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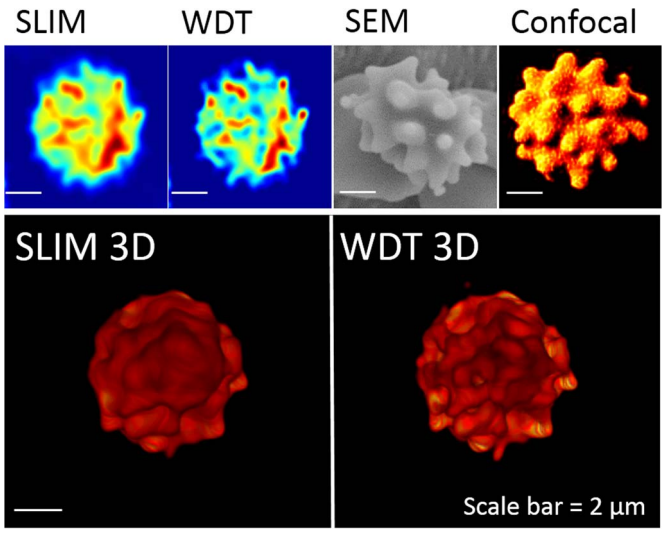
Taewoo Kim
Renjie Zhou
Lynford L. Goddard
Gabriel Popescu



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Breakthroughs in Photonics 2013: Quantitative Phase Imaging: Metrology Meets Biology

Taewoo Kim,[1] Renjie Zhou,[1,2] Lynford L. Goddard,[2] and Gabriel Popescu[1]

(Invited Paper)

[1]Quantitative Light Imaging Laboratory, Department of Electrical and Computer Engineering, Beckman Institute of Advanced Science and Technology, University of Illinois at Urbana–Champaign, Urbana, IL 61801 USA
[2]Photonic Systems Laboratory, Department of Electrical and Computer Engineering, Micro and Nanotechnology Laboratory, University of Illinois at Urbana–Champaign, Urbana, IL 61801 USA

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Manuscript received February 11, 2014; accepted February 25, 2014. Date of publication March 11, 2014; date of current version April 30, 2014. Corresponding author: G. Popescu (e-mail: gpopescu@illinois.edu). T. Kim and R. Zhou contributed equally to this work.

Abstract: Quantitative phase imaging (QPI) is an emerging optical approach that measures the optical path length of a transparent specimen noninvasively. Therefore, it is suitable for studying unstained biological tissues and cells with high sensitivity and resolution. This capability of QPI has fueled itself to grow rapidly as an active field of study for the past two decades. With this trend, QPI has experienced some breakthroughs in methods and applications in the past year. We briefly review some of these breakthroughs in method, including QPI through silicon marker-free phase nanoscopy and white-light diffraction tomography. Furthermore, some of the applications, such as quantitative phase measurement of cell growth and real-time blood testing, are introduced to show the importance and applicability of the field.

Index Terms: Optical imaging, microscopy, phase measurement, interferometry, tomography.

1. Introduction

Quantitative phase imaging (QPI) is an emerging optical approach, in which the optical path length introduced by a transparent specimen is measured at each point in the field of view [1]. Due to the interference phenomenon that it relies on, QPI renders high contrast images of samples that otherwise exhibit low contrast in common bright field imaging. In QPI, the image is obtained in a *label-free* mode, meaning that the biological specimen does not need to be tagged or stained with exogenous contrast agents (e.g., dyes or fluorophores). Furthermore, typical wavelengths used in QPI lie in the visible range, where unstained cells and tissues do not absorb significantly. As a result, live cells experience negligible damage in QPI compared to fluorescence imaging, where ultraviolet illumination is commonly used. Thus, QPI is virtually noninvasive, allowing investigation of live cells over long periods of time. QPI is an ideal tool for studying dynamic phenomena in cells over broad temporal and spatial scales. The *quantitative* nature of this imaging modality allows measurements of refractive index and thickness with great precision. A precise phase

measurement with sensitivity down to 1 mrad, can yield thickness change measurements on the order of 1 nm or, conversely, refractive index changes on the order of 10^{-4}. Thus, QPI can be used as a very precise *sizing* tool, while its refractometry capability can be converted into a *density* measurement of biological matter. Converting phase into biologically relevant knowledge has triggered important QPI technology development as well as explorations of new applications over the past 15–20 years. In the past year, we have witnessed a number of reports in high-impact journals in both directions. Below, we describe briefly some of these breakthroughs.

2. Breakthroughs in Methods

From a technology point of view, QPI builds upon phase-sensitive methods, such as phase contrast microscopy [2], [3], by combining them with holography [4], in which phase information is retrieved. Throughout the years, a number of techniques have been developed: digitally recorded interference microscopy with automatic phase shifting (DRIMAPS) [5], transport of intensity method [6], digital holographic microscopy [7]–[10], phase-resolved low-coherence interferometry [11]–[13], Fourier phase microscopy [14], [15], Hilbert phase microscopy [16], diffraction phase microscopy [17]–[19], spatial light interference microscopy [20], [21], to name just a few. Yet, in the past year, several new approaches have been published in high profile journals, suggesting that the technology development field is very much active, as follows.

2.1. Quantitative Phase Imaging Through Silicon

Silicon is the basis of integrated circuits. In recent years, *lab-on-a-chip* microfluidic devices [22], typically built upon silicon wafers, have gained popularity for studying intracellular processes and functionalities [23], [24], drug screening [25], [26], and bio-sensing [27]. On the other hand, QPI, a highly sensitive technique in both spatial and temporal dimensions, has been widely used in biological imaging, due to its label-free and high throughput nature. Last year, researchers from MIT and the University of Texas at Arlington published on using a quantitative phase imaging technique for studying structure and dynamics of cells on a silicon wafer [28]. In this work, a 980 nm Ti: Sapphire laser, accommodating both the silicon absorption and the detector quantum efficiency, was used as the illumination. A near common-path transmission interferometric QPI system was built to achieve nanometer optical path length sensitivity for quantitative phase measurement of live cells. The researchers used their system to measure the morphology of red blood cells (RBCs), in isotonic solution on the surface of a silicon wafer. In their setup, the near-infrared (NIR) laser beam traveled through both the RBCs and the silicon wafer, and then the interferometer to create an interferogram on the camera, where a phase image was retrieved. A phase image of RBCs is shown in Fig. 1(a), where the discocyte shape of RBC can be clearly observed. The phase and thickness profiles of an individual RBC are plotted in Fig. 1(b) for quantitative analysis purpose, and their values are found to be consistent with previously established results. Due to the high throughput and sensitivity of this technique, this system can be potentially applied to study mechanical, chemical, and electrical perturbation in cells. Thus, by integrating this system with a microfluidic lab-on-a-chip platform, as depicted in Fig. 1(c), it can perform measurements for different types of live cells, which can be used for disease diagnosis, drug screening, cell sorting, and bio-sensing.

2.2. Marker-Free Phase Nanoscopy

Unlike fluorescence microscopy, QPI uses the endogenous contrast coming from the refractive index distribution to obtain information about biological structures through measuring the complex electromagnetic field [1]. However, for most laser-based QPI techniques, due to the laser speckle phenomena and the low frequency coverage in the reconstruction, those systems typically have poor sensitivity and resolution. Earlier in 2013, Cotte *et al.* proposed a quasi-2π-digital holographic microscopy (2π-DHM) technique with complex deconvolution to achieve resolution beyond the diffraction limit, which allowed for reconstructing the 3D cellular structures nondestructively [29]. The

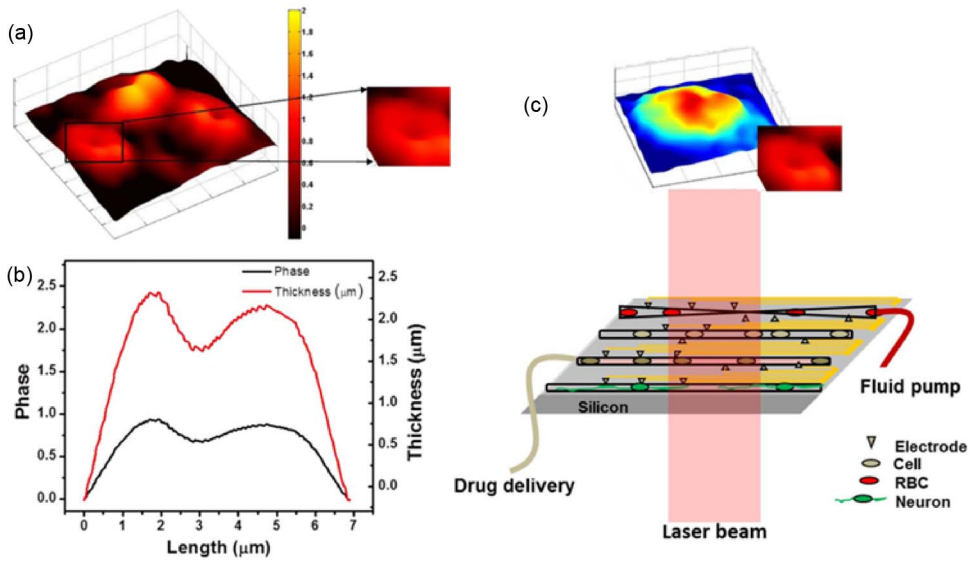

Fig. 1. (a) A quantitative phase image of RBCs, where the inset figure shows a single RBC. (b) The phase and thickness profiles of a single RBC, where the discocyte shape of the RBC can be clearly observed. (c) A schematic description of the QPI based lab-on-a-chip system for quantitative measurements of cells. Quantitative phase images of a human embryonic kidney cell and a RBC are shown on the top. Figures are adapted from reference [28] with permission.

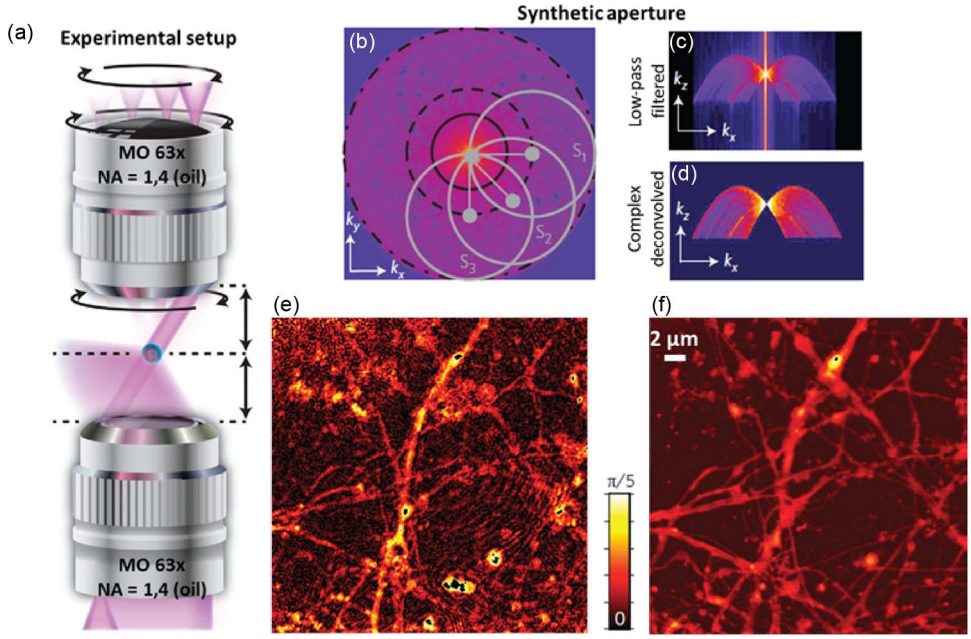

Fig. 2. (a) A schematic description of the 2π-DHM setup. (b) The synthetic aperture measurement description. (c) The (k_z, k_x) plane spatial frequency signal with low-pass filter by the system coherent transfer function. (d) The (k_z, k_x) plane spatial frequency signal after complex deconvolution. (e)–(f) A side-by-side comparison of the measurement under a conventional laser DHM system and the 2π-DHM system. Figures are adapted from reference [29] with permission.

foundation of this technique lies in the use of the synthetic aperture concept, which was experimentally realized by scanning the laser beam at different illumination angles, and collecting the scattered field for each illumination angle. A schematic description of this system is shown in Fig. 2(a).

Using this system, the 2π measurement in (k_x, k_y) plane can be obtained, as illustrated in Fig. 2(b). For 3D reconstruction, the (k_z, k_x) plane signals were also measured; Fig. 2(c) is the low-pass filtered signal (due to the system coherent transfer function) and Fig. 2(d) is the complex deconvolved (with the system transfer function) signal. A side by side comparison between the conventional laser DHM and the 2π-DHM is shown in Fig. 2(e) and (f), respectively. Through this comparison, one finds that 2π-DHM method can discern the dendrite structures that have sizes less than 100 nm, which demonstrates that this marker-free laser-based QPI technique is a promising tool for live cell morphology and dynamics study in the future.

2.3. White-Light Diffraction Tomography (WDT)

Non-invasive 3D object reconstruction is desired in biological imaging for studying morphology, growth and transportation, and dynamics in cells [30]–[32]. A new technique called white-light diffraction tomography (WDT) was recently demonstrated for label-free live 3D imaging of transparent biological objects [33]. WDT combines the concepts from diffraction tomography and low-coherence interferometry, and achieves 3D object reconstruction beyond the diffraction limit in both the lateral and axial dimensions. Importantly, WDT measures the signal in the image plane, instead of measuring in the far zone through scanning the illumination or the sample in traditional methods, and the depth dimension is obtained by simply scanning the focus through the object. The theory of WDT is a generalization of Wolf's diffraction tomography theory, and the experiment based on the theory is demonstrated by using a QPI technique called spatial light interference microscopy (SLIM) [20], [33]. Using WDT theory, the coherent transfer function of SLIM was first obtained numerically, which is related to the objective's numerical aperture and the white light coherence property. The calculated coherent transfer function for a 63x/1.4NA objective is shown in Fig. 3(a). A cross section plane of Fig. 3(a) at $k_y = 0$ is also shown in Fig. 3(b), where we can see that the coverage of k_z increases with k_x initially and then decreases due to the constraint from the objective's numerical aperture.

The calculated coherent transfer function was then used for deconvolution to render the 3D object structure. Fig. 3(c) and (d) show a comparison between the measured and deconvolved 3D image for a spiculated red blood cell (also known as echinocyte). Clearly, the deconvolution image reveals more membrane roughness. A slice of the 3D image is also taken to compare the measurement and the deconvolution, and sharper cell structures are observed in the deconvolved image. Shown in Fig. 3(e), the deconvolution result is also compared with the results from scanning electron microscopy (SEM) and confocal fluorescence microscopy to show the performance of WDT after deconvolution. As expected, WDT reveals similar structures as SEM and confocal fluorescence microscopy. Thus, we envision WDT to be a potential label-free complementary alternative to the widely used confocal fluorescence imaging system in the future.

3. Breakthroughs in Applications

In the past two decades, QPI has found numerous applications to biology: cell membrane dynamics [34], [35], intracellular transport [36], [37], cell tomography [29]–[31], [33], blood testing [34], [35], [38]–[50], tissue refractometry, scattering and diagnosis [51]–[58]. Below we highlight some recent breakthroughs in QPI applications.

3.1. Cell Growth

It has been shown that the quantitative phase map of a cell is proportional to the surface dry mass density of the cell [59]–[61]. This basic fact opened up new opportunities for studies of cell growth and proliferation [61]–[64]. In 2013, Sung *et al.*, with the Kirschner Group at Harvard, reported a study on size homeostasis in adherent cells by using a synthetic phase microscopy technique (SPM) [65]. SPM is an extension of single-shot, off-axis digital holography with laser illumination at arbitrary angles of up to 60° with respect to the optical axis. The authors obtained both amplitude and phase images and therefore the complex scattered field of the biological cells, at three different angles of illumination. These three complex fields were then numerically projected to the spatial frequency plane and

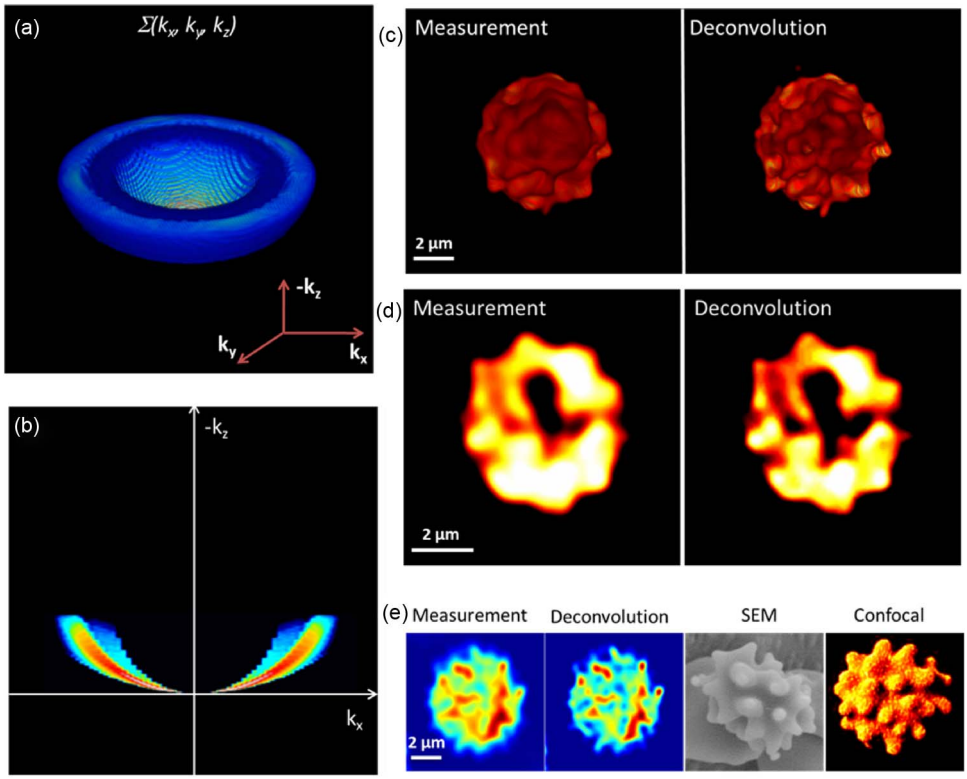

Fig. 3. (a) The calculated 3D coherent transfer function. (b) Cross-section plane of the 3D coherent transfer function at $k_y = 0$. (c) Rendered 3D image for a spiculated red blood cell using the measured raw data and the deconvolution, respectively. (d) A slice of the 3D red blood cell image using the measured raw data and its corresponding deconvolution. (e) A comparison between the measurement, deconvolution, SEM and confocal. Figures are adapted from reference [33] with permission.

synthesized to achieve larger spatial frequency coverage. Therefore, the transverse resolution of the system is comparable to that of high resolution optical diffraction tomography [66]. The refractive index of the sample can then be determined with high precision and sensitivity, down to 2.5 fg in the dry mass measurement. It is interesting to note that the dry mass measurement through SPM is almost independent of cell thickness, due to the large depth of field. Along with the high-resolution and high-sensitivity imaging ability, the system is also equipped with an on-stage cell culture system, allowing for measurements of live cells as they grow. Essentially, this system allows quantitative phase measurement of live cells in a non-invasive manner characterized by low light toxicity, no labeling, and proper incubation environment. SPM was applied to study cell division symmetry and size dependency of growth rate; the authors first measured the division symmetry by measuring the daughter cell mass ratio for cells that are adherent to the plate. For spherical L1210 lymphoblasts, the asymmetry ratio was measured to be 7.5 $\pm$ 4.8%, while for other two cell types, HT-29 and RKO human colon cancer cells, the asymmetry was significantly higher, 10.0 $\pm$ 6.4% and 13.0 $\pm$ 6.8%, respectively. This result shows that cell division is more asymmetric in adherent cells (HT-29 and RKO) than in suspended or slightly attached cells (L1210). Furthermore, the size dependency of cell growth was studied using the SPM measurements and the Collins-Richmond model [67], [68]. For all three cell types presented, the growth rate was found to be increasing as the cell mass increased, following the exponential growth model of cell growth [68], [69]. These results suggest the existence of a size-regulator that controls the cell cycle in the process of cell growth. Another QPI cell growth study from the same group, led by Cooper and Oh *et al.* [70], investigated the growth patterns of *chondrocytes*, the cells found in cartilage. The work revealed that this particular type of cell undergoes three developmental phases with distinct volume and mass trends.

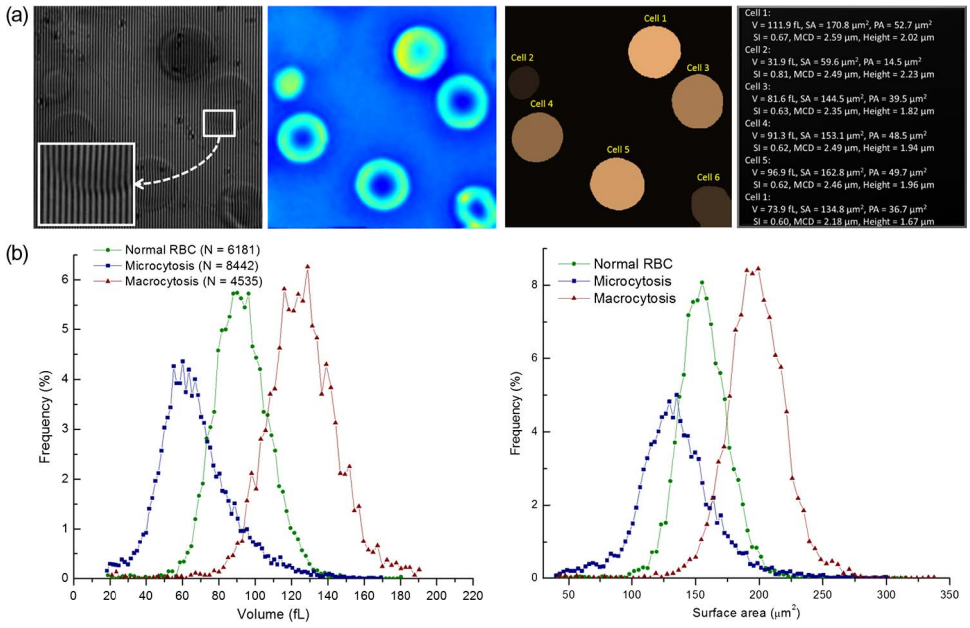

Fig. 4. Real-time blood testing using quantitative phase imaging [38]. (a) Process of blood testing is illustrated in steps from left to right. Obtained interferogram (left) is reconstructed to provide the phase information (middle left). The segmentation module segments and selects each cell (middle right), and for each cell, different parameters, such as volume, surface area, projected area, sphericity index, minimum cylindrical diameter, and mean height, are calculated (right). (b) Red blood cell volume distribution (left) and surface area distribution (right) are shown for normal, microcytic, and macrocytic RBCs.

3.2. Real-Time Blood Analysis

On the clinical side, Pham *et al.* [38] have shown real time blood testing by combining a QPI technique called diffraction phase microscopy (DPM) [17] and parallel computing. DPM is a single-shot off-axis QPI technique with the acquisition speed limited only by the acquisition speed of the detector and image-processing in computer. By using parallel computing through CUDA, real-time (40 frames/s) analysis at single cell level has been made possible. Combined with the large field of view of the imaging system, blood testing using DPM can be done at more than a thousand cells in five minutes. The blood testing procedure used in this paper is shown in Fig. 4(a). The interferogram obtained through DPM setup generates a phase image with multiple cells in the field of view. Then, the real-time blood-testing module segments the image to capture individual cells and runs the computation to return characteristic values of each cell. More specifically, the authors successfully demonstrated the use of cell morphology parameters, such as surface area, sphericity, and minimum cylindrical diameter for diagnosis of microcytic and macrocytic anemia, and showed that the results agree well with the current assessments in clinic. As shown in Fig. 4(b), normal, microcytic and macrocytic RBCs has shown significant difference in their volume and surface area distribution, indicating that the system can be used to successfully diagnose diseases.

4. Summary/Outlook

In summary, QPI has demonstrated huge potential for label-free biomedical imaging in a number of different applications. At the same time, despite some high profile publications in the past year, the QPI field is still to reach the critical mass that will result in the adoption by biologists at the large scale of these instruments. From this point of view, demonstrating new applications and, equally important, publishing the results in journals of broad audience will be the key in growing the field. Promising new class of applications include stem cell differentiation [71] and cancer drug screening [72]. Recently, there have been several companies active on the QPI market, which demonstrates

that this technology is ripe for commercialization. These companies may play a central role in turning research grade instrument into commercial, user-friendly, task specific systems, paving the way for large scale impact to biology.

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