count of each value was plotted with the “red” and “blue” curves corresponding to subspace and temporal binning reconstruction methods, respectively. The standard deviation of the voxel count across subjects was added as margins around the curve.

5.3.4 Comparison with other advanced reconstruction methods

In Figure 5.12, the angiography results were further compared against other advanced methods reconstructed with the same temporal resolution as the subspace method from the same k-space data. As all 144 frames were explicitly reconstructed, the *LLR-matched* approach had much higher computation time and memory requirements (300GB memory, 28hr reconstruction time) than the subspace method (130 GB memory, 4hr reconstruction time). In addition, since $12\times$ more frames were reconstructed than temporal binning without introducing additional regularization, LLR-matched exhibited degraded image quality and only the large arteries with strong signal intensity could be visualized while the small distal vessels were lost as shown in the green box. The reduced sampling per frame of LLR-matched

also increased its dependence on locally low rank regularization, which introduced artifacts in arteries highlighted by the red arrow. Extreme MRI used an even more sophisticated reconstruction with multi-scale low rank patches and resulted in better sharpness of small vessels than LLR-matched. However, SNR was low and image details were inferior to those of the subspace reconstruction as could be seen from the enlarged green box. Overall, the subspace results demonstrated the best temporal and spatial fidelity and resolution among these reconstruction methods.

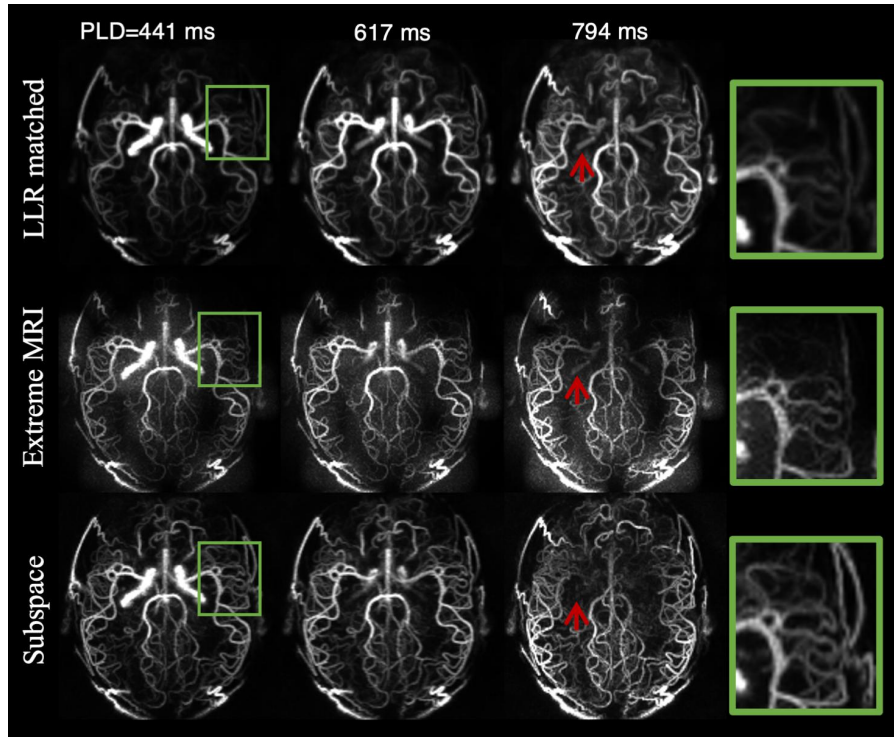


Figure 5.12: Comparison of subspace with other advanced reconstruction methods. LLR-matched adapted the temporal binning reconstruction to the same temporal resolution as subspace. Extreme MRI is a multi-scale low rank method and also had matched temporal resolution. Regions enlarged within the green box show loss of details in ExtremeMRI and LLR-matched results, but better clarity in subspace. Red arrows highlighted falsely reconstructed arteries in LLR-matched due to regularization. Further investigation of the effects of regularization weight in ExtremeMRI and LLR-matched is shown in Supporting Figures 5.4 and 5.5

5.4 Discussion

In this work, a subspace, generated by linearly compressing a kinetic model, was incorporated into the reconstruction of 4D dynamic angiograms to achieve ultra-high

temporal resolution (14.7ms) and improved spatiotemporal fidelity. Our proposed subspace reconstruction was optimized through numerical simulations, where the optimal number of subspace principal components was chosen to balance the relative fitting error and computational requirements. Simulations were also used to find the optimal regularization weight, which is challenging to do using in-vivo data where there is no ground truth. The reconstructed in-vivo results were compared between the subspace and temporal binning methods and validated against the simulation results both qualitatively (improvement of spatiotemporal fidelity) and quantitatively (improvement of physiological modeling accuracy). Additionally, the proposed method was shown to outperform other advanced methods (*LLR-matched* and *ExtremeMRI*[37]) when the same spatial and temporal resolution were used.

Incorporation of the modality specific prior knowledge (i.e., the kinetic model) was essential in obtaining ultra-high temporal resolution 4D angiograms without increasing scanning time (~ 6 min), as the high undersampling factor per frame presented a very ill-conditioned reconstruction problem. Taking advantage of compressed sensing[34] (e.g., low rank regularization) and adjusting the regularization weight could alleviate the problem of insufficient k-space sampling while also potentially introducing artifacts. As shown in Figures 5.4 and 5.5, both *LLR-matched* and *ExtremeMRI*[37] methods were evaluated with different regularization weights, and the results were either too noisy (i.e., under regularized) or too blurry (i.e., over regularized), with loss of distal vessel visibility. These results demonstrate that relying solely on locally low rank regularization limited the temporal variation to compensate for the insufficient sampling per frame and was not enough for faithful reconstruction of ultra-high temporal resolution 4D angiograms. In contrast, our subspace method incorporated a signal model of blood flow into the reconstruction, limiting the degrees of freedom. The fact that k-space samples acquired across the whole train of readouts can contribute to the estimation of each subspace coefficient map likely improves the spatial fidelity of the reconstruction. The subspace approach also avoids the temporal misallocation of signal which is inevitable in the temporal

binning method. In our subspace method, a locally low rank regularization term was also included on the coefficient maps to reduce noise.

Several characteristics of the sequence used to acquire our data also contributed to achieving ultra-high temporal resolution 4D angiograms. Firstly, the 3D golden angle[20] and repeat-first ordering[73] in the sequence guaranteed similar and approximately uniform k-space sampling at each timepoint, supporting a frame window size of one TR in the subspace reconstruction. Voxels at different timepoints were also assumed to be spatially aligned for the kinetic model constraint to be applicable voxel-wise. As the total readout time within each repeat is ~ 2 s, it is unlikely that significant motion will occur within each train of readouts. Since the between-repeat motion was shared for samples acquired across all TR periods, motion would be more likely manifested as blurriness rather than spatial misalignment between TRs, which is expected to make the subspace constrained reconstruction of 4D angiograms less motion sensitive.

Additionally, the proposed reconstruction was particularly advantageous for trajectories with lower sampling efficiency, such as 3D radial imaging, as can be seen from the simulation in Figure 5.6b. The poorer k-space coverage compared to the cone trajectory[13] means the radial approach benefits more from the effective sharing of information across timepoints that is achieved with a subspace reconstruction.

Compared to sliding window approaches like KWIC[73, 95, 96], which reconstruct each frame independently with gridding, our method took advantage of the sampling across the whole train of readouts without timepoint mismatch between acquisition and reconstruction(i.e., signal from multiple TRs was combined for image of a single timepoint). Additionally, the LLR regularization applied on the subspace coefficient maps improved SNR in the final images, whereas the gridding approach used in KWIC would not provide additional denoising. Although a sliding window approach could be also combined with compressed sensing to achieve additional noise suppression for high temporal resolution dynamic MRA, the computational requirements would be enormous. Compared to previously reported state-of-the-art work on 4D dynamic MRA, for which compromises had to be made either

in temporal resolution[73] (1 mm^3 spatial resolution with $\sim 100\text{ ms}$ temporal resolution) or in spatial resolution[74] (59 ms spatial resolution with 2 mm spatial resolution in slice direction), we achieved 1.1 mm isotropic spatial resolution, 14.7 ms temporal resolution and $200 \times 200 \times 125\text{ mm}$ acquisition FOV within a $\sim 6\text{ min}$ acquisition time.

The proposed subspace reconstruction method could be extended to further improve the image quality of dynamic MRA. For instance, it could be combined with time-encoded PCASL to boost SNR by allowing for larger flip angle readouts and better background suppression[94]. Incorporating the kinetic model informed reconstruction into such a protocol could combine the advantages of SNR and spatiotemporal resolution for better fidelity angiograms.

While the linear compression of the signal dictionary served as a close approximation for the true underlying signal model, there are several drawbacks to this approach. Modeling the angiography signal variation of the sequence in this work is complex as the labeled blood flows in the vessels while experiencing dispersion. Additionally, the in vivo transit time varied across a wide range from close to 0 to longer than 1.8 s according to our results, which is reflected as a temporal shift in the signal time series. Therefore, according to our simulations, 12 principal components were required to characterize 99.95% of signal variability in the dictionary. Further increasing the number of principal components gave marginal improvement in signal fitting but increased the computational time and memory significantly. In addition, using more principal components would have weakened the prior constraint, potentially leading to increased noise sensitivity. In some extreme cases, where transit time was short or dispersion sharpness was large, the signal variation could not be represented accurately by the compressed subspace, contributing to errors in the reconstructed images. Non-linear methods like autoencoders[101] are capable of representing complex signal variations with a smaller number of independent components (i.e., in the latent space), as demonstrated by Arefeen, et al.[102]. However, the computational convenience brought by the permutation of linear operators would be lost, and the optimization would need to be performed with a

subset of frames per iteration to accommodate limited memory. The balance between computational efficiency and representation accuracy remains to be explored in greater detail in future work.

Apart from the linearly compressed representation of the kinetic model being imperfect, the model itself might not be applicable to some complex flow scenarios present in patients. For example, modeling of the complex blood flow in an aneurysm is still the subject of ongoing research[103]. Therefore, the actual generalizability of subspace representation for the kinetic model to complex scenarios requires further investigation through testing in patient cohorts. By examining the residuals of model fitting voxel-wise and those with higher residuals might give us some clue in terms of how well data fit to the model.

In this preliminary study, a group of 8 subjects was scanned to prove the feasibility and advantage of the proposed model informed reconstruction for accurate qualitative and quantitative assessment. Patients with cerebrovascular disease should be recruited and studied in the future for a more comprehensive examination of the effectiveness of our method. An effort could also be made to acquire ground truth data for the validation of the accuracy of the angiography quantification results obtained from the proposed reconstruction (e.g. using a very long scan time reference).

5.5 Conclusion

In this work, we incorporated an angiographic kinetic model into the image reconstruction process and combined this with a subspace technique to achieve ultra-high temporal resolution 4D MRA. Our method took advantage of the prior knowledge of the angiographic signal time-course to compensate for reduced sampling per frame and disentangled time-varying blood signal at different timepoints. The spatial and temporal fidelity of the resulting angiograms were, therefore, both notably improved. Parameter maps derived from the subspace results also benefited from the improved temporal fidelity and achieved better accuracy than that of the conventional temporally binned images in numerical simulation. Investigation on a

group of healthy subjects demonstrated superior image quality and angiography parameter quantification using the proposed subspace reconstruction compared to the temporal binning method, consistent with the simulation results.

Code

The code for cone trajectory used in this work could be found at <https://github.com/Michaelsqj/TrajectoryDesign>.

The code for reconstruction and simulation could be found at https://github.com/Michaelsqj/dynamic_angio.

The fabber code for model fitting could be found at https://github.com/tomokell/fabber_models_asl/tree/capria.

6

Correction methods to improve robustness to motion using the CASPRIA sequence

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6.1 Introduction

MRI is susceptible to motion corruption due to prolonged scanning times. Subject motion, ranging from occasional nodding and coughing with healthy subjects to frequent and large-scale movements with disoriented patients, results in a decreased signal-to-noise ratio (SNR) and image artifacts. This degradation in image quality can negatively affect clinical diagnosis and increase costs due to the need for repeat scans [104, 105]. Different MRI modalities are affected by motion to different degrees. Arterial spin labeling (ASL)-based blood flow imaging is particularly susceptible to motion corruption since it relies on the difference between two images in which the static tissue signal dominates. Therefore, any changes due to motion can lead to large artifacts that obscure the signal of interest.

A variety of MRI based techniques have been developed to estimate subject motion during scans. One stream of methods acquires dedicated navigator images during scanning to determine the motion status by comparing the navigators with a reference. Prospective motion correction (PROMO) [106, 107], for instance, acquires 2D images on three orthogonal planes and compares them with the fixed reference navigator. Volumetric navigators were also used in some work [108–110], allowing a more straightforward comparison with the reference, while some methods perform motion estimation directly in k-space [111, 112]. However, insertion of additional navigators may alter the original contrast and increase scanning time. Self-navigated methods seek to use the existing readouts to correct for motion using data in existed sequence. For example, joint motion estimation and image reconstruction was proposed for multishot structural MRI [113]. Navigators can also be reconstructed from the k-space center of radial data [114].

However, the above mentioned methods could not be readily applied to correct for motion in a recently introduced ASL-based sequence called combined angiography, structural and perfusion radial imaging using ASL (CASPRIA) [60, 115], which has a global inversion pulse that leads to a time-varying signal during a train of spoiled

gradient-echo readouts (Figure 6.1 and Figure 6.2a). Note that it shares similar form, a magnetization preparation followed by a long train of readouts, to other widely used sequences like MP-RAGE [40], fast spin echo [116]. While the long train of readouts in each repeat potentially contains sufficient k-space information to reconstruct a single navigator, they cannot simply be combined because the image contrast varies across the navigator acquisition window due to the magnetization preparation. To address this, we propose to explicitly model the signal evolution across the readout train and incorporate it into a subspace-based reconstruction (similar to T_2 -shuffling [39] and the work described in the previous chapter) to reconstruct navigators with greatly reduced artifacts, thus improving registration accuracy.

Accurately estimated motion parameters using the subspace-based navigators were used to update k-space locations. However, methods like ASL require a subtraction between two sets of data with and without labeled blood (called label and control images), which is no longer feasible in k-space because the k-space sample locations are no longer matched after motion correction. Image space subtraction from separately reconstructed label and control images is possible, but it loses the advantage of artifact reduction by enforcing spatiotemporal regularization on the difference image. To mitigate artifacts in the subtracted image due to the different aliasing patterns of the strong background signal and residual motion, we propose a split-update method which jointly reconstructs the label and control images while imposing locally low rank (LLR) [36] regularization on their difference.

The proposed subspace-navigator approach was applied to correct for rigid brain motion on the three modalities generated by the CASPRIA sequence: angiography, perfusion and structural images, while the split-update method was applied to the angiography and perfusion image reconstruction to mitigate subtraction artifacts. These methods were tested in numerical simulations and in a group of 8 healthy subjects, demonstrating the feasibility and significant improvement in image quality on all three modalities with the proposed motion correction approach.

6.2 Method

6.2.1 Pulse sequence design

As illustrated in Figure 6.1, the CASPRIA [60] sequence is an ASL-based sequence consisting of multiple repeats. Consistent with the general form of sequences our motion correction method can be applied to, each repeat is composed of a magnetization preparation followed by a train of readouts. The magnetization preparation part of the sequence consists of three sequential modules: water suppression enhanced through T_1 effects (WET) [61] for pre-saturation of the imaging volume, PCASL [57] for labeling inflowing arterial blood, and a single adiabatic inversion pulse for background tissue suppression. Note that an interleaved scheme across repeats ensures the same k-space sample points are acquired for *label* and *control* images close together in time. Subtraction of label and control data isolates the labeled blood signal, whereas their summation gives the static tissue signal. The acquisition section is comprised of a train of readouts using non-Cartesian rotating cone trajectories [13] with 3D golden angle ordering [20]. A number of readouts at adjacent acquisition timepoints are combined across all repeats to achieve sufficient k-space sampling for the reconstruction of dynamic images.

Assuming within-repeat motion is negligible, i.e., there is minimal motion during each readout train of around 2 seconds, a navigator was reconstructed from all the k-space data acquired during each repeat, as shown in Figure 6.1. The relative motion between repeats can then be estimated from registration among the navigators and is used to update the k-space trajectories and data. The motion corrected images (i.e., angiography, perfusion and structural images) were reconstructed from the updated k-space data.

As the inversion pulse, used for background suppression, introduces a continuously varying contrast during the train of readouts, grouping all readouts within a repeat and reconstructing with conventional methods like conjugate gradient (CG) SENSE [28] or simple gridding [79] would generate images with significant artifacts

and blurring (Figure 6.2b). Therefore, a subspace-based method was developed to accommodate for the signal evolution within each repeat.

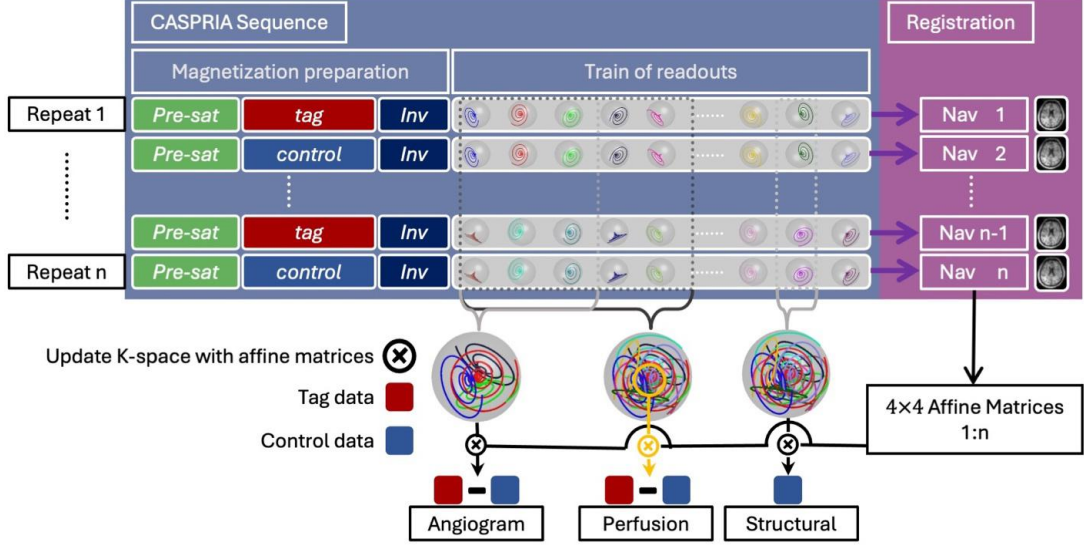


Figure 6.1: Overview of motion correction process using the CASPRIA sequence. Navigators 1 to n were reconstructed from the train of readouts in repeat 1 to n, respectively. Registration among all the navigators allows estimation of relative motion in the form of rigid transformation matrices. The matrices were then used to update the k-space trajectories and data, from which the motion corrected angiography, perfusion and structural images were reconstructed.

6.2.2 Subspace-based reconstruction of navigators

Figure 6.2a illustrates the process of reconstructing navigator images using a subspace method for one repeat (without loss of generality, repeat n was used in Figure 6.2a). Firstly, we modeled the time-course of the tissue signal during the train of readouts after the inversion pulse. This time-course is approximately identical across repeat 1~n (when ignoring the effects of the inflowing arterial PCASL labeled blood) and consists of a saturation-inversion T_1 recovery curve, modulated by the readout excitation pulses. The PCASL pulse would cause some magnetization transfer effect and affect the apparent T_1 .

Equation 6.1 describes how magnetization evolves from one readout to the next during one repeat. i denotes the i^{th} readout within the train of readouts and α_i denotes corresponding flip angle, which can vary across the readout train. Assuming

equilibrium magnetization $M_z = 1$, $M_{z_i}^-$, $M_{z_i}^+$ represents the longitudinal magnetization immediately before and after i^{th} RF pulse respectively. M_{xy_i} represents transverse magnetization after i^{th} RF pulse. As TE is short in the sequence, T2* decay is not included in the model. TR represents the duration of single readout. Following Equation 1, the tissue signal, M_{xy_i} , in one voxel can be sequentially calculated for each readout in a single repeat.

$$\begin{cases} M_{z_i}^- = 1 - \left(1 - M_{z_{i-1}}^+\right) * \exp\left(-\frac{TR}{T_1}\right) \\ M_{z_i}^+ = M_{z_i}^- * \cos(\alpha_i) \\ M_{xy_i} = M_{z_i}^- * \sin(\alpha_i) \end{cases} \quad (6.1)$$

Given the sequence parameters TR and α_i , the signal evolution is completely dependent on the T_1 of each voxel. Therefore, a subspace was used to constrain the navigator reconstruction with this T_1 dependent model. Firstly, a simulated dictionary of plausible signal time-courses was generated using Equation 1 with T_1 ranging from 250ms - 4000ms spaced by every 10ms. The parameters in Equation 6.1 followed the actual protocol described later. Secondly, principal component analysis (PCA) was used to linearly compress the dictionary. The first 3 principal components, $\Phi = [\phi_1 \ \phi_2 \ \phi_3]$, represent 98.7% of the signal variance in the dictionary. The time-course of each voxel in the 4D images, x , can be represented as linear combination of the principal components, Φ , the weights of which are the coefficient maps, α (different from flip angle α_i above), as proposed by [39]

$$x = \Phi\alpha \quad (6.2)$$

Given the subspace representation, the reconstruction of the coefficient maps from a single repeat can be formulated as:

$$\hat{\alpha} = \underset{\alpha}{argmin} \|PFC\Phi\alpha - y\|_2^2 + \lambda \|W\alpha\|_1 \quad (6.3)$$

where P represents the k-space sampling, F is the non-uniform fast Fourier transform (NUFFT), C is the coil sensitivities, W denotes Daubechies 4 wavelet transform, and λ is the regularization weight.

After reconstruction, a 4D time series x was obtained for each repeat where the contrast of each frame of x is matched with that of one readout. The frame

corresponding to 960 *ms* after inversion was selected as the actual navigator used for registration as it gives similar tissue contrast to MPRAGE [40], which is known to be well suited to accurate registration.

Because of the correct modeling of the signal evolution across the readouts, the subspace reconstructed navigator demonstrated clearer anatomical structure and boundaries compared to the navigators reconstructed with gridding and CG-SENSE, as shown in Figure 6.2b.

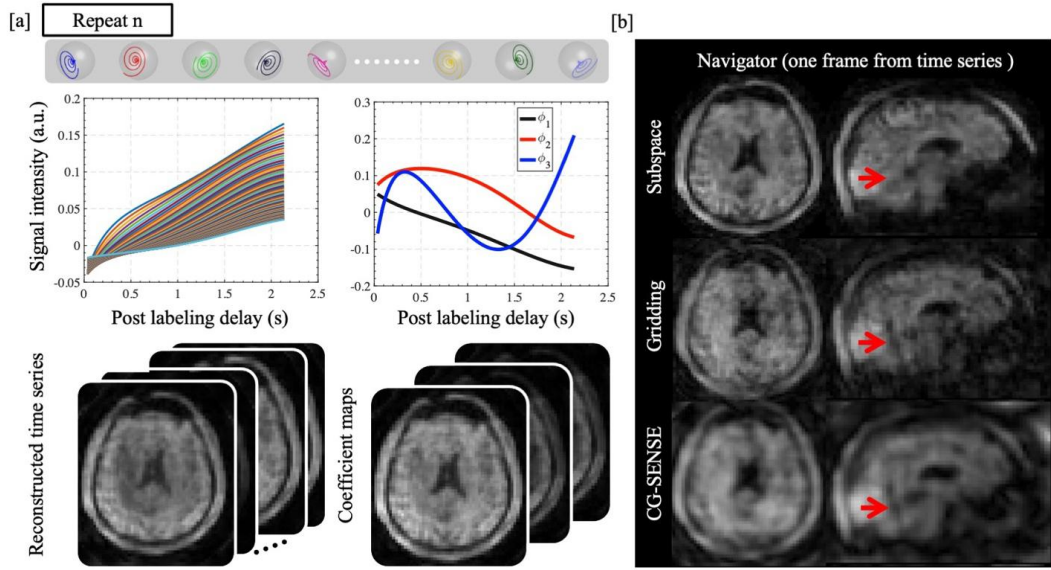


Figure 6.2: Reconstruction for subspace-based navigators. [a], for each repeat (without loss of generality, repeat *n* was shown as an example), the signal evolution of static tissue within each voxel follows a model dependent on sequence parameters and T_1 . Given the sequence, a dictionary of plausible 1D signal evolutions was simulated with various T_1 values. The dictionary could be efficiently linearly compressed with 3 principal components (ϕ_1 ϕ_2 ϕ_3). The **coefficient maps** α corresponding to the three principal components were reconstructed and then expanded to a full **time-series** of dynamic structural images using Equation 6.2 Each frame of the time-series corresponds to the tissue contrast in one readout. [b], Comparison between an example navigator reconstructed with subspace approach, gridding and CG-SENSE methods. The frame corresponding to 960 *ms* after inversion in the **time-series** was selected as the actual navigator for motion correction. Artifacts pointed by red arrows could only be seen in gridding and CG-SENSE results and were speculated to be caused by contrast mixing.

6.2.3 Registration among navigators

The navigators reconstructed from each repeat were used to estimate subject movement. The linear registration tool FLIRT [117] was used to register the

navigator from each repeat to that of the first repeat as shown in Figure 6.1 and generated affine transformation matrix for each repeat. These affine transformation matrices were then used to update the k-space in each repeat. Specifically, an image space rotation in each affine matrix corresponds to a rotation of the k-space trajectory around the center, while an image space translation corresponds to a phase ramp in the k-space data. Each repeat was updated with the separately estimated rotations and phase ramps. The updated k-space was grouped for reconstruction of perfusion, angiography and structural images described below.

However, when we manually check the registered result, there were some notable, though tiny, mismatch between brains of two certain navigators. It was speculated that the strong scalp signal drove the FLIRT registration, while matching the brain was of higher importance. Therefore, we developed a second stage registration refining process by registering again on the navigators updated by estimated motion in the first stage. To enforce the registration between brains, we adopted brain mask weighted registration in FLIRT. Traditional brain extraction method BET in FLIRT cannot generate accurate masks due to the limited quality of navigators. The deep learning based Synthstrip[118, 119], however, generated accurate brain masks, as shown in Figure 6.3. Experiments showed that brain mismatch was alleviated after stage 2. In practice, the second stage was used as supplementary to the first stage.

6.2.4 Split reconstruction of perfusion and angiographic images

Due to the high under-sampling factor used in CASPRIA acquisition, regularization is typically used to improve the conditioning of reconstruction. Conventionally, the label and control data are acquired with matched k-space trajectory and subtracted prior to the reconstruction of ASL perfusion and angiography images, i.e., only the difference image needs to be reconstructed. Therefore, a simple regularized reconstruction algorithm can be applied. However, with our proposed motion correction, the k-space trajectory in each repeat is updated with a different rotation matrix, so that the k-space trajectories in the label (odd repeat) and

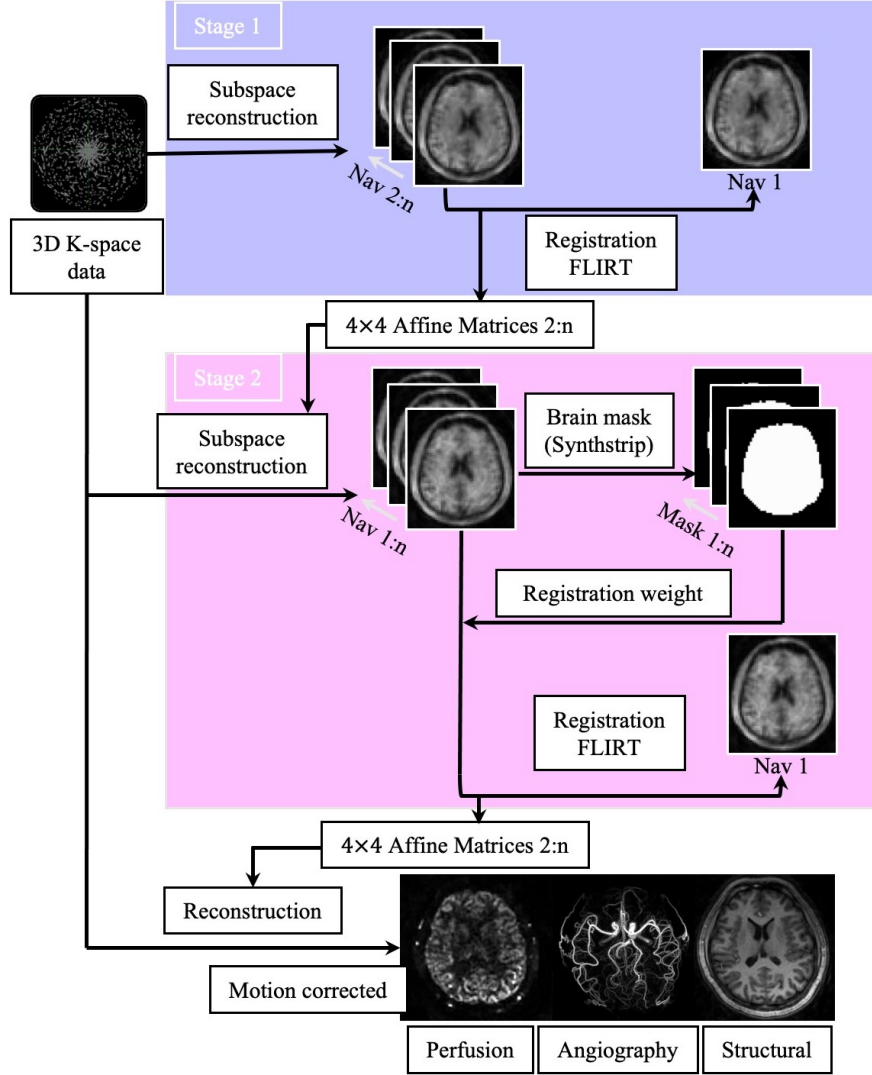


Figure 6.3: Two stage registration pipeline to refine brain registration accuracy.

control (even repeat) acquisition are no longer matched, making direct k-space subtraction infeasible. Additionally, during testing we found that subtraction of separately reconstructed label and control images led to significant artifacts due to the different aliasing patterns of the strong static tissue signal; this prevented us from leveraging spatiotemporal correlations in the blood signal itself for regularization. Hence, we propose a new scheme where the label and control images are jointly reconstructed with a locally low rank (LLR) [36] regularization enforced on their

difference, as shown in Equation 6.4:

$$\hat{x}_1, \hat{x}_2 = \underset{x_1, x_2}{\operatorname{argmin}} \|P_1 F C x_1 - y_1\|_2 + \|P_2 F C x_2 - y_2\|_2 + \lambda \sum_i \|R_i(x_1 - x_2)\|_* \quad (6.4)$$

where x_1, x_2 are label and control images, respectively, R_i is an operator for extraction of local patch i . and P_1, P_2 represent sampling trajectories for label and control data. A split-update method adapted from POGM [120] was used for optimization. To be more specific, the iterative optimization alternates between updating x_1 and x_2 , as shown in Equation 6.5:

$$\begin{cases} \hat{x}_1 = \underset{x_1}{\operatorname{argmin}} \|P_1 F C x_1 - y_1\|_2 + \lambda \sum_i \|R_i(x_1 - x_2)\|_* \\ \hat{x}_2 = \underset{x_2}{\operatorname{argmin}} \|P_2 F C x_2 - y_2\|_2 + \lambda \sum_i \|R_i(x_1 - x_2)\|_* \end{cases} \quad (6.5)$$

Where x_2 and x_1 are fixed when updating $\hat{x}_1$ and $\hat{x}_2$, respectively.

6.2.5 Subspace reconstruction for dynamic structural images

As shown in Figure 6.1, the dynamic structural image has the same temporal resolution as TR. The reconstruction still follows Equation 6.3 using the same subspace, except that y in Equation 6.3 now represents all data from PCASL control repeat.

6.2.6 Experiments: Numerical simulation

To evaluate the motion estimation accuracy, numerical simulations were performed based on data from one scan with minimal subject movement. The acquisition protocol used in simulation was the same as the in vivo scanning protocol described below. A motion trajectory specifying rotation and translation parameters for each repeat, shown as the black curves in Figure 6.3a (the complete set of parameters can be found in Figure 6.4), were used to corrupt the k-space data, simulating head movements during the scan. The navigator image for each repeat was reconstructed and registered following the methods described above. The residual uncorrected motion was calculated by multiplication of the estimated affine matrix and the ground-truth motion matrix, such that perfect motion estimation would result in an

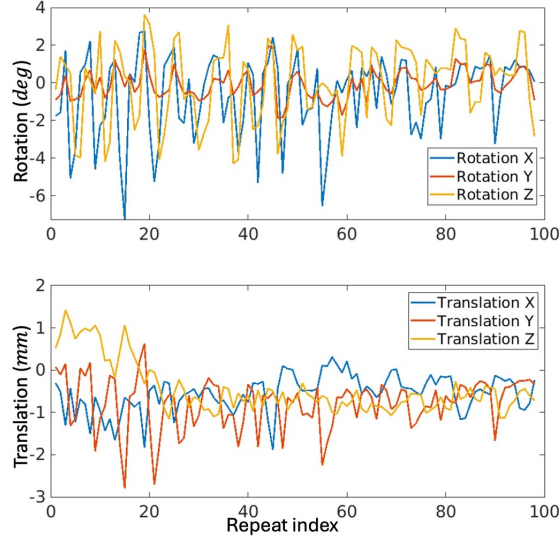


Figure 6.4: Motion parameters used for numerical simulations.

identity matrix. Residual motion parameters (rotation and translation on 3 axes) were then calculated from the residual affine matrix using the ‘avscale’ function in FLIRT [117]. For comparison, navigator images were also reconstructed with gridding [79] and CG-SENSE [28] and evaluated in the same manner to help assess the potential benefits of the proposed subspace approach.

Since perfusion images are most sensitive to motion, due to the weak blood signal relative to static tissue, simulated perfusion images were reconstructed from k-space data without motion, with added motion and with motion correction to qualitatively assess the efficacy of the proposed method.

Root-mean-square error (RMSE) was calculated with all residual rotation and translation parameters from all repeats as both rotation and translation have similar scales.

6.2.7 Experiments: In-vivo scanning protocol

Acquisition parameters

To assess the proposed motion correction method, a total number of 8 subjects were scanned on a 3T Prisma scanner (Siemens Healthineers, Erlangen, Germany) using a 32-channel receive-only head coil under a technical development protocol agreed by local ethics and institutional committees. Two back-to-back scans with

the same protocol were performed on each subject. In the first scan, subjects were instructed to move their head to follow a marker on the screen, which moves every 20 s. In the second scan, subjects were instructed to stay still. We termed the data for the first scan as *cued motion data* and the second as *reference data*.

For each scan, the protocol followed the settings used in our previous study [13]: briefly, after each PCASL preparation and single inversion pulse, a train of 144 readouts was acquired within each repeat. A quadratically varying flip angle scheme was used in each readout train, ranging between 3°-12°. The temporal resolution used to reconstruct perfusion and angiographic images was 384 ms and 192 ms, respectively. Dynamic structural images were reconstructed using the subspace approach with a temporal resolution equal to the readout TR (16 ms). 12 frames, 6 frames and 144 frames were reconstructed for angiography, perfusion and dynamic structural images respectively.

An additional MPRAGE [40] image was acquired for each subject as reference for evaluating motion correction accuracy. The sequence used $TI = 904\text{ ms}$, $TE = 3.4\text{ ms}$, echo spacing = 8.8 ms , turbo factor = 128, and spatial resolution = 1.7 mm isotropic.

Reconstruction parameters

Coil compression [77] was used to reduce the original 32 channel data to 8 channels for reconstruction. Coil sensitivity maps were estimated from a pseudo-structural image (reconstructed by regridding averaged label and control data from the final 360 ms of the readout train where the static tissue signal is more consistent) using the adaptive combine method [78]. Despite the presence of motion, we found that coil sensitivity maps can still be reliably estimated from the pre-correction pseudo-structural image. For both navigator and dynamic structural image reconstructions, 3 principal components were used and $\lambda = 1e - 4$ was empirically chosen as the weight for wavelet regularization. For perfusion and angiography reconstructions, $\lambda = 7e - 2$ was chosen empirically as the weight for LLR regularization. The locally low rank patch size was $5 \times 5 \times 5$ voxels.

The reconstruction matrix sizes for both angiography and structural images are $186 \times 196 \times 150$ with isotropic spatial resolution 1.13 mm . The navigator and perfusion images share same matrix size $62 \times 66 \times 50$ and isotropic spatial resolution 3.39 mm . Note that motion correction was not applied on the *reference data* except for the cases specifically mentioned below.

6.2.8 Quantitative evaluation

To investigate the effectiveness of our motion correction method quantitatively, Pearson correlation coefficient was calculated between images with and without cued motion before and after applying motion correction, where the reference images are the data without cued motion and reconstructed without the motion correction pipeline. To align the position of the two datasets without introducing blurriness due to image space interpolation, a pseudo-structural image was reconstructed for data acquired with and without cued motion. A transformation matrix was extracted by registering the pseudo-structural image of motion corrected data to reference data. The same transformation matrix was then multiplied with the affine matrices generated by the registration step for updating the k-space before reconstructing the final angiography, structural and perfusion images, such that the motion corrected images were aligned with the reference images.

A brain mask, used to calculate correlation for structural and perfusion images, was extracted using BET [121], while a dilated vessel mask, used to assess the angiographic data, was extracted following the steps described in the original 4D CAPRIA paper [115]. The voxel-wise correlation between the cued motion data and reference data was then calculated within the relevant mask for each frame separately as a metric of repeatability. The dynamic angiogram within the vessel mask was also fitted with FABBER [99] and the resulted transit time was displayed to demonstrate the effects of motion correction.

A multi-way ANOVA was performed on the Fisher transformed correlation coefficients to assess the statistical significance of differences before and after motion correction, with subject number and post labeling delay (PLD) as additional factors.

6.3 Results

6.3.1 Numerical simulation

Results from the numerical simulations are shown in Figure 6.5. The retrospectively added motion trajectory is plotted together with the residual motion after correction by navigators reconstructing using either the subspace or the gridding method. Motion could be largely estimated by registering the gridding reconstructed navigators, reflected by the 67% reduction of RMSE of motion parameters compared to without motion correction. However, mixture of contrast and unclear brain/tissue boundaries, as shown in Figure 6.2b, limited the motion estimation accuracy using gridding navigators. The subspace-based reconstruction, however, greatly reduced artifacts in the navigator images by correctly modeling the signal evolutions across time. Additional LLR regularization further reduced the non-Cartesian trajectory induced artifacts and improved the boundary clarity. Therefore, the retrospectively added rotation and translation were accurately estimated by registering the navigators reconstructed by the subspace method, as depicted by the red curve in Figure 6.5a, which achieved an additional 53% reduction in RMSE of residual motion compared to the gridding reconstructed navigators.

The visual quality of the perfusion images, especially last two frames, serves as a good indicator of how good a navigator was at accurately estimating motion because perfusion images are particularly susceptible to motion corruption and the last two frames have the lowest perfusion-to-tissue relative signal intensity ratio. Before adding retrospective motion to the raw data, our motion correction pipeline was first tested on the original data to ensure data quality was not degraded by the correction in cases with minimal motion, as shown in Figure 6.5b *correction w/o retro motion*. The high similarity between the *reference* and *correction w/o retro motion* demonstrates the stability of the proposed method. Simulation with retrospective motion addition was then performed. As shown in Figure 6.5b, the motion corrupted perfusion images were dominated by artifacts, almost without discernable brain structure. After correction with motion estimated from the gridded navigators,

more detail was recovered. The tissue structure, however, was still mixed with artifacts. In comparison, the perfusion images corrected with subspace reconstructed navigators revealed greatly improved tissue detail with the fewest artefacts.

The improved correlation ($r = 0.76$ in Figure 6.5b) between motion corrected and motion free reference perfusion images also demonstrated that subspace-based navigators could correct simulated motion more accurately.

6.3.2 In-vivo perfusion results

Like numerical simulation, the subspace-based navigator can also accurately estimate subjects' movement on in-vivo data with cued motion. As shown in Figure 6.6a, a subject moved intentionally during the scan, resulting in significant artifacts covering the whole brain. The tissue structures were mostly recovered after motion correction. Figure 6.6b showed another subject with more severe motion corruption. The data was virtually overwhelmed by motion induced artifacts before correction, preventing any kind of qualitative assessment. Our correction method successfully recovered tissue perfusion information. In the motion corrected images, more artifacts are observed at PLD=1728 ms compared to 1344 ms likely due to ineffective suppression of background tissue signals because of T1 relaxation (see Figure 6.2a).

6.3.3 In-vivo angiography results

Despite its strong signal intensity compared to perfusion imaging, angiography is also affected by motion because visualizing thin vessels with fidelity requires accurate alignment between repeats. The images before motion correction in Figure 6.7a demonstrate an example of the effects of motion on an angiogram acquired with cued motion. The thin vessels in Figure 6.7a were blurred and mixed with background tissue signal due to motion at PLD=480 ms. As the background tissue signal recovers with advancing PLD, the vessels become obscured by motion artifacts. As exemplified by the enlarged green box in Figure 6.7a, almost no discernible vessels could be identified before correction, but they were largely restored after correction.

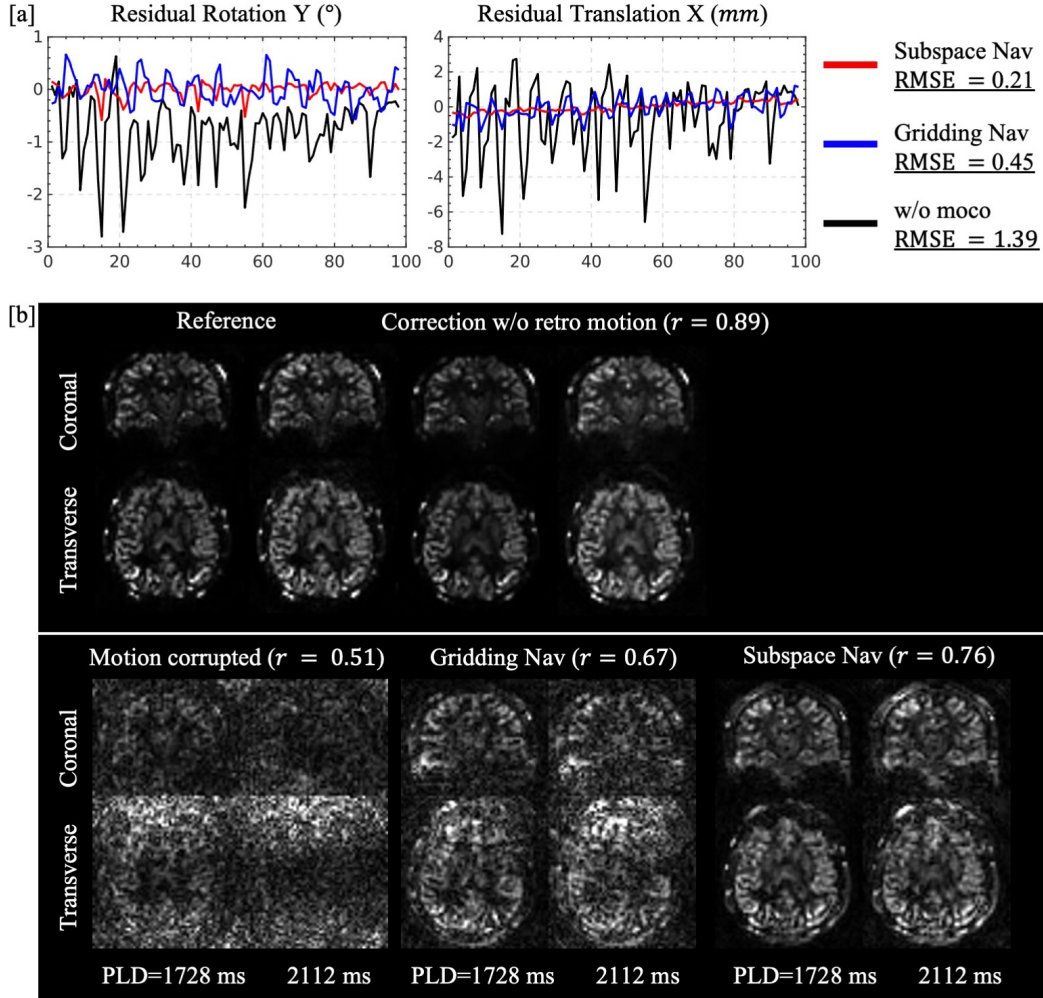


Figure 6.5: Numerical simulation with motion parameters retrospectively added onto a dataset with minimal subject motion. [a], Motion parameters retrospectively added onto the motion-free k-space data (black curve), and residual motion estimated with navigators reconstructed by gridding (blue) and subspace (red) methods. RMSE of 6 parameters of the residual motion was calculated for each case. [b], Perfusion images calculated from data with retrospectively added motion. Each dynamic perfusion image has six temporal frames, the last two of which are shown. The motion correction pipeline with subspace derived navigators was applied to the data without retrospectively added motion first to test robustness. Correlation (r) was calculated between the two frames of the reference image and those corrupted by motion, corrected with gridding navigators and subspace navigators.

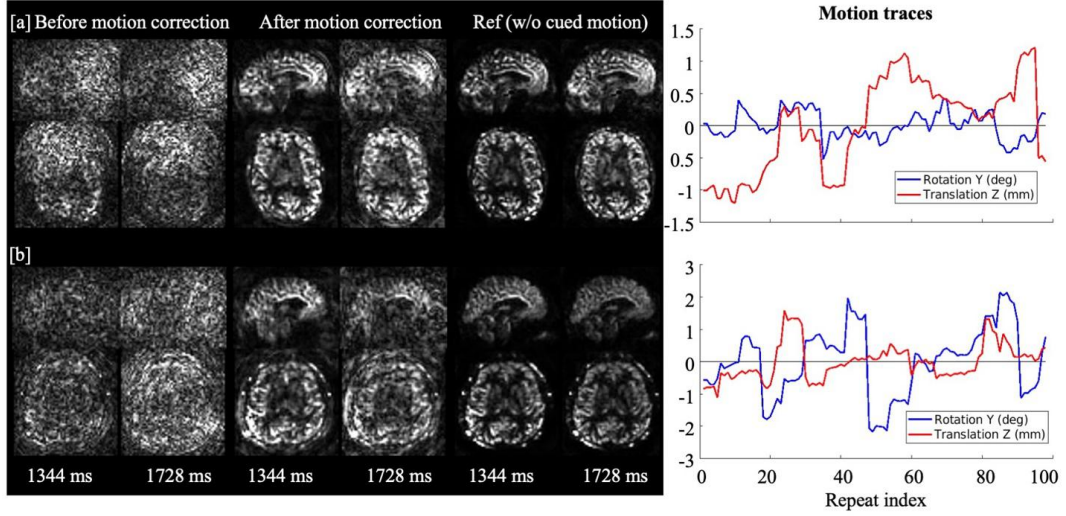


Figure 6.6: Perfusion images from the data acquired with cued motion compared to reference data. [a], this subject moved during perfusion scan with moderate amplitude and frequency as plotted on the right. The quality of the perfusion images improved after motion correction. [b], Data acquired from a different subject with more severe motion. Artifacts in the perfusion images were greatly reduced as well after motion correction, although some residual corruption remained, especially at PLD=1728 ms.

The misalignment between repeats not only caused impairment of vessel visibility, but also degradation of quantitative results. As shown in the white box in Figure 6.7b, the transit time estimated from motion corrupted data contained many more spurious values than the motion corrected one and deviated from the reference result.

During more extreme motion in a different subject, as displayed in Figure 6.7c, this angiogram suffered from almost complete loss of visible vessels. The motion traces for this severe case were plotted in Figure 6.8. However, fine details were recovered in the motion corrected images, further confirming the motion estimation accuracy of the proposed method.

6.3.4 In-vivo structural results

The structural images were reconstructed using the subspace method, and the frame corresponding to 960 ms after inversion pulse was compared to MP-RAGE in Figure 6.9. As shown in shown in Figure 6.9a, moderate motion resulted in relatively minor blurring of tissue structures which were visibly improved using the proposed motion correction method. In Figure 6.9b, the data affected by strong motion resulted

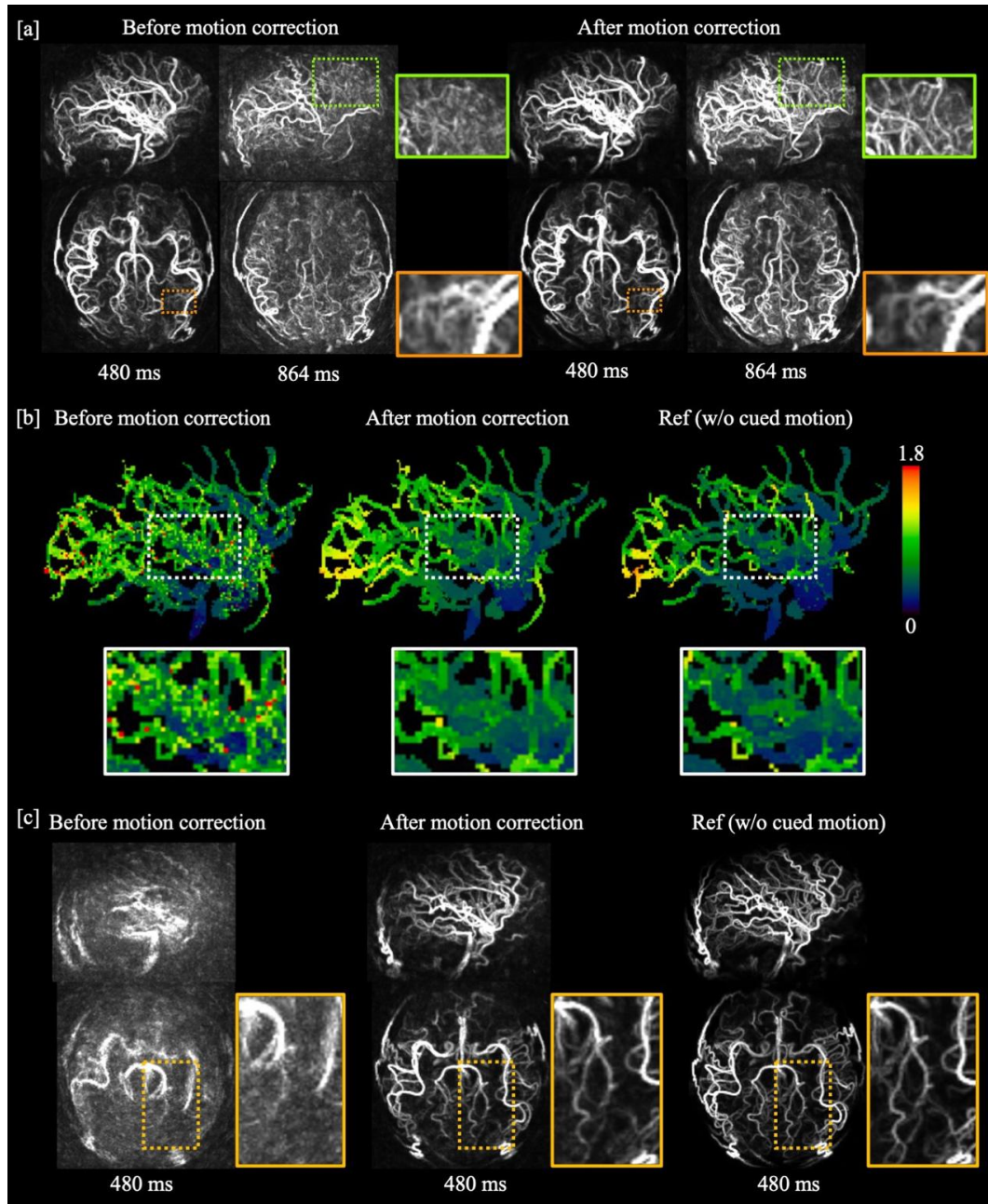


Figure 6.7: Comparison of angiography images before and after motion correction. [a], Angiography images still preserved fidelity under moderate motion. The effect of motion was mainly manifested as blurring of thin vessels at short PLDs when the background tissue signal was well suppressed. As the background suppression gets weaker due to recovery of the static tissue signal (e.g. at PLD=864 ms), motion resulted in a complete loss of visible small vessel signal, but this was recovered with the proposed motion correction approach. [b], Comparison of transit time estimation from the angiogram in [a] before and after motion correction. Spurious estimation caused by motion was mostly removed in motion corrected data. [c], A different dataset showing an angiogram affected by very large motion, which was still well recovered after correction. The corresponding motion traces can be found in Figure 6.8.

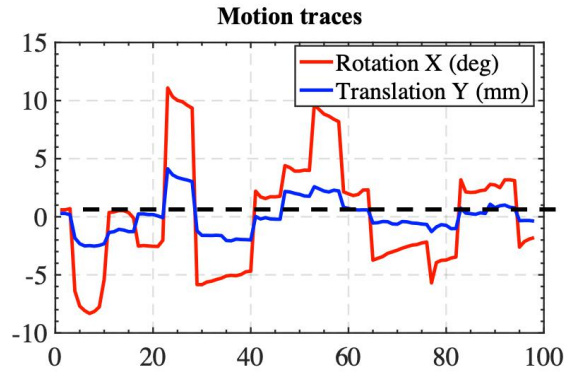


Figure 6.8: Motion traces for severe subject motion during one acquisition corrupting the angiography images in Figure 6.7c.

in much greater blurring. Nevertheless, motion correction greatly improved the image quality, and the tissue structure details were recovered.

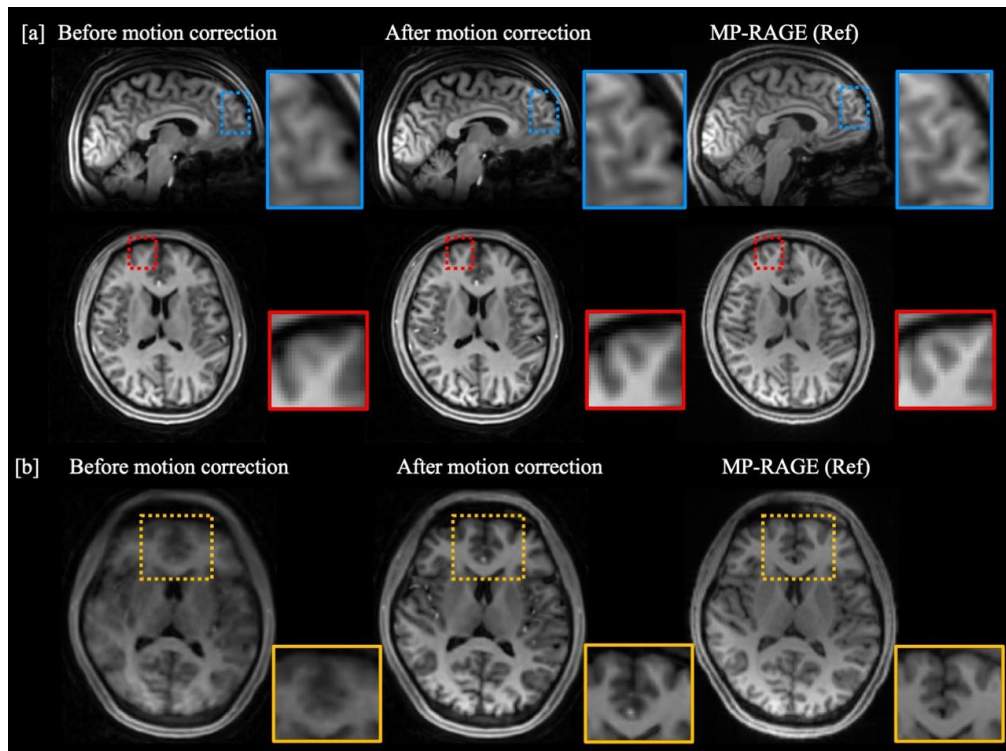


Figure 6.9: Comparison of structural images before and after motion correction. The data was acquired with cued motion. [a], Moderate motion caused blurriness in brain tissue structures. The structural discernability was noticeably improved after motion correction, as shown in the blue and red boxes. [b], Structural images affected by strong motion lost much more structural detail but could still be corrected with high quality compared to the reference motion-free MP-RAGE image, as shown in the yellow box.

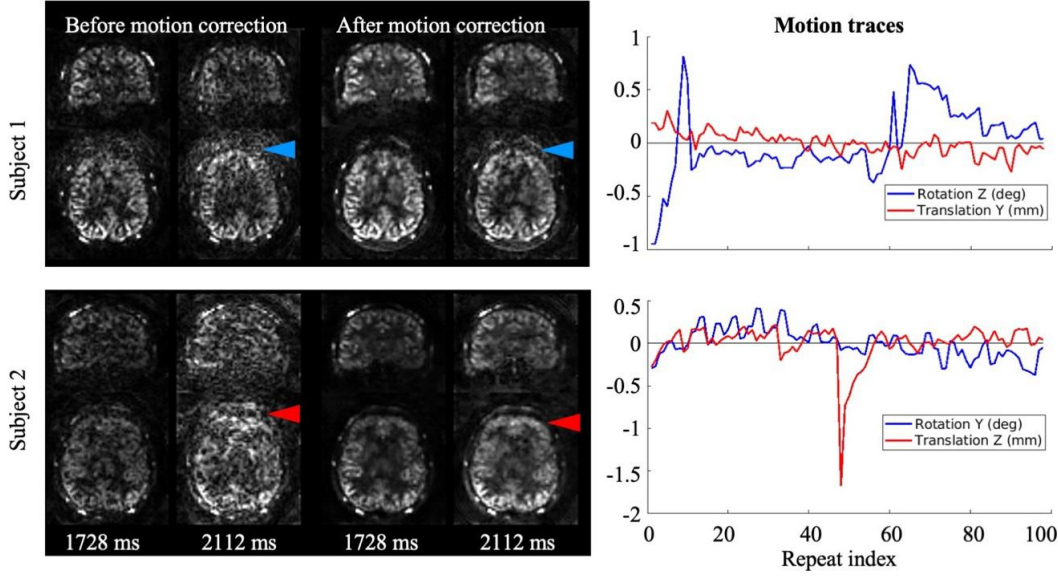


Figure 6.10: Perfusion images before and after motion correction for two datasets acquired without cued motion, but which still demonstrated some motion corruption. The images after correction showed noticeable reduction of artifacts in the frontal area (blue and red arrows).

6.3.5 Robustness to mild motion

One important motivation for this study originated from an observation of previous experiments that, even if a subject intends to stay still, mild and unintentional motion could still degrade the quality of perfusion images. In Figure 6.10, we demonstrated two such cases to prove that our subspace-based correction method is also robust when motion is small. These two cases were noticed being corrupted by motion artifacts among the data acquired without cued motion (reference data session). For one subject, the head position drifted during scanning accompanied by sudden rotations. The motion induced artifacts were mainly concentrated in frontal regions and exhibited similarity to noise. Motion induced artifacts for the second subject were more obvious, possibly due to larger and more frequent head movement. In both cases, the perfusion images were greatly improved after motion-correction, so they were still included as reference images when calculating the correlation with the case with cued motion in Figure 6.12.

6.3.6 Qualitative comparison between gridding and subspace-based correction

Image quality of in-vivo results corrected by subspace-based navigator also notably surpassed those by gridding-based navigator. Similar to numerical simulation, we also used perfusion results at long PLD as the indicator thanks to their sensitivity to k-space mismatch. In Figure 6.11, we compare the reconstruction results based on motion estimated by subspace navigators with that by gridding navigators using cued-motion data from one subject. Without motion correction, the perfusion images are dominated by artifacts without any discernible structures. Although many tissue structures were recovered after correction with the gridding-based navigators, the image quality was inferior to that of the subspace-based correction. This result is consistent with numerical simulation and confirms that subspace-based navigators can provide more accurate motion estimation than gridding-based navigators.

The quantitative comparison between results corrected by two navigators were also performed on the group level in Figure 6.12.

6.3.7 Quantitative results

Correlation coefficients calculated within the group of subjects on all three modalities are presented in Figure 6.12. Figure 6.12a shows the correlation of the motion corrected structural images with reference. As comparison on all 144 frames of dynamic structural images is computationally demanding, a representative frame corresponding to 960ms after inversion pulse with rich tissue contrast is chosen for evaluation. Consistent with the qualitative results, the structural images are less sensitive to motion compared to the perfusion and angiography images and thus have higher repeatability. As subjects moved differently in the scanner, the repeatability without motion correction has large variance. After motion correction, the repeatability has a higher average with limited variance.

Correlation coefficients of the perfusion images is shown in Figure 6.12b, here r-value of all 6 reconstructed frames is presented. The overall correlation coefficients were lower than the structural data as perfusion signal is weaker and can easily be

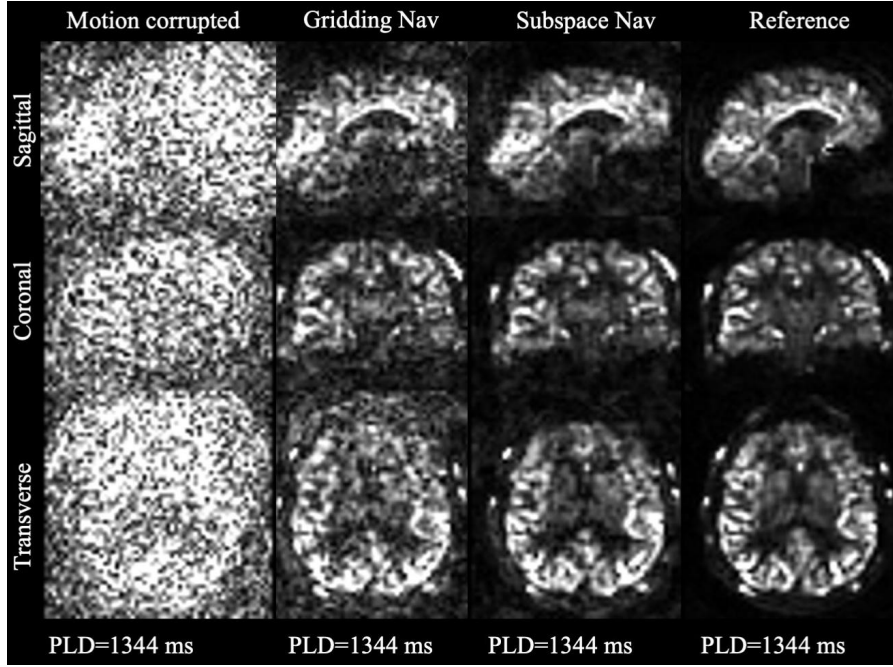


Figure 6.11: Comparison of one frame ($PLD = 1344\text{ ms}$) of the perfusion images from the cued motion scan with gridding-based and subspace-based navigators. From left to right are perfusion images reconstructed without motion correction, motion-corrected with gridding navigator, motion-corrected with subspace-based navigator, and motion-free reference data in a single subject.

corrupted by static tissue when label and control data is mismatched. Nevertheless, the subspace-based correction still led to 53% increase in correlation to reference compared to without correction across all frames and subjects, and 16% additional improvement compared to gridding-based navigators. As was observed in the CAPRIA paper [115], the standard deviation of correlation was increased in the last two frames but not necessarily due to uncorrected motion. The decreased correlation can also be attributed to weaker background suppression at long PLD, smaller perfusion signal and more significant effects of noise as well as residual static tissue artefacts. In Figure 6.12c, the angiography results also achieved significant improvements in correlation to reference, 159% and 11.2% compared to without correction and with gridding-based correction respectively. For reference, the correlation of two scans without motion should be close to Figure 4.18.

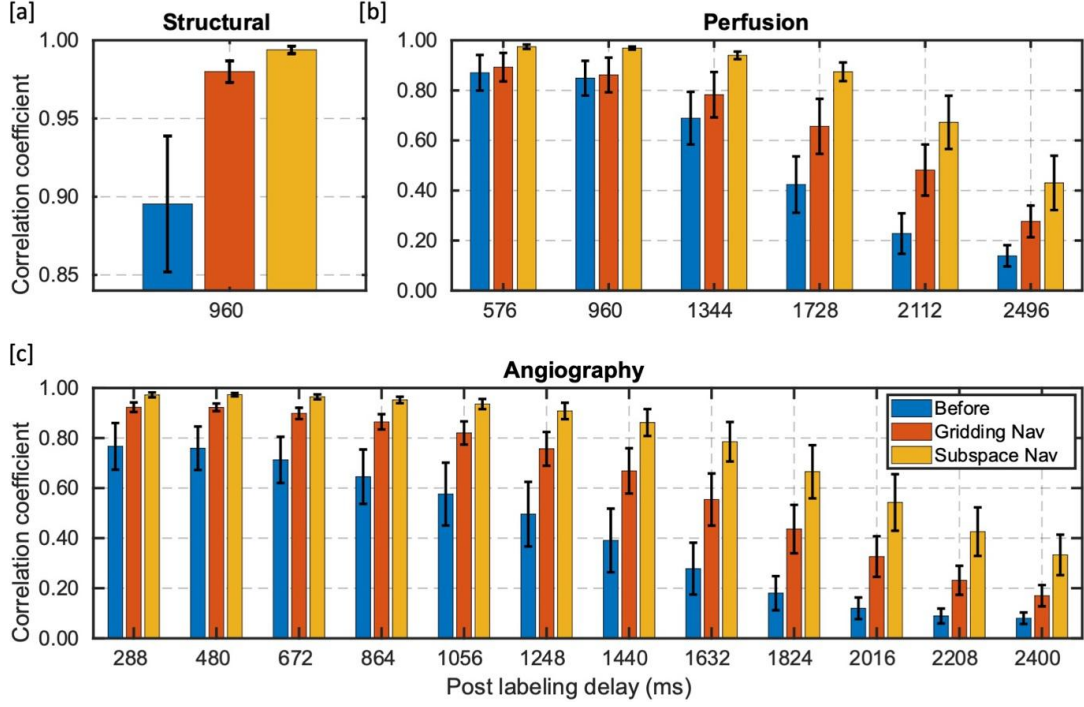


Figure 6.12: Comparison of correlation coefficient before and after gridding-based, subspace-based motion correction. Mean and standard deviation of correlation on the group of 8 healthy subjects were plotted per frame. Note that the mean values were plotted as columns where the standard deviation in the form of error bars were overlaid. [a], Bar plot of the correlation of structural images. The correlation was calculated on the frame with $PLD = 960$ ms. Subspace-based navigator improved 12% and 1.4% of correlation compared to before and after gridding-based correction respectively. [b] Bar plot of the correlation on all 6 frames of the perfusion. There were 53% and 16% improvement of correlation on average using subspace-based motion correction when compared to before and after gridding-based correction. [c], Bar plot of the correlation on all 12 frames of the angiographic images. 159% and 11.2% improvement of correlation were achieved on average with subspace-based correction versus before and after gridding-based correction respectively across all subjects and frames. In all cases, a significant ($p < 0.001$) increase in correlation was seen using subspace-based correction compared to without motion correction.

6.4 Discussion

Here, we proposed a method for reconstructing robust navigators for MRI acquisitions in which the contrast is changing over time. We showed that a subspace approach reconstructs navigators with better quality than conventional gridding or CG-SENSE methods when the contrast changes and gives much more robust motion estimation. We further proposed that, for methods which rely on subtraction, a split-update reconstruction can be used to incorporate spatiotemporal regularization on

the difference signal whilst accounting for the mismatched k-space sample locations between label and control conditions after being updated with different motion parameters. We demonstrate these improvements on the CASPRIA sequence in which structural, angiographic and perfusion images can be obtained from a single scan, showing large reductions in motion artifacts and significant improvements in repeatability.

This work extended the previous development of the CASPRIA sequence [60, 115] and the optimized cone trajectory [13], with a focus on improving the motion robustness with self-navigation. The self-navigated motion correction approach possesses several advantages: 1) the method does not prolong the total scanning time, which is crucial in clinical settings. Adding a navigator for each repeat would add a considerable amount of scan time considering the total number of repeats reaches ~ 100 ; 2) the original contrast is unaffected, avoiding the possibility of introducing unexpected signal change or artifacts; 3) the proposed motion correction method also only leads to a modest increase in reconstruction time and can be inserted as an initial step to existing reconstruction pipelines. Reconstruction and registration for each navigator using the subspace-based method takes 10-20 mins, and these could be run in parallel for each repeat. The memory and time consumption for the split-update reconstruction for each modality increased by less than twice. In contrast, the joint parameter estimation and reconstruction method [113] would be computationally infeasible when dealing with high-resolution dynamic images with ~ 100 sets of motion parameters.

The techniques developed, however, are not confined to the CASPRIA sequence itself and are suitable for translating to different applications. The subspace-based navigator could see its application in cases with long trains of readouts and varying contrast. For example, MP-RAGE [40], the signal curve of which is plotted in Figure 3.1, MPnRAGE [122]) and fast spin echo sequences [39, 116] could benefit from subspace navigators, as incorporating the signal model compensates for undersampling common in navigator reconstructions and correctly matches signal and contrasts at different timepoints, which, in turn, helps reduce artifacts

in reconstructed navigators and improves the registration accuracy. Nevertheless, it is not trivial to incorporate the subspace-based navigator into existed sequences for motion correction as the spatial encodings might need to be reordered.

The proposed split-update method is also generalizable for reconstruction of the ASL signal in other sequences. Previous ASL methods subtract the label and control signal either in k-space prior to reconstruction[123] or in image space post reconstruction[124]. K-space subtraction simplifies reconstruction by optimizing for the difference image only but is incompatible with any mismatch in k-space sampling points. Image space subtraction affords more flexibility in k-space trajectory but loses the benefit of image space regularization and reduces SNR. Our split-update method combines the advantages of the two. Integrating the two variable updates into a gradient method (e.g., POGM) resulted in convergence using iterations similar to single variable updates. Although image space subtraction methods have also been proposed by others [125, 126], they reconstruct each frame separately. Our method reconstructs the whole time series and incorporates LLR constraints [36] for effective denoising across frames. We also considered using the ADMM optimization algorithm [127] for joint label and control reconstruction, the formulation of which is in the ADMM Reconstruction section. But in preliminary experiments we found it difficult to adjust the parameters for results comparable to the split-update method. The data consistency step within each iteration is also iterative which makes reconstruction time for high resolution dynamic angiograms prohibitively long (~ 5 days).

Since the k-space of each motion state is applied with a transformation matrix to invert the motion, the coil profile of that motion state is also rotated accordingly. However, to reduce computational time and memory consumption, the sensitivity maps were not transformed accordingly within each repeat when incorporating the motion parameters into the reconstruction for the in-vivo results. To be more specific, the computational time and memory consumption scales linearly with the number of repeats (i.e., ~ 100) when incorporating the transformed sensitivity maps for each repeat, and therefore, prohibits running reconstructions on dynamic

perfusion or angiography images. This approximation, however, did not seem to severely impact the quality of the motion corrected images according to our results, as sensitivity maps are generally smoothly varying. The approximation still holds in large head movements. For example, in Figure 6.7c, the angiogram after motion correction showed high fidelity and sharpness compared to the reference while the rotation reached 15° .

As the complete train of readouts within each repeat was used to reconstruct one navigator, the minimal interval our method could discern between motion states was ~ 2 s. Nevertheless, a report examining fMRI data of 42874 subjects in UK Biobank [128] showed that the vast majority moved slower than 0.5 deg/s in rotation and 0.5 mm/s. Therefore, we believe the 2s interval used in this work could already correct for a considerable amount of motion.

In addition, within-repeat motion estimation might also be possible with the help of our subspace reconstruction method. Similar to the cloverleaf [112] method, subspace navigators could be used as a reference for each repeat while the motion status of each individual readout could be estimated by comparing to the reference in k-space, and achieve more sophisticated motion correction.

Although relatively small improvement in terms of correlation coefficient, the improved tissue clarity of structural images after correction can generate better segmentation and be used for partial volume correction for the perfusion quantification.

Another source of imperfect correction originated from the insufficient background suppression towards the end of the readout train as static tissue recovered after the inversion pulse. Insertion of an additional inversion pulses during the train of readouts would help to reduce the intensity of static tissue at long PLDs. Subspace-based navigators could still be reconstructed by explicitly modeling the additional inversion pulses. In conventional self-navigated ASL motion correction methods, background suppression is deliberately suboptimal for higher tissue contrast in the navigators [107]. However, this situation can be avoided, because the subspace-based method reconstructs the whole time-series and the frame with best tissue contrast can be selected as the navigator.

As a preliminary study, a group of 8 healthy subjects were scanned with and without cued motion. A broader comparison within a large group should be carried out in the future, examining our method in correcting for involuntary motion of healthy subjects as well as patients with more severe head motion.

6.5 Conclusion

In this work, we proposed a subspace-based method for reconstructing navigators in acquisitions with changing contrast and showed that the reconstructed navigators have better quality and registration accuracy than gridding with contrast-mixed signal. A split-update algorithm was also introduced to reconstruct from mismatched k-space sample locations while applying LLR regularization on the difference image. Both methods were applied to the CASPRIA sequence for motion corrected angiography, structural and perfusion images. The motion correction pipeline was evaluated comprehensively with numerical simulation and achieved 84% reduction in RMSE of the residual motion parameters. In scanning of healthy subjects, it also noticeably reduced motion artifacts. The correlation of the perfusion, structural and angiography images improved by 53%, 12% and 159%, respectively, after motion correction.

Code

The code used in the paper can be found at
https://github.com/Michaelsqj/capria_motion_correction

6.6 Appendix: ADMM for joint label and control reconstruction

Here we demonstrate the ADMM algorithm experimented for joint label-control reconstruction with LLR regularization on the label-control difference image.

$$\hat{x}_1, \hat{x}_2 = \arg \min_{x_1, x_2} \left\| \begin{bmatrix} P_1 F C_1 & 0 \\ 0 & P_2 F C_2 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} - \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} \right\|_2^2 + \lambda \sum_i \left\| R_i \left(\begin{bmatrix} 1 & -1 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} \right) \right\|_* \quad (6.6)$$

P_1FC_1 , P_2FC_2 represents k-space sampling, Fourier transform, and coil sensitivity corresponds to repeats with label and control. x_1 , x_2 represents label and control images to reconstruct. y_1 , y_2 represents k-space data of repeats with label and control. R_i represents operation for extracting LLR patches as in Equation 6.4.

For convenience, Equation 6.6 is rewritten as

$$\arg \min_{x_1, x_2} \|AX - Y\|_2^2 + \lambda \sum_i \|R_i(Z)\|_* \quad (6.7)$$

where,

$$BX - Z = 0$$

$$B = \begin{bmatrix} 1 & -1 \end{bmatrix}$$

$$A = \begin{bmatrix} P_1FC_1 & 0 \\ 0 & P_2FC_2 \end{bmatrix}$$

$$X = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$$

$$Y = \begin{bmatrix} y_1 \\ y_2 \end{bmatrix}$$

And ADMM updates become

$$X^{(k)} = \arg \min_X \|AX - Y\|_2^2 + \frac{\rho}{2} \|BX - Z^{(k-1)} + w^{(k-1)}\|_2^2 \quad (6.8)$$

$$Z^{(k)} = \arg \min_Z \frac{\rho}{2} \|BX^k - Z + w^{(k-1)}\|_2^2 + \lambda \sum_i \|R_i(Z)\|_* \quad (6.9)$$

$$w^k = w^{k-1} + BX^k - Z^k \quad (6.10)$$

ρ and λ are two parameters to adjust and w is a variable introduced by the Augmented Lagrangian method.

Equation 6.8 could be solved using the iterative conjugate gradient method [129] which is the most time consuming step in ADMM updates due to the iterative NUFFT [79] calculation, but is prohibited using the method for reconstructing dynamic angiography and perfusion images. Equation 6.9 is solved by applying locally low rank denoising on Z .

7

Summary and future work

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In this chapter, I will summarize the methods that I have developed and give a more general discussion about the benefits and limitations. Finally, I will discuss about future directions for better image quality, more accurate quantification, potential clinical applications and physiological analysis.

7.1 Summary

The aim of this thesis is to optimize combined angiography, structural and perfusion imaging using ASL. This includes improving the spatial resolution with the development of an efficient sampling trajectory, pushing the temporal resolution with the model-constrained reconstruction and improving motion robustness for the sequence.

7.1.1 Technical development

In the first project, we started from the combined imaging sequence with radial acquisition and aimed at improving the k-space sampling efficiency. Though easy to implement, radial spokes do not have much flexibility and generate sampling density proportional to $1/r^2$, leaving large sampling gaps in peripheral k-space. Yet, the radial approach combined with Song ordering [73] and golden ratio [20] increments can be arbitrarily segmented and grouped for different temporal resolution, making it particularly well suited for dynamic imaging. Therefore, the goal was finding an alternative to radial sampling while preserving this flexibility. Cone trajectories [24, 66] had potential for this work, given that they sample k-space more uniformly and efficiently and have higher degrees of freedom to customise the design for specific applications. To further improve upon existing designs [24, 66], we got rid of the analytical solutions, which are more suitable for scenarios in which full Nyquist sampling is required, parameterized the key aspects of the trajectory and adopted the time-optimal gradient algorithm [25]. All these modifications prepared us for optimizing trajectories for our specific application. A two-stage process combining numerical simulation and phantom scanning helped us better identify the optimal trajectory shape.

Based on the first project, we identified that the temporal resolution can be further improved as the Song ordering we adopted facilitates arbitrary grouping along train of readouts while still maintaining relatively uniform sampling. An angiography model [90] was used to constrain the reconstruction voxel-wise. A subspace [39] method was further used to compress the model and reduce computational requirements. This project pushed temporal resolution to an unprecedented $\tilde{15}\text{ms}$,

an huge leap from the previous best 50 ms [74]. The finer temporal resolution allowed more accurate quantification of physiological parameters.

During the experiments for the first two projects, we noticed perfusion images were likely to be contaminated by the motion induced artifacts, meaning the scan might need to be discarded since we did not have the proper tools to correct for that. Therefore, we aimed at developing a motion correction method for the combined imaging sequence. Drawing inspiration from the second project, we introduced the subspace method to reconstruct navigator images without contrast-mixing artifacts for accurate motion estimation. A split-update method was further developed to allow label-control joint reconstruction with spatiotemporal regularization applied on the difference image.

7.1.2 Benefits and limitations

The cone trajectory design is very efficient even if the maximum gradient and slew rate is heavily limited. The optimization process we used included phantom scanning which made sure that real-world artifacts were considered when choosing parameters. Once the parameters have been decided, the gradient waveforms to generate that trajectory are computed online, meaning the scanner operator can change protocols flexibly without a tedious process of rerunning the gradient calculations on standalone machine and importing them to the scanner. As the trajectory starts from the k-space center, it is also minimally affected by the T_2^* decay. The trajectory maintains flexibility of radial trajectories while providing much more efficient k-space sampling, especially if we want to minimize the number of excitation pulses. Combining the cone trajectory with the subspace method, we can achieve both high spatial and temporal resolution without significantly increasing computational requirements. Our retrospective self-navigated motion correction pipeline can further improve the motion robustness for the CASPRIA method without changing the sequence. The benefits of these three techniques can be integrated with each other seamlessly, greatly improving the quality of the angiographic, structural and perfusion images.

Nevertheless, these methods still have some limitations. Firstly, the cone trajectory sampling is not perfectly uniform or isotropic. Additionally, it remains an open question how best to evaluate different sampling trajectories, due to the complex interactions of the trajectory design with coil sensitivity profiles, sophisticated image reconstruction algorithms and the structure of the data and artefacts themselves. The potential for non-Cartesian trajectories has not been fully exploited for certain, but determining how to progress this field further is challenging. Secondly, the subspace-based angiography reconstruction is faced with two major limitations. On the one hand, the constructed subspace is not a perfect representation for the kinetic model which suffers inaccuracies during sharp changes in the signal. On the other hand, the kinetic model itself contains some assumptions, so it cannot guarantee to describe every possible signal evolution, particularly in the presence of artefacts. Since model-based reconstruction allows reconstruction at an arbitrarily high temporal resolution – limited only by the model of choice, it is currently also difficult to validate using alternative methods. Finally, the currently developed motion correction methods are still limited in the temporal resolution of the navigators (currently only once per ASL preparation) and sub-optimal background suppression.

7.1.3 Extension and generalization

Despite these limitations, the developed methods can still be advantageous when generalizing to other applications. The cone trajectory can see its application in virtually all dynamic imaging cases to replace currently used radial trajectories. As discussed above, the subspace-based navigators can also be generalized to other applications where sampling is sufficient but suffer from contrast mixing, like fast spin echo[39], or MP-nRAGE[122].

7.2 Future directions

To improve ASL based brain blood flow imaging, extensive works from different perspectives are required for fast imaging and better diagnosis and analysis. Based

on the techniques developed in the thesis, several future works can be envisioned.

7.2.1 Clinical applications

The first and foremost thing to do is to actively seek opportunities to test the developed techniques on patients in clinical settings. Although, techniques for higher spatiotemporal resolution have been developed as covered by the thesis, they have never been tested on patients with cerebrovascular diseases such as stroke or moyamoya disease. To test on patients in a hospital setting may require refining sequence code to minimise the potential for bugs which could stop the scanners under certain conditions. Protocols also need to be optimized for efficiency and stability. Current reconstruction is implemented in MATLAB and run on a standalone server, which will not be compatible with clinical settings. That said, offline reconstruction might still be acceptable during the initial testing phase. To achieve this, we have been collaborating with other institutes who have strong links with hospital sites and are more easily able to test novel pulse sequences. Although the most updated sequence code, including the developed trajectories and reconstruction code, is yet to be transferred, we could potentially test these methods on a large number of patients. We will then try to scale dissemination of the sequence further to different sites and applications.

However, the current sequence is written under the Siemens IDEA platform preventing it from being accessed by wider group of researchers. One possible solution to this is to rewrite the CASPRIA sequence using vendor agnostic programming like Pulseseq[130]. The sequence could then be shared online for researchers interested in giving it a quick test, although some challenges relating to positioning the imaging region, background suppression regions and labelling plane on the scanner console may need to be overcome.

7.2.2 Further optimization for trajectory

The efficient cone trajectory developed can also be further optimized. Currently, the trajectory parameters, including cone angles and curvature, were decided based

numerical simulation as well as phantom scanning with minimized undersampling aliasing. However, since the trajectory is a conical shape, the search space is limited. The parameter combinations that were investigated were also limited. As shown in Figure 2.11, a numerically optimized trajectory [26, 71] can achieve a much better PSF than the cone trajectory, but it lacks the flexibility for adapting to different spatiotemporal resolutions or number of shots (i.e., window size in dynamic imaging). Therefore, an interesting avenue for future research would be to develop a numerically optimized shape of single shot. The full extent of k-space could then be covered by rotating the base shot in a similar fashion to our cone approach. We anticipated this may generate a much better PSF compared to analytically defined trajectories whilst maintaining some flexibility to adapt to different spatial resolution and temporal resolution requirements by adjusting the trajectory scaling and number of shots.

7.2.3 Corrections for non-Cartesian trajectories

Here in this section, I introduce two important problems to resolve. Although these two problems already have mature solutions, it is still important to implement a pipeline ourselves based on the CASPRIA sequence in order to push the blood flow imaging resolution further.

- **Gradient imperfection** It is often important to deal with trajectory shifts or distortions caused by imperfections in the gradient system, such as delays between the gradients and the ADC, delays between physical gradient axes or eddy current effects. The maximum gradient and slew rate were constrained in the work presented in this thesis to be very conservative, which avoided significant trajectory distortions. To push the spatial resolution further, however, it is expected that higher maximum gradient strengths and slew rates would result in better sampling efficiency, but also more noticeable trajectory imperfection issues. To deal with this, we could model the gradient system as linear time-invariant system, and measuring the the impulse response function for the gradient system[84], as illustrated in the pipeline in Figure

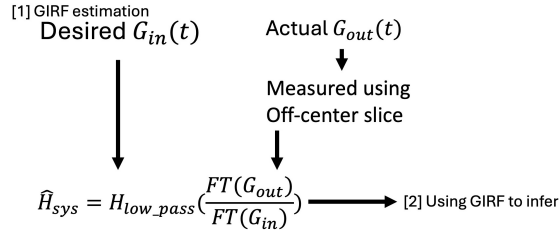


Figure 7.1: Pipeline for GIRF measurement and correction.

7.1. The actual correction process consists of two phases. In the first phase, the actual gradient waveform G_{out} of the input gradient waveform G_{in} is measured using off-center slice following [131]. The system response function is calculated from frequency space by dividing the G_{out} and G_{in} . Low pass filter is applied as well to remove high frequency noise. In the second phase, the obtained system response function can be used to predict the actual gradient waveform for arbitrary input gradient G_{in} .

- **Correct for off-resonance** Off-resonance is another issue that needs to be addressed, as B0 inhomogeneity (ΔB) induces a time-varying phase $\Delta\phi = \Delta Bt$ after the magnetisation is excited. Following [132], the data consistency term used in optimization becomes Eq. 7.1. A conventional Fourier reconstruction is then no longer possible, although time segmented methods have been suggested to make this computationally feasible.

$$\|P_t FC(\Delta Bt)x - y_t\|_2 \quad (7.1)$$

7.2.4 7T imaging for pushing spatiotemporal resolution

It is also worth taking advantage of the high SNR provided by scanning at 7T to improve the spatial and/or temporal resolution of blood flow imaging. Previously, PCASL at 7T was limited by low labeling efficiency due to the B0 inhomogeneity within the brain-feeding arteries at the labelling plane and high power deposition (SAR) due to the use of many labeling and background suppression pulses. Fortunately, these problems have recently been addressed by using dynamic B0 shimming [133] and VERSE optimized pulses [134]. Together with a trajectory

correction using e.g. the GIRF approach[84], it is expected that high resolution and SNR blood flow imaging could be performed.

7.2.5 Neural network representation for k-t-c space

It is known that k-space signals in dynamic imaging are spatiotemporally correlated. The signal among different coils is highly correlated as well. Instead of processing the signal compression explicitly and separately across coil dimensions and temporal dimensions, we propose to implicitly compress the signal on all dimensions x, y, z, t, c . In addition, the on-grid sampling in k-space need no longer be explicitly interpolated using a gridding algorithm, but implicitly interpolated on a manifold. One potential implementation is illustrated in Figure 7.2. The neural network could be trained and validated on single dataset. Once trained, the data corresponding to on-grid coordinates can be inferred for image reconstruction, avoiding many of the intermediate interpolation and gridding procedures that introduce inaccuracies [135, 136].

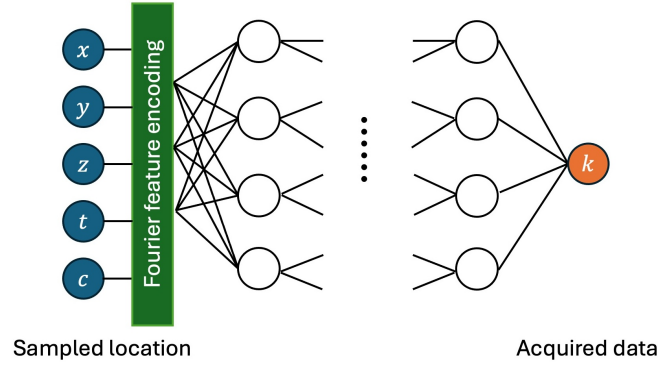


Figure 7.2: A neural network with k-space location, echo train index, coil index as input and k-space data as output.

7.2.6 Motion correction within k-space

The estimation accuracy for the motion correction work presented in this thesis could be further improved by comparing data in the k-space domain rather than the image space domain[112]. Figure 7.3 demonstrates one potential implementation. From the subspace-based navigator we proposed in this thesis, each readout from each repeat has a corresponding image, which is associated with one radial spoke

in k-space (can be extended to cone trajectory as well). However, since the head is rotated from its initial position, the actual sampled coordinates are modified from their intended position. Therefore, the navigator can be projected to spokes around the original spoke and the one with projected data that matches closest with the acquired data can be considered as the actual acquired trajectory. Translation can be more simply modelled by differences in phase. To be more specific, the translation and rotation can be solved by Equation 7.2. n indexes the projected spoke and $\Delta\Phi$ is associated with the translation. $A_n(k)e^{i\phi_n(k)}$, $A(k)e^{i\phi(k)}$ are the data on sampled point k on spoke n and the acquired spoke respectively. Given that motion within the readout train will be limited, the approximate solution of Equation 7.2 can be obtained by grid search.

$$\hat{n}, \Delta\hat{\Phi} = \arg \min_{n, \Delta\Phi} \sum_1^K \left| A_n(k)e^{i\phi_n(k)}e^{i\Delta\Phi} - A(k)e^{i\phi(k)} \right|_2^2 \quad (7.2)$$

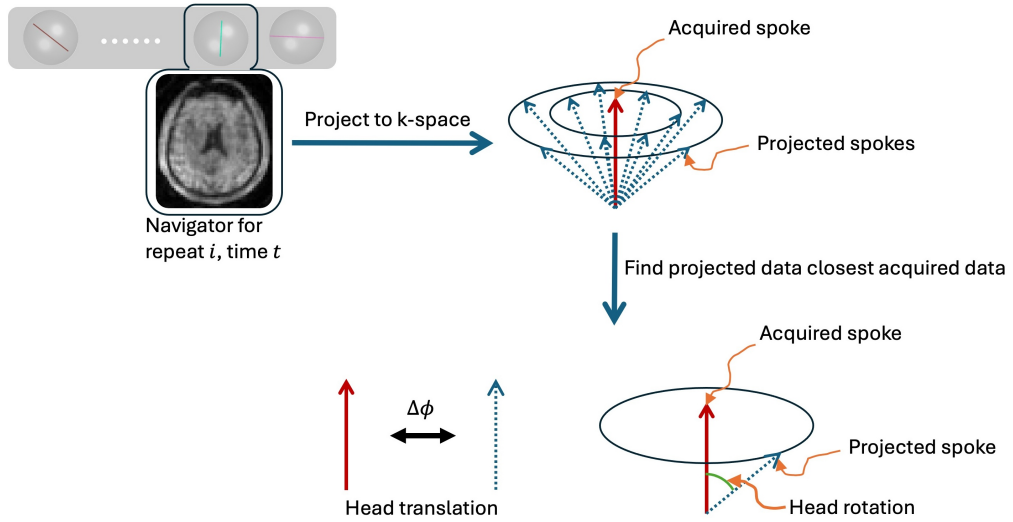


Figure 7.3: Pipeline for determining the head rotation and translation for one spoke.

7.2.7 Accurate perfusion quantification

Accurate perfusion quantification is difficult, as perfusion images generally have low temporal resolution and often contain macrovascular signal, especially at shorter PLDs. Although macrovascular signal can be taken account of by modeling the

two compartments, macrovascular and tissue perfusion[137], simultaneously, the accuracy for perfusion quantification is still constrained by the limited temporal resolution. CASPRIA has a unique advantage as the high resolution angiography and low resolution perfusion are perfectly registered as they are reconstructed from the same k-space data. Therefore, the quantification results of angiography can inform the perfusion quantification.

To be more specific, we can use the subspace method to obtain highly accurate angiographic quantification. The parameter maps like macrovascular blood volume, transit time and dispersion can be downsampled to the same resolution as the perfusion data. The macrovascular blood volume map can be directly used to help separate out this confounding factor on tissue perfusion quantification. In addition, as the tissue perfusion signal surrounding large vessels is likely share similar transit time and dispersion parameters with the macrovascular compartment, the downsampled parameter maps can be used as a prior to compensate for the limited temporal resolution of the perfusion images, helping to improve tissue perfusion quantification accuracy.

However, it would be non-trivial to validate the accuracy of the parameters obtained by the proposed method since there is no easy way to obtain ground-truth measurements. Validation shall be a important piece of future work in this area.

7.3 Conclusion

This thesis aimed to optimize combined angiography, structural, and perfusion imaging using arterial spin labeling (ASL) to address the limitations of ASL in visualizing the dynamic process of blood flow for diagnosing and monitoring cerebrovascular diseases.

The development of an efficient cone trajectory design significantly improved spatial resolution and SNR for angiographic and perfusion images acquired with 4D CAPRIA. The two-stage parametric cone design, combined with golden ratio rotations led to sharper vessel contours and improved resolution in tissue perfusion. Further improvement in temporal resolution was achieved by incorporating an

angiographic signal model and a subspace technique into the reconstruction process, resulting in ultra-high temporal resolution 4D MRA with an unprecedented temporal resolution of 15ms. This finer temporal resolution allowed for more accurate quantification of physiological parameters and improved visualization of blood flow dynamics. Motion robustness was significantly enhanced through a novel subspace-based method for reconstructing navigators in acquisitions with changing contrast. These navigators exhibited superior quality and registration accuracy compared to gridding with contrast-mixed signals. The split-update algorithm further mitigated subtraction artifacts, enabling the reconstruction of high-quality blood flow images from mismatched k-space data.

The combination of these techniques resulted in substantial improvements in combined angiography, structural, and perfusion imaging using ASL. The advancements in spatial resolution, temporal resolution, and motion robustness directly address the limitations of ASL outlined in the motivation, enabling more accurate and reliable visualization and quantification of brain blood flow. These improvements hold great potential for enhancing the diagnosis, treatment monitoring, and understanding of cerebrovascular diseases.

Appendices



Aliasing reduction for structural images in CASPRIA

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A.1 Introduction

Based on CAPRIA, 4D Combined Angiographic, Structural and Perfusion Radial Imaging using Arterial Spin Labeling (CASPRIA)[60] was developed recently, which enables the reconstruction of structural images with contrast flexibility. To reconstruct structural images from the sequence in Figure 4.1, data of tag and control repeat is added. The window size for each frame is equivalent between structural and perfusion images and the spatial resolution of structural and angiography images is same. After replacing the radial trajectory with a cone trajectory in 4D CASPRIA as we did for 4D CAPRIA, the structural images acquired had a

higher resolution, as was found in the angiography and perfusion images described above. However, the structural images also contained many more artefacts at the edge of the brain which were not obvious in those acquired with a radial trajectory. In this section, we first used numerical simulation to determine the cause of the artefacts in structural images, and then we implemented water excitation to suppress the fat signal and produced structural images with greatly reduced artefacts. Finally, we demonstrated the side-effects of using the water excitation approach on angiographic and perfusion images, which prohibited us from including water excitation in the main description above.

A.2 Methods

To investigate the impact of off-resonance on additional artefacts in the structural images, we performed a simulation based on a standard MPRAGE-T1 weighted scan. Firstly, we extracted the brain and scalp from the T1w image. Secondly, we separately transformed the brain and scalp to k-space. Thirdly, an additional phase was added to the data transformed from the scalp, representing the off-resonance effect of fat, which linearly increased with time after the start of the ADC. The final reconstruction was obtained by adding the k-space data of the scalp and brain together and transforming back into image space. The density compensated NUFFT and adjoint NUFFT were used to transform data between k-space and image space.

We compared the reconstruction without the off-resonance effect, with the off-resonance effect and with twice the intensity of the original scalp to facilitates visualizing the off-resonance effect. We also compared results between the cone and radial trajectories when adding the same frequency offset.

We used a 1:1 binomial pulse for water excitation as shown in Figure A.1 and compared it with the results acquired using a conventional excitation pulse. The flip angles were the same in both cases. The 1:1 binomial pulse splits a single pulse into two pulses with flip angle $\alpha/2$. As the water and fat difference in resonance has a difference of 420Hz in $3T$ scanner. The wait time between the two pulses $\Delta t = 0.5 \times \frac{1}{420} = 0.00119s$.

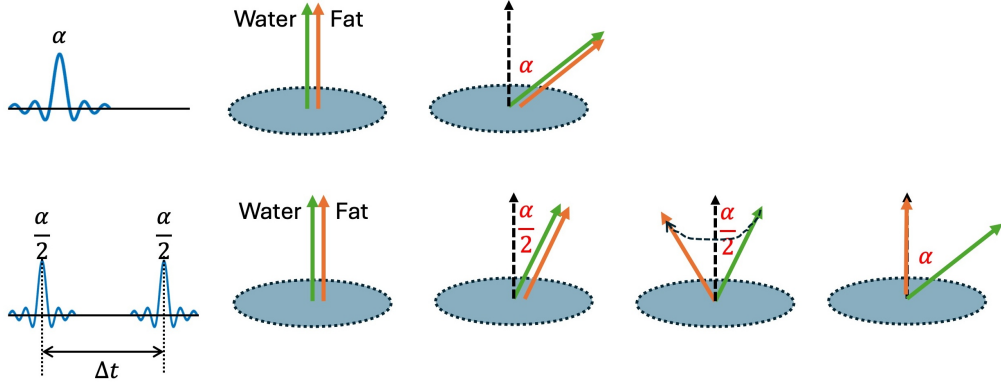


Figure A.1: Conventional excitation pulse only has single pulse with flip angle α , whereas the 1:1 binomial pulse is split into two $\alpha/2$ pulses spaced by Δt to null the transverse magnetization of fat.

Two subjects were scanned with the two protocols, one used the optimal cone protocol, and the other kept everything the same except replacing the normal excitation pulse with water excitation.

A.3 Results

A.3.1 Numerical simulation

As shown in Figure A.2, keeping the off-resonance frequency the same, but increasing the intensity of the scalp signal which represents fat, the scalp in the cone trajectory result becomes blurrier and encroaches into the brain, degrading the overall image quality. The gap between the scalp and the brain also contained aliased fat signal. The result from the radial trajectory also demonstrated a blurry and noisy scalp after adding the off-resonance effect. However, the scalp signal acquired with radial trajectory did not affect the image quality of the brain as much as the cone trajectory. The aliasing of the scalp in the radial trajectory also manifested in a structured streaking fashion, which is different from that in cone trajectory. Since no signal modulation from T1 relaxation was applied during simulation, this difference can be attributed to two factors: firstly, the cone trajectory traverses a larger region of k-space in an irregular twisting path, leading to a more complicated aliasing pattern when off-resonant signal is present. Secondly, the cone trajectory provides

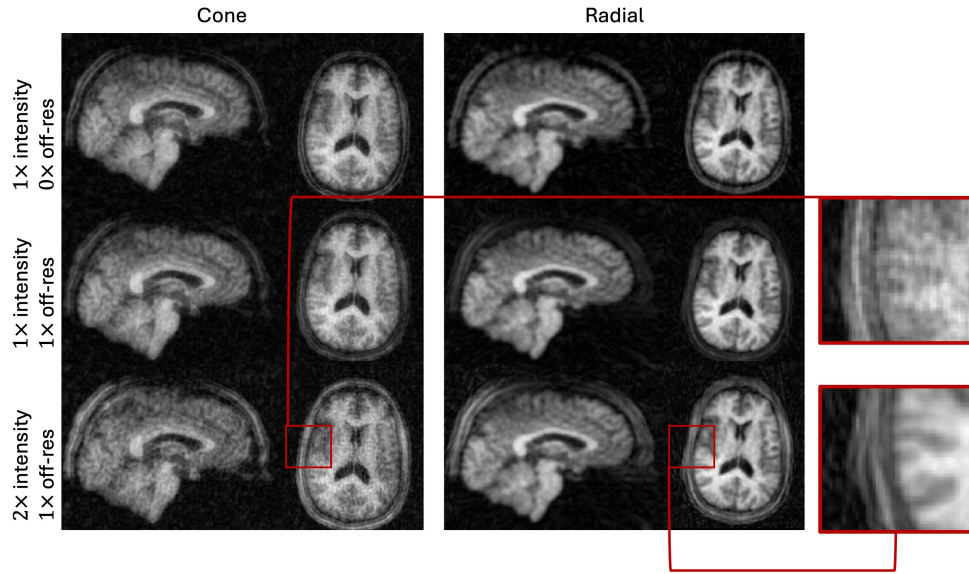


Figure A.2: Off-resonance simulations in CASPRIA structural imaging with a cone trajectory (left) and a radial trajectory (right): 1) without any signal modulation; 2) scalp with the off-resonance effect included; 3) scalp with twice the intensity and same off-resonance frequency shift. As the strength of the scalp signal increases, the off-resonance effect becomes more obvious and affects the image quality in the brain.

a higher spatial resolution, thus making the noise-like artefacts more clearly visible whereas artefacts in the radial trajectory were largely blurred out.

A.3.2 In-vivo structural comparison

As shown in Figure A.3, the structural images with normal excitation have a thicker region of signal around the scalp. A ring with a shape identical to the scalp appeared on the edge of the brain in both subjects. The amount of aliasing largely depended on the anatomy of each individual and varied a lot. For example in Figure A.4, the image of subject 1 only shows slight aliasing whereas that of subject 2 shows more significant aliasing. Off-resonance induced artifacts around the scalp are also dependent on the sampling trajectory adopted. Similar to the numerical simulation in Figure A.2, image acquired with radial trajectory in Figure A.4 shows blurred scalp but clean brain tissue whereas that acquired with cone trajectory has concentric rings around scalp and even intruding into the brain tissue. After switching to water excitation, both the scalp and brain tissue in the cone trajectory results become clean as indicated by the red arrow in Figure A.3.

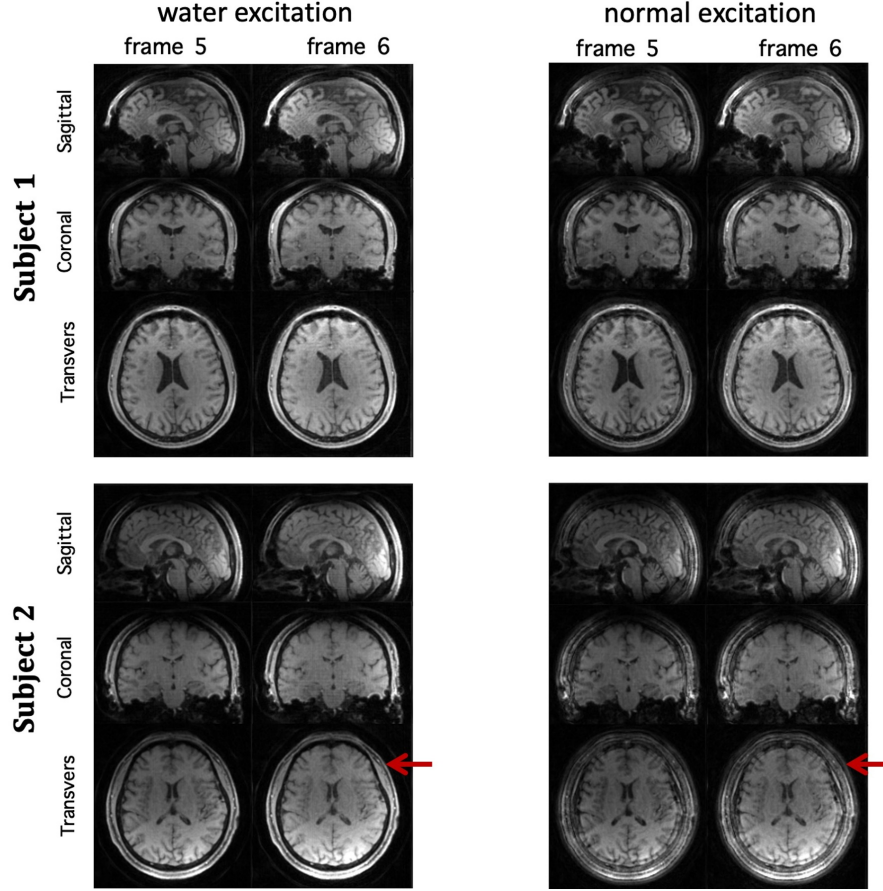


Figure A.3: Structural images acquired with cone trajectory. Results with water excitation showed clean separation between the scalp and the brain, while those with normal excitation contained many artefacts at the edge of the brain.

A.3.3 In-vivo angiography and perfusion

However, despite significant aliasing reduction in the structural images when using water excitation, the perfusion and angiography images were also affected. As indicated with the red arrows in Figure A.5, some tiny distal vessels were lost in the angiographic images with water excitation. The proximal arteries also showed some signal loss. In Figure A.6, when comparing the perfusion reconstructions, slight contrast changes were observed in both subjects, especially in the white matter. Additionally, the images acquired using water excitation showed more obvious residual signal in the scalp, which is much less obvious in those acquired with normal excitation. We suspect it might be related to some lack of robustness in the 1:1 binomial pulse, which could not perform stable water excitation as well

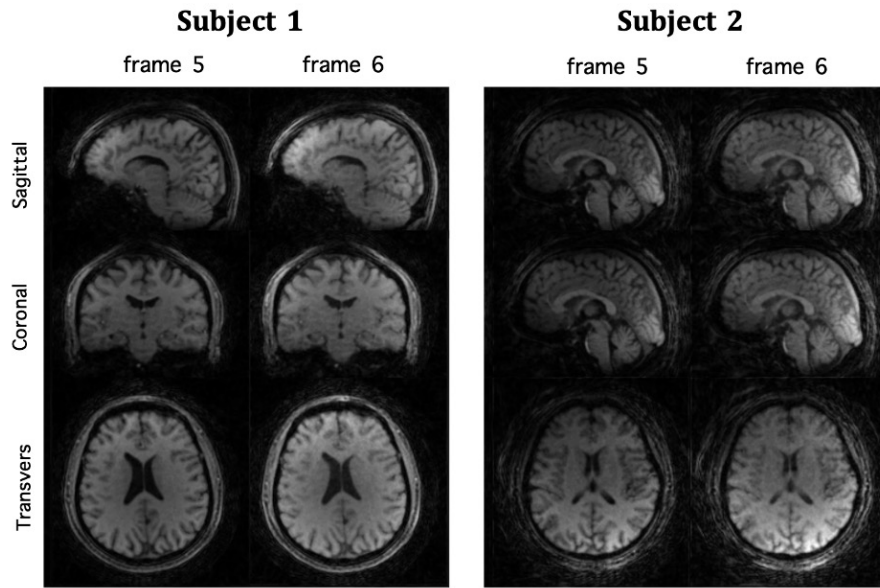


Figure A.4: Structural images acquired with a radial trajectory in the two subjects. The first subject has less fat signal in the scalp, and the aliasing caused by off-resonance is not obvious. The second subject has more fat signal in the scalp, and the off-resonance effect is more obvious but with a different pattern compared to the cone trajectory.

as 1:2:1 binomial pulse. Another probable cause might be longer TE required and greater sensitivity to off-resonance effects.

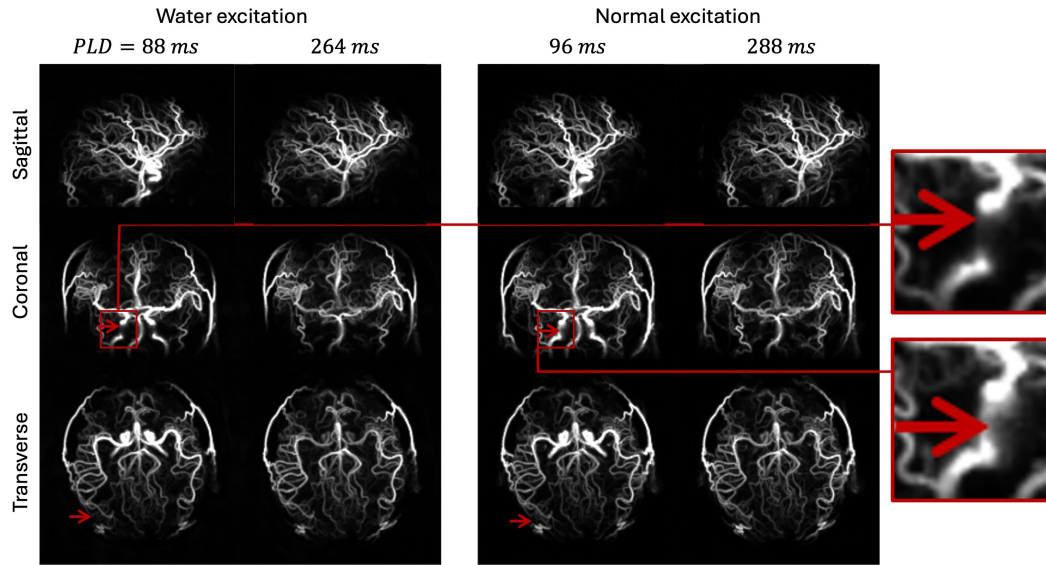


Figure A.5: Angiography images with and without water excitation. Although they have similar apparent spatial resolution, the angiography with water excitation loses tiny vessels (transverse view) and proximal arteries (coronal view) compared to the normal excitation (red arrows).

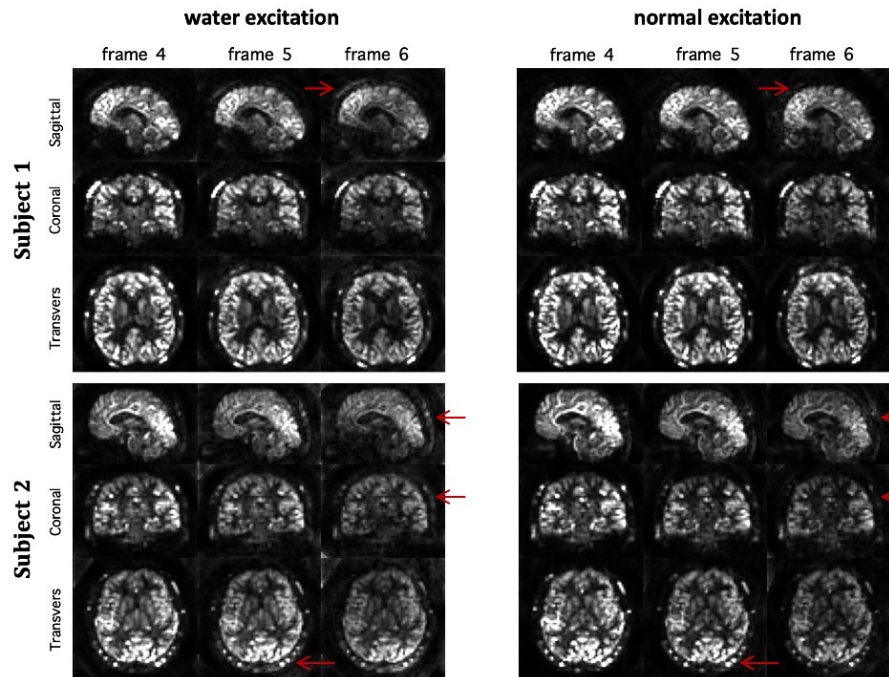


Figure A.6: Perfusion images with and without water excitation. In the transverse view, there is still some residual signal of scalp in water excitation acquisition, as pointed out by the red arrow. In the white matter region, the contrast is also different between with and without water excitation.

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