Physics-based Learned Design: Optimized Coded-Illumination for Quantitative Phase Imaging

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Abstract—Coded-illumination can enable quantitative phase microscopy of transparent samples with minimal hardware requirements. Intensity images are captured with different source patterns and are processed using non-linear phase retrieval to recover the quantitative phase. The non-linear nature of the processing makes optimizing the coded-illumination pattern designs complicated. Traditional techniques for experimental design (e.g., condition number optimization or spectral analysis) may not be ideal as they characterize linear measurement formation models for linear reconstructions. Deep neural networks (DNNs) offer an end-to-end framework which can efficiently represent the non-linear process and can be optimized over by training. However, DNNs require an enormous amount of training examples and parameters to properly learn the phase retrieval process, without making use of the known physical models. Here, we aim to use both our knowledge of the physics and the power of machine learning together. We develop a new data-driven approach to optimizing coded-illumination patterns for a LED array microscope to maximize performance of a given phase reconstruction algorithm. Our general formulation incorporates the physics of the measurement scheme as well as the non-linearity of the reconstruction algorithm into the design problem. This enables efficient parameterization of the problem, which allows us to use only a small number of training examples to learn designs that generalize well in the experimental setting without retraining. We show experimental results for both a well-characterized phase target and mouse fibroblast cells using coded-illumination patterns optimized for a sparsity-based phase reconstruction algorithm. Our results demonstrate similar accuracy to Fourier Ptychography with 69 measurements, while only using 2 measurements with our learned design.

Index Terms—Phase Imaging, LED Array Microscope, Unrolled Network, Physics-based, Experimental Design, Source Design.

I. INTRODUCTION

Quantitative Phase Imaging [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14] (QPI) enables stain-free and label-free imaging of transparent biological samples in vitro. QPI methods that use partially coherent illumination (as opposed to coherent illumination [4], [5]) achieve higher spatial resolution, more light throughput, and reduced speckle artifacts. Well-known practical examples of such systems include interference [5], [7] and defocus [3], [8], [9] as phase contrast mechanisms. More recently, coded-illumination microscopy [10], [11], [12], [13], [14] has offered an accurate and inexpensive scheme for QPI that can be realized without any moving parts, by replacing a commercial microscope’s illumination unit with a light-emitting diode (LED) array (see Fig. 1). This provides a flexible hardware platform for various QPI applications including super-resolution [10], [11], multi-contrast [16], and 3D [13], [14] imaging.

Coded-illumination microscopy of optically thin samples uses asymmetric source patterns [17] and multiple measurements to retrieve 2D phase information. Quantitative Differential Phase Contrast [18], [19], [20], [21] (qDPC), for example, captures four measurements with rotated half-circle source patterns, from which the phase is computationally recovered using a partially coherent linearized model. The practical performance of qDPC is predominantly determined by how the phase information is encoded in (via coded-illumination patterns) and decoded from (via phase recovery) the intensity measurements.

The half-circle illumination designs of qDPC were derived analytically based on a Weak Object Approximation [22], [23], [20] which linearizes the physics in order to make the inverse problem mathematically convenient. This linearized model enables one to derive a phase transfer function and analyze the spatial frequency coverage of any given source pattern [20], [21], [24], [25], however, the non-linearity of the exact model makes it impossible to predict an optimal source design without knowing the sample’s phase a priori. In addition, these types of analysis are inherently restricted to linear reconstruction algorithms and will not necessarily result in improved accuracy when the phase is retrieved via non-linear iterative methods.

Motivated by the success of deep learning [26] for image reconstruction problems [27], [28], [29], [30], [31], [32], data-driven approaches have been adopted as an alternative to learn coded-illumination patterns. For instance, researchers have used machine learning to maximize the phase contrast of each coded-illumination measurement [33], to improve accuracy on classification tasks [34], and to reconstruct phase [35]. The common theme between these techniques is to rely on learning the input-output relationship with a deep convolutional neural network (CNN) using training data. It is not straightforward to include the well-characterized system physics into these frameworks; hence, the CNN is required to learn the physical measurement formation and phase reconstruction processes by training of 10s to 100s of thousands of weights. This task requires an immense number of training examples to properly learn a model that generalizes in the experimental setting.

In this work, we introduce a new data-driven approach to optimize the source pattern design for coded-illumination phase retrieval by directly including both the system physics and the non-linear nature of a reconstruction algorithm in the...
learning process. Our approach unrolls \cite{46, 47, 48, 49, 50, 51} the iterations of a generic non-linear reconstruction algorithm to construct an unrolled network. Similar to CNNs, our unrolled network consists of several layers (one for each iteration); however, now each layer consists of well-specified operations to incorporate measurement formation and sparse regularization, instead of standard operations such as generic convolutions. The key aspects of the proposed approach are:

- incorporation of the system physics and reconstruction non-linearities in the illumination design process.
- efficient parameterization of the unrolled network.
- incorporation of physically-desirable constraints.
- reduced number of training examples required.

We deploy our data-driven approach to learn improved coded-illumination patterns for phase reconstruction. Each layer of the unrolled network is parameterized by only a few variables (LED brightness values), enabling an efficient use of training data (i.e. < 100 simulated training examples). We compare the phase reconstruction performance of our learned designs to previous work and demonstrate that ours generalize to standard operations such as generic convolutions.

II. QUANTITATIVE PHASE IMAGING

qDPC recovers a sample’s complex transmittance function from several coded-illumination measurements by phase recovery optimization. The optimization aims to minimize the Euclidean norm of error between the experimental measurements and the expected measurements formed with the current phase estimate. The phase estimate is iteratively updated using a gradient-based procedure. Once converged, the phase reconstructed achieves a resolution up to twice the coherent diffraction limit. In this section, we mathematically detail the measurement formation process and phase recovery optimization.

\subsection*{A. System Modelling}

A thin sample’s transmission function can be approximated as a two-dimensional complex function, \(o(r) = e^{i\phi(r) - \mu(r)}\), characterized by its absorption, \(\mu(r)\), and phase, \(\phi(r) = \frac{2\pi}{\lambda} \Delta n(r) d(r)\), where \(r\) are two dimensional spatial coordinates, \(\lambda\) is the wavelength of the illumination, \(d(r)\) is the physical thickness of the sample, and \(\Delta n(r)\) is the change in refractive index from the background. Intensity measurements, \(y(r)\), of the sample are a non-linear function of \(o(r)\) and can be mathematically described by,

\[
y(r) = |p(r) * (s(r) \cdot o(r))|^2,
\]

where \(|\cdot|^2\) is the squared absolute value, \(*\) denotes convolution, \(\cdot\) denotes elementwise multiplication, \(s(r)\) is the illumination’s complex-field at the sample plane and \(p(r)\) is the point spread function of the microscope. The illumination from each LED is approximated as a tilted plane wave, \(s(r) = e^{\pi u_{\text{pos}} \cdot r}\), with tilt \(u_{\text{pos}}\) determined by the physical position of the LED relative the microscope \cite{42}.

Because the measured image in Eq. \[\text{1}\] is non-linear with respect to the sample’s transmission function, recovering phase generally requires non-convex optimization. However, biological samples in closely index-matched fluid have a small scatter-scatter term. This means that a weak object approximation can be made; linearizing the measurement formation model such that phase recovery requires only a linear deconvolution of the measurements with their respective weak object transfer functions, WOTFs \cite{22, 19, 23, 21, 20}. Further, the predominant contrast for many biological samples is phase and not amplitude, Thus we consider the samples to be weakly absorbing (i.e. \(\mu(r)\) is small). With these approximations, we can express each intensity measurement as a linear system with contributions from the background and phase contrast. In Fourier space,

\[
\hat{y}(u) \approx B\delta(u) + ih(u)\hat{\phi}(u),
\]
where \( \vec{\phi} \) denotes Fourier transform, \( \mathbf{u} \) are two-dimensional spatial frequency coordinates, \( B \) is background energy of the measurement concentrated at the DC and \( h(\mathbf{u}) \) is the phase WOTF. The phase WOTFs can be described as a function of the illumination source and pupil distributions of the microscope [20]; for a single LED we have,

\[
    h^{(\text{single})}(\mathbf{u}) = i\hat{\mathbf{p}}(\mathbf{u}) * \hat{s}(\mathbf{u}) - \hat{s}(\mathbf{u}) * \hat{\mathbf{p}}(\mathbf{u}),
\]

\[ \text{ where } * \text{ is the correlation operator.} \]

In [20], multiple LEDs are turned on simultaneously to increase signal-to-noise (SNR) and phase contrast. Because the fields generated by each single LED’s illumination are spatially incoherent with each other, the measurement from multiple LEDs will simply be the weighted sum of each LED’s measurement, where the weights correspond to the LEDs’ brightness values. The phase WOTF for illumination by multiple LEDs will also be the weighted sum of the single-LED phase WOTFs. Mathematically,

\[
    \hat{y}^{(\text{multi})}(\mathbf{u}) = \sum_{w \in \mathcal{W}} c_w \hat{y}^{(\text{single})}(\mathbf{u})
\]

\[
    \hat{h}^{(\text{multi})}(\mathbf{u}) = \sum_{w \in \mathcal{W}} c_w h^{(\text{single})}(\mathbf{u}),
\]

where \( \mathcal{W} \) is the set of LEDs turned on and \( c_w \geq 0 \) are the LEDs’ brightness values.

Following the common practice [43], we discretize the 2D spatial distributions and format them as vectors (bold lower case) (e.g. \( \phi \) represents the 2D spatial phase distribution). Accordingly, the forward model is discretized on the spatial frequency grid so that the measurements [4] are described in Fourier space as \( \hat{\mathbf{y}} = A\hat{\phi} \) with system function \( A = \text{diag}(h) \).

Based on this, we define \( \mathbf{Y} \in \mathbb{R}^{M \times S} \) as the Fourier transform of \( S \) single LED measurements, \( \hat{\mathbf{y}} \), along the columns. Then, \( \mathbf{C} \in \mathbb{R}^{S \times K} \) is defined as the \( S \) single LED weights for each of \( K \) measurements, and \( c_k \in \mathbb{R}^S \) is the \( k^{th} \) column of \( \mathbf{C} \). The product \( \hat{\mathbf{y}}_k = \mathbf{Y} c_k \) simulates the \( k^{th} \) multiple LED measurement in Fourier space. Similarly, we define \( \mathbf{H} \in \mathbb{R}^{N \times S} \) as \( S \) single LED phase WOTFs, \( \hat{\mathbf{h}} \), along the columns, such that the product \( \mathbf{A}_k = \text{diag}(\mathbf{H} c_k) \) gives the corresponding multiple LED phase WOTF for the \( k^{th} \) measurement.

B. Phase Recovery

Phase recovery using the forward model in Sec. II-A can be formulated as a regularized linear inverse problem,

\[
    \hat{\phi}^* = \mathcal{R}(\hat{\mathbf{y}}_k^{K=1}, \mathcal{P}(\cdot))
\]

\[
    = \arg \min_{\phi} \frac{1}{2K} \sum_{k=1}^{K} \| \hat{\mathbf{y}}_k - \mathbf{A}_k \hat{\phi} \|_2^2 + \mathcal{P}(\hat{\phi}),
\]

\[ \text{ where } \hat{\phi}^* \text{ is the recovered phase, } K \text{ is the number of measurements acquired, } \hat{\mathbf{y}}_k \text{ is the Fourier transform of the } k^{th} \text{ measurement and } \mathcal{P}(\cdot) \text{ is a user-chosen regularizer.} \]

We solve this optimization problem efficiently using the accelerated proximal gradient descent (APGD) algorithm by iteratively applying an acceleration update, a gradient update and a proximal update [44]. The algorithm is detailed in Alg. 1.

Algorithm 1 Accelerated Proximal Gradient Descent (APGD) for Phase Recovery

\[
\begin{align*}
    1: & \quad \text{procedure } \text{APGD}(\hat{\mathbf{y}}_k^{K=1}, N, \alpha, \mathcal{P}(\cdot)) \quad \\
    2: & \quad \hat{\phi}^{(0)} = 0, \hat{\phi}^{(-1)} = 0 \quad \\
    3: & \quad \text{for } n \in \{1...N\} \text{ do} \quad \\
    4: & \quad \hat{s}^{(n)} \leftarrow \hat{\mu}^{(n)} \hat{\phi}^{(n-1)} + \left(1 - \hat{\mu}^{(n)}\right) \hat{\phi}^{(n-2)} \quad \\
    5: & \quad \hat{z}^{(n)} \leftarrow \hat{\phi}^{(n)} - \alpha \sum_{k=1}^{K} (-A_k^H)(\hat{\mathbf{y}}_k - A_k \hat{s}^{(n)}) \quad \\
    6: & \quad \hat{\phi}^{(n)} \leftarrow \text{prox}_{\alpha \mathcal{P}}(\hat{z}^{(n)}) \quad \\
    7: & \quad \text{end for} \quad \\
    8: & \quad \text{return } \hat{\phi}^{(N)} \quad \\
    9: & \quad \text{end procedure}
\end{align*}
\]

\[
\text{where } \alpha \text{ is the gradient step size, } N \text{ is the number of iterations, } s \text{ and } z \text{ are intermediate variables, } \mu^{(n)} \text{ is the acceleration parameter derived by the recursion, } \mu^{(n)} = \frac{1+\sqrt{1+4\mu^{(n-1)}\mu^{(n-2)}}}{2} \text{ [45], and } \text{prox}_{\cdot}(\cdot) \text{ is the proximal operator corresponding to the user-chosen regularizer } \mathcal{P}(\cdot) [44].}
\]

III. Physics-Based Learned Design

Given the phase recovery algorithm outlined in Sec. II-B we now focus on the main contribution of learning the coded-illumination designs for a given reconstruction algorithm and training set. We define an unrolled network architecture, the optimization’s objective and physical constraints, and the backpropagation algorithm, which calculates the analytic gradient with respect to the design parameters.

A. Physics-based Unrolled Network

Traditionally, DNNs contain many layers of weighted linear mixtures and non-linear activation functions [26]. Here, we consider specific linear functions which capture the system physics of measurement formation and specific non-linear activation functions which promote sparsity. Starting from Alg. 1, we treat each iteration as a layer such that when unrolled they form a network of \( N \) layers, denoted \( \mathcal{R} \) (Fig. 2). Each layer of \( \mathcal{R} \) contains a module for each of the iterative algorithm’s updates (i.e. an acceleration module, a gradient module (incorporates system physics), and proximal module (incorporates sparsity)). The regularization and step size parameters specified for Alg. 1 are fixed. The network’s inputs comprise \( \hat{\mathbf{y}}_k^{K=1} \) and the network’s output is \( \hat{\phi} \). The design parameters of the network, which will be learned, govern the relative brightness of the LEDs and are incorporated in the measurement formation and the system transfer functions.

B. Learning Objective

Our learning objective is to minimize the phase reconstruction error of the training data over the space of possible
LED configurations subject to constraints that enforce physical feasibility and eliminate degenerate and trivial solutions:

\[
C^* = \arg \min_C \mathcal{F}(C) \\
\text{s.t. } c_k \geq 0 \quad \text{(positivity)} \tag{9} \\
\|c_k\|_1 = 1 \quad \text{(power)} \tag{10} \\
m_k \cdot c_k = 0 \quad \text{(geometric)} \tag{11}
\]

where,

\[
\mathcal{F}(C) = \frac{1}{L} \sum_{l=1}^{L} \mathcal{F}_l(C) = \frac{1}{2L} \sum_{l=1}^{L} \|\mathcal{R}((Y_l c_k)_{k=1}^{K}) - \hat{\phi}_l\|_2^2. \tag{12}
\]

Here, \((Y_l, \phi_l')_{l=1}^{L}\) are \(L\) training pairs for which \(Y_l\) is a matrix of the Fourier transform of single LED measurements for the \(l\)th sample with optical phase, \(\phi_l'\), is the elementwise product operator and \(m_k\) is a geometric constraint mask for the \(k\)th measurement.

The positivity constraint (Eq. 9) enforces the brightness of each LED to be positive, to prevent non-physical solutions. The power constraint (Eq. 10) enforces that each coded-illumination design must have weights with sum equal to 1. This eliminates arbitrary scalings of the same coded-illumination design. The geometric constraint (Eq. 11) enforces that the coded-illumination designs do not use conjugate-symmetric LED pairs to illuminate the sample within the same measurement, since these would also result in degenerate solutions (e.g. two symmetric LEDs produce opposite phase contrast measurements that would cancel each other out). To prevent this, we force the source patterns for each measurement to reside within only one of the major semicircle sets (e.g. top, bottom, left, right).

We solve Eq. 8 subject to constraints iteratively via accelerated projected gradient descent (Alg. 2). At each iteration, the coded-illumination design for each measurement is updated with the analytical gradient, projected onto the constraints (denoted by \(B(\cdot)\)) and updated again with a contribution from the previous iteration (weighted by \(\beta(t)\)).

**Algorithm 2** Physics-based Learned Design Algorithm to solve for source patterns

1. procedure CLA((\(Y_l, \phi_l'\))\(_{l=0}^{L}\), \(C, \gamma, T\)) \>
   \begin{align*}
   &\text{for } t \in \{0..T\} \text{ do} \quad \text{Gradient descent loop} \\
   &\text{for } l \in \{1..L\} \text{ do} \quad \text{Training data loop} \\
   &\quad r_l \leftarrow \mathcal{R}((Y_l c_k)_{k=1}^{K} - \hat{\phi}_l) \\
   &\quad G_l \leftarrow \text{BackPropagation}(r_l) \\
   &\quad \text{end for} \\
   &\quad C(t+1) \leftarrow B(C(t)) - \gamma \sum_{l=1}^{L} G_l \\
   &\quad C(t+1) \leftarrow \beta(t) C(t+1) + (1 - \beta(t)) C(t) \\
   &\text{end for} \\
   &\text{return } C(T)
   \end{align*}

**C. Gradient Update**

The gradient with respect to the design parameters has contributions at every layer of the unrolled network (Fig. 2) through both the measurement terms, \(\hat{y}_k\), and the phase WOTF terms, \(A_k\), for each measurement \(k \in \{1..K\}\). Here, we outline our algorithm for updating the coded-illumination design weights via a two-step procedure: backpropagating the error from layer to layer and computing each layer’s gradient contribution. For simplicity, we outline the gradient update for only a single training example, \(l\), as the gradient for all the training examples is the sum of their individual gradients.

Unlike pure gradient descent, where each iteration’s estimate only depends on the previous’, accelerated methods like Alg. 1 linearly combine the previous two iteration’s estimates to improve convergence. As a consequence, backpropagating error from layer to layer requires contributions from both successive layers. Specifically, we compute the error at all \(N\) layers with the recursive relation,
for which,

\[ \nabla_C F_l(C) = \sum_{n=0}^{N} Q^{(n)}, \quad (15) \]

Here, \( \left( \frac{\partial \alpha}{\partial \phi} \right) \) backpropagates the error through the proximal operator and other partials with respect to \( C \) relate the backpropagated error at each layer to the changes in \( C \). Derivations of these partial gradients are included in the supplementary sections. Below, we unite these two steps to form a recursive algorithm which efficiently computes the analytic gradient for a single training example (Alg. 3).

Algorithm 3 Gradient Update for Single Training Example

1: procedure BACKPROPAGATION(BP)(r(N))
2: for \( n \in \{N, \ldots, 0\} \) do
3: \( b^{(n)} \leftarrow \phi \frac{\partial r}{\partial \phi}(n) \)
4: \( v^{(n)} \leftarrow (I - \mu(n) \sum_k A_k^H A_k) b^{(n)} \)
5: \( r^{(n-1)} \leftarrow \mu(n) v^{(n)} + (1 - \mu(n+1)) v^{(n+1)} \)
6: \( Q^{(n)} \leftarrow \frac{\alpha}{K} \sum_{k=1}^{K} \frac{\partial A_k^H \hat{y}_k}{\partial C} - \frac{\partial A_k^H A_k}{\partial C} s^{(n-1)} b^{(n)} \)
7: end for
8: return \( \sum_{n=0}^{N} Q^{(n)} \)
9: end procedure

IV. RESULTS

Our proposed method learns the coded-illumination design for a given reconstruction and training set (Fig. 3a), yet up to this point we have not detailed specific parameters of our phase reconstruction. In our results, we set the parameters of our reconstruction algorithm (Alg. 1) to have a fixed CPU time (i.e., a fixed number of iterations). We set the number of iterations to be \( N = 40 \) and the step size to \( \alpha = 0.2 \). In addition, the regularization term, \( P(\phi) \), has been defined generally (e.g., \( \ell_1 \) penalty, total variation (TV) penalty \( 46 \), BM3D \( 47 \)). Here, we choose to enforce TV-based sparsity (Eq. 17). Mathematically, that means,

\[ \mathcal{P}(\phi) = \tau \sum_i ||D_i \phi||_1, \quad (17) \]

where \( \tau = 1e^{-3} \) is set to trade off the “total-variation” cost with the data consistency cost and \( D_i \) is the first-order difference operator along the \( i \)th image dimension. We efficiently implement the proximal operator of Eq. 17 in closed form via parallel proximal method \( 48 \) (details in supplementary sections).

A. Learning

To train our coded-illumination design parameters using Alg. 3 we generate a dataset of 100 examples (90 for training, 10 for testing). Given a large image, each example contains ground truth phase from a small region (95 × 95 pixels) and 69 simulated single LED measurements (using Eq. 1 of that patch. The LEDs are uniformly spaced within a circle (with \( N_{\text{illum}} = 0.25 \)), such that each single LED intensity measurement is a brightfield measurement. The physical system parameters used to generate the phase WOTFs and simulate the training data measurements are \( \lambda = 0.532 \mu \text{m} \), pixel pitch = 6.5 \mu \text{m} \), magnification = 20×, and \( N_{\text{obj}} = 0.25 \). To train, we use \( \ell_2 \) cost between reconstructed phase and ground truth phase as our loss function and approximate the full gradient of Eq. 8 with a batch gradient from random batches using 10%
Fig. 4. Phase reconstruction comparison with different coded-illumination designs and simulated measurements (as in Sec. IV). The illumination schemes tested are: traditional qDPC, annular illumination, condition number optimization, A-optimal design, and our proposed physics-based learned designs. We show results for the cases of (a) four, (b) three, and (c) two measurements allowed for each phase reconstruction. Absolute error maps are shown below each reconstruction.

| # Meas. | Traditional qDPC | Annular Illumination | Cond. Number Opt. | A-optimal Design | Physics-based Learned Design |
|---------|-------------------|----------------------|-------------------|-----------------|----------------------------|
| 4       | 15.67             | 20.40                | 20.37             | 17.94           | 28.46                      |
| 3       | 15.28             | 20.44                | 19.33             | 18.05           | 28.04                      |
| 2       | 14.87             | 20.21                | 17.19             | 18.08           | 23.73                      |

TABLE I

PSNR RESULTS: AVERAGE PSNR (dB) OF PHASE RECONSTRUCTION ON THE SIMULATED TESTING EXAMPLES WITH PARAMETERS OUTLINED IN SEC. IV USING DIFFERENT ILLUMINATION SCHEMES AND DIFFERENT NUMBERS OF MEASUREMENTS.

of the training pairs at each iteration. We use a learning rate of $\gamma = 1e^{-2}$.

Traditional qDPC uses 4 measurements to adequately cover frequency space. Our learned designs are more efficient and may require fewer measurements; hence, we show learned designs for the cases of 4, 3 and 2 measurements. The designs and their corresponding phase WOTFs are shown in Fig. 3.

Comparing our learned designs with previous work, Fig. 4 shows the phase reconstruction for a single simulated testing example given 4, 3 and 2 measurements. The ground truth phase is shown next to phase reconstructed using traditional qDPC [20], annular illumination [20], condition number optimized designs, A-optimal designs [49], and our physics-based learned designs. Table I reports the average peak SNR (PSNR) of the phase reconstructions using $R$ evaluated on our set of testing examples. Our learned designs give significant improvement, recovering both the highest frequencies and the lowest frequencies (where energy is concentrated) more accurately.

B. Experimental Validation

To demonstrate that our learned designs generalize well in the experimental setting, we implement our method on an LED array microscope. A commercial Nikon TE300 microscope is
equipped with a custom quasi-Dome [15] illumination system (581 programmable RGB LEDs: $\lambda_R = 625$ nm, $\lambda_G = 532$ nm, $\lambda_B = 450$ nm) and a PCO.edge 5.5 monochrome camera ($2560 \times 2160$, 6.5$\mu$m pixel pitch, 16 bit). We image two samples: the USAF phase target from Benchmark Technologies and fixed 3T3 mouse fibroblast cells prepared as detailed in the supplementary sections. In order to validate our method, we compare all reconstructions with phase experimentally estimated via pupil-corrected Fourier Ptychography (FP) [42], [50], [12] with equivalent bandwidth. FP may also suffer reconstruction artifacts, but uses significantly more measurements (69 single-LED measurements) and a non-linear reconstruction process to ensure accuracy.

Using the USAF phase target, we compare the phase reconstruction using FP (Fig. 5a) with phase reconstructions using traditional qDPC and phase reconstructions using our learned design measurements. With traditional qDPC, the phase reconstruction consistently under-estimates the phase values. However, phase reconstructions using our learned design measurements (Fig. 5c) are similar to phase estimated with FP (see cross-sections in Fig. 5d). As the number of measurements is reduced, the performance quality of the reconstruction using traditional qDPC degrades, while the reconstruction using the learned design remains accurate.

To demonstrate our method with live biological samples, we repeated the experiments with 3T3 mouse fibroblast cells. Figure 6 shows that phase reconstructions from traditional qDPC again consistently under-estimate phase values, while phase reconstructions using learned design measurements well match the phase estimated with FP.

V. DISCUSSION

Our proposed experimental design method efficiently learns the coded-illumination designs by incorporating both the system physics and the non-linear nature of iterative phase recovery. Learned design with only 2 measurements can efficiently reconstruct phase quality similar to Fourier Ptychography (69 measurements), giving an improvement in temporal resolution by a factor of 2 over traditional qDPC (which uses 4 measurements) and by an order of magnitude over FP.
Additionally, we demonstrate (Table 1) that the performance of our designs on a set of testing examples is superior to previously proposed coded-illumination designs [20]. Visually, our learned design produces phase reconstructions that closely resemble the ground truth phase, with both low-frequency and high-frequency information accurately recovered.

Phase recovery with the learned designs’ measurements are trained to produce high-quality reconstructions for a given number of reconstruction iterations (e.g. determined by a CPU budget). This makes our method particularly well-suited for real-time processing, which would ordinarily be inhibited by traditional qDPC’s low sensitivity to low-frequency information, which causes a need for a large number of iterations to properly decode from the measurements. As highlighted in experiments, for a given number of iterations our learned designs produce phase reconstructions similar to those of the FP reconstruction, while traditional qDPC underestimates low-frequency information in the phase reconstructions.

By parameterizing our learning problem with only a few weights per measurement we have enabled our method to efficiently learn an experimental design with a small simulated dataset that generalizes well to the experimental setting. Our designs recover the phase of testing examples with a high fidelity, and generalize well in the experimental setting. This is reinforced by results in Sec. IV-B, where the learned design produces phase reconstructions similar to those of the previously proposed coded-illumination designs [20]. Visually, our learned designs on a set of testing examples is superior to FP reconstruction experimentally without the need for retraining.

VI. OUTLOOK

As outlined, our method is general to the problem of experimental design. Similar to QPI, many fields (e.g. Magnetic Resonance Imaging (MRI), Fluorescence Microscopy (FM)) use physics-based non-linear iterative reconstruction techniques to achieve state-of-the-art performance. With the correct model parameterization and physically-relevant constraints, our method could be applied to learn optimal design for these applications (e.g. undersampling patterns for compressed sensing MRI [51], point spread functions for FM [52]).

Requirements for our method’s application in other fields are simple: the reconstruction algorithm’s updates must be differentiable (e.g. gradient update and proximal update) so that analytic gradients can be computed with respect to the design parameters. Of practical importance, the proximal operator of the regularizer should be chosen so that it has a closed form. While this is not a strict requirement, if the operator itself requires an additional iterative optimization, error will have to be backpropagated through an excessive number of iterations. Here, we choose to penalize anisotropic TV, whose proximal operator can be approximated in closed form [48]. Further, including an acceleration update improves the convergence of gradient-based reconstructions. As a result, the unrolled network can be constructed using fewer layers than its unaccelerated counterpart. This will reduce both computation time for phase reconstruction as well as training.

VII. CONCLUSION

We have presented a general framework for incorporating the non-linearities of regularized reconstruction and known system physics to learn optimal experimental design. Here, we have applied this method to learn coded-illumination source designs for quantitative phase recovery. Our coded-illumination designs can improve the temporal resolution of the acquisition, enable real-time processing while maintaining high accuracy and outperform both traditional and previous designs. Finally, our learned designs achieve high-quality reconstructions experimentally without the need for retraining.

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REFERENCES

[1] G. Popescu, Quantitative Phase Imaging of Cells and Tissues, ser. McGraw-Hill biophotonics. McGraw-Hill Education, 2011.
[2] M. Mir, B. Bhaduri, R. Wang, R. Zhu, and G. Popescu, Quantitative Phase Imaging. Elsevier Inc., Jul. 2012, vol. 57.
[3] T. E. Gureyev, A. Roberts, and K. A. Nugent, “Partially coherent fields, the transport-of-intensity equation, and phase uniqueness,” J. Opt. Soc. Am. A., vol. 12, no. 9, pp. 1942–1946, Sep 1995. [Online]. Available: http://josaa.osa.org/abstract.cfm?URI=josaa-12-9-1942.
[4] B. Rappaz, B. Breton, E. Shaffer, and G. Turcatti, “Digital holographic microscopy: A quantitative label-free microscopy technique for phenotypic screening,” Combinatorial Chemistry & High Throughput Screening, vol. 17, no. 1, pp. 80-88, January 2014.
[5] E. Cuche, P. Marquet, and C. Depeursinge, “Simultaneous amplitude-contrast and quantitative phase-contrast microscopy by numerical reconstruction of fresnel off-axis holograms,” Applied optics, vol. 38, no. 34, pp. 6994–7001, 1999.
[6] B. Bhaduri, H. V. Pham, M. Mir, Must, and G. Popescu, “Diffraction phase microscopy with white light,” pp. 1–3, Mar. 2012.
[7] Z. Wang, L. Millet, M. Mir, H. Ding, S. Unarunotai, J. Rogers, M. U. Gillette, and G. Popescu, “Spatial light interference microscopy (SLIM),” Optics express, vol. 19, no. 2, pp. 1016–1026, January 2011. [Online]. Available: http://www.opticsexpress.org/abstract.cfm?url=/oe-19-2-1016.
[8] N. Streibl, “Phase Imaging by the Transport Equations of Intensity,” Optics Communications, vol. 49, no. 1, pp. 6–10, Feb. 1984.
[9] L. Waller, L. Tian, and G. Barbabastis, “Transport of intensity phase-amplitude imaging with higher order intensity derivatives,” Optics express, vol. 18, no. 12, pp. 12552–12561, June 2010.
[10] L. Tian, Z. Liu, L.-H. Yeh, M. Chen, J. Zhong, and L. Waller, “Computational illumination for high-speed in vitro fluoroury froughraphic microscopy,” pp. 1–19, Sep. 2015.
[11] G. Zheng, R. Horstmeyer, and C. Yang, “Wide-field, high-resolution Fourier ptychographic microscopy,” Nature Photonics, vol. 7, no. 9, pp. 739–745, 2013.
[12] L. Tian, X. Li, K. Ramchandran, and L. Waller, “Multiplexed coded illumination for fluoroury froughraphic with an led array microscope,” pp. 1–14, Jun. 2014.
[13] L. Tian and L. Waller, “3D intensity and phase imaging from light field measurements in an LED array microscope,” Optica, vol. 2, no. 2, pp. 104–111, February 2015.
R. Ling, W. Tahir, H.-Y. Lin, H. Lee, and L. Tian, “High-throughput intensity diffraction tomography with a computational microscope,” pp. 1–20, Jan. 2018.

Z. Phillips, R. Eckert, and L. Waller, “Quasi-Dome: A Self-Calibrated High-NA LED Illuminator for Fourier Ptychography,” in Imaging and Applied Optics 2017 (3D, AFO, COSI, IS, MATH, pcAOP). Optical Society of America, 2017, p. 1W4E.5.

Z. Liu, L. Tian, S. Liu, and L. Waller, “Real-time brightfield, darkfield, and phase contrast imaging in a light-emitting diode array microscope,” Journal of biomedical optics, vol. 19, no. 10, p. 106002, 2014.

B. Kachar, “Asymmetric illumination contrast: a method of image formation for video light microscopy,” Science, vol. 227, no. 4686, pp. 756–768, 1985. [Online]. Available: http://science.sciencemag.org/content/227/4688/766

D. K. Hamilton and C. J. R. Sheppard, “Differential phase contrast in scanning optical microscopy,” Journal of Microscopy, vol. 133, no. 1, pp. 27–39. [Online]. Available: https://journals.lww.com/jmicro/mol.2008.03.004.x

D. K. Hamilton, C. J. R. Sheppard, and T. Wilson, “Improved imaging of phase gradients in scanning optical microscopy,” Journal of Microscopy, vol. 135, no. 3, pp. 275–286. [Online]. Available: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2818.1984.tb00460.x

N. Streibl, “Three-dimensional imaging by a microscope,” J. Opt. Soc. Am. A, vol. 2, no. 2, pp. 121–127, Feb 1985. [Online]. Available: http://doi.org/10.1364/JOSAA.2.000121

J. Li, Q. Chen, J. Zhang, Y. Zhang, L. Lu, and C. Zuo, “Efficient quantitative phase microscopy using programmable annular led illumination,” Biomed. Opt. Express, vol. 8, no. 10, pp. 4687–4705, Oct 2017. [Online]. Available: http://www.osapublishing.org/boe/publication.cfm?URID=boe-8-10-4687

Y.-Z. Lin, K.-Y. Huang, and Y. Luo, “Quantitative differential phase contrast imaging at high resolution with radially asymmetric illumination,” Optics Letters, vol. 43, no. 12, pp. 2973–4, 2018.

Y. LeCun, Y. Bengio, and G. Hinton, “Deep learning,” Nature, vol. 521, no. 7553, pp. 436–444, May 2015.

K. H. Jin, M. T. McCann, e. Froustey, and M. Unser, “Deep convolutional neural network for inverse problems in imaging,” pp. 1–20, Nov. 2016.

S. Wang, Z. Su, L. Ying, X. Peng, S. Zhu, F. Liang, D. Feng, and D. Liang, “Accelerating magnetic resonance imaging via deep learning,” in 2016 IEEE 13th International Symposium on Biomedical Imaging (ISBI), April 2016, pp. 514–517.

Y. Rivenson, Y. Zhang, H. Ginaydin, D. Teng, and A. Ozcan, “Phase recovery and holographic image reconstruction using deep learning in neural networks,” Light: Science &amp; Applications, vol. 7, p. 17141.

A. Sinha, J. Lee, S. Li, and G. Barbastathis, “Lensless computational imaging through deep learning,” Optica, vol. 4, no. 9, pp. 1117–1125, Sep 2017. [Online]. Available: http://www.osapublishing.org/optica/abstract.cfm?URI=optica-4-9-1117

Y. Rivenson, Z. Gintovits, H. Ginaydin, Y. Zhang, H. Wang, and A. Ozcan, “Deep learning microscopy,” Optica, vol. 4, no. 11, pp. 1437–1443, Nov 2017. [Online]. Available: http://www.osapublishing.org/optica/abstract.cfm?URI=optica-4-11-1437

T. Nguyen, Y. Xue, Y. Li, L. Tian, and G. Nehmetallah, “Convolutional neural network for fourier ptychography video reconstruction: learning temporal dynamics from spatial ensembles,” CoRR, vol. abs/1805.00334, 2018. [Online]. Available: http://arxiv.org/abs/1805.00334

B. Diederich, R. Wartmann, H. Schadwinkel, and R. Heintzmann, “Using machine-learning to optimize phase contrast in a low-cost cellphone microscope,” PLoS ONE, vol. 13, no. 3, pp. e0192937–20, Mar. 2018.

R. Horstmeyer, R. Chen, B. Kappes, and B. Judkewitz, “Convolutional neural networks that teach microscopes how to image,” pp. 1–14, Sep. 2017.

A. Robey and V. Ganapati, “Optimal Physical Preprocessing for Example-Based Super-Resolution,” ArXiv e-prints, Jul. 2018.