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Blood oxygenation level-dependent functional MRI signal turbulence caused by ultrahigh spatial resolution: numerical simulation and theoretical explanation

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Abstract

High-spatial-resolution functional MRI (fMRI) can enhance image contrast and improve spatial specificity for brain activity mapping. As the voxel size is reduced, an irregular magnetic fieldmap will emerge as a result of less local averaging, and will lead to abnormal fMRI signal evolution with respect to the image acquisition TE. In this article, we report this signal turbulence phenomenon observed in simulations of ultrahigh-spatial-resolution blood oxygenation level-dependent (BOLD) fMRI (voxel size of less than $50 \times 50 \times 50 \mu\text{m}^3$). We present a four-level coarse-to-fine multiresolution BOLD fMRI signal simulation. Based on the statistical histogram of an intravoxel fieldmap, we reformulate the intravoxel dephasing summation (a form of Riemann sum) into a new formula that is a discrete Fourier transformation of the intravoxel fieldmap histogram (a form of Lebesgue sum). We interpret the BOLD signal formation by relating its magnitude (phase) to the even (odd) symmetry of the fieldmap histogram. Based on multiresolution BOLD signal simulation, we find that the signal turbulence mainly emerges at the vessel boundary, and that there are only a few voxels (less than 10%) in an ultrahigh-resolution image that reveal turbulence in the form of sparse point noise. Our simulation also shows that, for typical human brain imaging of the cerebral cortex with millimeter resolution, $TE < 30$ ms and $B_0 = 3$ T, we are unlikely to observe BOLD signal turbulence. Overall, the main causes of voxel signal turbulence include a high spatial resolution, high field, long TE and large vessel.

Keywords

BOLD fMRI; BOLD signal simulation; intravoxel dephasing; multiresolution; phasor turbulence; fieldmap histogram; intravascular and extravascular partition; voxel symmetry

INTRODUCTION

Blood oxygenation level-dependent (BOLD) functional MRI (fMRI) has been widely used to map brain activity. The BOLD signal is a T_2^* signal formed by intravoxel dephasing

summation over proton precessions in a BOLD-induced magnetic fieldmap (1). As BOLD signal detection involves a spatial average over the voxel space (different from summation by a constant scale), it is understandable that the spatial specificity of BOLD fMRI can be improved by reducing the voxel size. For a human fMRI study, the standard voxel dimension is in the millimeter range (1–3 mm resolution), and high-spatial-resolution fMRI is in the submillimeter range (2–4). In animal fMRI, the spatial resolution can approach 100 μm (5–7). In this article, we use the term ‘ultrahigh spatial resolution’ and consider cases in which the resolution is less than 50 μm .

Numerical simulation of multiresolution BOLD data (8) has shown that the dephasing signal degeneration caused by the intravoxel average can be mitigated by voxel subdivision, thereby bringing an additional contrast to resolution-refined images. As we move from coarse to fine multiresolution analysis, more BOLD field irregularities emerge as the voxel size is reduced. Through the multiresolution signal analysis in this article, we demonstrate that some BOLD signal timeseries at high-resolution levels may evolve in a chaotic manner, called ‘signal turbulence’, which defines the instability and unpredictability of the timeseries subject to a slight variation of parameter setting. To some extent, our work is related to previous reports on ‘spin turbulence’ (9,10) and ‘chaotic dynamics’ (11) observed in liquid-state nuclear magnetic resonance.

The BOLD fMRI signal is, in its nature, a complex-valued timeseries (with respect to TE), representing the average BOLD activity within a voxel. Conventionally, we decompose the complex timeseries into magnitude and phase components, and thereby address the magnitude and phase behavior separately (8,12–16). A complex variable can be represented by a phasor (phase vector) in a polar system (17). In a similar way, we can depict the evolution of a BOLD signal timeseries by a dynamic phasor (18), which usually manifests as a spiral, in which the shortening radial distance represents the magnitude decay and the spiraling indicates the phase angle accumulation with respect to time. Adopting the phasor diagram for BOLD signals, we can observe both the magnitude and phase behaviors simultaneously in a single figure; more importantly, we can manipulate the phasors algebraically (rather than trigonometrically). In most scenarios, the BOLD signals evolve in the form of inward spirals in phasor diagrams. However, as the voxel size is reduced, we demonstrate that the BOLD phasors do not follow inward spirals, and instead manifest as knotting, leaping and other disordered patterns. Collectively, we describe the nonspiral evolutions as ‘turbulence’. In the following, we use the terms ‘voxel signal’, ‘BOLD signal’ and ‘signal’ exchangeably, which are expressed in complex format and are represented graphically by phasors.

Numerical simulation allows us to look inside the relationship between neuroactivity-induced biomagnetic disturbance and the intravoxel dephasing signal or image formation in a controllable manner (19–23). To implement the simulation, we first define the parameter values for a cortical voxel (e.g. voxel dimension, intravoxel vasculature configuration and biomagnetic characterization) and define a protocol for fMRI scanning (e.g. main field strength, TE, image matrix) (8,22,24,25). We represent a voxel by a support matrix (size, $512 \times 512 \times 512$; in which each element represents a spin packet or isochromat) and carry out the fine-to-coarse multiresolution synthesis by subvoxel rebinning. The intravoxel

vasculature configuration has advanced from simple geometrical primitives (balls and cylinders) to arbitrary vascular networks (8,23,24,26). The BOLD fieldmap induced by vasculature magnetization can be efficiently calculated by a Fourier transform method (23,27,28).

The BOLD fieldmap over a voxel space assumes the same support matrix representation as used for voxel digitization. By counting the numbers of matrix elements that have equal fieldvalues, we obtain a fieldmap histogram that describes the statistical fieldvalue distribution of the fieldmap by completely ignoring the spatial population information. The histogram of the intravoxel BOLD fieldmap can be used to compute the BOLD signal (28,29). The intravoxel dephasing summation for BOLD signal formation amounts to a Riemann sum (30): a sum of spin packets over a three-dimensional voxel domain. Given a histogram for a BOLD fieldmap, we show that the Riemann sum formula for intravoxel dephasing can be reformatted into a Lebesgue sum (31): a sum of binned fieldvalues over a one-dimensional fieldvalue range of the fieldmap. Using this formulation, we propose a histogram-based dephasing algorithm for fast BOLD signal calculation, and we can interpret the BOLD signal turbulence as caused by fieldmap histogram irregularity.

Currently, millimeter and submillimeter resolutions have been achieved for fMRI studies, and the pursuit of higher spatial resolutions continues (4,6). The promise of high-spatial-resolution fMRI is to underpin the neuronal activity with more details and improved specificity (2,4). However, the pursuit of high-spatial-resolution fMRI also poses some challenges (5), one of which is the boost of noise. Our report is helpful for understanding the sparse point noise in ultrahigh-resolution images from the perspective of turbulent signals.

THEORY AND METHODOLOGY

Overall topic

The BOLD fMRI signal is attributed to a fieldmap established via the magnetization of an inhomogeneous susceptibility distribution induced by cerebral blood oxygenation and deoxygenation associated with brain activity. To implement the BOLD fMRI simulation, we first configure the cortical vasculature in a voxel of interest. Figure 1a shows a cortical voxel filled with F1 3- μ m-radius vasculature with a blood volume fraction (*bfrac*) of 2%. Next, we define the parameters for the MRI scanning protocol and proceed to calculate the BOLD fieldmap and the BOLD voxel signal. For subdivided subvoxels, we calculate the subvoxel signals based on the subdivided fieldmaps. The BOLD signal is a complex-valued timeseries consisting of a pair of magnitude and phase components, as displayed separately in Figure 1b, c. We can also represent the complex timeseries by a phasor in a polar system, as shown in Figure 1d, in which a spiraling phasor (a spiral segment in the black plot) represents both the magnitude decay and the phase angle accumulation behaviors with respect to time. It is shown in Figure 1 that the voxel signal $s_0(t)$ reveals a fall-off magnitude decay in Figure 1a, a linear phase angle accumulation in Figure 1c and a spiraling phasor in Figure 1d (black plots); in comparison, the subvoxel signal $s_4(t)$ reveals a turbulent evolution in the form of an oscillating magnitude decay in Figure 1b, an oscillating phase angle accumulation in Figure 1c and a nonspiraling phasor in Figure 1d (red plots). In this section, we address the phasor turbulence phenomenon by multiresolution analysis theory and attempt to understand

the causes by reformatting the subvoxel fieldmap into a histogram and relating it to subvoxel signal formation.

Multiresolution voxel decomposition

We simulate a cortex voxel V_0 by filling it with a random capillary vasculature under the condition of $bfrac = 2\%$. Let us suppose the voxel size is $D_0 \times D_0 \times D_0$; then V_0 can be expressed by:

$$V_0(x, y, z) = \begin{cases} 1, & (x, y, z) \in \text{vessel} \\ 0, & \text{otherwise} \end{cases} \quad \Omega \quad [1]$$

$$\text{supp}(V_0) = \begin{cases} |x| \leq \frac{D_0}{2}, |y| \leq \frac{D_0}{2}, |z| \leq \frac{D_0}{2} \\ 0, & \text{otherwise} \end{cases}$$

where Ω_0 denotes the voxel spatial domain. By discretizing V_0 with a grid resolution element (gridel) $\Omega_\varepsilon = \varepsilon \times \varepsilon \times \varepsilon$ ($\varepsilon \ll D_0$), we represent V_0 by a three-dimensional support matrix with a size of $N_\varepsilon \times N_\varepsilon \times N_\varepsilon$, typically $N_\varepsilon = 512 \gg 1$. The j -level multiresolution analysis ($1 < j < N_\varepsilon$) on V_0 produces an octadic tree (in which each parent node is decomposed into eight children nodes) (32), denoted by $\text{octree}_j(V_0)$. Adopting a j -tuple notation (8), we can designate a subvoxel at j level by $V_j(k^1, k^2, \dots, k^j)$. The multiresolution voxel decomposition scheme can be applied to the fieldmap partition and signal decomposition in a similar manner. We refer the reader to our previous publication (8) for more details.

Multiresolution intravascular/extravascular partitions

The intravascular (IV) and extravascular (EV) partitions (denoted by intravascular/extravascular or IV/EV partition) of a cortical voxel (as shown in Figure 2) and their subvoxels can be expressed by:

$$\begin{aligned} \Omega &= \Omega_j^{IV} \cup \Omega_j^{EV}, j=0, 1, 2, \dots \\ &= \{(i_x, i_y, i_z) \mid V_j(i_x, i_y, i_z) = 1\} \cup \{(i_x, i_y, i_z) \mid V_j(i_x, i_y, i_z) = 0\} \quad [2] \\ &= \{(i_x, i_y, i_z) \mid V_j(i_x, i_y, i_z) = 1\} \cup \{(i_x, i_y, i_z) \mid V_j(i_x, i_y, i_z) = 0\} \end{aligned}$$

where Ω_j denotes the spatial support of subvoxel V_j . In the sense of three-dimensional masks, we use this IV/EV partition scheme to spatially partition the BOLD fieldmap and thereby to decompose the resulting BOLD signals. In practice, the IV signal is inseparable from the EV signal during signal detection. Nevertheless, the numerical simulation allows us to separate the contribution of IV from that of EV to the BOLD voxel signal.

Multiresolution BOLD fieldmap partitions

Given a vasculature-filled voxel V_0 , we proceed to calculate the BOLD fieldmap $B(i_x, i_y, i_z)$ therein. For simple and regular geometrical primitives, such as balls and cylinders, the BOLD fieldmap can be calculated by a three-dimensional convolution of the magnetic susceptibility distribution with the point magnetic dipole field kernel. For arbitrary vasculature, an efficient way to calculate the BOLD fieldmap is by a Fourier technique (23,27,28,33), as expressed by:

$$\Delta B(i_x, i_y, i_z) = IFT \left\{ \left(\frac{k_z^2}{k_x^2 + k_y^2 + k_z^2} - \frac{1}{3} \right) \cdot FT \{V_0(i_x, i_y, i_z)\} \right\} \cdot (1 - Y) \cdot Hct \cdot \chi_{do} \cdot B_0 \quad [3]$$

where Hct is the blood hematocrit, χ_{do} is the susceptibility difference between oxygenated and deoxygenated blood, Y is the blood oxygenation level, B_0 is the main magnetic field, FT is the Fourier transform, IFT is the inverse Fourier transform and (k_x, k_y, k_z) is the Fourier domain. The FT technique is of global transformation, which accounts for the interactions among the magnetizations of the cerebral cortex vasculature, and therefore must be applied to the whole voxel space as represented in a large fine grid support matrix at level $j = 0$ for the BOLD fieldmap calculation.

On completion of the BOLD fieldmap $B(i_x, i_y, i_z)$, we can spatially partition it according to the multiresolution voxel partition scheme, thereby producing a BOLD fieldmap octree:

$${}^c_j(\Delta B) = \left\{ \Delta B, \Delta B_1({}^1k), \Delta B_2({}^1k, {}^2k), \dots, \Delta B_j({}^1k, {}^2k, \dots, {}^jk) \mid j \in K_8, j=0, 1, 2, \dots, j \right\} \quad [4]$$

with $\Delta B_j({}^1k, {}^2k, \dots, {}^jk) = \Delta B \cdot \Omega_j({}^1k, {}^2k, \dots, {}^jk)$

where B_0 refers to B , and the notation of the spatial location (i_x, i_y, i_z) is omitted. In the same way as the multiresolution IV/EV space partition on a voxel or subvoxel in Equation (2), we can carry out multiresolution IV/EV fieldmap partition by $\Delta B_j = \Delta B_j^{IV} + \Delta B_j^{EV}$.

The BOLD fieldmap $B(i_x, i_y, i_z)$ over Ω_0 assumes positive and negative fieldvalues, distributed in a finite fieldvalue range of $[\min(B), \max(B)]$, which is usually asymmetrical about zero [that is $|\min(B)| \neq |\max(B)|$]. By partitioning the fieldvalue range into a sequence of fieldvalue bins and counting the fieldvalues that fall into bins, as presented in APPENDIX A, we can calculate a statistical histogram for the fieldmap.

For the sake of histogram processing (see later), we define a symmetrical fieldvalue range by $[-\max(|B|), \max(|B|)]$ and partition it into $N + 1$ bins, $\{b_n, n = [-N/2, N/2]\}$; we can then calculate a histogram for the BOLD fieldmap, denoted by $h(n)$. In APPENDIX A, we only address the fieldmap histogram for a voxel. In a similar manner, we can calculate the fieldmap histograms for subvoxels, with and without IV/EV partition. As a result of the disjoint IV/EV partition and the histogram additivity, the fieldmap histograms satisfy the following relations:

$$\begin{aligned}
 &= h_j^{IV}(n) + h_j^{EV}(n) \\
 &= \sum_{n=-N_\varepsilon}^N h_j^{IV}(n) + \sum_{n=-N_\varepsilon}^N h_j^{EV}(n) = N_\varepsilon^3 / 8^j \quad [5]
 \end{aligned}$$

Given a histogram $h(n)$, we propose to decompose it into an even symmetrical component and an odd symmetrical component (denoted by even/odd decomposition $h = {}^eh + {}^oh$) using Equation (A10) (APPENDIX A). Figure 3 shows a histogram function and its even/odd decomposition. The histogram function is nonnegative [$h(n) \geq 0$], and so is its even component (${}^eh \geq 0$). Concerning the fact that the even function eh usually has an overwhelming mode at the symmetrical center at $B = 0$ (at $n = 0$), we propose to characterize the spread of symmetrical ${}^eh(n)$ by a parameter B_{spread} , as defined by:

$$B_{\text{spread},j} = \sum_{n>0} n \cdot {}^eh_j(n), {}^eh_j(n) \geq 0 \quad [6]$$

which represents the centroid of the quadrature of one-sided ${}^eh(n)$ ($n > 0$). A large B_{spread} value implies a wide spread of off-resonances. In the special case of ${}^eh(n) = \delta(n)$ [where $\delta(n)$ is the Dirac delta function], $B_{\text{spread}} = 0$, indicating no off-resonance or no BOLD activity. In the sense of the centroid in Equation (6), B_{spread} can be used to estimate the overall off-resonance effect of the BOLD fieldmap, as illustrated in Figure 3c. In comparison, the odd histogram component ${}^oh(n)$ is antisymmetrical about $B = 0$ (at $n = 0$), and usually assumes one positive lobe at one side and a negative lobe on the other side, that is ${}^oh(-n) = -{}^oh(n)$ and ${}^oh(n = 0) = 0$. Therefore, we propose to characterize the asymmetrical oh distribution by a parameter B_{shift} , as defined by:

$$B_{\text{shift},j} = \sum_{n>0} n \cdot {}^oh_j(n) \quad [7]$$

Again, B_{shift} represents a centroid of one-sided ${}^oh(n)$ ($n > 0$). It should be noted that, in contrast with the nonnegative $h(n)$ and ${}^eh(n)$, ${}^oh(n)$ always assumes positive and negative distributions on two sides with respect to the center at $n = 0$. In some cases, a positive mode and a negative mode may happen on one side of oh simultaneously, as illustrated in Figure 3d. If the positive quadrature and negative quadrature are not completely cancelled in Equation (7), it produces a nonzero centroid ($B_{\text{shift}} \neq 0$).

A histogram of a BOLD fieldmap usually assumes a unimodal distribution with a peak at the on-resonance frequency (at $B = 0$). In such cases, its even component is also unimodal (usually sitting at the symmetrical center) with a distributive width of B_{spread} , whereas its odd component always assumes an antisymmetrical multimodal distribution, in which the mode shift from the origin can be measured by B_{shift} . Along the course of multiresolution analysis on voxels, the fieldmap histograms resulting from subvoxels show more irregular distributions, which are characteristic of large B_{spread} and B_{shift} values (as demonstrated later).

Multiresolution BOLD signals

Intravoxel dephasing is the underlying principle for BOLD signal formation, which is formulated as a sum of spin precessions [strictly spin packet processions in numerical simulation (18)]. In the computation implementation, the signal of a spin packet at (i_x, i_y, i_z) in V_0 is expressed by:

$$s_\varepsilon(i_x, i_y, i_z, t) = \exp(-i \cdot \gamma \cdot \Delta B(i_x, i_y, i_z) \cdot t) \quad [8]$$

which is represented by a rotation on a unit circle (no amplitude decay $|s_\varepsilon(t)| = 1$) with respect to time t in the phasor diagram (t is interpreted as TE). The BOLD signal S_0 for the voxel V_0 is generated by the intravoxel dephasing summation over a number of N_ε^3 spin packets. Considering the fact that the makeup of a cerebral cortex includes IV blood and EV brain parenchyma, which can be modeled as a water-equivalent soft tissue, we assume a uniform distribution of water molecules (corresponding to spin packets in the numerical simulation) in a cortical voxel. With the uniform spin density assumption, the multiresolution BOLD signals (non-normalized) are calculated by:

$$S_j(t; {}^1k, {}^2k, \dots, {}^jk) = \sum_{(i_x, i_y, i_z) \in \Omega_j} s_\varepsilon(i_x, i_y, i_z, t) \quad [9]$$

This dephasing formula is also applicable to IV/EV spaces of a voxel or subvoxel [APPENDIX B, Equation (B1)]. The IV/EV signal decomposition is expressed by:

$$\begin{aligned} & S_j(t; {}^1k, {}^2k, \dots, {}^jk) \\ &= S_j^{IV}(t; {}^1k, {}^2k, \dots, {}^jk) \\ &+ S_j^{EV}(t; {}^1k, {}^2k, \dots, {}^jk) \end{aligned} \quad [10]$$

where:

$$\begin{cases} S_j^{IV}(t; {}^1k, {}^2k, \dots, {}^jk) \\ = \sum_{(i_x, i_y, i_z) \in \Omega_j^{IV}} s_\varepsilon(i_x, i_y, i_z, t) \\ S_j^{EV}(t; {}^1k, {}^2k, \dots, {}^jk) \\ = \sum_{(i_x, i_y, i_z) \in \Omega_j^{EV}} s_\varepsilon(i_x, i_y, i_z, t) \end{cases} \quad [11]$$

The spatial summation over a voxel (or a subvoxel) can be alternatively achieved by a summation over the fieldmap histogram. In APPENDIX A, we develop a discrete Fourier transform (DFT) implementation for the histogram-based BOLD signal calculation. In the presence of IV/EV partition, the multiresolution BOLD signals are calculated by:

$$\begin{aligned}
& S_j^\lambda(t; {}^1k, {}^2k, \dots, {}^jk) \\
& = DFT \left\{ h_j^\lambda(n; \Delta B_j({}^1k, {}^2k, \dots, {}^jk)) \right\}, \lambda \\
& = \{ 'IV', 'EV', 'void' \}
\end{aligned} \quad [12]$$

where $\lambda = \text{'void'}$ represents the case of no IV/EV partition.

Given a complex signal, we can extract its magnitude and phase parts by:

$$\begin{cases}
\lambda_j(t; {}^1k, {}^2k, \dots, {}^jk) \\
= |S_j^\lambda(t; {}^1k, {}^2k, \dots, {}^jk)| \\
\Theta_j^\lambda(t; {}^1k, {}^2k, \dots, {}^jk) \\
= \angle S_j^\lambda(t; {}^1k, {}^2k, \dots, {}^jk)
\end{cases} \quad [13]$$

where $|\cdot|$ denotes the absolute value and $\angle$ the phase angle. It should be noted that the phasor representation allows simple algebraic operations (vector or complex addition) in Equation (10). However, this advantage is not maintained for the magnitude and phase components because of the nonlinearity of the complex modulo and argument operations in Equation (13). In general, we observe the following inequities:

$$\begin{cases}
j(t; {}^1k, {}^2k, \dots, {}^jk) \\
\neq A_j^{IV}(t; {}^1k, {}^2k, \dots, {}^jk) + A_j^{EV}(t; {}^1k, {}^2k, \dots, {}^jk) \\
\Theta_j(t; {}^1k, {}^2k, \dots, {}^jk) \\
\neq \Theta_j^{IV}(t; {}^1k, {}^2k, \dots, {}^jk) + \Theta_j^{EV}(t; {}^1k, {}^2k, \dots, {}^jk)
\end{cases} \quad [14]$$

Not only can a histogram be decomposed into IV and EV components according to spatial occupancy, it can also be decomposed into even and odd components as a mathematical trick (APPENDIX A). Exploiting the linearity of DFT and the properties of even and odd functions, we extend Equation (A12) to subvoxels:

$$\begin{cases}
\lambda_j(t_n) = |S_j^\lambda(t_n)| = \frac{1}{2} \\
\sqrt{\left(DCT \left\{ e h_j^\lambda(n) \right\} \right)^2 + \left(DST \left\{ o h_j^\lambda(n) \right\} \right)^2} \\
\Theta_j^\lambda(t_n) = \angle S_j^\lambda(t_n) \\
= \arctan \left(\frac{DST \left\{ o h_j^\lambda(n) \right\}}{DCT \left\{ e h_j^\lambda(n) \right\}} \right)
\end{cases} \quad [15]$$

where DCT and DST are the discrete cosine and sine transforms, respectively, and t_n is the discrete time. The histogram-based BOLD signal calculation formula in Equation (15) allows us to interpret the BOLD signal magnitude and phase parts using Equation (A14).

So far, we have addressed a coarse-to-fine multiresolution analysis on voxel, field and signal, with and without IV/EV partition. In a reverse manner, we can render a fine-to-coarse multiresolution synthesis. For the children-to-parent synthesis of the BOLD signals along an octree, there exists a rebinning invariance (8) (additivity of complex signals),

which is also applicable to IV/EV partitioned histograms and to IV/EV signals (valid for non-normalized signals). However, for the normalized IV/EV signals [Equation (B2)], we show in APPENDIX B that the BOLD signal formation involves a convex combination (34) of *bfrac*-weighted IV/EV partition by Equation (B3). For a subvoxel signal, the IV/EV partition is governed by:

$$s_j(t) = bfrac_j \cdot s_j^{IV}(t) + (1 - bfrac_j) \cdot s_j^{EV}(t) \quad [16]$$

where *bfrac_j* denotes the blood volume fraction in a subvoxel at level *j*; it changes not only from a parent voxel to a child subvoxel across resolution levels (*bfrac_j* → *bfrac_j*), but also between sibling subvoxels at the same resolution level [*bfrac_j*(¹*k*, ²*k*, ..., ^j*k*) → *bfrac_j*(¹*k*, ²*k*, ..., ^j*k*')] as a result of the nonuniform distribution of cortical vasculature in the field of view (the root voxel with *bfrac* = *bfrac₀* = 2% in our simulation). At high-resolution levels, a small subvoxel may contain no vessels (*bfrac_j* = 0) or completely be embedded inside a large vessel (*bfrac_j* = 100%); thus 0 ≤ *bfrac_j* ≤ 100%.

Occurrence rate of BOLD signal turbulence

Given a cortical voxel, its BOLD signal is determined by the intravoxel BOLD fieldmap, which is, in turn, determined by the cortical vasculature therein. We demonstrate in the next section that, as a voxel is decomposed into subvoxels, there are only a fractional number of the subvoxel signals that may exhibit turbulence. We propose to numerically characterize the turbulence occurrence rate by a fractional number as defined by *turfrac* = (# of turbulent phasors)/(# of total phasors), where # denotes the numbers. For a practical setting, there are many factors that may affect the *turfrac* value. For multiresolution BOLD signals, *turfrac* is explicitly affected by the resolution level *j* and TE; therefore, we customize *turfrac* by:

$$turfrac_j(t) = \frac{\# \text{ of turbulent } s_j(t; {}^1k, {}^2k, \dots, {}^jk)}{8^j} \quad [17]$$

where 8^j is the total number of subvoxel phasors at level *j* and 0 < *turfrac_j* < 1. Another important factor that has a significant effect on the BOLD signal turbulence and on *turfrac* is the vessel size. We simulate the vessel size effect by configuring a cortical voxel (*V₀*) with random cylinders of a specific radius (for monosized vasculature) or with a range of radii (for mixed vasculature) under the condition of *bfrac* = 2%.

A turbulent signal behaves with a rapid and unpredictable evolution in a phase diagram because of its extreme sensitivity to a subtle variation in the imaging condition. At a given TE, the values for all the subvoxel signals are presented as a three-dimensional image, in which there are up to *turfrac* entries which behave as image point noise; therefore, the turbulence occurrence rate *turfrac* can be interpreted as the noise sparsity. For cerebral cortex imaging, we show that there are about 10% of voxels in a high-resolution image (*turfrac₄* ≈ 10% for a vessel radius of 3 μm, *bfrac₀* = 2% and a resolution of 20 μm) which will show turbulence. We refer readers to our previous publication (8) for the image presentation of multiresolution BOLD signals, in which the extreme values of the image

entries are described in terms of statistical ‘wildness’ and outliers, which correspond to the turbulent signals herein.

RESULTS

In this section, we demonstrate the emergence of BOLD signal turbulence as a result of a four-level, coarse-to-fine multiresolution voxel decomposition ($j = \{0, 1, 2, 3, 4\}$ corresponding to voxel sizes of $\{320 \times 320 \times 320, 160 \times 160 \times 160, 80 \times 80 \times 80, 40 \times 40 \times 40, 20 \times 20 \times 20\} \mu\text{m}^3$, respectively). At the beginning, we configure a cortical voxel (V_0) by defining a cube with a size of $320 \times 320 \times 320 \mu\text{m}^3$ and filling it with a typical capillary vasculature (vessel radius, $5 \mu\text{m}$; $bfrac = 2\%$). The voxel is finely discretized into a large support matrix with a size of $512 \times 512 \times 512$ with a grid resolution $\epsilon = 0.625 \mu\text{m}$ ($= 320 \mu\text{m}/512$). We then calculate the BOLD fieldmap using Equation (3) with the parameter settings (23): $B_0 = 3 \text{ T}$, $Hct = 0.4$, $Y = 0.5$ and $\chi_{do} = 0.27 \times 4\pi \text{ ppm}$. Given a voxel fieldmap (a global fieldmap over the space of the root voxel), we calculate the BOLD voxel signal at level $j = 0$ for $TE = [0, 120] \text{ ms}$ using Equation (9). By decomposing the voxel into smaller subvoxels, we repeat the subvoxel BOLD signal calculation using Equation (9). It should be noted that the subvoxel fieldmap is taken from a part of the global voxel fieldmap, rather than being recalculated from the subvoxel by Equation (9). We show that the multiresolution voxel decomposition incurs phasor turbulence in the form of the manifestation of nonspiral or rapid evolutions. By decomposing the multiresolution BOLD signals into IV/EV contributions, we testify that the IV signals are responsible for the turbulence.

Multiresolution phasors

The multiresolution BOLD signals calculated for the four-level F4 voxel decompositions are displayed in Figure 4, in which the BOLD signal $s_0(t)$ of the root voxel V_0 (at level $j = 0$) is copied in all four-level panels for visual comparison with the subvoxel signals. It can be seen that some phasors at $j = 2$ begin to oscillate, then become turbulent at $j = 3$ and quickly become entangled at level $j = 4$. The number of phasors increases by 8^j as a result of octadic decomposition, which are displayed in different colors for visual distinction. Of the 8^j subvoxel phasors, only a fraction of the total subvoxel phasors (about 8% for a vessel radius of $5 \mu\text{m}$ and $bfrac = 2\%$) reveal turbulence at $j = 3$ (resolution, $40 \mu\text{m}$) and $j = 4$ (resolution, $20 \mu\text{m}$).

As shown in Figure 4, almost all the low-resolution signals (at $j = 1, 2$) behave as spirals, and high-resolution signals (at $j = 3, 4$) prolong the spirals and some become turbulent. The phasor turbulence appears in the form of knotting, leaping, oscillation and other nonspiral involutions. In particular, we note that all of the subvoxel phasors behave as inward spirals around the common starting point (radial length, 1; polar angle, 0), implying no turbulence in the small-angle regime ($\exp(i\phi) \approx 1 + i\phi$ for a small phase angle $\phi \ll 1$ that can be reached by a small TE, usually for $\phi < 0.1 \text{ radian} = 5.7^\circ$).

In Figure 4, we observe that, as the resolution level increases, the number of phasors proliferates (according to 8^j), the phasor lengths become prolonged and some develop into turbulence (manifesting as self-entanglement, intertwining, rapid looping and oscillating spiraling). To demonstrate a specific turbulent subvoxel phasor, we trace a four-level voxel

decomposition of a subtree along a trunk path of $(^1k, ^2k, ^3k) = (^11, ^21, ^34)$ in the voxel decomposition tree and display it in Figure 5. In the four panels, we display the BOLD fieldmap (a two-dimensional slice), the fieldmap histogram and the phasor for the four-level subvoxels. We demonstrate that the subvoxels that are located at vessel boundaries produce irregular fieldmap histograms (asymmetry and multimode) and turbulent signals (see panel 3 for $j = 3$ and panel 4 for $j = 4$ in Figure 5).

Multiresolution fieldmap histograms and even/odd decomposition

The positive portion of the BOLD fieldmap is not always equal to the negative portion because of the random vasculature in the cortical cortex, thus producing an asymmetrical histogram distribution about $B = 0$. In order to render the even/odd histogram, we need to set up a sequence of bins with the center at $B = 0$. For example, we may define a fieldvalue range of $[-15, 15]$ ppmT for a BOLD fieldmap with $\max(|B|) = 14.6$ ppmT, and partition it into 241 bins ($N = 240$). Figure 6 displays the subvoxel fieldmap histograms for a subtree along a branch path $(^1k, ^2k, ^3k) = (^11, ^21, ^34)$, together with the calculated values for B_{spread} and B_{shift} using Equations (6) and (7). In each panel, we demonstrate the children-to-parent histogram synthesis: the sum of eight children histograms in the first eight subpanels produces the parent histogram in the last subpanel at the bottom right corner. The irregular subvoxel BOLD disturbance is featured by large B_{spread} and B_{shift} values. It can be seen that, as the spatial resolution increases, the fieldmap histograms at reduced subvoxels have multimodal and irregular distributions, implying the emergence of BOLD field irregularity in the subvoxels.

Multiresolution BOLD signal calculation by two algorithms

In the previous section, we presented two algorithms for BOLD signal calculation: one is the conventional intravoxel dephasing algorithm [in the form of the Riemann sum in Equation (9)] and the other is the DFT on the fieldmap histogram [in the form of the Lebesgue sum in Equations (12) and (A5)]. Figure 7 shows that the two algorithms produce similar results for the four-level multiresolution signals. It is known that the Riemann sum and Lebesgue sum produce the same result when $N + 1 = N^3/8^j$ (no binning effect on the histogram calculation). With the correspondence between Figures 7 and 6, we see that irregular multimodal fieldmap histograms lead to phasor turbulence; therefore, the Lebesgue sum algorithm offers a means that allows us to look into the relationship between the BOLD voxel signal behavior and intravoxel vascular structure via the fieldmap histogram.

Multiresolution IV/EV partitions

Although the IV and EV BOLD signal components are inseparable in BOLD fMRI, we can examine the IV/EV contributions to the voxel or subvoxel signals by numerical simulation in the F8 static dephasing regime. Figure 8 shows the IV/EV partition on the BOLD fieldmap, fieldmap histogram and complex-valued voxel signal (level $j = 0$). We should point out that the normalized IV/EV signals combine into the BOLD signal according to their spatial occupancies by a convex combination (34) [see APPENDIX B, Equation (B3)].

The multiresolution IV/EV partition on the BOLD fieldmap can be described statistically by the IV/EV histograms. Figure 9 shows the IV/EV histograms for a subtree along a trunk path

of $(^1k, ^2k, ^3k) = (^11, ^21, ^34)$, and Figure 10 shows the corresponding IV/EV signals. With the correspondence of Figures 9 and 10, we see that irregular IV histograms are responsible for the extreme IV signal turbulence. As the subvoxel synthesis of normalized IV/EV signals follows a convex combination using Equation (16), the extreme IV signal turbulences are greatly suppressed by a small coefficient $bfrac_j$ in subvoxel signals $s_j(t)$ (note that, because the resolution of 20–320 μm is larger than the 5-mm-radius vessel, a subvoxel cannot sit inside a vessel, and therefore $bfrac_j < 100\%$ in Figure 10). Nevertheless, the IV signal is the main character in the play of the BOLD signal turbulence. As the spatial resolution increases, the subvoxel decreases, such that some subvoxels may completely sit in the IV space (when the voxel size is less than the vessel size) and some may intercept an IV boundary; all of these cases produce a large B_{shift} and a large $bfrac_j$, which are responsible for rapid phasor evolutions (see rapid spiraling and nonspiraling turbulences in Figure 10).

Sparsity of the occurrence of BOLD signal turbulence

A complex-valued voxel signal is represented by a phasor. As the voxel is decomposed into subvoxels, it produces the same number of phasors. Of the multitude of subvoxel phasors, only a fraction reveals nonspiraling and rapid spiraling turbulence. On the observation of the multiresolution BOLD signals, we note that the conspicuous phasor turbulence primarily occurs at the large vessel boundary. As a BOLD fMRI study captures a timeseries of brain physiological states by snapshot imaging with a single TE value (except for multi-echo imaging) rather than a range of TE, the effect of signal turbulence on the multivoxel image is manifested as unstable voxel values that may quickly change with a slight variation in imaging conditions. However, only a fractional number of voxels, as expressed by $turfrac_j$ in Equation (17) may reveal irreproducible image point noise. In our simulation, we observed the multiresolution signal phasors (displayed on a computer with a semiautomatic program) and classified them into normal spiral phasors and abnormal nonspiral phasors (including nonspiraling and rapid spiraling). The count numbers are presented in Table 1 and the parameters T1 $turfrac_j$ were numerically characterized using Equation (17).

It is seen that large vessels may reveal signal turbulence at a relatively low resolution level (e.g. $j = 1$ for the signal turbulence emergence of 9- μm -radius vasculature). As the resolution level increases, the parameter $turfrac_j$ tends to decrease. As the different vasculature voxels V_0 (at $j = 0$) are configured under the same condition of $bfrac = 2\%$, a voxel filled with large vessels has less vessel surface area than a voxel filled with small vessels, which explains why the 9- μm -radius vasculature voxel in Table 1 reaches the smallest $turfrac_j$ value (6%). Thus, there is only a small fraction of voxels in an image acquired by high-resolution fMRI which may assume unstable values (or irreproducible values), thus manifesting as image point noise: a small change in imaging conditions may cause some image points to change their values too quickly to be predictable. Therefore, the parameter $turfrac_j$ can be interpreted as the sparsity of image point noise.

DISCUSSION

For numerical simulation of multiresolution voxel and BOLD signal decomposition, we should clearly distinguish two spatial resolutions: one is the grid resolution for the

discretization of a cortical voxel by a three-dimensional matrix and the depiction of the vessels therein in digital geometry; the other is the imaging resolution for presenting the detected MRI signals by an image array. Figure 2 provides an intuitive illustration for a three-level multiresolution voxel decomposition that produces multiresolution image arrays. In the implementation, a cortical voxel space is represented in a large support matrix at a fine grid resolution and multiresolution analysis is carried out by subvoxel rebinning. High-spatial-resolution fMRI may increase the magnitude and phase image contrast. Multiresolution BOLD signal analysis has shown that the phase image contrast increases more rapidly than the magnitude image contrast as the resolution increases (8), which corresponds to the phasor turbulent phenomenon as demonstrated in this article. On the one hand, as more field irregularities emerge in the high-resolution phase image, the contrast is enhanced. On the other, the contrast enhancement resulting from high-spatial-resolution imaging may be manifested as unstable image point noise: some bright image points may suddenly turn dark, and vice versa, because of a slight change in the parameter settings, such as TE and field strength. As the phase angle of a spin precession is proportional to the field strength at a location [$\phi(x, y, z) \propto B(x, y, z)$], as the voxel size is reduced in high-resolution imaging, the intravoxel average effect on the signal phase is decreased, which yields the emergence of large fieldvalues (as a result of less average effect) that prolong phasors. In extreme cases, the emergence of fieldvalue peaks in reduced subvoxels leads to rapid phasor evolution and turbulence. As can be seen in Equation (2), the inhomogeneous fieldmap is determined by the cortical vasculature; a fieldvalue jump occurs close to the vessel boundary because of the spatial derivative characteristics of the three-dimensional filtering with a bipolar-valued filter therein. It is understandable that the reduced voxel size allows more field irregularities to emerge because of less average effect. Therefore, the phasor turbulence is always observed at vessel boundaries in high-resolution images.

The intravoxel dephasing BOLD signal is conventionally calculated by counting the spin packets over the support matrix of a voxel (or a submatrix for a subvoxel), which is a form of Riemann sum: summing up the spin signals over the three-dimensional voxel space. By reformatting the Riemann sum, we can calculate the BOLD signal by performing a DFT on the fieldmap histogram, which is a form of Lebesgue sum: summing up the fieldvalue-sorted spin signals over the one-dimensional fieldvalue range (the fieldmap histogram). The two algorithms produce similar results. The approximation associated with the Lebesgue sum is a result of fieldvalue discretion (fieldvalue bin). As the bin width decreases, the Lebesgue sum approaches the Riemann sum.

The vessel size has a strong effect on the occurrence of phasor turbulence. By filling a voxel V_0 with vasculature with different vessel sizes (radii = {3, 5, 9} μm) under the same blood volume fraction condition ($bfrac = 2\%$), our simulation shows that we can readily observe phasor turbulence for large-vessel (radius, 9 μm) voxels by just one-level voxel decomposition (emergence at $j = 1$). High-resolution voxel decomposition and long TE will quickly prolong the phasor length and dramatically turn the phasor into turbulence. In comparison, we note that tiny cortical capillaries (radius, <3 μm) are unlikely to reveal noticeable signal turbulence, even if at ultrahigh-resolution imaging (voxel size of $40 \times 40 \times$

40 μm^3 or smaller). Based on this observation, the observed turbulence will not occur for high-spatial-resolution, small-animal fMRI at high field because of the small vessel size.

For the parameter setting of $\text{TE} = [0, 120]$ ms and $B_0 = 3$ T, we have demonstrated in Figure 4 that high-resolution imaging could incur signal turbulence at long TE, and that the signal turbulence could be avoided either at low resolution ($j=0, 1$) or with a short TE for high-resolution imaging (as indicated in the small-angle regime circles therein). During a short TE (<30 ms), we did not observe phasor turbulence. The largest phasor turbulence happens at long TE (>30 ms) and at high resolution levels ($j = \{3, 4\}$). As the spin precession angle $\phi(x, y, z)$ is proportional to $B(x, y, z)\text{TE}$, and the BOLD fieldmap $B(x, y, z)$ is proportional to B_0 , a high field contributes to the BOLD signal, similar to a long TE in a static regime (24). Therefore, it is understandable that the ‘spin turbulence’ phenomenon occurs at both high field strengths (9,11) and long TEs (10) in liquid-state NMR. In contrast, in this article, we report a BOLD signal turbulence phenomenon that occurs during other imaging conditions: high spatial resolution and large vessel size. As a result of the equivalence of long TE and high field to the phase angle increase (via $\phi = \gamma\text{TE} \cdot B$) (24), our multiresolution simulations with long TE = 120 ms may also be considered as a high-field BOLD fMRI simulation (TE < 30 ms). However, this equivalence is only valid when the diffusion effect can be neglected.

By partitioning the BOLD fieldmap into IV/EV spaces and calculating the IV/EV signals, we find that the IV signal undergoes much stronger variation than the EV signal during multiresolution voxel decomposition. At low spatial resolutions, the IV occupancy of a cortical voxel only assumes a small fraction number, as expressed by $b\text{frac}_j \approx 2\%$, so that the IV contribution to the observable voxel signal is greatly compromised by the weight of $b\text{frac}_j$. As the spatial resolution increases (voxel size decreases), the parameter $b\text{frac}_j$ varies among subvoxels in the range 0–100%. It is understandable that $b\text{frac}_j$ may assume a value of zero when a subvoxel contains no vessels or a fraction at very high resolution ($<50 \mu\text{m}$). For example, $s_3(t;1,1,3)$ in Figure 10 contains no IV contribution, and is a special case of $b\text{frac}_j = 0$, and $s_3(t;1,1,6)$ reveals rapid spiraling, and is an extreme case of $b\text{frac}_j \rightarrow 100\%$. The extreme IV signal turbulence may be attributed to the strong field disturbance (large $|B|$ value) and statistical fieldmap asymmetry ($\epsilon_h \neq 0$) within blood vessels. We should point out that the IV/EV signal simulation is valid for a static dephasing regime, where we do not involve the water proton diffusion across the IV/EV boundary.

We can also decompose a fieldmap histogram into even and odd components, as presented in APPENDIX A, where we find that the even fieldmap histogram is responsible for the signal magnitude and the odd fieldmap component for the signal phase. As the fieldmap histogram symmetry is very closely related to the fieldmap symmetry (not deterministic because of statistical binning), and the fieldmap symmetry is, in turn, determined by the intravoxel vasculature symmetry (in the absence or ignorance of the surrounding extravoxel vasculature), we reason that the BOLD signal is, to a great extent, caused by the voxel vasculature symmetry: the even vasculature symmetry is responsible for the magnitude and the odd vasculature symmetry (vasculature asymmetry) for the signal phase. The relationship between fieldmap histogram irregularity and signal turbulence can be perceived by observing the correspondence between the demonstrations in Figures 9 and 10. As

discussed in APPENDIX A, we note that the intravoxel vasculature asymmetry is responsible for the nonspiral signal turbulence, and the fieldvalue jumps for the rapid phase angle accumulation ($\phi \propto B$). These phenomena are usually observed at voxels located at the large vessel boundary, especially in high-resolution images where the partial volume effect is pronounced because of the digital geometry. Therefore, we conclude that the BOLD signal turbulence is mainly observed at large vessel boundaries in high-resolution imaging.

In this article, we only address the static dephasing regime without diffusion. More realistic dephasing mechanisms should take into account the spin diffusion effect. It is expected that the signal turbulence will be ameliorated slightly in the presence of spin diffusion because the random diffusion may suppress the field irregularity as a result of the blurring effect. Therefore, diffusion will suppress the occurrence of signal turbulence to some extent.

CONCLUSIONS

In this article, we report a BOLD signal turbulence phenomenon that occurs at ultrahigh-resolution fMRI (voxel size, $<50 \times 50 \times 50 \mu\text{m}^3$) by numerical simulation. The phenomenon is demonstrated with multiresolution BOLD signals in the form of a phasor diagram (resulting from four-level multiresolution voxel sizes: $320 \times 320 \times 320$, $160 \times 160 \times 160$, $80 \times 80 \times 80$, $40 \times 40 \times 40$, $20 \times 20 \times 20 \mu\text{m}^3$). We attempt to understand the phasor turbulences from the fieldmap histogram-based dephasing signal algorithm: the even histogram component is responsible for magnitude decay and the odd histogram component for phase angle accumulation. The emergence of irregular BOLD field disturbance as a result of the reduced intravoxel average effect is reflected in an irregular and multimodal histogram, which can be characterized by the centroids of the one-sided even and odd components. Intuitively, we may relate the even/odd symmetry of the fieldmap histogram to the geometrical symmetry of the intravoxel vasculature, thereby interpreting the BOLD signal turbulence from the perspective of the intravoxel microstructure. Future work should examine the relationships among the parameters (vessel size, $bfrac_j$, $turfrac_j$, resolution level, grid resolution and TE) in order to better understand high-resolution BOLD fMRI.

The pursuit of high-spatial-resolution BOLD fMRI may lead to signal turbulence (at a resolution of less than $50 \mu\text{m}$), which is manifested as sparse point noise in an image: there is a fraction of voxels (typically less than 10%) which may assume unpredictable values because of a subtle variation in imaging conditions. Our numerical demonstration shows that the IV signal is highly prone to turbulence; however, its contribution to the BOLD signal is greatly suppressed if the blood volume fraction is very small at low resolutions ($bfrac \ll 100\%$). The BOLD signal turbulence may be reduced or avoided by a short TE, a low field or a low spatial resolution. For fMRI at submillimeter resolution, it is unlikely that we will observe signal turbulence for $TE < 30 \text{ ms}$ and $B_0 = 3 \text{ T}$.

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APPENDIX A: BOLD FIELDMAP HISTOGRAM

The intravoxel BOLD fieldmap statistics can be characterized by a histogram. This Appendix reports a BOLD fieldmap histogram calculation method and a histogram-weighted BOLD signal algorithm.

Let $\max(|B|)$ denote the largest disturbance (deviation from zero) of the BOLD fieldmap $B(i_x, i_y, i_z)$ over voxel V_0 ; we define a fieldvalue range $[-\max(|B|), \max(|B|)]$, such that it has a center at zero, and partition the one-dimensional interval into $N + 1$ equally spaced bins by:

$$\frac{b_n = 2 \max(|\Delta B|)}{n} n = n \cdot \delta b, n \in [-N/2, N/2] \quad (\text{A1})$$

Hence, the n th bin is defined by a small subinterval $(b_n - \delta b/2, b_n + \delta b/2)$. It should be noted that the interval $[-\max(|B|), \max(|B|)]$ is symmetric in length about $|B| = 0$ (at $b_n = 0$ or $n = 0$), and so allows a function (that is defined over $[-\max(|B|), \max(|B|)]$) to be flipped for even and odd function decomposition (as used later). The BOLD fieldmap histogram over the voxel domain Ω_0 can be calculated by:

$$h(n) = \text{card} \{ (i_x, i_y, i_z) | b_n - \delta b/2 \leq \Delta B(i_x, i_y, i_z) < b_n + \delta b/2 \forall (i_x, i_y, i_z) \in \Omega_0 \} \quad (\text{A2})$$

It should be noted that $h(n)$ is inherently non-negative, that is $h(n) \geq 0$, and that the three-dimensional fieldmap spatial distribution information is completely lost in the one-dimensional histogram. We show that a summation over a three-dimensional spatial distribution can be alternatively achieved by a summation over its one-dimensional histogram.

Conventionally, the BOLD signal $S_0(t)$ as a result of intravoxel dephasing summation in the static regime (in the absence of diffusion) is expressed by:

$$S_0(t) = \sum_{(i_x, i_y, i_z) \in \Omega_0} \exp[-i \cdot \gamma \cdot \Delta B(i_x, i_y, i_z) \cdot t] \quad (\text{A3})$$

which is a summation of spin precessions over the three-dimensional voxel domain Ω_0 . Given that both the three-dimensional index summation over Ω_0 and the one-dimensional histogram summation over the fieldvalue bins give rise to the total gridel number N_ε^3 , that is:

$$\sum_{(i_x, i_y, i_z) \in \Omega_0} = \sum_{n=0}^N h(n) = N_\varepsilon^3 \quad (\text{A4})$$

we can reformat Equation (A3) into:

$$S_0(t) \approx \sum_{n=0}^N h(n) \cdot \exp(-i \cdot b_n \cdot \gamma \cdot t) \quad (\text{A5})$$

where the approximation ‘ $\approx$ ’ accounts for the intrabin average effect (discreteness of the fieldvalue range), which will diminish as $N+1 \rightarrow N_\epsilon^3$. Mathematically, Equation (A3) is a Riemann sum (30), and Equation (A4) is a Lebesgue sum (31), both carrying out the intravoxel dephasing summation for BOLD signal formation. It can be seen that Equation (A5) takes on a form of DFT with the kernel of $\exp(-i\gamma b_n t)$. Therefore, we suggest a DFT implementation for intravoxel dephasing signal calculation.

Histogram-weighted intravoxel dephasing algorithm

The inputs are as follows: BOLD fieldmap histogram $h(n)$, fieldvalue bin width δb , number of fieldvalue bins $N+1$ and TE.

Step 1: partitioning TE into $N+1$ equally spaced time bins by:

$$t_n = \frac{TE}{N} n = n \cdot \delta t, n \in [0, N] \quad (\text{A6})$$

Step 2: setting the DFT kernel:

$$W = \exp(-i \cdot \gamma \cdot \delta b \cdot \delta t) \quad (\text{A7})$$

with $\delta b = 2\max(|\Delta B|)/N, \delta t = TE/N$

Step 3: performing DFT on $h(n)$:

$$\begin{aligned} S_0(t_n) &= \sum_{n'=0}^N h(n') \exp(-i \cdot \gamma \cdot b_{n'} \cdot t_n) = W^{nN/2} \sum_{n'=0}^N h(n') W^{nn'} \\ &= W^{nN/2} DFT\{h(n)\} \end{aligned} \quad (\text{A8})$$

Step 4: outputting the BOLD signal with 1 – normalization [$s_0(t=0) = 1$]:

$$s_0(t_n) = S_0(t_n) / S(t_0) \quad (\text{A9})$$

It should be noted that the histogram-weighted BOLD signal algorithm in Equation (A8) suffers an intrabin average effect (for both fieldvalue bins and time bins, because of the discreteness of the continuous fieldvalue and time). The DFT algorithm requires the discretization of the TE into $(N+1)$ time bins in Equation (A6), such that both $\{S(t_n)\}$ and $\{b_n\}$ assume the same sequence length for fast algorithm implementation.

In addition to the fast implementation by DFT in Equation (A8), the histogram-weighted intravoxel dephasing algorithm provides a perspective on the magnitude and phase mechanisms of a BOLD signal from the statistical symmetry of the intravoxel fieldmap.

Given the fieldmap histogram $h(n)$ calculated for $N + 1$ fieldvalue bins in the symmetrical fieldvalue range $[-\max(|B|), \max(|B|)]$, we decompose $h(n)$ into even and odd components by:

$$\begin{aligned} h(n) &= {}^e h(n) + {}^o h(n) \\ &= \frac{h(n) + h(-n)}{2} + \frac{h(n) - h(-n)}{2} \end{aligned} \quad (\text{A10})$$

Given that the FT of an even function only produces a real part, and that of an odd function only produces an imagery part, we reformat Equation (A5) as follows:

$$\begin{aligned} S_0(t_n) &= \sum_{n'=-N/2}^{N/2} h(n') \exp(-i \cdot \gamma \cdot b_{n'} \cdot t_n) \\ &= \sum_{n'=-N/2}^{N/2} \left[{}^e h(n') + {}^o h(n') \right] \exp(-i \cdot \gamma b_{n'} \cdot t_n) \\ &= \sum_{n'=-N/2}^{N/2} {}^e h(n') \cdot \exp(-i \cdot \gamma b_{n'} \cdot t_n) + \sum_{n'=-N/2}^{N/2} {}^o h(n') \cdot \exp(-i \cdot \gamma b_{n'} \cdot t_n) \\ &= {}^e h(N/2) + 2 \sum_{n'=1}^{N/2} {}^e h(n') \cdot \cos(-\gamma b_{n'} t_n) + i \cdot 2 \sum_{n'=1}^{N/2} {}^o h(n') \cdot \sin(-\gamma \cdot b_{n'} \cdot t_n) \\ &= \text{DCT} \{ {}^e h(n) \} / 2 + i \cdot \text{DST} \{ {}^o h(n) \} / 2 \end{aligned} \quad (\text{A11})$$

where DCT and DST represent the discrete cosine and sine transforms, respectively. Therefore, the BOLD signal magnitude and phase are given by:

$$\begin{aligned} |S_0(t_n)| &= \frac{1}{2} \sqrt{[\text{DCT} \{ {}^e h(n) \}]^2 + [\text{DST} \{ {}^o h(n) \}]^2} \\ \Theta_0(t_n) &= \angle S_0(t_n) = \arctan \left[\frac{\text{DST} \{ {}^o h(n) \}}{\text{DCT} \{ {}^e h(n) \}} \right] \end{aligned} \quad (\text{A12})$$

As DCT produces a few large coefficients (including the dominant DC term corresponding to the function energy), which are greater than DST coefficients for the first few low harmonics (a few entries indexed by small t_n corresponding to a short TE), we can utilize the following series approximation:

$$\begin{aligned}\sqrt{1+x^2} &= 1 + \frac{x^2}{2} - \frac{x^4}{8} + \dots \approx 1 + \frac{x^2}{2} \approx \quad \text{for } |x| < 1 \\ \arctan x &= x - \frac{x^3}{3} + \frac{x^5}{5} - \dots \approx x \quad \text{for } |x| < 1\end{aligned}\quad (\text{A13})$$

to estimate the signal magnitude and phase parts, thus:

$$\begin{cases} \rho(t_n) \approx \frac{DCT\{e h(n)\}}{2} \left(1 + \left| \frac{DST\{o h(n)\}}{DCT\{e h(n)\}} \right|^2 \right) \approx \frac{DCT\{e h(n)\}}{2}, \\ \text{for } \gamma b_n t_n < 1 \forall n' \in [0, N] \\ \Theta_0(t_n) \approx \frac{DST\{o h(n)\}}{DCT\{e h(n)\}} \end{cases} \quad (\text{A14})$$

For a special case of perfect statistical even symmetry of the intravoxel fieldmap, that is $h = e h$ and $o h = 0$, we have $DST\{o h(n)\} = 0$ and:

$$\begin{cases} \rho(t_n) = DCT\{h(n)\} / 2 \\ \text{for } h = e h \text{ and } o h = 0 \\ \Theta_0(t_n) = 0 \end{cases} \quad \text{A15}$$

which implies that, for a voxel that has a perfect even symmetrical fieldmap histogram, it only produces a magnitude decay signal and no phase accumulation (phase contrast = 0). Imagine another extreme case of ideal statistical odd symmetry of the intravoxel fieldmap, that is $h = o h$ and $e h = 0$; we have $DCT\{e h(n)\} = 0$ and:

$$\begin{cases} \rho(t_n) \rightarrow 0, \\ \text{for } h = o h \text{ and } e h = 0 \text{ (imaginary case)} \\ \Theta_0(t_n) \rightarrow \infty \end{cases} \quad (\text{A16})$$

which implies that there is no magnitude and that the phase behavior is completely unpredictable. In practice, this imaginary case never happens because the $e h$ component of a nonzero $h(n)$ could not be zero. However, from Equation (A16), we may understand that as $o h$ increases and $e h$ decreases, the BOLD signal only has a phase accumulation that tends to be turbulent. In particular, we may attribute the BOLD signal phase to the statistical asymmetry of the intravoxel fieldmap. As the fieldmap is a linear convolution transformation of the vasculature [in Equation (3)], the fieldmap symmetry (or asymmetry) is determined by that of the intravoxel vasculature. Given that the vasculature asymmetry mainly happens at the vessel boundary, especially for large vessels and small voxels, we can explain why the vessel boundary can produce significant phase angles.

APPENDIX B: IV/EV BOLD SIGNAL COMBINATION

The IV/EV partition is established on the basis of the voxel vasculature. We can apply it to the intravoxel BOLD fieldmap distribution and thereby to calculate the IV and EV dephasing signals separately. Let us suppose that the IV and EV compartments have the

same spin density (a valid assumption for the cerebral cortex); then, the IV/EV signals can be calculated by:

$$\begin{aligned}
 &= \sum_{(i_x, i_y, i_z) \in \Omega_0^{IV}} S_0^{IV}(t) S_\varepsilon(i_x, i_y, i_z, t) \\
 &= \sum_{(i_x, i_y, i_z) \in \Omega_0^{EV}} S_0^{EV}(t) S_\varepsilon(i_x, i_y, i_z, t) \quad (B1) \\
 &= S_0^{IV}(t) + S_0^{EV}(t)
 \end{aligned}$$

The summation in Equation (B1) is dependent on the grid resolution, which determines the number of spin packets in Ω_0 . Conventionally, we use 1 – normalized signals as defined by:

$$\begin{aligned}
 &= \frac{S_0^{IV}(t)}{S_0^{IV}(t=0)} = \frac{\sum_{(i_x, i_y, i_z) \in \Omega_0^{IV}} s_\varepsilon(i_x, i_y, i_z, t)}{\text{card}\{\Omega_0^{IV}\}} \\
 &= \frac{S_0^{EV}(t)}{S_0^{EV}(t=0)} = \frac{\sum_{(i_x, i_y, i_z) \in \Omega_0^{EV}} s_\varepsilon(i_x, i_y, i_z, t)}{\text{card}\{\Omega_0^{EV}\}} \quad (B2) \\
 &= \frac{S_0(t)}{S_0(t=0)} = \frac{S_0(t)}{\text{card}\{\Omega_0\}}
 \end{aligned}$$

which are governed by:

$$s_0(t)^0 = (bfrac) s_0^{IV}(t) + (1 - bfrac) s_0^{EV}(t) \quad (B3)$$

where *bfrac* denotes the blood volume fraction of the voxel V_0 . Equation (B3) shows that the normalized BOLD signal of a voxel is a convex combination of the normalized IV and EV components, for which the IV contribution is weighted by the blood volume fraction (typically *bfrac* = 2% for cerebral cortex). For high-spatial-resolution fMRI, the parameter *bfrac* changes quickly from voxel to voxel: a small voxel may contain no vessel (*bfrac* = 0) or sit completely inside a vessel (*bfrac* = 100%), or at a vessel boundary ($0 < bfrac < 100\%$).

Abbreviations used

bfrac	blood volume fraction
BOLD	blood oxygenation level dependent
DCT	discrete cosine transform
DFT	discrete Fourier transform
DST	discrete sine transform
EV	extravascular

fMRI	functional MRI
FT	Fourier transform
IFT	inverse Fourier transform
IV	intravascular
turfrac	turbulent signal fraction

REFERENCES

1. Buxton, RB. Introduction to Functional Magnetic Resonance Imaging: Principle and Techniques. Cambridge University Press; Town: 2002.
2. Soltysik DA, Hyde JS. High spatial resolution increases the specificity of block-design BOLD fMRI studies of overt vowel production. *Neuroimage*. 2008; 41(2):389–397. [PubMed: 18387825]
3. Kirwan CB, Jones CK, Miller MI, Stark CE. High-resolution fMRI investigation of the medial temporal lobe. *Hum. Brain Mapp*. 2007; 28(10):959–966. [PubMed: 17133381]
4. Harel N, Bolan J, Turner R, Ugurbil K, Yacoub E. Recent advances in high-resolution MR application and its implications for neurovascular coupling research. *Front. Neuroenergetics*. 2010; 2(2):1–9. [PubMed: 20162100]
5. Kriegeskorte N, Bandettini P. Analyzing for information, not activation, to exploit high-resolution fMRI. *Neuroimage*. 2007; 38(4):649–662. [PubMed: 17804260]
6. Kim S, Ugurbil K. High-resolution functional magnetic resonance imaging of the animal brain. *Methods*. 2003; 30(1):28–43. [PubMed: 12695101]
7. Bridge H, Clare S. High-resolution MRI: in vivo histology? *Philos. Trans. R. Soc. London B: Biol. Sci*. 2006; 361(1465):137–146. [PubMed: 16553313]
8. Chen Z, Calhoun VD. Magnitude and phase behavior of multiresolution BOLD signal. *Concepts Magn. Reson*. 2010; 37B(3):129–134.
9. Datta S, Huang S, Li Y. Understanding spin turbulence in solution magnetic resonance through phase space dynamic and instability. *Concepts Magn. Reson. A*. 2006; 28A(12):410–421.
10. Abergel D, Joseph AL. Generating spin turbulence through nonlinear excitation in liquid NMR. *J. Magn. Reson*. 2009; 196:115–128. [PubMed: 19013087]
11. Lin YY, Lisitz N, Ahn S, Warren WS. Resurrection of crushed magnetization and chaotic dynamics in solution NMR spectroscopy. *Science*. 2000; 290(5489):118–122. [PubMed: 11021793]
12. Arja SK, Feng Z, Chen Z, Caprihan A, Kiehl KA, Adali T, Calhoun VD. Changes in fMRI magnitude data and phase data observed in block-design and event-related tasks. *Neuroimage*. 2009; 59(4):3748–3761.
13. Feng Z, Caprihan A, Blagoev KB, Calhoun VD. Biophysical modeling of phase changes in BOLD fMRI. *Neuroimage*. 2009; 47(2):540–548. [PubMed: 19426815]
14. Rowe DB. Modeling both the magnitude and phase of complex-valued fMRI data. *Neuroimage*. 2005; 25(4):1310–1324. [PubMed: 15850748]
15. Rowe DB. Magnitude and phase signal detection in complex-valued fMRI data. *Magn. Reson. Med*. 2009; 62(5):1356–1357. [PubMed: 19705465]
16. Zhao F, Jin T, Wang P, Hu X, Kim SG. Sources of phase changes in BOLD and CBV-weighted fMRI. *Magn. Reson. Med*. 2007; 57(3):520–527. [PubMed: 17326174]
17. Giancoli, D. Physics for Scientists and Engineers. Prentice Hall; Town: 1989.
18. Chen Z, Calhoun V. A computational multiresolution BOLD fMRI model. *IEEE Trans. Biomed. Eng*. 2011; 58(10):2995–2999. [PubMed: 21652281]
19. Boxerman JL, Bandettini PA, Kwong KK, Baker JR, Davis TL, Rosen BR, Weisskoff RM. The intravascular contribution to fMRI signal change: Monte Carlo modeling and diffusion-weighted studies in vivo. *Magn. Reson. Med*. 1995; 34(1):4–10. [PubMed: 7674897]

20. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. *Magn. Reson. Med.* 1995; 34(4):555–566. [PubMed: 8524024]
21. Kiselev VG, Posse S. Analytical theory of susceptibility induced NMR signal dephasing in a cerebrovascular network. *Phys. Rev. Lett.* 1998; 81(25):5696–5699.
22. Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc. Natl. Acad. Sci. USA.* 1992; 89(13):5951–5955. [PubMed: 1631079]
23. Martindale J, Kennerley AJ, Johnston D, Zheng Y, Mayhew JE. Theory and generalization of Monte Carlo models of the BOLD signal source. *Magn. Reson. Med.* 2008; 59(3):607–618. [PubMed: 18224696]
24. Chen Z, Caprihan A, Calhoun VD. Effect of surrounding vasculature on intravoxel BOLD signal. *Med. Phys.* 2010; 37(4):1778–1787. [PubMed: 20443500]
25. Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K. Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. *Biophys. J.* 1993; 64(3):803–812. [PubMed: 8386018]
26. Pathak AP, Ward BD, Schmainda KM. A novel technique for modeling susceptibility-based contrast mechanisms for arbitrary microvascular geometries: the finite perturber method. *Neuroimage.* 2008; 40(3):1130–1143. [PubMed: 18308587]
27. Bhagwandien R, Moerland MA, Bakker CJ, Beersma R, Lagendijk JJ. Numerical analysis of the magnetic field for arbitrary magnetic susceptibility distributions in 3D. *Magn. Reson. Imaging.* 1994; 12(1):101–107. [PubMed: 8295497]
28. Marques JP, Bowtell RW. Using forward calculations of the magnetic field perturbation due to a realistic vascular model to explore the BOLD effect. *NMR Biomed.* 2008; 21(6):553–565. [PubMed: 18078307]
29. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. *Magn. Reson. Med.* 1994; 31(1):9–21. [PubMed: 8121277]
30. Weisstein, EW. Riemann Sum. From MathWorld – A Wolfram Web Resource. Available at: <http://mathworld.wolfram.com/Riemann-Sum.html> [accessed February 2012]
31. Weisstein, EW. Lebesgue Sum. From MathWorld – A Wolfram Web Resource. Available at: <http://mathworld.wolfram.com/LebesgueSum.html> [accessed February 2012]
32. Chen Z, Ning R. Breast volume denoising and noise characterization by 3D wavelet transform. *Comput. Med. Imaging Graph.* 2004; 28(5):235–246. [PubMed: 15249069]
33. Marques JP, Bowtell R. Application of a Fourier-based method for rapid calculation of field inhomogeneity due to spatial variation of magnetic susceptibility Concepts. *Magn. Reson.* 2005; 25B(1):65–78.
34. Chen Z, Ning R. Filling the Radon domain in computed tomography by local convex combination. *Appl. Opt.* 2003; 42(35):7043–7051. [PubMed: 14674649]

Figure 1.

Demonstration of a low-resolution spiral phasor versus a high-resolution turbulent phasor. (a) A cortical voxel (large box) and one of its subvoxels at $(^1k, ^2k, ^3k, ^4k) = (17, 25, 35, 45)$ (small red box). The large voxel produces a blood oxygenation level-dependent (BOLD) signal $s_0(t)$ and the subvoxel produces $s_4(t)$. (b) Intensity timeseries [black, $|s_0(t)|$; red, $|s_4(t)|$]. (c) Phase angle timeseries [black, $\angle s_0(t)$; red, $\angle s_4(t)$]. (d) Phasor diagrams [black, $s_0(t)$; red, $s_4(t)$]. It should be noted in (d) that $s_0(t)$ evolves as a spiral segment, whereas $s_4(t)$ manifests a nonspiral evolution (turbulence).

Figure 2.

Illustration of three-level multiresolution voxel decomposition. The labels for eight subvoxels are shown at level $j = 1$ (defined for K_8). The subvoxel at level $j = 3$ (marked in a red box) is labeled by $(^1k, ^2k, ^3k) = (18, 26, 36)$. All the voxel and subvoxels are represented as matrices at the same grid resolution (indicated by gridel).

Figure 3.

Illustration of the even/odd histogram decomposition and the B_{spread} and B_{shift} connotations. (a) A blood oxygenation level-dependent (BOLD) fieldmap histogram $h(n)$ (a non-negative function with the on-resonance at $n = 0$). (b) The even/odd decomposition: $h = {}^e h + {}^o h$. (c) B_{spread} representing the centroid of one-sided ${}^e h(n)$ for $n > 0$. (d) B_{shift} representing the centroid of one-sided ${}^o h(n)$ for $n > 0$ [one positive and one negative lobe occur at the same side of ${}^o h(n)$, but their quadratures are not completely cancelled, thus producing $|B_{\text{shift}}| \neq 0$].

Figure 4.

Phasor diagrams for four-level multiresolution blood oxygenation level-dependent (BOLD) signals generated from a cortical voxel [V_0 : $320 \times 320 \times 320 \mu\text{m}^3$ in a support matrix of $512 \times 512 \times 512$; vessel radius, $5 \mu\text{m}$; blood volume fraction ($bfrac$) = 2%]. The phasors are displayed in different colors for visualization. At level $j = 4$, about 10% of subvoxel phasors become turbulent in the form of nonspiral evolutions, such as knotting, leaping and oscillation. It should be noted that, as the resolution level increases, the number of phasors increases exponentially, all the phasors become prolonged and some become turbulent. There is no turbulence in the small-angle regime [$\exp(i\phi) \approx 1 + i\phi$], as marked by broken circles.

Figure 5.

Demonstration of multiresolution analysis on the voxel, blood oxygenation level-dependent (BOLD) fieldmap, fieldmap histogram and phasor signal with a path of $(^11, ^21, ^34, ^44)$ in $\text{octree}_4(V_0)$. Subvoxel phasors become turbulent in the form of leaping at $j = 3$ and in the form of knotting at $j = 4$. The subvoxel field disturbances (at a slice) and fieldmap histograms are provided. The subvoxel fieldmap slices are zoomed in accordance with the multiresolution levels, thus explaining the ever-increasing vessels in the slice images. The subvoxels are displayed with nested boxes. Note the irregular and multimodal histogram for the knotted phasor at $j = 4$ (voxel size: $20 \times 20 \times 20 \mu\text{m}^3$).

Figure 6.

Demonstration of multiresolution subvoxel blood oxygenation level-dependent (BOLD) fieldmap histograms $h_i(B; {}^1k, {}^2k, {}^3k)$ for an octadic subtree with the trunk path of $({}^1k, {}^2k, {}^3k) = ({}^11, {}^21, {}^34)$ in $\text{octree}_4(V_0)$. At each panel, the histogram at the last subpanel (at the bottom right corner subplot) is the sum of the other eight histograms. All the fieldmap histograms at different levels assume the same fieldvalue bins. The irregular and multimodal histograms are characteristic of large B_{spread} and B_{shift} values. The on-resonance at $B = 0$ is indicated by a vertical line.

Figure 7.

Demonstration of multiresolution blood oxygenation level-dependent (BOLD) signals calculated by conventional intravoxel dephasing (black plots, ‘Riemann’) and histogram discrete Fourier transform (DFT) algorithm (red plots, ‘Lebesgue’). The ‘Lebesgue sum’ algorithm with the settings of {fieldvalue bin $\delta b = 0.0138$ ppmT, time bin $\delta t = 0.5$ ms, TE = 120 ms} produced similar signals to the conventional dephasing algorithm (the ‘Riemann sum’ algorithm). The children-to-parent synthesis is demonstrated in each panel. The phasor turbulences can be understood by referring to the corresponding fieldmap histograms in Fig. 6.

Figure 8.

Demonstration of an intravascular/extravascular (IV/EV) decomposition on a blood oxygenation level-dependent (BOLD) fieldmap distribution, fieldmap histogram and BOLD signal at level $j = 0$. (a) Two-dimensional slices for B^{IV} , B^{EV} and $B = B^{IV} + B^{EV}$. (b) Fieldmap histograms $h(B^{IV})$, $h(B^{EV})$ and $h(B) = h(B^{IV}) + h(B^{EV})$. (c) Signals $s^{IV}(t)$, $s^{EV}(t)$ and $s(t) = (bfrac)s^{IV}(t) + (1 - bfrac)s^{EV}(t)$ with $bfrac = 2\%$. It should be noted that the extreme turbulence of the IV contribution in (c1) is greatly suppressed (by a factor of $bfrac = 2\%$) in the total voxel BOLD signal in (c3), thus revealing a short spiral phasor. $bfrac$, blood volume fraction.

Figure 9.

Multiresolution subvoxel intravascular/extravascular (IV/EV) histograms for the octadic subtree along a trunk path of $(^1k, ^2k, ^3k) = (^11, ^21, ^34)$ in $\text{octree}_4(V_0)$. In each panel, the children-to-parent synthesis is demonstrated. It should be noted that the IV histogram (marked in red at the left-hand side) uses different ordinates from the EV histogram (marked in black at the right-hand side) in the same subplot, and that some subvoxels at $j = 3$ and $j = 4$ contain no vessels (there is no IV signal for a ‘no vessel’ subvoxel). Note the irregular and multimodal histograms of the IV field disturbance which are responsible for the IV signal turbulence in Fig. 10.

Figure 10.

Demonstration of multiresolution subvoxel intravascular/extravascular (IV/EV) signal decomposition. In each panel, the phasor in the bottom right subplot is an average of the children phasors in other subplots. The phasor turbulences can be understood by referring to the corresponding fieldmap histograms in Fig. 9. It should be noted that the IV components are the main players of blood oxygenation level-dependent (BOLD) signal turbulence, but its contribution to the voxel signal is greatly suppressed by a small blood volume fraction ($bfrac_j$) at $j = \{0,1\}$, and increasingly retained for large $bfrac_j$ at $j = \{3,4\}$.

Table 1

The turbulent signal fraction ($turfrac_j$) values of four-level multiresolution voxel decompositions for three cortical voxels (vessel radii = {3, 5, 9} μm , $bfrac_0 = 2\%$, TE = 120 ms, $B_0=3$ T)

Resolution level j		$j=0$	$j=1$	$j=2$	$j=3$	$j=4$
Voxel size V_j (μm^3)		$320 \times 320 \times 320$	$160 \times 160 \times 160$	$80 \times 80 \times 80$	$40 \times 40 \times 40$	$20 \times 20 \times 20$
$turfrac_j$	Radius = 3 μm	0 (=0/8 ^j)	0 (=0/8 ^j)	0 (=0/8 ^j)	0.08 (=39/8 ^j)	0.10 (=385/8 ^j)
	Radius = 5 μm	0 (=0/8 ^j)	0 (=0/8 ^j)	0.18 (=12/8 ^j)	0.16 (=84/8 ^j)	0.08 (=327/8 ^j)
	Radius = 9 μm	0 (=0/8 ^j)	0.13 (=1/8 ^j)	0.20 (=13/8 ^j)	0.11 (=58/8 ^j)	0.06 (=240/8 ^j)