Studies of signal estimation bias in grating-based x-ray multicontrast imaging

Xu Ji, Yongshuai Ge, and Ran Zhang

Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Ke Li and Guang-Hong Chen^{a)}

Department of Medical Physics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

(Received 10 November 2016; revised 8 March 2017; accepted for publication 12 March 2017; published 12 May 2017)

Purpose: In grating-based x-ray multi-contrast imaging, signals of three contrast mechanisms—absorption contrast, differential phase contrast (DPC), and dark-field contrast—can be estimated from the same set of acquired data. The estimated signals, N_0 (related to absorption), N_1 (related to dark-field), and ϕ (related to DPC) may be intrinsically biased. However, it is yet unclear how large these biases are and how the data acquisition parameters affect the biases in the extracted signals. The purpose of this paper was to address these questions.

Methods: The biases of the extracted signals (i.e., N_0 , N_1 and ϕ) were theoretically studied for a well-known signal estimation method. Experimental data acquired from a grating-based x-ray multi-contrast benchtop imaging system with a photon counting detector were used to validate the theoretical results for the signal biases of the three contrast mechanisms.

Results: Both theoretical and experimental studies showed the following results: (1) The bias of signal estimation for the absorption contrast signal is zero; (2) The bias of signal estimation for N_1 is inversely proportional to the number of phase steps and to the average fringe visibility of the grating interferometer, but the ratio between the bias and the signal level (i.e., the relative bias) is independent of the number of phase steps; (3) The bias of signal estimation for ϕ depends on the mean DPC signal level, the total exposure level of the multi-contrast data acquisition, and the mean fringe visibility of the interferometer.

Conclusions: In grating-based x-ray multi-contrast imaging, the estimated absorption contrast signal is unbiased; the estimated dark-field contrast signal is biased, but the relative bias is only dependent on the mean fringe visibility of the interferometer and the exposure level. The estimated DPC signal may be biased, and the bias level depends on the mean signal level, the exposure level, and the interferometer performance. © 2017 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12235]

Key words: signal bias, x-ray dark-field contrast imaging, x-ray imaging, x-ray phase-contrast imaging

1. INTRODUCTION

Recently, grating-based x-ray multicontrast imaging has attracted a lot of interest in the medical imaging field.^{1–14} By incorporating three x-ray gratings, a conventional x-ray absorption contrast imaging system can be upgraded into an x-ray multicontrast imaging system, which can generate three sets of images with distinctive and endogenous contrast mechanisms: the conventional absorption contrast, the differential phase-contrast (DPC), and the dark-field contrast. The DPC and dark-field contrast have been found to be complementary to the conventional absorption contrast. Therefore, the three contrast mechanisms can potentially be used in a synergistic way to improve the imaging performance for tissue differentiation, material characterization, and lesion detection.

A typical x-ray multicontrast image acquisition process often involves a phase stepping procedure, in which one of the gratings is translated laterally over its period in a total of M phase steps, and an x-ray intensity measurement is performed at each phase step. In the absence of noise, a phase stepping measurement leads to the following sinusoidal intensity modulation for each detector pixel:^{1–3}

$$\bar{N}^{(k)} = N_0 + N_1 \cos\left(\frac{2\pi k}{M} + \phi\right), \quad (1)$$

where $\bar{N}^{(k)}$ ($k = 1, 2, \dots, M$) is the expected x-ray intensity measured at each phase step. The three characteristic parameters, N_0 , N_1 , and ϕ , are related to the signals of the absorption, dark-field, and phase-contrast mechanism, respectively.

In reality, each x-ray intensity measurement is always contaminated by noise. In order to accurately extract signals of the three contrast mechanisms, the intensity measurements can be repeated many times and averaged at each phase step, so that the expected photon number at each phase step (i.e., $\bar{N}^{(k)}$) can be estimated before Eq. (1) is used to extract the three parameters. However, repeated x-ray measurements are impractical in medical imaging due to the concerns of potential risks associated with ionizing radiation and prolonged imaging time. Therefore, the question encountered in the multicontrast signal extraction process is, how does one estimate the three characteristic parameters from a single set of phase stepping measurements? Namely, how does one seek for a set of three parameters, $\{N_0, N_1, \phi\}$, that best fit the measured set of data $N^{(k)}$? The least squares method is a

natural choice to address this problem, and it was used implicitly¹ or explicitly¹⁵ to accomplish this goal. A closed-form solution for $\{N_0, N_1, \phi\}$, denoted as $\{\hat{N}_0, \hat{N}_1, \hat{\phi}\}$, has been derived from the least squares optimization problem and is widely used in literature.^{1,2,15}

However, one fundamental question that remains to be addressed is how accurate are the multicontrast signals when the aforementioned least squares method is used? To better illustrate the rationale behind the question, let us assume that the x-ray intensity measurement at each phase step can be repeated many times to collect an ensemble of data under identical experimental conditions. In this case, one can use two different methods to extract the three characteristic parameters of interest. The first method is to take the experimental mean of the measured photon number at each phase step to estimate $\bar{N}^{(k)}$ before applying the least squares method to extract the three parameters: N_0 , N_1 , and ϕ . Alternatively, one can use the least squares method to estimate the three parameters ($\hat{N}_0, \hat{N}_1, \hat{\phi}$) from each set of phase stepping measurements. Then, one can calculate their mean values, $\langle \hat{N}_0 \rangle$, $\langle \hat{N}_1 \rangle$, and $\langle \hat{\phi} \rangle$, from the repeated experiments. Whether the estimated multicontrast signals are biased or not depends on the agreement in the outcome between the above two methods. If the two methods generate the same outcome, the least squares multicontrast signal estimation method is defined as an unbiased estimator. Otherwise, the method is defined as a biased estimator. If an estimator is found to be a biased one, then it is important to address the following two intriguing questions: (a) how large is the bias? and (b) how does the bias depend on the signal itself and the data acquisition system?

Note that the statistical variances of multicontrast signals estimated using the least squares method have been extensively studied in previous works.^{15–23} To the best of the authors' knowledge, the potential bias of the estimated multicontrast signals, which is essentially a quantitative descriptor of the multicontrast signal accuracy, has not yet been fully addressed in the literature. The purpose of this work was to conduct both theoretical and experimental studies on this important topic in grating-based x-ray multicontrast imaging.

2. BRIEF REVIEW OF THE LEAST SQUARES SIGNAL ESTIMATION METHOD IN X-RAY MULTICONTRAST IMAGING

With the acquired data, $N^{(k)}$ ($k = 1, 2, \dots, M$), the least squares-based signal estimation can be formulated by solving the following minimization problem:

$$\{\hat{N}_0, \hat{N}_1, \hat{\phi}\} = \arg \min_{N_0, N_1, \phi} \sum_{k=1}^M \{N^{(k)} - [N_0 + N_1 \cos(\frac{2\pi k}{M} + \phi)]\}^2. \quad (2)$$

By negating the partial derivatives of the least-squared objective function with respect to the parameters N_0, N_1 , and ϕ , a closed-form solution to the minimization problem in Eq. (2) can be readily derived as follows:

$$\hat{N}_0 = \frac{1}{M} \sum_{k=1}^M N^{(k)}, \quad (3)$$

$$\hat{N}_1 = \frac{2}{M} \sqrt{\left[\sum_{k=1}^M N^{(k)} \sin \frac{2\pi k}{M}\right]^2 + \left[\sum_{k=1}^M N^{(k)} \cos \frac{2\pi k}{M}\right]^2}, \quad (4)$$

$$\hat{\phi} = \text{Arg}\left(\sum_{k=1}^M N^{(k)} \cos \frac{2\pi k}{M} - i \sum_{k=1}^M N^{(k)} \sin \frac{2\pi k}{M}\right), \quad (5)$$

where $\text{Arg}(z)$ denotes the principal value of the argument of a complex number z . The range of the principal value is limited to $(-\pi, +\pi]$ in this paper. When the actual differential phase signal ϕ is beyond the range of the principal value, it is folded back to the principal range by a modulus operation $\text{Arg}(z) = \arg(z) + 2m\pi$, where m is an integer. This folding process has been widely referred to as phase wrapping in phase retrieval. Eq. (3)–(5) were widely used in most of the published literature to extract multicontrast signals in grating-based systems, although the explicit least-squares fitting procedure may not have been used. Note that when the least squares method was not explicitly used, then it was the following assumption that was implicitly used to derive the same solution, that is, a single measurement of $N^{(k)}$ can be used to replace the expected signal level in Eq. (1). As a matter of fact, this assumption is just a direct statement of the least-squares solution without tracking its mathematical foundation.

3. BIAS OF SIGNAL ESTIMATION USING THE LEAST SQUARES METHOD: THEORY

3.A. General method to estimate the potential bias of an estimator in statistics

In statistics, the bias of an estimated parameter, $\hat{\theta}$, is defined as the statistical mean of the difference between the estimated value and the truth, θ .

$$b_{\theta}(\hat{\theta}) = E(\hat{\theta} - \theta) = \int [\hat{\theta}(\mathbf{x}) - \theta] P(\mathbf{x}; \theta) d\mathbf{x}, \quad (6)$$

where $\mathbf{x}$ is the measured data vector from which the estimator, $\hat{\theta}$, is extracted, and $P(\mathbf{x}; \theta)$ is the probability density function (PDF) of $\mathbf{x}$ for given θ . Theoretically speaking, if $\hat{\theta}(\mathbf{x})$ and $P(\mathbf{x}; \theta)$ can be written as explicit forms, the bias of $\hat{\theta}$ can be directly calculated. However, in many cases, a direct analytical calculation of the integration in Eq. (6) may not be possible. In this case, one can proceed by using the Taylor series expansion method to approximate $\hat{\theta}$ around $\bar{\mathbf{x}}$ as follows:

$$\begin{aligned} \hat{\theta}(\mathbf{x}) &= \hat{\theta}(\mathbf{x} - \bar{\mathbf{x}} + \bar{\mathbf{x}}) \approx \hat{\theta}(\bar{\mathbf{x}}) + \sum_i \frac{\partial \hat{\theta}}{\partial x_i} \bigg|_{\bar{\mathbf{x}}} (x_i - \bar{x}_i) \\ &\quad + \frac{1}{2} \sum_{i,j} \frac{\partial^2 \hat{\theta}}{\partial x_i \partial x_j} \bigg|_{\bar{\mathbf{x}}} (x_i - \bar{x}_i)(x_j - \bar{x}_j), \end{aligned} \quad (7)$$

where x_i denotes the i^{th} element in the data vector $\mathbf{x}$. The expansion above assumes that $\hat{\theta}(\mathbf{x})$ is continuous everywhere.

Under this approximation, the statistical mean of the estimated value is given by

$$\begin{aligned}
 E(\hat{\theta}(\mathbf{x})) &\approx \left\langle \hat{\theta}(\bar{\mathbf{x}}) + \sum_i \frac{\partial \hat{\theta}}{\partial x_i} \bigg|_{\bar{\mathbf{x}}} (x_i - \bar{x}_i) \right. \\
 &\quad \left. + \frac{1}{2} \sum_{ij} \frac{\partial^2 \hat{\theta}}{\partial x_i \partial x_j} \bigg|_{\bar{\mathbf{x}}} (x_i - \bar{x}_i)(x_j - \bar{x}_j) \right\rangle \\
 &= \hat{\theta}(\bar{\mathbf{x}}) + \sum_i \frac{\partial \hat{\theta}}{\partial x_i} \bigg|_{\bar{\mathbf{x}}} \langle x_i - \bar{x}_i \rangle \\
 &\quad + \frac{1}{2} \sum_{ij} \frac{\partial^2 \hat{\theta}}{\partial x_i \partial x_j} \bigg|_{\bar{\mathbf{x}}} \langle (x_i - \bar{x}_i)(x_j - \bar{x}_j) \rangle. \quad (8)
 \end{aligned}$$

If the elements in $\mathbf{x}$ are uncorrelated, the following results can be readily derived:

$$\hat{\theta}(\bar{\mathbf{x}}) = \theta; \quad (9)$$

$$\langle x_i - \bar{x}_i \rangle = 0; \quad (10)$$

$$\langle (x_i - \bar{x}_i)(x_j - \bar{x}_j) \rangle = \text{cov}(x_i, x_j) = \sigma_{x_i}^2 \cdot \delta_{ij}, \quad (11)$$

where $\sigma_{x_i}^2$ is the variance of x_i and δ_{ij} is the Kronecker delta. In practice, one uses the corresponding signals extracted from the sample mean of the measurement in order to define the truth in the definition of bias, which leads to Eq. (9). Equation (11) assumes that the measurements are independent. Using Eq. (6) and (8), the bias of an estimator $\hat{\theta}$ can be approximately calculated as follows:

$$b_{\theta}(\hat{\theta}) = E(\hat{\theta} - \theta) \approx \frac{1}{2} \sum_i \frac{\partial^2 \hat{\theta}}{\partial x_i^2} \bigg|_{\bar{\mathbf{x}}} \sigma_{x_i}^2. \quad (12)$$

Namely, the bias of θ is related to the second-order derivative of the estimator calculated based on the expected value of $\bar{\mathbf{x}}$ and the variance of the measured data ($\sigma_{x_i}^2$).

3.B. Biases of multicontrast signal estimators

3.B.1. Bias of the absorption contrast signal estimator

Using the closed-form solution of $\hat{N}_0$ given in Eq. (3), the following result can be found:

$$\frac{\partial^2 \hat{N}_0}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} = 0, \quad (13)$$

Notice, additionally, that all of the higher order derivatives are also equal to zero because $\hat{N}_0$ is linearly related to $N^{(k)}$, which immediately leads to the following exact result:

$$b(\hat{N}_0) = 0. \quad (14)$$

Namely, the absorption contrast signal estimator is an unbiased estimator.

3.B.2. Bias of the dark-field contrast signal estimator

Based on the closed-form solution of $\hat{N}_1$ given in Eq. (4), the following result can be obtained:

$$\frac{\partial^2 \hat{N}_1}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} = \frac{4 \sin^2(\frac{2\pi k}{M} + \bar{\phi})}{M^2 \bar{N}_1}. \quad (15)$$

For quantum-limited photon-counting x-ray imaging systems, the recorded number of photons usually follows the Poisson distribution, which means that the variance of $N^{(k)}$ is equal to its mean value, namely:

$$\begin{aligned}
 \sigma_{N^{(k)}}^2 &= \bar{N}^{(k)} \\
 &= \bar{N}_0 + \bar{N}_1 \cos\left(\frac{2\pi k}{M} + \bar{\phi}\right). \quad (16)
 \end{aligned}$$

Therefore, the bias for the dark-field signal estimator is given by

$$\begin{aligned}
 b(\hat{N}_1) &\approx \frac{1}{2} \sum_{k=1}^M \frac{\partial^2 \hat{N}_1}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 \\
 &= \frac{1}{2} \sum_{k=1}^M \frac{4 \sin^2(\frac{2\pi k}{M} + \bar{\phi})}{M^2 \bar{N}_1} \left[\bar{N}_0 + \bar{N}_1 \cos\left(\frac{2\pi k}{M} + \bar{\phi}\right) \right] \\
 &= \frac{1}{M\bar{\epsilon}}, \quad (17)
 \end{aligned}$$

where $\bar{\epsilon} = \frac{\bar{N}_1}{\bar{N}_0}$, and it describes the mean fringe visibility of the grating interferometer. In practice, it is the fringe visibility that is used to define the dark-field contrast signal. Therefore, it would be interesting to directly study the potential bias of the following fringe visibility estimator:

$$\hat{\epsilon} = \frac{\hat{N}_1}{\hat{N}_0} \quad (18)$$

With a few more straightforward calculations (please see APPENDIX C for details of the derivation), the bias of $\hat{\epsilon}$ is found to be

$$b(\hat{\epsilon}) \approx \frac{1}{M\bar{N}_0\bar{\epsilon}}. \quad (19)$$

Based on Eqs. (17) and (19), the dark-field signal estimator is a biased estimator, and the bias level depends on the total number of phase steps, the exposure per phase step used in data acquisitions, and the mean fringe visibility of the grating interferometer.

3.B.3. Bias of the differential phase-contrast signal estimator

Note that the Arg function that relates the estimator $\hat{\phi}$ to the measured data $N^{(k)}$ is not a continuous function everywhere. This point can be easily illustrated using the function $\hat{\theta} = \text{Arg}(-1 + ix)$ as an example. When x varies continuously from $-\epsilon$ to ϵ , where $\epsilon \rightarrow 0^+$, the value of $\hat{\theta}$ changes abruptly from $-\pi$ to π , indicating a discontinuity in this

function. As a result, Eq. (12) cannot be used to calculate the bias of $\hat{\phi}$.

To study the potential bias of the DPC signal estimator, an alternative method must be employed. Actually, due to phase wrapping, the following wrapped normal distribution²⁴ can be used to model the statistical distribution of the estimated $\hat{\phi}$:

$$f(\hat{\phi}) = \sum_{k=-\infty}^{+\infty} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(\hat{\phi}-\bar{\phi}+2k\pi)^2}{2\sigma^2}}, \quad (20)$$

where $\hat{\phi} \in (-\pi, \pi]$ and $\sigma^2 = \frac{2}{MN_0\bar{\epsilon}^2}$ denotes the variance of the phase-contrast signal, which has been well investigated both theoretically and experimentally.^{15–22} Using Eq. (6) and the wrapped normal distribution in Eq. (19), the bias of $\bar{\phi}$ can be calculated as follows (details are presented in Appendix A):

$$b(\hat{\phi}) = \pi \left[\operatorname{erf}\left(\frac{\pi - \bar{\phi}}{\sqrt{2\sigma^2}}\right) - \operatorname{erf}\left(\frac{\pi + \bar{\phi}}{\sqrt{2\sigma^2}}\right) \right] + b_r(\bar{\phi}, \sigma) \quad (21)$$

and

$$b_r(\bar{\phi}, \sigma) = \pi \sum_{k=1}^{+\infty} \left\{ \operatorname{erf}\left[\frac{(2k+1)\pi}{\sqrt{2\sigma^2}}(1 - \Delta_k)\right] - \operatorname{erf}\left[\frac{(2k+1)\pi}{\sqrt{2\sigma^2}}(1 + \Delta_k)\right] \right\}, \quad (22)$$

where the error function $\operatorname{erf}(x)$ and parameter Δ_k are defined as follows:

$$\operatorname{erf}(x) =: \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} dt, \quad (23)$$

$$\Delta_k =: \frac{\bar{\phi}}{(2k+1)\pi}. \quad (24)$$

Since $|\Delta_k| = \frac{|\bar{\phi}|}{(2k+1)\pi} \leq \frac{1}{3}$ for any $k \geq 1$, Δ_k can be used as a small quantity to approximate the error function $\operatorname{erf}\left[\frac{(2k+1)\pi}{\sqrt{2\sigma^2}}(1 - \Delta_k)\right]$ using the Taylor series expansion method. As a result, the infinite summation over k in Eq. (21) can be approximated as follows:

$$\begin{aligned} b_r(\bar{\phi}, \sigma) &\approx -\frac{2\pi\bar{\phi}}{\sqrt{2\sigma^2}} \sum_{k=1}^{\infty} \operatorname{erf}'\left[\frac{(2k+1)\pi}{\sqrt{2\sigma^2}}\right] \\ &= -\frac{4\pi\bar{\phi}}{\sqrt{2\pi\sigma^2}} \sum_{k=1}^{+\infty} \exp\left[-\frac{\pi^2}{2\sigma^2} \times (2k+1)^2\right] \\ &\approx -\bar{\phi} \left[1 - \operatorname{erf}\left(\frac{\pi}{\sqrt{2\sigma^2}}\right)\right] \\ &\quad + \frac{\sqrt{2\pi}\bar{\phi}}{\sigma} \left(1 - \frac{\pi^2}{6\sigma^2}\right) \exp\left(-\frac{\pi^2}{2\sigma^2}\right). \end{aligned} \quad (25)$$

As shown in Appendix B, the Euler–MacLaurin summation formula can be used to approximate the summation in the last line of Eq. (25). By substituting the above result into

Eq. (21), the following major theoretical result is obtained for the bias of the phase-contrast signal estimator:

$$\begin{aligned} b(\hat{\phi}) &\approx \pi \left[\operatorname{erf}\left(\frac{\pi - \bar{\phi}}{\sqrt{2\sigma^2}}\right) - \operatorname{erf}\left(\frac{\pi + \bar{\phi}}{\sqrt{2\sigma^2}}\right) - \frac{\bar{\phi}}{\pi} \left[1 - \operatorname{erf}\left(\frac{\pi}{\sqrt{2\sigma^2}}\right)\right] \right] \\ &\quad + \frac{\sqrt{2\pi}\bar{\phi}}{\sigma} \left(1 - \frac{\pi^2}{6\sigma^2}\right) \exp\left(-\frac{\pi^2}{2\sigma^2}\right). \end{aligned} \quad (26)$$

The above analytical formula is asymptotically valid for all $\bar{\phi}$ and σ , since the only condition used in the derivation is that $\Delta_k = \frac{|\bar{\phi}|}{(2k+1)\pi}$ is a small quantity, and this is generally true for $k \geq 1$. As shown in Fig. 1, the approximate result in Eq. (26) is consistent with the brute force summation from $k = 1$ to 1000 in Eq. (21) for various $\bar{\phi}$ and σ . To gain further insight into the above results, several limiting cases were discussed as follows:

- Small σ limit, that is, $\sigma \ll \pi$. This corresponds to the high exposure limit in grating-based x-ray multicontrast imaging. In this case, $\operatorname{erf}\left(\frac{\pi}{\sqrt{2\sigma^2}}\right) \rightarrow 1$, $\left(1 - \frac{\pi^2}{6\sigma^2}\right) \exp\left(-\frac{\pi^2}{2\sigma^2}\right) \rightarrow 0$, and Eq. (26) can be approximated as follows:

$$b(\hat{\phi}) \approx \pi \left[\operatorname{erf}\left(\frac{\pi - \bar{\phi}}{\sqrt{2\sigma^2}}\right) - \operatorname{erf}\left(\frac{\pi + \bar{\phi}}{\sqrt{2\sigma^2}}\right) \right]. \quad (27)$$

As shown in Fig. 1, this simple expression is valid up to $\sigma \approx 1$. Another observation is that $b(\hat{\phi})$ is exactly zero when $\bar{\phi} = 0$, and the bias becomes larger when $\bar{\phi}$ deviates from zero. Therefore, the degree of bias in DPC signal estimation depends on the actual signal amplitude.

- Large σ limit, that is, $\sigma \gg \pi > |\bar{\phi}|$. This corresponds to the low exposure limit in x-ray multicontrast imaging. In this case, the Taylor series expansion can be used to obtain the following approximations:

$$\begin{aligned} \pi \left[\operatorname{erf}\left(\frac{\pi - \bar{\phi}}{\sqrt{2\sigma^2}}\right) - \operatorname{erf}\left(\frac{\pi + \bar{\phi}}{\sqrt{2\sigma^2}}\right) \right] &\approx -\frac{2\sqrt{2\pi}\bar{\phi}}{\sigma} \\ -\bar{\phi} \left[1 - \operatorname{erf}\left(\frac{\pi}{\sqrt{2\sigma^2}}\right) \right] &\approx -\bar{\phi} \left(1 - \frac{\sqrt{2\pi}}{\sigma}\right) \\ \frac{\sqrt{2\pi}\bar{\phi}}{\sigma} \left(1 - \frac{\pi^2}{6\sigma^2}\right) \exp\left(-\frac{\pi^2}{2\sigma^2}\right) &\approx \frac{\sqrt{2\pi}\bar{\phi}}{\sigma}. \end{aligned} \quad (28)$$

Using the above approximations, Eq. (26) gives the following simple result:

$$b(\hat{\phi}) \approx -\frac{2\sqrt{2\pi}\bar{\phi}}{\sigma} + \bar{\phi} \left(-1 + \frac{\sqrt{2\pi}}{\sigma}\right) + \frac{\sqrt{2\pi}\bar{\phi}}{\sigma} = -\bar{\phi}. \quad (29)$$

Namely, the amplitude of the bias of the DPC signal at the low exposure limit is as large as the signal amplitude itself. This seemingly surprising result can be explained as follows: At extremely low exposure levels, the variance σ is so large that the wrapped normal distribution function approaches a uniform distribution for $\hat{\phi} \in [-\pi, +\pi]$. As a result, the expected value of $\hat{\phi}$ is zero, and thus its bias is $-\bar{\phi}$. This result agrees with what has been reported in Ref. [25].

FIG. 1. Comparison of $b(\hat{\phi})$ given by Eq. (21) and the approximate form given by Eq. (26) for different $\hat{\phi}$ and σ values.

In the following section, experimental studies were performed to validate the above theoretical results regarding the biases of the multicontrast signal estimators.

4. EXPERIMENTAL VALIDATION STUDIES

Experimental studies were performed on a grating-based x-ray multicontrast benchtop imaging system. The imaging system uses a medical grade rotating-anode x-ray tube with 1.0 mm nominal focal spots (model G1582, Varian Medical Systems, Inc., Salt Lake City, UT) and a CdTe-based photon counting detector (model XC-XFLITE X1, XCounter AB, Sweden). The detector has a 1536×128 array of $100 \mu\text{m}$ pixels. The grating interferometer consists of a source grating G0, a phase grating G1, and an analyzer grating G2. Specifically, the source grating G0 has a pitch size of $20.7 \mu\text{m}$ and a duty cycle of 35%; the phase grating G1 has a pitch size of $4.3 \mu\text{m}$ and a duty cycle of 50%. The analyzer grating G2 has a pitch size of $2.4 \mu\text{m}$ and a duty cycle of 50%. The G1 grating is a π -phase grating designed for 28 keV x-rays. The distance between G0 and G1 was set to 150.8 cm, and the distance between G1 and G2 was 17.5 cm. During the data acquisition, the tube potential was fixed at 40 kVp (mean energy of 28 keV). The fringe visibility of the system is approximately 0.2 under the aforementioned data acquisition conditions. The tube current was set at 15 mA, and the exposure time per phase step ranged from 8.33 ms to 333 ms. With this acquisition setup, the value of $\bar{N}_0$ ranged from 7 to 280. The total number of phase steps (M) ranged from 4 to 16.

For a given set of $\bar{N}_0$ and M , the measurements were repeated 200 times. Figure 2 illustrates the data processing procedure. First, the 200 sets of phase stepping data were averaged to get $\bar{N}^{(k)}(x, y)$, which was used to extract $\bar{N}_0(x, y)$, $\bar{N}_1(x, y)$, and $\bar{\phi}(x, y)$. Next, the estimators corresponding to each individual set of phase stepping data were generated based on Eq. (3)–(5). Finally, ensemble averaging was performed for each estimator.

4.A. Preparation of experimental system

It is well-known that a baseline phase drift may occur in experimental Talbot–Lau data acquisition systems due to thermal expansions caused by the heat dissipation of the x-ray tube and the establishment of thermal equilibrium between the data acquisition system and the environment. To eliminate the confounding effect of the thermal phase drift to the measurements of the signal bias in this paper, the system was warmed up for more than an hour to ensure that the needed thermal equilibrium conditions were established and the potential phase drifts were effectively suppressed. To examine the thermal stability of the system during the approximately 20 min required to obtain 200 measurements of $\hat{N}_1$ and $\hat{\phi}$ (16 phase steps $\times$ 333 ms per phase step $\times$ 200 measurements), a region of interest (ROI) was chosen and the mean of the ROI was plotted versus the temporal indices of the measurements. As shown in Fig. 3, the potential phase drifts were effectively eliminated in our data acquisitions.

4.B. Validation of $b(\hat{N}_0)$

According to the data processing procedure shown in Fig. 2 and the signal extraction formula for $\hat{N}_0$ shown in Eq. (3), $\bar{N}_0$ and $\langle \hat{N}_0 \rangle$ are given by

$$\begin{aligned} \bar{N}_0 &= \frac{1}{M} \sum_{k=1}^M \bar{N}^{(k)} = \frac{1}{M} \sum_{k=1}^M \frac{1}{200} \sum_{j=1}^{200} N_j^{(k)} \\ &= \frac{1}{200M} \sum_{k=1}^M \sum_{j=1}^{200} N_j^{(k)}, \end{aligned} \quad (30)$$

and

$$\begin{aligned} \langle \hat{N}_0 \rangle &= \frac{1}{200} \sum_{j=1}^{200} \langle \hat{N}_0 \rangle_j = \frac{1}{200} \sum_{j=1}^{200} \frac{1}{M} \sum_{k=1}^M N_j^{(k)} \\ &= \frac{1}{200M} \sum_{j=1}^{200} \sum_{k=1}^M N_j^{(k)}, \end{aligned} \quad (31)$$

respectively. In the above two equations, $N_j^{(k)}$ denotes the j^{th} repeated intensity measurement at the k^{th} phase step position, and $\langle \hat{N}_0 \rangle_j$ indicates the estimated $\hat{N}_0$ from the j^{th} phase stepping measurement using Eq. (3). The bias of $\hat{N}_0$ is given by

$$b(\hat{N}_0) = \langle \hat{N}_0 \rangle - \bar{N}_0 = 0. \quad (32)$$

Therefore, $\hat{N}_0$ is an exact unbiased estimator. This result can be readily observed by comparing Eqs. (30) and (31). The result is also a direct consequence of the fact that the extraction of the absorption contrast signal described in Eq. (3) is a linear process.

4.C. Validation of $b(\hat{N}_1)$

Figure 4 shows images of $\bar{N}_1$, $\langle \hat{N}_1 \rangle$, $b_m(\hat{N}_1)$, and $\bar{\epsilon}$ at 0.5 mAs per phase step and the number of phase steps

(a) Signal extraction process for $\bar{N}_0$, $\bar{N}_1$, $\bar{\phi}$ (b) Signal extraction process for $\hat{N}_0$, $\hat{N}_1$, $\hat{\phi}$ FIG. 2. Flow chart of the signal extraction process for $\bar{N}_0$, $\bar{N}_1$, $\bar{\phi}$ and $\langle \hat{N}_0 \rangle$, $\langle \hat{N}_1 \rangle$, $\langle \hat{\phi} \rangle$

$M = 4$. The image of $\langle \hat{N}_1 \rangle$ appears to be much brighter than that of $\bar{N}_1$, indicating a positive bias of $\hat{N}_1$. The experimental result of bias $b_m(\hat{N}_1)$ is shown in Fig. 4(c). According to Section 3, the product of $b(\hat{N}_1)$ and fringe visibility should be inversely proportional to the number of phase steps, namely,

$$b_m(\hat{N}_1)\bar{\epsilon} \approx \frac{1}{M}. \quad (33)$$

In other words, the pixel-wise Hadamard product of the $b_m(\hat{N}_1)$ and the $\bar{\epsilon}(x, y)$ images should yield an image with constant pixel value. The experimental image generated by this pixel-wise Hadamard product was shown in Fig. 4(e), and the histogram of this product was shown in Fig. 4(f). The mean $\pm$ standard deviation of this image was 0.28 ± 0.02 . Compared with the theoretical value of $1/M = 0.25$, the experimental result was in good agreement with the theoretical prediction.

The same data analysis method was applied to data acquired with other mAs and M values. For a given mAs, the experimental values of $b_m(N_1)\bar{\epsilon}$ were plotted against $1/M$, and the results are presented in Fig. 5. Based on the linear fit of the data, the measured bias of N_1 has a good agreement with the theoretical prediction. Since the slope of the linear regression in Fig. 5 varied slightly for different mAs, the experimental values of $b_m(N_1)\bar{\epsilon}$ were then plotted across different mAs levels for a given M value. As shown by Fig. 6, the results were nearly independent of mAs except at extremely low exposure levels.

4.D. Validation of $b(\hat{\epsilon})$

Figure 7 shows images of $\bar{\epsilon}$, $\langle \hat{\epsilon} \rangle$, and $b(\hat{\epsilon})$ for the case of 0.5 mAs per phase step and $M = 4$ phase steps. It demonstrates that there is a positive bias of $\hat{\epsilon}$. In Fig. 8, the bias of $\hat{\epsilon}$ is drawn as a function of the number of phase steps and the

mAs per phase step. The experimental results (represented by the points with error bars) and the theoretical predictions (represented by the solid lines) agree well. The bias decreases

when M increases or when mAs per phase step increases. Generally speaking, increasing the total exposure ($M\bar{N}_0$) decreases the bias of $\hat{\epsilon}$, which is consistent with Eq. (19).

FIG. 3. Demonstration of elimination of potential phase drift in experimental acquisitions.

FIG. 4. Experimental images of $\bar{N}_1$, $\langle \hat{N}_1 \rangle$, $b_m(\hat{N}_1)$, $\bar{\epsilon}$, $b_m(\hat{N}_1) \circ \bar{\epsilon}$ (0.5 mAs per phase step, $M = 4$), and the histogram of $b_m(\hat{N}_1) \circ \bar{\epsilon}$. The display range for both $\bar{N}_1$ and $\langle \hat{N}_1 \rangle$ was matched at [4,10].

FIG. 5. Plot of $b_m(\hat{N}_1)\bar{\epsilon}$ vs. $1/M$. The circular points were taken from the DC value of the $\{b_m(\hat{N}_1) \circ \bar{\epsilon}\}$ images. The error bar was given by the standard deviation of each $\{b_m(\hat{N}_1) \circ \bar{\epsilon}\}$ image. The solid straight lines are the linear fit of the experimental data points.

FIG. 6. Plot of $b_m(\hat{N}_1)\bar{\epsilon}$ vs. mAs per phase step.

4.E. Validation of $b(\hat{\phi})$

Figure 9 shows the measured $\bar{\phi}$, $\langle \hat{\phi} \rangle$, and $b(\hat{\phi})$ at 2.5 mAs per phase step and $M = 8$. Images of $\bar{\phi}$ and $\langle \hat{\phi} \rangle$ looked similar, and there was no obvious bias in $\bar{\phi}$ except in the bright or dark region at the edge of the $b_m(\hat{\phi})$ image, where $\bar{\phi}$ is close to $\pm\pi$. These experimental observations are consistent with the theoretical prediction made in Eq. (26).

To further validate Eq. (26), the experimentally measured bias of $\hat{\phi}$ was plotted against the theoretically derived $b(\hat{\phi})$ in Fig. 10(a). A linear regression was performed and the coefficients are shown in the same figure. Bland–Altman plot [Fig. 10(b)] was also used to compare the experimental and theoretical results. Both figures demonstrated good agreement between the experimental and theoretical data.

Figure 11 shows $b(\hat{\phi})$ -mAs curves for different M and $\bar{\phi}$ values. The dashed lines in the plot represent the theoretically derived biases given in Eq. (26). The measured data agree well with the theoretical predictions. Figure 11 also shows that the bias of $\hat{\phi}$ becomes larger when the total exposure (i.e., mAs per phase step multiplied by the number of phase steps M) decreases. When $\bar{\phi}$ approaches $\pm\pi$, $b(\hat{\phi})$ becomes

larger. These observations are further confirmed by the experimental results shown in Figs. 12 and 13.

5. DISCUSSION

This work investigated the potential biases of x-ray multi-contrast image signals extracted using the well-known closed-form solution given in Eq. (3)–(5). Analytical results were derived and experimentally validated. For the absorption related signal $\hat{N}_0$, there is no bias.

For the dark-field related signal $\hat{N}_1$, the bias is inversely proportional to the product of the total number of phase steps and the average fringe visibility of the grating interferometer. To understand the practical implications of the bias $b(\hat{N}_1)$, it is beneficial to investigate the relative error introduced by the bias, that is,

$$\frac{b(\hat{N}_1)}{\hat{N}_1} = \frac{1/(M\bar{\epsilon})}{\bar{N}_0\bar{\epsilon}} = \frac{1}{M\bar{N}_0\bar{\epsilon}^2}. \quad (34)$$

If $M \geq 5$, $\bar{N}_0 \geq 200$, and visibility $\bar{\epsilon} \geq 0.1$, the above relative error is smaller than 0.1, which may not be significant. If the product of $M\bar{N}_0\bar{\epsilon}^2$ is smaller than 10, the relative error can be more than 10%. In this case, the inaccuracy caused by the estimator bias may not be negligible. From Eq. (17), it could be misleading to conclude that more phase steps would reduce the bias. In fact, when $M\bar{N}_0$ (proportional to total exposure level) is fixed, the relative error $b(\hat{N}_1)/\hat{N}_1$ is solely determined by the fringe visibility $\bar{\epsilon}$. Therefore, an increase in M under the condition of fixed total exposure level does not influence the relative bias of $\hat{N}_1$.

For the fringe visibility signal $\hat{\epsilon}$, the bias is inversely proportional to the product of the total number of phase steps M , the number of incident photons per phase step $\bar{N}_0$ (viz., radiation exposure level $M\bar{N}_0$) and the mean fringe visibility of the grating interferometer $\bar{\epsilon}$. Therefore, for a system with acquisition parameters of $M \geq 5$, $\bar{N}_0 \geq 200$, and visibility $\bar{\epsilon} \geq 0.1$, the bias of $\hat{\epsilon}$ is smaller than 0.01 and thus can be considered as insignificant. However, if the exposure level satisfies the condition of $M\bar{N}_0\bar{\epsilon} \ll 100$, then the bias can be much larger than 0.01 and thus it may not be negligible.

Since both the signal bias and signal standard deviation contribute to the final mean square error of the signal, that is,

FIG. 7. Experimental images of $\bar{\epsilon}$, $\langle \hat{\epsilon} \rangle$, and $b(\hat{\epsilon})$ (0.5 mAs per phase step, $M = 4$).

the overall signal variability, it would be interesting to compare the relative amplitude of the two contributions. Using the well-known error propagation formula, one can approximate the standard deviation of the visibility signal as follows:

$$\sigma_{\hat{\epsilon}}^2 = \left(\frac{\partial \hat{\epsilon}}{\partial \hat{N}_0} \right)^2 \sigma_{\hat{N}_0}^2 + \left(\frac{\partial \hat{\epsilon}}{\partial \hat{N}_1} \right)^2 \sigma_{\hat{N}_1}^2 = \frac{2 + \bar{\epsilon}^2}{M \bar{N}_0} \approx \frac{2}{M \bar{N}_0}, \quad (35)$$

FIG. 8. Plots of $b(\hat{\epsilon})$ vs. $1/M$. The circular points represent the experimental results and the solid lines are the theoretical predictions from Eq. (19). The three solid lines correspond to three different exposure levels: 1.5 mAs, 3 mAs, and 5 mAs per phase step.

where $\sigma_{\hat{N}_0}^2$ and $\sigma_{\hat{N}_1}^2$ have been investigated in the previous studies.^{15,23} Using this result and Eq. (19), the ratio between the bias and the standard deviation of the fringe visibility is proportional to the inverse of the mean fringe visibility as follows:

$$\frac{b(\hat{\epsilon})}{\sigma_{\hat{\epsilon}}} \approx \frac{1}{2\bar{\epsilon}}. \quad (36)$$

For a fixed fringe visibility, the above result dictates that the bias of $\hat{\epsilon}$ (i.e., $b(\hat{\epsilon})$) is proportional to $\sigma_{\hat{\epsilon}}^2$. As a consequence, when the exposure level is lowered for the purpose of radiation dose reduction, both signal bias and signal standard deviation increase and thus both contribute to the increase of the mean square error.

For the estimator of the DPC signal, $\hat{\phi}$, its bias depends on the phase-contrast signal amplitude, the radiation exposure level, and the fringe visibility of the grating interferometer. As shown in Eq. (26) and Fig. 1, the amplitude of the bias, $|b(\hat{\phi})|$, increases either when σ increases or when $|\bar{\phi}|$ approaches π . Based upon this property, one can deduce the following important implications for the practical use of DPC imaging:

First of all, this property indicates that if one hopes to keep the bias of DPC signal negligible, then a minimal amount of exposure is required. In fact, Eq. (26) can be used as a guideline to set such a minimal exposure level. For example, if $|b(\hat{\phi})|$ is required to be smaller than 0.1 for the range of $\phi \in [-\pi/2, \pi/2]$, then $\sigma \leq 0.6$ is required, as shown in Fig. 1. Using the relationship $\sigma^2 = \frac{2}{M \bar{N}_0 \bar{\epsilon}^2}$, the total number of detected photons must be larger than the following lower limit, $(M \bar{N}_0)_{\min}$,

FIG. 9. Images of $\bar{\phi}$, $\langle \hat{\phi} \rangle$, and $b_m(\hat{\phi})$. (2.5 mAs per phase step, $M = 8$). The display range for both (a) and (b) was matched at $[-\pi, \pi]$.

FIG. 10. (a) Plot of experimental $b(\hat{\phi})$ vs. theoretical $b(\hat{\phi})$. A linear regression was performed on the paired points, and the correlation coefficients are shown in the figure. (b) Bland-Altman plot of the experimental and theoretical $b(\hat{\phi})$.

FIG. 11. Plot of $b_m(\hat{\phi})$ vs. mAs per phase step for different M and $\bar{\phi}$ values. The dashed lines represent the theoretical derived biases. [Color figure can be viewed at wileyonlinelibrary.com]

$$(MN_0)_{\min} = \frac{2}{\sigma^2 \bar{\epsilon}^2} \approx 140, \quad (37)$$

where $\bar{\epsilon}$ is assumed to be around 0.2 for a typical x-ray interferometer system. Similarly, if the unbiased range of $\bar{\phi}$ is expanded, σ needs to be smaller, and a larger number of detected photons is required.

Second, in DPC imaging, it is the difference of the estimated signals between a scan with the image object present and a background scan without the object that generates the final DPC image. As a result, the signal bias in the background scan will introduce additional bias for the final DPC signals of the target of interest. Using the result derived and validated in this paper, to reduce the additional bias caused by the background scan, one can adjust the starting position of the phase stepping procedure, so that $|\bar{\phi}|$ can be close to zero for most of the image pixels.

Last but not least, both the signal magnitude and signal-to-noise ratio (SNR) of DPC imaging are related to the sensitivity of the grating interferometer, with higher sensitivity corresponding to higher signal magnitude and SNR.²⁶ However, this work shows that higher signal level may also generate higher bias in the estimated DPC signal. Under a given radiation dose constraint, the sensitivity of the grating interferometer can be optimized to achieve the

FIG. 12. Plot of $b_m(\hat{\phi})$ vs. total mAs for different $\bar{\phi}$ values. [Color figure can be viewed at wileyonlinelibrary.com]

needed balance between SNR and signal accuracy for a specific imaging task.

As a final remark, it is important to emphasize that the theoretical analysis of the signal bias in this work is based upon point statistics and thus its applicability is limited to the local signal estimation method. It is not clear yet

FIG. 13. Plot of $b_m(\hat{\phi})$ vs. $\bar{\phi}$ for different M value and mAs per phase step. The dashed lines represent the theoretical derived biases. [Color figure can be viewed at wileyonlinelibrary.com]

whether the same conclusion regarding signal bias holds true for other nonlocal phase retrieval acquisition methods such as the single-shot acquisition method proposed by the authors' group,^{27,28} or the conjugate ray method by others.²⁹ It would also be interesting to investigate the potential signal bias in these nonlocal signal retrieval methods, but these investigations are clearly beyond the scope of the present paper.

6. CONCLUSIONS

In conclusion, the potential biases for all three contrast mechanisms in grating-based x-ray multicontrast imaging have been studied. Analytical results have been derived to characterize the level of biases and the dependence of biases on imaging parameters. The theoretical results were validated by extensive experimental studies. The results demonstrated that the estimated absorption contrast signal is unbiased while the estimated dark-field contrast signal is biased, but this bias decreases with improved visibility of the grating interferometer. In contrast, whether the estimated DPC signal is biased or not depends on the mean signal level, the radiation exposure level, and the average fringe visibility of the grating interferometer.

ACKNOWLEDGMENTS

The authors thank Daniel Gomez-Cardona, John Hayes, Kayla Gomez-Cardona, and Evan Harvey for their editorial assistance. This work was partially supported by the National Institute of Biomedical Imaging and Bioengineering of the National Institutes of Health under Award Number R01EB020521, and by the Office of the Assistant Secretary of Defense for Health Affairs, through the Breast Cancer Research Program, under Award No. W81XWH-16-1-0031. However, opinions, interpretations, conclusions, and recommendations are those of the authors; they do not necessarily represent the official views of the funding agencies, nor necessarily endorsed by the federal funding agencies.

APPENDIX A

BIAS WITH WRAPPED NORMAL DISTRIBUTION

In this Appendix, mathematical details of the derivation of Eq. (21) are presented. Given the wrapped normal distribution function,

$$f(\hat{\phi}) = \sum_{k=-\infty}^{+\infty} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(\hat{\phi}-\bar{\phi}+2k\pi)^2}{2\sigma^2}}, \quad \hat{\phi} \in (-\pi, \pi], \quad (\text{A1})$$

the bias is calculated as follows:

$$b(\hat{\phi}) = \langle \hat{\phi} \rangle - \bar{\phi} \quad (\text{A2})$$

$$\begin{aligned} &= \int_{-\pi}^{\pi} (\hat{\phi} - \bar{\phi}) f(\hat{\phi}) d\hat{\phi} \\ &= \int_{-\pi}^{\pi} (\hat{\phi} - \bar{\phi}) \sum_{k=-\infty}^{+\infty} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(\hat{\phi}-\bar{\phi}+2k\pi)^2}{2\sigma^2}} d\hat{\phi} \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} \int_{-\pi}^{\pi} (\hat{\phi} - \bar{\phi}) e^{-\frac{(\hat{\phi}-\bar{\phi}+2k\pi)^2}{2\sigma^2}} d\hat{\phi} \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} \int_{(2k-1)\pi-\bar{\phi}}^{(2k+1)\pi-\bar{\phi}} (\zeta - 2k\pi) e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \quad (\zeta = \hat{\phi} - \bar{\phi} + 2k\pi) \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} \int_{(2k-1)\pi-\bar{\phi}}^{(2k+1)\pi-\bar{\phi}} \zeta e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \\ &\quad + \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} \int_{(2k-1)\pi-\bar{\phi}}^{(2k+1)\pi-\bar{\phi}} -2k\pi e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{+\infty} \zeta e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \\ &\quad + \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} \int_{(2k-1)\pi-\bar{\phi}}^{(2k+1)\pi-\bar{\phi}} -2k\pi e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \\ &= \frac{1}{\sqrt{2\pi\sigma^2}} \sum_{k=-\infty}^{+\infty} (-2k\pi) \int_{(2k-1)\pi-\bar{\phi}}^{(2k+1)\pi-\bar{\phi}} e^{-\frac{\zeta^2}{2\sigma^2}} d\zeta \quad (\text{A3}) \end{aligned}$$

$$= \sum_{k=-\infty}^{+\infty} -k\pi \left[\operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) - \operatorname{erf} \left(\frac{(2k-1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) \right],$$

where the error function defined in Eq. (24) is used. By changing the dummy variable k in the summation, $b(\hat{\phi})$ can be written as

$$\begin{aligned} b(\hat{\phi}) &= \pi \sum_{k=-\infty}^{+\infty} \operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) \\ &= \pi \sum_{k=0}^{+\infty} \operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) + \pi \sum_{k=-\infty}^{-1} \operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) \\ &= \pi \sum_{k=0}^{+\infty} \operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) + \pi \sum_{k=0}^{+\infty} \operatorname{erf} \left(-\frac{(2k+1)\pi + \bar{\phi}}{\sqrt{2}\sigma^2} \right) \\ &= \pi \sum_{k=0}^{+\infty} \left[\operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) - \operatorname{erf} \left(\frac{(2k+1)\pi + \bar{\phi}}{\sqrt{2}\sigma^2} \right) \right] \\ &= \pi \left[\operatorname{erf} \left(\frac{\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) - \operatorname{erf} \left(\frac{\pi + \bar{\phi}}{\sqrt{2}\sigma^2} \right) \right] + b_r(\bar{\phi}, \sigma), \end{aligned}$$

where

$$\begin{aligned} b_r(\bar{\phi}, \sigma) &= \pi \sum_{k=1}^{+\infty} \left[\operatorname{erf} \left(\frac{(2k+1)\pi - \bar{\phi}}{\sqrt{2}\sigma^2} \right) \right. \\ &\quad \left. - \operatorname{erf} \left(\frac{(2k+1)\pi + \bar{\phi}}{\sqrt{2}\sigma^2} \right) \right]. \end{aligned} \quad (\text{A4})$$

This is Eq. (21) in the manuscript.

APPENDIX B

EULER–MACLAURIN SUMMATION

Using the Euler–Maclaurin summation formula,³⁰

$$\sum_{k=1}^{+\infty} f(k) \approx \int_0^{+\infty} f(x) dx - \frac{1}{2}f(0) - \frac{1}{12}f'(0). \quad (\text{B1})$$

The summation in Eq. (25) can be written as

$$\begin{aligned} \sum_{k=1}^{+\infty} \exp \left[-\frac{\pi^2}{2\sigma^2} \times (2k+1)^2 \right] &\approx \frac{\sigma}{2\sqrt{2}\pi} \left[1 - \operatorname{erf} \left(\frac{\pi}{\sqrt{2}\sigma^2} \right) \right] \\ &\quad - \frac{1}{2} \left(1 - \frac{\pi^2}{6\sigma^2} \right) e^{-\frac{\pi^2}{2\sigma^2}}. \end{aligned} \quad (\text{B2})$$

The above result lead to the final result in Eq. (26).

APPENDIX C

BIAS OF THE FRINGE VISIBILITY $\hat{\epsilon}$

Based on Eq. (12), the bias of the fringe visibility is given approximately by the following formula:

$$b(\hat{\epsilon}) \approx \frac{1}{2} \sum_{k=1}^M \frac{\partial^2 \hat{\epsilon}}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2. \quad (\text{C1})$$

Notice that $\hat{\epsilon} = \frac{\hat{N}_1}{\hat{N}_0}$. Using the chain rule of differentiation, one may obtain the second order derivative as follows:

$$\begin{aligned} \frac{\partial^2 \hat{\epsilon}}{\partial (N^{(k)})^2} &= \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_0^2} \left(\frac{\partial \hat{N}_0}{\partial N^{(k)}} \right)^2 + \frac{\partial \hat{\epsilon}}{\partial \hat{N}_0} \frac{\partial^2 \hat{N}_0}{\partial (N^{(k)})^2} \\ &\quad + \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1^2} \left(\frac{\partial \hat{N}_1}{\partial N^{(k)}} \right)^2 + \frac{\partial \hat{\epsilon}}{\partial \hat{N}_1} \frac{\partial^2 \hat{N}_1}{\partial (N^{(k)})^2} \\ &\quad + 2 \times \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1 \partial \hat{N}_0} \frac{\partial \hat{N}_1}{\partial N^{(k)}} \frac{\partial \hat{N}_0}{\partial N^{(k)}}. \end{aligned} \quad (\text{C2})$$

Therefore,

$$\begin{aligned} b(\hat{\epsilon}) &\approx \frac{1}{2} \sum_{k=1}^M \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_0^2} \left(\frac{\partial \hat{N}_0}{\partial N^{(k)}} \right)^2 \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 + \frac{1}{2} \sum_{k=1}^M \frac{\partial \hat{\epsilon}}{\partial \hat{N}_0} \frac{\partial^2 \hat{N}_0}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 + \\ &\quad \frac{1}{2} \sum_{k=1}^M \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1^2} \left(\frac{\partial \hat{N}_1}{\partial N^{(k)}} \right)^2 \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 + \frac{1}{2} \sum_{k=1}^M \frac{\partial \hat{\epsilon}}{\partial \hat{N}_1} \frac{\partial^2 \hat{N}_1}{\partial (N^{(k)})^2} \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 + \\ &\quad \sum_{k=1}^M \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1 \partial \hat{N}_0} \frac{\partial \hat{N}_1}{\partial N^{(k)}} \frac{\partial \hat{N}_0}{\partial N^{(k)}} \bigg|_{\bar{N}^{(k)}} \sigma_{N^{(k)}}^2 \\ &= \frac{1}{2} \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_0^2} \bigg|_{\bar{N}^{(k)}} \sigma_{\hat{N}_0}^2 + \frac{\partial \hat{\epsilon}}{\partial \hat{N}_0} \bigg|_{\bar{N}^{(k)}} b(\hat{N}_0) + \frac{1}{2} \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1^2} \bigg|_{\bar{N}^{(k)}} \sigma_{\hat{N}_1}^2 \\ &\quad + \frac{\partial \hat{\epsilon}}{\partial \hat{N}_1} \bigg|_{\bar{N}^{(k)}} b(\hat{N}_1) \\ &\quad + \frac{\partial^2 \hat{\epsilon}}{\partial \hat{N}_1 \partial \hat{N}_0} \bigg|_{\bar{N}^{(k)}} \operatorname{cov}(\hat{N}_1, \hat{N}_0), \\ &= \frac{1}{2} \times \frac{2\bar{N}_1}{\bar{N}_0^3} \times \frac{\bar{N}_0}{M} + 0 + 0 + \frac{1}{\bar{N}_0} \times \frac{1}{M\bar{\epsilon}} - \frac{1}{\bar{N}_0^2} \times \frac{\bar{\epsilon}\bar{N}_0}{M}, \\ &= \frac{1}{M\bar{N}_0\bar{\epsilon}}. \end{aligned} \quad (\text{C3})$$

^{a)} Author to whom correspondence should be addressed. Electronic mail: gchen7@wisc.edu.

REFERENCES

1. Momose A, Kawamoto S, Koyama I, Hamaishi Y, Takai H, Suzuki Y. Demonstration of x-ray Talbot interferometry. *Jpn J Appl Phys.* 2003;42:866–8.
2. Weitkamp T, Diaz A, David C, et al. X-ray phase imaging with a grating interferometer. *Opt Exp.* 2005;12:6296–304.
3. Pfeiffer F, Weitkamp T, Bunk O, David C. Phase retrieval and differential phase-contrast imaging with low-brilliance x-ray sources. *Nat Phys.* 2006;2:258–261.
4. Pfeiffer F, Bech M, Bunk O, et al. Hard-x-ray dark-field imaging using a grating interferometer. *Nat Mater.* 2008;7:134–137.
5. Stamparoni M, Wang Z, Thüning T, et al. The first analysis and clinical evaluation of native breast tissue using differential phase-contrast mammography. *Invet Radiol.* 2011;46:801–6.
6. Stutman D, Beck TJ, Carrino JA, Bingham CO. Talbot phase-contrast x-ray imaging for the small joints of the hand. *Phys Med Biol.* 2011;56:5697–720.
7. Tapfer A, Bech M, Velroyen A, et al. Experimental results from a pre-clinical X-ray phase-contrast CT scanner. *Proc Natl Acad Sci USA.* 2012;109:15691–6.

8. Li K, Garrett J, Chen G-H. Correlation between human observer performance and model observer performance in differential phase contrast CT. *Med Phys*. 2013;40:111905.
9. Li K, Ge Y, Garrett J, Bevins N, Zambelli J, Chen G-H. Grating-based phase contrast tomosynthesis imaging: proof-of-concept experimental studies. *Med Phys*. 2014;41:011903.
10. Garrett J, Ge Y, Li K, Chen G-H. Anatomical background noise power spectrum in differential phase contrast and dark field contrast mammograms. *Med Phys*. 2014;41:120701.
11. Koehler T, Daerr H, Martens G, et al. Slit-scanning differential x-ray phase-contrast mammography: proof-of-concept experimental studies. *Med Phys*. 2015;42:1959–1965.
12. Miao H, Gomella AA, Harmon KJ, et al. Enhancing tabletop x-ray phase contrast imaging with nano-fabrication. *Sci Rep*. 2015;5:13581.
13. Miao H, Panna A, Gomella AA, et al. A universal moiré effect and application in X-ray phase-contrast imaging. *Nat Phys*. 2016;12:830–834.
14. Birnbacher L, Willner M, Velroyen A, et al. Experimental realisation of high-sensitivity laboratory x-ray grating-based phase-contrast computed tomography. *Sci Rep* 2016;6:24022.
15. Weber T, Bartl P, Bayer F, et al. Noise in x-ray grating-based phase-contrast imaging. *Med Phys*. 2011;38:4133.
16. Revol V, Kottler C, Kaufmann R, Straumann U, Urban C. Noise analysis of grating-based x-ray differential phase contrast imaging. *Rev Sci Instrum*. 2010;81:073709.
17. Chen G-H, Zambelli J, Li K, Bevins N, Qi Z. Scaling law for noise variance and spatial resolution in differential phase contrast computed tomography. *Med Phys*. 2011;38:584.
18. Raupach R, Flohr TG. Analytical evaluation of the signal and noise propagation in x-ray differential phase-contrast computed tomography. *Phys Med Biol*. 2011;56:2219–44.
19. Köhler T, Jürgen Engel K, Roessl E. Noise properties of grating-based x-ray phase contrast computed tomography. *Med Phys*. 2011;38: Suppl 1S106.
20. Tang X, Yang Y, Tang S. Characterization of imaging performance in differential phase contrast CT compared with the conventional CT-Noise power spectrum NPS(k). *Med Phys*. 2011;38:4386.
21. Li K, Bevins N, Zambelli J, Qi Z, Chen G-H. Detection performance study for cone-beam differential phase contrast CT. In: Pelc NJ, Nishikawa RM, Whiting BR, eds. *Medical Imaging Physics of Medical Imaging*, Vol. 8313, (Proc. SPIE, 2012); 2012: 83131L.
22. Li K, Bevins N, Zambelli J, Chen G-H. Fundamental relationship between the noise properties of grating-based differential phase contrast CT and absorption CT: theoretical framework using a cascaded system model and experimental validation. *Med Phys*. 2013;40:021908.
23. Ge Y, Li K, Chen G-H. Cramer-rao lower bound in differential phase contrast imaging and its application in the optimization of data acquisition systems. *Proc SPIE* 9033, 2014:90330F–90330F–6.
24. Fisher NI. *Statistical Analysis of Circular Data*. Cambridge: Cambridge University Press; 1996.
25. Chabior M. Contributions to the characterization of grating-based x-ray phase-contrast imaging, Ph.D. thesis, der Technischen Universität Dresden; 2011.
26. Modregger P, Pinzer BR, Thüning T, Rutishauser S, David C, Stampf M. Sensitivity of x-ray grating interferometry. *Opt Express* 2011;19:18324–18338.
27. Ge Y, Li K, Garrett J, Chen G-H. Grating based x-ray differential phase contrast imaging without mechanical phase stepping. *Opt Express* 2014;22:14246–14252.
28. Bevins N, Zambelli J, Li K, Qi Z, Chen G-H. Multi-contrast x-ray computed tomography imaging using talbot-lau interferometry without phase stepping. *Med Phys*. 2012;39:424–428.
29. Zhu P, Zhang K, Wang Z, et al. Low-dose, simple, and fast grating-based x-ray phase-contrast imaging. *Proc Natl Acad Sci USA*. 2010;107:13576.
30. Abramowitz M, Stegun IA. eds., *Handbook of Mathematical Functions with Formulas, Graphs, and Mathematical Tables*. New York: Dover Publications; 1972.