Isotropic quantitative differential phase contrast microscopy using radially asymmetric color-encoded pupil

Yu-Hsiang Lin\textsuperscript{1,2}\textsuperscript{*}, An-Cin Li\textsuperscript{1}, Sunil Vyasa, Yi-You Huang\textsuperscript{3,4}, J Andrew Yeh\textsuperscript{2,}\textsuperscript{*} and Yuan Luo\textsuperscript{1,3,5,6,}\textsuperscript{*}

\textsuperscript{1} Institute of Medical Device and Imaging, National Taiwan University, Taipei 10051, Taiwan, R. O. C.
\textsuperscript{2} Department of Power Mechanical Engineering, National Tsing Hua University, Hsinchu 30013, Taiwan, R. O. C.
\textsuperscript{3} Department of Biomedical Engineering, National Taiwan University, Taipei 10051, Taiwan, R. O. C.
\textsuperscript{4} National Taiwan University Hospital, Taipei 10051, Taiwan, R. O. C.
\textsuperscript{5} National Taiwan University, Molecular Imaging Center, Taipei 10672, Taiwan, R. O. C.
\textsuperscript{6} National Taiwan University, YongLin Institute of Health, Taipei 10087, Taiwan, R. O. C.

\textsuperscript{*} Authors to whom any correspondence should be addressed.
E-mail: jayeh@pme.nthu.edu.tw and yuanluo@ntu.edu.tw

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Abstract
Differential phase contrast (DPC) microscopy provides isotropic phase images by applying asymmetric illumination patterns on the sample. The movement of specimens during series image acquisition may lead to motion blur artifacts, which are difficult to prevent. Here, we propose a new method based on pupil engineering and color multiplexing to obtain an isotropic phase transfer function and to reduce the required frames simultaneously. Radially asymmetric color pupils are implemented in a DPC microscope using a programmable thin-film transistor as a digital pupil, which gives flexibility and dynamic control for projecting illumination patterns on samples. With our approach, an isotropic quantitative phase map can be obtained using only pairwise color images for phase reconstruction. A radially asymmetric color pupil is synthesized by encoding the red, green, and blue colors. To recover accurate phase values, a color-leakage correction algorithm is applied to calibrate each color channel. Compared to a half-circle illumination pupil, our method can significantly enhance the image acquisition speed. The phase recovery accuracy is more than 97%. To show the imaging performance of our proposed method, quantitative phase imaging of living 3T3 mouse fibroblast cells is performed. Our quantitative phase measurement method may find important applications in biomedical research.

1. Introduction
Quantitative phase imaging (QPI) is a label-free imaging technique which is used to obtain phase information from translucent specimens. In the last decade, QPI has become an advanced imaging tool for obtaining valuable quantitative biophysical information \cite{1-4} for investigating cells and tissues \cite{3, 4}. Among the many QPI techniques, differential phase contrast (DPC) microscopy offers many advantages, such as higher resolution, reconstruction of accurate quantitative phase maps, and simple experimental configuration. DPC imaging can be performed in a qualitative as well as a quantitative manner. In the quantitative DPC (qDPC) method, phase values can be evaluated by deconvolving DPC images with the phase transfer function (PTF) based on the weak object function \cite{5, 6}. Typically, four images corresponding to four half-circle illumination patterns are required to calculate qDPC images in the two-axis measurement method \cite{5}. However, the missing frequencies of the PTF not only decrease the reconstruction accuracy, but also generate artifacts in two-axis measurements. To mitigate this issue, a strategy of achieving isotropic PTF using 12-axis measurements has been introduced \cite{5}. The accuracy can be improved by increasing the number of measurements with more axes, but it results in a low imaging speed. Moreover, fast-moving samples bring about motion blur artifacts, due to the temporal resolution limitations \cite{7}. It is a trade-off between reconstruction accuracy and imaging speed in traditional half-circle illumination patterns \cite{5}.
Pupil engineering can provide novel strategies to overcome this limitation by modulating the amplitude distribution of the pupil function. By designing pupil functions with specific amplitude variations, we can accomplish isotropic PTF even with a few intensity measurements. To implement pupil functions, LED arrays or thin-film transistor (TFT)-LCDs have been used as key components. These components serve as digital pupils in the qDPC microscope. It is important to note that only with digital pupils can transmittance be dynamically manipulated at each point across the pupil; this is not possible with conventional hardware pupils [8]. It is convenient to embed the digital pupil in the Fourier plane of the illumination part of the microscope, and modulate the amplitude distribution according to the requirement. In addition, digital pupils are dynamic and reconfigurable, and can be rotated or shifted without any mechanical movements, such that the system maintains high stability and robustness. In the pupil engineering approach, there are two main methods, namely the monochrome pupil and color pupil method. To obtain isotropic PTF, several monochrome pupils have been proposed, including a gradient pupil [9], radially asymmetric pupil [10], and optimal pupil [11]. These monochrome pupils are displayed on the TFT-LCD panel rather than being synthesized by the LED array for illumination. Since the pixel pitch of the TFT-LCD is smaller by at least one order of magnitude than the LED array, it not only generates uniform illumination but also continuously modulates the amplitude across the entire pupil. To achieve isotropic PTF, four intensity measurements are required for the gradient pupil and optimal pupil, while the radially asymmetrical pupil requires six intensity measurements. In the annular illumination approach, the transmittance of the optimal pupil is severely limited despite its capability to provide a high signal-to-noise ratio [11]. Besides the above limitation, it also requires a high-power light source to prevent poor image brightness.

In color pupil engineering methods, pupils are encoded with different colors to reduce the number of required frames for reconstruction. The different color images corresponding to color illumination can be separated before phase reconstruction. To reduce the image acquisition time, various pupil patterns have been designed by encoding red, blue, and green colors [8, 12–14]. The half-circle color pupil and trisection circle color pupil [12] require only one frame to reconstruct the phase, but isotropy of the PTF cannot be achieved. In contrast, an optimal color pupil can provide isotropic PTF with two frames but suffers from low-illumination images [14]. Moreover, color leakage between the illumination source and color camera will affect the reconstruction accuracy significantly [12]. Inevitably, there exists an overlap area of spectral response between different channels of the color camera. As a result, the other two channels will get a signal even when illuminated with one-color illumination. A color-leakage correction (CLC) algorithm has been developed to alleviate color-leakage phenomena by pre-measuring the color-leakage matrix for calibration [12].

In this work, color-multiplex isotropic qDPC microscopy is proposed. Based on color pupil engineering, a radially asymmetric color pupil is designed and implemented to speed up the image acquisition. To improve the phase reconstruction, a CLC algorithm is applied. A radially asymmetric color pupil is synthesized by encoding red, green, and blue colors. By illuminating the TFT with the synthesized pupil, pairwise color images are acquired. After calibration using CLC, the phase map can be accurately reconstructed. The performance of radially asymmetric color pupils is compared with the other proposed color pupils. Our method not only provides isotropic PTF with two measurements, but also offers high illumination efficiency. To demonstrate the potential of our method for biomedical applications, high-resolution three-dimensional (3D) phase imaging of live 3T3 mouse fibroblast cells is performed. The fine structural details of the cell, such as pseudopodia, can be observed with our system [15].

2. Method and theory

2.1. System configuration
The system configuration of the isotropic qDPC microscope is shown in figure 1. The microscope is configured with a programmable TFT panel, which is located at the front focal plane of the condenser lens. The radially asymmetric color pattern, projected onto the TFT panel, is shown in figure 2. Amplitude patterns were predesigned for qDPC measurements.

2.2. Radially asymmetric color pupils
The radially asymmetric color pupils in figure 2(a3)–(a8) are designed using equation (1). The pupil function \( S_{\lambda_i j}(r, \theta) \) is defined in polar coordinates, where \( r, \theta \) represent the radius and polar angle. \( \lambda_i \) is the wavelength of the color pupil, where \( i = 1, 2, 3 \) in our design and \( j \) denotes different color pupils.

The pupil design is composed of two functions, \( M_{\lambda_i j}(\theta) \) in equations (2) and (3) and \( \text{circ}(\theta) \) in equation (4)

\[
S_{\lambda_i j}(r, \theta) = M_{\lambda_i j}(\theta) \text{circ}(r).
\] (1)
Figure 1. Schematic diagram of isotropic qDPC microscope. Amplitude patterns displayed on TFT panel were employed as the color pupil, which is located at the front focal plane of the condenser under Koehler illumination condition. By utilizing different amplitude patterns, color images are captured by color camera.

In equation (2), $M_{\lambda i,j}(\theta)$ decides the transmittance of each pixel located at different polar angles, and $\theta_{as}$ represents the axis of symmetry of each pupil, which is defined by equation (3):
circ(r) = \begin{cases} 
1, & r \leq \rho_c \\
0, & r > \rho_c
\end{cases}, \quad \rho_c = \frac{NA_{\text{condenser}}}{\lambda},
(4)

where $NA_{\text{condenser}}$ is the numerical aperture of the condenser and $\lambda$ is the operating wavelength. As shown in figures 2(a1) and (a2), our radially asymmetric color pupil is synthesized by encoding the red, green, and blue colors, which can be represented by equation (5):

$$S_{\text{color}, j} = S_{\lambda 1, j} + S_{\lambda 2, j} + S_{\lambda 3, j}, \quad j = 1, 2.$$  
(5)

Figure 2(c) shows the composition of different colors in the pupil. The axis of symmetry of the color pupil can be obtained by equation (3, 4).

To describe the amplitude variation in the single color pupil we illustrate a grey-level pupil, function as shown in figure 3(a). The green and orange dashed lines show the amplitude distribution along different polar angles when the radius is equal to $\rho_c$ and $\rho_c/2$. The red and yellow arrows show the amplitude distribution along different radii, when $\theta = \pi/3$ and $2\pi/3$, respectively. Figure 3(b) shows the amplitude distribution along different polar angles, which follows equation (2). Following equation (4), the variation of the amplitude with the radius is shown in figure 3(c). From the figures, we can observe that the radially asymmetric pupil function depends only on the polar angle. The advantage of our color pupil is that at each pixel, the amplitude is modulated by all the constituent color components, which results in uniformity of illumination.

2.3. CLC model

Color leakage is the cross-talk phenomenon between the illumination wavelength and the spectral response between different channels of the color camera. When applying the TFT panel as a digital pupil, color filters inside the TFT panel can be treated as a band-pass filter. Different wavelengths of light will be filtered from the transmitted light according to the different wavelength band characteristics of the red, green, and blue filters. On the other hand, due to the overlap area of the spectral response area for each channel, the other two channels will get signals even when illuminating with a single color source. This will affect the reconstruction result owing to the deviation of qDPC image calculations.

In order to correct the color leakage, the cross-talk between each channel is modeled as [13]

$$\begin{bmatrix}
I_{\text{sensor}}^r \\
I_{\text{sensor}}^g \\
I_{\text{sensor}}^b
\end{bmatrix} = M_{\text{CL}} \begin{bmatrix}
I_{\text{illu}}^R \\
I_{\text{illu}}^G \\
I_{\text{illu}}^B
\end{bmatrix} = \begin{bmatrix}
\Re^R \\
\Re^G \\
\Re^B
\end{bmatrix} \begin{bmatrix}
I_{\text{illu}}^R \\
I_{\text{illu}}^G \\
I_{\text{illu}}^B
\end{bmatrix}.$$
(6)

$I_{\text{illu}}^R$ represents the average intensity from a single color under illumination in one color source and $I_{\text{sensor}}^r$ represents the signal from one color channel of the camera. $M_{\text{CL}}$ is a $3 \times 3$ color-leakage matrix, and for each element $\Re^R$, $\Re^G$, and $\Re^B$ is the ratio equal to the average value of one channel over the summation of the average value of three channels. $\Re^R$ is given as

$$\Re^R = \frac{I_j}{I^R + I^G + I^B}.$$  
(7)
Multiplying the inverse of the color-leakage matrix with each color image, the color leakage can be obtained:

$$\begin{bmatrix}
I_{\text{G, \text{illa}}} \\
I_{\text{B, \text{illa}}} \\
I_{\text{G, \text{illa}}}
\end{bmatrix} = M^{-1} \begin{bmatrix}
I_{\text{sensor}} \\
I_{\text{sensor}} \\
I_{\text{sensor}}
\end{bmatrix}. \tag{8}
$$

### 2.4. Principle of DPC microscopy

In DPC imaging, a weak phase object $O(r)$, consisting of weak absorption ($\alpha$) and phase delay ($\varphi$), can be approximated by ignoring the high-order terms in the Taylor expansion [6], and writing as

$$O(r) = e^{-\alpha(r)}e^{\varphi(r)} \approx 1 - \alpha(r) + \varphi(r). \tag{9}$$

The image from the DPC microscope is given by [6]

$$I(r) = \iint \left| \mathcal{F} \left\{ \mathcal{F} \left[ S(u) e^{2\pi i u \cdot O(r)} \right] P(u) \right\} \right| d^2u,$$ \tag{10}

where $\mathcal{F}$ denotes the Fourier transform, $S(u)$ denotes the amplitude illumination pattern, $O(r)$ represents the object function, $P(u)$ is the pupil function, $r$ denotes the spatial coordinate of $(r_x, r_y)$, and $u$ is the spatial-frequency coordinate of $(u_x, u_y)$. The integration with respect to the coordinate $u$ represents the intensity superposition from each point source of $S(u)$ on the image plane. After substituting equation (10) with equation (9), the equation can be written as [16]

$$\bar{I}(u) = \bar{I}_b \cdot \delta(u) + \bar{H}_{\text{amp}} \cdot \bar{\alpha}(u) + i\bar{H}_{\text{pha}} \cdot \bar{\varphi}(u). \tag{11}$$

Equation (11) is composed of three terms: the intensity of background $\bar{I}_b$, amplitude transfer function $\bar{H}_{\text{amp}}$, and PTF $\bar{H}_{\text{pha}}$, where $\mathcal{F}$ represents the Fourier transform.

A DPC image obtained by pairwise intensity measurement by complementary illumination is given by [6], and in our case is

$$I_{\lambda, \text{DPC}}(r) = \frac{I_{\lambda,1}(r) - I_{\lambda,2}(r)}{I_{\lambda,1}(r) + I_{\lambda,2}(r)} \tag{12}$$

where $\lambda_i$ are $\lambda_1$, $\lambda_2$, and $\lambda_3$, which are different colors of pupils. The qDPC reconstruction algorithm follows equation (13) to recover the phase

$$\varphi(r) = \mathcal{F}^{-1} \left\{ \frac{\sum_{\lambda_i} \bar{H}_{\text{DPC,} \lambda_i}(u) \cdot \bar{I}_{\text{DPC,} \lambda_i}(u)}{\sum_{\lambda_i} \left| \bar{H}_{\text{DPC,} \lambda_i}(u) \right|^2 + \gamma} \right\}. \tag{13}$$

The phase reconstruction flowchart of the proposed isotropic qDPC microscopy is shown in figure 4. The input images are the raw images obtained from the color camera. The effect of color illumination is visible at each portion of the raw images. The raw image is composed of three colors: red, green, and blue. The different color images are separated into three color channels in step (b). The CLC algorithm is used to calibrate each color channel as shown in step (c). In step (d), the DPC intensity images are obtained from equation (12). In step (e), using equation (13), the intensity images from the three channels are combined to obtain the final qDPC images as shown in step (f).

### 2.5. PTF

The calculated results of the PTF of the radially asymmetric color pupil and the conventional half-circle pupil for 12-axis measurements are shown in figure 5. The PTF corresponding to the three different colors is shown in figure 5(a1)–(a3). The isotropic PTF corresponding to the radially asymmetric color pupil is shown in (b1). In earlier studies, it was shown that to obtain isotropy of the PTF, at least 12-axis measurements are essential. Figure 5(b2) shows the PTF of 12-axis measurements. It should be noted that with our proposed color pupil, isotropy of the PTF can be achieved even with two intensity measurements. To show the isotropy of the PTF, we calculated the difference between the radially asymmetric color pupils in two intensity measurements, as shown in figure 5(c).
Figure 4. The phase reconstruction flowchart of isotropic qDPC microscopy. (a) Raw images obtained from color camera, (b) color channel separation, (c) color-leakage correction, (d) DPC image calculations, (e) reconstruction of qDPC images, and (f) quantitative phase image.

Figure 5. Comparison of PTF between radially asymmetric color pupil and half-circle pupil with 12-axis measurement. (a1)–(a3) PTF of one-axis measurement for radially asymmetric color pupil. (b1) PTF of radially asymmetric color pupil with two intensity measurements. (b2) PTF of half-circle pupil with 12-axis measurements. (c) Difference of PTF between (b1) and (b2).

3. Experimental measurements

3.1. System specification of experimental setup

The system specification of the isotropic qDPC microscope is discussed below. The light source is a tungsten halogen lamp of a commercial inverted microscope system. The commercial inverted microscope (Leica DMI3000 B) was installed with a TFT panel (2.8′′ TFT Touch Shield), and controlled by an Arduino control board (UNO32). For the TFT panel module, the pixel size of the TFT panel is 180 µm and the number of pixels is 240 × 320 pixels. In our experiment, 10X NA0.3 objectives (HCX PL Fluotar 10x/0.30) and a Leica S28 NA0.55 condenser system were adopted. The camera module is a 5.0MP color scientific camera (TCH-5.0ICE) with 3.4 µm pixel size and 2580 × 1944 pixels.

Following equations (1)–(5), the amplitude patterns were pre-designed and generated using MATLAB software. The TFT panel module is controlled by the Arduino control board to display the amplitude patterns as a color pupil. Figure 6(a) shows the experimental setup of the isotropic qDPC microscope equipped with the TFT panel, and figure 6(b) shows the color illumination patterns generated from the TFT panel.

3.2. CLC

The results of CLC are shown in figure 7. Figure 7(a1) shows that around 12.38% of the green signal and 2.01% of the blue signal are detected under the red illumination. Figure 7(a2) shows that around 18.8% of the red signal and 31.0% of the blue signal are detected under the green illumination. For blue illumination, as shown in figure 7(a3), around 1.4% of the red signal and 26.2% of the green signal are detected. From figure 7(b) we can see that by implementing the color-leakage algorithm, the leakage from one color illumination to the other color channel can be significantly reduced. The ratio of color is over 97% in each color channel, which prevents cross-talk among different colors. The experimental results demonstrate that CLC calibrates each color channel and significantly suppresses leakage.
Figure 6. (a) Isotropic qDPC microscopy based on a commercial inverted microscope (Leica DMI3000 B); TFT panel is placed at the front focal plane of condenser lens, marked with red dashed box. (b) Color illumination generated from the TFT panel (highlighted with orange dashed box).

Figure 7. The percentage of each color channel among uncorrected images is shown in (a) and (b). (a1)–(a3) The each color channel of uncorrected images under red, green, and blue illumination. (b1)–(b3) The percentage of each color channel of corrected images under red, green, and blue illumination.

3.3. Accuracy and validation of reconstruction

To verify the accuracy of phase retrieval with our method, we performed phase imaging of 10 µm polystyrene microspheres. We measured the phase values and compared them with the theoretically calculated results. The phase reconstruction result of 10 µm polystyrene microspheres is shown in figure 8(a). Equation (14) is used to estimate the phase of microspheres. The estimated value is 3.54 rads. The refractive index of the microspheres is 1.59, the refractive index of the surrounding medium (immersion oil) is 1.56, and the operating wavelength is 532 nm.

\[
\Delta \phi = \frac{2\pi D(n_{\text{bead}} - n_{\text{solution}})}{\lambda}.
\]

(14)
Figure 8. (a) Reconstruction phase image of 10 \( \mu \)m polystyrene microspheres, with refractive index of surrounding medium equal to 1.56 (immersion oil). (b) Measured phase distribution of the cross-section along the red dashed lines of a zoomed-in microsphere at the solid box region of (a).

Figure 8(b) shows the phase distribution along the red dashed line in figure 8(a). The measured phase of microspheres with our method is 3.55 rads, which indicates that the error is only 2.8%. The source of the error may be due to the tolerance of the microsphere size and the chromatic aberration of the objective under color illumination.

3.4. Phase imaging of living cells

To demonstrate the imaging performance of our method, we performed live cell imaging of 3T3 mouse fibroblast cells. Figure 9(a) shows the raw images of 3T3 cells under color illumination. The reconstructed phase images are shown in figure 9(b). The 3D phase distribution of the zoomed-in images corresponding to the solid box region is shown in figure 9(c). The pseudopodia of 3T3 cells can be clearly observed in figure 9(c1), while compared with figure 9(c2), apoptosis of 3T3 cells can be observed easily by the change of phase. From these images it is obvious that our method reconstructs high-resolution phase images of living cells.

4. Discussion

Various color pupils have been proposed for qDPC imaging. The performance characteristics of different color pupils is compared in table 1. Several estimation indexes, including the number of axes of measurement, illumination hardware, number of frames, isotropy of PTF, and luminous exitance, are taken into account. Among these indexes, luminous exitance is a main factor to estimate the illumination efficiency of color pupils. Luminous exitance [17] can be defined as the luminous flux per unit area emitted from a surface. The luminous exitance of color pupils, shown in table 1, can be estimated by the function \( \bar{T} \) as below:

\[
\bar{T} = \frac{\int M(\theta)\text{circ}(r)drd\theta}{\int \text{circ}(r)drd\theta}.
\]

In equation (15), \( \bar{T} \) integrates the amplitude distribution within the pupil normalized to the same pupil area.

Although the luminous exitance in the trisection circle color pupil and half-circle color pupil can have higher values, they cannot achieve isotropic PTF. In contrast, both the radially asymmetric color pupil and optimal illumination pupil can realize isotropic PTF. The optimal illumination pupil has the advantage of high signal-to-noise ratio, but it suffers with very low \( \bar{T} \) during imaging. This limitation can be overcome by using a longer exposure time setting of the camera or a high-power lamp source. However, both solutions generate more hardware issues, including motion blur artifacts and low illumination efficiency. By calculating \( \bar{T} \), the advantages of radially asymmetric pupils are not only isotropic PTF achievement within two intensity measurements, but also providing higher \( \bar{T} \).
Table 1. Comparison table of color-multiplexing method in DPC. In this table, different estimation indexes are used, including the axis of measurement, illumination hardware design approach, reconstruction required frames, isotropic PTF achievement, and luminous exitance. * The area of annular ring illumination depends on the width of the ring.

| Pupil design | Axis of illumination | Illumination approach | Reconstruction required frame | Isotropic PTF | Luminous exitance (T) |
|--------------|----------------------|-----------------------|------------------------------|---------------|-----------------------|
| Radially asymmetric color pupil (this work) | Three-axis | White light source + TFT-LCD | Two frames | Achieved | 100% |
| Radially asymmetric two-color pupil [13] | Three-axis | White light source + TFT-LCD | Three frames | Achieved | 100% |
| Optimal illumination color pupil [14] | Three-axis | White light source + TFT-LCD | Two frames | Achieved | Depends on illuminating area* |
| Trisection circle color pupil [12] | Four-axis | White light source + PET color filters | One frame | Unachieved | 100% |
| Half-circle color pupil [9] | Three-axis | Color LED array | One frame | Unachieved | 100% |
5. Conclusions

In conclusion, using radially asymmetric color pupils, a new method of qDPC microscopy is proposed. We show that radially asymmetric color pupils can achieve isotropic PTF in a circular symmetric shape with only two intensity measurements. As a result, there is a 12 times enhancement of the image acquisition speed as compared to the standard 12-axis measurement method. In addition, our pupil provides higher luminous exitance to avoid limitations such as motion blur and low illumination efficiency, which may be useful for reconstructing phase values at video rate. The minimum number of frames will help in achieving real-time qDPC imaging. We also demonstrate that color leakage can be suppressed by adopting the CLC algorithm. Around 97% color can be corrected in each color channel. The accuracy of phase recovery is very high and the error is smaller than 2.8%. The reconstructed 3D phase map of living cells demonstrates the capability of our system to obtain accurate quantitative phase values, which may give impetus to many biomedical applications.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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ORCID iDs

Yu-Hsiang Lin  https://orcid.org/0000-0003-0581-257X
Yuan Luo  https://orcid.org/0000-0001-9776-7897

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