Abstract
A new intriguing paradigm recently emerged in bio-photonics, in which a single biological element such as a simple cell can be used as an optical or photonic component having well-defined features. Based on this novel concept, the interactions between light and biological matter can be exploited in many circumstances as useful tools in various fields of science and technology. In fact, it is surprising as well as exciting that the optical behavior of living cells permits their use as microlenses for imaging, photonic microresonators or optical waveguides. Moreover, it has been demonstrated that biological cells can behave as advanced probes for optical tweezing, able to manipulate matter at the nanoscale and also as subwavelength probes of localized fluorescence. Here, we present an overview of these fascinating applications of biological lenses. The aim of the present Topical Review is to introduce a completely new scenario to the community of scientists working in optics and photonics. A developing research field is presented, in which live cells can be employed and exploited as optical components for incredible applications ranging from simple imaging, to manipulation of soft matter, to biomedical diagnosis. Several of the most significant studies and discoveries will be illustrated and discussed.

1. Introduction
Bio-photonics is the research field that embraces all the technologies based on the interactions of light with living matter. Its development has been possible thanks to the intersection of medicine, engineering and the sciences (physics, biology and chemistry), in other words, bio-photonics’ soul is rooted in multidisciplinarity [1]. The most important technologies range from imaging (spectroscopy, fluorescence and label-free phase-contrast microscopies), single-cell manipulation in the form of optical tweezers [2, 3], up to tissue repair or surgery, as in the case of laser therapy. The impact of bio-photonic technologies on society has been disruptive over the last 50 years because it has allowed the development of diagnostic and therapeutic tools that are less invasive and cheaper. Furthermore, such new technologies give access to more specific identification of diseases, thus contributing to paving the way for personalized medicine, that will be the route to the future.

Within this wide framework, a new paradigm has recently emerged in photonics. Nature gives us the inspiration not only for creating new structures to manipulate light, but also for using living and already-existing objects in photonics applications. In fact, a new field of investigation has recently emerged, where living objects interact with light and are able to perform optical tasks as real optical elements (i.e. microlenses, resonators, waveguides or gratings [4, 5]). Conversely, by observing nature, many examples of optical and photonic intriguing effects can be found [6]. This simple but effective observation is the foundation of many remarkable papers describing the realization of bio-inspired photonic architectures and bio-inspired structures [7, 8]. However, the natural attitude of live samples to managing light or controlling it can also be investigated also to develop a new paradigm based on the integration of biological objects into the technology of optics and photonics [9–15]. In this review, we will call this new insight ‘optobiology’.

Research in this area is also motivated by the lack of biocompatibility of synthetic structures, which is a
fundamental aspect of biological and medical applications, particularly when contact with the sample is needed, for example in endoscopy [16, 17]. A further driving reason for developing optobiology is that fabrication techniques at the micro- or nanoscale are complex and multistep processes, while living cells are abundant in nature and many different types are available. Therefore, why not use biological objects themselves in optics and photonics? If this new scenario could be affirmed in the future, this would avoid sophisticated fabrication processes.

The aim of the present paper is to shed light on this area of interest, drawing the attention of the community to the recent advancements in light manipulation through living organisms. This review will describe and illustrate some of most exciting possibilities offered by biological matter to be exploited as living materials, able to accomplish optical and photonics operations. In particular, biological live cells such as fibroblasts, red blood cells (RBCs), yeast cells and bacteria, to name a few, will be considered as possible candidates for optical tools. The exciting matter described here can really open incredible perspectives, in which live cells could be used as an optical magnifying lens at the micro- and nanoscales or as laser cavity media, able to sustain laser emission that could revolutionize photonics devices. On the basis of this new paradigm we can foresee a near future in which cells can be used, for example, in lithography processes or as imaging optical elements in the human body. Furthermore, this kind of research will open new scenarios, in which new approaches could be developed for diagnosis and therapy in biomedical sciences.

2. Lasing through living cells

New possibilities are opened up by the possibility of lasing through living samples [9, 18–22]. Several modalities to realize lasers by integration with single cells have been demonstrated. The first attempt was with a single live cell expressing a green fluorescent protein used as a gain medium in a high-Q microcavity for laser emission [9]. Later, it was demonstrated that lasing can be achieved by introducing a whispering gallery mode (WGM) microresonator into the cytoplasm of adherent cells [20, 23], as shown in figure 1. Laser emission through living samples is one of the latest frontiers in biophotonics [24, 25, 26]. Specificity in the biosensing of live samples is related to their interactions with laser light, as shown in figure 2. Laser emission that is directly integrated and scaled at the single-cell level allows improvement of sensing and imaging capabilities. Indeed, thanks to the photonic principles of optical resonance and stimulated emission the spectral narrowing of fluorescent probes via coherent gain has been made possible, thus enabling a change of probing methodology from fluorescence-based to laser emission-based detection.
3. Imaging by biological lenses

The lensing effect of biological samples has started to be investigated by different research groups across the globe. The two main driving motivations of scientists are based on biocompatibility and super-resolution, i.e. the possibility to go beyond the optical diffraction limit [14, 27, 28]. In this scenario, it has been demonstrated that erythrocytes, or red blood cells (RBCs), can behave as a sort of optofluidic microlenses, having the proper focal length and magnification. In fact, healthy and mature human RBCs have a globular structure and, most importantly, they lack nuclei and organelles. RBCs can be regarded as disk-shaped micro-envelopes filled with a uniform liquid [10]. Furthermore, variation of the RBCs’ morphology can be easily achieved by changing the liquid buffer osmolarity. These two simple observations are the basis of the idea that RBCs could be considered as tunable liquid microlenses [10, 29, 30].

The nucleus of the model rests on the assumption that, when a monochromatic plane wave propagates through an RBC, the RBC behaves as a lens with certain aberrations [28], so that the diffracted wavefront at its exit pupil can be expressed as a linear combination of Zernike polynomials [30]:

$$\varphi(x, y) = \sum_j a_j Z_j(x, y)$$

In case of a normal (healthy) RBC, i.e. a discocyte, the main contributions to the wavefront are given by the focus-shift term and the third-order spherical aberration, whose coefficients are $a_4$ and $a_{12}$, respectively. By modifying the ideal biconcave shape and simulating a spherocyte (an RBC with a spherical shape) only one term is responsible for the diffraction through the cell, i.e. the focus-shift term, $a_4$ [10]. This model was validated through a digital holographic (DH) microscope configured for transmission. Digital holography is one of the most developed fields for quantitative phase imaging (QPI) in biological applications [31–33]. The wrapped quantitative-phase map (QPM) from the refocused complex wavefront is processed by PUMA code for the unwrapping process in order to correct the phase discontinuities (mod 2\pi) [34, 35]. The results of the simulation and the corresponding experiment are reported in figure 3(a) where the model and real phase maps for discocytes and spherocytes are compared. Figure 3(a) also shows a scan of the amplitude along the axis that highlights the presence of both real and virtual foci for the discocyte and a single real focal spot for the spherocyte. This experiment was designed to evaluate the temporal evolution from discocyte to...
spherocyte, thus proving the lens effect and also the RBC’s dynamic tunability. This evolution is obtained by changing the chemistry of the buffer, passing from an isotonic to a hypotonic solution, inducing swelling of the RBC in about 10 s. The temporal evolution of the main Zernike coefficients is shown in figure 3(b); the coefficient of the spherical aberration goes to zero when changing from the isotonic to the hypotonic buffer and, at the same time, the coefficient representing the focus-shift increases. A specific experiment was also performed to test the imaging performance of RBC lenses. A spherical-shaped RBC was displaced along the optical axis. The object to be imaged was the surface of a DVD, where submicron gratings were engraved (figure 3(c)). The experimental test demonstrated the possibility of getting true imaging by using a live biological cell (i.e. an RBC). The results clearly show that the DVD grating surfaces were correctly imaged, and a magnification of about 22% was also obtained [10]. Figure 3(d) shows the axial tracking of the focal spots generated by discocytes (first line) and sphere-like erythrocytes (second line). The focal points are both real (in blue) and virtual (in green) for discocytes, while they are only in the real plane for the spherocytes.

A very interesting paper, [37], furnishes another example where sub-diffraction imaging through a biological cell was demonstrated. Optical tweezers, obtained on a fiber tip, manipulated a cell that was acting as a biomagnifier lens. The interesting results revealed in the manuscript by Li and coworkers [37] show that a biological lens can offer a very high-precision tool for sensing, assembly of bionanomaterials and optical imaging. In figure 4(a), the optical setup with the cell and the imaged nanostructures is shown. Furthermore, in [37] the imaging capabilities achieved by using different types of cells are shown, such as bacterial, yeast, red blood and stem cells. Even though imaging by an RBC lens was already demonstrated by Miccio et al [10], it is noteworthy that this recent research work significantly extended the imaging capability to almost any other kind of cell, thus opening the route for further applications. Nanostructures with a resolution of 100 nm (λ/5.5) under white-light microscopy were magnified by the cellular lens and imaged, as shown in figure 5. From observing the results shown in figure 5, spherical aberrations are clearly present in the imaged patterns.

Figure 3. (a) Phase-shifts in the (x-y) plane for a single RBC, simulated and real, both discocyte and spherocyte, and the corresponding light intensity distributions along the optical axis, for a plane monochromatic wave propagating through the cell. Scanning range was between — 15 and 15 µm. (b) The theoretical and experimentally-measured energy percentages of the Zernike coefficients during swelling. (c) The magnification property of a single spherical RBC. The cell is trapped by an optical tweezer and displaced to the proper distance from a DVD grating to get the magnifying-lens effect. (d) The results of the axial tracking of the focal points for discocytes (first line) and sphere-like erythrocytes (second line). The focal-point positioning and the relative thickness maps are shown. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature Communications [10] 2015. Reproduced with permission from [36].
It is interesting to note that one of the tricks adopted by the authors of [37] consists of using a biological lens positioned accurately at the boundary of the air–liquid interface. This is a very smart strategy, as the refractive index of the cell is very close to that of water. In this case, having half of the spherical lens in air, the focal power is considerably improved thus making it possible to use the biological lens for different applications. Figure 6 shows dark-field images of 644 nm red light (d), 532 nm green light (e), and 473 nm blue light (f) transmitted through a ‘cell biomagnifier’ and focused into subwavelength light spots with waist radii of 370, 300, and 270 nm, respectively. Quite sharp focal spots are visible for the three light wavelength sources. Further results revealed in reference [37] show that the focal spots of the cell biomagnifier also acted as sort of nano-optical trapping tool, thus allowing the accurate manipulation of single nanoparticle having a 50 nm radius.

A further application reported in [37] is the possibility of using a biological lens for imaging the subcellular structures of a human epithelial cell. A comparison between a conventional optical microscope
Figure 6. Dark-field images showing 644-nm red light (d), 532-nm green light (e), and 473-nm blue light (f) transmitted through a 'cell biomagnifier' and focused into subwavelength light spots with waist radii of 370, 300, and 270 nm, respectively. Reproduced from [37]. CC BY 4.0.

Figure 7. (a) Near real-time RBC’s pre-screened by analyzing intensity spots in the virtual focus plane. Healthy discocytes are denoted by a quasi-circular intensity spot (in green); red spots denote doubtful cases. Blue histograms represent the number of RBCs detected, green and red histograms are the percentage of healthy and doubtful cases, respectively. The corresponding intensity image is also reported. (b) A sketch of the experiment (first column), aberrations and point spread functions (columns two to five) of the transmitted wavefront during RBC shrinking and stretching. [38] John Wiley & Sons. © 2017 International Society for Advancement of Cytometry.

4. Biomedical applications using the concept of the biological lens

Here we show that modeling a biological cell as an optical element opens new routes in diagnostic fields, because their optical fingerprint allows the discernment of healthy versus unhealthy samples. As described previously, the optical characteristics of RBCs are related to morphological modifications and also to membraned fluctuations. Many blood diseases are indeed reflected by a modification of the RBC shape. The first evidence of diagnostic capabilities is described in [10], where quasi real-time pre-screening of a RBC sample is realized by means of the evaluation of their focal spots in the virtual focus plane. The test output confirms the percentage of healthy and doubtful cases, based on a threshold value of the spot ellipticity. In figure 7(a), the results of pre-screening are shown, the green-colored spots representing healthy cells and a biomagnifier cell shows an impressive performance of the bio-lens. In fact, the cell is able to resolve the fibrous cytoskeleton inside it and two-layer structures on the cell membrane [37].
Figure 8. Anemia identification through Gaussian ellipsoids obtained by the statistical analysis of the three main Zernike coefficients used to identify biolenses, i.e. the piston, the focus-shift and the third order spherical aberration. Reprinted with permission from [40]. Copyright 2018 American Chemical Society.

Figure 9. The results of in-flow Tomographic Phase Microscopy applied to RBCs with morphological anomalies: (a) one-side concavity, (b) speculated, (c) iron-deficiency anemic and (d) thalassemic RBCs. For each cell, quantitative phase images and the retrieved tomogram are shown. The refractive index (RI) distributions at the $z = 0$ and $y = 0$ planes, the healthiness parameter ($H$), the average refractive index (ARI), the volume ($V$) and the corpuscular hemoglobin (CH) are also shown. Reproduced from [41]. CC BY 4.0.

(ellipticity >0.8). Red-colored spots represent cells whose ellipticity is under the threshold. A deeper analysis of the focal spots, based on a phase-retrieval approach and Zernike analysis, allows the retrieval of a full tridimensional rendering of each RBC in the ensemble. Indeed, any deviation from a healthy RBC shape is reflected by a modification of the Zernike coefficients’ corresponding weights. This approach has been implemented to measure the modification induced in the RBC membrane by a holographic optical tweezer (HOT) setup [38] or by shear stress inside a microfluidic chip [39]. The deformation optically induced by an HOT is measured by the Zernike method, thus establishing a direct relation between the RBC elasticity and the optical properties. In figure 7(b), the aberrations and point spread functions of a wavefront transmitted by a single cell are reported for the case of full symmetric stretching. In particular, focus shift and astigmatisms, third order spherical aberration and secondary astigmatisms and coma components are measured to quantitatively evaluate the effect of the stretching.

A direct biomedical application of this new paradigm has been investigated for the analysis of inherited anemias [40]. It has been proved that RBCs from patients with different types of anemia can be distinguished from healthy ones and, also, RBCs from different anemia types can be specifically identified. Specifically, RBCs were analyzed as biolenses in cases of iron-refractory iron-deficiency anemia, thalassemia, hereditary spherocytosis, and congenital dyserythropoietic anemia, types I and II. The standard QPM morphometric parameters can be calculated (i.e. the mean corpuscular hemoglobin (MCH), diameters, MCH surface density (MCHSD), and sphericity) but, comparing their probability-density functions, it is not possible to identify anemia’s phenotypes. Moreover, a joint observation using multivariate statistical analysis is impracticable because of their mathematical correlations. Conversely, as Zernike polynomials constitute a base for the wavefront [30], all the terms considered are independent of each other, so they can be used for multivariate statistical analysis. Thus the QPMs (figures 8(a)–(e)), when fitted as a weighted combination of Zernike polynomials, allow the separation of the data populations identifying anemia’s phenotypes [40].
Figure 10. The light-scattering characteristics of (a) hRBCs and (b) iRBCs. f_r and f_v represent the real focus and virtual focus, respectively. A comparison of six features extracted from the light-intensity distribution maps of hRBCs and iRBCs. (c) The real focal length f_r. (d) The virtual focal length f_v. (e) The average vertical distance between the foci and the z-axis. (f) The maximum intensity in raw light-intensity distribution maps. (g) The average of the normalized light-intensity distribution maps. (h) The standard deviation (SD) of normalized light-intensity distribution maps. The scale bars are 5 μm. *P < .001. [46] John Wiley & Sons. © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

In figure 10, light-scattering characteristics for healthy (hRBCs) and malaria-infected (iRBCs) are shown, together with six extracted features for both populations.

5. Lithography

Optical bio-phololithography (bio-PL) is a further functionality of a biological lens array. It has been shown that the focusing properties of an array of RBCs can successfully be used to transfer phase modulation onto a photo-activated and biocompatible material, i.e. iron doped Lithium Niobate (Fe:LN) [47]. The RBC array acts as a photomask that is analogous to the mask used in photolithographic technological processes, where light illumination is responsible for transferring a pattern from a mask to a photoresistant material. In the case of [47], the photosist was replaced by Fe:LN crystal, which is a ferroelectric and photorefractive (PR) material already employed for the manipulation of biological samples. PR imprinting onto LN was previously demonstrated to generate negative lens-like structures, diffraction gratings or waveguides [48, 49, 50], thus opening the possibility of PR writing by bio-lenses. In figure 11(a) a schematic view for bio-PL is displayed, while in figures 11(b)–(c) a comparison between the focusing properties of RBCs and their corresponding imprints is shown. Actually, optical bio-PL is one of the various expressions of using biological samples as...
Figure 11. (a) A schematic view of bio-PL. (b)–(c) A comparison between the (b) focusing properties of RBCs and (c) their corresponding imprints. Reprinted with permission from [47]. Copyright 2019 American Chemical Society.

Figure 12. Direct-PL by cells in PDMS structures. The technique allows cells to be guided into the cavities of cell-imprinted substrates by introducing direct-cell photolithography and soft contact photolithography using cell-imprinted substrates. Reprinted (part of figure 1) with permission from [50]. Copyright (2019) American Chemical Society.

photomasks. Indeed, in [50], the authors demonstrated direct-PL of cells in polydimethylsiloxane (PDMS) structures in order to be more efficient in cell-imprinting experiments (figure 12). Jung et al demonstrated that DNA can also be used as photomask to create patterns in polymer membranes [51]. In the case of optical bio-PL, the novelty exists in generating bulk refractive index modifications and surface potentials at the same time at the cellular scale. Optical bio-PL offers new challenges in cell-to-material interactions.
and, furthermore, it can be seen as a tool to fix the optical fingerprint of living samples into a solid material.

6. Conclusions

Optobiology is a new point of view in optics and photonics, where biological samples can act as optical and photonics elements. Such biological optical elements can be actively integrated into systems and devices, thus providing specific functionalities. The optobiology concept has started to be employed in different fields, as testified by very recent publications.

Direct developments in the near future will definitely be in the less invasive and biocompatible diagnostic and prognostic technologies with lower costs. This trend can drive the further development and exploitation of ‘Optobiology’.

Furthermore, the optical signature of each single cell in an array can be intrinsically exploited as a label-free biomarker for identifying cell phenotypes and thus labeling an ‘optical fingerprint’ directly related to a cellular disease. In biomedical imaging, the machine-learning approach is the most rapidly developing field of the near future, because of its ability to classify different populations by managing a large amount of data. Label-free and quantitative images seem to be a really good candidate for machine-learning classification, due to the large amount of encoded information [45, 52]. A possible valuable application would be the identification and classification of cancer cells, for example in liquid biopsies [53–56].

Advances at the interface of medicine, biology and physics will supply innovations that will open up further possibilities for biomedical research, either in diagnostics or treatments.

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