Review

Holographic Optical Tweezers: Techniques and Biomedical Applications

Hui-Chi Chen 1,* and Chau-Jern Cheng 2

1 Department of Physics, Fu Jen Catholic University, New Taipei City 24206, Taiwan
2 Institute of Electro-Optical Engineering, National Taiwan Normal University, Taipei 11114, Taiwan
* Correspondence: 064783@mail.fju.edu.tw

Abstract: Holographic optical tweezers (HOT) is a programmable technique used for manipulation of microsized samples. In combination with computer-generation holography (CGH), a spatial light modulator reshapes the light distribution within the focal area of the optical tweezers. HOT can be used to realize real-time multiple-point manipulation in fluid, and this is useful in biological research. In this article, we summarize the HOT technique, discuss its recent developments, and present an overview of its biological applications.

Keywords: optical tweezers; holographic optical tweezers; holographic tomography; computer-generated hologram

1. Introduction

Optical tweezers (OT) [1] utilize a highly focused laser beam to manipulate a microscale-to-nanoscale [2,3] particle or single atom [4]. The particles in Brownian motion are restricted within the focal region because of the intensity gradient change and momentum transfer. For decades, optical tweezers have been widely used in biological research [5–8] to detect biological samples, using suitable wavelengths, without damaging them. Based on particle size, two theoretical models are used for force analysis—the ray optics model [9] for micro-sized particles and the Rayleigh model [10] for nanosized particles. This review focuses on biological cells or bacteria within the ray optics regime.

Ashkin, the inventor of OT, demonstrated his potential in biological research [11,12]. His research group utilized gradient laser to trap Escherichia coli, yeast cells, red blood cells, organelles, and viruses within bio-environments and aqueous solutions. Their results demonstrated that bio-samples could be reproduced without apparent damage after optical manipulation. Thus, OT enables signaling from a single living bio-sample within a crowded fluid can be detected. For example, laser tweezers Raman spectroscopy (LTRS) [13–16], also known as Raman tweezers, can be used to determine the vibration modes of a single molecule, enabling the detection and identification of unknown and rare bio-samples in complex liquid or fluid environments. In addition, OT can indirectly stretch long molecules and simultaneously measure their mechanical properties [6,17,18] by adhering to trapped microparticles. This technique is called photonic force microscopy (PFM) [19] and can be applied inside or outside living bio-samples to measure membrane elasticity [7,8,20].

Several methods were proposed in the 1990s to achieve programmable multi-particle manipulation by using OT. Position manipulation of single particles was realized by using galvano-mirrors [21,22], acousto-optic deflectors [23], and deformable mirrors [24]. Moreover, for two-particle position manipulation, beamsplitters and steerable mirrors were used to provide dual-beam control [25,26], enabling the manipulation of the positions for two particles simultaneously but independently. These systems used mechanical devices to modulate the direction of the beam entering the objective, which easily exceeds the entrance pupil of the optical system. However, none of the above systems could simultaneously provide dynamic, 3D area, and multiple-particle manipulation functions.
Computer-generated hologram (CGH) was proposed as an alternative approach to the aforementioned tasks [27]. A precalculated CGH, containing amplitude and/or phase information [28,29], can be used to induce the designed light fields on the target regions. By using a suitable device to encode CGH, the wavefront shaping technique can expand the OT’s ability to the 3D real-time multiple manipulations. This technique is called holographic optical tweezers (HOT) [30–34]. Three primary research groups contributed to the early development of HOT [30–40]—Tizani et al., (Stuttgart University) [30,31], Grier et al., (Chicago University) [32,33,35,37,38,41] and Padgett et al., (Glasgow University) [34,40]. They adopted spatial light modulators (SLMs) to encode the CGH information and used it as the input of the optical system. In preliminary attempts, Grier et al. [41] utilized a commercial diffractive pattern generator to produce a square array of spots on the trapping plane. Later, they simulated an optimized phase-only CGH to create arbitrary configurations of optical tweezers and fabricated a diffractive optical element (DOE), using the photolithographic technique [35]. This system achieved 3D manipulation of multiple particles; however, researchers usually require prefabricated DOEs. With further advancements of technology, programmable liquid crystal displays (LCDs) have been utilized as SLMs [42]. To the best of our knowledge, Reicherter et al. [30] first introduced LCDs into the OT system. They calculated the CGH to generate desired light fields on the Fourier plane of the LCD. Then they projected the CGH by using transmissive LCD into OTs and implemented the lateral manipulation dynamically on the focal plane. Later, they performed axial manipulation [31] by combining a virtual lens function into the CGH simulation. Grier’s group also conducted a similar study [32], but they applied the Gerchberg–Saxton algorithm (GSA) [43] to optimize the phase-only CGH. However, these CGH designs offered only a single defocus trapping plane. To shape a desired 3D field, Padgett et al. [34] developed the first HOT with multiple trapping planes. Using the iterative 2D-GSA [44] for multiple planes and summing the phases corresponding to the same pixels in each plane, they calculated a single phase-only CGH to produce multiple discrete trapping planes.

Owing to its ability to manipulate multiple particles dynamically, HOT has been applied in various fields of assembly [45,46], microstructure fabrication [47–50], and transport [48,51–60]. Another important application of HOT has been in the orientation control of microparticles [40,61]. Additionally, it has been used in microscopy for detection from different perspectives. For instance, HOT is often incorporated with digital holographic microscopy (DHM) [62,63] to perform holographic tomography (HT) [64–67] to estimate the 3D refractive index information of the bio-samples.

CGH can also be used to modulate the angular momentum and polarization of the light [68]. Trapping light with orbital angular momentum transfers the angular momentum to the trapping particle [69–73] and endows the trapping particle with rotational or spin motion. This technique is useful for absorptive particles because they cannot be constrained within the focal region of a Gaussian beam. Polarization control is often related to spin angular momentum [72]. Vectorial light can trap and arrange polarization-sensitive objects. This review focuses on the spatially modulated technique since it has more applications in biomedical issues.

For more than ten years, our team has also been working on the development and bio-application of OT, HOT. We applied LTRS to study the vibration modes of the newly discovered living cyanobacterium [14] and oleaginous microorganisms [16], and the results provided the information for revealing the characteristics of these microbials. To manipulate and observe the opaque particle, we implemented the optical vortex to manipulate the angular motion of magnetic ferric oxide nanoparticle clusters [74]. Later, in order to observe the signal from the sides of cylinder, we performed the orientation control [75] on the rod-shaped sample by using HOT. We then combined this technique with DHM to perform all-optical dual-tomography [65–67].

There are some other types of tweezers that can manipulate particles, such as magnetic tweezers [76], acoustical tweezers [77], plasmonic tweezers [78], and opto-thermoelectric...
whereas the direct-search algorithm exhibits a higher computing speed. To reconstruct the image within the liquid, the programmable LCD encodes and inputs the precalculated CGH into the OT system. After passing through the CGH on the LCD, the laser light is reshaped to the desired structured light within the trapping region. The sample within the fluid on the cover glass is placed on the focal plane of the objective lens. An optical source, such as an LED, is used to illuminate the sample region and image it onto the image sensor.

Figure 1. A typical HOT system.

2.2. CGH Simulation Methods

Under the currently used display resolutions, LCD–SLM can encode only a part of the entire CGH information. In HOT applications, a phase-only CGH, which discards the amplitude and retains only the phase information, is typically utilized to regenerate the light field in a 3D field or multiple planes. Therefore, an iterative or non-iterative algorithm [43,82–88] is required to optimize and synthesize CGH.

Several papers [87,89,90] reviewed the computational algorithms used in HOT system and compared their performance. In this context [87,90], the iterative algorithm exhibits better diffraction efficiency and image uniformity to generate a higher-quality optical trap, whereas the direct-search algorithm exhibits a higher computing speed. To reconstruct the desired amplitude, scalar theory was applied to calculate the phase hologram, \( \phi_k(x_k, y_k) \), for M traps. The complex amplitude from the \( k \)th pixel, location \((x_k, y_k)\) of SLM under...
uniform illumination is \( u_k = |u|e^{i\phi_k} \). After passing through the lens (focal length \( f \)), the complex amplitude, \( U_m \), of the \( m \)th trap point \((x_m, y_m, z_m)\) can be written as follows:

\[
U_m = \frac{e^{2\pi i (2f + z_m)/\lambda}}{j} \frac{d}{\lambda f} \sum_{k=1-K} |u|e^{i(\phi_k - \Delta_k^n)}
\]

where \( d \) is the pixel size and

\[
\Delta_k^n = \frac{\pi z_m}{\lambda f^2} \left( x_k^2 + y_k^2 \right) + \frac{2\pi}{\lambda f} (x_k x_m + y_k y_m)
\]

Random mask encoding (RM) [88] divides the SLM pixels into subdomains by randomly encoding the information from each CGH. The phase-only hologram of RM is denoted by \( \phi_{k,RM} = \Delta_k^{R,M} \), where the integer \( m_k \) is in the range of 1–M for each pixel. The method of superposition of prisms and lens (S) [30,31] sums up all single trap hologram, \( \phi_{k,S} = \arg \left( \sum m e^{i\Delta_k^n} \right) \), to composite CGH. RM and S perform with very poor efficiency but very fast computation. By further adding a random phase \( \theta_m, \phi_{k,SR} = \arg \left( \sum m e^{i(\Delta_k^n + \theta_m)} \right) \), a random superposition algorithm (SR) [91] has been shown to have the best performance in direct-search algorithms.

The iterative algorithm, mainly based on the Gerchberg–Saxton (GS) algorithm, includes a generalized adaptive–additive algorithm (GAA) [32], weighted GS (GSW) [89], 2D-GSA [34], and 3D-GSA [92]. At the beginning of GS, \( \phi_k \) was set as \( \phi_{k,SR} \), and then we computed \( V_m = \frac{1}{K} \sum_{k=1-K} e^{i(\phi_k - \Delta_k^n)} \), and \( \phi_k = \arg \left( \sum_m e^{i\Delta_k^n} \frac{V_m}{|V_m|} \right) \) in an iterative procedure until it converged. The diffraction efficiency of GS is high, but the uniformity is not satisfactory. Therefore, GAA adds the bias, \( \xi \), and GSW introduces the weighted factor, \( \omega_m \), to improve the uniformity. The phase information for GAA and GSW during the interaction is modified as \( \phi_{k,GAA} = \arg \left( \sum_m e^{i\Delta_k^n} \frac{V_m}{|V_m|} \left( 1 - \xi + \frac{\xi}{|V_m|} \right) \right) \), and \( \phi_{k,GSW} = \arg \left( \sum_m e^{i\Delta_k^n} \omega_m V_m \right) \). Both the GAA and GSW perform with high diffraction efficiency and uniformity, but GSW shows remarkable uniformity.

HOT often uses FT-based GSA to calculate CGH. Moreover, when 2D-GSA and 3D-GSA use the fast FT, they can generate the CGH to shape the desired amplitude on the multiple planes or in the 3D area. As depicted in Figures 1 and 2, the light with CGH information, \( u_c(p, q) \), is resized by the lenses, \( L_1 \) and \( L_2 \), and projected onto the front focal plane \((x, y)\) of the objective, i.e., \( u(x, y) = u_c \left( \frac{x f}{M}, \frac{y f}{M} \right) \). Then the light distribution, \( u(x, y) \), is Fourier transformed (FT) to the trapping area by the objective. Based on Fresnel diffraction, the light distribution on the back focal plane \((z = f)\) of the objective (real lens) can be expressed as follows:

\[
U(\xi, \eta, z = f) = \frac{1}{\lambda f} \exp \left[ j \frac{\pi}{\lambda f} \left( 1 - \frac{d}{\lambda f} \right) (\xi^2 + \eta^2) \right] \int_{-\infty}^{\infty} u(x, y) \exp \left[ -j \frac{2\pi}{\lambda f} (x \xi + y \eta) \right] dx dy
\]

where \( d \) denotes the distance between the plane \((x, y)\) and the front focal plane of the real lens. In this HOT system, the \((x, y)\) plane is on the front focal plane of the objective; hence, the distance, \( d \), is taken to be equal to the objective’s focal length, \( f \). Then the light field on the back focal plane of the objective can be expressed as the FT of the resized CGH, i.e., \( U(\xi, \eta, z = f) = \frac{1}{\lambda f} \Im \{ u(x, y) \} \).

Furthermore, 2D-GSA is used to calculate the light fields back and forth between the CGH and each regeneration plane, producing a single CGH for multiple regeneration planes. Figure 2 depicts the flowchart of 2D-GSA for M-plane regeneration. On the \( n \)th recursion, the CGH plane’s light field is denoted by \( u_n(x, y) \), and the \( m \)th regeneration plane’s light distribution is denoted by \( U_{m,n}(\xi, \eta, z) \). The amplitude of the desired regenerated image is \( T_m(\xi, \eta) \), and the distance of the regeneration plane from the focal plane is denoted by \( \Delta_m \), where \( m = 1 \sim M \). To postpone the regeneration plane away from
the focal plane, 2D-GSA introduces a virtual lens (focal length \( f_{vm} = -\frac{f^2}{\lambda_m} \)) into the CGH calculation. The calculation procedure is as follows.

**Figure 2.** Light field generation away from the real lens’s focal plane by 2D-GSA.

Step 1. If \( n = 0 \), configure the CGH’s plane function, \( u_n(x, y) = a_0 e^{i\varphi_n(x,y)} \), with random phase, \( q_0(x, y) = \text{random}(0 \sim 2\pi) \), and constant amplitude, \( a_0 \).

Step 2. Calculate the light field on the \( m \)th regeneration plane by using FT and then replace the amplitude distribution with the desired image, \( T_m \):

\[
U_{mn}(\xi, \eta) = \frac{1}{\sqrt{f}} \sum_{n=n+1} \left\{ u_n(x, y) e^{\frac{j}{\lambda_m} \left( x^2 + y^2 \right)} \right\} = A_{mn}(\xi, \eta) e^{i\varphi_{mn}(\xi, \eta)} \rightarrow T_{mn}(\xi, \eta) e^{i\varphi_{mn}(\xi, \eta)}. \tag{4}
\]

Step 3. Calculate the standard deviation, \( \epsilon \), between \( A_{mn} \) and \( T_m \). If \( \epsilon \leq \epsilon_0 \), the process is terminated, and \( u_n(x, y) \) is output as the final CGH function.

Step 4. Take inverse Fourier transform (iFT) to be the regeneration function and pass through a virtual lens, \( -f_{vm} \), back to the CGH field:

\[
\frac{1}{\sqrt{f}} \sum_{n} \left\{ T_{mn} e^{i\varphi_{mn}(\xi, \eta)} \right\} e^{-\frac{j}{\lambda_m} \left( x^2 + y^2 \right)} = a_{m,n+1} e^{i\varphi_{n+1}(x,y)} \tag{5}
\]

Step 5. Sum each phase term corresponding to the same pixel to obtain a single CGH function, \( u_{n+1}(x, y) \), corresponding to the \((n+1)\)th recursion:

\[
\varphi_{n+1}(x, y) = \sum_{m=1}^{M} \varphi_{m,n+1}(x, y) \tag{6}
\]

\[
u_{n+1}(x, y) = a_{0} e^{i\varphi_{n+1}(x,y)} \tag{7}
\]

Furthermore, 2D-GSA with 2D-FT for multiplane regeneration usually converges after a few tens of iterations. However, the uniformity and efficiency of the generated patterns are not very good. Moreover, although the resolution along the z-axis depends on the plane number, \( M \), overly large values of \( M \) increase the calculation time and required resource.

Whyte et al. [93] generated light fields over a continuous 3D volume, instead of merely on multiple discrete planes, using a 3D-GSA based on iterative 3D-FT between the CGH plane and the regenerated area. Figure 3 depicts the 3D-GSA scheme. During each iteration, the 3D-GSA captures the hemisphere’s phase within the CGH area and projects it onto a...
single-plane CGH. Based on this, Chen et al. [92] applied the HOT to a continuous space. However, despite the good 3D performance, the efficiency of CGH in their system is lower than that of 2D-GSA, as it captured only the hemispheric information for encoding onto the SLM.

![Diagram](image1)

**Figure 3.** The scheme of 3D-GSA.

Other methods have also been proposed for this purpose. The direct binary search (DBS) algorithm [45,94] exhibits a relatively slow simulation speed but is more suited for complex structures. The Wirtinger flow method [95,96] recovers the phase pattern for complex objects under noisy environments from magnitude measurement with low computational cost. Recently, Cai et al. proposed a tilted-plane weighted GSA [97] to reduce the required calculations from the 3D region to the 2D plane. They generated multiple points on a tilted plane and performed 3D optical manipulation by rotating the tilt angle.

### 2.3. Optical Orientation Control

Cell rotation is an important technique to study cell mechanism [98]. HOT can also be used for orientation control for non-spherical particles. Agarwal et al. [99] and Li et al. [100] performed the orientation rotation of nanowires by three trapping spots. However, the rotational movement was constrained to the focal plane, and the long axis of the nanowire was maintained on the focal plane. Particle orientation in OT depends on its shape and force equilibrium. This limits the measured signal from only one side of the sample. For example, Figure 4a depicts a rod-shaped particle that floats into the region of the Gaussian beam. The higher intensity near the optical axis of the light beam exerts greater force and torque to the sample, rotating its long axis until it is aligned with the optical axis (z-axis) of the trapping light. In addition, the signal detected by the objective corresponds to the round end face. In addition, the signal from the side of the cylinder may be lost during measurement.

Dragging the long axis away from the optical axis requires additional force to oppose the optical force. Kobayashi et al. [101] trapped and rotated a spherical living cell, by splitting a laser into two proximal focused beams using a half mirror and illuminating them from opposite directions. This system requires precise calibration for the appropriate alignment of the two spots in opposite directions. In 2010, H. Höner et al. [102] demonstrated full 3D translational and rotational control for rod-shaped bacteria. Using 2D-GSA and LCD-SLM, they proposed a two-spot set to trap the two ends of the sample and rotate its long axis. We also performed similar studies to control the orientation of the rod-shaped bacterium, *Thermosynechococcus elongatus* (TA) [75], that are 5–8 μm in length and 1–2 μm in diameter. As depicted in Figure 4b, two designed spots were designed on the y–z plane. The precalculated CGH fixed one on the focus plane and moved the other along the round path with a 3 μm radius. Figure 4c illustrates the experimental observations. Later, Cao et al. [61] also utilized two-spot trapping to manipulate a live spherical cell and rotated it through 360°.
Figure 4. The rotational motion of the cylindrical sample in OT and HOT. Schematic diagram (a) in a Gaussian beam trapping and (b) under a two-spot set for orientation control. (c) The experimental results for the bacteria *Thermosynechococcus elongatus* (TA) rotating on the (i–iii) y–z plane and (iv) x–y plane [75].

3. HOT Technique for Bio-Application

In biological research, fluid environments and the presence of diverse components usually increase the complexity of measurement and limit its accuracy. This issue can be addressed by rearranging microparticles at design points, using HOT, enabling long-term observation or further applications without physical contact. Thus, it serves as a powerful tool in fluid microenvironments. The advantages and characteristics of HOT for bioapplications are summarized in Figure 5.

Figure 5. The advantages and characteristics of HOT in bio-applications.

In this section, we summarize the bio-applications of HOT. As depicted in Figure 6, HOT provides the functions of multiple spots’ manipulation and orientation control. The
multiple spot manipulations can be used to guide and assemble bio-samples for further applications, such as bio-fabrication for micro-robots, micro-tools, and microstructures; moreover, the orientation control can increase the potential of design. HOT can also extend the parallel ability of detection systems to sustain the studied organelles within the sample on the same plane. Finally, HOT can also be used to control biological sample orientations to aid detection systems, such as DHM, in studying cellular mechanics.

Figure 6. Bio-applications of HOT.

3.1. Assembly and Bio-Structure Fabrication

HOT can be used to program the assembly of nano- and microsized particles [45,46] into crystal growths [47] or microstructures [103]. Several research groups have verified the feasibility of HOT-driven in 3D space. Padgett et al. [45,48] lined up several silica spheres and then moved them into a 3D structure. They also constructed 3D crystal templates for photonic bandgap materials [50] by using microspheres ranging from 0.8 to 3 µm. Other studies [104,105] have reported the assembly of microsized particles into crystalline photonic heterostructures.

On the other hand, Dufresne et al. [46] adopted real-time feature recognition to automate the assembly and sorting of colloidal silica by size. Subsequently, Shaw et al. [106] improved the throughput of automation via efficient path planning and particle identification. The assembly technique can be extended to crystal growth and fabrication [47] by combining it with a fixing process, such as polymerization [49,107].

The assembly function of HOT is also suitable for microfluidic cytometry and lab-on-a-chip devices [55,108,109]. Akselrod et al. [109] were the first to assemble living bacteria into the designing 2D and 3D arrangements in hydrogels without losing viability. Later, Leach et al. [110] arranged the live embryonic stem cells of mice along straight lines, curves, and circles and studied the interaction between multiple bio-samples. Using a suitable gelatin medium, Jordan et al. [111] and Mirsaidov et al. [112] created permanent 3D arrangements of isolated \( E. \ coli \). The fabricated structures remained intact, and the \( E. \ coli \) survived for several days even after removing the laser beam. However, the aforementioned bio-sample matrix array is insufficient to study the bio-system. The surrounding microenvironment also affects system operation. Even in this context, HOT can be used to assemble biological structures and manufacture complex cellular structures accurately [113,114].

Additionally, HOT has been applied to the fields of micro-robotics and micro-tools. Barroso et al. [115] employed HOT to fabricate living micro-robots comprising a rod-shaped prokaryotic bacterium and a single elongated zeolite L crystal. As depicted in Figure 7, HOT controls the orientation of zeolite L crystal and the position of bacterium and then assembles them together. After the trapping laser is turned off, the bacterium-zeolite L living machine can swim itself by using the bacterium’s flagella. Unlike the aforementioned studies that used mobile bacteria for transport, Sun et al. focused on automatically transporting [54,56,57,60] by moving laser spots. They fabricated a micro-
tool to transport biological cells indirectly. Figure 8 depicts the design of the micro-tool and the transportation results. Three trapping spots generated via HOT are used to manipulate the position and orientation of the micro-tool and transport the biological cell. Three-spots tweezers trap the micro-tool and indirectly move the cell along the designed path (dash line) to the desired position. The images during transportation are shown in Figure 8a–d.

Figure 7. Optical assembly of bio-hybrid micro-robot [115]. (a) HOTs trap bacterium and zeolite L crystal. (b) The orientation of zeolite L crystal is rotated by a two-spots HOT. (c) HOT assembles them together. (d) Trapping laser is turn off, then bacterium–zeolite L living machine utilizes the bacterium’s flagella to swim on its own. (e–h) Top views of the experiment during the assembling process (a–d).

Figure 8. The indirect transportation of biological cells with HOT [60]. (a) Three-spots HOTs trap and move the microtool. The microtool push the cell. (b) The cell is carried to the waypoint to avoid the obstacle. (c) The moving direction of the microtool is redirected to the desired position. (d) Cell is transported to the desired location.

3.2. Parallel Measurement of the Bio-Samples in a Fluid

HOT can be used to sustain multiple sample positions in a fluid, enabling parallel measurement and study of a single cell [116]. For instance, fluorescence microscopy can be used to acquire image stacks to extract quantitative data with high spatial and temporal protein distributions. Eriksson et al. [117] combined 3D CGH, HOT, and image analysis to optimize the axial position of trapped cells in an array. As depicted in Figure 9a,c, via 2D optical trapping, all trapping points are aligned on the same plane. To obtain better images of all nuclei, their automated system displaced the nuclei onto a single imaging plane (Figure 9b,d), and a greater number of images could be obtained via time-lapse experiments before photobleaching. HOT can also be used to increase the parallel processing capability of digital holographic microscopy. Kemper et al. [118] aligned several bacterial cells precisely on the surface of living host cells by using HOT and simultaneously monitored them via self-interference digital holographic microscopy. Their system enables the 3D modeling and imaging of infection scenarios on the single-cell level.
Then they studied chemo-mechanical processes via force measurement. As depicted in via spectroscopy. From the spectral results, polystyrene particles and yeast cells were identified. The HOT then transported the polystyrene particles away.

The incorporation of HOT also enhances the performance of Raman spectroscopy [119,120]. Raman spectroscopy [121] can be used to probe the biochemical composition of microorganisms without preprocessing. However, the floating motion of motile microbial samples influences the temporal and spatial resolution of the Raman signal. By integrating it with optical trapping, Raman tweezers [13,15] enable the spectroscopic study of the optically immobilized single microorganism under animate conditions [14]. Parlatan et al. [122] sorted and transported yeast cells and polystyrenes by using Raman tweezers. Initially, HOT was used to trap eight particles, and the Raman spectra of the particles were obtained via spectroscopy. From the spectral results, polystyrene particles and yeast cells were identified. The HOT then transported the polystyrene particles away.

OT can also be applied in photonic force microscopy (PFM) [19] to measure forces in the pico-Newton range by detecting the Brownian motion of single trapped samples. This enables the study of the viscoelasticity of the bio-sample. The use of CGH enhances the dynamic control ability and lets HOT manipulate the movement of beads in vivo. For instance, Hömer et al. [123] injected fluorescent beads into zebrafish embryos and then applied HOT to control the movement of the beads in vivo to investigate the viscoelastic properties of the embryos, enabling the study of embryonic development without invasive intervention.

Moreover, the incorporation of CGH enables the simultaneous study of multiple cells or molecules by using PFM. Mejean et al. [124] measured the mechanical coupling between an Aplysia growth cone and a bead functionalized with the neuronal cell adhesion molecule, apCAM. As depicted in Figure 10, HOT was used to position several beads near the leading edge of the growth cone—subsequently, the cell pulled the beads, which escaped from the optical force. Cell adhesion and related motility were then measured. HOT can also be applied to the measurement of the viscoelasticity of proteins and membranes [125]. In this case, the ends of the extended molecule stick to the particles, and then the particle is manipulated by HOT to measure the relation between the force and the particles’ separation. Uhrig et al. [126] demonstrated this application in a microfluidic environment. As illustrated in Figure 11, they constructed a biomimetic quasi-two-dimensional actin network on an array of polystyrene microspheres trapped inside a microfluidic chamber. Then they studied chemo-mechanical processes via force measurement. As depicted in Figure 12, Streichfuss et al. [127] also programmed three spot locations and used them to measure forces between two single actin filaments during bundle formation.
Figure 10. Growth cone study based on multiple force measurement [124]. (a) HOT hold the position of beads near the leading edge of the growth cone. (b,c) The force measured when the cell pulls the bead.

Figure 11. Actin network construction and optical force sensor array [126]. (a–c) A constructed biomimetic quasi-two-dimensional actin network. (d) Measuring force on beads with HOT.

Figure 12. Two single actin filaments during bundle formation [127]. (a–c) Sequential fluorescence images of the bunding filaments. Yellow circle indicates the attachment between filaments, yellow arrow indicates the bunding axis.
3.3. Digital Hologram

Digital holography microscopy (DHM) [62,128–130] is a label-free optical microscopic imaging system which is suitable for the study of biological samples study [64,131]. The computer program can numerically reconstruct the quantitative refractive index (RI) distribution inside bio-samples by digitally recording the interference pattern as a hologram. OT can rotate the orientation of the sample to a specified angle to gather part of the sample’s information. Bernecker et al. [132] measured the RI distribution for RBCs (red blood cells) from two perspective angles—when the long axis lies on the slide and when it is rotated by the OT to perpendicular to the slide. This application is extended to real 3D imaging in holographic tomography [66,133–136], which employs beam-rotation [137,138] or sample-rotation schemes [63,67,136,139,140] to scan entire samples under the different angles of illumination and calculate the integral phase. The beam-rotation method can be implemented by using a galvano-mirror, LCD, or digital micro-mirror device (DMD), which keeps the sample and the observation system static. The beam-rotation method exhibits a limited measuring angle, leading to an anisotropic resolution with incomplete spatial frequency coverage [141,142]. However, the sample-rotation method retains an illumination system with better reconstruction features.

Among the multiple techniques used for sample rotation, HOT offers an all-optical setup [67,139,140,143,144] with stable control and exhaustive measuring angles. Habaza et al. [140] applied the HOT technique to rotate samples during recording processing in tomography-phase microscopy. They utilized a two-spot trap to orient a yeast cell on the y–z plane over 180° in angular steps of 5° and captured the off-axis interferogram at each stage. Our team [67,139] also proposed a two-spot trap to implement full-angle rotation for living yeast cells and Candida rugosa in a fluid and acquired an entire symmetric spectrum for tomography reconstruction. Figure 13 depicts the HT-HOT joint system. Green laser light with 2D-GSA CGH information was used to illuminate the sample area to hold the sample and rotate its orientation. The HT system was built up by using the red laser, and the 3D-RI distribution of the sample was recorded.

![Figure 13. HT-HOT joint system [67]. (a) Optical system. (b) The schematic diagram. (c) The measuring index distributions of yeast cell.](image)

To extend the application of HOT and DHM to arbitrarily shaped samples, Park et al. proposed the tomographic molds for optical trapping (TOMOTRAP) [143,144]. Initially, their system measured the 3D-RI distributions of the samples. Then, based on them, they applied a 3D-GSA to generate a continuous light field distribution for the optical trapping.
This 3D reconstructed beam intensity distribution is identical to the sample volume and can be used to manipulate the sample. They demonstrated orientation control, folding, and assembly of RBCs and eukaryotic cells [143]. They recently developed isotropically resolved label-free tomographic imaging based on tomographic molds for optical trapping [144]. As illustrated in Figure 14, their proposed method yields an isotropic resolution of 230 nm and captures the structural details of live RBCs.

![Figure 14. 3D refractive index reconstruction [144] of (a,b) normal RBCs and (c,d) echinocyte, by (a,c) conventional optical diffraction tomography and (b,d) TOMOTRAP system.](image)

4. Summary and Outlook

Optical tweezers have been widely applied in biotechnology for more than 30 years. Arthur Ashkin was awarded the 2018 Nobel Prize in physics for introducing OT and its diverse applications. On the other hand, CGH endows the ability of OT to the purpose of dynamical manipulation for multiple samples. This article reviewed the development and technology of HOT and its application in biological research. Gerchberg–Saxton is the most commonly used interactive algorithm to produce CGH for shaping spatial amplitude distribution in the HOT system. Moreover, 2D-GSA simulates the optical field on multiple planes with a higher diffraction efficiency; however, 3D-GSA calculates the 3D optical field more directly but uses more computing resource. Researchers are still working on developing algorithms with higher computing speed and diffraction efficiency.

The reconstructed optical field of HOT enables the assembly and arrangement of the microsamples in the crowded and complex fluid. Thus, combining other measurement technologies, HOT provides a platform to study bio-samples or their interactions. In addition to reconstructing the spatial distribution of light, CGH can also shape the polarization [145] of the trapping light or transfer orbital angular momentum to the trapped particles [146]. Thus, it can be used to study bio-samples with polarity, such as RBC. In addition, most bio-applications of HOT have been conducted in vitro. Recently, Leite et al. [147] demonstrated a 3D HOT, using a high-NA soft-glass multimode fiber. Their system provides a possible solution for medical purple in vivo.

**Author Contributions:** Conceptualization, all authors; methodology: all authors; writing—original draft preparation, H.-C.C.; writing—review and editing, C.-J.C. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Ministry of Science and Technology in Taiwan under Grant No. MOST 103-2221-E-030-006.
Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ashkin, A.; Dziedzic, J.M.; Bjorkholm, J.E.; Chu, S. Observation of a single-beam gradient force optical trap for dielectric particles. Opt. Lett. 1986, 11, 288–290. [CrossRef] [PubMed]
2. Bradas, C. Nanoscale Optical Trapping: A Review. Adv. Opt. Mater. 2018, 6, 1800005. [CrossRef]
3. Kolbow, J.D.; Lindquist, N.C.; Ertsgaard, C.T.; Yoo, D.; Oh, S.H. Nano-Optical Tweezers: Methods and Applications for Trapping Single Molecules and Nanoparticles. ChemPhysChem 2021, 22, 1409–1420. [CrossRef] [PubMed]
4. Samoylenko, S.R.; Lisitsin, A.V.; Schepanovich, D.; Bobrov, I.B.; Straupe, S.S.; Kulik, S.P. Single atom movement with dynamic holographic optical tweezers. Laser Phys. Lett. 2020, 17, 8. [CrossRef]
5. Svoboda, A.K.; Block, S.M. Biological Applications of Optical Forces. Annu. Rev. Biophys. Biomol. Struct. 1994, 23, 247–285. [CrossRef]
6. Wang, M.D. Manipulation of single molecules in biology. Curr. Opin. Biotechnol. 1999, 10, 81–86. [CrossRef]
7. Xin, H.; Li, Y.; Liu, Y.-C.; Zhang, Y.; Xiao, Y.-F.; Li, B. Optical Forces: From Fundamental to Biological Applications. Adv. Mater. 2020, 32, 2001994. [CrossRef]
8. Favre-Bulle, I.A.; Stilgoe, A.B.; Scott, E.K.; Rubinsztein-Dunlop, H. Optical trapping in vivo: Theory, practice, and applications. Nanophotonics 2019, 8, 1023–1040. [CrossRef]
9. Ashkin, A. Forces of a single-beam gradient laser trap on a dielectric sphere in the ray optics regime. Biophys. J. 1992, 61, 569–582. [CrossRef]
10. Ashkin, A. Trapping of Atoms by Resonance Radiation Pressure. Phys. Rev. Lett. 1978, 40, 729–732. [CrossRef]
11. Ashkin, A.; Dziedzic, J.M.; Yamane, T. Optical trapping and manipulation of single cells using infrared laser beams. Nature 1987, 330, 769–771. [CrossRef]
12. Ashkin, A.; Dziedzic, J.M. Optical Trapping and Manipulation of Viruses and Bacteria. Science 1987, 235, 1517–1520. [CrossRef]
13. Xie, C.; Dinno, M.A.; Li, Y.-q. Near-infrared Raman spectroscopy of single optically trapped biological cells. Opt. Lett. 2002, 27, 249–251. [CrossRef]
14. Leu, J.-Y.; Lin, T.-H.; Selvamani, M.J.P.; Chen, H.-C.; Liang, J.-Z.; Pan, K.-M. Characterization of a novel thermophilic cyanobacterial strain from Taian hot springs in Taiwan for high CO$_2$ mitigation and C-phycocyanin extraction. Process Biochem. 2013, 48, 41–48. [CrossRef]
15. Lankers, M.; Popp, J.; Kiever, W. Raman and Fluorescence Spectra of Single Optically Trapped Microdroplets in Emulsions. Appl. Spectrosc. 1994, 48, 1166–1168. [CrossRef]
16. Pan, K.-M.; Shen, W.-T.; Wu, Y.; Hung, S.; Leu, J.-Y.; Liang, J.-Z.; Chen, H.-C. Raman study of Taiwan local oil-producing microorganisms and fatty acids. In Proceedings of the Optics & Photonics Taiwan International Conference, Taipei, Taiwan, 3–4 December 2010; p. OPT6-O-032.
17. Block, S.M.; Goldstein, L.S.B.; Schnapp, B.J. Bead movement by single kinesin molecules studied with optical tweezers. Nature 1990, 348, 348–352. [CrossRef]
18. Wang, M.D.; Yin, H.; Landick, R.; Gelles, J.; Block, S.M. Stretching DNA with optical tweezers. Biophys. J. 1997, 72, 1335–1346. [CrossRef]
19. Pralle, A.; Florin, E.L.; Stelzer, E.H.K.; Hörber, J.K.H. Photonic Force Microscopy: A New Tool Providing New Methods to Study Membranes at the Molecular Level. 2000, 1, 129–133. [CrossRef]
20. Nussenzveig, H.M. Cell membrane biophysics with optical tweezers. Eur. Biophys. J. 2018, 47, 499–514. [CrossRef]
21. Sasaki, K.; Koshioka, M.; Misawa, H.; Kitamura, N.; Masuhara, H. Pattern formation and flow control of fine particles by laser-scanning micromanipulation. Opt. Lett. 1991, 16, 1463–1465. [CrossRef]
22. Sasaki, K.; Koshioka, M.; Misawa, H.; Kitamura, N.; Masuhara, H. Optical trapping of a metal particle and a water droplet by a scanning laser beam. Appl. Phys. Lett. 1992, 60, 807–809. [CrossRef]
23. Martinez, I.A.; Petrov, D. Force mapping of an optical trap using an acousto-optical deflector in a time-sharing regime. Appl. Opt. 2012, 51, 5522–5526. [CrossRef]
24. Ota, T.; Kawata, S.; Sugiyama, T.; Booth, M.J.; Neil, M.A.A.; Juškaitis, R.; Wilson, T. Dynamic axial-position control of a laser-trapped particle by wave-front modification. Opt. Lett. 2003, 28, 465–467. [CrossRef]
25. Fällman, E.; Axner, O. Design for fully steerable dual-trap optical tweezers. Appl. Opt. 1997, 36, 2107–2113. [CrossRef]
26. Sivaramakrishnan, S.; Sung, J.M.; Dunn, A.R.; Spudich, J.A. Dual-Beam Optical Tweezers. In Encyclopedia of Biophysics; Roberts, G.C.K., Ed.; Springer: Berlin/Heidelberg, Germany, 2013; pp. 522–526.
27. Brown, B.R.; Lohmann, A.W. Computer-generated Binary Holograms. IBM J. Res. Dev. 1969, 13, 160–168. [CrossRef]
28. Davis, J.A.; Capello, D.M.; Cottrell, D.M. Encoding amplitude and phase information onto a binary phase-only spatial light modulator. Appl. Opt. 2003, 42, 2003–2008. [CrossRef]
29. Davis, J.A.; Cottrell, D.M.; Campos, J.; Yzuel, M.J.; Moreno, I. Encoding amplitude information onto phase-only filters. Appl. Opt. 1999, 38, 5004–5013. [CrossRef]
30. Reicherter, M.; Haist, T.; Wagemann, E.U.; Tizziani, H.J. Optical particle trapping with computer-generated holograms written on a liquid-crystal display. Opt. Lett. 1999, 24, 608–610. [CrossRef]
31. Liesener, J.; Reicherter, M.; Haist, T.; Tiziani, H.J. Multi-functional optical tweezers using computer-generated holograms. Opt. Commun. 2000, 185, 77–82. [CrossRef]
32. Curtis, J.E.; Koss, B.A.; Grier, D.G. Dynamic holographic optical tweezers. Opt. Commun. 2002, 207, 169–175. [CrossRef]
33. Grier, D.G. A revolution in optical manipulation. Nature 2003, 424, 810–816. [CrossRef] [PubMed]
34. Sinclair, G.; Leach, J.; Jordan, P.; Gibson, G.; Yao, E.; Laczik, Z.J.; Padgett, M.J.; Courtial, J. Interactive application in holographic optical tweezers of a multi-plane Gerchberg-Saxton algorithm for three-dimensional light shaping. Opt. Express 2004, 12, 1665–1670. [CrossRef] [PubMed]
35. Dufresne, E.R.; Spalding, G.C.; Dearing, M.T.; Sheets, S.A.; Grier, D.G. Computer-generated holographic optical tweezer arrays. Rev. Sci. Instrum. 2001, 72, 1810–1816. [CrossRef]
36. Lyng Eriksen, R.; Ricardo Daria, V; Glickstad, J. Fully dynamic multiple-beam optical tweezers. Opt. Express 2002, 10, 597–602. [CrossRef]
37. Grier, D.G.; Roichman, Y. Holographic optical trapping. Appl. Opt. 2006, 45, 880–887. [CrossRef]
38. Sun, B.; Roichman, Y.; Grier, D.G. Theory of holographic optical trapping. Opt. Express 2008, 16, 15765–15776. [CrossRef]
39. Reicherter, M.; Zwick, S.; Haist, T.; Kohler, C.; Tiziani, H.; Osten, W. Fast digital hologram generation and adaptive force measurement in liquid-crystal-display-based holographic tweezers. Appl. Opt. 2006, 45, 888–896. [CrossRef]
40. Bingelyte, V.; Leach, J.; Courtial, J.; Padgett, M.J. Optically controlled three-dimensional rotation of microscopic objects. Appl. Phys. Lett. 2003, 82, 829–831. [CrossRef]
41. Dufresne, E.R.; Grier, D.G. Optical tweezer arrays and optical substrates created with diffractive optics. Rev. Sci. Instrum. 1998, 69, 1974–1977. [CrossRef]
42. Cho, D.J.; Thurman, S.T.; Donner, J.T.; Morris, G.M. Characteristics of a 128 × 128 liquid-crystal spatial light modulator for wave-front generation. Opt. Lett. 1998, 23, 969–971. [CrossRef]
43. Gerchberg, R.W. A practical algorithm for the determination of the phase from image and diffraction plane pictures. Optik 1972, 35, 237–246.
44. Haist, T.; Schönleber, M.; Tiziani, H.J. Computer-generated holograms from 3D-objects written on twisted-nematic liquid crystal displays. Opt. Commun. 1997, 140, 299–308. [CrossRef]
45. Sinclair, G.; Jordan, P.; Courtial, J.; Padgett, M.; Cooper, J.; Laczik, Z.J. Assembly of 3-dimensional structures using programmable holographic optical tweezers. Opt. Express 2004, 12, 5475–5480. [CrossRef]
46. Chapin, S.C.; Germain, V.; Dufresne, E.R. Automated trapping, assembly, and sorting with holographic optical tweezers. Opt. Express 2006, 14, 13095–13101. [CrossRef]
47. Leach, J.; Sinclair, G.; Jordan, P.; Courtial, J.; Padgett, M.J.; Cooper, J.; Laczik, Z.J. 3D manipulation of particles into crystal structures using holographic optical tweezers. Opt. Express 2004, 12, 220–226. [CrossRef]
48. Korda, P.; Spalding, G.C.; Dufresne, E.R.; Grier, D.G. Nanofabrication with holographic optical tweezers. Rev. Sci. Instrum. 2002, 73, 1956–1957. [CrossRef]
49. Jordan, P.; Clare, H.; Flendrig, L.; Leach, J.; Cooper, J.; Padgett, M. Permanent 3D microstructures in a polymeric host created using holographic optical tweezers. J. Mod. Opt. 2004, 51, 627–632. [CrossRef]
50. Benito, D.C.; Carberry, D.M.; Simpson, S.H.; Gibson, G.M.; Padgett, M.J.; Rarity, J.G.; Miles, M.J.; Hanna, S. Constructing 3D crystal templates for photonic band gap materials using holographic optical tweezers. Opt. Express 2008, 16, 13005–13015. [CrossRef]
51. Korda, P.T.; Taylor, M.B.; Grier, D.G. Kinetically locked-in colloidal transport in an array of optical tweezers. Phys. Rev. Lett. 2002, 89, 4. [CrossRef]
52. Grier, D.G. Colloidal transport in holographic optical tweezer arrays. Abstr. Pap. Am. Chem. Soc. 2003, 226, U292.
53. Roichman, Y.; Wong, V.; Grier, D.G. Colloidal transport through optical tweezer arrays. Phys. Rev. E 2007, 75, 4. [CrossRef]
54. Hu, S.Y.; Sun, D. Automated Transportation of Single Cells Using Robot-Tweezer Manipulation System. JALA J. Assoc. Lab. Autom. 2011, 16, 263–270. [CrossRef]
55. Pagliara, S.; Schwall, C.; Keyser, U.F. Optimizing Diffusive Transport Through a Synthetic Membrane Channel. Adv. Mater. 2013, 25, 844–849. [CrossRef]
56. Chen, H.Y.; Wang, C.; Li, X.J.; Sun, D. Transportation of Multiple Biological Cells Through Saturation-Controlled Optical Tweezers In Crowded Microenvironments. IEEE-ASME Trans. Mechatron. 2016, 21, 888–899. [CrossRef]
57. Hu, S.Y.; Chen, S.X.; Chen, S.; Xu, G.; Sun, D. Automated Transportation of Multiple Cell Types Using a Robot-Aided Cell Manipulation System With Holographic Optical Tweezers. IEEE-ASME Trans. Mechatron. 2017, 22, 804–814. [CrossRef]
58. Stuart, D.; Kuhn, A. Single-atom trapping and transport in DMD-controlled optical tweezers. New J. Phys. 2018, 20, 9. [CrossRef]
59. Quinto-Su, P.A. Microparticle transport networks with holographic optical tweezers and cavitation bubbles. Opt. Lett. 2019, 44, 4610–4613. [CrossRef]
60. Hu, S.Y.; Xie, H.; Wei, T.Y.; Chen, S.X.; Sun, D. Automated Indirect Transportation of Biological Cells with Optical Tweezers and a 3D Printed Microtool. Appl. Sci. 2019, 9, 15. [CrossRef]
61. Cao, B.; Kelbauskas, L.; Chan, S.; Shetty, R.M.; Smith, D.; Meldrum, D.R. Rotation of single live mammalian cells using dynamic holographic optical tweezers. Opt. Lasers Eng. 2017, 92, 70–75. [CrossRef]
62. Cuche, E.; Marquet, P.; Depeursinge, C. Simultaneous amplitude-contrast and quantitative phase-contrast microscopy by numerical reconstruction of Fresnel off-axis holograms. Appl. Opt. 1999, 38, 6994–7001. [CrossRef]
95. Wei, Z.; Chen, W.; Yin, T.; Chen, X. Robust phase retrieval of complex-valued object in phase modulation by hybrid Wirtzinger flow method. Opt. Eng. 2017, 56, 093106. [CrossRef]

96. Candès, E.J.; Li, X.; Soltanolkotabi, M. Phase Retrieval via Wirtzinger Flow: Theory and Algorithms. IEEE Trans. Inf. Theory 2015, 61, 1985–2007. [CrossRef]

97. Cai, Y.N.; Yan, S.H.; Wang, Z.J.; Li, R.Z.; Liang, Y.S.; Zhou, Y.; Li, X.; Yu, X.H.; Lei, M.; Yao, B.L. Rapid tilted-plane Gerchberg-Saxton algorithm for holographic optical tweezers. Opt. Express 2020, 28, 12729–12739. [CrossRef] [PubMed]

98. Tang, T.; Hosokawa, Y.; Hayakawa, T.; Tanaka, Y.; Li, W.; Li, M.; Yalikun, Y. Rotation of Biological Cells: Fundamentals and Applications. Engineering 2022, 10, 110–126. [CrossRef]

99. Agarwal, R.; Ladavac, K.; Roichman, Y.; Yu, G.H.; Lieber, C.M.; Grier, D.G. Manipulation and assembly of nanowires with holographic optical traps. Opt. Express 2005, 13, 8906–8912. [CrossRef]

100. Li, J.; Du, G. Manipulation and assembly with ZnO nanowires with single holographic optical tweezers system. Appl. Opt. 2014, 53, 351–355. [CrossRef]

101. Kobayashi, H.; Ishimaru, I.; Hyodo, R.; Yasokawa, T.; Ishizaki, K.; Kurita, S.; Komatsu, T.; Nakai, S.; Takegawa, K.; Tanaka, N. A precise method for rotating single cells. Appl. Phys. Lett. 2006, 88, 131103. [CrossRef]

102. Horner, F.; Woerdemann, M.; Muller, S.; Maier, B.; Denz, C. Full 3D translational and rotational optical control of multiple rod-shaped bacteria. J. Biophotonics 2010, 3, 468–475. [CrossRef]

103. Gould, O.E.C.; Qu, H.B.; Lunn, D.J.; Rowden, J.; Harmann, R.L.; Hudson, Z.M.; Winnik, M.A.; Miles, M.J.; Manners, I. Transformation and patterning of supermicelles using dynamic holographic assembly. Nat. Commun. 2015, 6, 7. [CrossRef]

104. Roichman, Y.; Grier, D.G. Holographic assembly of quasicrystalline photonic heterostructures. Opt. Lett. 2009, 34, 364–366. [CrossRef]

105. Ovanesyan, Z.; Pudasaini, P.R.; Gangadharan, A.; Marucho, M. Three-dimensional quasicrystalline photonic material with five-fold planar symmetry for visible and infrared wavelengths by holographic assembly of quasicrystalline photonic heterostructures. Opt. Mater. Express 2013, 3, 1332–1337. [CrossRef]

106. Shaw, L.A.; Chizari, S.; Hopkins, J.B. Improving the throughput of automated holographic optical tweezers. Appl. Opt. 2018, 57, 6396–6402. [CrossRef]

107. Shaw, L.A.; Chizari, S.; Panas, R.M.; Shusteff, M.; Spadaccini, C.M.; Hopkins, J.B. Holographic optical assembly and photopolymerized joining of planar microspheres. Appl. Opt. 2016, 41, 3571–3574. [CrossRef]

108. Padgett, M.; Di Leonardo, R. Holographic optical tweezers and their relevance to lab on chip devices. Lab Chip 2011, 11, 1196–1205. [CrossRef]

109. Akselrod, G.M.; Timp, W.; Mirsaidov, U.; Zhao, Q.; Li, C.; Timp, R.; Timp, K.; Matsuda, M.; Timp, G. Laser-guided assembly of heterotypic three-dimensional living cell microarrays. Biophys. J. 2006, 91, 3465–3473. [CrossRef]

110. Leach, J.; Howard, D.; Roberts, S.; Gibson, G.; Gotthard, D.; Cooper, J.; Shakesheff, K.; Padgett, M.; Buttery, L. Manipulation of live mouse embryonic stem cells using holographic optical tweezers. J. Mod. Opt. 2009, 56, 448–452. [CrossRef]

111. Jordan, P.; Leach, J.; Padgett, M.; Blackburn, P.; Isaacs, N.; Goksor, M.; Hanstorp, D.; Wright, A.; Girkin, J.; Cooper, J. Creating permanent 3D arrangements of isolated cells using holographic optical tweezers. Lab Chip 2005, 5, 1224–1228. [CrossRef]

112. Mirsaidov, U.; Scrimgeour, J.; Timp, W.; Beck, K.; Mir, M.; Matsuda, M.; Timp, G. Live cell lithography: Using optical tweezers to create synthetic tissue. Lab Chip 2008, 8, 2174–2181. [CrossRef]

113. Dinu, C.Z.; Chakrabarty, T.; Lunsford, E.; Mauer, C.; Plewa, J.; Dordick, J.S.; Chrisey, D.B. Optical manipulation of microtubes for directed biomolecule assembly. Soft Matter 2009, 5, 3818–3822. [CrossRef]

114. Kirkham, G.R.; Britchford, E.; Upton, T.; Ware, J.; Gibson, G.M.; Devaud, Y.; Ehrbar, M.; Padgett, M.; Allen, S.; Buttery, L.D.; et al. Precision Assembly of Complex Cellular Microenvironments using Holographic Optical Tweezers. Sci. Rep. 2015, 5, 7. [CrossRef]

115. Barroso, A.; Landwerth, S.; Woerdemann, M.; Altmann, C.; Buscher, T.; Becker, M.; Studer, A.; Denz, C. Optical assembly of bio-hybrid micro-robots. Biomed. Microdevices 2015, 17, 8. [CrossRef]

116. Ramser, K.; Hanstorp, D. Optical manipulation for single-cell studies. J. Biophotonics 2010, 3, 187–206. [CrossRef]

117. Eriksson, E.; Engstrom, D.; Scrimgeour, J.; Goksor, M. Automated focusing of nuclei for time lapse experiments on single cells using holographic optical tweezers. Opt. Express 2009, 17, 5585–5594. [CrossRef]

118. Kemper, B.; Barroso, A.; Woerdemann, M.; Dewenter, L.; Vollmer, A.; Schubert, R.; Hellmam, A.; von Bally, G.; Denz, C. Towards 3D modelling and imaging of infection scenarios at the single cell level using holographic optical tweezers and digital holographic microscopy. J. Biophotonics 2013, 6, 260–266. [CrossRef]

119. Creely, C.M.; Volpe, G.; Singh, G.P.; Soler, M.; Petrov, D.V. Raman imaging of floating cells. Opt. Express 2005, 13, 6105–6110. [CrossRef]

120. Zhang, P.; Kong, L.; Setlow, P.; Li, Y-q. Multiple-trap laser tweezers Raman spectroscopy for simultaneous monitoring of the biological dynamics of multiple individual cells. Opt. Lett. 2010, 35, 3321–3323. [CrossRef]

121. Raman, C.V. Part II.—The Raman effect. Investigation of molecular structure by light scattering. Trans. Faraday Soc. 1929, 25, 781–792. [CrossRef]

122. Parlatan, U.;Basar, G.;Basar, G. Sorting of micron-sized particles using holographic optical Raman tweezers in aqueous medium. J. Mod. Opt. 2019, 66, 228–234. [CrossRef]

123. Horner, F.; Meissner, R.; Polali, S.; Pfeiffer, J.; Betz, T.; Denz, C.; Raz, E. Holographic optical tweezers-based in vivo manipulations in zebrafish embryos. J. Biophotonics 2017, 10, 1492–1501. [CrossRef]
124. Mejean, C.O.; Schaefer, A.W.; Millman, E.A.; Forscher, P.; Dufresne, E.R. Multiplexed force measurements on live cells with holographic optical tweezers. *Opt. Express* 2009, 17, 6209–6217. [CrossRef]
125. Farre, A.; van der Horst, A.; Blab, G.A.; Downing, B.P.B.; Forde, N.R. Stretching single DNA molecules to demonstrate high-force capabilities of holographic optical tweezers. *J. Biophotonics* 2010, 3, 224–233. [CrossRef] [PubMed]
126. Uhrig, K.; Kurre, R.; Schmitz, C.; Curtis, J.E.; Haraszti, T.; Clemen, A.E.M.; Spatz, J.P. Optical force sensor array in a microfluidic device based on holographic optical tweezers. *Lab Chip* 2009, 9, 661–668. [CrossRef] [PubMed]
127. Streichfuss, M.; Erbsd, F.; Uhrig, K.; Kurre, R.; Clemen, A.E.M.; Bohm, C.H.J.; Haraszti, T.; Spatz, J.P. Measuring Forces between Two Single Actin Filaments during Bundle Formation. *Nano Lett.* 2011, 11, 3676–3680. [CrossRef] [PubMed]
128. Huang, T.S. Digital holography. *Proc. IEEE* 1971, 59, 1335–1346. [CrossRef]
129. Schnars, U.; Jüptner, W. Direct recording of holograms by a CCD target and numerical reconstruction. *Appl. Opt.* 1994, 33, 179–181. [CrossRef]
130. Kim, M. Principles and techniques of digital holographic microscopy. *SPIE Rev.* 2010, 1, 018005. [CrossRef]
131. Jin, D.; Zhou, R.; Yaqoob, Z.; So, F.T.C. Tomographic phase microscopy: Principles and applications in bioimaging [Invited]. *J. Opt. Soc. Am. B* 2017, 34, B64–B77. [CrossRef]
132. Bernecker, C.; Lima, M.; Ciubotaru, C.D.; Schlenke, P.; Dorn, I.; Cojoc, D. Biomechanics of Ex Vivo-Generated Red Blood Cells Investigated by Optical Tweezers and Digital Holographic Microscopy. *Cells* 2021, 10, 18. [CrossRef]
133. Lauer, V. New approach to optical diffraction tomography yielding a vector equation of diffraction tomography and a novel tomographic microscope. *J. Microsc.* 2002, 205, 165–176. [CrossRef]
134. Lin, Y.-C.; Cheng, C.-J. Determining the refractive index profile of micro-optical elements using transmissive digital holographic microscopy. *J. Opt.* 2010, 12, 115402. [CrossRef]
135. Lin, Y.-C.; Cheng, C.-J. Sectional imaging of spatially refractive index distribution using coaxial rotation digital holographic microtomography. *J. Opt. Appl.* 2014, 16, 065401. [CrossRef]
136. Choi, W.; Fang-Yen, C.; Badizadegan, K.; Oh, S.; Lue, N.; Dasari, R.R.; Feld, M.S. Tomographic phase microscopy. *Nat. Methods* 2007, 4, 717–719. [CrossRef]
137. Kostencka, J.; Kozacki, T.; Kuś, A.; Kemper, B.; Kujawińska, M. Holographic tomography with scanning of illumination: Space-domain reconstruction for spatially invariant accuracy. *Biomed. Opt. Express* 2016, 7, 4086–4101. [CrossRef]
138. Haeberle, O.; Belkebir, K.; Giovaninni, H.; Sentenac, A. Tomographic diffractive microscopy: Basics, techniques and perspectives. *J. Mod. Opt.* 2010, 57, 686–699. [CrossRef]
139. Kujawińska, M.; Krauze, W.; Kuś, A.; Kostencka, J.; Kozacki, T.; Kemper, B.; Dudek, M. Problems and Solutions in 3-D Analysis of Phase Biological Objects by Optical Diffraction Tomography. *Int. J. Optomechatronics* 2014, 8, 357–372. [CrossRef]
140. Gilboa, M.H.B.; Roichman, Y.; Shaked, N.T. Tomographic phase microscopy with 180 degrees rotation of live cells in suspension by holographic optical tweezers. *Opt. Lett.* 2015, 40, 1881–1884. [CrossRef]
141. Balasubramani, V.; Montresor, S.; Tu, H.Y.; Huang, C.H.; Picart, P.; Cheng, C.J. Influence of noise-reduction techniques in sparse-data sample rotation tomographic imaging. *Opt. Appl.* 2021, 60, B81–B87. [CrossRef]
142. Curtis, J.E.; Grier, D.G. Structure of optical vortices. *Phys. Rev. Lett.* 2003, 90, 4. [CrossRef] [PubMed]
143. Leite, I.T.; Turtel, S.; Jiang, X.; Siler, M.; Cuschieri, A.; Russell, P.S.; Cizmar, T. Three-dimensional holographic optical manipulation through a high-numerical-aperture soft-glass multimode fibre. *Nat. Photonics* 2018, 12, 33–39. [CrossRef]