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GSURE criterion for unsupervised regularized reconstruction in Tomographic Diffractive Microscopy

L. DENNEULIN^{1,*}, F. MOMEY¹, D. BRAULT¹, M. DEBAILLEUL², A. M. TADDESE², N. VERRIER², AND O. HAEBERLÉ²

¹Laboratoire Hubert Curien UMR CNRS 5516, Université Jean Monnet, F-42000 Saint-Étienne, France

²Institut Recherche en Informatique, Mathématiques, Automatique et Signal (IRIMAS UR UHA 7499), Université de Haute-Alsace, IUT Mulhouse, 61 Rue Albert Camus, 68093 Mulhouse Cedex, France

*Corresponding author: laurence.denneulin@univ-st-etienne.fr

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We propose an unsupervised regularized inversion method for the reconstruction of the 3D refractive index map of a sample in Tomographic Diffractive Microscopy (TDM). It is based on the minimization of the Generalized Stein's Unbiased Risk Estimator (GSURE) to automatically estimate optimal values for the hyperparameters of one or several regularization terms (sparsity, edge-preserving smoothness, Total Variation). We evaluate the performance of our approach on simulated and experimental limited-view data. Our results show that GSURE is an efficient criterion to find suitable regularization weights, that is a critical task, particularly in the context of reducing the amount of required data to allow faster **yet efficient** acquisitions and reconstructions. © 2021 Optical Society of America

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1. INTRODUCTION

Optical microscopy techniques constitute the reference tools for the study of biological phenomena, thanks to their capability of imaging living specimens. Among them, three dimensional (3D) imaging techniques are of great interest because they allow the observed specimens to keep their natural 3D structure and properties. In this context, advanced fluorescence nanoscopy methods (STED [1], PALM/STORM [2–4]) are able to achieve high resolved 3D images above ten times beyond the diffraction limit. However, they require long acquisition times which can be incompatible with live imaging. Moreover, the required labelling of the sample is a complex and invasive technique that can degrade the specimen. In this case, label-free imaging techniques are preferred but must be adapted to observe transparent samples. Optical diffraction tomography (ODT) or Tomographic Diffractive Microscopy (TDM) is an emergent technique, which permits to image transparent specimens in 3D [5], without preparation or staining. TDM brings a morphological information about the observed objects. It is less specific and less resolved than fluorescence-based nanoscopy techniques which focus on precise metabolic targets (kernels, mitochondria, etc.). However,

this information is complementary as it can allow to register anatomical (TDM) and functional (fluorescence) phenomena. Moreover, TDM allows for the imaging of a wider field-of-view at a resolution up to twice larger than the diffraction limit, and possibly at a very fast acquisition range. It is almost similar to Structured Illumination Microscopy (SIM) that also performs a kind of synthesis aperture of the object's spectral content, and can go further than twice the diffraction limit.

TDM is an *interferometric* imaging technique based on digital holographic measurements in tomographic mode, *i.e.* for multiple illuminations and/or sample orientations. Thus, acquisitions are performed by either a specimen rotation or an illumination scanning (one projection orientation per hologram). It gives access, by image reconstruction, to the 3D refractive index (RI) map of a specimen.

Several reconstruction methods from TDM measurements have been proposed in the last decades. The first Born or Rytov approximation allows for a direct 3D mapping of the object in the Fourier space, combining each view's 2D Fourier spectrum. Thus, an isotropic exploration of the object, for example by combination of illumination orientations and sample rotations, leads to a fully-3D mapping of the object's spectrum and allows to reach an isotropic resolution in the 100nm range [6, 7]. However, this reconstruction quality requires a huge number of holograms with almost isotropic exploration. Moreover, the Born or Rytov inversion is limited to weakly scattering samples. To overcome limitations involved in classical inversion, one has to turn to more sophisticated approaches. The Gerchberg-Papoulis algorithm [8] proposes an iterative framework based on the alternating projections principle - similar to the so-called Fienup Error Reduction algorithm in 2D digital holography [9] - with the imposition of a positivity (or negativity) constraint on the RI difference map. This algorithm is a representative of what we call inverse problems approaches [8, 10, 11]. These last are mostly based on the minimization of a global penalty criterion constructed as a combination of two components: a so-called data-fidelity term measuring the error between the data and an image formation model, and one or several priors taking the form of regularization terms or bound constraints. Inverse approaches are more flexible because they allow for the use of more accurate models, *e.g.* multiple-scattering based approaches

[12–15]. Thanks to this gain of accuracy, the data information is better exploited. Therefore, the useful amount of measurements can be drastically reduced if an appropriate trade-off is found between the relative influences given on both the data-fidelity and the *a priori* information on the targeted object. This trade-off is most of the time achieved by weighting properly the regularization penalty terms in the global criterion. These scalar weights are called hyperparameters, and their tuning is critical to ensure the consistency of the inverse problem and thus its solution.

The optimal hand tuning of the hyperparameters is a too fastidious task, so finding unsupervised tuning approaches is of great interest in image reconstruction. If the ground truth was known, the optimal hyperparameters' values would be those that minimize an error between the reconstruction and the ground truth (e.g. the estimation Mean Square Error). Obviously in practice, such a ground truth being unknown, unsupervised tuning approaches consist in using a "blind" criterion to find optimal values for the hyperparameters. Popular methods in this context are the generalized cross-validation (GCV:[16]), the *L*-curve [17], hierarchical Bayesian strategies [18] and the Generalized Stein unbiased Risk Estimator (GSURE: [19, 20]). Lately, some hyperparameters-free methods have exploited neural networks for learning appropriate regularizers [21, 22].

In this work, we discuss the performance of GSURE for the unsupervised tuning of the regularization hyperparameters in the context of TDM reconstruction. The application of GSURE in such a context constitutes the main contribution of this work. Our paper is organized as follows. In Section 2 we introduce the TDM principle with some mathematical notations, and present the forward model used in our experiments. In Section 3, we present a regularized inverse approach for TDM reconstruction that involves popular regularization terms (sparsity, edge-preserving, Total Variation), which we "plug" in a minimization procedure of the GSURE criterion to estimate optimal regularization hyperparameters. Finally, in Section 4, we evaluate the performance of our unsupervised reconstruction approach using GSURE, on both simulated and real data. Our datasets consist in realistic simulations of TDM acquisitions of a single transparent bead (5 and 10 μm diameter), using a Lorenz-Mie scattering model [23], and experimental TDM acquisitions of a Jerusalem artichoke pollen grain ($\sim 30 \mu\text{m}$ diameter). We perform the reconstructions from very limited TDM views to show how the optimal trade-off between the data-fidelity and the regularization is helpful in this context. Our results tend to demonstrate this claim.

2. TDM DATA ACQUISITION PRINCIPLE AND FORWARD MODEL

A. Object and data models

We consider a single object (e.g. a bead as in Fig. 1), or a distribution of objects, immersed in a medium of RI n_0 . In the following, the object in the medium is sampled and considered as the three dimensional (3D) array $\mathbf{n} \in \mathbb{C}^K$, where K is the total number of voxels. Each voxel value \mathbf{n}_k , for $k \in \{1, \dots, K\}$, is the complex RI difference of the object with the medium in this voxel. Hence each \mathbf{n}_k can be decomposed into two components $\Re(\mathbf{n}_k)$ and $\Im(\mathbf{n}_k)$, defining its respective real and imaginary parts such that $\mathbf{n}_k = \Re(\mathbf{n}_k) + j\Im(\mathbf{n}_k)$. Moreover, $\mathbf{n}_k = 0$ means that the voxel $k \in \{1, \dots, K\}$ contains only the medium.

A TDM dataset consists in the recording, on a digital sensor of M pixels, of L complex holograms obtained by the diffraction and

propagation into the sample of L respective coherent illumination plane waves $\underline{u}_\ell^{(inc)}$ that are tilted with respect to the sensor plane (see Fig. 1). We denote $\mathbf{d}_\ell^* \in \mathbb{C}^M$ the ℓ^{th} sampled complex hologram corresponding to a unique tilted view of parameter ϕ_ℓ .

The model of the respective noisy data acquired by the camera is given as:

$$\mathbf{d}_\ell = \mathbf{d}_\ell^* + \boldsymbol{\eta}_\ell \quad (1)$$

where $\boldsymbol{\eta}_\ell$ corresponds to a vector of M noise values.

B. The hologram formation model

In practice, the true complex holograms $\mathbf{d}_\ell^* \in \mathbb{C}^M$ are unknown. Several methods exist [14] to calculate an approximation of these projections as the first Born or Rytov approximation [5, 24–26], the beam propagation method (BPM) and similar strategies such the wave propagation method (WPM) [10, 27], the Lippmann-Schwinger model [28], etc. We denote by $u_\ell(\mathbf{n})$ the hologram formation model. In this work, we focus on BPM that performs a cascading propagation of the diffracted wave through the sample - from the "top" to the "bottom" - decomposed in several slices, each one interacting successively with the upper wave (multiplication of the wave with the transmittance slice). This model is adapted to simulate multiple scattering (in the propagation direction) into a dense volume. However, the unsupervised method proposed in this paper can be applied using another hologram formation model. The forward-model, approximating the true data formation process, is thus the following:

$$\mathbf{d}_\ell \approx u_\ell(\mathbf{n}) + \boldsymbol{\eta}_\ell \quad (2)$$

Note that this model is now an approximation of the true data formation process in Eq. (1) because of the additional modeling errors.

3. PROPOSED METHOD

A. Regularized inverse approach

We aim at retrieving $\mathbf{n} \in \mathbb{C}^K$ from the complex dataset $(\mathbf{d}_\ell)_{\ell \in \{1, \dots, L\}}$. The classical inverse approach is to find \mathbf{n} mini-

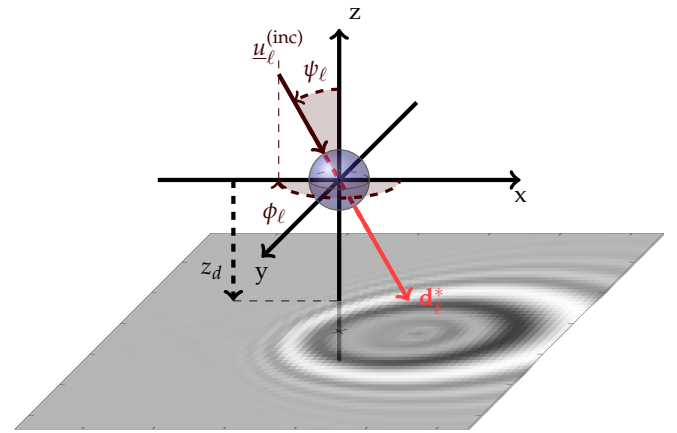


Fig. 1. Scheme of the TDM principle for the ℓ -th hologram acquisition \mathbf{d}_ℓ^* of a sample (here a bead). The hologram is acquired for an orientation of illumination wave $\underline{u}_\ell^{(inc)}$, parametrized by the angles ψ_ℓ in the (z, x) plane and ϕ_ℓ in the (x, y) plane, at a distance z_d from the center of the object.

159 mizing the following cost function:

$$160 \quad f(\mathbf{n}) = \sum_{\ell=1}^L \frac{1}{2} \left\| \mathbf{d}_\ell - u_\ell(\mathbf{n}) \right\|_{\mathbb{C}}^2. \quad (3)$$

161 It is equivalent to the co-log-likelihood minimization under the
162 assumption that $\forall \ell \in \{1, \dots, L\}$, $\mathbf{d}_\ell \sim \mathcal{N}(u_\ell(\mathbf{n}), \sigma^2 \mathbf{Id}_M)$ (i.e.
163 the additive noise $\boldsymbol{\eta}_\ell$ follows a centered multidimensional Gaus-
164 sian distribution of diagonal covariance $\sigma^2 \mathbf{Id}_M$). However, the
165 minimization of the problem Eq. 3 alone can lead to strong arti-
166 facts in the reconstruction if the problem is ill-posed: a good
167 conditionment of the problem is critical to control and alleviate
168 modeling errors and noise amplification in the reconstruction
169 process.

170 To palliate this issue, a prior term g^ρ is added to the problem
171 Eq. 3, that can be a composition of one or several regularizers,
172 and parametrized by a set of hyperparameters ρ . This set is
173 composed of at least one hyperparameter per regularization
174 term to weight their contribution. The reconstruction problem
of the 3D RI map \mathbf{n} becomes:

$$175 \quad \hat{\mathbf{n}} \in \arg \min_{\mathbf{n} \in \Omega} \left\{ f(\mathbf{n}) + g^\rho(\mathbf{n}) \right\} \quad (4)$$

176 where $\Omega \subset \mathbb{C}^K$ is a set of separable bound constraints applied
on the real and imaginary part of each element of \mathbf{n} .

177 In this work we compare two regularizations: $g^{\text{EP}+\ell_1}$ that is
178 the combination of an Edge Preserving smoothing prior [29] and
179 the ℓ_1 -norm sparsity constraint (EP + ℓ_1) applied separately on
180 the real part $\Re(\mathbf{n})$ and imaginary part $\Im(\mathbf{n})$ of \mathbf{n} , and g^{TV} the
181 Total Variation (TV) [30]. On one hand, the EP+ ℓ_1 regularization,
182 given by:

$$183 \quad g^{\text{EP}+\ell_1}(\mathbf{n}) = \lambda^{\text{EP}} \sum_{n=1}^N \left(\sqrt{\|\mathbf{D}_n \mathbf{n}\|^2 + \mu^2} - \mu \right) \\ 184 \quad + \lambda^{\ell_1} \sum_{n=1}^N (|\Re(\mathbf{n}_n)| + |\Im(\mathbf{n}_n)|) \quad (5)$$

185 has the advantage of being differential (thanks to the relaxing
186 parameter $\mu > 0$) when all the voxels of \mathbf{n} are constrained to
187 have the same sign. \mathbf{D}_n is a finite difference operator at each
188 voxel n , giving a vector of six components: three gradient com-
189 ponents for both the real part $\Re(\mathbf{n})$ and imaginary part $\Im(\mathbf{n})$
190 of \mathbf{n} . Thus the squared norm $\|\mathbf{D}_n \mathbf{n}\|^2$ applied to this gradient
191 vector is the sum of its six squared components. When μ tends to
zero, the Edge Preserving Smoothing tends to TV. The ℓ_1 sparsity
prior applied on \mathbf{n} is there to ensure zero values outside of the
object, thus it acts as a support constraint. In such a case of regu-
larization, the set of hyperparameters is $\rho = (\lambda^{\text{EP}}, \mu, \lambda^{\ell_1})$. The
whole criterion in Eq. 4 is differentiable (smooth), so we achieve
the minimization using the VMLM-B algorithm [31], which is a
limited memory quasi-newton method with line search.

192 On the other hand, the Total Variation, given by:

$$193 \quad g^{\text{TV}}(\mathbf{n}) = \lambda^{\text{TV}} \sum_{n=1}^N \sqrt{\|\mathbf{D}_n \mathbf{n}\|^2}. \quad (6)$$

194 requires only one hyperparameter, thus $\rho = \lambda^{\text{TV}}$. This regular-
195 ization is not differentiable and the criterion in Eq. 4 is then a
196 sum of a smooth (f) and a non-smooth (g^{TV}) terms. This leads
197 to the use of proximal algorithms for the minimization of the
cost function. In this work, we use the primal-dual Condat-Vũ
algorithm with backtracking [32–34].

198 B. GSURE for unsupervised reconstruction

199 An appropriate tuning of the regularization hyperparameters
200 is essential to achieve a good reconstruction of the object. An
201 under-regularized reconstruction will lead to a wrong estimation
202 of the 3D map \mathbf{n} . For example, the "missing cone" effect, a
203 classical problem in TDM due to the limited angular coverage,
204 will be exhibited by the defective closure of the object in the axial
205 (z) direction. On the contrary, an over-regularized reconstruction
206 can yield over-smoothing, i.e. a loss of details. The tuning of
207 the hyperparameters can be achieved by finding the set ρ for
208 which the reconstruction optimizes a given quality criterion, for
209 example: the estimation Mean Square Error (MSE), the absolute
210 error, or the prediction Mean Square Error (pMSE). These three
211 quality criteria require the knowledge of the ground truth,
212 unknown in practice, but the pMSE can be estimated using
213 the Generalized Stein's Unbiased Risk Estimator [19, 20] which
214 requires only the knowledge of the data \mathbf{d}_ℓ .

215 We denote $\hat{\mathbf{n}}_\rho$ the reconstruction obtained for a given set of
216 hyperparameters ρ . The pMSE is defined as follows:

$$217 \quad \text{pMSE}(\hat{\mathbf{n}}_\rho) = \sum_{\ell=1}^L \mathbb{E} \left[\left\| \mathbf{d}_\ell^* - u_\ell(\hat{\mathbf{n}}_\rho) \right\|_{\mathbb{C}}^2 \right]. \quad (7)$$

218 where \mathbb{E} stands for the expectation. Note that the use of such a
219 criterion to find ρ for which the reconstructions is minimizing
220 the pMSE requires an accurate image formation model. In fact,
221 this criterion only "sees" the data and the modeling approxima-
222 tions. If it is not accurate enough, the pMSE minimization will
223 lead to a reconstruction minimizing these modeling errors at the
224 expense of its accordance to the ground truth object.

The GSURE criterion is given by:

$$225 \quad \text{GSURE}(\hat{\mathbf{n}}_\rho) = \sum_{\ell=1}^L \left[\frac{1}{2\sigma^2} \left\| \mathbf{d}_\ell - u_\ell(\hat{\mathbf{n}}_\rho) \right\|_{\mathbb{C}}^2 + 2\text{tr} \left(\frac{\partial u_\ell(\hat{\mathbf{n}}_\rho)}{\partial \mathbf{d}_\ell} \right) - M \right]. \quad (8)$$

226 where σ^2 is the variance of the noise in the data, tr stands for
227 the trace (sum of the diagonal elements) of a matrix, and M the
228 number of pixel in each hologram. Since GSURE is an estimator
of the pMSE, then

$$229 \quad \mathbb{E}[\text{GSURE}(\hat{\mathbf{n}}_\rho)] = \text{pMSE}(\hat{\mathbf{n}}_\rho) \quad (9)$$

and both criterion, as a function of ρ , achieve their minimum for
the same argument. Hence, we can find the optimal hyperparam-
eter set $\hat{\rho}$ minimizing the pMSE, by minimizing GSURE.

230 The trace term $\text{tr}(\partial u_\ell(\hat{\mathbf{n}}_\rho) / \partial \mathbf{d}_\ell)$ is equal to $\text{div} u_\ell(\hat{\mathbf{n}}_\rho)$ and is
231 obtained with the Monte-Carlo method presented in [35]. Its
232 principle is to generate a perturbed dataset \mathbf{d}_ℓ^δ by adding a ran-
233 dom deviation on the data $(\mathbf{d}_\ell)_{\ell \in \{1, \dots, L\}}$, with a centered Gaus-
234 sian noise of standard deviation ε . Then a reconstruction from
235 \mathbf{d}_ℓ^δ is performed to obtain a map $\hat{\mathbf{n}}_\rho^\delta$. From this reconstruction,
236 the computation of the trace is performed from the following
237 formula:

$$238 \quad \text{tr} \left(\frac{\partial u_\ell(\hat{\mathbf{n}}_\rho)}{\partial \mathbf{d}_\ell} \right) = \frac{\langle \mathbf{d}_\ell^\delta - \mathbf{d}_\ell, u_\ell(\hat{\mathbf{n}}_\rho^\delta) - u_\ell(\hat{\mathbf{n}}_\rho) \rangle}{\varepsilon^2}. \quad (10)$$

239 A good choice of ε is critical to ensure GSURE is a good estimate
of the pMSE. If chosen too small or too large, the trace will be
underestimated or overestimated, leading to a wrong GSURE
criterion. In this work we compute ε as the tenth of the median
of the real part of the data, which gives a good GSURE criterion
in practice.

246 To achieve the minimization of GSURE, the most intuitive
 247 method is to create a mapping of different hyperparameters
 248 set ρ , to proceed to the reconstruction on both datasets and
 249 perturbed datasets to compute GSURE for each ρ , and finally
 250 find on the mapping the set $\hat{\rho}$ that gives the minimum of the
 251 obtained discretized GSURE map. However, such a method can
 252 become computationally intractable when the set ρ is composed
 253 with two or more hyperparameters. Hence, an optimization of
 254 the GSURE criterion is performed using a Powell method [36],
 255 which does not require the computation of the gradient for the
 256 search of the minimum.

257 4. RESULTS

258 In this section, we observe and discuss the performance of our
 259 GSURE based unsupervised method on reconstructions from
 260 simulated and experimental data.

261 First, we consider simulated TDM measurements of a perfect
 262 sphere of diameter Δ , using the realistic Lorenz-Mie scattering
 263 model [23], that simulates the diffracted field from this kind
 264 of object almost perfectly. For the reconstruction, we choose
 265 the BPM model that fits at best the simulated one and over-
 266 comes the classical Born or Rytov model, particularly when the
 267 size of the object of interest or the RI gradient grows. More-
 268 over, the simplicity of the object of interest (a homogeneous
 269 sphere with sharp edges) corresponds exactly to the chosen
 270 Edge-Preserving and TV regularizers (promoting piecewise
 271 constant images) as its characteristics validate precisely such prior
 272 assumptions. Hence, our choices lead to a really good toy model
 273 and an "inverse crime"-less reconstruction, allowing the valida-
 274 tion of our method. We aim to prove that we can find optimal
 275 values of the hyperparameters in the sense of the prediction
 276 Mean Square Error (pMSE), under such controlled conditions.

277 Second, we consider experimental TDM acquisitions of a
 278 Jerusalem artichoke pollen grain. We aim to validate the conclu-
 279 sion obtained on simulated data.

280 A. Results on a simulated bead

281 We aim at reconstructing independently three non-centered
 282 spherical beads of different diameters Δ (see Table. 1), with
 283 a RI $n_{bead} = 1.45$ and immersed in a medium of RI $n_0 = 1.519$
 284 - mimicking a silica bead in immersion oil. For each bead, our
 285 datasets consist in L on-focus holograms \mathbf{d}_ℓ^* (i.e. $z_d = 0 \mu\text{m}$),
 286 simulated from an implementation of the Lorenz-Mie model [23].
 287 The incident wave orientations are displayed on Fig. 2

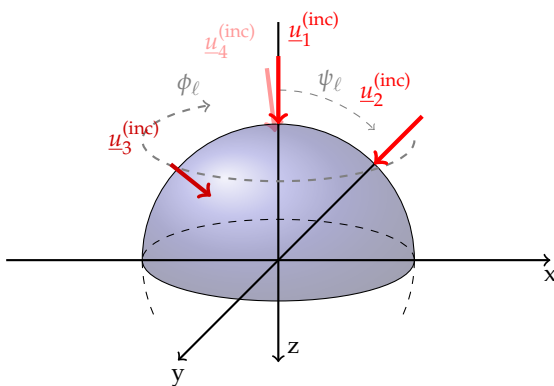


Fig. 2. Scheme of the L projections parametrized by the angles $\psi_\ell \in \{0^\circ, 45^\circ, 45^\circ, 45^\circ\}$ and $\phi_\ell \in \{0^\circ, 0^\circ, 120^\circ, 240^\circ\}$.

288 and the size of the holograms are given in Table. 1. Finally, we
 289 compute the data following Eq. 1, where each element η_k of the
 290 additive noise vector $\boldsymbol{\eta}$ is randomly generated using a stationary
 291 complex normal law $\mathcal{CN}(0, 2\sigma^2)$ with $\sigma^2 = 0.1$. Table. 1 summa-

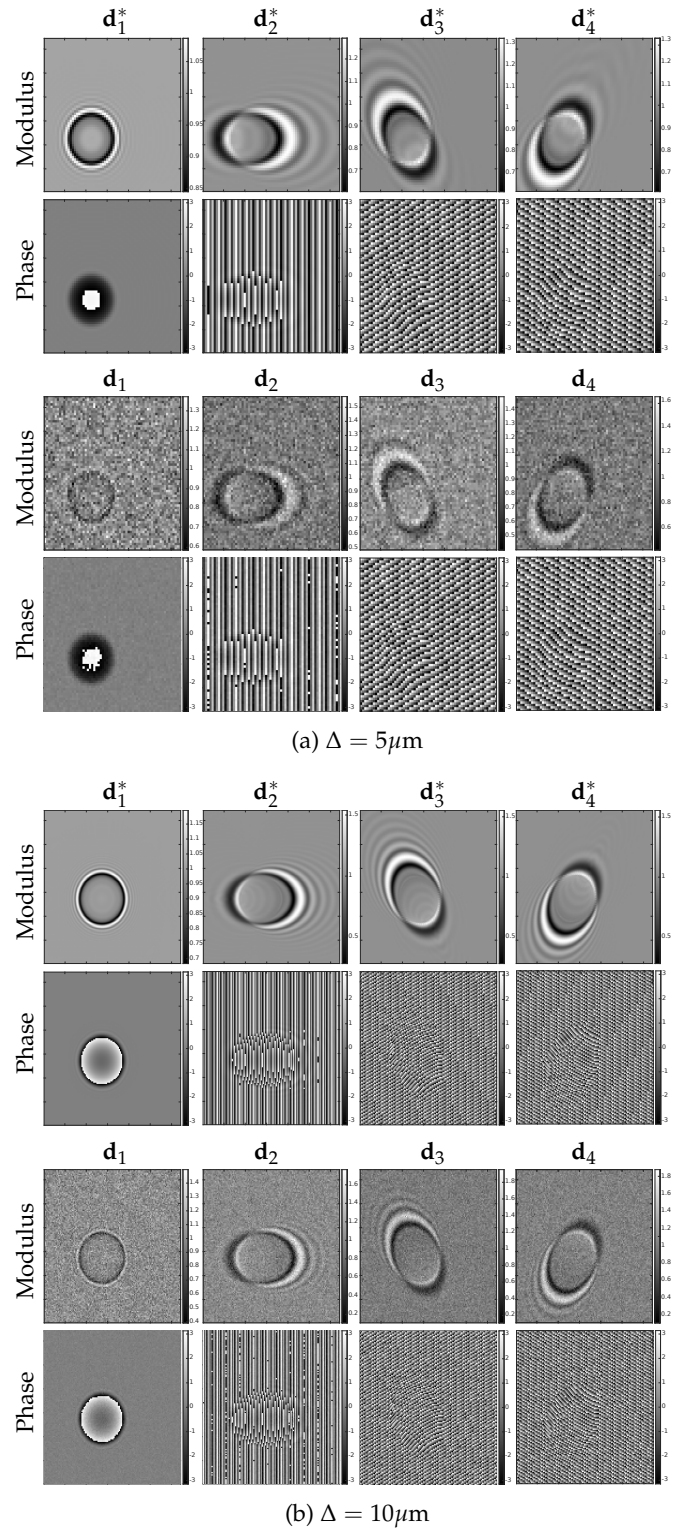


Fig. 3. Moduli and phases of the true holograms \mathbf{d}_ℓ^* and of the related data \mathbf{d}_ℓ , for $\ell \in \{1, \dots, 4\}$, simulated with the Lorenz-Mie model for the parameters summarized in Table. 1.

Table 1. Summary of the beads and data properties, and list of the regularization hyperparameters obtained with the Powell minimization of the GSURE criterion.

case	Δ	$(x_{\text{bead}}, y_{\text{bead}}, z_{\text{bead}})$	ψ_L	L	M	N	$\rho^{\text{EP}+\ell_1}$	ρ^{TV}
(a)	$5\mu\text{m}$	$(-2.3467\mu\text{m}, -2.3467\mu\text{m}, 0\mu)$	45°	4	64×64	$64 \times 64 \times 64$	$(10^{0.38}, 10^{-0.27}, 10^{-0.99})$	$10^{-0.67}$
(b)	$10\mu\text{m}$	$(-2.3467\mu\text{m}, -2.3467\mu\text{m}, 0\mu)$	45°	4	128×128	$128 \times 128 \times 128$	$(10^{1.53}, 10^{0.44}, 10^{-1.4})$	$10^{0.49}$

292 rizes the simulations parameters. The modulus and the phase of
293 the Lorenze-Mie simulations for **all the incidences** are displayed
294 on Fig. 3 along with the modulus and the phase of the data.

295 Since the difference between the Lorenze-Mie model and
296 BPM is growing with the RI difference and with the size, the
297 case (a) in Table 1 is an **intermediate** case and the case (b) is
298 the harder case. We only consider $L = 4$ projections. More
299 projections could make the task **easier** but we make the choice
300 to show configurations where the tuning of regularizations is
301 critical to get the best trade-off with the accordance to the data
302 model.

303 Fig. 4 presents the maps (respectively curves), of pMSE values
304 and GSURE, for the EP+ ℓ_1 regularization (respectively TV). First
305 of all, we can see that the minimal arguments on both criteria,
306 are close. In the case of EP+ ℓ_1 , the μ hyperparameter is fixed to
307 the best hyperparameter obtained with the Powell method. For
308 this regularization GSURE seems to be less sensitive to the ℓ_1

309 norm, which can be problematic since the sparsity constraint is
310 important to have a good support of the object, *i.e.* to have zero
311 values outside of the object.

312 Fig. 5 shows the 3D reconstructions of the bead compared to
313 the ground truth in the different configurations. For each case
314 and each regularization, the bead is well reconstructed. The
315 reconstructions with the EP + ℓ_1 regularization seems noisier
316 than with the TV regularization and the edges of the object are
317 smoother. Such an observation is coherent with the assertion
318 that for EP + ℓ_1 the GSURE criterion is less sensitive to the ℓ_1
319 norm. In fact, since the reconstruction is under-regularized for
320 the sparsity-promoting part, the values outside the support of
321 the object are not sufficiently constrained to zero. Moreover,
322 it leads to a smoothing of the edges along the z-axis. On the
323 opposite, the edges in the reconstructions with TV are sharp,
324 and the medium is uniform and noiseless. The reconstruction
325 with TV is thus satisfying and seems really close to the ground

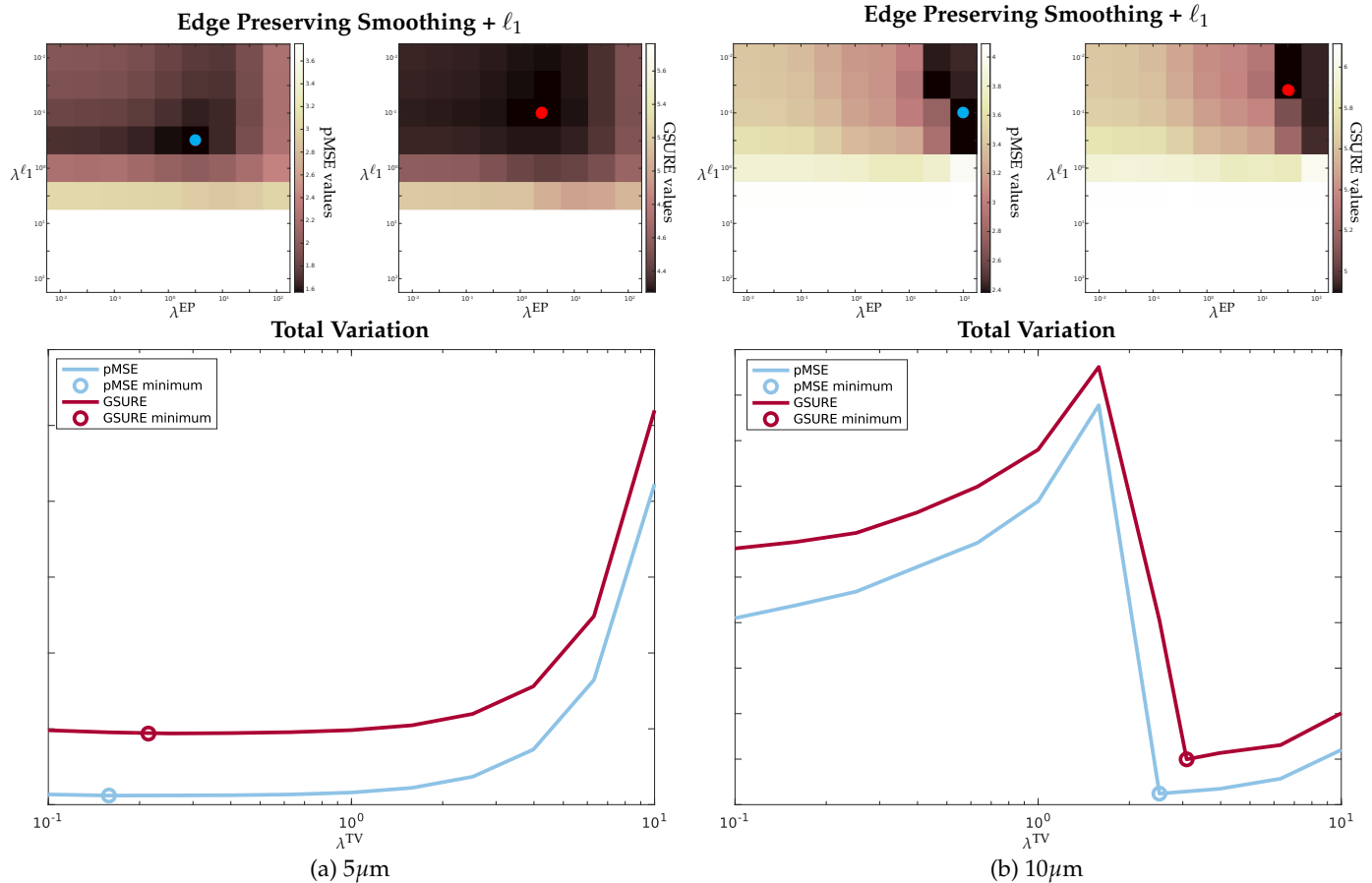


Fig. 4. Maps of pMSE and GSURE values for both regularizations and for each case presented in Table 1. For EP+ ℓ_1 , the values of μ are fixed to those **estimated** (see Table. 1). The minimum of the pMSE (respectively GSURE) values are marked with a blue (respectively red) circle.

326 truths.

327 An overview of under-regularized and over-regularized re-
 328 constructions, **in the case of the TV regularization**, is presented
 329 in Fig. 6. For the under-regularized case, the object is not well
 330 defined. The edges and the inner region are lost. This highlights
 331 the fact that the amount of data, in this simulation configuration
 332 and with such hyperparameters, is not sufficient to reconstruct
 333 the bead correctly, evidencing the need of appropriately tuned
 334 regularizations. For the over-regularized case, the bead is well
 335 defined but some artifacts are appearing.

336 Overall, the GSURE criterion seems to be an effective tool to

337 select automatically a good set of hyperparameters for the recon-
 338 struction as it manages to capture a set of optimal regularization
 339 weights **ensuring a satisfactory solution that fits at best the data**
 340 **model and the prior constraint**.

341 To compare which regularization term, for the best set of
 342 hyperparameters estimated by GSURE, gives the best perfor-
 343 mances, we perform a quantitative study of the RI difference
 344 distribution in the reconstructed bead in Fig. 7. In case (a) and
 345 (b), the median with $EP+\ell_1$ is closer to the true RI than with TV.
 346 However, the interquartile range is smaller with TV than with
 347 $EP+\ell_1$. In the end, with $EP+\ell_1$, since the bead is less compact

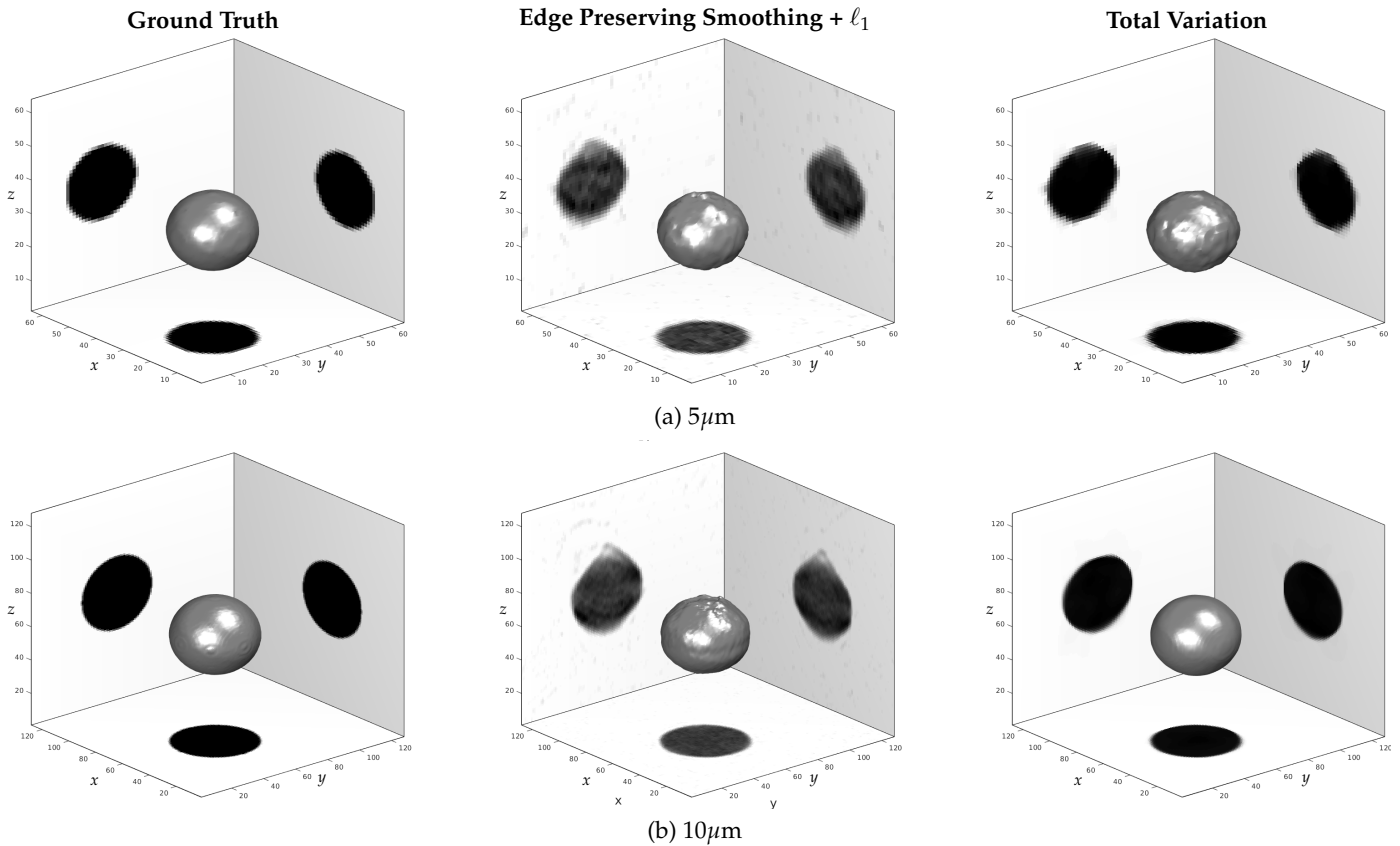


Fig. 5. 3D segmented views of the ground truth and reconstructed beads obtained with optimal regularization weights minimizing GSURE, for both regularization terms $EP + \ell_1$ and TV, and each case presented in Table 1. Side views displays the xy , xz and yz orthogonal slices through the object's center.

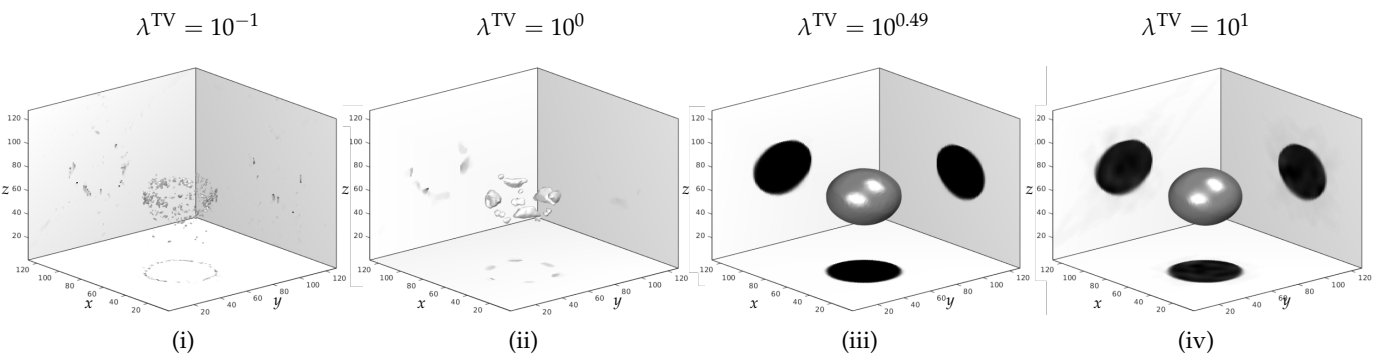


Fig. 6. Reconstructions of the bead (b) with the TV regularization for several choices of hyperparameters and with the optimal parameter obtained with the minimization of the GSURE criterion. Case (i) and (ii) are under-regularized reconstructions, case (iii) is the reconstruction minimizing the GSURE criterion and case (iv) is over-regularized.

348 due to an under-regularization, the precision on the RI difference
 349 is worse than with TV. Yet, with TV, the average RI difference
 350 obtained in the bead is smaller than the ground truth. Note that
 351 a loss of intensity is common with TV.

352 To conclude, in these simulations GSURE is effective to tune
 353 automatically the hyperparameters leading to reconstruction
 354 with a satisfying quality, a difficult task due to the low amount
 355 of data in this context. The reconstruction with TV gives better
 356 results than with $EP+\ell_1$ because GSURE is less sensitive to the
 357 sparsity-promoting constraint. However, it suffers from a bias in
 358 the reconstructed RI difference in the bead. Note that this object
 359 has a piecewise constant gradient, thus the TV regularization is
 360 at ease in this context. With a more detailed object such a prior
 361 can be too strong and lead to the flattening of some structures.
 362 This is why in the following we still apply both regularizers.

363 B. Results on a pollen grain sample

364 We used the GSURE criterion to reconstruct the 3D index map
 365 of a Jerusalem artichoke pollen grain. These data are given

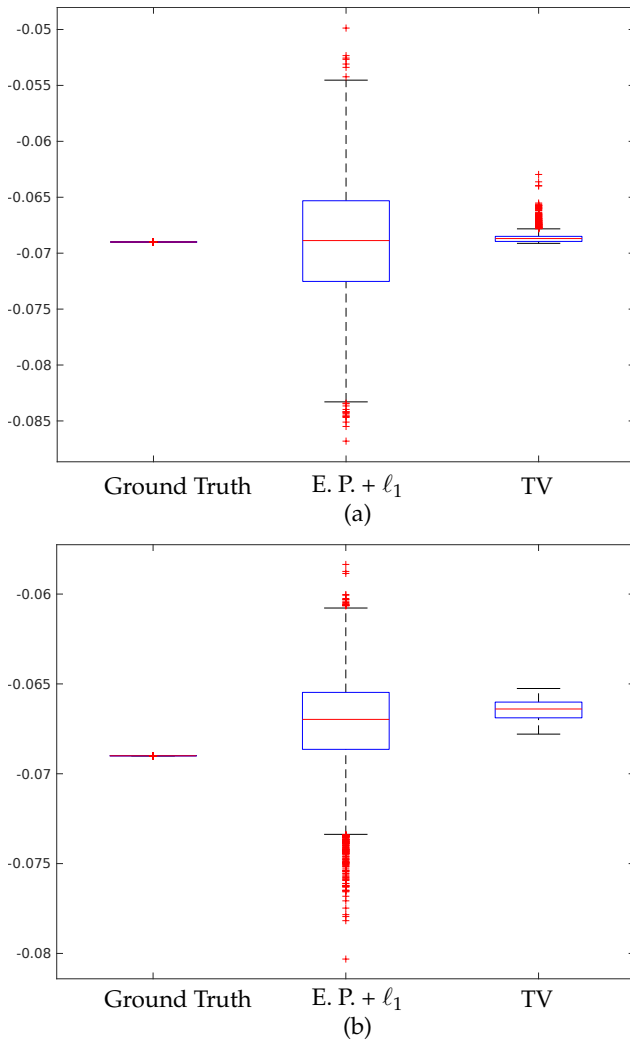


Fig. 7. Distribution of the RI difference value of the reconstructed beads giving the best GSURE for both regularization and each case presented in Table 1. Each blue boxes corresponds to the interquartile range and the red line is the median. The red crosses represent the outliers.

366 with the courtesy of the IRIMAS laboratory, Mulhouse, France.
 367 A detailed description of the TDM setup that performed the
 368 measurements can be found in [7]. It is based on holographic
 369 measurements in off-axis configuration. In our reconstructions,
 370 the considered dataset is the measured complex diffracted waves
 371 on the sensor plane (focal plane of the setup), extracted from the
 372 raw off-axis measurements.

To estimate the noise in the data, we suppose it is an homogeneous Gaussian noise and estimate its variance on a patch containing only background. We proceed to the GSURE optimization for the reconstruction with $EP+\ell_1$ and TV regularizations respectively, using only $L = 20$ projections. These projections are chosen by the following method. First we sort the entire set of 600 projections by their angles ϕ_ℓ and group them in 20 subsets. Thus, we ensure that the 20 subsets are covering the entire circle on which ϕ_ℓ evolves. Then, one projection is randomly chosen in each subset to create the dataset. Since problem Eq. 4 is non-convex due to the BPM approximation, to avoid the convergence to a local minimum [12], we initiate the reconstruction obtained with an unregularized inversion using the first Born approximation [5, 24–26]. We made the hypothesis that the object has no absorption (*i.e.* $\Im m(\mathbf{n}_k) = 0$ for all $k \in \{1, \dots, N\}$) and that the object's absolute RI values are larger than the medium RI value n_0 (the RI difference is greater or equal to 0), leading to the following separable bound constraints set:

$$\Omega = \{\mathbf{n} \in \mathbb{R}^N \mid \forall k \in \{1, \dots, N\}, \mathbf{n}_k \geq 0\}. \quad (11)$$

391 Figure 8 presents different views of the object reconstructed
 392 with a direct inversion using Rytov approximation for $L = 600$
 393 without any constraint or regularization (courtesy from IRIMAS
 394 team), with the Gerchberg-Papoulis (GP [8]) method including
 395 a non-negativity constraint for $L = 600$ and $L = 20$, and
 396 with the presented method for both regularization terms. The
 397 set of hyperparameters obtained for the reconstructions are
 398 $\rho^{EP+\ell_1} = (10^{0.61}, 10^{-3.53}, 10^{0.84})$ and $\rho^{TV} = 10^{-0.26}$.
 399 First, comparing Rytov and GP reconstructions for $L = 600$, we
 400 see that the constraint on the sign of the RI difference improves
 401 clearly the contrast and, as in [8], alleviate the underestimation
 402 of RI values. Thus, the reconstruction with GP seems better, and
 403 this is why we consider it as our “ground truth” for our compar-
 404 isons with $L = 20$.

405 For both reconstructions using our method, the object is well
 406 reconstructed and the contrast is enhanced compared with GP
 407 for $L = 20$. On the TV reconstruction, even if the apparent res-
 408 olution is lower than for the Rytov and GP reconstructions (for
 409 $L = 600$), we can observe the same structured features inside
 410 the object. For example, in Fig. 8: (a)-(c) and (e), we high-
 411 lighted some dense regions with red arrows and kind of porosities
 412 with purple arrows. These features are better reconstructed with
 413 our methods than with GP for $L = 20$. However, the reconstruc-
 414 tion with $EP+\ell_1$ is a little smoother than the reconstruction
 415 with TV, leading to the loss of these small features. Finally,
 416 our methods deal better with the zero values outside the object
 417 (support estimation). It is mainly visible in the 3D views in
 418 rows (e) and (g) and for the central frame (*i.e.* $z = 256$)
 419 shown on row (b). Furthermore, we can see on row (f) that our
 420 methods deal also better with the missing cone effect.

421 Fig. 9 presents wrongly tuned reconstructions of the pollen
 422 grain with the TV regularization. We can see that in the under-
 423 regularized case, the contrast is slightly lighter, and some poro-
 424 sities are lost in case (a) and (b). However, the reconstruction
 425 is close to the reconstruction obtained with GSURE even though

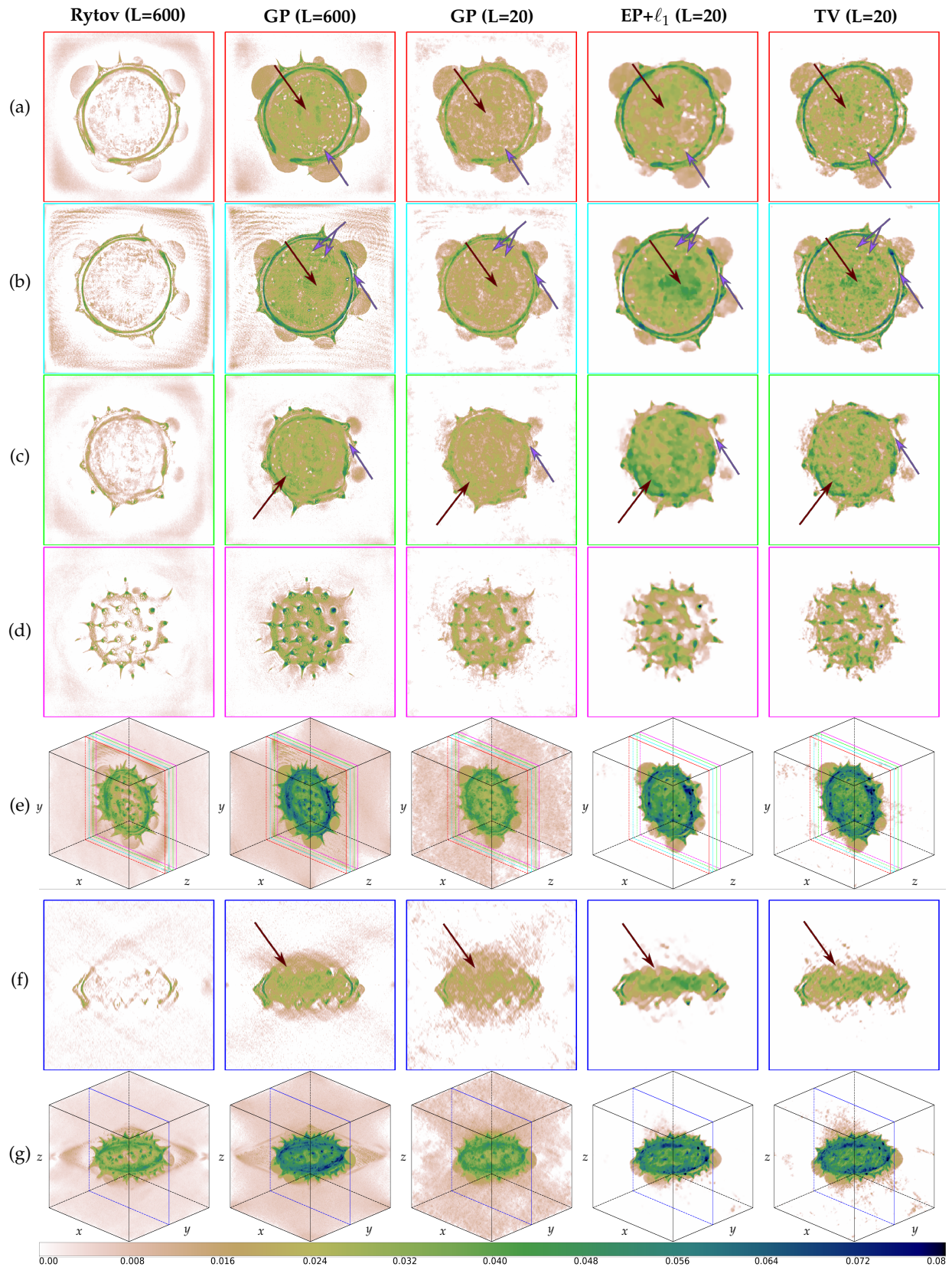
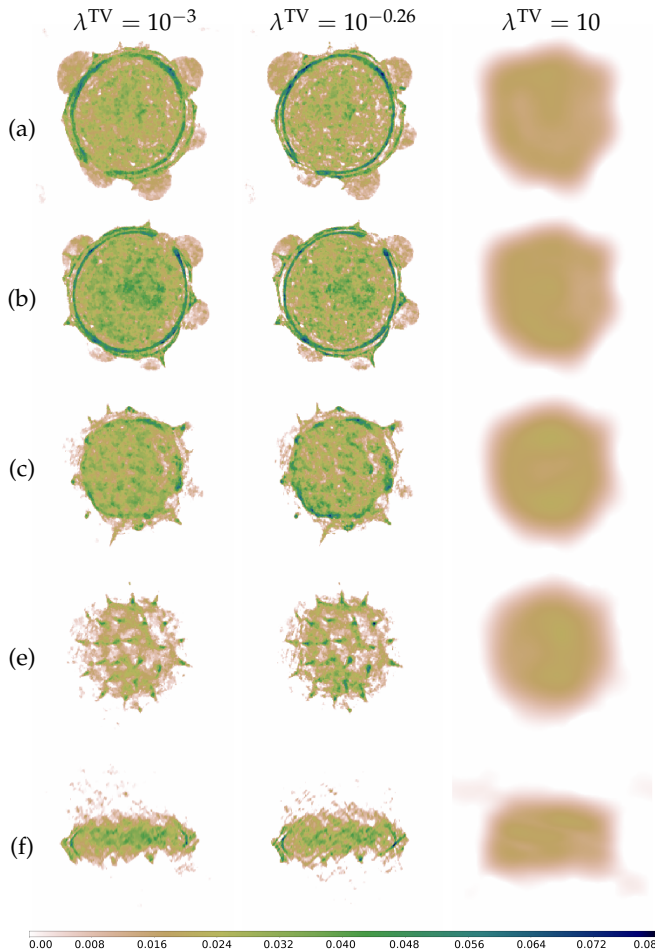


Fig. 8. Views of the Jerusalem artichoke pollen grain for the Rytov inversion and with the GP method for $L = 600$ projections, and the reconstructions with the GP method and giving the best GSURE values for the $EP+\ell_1$ and TV regularizations for $L = 20$ projections. Rows (a)-(d) represents the (x, y) slices for $z \in \{231, 256, 282, 303\}$ and are highlighted on the (x, y, z) 3D view on row (e) with the same colored frames. Row (f) is the (x, z) view for $y = 256$ and is highlighted on the (x, z, y) 3D view on row (g) with the same colored frame.

426 the hyperparameter is a lot smaller. In the over-regularized case, 444
 427 all the details are lost. The reconstruction is really different from 445
 428 the reconstruction obtained with GSURE even though the hyper- 446
 429 parameter is not far from the optimal one (in the sense of the 447
 430 pMSE). 448

431 In conclusion, in this experimental case, when using the 449
 432 TV regularization, the optimization of the GSURE criterion 450
 433 is effective to achieve a satisfying reconstruction. In the case 451
 434 of $EP + \ell_1$, some further hand tuning could help lower the 452
 435 regularization and recover the features inside the object. Thus, 453
 436 it only gives a starting set. Overall, an important point in 454
 437 these experiments is the demonstration that an appropriate 455
 438 tuning of the regularization hyperparameters can favor a better 456
 439 exploitation of the data by the model, opening the way to 457
 440 drastically reduce the amount of useful TDM projections (from 458
 441 an order of magnitude in this experiment) while preserving a 459
 442 satisfying reconstruction in terms of contrast and resolution. 460
 443



444 **Fig. 9.** Comparison of reconstructions of the pollen grain, on 445
 446 the slices Fig. 8-(a) to (c), (e), and (f), with the TV regularization 447
 448 for different hyperparameters. From the left to the right : an 449
 450 under-regularized reconstruction, the reconstruction giving 451
 452 the best GSSURE value and an over-regularized reconstruction. 453

444 5. CONCLUSION

445 In this work, we propose an unsupervised method for auto- 446
 447 matically tune the hyperparameters of a regularized 3D recon- 448
 449 struction method from TDM measurements using GSURE. We 450
 451 applied it with both differentiable and non-differentiable regu- 452
 453 larization terms. We prove its capability to find a good tuning of the 454
 455 regularization hyperparameters on both simulated and experi- 456
 457 mental data. This work show how an appropriate tuning of the 458
 459 regularization hyperparameters helps to exploit at best the data information, 460
 461 which is particularly critical when the amount of measurements 462
 462 is or has to be reduced, for example for experiment or setup 463
 464 optimization purposes. 465

466 However, this work only presents a brief application of 467
 468 GSURE and raises several perspectives. First, it would be inter- 469
 470 esting to study how GSURE behaves with other models (*e.g.* 471
 472 the first Born Approximation). Second, an empirical study of 473
 474 how the GSURE minimal argument varies with the number of 475
 476 projections used for the reconstruction could be useful to see if 477
 478 it is predictable. Such a case would allow us to tune the hyper- 479
 480 parameters only on a few holograms (the minimum required) 481
 482 and then perform a reconstruction with all the data (or a suffi- 483
 484 cient amount to have the best quality). **Third, an optimization 485
 486 of the computational time could be done. In fact, it takes two 487
 488 reconstructions to compute one iteration of GSURE and several 489
 490 iterations are needed to converge to its minimum. Depending on 491
 492 the complexity of the hologram formation model (Born or BPM), 493
 494 it can take several hours to several days.** Finally, a comparison 495
 496 with other autotuning method should be performed. 497

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478 8. DISCLOSURES

479 The authors declare no conflict of interest.

480 9. DATA AVAILABILITY

481 **Data underlying the results presented in this paper are not pub- 482
 483 licly available at this time but may be obtained from the authors 484
 485 upon reasonable request.**

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