Signal-to-noise criterion for free-propagation imaging techniques at free-electron lasers and synchrotrons

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Abstract: We propose a signal-to-noise criterion which predicts whether a feature of a given size and scattering strength, placed inside a larger object, can be retrieved with two common X-ray imaging techniques: coherent diffraction imaging and projection microscopy. This criterion, based on how efficiently these techniques detect the scattered photons and validated through simulations, shows in general that projection microscopy can resolve smaller phase differences and features than coherent diffraction imaging. Our criterion can be used to design optimized imaging experiments and perform feasibility studies for sensitive biological materials in free-electron lasers, where the number of photons per pulse is limited, or in synchrotron experiments, for both techniques.

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References and links

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1. Introduction

The non-destructive imaging of soft biological material, such as bacteria, cells or tissue at a resolution of few tens of nanometers or less, is a widespread wish within the biology community [1, 2]. Modern X-ray techniques have been proved to be serious candidates for this task [3]. The debate on the ultimate achievable spatial resolution in coherent diffraction imaging, has been addressed in [4]. For continuous irradiation of the sample, as typically happens in a synchrotron, the resolution limit is dictated by radiation damage, and was claimed to be 10 nm for biological material [4]. As an alternative, the ultrashort and ultraintense X-ray pulses delivered by free-electron lasers (FELs) may serve to outrun the radiation damage [5], thus shifting the origin of the resolution limit from the maximal dose that can be deposited on the sample to the number of photons in an FEL X-ray pulse. These two approaches are the subject of the present work, which aims to shed light on the questions: (a) whether the resolution achievable on a single feature is hampered by the feature being embedded in a larger area illuminated with X-rays, and (b) if different imaging techniques exhibit different efficiency. For this comparison, we considered coherent diffraction imaging (CDI) [6] and propagation-based projection microscopy (PM) in holographic regime [7], as representative of reciprocal and real
space methods, respectively.

PM imaging techniques require a small X-ray source [7], which may be a secondary focus [8], and were recently employed at synchrotron sources [9] achieving sub-100nm spatial resolution [10]. As illustrated in Fig. 1(a), the sample is placed at a small distance \( z_1 \) downstream the source. The detector is positioned at a distance \( z_2 \) further downstream to record a magnified Fresnel diffraction pattern, which forms according to Gabor’s holographic principle [11]. With a single diffraction pattern, the phase retrieval schemes are applicable only in special cases, for example for pure-phase objects [12, 13], and the retrieved phase generally is not reproduced quantitatively. A quantitative phase reconstruction, with a single diffraction pattern, can be achieved in some special cases, such as, single-material objects [14]. In general, this becomes possible if a number of patterns (typically 3 to 5) are acquired at different source-to-sample distances \( z_1 \) [15–18], which ensures non-zero values of the contrast transfer function [15]. Another option is to use iterative approaches which impose constraints in the sample and detector planes [18]. The spatial resolution of the reconstructed phase map is in principle limited by the source size.

As an alternative imaging technique, we use CDI with plane wave illumination, typically achieved by focusing the beam at the sample position with a transversal size larger than the sample extension. A Fraunhofer diffraction pattern is detected in the far field, as shown in Fig. 1(b). The resolution is in principle given by the largest angle at which the intensity signal can be measured. Quantitative reconstruction of sample transmission amplitudes and phases from the measured intensity can be achieved by means of iterative transform algorithms (ITA) [6, 19], which rely on imposing additional constraints to the sample, for example a compact support.

The paper is organized as follows: in the next section we develop our signal-to-noise (SNR) criterion, based on Gaussian scatterers, which allows us to predict whether a feature of a given size and scattering contrast, placed inside a larger object can be retrieved for PM and CDI. In Section 3, we validate our model simulating both imaging techniques and evaluating the quality of the reconstructions. In Section 4, we apply our criterion to synchrotron and FEL experiments for the imaging conditions described in Section 3.

2. Signal-to-noise criterion

In this section, we develop a mathematical model, based on Gaussian scatterers, to predict the SNR for both techniques. Using the projection approximation [20] a 2D Gaussian scatterer is described by its transmission

\[
t(x, y) = e^{-j(\hat{\phi} + \Delta\phi(x, y))},
\]

Fig. 1. (a) PM setup, \( z_1 \) is the source to sample distance (\( \sim 10 \mu m \)), and \( z_2 \) is the sample to detector distance (\( \sim 1 m \)). (b) CDI setup, \( z \) is the distance from sample to detector.
where is the average phase of the object and is the relative phase shift due to the Gaussian scatterer. In principle, and are complex valued. In this model the relative phase is given by

\[ \Delta \phi(x, y) = \phi_{\text{max}} e^{-\frac{(x^2 + y^2)}{2\sigma^2}}, \tag{2} \]

where is the Gaussian width or standard deviation and is related to the size of our feature, is the maximum phase shift acquired by the wave front after crossing the scatterer, is the wavelength, is the refractive index of the Gaussian scatterer, is the refractive index of the background (e.g., water), and is the maximum thickness of the scatterer. Within this article, we restrict the attention to weak pure phase objects. Biological material at photon energies between 2 and 20 keV is a prominent example, being the real part of the refraction index small but orders of magnitude larger than its imaginary part. The parameter , at the energies we are studying, fulfills \( \Delta \delta \ll 1 \), leading to a weak-phase approximation \( \phi_{\text{max}} \ll 1 \), which allows us to expand the exponential for the term in Eq. (1).

In the following, we are going to discuss the circumstances under which nanoscale features can be imaged with PM and CDI methods. As a first step, we quantify the X-ray intensities diffracted by a single Gaussian feature (Eq. (2)) and measured with a pixel detector, using the weak-phase approximation. We calculate the SNR for both imaging techniques assuming Poissonian noise.

The parameters for the PM setup are shown in Fig 1(a). The beam with fluence \( \Phi \) emerging from a source of size \( f \) illuminates the sample uniformly over a field of view \( \text{FOV}_{\text{PM}} \). The defocusing distance is \( z = (z_1 z_2)/(z_1 + z_2) \) [21] and the magnification is \( M = (z_1 + z_2)/z_1 \). We use demagnified coordinates \((x, y) = (x_d, y_d)/M \) to specify positions on the detector plane, corresponding to the physical coordinates \((x_0, y_0)\). The X-ray intensity can be expressed by the sum of the non-scattered illumination \( I_0 \) plus the intensity containing the scatterer interaction \( I_{\text{sig}} \).

\[ I(x, y; z) = I_0 + I_{\text{sig}}(x, y; z). \tag{3} \]

In the limit of Poisson noise statistics and using the weak-phase approximation, the SNR for PM is given by (see for details [appendixA]Appendix A).

\[ \text{SNR}_{\text{PM}}(x, y; z) = \frac{I_{\text{sig}}(x, y; z)}{\sqrt{I(x, y; z)}} = \frac{I_{\text{sig}}(x, y; z)}{\sqrt{I_0}} \approx 2 \sqrt{N_S} |\Phi| |A| e^{-\frac{x^2 + y^2}{2\sigma^2} \Re(A)} \left| \sin \left( \phi_0 - \frac{x^2 + y^2}{2\sigma^2} \Im(A) \right) \right|, \tag{4} \]

where

\[ A = \frac{1}{1 + \frac{j x \Phi}{2 \pi N_F}} = |A| e^{j \phi_0}, \tag{5} \]

\( N_F = \sigma^2/\lambda z \) is the Fresnel number, \( \omega = (p_x/\sigma^2)/\pi \) is related to the ratio between the sampling size \( p_x \) and the Gaussian feature width, and \( N_S \) is the total number of scattered photons

\[ N_S = \Phi \sigma_S = \Phi \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} |1 - t(x, y)|^2 \ dx \ dy = \Phi \pi \sigma^2 |\phi_{\text{max}}|^2, \tag{6} \]

where \( \sigma_S \) is the total scattering cross section, as described in [4].

For CDI as depicted in Fig. 1(b), we illuminate with a fluence \( \Phi \) a sample over a field of view \( \text{FOV}_{\text{CDI}} \). We will assume for the rest of the paper that our object covers an area smaller
than half of the illuminated area by the \( \text{FOV}_{\text{CDI}} \). In case that our object is bigger than the illuminating beam, we would require a mask to fulfill the compact support condition \cite{ref22}. In this scenario, the \( \text{FOV}_{\text{CDI}} \) can be reinterpreted as \( \sqrt{2} \times L \), where \( L \) is the biggest dimension of the mask. Positions on the detector plane, located at a distance \( z \) downstream, are given in terms of reciprocal space coordinates \( (q_x, q_y) = 2\pi / (\lambda z)(x_0, y_0) \). The SNR for CDI away from the direct beam \( (q_x \neq 0, q_y \neq 0) \) is given by (see for details [appendixA]Appendix A)

\[
\text{SNR}^{\text{CDI}}(q_x, q_y) = \sqrt{I(q_x, q_y)} = \sqrt{N_S} \frac{2\sqrt{\pi \sigma \text{FOV}_{\text{CDI}}}}{\text{FOV}_{\text{CDI}}} e^{-\frac{q_x^2 + q_y^2}{\lambda}}
\]

where \( I(q_x, q_y) \) is the total intensity on the detector.

From Eqs. (4) and (7) it is clear that for both techniques the SNRs are proportional to \( \sqrt{N_S} \). As a consequence, to compare both methods, it is crucial to understand how efficiently both techniques handle the scattered photons. We proceed by defining, for both imaging approaches, an effective SNR level which we will use later as imaging requirement to predict if a Gaussian feature embedded in a larger object can be recovered inside the retrieved overall image. In the \( N_F \ll 1 \) approximation, we require to detect the oscillation amplitude in Eq. (4). Thus we define

\[
\text{SNR}_\text{eff}^{\text{PM}} = 2\sqrt{N_S} |A| \approx 2\sqrt{N_S} \frac{4\beta}{\pi \text{FOV}_{\text{PM}}},
\]

where \( \beta = p_s / t_w \) and we have assumed a diffraction limited source \( (\lambda z = \pi \text{FOV}_{\text{PM}} t_w / 4) \).

For CDI, we require to have a significant SNR over the area given by \( q_{\text{max}} = \sqrt{q_x^2 + q_y^2} = \pi / \sigma \) with the sampling given by the \( \text{FOV}_{\text{CDI}} \) \( (\Delta q = 2\pi / \text{FOV}_{\text{CDI}}) \)

\[
\text{SNR}^{\text{CDI}} \equiv \sqrt{N_S} \frac{2\sqrt{\pi \sigma \text{FOV}_{\text{CDI}}}}{\pi q_{\text{max}}^2} \int_{0}^{q_{\text{max}}} q \ e^{-\frac{q_x^2 + q_y^2}{\lambda}} dq \approx \sqrt{N_S} \frac{2\sigma}{\pi \text{FOV}_{\text{CDI}}}. \]

In the case that our feature is not isolated and it is embedded in a larger object, which scatters isotropically and more than our feature, we can reduce our effective signal-to-noise criterion by a factor 2, as our feature signal is dominated by the interference term \cite{ref22}. We have already included this factor 2 in Eq. (9) and for the rest of the paper we will use this factor as this is generally the case for small features inside biological samples. In case the interference is negligible, such as for example when the feature is isolated and there are not other significant scatterers, one should divide Eq. (9) by this factor 2. The reader should notice that the CDI requirement derived in Eq. (9) reduces to Eq. (4) in [4] for the special case where the feature of interest is half of the \( \text{FOV}_{\text{CDI}} \), i.e., our feature is isolated or we use a tight support around the feature \cite{ref22}.

As imaging criterion we propose

\[
\text{SNR}_\text{eff} \geq 5, \tag{10}
\]

as suggested by the Rose criterion \cite{ref23}, the implications of using a \( 3\sigma \) criterion are described in [appendixB]Appendix B. We consider for example a feature of 20 nm (\( \sigma = 10 \) nm) in an object covering a \( 0.5 \times 0.5 \) \( \mu \text{m}^2 \) area, using a perfect coherent illumination with \( 10^{13} \) photons per image at an energy of 4 keV. In order to achieve the desired resolution with PM, we require \( f_w \) to be smaller or equal to the feature size (20 nm). Assuming a Gaussian beam distribution with \( f_w = 10 \) nm at 4 keV, the beam waist at a distance of \( z_1 \approx 12.6 \) \( \mu \text{m} \) defines the \( \text{FOV}_{\text{PM}} = \)}
0.5 \mu m covering the whole object. For our PM geometry with big magnification \( z_2 \gg z_1 \) as shown in Fig. 1(a), \( z \approx z_1 = 12.6 \mu m \). For this PM scenario, \(|A| \approx 0.16 \) and taking a sampling in real space of a third of the feature size \((p_s = 0.67 \text{ nm})\) as suggested in [24], \( \omega \approx 0.14 \). Therefore from Eq. (8) the \( \text{SNR}_{\text{PM}} \approx 0.12 \sqrt{N_S} \). Using the detectability threshold in Eq. (10) we impose a condition over the number of scattered photons \( N_S^{\text{PM}} \gtrsim 1800 \) photons. Using Eq. (6), the achievable phase sensitivity \( (\phi_{\text{max}}) \) in the described PM geometry for a feature of 20 nm is \( \phi_{\text{max}}^{\text{PM}} \gtrsim 3 \text{ mrad} \).

Analogously for CDI, the focusing requirement is relaxed to two times the sample size (\( \text{FOV}_{\text{CDI}} = 1 \mu m \)), in order to fulfill the solution criterion for the iterative phase retrieval algorithms [19]. Conversely, PM does not require this sampling constraint. From Eqs. (9) and (10) we can obtain the condition for the number of scattered photons for CDI \( N_S^{\text{CDI}} \gtrsim 1.6 \cdot 10^4 \) photons. Thus the achievable sensitivity is \( \phi_{\text{CDI}}^{\text{max}} \gtrsim 7 \text{ mrad} \).

3. Simulation and validation

In order to numerically validate the sensitivity calculations for both methods with our model, we create a pure-phase phantom. This phantom has a background support with \( \phi_{\text{max}} = 10 \text{ mrad} \), which is on the order of magnitude of the phase shift expected for a biological sample in water or ice at multi-keV X-rays [25], covering approximately a \( \sim 0.5 \times 0.5 \mu m^2 \) area. Inside of this object we add three Gaussian scatterers, as depicted in Fig. 2(a). The values of the phase shifts \( (\phi_{\text{max}}) \) of the scatterers are chosen according to the values calculated with our imaging criterion.

We simulate both imaging geometries with the above discussed FOVs at the object plane and the same sampling in real space \((p_s)\). Using the projection approximation to describe the object, paraxial propagation [26], and Poissonian noise, we simulate the intensities on the detector. For PM we consider that the focal spot has a finite size, therefore we convolve our intensity pattern.
with the source size. To retrieve the phases from the PM images, we use phase retrieval based on contrast transfer function (CTF) algorithms [12, 13] with a single distance input. For CDI images, we have averaged over 20 reconstructions from different random seeds (starting guess) performed in 10 series alternating 45 hybrid input output algorithm (HIO) with 5 iterations of error reduction algorithm (ER) [27, 28], each with a tight support. Figures 2(b) and (c), show the retrieved phase of the phantom for PM and CDI respectively.

To evaluate if each feature has been properly imaged, we compute the Fourier Ring Correlation (FRC) [29] with the half bit threshold criterion [24], as implemented in [30], between the reconstructed objects and the reference object. The resolution values are reported in Fig. 3 as a function of $\phi_{\text{max}}$ of nine features included in distinct simulations. The horizontal lines represent the resolution thresholds which we use to discriminate between successful and unsuccessful reconstruction of a feature. For CDI, we set the threshold at $2\sigma = 20$ nm. For PM, we correct the threshold to $\sqrt{(2\sigma)^2 + f_w^2} = 23$ nm to account for the source size.

Equations (8) and (9) predict sensitivity thresholds $\phi_{\text{PM}}^{\text{max}} \simeq 3$ mrad and $\phi_{\text{CDI}}^{\text{max}} \simeq 7$ mrad, respectively, which means that in Fig. 3 full square PM data points should be below or compatible with the horizontal dashed line ($\phi_{\text{PM}}^{\text{max}} > 3$), while for CDI the full circle points ($\phi_{\text{max}} > 7$ mrad) should be below or compatible with the continuous horizontal line. The asymmetric error bars are due to the interpolation of the discrete FRC. We therefore note a discrepancy in the sensitivity thresholds for both PM and CDI, which we attribute to the non-perfect efficiency of the phase retrieval algorithm. The reader should notice that we have not included the efficiency of the phase retrieval algorithms in our theoretical model. This factor is out of the scope of this work because it is dependent on the sample, experimental uncertainties, and on the amount of prior knowledge that is brought to bear in the reconstruction procedure. Our result can be interpreted as a best case scenario with a fully efficient phase retrieval algorithm. The relevant prediction that PM can image weaker features than CDI remains valid. However, the data points indicate that for resolvable phase shifts CDI can achieve a better resolution, well below the feature size, not possible in PM because of the source extent.

4. Application to synchrotron and FEL experiments

In this section, we study the application and implications of our criterion for FEL and and synchrotron. For single pulse imaging with FEL [5] the radiation damage does not play a role. We study the sensitivity for both techniques as a function of the desired resolution. For this calculation we simulate a realistic geometry for both setups, neglecting any experimental limitation (achievable $f_w$, sample positioning precision), with a sample size of 0.5 $\mu$m size, uniformly illuminated by $10^{12}$ photons, with features of the desired resolution. The results of these calculations, for an energy of 4 keV, using Eqs. (6), (8), (9), and (10) are summarized in Fig. 4 (Fig. 6 in Appendix B shows an analogous calculation using a $3\sigma$ criterion for the SNR$_{\text{eff}}$).

Conversely, for synchrotron experiments, where the radiation damage plays a crucial role, this model can be used to evaluate the fluence required to image certain scatterers (fixing the scattering cross section) at a certain resolution in a realistic geometry for PM and CDI. To illustrate this we use our Gaussian model, with a maximum thickness $t_0 = 2\sigma$, to evaluate scatterers given by the protein model in vacuum used in [4] with the corresponding size to the desired resolution at 4 keV, inside a support of 0.5 $\mu$m (like our example). We have neglected any technical limitation to achieve the necessary focal spot for each resolution and the focus to sample distance ($z_1$) for PM. From the results shown in Fig. 5, one can see that PM requires less fluence than CDI in these imaging scenarios (the same conclusions can be extracted from Fig. 7 in Appendix B for SNR$_{\text{eff}} = 3$).
Fig. 3. Resolution as a function of the maximum phase shift in the sample ($\phi_{\text{max}}$) for PM and CDI using FRC with half bit threshold criterion. We have computed the FRC of each Gaussian scatterer with a square from $[-5\sigma, 5\sigma]$ for PM and CDI with our phantom image and an analogous phantoms with features with a phase shift of 1, 2, 5, 6, 9, and 13 mrad. The resolution for PM (CDI) is represented with square (circle) markers. The expected resolution of 23 and 20 nm is represented by the horizontal dashed and continuous lines for PM and CDI, respectively.

Fig. 4. Best sensitivity as a function of the feature size ($2\sigma$) for $10^{12}$ photons uniformly distributed over the whole FOV. The dashed, continuous, and dotted-dashed lines represent the best sensitivity for PM, CDI, and the criterion of [4], respectively.

5. Conclusions

In summary, we have proposed a criterion based on a SNR threshold which predicts whether a feature of given size and scattering strength, placed inside a larger object, can be properly retrieved with PM and CDI imaging methodologies. This is useful to design imaging experi-
ments and feasibility studies at FELs and synchrotron sources. Simulations of the experiments provide a qualitative validation of the criterion. In contrast to previous suggestions, our criterion explicitly accounts for the size of the full object, and predicts deterioration of the imaging performance with increasing object size. PM is more suitable to identify weaker features than CDI, although the latter has the potential to provide better resolution as it overcomes the effects of the finite source extension.

Appendix A: Signal-to-noise calculations

In this appendix we report the calculation of the signal-to-noise ratio (SNR) for our Gaussian scatter model for coherent diffraction imaging (CDI) and projection microscopy (PM).

Describing our the transmissivity as in Eq. (1)

\[ t(x,y) = e^{i(\phi + \Delta \phi(x,y))} \approx e^{i\bar{\phi}}(1 + j \Delta \phi(x,y)) , \]  

(11)

where \( \bar{\phi} \) is the average phase of the object and \( \Delta \phi(x,y) \) is the variation of the phase along the different positions over the field of view (FOV). We have assumed a weakly scattering object \( \Delta \phi \ll 1 \), given by a Gaussian scatterer

\[ \Delta \phi(x,y) = \phi_{\text{max}} e^{-\frac{(x^2+y^2)}{2\sigma^2}} , \]  

(12)

where \( \phi_{\text{max}} \) is the maximum phase acquired by the wave front after crossing the scatterer and \( \sigma \) is the scatterer width. Therefore the wave front after our scatter, assuming projection approximation, is given by

\[ \psi(x,y) \approx \sqrt{\Phi} \left( 1 + j \phi_{\text{max}} e^{-\frac{(x^2+y^2)}{2\sigma^2}} \right) , \]  

(13)

as a function of the incident fluence \( \Phi \) and neglecting the global phase.
We have assumed for simplicity that our intensity is constant within each sampling area. The sample and the detector over the optical axis, and where $λ$ is the wavelength, $k = 2π/λ$ is the wavenumber, $z$ is the propagating distance between the sample and the detector over the optical axis, and $x$ and $y$ are the detector coordinates. We obtain propagating our wavefront, Eq. (13), and neglecting global phase factors

$$I(λ, z) = N_S(λ) e^{−2πN_0}$$

Thus, we calculate the CDI SNR for the scattering signal

$$\text{SNR} (q_x, q_y) = \frac{I(q_x, q_y)}{\sqrt{I(q_x, q_y)}}$$

where $q_x$ and $q_y$ are our sampling, $N_F = σ^2/(λz)$ is the Fresnel number, $ω = (p_s/σ)^2/π$ is related to the ratio of our sampling and the Gaussian width, and $N_S$ is the total number of scattered photons. We have use the fact that the total number of scattered photons is given by $N_S = Φσ_S$, where $σ_S$ is the total scattering cross section given by

$$σ_S = \int_{−∞}^{+∞} |1 − t(x, y)|^2 dx dy = \piσ^2|φ_{max}|^2$$

We have assumed for simplicity that our intensity is constant within each sampling area. The intensity for CDI can also be written as a function of the sampling solid angle,

$$I(λ, z) = \frac{N_S(λ) e^{−2πN_0}}{\sqrt{2π}}$$

where $Δq = 2π/\text{FOV}$ is the Shannon sampling. Therefore the intensity can be written as

$$I(q_x, q_y) = Φ \left( \int_{−∞}^{+∞} |1 − t(x, y)|^2 dx dy \right)^2$$

Thus, we calculate the CDI SNR for the scattering signal

$$\text{SNR} (q_x, q_y) = \frac{I(q_x, q_y)}{\sqrt{I(q_x, q_y)}}$$

$$= \sqrt{N_S(λ) e^{−2πN_0}}$$

$$= \sqrt{N_S(λ) e^{−2πN_0}}$$
PM signal-to-noise ratio

Now we calculate the propagated field after a distance $z$ close to the object in the Fresnel approximation. Thus neglecting global phase factors

$$
\psi(x, y; z) = \frac{\sqrt{\Phi}}{j\lambda z} \int_{-\infty}^{\infty} \left(1 + j \Delta \phi(\varepsilon_x, \varepsilon_y)\right) e^{jk \frac{(\varepsilon_x - x)^2 + (\varepsilon_y - y)^2}{2z}} \, d\varepsilon_x d\varepsilon_y
$$

$$
= \frac{\sqrt{\Phi}}{1 + j \frac{x^2 + y^2}{2\sigma^2}} \left(1 + j \phi_{max} A e^{-\frac{x^2 + y^2}{2\sigma^2}}\right),
$$

(21)

where the parameter $A$ is given by

$$
A = \frac{1}{1 + j \frac{x^2 + y^2}{2\sigma^2}} = \frac{1}{1 + j \frac{1}{2\sigma N_F}} = |A| e^{i\phi_A},
$$

(22)

and the phase distribution in 2D ($\Delta \phi(x, y)$) is given by Eq. (12).

This allows us to calculate the number of photons registered per sampling pixel

$$
I(x, y; z) = \Phi \rho^2 \left(1 + |\phi_{max}|^2 |A|^2 e^{\frac{i(x^2 + y^2)}{2\sigma^2} ReA} + 2 |\phi_{max}| |A| e^{\frac{i(x^2 + y^2)}{2\sigma^2} ReA} \sin(\phi_A - \frac{x^2 + y^2}{2\sigma^2} ImA)\right)
$$

$$
\approx \Phi \rho^2 \left(1 + 2 |\phi_{max}| |A| e^{\frac{i(x^2 + y^2)}{2\sigma^2} ReA} \sin(\phi_A - \frac{x^2 + y^2}{2\sigma^2} ImA)\right).
$$

(23)

We have neglected high order contribution on $\phi_{max}$ as we are in the weak-phase approximation. We have assumed that the intensity does not change over the pixel area significantly, this is a good approximation for $N_F \ll 1$.

The X-ray intensity can be expressed by the sum of a background signal, arising from the non-scattered photons ($I_0$), plus the signal originating from the interaction with the sample ($I_{sig}$)

$$
I(x, y; z) = I_0 + I_{sig}(x, y; z),
$$

(24)

where $I_0$ is the background component given by

$$
I_0 = \Phi \rho^2,
$$

(25)

and $I_{sig}$ contains the scattering signal and up to first order in $\phi_{max}$ is given by

$$
I_{sig}(x, y; z) = 2 \Phi \rho^2 |\phi_{max}| |A| e^{\frac{i(x^2 + y^2)}{2\sigma^2} ReA} \sin(\phi_A - \frac{x^2 + y^2}{2\sigma^2} ImA).
$$

(26)

We define our SNR as

$$
\text{SNR}(x, y; z) = \frac{I_{sig}(x, y; z)}{\sqrt{I(x, y; z)}} \approx \frac{I_{sig}(x, y; z)}{\sqrt{I_0(x, y; z)}}
$$

$$
= 2 \sqrt{N_F} \omega |A| e^{\frac{-i(x^2 + y^2)}{2\sigma^2} ReA} |\sin(\phi_A - \frac{x^2 + y^2}{2\sigma^2} ImA)|.
$$

(27)

Appendix B: 3σ imaging criterion

In this appendix we explore the implications of changing our imaging criterion used in Eq. (10) to a 3σ criterion.

Using the same imaging conditions described in Section 3 and analogous calculations as in Section 4, we calculate the best sensitivity, illuminating with $10^{12}$ photons, for FEL experiments, the results are depicted in Fig. 6. We can observe that PM becomes more sensitive than
the criterion of [4] for features larger than 50 nm inside of a field of view of 500 µm. On the other hand, our CDI criterion for features smaller than 100 nm achieves values less sensitive than the results obtained in [4]. It must be reminded that different field of views will report different phase sensitivities, which is not the case for the criterion in [4]. Above all, the 3σ criterion reports better phase sensitivity than the values for the 5σ shown in Fig. 4, as expected from Eqs. (8) and (9), because the $\phi_{\text{max}}$ functional dependence with the SNR$_{\text{eff}}$ for both techniques is given by

$$\phi_{\text{max}} \propto \text{SNR}_{\text{eff}}.$$  \hspace{1cm} (28)

Fig. 6. Best sensitivity for SNR$_{\text{eff}} = 3$ as a function of the feature size (2σ) for $10^{12}$ photons uniformly distributed over the whole FOV. The dashed, continuous, and dotted-dashed lines represent the best sensitivity for PM, CDI, and the criterion of [4], respectively.

Fig. 7. Required imaging fluence for SNR$_{\text{eff}} = 3$ as a function of the feature size (2σ). The dashed, continuous, and dashed-dotted lines represent the required fluence for resolution for PM, CDI, and the criterion of [4], respectively. The horizontal dashed line represents a typical order for the fluence in a single FEL shot.
For synchrotron experiments, we evaluate the fluence required to image the features described in Section 4. This calculation is summarized in Fig. 7. According to the criterion in [4] we would be able to resolve with $10^{12}$ photons features of 4 nm neglecting the radiation damage threshold. On the other hand, we predict around 10 nm and 20 nm resolution approximately for PM and CDI, respectively. For the range of the study we can see that we require more photons than the predicted by the criterion of [4], in spite of using a $3\sigma$ criterion. Above all, the $3\sigma$ criterion reports better fluence requirements than the values for the $5\sigma$ shown in Fig. 5, because, from Eqs. (8) and (9), the $\Phi$ dependence with the SNR$_{eff}$ for both techniques is given by

$$\Phi \propto \text{SNR}^2_{\text{eff}}.$$  \hspace{1cm} (29)

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