Fast and accurate aberration estimation from 3D bead images using convolutional neural networks

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Estimating optical aberrations from volumetric intensity images is a key step in sensorless adaptive optics for microscopy. Here we describe a method (PHASENET) for fast and accurate aberration measurement from experimentally acquired 3D bead images using convolutional neural networks. Importantly, we show that networks trained only on synthetically generated data can successfully predict aberrations from experimental images. We demonstrate our approach on two data sets acquired with different microscopy modalities and find that PHASENET yields results better than or comparable to classical methods while being orders of magnitude faster. We furthermore show that the number of focal planes required for satisfactory prediction is related to different symmetry groups of Zernike modes. PHASENET is freely available as open-source software in Python.

1. INTRODUCTION

Image quality in volumetric microscopy of biological samples is often severely limited by optical aberrations due to refractive index inhomogeneities inside the specimen [1, 2]. Adaptive optics (AO) is widely used to correct for these distortions via optical elements like deformable mirrors or spatial light modulators [3, 4]. Successful implementation of AO requires aberration measurement at multiple locations within the imaging volume [5]. This can be achieved by creating point sources such as embedded fluorescent beads [6] or optically induced guide stars [7], and then sensing the wavefront either directly via dedicated hardware (e.g. Shack-Hartman wavefront sensors [8, 9]) or indirectly from the intensity image of the point source (PSF) alone [10, 11]. Due to its special hardware requirements, and its reliance on a point-scanning configuration, direct wavefront sensing can be cumbersome to implement and too slow for volumetric imaging of living samples [12]. In contrast, indirect wavefront sensing - or phase retrieval - offers the possibility to infer the aberration at multiple locations, across the entire volume simultaneously, without additional optical hardware [13, 14]. Establishing a fast and accurate phase retrieval method from intensity images of point sources is therefore an important step for making AO more accessible to live imaging of large biological samples.

Classical approaches to phase retrieval include alternating projection methods such as Gerchberg-Saxton (GS) [11, 15] or parameterized PSF fitting methods such as ZOLA [16]. While projection methods are typically fast but can perform poorly especially for noisy images, PSF fitting methods can achieve excellent results yet are relatively slow. In recent years, convolutional neural networks (CNNs) have proven to be powerful and computationally efficient tools for image-based classification and regression tasks [17–19]. Recently, CNN-based phase retrieval has been shown to achieve promising results on purely synthetic data [20–22]. Whether such an approach can be extended to experimental microscopy data and how it compares to state-of-the-art classical methods, however, still needs to be established.

In this paper we demonstrate that CNNs trained on appropriately generated synthetic data can be successfully applied to real images acquired with different microscopy modalities. Specifically, we generate synthetic 3D bead images with random aberrations via a realistic image formation model that matches the microscope setup, and we use a simple CNN architecture (which we call PHASENET) to directly predict these aberrations from the given volumetric images. We demonstrate our approach on two distinct microscopy modalities: i) a point-scanning microscope where single-mode aberrations were introduced in the illumina-
we avoid the acquisition of experimental training images with precisely known aberrations, which often is difficult or outright impossible. The wavefront aberration \( \phi(x, y) \) is then decomposed as a sum of Zernike polynomials/modes

\[
\phi(x, y) = \sum_i a_i Z_i(x, y)
\]

with \( Z_i(x, y) \) being the \( i \)-th (Noll indexed) Zernike mode and \( a_i \) the corresponding amplitude [23, 24]. The problem of phase retrieval is then to infer these amplitudes \( a_i \) from experimental bead images \( h_{\text{real}} \). The predicted amplitudes \( \tilde{a}_i \) are then used to reconstruct the wavefront.

2. METHODS

Let \( h(x, y, z) \) be the acquired image of a bead (point spread function, PSF) and let \( \phi(x, y) \) be the wavefront aberration, i.e. the phase deviation from an ideal wavefront defined on the back pupil with coordinates \( x_i, y_i \). The wavefront aberration \( \phi \) is then decomposed as a sum of Zernike polynomials/modes

\[
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with \( Z_i(x, y) \) being the \( i \)-th (Noll indexed) Zernike mode and \( a_i \) the corresponding amplitude [23, 24]. The problem of phase retrieval is then to infer these amplitudes \( a_i \) from \( h(x, y, z) \). Our approach (PHASENET) uses a CNN model that takes a 3D image as an input and directly outputs the amplitudes \( a_i \). Importantly, the model is trained on synthetically created data first and only then applied to real microscopy images (cf. Fig. 1). That way, we avoid the acquisition of experimental training images with known aberrations, which often is difficult or outright impossible (e.g. for sensorless setups).

A. Synthetic training data

To generate training data for a specific microscope setup, we synthetically create pairs \( (a_i^o, h_{\text{synth}}^o) \) of randomly sampled amplitudes \( a_i^o \) and corresponding 3D PSFs \( h_{\text{synth}}^o \). We use only the first 11 non-trivial Zernike modes \( a_i^o = (a_{5}^o, \ldots, a_{11}^o) \), excluding \( \text{piston}, \text{tip}, \text{tilt} \) and \( \text{defocus} \), and generate randomly aberrated PSFs by uniformly sampling \( a_i^o \in [-0.075, 0.075] \). Given a wavefront \( \phi^o = \sum_i a_i^o Z_i \), we compute the corresponding intensity image as:

\[
h_{\text{synth}}^o(x, y) = |\mathcal{F}[P(k_x, k_y) \cdot e^{2\pi i \phi^o(k_x, k_y)/\lambda} \cdot e^{-2\pi i \sqrt{k_x^2 + k_y^2}/\lambda}]|^2
\]

where \( \mathcal{F}[\cdot] \) is the Fourier transform, \( \lambda \) is the wavelength, \( n_0 \) is the refractive index of the immersion medium, \( \phi^o = \sum_{i=5}^{11} a_i^o Z_i(k_x, k_y) \) is the wavefront aberration, and \( P(k_x, k_y) \) is the amplitude of the pupil function [25]. Since we do not consider amplitude attenuation, we simply set \( P(k_x, k_y) = 1_{|k_x|+|k_y|<(NA/\lambda)^2} \) with \( NA \) being the numerical aperture of the objective. To accommodate for a finite bead size, we then convolve \( h_{\text{synth}}^o \) with a sphere of appropriate diameter (depending on the experiment) and add realistic Gaussian and Poisson noise.

B. PHASENET

The CNN architecture (PHASENET) is shown in Fig. 1 and consists of five stacked blocks, each comprising two \( 3 \times 3 \times 3 \) convolutional layers and one max-pooling layer, followed by two dense layers with the last having the same number of neurons as the number of Zernike amplitudes to be predicted (11 in our case). This results in a rather compact CNN model with a total of 0.9 million parameters. We use \( \text{tanh} \) as activation function for all layers except the last, where we use linear activation. We simulate 3D PSFs \( h_{\text{synth}}^o \) and the corresponding amplitudes \( a_i^o \) which form the input and output of the network, respectively (cf. Fig. 1). To prevent overfitting, we use a data generator to continuously create random batches of training data pairs during the training process. We minimize the mean squared error (MSE) between predicted and ground truth (GT) amplitudes during the training process. We minimize the mean squared error between predicted and ground truth (GT) amplitudes during the training process. We minimize the mean squared error between predicted and ground truth (GT) amplitudes during the training process. We minimize the mean squared error between predicted and ground truth (GT) amplitudes during the training process.

C. Experimental data

We use two different microscope setups (POINT SCANNING and WIDEFIELD) to demonstrate the applicability of this technique on real microscopy data.

POINT SCANNING This is a point-scanning microscope designed for STED microscopy, equipped with a 1.4 NA oil immersion (\( n_0 = 1.518 \)) objective and a \( \lambda = 755 \text{nm} \) illumination laser (cf. Supp. Fig. S1a and described in [28]). For these experiments, the system was operated without the STED function activated – in effect as a point scanning confocal microscope with open pinhole. Single Zernike mode aberrations for Z5 (oblique astigmatism) to Z15 (oblique quadrafoil) within an amplitude range of \( \pm 0.11 \mu \text{m} \) were introduced in the illumination path via a spatial light modulator (SLM). The backscattering signal of 80nm gold beads was then measured using a photomultiplier tube and the stage axially and laterally shifted resulting in \( n = 198 \) aberrated 3D bead images of size \( 32 \times 32 \times 32 \) with isotropic voxel size 30nm. We generated synthetic training data using the given microscope parameters and random amplitudes \( (a_{5}^o, \ldots, a_{11}^o) \) in the range of \( \pm 0.025 \mu \text{m} \) (cf. Section A). We then trained a PHASENET model as explained in Section B.

WIDEFIELD This is a custom-built epifluorescence microscope with a 1.1 NA water immersion objective and a \( \lambda = 488 \text{nm} \) illumination laser (cf. Supp. Fig. S1b). Mixed Zernike mode aberrations comprising \( Z_5 - Z_{10} \) (lower order) or \( Z_5 - Z_{15} \) (higher order) were introduced in the detection path via a deformable
Fig. 2. Measurement of single Zernike mode aberrations for POINT SCANNING data. a) PHASENET predictions on images with experimentally introduced oblique astigmatism $Z_5$ (see Supp. Fig. S2 for modes $Z_6 - Z_{15}$). Shown are ground truth $a_5$, the predicted amplitude $a_5$ (black dots), perfect prediction (solid black line), and the upper/lower bounds of amplitudes used during training (gray arrow). The inset shows the distribution of predicted non-introduced modes $a_6, \ldots, a_{15}$. b) Same results for experimentally introduced vertical coma $Z_7$. Scalebar 500nm. c) RMSE for PHASENET and compared methods (GS and ZOLA) on all images. Boxes show interquartile range (IQR), lines signify median, and whiskers extend to 1.5 IQR.

mirror (DM). We used an amplitude range of $\pm 0.075 \mu m$ for each mode. The images of 200nm fluorescent beads were recorded at different focal positions, resulting in $n = 100$ aberrated 3D bead images of size $50 \times 50 \times 50$ with a voxel size of $80nm$ laterally and $100nm$ axially. As before, we generated similar synthetic training data using the respective microscope parameters and trained a PHASENET model.

D. Evaluation and comparison with classical methods

We compare PHASENET against two classical iterative methods, GS (Gerchberg-Saxton, code from [11]) and ZOLA [16]. GS is an alternating projection method that directly estimates the wavefront aberration $\phi$. ZOLA fits a realistic PSF model to the given image and returns the present Zernike amplitudes (Supp. Notes A). For both GS and ZOLA, we used 30 iterations per image, ZOLA additionally leveraging GPU-acceleration (NVIDIA Titan Xp). For every method we quantify the prediction error by first reconstructing the wavefront from the predicted Zernike amplitudes (for PHASENET and ZOLA) and then computing the root mean squared error (RMSE, in $\mu m$) of the difference between the predicted and the ground truth wavefront.

3. RESULTS

A. POINT SCANNING

We first investigated the performance of PHASENET on the data from POINT SCANNING microscope with experimentally introduced single-mode aberrations (cf. Fig. 2). This gives us the opportunity to assess the performance of all methods for each Zernike mode and amplitude in isolation. Here, the respective PHASENET model trained on synthetic PSFs achieved good wavefront reconstruction with the predicted and ground truth wavefront having a median RMSE of 0.025$\mu m$ (compared to the RMSE 0.15$\mu m$ of the input wavefronts), thus validating our approach (cf. Supp. Fig. S2). We then applied the model on the experimental images, yielding amplitude predictions ($a_5, \ldots, a_{15}$) for each 3D input. In Fig. 2a) we show the results for $Z_5$ (oblique astigmatism). As can be seen, the predicted amplitude $a_5$ exhibits good agreement with the experimental ground truth, even outside the amplitude range used for training (indicated by the gray arrow). Importantly, the predicted amplitudes for the non-introduced modes ($a_6, \ldots, a_{15}$) were substantially smaller, indicating only minor cross-prediction between modes (cf. inset in Fig. 2a). The same can be observed for vertical coma $Z_7$ (Fig. 2b) and all other modes $Z_6 - Z_{15}$ (cf. Supp. Fig. S3 & Supp. Fig. S4 for reconstructed wavefronts).

We next quantitatively compared the results of PHASENET with predictions obtained with GS and ZOLA. Here, PHASENET achieves a median RMSE between predicted and ground truth wavefronts of 0.028$\mu m$ across all acquired images ($n = 198$), which is comparable to the prediction error on synthetic PSFs. At the same time GS (0.039$\mu m$) and ZOLA (0.031$\mu m$) performed slightly worse (cf. Fig. 2b). This demonstrates that a PHASENET model trained only on synthetic images can indeed generalize to experimental data and achieve better performance than classical methods. Crucially, predictions with PHASENET were obtained orders of magnitude faster than with both GS and ZOLA (cf. Table 1). Whereas it took only $4ms$ for PHASENET to process a single image, it required 0.12s for GS and 17.1s for ZOLA. The speed advantage of PHASENET is even more pronounced when predicting batches of several images simultaneously (cf. Table 1).

| Method     | single ($n = 1$) | batched ($n = 50$) |
|------------|------------------|---------------------|
| GS         | 0.120 s          | 6.2 s               |
| Zola       | 17.1 s           | 838 s               |
| **PHASENET** | **0.004 s**     | **0.033 s**         |

Table 1. Runtime of all methods for aberration estimation from a single ($n = 1$) and multiple ($n = 50$) PSFs of size $32 \times 32 \times 32$.

B. WIDEFIELD

We next explored the applicability of our approach to the WIDEFIELD microscope modality, where mixed-mode aberrations were randomly introduced. The PHASENET model trained on appropriate synthetic data achieved a median RMSE of 0.022$\mu m$ (compared to RMSE 0.15$\mu m$ of the input wavefronts) indicating again good wavefront reconstruction (Supp. Fig. S5). We then applied the trained model on the experimental bead images. In Fig. 3a we show results for PHASENET, GS, and ZOLA for images with introduced modes $Z_5 - Z_{10}$ (lower order). The re-
higher order aberration (5-15)

Although Zₐ yields slightly better RMSE than PHASENET for this dataset, PHASENET again vastly outperforms ZOLA and GS in terms of prediction time by being orders of magnitude faster (cf. Supp. Table S2).

C. Number of input planes

In both experiments so far, the 3D input of PHASENET consisted of many defocus planes (nₓ = 32 for POINT SCANNING and nₓ = 50 for WIDEFIELD). We set out to determine, whether accurate aberration prediction is still possible with substantially fewer planes. We therefore trained several PHASENET models with varying nₓ and applied them to experimental images (cf. Supp. Notes B). In Fig. 4a/b we show predictions with nₓ ∈ {1, 2, 32} for single-mode aberrations Z₅ (oblique astigmatism) and Z₇ (vertical coma). Interestingly, we find that in the case of Z₅ at least nₓ ≥ 2 planes are needed for meaningful predictions, whereas in the case of Z₇ already a single plane (nₓ = 1) yields satisfactory results. This can be explained by observing that for purely Z₅ aberrations (i.e. a₃≠5 = 0), flipping the sign of the aberration amplitude a₅ = −a₅ leads to a 3D PSF that is mirrored along the optical axis. Predicting the amplitude a₅ from a single image plane is therefore inherently ambiguous. To further examine this, we grouped the Zernike modes into the classes even and odd depending on the symmetry of the wavefront (even: Z₁, Z₃, Z₅, . . ., odd: Z₂, Z₄, Z₆, . . .) and calculated the prediction for each class separately. As expected, the RMSE decreases with increasing nₓ (Fig. 4c) for both classes. However, for even Zernike modes the prediction error is significantly higher than for odd modes, especially when using only few planes, in line with our earlier observation.

4. CONCLUSION

We demonstrated how a simple CNN architecture (PHASENET), together with synthetic training data, allows for accurate and efficient aberration estimation from experimental 3D bead images. On datasets from two different microscopy modalities we showed that PHASENET yields better or comparable results than classical methods, while being orders of magnitude faster. This opens up the interesting possibility of using PHASENET to perform aberration estimation from multiple beads or guide stars across an entire volumetric image in a real-time setting on the microscope during acquisition. We further investigated how prediction quality depends on the number of defocus planes nₓ and found that odd Zernike modes are substantially easier to predict than even modes for the same nₓ.

Still, our approach may not be applicable to cases where the
Fig. 4. Results for varying number of input planes \( n_z \): a) Ground truth vs. the predicted amplitude \( a_7 \) (oblique astigmatism) for single mode data POINT SCANNING and using PHASENET models with \( n_z = 1, 2, 32 \). b) The same for \( a_5 \) (vertical coma). c) Prediction error (RMSE) on WIDEFIELD data (50 images) for PHASENET models trained with different \( n_z \). We show the RMSE for odd (orange) and even (blue) Zernike modes separately. Boxes depict interquartile range (IQR), lines signify median, and whiskers extend to 1.5 IQR.

synthetic PSF model is inadequate for the microscope setup or where experimental data is vastly different from the data seen during training (a limitation that applies to most machine learning based methods). Furthermore, our experimental data so far included only Zernike modes \( Z_n \leq 15 \), leaving the question open whether our approach would behave similarly for larger Zernike modes. Additionally, more advanced network architectures that explicitly leverage the physical PSF model might improve prediction accuracy.

We believe that in future our method can serve as an integral computational component of practical adaptive optics systems for microscopy of large biological samples.

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**SUPPLEMENTAL DOCUMENTS**

See Supplement for supporting notes, tables, and figures.

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