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Transport-of-intensity diffraction tomography with nonuniform axial sampling (TIDT-NAS)

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Abstract

Transport-of-intensity diffraction tomography (TIDT) extends the *transport-of-intensity equation* (TIE) from 2D phase retrieval to 3D refractive index (RI) tomography, enabling non-interferometric volumetric imaging under partially coherent illumination. By combining parallel spectral filling with reduced sensitivity to coherence noise and strong optical sectioning capability, TIDT provides high-fidelity RI reconstruction while retaining compatibility with a standard bright-field microscope. However, its volumetric imaging throughput is constrained by the need for densely and uniformly sampled axial intensity stacks, which are required to preserve tomographic resolution but impose substantial data burdens and limit imaging speed. Here, we introduce TIDT-NAS, a nonuniform axial-sampling framework that preserves full tomographic resolution while substantially reducing acquisition requirements. Dense sampling over the specimen-containing axial range captures high-frequency structural details, whereas coarse sampling over the extended defocus range retains low-frequency volumetric information. A physics-guided, alias-aware Fourier fusion integrates these complementary stacks into an alias-free 3D spectrum, enabling accurate volumetric reconstruction using only a minimal fraction of the data required by conventional TIDT. Experiments on live cells show that TIDT-NAS reduces the measurement burden to ~30% while maintaining reconstruction fidelity comparable to conventional TIDT, enabling sustained ~1-Hz 4D ($x - y - z - t$) RI imaging over extended periods. These results establish TIDT-NAS as a high-throughput, high-resolution tomographic method that overcomes TIDT's long-standing acquisition bottleneck and significantly broadens its utility to long-term, dynamic volumetric imaging of thick biological samples.

Keywords: Computational optical microscopy, Label-free microscopy, Optical diffraction tomography

Introduction

Quantitative phase imaging (QPI) [1–3] provides high-content, label-free visualization of cells and tissues by exploiting refractive index (RI) as intrinsic contrast, offering a powerful non-invasive optical microscopic tool for biomedical studies. As the core of

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QPI, quantitative phase information can be obtained either by demodulating interferometric holograms [4–7] or, alternatively, by retrieving phase from various forms of phase diversity induced by illumination or pupil modulations. Representative non-interferometric techniques of the latter category, including differential phase contrast microscopy (DPC) [8–11], Fourier ptychographic microscopy (FPM) [12–19], and quantitative Zernike phase contrast microscopy [20–23], have attracted substantial attention owing to their flexible implementation, non-interferometric optical path, and speckle-free imaging performance. Among these methods, the transport-of-intensity equation (TIE) technique is a pioneering and well-established approach for phase retrieval that has been continuously studied in the past decades [24–27]. By relating the phase distribution of a light field to measured axial intensity variations, TIE provides a simple yet effective way for QPI that is highly compatible with standard bright-field microscopes and partially coherent illumination.

The central challenge of TIE lies in accurately estimating the axial intensity derivative. The classic two-plane finite-difference approach inevitably involves a trade-off when choosing the defocus distance [28]. A small defocus leads to cloud-like artifacts due to the poor signal-to-noise ratio (SNR) in low-frequency transfer, whereas a large defocus introduces nonlinear errors that blur high-frequency details [29]. Employing a higher-order Taylor expansion provides a more accurate representation of the intensity derivative [30–32], but requires additional measurements at multiple, distinct planes. The advantage of multi-plane acquisition in TIE can also be interpreted by the contrast transfer function (CTF) [33], which reveals that intensity images recorded at small and large defocus distances provide complementary high- and low-frequency phase information, respectively [28, 34]. However, acquiring images by scanning the sample over a large axial range is highly time-consuming.

Importantly, redundancy exists within this through-focus scanning process. For example, the measured phase contrast, equivalently the CTF response, varies relatively slowly along the z -axis in the large-defocus region, where densely sampled axial measurements provide limited additional information. This observation has motivated the use of unequally spaced intensity measurements to reduce redundant acquisitions [35, 36]. Such flexibility requires corresponding modifications to the reconstruction algorithms, for example, by fitting the measured data in Fourier space using polynomials or by applying appropriately weighted summation strategies. Meanwhile, the derivation of CTF provides a more straightforward TIE solver [37, 38], which is naturally compatible with reconstruction from unequally spaced intensity measurements. As a unique advantage, guided by the calculated CTFs, phase maps acquired at different defocus distances can be fused with high SNR by selectively combining their respective advantageous frequency components [39, 40]. Furthermore, by generalizing the coherent CTF to the weak object transfer function (WOTF) [34], the spatial coherence of the source can be incorporated into TIE, enabling illumination modulation to improve both phase resolution and contrast amplitude [41]. In general, well-established methodologies now exist for implementing unequally sampled TIE, allowing an effective balance between imaging quality and efficiency to enable high-fidelity QPI.

This nonuniform through-focus sampling strategy suggests a route to reducing the data burden of axial-scanning 3D phase tomographic microscopy. By combining TIE

with the theory of optical diffraction tomography (ODT) [42, 43], the transport-of-intensity framework can be extended from “2D planar transport” to “3D volumetric transport” for depth-resolved RI reconstruction [25, 44–47]. Distinct from angular-scanning ODT [48–55], this axial-scanning formulation naturally operates under partially coherent illumination and has therefore also been referred to as partially coherent ODT (pc-ODT) [45, 56, 57]. In this work, we use the term *transport-of-intensity diffraction tomography* (TIDT) [58] to emphasize its connection to TIE-based intensity transport and to maintain consistency throughout the following analysis. TIDT can be viewed as a bright-field implementation of 3D deconvolution microscopy [59] for phase retrieval, in which the RI volume is reconstructed by deconvolving a through-focus intensity stack with the system’s 3D WOTF. Benefiting from the use of partially coherent illumination, TIDT avoids the laser source and interferometric detection typically required in coherent angular-scanning ODT, thereby improving speckle suppression, experimental stability, and compatibility with standard bright-field microscopes. More importantly, partial coherence provides a depth-gating effect during through-focus scanning, leading to enhanced optical sectioning and reduced scattering-induced artifacts in thick specimens [46, 60, 61]. Beyond these acquisition advantages, the 3D transfer characteristics of TIDT can be further engineered through illumination design. This can be achieved either with a single optimized illumination pattern, such as Gaussian or annular illumination [62, 63], or with multiple illumination patterns whose synthetic transfer function is jointly optimized [64, 65]. Compared with a single intensity stack acquired under a fixed illumination condition, illumination engineering provides more complete and balanced transfer of 3D spatial frequencies, thereby improving the fidelity of volumetric RI reconstruction.

A central limitation of ODT is its acquisition throughput, as faithful volumetric reconstruction generally requires substantially larger datasets than 2D QPI to provide sufficient coverage of the 3D Fourier space. For angular-scanning ODT, the data burden has been reduced by multiplexing illumination angles [66, 67], spatial-frequency spectra [68, 69], or wavelengths [70], as well as by sparse angular sampling [71, 72]. Motion artifacts associated with limited frame rates can also be mitigated by jointly reconstructing the sample and its motion [73–77], or by incorporating temporal sparsity priors [78–81]. In contrast, the throughput of depth-scanning TIDT remains fundamentally constrained by its axial acquisition protocol. Under conventional uniform through-focus scanning, the axial step size must be sufficiently small to satisfy the Nyquist criterion with respect to the axial frequency support of the 3D WOTF, thereby avoiding aliasing of depth-dependent information. At the same time, the axial scanning range must be sufficiently large to ensure fine axial spectral sampling for reliable recovery of low-frequency volumetric components. These two requirements must be satisfied simultaneously over the entire scanning range, so a typical TIDT acquisition often comprises more than 100 axial planes [45, 64, 82, 83]. This leaves limited room for data reduction within the conventional uniform axial-sampling framework.

Inspired by nonuniform axial sampling in TIE-based QPI [35, 36], a natural question is whether a similar strategy can reduce the number of raw intensity images required by TIDT. From an acquisition perspective, such a strategy is physically well motivated. In practical TIDT implementations, the axial scanning range is often extended beyond the actual specimen thickness to ensure sufficient axial spectral resolution. The intensity

measurements outside the specimen region are dominated mainly by slowly varying low-frequency defocus contrast [32], rather than high-frequency structural information. Therefore, similar to unequally sampled TIE, these out-of-specimen axial regions are expected to tolerate a larger sampling step, instead of being sampled at the small axial interval strictly dictated by the system's axial resolution. However, from a reconstruction perspective, directly applying nonuniform axial sampling to TIDT is nontrivial. Conventional TIDT reconstruction is based on 3D deconvolution with the system transfer function [56, 57], which assumes that the measured through-focus intensity stack is sampled on a uniform 3D grid so that the forward model can be discretized as a shift-invariant convolution. A nonuniformly sampled axial stack does not directly satisfy this discrete convolutional formulation, making standard transfer-function-based deconvolution inapplicable without further treatment. Therefore, although nonuniform axial acquisition is promising for high-throughput TIDT, a systematic analysis of the sampling strategy and a corresponding reconstruction framework remain lacking.

To address this gap, we introduce transport-of-intensity diffraction tomography with nonuniform axial sampling (TIDT-NAS), a complete acquisition and reconstruction framework for high-throughput TIDT. In TIDT-NAS, the axial scan is divided into two sampling regimes: a densely sampled segment, determined by the system's axial resolution and confined to the specimen region, and a sparsely sampled segment that spans the full axial range. The two resulting intensity stacks provide complementary spectral information. The densely sampled stack preserves high-frequency structural details within the specimen, whereas the sparsely sampled full-range stack retains low-frequency volumetric information with sufficient axial spectral resolution. To jointly exploit these complementary measurements, we develop a physics-guided, alias-aware Fourier-domain fusion strategy that combines the reconstructed spectra of the two stacks into an alias-free 3D spectrum, enabling accurate RI reconstruction from a substantially reduced dataset. This sparse acquisition strategy has been demonstrated to be compatible with existing TIDT frameworks employing diverse illumination schemes [44, 84]. Experimental validation on benchmark samples and biological specimens, including live HeLa cells and human hepatocellular carcinoma cells, demonstrates that TIDT-NAS achieves reconstruction quality comparable to conventional uniformly sampled TIDT while requiring only approximately 30% of the original axial measurements.

Results

Principle of TIDT-NAS

TIDT is implemented on a conventional transmission bright-field microscope by acquiring a through-focus intensity stack while axially scanning the focal plane through the specimen, which in this work is realized using a self-developed motorized setup (see Fig. 1a). Under partially coherent illumination generated by a programmable LED array, the volumetric imaging process can be described by a 3D weak-object transfer-function model [44, 58, 65]. The specimen is characterized by its scattering potential (SP)

$$f(\mathbf{x}) = k_0^2 [n^2(\mathbf{x}) - n_m^2], \quad (1)$$

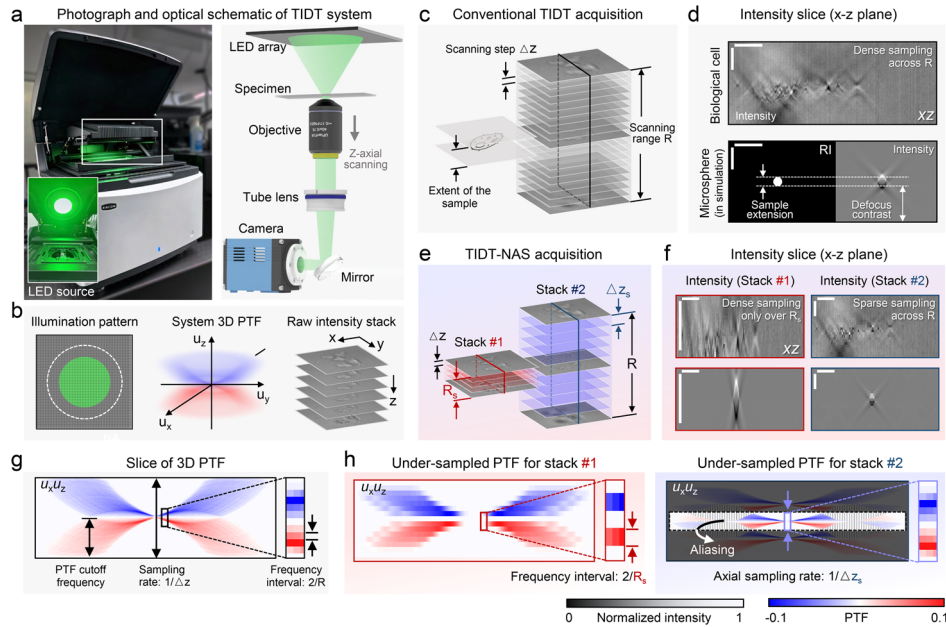


Fig. 1 Comparison of conventional TIDT and TIDT-NAS. **a** Photograph and optical schematic of TIDT system (Zircon optoelectronics, China). The intensity stack is acquired by axially translating the objective lens under partially coherent illumination provided by LED source. **b** The volumetric imaging characteristics are described by the 3D PTF, which is determined by the illumination pattern. **c** Schematic of the data acquisition process in conventional TIDT, characterized by the axial sampling step Δz and the scanning range R . **d** Representative x - z slices of TIDT intensity stacks for biological cells and microspheres. **e** Schematic of the data acquisition strategy in TIDT-NAS, where stack #1 is densely sampled over a reduced range R_s with step Δz , and stack #2 is sparsely sampled over the full range R with step Δz_s . **f** Representative x - z slices of intensity stacks #1 and #2 for biological cells and microspheres acquired using TIDT-NAS. **g** Well-sampled PTF of conventional TIDT shown in the $u_x - u_z$ plane. The inset highlights the axial frequency interval of $2/R$. **h** Undersampled PTFs corresponding to stacks #1 and #2. PTF #1 exhibits pronounced spectral discretization due to the limited scanning range R_s , whereas PTF #2 exhibits axial aliasing due to the enlarged sampling step Δz_s . Regions overlaid with line-patterned shading indicate aliased spectral components that should be excluded from the subsequent fusion. Scale bar: 10 μm

where $\mathbf{x} = (x, y, z)$ denotes the spatial coordinates, $k_0 = 2\pi/\lambda_0$ is the wavenumber in free space, and $n(\mathbf{x})$ and n_m are the RI distributions of the specimen and surrounding medium, respectively. Under the first-order Born approximation, the measured 3D intensity spectrum can be written as [45, 85]

$$I(\mathbf{u}) = I_0\delta(\mathbf{u}) + H_a(\mathbf{u})A(\mathbf{u}) + iH_\phi(\mathbf{u})\Phi(\mathbf{u}), \quad (2)$$

where $\mathbf{u} = (u_x, u_y, u_z)$ is the spatial-frequency coordinate, $I_0\delta(\mathbf{u})$ is the zero-order background term, and $A(\mathbf{u})$ and $\Phi(\mathbf{u})$ are the Fourier transforms of the absorption and phase components of the SP, respectively. The 3D weak-object transfer function (WOTF) consists of the absorption transfer function (ATF) $H_a(\mathbf{u})$ and the phase transfer function (PTF) $H_\phi(\mathbf{u})$, which describe the system responses to absorption and phase contrast in the measured intensity stack.

In general, recovering both $A(\mathbf{u})$ and $\Phi(\mathbf{u})$ requires illumination or pupil diversity [44, 60]. In this work, we focus on weakly absorbing biological specimens and adopt the pure-phase approximation, for which the absorption component is neglected. Under this assumption, the measured intensity is dominated by the phase transfer term, allowing the RI-related SP to be reconstructed from a single illumination pattern (see Fig. 1b). The corresponding 3D

PTF under partially coherent illumination is given by (see Supporting Information S1 for the derivation)

$$H_\phi(\mathbf{u}) = P(-\mathbf{u}) \otimes [S(\mathbf{u})P^*(\mathbf{u})] - P^*(\mathbf{u}) \otimes [S(-\mathbf{u})P(-\mathbf{u})], \quad (3)$$

where $\otimes$ denotes 3D convolution and $(\cdot)^*$ denotes complex conjugation. $P(\mathbf{u})$ is the objective pupil function projected onto the Ewald sphere, also known as the generalized aperture or 3D pupil function [86]. $S(\mathbf{u})$ has a similar geometric form and represents the 3D spatial-frequency coordinates associated with the illumination angles defined by the source pattern. They can be expressed as

$$\begin{aligned} P(\mathbf{u}) &= P(\mathbf{u}_T) \delta \left(u_z - \sqrt{\left(\frac{n_m}{\lambda_0} \right)^2 - |\mathbf{u}_T|^2} \right), \\ S(\mathbf{u}) &= S(\mathbf{u}_T) \delta \left(u_z - \sqrt{\left(\frac{n_m}{\lambda_0} \right)^2 - |\mathbf{u}_T|^2} \right), \end{aligned} \quad (4)$$

where $\mathbf{u}_T = (u_x, u_y)$ is the transverse spatial-frequency coordinate, and $P(\mathbf{u}_T)$ and $S(\mathbf{u}_T)$ are the 2D objective pupil function and source intensity distribution, respectively. For the symmetric illumination pattern used in this work, $H_\phi(\mathbf{u})$ can be computed analytically, avoiding explicit 3D convolution or numerical integration [87, 88]. The resulting PTF is odd-symmetric along the u_z -axis.

We next analyze conventional TIDT acquisition from the perspective of axial sampling. During through-focus scanning, a continuous 3D intensity distribution is discretely recorded at successive axial planes. Two parameters are critical for this process: the axial sampling step Δz and the axial scanning range R (see Fig. 1c). The sampled intensity stack $I_s(\mathbf{x})$ can be modeled as the product of the continuous intensity distribution $I(\mathbf{x})$, a Dirac comb describing axial sampling, and a finite axial window describing the scan range:

$$I_s(\mathbf{x}_T, z) = I(\mathbf{x}_T, z) \left[\sum_{n=-\infty}^{+\infty} \delta(z - n\Delta z) \right] \text{rect}\left(\frac{z}{R}\right), \quad (5)$$

where $\mathbf{x}_T = (x, y)$ and

$$\text{rect}\left(\frac{z}{R}\right) = \begin{cases} 1, & |z| \leq R/2, \\ 0, & |z| > R/2. \end{cases} \quad (6)$$

After Fourier transformation, the spectrum of the sampled stack becomes (see Supporting Information S2)

$$I_s(\mathbf{u}_T, u_z) = \frac{R}{\Delta z} \left[\sum_{n=-\infty}^{+\infty} I\left(\mathbf{u}_T, u_z - \frac{n}{\Delta z}\right) \right] \otimes \text{sinc}(Ru_z), \quad (7)$$

where $\text{sinc}(x) = \sin(\pi x)/(\pi x)$. Equation 7 shows that the axial sampling step and scanning range affect the measured spectrum in different ways. The discrete axial sampling with step Δz replicates the spectrum along the u_z -axis with a period of $1/\Delta z$. To avoid axial spectral aliasing, Δz must satisfy the Nyquist criterion

$$\Delta z \leq \frac{1}{2u_{z,\max}}, \quad (8)$$

where $u_{z,\max}$ denotes the maximum axial spatial frequency supported by the 3D PTF. In contrast, the finite scan range R determines the axial spectral sampling interval through the convolution with $\text{sinc}(Ru_z)$, whose main-lobe width is $2/R$. A shorter scan range therefore leads to coarser axial spectral sampling and degraded recovery of low-frequency volumetric information.

Therefore, conventional TIDT must simultaneously satisfy two requirements: a sufficiently small Δz to avoid axial aliasing and a sufficiently large R to ensure adequate axial spectral resolution. These two constraints explain why conventional uniformly sampled TIDT typically requires a large number of axial measurements. Reducing the scanning range mainly degrades the low-frequency volumetric components by coarsening the axial spectrum, whereas increasing the axial step size mainly introduces aliasing by overlapping periodically replicated PTF supports. These two downsampling effects are illustrated in Fig. 1h, Visualization 1, and further validated using experimental data in Supporting Information S3 and Supporting Information S4. In the right panel of Fig. 1h, the line-patterned overlays denote aliased spectral regions caused by overlap between periodically replicated PTF supports, whereas the unshaded single-covered regions represent the effective alias-free support.

The above sampling analysis motivates a nonuniform axial-sampling strategy for TIDT. The key observation is that the frequency content of a through-focus intensity stack is not uniformly distributed along the axial direction. As shown by both experimental and simulated examples in Fig. 1d, the RI distribution of the specimen gives rise to high-frequency intensity contrast primarily near the in-focus region, whereas the extended out-of-specimen defocus regions mainly contain slowly varying low-frequency diffraction contrast. Therefore, dense axial sampling is most critical within the specimen region to preserve high-frequency structural information, whereas a larger axial step can be used over the extended defocus range to capture low-frequency volumetric information.

Based on this principle, TIDT-NAS acquires two complementary intensity stacks within the same axial scanning sequence (see Fig. 1e, f). Stack #1 is acquired over a reduced range R_s comparable to the axial extent of the specimen, using the small step size Δz that satisfies Eq. 8. This stack preserves high-frequency structural details within the specimen. However, stack #1 alone is insufficient for high-fidelity reconstruction because its limited scan range leads to coarse axial spectral sampling and poor recovery of low-frequency volumetric components, as indicated by the discretized PTF in the left panel of Fig. 1h.

Stack #2 is acquired over the full scanning range R using a larger step size Δz_s . Although this enlarged step size introduces axial aliasing, the non-overlapped low-frequency support of stack #2 remains available for reconstruction. This effective alias-free region can be identified from the periodically replicated 3D PTF support. Because the out-of-specimen defocus contrast is dominated by low-frequency content, stack #2 can preserve the dominant low-frequency volumetric information despite the enlarged axial step. As a result, stack #1 and stack #2 provide

complementary spectral information: the former supplies densely sampled high-frequency details near the specimen, while the latter supplies full-range low-frequency information with fine axial spectral resolution.

By employing different axial sampling steps in different axial regions, TIDT-NAS substantially reduces the number of acquired images while retaining the spectral information required for high-fidelity RI reconstruction. The following section describes how the two spectra are reconstructed and fused in Fourier space using an alias-aware mask, such that aliased components from the sparsely sampled stack are excluded while its useful low-frequency information is retained.

Reconstruction workflow of TIDT-NAS

In the data acquisition procedure of TIDT-NAS, the through-focus intensity stack is recorded within a single axial-scanning sequence using nonuniform axial steps and is subsequently separated into stack #1 and stack #2 for reconstruction (see Fig. 2a). Four acquisition parameters determine the final reconstruction quality: the reduced scanning range R_s and dense axial step Δz for stack #1, and the full scanning range R and sparse axial step Δz_s for stack #2. The dense step Δz is chosen to satisfy the Nyquist criterion determined by the axial frequency support of the 3D PTF, while R_s is selected to cover the axial extent of the specimen with an appropriate safety margin. The full scanning range R extends beyond the specimen to ensure sufficient axial spectral resolution for low-frequency volumetric recovery, as discussed in the preceding section and Supporting Information S3. The sparse step Δz_s determines the usable low-frequency spectral components under aliasing and is chosen as an integer multiple of Δz ,

$$\Delta z_s = m\Delta z, \quad m \in \mathbb{N}^+, \quad (9)$$

so that a subset of the planes acquired for stack #1 can be reused in stack #2, further reducing the total number of raw images.

In Step 2 (see Fig. 2b), stack #1 is extended along the z -axis by zero-padding. Because stack #1 is acquired only over the reduced scanning range R_s , the padding operation virtually unifies its axial extent with that of stack #2, enabling both stacks to be processed on the same reconstruction grid. Zero-padding in the spatial domain is a standard operation in computational microscopy for mitigating boundary artifacts [89–92]. From a Fourier perspective, padding corresponds to spectral interpolation and does not introduce additional physical information. Therefore, the padded stack #1 should not be interpreted as providing additional low-frequency volumetric information; rather, its role in the final fusion is mainly to supply the high-frequency structural components that are densely sampled within the specimen region.

After padding, stack #1 is deconvolved using the PTF computed over the full reconstruction range, denoted as PTF #1, following the standard regularized PTF-based deconvolution used in TIDT [45, 56]. This operation yields the SP spectrum $f_1(\mathbf{u})$. Owing to the limited original scanning range R_s , this estimate preserves high-frequency structural information within the specimen but suffers from insufficient low-frequency volumetric recovery.

In Step 3 (see Fig. 2c), stack #2 is deconvolved following the same procedure to obtain $f_2(\mathbf{u})$. Because the padded stack #1 and stack #2 share the same axial extent

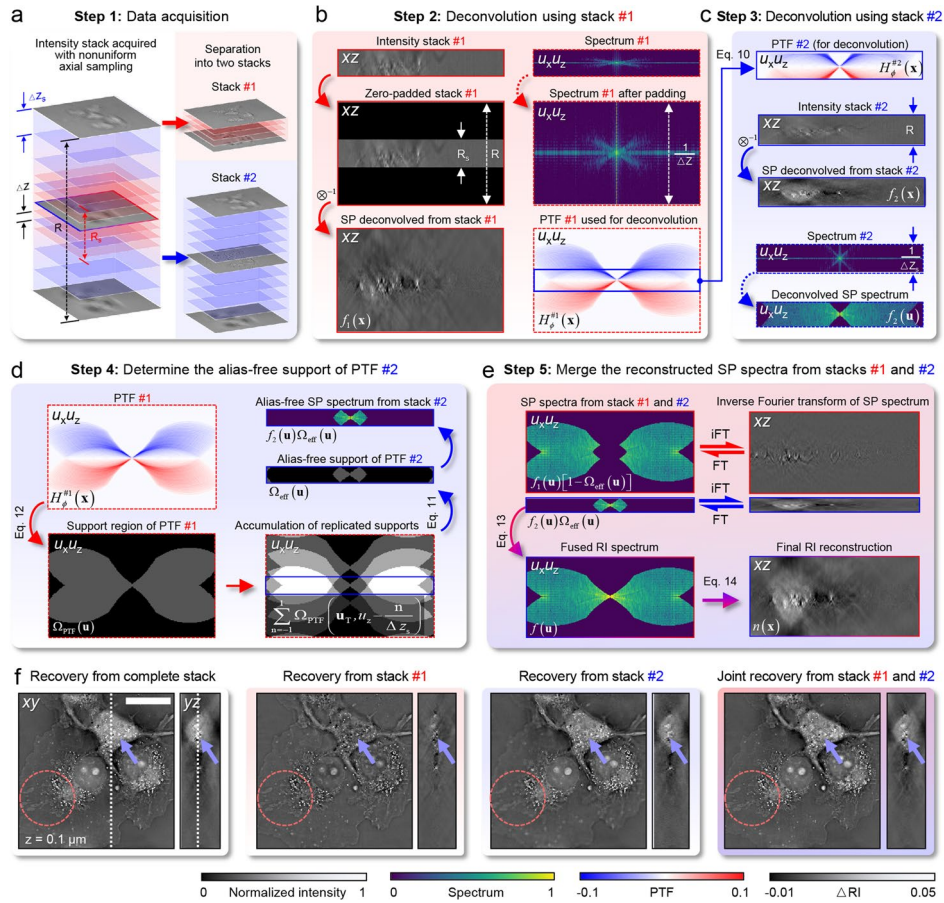


Fig. 2 Reconstruction workflow of TIDT-NAS. **a** A nonuniformly sampled through-focus intensity stack is separated into a densely sampled stack #1 around the specimen and a sparsely sampled full-range stack #2. **b, c** Stack #1 and stack #2 are separately deconvolved with their corresponding PTFs to obtain the SP spectra $f_1(\mathbf{u})$ and $f_2(\mathbf{u})$. **d** The alias-free support of PTF #2 is determined by accumulating periodically replicated supports of PTF #1 according to the sparse sampling interval Δz_s . **e** The alias-free low-frequency spectrum from stack #2 is fused with the complementary spectrum from stack #1 in the Fourier domain to generate an alias-free 3D RI spectrum and the final RI reconstruction. **f** Comparison of reconstructions from the fully sampled stack, stack #1 alone, stack #2 alone, and the joint TIDT-NAS reconstruction. The joint reconstruction preserves both high-frequency structural details and low-frequency volumetric information while using substantially fewer axial measurements. Scale bar: 20 μm

but are sampled with different axial steps, their corresponding spectra have identical frequency intervals while differing in their axial Nyquist bandwidths. Accordingly, the PTF for stack #2, denoted as PTF #2, is computed by extracting the low-frequency band from PTF #1 that lies within the passband supported by the axial sampling rate of stack #2:

$$H_{\phi}^{\#2}(\mathbf{u}_T, u_z) = H_{\phi}^{\#1}(\mathbf{u}_T, u_z), \quad |u_z| \leq \frac{1}{2\Delta z_s}. \quad (10)$$

It should be noted that part of the spectrum of stack #2 is contaminated by aliasing and should be excluded before spectral fusion. Therefore, in Step 4, we determine the effective alias-free support of PTF #2 by accumulating the periodically replicated support regions of PTF #1 according to the aliasing period imposed by Δz_s (for detailed

procedures, see Supporting Information S5). This operation forms a binary mask that isolates the non-overlapping spectral region of stack #2 (see Fig. 2d), denoted as

$$\Omega_{\text{eff}}(\mathbf{u}) = \begin{cases} 1, & \sum_{n=-1}^1 \Omega_{\text{PTF}}\left(\mathbf{u}_T, u_z - \frac{n}{\Delta z_s}\right) = 1, \\ 0, & \sum_{n=-1}^1 \Omega_{\text{PTF}}\left(\mathbf{u}_T, u_z - \frac{n}{\Delta z_s}\right) \neq 1, \end{cases} \quad (11)$$

where the support region of PTF #1 is represented as

$$\Omega_{\text{PTF}}(\mathbf{u}) = \left\{ \mathbf{u} \in \mathbb{R}^3 : \left| H_{\phi}^{\#1}(\mathbf{u}) \right| > 0 \right\}. \quad (12)$$

In practice, spectral regions outside the support of PTF #1 are assigned zero by default, whereas regions with overlapping replicated supports are regarded as aliased and are excluded from the subsequent fusion.

In Step 5, the alias-free low-frequency components from stack #2 are fused with the complementary spectrum from stack #1 in the Fourier domain (see Fig. 2e). The fused SP spectrum is computed as

$$f(\mathbf{u}) = f_1(\mathbf{u})[1 - \Omega_{\text{eff}}(\mathbf{u})] + f_2(\mathbf{u})\Omega_{\text{eff}}(\mathbf{u}). \quad (13)$$

Here, stack #2 contributes the reliable alias-free low-frequency volumetric information, while stack #1 supplies the remaining complementary spectral components, especially the high-frequency structural information preserved by dense sampling around the specimen. The fused SP spectrum is then transformed back to the spatial domain and converted to the RI distribution according to the definition of the scattering potential [42]:

$$n(\mathbf{x}) = \sqrt{n_m^2 + \frac{f(\mathbf{x})}{k_0^2}}. \quad (14)$$

Visualization 1 more detailedly illustrates the reconstruction procedures using the two stacks. The reconstruction in Eqs. 13 and 14 is conceptually related to previous Fourier-domain fusion approaches [32, 64, 87], in which spectra acquired under different defocus distances or illumination patterns are combined to improve the SNR and frequency coverage of QPI or ODT. Here, we extend this concept to improve imaging throughput by fusing spectra obtained from different axial sampling rates.

In Fig. 2f, we demonstrate the effectiveness of TIDT-NAS in recovering high-fidelity RI volumes from compressed axial measurements by jointly exploiting stack #1 and stack #2. Reconstructions obtained from stack #1 alone, stack #2 alone, and the proposed joint TIDT-NAS reconstruction are compared with the fully sampled TIDT result. The fully sampled reference accurately resolves both global volumetric features, such as the nucleus indicated by blue arrows, and fine subcellular structures, such as mitochondria highlighted by red circles. In contrast, reconstruction from stack #1 alone preserves fine structural details but fails to recover low-frequency volumetric information because of the reduced scanning range. Reconstruction from stack #2 alone retains global low-frequency features but loses high-frequency details due to the enlarged axial

sampling step. By fusing the complementary spectral information from the two stacks, TIDT-NAS achieves accurate 3D RI reconstruction from compressed measurements, yielding a result comparable to the fully sampled TIDT reconstruction.

Analysis of acquisition-parameter selection for RI tomography in hepatocellular carcinoma cells

To further validate and analyze the influence of acquisition-parameter selection on RI reconstruction, we apply the proposed method to human hepatocellular carcinoma cells, as illustrated in Fig. 3. The raw dataset was acquired using a water-immersion objective ($40\times$, 1.1 NA) for conventional equally-sampled TIDT with parameters of $R = 50\text{ }\mu\text{m}$ and $\Delta z = 0.32\text{ }\mu\text{m}$. Figure 3a shows the RI reconstruction of several adherent cells which are closely attached, presented in the x - y , x - z ,

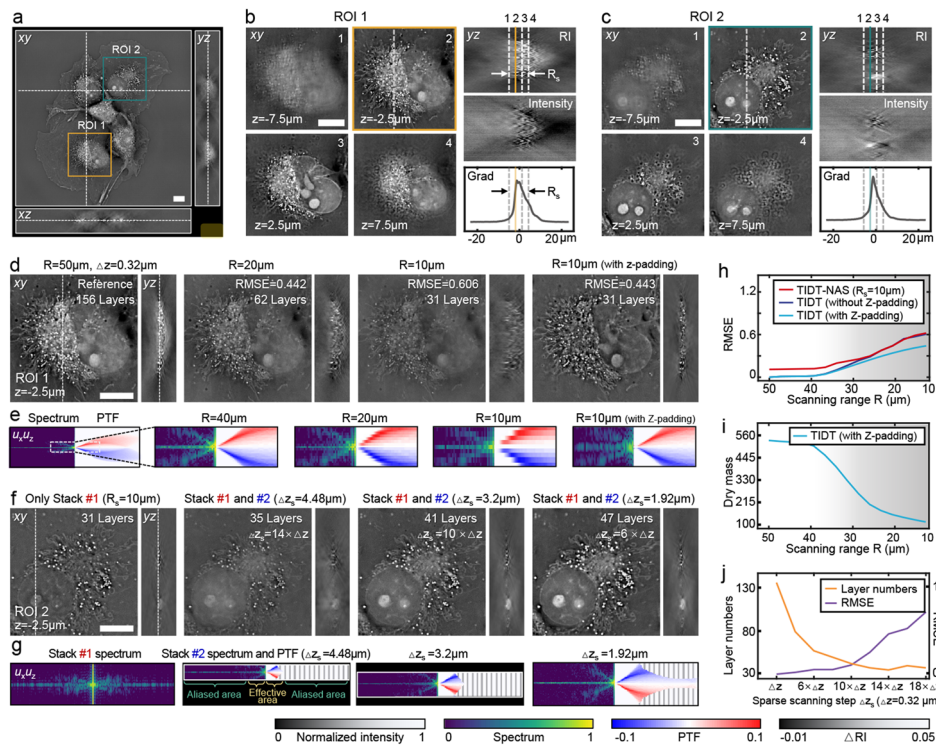


Fig. 3 Comparative experimental results of TIDT-NAS under different acquisition parameters. **a** Full-FOV reconstructed RI distributions shown in the x - y , x - z , and y - z planes. **b, c** RI distributions of ROI 1 and ROI 2 at multiple axial planes. The RI and intensity distributions shown in the x - z plane, together with the axial gradient curves, computed as the mean gradient of each RI slice along the z -axis, indicate that the high-frequency intracellular structures are confined within a $\sim 10\text{ }\mu\text{m}$ depth range. **d** RI reconstructions of ROI 1 in the x - y and x - z planes using axial scanning ranges of $50\text{ }\mu\text{m}$, $20\text{ }\mu\text{m}$, and $10\text{ }\mu\text{m}$, as well as reconstruction from the same intensity stack with z -axis padding. **e** Intensity spectra and corresponding discretely sampled PTFs along the u_x - u_z direction under the same scanning conditions as in **(d)**. **f** RI reconstructions of ROI 2 in the x - y and x - z planes obtained using only stack #1 ($10\text{ }\mu\text{m}$ range) and jointly with stack #2 acquired at axial steps of $4.48\text{ }\mu\text{m}$, $3.2\text{ }\mu\text{m}$, and $1.92\text{ }\mu\text{m}$. **g** Intensity spectra of stack #1 and #2 corresponding to the RI reconstruction in **(f)**, where #2 shows higher low-frequency spectrum resolution than #1. The PTF and the line-patterned region indicate the aliased and unaliased region in the spectrum. **h** Line charts of RMSE respective to scanning range, for TIDT-NAS and TIDT with and without z -axis padding. **i** Line chart of measured cell dry mass with respective to scanning range. **j** Line curve of used layer numbers and RMSE with respective to sparse scanning step Δz_s . Scale bar: $10\text{ }\mu\text{m}$

and y - z planes. The RI distributions at four axial depths within ROI 1 and ROI 2 are depicted in Fig. 3b and c. By analyzing the cellular structural variations along the z -axis via the mean gradient of each slice, we determine that high-frequency structural details are confined within a depth of approximately $10\ \mu\text{m}$. Accordingly, TIDT-NAS is evaluated on this dataset using $R_s = 10\ \mu\text{m}$.

To examine the impact of spectral resolution on low-frequency recovery, RI volumes were reconstructed using different subsets of raw images corresponding to varying scanning ranges R , with results shown in Fig. 3d. The reconstruction obtained with $R = 50\ \mu\text{m}$ clearly resolves the low-frequency components of the nucleus and surrounding regions in both the x - y and y - z planes. As R decreases, the reconstruction quality deteriorates (see Fig. 3e). This trend is further quantified in Fig. 3h, where the reconstruction error, defined as the RMSE relative to the $R = 50\ \mu\text{m}$ result, shows a noticeable increase when R falls below $40\ \mu\text{m}$. Moreover, since the z -axis padding avoids the artifacts induced by boundary problem, it also significantly affects the result, which can be seen from the comparison between last two results in Fig. 3d. However, although z -axis padding virtually increases the spectral resolution, the low-frequency information is still not correctly recovered since this part of information is inherently lost in acquisition process. Equally, Fig. 3h indicates that the scanning range of the second stack is crucial for achieving high-fidelity reconstruction in TIDT-NAS, and it can be satisfied in a compressed manner. Moreover, high-fidelity RI reconstruction is essential for accurate analysis of cellular morphology, as insufficient low-frequency recovery can substantially bias quantitative metrics, such as dry mass, obtained from the reconstructed RI volume (see Fig. 3i). Overall, this experimental evaluation provides a practical reference for selecting the axial scanning range in both TIDT-NAS and conventional TIDT.

Another key parameter of TIDT-NAS is the axial scanning step of the second stack, Δz_s , which determines the amount of usable low-frequency spectrum under aliasing. Figure 3f first presents the RI reconstruction using only stack #1 ($R_s = 10\ \mu\text{m}$, $\Delta z = 0.32\ \mu\text{m}$), which lacks essential low-frequency components. When stacks #1 and #2 are jointly used, the reconstruction quality is substantially improved due to the increased spectral resolution in low frequency, as is indicated by the corresponding spectra shown in Fig. 3g. As Δz_s decreases, more unaliased spectral region can be used for RI reconstruction (indicated by the PTF in Fig. 3g; aliasing region indicated by the hatched pattern). To further quantify the effect of Δz_s , RI volumes were reconstructed with Δz_s varying from Δz to $18 \times \Delta z_s$, as shown in Fig. 3j. The reconstruction error exhibits a relatively gradual increase when $\Delta z_s < 10 \times \Delta z$, suggesting that this axial step-size threshold is sufficient to preserve the low-frequency spectral support required for accurate RI reconstruction. Accordingly, this value can serve as a practical reference for parameter selection. The corresponding numbers of acquired images for both stacks are also summarized in Fig. 3j. Notably, choosing Δz_s as an integer multiple of Δz allows partial sharing of layers between stacks, further reducing data redundancy. Overall, with the scanning range set to $40\ \mu\text{m}$, TIDT-NAS reduces the required data volume from 125 to 41 axial layers, which corresponds to approximately 30% of that required by conventional TIDT, while preserving reconstruction fidelity.

Comparison of TIDT-NAS and TIDT for 3D RI tomography on HeLa cells

To evaluate the RI tomographic performance of TIDT-NAS under compressed acquisition, we further compared conventional TIDT and TIDT-NAS on live HeLa cells using a $40\times/0.75$ NA objective lens. For conventional TIDT, the raw intensity stack was acquired with an axial step of $0.64\ \mu\text{m}$ over a scanning range of $45\ \mu\text{m}$, resulting in a total of 71 axial images. For TIDT-NAS, 26 images were extracted from the same dataset using the parameters $R_s = 13\ \mu\text{m}$ and $\Delta z_s = 3.2\ \mu\text{m}$. The reconstructed RI distributions obtained with TIDT-NAS in the x - y , x - z , and y - z planes are shown in Fig. 4a. A 3D volume rendering over a $200\ \mu\text{m} \times 200\ \mu\text{m} \times 45\ \mu\text{m}$ region is presented in Fig. 4b, with an additional viewing perspective provided in Fig. 4c. These results show that TIDT-NAS recovers the volumetric RI distribution of multiple live HeLa cells over a large field of view

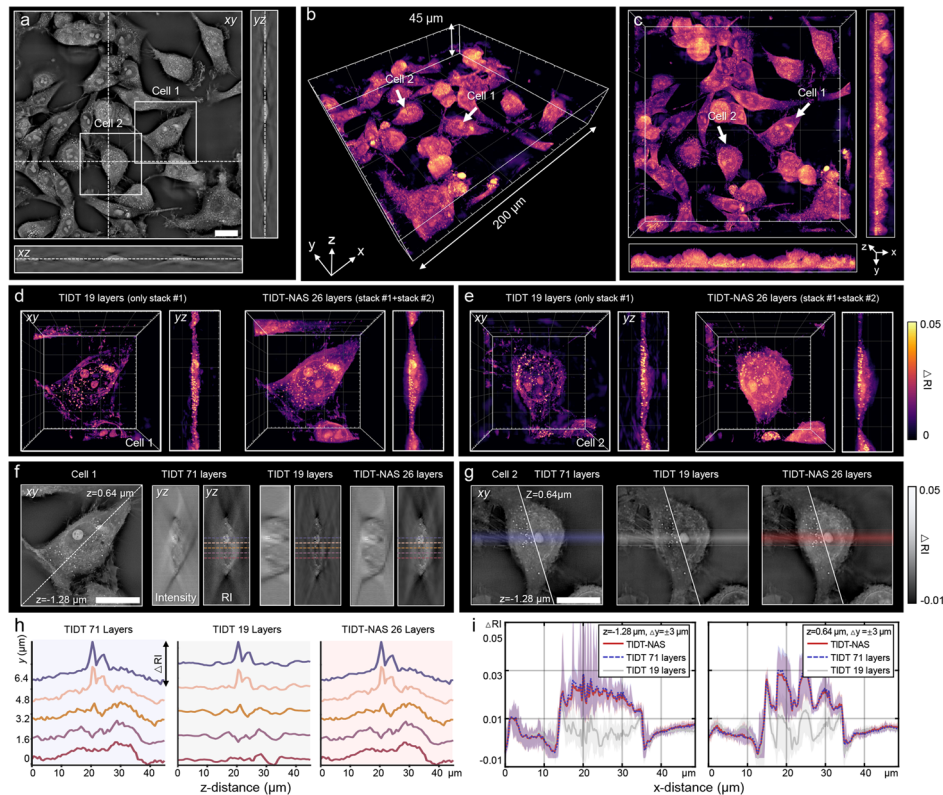


Fig. 4 Comparative experimental results of TIDT-NAS and conventional TIDT for 3D RI tomography of HeLa cells. **a** Full-FOV RI reconstruction obtained by TIDT-NAS, shown in the x - y , x - z , and y - z planes. Two representative cells, Cell 1 and Cell 2, are marked for detailed comparison. **b**, **c** 3D volume-rendered views of the reconstructed HeLa cells from different perspectives, showing the full volumetric RI distribution over a $200\ \mu\text{m}$ field of view and a $45\ \mu\text{m}$ axial range. **d**, **e** 3D volume-rendered comparison of Cell 1 and Cell 2 reconstructed using conventional TIDT with reduced acquisition and TIDT-NAS. The x - y and y - z views show that TIDT-NAS recovers a more complete cellular morphology under compressed acquisition. **f** Representative RI reconstruction of Cell 1 comparing fully sampled TIDT, reduced-acquisition TIDT, and TIDT-NAS. The x - y slice and corresponding y - z profiles illustrate the recovery of both lateral cellular structures and axial RI distribution. **g** Representative RI reconstruction of Cell 2 under the same three conditions, further showing the improved volumetric fidelity of TIDT-NAS compared with reduced-acquisition TIDT. **h** Axial RI profiles extracted from Cell 1, comparing the depth-dependent RI distributions reconstructed by fully sampled TIDT, reduced-acquisition TIDT, and TIDT-NAS. **i** Lateral RI profiles extracted from Cell 2 at representative axial planes. The shaded regions indicate the range of RI variations within a lateral band of $\pm 3\ \mu\text{m}$ around the selected line profiles. Scale bars: $20\ \mu\text{m}$

while preserving subcellular RI heterogeneity. We then selected two representative cells, Cell 1 and Cell 2, labeled in Fig. 4a, for detailed comparison among fully sampled TIDT, reduced-acquisition TIDT (only using stack #1), and TIDT-NAS. The 3D renderings in Fig. 4d and e compare the reconstructions obtained using reduced-acquisition TIDT and TIDT-NAS. Although both methods use a compressed number of axial measurements, reduced-acquisition TIDT reconstructs mainly high-frequency cellular features and exhibits incomplete axial morphology, whereas TIDT-NAS recovers a more continuous and complete cellular volume by incorporating the sparsely sampled full-range stack.

Slice-wise comparisons further confirm this improvement. For Cell 1, the x - y RI slice and corresponding y - z views in Fig. 4f show that fully sampled TIDT resolves both lateral subcellular structures and the axial RI distribution. When only the reduced-range stack is used in conventional TIDT, low-frequency volumetric information is poorly recovered, leading to weakened axial continuity and distorted RI contrast. In contrast, TIDT-NAS restores the missing low-frequency components while preserving fine structural details. Similar behavior is observed for Cell 2 in Fig. 4g, where TIDT-NAS produces an RI distribution that is much closer to the fully sampled TIDT reference than the reduced-acquisition TIDT result. The profile comparisons in Fig. 4h and i provide a quantitative assessment of the reconstruction fidelity. Axial RI profiles extracted from Cell 1 show that reduced-acquisition TIDT underestimates depth-dependent RI variations, whereas TIDT-NAS closely follows the fully sampled TIDT reference across multiple depths. Lateral RI profiles extracted from Cell 2 at representative axial planes further demonstrate that TIDT-NAS preserves both the amplitude and spatial variation of the RI signal, while reduced-acquisition TIDT exhibits reduced contrast and incomplete structural recovery. Together, these results demonstrate that TIDT-NAS substantially reduces the number of required axial measurements while maintaining the volumetric accuracy and structural fidelity of fully sampled TIDT. A more detailed comparison is provided in Visualization 2. Additional comparative experiments on benchmark samples are presented in Supporting Information S6, providing an objective assessment of the tomographic performance of TIDT-NAS.

To further evaluate the capability of TIDT-NAS for high-temporal-resolution 4D RI imaging, we performed dynamic tomographic imaging of live HeLa cells over a duration of 2 min using both TIDT-NAS and conventional TIDT under the same imaging conditions. Representative full-FOV RI frames acquired by TIDT-NAS at 1 fps and by conventional TIDT at 0.3 fps are shown in Fig. 5a and f, respectively. Two regions of interest, corresponding to the cytomembrane and nucleus, were selected for detailed comparison at representative axial planes. The time-lapse RI images in Fig. 5b and c show the temporal evolution of the cytomembrane and nucleus regions captured by TIDT-NAS at representative time points. The corresponding results obtained by conventional TIDT are shown in Fig. 5g and h. To compare the ability of the two methods to track dynamic subcellular activities, we extracted RI profiles along the indicated line positions and generated x - t kymographs. As shown in Fig. 5d and e, TIDT-NAS resolves continuous temporal RI variations at the cytomembrane and inside the nucleus, including fluctuations at the cell-medium boundary and nucleolar motion. In contrast, the conventional TIDT kymographs in Fig. 5i and j show more pronounced frame-to-frame discontinuities because of the lower volumetric frame rate. These results demonstrate

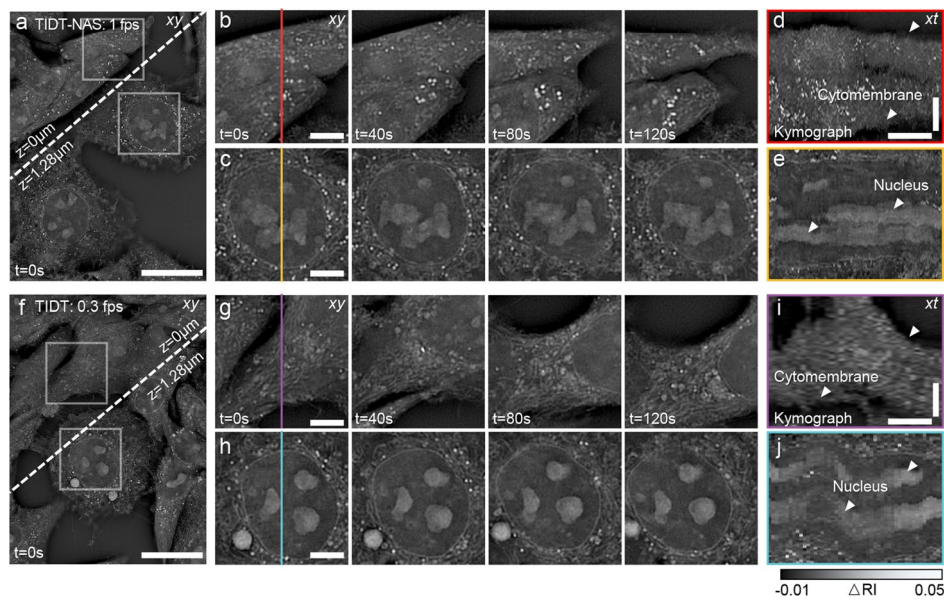


Fig. 5 Comparison of TIDT-NAS and conventional TIDT for dynamic 3D RI tomography of live HeLa cells. **a** Representative full-FOV RI frame acquired by TIDT-NAS at 1 fps. Two regions of interest corresponding to the cytomembrane and nucleus are marked, and the selected axial planes are indicated. **b, c** Time-lapse RI images of the cytomembrane and nucleus regions acquired by TIDT-NAS at representative time points. **d, e** Kymographs showing the temporal evolution of RI along the indicated line profiles in the cytomembrane and nucleus regions for TIDT-NAS. **f** Representative full-FOV RI frame acquired by conventional TIDT at 0.3 fps under the same imaging conditions. **g, h** Time-lapse RI images of the cytomembrane and nucleus regions acquired by conventional TIDT at representative time points. **i, j** Corresponding kymographs of RI dynamics in the cytomembrane and nucleus regions for conventional TIDT. Compared with conventional TIDT, TIDT-NAS provides denser temporal sampling and smoother visualization of dynamic subcellular RI variations. Scale bars: 20 μm in full-FOV images, 5 μm in time-lapse images, and 20 s in kymographs

that TIDT-NAS improves temporal sampling while maintaining volumetric RI contrast, enabling smoother visualization and more reliable tracking of dynamic subcellular RI variations than conventional TIDT under compressed axial acquisition.

Comparative of TIDT-NAS under different illumination strategies on HeLa cells

The proposed efficient non-uniform axial sampling scheme can be readily generalized to different illumination schemes commonly used in TIDT [44, 63]. To demonstrate this flexibility, we perform TIDT-NAS under three representative illumination patterns, the circle, the half circle with four directions, and the annulus, as shown in Fig. 6. The acquisition parameters are consistent with Fig. 5 except for the illumination. Since the circular pattern can be represented as the sum of semi-circular patterns, the intensity measurement under the former can be generated by synthesizing the latter with complementary directions.

For a bright-field microscope, the illumination function determines both the support and amplitude distribution of the 3D transfer function. In TIDT-NAS, changing the illumination pattern modifies the alias-free spectral region available in Stack #2, as illustrated in Fig. 6(a3) and (c3). For the circular and annular illumination schemes considered here, this variation has only a minor effect on the recovered low-frequency components (see Fig. 6(a4) and (c4)). It nevertheless suggests an additional

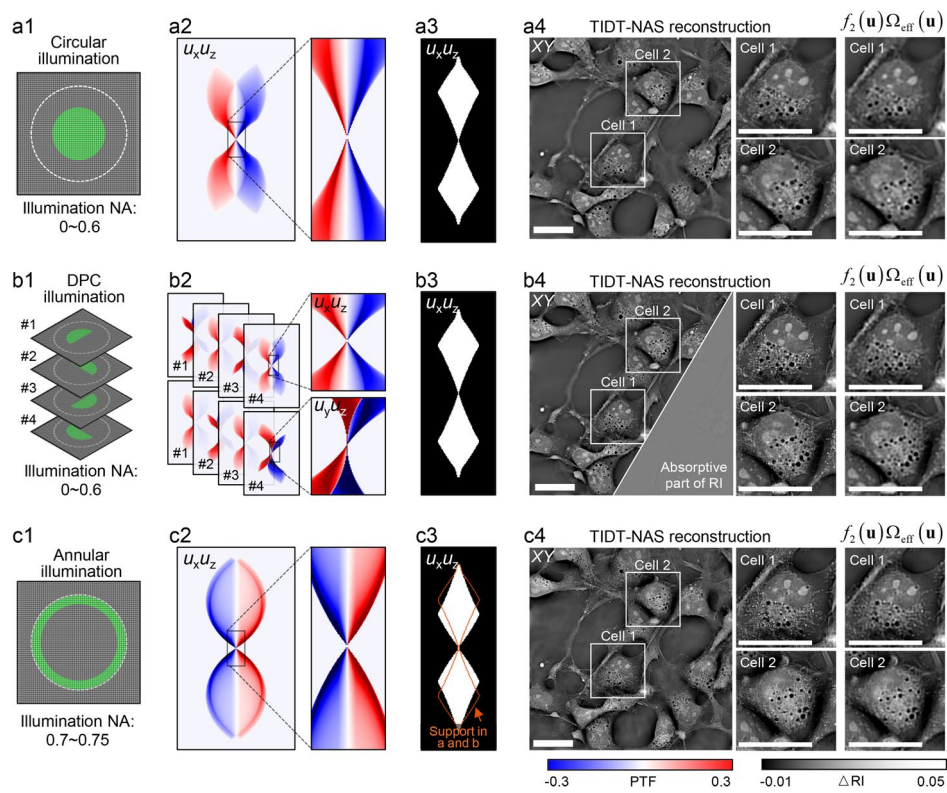


Fig. 6 Comparison of TIDT-NAS reconstructions under different illumination strategies. **a1–a4** Circular illumination with an illumination NA of 0–0.6. **b1–b4** Four-direction DPC illumination with the same illumination NA. **c1–c4** Annular illumination with an illumination NA of 0.7–0.75. Panels 1–4 show the illumination patterns, slices of 3D PTF, and their low-frequency magnifications, effective alias-free support masks $\Omega_{eff}(\mathbf{u})$ at $\Delta z_5 = 3.2 \mu\text{m}$, and TIDT-NAS reconstructions, respectively. Panels 4 show magnified views of Cells 1 and 2 and the corresponding RI components $f_2(\mathbf{u})\Omega_{eff}(\mathbf{u})$ retained within the low-frequency alias-free region. **b3** shows the alias-free support determined from the combined transfer function under the four directional illuminations. **b4** also shows the absorptive part of RI reconstructed from DPC measurement. The orange contour in **c3** indicates the effective supports for circular and DPC illumination as the comparison. Scale bars: $20 \mu\text{m}$

degree of freedom for optimization: Stack #2 may employ a dedicated illumination pattern to selectively enhance the PTF response within the alias-free low-frequency region. Figure 6b further demonstrates that TIDT-NAS is compatible with reconstruction from multiple illumination patterns. Because the synthesized PTF support of the four-direction DPC measurements is essentially identical to that of circular illumination with the same maximum illumination NA (see Fig. 6(a3) and (b3)), the recovered low-frequency components in Fig. 6(a4) and (b4) are nearly identical. The improved phase sensitivity and structural contrast under DPC illumination arise primarily from its stronger synthesized PTF response within the supported spatial-frequency region. Moreover, the multiple directional measurements enable recovery of both the real and imaginary components of the refractive index without invoking the pure-phase approximation. Overall, TIDT-NAS is a raw-data reduction strategy that reduces the number of required measurements by optimizing axial acquisition efficiency, while remaining broadly applicable to the selection and optimization of illumination functions.

Experimental results of long-term dynamic RI tomography on HeLa cells

To demonstrate the capability of TIDT-NAS for long-term 4D RI imaging of live cells, we applied the proposed method to time-lapse RI tomography of HeLa cells. The acquisition parameters were identical to those used in Fig. 4, with 26 images collected across

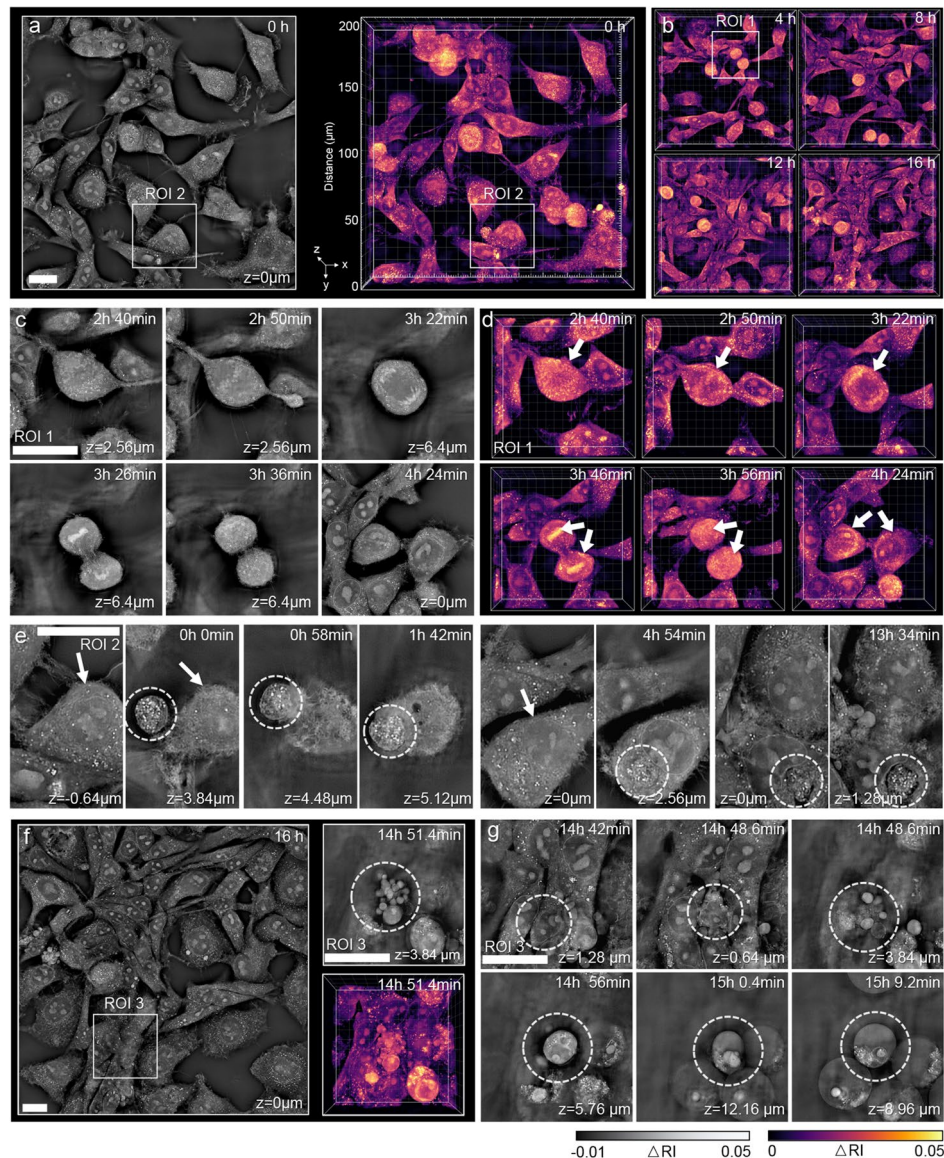


Fig. 7 Long-term time-lapse RI tomography of live HeLa cells using TIDT-NAS. **a** Representative full-FOV RI reconstruction at the initial time point, shown as an x-y slice at $z = 0 \mu\text{m}$ and a corresponding 3D volume rendering. **b** Time-lapse 3D volume renderings of the full-FOV RI reconstruction over 16 h, shown at representative time points. **c**, **d** Time-lapse RI imaging of ROI 1 during cell mitosis. Representative x-y RI sections at different axial positions are shown in **c**, while the corresponding 3D volume renderings in **d** visualize the volumetric morphological changes during mitotic progression. **e** Time-lapse x-y RI sections of ROI 2 at selected axial planes, showing a cell-cell interaction/cytophagic-like process over the long-term recording. **f** Full-FOV RI reconstruction at a later time point and magnified views of ROI 3, showing intracellular vacuole-like structures in both x-y RI sections and 3D volume rendering. **g** Time-lapse x-y RI sections of ROI 3 at multiple axial positions, visualizing the temporal evolution and volumetric distribution of the vacuole-like structures. Scale bars: $20 \mu\text{m}$

a 45- μm axial range for each 3D volume. With an exposure time of 30 ms per image, the resulting volumetric imaging rate was approximately 1 Hz when including the overhead associated with axial scanning. Figure 7a shows a representative full-FOV RI reconstruction at the initial time point, including both an x - y section at $z = 0\ \mu\text{m}$ and the corresponding 3D volume rendering. The full-FOV time-lapse 3D renderings in Fig. 7b show the evolution of the cell population over 16 h, during which the cells gradually increased in density and spatial coverage. The complete time-lapse video is provided in Visualization 3.

We further highlight several representative subcellular and cellular events observed during the long-term recording. In ROI 1, TIDT-NAS captures a complete mitotic process lasting approximately 2 h (see Fig. 7c, d and Visualization 4). The time-lapse x - y RI sections in Fig. 7c, acquired at different axial positions, show the progressive morphological changes during mitosis, including cell rounding, intracellular RI redistribution, and subsequent cell division. The corresponding 3D renderings in Fig. 7d provide a volumetric view of the mitotic progression, where the white arrows highlight characteristic changes in cell morphology and internal high-RI structures. These results demonstrate that TIDT-NAS can follow dynamic mitotic events while preserving depth-resolved RI information.

In ROI 2, we observed a long-term cell–cell interaction with cannibalism-like characteristics during the time-lapse recording (see Fig. 7e). Multiple x - y sections at selected axial positions are shown to visualize the event across depth. At the initial stage, a rounded cell-like structure is located adjacent to a neighboring HeLa cell, as indicated by the arrows and dashed circles. Over the following hours, this structure remains closely associated with the neighboring cell and gradually becomes embedded within or surrounded by the host-cell region. Even after more than 13 h, the internalized structure remains morphologically distinguishable, suggesting slow or incomplete degradation. This observation is consistent with previously reported cannibalism-like cell-in-cell behavior in tumor cells [93, 94]. We note that TIDT-NAS enables this process to be visualized label-free across multiple axial planes, providing both temporal continuity and volumetric context.

Finally, ROI 3 captures the emergence and evolution of intracellular vacuole-like structures under high cell-density conditions (see Fig. 7f, g and Visualization 5). Figure 7f shows a later full-FOV RI reconstruction and magnified views of ROI 3, where multiple high-contrast intracellular structures are visible in both x - y sections and 3D rendering. The time-lapse sections in Fig. 7g, acquired at different axial positions, reveal the depth-dependent distribution and temporal evolution of these vacuole-like structures over tens of minutes. The dashed circles highlight their appearance, growth, and redistribution within the cell volume. Overall, these long-term observations demonstrate that TIDT-NAS can record dynamic cellular events over extended periods while maintaining sufficient volumetric resolution to resolve depth-dependent subcellular RI changes.

Discussion and conclusion

Compared with angular-scanning ODT, TIDT offers several advantages by operating under partially coherent illumination. Reduced spatial coherence suppresses speckle noise and multiple-scattering-induced artifacts, providing a cleaner background and

improved stability for biological RI tomography. By reconstructing volumetric information from a through-focus intensity stack rather than coherent angular scattering measurements, TIDT is also less sensitive to interferometric instability and model mismatch. However, its throughput is limited by the need for densely sampled axial measurements. Even when high-speed electrically tunable lenses (ETLs) replace mechanical scanning, the acquisition time remains dominated by the cumulative camera exposure required for a large number of axial frames, typically on the order of ~ 100 measurements [45, 64, 82, 83, 95, 96]. This data burden remains substantially higher than that of angular-scanning ODT, where optimized angular sampling can often reduce the acquisition to fewer than 30 measurements [97, 98].

Here we present TIDT-NAS, a nonuniform axial-sampling framework that reduces the number of axial measurements required for TIDT while preserving high-fidelity volumetric reconstruction. Inspired by nonuniform defocus sampling in 2D TIE-based phase retrieval [35], TIDT-NAS exploits the different axial sampling requirements of distinct spectral components. Dense sampling is confined to the specimen-containing region to preserve high-frequency structural information, whereas sparse sampling over the extended defocus range retains low-frequency diffraction contrast. The two resulting intensity stacks provide complementary spectral information and are combined through alias-aware Fourier-domain fusion, enabling accurate volumetric RI reconstruction with substantially reduced acquisition overhead.

The spectral fusion strategy is conceptually related to TIE-based methods that combine measurements acquired at different defocus distances through optimal frequency selection [32] or SNR-based weighting [99]. In TIDT-NAS, the fusion is instead designed to reject aliased components introduced by sparse axial sampling while retaining reliable low-frequency information from the full-range stack. Beyond TIDT, the frequency-aware sampling concept may also inform other axial-scanning volumetric microscopy modalities, including 3D fluorescence deconvolution microscopy [100, 101], 3D structured illumination microscopy [102, 103], and light-sheet microscopy [104, 105]. Although their contrast mechanisms differ from that of TIDT, these modalities are also governed by modality-specific 3D transfer functions and frequency-dependent sampling requirements. This suggests that appropriately designed nonuniform axial sampling may help reduce volumetric acquisition burden while retaining reconstruction-relevant information.

Several limitations remain. First, TIDT-NAS is most effective for specimens with a confined axial extent, such as adherent cells and tissue sections, where dense sampling is required only over a limited depth range. For substantially thicker specimens, such as organoids [106], the dense sampling range should be enlarged accordingly; when the specimen occupies most of the axial range, the benefit of nonuniform sampling may diminish and conventional uniform scanning may be more appropriate. Second, the illumination function represents an additional degree of freedom that can be further optimized within the TIDT-NAS framework. The PTF can be improved using annular [63] or Gaussian [62] illumination, or synthesized from multiple illumination patterns [64, 65] to enhance frequency coverage and SNR. Illumination diversity may also facilitate the decoupling of phase and absorption components of the scattering potential [44], although the number of patterns should be balanced against temporal resolution [83]. Joint optimization

of illumination design and axial sampling is therefore a promising direction. More flexible compressive axial-sampling schemes may also be explored. For example, exponentially spaced axial sampling, previously studied in TIE-based phase retrieval [35], could be extended to TIDT to allow progressively larger axial steps at increasing defocus distances. Such nonlinear sampling would require reconstruction algorithms capable of handling measurements acquired at arbitrary axial positions. Finally, the present implementation is limited by mechanical axial translation. Replacing mechanical scanning with an ETL would enable rapid, inertia-free axial modulation [82, 107], making the volumetric imaging speed primarily limited by camera exposure time and signal level.

Methods

Hardware

All experiments were performed on a fully motorized commercial inverted bright-field tomographic microscope (SC3000, Zircon Optoelectronics, Suzhou, China). Two objective lenses were used: a 40×/1.1 NA water-immersion objective (UAPON40XW340, Olympus) and a 40×/0.75 NA objective (UPLFLN40X, Olympus). The intensity stacks were recorded using a high-speed 16-bit sCMOS camera (PCO.edge 5.5 CLHS). Illumination was provided by a dense programmable LED array (51×51 elements) with a pitch of 1.875 μm , positioned 106.6 μm above the sample plane. The LEDs emitted green light with a center wavelength of 520 nm, and a circular illumination pattern corresponding to a 0.6 NA was adopted. All computations were carried out on a workstation equipped with an Intel Core i7-14700KF CPU (3.40 GHz), 64 GB RAM, running Windows 11 Pro for Workstations.

Sample preparation

Live hepatoma carcinoma cells (PLC/PRF/5) and HeLa cells (ATCC CCL-2) were obtained from the National Collection of Authenticated Cell Cultures (China). Both cell lines were maintained in Minimum Essential Medium (MEM; Thermo Fisher Scientific) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Cells were cultured in a humidified incubator at 37°C with 5% CO_2 . For imaging experiments, cells were seeded in glass-bottom confocal dishes at a density of 8×10^5 cells per dish and allowed to adhere overnight. Prior to imaging, the culture medium was replaced with fresh pre-warmed MEM to maintain physiological conditions during long-term time-lapse acquisition. All samples were handled under aseptic conditions to prevent contamination.

Data processing and analysis

For RI tomography of hepatoma carcinoma cells, an intensity volume of $1024 \times 1024 \times 156$ (x - y - z) was acquired using a 40×/1.1NA objective. The axial sampling interval was 0.32 μm , and each slice was recorded with an exposure time of 30 ms. Accounting for axial movement, the total acquisition time for one volumetric dataset was approximately 6.2 s. For long-term RI tomography of HeLa cells, time-lapse imaging was performed over a duration exceeding 15 h. The first volumetric frame was acquired with the full TIDT protocol with the intensity volume of $1024 \times 1024 \times 71$ using a 40×/0.75NA objective. The axial sampling interval was 0.64 μm . These fully sampled

datasets served as reference reconstructions for performance analysis and comparison with the proposed TIDT-NAS. Subsequent frames were acquired using the TIDT-NAS scheme, which records only 26 axial layers. With the same exposure time, the total acquisition time per 3D frame was reduced to approximately 1 s, enabling dynamic live-cell RI imaging at a frame rate of 1 Hz.

All RI reconstruction algorithms for both TIDT and TIDT-NAS were implemented in MATLAB R2024b. 3D volume renderings of the reconstructed RI datasets were generated using Fiji. On the computational platform described previously, the total processing times, including image loading and reconstruction, were approximately 31 s for TIDT and TIDT-NAS, respectively.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s43074-026-00290-y>.

Supplementary Material 1

Authors' contributions

C.Z., Y.S. and J.S. conceived the project. C.Z., J.S., and Q.C. supervised the research. Y.S. and S.Z. derived and validated the theory. Y.S. and A.T. performed experiments and analyzed the data. C.Z. supervised the experiments. All authors discussed the results and contributed to writing the paper.

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Data availability

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

There is no ethics issue for this paper.

Consent for publication

All authors agreed to publish this paper.

Competing interests

The authors declare that they have no competing interests.

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