Chapter

Optical Tweezers in Biotechnology

Zhiyong Gong and Yuchao Li

Abstract

Three-dimensional optical manipulation of microparticles, cells, and biomolecules in a noncontact and noninvasive manner is crucial for biophotonic, nanophotonic, and biomedical fields. Optical tweezers, as a standard optical manipulation technique, have some limitations in precise manipulation of micro-objects in microfluidics and in vivo because of their bulky lens system and limited penetration depth. Moreover, when applied for trapping nanoscale objects, especially with sizes smaller than 100 nm, the strength of optical tweezers becomes significantly weak due to the diffraction limit of light. The emerging near-field methods, such as plasmon tweezers and photonic crystal resonators, have enabled surpassing of the diffraction limit. However, these methods msay lead to local heating effects that will damage the biological specimens and reduce the trapping stability. Furthermore, the available near-field techniques rely on complex nanostructures fixed on substrates, which are usually used for 2D manipulation. The optical tweezers are of great potential for the applications including nanostructure assembly, cancer cell sorting, targeted drug delivery, single-molecule studies, and biosensing.

Keywords: optical tweezers, optical force, optical manipulation, biophotonics, biotechnology

1. Introduction

As early as the 1970s, Maxwell revealed that electromagnetic waves can carry momentum in his famous electromagnetic field theory. When electromagnetic waves are applied to objects, they will transmit momentum. Therefore, electromagnetic waves can exert force on objects, and then the concept of electromagnetic force is proposed [1]. Until the beginning of the twentieth century, Einstein proposed the concept of photonic quantum, which believes that light is composed of a group of photons with both mass and momentum. When light is irradiated on the surface of the object, it can cause changes in the photon momentum to produce radiation pressure on the object due to the scattering and absorption of light. Subsequently, Lebedev, Nichol, and Hull first demonstrated the existence of radiation pressure experimentally. The experiment used arc lamps and torsion scales to observe the effect of light in the macroscopic physical world. However, the light produced by the arc lamp is very weak and difficult to practically apply. Until 1960, the invention of the laser provided a high-intensity optical source for studying optical force, which greatly promoted the application of optical manipulation. Arthur Ashkin, a scientist at Bell Experiments in the United States, first used the radiation pressure generated by the laser beam to push tiny particles in the liquid environment [2] and then used two opposing laser beams to capture microparticles and even atoms. However, the experimental setup used in the dual-beam capture method is too complex and can

only limit microparticles in a two-dimensional plane. Scientists hope to use a single laser to achieve three-dimensional trapping of microparticles. To this end, in 1986, Ashkin et al. used a high-numerical-aperture objective to focus a single laser to trap microparticles and named the technology "single beam gradient force trap" [3]. A year later, Ashkin et al. continued to improve this technology and achieved optical trapping and manipulation of tiny bacteria and viruses. They officially named the technology "optical tweezers" [3]. Compared with traditional macro-mechanical tweezers, the optical tweezers have the advantages of noncontact and no damage and can perform high-precision manipulation of microscopic particles. Therefore, since the birth of the optical tweezer technology, it has played an important role in the fields of biomedicine and physical chemistry.

1.1 Traditional optical tweezers

1.1.1 Basic principles

The core component of the traditional optical tweezers is a highly focused beam, as shown in **Figure 1a** [4]. When the incident laser (usually a near-infrared laser with a wavelength of 1064 nm) is focused by a high-numerical-aperture objective lens, the microparticles in the liquid environment will be exposed to optical force near the focus. This force is derived from the momentum transfer effect between light and particles. Specifically, the optical forces are divided into two components: one component along the direction of the optical gradient, called the optical gradient force, which is caused by the microparticles being in a nonuniform optical field, and the optical gradient force, which drives the particles to the area where the optical intensity is greatest; another component along the direction of optical propagation, called optical scattering force, is caused by the scattering and absorption of particles, and the optical scattering force causes the microparticles to move along the direction of optical propagation. By modulating the focused beam, the magnitude of two forces can be varied to achieve different functions such as capture, acceleration, and rotation of the microparticles. For traditional optical tweezers to construct a stable trap, it is necessary to focus the incident laser with a high-numerical-aperture (generally NA = 1.0~1.4) objective lens. The resulting

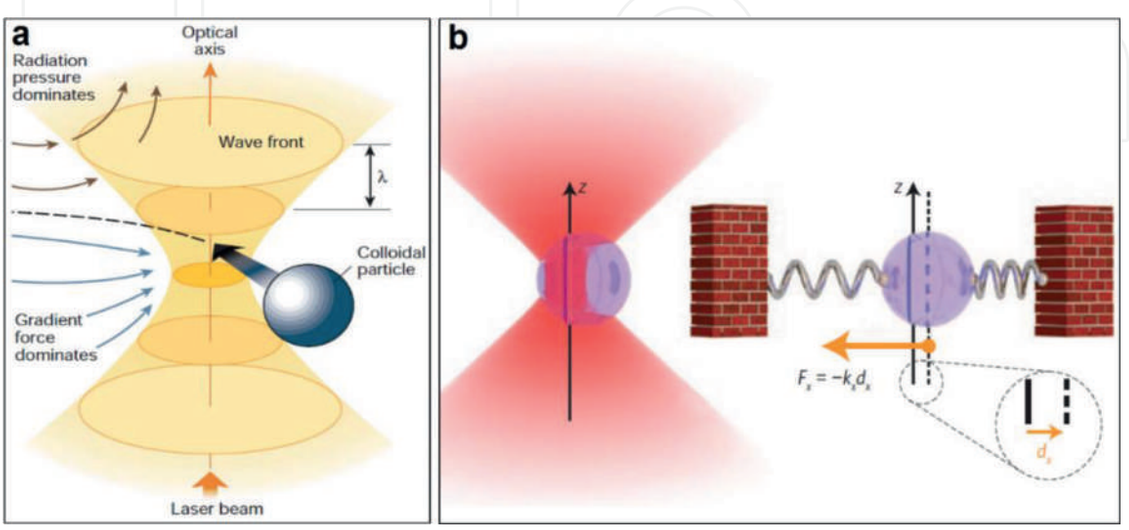

Figure 1.
Schematic diagram of the traditional optical tweezers. (a) A single microparticle is trapped to the focused spot of a laser beam by gradient force and scattering force to [4]. (b) A simple harmonic oscillator model for the optical trapping of the microparticle.

optical gradient force is greater than the optical scattering force, so the microparticles or the cells can be stably trapped in the focus of light [5].

The model in which the object is trapped by the optical tweezers can be equivalent to a simple oscillator, as shown in **Figure 1b**. The magnitude of the object's received optical force (F) is proportional to the object's distance from the focus (d), which is

$$F = -kd \tag{1}$$

where the constant k represents the spring constant of the spring oscillator and the strength of the trap. Therefore, when we know the motion of an object in a trap, the magnitude of the optical force can be calculated by Formula 1. However, in the more general case, we want to quantitatively analyze the optical force when the unknown object motions and then other optical theories are needed. The theoretical analysis of optical tweezers needs to be determined according to the size of the object, specifically divided into three cases: first, when the radius (R) of the particle is much larger than the wavelength (λ) of the incident light, then a simple geometric optical method can be used to analyze the force of the object; second, if the size of the particle is much smaller than the wavelength of the incident light, the particle can be equivalent to the dipole in the electric field, and a dipole approximation model is needed; and third, if the size of the particles is close to the wavelength of the light, the situation becomes complicated, and the Maxwell equation is needed to solve the problem.

We first analyze the Rayleigh nanoparticle ($R << \lambda$). At this time, the nanoparticle can be regarded as a dipole in a nonuniform electromagnetic field, and the optical gradient force ($\boldsymbol{F}_{grad}$) of the dipole in the electromagnetic field can be expressed as

$$\boldsymbol{F}_{\text{grad}} = \frac{1}{2}|\alpha|\ \nabla\langle \boldsymbol{E}^2\rangle, \tag{2}$$

where α is the polarizability of the dipole, $\boldsymbol{E}$ is the electric field, parentheses indicate the time average, and $|\boldsymbol{E2}|$ is proportional to the intensity of the electromagnetic field. It can be seen from Formula 2 that the direction of the optical gradient force $\boldsymbol{F}_{grad}$ is along the direction of the optical intensity gradient. Thus, for a highly concentrated beam, the particles are drawn to the focus of the spot. Here, the polarizability α is a crucial parameter that directly determines the intensity of the interaction of light with object. For spherical nanoparticles, α can be expressed as [6]

$$\alpha = \alpha_0 \left(1 - \frac{ik^3\alpha_0}{6\pi\varepsilon_0}\right)^{-1}, \tag{3}$$

where $k = 2\pi n/\lambda$ is the scalar of the incident light wave vector, ε is the dielectric constant of the particle, ε_0 is the dielectric constant of the vacuum, α_0 is the quasi-static polarizability of the nanoparticle, and α_0 can be given by the Clausius-Mossotti relation [6]:

$$\alpha_0 = 4\pi\varepsilon_0 R^3 \frac{\varepsilon - 1}{\varepsilon + 2}, \tag{4}$$

The radiation pressure ($\boldsymbol{F}_{rad}$) is produced by the scattering and absorption of light by the surface of the particles, which can be expressed as [7]

$$\boldsymbol{F}_{\text{rad}} = \frac{n\langle \boldsymbol{P}\rangle}{c}\sigma, \tag{5}$$

where n is the refractive index of the surrounding environment, c is the speed of light in the vacuum, and $\langle \mathbf{P} \rangle$ is the time-averaged Poynting vector, which can be expressed as

$$\langle \boldsymbol{P} \rangle = \frac{1}{2} Re(\boldsymbol{E} \times \boldsymbol{H}^*). \tag{6}$$

The σ in Formula 6 reflects the characteristics of the nanoparticle, which indicates the extinction cross section of the nanoparticle, including the scattering cross section (σ_{scat}) and the absorption cross section (σ_{abs}), and σ is determined by the following formula [8]:

$$\sigma = \sigma_{scat} + \sigma_{abs} = \frac{k^4 |\alpha|^2}{4\pi} + k\,\alpha'', \tag{7}$$

where α'' is the imaginary part of the particle polarizability α, which represents the absorption of light by the particles. For transparent media particles, this term is approximately equal to zero and can be ignored. It can be seen from Formula 5 that the direction of the optical scattering force coincides with the direction of the glass booth vector, that is, the direction in which the optical scattering force propagates along the light. When $\boldsymbol{F}_{grad} > \boldsymbol{F}_{rad}$, the trapping of particles can be achieved.

The dipole approximation model is only applicable to spherical nanoparticles. When the shape of the captured object is irregular or the size is the same magnitude as the wavelength, it needs to be solved from the most basic Maxwell equations using simulation software. This method is based on the Maxwell stress tensor integral of the surface S of the object, as defined below:

$$F_O = \oint_S (\langle T_M \rangle \cdot n) dS, \tag{8}$$

where $\boldsymbol{n}$ is the normal vector of the surface of the object and $\langle \mathbf{TM} \rangle$ is the time-averaged Maxwell stress tensor. The expression is

$$\langle \boldsymbol{T}_M \rangle = \frac{1}{2} Re\left[\varepsilon \boldsymbol{E}\boldsymbol{E}^* + \mu \boldsymbol{H}\boldsymbol{H}^* - \frac{1}{2}\left(\varepsilon |\boldsymbol{E}|^2 + \mu |\boldsymbol{H}|^2\right)\boldsymbol{I}\right], \tag{9}$$

where $\boldsymbol{E}$ and $\boldsymbol{H}$ are the electric field vector and the magnetic flux vector in the electromagnetic field, $\boldsymbol{E}^*$ and $\boldsymbol{H}^*$ are complex conjugates, $\boldsymbol{I}$ is an isotropic tensor, and ε and μ represent the dielectric constant and magnetic permeability, respectively. After calculating the optical force, the torque of the object can also be calculated by the following formula:

$$\boldsymbol{T} = \int \boldsymbol{r}p \times d\boldsymbol{F}p, \tag{10}$$

where $d\boldsymbol{F}p$ represents the unit force at the point of action p and $\boldsymbol{r}p$ is the position vector from the center of the object to the point of action p.

1.1.2 Applications of the optical tweezers

Professor Ashkin, the pioneer of optical tweezers, predicted that optical tweezers as the manipulation technology of tiny particles will be widely used in the research of molecular biology, cell biology, and mesoscopic physics, especially to promote the development of many interdisciplinary subjects [9]. As an example, we will introduce some of the applications of the optical tweezers in the following aspects:

1.1.2.1 Capture, separation, and assembly of microparticles and cells

The invention of optical tweezers was used to capture and manipulate tiny particles such as polystyrene microspheres, biological cells, viruses, and bacteria [12]. By capturing these tiny particles, the Brownian motion of particles can be overcome and fixed in the field of the microscope for the researcher to observe and detect. When the particles are stably captured, they can be moved to a specific position and arranged in a regular pattern, which is applied to the ordered assembly of particles and cell arrays (as shown in **Figure 2a**), giving it a specific function. Further, by measuring the mechanical properties of particles and cell array, the interaction between the particles or cells can be studied. In addition, since different types of particles and cells are affected by the magnitude and direction of optical force, separation and screening of particles and cells can be achieved. With the maturity of optical tweezer technology, the system of optical tweezers is gradually combined with Raman technology, fluorescence technology [13], confocal technology, and femtosecond laser technology and achieves real-time detection of captured targets, which will enrich the applications of optical tweezers in cell biology and colloidal physics.

1.1.2.2 Study of optical tweezers and single molecules

The optical technology has a high mechanical resolution (10^{-12}–10^{-15} N), which is sufficient for the study of individual biomacromolecules. For example, the basic laws of life movement are explained by measuring the physical forces such as the tiny force of biological single molecule and the motion step size. Optical tweezer technology has become an indispensable tool for quantitatively studying life processes and transforming life activities. Since the diameter of biomolecules is generally between 1 and 10 nanometers, the optical tweezer system cannot directly observe and manipulate. In order to see a single molecule, it is necessary to combine fluorescence imaging technology; in order to manipulate a single molecule, it is necessary to connect the molecule to the microsphere and indirectly manipulate and measure by using the small microsphere as the "handle" of the manipulation. For example, the

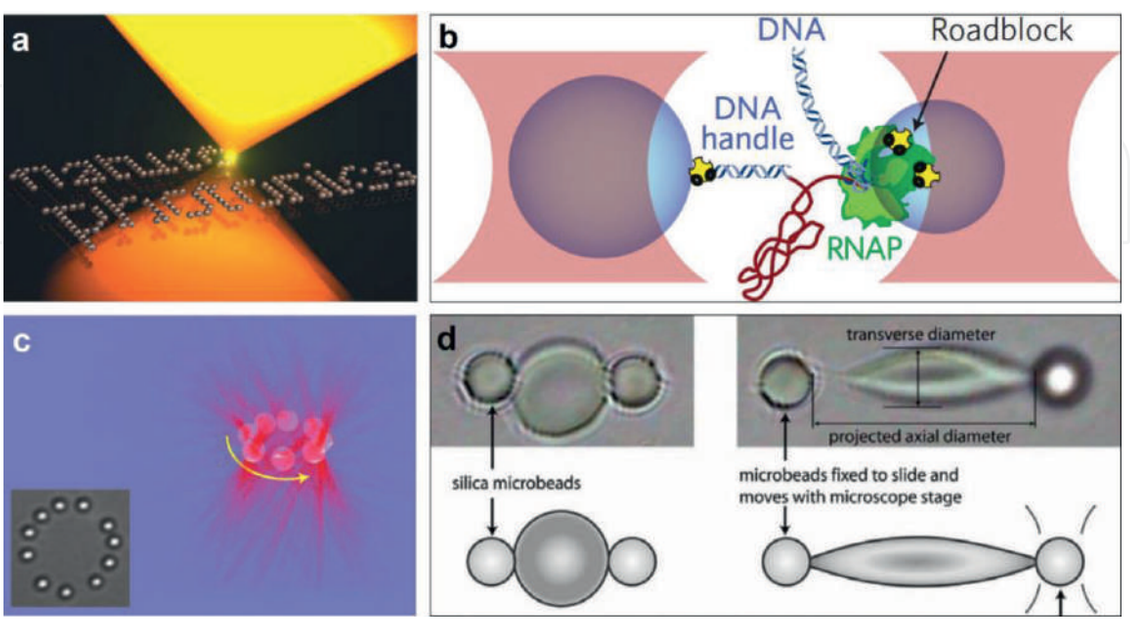

Figure 2.
Several application examples of traditional optical tweezers. (a) Order and assemble microparticles and cells. (b) Study the interaction of nucleic acid molecules using micron media balls as handles [10]. (c) Rotating the microspheres using a vortex beam [11]. (d) Stretching human red blood cells using a micron media ball as a handle.

two ends of the DNA molecular chain are, respectively, connected to two microspheres, and the microspheres are manipulated by a double-beam tweezers to stretch the DNA molecular chain and measure its elastic properties (as shown in **Figure 2b**) [10]. By rotating the two microspheres in the opposite direction, the binding force of the DNA molecular chain can be calculated. Using similar methods, researchers can also study the properties of various biomacromolecules: RNA transcription, kinesin movement, the role of polymerases, etc. These are the basic processes of life activities. Its high-precision measurement can reveal the basic laws of life activities and lay the foundation for the research and application of biomedicine.

1.1.2.3 Optical rotator

The optical rotator is a branch of the optical tweezers that not only captures the microparticles but also allows the angular rotation of the microparticles as shown in **Figure 2c** [11]. This technique is based on the moment applied by the angular momentum of the light to the object. In order to achieve the rotation of the particles, the optical rotator requires a special beam of angular momentum, such as a Laguerre-Gauss beam [14]. Rotating particles or cells are used in many fields, such as rotating a tiny mechanical motor in a liquid environment to control the movement of local water flow. In addition, by rotating living cells, it can be imaged at various angles, which is beneficial to observe the full three-dimensional appearance of cells.

1.1.2.4 Optical stretchers

Stretching cells can study the elasticity of cell membranes, and the elasticity of cell membranes is closely related to many cellular diseases and can be used to reflect the activity of cells and even the health of the human body. There are many optical stretching methods based on optical tweezers, such as direct stretching of double-beam tweezers, stretching by microsphere handle, time-division multiplexed stretching, and so on. The method based on the microsphere handle-stretching method is more commonly used because of the high measurement precision. The method is shown in **Figure 2d**: two microspheres are adhered to the cell surface by chemical coupling, and then the microspheres are controlled to move in opposite directions by the tweezers. At this time, the cell membrane is stretched by shearing force. By recording the shape variables of the cells and measuring the force of stretching the microspheres, physical parameters such as the elastic modulus of the cell membrane can be calculated.

1.2 Holographic optical tweezers

1.2.1 Basic principles

Traditional optical tweezers based on single beam can only capture and manipulate one or a few particles at a time. However, researchers want to improve the efficiency of capture, such as controlling multiple particles at the same time. Based on this goal, scientists invented holographic optical tweezers. The core component of holographic optical tweezers is a hologram element: an interference pattern formed by recording the object light and reference light through the film. The wave front can be adjusted by holographic elements to construct a light field with a specific function. The holographic optical tweezers were firstly invented in 1998 by Professor Grier of the University of Chicago and his collaborators [15]. They used a holographic element (diffraction grating) to split the collimated single laser beam

into multiple independent beams, and then an array of grating is formed by focusing the lens to capture a large number of microparticles. The earliest holographic elements were prepared by coherent-optical interferometry, but the holographic elements obtained by this method have low diffraction efficiency and poor versatility, and thus this method has not been widely used. In order to improve diffraction efficiency and applicability, conventional holographic elements are often composed of spatial light modulators. The spatial light modulators include liquid crystal spatial light modulators, acousto-optic modulators, and digital microlens arrays. The spatial light modulator is controlled by a computer, and each focused beam can be individually controlled by changing the hologram element so that the formed trap well can be dynamically changed. Such holographic optical tweezers not only capture a plurality of microparticles at the same time but also control the movement of each microparticle to be arranged in different shapes, thereby achieving ordered assembly of the microparticles.

1.2.2 Applications of the holographic optical tweezers

As an emerging optical technology, holographic optical tweezers can trap and manipulate a large number of particles, showing great application prospects in the fields of particle assembly and construction of three-dimensional cell microstructure (**Figure 3**). For example, Glen R. Kirkham et al. of the United Kingdom used holographic optical tweezers to assemble one-, two-, and three-dimensional embryonic stem cell array structures (as shown in **Figure 4**) to provide a new means to study the directed differentiation of stem cells [16]. Moreover, Jesacher and his colleagues from Austria regulated the amplitude and phase of the incident light field through a liquid crystal spatial light modulator, which not only realized trapping potential wells of special shapes such as line, cross, circle, and rectangle but also controlled the microparticle movement along a specific path. In addition, holographic optical tweezer technology can also produce beams with special modes, such as Bessel beams, Laguerre-Gauss beams, and Airy beams [18]. These special-mode beams have peculiar phase distribution and propagation characteristics and can generate trapped potential wells with special functions, such as rotating particles with a Laguerre-Gauss beam, which can be used to construct micro- and nano-motors and study the transfer of orbital angular momentum; Airy beam or Bessel beam can be used to transport particles for sorting different types of particles and cells.

1.3 Fiber-based optical tweezers

1.3.1 Basic principles

Due to the low integration of conventional optical tweezer systems, it is difficult to manipulate particles located in a narrow position, such as particles inside a microfluidic channel or red blood cells in a blood vessel. The newly developed fiber-based optical tweezers are promising candidates because of its compact structure and flexible operation, which can overcome the problems of traditional optical tweezers [19]. Fiber-based optical tweezers use the output light from the end face of the fiber to achieve particle capture and manipulation, as shown in **Figure 5a**. When the laser beam passes into the fiber, it converges through the end of fiber and form a highly focused beam. The microparticles located near the tip of the fiber will be captured by the longitudinal gradient force onto the optical axis of the fiber and then captured by the lateral gradient force at the focus of the emitted light or move along the optical axis under the action of optical scattering force. For

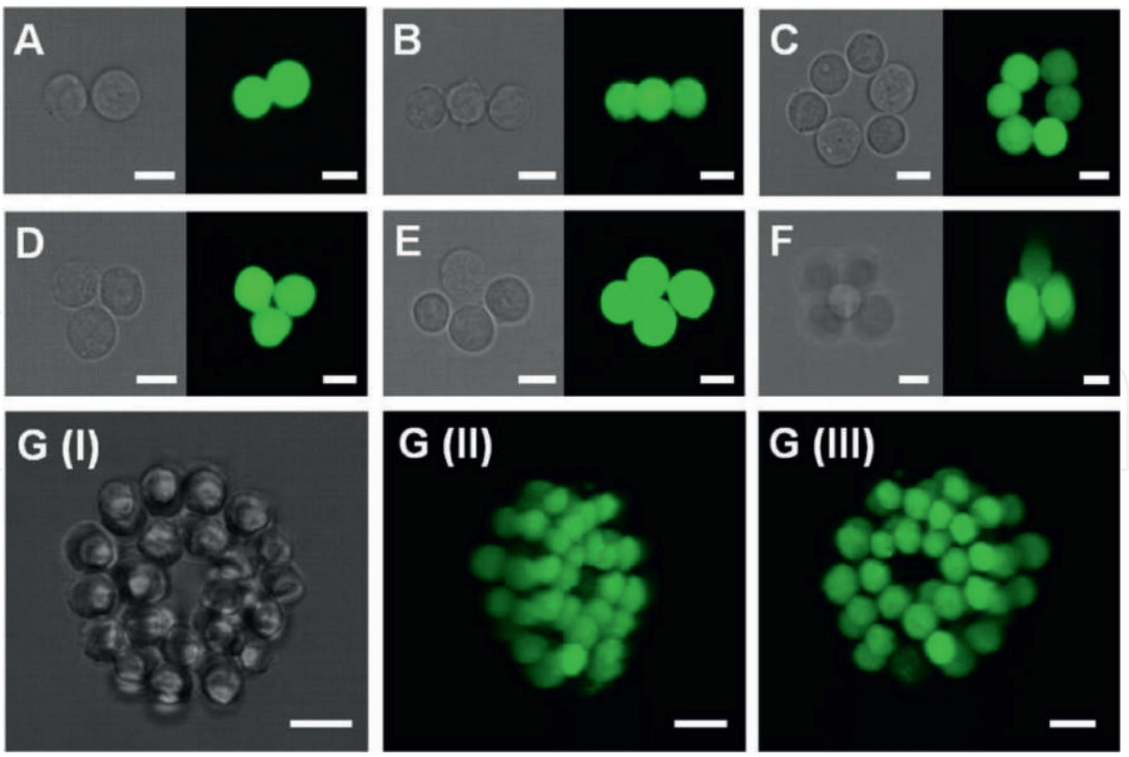

Figure 3.
Bright-field optical micrographs and confocal fluorescence micrographs of one-, two-, and three-dimensional microarray structures of embryonic stem cells assembled by holographic optical tweezers [16].

fiber-based optical tweezers, the distribution of the exiting light field depends on the shape of the fiber tip, which is a highly focused beam, to create a three-dimensional trapping potential. Currently, the tip of the fiber-based optical tweezers is generally designed as a parabolic, spherical, or conical structure. Different shapes of fiber tip can be prepared by physical polishing, heating stretching, chemical etching, and femtosecond laser processing. By changing the physical parameters of the preparation method, such as temperature, speed, time, etc., the shape and size of the fiber tip can be controlled to achieve different functions. **Figure 5b** shows the output light field distribution of a typical tapered fiber. It can be seen that the light is concentrated at the front end of fiber so that the cells can be trapped on the axis of the front end of the fiber and arranged into an ordered structure, as shown in **Figure 5c** [17].

1.3.2 Application of fiber-based optical tweezers

Since the fiber-based optical tweezers have the advantages of simple fabrication, flexible operation, compact structure, and easy integration, it has applications in many fields. For example, Xin et al. used a flame heating and melting taper to prepare a fiber-based optical tweezers with a tapered tip, which enables the capture of submicron-sized polystyrene particles and *E. coli* cells [20, 21]. Xu et al. realized the rotation of single silver nanowires using two tapered fibers, which provide a controlled and optical method for assembling plasmonic nanostructures [22]. Fiber-based optical tweezers will be developed in the direction of high integration and multifunctionality to adapt to lab-on-a-chip and in vivo requirements. In the future, the fiber-based optical tweezers may integrate multiple functions on a single-fiber probe, as shown in **Figure 6**, such as simultaneously capturing, transporting, sorting, stretching, deforming, and rotating various cells and pathogens in the microfluidics or living blood.

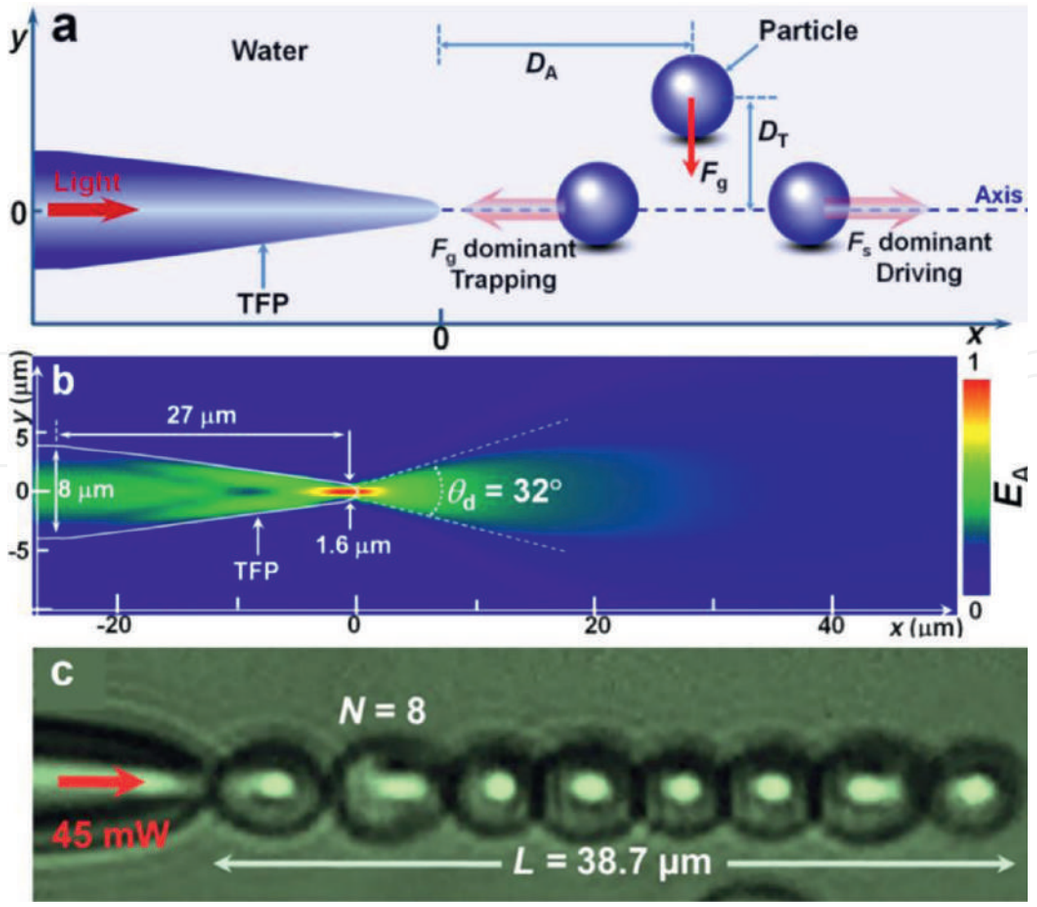

Figure 4.
The basic principle of the fiber-based optical tweezers. (a) Schematic diagram of the optical gradient force (Fg) and scattering force (Fs) applied to the microparticles by the fiber-based optical tweezers. (b) Simulation of electric field intensity distribution of the fiber-based optical tweezers. (c) A chain of yeast cells was trapped by the fiber-based optical tweezers [17].

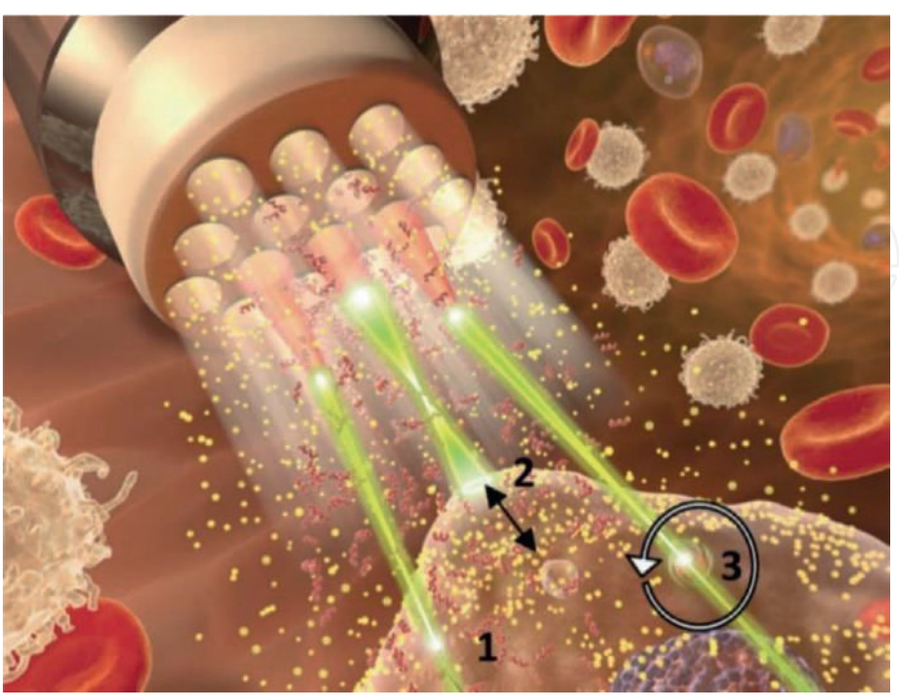

Figure 5.
This schematic shows a versatile fiber-based optical tweezers: number 1 indicates the capture, transport, and sorting of cells, number 2 indicates the optical stretching and deformation of cells, and numbers 3 indicates the optical rotation of cells.

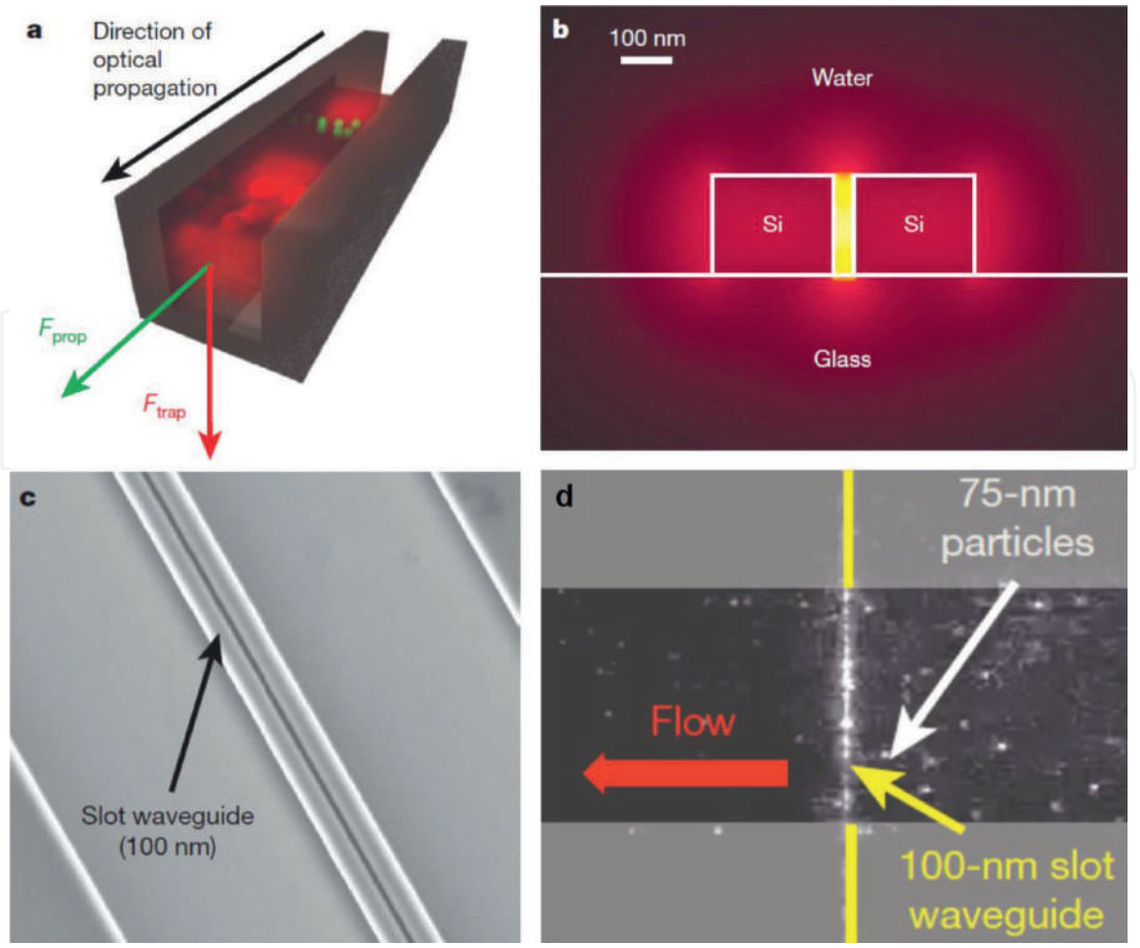

Figure 6.
Slot waveguide optical tweezers. (a) Schematic diagram of the optical gradient force and scattering force of nanoparticles in the slot waveguide. (b) A simulation result of the light intensity distribution of the slot waveguide in an aqueous environment. (c) An electron scanning micrograph of a waveguide having a slit of 100 nm. (d) The slot waveguide captures a large number of polystyrene particles of 75 nm in diameter in the water flow [23].

1.4 Nano-optical tweezers

1.4.1 Planar waveguide optical tweezers

When the light is transmitted in the waveguide, an evanescent wave is generated on the surface of the waveguide due to the total reflection. The evanescent wave is limited to a near-field range of 100 nanometers from the surface of the waveguide. When a nanoparticle enters the evanescent wave, the gradient of the light intensity changes greatly in the direction perpendicular to the waveguide, so the nanoparticles will be trapped on the surface of the waveguide by a strong optical gradient force. In the direction of light propagation, the evanescent wave can be considered to be uniformly distributed. Therefore, there is no optical gravity force in this direction. Only the optical scattering force exists. The nanoparticles move along the direction of light propagation due to the optical scattering force. Therefore, planar waveguide optical tweezers are often used for the transport of nanoparticles. Moreover, since the optical waveguide device is easily integrated into the microfluidic chip, the planar waveguide optical tweezers play an important role in the field of microfluidics. Current planar waveguide optical tweezers can be classified into three types: rectangular waveguide optical tweezers, slot waveguide optical tweezers, and nanofiber waveguide optical tweezers.

The manipulation of microparticles by a rectangular waveguide optical tweezers was first implemented by Kawata et al. [5]. They use rectangular waveguides to perform noncontact optical transport of different sizes of microparticles. This method can deliver cells or drugs over long distances. After this groundbreaking work, more and more researchers have entered this field and designed rectangular waveguides with different structures for transporting metal particles, media particles, microbial cells, etc. [5].

Since the evanescent wave of the rectangular waveguide has limited light confinement, it is challenging for the rectangular waveguide to capture particles and biomolecules below 100 nm. To solve this limitation, the researchers developed slot waveguide nanotweezers [23]. The slot waveguide is an air slit having a width of nanometers by photolithography or electron beam etching. The large refractive index contrast between low refractive index slot and high refractive index waveguide material makes the light energy highly confined in the slot region, which produces a strong optical gradient force and scattering force on the nanoparticles entering the slot. Using this property, Yang et al. achieved capture and transport of polystyrene particles and DNA molecules with sizes below 100 nanometers (as shown in **Figure 7**) [23].

A common problem with rectangular waveguide optical tweezers and slot waveguide optical tweezers is that they must be fixed on the substrate, making it difficult to operate. The emerging nanofiber waveguide optical tweezers can solve this problem. Li et al. used fibers with a diameter of 500–700 nm to achieve stable trap, bidirectional transport, optical separation, and controlled release of nanoparticles and micro-pathogens in microfluidics [26, 27]. The nanofiber waveguide optical tweezers have the advantages of low cost, production, and large control range and have important research value and application prospects in cell transportation, drug delivery, and particle collection.

1.4.2 Photonic crystal optical tweezers

Optical tweezers based on rectangular waveguides, slot waveguides, and nanofiber waveguides can only move particles along the waveguide surface but cannot be used to stably trap nanoparticles. In order to stably capture the nanoparticles, a photonic crystal optical tweezers were developed. The photonic crystal optical tweezers are based on one- or two-dimensional photonic crystal resonator structures (as shown in **Figure 8**) [24, 25]. When the laser that satisfies the wavelength matching condition is coupled into the photonic crystal resonator, static

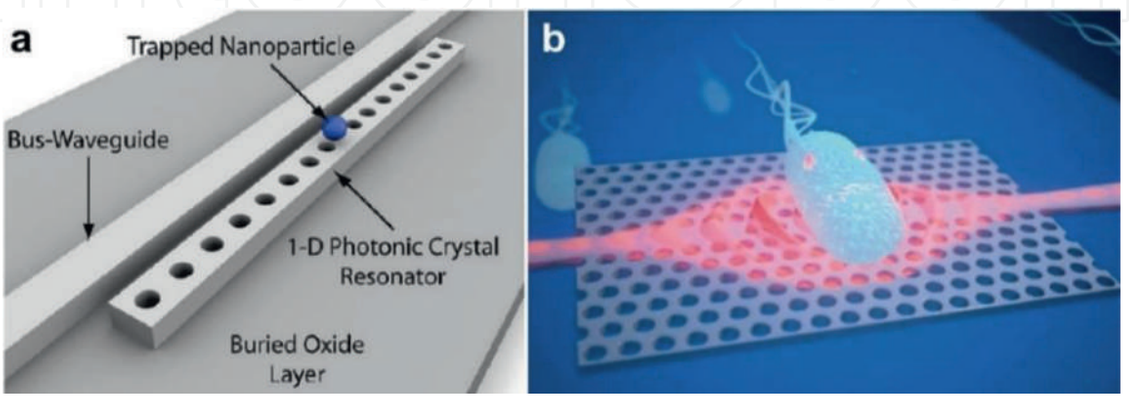

Figure 7.
Photonic crystal optical tweezers. (a) Schematic representation of a single-dimensional photonic crystal resonator capturing a single nanoparticle [24]. (b) Schematic representation of a two-dimensional photonic crystal resonator capturing a single E. coli [25].

interference will occur in the cavity. With the resonance effect, the intensity of the light is greatly enhanced, and the size of the light spot is strongly suppressed, thereby enhancing the optical force of nanoparticles. Based on this principle, Erickson and Mandal et al. achieved stable capture and controlled release of nano-objects such as polystyrene particles, semiconductor quantum dots, and serum protein molecules in a liquid environment [30]. In addition, this method can also be used to study the angular rotation of silver nanowires or carbon nanotubes [31].

1.4.3 Plasmon optical tweezers

Plasmon is a near-field electromagnetic wave formed by the resonance of free electrons on a metal surface and incident photons. Under such resonance conditions, the energy of the electromagnetic field will be converted into the collective vibrational energy of the free electrons on the metal surface, thereby forming a special electromagnetic field: the light is confined to the sub-wavelength of the

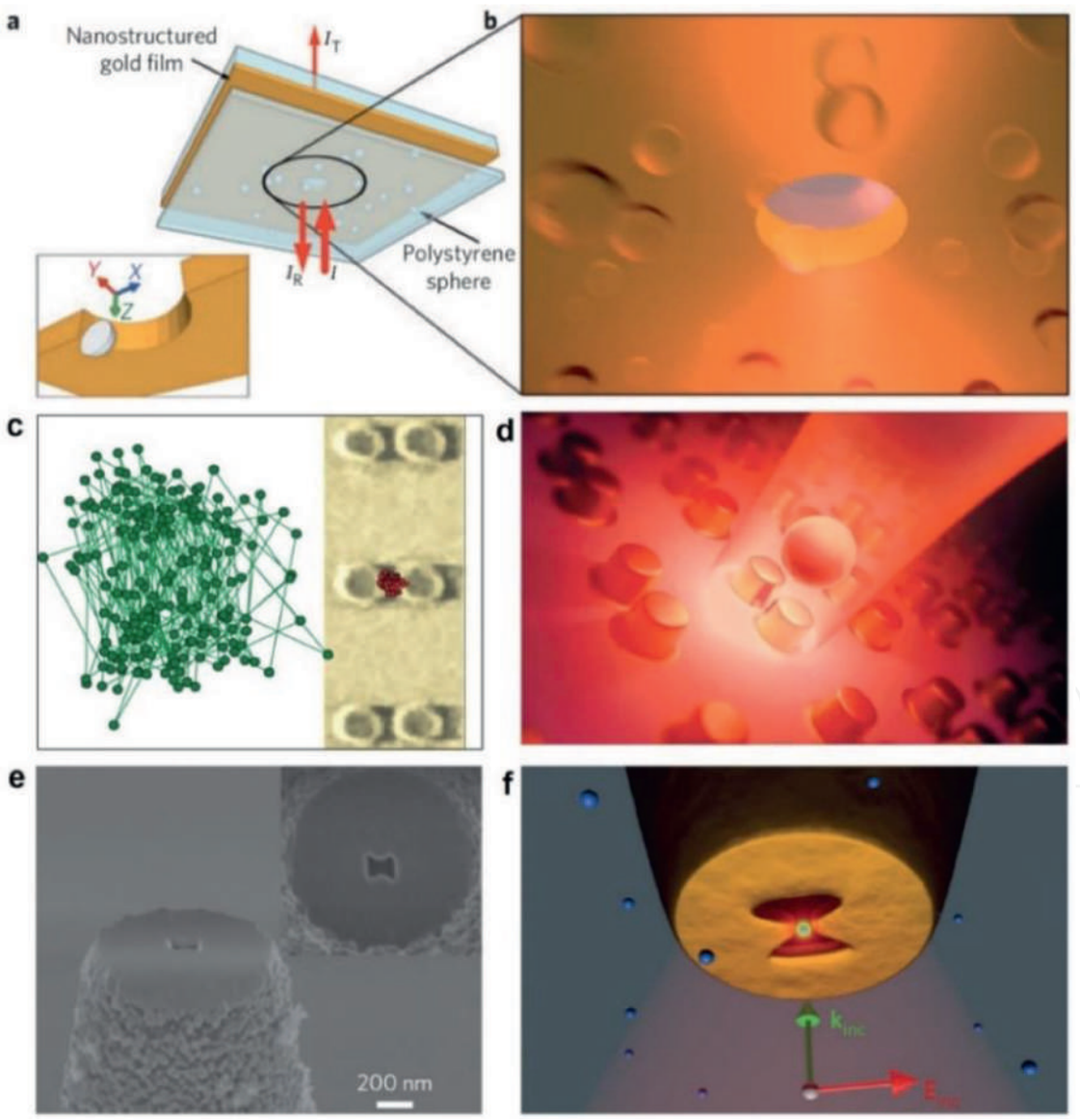

Figure 8.
Plasmon optical tweezers. (a) Schematic diagram of a metal film having nanopores. (b) Schematic diagram of magnified metal nanopore capture nanoparticles. (c) SEM image of the metal nano-antenna structure and motion trajectory after the nanoparticles are captured. (d) Schematic representation of metal nano-antenna structures [28]. (e) SEM image of a metal nano-bowtie structure. (f) Schematic diagram of metal bow nanostructure [29].

metal surface and greatly enhanced. The effect is called the plasmon effect. Since the plasmon effect localizes the light in the near-field range of the nanometer order, it is widely used in the fields of fluorescence signal enhancement, near-field super-resolution imaging, high-density optical storage, integrated optical circuits, etc. [32]. In recent years, the plasmon effect has also been applied in the field of optical trapping and manipulation. The plasmon effect is divided into two types: surface plasmon resonance (SPR) and local surface plasmon resonance (LSPR), both of which can be used to enhance optical force. Researchers used a prismatic total internal reflection to couple incident light into a metal micro-disk on the substrate, which will increase the optical force of the particle by two orders of magnitude and realize the capture of the microparticle. However, the SPR-based optical tweezers can only enhance the optical force of the particle in a two-dimensional plane. Therefore, researchers have proposed an LSPR-based nano-optical tweezers to enhance the optical force of the nanoparticle in three dimensions, including metal nanopores (**Figure 8a, b**), metal nano-antennas (**Figure 8c, d**) [28], metal nano-bows (**Figure 8e, f**) [29], and metal nano-double holes [33]. By using these nano-optical tweezers to achieve trapping of various nanoparticles, such as polystyrene particles, protein molecules, gold particles, micro-pathogenic bacteria, and so on.

2. Conclusions

The noncontact and noninvasive optical trapping and manipulation of microparticles, cells, and biomolecules in liquid environments has broad application prospect in the fields of biomedicine and nanomaterial science [34–47]. Traditional optical tweezers and holographic optical tweezers play an important role in the study of microscale optical manipulation. However, in the rapid development of nanoscience, traditional optical tweezers and holographic optical tweezers are difficult to adapt integration and nano-precision requirements due to the large volume and diffraction limitations. The developed nano-optical manipulation techniques, such as planar waveguides, plasmon optical tweezers, and photonic crystal resonators, can overcome the problem of difficult integration and diffraction limitations of conventional optical tweezers and holographic optical tweezers, which hold great promise in biophotonic and biomedical applications.

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Conflict of interest

The authors declare no competing financial interests.

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Chapter

Nanolithography by Scanning Probes for Biorecognition

Javier Martinez

Abstract

With the invention of the scanning tunneling microscope (STM) and subsequently with the atomic force microscope (AFM), the human being was able to enter in the nanoscale world. At first, these devices were only used for imaging samples, but with a small modification of its electronics, they can be used for a precise and controlled manipulation of the scanning probe, creating different types of nanolithographed motifs. The development of this type of lithography has allowed the manufacture of nanometric-scale structures that have led spectacular advances in the field of nanotechnology. In this book chapter, we present the most innovative and reliable probe nanolithography techniques. All of them are based on the spatial confinement of a chemical reaction within a nanometric size region of the sample surface. In that way, 2D or even 3D nanostructures can be fabricated. The full potential of probe nanolithography techniques is demonstrated by showing a range of applications such as the controlled deposition of molecules with high precision or nanotransistors that can be used as sensors for biorecognition processes.

Keywords: AFM, nanotechnology, lithography, nanodevices, scanning probe

1. Introduction

Since the 1960s, the size of electronic devices has been reduced through the use of optical, electronic lithography and lately by immersion lithography. All these techniques are very efficient and allow the fabrication of very complex microelectronic devices, but they have a high cost, are not modifiable, are always made on silicon wafers, and are bounded within the standards of clean rooms. Due to these limitations, in the 1990s, new manufacturing techniques began to be developed that could perform nanometric motifs of different materials in different environments and with lower costs: nanoimprint, soft lithography, and scanning probe nanolithography [1–3].

These new nanofabrication techniques have allowed a great variety of structures to be made, and they have also been able to position and manipulate with nanometric precision different organic and inorganic materials. This chapter wants to provide an overview of the most relevant nanolithography techniques using a local probe that will allow the manufacture of a wide variety of different structures and the creation of functional nanoscale devices for biorecognition.

In order to perform this type of lithography, an atomic force microscope (AFM) is needed, which permits us to obtain high-resolution images in air, in liquids, or in vacuum of all types of conductive, semiconductor, and insulating surfaces. The main elements of the AFM microscope are shown in **Figure 1**. In addition to

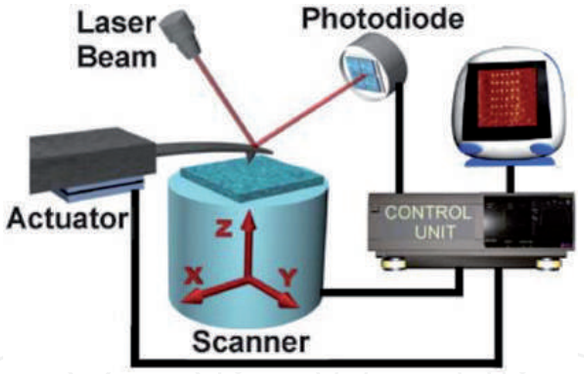

Figure 1.
Main elements of an atomic force microscope system (from Ref. [28]).

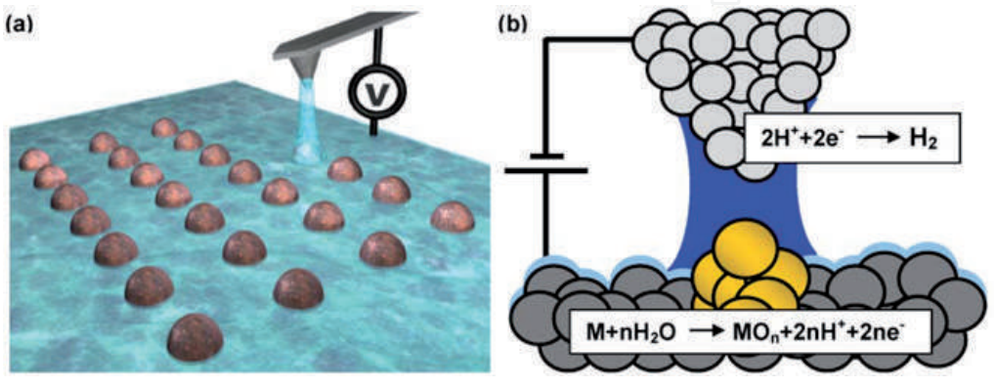

Figure 2.
Local oxidation nanolithography process by AFM. (a) Formation of the liquid meniscus. (b) Chemical reactions in a metallic sample (from Ref. [28]).

generating the image, the control electronics can be configured to use the scanning probe as a powerful tool that can atomically modify the surface with nanometric accuracy. This type of nanometric modifications can be chemical, electrostatic, mechanical, or thermal [4–10].

Nanolithography can be performed under different conditions such as ultrahigh vacuum and low temperature, but the patterning disappears as soon as these conditions are lost, so we will focus on the nanolithography processes at room temperature and without vacuum. In order to perform lithography on a surface, the spatial confinement of a chemical reaction within a nanometric size region is necessary. For this, it is necessary that the probe tip is sufficiently close to the sample so that a liquid meniscus (**Figure 2**) can be formed spontaneous or with the aid of an electric field and also a thermal gradient or a mechanical indentation can be applied.

In a first stage, local oxidation with AFM will be studied in detail. In this case the liquid meniscus that forms between the tip and the sample is water due to relative humidity [10–12]. This type of nanolithography will allow the development of patterns with different shapes [13, 14], and its operating principle can be used to lithograph large areas [15–17]. With this technology, silicon transistors have been made [18, 19]. Afterward it has been observed that these nanotransistors can be used for molecular recognition [20]. In recent years this technique has served to manipulate two-dimensional materials of high scientific interest [21, 22].

By altering the atmosphere where the AFM is housed, nanolithography of different materials can be performed. With octane vapors, extremely small motifs can be obtained [23]. This patterning can be used later for the growth of biological molecules [24]. And by changing to an atmosphere of CO_2, gas molecules can be converted into solid deposits on the surface by applying an electric field [25, 26].

In recent years, a new 3D lithography technique has been developed [27]. In this case, a standard AFM probe has been replaced by a thermal one that reaches a high temperature at its final tip, and the polymer that is deposited on the surface is thermally moldable in three dimensions by scanning with this thermal probe.

2. Local anodic oxidation

Local oxidation of semiconductor, metallic, and organic surfaces by atomic force microscopy (AFM) has established itself as a robust, reliable, and flexible lithographic method for the fabrication of nanometer-scale structures and devices [28, 29].

The invention of this technique appeared in 1990, when Dagata and his collaborators realized that by applying a voltage between the tip of an STM and a silicon sample, their surface was modified and they were able to demonstrate that it was an oxide by mass spectroscopy [12]. A few years later, in 1993 it was done through AFM [30].

The application of a voltage pulse between the tip and the sample polarizes the water molecules in the gas phase and those absorbed on the sample surface. When the voltage is above a certain threshold value, a field-induced liquid meniscus is formed between the tip and sample surface (**Figure 2a**). The water meniscus provides both the chemical species (**Figure 2b**) and the spatial confinement for the anodic oxidation of a nanometer size region of the sample surface [28, 31]. The AFM tip is used as a cathode, and the water meniscus provides the electrolyte.

The size of the oxide motifs can be modified by applying different values of the voltage pulse since it depends linearly. In this way, structures of less than 10 nm have been made reproducible. The voltage pulses are generally between 10 and 30 V and the duration a few milliseconds. The heights of the oxides are a few nanometers, and only 60% of the oxide is above the surface of the sample; the rest is buried in the silicon sample.

This nanofabrication technique allows to perform all types of patterning as can be seen in **Figure 3**: arrays of points, circles, or even the first lines of *Don Quixote* [28].

The process is rather general because many different materials have been patterned such as semiconductors [32], metals [33], dielectrics [34], perovskite oxides [35], or self-assembled monolayers [36].

Figure 3.
Examples of local oxidation nanopatterns (from Ref. [28]).

Although nanometric patterns can be generated quite accurately, the main disadvantage of this technology is that AFM is a slow technique and can only cover small areas of a few square microns. To scale this process, a nanoimprint stamp has been developed with millions of protrusions similar to the AFM probe. The stamp has been metallized in order to apply an electric field that allows the oxidation process (**Figure 4a**). The areas of square centimeters with nanometric patterning can be oxidized [16, 17]. An example of that oxidation can be shown in **Figure 4b**, the area is only 5 × 5 μm due to the scan of the AFM, but the oxide patterns are in the whole sample of 1 × 1 cm.

In many of the cases, during the nanofabrication different charges are trapped inside the oxide lines, and that can be used for the selective positioning of molecules [37]. As an example, in **Figure 5** one can observe a controlled deposition of ferritin molecules on the oxide lines made by AFM. For a better positioning, it is necessary to deposit on the silicon sample a self-assembled monolayer of octadecyltrichlorosilane (OTS) and to deposit a monolayer of aminopropyltriethoxysilane (APTES) after the local oxidation [38].

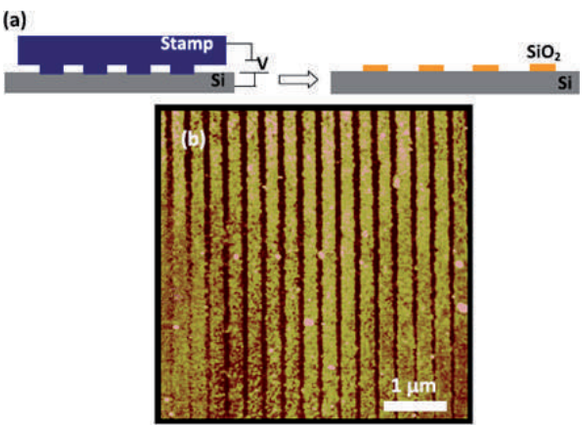

Figure 4.
(a) Scheme of parallel oxidation lithography process with a nanoimprint stamp. (b) AFM image of the silicon oxide line pattern (from Ref. [17]).

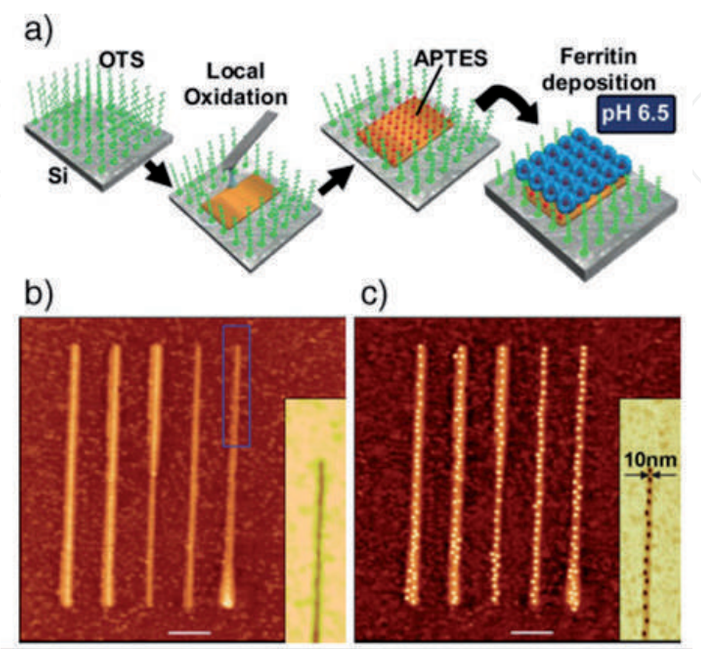

Figure 5.
Patterning of ferritin molecules by local oxidation nanolithography and surface functionalization (from Ref. [38]).

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Also with this technology, it is possible to create functional devices. An example, in **Figure 6**, a transistor with a 4 nm silicon nanowire made by local oxidation is shown [18].

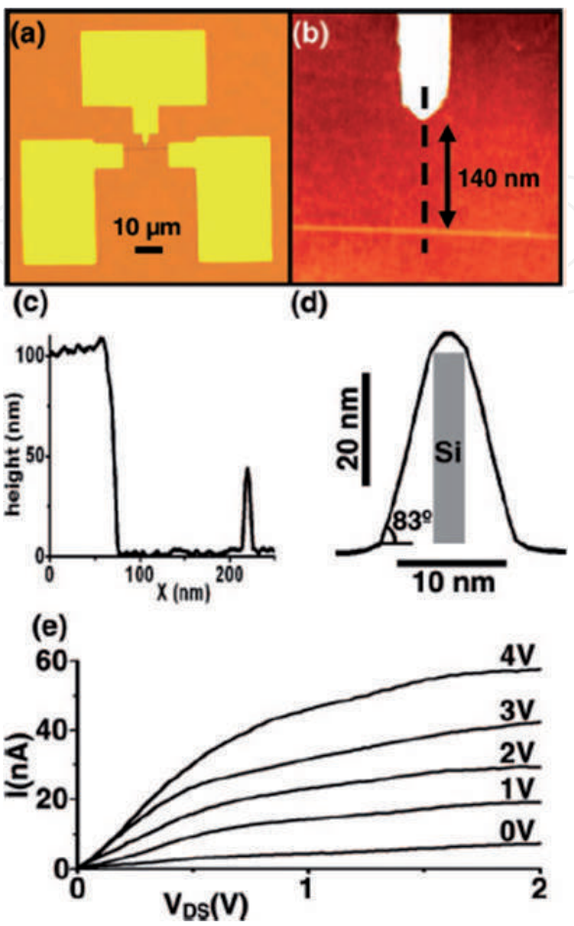

Figure 6.
Silicon nanowire transistor fabricated by local oxidation nanolithography (from Ref. [18]).

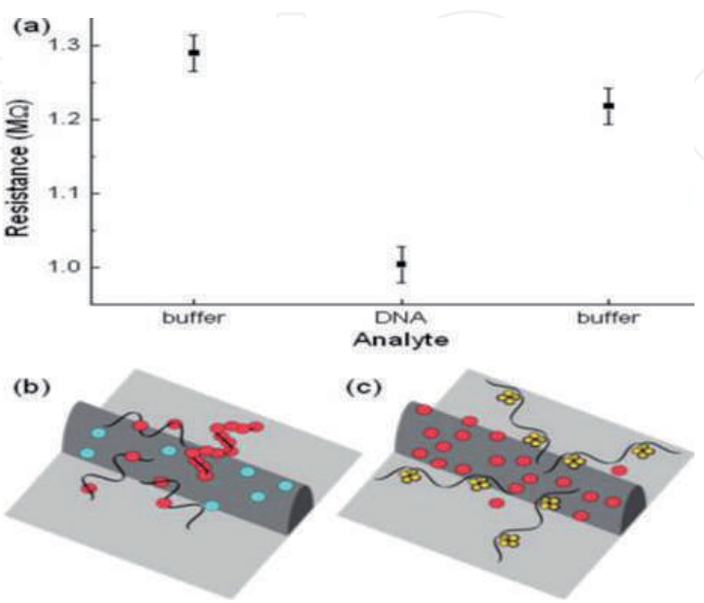

Figure 7.
The silicon nanowire sensor changes its electrical behavior in the presence of DNA and is able to recover its resistance after cleaning (from Ref. [20]).

In this case a silicon on insulator (SOI) wafer was used. The gate, drain, and source contacts were first made by optical lithography. Between these last two, a local oxidation line was made that serves as a mask for the following etching of the top silicon by reactive ions (RIE). In this way the silicon nanowire is free, and after a second stage of lithography and metallization, the source and the drain are in contact with the nanowire forming a nanotransistor.

These nanowire sensors can subsequently be functionalized with different molecules to perform molecular recognition of different agents [19, 20]. In **Figure 7**, a nanowire is used for measuring the early stages of recombinational DNA repair by RecA protein [20].

3. Chemical nanofabrication

Changing the atmosphere surrounding the AFM can produce other chemical reactions between the tip and the samples, which will allow us to manufacture motifs or materials that are not oxides.

For doing this, it is necessary to introduce the AFM into a glove chamber or in a closed environment where it is possible to remove the relative humidity from the environment by a nitrogen flow. Subsequently, the gas to be used for nanolithography is introduced, and an electric field is applied again between the tip and the sample.

Thanks to this type of lithography, polymeric motifs as small as 2 nm resolution at 3 nm at half pitch in ambient conditions have been achieved [23]. This is the smallest periodic pattern fabricated on silicon at atmospheric pressure and room temperature.

The method is based on the formation of a nanoscale octane liquid meniscus between a sharp conductive protrusion and a silicon (100) surface. The application of a high electrical field (10 V/nm) produces the polymerization and cross-linking of the octane molecules within the meniscus followed by their deposition. The manufactured motifs can be seen in **Figure 8**.

This technology can also be used to break up very stable gaseous molecules such as CO_2 and turn them into solid motifs. Thus, if the AFM is introduced into a CO_2

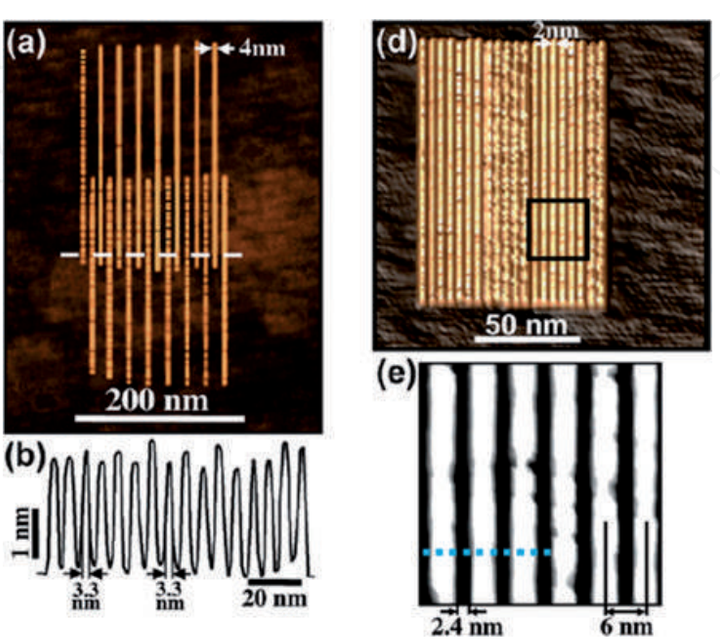

Figure 8.
AFM images and cross sections of the polymeric nanostructures (from Ref. [23]).

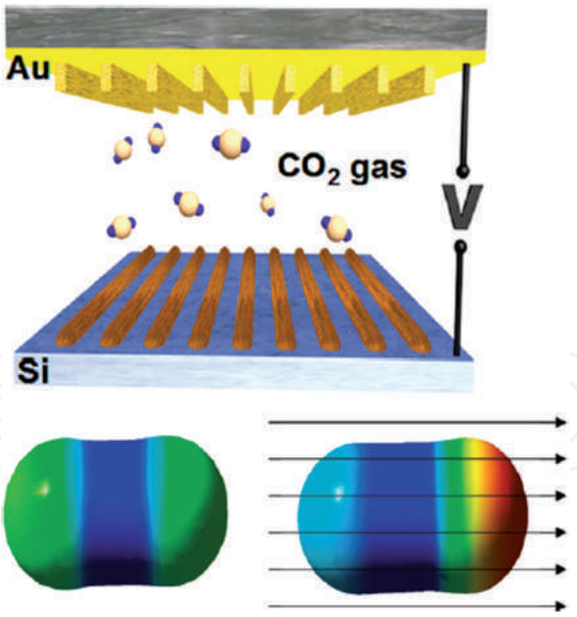

Figure 9.
Conversion of CO_2 gas molecules in solid nanometric motives by applying an electric field (from Ref. [25]).

atmosphere and later an electric field is applied, the CO_2 molecules are able to break due to the high electric field at the end of the tip [25, 26]. This happens for an electric field above 40 V/nm. This technology can be scaled again using PDMS stamp of several square centimeters with thousands of protrusions like in the scheme of **Figure 9**.

The possibilities of generating different nanolithography with different materials are enormous since they only depend on the atmosphere in which the AFM is inserted. The only disadvantage is the need for a spectroscopy analysis after lithography to identify the nature of the motives created.

4. Nanofabrication in 3D

In recent years, micro nanofabrication technologies have advanced quite a bit and are allowing more and more sophisticated AFM tips. Thus, in 2010, IBM laboratories in Zurich made an AFM probes that were doped at their end so that they could behave with a thermal tip when a current is applied [27].

The high temperature at the end of the AFM tip was used to perform a patterning on a glassy organic resist. This local desorption allowed to make structures at a half pitch down to 15 nanometers without proximity corrections. These patterns can be transferred to other substrates, and the material can be removed in successive steps in order to fabricate complex three-dimensional structures (**Figure 10**).

This technique is in continuous development and has great future potential, but it also depends on the thermal tip and on the optimization of the appropriate resins that allow its elimination layer by layer. As can be seen in **Figure 11**, it was possible to make a replica of the Matterhorn mountain in Switzerland first on the resist and then transfer its pattern to silicon.

5. Conclusions

Although the AFM began as a technique to visualize images of a few microns, its potential was seen to be able to manipulate materials in the nanoscale due to various

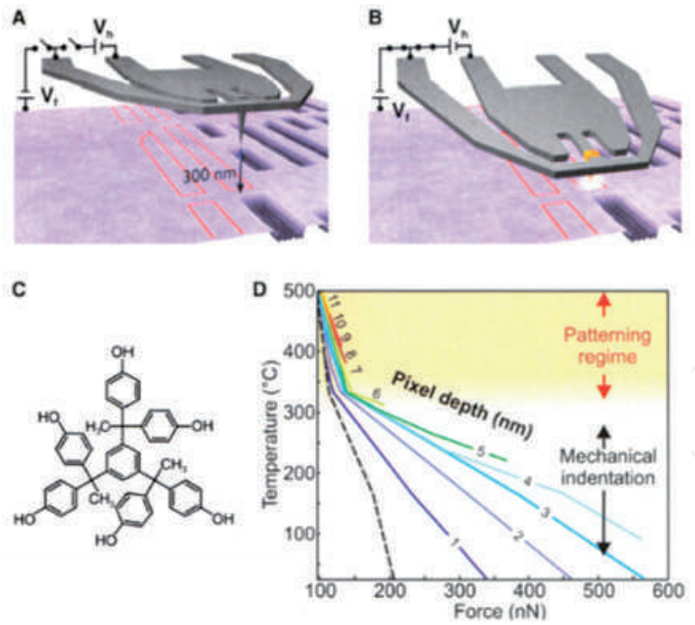

Figure 10.
AFM thermal probe making 3D nanopatterning over a resist (from Ref. [27]).

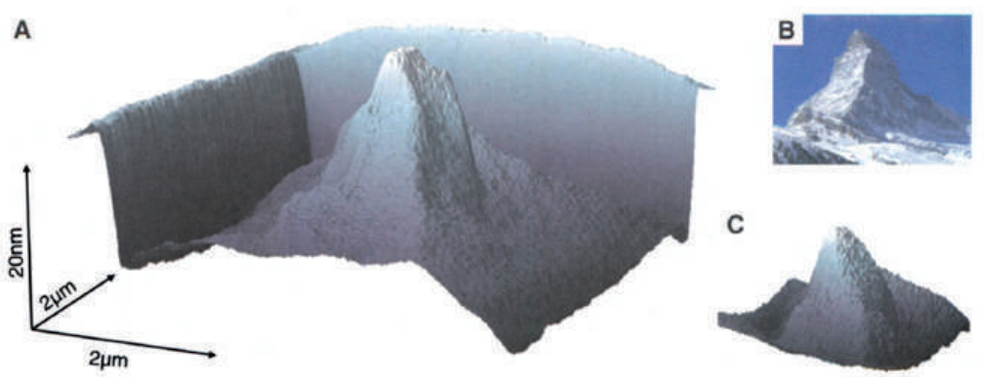

Figure 11.
(A) AFM picture of the Matterhorn replica in the molecular glass resist. (B) Picture of the Matterhorn mountain. (C) AFM replica in silicon (from Ref. [27]).

reasons. The first of these reasons is the high precision of the piezoelectric devices that allow the AFM tip to be positioned in the right place, and the closed loop control electronics allow a repetitive positioning better than an interferometric stage. On the other hand is the small size of the AFM tip, usually 10 nm or smaller. This allows to obtain liquid menisci of very small volumes in which chemical reactions of various kinds can be created. The small size of the tip also facilitates that with low voltage, high electric fields are obtained at the interface between the tip and the sample, allowing to oxidize different materials or make solid deposits of molecules that are in the vapor phase. Finally in recent years the microelectronic industry has been able to make more sophisticated probes in which they can get the final apex of the tip at very high temperature. This type of tips can modify or even sublimate resins on a surface and can create 3D lithographic motifs that can then be transmitted to the different materials.

With these lithography techniques by scanning probes, great nanotechnological advances have been achieved. The first was to be able to create smaller structures than those achieved by electron beam lithography. It has made possible to lithograph different designs on all types of materials from conductors, semiconductors, or even insulators and more recently in 2D materials like graphene or dichalcogenides.

The second advance was that nanolithographed structures have shown selective positioning of different molecules due to the charges trapped in lithographed motifs. On the other hand, lithographed motifs by scanning microscopy can be used as masks to perform more complex devices such as memories, sensors, or field-effect nanotransistors. These nanotransistors are ideal for its use as sensors for single molecule biorecognition.

In summary, scanning probe nanolithography techniques are very precise and very versatile and constitute an adequate tool for the development of nanotechnology without the need for large and expensive conventional lithography equipment. In addition, the motifs that are capable of manufacturing can be easily scaled for the macroscale simply with the use of nanoimprint techniques.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter

Biophotonics in Africa Powered by Light Technology Applied to Medical Work

Klaudia Freire

Abstract

Biophotonics technologies can be designed to provide unique, dynamic information about tissue structure and biochemical composition. Their impact spans from medical diagnostic and therapeutic devices to consumer-based wearable sensors. With advances in device miniaturization and high-performance biophotonics components, the line between conventional medical instruments and consumer devices is becoming increasingly blurred. Health care economic pressures are further accelerating this ambiguity by shifting clinical attention from expensive disease treatments to strategies for cost-effective disease management and prevention. This clinical research collaboration introduces emerging biophotonics technologies that are capable of characterizing brain tissue structure and biochemical composition spanning from micro to macroscopic regimes.

Keywords: biophotonics, Africa, health technology, light, point of care, medicine

1. Introduction

Biophotonics is a scientific field merging biology and photonics, with photonics being the science and technology of generation, manipulation, and detection of photons, quantum units of light. Research in biophotonics is focused on the development of innovative applications in clinical diagnosis of cancer and related therapies involving fluids, cells, and tissues using light-based tools to excite matter and to transfer information back to the biological operating system.

"Today, healthcare is moving from a treatment-oriented system to a diagnostic oriented one, the end-goal being companioned diagnostic, which is promising but still far away. All these issues have in common a strong need to study real-time evolution of complete living organisms, or part of them (tissues, organs, cells, proteins, DNA, etc.) [1]" and "Therefore, it's essential to develop technologies for quality and process control, as well as rapid microbiological methods suited to the entire production system," says Jacques Cochard, Founder of Tematys.

Global Health Care systems are currently focused on the creation of a well-structured coordination of research effort at global scale aiming to find and implement innovative solutions for sustainable biophotonics devices production and light use as a resource and therefore centered on the need of developing a long term and sustainable partnership in the biophotonics research area that will develop a set of actions devoted to deliver an implementation plan able to stir it and make it effective and operative in terms of sustainable solutions for Health Care systems dealing

with new challenges that arise from climate change non described potential epidemics leading to new avenues exploration in terms of scientific research to develop new tools for clinical practice to be applied at point of care in order to improve better clinical protocols outcomes both at low cost and patient patient-centered health care delivery policies.

Diagnosis security is globally recognized as one among the major challenges our society is facing in health care systems. Neurodegenerative diseases are a serious emerging problem in Africa that health care systems need to cope with but the strategies to this novel epidemic ecosystem is far from the optimal resources to ensure the control of epidemical dimension of the problem in Africa. This is particularly the case in rural areas, the most vulnerable regions, exposed to multiple challenges. At the same time, the health care system still plays a key role in improving the life quality in populations by providing support to local rural and urban ecosystems. In fact, health sectors are strategic in the whole African area in terms of future social development, of rural population and territorial development of population in Africa. While natural resources are under climate and population stress, clinical practice must cope with quality requirements imposed by patients and by their ever-changing health patterns. How to apply new diagnostic systems on the population and safeguard their biological machinery health for future quality of life is a great challenge in this area.

Given the scarcity of these biophotonic resources and the increasing neurodegenerative diseases in Africa's population, proper biophotonic research and market output is one of the most crucial issues for the sustainable future of African health care systems. In addition, the challenge of low-cost biophotonic diagnostic devices' scarcity is closely linked to the lack of biophotonic researches, as diseases epidemics in Africa human ecosystem has resulted in an overexploitation of nonscientific based clinical resources and the subsequent risk for population health safety.

This issue requires a more focused approach where the long-term impacts of health care management and biophotonics research use should be considered for ensuring sustainable health care on diseases epidemics provision without harmful effects on the population and the patients in particular. Cooperation in research and innovation is considered of particular importance in order to tackle the most pressing challenges of the biophotonics research area in particular through the development of innovative solutions and the promotion of their adoption for improving the efficiency and sustainability of low-cost biophotonics-based diagnostic devices' production and the safety of clinical practice to treat neurodegenerative diseases in Africa.

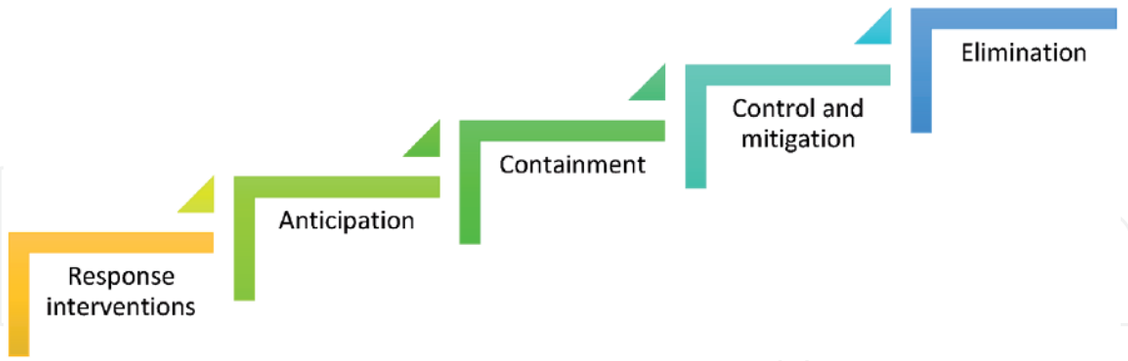
2. Africa health care solutions and epidemics overview

Africa is a continent with a complex ecosystem concerning biological entities and specific climate characteristics that enable systematic events of diseases epidemics over population leading to a process phase that we can describe in schematic phases according to World Health Organization monitoring epidemic events assessment identification from level emergence, localized transmission, amplification to reduced transmission being this one the last phase of the process in epidemics. World Health Organization proposal strategic planification to provide response in diseases epidemic events in Africa for the different previous identified phases of diseases epidemics process are first anticipation, containment, mitigation and last eradication.

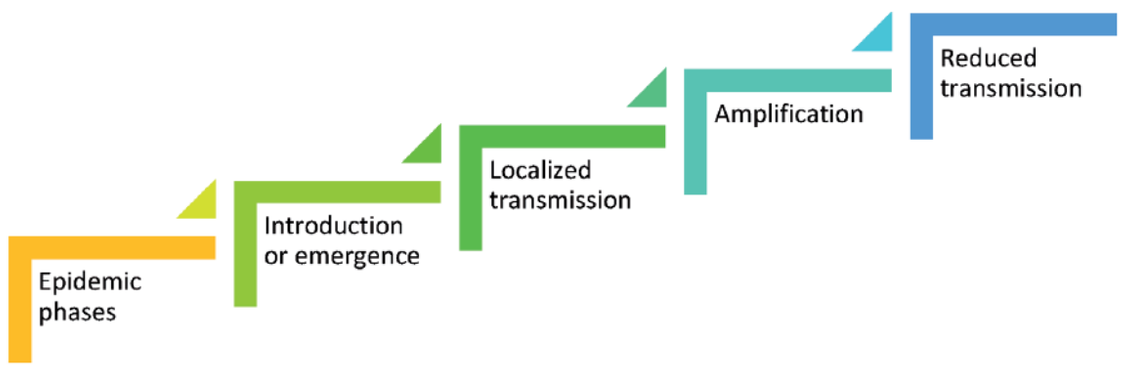
The standard approach based on emergency plan formula with similar parallel to the territory planning in terms of human demographics criteria often deliver poor cost-effective results as the target for the emergency plan is a group of individuals that are subject to different epigenetics that may present different results on

standard protocols applications as current world wide programs apply over African territories for epidemic treatment approach.

According to World Health Organization [2] the response interventions are



and epidemic phases are



African regions face several epidemic outbreaks that are still a severe threat to national health care systems, which are low-resource settings representing a risk to population health management in the long term.

In order to deal with this critical and systemic situation, African regions receive support from the United Nations World Health Organization and several other global players such as the Gates Foundation Programs, to provide health care solutions for managing epidemics in Africa.

One of the potential solutions for African Governments to accelerate effective response to the epidemics in African regions could be the acquisition of low-cost "top notch equipment," powered by biophotonics technology to enable further impact on the epidemic's detection and eradication.

In recent years, African regions have received significant scientific support concerning biophotonics tools applied to health care with focus on how to "develop cost-effective health care for underserved populations," according to Gerard L. Coté—Director, NSF-ERC on Precise Advanced Technologies and Health Systems for Underserved Populations (PATHS-UP) [3] project development to serve Health Care System on malaria diagnosis in Rwanda with photonics designed technology.

Image: Paths Up Project.

Another example of biophotonics technology applied to health care systems in Africa can be found in Nairobi, Kenya, developed by Prof. Katarina Svanberg [4], leading work in oncology with research work applied to medical lasers to accelerate biomedicine solutions in Africa, empowered by her academic work based at the Department of Oncology in Lund University. Prof. Katarina Shanberg [5] ignited biophotonics education in Senegal. Prof. Katarina Shanberg's group promoted doctor training and offered the medical community photonics-based fluorosensor instruments for trained doctors to perform further biophotonics treatment protocols in Dakar, Senegal, in collaborative work with Sheikh Anta Diop University.

Prof. Katarina Svanberg urges health care systems in Africa to promote the application of biophotonics -based clinical tools at point of care in remote rural areas where patients cannot access health care systems facilities in cities.

The scientific community in Africa is developing one of the firmest research communities dedicated to the exploration of biophotonics applications due to the lack of current medical conventional solutions in African regions, to serve the population suffering from African continent-specific epidemic contexts. This contextual situation is leading to a new generation of African students with academic training in physics and light-based sciences like optics, photonics, and biophotonics searching for solutions in order to accelerate production of light-based clinical instruments to serve African regions in terms of contributing toward health care; according to Zghal [6] "African countries definitely need better-prepared researchers and teachers in optics and photonics to pass on their skills to younger generations."

Africa region is a potential area at global scale that can deliver sustainable biophotonics research and clinical instruments development as Africa needs to accelerate practical low cost solutions to provide innovative Health Care systems with diagnosis and therapeutics for clinical work in African countries, collaborative work has been already ignited with education and training in Africa with the celebration of some events "organized by universities throughout Africa to provide education and training for advanced graduate students and post-doctoral faculty in optics, laser science and technology [7]." like the First African Summer School on Optics and Applications to Sustainable Development [8].

Image: SPIE CEO Eugene Arthurs (at center holding "are" sign) and participants of the Lighting up Africa with Lasers, Optics, and Fibers event in March. In Promoting Optics in Africa https://spie.org/news/spie-professional-magazine/2015-july/optics-in-africa?SSO=1

Africa dares to innovate with biophotonics scientific development in a low resources ecosystem to cope with constant critical epidemic problematics re-emergence that challenge current applied treatments that show less effective

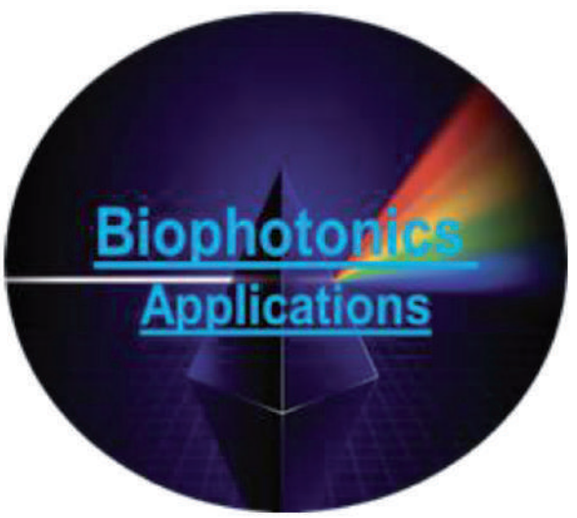
solution than biophotonics approach being the critical point for this structural problem in Africa the lack of scientific infrastructures and consolidated educational and training programs in the African Universities and a high level of dependence on educational skills leading to poor scientific results outcomes without external support from other scientific communities participating and contributing to a balanced educational and training environment that is crucial for Africa to mitigate epidemics with a knowledge based own scientific community inside the African territory to increase collaborative research work in the field in a systematic way by monitoring the factors driving to replication and mutation of epidemics outbreaks that requires multidisciplinary scientific and clinical research multidisciplinary approaches for consolidated results.

Investment on biophotonics education and research should be a priority for African Governments to advance with innovative solutions for health care systems "because epidemics are social problems as much as medical ones, we need to move beyond the traditional biomedical approaches to them." as World Health Organization suggests [9], for making progress in emerging health issues in Africa.

Biophotonics represents Africa pipeline focus in sustainable Health Care systems management towards effective results over efforts to eradicate debilitating epidemics in Africa leading to rapid cost-effective growth biophotonics health technology in Africa to deliver smart point of care diagnosis and therapeutic assessments for population health improvement with biophotonics applied to medical protocols. Biophotonics is consequently a significant and promising scientific resource to empower Health Care systems with light based clinical instruments in Africa.

3. Biophotonics for health tech delivery

Biophotonics [10] is the use of light-based technologies in biomedical sciences with a multidisciplinary approach involving the interaction of biology, physics, neuroscience, nanotechnology, and other related fields of scientific knowledge that can provide innovative solutions to products and services development, in this case applied to health care systems.



Biophotonics technologies can be designed to provide unique, dynamic information about clinical conditions. The use of biophotonics technology to develop medical diagnostic and therapeutic devices for clinical applications is a growing field of clinical research work worldwide. With advances in devices miniaturization and high-performance biophotonics components, the frontier between conventional

medical instruments and innovative light-based clinical application devices is becoming a challenge to doctors that are adapting their own professional skills and resources into a more effective operational clinical work with biophotonics tools.

This issue requires a more holistic approach where the long-term impacts of health care management and biophotonics research use should be jointly considered for ensuring sustainable health care on diseases provision without harmful effects on the population and the patients in particular. Cooperation in research and innovation is considered of particular importance in order to tackle the most pressing challenges in the field of biophotonics in particular through the development of innovative solutions and the promotion of their adoption for improving the efficiency and sustainability of low-cost biophotonics-based diagnostic devices' production and the safety of clinical practices to treat diseases at a global scale.

Biophotonics educational and scientific development practices and policies, through action and investigative research activities, are urgent to promote educational and scientific improvement, and clinical practice resulting in optimal development and high levels of achievement and accomplishments for biophotonics as a leading health technology resource that must be available in the market to health care providers in order to accelerate the development of health innovative products and services with biophotonics technology and related fields of knowledge to serve patients population at global scale because to health care systems, search for information is perhaps the most important problem to minimize the clinical assessment error. In addition, in health care systems, frequently, much time is lost in the search for correct information: this results in downtime and patient's mortality.

Biophotonics systems applied to health care offer the point of integration between the different health care systems and the health care provider operator himself, who performs operations and is the only one who can make decisions and take the actions needed in a very short time, thus reducing costs involved in health care assistance to patient with high quality, which requires smart solutions but simple and inexpensive to simplify clinical protocols at Point Of Care (POC) activities of the assembly operators, in order to reduce errors and increase health care systems' efficiency.

Main economic benefits of biophotonics applied to health

The main benefits for health care providers implementing biophotonics technology systems are:

a. increase in clinical performance because they can get the same health care services delivery at a much lower cost;

b. greater competitiveness in the market;

c. reduction in response times to patients;

d. simplification of clinical protocols activities by health care providers and decision-making processes.

The main end users of biophotonics technology applied to health care are health care provider companies, mainly hospitals, clinics, government NHCS, who often seek to invest in new technologies and improve their health care system services' processes, from older technological systems in departments to flexible and efficient services delivered at point of care with focus on ITC technologies integrations like e-health, telemedicine, and other clinical protocols.

This solution could be particularly attractive for health care providers operating in the market given the expected significant savings in terms of costs.

Time saving + cost and brain diagnosis time waste reduction + elimination of the dependence on other systems + simplification of activities → more efficiency → higher competitiveness

Biophotonics light-based devices for fast diagnosis and theragnostics of low cost and that are intuitive to use are particularly suitable for dynamic realities

a. seeking not too structured systems, flexible to point of care remote clinical needs and

b. wanting fast and simple systems to use and implement.

Rapid demographic, socioeconomic, and climate change factors are threatening the sustainable development of global societies where health care systems must be able to cope with increased demand for innovative diagnostic instruments' production in a scenario of non-invasive diagnostic devices' scarcity in the health care market.

- distributing to the various e-health workstations the ability to decide,
- simplifying and speeding up the decision-making activities in clinical protocols,
- streamlining the activities to be fulfilled by the health care systems elements/operators.

To perform the evaluation and analysis of biophotonics-based innovative solutions from the lab to the marketplace from a technical point of view, several stages of innovation are necessary during systems validation; therefore, technical feasibility studies must be focused on details such as:

- Redesign of the production system
- Device control test
- Detailed energy consumption analysis
- Study on the integration of devices with different production systems
- Control of the information flow
- Compliance with regulatory and safety requirements.

Once the technical feasibility studies are completed, several tests will be performed simulating real working conditions.

The solution will have to be further analyzed from a logistic and from an environmental point of view, to evaluate the clinical diagnosis impacts of the systems to be used.

Integrated systems for biophotonics clinical assessment already exist in the market, in particular, devices for point of care and low-cost applications to be used in smartphones applied to pathologies diagnosis that are able to integrate with

- e-health systems
- health care providers

- national governments' management of healthcare systems

Advantages of biophotonics applied to health care innovative solutions:

- Fewer indirect clinical structures
- Less clinical delivery time
- Ability to keep under control the health care system from all points of view with encrypted data collection but with a real-time action control system
- Monitoring of patient health status in direct time and reducing unnecessary clinical resources waste.

The rationale of the innovation with biophotonics approach health technology is the importance given to innovation which finds solutions that can reinforce competitiveness and better health care results for all the elements involved in the health care process with focus on patient centered clinical assessment for excellent clinical outcomes and patients benefits.

The current challenge for Biophotonics science applied to health care market is to be able to disrupt the medical applications conventional market with powerful clinical tools light based as "Biophotonics research is a field with a history of more than 50 years. Giants like Britton Chance were one of the first scientists to realize the potential of using light in medical applications. Until his death at the age of 96 he was a world leader in the field. He very early transformed theoretical science into useful biomedical applications" [5] for a sustainable diagnosis and theragnosis delivery with light based clinical tools to accelerate global health balance with Biophotonics powered by light technology for the benefit of Humanity. The missing link for sustainable democratic health care systems is technology enabled by biophotonics.

4. Research impact of biophotonics in Rwanda

Current stage of innovation development of BioAdd device has been studying the solution since 2016. Following the Technology Readiness Levels classification, the proposed business innovation project is positioned at TRL 3: technology demonstrated in relevant environment.

All the preceding TRLs (from 1 to 3) have been already tackled and successfully overcome during previous research works. In particular, three major milestones have marked the completed phase "from idea to application" enabling the project to enter the next step "from lab to market":

(M1) Preliminary study and research: this phase was conducted internally in VB lab, through the (human and material) resources of the company. The initial goal was to study how the internal production lines could be improved. Later, an exchange of views with some clients was conducted to verify their needs.

(M2) Construction of an experimental pilot room lab: an experimental system was built (experimental but currently functioning).

(M3) Experimentation successfully carried out on the small pilot room lab, in which some of the technologies here proposed have been tried, obtaining very good feedback from partner to VB Company: IBM Finland.

We can find BioAdd as a diagnosis advanced system applying biophotonics by observing the offered solution:

- Monitoring can take place anywhere and can be done by anyone
- Monitoring can be as frequent as needed with low-cost screening device and App
- Results compare to/beat those obtained by current oncological invasive lab protocols
- Results are available in minutes warning to doctor can be sent within minutes of a test Effectiveness of protocol can be monitored in real time
- Instant analysis and availability of related data improve speed and effectiveness of cancer treatments.

5. Conclusion

Biophotonics represents Africa pipeline focus in sustainable Health Care systems management towards effective results over efforts to eradicate debilitating epidemics in Africa leading to rapid cost-effective growth biophotonics health technology in Africa to deliver smart point of care diagnosis and therapeutic assessments for population health improvement with biophotonics applied to medical protocols. Biophotonics is consequently a significant and promising scientific resource to empower health care systems with light-based clinical instruments in Africa.

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Conflict of interest

The author declares no conflict of interest.

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