

# MicroFM: Physics-guided Flow Matching for Isotropic Microscopy Reconstruction

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## Abstract

*Isotropic microscopy reconstruction remains challenging because the anisotropic point spread function in optical systems yields much poorer axial resolution and hampers accurate 3D analysis. Hardware strategies can approach isotropy, yet they are complex, costly, susceptible to side-lobes, and introduce phototoxicity. Deep learning approaches reduce acquisition burden, yet synthetic pipelines often rely on Gaussian blur mismatched to physical degradation, resulting in low-fidelity reconstructions. To address these challenges, we present MicroFM, which synthesizes realistic training data using physical PSFs matched to the target microscope. MicroFM also introduces a physics-guided flow-matching framework for isotropic microscopy reconstruction, guided by a continuous implicit geometry prior to achieve high-fidelity isotropic recovery. Across four fluorescence microscopy systems and datasets, MicroFM achieves state-of-the-art (SOTA) performance, producing sharper structures, more isotropic spectra, and substantial gains in both full-reference and no-reference metrics.*

## 1. Introduction

3D fluorescence microscopy reveals subcellular structures, cell-cell interactions, and tissue architecture [7, 23] and enables live cell imaging. However, optical microscopy is fundamentally constrained by the diffraction limit, which yields a highly anisotropic point spread function (PSF) in most imaging systems. Consequently, the axial resolution is typically two to three times worse than the lateral resolution [29, 32], imposing substantial limitations on accurate 3D visualization and quantitative analysis. This inherent anisotropy has motivated a wide range of optical and computational strategies aimed at restoring axial resolution.

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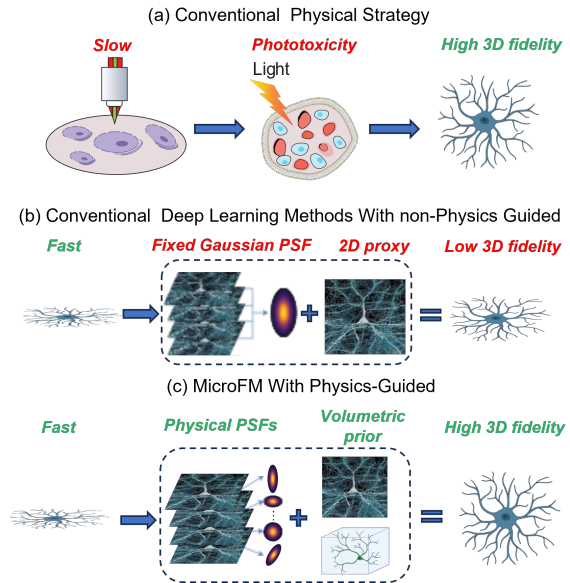


Figure 1. Background and concept of MicroFM. (a) Conventional 3D fluorescence microscopy yields nearly isotropic, high-fidelity volumes, yet acquisition is slow and costly and causes phototoxicity in live samples. (b) Conventional deep learning pipelines are fast and low cost; they often assume a fixed Gaussian PSF and rely on 2D slice proxies, which mismatch real optical degradation and ignore volumetric geometry, leading to low 3D fidelity. (c) MicroFM combines physics-based, spatially varying PSF estimation with an implicit volumetric prior that guides a Flow Matching reconstruction network, enabling fast, low-cost imaging with high-fidelity isotropic 3D reconstruction.

A broad set of strategies exists to address this anisotropy, falling into two classes: optical approaches that modify the PSF through hardware and computational methods that restore isotropy from standard acquisitions. Optical solutions such as beam shaping, multiview imaging, and PSF engineering [1, 5, 12, 33] can improve axial resolution but often involve high complexity and phototoxicity. As a result, computational reconstruction has become the main route to scalable isotropic 3D fluorescence imaging.

Building on this shift, computational reconstruction

methods have advanced rapidly, evolving from classical deconvolution to learning-based models, including zero-shot, nonblind, and blind variants [6, 13, 35, 39, 41]. Deep learning now dominates practice because it improves reconstruction quality, reduces acquisition burden, and increases robustness to unknown blur, with unsupervised and self-supervised strategies [14, 15] widely used.

Supervised methods [4, 9, 30] achieve high accuracy but require large paired volumes of blurred and sharp data, which are difficult to acquire and register. Unpaired frameworks such as CycleGAN [45], OT-CycleGAN [31], and UTOM [19] relax this requirement through cycle consistency or saliency constraints, yet they often introduce hallucinations and structural distortions. Recent self-supervised methods, including SSAI-3D [10] and the Content-Aware Image Restoration network (CARE) [42], synthesize training pairs by convolving lateral high-resolution images with Gaussian PSFs of varying standard deviations and then train networks to deblur and denoise axial views.

Despite progress, these networks face two central limitations (see Fig. 1(b)). The first limitation is the mismatch between synthetic training data and real optical image formation. Most pipelines approximate axial blur using Gaussian kernels [10, 25, 42], which overlook the anisotropy, aberrations, depth variation, and sample-induced changes of real PSFs. Models trained on such simplified degradations learn to invert Gaussian blur rather than the true imaging process and therefore generalize poorly to axial views. The second limitation is the lack of explicit volumetric geometry constraints. Slice-wise 2D reconstruction ignores cross-slice continuity and geometric structure, often producing distorted morphologies such as cylinders reconstructed as spheres. Quasi-3D inputs [10, 29] and axial-lateral similarity cues [19, 31] offer only weak regularization and frequently fail in tissues with strong directionality or anisotropy.

To overcome two central limitations, we present MicroFM, an isotropic Microscopy Reconstruction using Flow Matching, which couples physics-grounded PSF estimation with geometry-aware reconstruction. First, we train SFE-Net [34] on high-fidelity lateral images to infer a PSF that captures axial blur and the characteristics of the target microscope. Then, we use the predicted PSFs to synthesize paired training data by degrading lateral images, and we pretrain a continuous implicit neural representation (INR) that encodes a volumetric geometry prior. Guided by this prior, we train a Flow Matching Reconstruction Network on the synthetic lateral pairs and apply it to isotropic 3D reconstruction. To our knowledge, this is the first application of Flow Matching to isotropic microscopy reconstruction. Initializing the probability flow with inputs anchored to low-quality images and conditioning on the volumetric prior reduces hallucinations, preserves morphology, and en-

ables fast and stable sampling. Experiments across four fluorescence microscopy systems demonstrate state of the art performance on full reference and no reference metrics, with clear gains in fidelity and perceptual quality.

Our contributions to isotropic microscopy reconstruction are summarized as follows.

- We estimate instrument-matched, spatially varying PSFs from axial views using SFE-Net and use them to synthesize realistic paired training data, significantly narrowing the gap between simulated and physical image formation.
- We introduce the physics-guided Flow Matching framework for isotropic microscopy reconstruction, anchored to low-quality inputs and guided by a continuous implicit 3D prior to preserve morphology, suppress hallucinations, and enable fast, stable sampling.
- We achieve SOTA performance across four fluorescence microscopy systems against six representative baselines on full-reference and no-reference evaluations. Ablation studies further confirm the benefits of physical PSF synthesis, the volumetric prior, and anchored flow sampling.

## 2. Related Works

### 2.1. Isotropic Restoration in Microscopy

3D imaging is essential in biomedicine; however, anisotropic PSF results in lower axial resolution compared to lateral resolution and fails to maintain isotropy. Optical solutions can approach isotropy but remain complex, costly, and phototoxic [18, 27]. To achieve lower-cost generalized solution, computational routes span classic deconvolution [24, 36, 40], supervised CNNs [8, 20, 42], and unpaired adversarial learning [19, 31, 45]. An algorithm-based deconvolution network has been used to overcome the limitations [24, 36, 40]. Supervised CNNs deliver strong results yet require large paired data that are hard to acquire [8, 20, 42]. Unpaired GANs allow unpairing data via cycle consistency or saliency cues but may hallucinate structures and distort morphology [19, 31, 45]. Self-supervised learning reduces pairing needs by exploiting lateral axial similarity, such as Self-Net, and physics-informed self-supervised designs, such as SSAI-3D, use sparse fine-tuning to improve cross-system generalization [10, 29]. Despite progress, most approaches still depend on lateral axial similarity and remain vulnerable to artifacts, which limits robust isotropic restoration.

### 2.2. Flow Matching

Generative modeling, including GANs [19, 29], has been used for isotropic, enabling unpaired training but is vulnerable to artifacts. Diffusion model also provides valid outcomes but requires a high computational cost [21]. Continuous Normalizing Flows (CNFs) [3, 17] emerged as another generative approach, modeling probability paths in

continuous time, but their reliance on costly ordinary differential equation simulations limited scalability. Attempts to accelerate CNFs through regularization or explicit path design faced biased gradients and integration challenges. Flow Matching [22] overcomes these limitations by enabling simulation-free training through direct probability flow matching, providing unbiased gradients and efficient scaling to high-dimensional data.

### 2.3. PSF Modeling

Traditional PSF analysis has largely relied on the Gaussian PSF, which simplifies optical modeling [38] but fails to capture the complex aberrations inherent in microscopy images. Besides Gaussian, there are other physics-informed priors proposed to minimize deviation from realistic PSF and adaptability to complex environments. Zernike polynomials [16] have become a standard tool for representing wavefront aberrations such as defocus, astigmatism, and coma in a compact and flexible form. Additionally, parameters like numerical aperture [11] and pupil apodization [28] are integrated to account for resolution limits and intensity variations across the aperture, influencing image contrast and sidelobe suppression. Depth-dependent aberrations [2, 26], caused by refractive index mismatches and spherical aberration, are also modeled to capture axial variations in PSF structure, which is an essential factor for 3D imaging. Utilizing these PSF calculation methods, learning-based restoration models have emerged as powerful alternatives. CARE [42] enables accurate fluorescence microscopy restoration without requiring laborious manual generation of training data; however, it relies on supervised training with paired high-quality ground truth data.

## 3. Method

### 3.1. Overview of MicroFM

Fluorescence microscopy usually exhibits much lower axial resolution than lateral resolution. Common synthetic pipelines use Gaussian kernels to mimic axial blur and ignore the true instrument-specific PSF, so degrading lateral images cannot reproduce axial blur, and the trained models perform poorly on axial restoration. Many methods also process axial slices in isolation with only 2D context, which weakens volumetric constraints and discards the original 3D relationships. To address these issues, we introduce MicroFM, a two-stage physics-guided framework. The first stage predicts physical PSFs from low-resolution images and calibrates them to the target instrument; the estimated functions are then used to degrade lateral high-resolution slices and to build training pairs that match the optical characteristics of the microscope. The second stage performs isotropic recovery with joint 3D and 2D context. We learn a continuous implicit neural representation (INR) that ren-

ders an isotropic volume and provides a slice-wise geometry prior. Guided by the INR-derived prior, the Flow Matching Reconstruction Network progressively transports degraded observations to realistic axial images and reconstructs high-fidelity isotropic 3D fluorescence volumes.

### 3.2. Physics PSF Prediction

We first use Zernike wavefronts at the pupil plane to generate physically consistent PSFs and synthesize low-resolution (LR) images. We train an SFE-network [34] to blindly infer PSF from LR, then apply it to the axial images of anisotropic 3D data to estimate the microscope PSF and blur lateral high-resolution slices, yielding training pairs matched to the imaging characteristics of the target system.

To generate physical degradations, we model the pupil plane wavefront with a compact Zernike basis. Specifically, we adopt 25 Zernike modes covering piston, tilt, defocus, astigmatism, coma, spherical, and higher-order aberrations. For each training sample, a coefficient vector  $\mathbf{a} = [a_0, \dots, a_{24}]^\top$  is drawn at random and the aberration phase on the normalized pupil  $(\rho, \theta)$  is

$$\phi(\rho, \theta) = \sum_{n=0}^{24} a_n Z_n(\rho, \theta). \quad (1)$$

Under the Fraunhofer approximation, the aberrated complex pupil is

$$P(\rho, \theta) = A(\rho) e^{i\phi(\rho, \theta)}, \quad (2)$$

where  $A(\rho)$  denotes the circular apodization determined by the emission wavelength and the detection NA. The incoherent PSF is obtained by Fourier propagation,

$$h(x, y) = |\mathcal{F}\{P(\rho, \theta)\}|^2. \quad (3)$$

Let  $S$  denote high-resolution images. A realistic low-resolution image is synthesized by convolving with  $h$ , injecting Poisson shot noise and additive Gaussian read noise, and downsampling to the microscope's axial sampling rates:

$$I_{\text{LR}} \sim \mathcal{D}(\text{Poisson}(S * h) + \eta), \quad \eta \sim \mathcal{N}(0, \sigma^2). \quad (4)$$

We use the trained SFE-Net [34] to estimate a bank of PSFs from axial images acquired with the target microscope. Each axial image yields a distinct function, which agrees with the spatially varying instrument response. We then build paired training data by convolving lateral slices with these functions to synthesize degraded inputs. For every axial image, we randomly sample seven predicted functions to produce seven degraded images. This design exposes the model to the full range of axial degradation. The physics-grounded pairing reduces mismatch relative to fixed Gaussian kernels and improves generalization on axial planes by capturing position dependence and both optical and sample-induced aberrations.

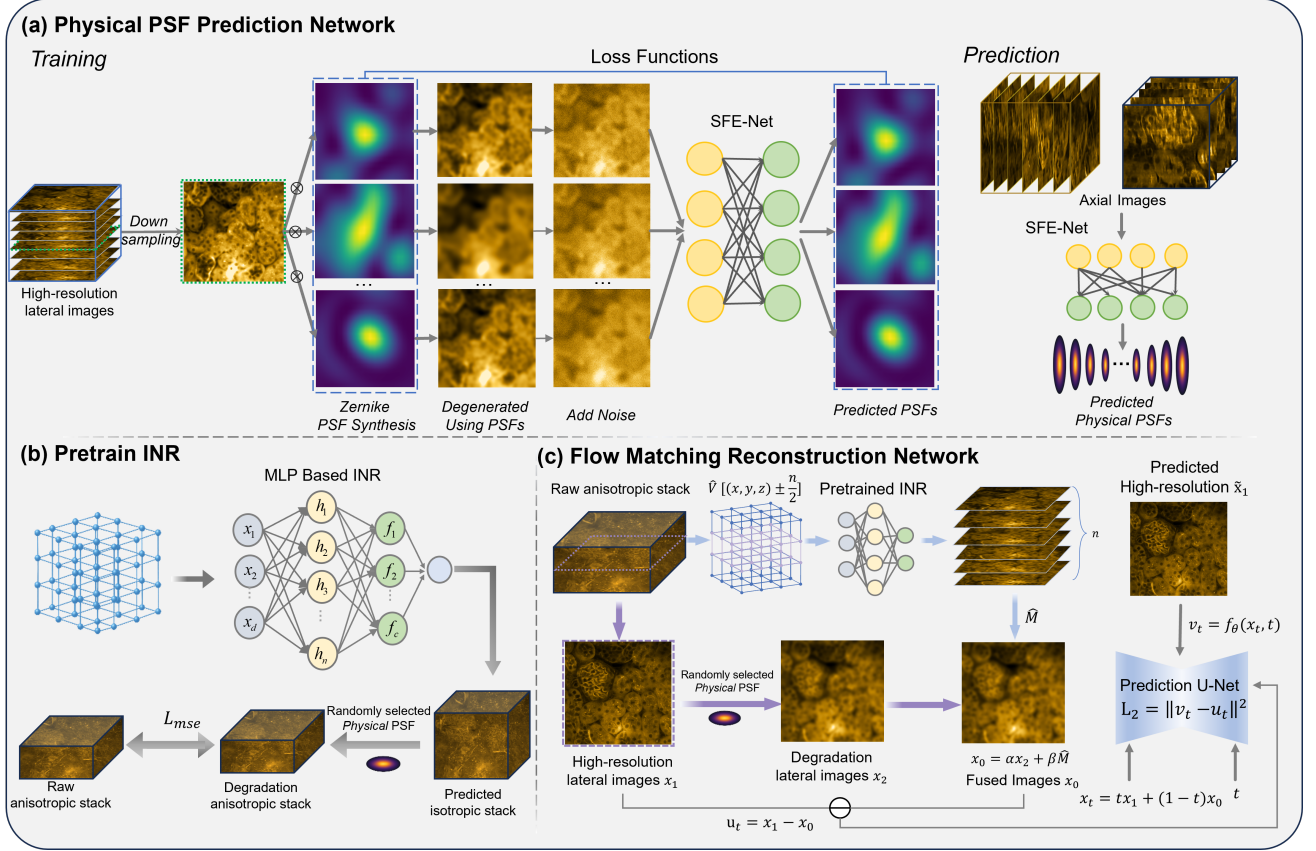


Figure 2. Overall framework of the proposed method. **(a) Physical PSF Prediction:** SFE-Net is trained with Zernike-based synthetic degradations and noise to regress spatially varying physical PSFs from axial images; the predicted PSFs are then used to synthesize training pairs matched to the target microscope. **(b) Pretrain INR:** Using the predicted PSFs as the physics operator, an MLP-based implicit neural representation renders an isotropic volume and serves as a volumetric geometry prior. **(c) Flow Matching Reconstruction Network:** Starting at  $x_0$  formed by fusing the degraded input slice with the INR prior, Flow Matching transports  $x_0$  to a high-quality slice; reconstructions from axial images are fused to obtain an isotropic 3D volume.

### 3.3. Isotropic Recovery

Isotropic recovery restores each axial slice with joint 3D and 2D context rather than isolated 2D processing. Accordingly, the pipeline contains two components: *volumetric geometry prior synthesis* and a *Flow Matching Reconstruction Network*. We first build a 3D geometry prior using an implicit neural representation [37], then train a Flow Matching Reconstruction Network [44] conditioned on the axial input and this prior to produce morphology-preserving isotropic reconstructions.

**Implicit isotropic volume.** We represent the target isotropic 3D volume as a continuous implicit neural field  $f_\theta : \mathbb{R}^3 \rightarrow \mathbb{R}$ . Given an anisotropic acquisition  $G \in \mathbb{R}^{Z_{\text{low}} \times Y \times X}$ , the network renders an isotropic volume via a fixed positional encoding  $\gamma$ :

$$\hat{V}(y, x, z) = f_\theta(\gamma(y, x, z)). \quad (5)$$

To learn  $f_\theta$ , we simulate the axial image formation by

first downsampling only along the  $z$ -axis and then convolving with the randomly selected predicted physical PSF  $p$ . Denote this degradation operator by  $\mathcal{A}(\cdot) = p * D_z(\cdot)$ . During training we sample contiguous 3D subvolumes  $\Omega$  uniformly at random from  $\hat{V}$  and minimize the mean-squared error between the simulated observation and the acquired stack:

$$\mathcal{L}_{\text{INR}} = \mathbb{E}_\Omega \left\| \mathcal{A}(\hat{V}|_\Omega) - G|_\Omega \right\|_2^2. \quad (6)$$

At inference, the trained field produces an explicit geometry prior for any prescribed slice. For a lateral slice index  $Z_s \in \{0, \dots, Z_{\text{low}} - 1\}$ , to generate an explicit volumetric geometry prior to  $\hat{M}_s$ , we aggregate  $n$  synthetic slices from a symmetric neighborhood around  $Z_s$ . Let  $\mu = (n + 1)/2$  and define equally spaced depth offsets  $\Delta_k = (k - \mu)$  for  $k = 1, \dots, n$ . The slice prior is the Gaussian weighted average

$$\hat{M}_s(y, x) = \sum_{k=1}^n w_k f_\theta(\gamma(y, x, z_s + \Delta_k)), \quad (7)$$

$$w_k = \frac{\exp(-\frac{(k-\mu)^2}{2\sigma^2})}{\sum_{j=1}^n \exp(-\frac{(j-\mu)^2}{2\sigma^2})}. \quad (8)$$

We set  $n = 6$  in MicroFM. The YZ and XZ planes are handled analogously by fixing  $x$  or  $y$  and repeating the construction.

**Flow Matching Reconstruction Network.** Building on the axial training pairs constructed in Section 3.2, we commence training of the Flow Matching Reconstruction Network. Given a degraded lateral slice  $x_2$  and a volumetric geometry prior  $\widehat{M}$  rendered by an implicit neural field, we define the start of the flow  $x_0$  as a convex blend of LR and prior. Let  $\alpha$  and  $\beta$  lie in  $[0, 1]$  with  $\alpha + \beta = 1$ , and set

$$x_0 = \alpha x_2 + \beta \widehat{M}. \quad (9)$$

This follows Equation 7 in the implicit isotropic volume module so that continuity and topological cues are injected across XY, YZ, and XZ, which compensates for the missing volumetric constraints that arise when processing 2D slices independently. Starting from the observed degraded slice guides the network to learn effective resolution enhancement under the true data distribution and reduces hallucination that often appears when the trajectory begins from pure noise.

We model resolution recovery as a deterministic probability flow that transports  $x_0$  which already carries the 3D prior toward the target high-quality slice  $x_1$  rather than starting from noise. It forces the network to learn effective resolution enhancement under the true data distribution and reduces hallucination that often appears when the trajectory begins from pure noise. Specifically, given the target high-quality slice  $x_1$  and the start  $x_0$ , for any time  $t$  with  $0 < t \leq 1$  we define the interpolation point and the ideal velocity as

$$v^*(x_t) = x_1 - x_0, \quad x_t = t x_1 + (1 - t)x_0. \quad (10)$$

We learn a conditional velocity field  $v_\theta[x_t, t \mid x_0]$  that approximates the oracle  $v^*$ . Following Consistency Flow Matching CFM, we impose endpoint consistency through

$$\begin{cases} f(t, x_t) \approx f(r, x_r), \\ f(t, x_t) = x_t + (s(t) - t) v_\theta(x_t, t). \end{cases} \quad (11)$$

Here  $r = \min\{t + \delta, 1\}$  and  $s(t)$  denote the end of the segment that contains time  $t$  under a multi-segment piecewise training schedule, which induces a piecewise linear path within each segment. The objective is equivalent to requiring that one step Euler predictions, obtained by advancing from different start times along the current velocity up to the segment end, arrive at a common endpoint. This straightens

Table 1. Datasets summary used in MicroFM.

| Datasets             | Source        | System     | Pixel number<br>(X, Y, Z) |
|----------------------|---------------|------------|---------------------------|
| Dense neuron cluster | Self-Net [29] | CS-fMOST   | (893, 1153, 194)          |
| Cleared Thy1-GFP     | Self-Net [29] | Confocal   | (1024, 1024, 92)          |
| Mouse Kidney         | Self-Net [29] | Two-photon | (1024, 1024, 150)         |
| Mouse Liver          | Self-Net [29] | Wide-field | (1800, 1700, 246)         |

the ODE trajectory, enables effective Euler sampling with few steps, and limits the accumulation of discretization error.

During training we sample  $t \sim \mathcal{U}[\varepsilon, 1]$  and set  $r = \text{clamp}[t + \delta, 1]$  for each example. We form the pair  $x_t, x_r$  with corresponding velocities  $v_t, v_r$  and minimize

$$\begin{aligned} \mathcal{L}_{\text{cons}} = & \|f(t, x_t) - f(r, x_r)\|_2^2 \\ & + \lambda_{\text{vel}} \mathbf{1}[t < b] \mathbf{1}[d_t > \tau] \|v_t - v_r\|_2^2. \end{aligned} \quad (12)$$

Here,  $b$  denotes the end time of the current segment,  $d_t$  is the distance from time  $t$  to the segment end, and  $\tau$  is a small threshold. The indicator  $\mathbf{1}[t < b]$  activates the velocity consistency term only for points strictly inside the current segment, while  $\mathbf{1}[d_t > \tau]$  disables this term near the segment endpoint to avoid degenerate zero-length updates.

## 4. Experiments

### 4.1. Experiment Settings

**Datasets and Metrics.** To validate the advantages of our model for isotropic resolution recovery, we evaluate reconstructions on four anisotropic fluorescence microscopy datasets that are widely used for isotropic verification [10, 29] and were acquired on four different fluorescence microscopes, as summarized in Table 1.

For lateral evaluation, we extract high-resolution lateral images from each anisotropic stack by slicing along the  $z$  axis, then synthesize degraded lateral inputs following the pipeline in Section 3.3. We use an eight to two split for training and testing. For axial evaluation, the reconstruction pipeline preserves a five fold disparity between lateral and axial sampling, which reflects the characteristic anisotropy of these modalities. We follow Volume Tells [21] to build our evaluation system; see the appendix for details.

**Implementation Details.** Real 2D slices from distinct 3D volumes vary in shape. We extract  $512 \times 512$  training patches with fixed spatial cropping so that the field of view remains consistent. Optimization uses Adam with initial learning rate  $5 \times 10^{-4}$  and  $\beta_1 = 0.9$ . The model includes a 3D implicit neural representation prior with weight  $\beta = 0.5$ , which preserves consistency across the volume. The proposed Consistency Flow Matching model adopts an NCSN++ backbone with 2.48 million parameters and

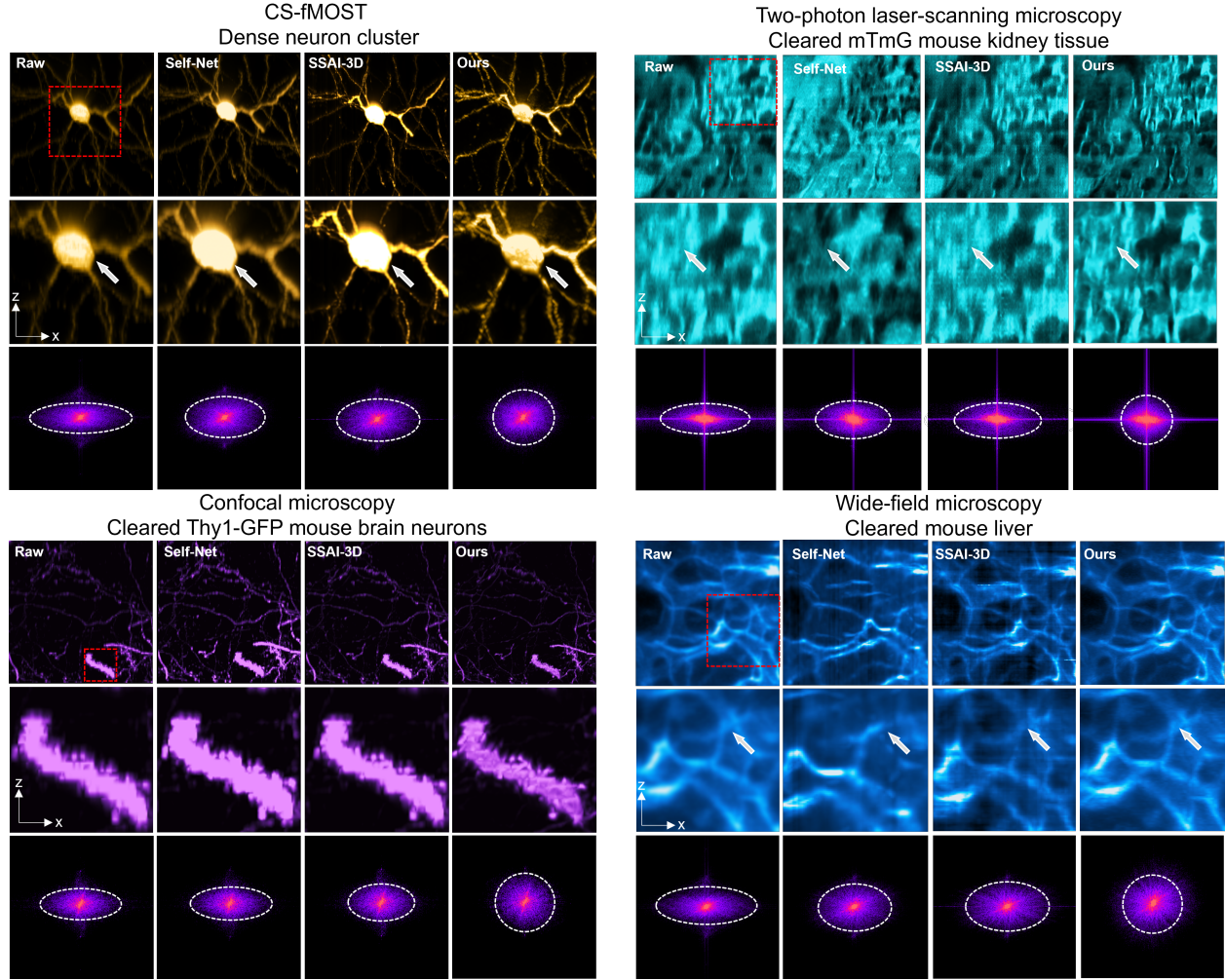


Figure 3. MicroFM enables isotropic-resolution recovery across diverse imaging systems and specimens. Each example shows the raw input and the restorations produced by Self-Net, SSAI-3D, and MicroFM, together with zoomed-in views (white boxes; middle row) and the corresponding Fourier magnitude spectra (bottom row). (a) Dense neuron cluster with Cyclosporine-fluorescence micro-optical sectioning tomography (CS-fMOST) imaging (b) Cleared mTmG mouse kidney tissue acquired with second-harmonic generation (SHG) microscopy; (c) cleared Thy1-GFP mouse brain neurons acquired with confocal microscopy; (d) cleared mouse liver acquired with wide-field microscopy.

applies two step sampling during training and inference. Training uses a batch size of 12 for 200,000 iterations on an AMD EPYC 7742 64 core processor and an NVIDIA H100 80 GB HBM3 GPU.

#### 4.2. Comparison with SOTA methods

We further assess the impact of our approach MicroFM against established three self-supervised models [10, 29, 31] and three unsupervised learning models [19, 43, 45].

**Baseline Comparison.** As shown in Table 2, across four fluorescence microscopy systems and four datasets, *MicroFM* achieves the best or tied for best fidelity on a lat-

eral test images as measured by PSNR, SSIM, and VIF, together with superior perceptual consistency reflected by lower LPIPS. On axial test images, it also shows a more stable advantage on the no reference metrics NIQE, PIQE, and NRQM. A few methods occasionally obtain higher scores on specific perceptual metrics, for example higher NRQM on Liver or lower LPIPS on Kidney, but these cases coincide with degraded lateral image full reference fidelity or unstable axial quality.

We further observe that three unsupervised baselines, CycleGAN, CycleDiffusion, and UTOM, are trained under the assumption that lateral and axial distributions are similar. This assumption is violated in strongly anisotropic sam-

Table 2. Quantitative comparison on four datasets acquired from different fluorescence microscopy systems. Full Reference Metrics are computed on lateral (XY) test images, while No Reference Metrics are computed on axial (XZ/YZ) test images. Multiple complementary metrics are adopted to enable a fair and comprehensive evaluation. Arrows indicate the preferred direction for each metric:  $\uparrow$  means higher is better and  $\downarrow$  means lower is better. **Bold** entries denote the best performance, and underlined entries denote the second best.

| Dataset                              | Method                | Full Reference Metrics   |                         |                         |                         | No Reference Metrics     |                          |                         |
|--------------------------------------|-----------------------|--------------------------|-------------------------|-------------------------|-------------------------|--------------------------|--------------------------|-------------------------|
|                                      |                       | PSNR $\uparrow$          | SSIM $\uparrow$         | LPIPS $\downarrow$      | VIF $\uparrow$          | NIQE $\downarrow$        | PIQE $\downarrow$        | NRQM $\uparrow$         |
| Dense neuron cluster                 | CycleGAN [45]         | 25.716 $\pm$ 1.36        | 0.876 $\pm$ 0.02        | 0.209 $\pm$ 0.03        | 0.120 $\pm$ 0.02        | 21.033 $\pm$ 1.79        | 92.589 $\pm$ 5.01        | 3.751 $\pm$ 0.92        |
|                                      | UTOM [19]             | 30.514 $\pm$ 2.75        | 0.848 $\pm$ 0.05        | 0.209 $\pm$ 0.08        | 0.052 $\pm$ 0.03        | 23.432 $\pm$ 11.56       | 82.289 $\pm$ 14.29       | 3.885 $\pm$ 1.18        |
|                                      | Neuroclear [31]       | 27.655 $\pm$ 2.02        | 0.714 $\pm$ 0.00        | 0.198 $\pm$ 0.04        | 0.103 $\pm$ 0.08        | <u>18.064</u> $\pm$ 1.60 | <u>81.104</u> $\pm$ 3.31 | 3.153 $\pm$ 0.58        |
|                                      | CycleDiffusion [43]   | 27.842 $\pm$ 2.11        | 0.862 $\pm$ 0.03        | 0.205 $\pm$ 0.05        | 0.088 $\pm$ 0.04        | 19.487 $\pm$ 1.52        | 88.734 $\pm$ 4.36        | 3.894 $\pm$ 0.69        |
|                                      | Self-Net [29]         | 29.078 $\pm$ 6.15        | 0.791 $\pm$ 0.13        | 0.182 $\pm$ 0.04        | 0.201 $\pm$ 0.09        | 19.492 $\pm$ 1.84        | 90.992 $\pm$ 4.74        | 3.790 $\pm$ 0.48        |
|                                      | SSAI-3D [10]          | 30.745 $\pm$ 3.32        | 0.889 $\pm$ 0.07        | 0.168 $\pm$ 0.04        | 0.210 $\pm$ 0.09        | 19.090 $\pm$ 2.60        | 89.197 $\pm$ 3.54        | 3.943 $\pm$ 0.60        |
|                                      | <b>MicroFM (Ours)</b> | <b>40.186</b> $\pm$ 8.55 | <b>0.964</b> $\pm$ 0.08 | <b>0.075</b> $\pm$ 0.07 | <b>0.378</b> $\pm$ 0.06 | <b>17.472</b> $\pm$ 1.54 | <b>78.925</b> $\pm$ 3.86 | <b>4.189</b> $\pm$ 0.57 |
| Cleared Thy1-GFP Mouse Brain neurons | CycleGAN [45]         | 20.203 $\pm$ 1.85        | 0.873 $\pm$ 0.01        | 0.284 $\pm$ 0.04        | 0.060 $\pm$ 0.02        | 17.414 $\pm$ 0.99        | 93.310 $\pm$ 4.09        | 3.706 $\pm$ 0.66        |
|                                      | UTOM [19]             | 30.126 $\pm$ 2.74        | 0.758 $\pm$ 0.06        | 0.284 $\pm$ 0.04        | 0.051 $\pm$ 0.01        | 18.078 $\pm$ 4.63        | <b>66.314</b> $\pm$ 9.86 | 3.257 $\pm$ 0.81        |
|                                      | Neuroclear [31]       | 28.578 $\pm$ 2.34        | 0.778 $\pm$ 0.01        | <u>0.264</u> $\pm$ 0.04 | 0.102 $\pm$ 0.05        | <u>15.162</u> $\pm$ 1.00 | <u>84.886</u> $\pm$ 3.68 | 2.996 $\pm$ 0.43        |
|                                      | CycleDiffusion [43]   | 24.918 $\pm$ 2.27        | 0.821 $\pm$ 0.04        | 0.268 $\pm$ 0.05        | 0.056 $\pm$ 0.02        | 16.203 $\pm$ 0.93        | 89.742 $\pm$ 4.51        | 3.842 $\pm$ 0.62        |
|                                      | Self-Net [29]         | 33.098 $\pm$ 3.78        | 0.950 $\pm$ 0.02        | 0.337 $\pm$ 0.05        | 0.461 $\pm$ 0.12        | 15.161 $\pm$ 1.18        | 85.828 $\pm$ 5.98        | 4.596 $\pm$ 0.70        |
|                                      | SSAI-3D [10]          | 29.090 $\pm$ 1.21        | 0.862 $\pm$ 0.03        | 0.274 $\pm$ 0.06        | 0.141 $\pm$ 0.05        | <u>14.440</u> $\pm$ 1.01 | 89.090 $\pm$ 2.68        | 3.835 $\pm$ 0.35        |
|                                      | <b>MicroFM (Ours)</b> | <b>47.363</b> $\pm$ 5.92 | <b>0.963</b> $\pm$ 0.08 | <b>0.032</b> $\pm$ 0.03 | <b>0.570</b> $\pm$ 0.13 | <b>13.154</b> $\pm$ 1.06 | <u>81.386</u> $\pm$ 4.51 | <b>4.999</b> $\pm$ 0.66 |
| Mouse Kidney                         | CycleGAN [45]         | 17.891 $\pm$ 2.61        | 0.658 $\pm$ 0.02        | 0.535 $\pm$ 0.03        | 0.172 $\pm$ 0.02        | 9.702 $\pm$ 0.43         | 77.471 $\pm$ 1.08        | 4.033 $\pm$ 0.96        |
|                                      | UTOM [19]             | 18.960 $\pm$ 2.88        | 0.579 $\pm$ 0.03        | <b>0.320</b> $\pm$ 0.01 | 0.059 $\pm$ 0.01        | 8.088 $\pm$ 0.86         | 70.886 $\pm$ 5.11        | 4.111 $\pm$ 0.36        |
|                                      | Neuroclear [31]       | 18.040 $\pm$ 1.03        | 0.655 $\pm$ 0.03        | 0.416 $\pm$ 0.01        | 0.135 $\pm$ 0.00        | 8.052 $\pm$ 0.62         | 69.511 $\pm$ 1.02        | 3.655 $\pm$ 0.10        |
|                                      | CycleDiffusion [43]   | 18.437 $\pm$ 2.18        | 0.621 $\pm$ 0.03        | 0.412 $\pm$ 0.02        | 0.113 $\pm$ 0.02        | 8.913 $\pm$ 0.59         | 73.286 $\pm$ 1.12        | 3.874 $\pm$ 0.21        |
|                                      | Self-Net [29]         | 20.457 $\pm$ 4.27        | <u>0.734</u> $\pm$ 0.02 | 0.659 $\pm$ 0.02        | <b>0.296</b> $\pm$ 0.04 | 9.376 $\pm$ 0.27         | 74.286 $\pm$ 1.04        | 3.989 $\pm$ 0.16        |
|                                      | SSAI-3D [10]          | <u>20.721</u> $\pm$ 3.94 | 0.686 $\pm$ 0.04        | 0.583 $\pm$ 0.03        | 0.172 $\pm$ 0.04        | <u>7.971</u> $\pm$ 0.58  | <u>61.888</u> $\pm$ 3.71 | <u>4.688</u> $\pm$ 0.29 |
|                                      | <b>MicroFM (Ours)</b> | <b>30.555</b> $\pm$ 3.58 | <b>0.854</b> $\pm$ 0.02 | 0.483 $\pm$ 0.03        | <u>0.266</u> $\pm$ 0.03 | <b>7.569</b> $\pm$ 0.64  | <b>56.453</b> $\pm$ 3.29 | <b>5.099</b> $\pm$ 0.31 |
| Mouse Liver                          | CycleGAN [45]         | 17.092 $\pm$ 0.43        | 0.437 $\pm$ 0.01        | 0.451 $\pm$ 0.02        | 0.055 $\pm$ 0.01        | 8.857 $\pm$ 1.02         | 82.330 $\pm$ 2.42        | 2.505 $\pm$ 0.42        |
|                                      | UTOM [19]             | 21.409 $\pm$ 0.36        | 0.622 $\pm$ 0.02        | 0.379 $\pm$ 0.02        | 0.080 $\pm$ 0.01        | 9.002 $\pm$ 0.86         | 81.544 $\pm$ 7.68        | <b>3.340</b> $\pm$ 0.52 |
|                                      | Neuroclear [31]       | 19.005 $\pm$ 1.36        | 0.714 $\pm$ 0.01        | 0.402 $\pm$ 0.01        | 0.092 $\pm$ 0.01        | <b>7.904</b> $\pm$ 0.28  | <b>80.136</b> $\pm$ 3.48 | 2.489 $\pm$ 0.76        |
|                                      | CycleDiffusion [43]   | 19.684 $\pm$ 0.98        | 0.561 $\pm$ 0.02        | 0.412 $\pm$ 0.03        | 0.071 $\pm$ 0.02        | 8.532 $\pm$ 0.87         | 81.945 $\pm$ 2.13        | 2.713 $\pm$ 0.51        |
|                                      | Self-Net [29]         | 19.136 $\pm$ 0.75        | 0.676 $\pm$ 0.02        | 0.460 $\pm$ 0.03        | 0.196 $\pm$ 0.02        | 9.741 $\pm$ 0.30         | 90.700 $\pm$ 0.75        | 2.979 $\pm$ 0.16        |
|                                      | SSAI-3D [10]          | <u>21.606</u> $\pm$ 1.63 | <u>0.759</u> $\pm$ 0.03 | <u>0.377</u> $\pm$ 0.03 | <u>0.221</u> $\pm$ 0.04 | 8.640 $\pm$ 0.34         | 81.230 $\pm$ 1.64        | 2.424 $\pm$ 0.13        |
|                                      | <b>MicroFM (Ours)</b> | <b>33.005</b> $\pm$ 2.85 | <b>0.946</b> $\pm$ 0.01 | <b>0.193</b> $\pm$ 0.03 | <b>0.498</b> $\pm$ 0.04 | <u>8.107</u> $\pm$ 0.81  | <u>80.141</u> $\pm$ 5.61 | <u>3.091</u> $\pm$ 0.32 |

ples such as *Mouse Kidney* and *Mouse Liver*, where their performance is generally weaker. A typical outcome is that lateral image appears sharper while axial structures become distorted or fluctuate, which makes it difficult to improve lateral images full reference and axial images no reference metrics at the same time. These observations align with the two bottlenecks highlighted in the introduction: axial resolution is substantially poorer than lateral resolution, and current models rely on mismatched degradation which lack an explicit volumetric geometry prior. *MicroFM* addresses these issues through physically consistent PSF pairing, a volumetric geometry prior, and flow matching that starts from the observations, thereby delivering consistent gains on anisotropic kidney and liver tissues and maintaining the same trend on the two brain datasets.

**Qualitative Comparison.** Fig. 3 presents side-by-side restorations with zoomed crops and their Fourier magnitude spectra. *MicroFM* yields crisp capillaries, dendritic shafts,

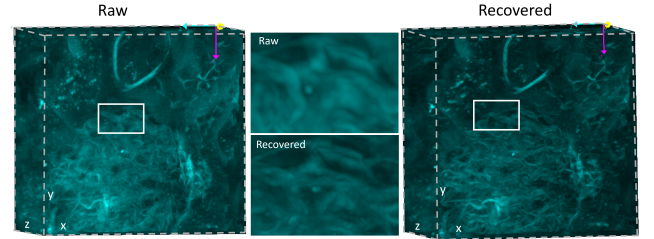


Figure 4. Comparison of cleared mTmG mouse kidney tissue before and after 3D reconstruction.

and collagen fibers with well-defined boundaries. The spectra recover stronger high-frequency content and trend toward an isotropic energy distribution along depth. Competing models often oversmooth or hallucinate fine texture, and residual anisotropy remains evident in their spectra. To more intuitively demonstrate the reconstruction effect of *MicroFM*, Fig. 4 compares the mouse whisker volume before and after reconstruction. The reconstructed volume is clearer, and its structures are more distinctly delineated.

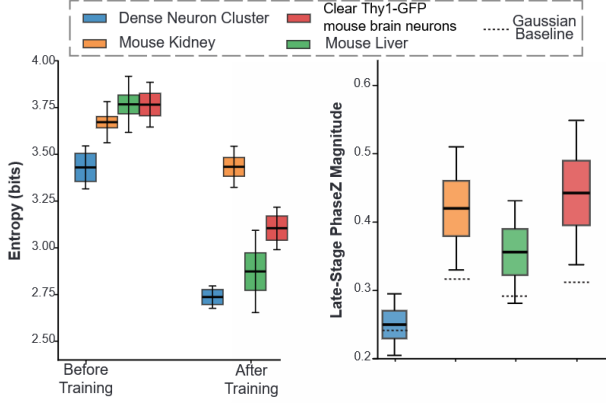


Figure 5. Left: entropy of the PSF bank before and after training. Lower entropy after training indicates greater concentration with limited residual dispersion, which agrees with the bounded spatial variability expected within a single microscope. Right: Late-stage PhaseZ magnitude for four fluorescence microscopy systems, highlighting systematic differences across instruments.

### 4.3. Ablation Studies

**Ablation of Key Components.** Table 3 indicates that each module is indispensable. Replacing instrument-matched physical PSFs with Gaussian kernels decreases PSNR by 22% and lowers SSIM by 13%, indicating that mismatched degradation models substantially limit axial reconstruction quality. Starting the probability flow from the low-resolution image  $x_0$  instead of noise increases PSNR from 32.614 to 40.186 and SSIM from 0.889 to 0.964, suppressing hallucinations and improving fidelity. Removing the volumetric prior reduces PSNR and SSIM, revealing its role in propagating cross-plane geometry and preserving morphology lost in slice-wise processing.

**Impact of Volumetric Prior.** We examine how the strength of the volumetric prior affects reconstruction quality by varying the prior weight  $\beta$ , as shown in Table 4. Performance peaks at  $\beta = 0.50$  with PSNR 40.186, SSIM 0.964, VIF 0.378, and LPIPS 0.075, corresponding to about a 20% increase in PSNR and about a 4% increase in SSIM relative to  $\beta = 0$ . Lower weights from 0.00 to 0.25 provide insufficient volumetric cues and keep PSNR near 33.5. Larger weights from 0.75 to 1.00 impose excessive regularization and reduce fidelity, for example, PSNR 31.758 and SSIM 0.908 at  $\beta = 1.00$ . We adopt  $\beta = 0.50$  for all experiments.

**PSF Analysis.** Fig. 5 summarizes the properties of the predicted PSFs. In the left panel, the Shannon entropy of the predicted PSF bank decreases after training, indicating more concentrated yet still spatially varying PSFs, as expected from microscope physics. In the right panel, the late-stage PhaseZ magnitude distributions show clear differences across microscopy systems. Three datasets, including Mouse Kidney, Mouse Liver, and Clear Thy1-GFP mouse

Table 3. Ablation of MicroFM components on the Dense Neuron Cluster dataset. Best result in each column is shown in **bold**. The base model removes the physical PSFs, the volumetric prior, and the flow that starts from low-quality images, while MicroFM includes all three components.

| Ablation setting                 | PSNR          | SSIM         |
|----------------------------------|---------------|--------------|
| Base model                       | 29.847        | 0.742        |
| w/o flow from low quality images | 32.614        | 0.889        |
| w/o physical PSFs                | 31.392        | 0.836        |
| w/o volumetric prior             | 33.490        | 0.926        |
| <b>MicroFM (Ours)</b>            | <b>40.186</b> | <b>0.964</b> |

Table 4. Ablation of the volume prior weight  $\beta$  on the Dense Neuron Cluster dataset. Best result is shown in **bold**.

| Prior Weight $\beta$ | Full Reference Metrics |                 |                |                    |
|----------------------|------------------------|-----------------|----------------|--------------------|
|                      | PSNR $\uparrow$        | SSIM $\uparrow$ | VIF $\uparrow$ | LPIPS $\downarrow$ |
| 0.00                 | 33.490                 | 0.926           | 0.304          | 0.129              |
| 0.25                 | 33.653                 | 0.939           | 0.372          | 0.086              |
| 0.50                 | <b>40.186</b>          | <b>0.964</b>    | <b>0.378</b>   | <b>0.075</b>       |
| 0.75                 | 34.335                 | 0.941           | 0.337          | 0.117              |
| 1.00                 | 31.758                 | 0.908           | 0.262          | 0.158              |

brain neurons, lie noticeably above the Gaussian reference line, while Dense Neuron Cluster is closer to the Gaussian baseline. This result suggests that real fluorescence microscopes generally deviate from a space-invariant Gaussian blur, although the degree of deviation varies across systems.

## 5. Conclusion

We present MicroFM, a physics guided framework for isotropic microscopy reconstruction. It combines physical point spread function estimation with an implicit volumetric prior and a consistency Flow Matching Reconstruction Network. This design reduces mismatch between synthetic and physical degradation, preserves cross-plane morphology, and suppresses hallucination in axial views. Across four fluorescence microscopy systems, MicroFM consistently improves both full reference and no reference metrics and yields sharper structures and cleaner spectra. Ablations validate the role of physical PSF pairing, the volumetric prior, and an observation anchored start of the probability flow. Future work includes joint learning of PSF and reconstruction, online calibration, and extensions to multichannel and time lapse imaging.

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## References

- [1] Daniel Aquino, Andreas Schönle, Claudia Geisler, Claas V Middendorff, Christian A Wurm, Yosuke Okamura, Thorsten Lang, Stefan W Hell, and Alexander Egner. Two-color nanoscopy of three-dimensional volumes by 4pi detection of stochastically switched fluorophores. *Nature Methods*, 8(4): 353–359, 2011. 1
- [2] Muthuvel Arigovindan, John W Sedat, and David A Agard. Effect of depth dependent spherical aberrations in 3d structured illumination microscopy. *Optics Express*, 20(6):6527–6541, 2012. 3
- [3] Changyou Chen, Chunyuan Li, Liqun Chen, Wenlin Wang, Yunchen Pu, and Lawrence Carin Duke. Continuous-time flows for efficient inference and density estimation. In *International Conference on Machine Learning*, pages 824–833. PMLR, 2018. 2
- [4] Jiji Chen, Hideki Sasaki, Hoyin Lai, Yijun Su, Jiamin Liu, Yicong Wu, Alexander Zhovmer, Christian A Combs, Ivan Rey-Suarez, Hung-Yu Chang, et al. Three-dimensional residual channel attention networks denoise and sharpen fluorescence microscopy image volumes. *Nature Methods*, 18(6):678–687, 2021. 2
- [5] Raghav K Chhetri, Fernando Amat, Yinan Wan, Burkhard Höckendorf, William C Lemon, and Philipp J Keller. Whole-animal functional and developmental imaging with isotropic spatial resolution. *Nature Methods*, 12(12):1171–1178, 2015. 1
- [6] Tomáš Chobola, Gesine Müller, Veit Dausmann, Anton Theileis, Jan Taucher, Jan Huysken, and Tingying Peng. Leveraging classic deconvolution and feature extraction in zero-shot image restoration. In *Proceedings of the IEEE/CVF International Conference on Computer Vision*, pages 3874–3883, 2023. 2
- [7] Chunyu Fang, Tingting Yu, Tingting Chu, Wenyang Feng, Fang Zhao, Xuechun Wang, Yujie Huang, Yusha Li, Peng Wan, Wei Mei, et al. Minutes-timescale 3d isotropic imaging of entire organs at subcellular resolution by content-aware compressed-sensing light-sheet microscopy. *Nature Communications*, 12(1):107, 2021. 1
- [8] Min Guo, Yue Li, Yijun Su, Talley Lambert, Damian Dalle Nogare, Mark W Moyle, Leighton H Duncan, Richard Ikegami, Anthony Santella, Ivan Rey-Suarez, et al. Rapid image deconvolution and multiview fusion for optical microscopy. *Nature biotechnology*, 38(11):1337–1346, 2020. 2
- [9] Xinyi Guo, Fang Zhao, Jingtian Zhu, Dan Zhu, Yuxuan Zhao, and Peng Fei. Rapid 3d isotropic imaging of whole organ with double-ring light-sheet microscopy and self-learning side-lobe elimination. *Biomedical Optics Express*, 14(12): 6206–6221, 2023. 2
- [10] Jiashu Han, Kunzan Liu, Keith B Isaacson, Kristina Monakhova, Linda G Griffith, and Sixian You. System-and sample-agnostic isotropic three-dimensional microscopy by weakly physics-informed, domain-shift-resistant axial deblurring. *Nature Communications*, 16(1):745, 2025. 2, 5, 6, 7
- [11] SB Ippolito, BB Goldberg, and MS Ünlü. Theoretical analysis of numerical aperture increasing lens microscopy. *Journal of Applied Physics*, 97(5), 2005. 3
- [12] Shu Jia, Joshua C Vaughan, and Xiaowei Zhuang. Isotropic three-dimensional super-resolution imaging with a self-bending point spread function. *Nature photonics*, 8(4):302–306, 2014. 1
- [13] Runmin Jiang, Jackson Daggett, Shriya Pingulkar, Yizhou Zhao, Priyanshu Dhingra, Daniel Brown, Qifeng Wu, Xiangrui Zeng, Xingjian Li, and Min Xu. Boe-vit: Boosting orientation estimation with equivariance in self-supervised 3d subtomogram alignment. In *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition*, pages 29352–29362, 2025. 2
- [14] Runmin Jiang, Wanyue Feng, Yuntian Yang, Shriya Pingulkar, Hong Wang, Xi Xiao, Xiaoyu Cao, Genpei Zhang, Xiao Wang, Xiaolong Wu, et al. Towards foundation models for cryo-et subtomogram analysis. *arXiv preprint arXiv:2509.24311*, 2025. 2
- [15] Runmin Jiang, Genpei Zhang, Yuntian Yang, Siqi Wu, Minhao Wu, Wanyue Feng, Yizhou Zhao, Xi Xiao, Xiao Wang, Tianyang Wang, et al. Cryoccd: Conditional cycle-consistent diffusion with biophysical modeling for cryo-em synthesis. *arXiv preprint arXiv:2505.23444*, 2025. 2
- [16] Yuncheng Jin, Yiye Zhang, Lejia Hu, Haiyang Huang, Qiaoqi Xu, Xinpei Zhu, Limeng Huang, Yao Zheng, Hui-Liang Shen, Wei Gong, et al. Machine learning guided rapid focusing with sensor-less aberration corrections. *Optics Express*, 26(23):30162–30171, 2018. 3
- [17] Ivan Kobyzev, Simon JD Prince, and Marcus A Brubaker. Normalizing flows: An introduction and review of current methods. *IEEE transactions on pattern analysis and machine intelligence*, 43(11):3964–3979, 2020. 2
- [18] Uros Krzic, Stefan Gunther, Timothy E Saunders, Sebastian J Streichan, and Lars Hufnagel. Multiview light-sheet microscope for rapid in toto imaging. *Nature Methods*, 9(7): 730–733, 2012. 2
- [19] Xinyang Li, Guoxun Zhang, Hui Qiao, Feng Bao, Yue Deng, Jiamin Wu, Yangfan He, Jingping Yun, Xing Lin, Hao Xie, et al. Unsupervised content-preserving transformation for optical microscopy. *Light: Science & Applications*, 10(1): 44, 2021. 2, 6, 7
- [20] Yue Li, Yijun Su, Min Guo, Xiaofei Han, Jiamin Liu, Harshad D Vishwasrao, Xuesong Li, Ryan Christensen, Titas Sengupta, Mark W Moyle, et al. Incorporating the image formation process into deep learning improves network performance. *Nature Methods*, 19(11):1427–1437, 2022. 2
- [21] Zelin Li, Chenwei Wang, Zhaoke Huang, Yiming Ma, Cumming Zhao, Zhongying Zhao, and Hong Yan. Volume tells: Dual cycle-consistent diffusion for 3d fluorescence microscopy de-noising and super-resolution. In *Proceedings of the Computer Vision and Pattern Recognition Conference*, pages 16091–16100, 2025. 2, 5
- [22] Yaron Lipman, Ricky T. Q. Chen, Heli Ben-Hamu, Maximilian Nickel, and Matt Le. Flow matching for generative modeling. *arXiv:2210.02747*, 2022. 3
- [23] Chang Liu, Binxiang Pan, Baoju Wang, Qi Zhao, Yue Ni, Hui Wu, Zewei Luo, Tongsheng Chen, and Qiuqiang

- Zhan. Sub-60-nm isotropic 3d super-resolution microscopy through self-interference field excitation. *Optica*, 11(9): 1324–1333, 2024. [1](#)
- [24] Leon B Lucy. An iterative technique for the rectification of observed distributions. *Astronomical Journal*, Vol. 79, p. 745 (1974), 79:745, 1974. [2](#)
- [25] Chenxi Ma, Weimin Tan, Ruian He, and Bo Yan. Pre-training a foundation model for generalizable fluorescence microscopy-based image restoration. *Nature Methods*, 21(8):1558–1567, 2024. [2](#)
- [26] Ryan McGorty, Joerg Schnitzbauer, Wei Zhang, and Bo Huang. Correction of depth-dependent aberrations in 3d single-molecule localization and super-resolution microscopy. *Optics letters*, 39(2):275–278, 2014. [3](#)
- [27] Gustavo de Medeiros, Nils Norlin, Stefan Gunther, Marvin Albert, Laura Panavaite, Ulla-Maj Fiuza, Francesca Peri, Takashi Hiiragi, Uros Krzic, and Lars Hufnagel. Confocal multiview light-sheet microscopy. *Nature Communications*, 6(1):8881, 2015. [2](#)
- [28] Christos Messinis, Manashee Adhikary, Tamar Cromwijk, Theodorus TM van Schaijk, Stefan Witte, Johannes F de Boer, and Arie den Boef. Pupil apodization in digital holographic microscopy for reduction of coherent imaging effects. *Optics Continuum*, 1(5):1202–1217, 2022. [3](#)
- [29] Kefu Ning, Bolin Lu, Xiaojun Wang, Xiaoyu Zhang, Shuo Nie, Tao Jiang, Anan Li, Guoqing Fan, Xiaofeng Wang, Qingming Luo, et al. Deep self-learning enables fast, high-fidelity isotropic resolution restoration for volumetric fluorescence microscopy. *Light: Science & Applications*, 12(1): 204, 2023. [1](#), [2](#), [5](#), [6](#), [7](#)
- [30] Mingjie Pan, Yulu Gan, Fangxu Zhou, Jiaming Liu, Ying Zhang, Aimin Wang, Shanghang Zhang, and Dawei Li. Diffuseir: diffusion models for isotropic reconstruction of 3d microscopic images. In *International Conference on Medical Image Computing and Computer-Assisted Intervention*, pages 323–332. Springer, 2023. [2](#)
- [31] Hyoungjun Park, Myeongsu Na, Bumju Kim, Soohyun Park, Ki Hean Kim, Sunghoe Chang, and Jong Chul Ye. Deep learning enables reference-free isotropic super-resolution for volumetric fluorescence microscopy. *Nature Communications*, 13(1):3297, 2022. [2](#), [6](#), [7](#)
- [32] Pawel A Penczek. Resolution measures in molecular electron microscopy. In *Methods in enzymology*, pages 73–100. Elsevier, 2010. [1](#)
- [33] Thomas A Planchon, Liang Gao, Daniel E Milkie, Michael W Davidson, James A Galbraith, Catherine G Galbraith, and Eric Betzig. Rapid three-dimensional isotropic imaging of living cells using bessel beam plane illumination. *Nature Methods*, 8(5):417–423, 2011. [1](#)
- [34] Chang Qiao, Haoyu Chen, Run Wang, Tao Jiang, Yuwang Wang, and Dong Li. Deep learning-based optical aberration estimation enables offline digital adaptive optics and super-resolution imaging. *Photonics Research*, 12(3):474–484, 2024. [2](#), [3](#)
- [35] Dongwei Ren, Kai Zhang, Qilong Wang, Qinghua Hu, and Wangmeng Zuo. Neural blind deconvolution using deep priors. In *Proceedings of the IEEE/CVF Conference on Computer Vision and Pattern Recognition (CVPR)*, pages 3341–3350, 2020. [2](#)
- [36] William Hadley Richardson. Bayesian-based iterative method of image restoration. *Journal of the optical society of America*, 62(1):55–59, 1972. [2](#)
- [37] Vincent Sitzmann, Julien Martel, Alexander Bergman, David Lindell, and Gordon Wetzstein. Implicit neural representations with periodic activation functions. *Advances in neural information processing systems*, 33:7462–7473, 2020. [4](#)
- [38] Sjoerd Stallinga and Bernd Rieger. Accuracy of the gaussian point spread function model in 2d localization microscopy. *Optics Express*, 18(24):24461–24476, 2010. [3](#)
- [39] P Topor, M Zimanyi, and A Mateasik. Increasing axial resolution of 3d data sets using deconvolution algorithms. *Journal of Microscopy*, 243(3):293–302, 2011. [2](#)
- [40] Wes Wallace, Lutz H Schaefer, and Jason R Swedlow. A workingperson’s guide to deconvolution in light microscopy. *Biotechniques*, 31(5):1076–1097, 2001. [2](#)
- [41] Martin Weigert, Loic Royer, Florian Jug, and Gene Myers. Isotropic reconstruction of 3d fluorescence microscopy images using convolutional neural networks. In *International Conference on Medical Image Computing and Computer-Assisted Intervention*, pages 126–134. Springer, 2017. [2](#)
- [42] Martin Weigert, Uwe Schmidt, Tobias Boothe, Andreas Müller, Alexandr Dibrov, Akanksha Jain, Benjamin Wilhelm, Deborah Schmidt, Coleman Broadus, Siân Culley, et al. Content-aware image restoration: pushing the limits of fluorescence microscopy. *Nature Methods*, 15(12):1090–1097, 2018. [2](#), [3](#)
- [43] Chen Henry Wu and Fernando De la Torre. A latent space of stochastic diffusion models for zero-shot image editing and guidance. In *ICCV*, 2023. [6](#), [7](#)
- [44] Ling Yang, Zixiang Zhang, Zhilong Zhang, Xingchao Liu, Minkai Xu, Wentao Zhang, Chenlin Meng, Stefano Ermon, and Bin Cui. Consistency flow matching: Defining straight flows with velocity consistency. *arXiv preprint arXiv:2407.02398*, 2024. [4](#)
- [45] Jun-Yan Zhu, Taesung Park, Phillip Isola, and Alexei A. Efros. Unpaired image-to-image translation using cycle-consistent adversarial networks, 2020. [2](#), [6](#), [7](#)