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Inverse problems based self-calibrated reconstruction for tomographic diffractive microscopy

Brault D.^a, Momey F.^a, Debailleul M.^b, Verrier N.^b, and Haeberlé O.^b

^aUniversité de Lyon, UJM-Saint-Étienne, CNRS, Institut d'Optique Graduate School, Laboratoire Hubert Curien UMR 5516, F-42023, Saint-Étienne, France

^bInstitut de Recherche en Informatique, Automatique, Automatique et Signal IRIMAS - EA7499, Université de Haute-Alsace (UHA), 61 rue Albert Camus F-68093 Mulhouse Cedex, France

ABSTRACT

In this work we propose an inverse problems based iterative reconstruction method for tomographic diffractive microscopy, involving measurements in off-axis configuration. More precisely, we propose a strategy that aims to eliminate reconstruction errors that can be caused by perturbations in the illumination wave of the reference arm. Our original contribution is to build the inverse problem considering as unknowns both the targeted 3D sample map and the perturbation map, that are jointly reconstructed and unmixed during the iterative process. This self-calibration process is rendered possible by the multiplicity of sample observations from multiple views, where the reference perturbed background remains invariant. We validate the feasibility of our approach on reconstructions from simulated data under different experimental conditions.

Keywords: Holography, tomographic diffractive microscopy, inverse problems, model-based iterative reconstruction, self-calibration, unmixing

1. INTRODUCTION

Tomographic diffractive microscopy (TDM) is a quantitative phase imaging technique, under coherent illumination, allowing to observe unlabelled samples at high resolution (twice the conventional resolution of 2D holography).^{1,2} This technique is implemented based on digital holography setups. When an off-axis configuration is used, measurements consist in sequentially recording a stack of digital images (holograms) of the intensity of the interference between an invariant reference plane wave (reference arm), tilted from the optical axis, and waves diffracted by the sample illuminated by incident plane waves also tilted under several angles (tomographic views on the object arm). The sample is retrieved by a reconstruction process, and take the form of a 3D map of its refractive index embedding morphological, absorbing and refractive properties of the objects of interest in the field of view, at a resolution twice larger than conventional 2D holography. While less resolved, TDM can bring additional information to functional phenomena targeted by fluorescence-based nanoscopy techniques, on a larger field of view and with faster acquisition times. Another important point compared with these previous techniques is that TDM does not require any labeling of the sample.

The most usual reconstruction process is direct, and is based on the Fourier diffraction theorem derived from the first Born approximation.^{3,4} Similarly to structured illumination microscopy (SIM), it performs a synthesis aperture on the object's spectral content: the Fourier transform of each hologram view corresponds to a translated spherical cap in the object's 3D Fourier spectrum, allowing to fill it and then reconstruct the 3D map by Fourier inversion. Based on this principle, alternated projections schemes inspired the the Gerchberg-Saxton method^{5,6}) can be also applied.

From off-axis measurements, such reconstruction methods require a pre-processing step consisting in extracting the complex-valued sample diffracted wave from the 1st order component of the total wave intensity - that is separated from order 0 in the Fourier domain thanks to the modulation produced by the reference wave.

Send correspondence to Fabien Momey

Fabien Momey: E-mail: fabien.momey@univ-st-etienne.fr

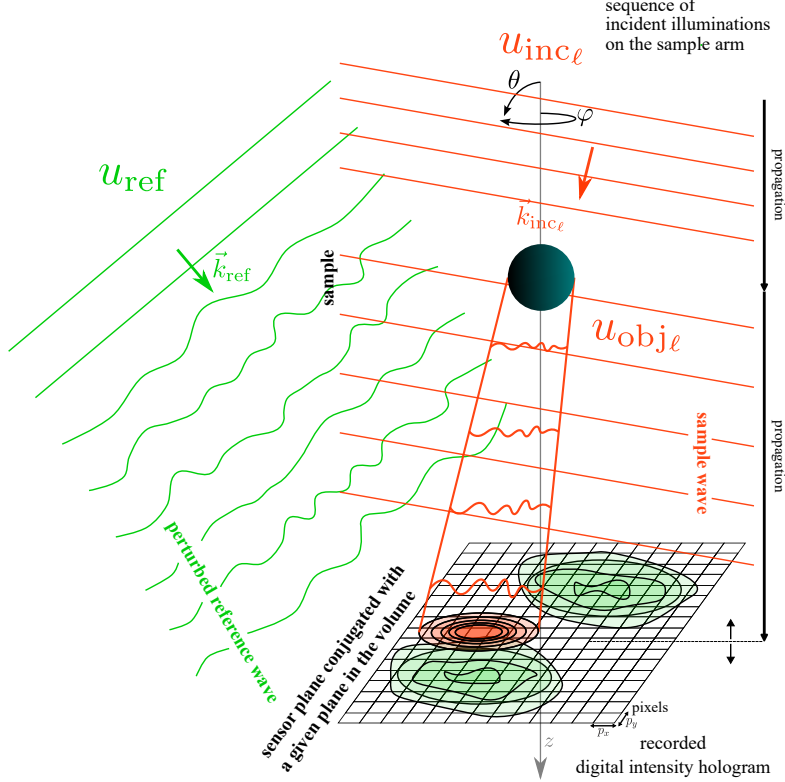


Figure 1. Scheme of TDM principle.

This process makes the hypothesis that the reference wave is "perfect", involving only a strict separation of the orders. Thus, it does not take into account possible perturbations in the illumination path in the reference arm of the setup (optical aberrations, dust, miscalibration, etc.). If so, such perturbations will re-appear in the reconstructed sample map.

In this work, we propose to perform an inverse problems based reconstruction, largely used in the context of digital holography,⁷⁻¹⁰ modeling the whole acquisition process, also including these perturbations as unknowns. We focus on the perturbations involved in the reference arm, that are modeled as a complex transmittance map that will non-uniformly dephase and attenuate the reference wave. This map is supposed to be invariant on each hologram view. This redundancy of information is exploited to jointly estimate the sample map and this perturbation map in the reconstruction process, allowing to unmix them and obtain a clean sample restitution. Thus, our method can be assimilated to a self-calibration, in the methodological sense, of the reference illumination in the reconstruction process.

We validate the feasibility of our approach on reconstructions from simulated data under different experimental conditions.

2. MATERIALS AND METHODS

In this section, we develop the principle of usual TDM reconstruction and identify some errors that can appear due to uncertainties in the reference wave. We then propose how to address it.

In the following, we take directly into account the digitalization process due to the recording of the data, by modeling all the physical quantities (complex wave maps, intensity maps, transmittance plane maps, 3D sample map) as discretized multi-dimensional arrays, which will be written in bold.

2.1 Identification of uncertainties on the reference illumination

Let $\mathbf{d} = (\mathbf{d}_\ell)_{\ell \in \{1, \dots, L\}}$ be the dataset of digital intensity holograms resulting from the interference between the invariant tilted reference wave \mathbf{u}_{ref} , and waves $\mathbf{u}_{\text{obj}_\ell}$ diffracted by the sample illuminated by incident plane waves at the tilted orientations indexed by ℓ :

$$\begin{aligned} \mathbf{d}_\ell &= |\mathbf{u}_{\text{tot}_\ell}|^2 = |\mathbf{u}_{\text{ref}} + \mathbf{u}_{\text{obj}_\ell}|^2 \\ &= \underbrace{|\mathbf{u}_{\text{ref}}|^2 + |\mathbf{u}_{\text{obj}_\ell}|^2}_{\text{order 0}} + \underbrace{\mathbf{u}_{\text{ref}}^* \mathbf{u}_{\text{obj}_\ell}}_{\text{order 1}} + \underbrace{\mathbf{u}_{\text{ref}} \mathbf{u}_{\text{obj}_\ell}^*}_{\text{order -1}} \end{aligned} \quad (1)$$

To separate the different diffraction orders in the Fourier domain, \mathbf{u}_{ref} must be a tilted plane wave. By cropping the 1st diffraction order in each hologram's spectrum, one can get the stack of sample's diffracted waves $\mathbf{u}_{\text{obj}_\ell}$.

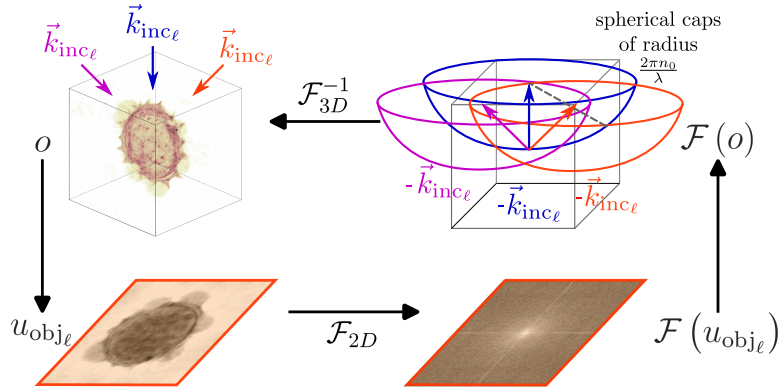


Figure 2. Illustration of direct inversion strategy by applying the Fourier diffraction theorem. \mathcal{F}_{nD} stands for the Fourier transform in nD (2 or 3).

From this pre-processing step, it is then possible to apply the Fourier diffraction theorem by filling the 3D Fourier spectrum of the map \mathbf{o} of the sample to be retrieved, with the 2D Fourier spectrum of each wave $\mathbf{u}_{\text{obj}_\ell}$ (cf. Fig. 2).

However, \mathbf{u}_{ref} may not be perfectly plane and can embed phase and absorption perturbations on its path:

$$\mathbf{u}_{\text{ref}} = \mathbf{u}_{\text{err}} \odot \bar{\mathbf{u}}_{\text{ref}} \quad (2)$$

where $\bar{\mathbf{u}}_{\text{ref}}$ models the perfect reference wave and \mathbf{u}_{err} models a complex perturbation wave, that is referred to as *error map* or *perturbation map* in the following. \odot corresponds to the element-wise product. Thus, this error map is captured in the extracted stack of diffracted waves $\mathbf{u}_{\text{obj}_\ell}$, and is then injected in the reconstructed map \mathbf{o} on the focal plane conjugated with the sensor plane (that often intersects the volume of interest), as illustrated in Fig. 3. When a regularized reconstruction approach is used, these undesirable artefacts can also spread over the volume, dramatically biasing the reconstruction.

2.2 Our solution: jointly reconstruct the sample map and the perturbation map, a self-calibration task

We propose to unmix the perturbation map \mathbf{u}_{err} from the sample map \mathbf{o} , by considering both as unknowns and therefore jointly estimating them during the reconstruction process. To this aim, we have to process the raw data directly, that is to say that we avoid the preliminary step of extracting the stack of diffracted waves $\mathbf{u}_{\text{obj}_\ell}$ from the off-axis measurements. Doing so, we can inject the error map \mathbf{u}_{err} in the end-to-end off-axis hologram formation model for the view ℓ :

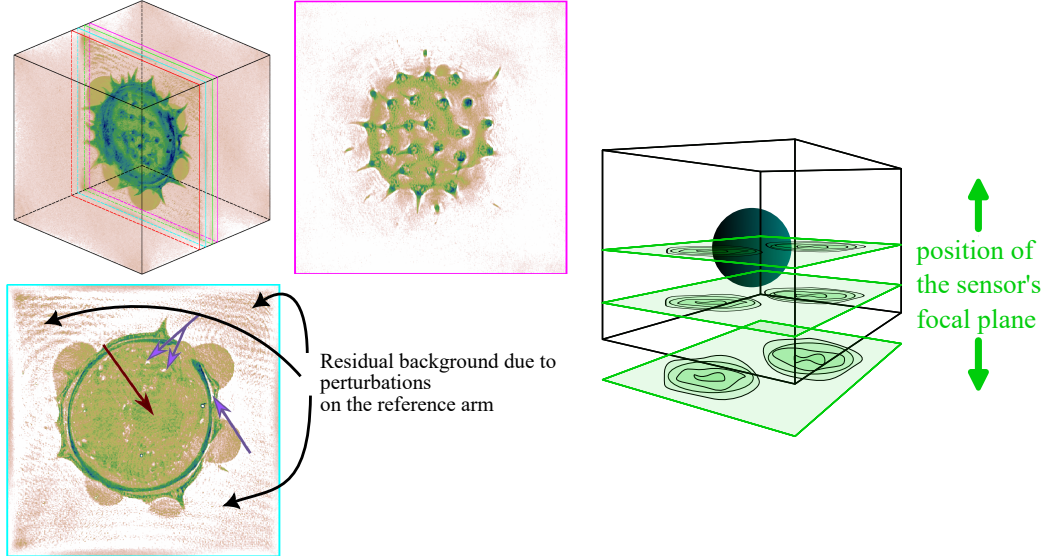


Figure 3. Illustration of the injection of perturbations of the reference wave in TDM reconstruction. Sample: Jerusalem artichoke pollen ($\approx 50\mu m$).

$$\mathcal{M}_\ell(\mathbf{o}, \mathbf{u}_{\text{err}}) = |\mathbf{u}_{\text{err}} \odot \bar{\mathbf{u}}_{\text{ref}} + \mathbf{u}_{\text{obj}_\ell}(\mathbf{o})|^2, \quad (3)$$

depending on the sample map \mathbf{o} and the error map \mathbf{u}_{err} . $\mathbf{u}_{\text{obj}_\ell}(\mathbf{o})$ models the wave diffracted by the sample \mathbf{o} , for which we can consider any propagation model through a volume. In this work, we use the beam propagation method (BPM)¹¹ that takes into account multiple scattering phenomena, and is thus more accurate than the popular Born or Rytov models.

The global TDM reconstruction problem is addressed with an inverse problems based strategy, minimizing the following criterion:

$$\{\mathbf{o}^+, \mathbf{u}_{\text{err}}^+\} = \arg \min_{\{\mathbf{o} \in \Omega, \mathbf{u}_{\text{err}}\}} \sum_\ell \|\alpha \mathcal{M}_\ell(\mathbf{o}, \mathbf{u}_{\text{err}}) - \mathbf{d}_\ell\|_{\mathbf{W}}^2 + \sum_r \mu_r \mathcal{R}_r(\mathbf{o}) \quad (4)$$

composed of a data-fidelity term penalizing, for the current estimates \mathbf{o} and \mathbf{u}_{err} , the deviation between the data \mathbf{d}_ℓ and the hologram formation model \mathcal{M}_ℓ for each view ℓ (we choose here a classical weighted least squares), and a set of regularization terms \mathcal{R}_r (weighted by scalars μ_r that can be tuned automatically¹⁰) and/or bound constraints on a restricted domain Ω , that enforce prior information on the targeted object of interest. In this work, we use an edge-preserving regularizer¹² that favors piecewise smooth solutions. α is a scalar (automatically tuned) for adjusting the intensity level between the model and the data. The minimization of the problem 4 is performed by a convex differentiable algorithm of type L-BFGS under bound constraints, called VMLM-B.¹³

The efficiency of our proposed unmixing approach resides on two points: (i) since \mathbf{u}_{err} is invariant on each view, a natural strong redundancy constraint is set on the map \mathbf{u}_{err} in the data domain, while the contribution of the sample varies from one view to another ; (ii) the flexibility of model-based regularized reconstruction strategies (inverse problems) allows the use of very accurate modeling of data formation, combined with strong prior enforcement that favor features in the sample map \mathbf{o} that exclude the error map \mathbf{u}_{err} from the volume.

3. RESULTS

In this section, we apply our proposed reconstruction method on simulated holograms to demonstrate its efficiency. We reconstruct simulated data in in- and out-of-focus cases to show that the proposed reconstruction algorithm performs well in the out-of-focus case, that is to say when the volume of interest is spatially separated from the focal plane where errors issuing from the perturbed part of the reference wave appear.

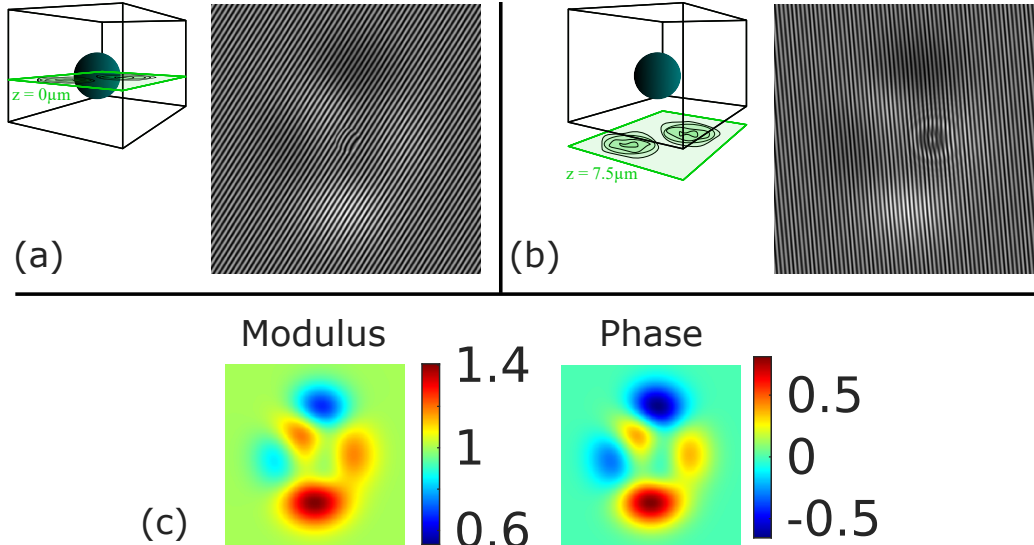


Figure 4. Examples of (a) in-focus and (b) out-of-focus simulated holograms. In green, the plane where the reference and sample waves interfere. (c) Simulated perturbation map on the reference wave.

3.1 Simulation parameters

We have simulated TDM data of a spherical bead for which we have added a low frequency perturbation map on the reference wave (see Fig. 4). Experimental parameters are summarized in Table 1. We have considered a TDM setup with an illumination wavelength of 632.8 nm and varying illumination angles such that $\theta \in [0^\circ, 30^\circ]$ and $\phi \in [0^\circ, 360^\circ]$. 20 holograms of a 4 μm -diameter silica bead ($n = 1.45$) diluted in an immersion oil of refractive index 1.52 have been simulated. Each hologram is a 256×256 image with a pixel pitch of 184.8 nm. An arbitrary low frequency perturbation map has been simulated in the modulus and phase of the reference wave (see Fig. 4(c)). The induced dephasing and absorption are not negligible and can drastically impinge the reconstruction quality as we will show in the results.

Wavelength	632.8nm
Pixel pitch	184.8nm
Total field of view	$47.3 \times 47.3 \mu\text{m}$ (256×256 pixels)
Bead diameter	4 μm
Beads refractive index	1.45 (silica)
Refractive index of immersion medium	1.52

Table 1. Experimental parameters for simulations

Traditionally, TDM consider in-focus sample measurements. As described in Section 2.1, the reference wave \mathbf{u}_{ref} and the diffracted wave $\mathbf{u}_{\text{obj}_\ell}$ at view ℓ interfere at the sensor plane, that is conjugated with a focal plane located in the sample's volume to be reconstructed (see Fig. 3). The perturbation map \mathbf{u}_{err} injected in the reference wave tend to appear on this focal plane in the volume, as it is considered as part of the object of interest, precisely located on this focal plane (the plane of invariance whatever the orientation ℓ), in the reconstruction process. To avoid these reconstruction artefacts, we propose to test the influence of acquiring out-of-focus holograms, such that the angular diversity of the measurements would be enhanced as holograms are shifted from one view to another due to the geometrical projection effect, while the error map remains static. Hence, unmixing the contributions of \mathbf{u}_{ref} and $\mathbf{u}_{\text{obj}_\ell}$ could be facilitated. To demonstrate this hypothesis, we apply our reconstruction approach on both in and out-of-focus simulated data. The out-of-focus data have been simulated with a defocusing distance of $7.5 \mu\text{m}$ such that the reference and sample's wave interfere outside of the reconstruction volume. In both cases we seek to retrieve a $256 \times 256 \times 84$ sample map and a 256×256 complex error map of the reference wave. To compare both reconstruction approaches we consider the same edge-preserving regularization with the same hyperparameter ($\mu_r = 0.1$).

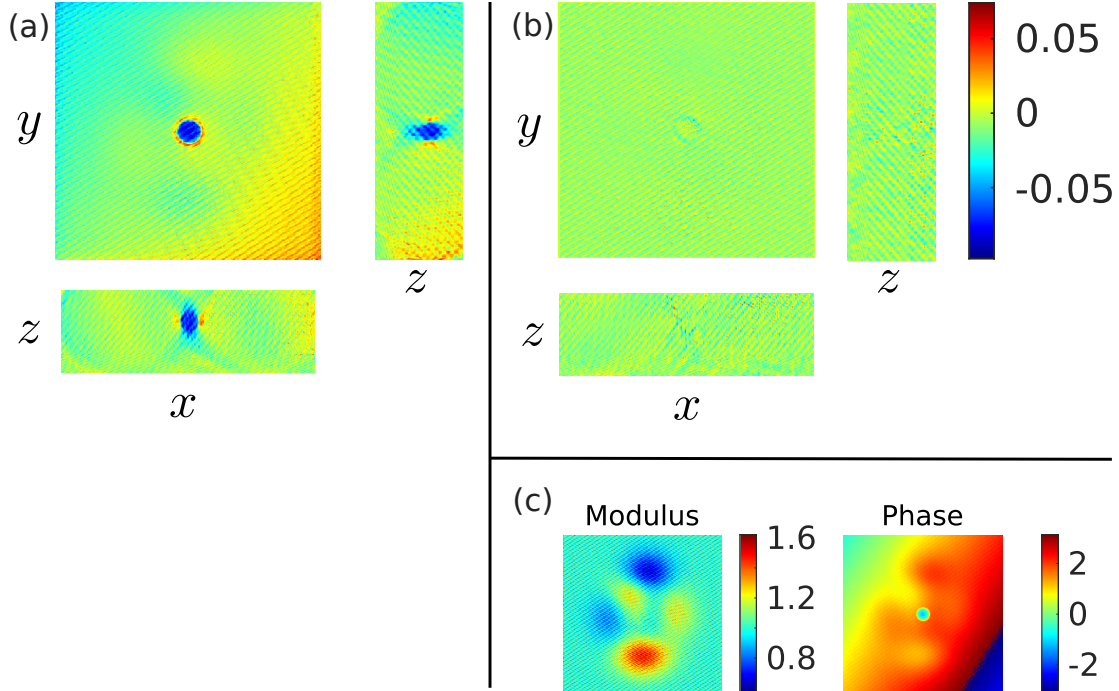


Figure 5. Reconstructed phase volume for in-focus simulated data. (a) Without estimating the perturbation map \mathbf{u}_{err} , (b) With the estimation of \mathbf{u}_{err} provided in (c)

3.2 In-focus hologram reconstructions

In this section, we discuss the reconstruction results from in-focus holograms. In these simulated data, the reference wave \mathbf{u}_{ref} and the diffracted wave $\mathbf{u}_{\text{obj}_\ell}$ at view ℓ interfere on the central axial plane in the reconstructed volume. As can be seen in Fig. 5, the reconstruction Fig. 5(a) without estimating the perturbation map shows artefacts due to errors in the image formation model. Indeed, strong phase ramp artifacts and low frequencies structures issuing from the perturbation map can be seen in the reconstruction, dramatically polluting it. However, in the reconstruction Fig. 5(b) using the proposed approach, the object of interest is not anymore in the reconstructed volume as it is captured by the error map Fig. 5(c). Indeed, as previously explained in Section 3.1, the angular diversity of the measurements is not exploited correctly to unmix both waves: the wave diffracted by the bead is projected on the invariance focal plane (conjugated with the sensor plane), producing a quasi-invariant footprint that can be considered as originating from the reference arm, misleading the solution searched by the reconstruction algorithm.

To overcome this issue, one must consider out-of-focus holograms.

3.3 Out-of-focus hologram reconstructions

In this section, we discuss the reconstruction results from out-of-focus holograms. Fig. 6 shows the phase of the reconstructed volume from the set of out-of-focus holograms. The reconstruction is biased by the perturbation map when they are not taken into account in the image formation model. Indeed, the perturbations are directly reconstructed in the volume and the resulting artefacts spread over the volume. With our approach Fig. 6(b), the sample map has been correctly separated from the perturbation map that is estimated apart. Moreover, the reconstruction of the perturbation map Fig. 6(c) is quantitatively close to the simulated one Fig. 4(c). This result demonstrates our hypothesis that out-of-focus acquisitions make the unmixing strategy successful.

One can notice that an appropriate tuning of the regularization could help limiting the reconstruction error when the unmixing strategy is not plugged, however it is known that overregularization can also be a source of bias. To verify it, reconstructions from out-of-focus data have been performed using multiple regularization weights. Fig. 7 shows the reconstruction results for these different weights. On the reconstruction performed

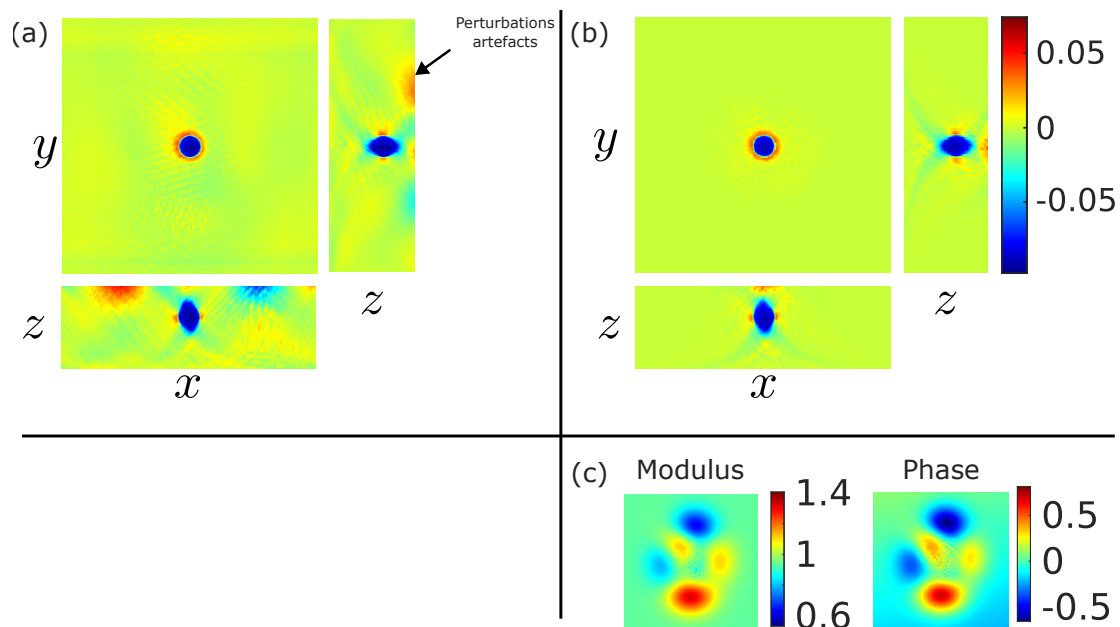


Figure 6. Reconstructed phase volume for out-of-focus simulated data. (a) Without estimating the perturbation map \mathbf{u}_{err} , (b) With the estimation of \mathbf{u}_{err} provided in (c).

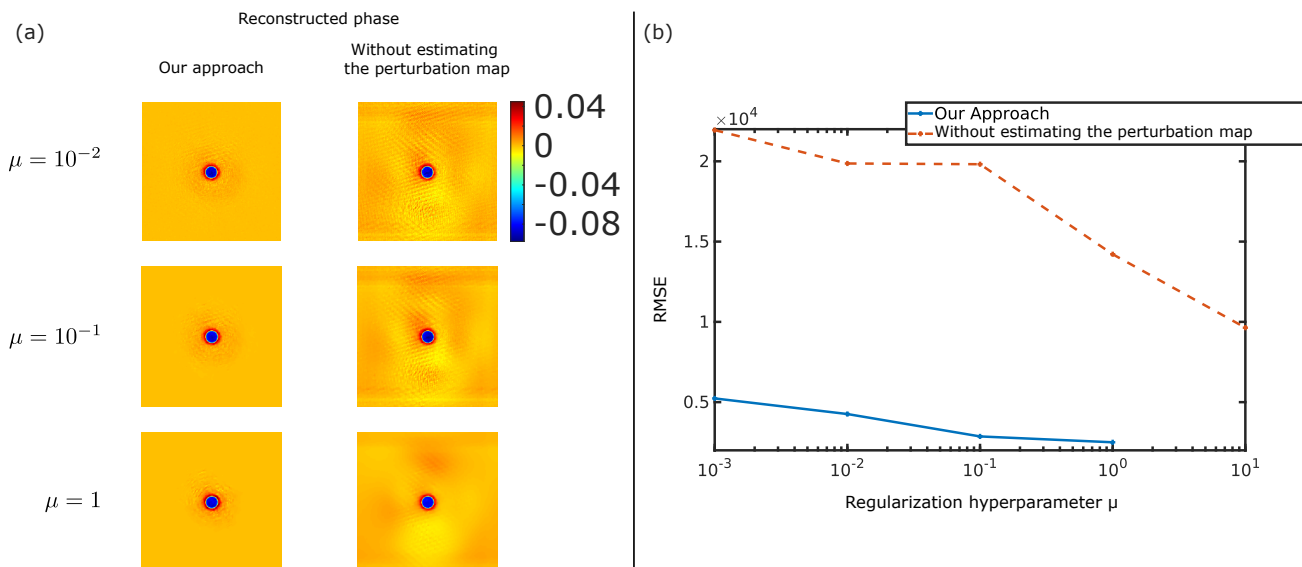


Figure 7. (a) Reconstructions shown at the central axial slice with and without estimating the perturbation map for several regularization weights, (b) RMSE on the reconstructions depending on the regularization weight.

without unmixing, increasing the regularization influence clearly reduces the perturbation artefacts. However, they are still quite visible in the reconstructed volume. With unmixing, the reconstruction still remains free of error map artefacts, and thus the regularization seems to have a finer influence on the object of interest. These results are confirmed with the calculation of root mean square errors (RMSE) between the reconstructions and the ground truth, provided in Fig. 7(b). Whatever the regularization weight, the RMSE on the reconstruction is always lower with our approach. Thus, our unmixing approach improves the reconstruction qualitatively and quantitatively.

4. CONCLUSION AND PERSPECTIVES

We have proposed an optimal strategy to address the issue of reconstruction artefacts due to perturbations of the reference wave in TDM. We have shown that jointly estimating the sample map and the perturbation map of the reference improves qualitatively and quantitatively the reconstructions. However, to efficiently unmix the two contributions, the proposed method requires out-of-focus acquisitions. Indeed, out-of-focus acquisitions reconstruction can fully exploit the angular diversity as the sample's contribution is shifted while the reference contribution remains static. We have demonstrated the relevance of this approach on simulations. Our results are encouraging as they provide more quantitative reconstructions in TDM. More broadly, this work shows that modeling precisely the data formation process and automatically adjust the calibration of the setup, can drastically enhance the reconstruction quality, in particular by allowing regularizations to have a more targeted action. In this context, the flexibility brought by the inverse problems based methodology, in terms of modeling and regularization, is important to make such task successful. Nevertheless, the proposed approach needs to be further explored, in particular by validating it on experimental data, and considering other self-calibration problems involved in a TDM setup (e.g. taking into account perturbations on the sample arm, refining illumination angles on both arms, etc.).

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