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Polarimetric coherent diffraction imaging on cancer-associated fibroblasts and SARS-CoV-2 viruses

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Abstract: Simultaneously non-destructive, high resolution and label-free imaging are of paramount importance for studies of complex biological systems, from viruses to cell cultures. Electron imaging techniques achieve extreme resolution but require slicing the sample to obtain volumetric information. On the other hand, X-rays’ high penetrative ability combined with cryogenic temperatures allows access to high resolution while preserving the sample’s structure. However, both X-ray and electron techniques do not currently allow label-free imaging with tissue specificity. Here, we combine a polarimetric approach with coherent diffractive imaging to reveal new ways to overcome this by mapping variations of anisotropy in the complex refractive index of cellular structures to differentiate between various tissues without chemical labeling. In this article, we demonstrate imaging of cancer-associated fibroblasts using birefringent coherent diffractive imaging with enhanced sensitivity to fibrous structures and their orientation as well as the possibility to differentiate the nucleus of the cell. We also propose a modeled soft X-ray experiment on the SARS-CoV-2 virus to address the possibility of leveraging the polarimetric birefringent contrast to spatially resolve the dynamical interaction of the virus with its host environment. We hope that our approach can open up avenues in the future to map and understand how SARS viruses bind with human epithelial cells.

Keywords: birefringence; polarimetric; coherent diffraction imaging; SARS-CoV-2; phase contrast

0. Introduction

0.1. X-ray imaging on biological cellular structures and viruses

X-ray imaging on biological specimens has been under intense development in the last decade. In general, biological cellular structures are weakly-scattering objects. Their diffraction intensities are relatively low compared to the hard condensed matter materials. The nature of X-ray imaging preserves the native environments of the sample structures without the need to section

the specimens, while high-resolution electron microscopy sections the samples into thinner parts that might perturb the native state of the specimen. Radiation damage is particularly important in X-ray imaging. Research shows that hard X-ray imaging results in less damage [1] due to the large penetration depth into the specimen, resulting in the lower radiation damage per unit volume illuminated by the X-rays. In hard X-ray imaging, phase contrast is the main contrast mechanism in cellular imaging, and a lot of progress has been made in this active research field in recent years [2,3].

In contrast to hard X-rays, soft X-ray imaging benefits from a high absorption contrast, especially the ability to image with X-ray energy near the carbon absorption edge (because most of the cellular structures are made of carbon). Also, the accessibility of X-ray energies in the water window (from the K-edge of carbon at about 282 eV to the K-edge of oxygen at about 533 eV) enables higher contrast imaging of the specimen because of the enhanced carbon absorption contrast, and water is almost transparent.

0.2. Coherent diffraction imaging

Coherent diffraction imaging (CDI)[4] is a lensless imaging technique that requires a high degree of coherence to iteratively invert the diffraction patterns with interference patterns from reciprocal space to the real space. The coherent diffraction intensities are then fed into the algorithms that iterate between real-space and reciprocal-space, resulting in the solutions of the real-space sample complex wave functions. This is made possible due to the oversampled coherent intensities in reciprocal-space that satisfy the oversampling criterion[5]. While most of the lens-based imaging methods heavily depend on the best available lithographic capabilities, CDI overcomes the limitation of lithography with the potential to achieve diffraction-limited spatial resolution. The ‘phase problem’ is indirectly solved by iterative algorithms. The iterative algorithm uses the measured diffraction intensities as the Fourier constraint, while a finite support constraint is used as a real-space constraint that confines the electronic densities of the specimen in a defined region. CDI provides non-destructive high-resolution phase-contrast imaging on various types of samples, including crystalline and amorphous structures. Furthermore, the variants of the technique, such as polarimetric CDI, provide additional information on the anisotropy of the specimen’s properties under investigation. One notable variant of CDI is ptychography[6–8], which is the subtle amalgamation of scanning transmission X-ray microscopy (STXM) with CDI. Ptychography is used to image extended objects with an unlimited field-of-view and simultaneously reconstruct the probe and the sample independently. Previous

research performed on the biological specimens by CDI[9–11] has shown the fascinating potential of the technique. Both CDI and ptychography can be implemented to image cancer-associated fibroblasts and the virus cellular structure of SARS-CoV-2 to better understand their intricate structural properties.

1. Results

1.1. Polarimetric coherent diffraction imaging on cancer-associated fibroblasts

Polarimetric CDI[12] combines both CDI and the polarization of the photon states to image specimens with polarization anisotropies. The differences in absorption constant in the birefringent/polarimetric materials generate the phase contrast in coherent diffraction patterns in the orthogonal polarization directions. The anisotropy of properties—dielectric permittivity—, of the birefringent/polarimetric specimen in the orthogonal directions, induces exceptionally notable contrast in the sample exit wave function and their coherent diffraction intensities. The coherent diffraction patterns can be inverted to the real-space sample complex wave function that encodes the phase and/or absorption differences (differences in the refraction and/or the absorption parts of the complex refractive indices) in the birefringent/polarimetric specimen.

Our goal was to model the diffraction patterns with different polarizer and analyzer settings, and to compare the resulting diffractions with modeled real space images (see Figure 1). The principal scheme of the simulation is shown in Figure 1A. First, we construct a polarized beam by combining the beam mask and desired Jones vector. Next, we construct the sample as multiple masks with specific polarization matrices. Both the sample matrix and the beam vector are later combined to form the object that is propagated to the analyzer plane. The propagated components of the polarization matrix are multiplied with the vector representation of the analyzer and displayed as the intensity distribution.

In the calibration model, we use a model sample composed of vertical stripes with alternating right-hand circular and +45° linear polarization. The model shows that in real space the combination of orthogonal linear polarizer

and analyzer misses the presence of the stripes (see Figure 1D). At the same time the presence of stripes is clearly indicated by the corresponding diffraction patterns (see Figure 1C). This suggests the possibility of extracting information on the optical anisotropy from the reconstruction of the diffraction patterns.

The polarimetric CDI experiments in our study were performed with a HeNe laser source, with the additional tools that enable the tunable polarization of the visible light generated by the laser. A polarization state analyzer is placed between the sample and the area detector for carefully selecting the diffraction intensities in a particular polarization direction. A typical experimental setup of this study is shown in Figure 2. With the polarization state generator, we can produce light with vertical, horizontal, right-hand circular, left-hand circular, and several elliptical polarization states. The polarization channels generated in our measurements are the ensemble of the full Jones vectors. The most notable and particularly interesting contrast was produced in the birefringent-polarization channel CDI measurements. Figure 3 displays the conventional microscopy absorption-contrast image of the cancer-associated fibroblasts, alongside a confocal image and the reconstructions of the polarimetric CDI measurements on the same sample, with the birefringent contrast. The birefringent contrast in Figure 3D is particularly insightful, and the fine features in the image are of high fidelity.

1.2. Simulations of model anisotropic samples using polarimetric CDI

To further understand how polarimetric CDI could determine anisotropies in biological cell structures, simulations were carried out with the polarimetric version of the cell system with a set of polarization channels of electromagnetic illumination. Figure 4 (A-D) illustrates the model polarization-dependent cell amplitude structures that are comprised of structures for 3 polarization channels. The vertical polarization, the +45° polarization, and right-hand circular polarization components all have uniquely defined amplitude structures in our simulated study. The simulated coherent diffraction intensities of a set of combinations of the polarized illumination

and the polarization-sensitive polarization state analyzers on the cell model are displayed in Figure 4 (E-G). The separate polarization channels' cell structures are expected to be recovered from the uniquely defined coherent diffraction intensities by polarimetric CDI.

1.3. Simulated polarimetric CDI experiments on SARS-CoV-2 viruses/tissue structure

Members of the family of Coronaviridae are enveloped viruses, 80–220 nm in size, pleomorphic although often spherical (coronaviruses), or 120–140 nm in size and disc, kidney, or rod-shaped (toroviruses and bafiniviruses)[14]. SARS-CoV-2 is an enveloped virus $\approx 0.1\mu\text{m}$ in diameter [15]. Both SARS-CoV-2 viruses and cancer-associated fibroblasts are highly-anisotropic in their structures; polarimetric CDI is ideal for retrieving polarization-dependent structural anisotropies. Nevertheless, SARS-CoV-2 viruses are about 1000 times smaller than cancer-associated fibroblasts; therefore, visible light microscopy can not yield sufficient resolution, and X-rays are needed to reconstruct the complex nanostructures of SARS-CoV-2 viruses. Many synchrotron facilities can produce X-ray pulses of tens of picoseconds long, and in many XFEL (X-ray free-electron laser) facilities, femtosecond x-ray pulses are available for the pump-probe measurements. Recent research shows UV-C irradiation could sterilize SARS-CoV-2 viruses[13]. Understanding how the cell's structural anisotropy in the surrounding chemical environment alters when infected with SARS-CoV-2 viruses is fundamentally important for the development of effective treatments, and polarimetric CDI at cryogenic temperatures can be implemented to maximize the diversity of the contrasts (due to the access of polarization) by the high dose of X-rays produced by the XFEL pulses.

To investigate the sensitivity of the proposed method to the viral particles we used the results of the experiment with the cancer cell to design a numerical simulation of the interaction between the virus-tissue interface and the polarized coherent X-ray radiation. To have finer control over the model we numerically generated the tissue-virus interface (see Figure 5).

The tissue texture was generated using Perlin noise. The shape of the viral particles was

procedurally generated starting with an elliptical shape with randomized semi-minor, semi-major axes, and rotation. The ellipse was then also seeded with Perlin texture and its shape was dilated by 10 pixels (modeling pixel size is 0.5 nm) with diffusion at each step. These operations allowed us to create a more realistic shape that will not contribute to artifacts in the propagation. To model the spikes at the surface of the viral particle we marked radial locations and generated fractal trees.

Since each element of the model (tissue, viral particles, and spikes) is generated separately it is possible to mask them and assign polarization components. We assigned the viral body weak circular polarizability of 5%. While the spikes were given 5% linear polarizability. The average electron density used in the model was $0.3 e^- / \text{\AA}^3$. The assembled viral particles are then placed in the tissue-free area of the model with a linear gradient of placement probability towards the tissue interface. We then perform a simulated scattering experiment using 495.93 eV X-rays and a propagation distance of 0.7 m. The resultant diffraction patterns (see Figure 5 C-G) show that even with a small amount of polarizability, there is a change in the distribution of the scattered intensities, suggesting that the method can offer sufficient sensitivity to image the viral structures. Polarimetric CDI is an effective imaging technique on virus specimens because of the promised diffraction-limited spatial resolution with phase, polarization, and elemental sensitivities.

2. Discussion

2.1. Limitation of polarimetric coherent diffraction imaging and ptychography experiments on SARS-CoV-2 virus

Although polarimetric CDI is a novel imaging technique that gives near-diffraction-limited spatial resolution and phase contrast mechanism, the data acquisition time depends mainly on the exposure time needed for a specific specimen and the field-of-view under study. When a specimen is a weak scatterer, such as most biological structures, a longer exposure time is usually required to achieve a sufficient signal-to-noise ratio. Due to the scanning nature of ptychography, studying a large field-of-view

may require a large number of scanning positions, which could result in increased data acquisition time needed. Nevertheless, the diffraction-limited synchrotron facilities are expected to significantly increase coherent flux for the experiments to overcome these limitations, thus reducing the total acquisition time needed for the measurements using polarimetric CDI and ptychography. Furthermore, sample vibration or instability could result in a reduction of the spatial resolution of the results. Therefore, experimental setups need to be carefully designed to accommodate these factors.

3. Conclusions

We report the imaging of cancer-associated fibroblasts using a developed polarimetric coherent diffractive imaging with a HeNe Laser source. The multi-modal contrast mechanism of this technique allows us to not only map the structure of cancer-associated fibroblasts but also demonstrate modeled experiments of x-ray polarimetric coherent diffractive imaging on the SARS-CoV-2 virus and its environment. Polarimetric coherent diffraction imaging is developed and proposed as a powerful imaging tool for soft matter such as biological cells, tissues, and novel pathogens such as the SARS-CoV-2 virus. Due to the multimodal polarimetric contrast mechanisms such as circular/linear dichroism, circular/linear birefringence, and depolarization, etc, this technique is capable of spatially resolving the internal structure and host environment in a wide variety of soft and even hard matter systems. This technique is also non-destructive in nature with the guarantee of diffraction-limited spatial resolution with phase (refraction) and polarization sensitivities.

Our measurements (on cancer-associated fibroblasts) using HeNe Laser Polarimetric CDI and simulated experiments (on the SARS-CoV-2 virus) using Synchrotron x-ray polarimetric CDI strongly demonstrates the feasibility of studying a host of soft biological matter systems. With the current upgrades in beam coherence at 3rd generation light sources such as the advanced photon source and the emergence of X-ray free-electron laser sources, polarimetric CDI is proposed to play a major role. The imaging of not only soft biological matter but also extensions to condensed matter systems such as

Figure 1. The concept and results of birefringent CDI. (A) Illustration of the setups of the simulated experiments. (B) The polarimetric test sample was used in the simulations. (C) The coherent diffraction pattern generated by various combinations of polarization state generator and polarization state analyzer for the amplitude test sample displayed in (B). (D) Real-space representations of the combination of orthogonal linear polarizer and analyzer used in our simulations. L: left-hand circular polarization, R: right-hand circular polarization, V: vertical polarization, H: horizontal polarization. RL (right-hand circular polarization state generator and left-hand circular polarization state analyzer).

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magnetic, ferroelectric, and even superconducting systems where symmetry-breaking features can be manifested as dichroism or birefringence at the x-ray frequency is expected.

4. Materials and Methods

4.1. Cancer-associated fibroblasts sample preparation

The TB129 cancer-associated fibroblasts were provided by Dr. Julia Tchou's laboratory of the Perleman Center for Advanced Medicine at the University of Pennsylvania. Isolation and maintenance protocols of these CAFs have been described [17,18]. The TB129 cancer-associated fibroblasts were plated on collagen, fibronectin, or laminin extracellular matrix proteins (5 $\mu\text{g}/\text{mL}$). 24 hours later, cells were fixed and stained for the nucleus (blue), actin cytoskeleton (green), and PEAK1 kinase (red).

4.2. Polarimetric Coherent Diffraction Imaging

Polarimetric coherent diffractive imaging measurements were performed with a 633 nm HeNe laser with high stability and coherence. A 30 μm pinhole, and a 50 mm plano-convex

lens was placed downstream to generate a spatially-filtered and parallel propagating laser beam. A tunable optical polarizing element (first polarizer) was used to prepare and generate polarized light of a given polarization state. A second polarizing element (that is an analyzer) is placed upstream of the first polarizer. A sample is mounted in between the polarizer and analyzer. By orienting the polarization states of the analyzer with respect to the polarizer, we can obtain information about the anisotropy of the sample in microscopy of diffraction mode. With the cancer-associated fibroblasts sample mounted, we can utilize the polarimetric contrast to map out the structural anisotropy. The accessible polarimetric contrast mechanisms include dichroic, birefringence, depolarization to name a few. A CCD camera (pco.pixelfly) was used to record the coherent diffraction patterns, and the sample-to-detector distance was chosen to be 10 mm. An 80 μm pinhole was used to select the probe's size for the CDI experiment. Diffraction intensities were accumulated for 400 frames to increase the signal-to-noise ratio, and dark-noise corrections were performed for each dataset. An

Figure 4. Model of polarizing structures. (A) Overlay of 3 polarizing channels in the model. (B)-(D) Individual structures with the property of polarizing incoming light into (B) linear +45° polarization. (C) linear right-hand circular polarization. (D) linear vertical polarization. (E)-(G) Diffraction patterns produced by the model structure, (E) using a linearly vertically polarized incident beam, and left-hand circular analyzer, (F) using a linearly horizontally polarized incident beam, and linear vertical analyzer. (G) using a right-hand circular polarized incident beam, and a left-hand circular analyzer. (H) Line plots of the normalized intensity profiles along the blue line in the panels e-g. The scale bar represents 50 μm

Figure 5. Model of the virus-tissue interface. (A) Simulated structure of viruses near the tissue. (B) Map of encoded polarizing properties of the simulated structures with green indicating spikes that were encoded with linear +45° polarization, red indicating viral particles that were encoded with right-hand circular polarization, and blue are the structures that show no polarizing property. (C-F) the diffraction pattern produced, (C) by the model structure and unpolarized beam, (D) by the model structure, linearly vertically polarized incident beam, and left-hand circular analyzer, (E) by the model structure, linearly horizontally polarized incident beam, and linear vertical analyzer, (F) by the model structure, right-hand circular polarized incident beam, and left-hand circular analyzer. (G) Line plots of the normalized intensity profiles along the blue line in the panels c-f. The scale bar represents 100 nm.

exposure time of 65 μ s was chosen to increase the signal-to-noise ratio and the measured datasets' quality.

5. Data availability

The data supporting the findings of this study are available from the corresponding author upon request.

Author Contributions: D.K., X.S., J.K. and E.F. planned and organized the experiments. E.F. and D.K. performed the experiments. The data was analyzed by E.F., D.K., X.S. The manuscript was written by D.K., X.S. and E.F. with contributions from all authors.

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Figures

Figure 1

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