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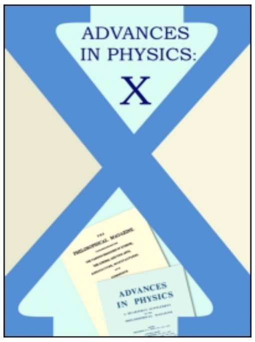

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REVIEW

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Nonlinear optical response and self-trapping of light in biological suspensions

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ABSTRACT
In the past decade, the development of artificial materials exhibiting novel optical properties has become a major scientific endeavor. One particularly interesting system is synthetic soft matter, which plays a central role in numerous fields ranging from life sciences, chemistry to condensed matter and biophysics. In this paper, we review briefly the optical force-induced nonlinearities in colloidal suspensions, which can give rise to nonlinear self-trapping of light for enhanced propagation through otherwise highly scattering media such as dielectric and plasmonic nanosuspensions. We then focus on discussing our recent work with respect to nonlinear biological suspensions, including self-trapping of light in colloidal suspensions of marine bacteria and red blood cells, where the nonlinear response is largely attributed to the optical forces acting on the cells. Although it is commonly believed that biological media cannot exhibit high optical nonlinearity, self-focusing of light and formation of soliton-like waveguides in bio-soft matter have been observed. Furthermore, we present preliminary results on biological waveguiding and sensing, and discuss some perspectives towards biomedical applications. The concept may be developed for subsequent studies and techniques in situations when low scattering and deep penetration of light is desired.

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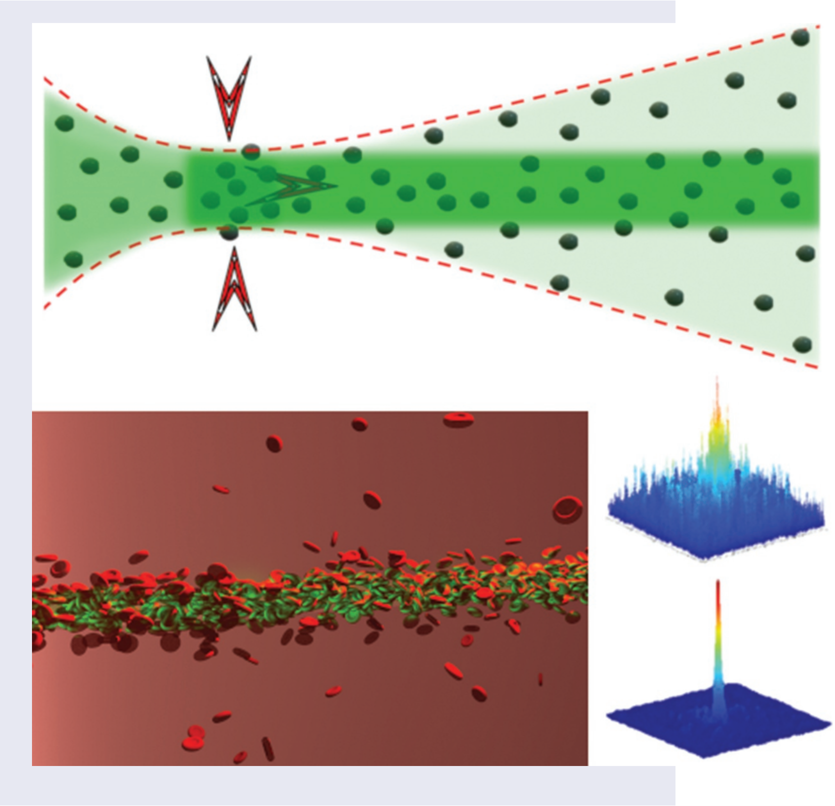

Introduction

Materials that are easily deformed or structurally altered by thermal fluctuations and external forces are defined as soft matter. Alternatively, they are called complex or structured fluids with an intermediate fluidity between a crystalline solid and a liquid [1,2]. Numerous liquids, colloids, gels, and liquid crystals can be loosely classified into this material category. The hierarchical molecular order of soft materials is governed by the self-organization of the basic structural units based on weak interactions such as Van der Waals interactions, π-stacking or hydrogen bonding [1–3]. Such materials are particularly interesting since the mesoscopic length scales of their basic structural units, along with their physical properties, can be manipulated at ease. New advances in the soft matter field contribute significantly to the development of photonics, electro-optic modulators, fiber optics, optical switches and nanoscale devices [2,4–6]. On the other hand, understanding the material properties in soft matter systems still constitutes a challenge due to their intrinsically heterogeneous structure, complex interactions across different length scales, and slow dynamics [1,2]. Noteworthy, optical tools have shown a great potential in evaluating material properties and manipulating the physical behaviors of soft matter systems. Traditional techniques, such as bright and dark field, polarization-based, phase contrast and total internal reflection microscopy, along with absorption and fluorescence spectroscopy, have been widely used to examine and characterize soft materials [3,7–9]. The integration of optics and photonic concepts with the soft matter field not only helps with the characterization of materials but also greatly contributes towards the modification and synthesis of advanced materials.

A variety of biological materials such as biofluids, cells, biopolymers (nucleic acid, proteins, polysaccharides) exhibits significant resemblance with man-made soft matter [2]. Such materials are flexible and easily deformable with only small external perturbations. Understanding the fundamental interactions in these systems and the microscopic mechanical properties of biomaterials is essential to comprehend their biological function, as well as use these materials for applications in such fields as drug delivery and biomedicine [10–12]. Recently, optical force-based techniques have shown potential to offer non-invasive means to understand various biological processes spanning proteins self-assembling, single molecule dynamics, DNA-protein binding and cell-cell interactions diagnosis [13–15]. Furthermore, the integration of microfluidics with optical forces (optical tweezers), as seen in optofluidics, provides a robust platform for cell-sorting, sensing and diagnosis [15,16].

Unfortunately, in soft and bio-soft matter systems, light-matter interactions are generally dominated by strong scattering effects, which typically limit the range of optical beam propagation. In this context, nonlinear optical techniques have been employed to provide a powerful tool to overcome such limitations and achieve enhanced transmission. For instance, two-photon fluorescence, sum-frequency generations, and coherent Raman scattering have been implemented to obtain deeper penetration and higher resolution [9,17–19]. In contrast to conventional single-photon excitation schemes, these techniques involve multiple excitation photons and utilize the intrinsic and/or extrinsic nonlinear optical responses of the soft matter system. Another example comes from the study of nonlinear light propagation in colloids, nanosuspensions and other engineered structures which have attracted a great deal of interest in optofluidics and photonics in general [20–25]. These systems offer a fascinating platform for observing and analyzing the optically induced control of nonlinear waves and their instabilities in colloidal suspensions [25–27]. In principle, such optically induced processes can be exploited for initiating and regulating chemical reactions, for sorting different sub-micron/micron scale particles, and for the development of novel optically tunable nonlinear devices [28–31].

In this article, we provide a brief overview of tunable optical nonlinearities mediated by optical forces in dielectric and plasmonic nanosuspensions, with a focus on the recent work regarding self-trapping and nonlinear guiding of light in biological suspensions. We discuss the physical picture of nonlinear beam propagation mediated by optical forces, along with the formation of optical waveguides in bio-soft materials. These include colloidal suspensions of cyanobacterial cells, Escherichia coli (E. *coli*) cells, or red blood cells (RBCs) from both humans and animal models. Some prospects for biomedical applications of nonlinear bio-soft matter will be discussed, such as soliton-induced biological waveguides, nonlinearity-induced fluorescence enhancement, and nanoparticle-assisted guiding of fluorescent biomolecules for potential biomedical applications.

Nonlinear dielectric and plasmonic nanosuspensions

When a laser beam is sent into a mixture of solids and liquids – such as a glass of milk – incident light typically undergoes strong scattering in all directions. It is however possible to develop nonlinear mixtures or colloidal suspensions that behave in a significantly different way to minimize scattering losses. Indeed, liquid suspensions of dielectric particles present nonlinear properties that have been of great interest in the past few decades: following Ashkin's early pioneering work [32–34], a number of studies have considered a variety of nonlinear phenomena spanning modulation instability, self-focusing, spatial solitons, and self-induced transparency in dielectric suspensions [25–27,35-39]. A light beam propagating in such soft matter can in fact display complex nonlinear dynamics due to the light-induced variation of the suspension refractive index, thereby modifying its intrinsic properties by inducing an alternating interplay between nonlinear effects and the beam propagation characteristics.

This well-known effects due to nonlinear optics becomes more complex in colloidal suspensions, where enhanced scattering can occur even as optical beams self-focus to the point of catastrophically collapse - causing a dramatic drop in transmission. In general, a particle displays a positive polarizability (PP) whenever its refractive index exceeds that of the background medium, while, conversely, negative polarizability (NP) is associated with the opposite scenario. As illustrated in Figure 1, under the action of optical forces, PP particles are attracted towards the center of an optical beam where the intensity is higher, whereas their NP counterparts are repelled. In the latter case, not only is the scattering significantly reduced but this phenomenon also gives rise to a saturable nonlinearity for stable self-trapping of light [40]. In this framework, colloidal suspensions exhibiting NP were synthesized by Man et al., in which robust propagation as well as enhanced transmission of self-trapped light was observed over long distances (5 to 10 mm) that would have been otherwise impossible in conventional suspensions [27]. Specifically, by dissolving 200 nm polytetrafluoroethylene (PTFE) particles (n = 1.35) in a diluted glycerin-water

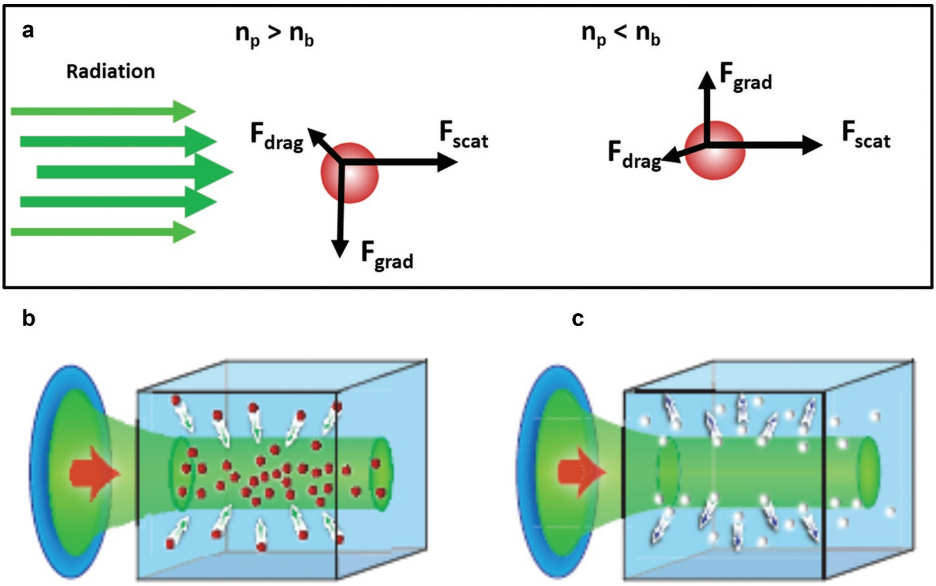

Figure 1. Schematic illustrations of light-particle interactions in colloidal suspensions. (a) Optical forces acting on the particle (b) positive-polarizability particles are attracted by an optical beam (c) negative-polarizability particles are expelled away. (b) and (c) are reproduced with permission from reference [27].

solution (n = 1.44), stable dielectric NP suspensions were realized, which led to the observation of a four-fold enhancement of transmission *via* non-linearly self-trapped light, compared to low-power linear propagation in the same scattering media [27]. In the case of such colloidal suspensions, light pushes the nanoparticles away from the main beam path, thus creating a waveguide with a lower than average concentration of scattering colloids within the suspension – the light essentially clearing away the particles in its path. Besides improving light guiding, this repulsion of the particles sideway with respect to the beam also enhances material transparency. This work represents an important step towards the engineering of optofluidic systems with active control of chemical reactions and light transmission.

In an independent work by Greenfield and co-workers [41] conducted over the same period, densely-packed suspensions of particles were studied using a different approach. Densely-packed suspensions are known to scatter light heavily and are usually opaque where the light diffuses, losing their directionality and localization. In this context, optical manipulation in strongly-scattering suspensions is considered impossible, because the optical field cannot be externally tailored to retain its spatial profile within the suspension. Greenfield *et al.* 2013, demonstrated theoretically and experimentally the optical manipulation of the local properties of scattering suspensions, and further showed that the optical forces exerted by multiply-scattered light give rise to shock-fronts of dense particle concentration, propagating deep inside the suspensions. Using these shock waves, they presented a new approach for optical manipulation, overcoming the usual limitations associated with the tailoring of the optical field within opaque suspensions. They demonstrated, among others, optical transport of large populations of nanoparticles and the ability to clear volumes of opaque solutions from particles as a probable outcome. At high concentrations, they also observed light-induced suspension-to-gel phase transition leading to the formation of small gel balls which can be remotely manipulated or positioned at preselected locations. The directionally localized and deeply penetrating (observed up to 15 photon scattering lengths or mean free paths) optical manipulation in scattering fluids stands in sharp contrast with the diffusive behavior expected from light experiencing multiple scattering. These nonlinear phenomena are in fact driven by the interplay between the optical gradient force and the radiation pressure acting on the particles, while no thermal effects are involved [41].

In 2014, Fardad *et al.* took the above work one step further [20]: they created gold-coated nanoparticles in nanosuspensions that demonstrated tunable optical nonlinearities. Surface plasmons, associated with metallic nanoparticles, are coherent excitations of conduction electrons near the metal surfaces, *i.e.* near metal-dielectric interfaces. Two main electromagnetic resonances are associated with these surface plasmons, where the extended metallic structures (e.g. films) generates surface plasmon polaritons (SPPs), while in metal nanoparticles the response arises from localized surface plasmons (LSPs). Excitation of nanostructures at the wavelength of LSP/SSP leads to the enhancement of nonlinear effect (nonlinear susceptibility) owing to the field enhancement near the metal-dielectric interface [42]. Plasmonics plays an important role in nonlinear optics by allowing nonlinear effects to be utilized towards combining a reduced laser power and the ultrafast response of the resonance excitation. Plasmonic nanostructures such as core–shell metallic particles, nanorods, and spheres have been shown to display tunable polarizabilities depending on their size, shape, and composition, as well as on the illumination wavelength. Theoretically, nonlinear propagation and soliton effects in plasmonic structures have also been extensively studied [43,44]. In the work of Fardad and co-workers with plasmonic nanosuspensions, nonlinear self-trapping of light beams and their robust soliton-like propagation were experimentally demonstrated over distances up to 25 diffraction lengths [20]. This self-trapping effect experienced by light beams in turn allows for the deep penetration of long needles of light through otherwise highly diffractive colloidal media. Furthermore, guiding light by light based on plasmonic resonant solitons was demonstrated, in which an infrared (IR) probe beam (1064 nm) by itself does not experience appreciable nonlinear self-action but is guided by a low-power visible beam (532 nm). The 532 nm laser beam acted as an optical pump in the gold nanoparticle suspension to enable the formation of a plasmonic resonant soliton-waveguide [23].

These findings may bring about new opportunities in synthesizing novel soft-matter media with tailored optical nonlinearities, which in turn would facilitate the development of optical switches, plasmonic devices, nanosensors *etc*. Additionally, by increasing the penetration depth of such ‘light needles’ into dissipative colloidal systems, it may become possible to overcome several scattering limitations by engineering tunable soft-matter systems towards applications like optical trapping and guiding, or by developing highly efficient spectroscopic techniques (such as surface-enhanced Raman spectroscopy and fluorescence) in settings that are otherwise inaccessible due to scattering losses. Furthermore, the work on dielectric (PP and NP) and metallic suspensions provide the necessary foundation to gain insight into both theoretical analysis and underlying physics of optical forces, which is important for exploring and understanding nonlinear dynamics in bio-soft matter systems.

Theoretical analysis of optical forces

In this section, we briefly discuss the theory behind optical forces. In most cases, the particle polarizability plays an important role in dictating the optical forces and concomitant nonlinear response of the particles [33,40]. The polarization of a spherical dielectric particle (P) as a function of an applied electric field (E) under Rayleigh scattering is given by:

$$P = 4\pi\varepsilon_0 n_b^2\left(\frac{m^2-1}{m^2+2}\right)r^3E \;=\; \alpha E \tag{1}$$

where $m = \frac{n_p}{n_b}$, n_b is the refractive index of the surrounding medium, n_p is the refractive index of the particle, r is its radius, and α is the effective polarizability of the particle. In the presence of an optical field, a particle experiences two main forces, the gradient force (F_g) and the scattering force (F_{sc}), which under appropriate conditions can, respectively, be simplified as [45–48]:

$$F_g = \frac{\alpha\nabla I}{4} \text{ and } F_{sc} = \frac{I\sigma n_b}{c} \tag{2}$$

where the scattering cross section of the particle σ is equal to $\frac{128\pi^5 r^6 n_b^4}{3\lambda^4}\left(\frac{m^2-1}{m^2+2}\right)^2$, $I = \frac{cn\varepsilon_0}{2}|\mathrm{E}|^2$ corresponds to the optical intensity, λ is the wavelength of the laser source, c is the speed of light in free space, n is the refractive index of the medium, and ε_0 is the vacuum permittivity. Due to the conjoint action of the optical gradient and scattering forces, the dielectric particles can be either attracted towards or repelled away from the beam path in the suspensions, leading to what Ashkin called 'artificial nonlinearity' [32]. Such nonlinearity can exhibit self-focusing effects and can be employed for self-guiding of light in an analogous manner to the formation of optical spatial solitons.

If the gradient force is the predominantly acting force that balances the particle diffusion, the steady-state of the particle concentration ρ_I in the system can be described as [35,37,40,49]:

$$\rho_I \frac{D}{k_B \mathrm{T}} \frac{\alpha \nabla I}{4} - D \nabla \rho_I = 0 \tag{3}$$

where D is the diffusion coefficient and $k_B\mathrm{T}$ is the thermal energy at temperature T. This partial differential equation has the solution $\rho_I = \rho_0 e^{\frac{\alpha I}{4k_B\mathrm{T}}}$ where ρ_0 is the unperturbed uniform particle density in the absence of a light field. Similarly, the volume filling factor of the colloidal particles in the presence of a light beam also follows a Boltzmann distribution: $f_I = f_0 e^{\frac{\alpha I}{4k_B\mathrm{T}}}$. Under the influence of an incident field, the PP particles ($n_p > n_b$) are attracted towards the center of the optical beam (where the intensity is higher), whereas the NP particles ($n_p < n_b$) are pushed away from the beam center. However, in both scenarios, the local refractive index effectively increases along the beam path, resulting in a self-focusing nonlinearity as illustrated in Figure 1. Under appropriate conditions, this effective nonlinear local change of refractive index is calculated as $\Delta n_{NL} = \left(n_p - n_b\right) V_p \rho_0 \left(e^{\frac{\alpha I}{4k_B\mathrm{T}}} - 1\right)$, where V_p is the volume of a particle. By writing the optical field as $E(x, y, z) = \varphi(x, y, z) e^{\mathrm{i}k_0 n_b z}$, the modified nonlinear Schrödinger equation describing the beam propagation can be written as [20,27,37,40]:

$$i\frac{\partial \varphi}{\partial z} + \frac{1}{2k_0 n_b} \nabla_\perp^2 \varphi + k_0 V_p \left(n_p - n_b\right) \rho_I \varphi + i\frac{\sigma}{2} \rho_I \varphi = 0 \tag{4}$$

where $k_0 = 2\pi/\lambda_0$ is the wavevector, φ is the field envelope, and $\left(\frac{\sigma \rho_I}{2}\right)$ is defined as the loss coefficient. The latter is seen to be proportional to the particle density, which implies that the scattering loss $\left(\sigma \rho_0 e^{\frac{\alpha I}{4k_B\mathrm{T}}}/2\right)$ also depends on the beam intensity.

Although the above nonlinear Schrödinger equation is just a very simplified model, it has been shown theoretically to support soliton dynamics and self-induced transparency in nonlinear nanosuspensions [40]. However, two other major factors also need to be considered when dealing with soft-matter environments. Firstly, in our recent studies in biological suspensions, we found it necessary to consider the forward scattering force in the theoretical analysis, in order to properly explain the dynamics and specific features observed experimentally. In this case, the optical forces acting on a suspended particle need to be defined as $\vec{F}_{ext}\ (\mathrm{I} = |\varphi|^2)\ = \alpha \quad I + \beta I\hat{z}$, which includes both the gradient and the forward scattering forces along the propagation direction z (the latter depends on a coefficient β) [21]. The gradient force acts by pulling the particles towards the central region of the laser beam, while the scattering force directs the particles along the beam path in PP suspensions, leading to a nonlocal dynamical self-guidance of light in the suspensions [21,22]. The other factor to be considered is related to the thermal effects due to light absorption by particles or cells [36]. When the absorption is significant, thermal effects as well as absorption forces become important, which could lead to thermal lensing or self-defocusing effects as well as absorption force-induced self-focusing effects. To include temperature dependent contributions, a thermal gradient term needs to be added into the above equation [20], which accounts for a refractive index gradient dn/dT due to a nonuniform heating of the medium. Suspended particles can move along such temperature gradient by thermophoresis, also known as the Soret effect [50,51]. Many nanoparticles and organic macromolecules move away towards colder regions, so that the refractive index typically decreases with increasing beam intensity. In this case, most of the thermal solutions or suspensions exhibit a self-defocusing nonlinearity and can therefore only support the formation of optical dark solitons [52]. However, exceptions have been observed where a self-focusing nonlinearity led to the formation of 'hot-particle' solitons in nanoparticle suspensions by virtue of thermophoresis [50]. In addition, recent experiments with metallic nanoparticle suspensions and solutions containing hemoglobin (Hb) or food-coloring dye molecules suggest that the absorption force could play a dominant role in the optical nonlinearity, especially when the scattering force is negligible for nano-sized particles [22,53,54]. Although the current optical force theory is yet to be optimized for better understanding nonlinear phenomena in nano- and bio-soft matter, it has already boosted the exploration of the nonlinear optical responses of various colloidal suspensions. Over the time, numerous studies were performed to understand the nonlinear optical properties of nanosuspensions and their application to generate optical spatial solitons [55–61]. These demonstrate various optical strategies which enables the formation of waveguides with different lengths and deeper light propagation. Furthermore, this research area has drawn considerable attention towards the development of waveguides in biocompatible materials such as silk, lipid bilayer, as well as DNA for biomedical applications [62]. However, long-distance propagation of light in active/living biological samples is particularly desirable due to the increasing demand for early diagnostic and *in vivo* therapies.

Nonlinear self-guiding of light in living biological suspensions

Understanding light interaction with living cells is of crucial importance in the development of bio-imaging, bio-fuels, bio-lasers and bio-optical microchips. It is also of fundamental interest in gaining insight into biophotonics, optofluidics, and soft-matter physics. Although nonlinear self-action of light was established in colloidal suspensions of stiff nanoparticles, as discussed above, research on optical forces and optical nonlinearity from biological objects is still at its infant stage. In fact, it is commonly thought that light cannot penetrate deeply into biological environments due to their strong scattering loss and weak optical nonlinearities. Interestingly, we recently demonstrated the presence of a significant nonlinear response in microorganisms involving both robust self-trapping and enhanced transmission of a light beam through biological suspensions of living cells, including marine bacteria [21] and red blood cells [22]. By deliberately altering the host environments of the cells, we demonstrated a dramatic change of the nonlinear dynamics associated with light propagation. Remarkably, the viability of the cells remained intact over the course of the experiments. To explain the observed behavior and the formation of 'biological' optical waveguides, we utilized the modified nonlinear Schrödinger equation discussed above (Eq. 4) and simulated a forward-scattering theoretical model. This work showed that a nonlocal nonlinearity, mediated by the combined optical forces acting on the cells, is indeed instrumental towards creating waveguides of light in biosuspensions. Here we review some of the key results.

In the experiments with marine bacterial suspensions [21], a laser beam (532 nm) was sent through biological suspensions of cyanobacteria (*Synechococcus sp*. cells) which present low absorption at this wavelength. We placed various concentrations of the bacteria in a 4-cm-long cuvette filled with seawater, and for each sample, a green laser beam with an initial width of about 50 μm at the sample input was sent through. With no bacteria present, the beam broadened to a width superior to 600 μm, due to linear diffraction and weak scattering in the buffer (seawater) solution. Once bacteria were added, two different situations were observed depending on the laser power. At low power (0.1 W), the addition of bacteria dramatically increased the random scattering experienced by the beam, the width of which more than doubled at the cuvette output to reach 1.25 mm. However, at high power (3 W), the beam experienced nonlinear self-trapping, overcoming the previous scattering effect to form a needle of light with an output width below 100 μm. Typical experimental results are summarized in Figure 2. The refractive index of cyanobacteria ($n_p = 1.38$) is slightly higher than that of seawater ($n_b = 1.33$), and thus the cells behave as dielectric particles with a PP as discussed earlier, and are pushed towards the center of the light beam due to the optical gradient force. It was noticed that

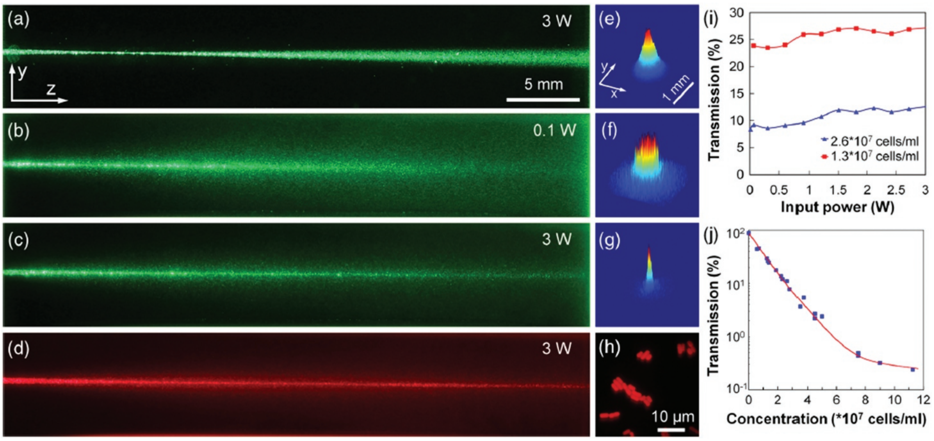

Figure 2. Nonlinear self-trapping of light through cyanobacteria in seawater. (a) Side view of normal diffraction of an intense laser beam in seawater, showing no self-action of the beam when no bacteria are present. (b), (c) When *Synechococcus* cells are suspended in seawater, the beam undergoes linear diffraction or scattering at low power (b), yet it experiences nonlinear self-trapping at high power (c). (d) Side view of the same beam in (c) imaged using autofluorescence of the cells (in red) when the green light is partially blocked, thus indicating survival of the trapped cells under laser illumination. (e)–(g) Corresponding 3D plots of the beam's normalized intensity profiles after 4 cm of propagation, captured by the CCD camera. (h) Image of the *Synechococcus* cells taken with an epifluorescence microscope using a 100x objective when excited by green light. (i) Transmission percentage measured as a function of input power for two different cell concentrations. (j) Semilogarithmic plot of transmission percentage as a function of cell concentration at a fixed input power of 3 W. Reproduced with permission from refernce [21].

the normalized transmission slightly increased with the laser power (due to self-guiding under nonlinear propagation) but decreases dramatically at high cell concentrations (due to enhanced scattering losses from an increased number of cells along the beam path). Additional systematic experiments showed a dramatic change of propagation dynamics from self-trapping to enhanced scattering when the background medium of the cyanobacteria was changed from seawater to a water-glycerol mixture featuring higher viscosity. Such characteristic of the background media reduces cells mobility and prevents them from being attracted or pushed (far) away from the beam's focus, thus hindering the formation of an effective waveguide [21].

As mentioned earlier, to explain the observed beam dynamics, our theoretical model included not only the optical gradient force but also a force due to the radiation pressure of light. The scattering force, which pushes objects in the propagation direction of the beam, plays a weak role for nanoparticles but becomes relatively important for bacteria given that cells are micron-sized objects and scatter light strongly. In numerical simulations, depicted in Figure 3, we indeed showed that the combination of

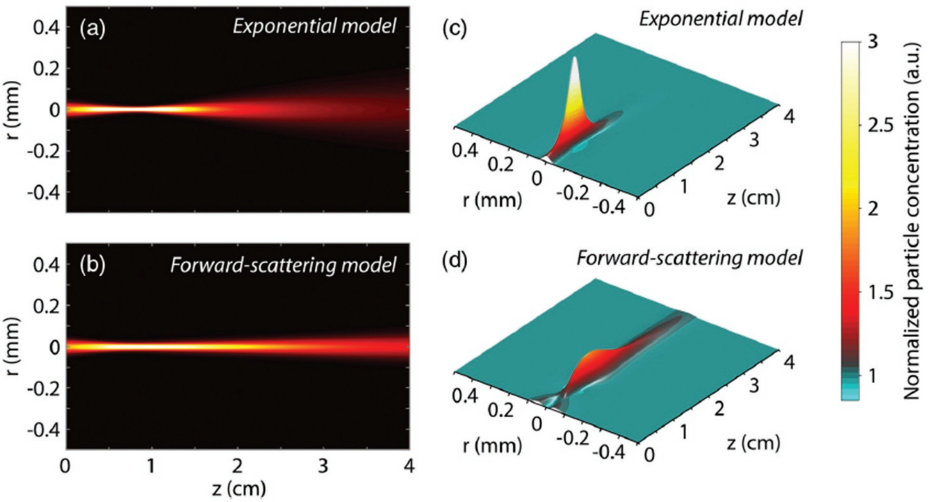

Figure 3. Comparison of two different models to describe nonlinear beam dynamics in biological suspensions. (a), (b) Side view of beam propagation (normalized linear scale) obtained numerically using (a) an optical gradient force only (exponential model) and (b) an optical gradient along with a forward-scattering force (forward-scattering model). (c), (d) Corresponding theoretical distributions of the normalized concentrations of bacteria-like particles induced by the respective types of light-particle interactions. Reproduced with permission from reference [21].

forward push and inward pull caused the bacteria to concentrate into a thin biological ‘fiber’ which prevented the beam from spreading out. As such, deep penetration of light without beam collapse was realized. Previously, such bio-waveguides have been observed with *E. coli* in the linear optical propagation regime using an abruptly tapered optical fiber seeded by a laser beam at 980 nm. However, the generated waveguide lasted only for few tens of microns (~55 μm) [63]. For those linear approaches, multiple *E. coli* cells had to be trapped individually and connected as a long chain, before being probed by a light beam. The propagating signal was detected on the other side of the chain using another abruptly tapered optical fiber [63].

In this framework, we performed comparable experiments with human RBC suspensions, and observed the qualitatively similar nonlinear propagation of a 532 nm laser beam experiencing self-trapping [22]. In this study, however, RBCs were suspended in different osmotic conditions allowing to manipulate the shape and associated refractive indices of the cells. As discussed in the previous section on theoretical analysis, refractive index is an important deciding factor for the nonlinear behavior of matter. To pursue more quantitative analysis, we also studied RBCs for both hypotonic and hypertonic buffer conditions, using a final concentration of ~10^5–10^6 cells/mL. Under physiological conditions (isotonic buffer) RBCs have a biconcave-disc shape and spatially uniform refractive index

(n ~ 1.42). However, in hypotonic and hypertonic conditions the RBCs acquire swollen spherical (n ~ 1.38) and irregular spiky (n ~ 1.44) shapes, respectively [64]. The optical self-trapping experiments were carried out with freshly washed RBC suspensions (to avoid any residual free Hb) in a 3-cm-long cuvette. Interestingly, it was observed that the RBCs suspended in the three osmotic conditions could exhibit different optical nonlinear responses and intrinsic random scattering properties, and that the optical beam (at the same wavelength) therefore required different powers to achieve optimal self-focusing (Figure 4). Self-trapping of light was observed when the beam power reached ~350 mW, 300 mW and 200 mW for hypotonic, isotonic and hypertonic suspensions, respectively. Evidently, the observed phenomenon arises from nonlinear self-focusing in each of the osmotic conditions, as the normalized transmission (output/input power) displayed a nonlinear trend with respect to the input power in all three RBC suspensions – in stark contrast with the background media without cells (Figure 5). Furthermore, these results show a variation in the initial transmission for the three different osmotic conditions considered here. This effect can be attributed to the difference in absorption and shape dependent scattering of the cells. Due to such shape modification, the refractive index, as well as the magnitude of the associated gradient force, follows the trend as hypertonic > isotonic >

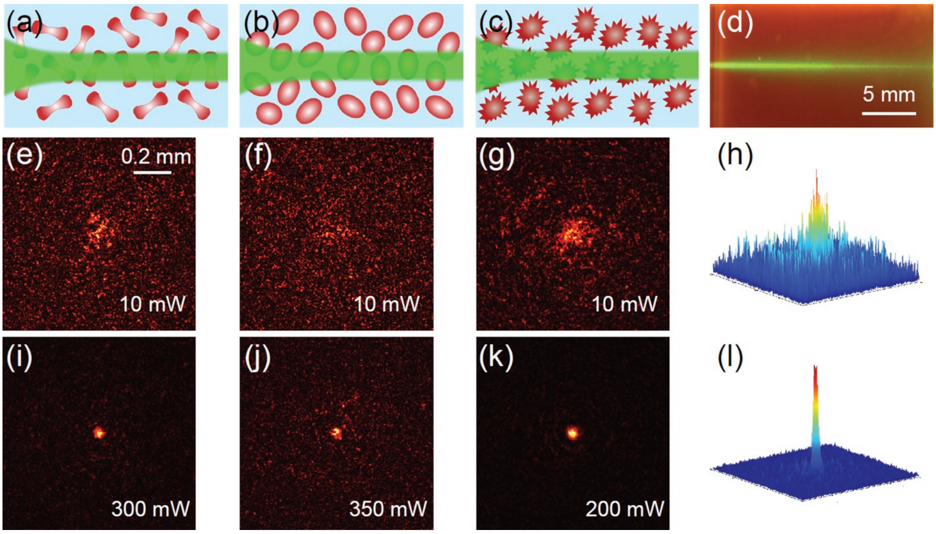

Figure 4. Self-trapping of light through *human* RBC suspensions under different osmotic conditions. (a–c) Illustrations of the beam dynamics in (a) isotonic, (b) hypotonic, and (c) hypertonic suspensions. (d) Side-view image of a self-trapped beam. (e–g) Observed output intensity patterns at a low power, which show the linear diffraction and strong scattering of the laser beam. (i–k) Corresponding patterns at high power, which demonstrate the beam localization due to nonlinear self-trapping. (h, l) 3D plots of the intensity patterns corresponding to (g, k), respectively. Reproduced with permission from reference [22].

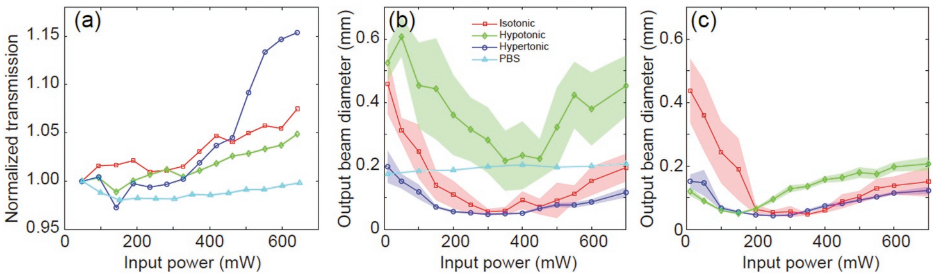

Figure 5. Normalized transmission and output beam size as a function of input power. (a) Measurement of the normalized transmission. (b) Output beam size change in fresh RBC suspensions of different buffer solutions. The cyan (triangle) curve depicts the results obtained from the PBS background solution without RBCs as a reference, which indicates no appreciable self-action of the beam in the buffer solution itself. The blue (circle), red (square), and green (diamond) curves show the data obtained from RBC suspensions in hypertonic, isotonic, and hypotonic solutions, respectively, where the error ranges in (b) are indicated by the shaded regions. (c) Corresponding results from the same blood sample but after the RBCs have been stored in a refrigerator for two weeks, showing that nonlinear focusing is dramatically enhanced in the hypotonic solutions. Reproduced with permission from reference [22].

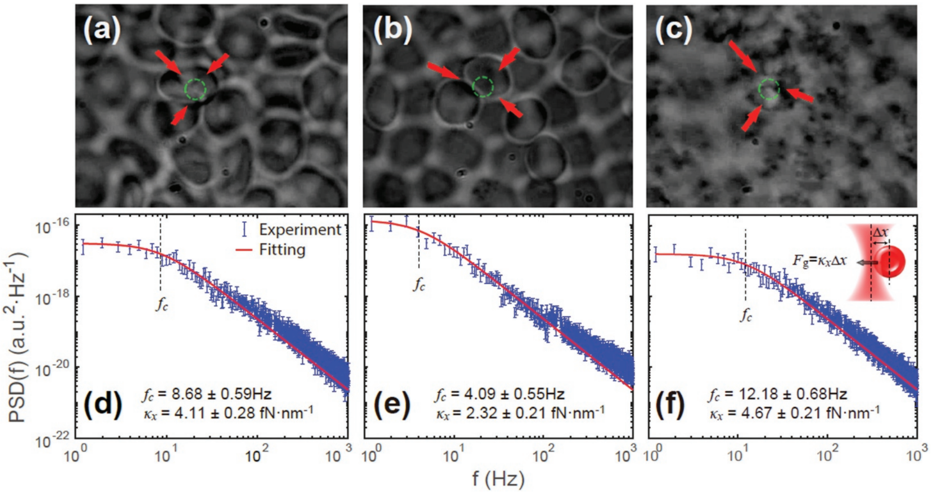

Figure 6. Optical gradient forces on *human* RBCs under different osmotic conditions examined by optical tweezers. (a–c) Snapshots of the RBC movement towards a 960-nm laser beam (position marked by a dashed green circle) in isotonic, hypotonic, and hypertonic solutions, respectively, as observed under a microscope. The red arrows illustrate the directional cell movement. (d–f) Power spectrum analyses showing the trap stiffness κ_x of a single RBC from the three suspensions in accordance with (a–c), where the vertical dashed lines mark the corner frequency f_c. The inset in (f) illustrates a single RBC that moves into the trap under the action of the gradient force. Reproduced with permission from reference [22].

hypotonic (Figure 6). In our analysis, the trapping forces were estimated from a Langevin equation [13,65] by assuming the RBCs as disk-shaped (prolate ellipsoid) objects in isotonic conditions, and spherical objects in the hypotonic and hypertonic conditions, having average diameters of 8.0 μm, 9.6 μm and 6.4 μm, respectively. Although this model is quite approximative, the trend followed by the optical forces (*i.e.* hypertonic > isotonic > hypotonic) was confirmed from direct measurements by optical tweezers experiments. Interestingly, we also found that in aged blood samples, which feature high free Hb content, the nonlinear beam dynamics is dramatically different (Figure 5(c)): at a higher concentration of Hb, a stronger self-focusing nonlinearity was observed first, and then thermal defocusing took over leading to shock-wave like patterns [22,66]. The underlying mechanism for optical nonlinearity-induced wave dynamics in such biological media certainly merits further studies.

In subsequent experiments, nonlinear self-trapping of a laser beam in suspensions of RBCs from an animal model was also observed for illuminations of a range of different wavelengths (Figure 7) [67]. For these results, sheep RBCs were used, which are slightly smaller than the human RBCs, and thus required relatively higher beam intensity to reach the desired nonlinear

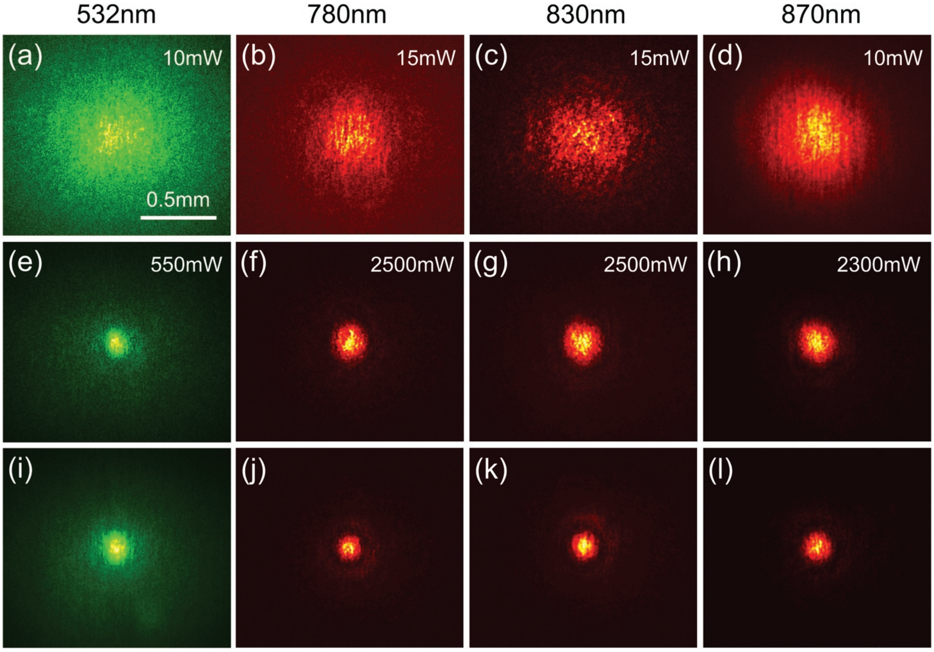

Figure 7. Self-trapping and guiding of light through colloidal suspensions of *sheep* RBCs. (a–d): Observed output intensity patterns of a light beam at low powers, corresponding to linear diffraction of the laser beam at different wavelengths. (e-h): Corresponding output intensity patterns at high powers when other conditions are unchanged, which illustrates the self-trapping of light at these wavelengths due to the nonlinear response of the RBC suspensions. (i-l) Guiding a low power probe beam at different wavelengths (j-l) by a green soliton-like beam, where (i) shows that the self-trapped 550 mW green beam remains intact in the presence of the probe beam at a different wavelength, while (i-l) pictures the guided output of a low power (100 mW) probe beam at different wavelengths.

response compared at the same green (532 nm) wavelength. As shown in Figure 7(a–d), a laser beam of a low power displays linear diffraction after propagating through the RBC suspensions at both visible and near-infrared (NIR) wavelengths. The formation of a self-trapped channel (soliton-like propagation) with an NIR laser beam requires a significantly higher power than that created with a green laser beam due to weaker nonlinear self-focusing effects at NIR wavelengths (Figure 7e–h)). As such, a pump-probe-like experiment is realized to examine the induced waveguide formed in the biological suspensions (Figure 7(i–l)): a 'master' beam at the green wavelengths forms a self-induced waveguide channel at 550 mW which can be used to guide a 'slave' beam at different NIR wavelengths, although the NIR laser beam itself does not show appreciable nonlinear self-focusing at low power levels (about 100 mW).

Apart from the nonlinearity-induced biological waveguides, we mention that, more recently, Li *et al*. constructed a living biosensor and micromotor using an *in vivo* RBC waveguide for pH sensing and particle transport [68]. They demonstrated that the light propagation mode of the RBC waveguide is related to the RBC morphology – which depends on the pH value of the blood, and therefore it could be used for pH sensing. In these experiments, two tapered fiber probes were inserted into a microfluidic channel from opposite directions, and a 980 nm light beam was used to trap the cells while the length of the formed RBC waveguide could be tuned by changing the trapping power. By varying the laser power from 1 to 25 mW, the RBC waveguide length was extended from 7 to 64 µm. This RBC waveguide also facilitated the propagation of a 532 nm laser beam (~100 µW) with a significant enhancement of transmission efficiency. Furthermore, an optical torque was applied to the RBC waveguide which allowed controllable delivery of microparticles to a target site [68]. Overall, these studies on linear and nonlinear light guides through scattering bio-soft matter show promising results that may lead to new development of photonic tools for noninvasive diagnosis [69,70].

Biomedical application perspectives

The growing demand of photomedicine calls for biocompatible optical devices as well as noninvasive diagnostic and therapeutic tools. To this end, exploring the nonlinear response of living cells can enable future developments in fabrication of tunable optical devices for applications such as *in vivo* sensing, drug delivery and phototherapy. As described above, for both bacterial and RBC suspensions under different conditions, nonlinear self-trapping and deep penetration of light was observed without noticeable photodamaging of the living cells [21,22,63,68]. The shape- and refractive-index-dependent variations of nonlinear optical responses of

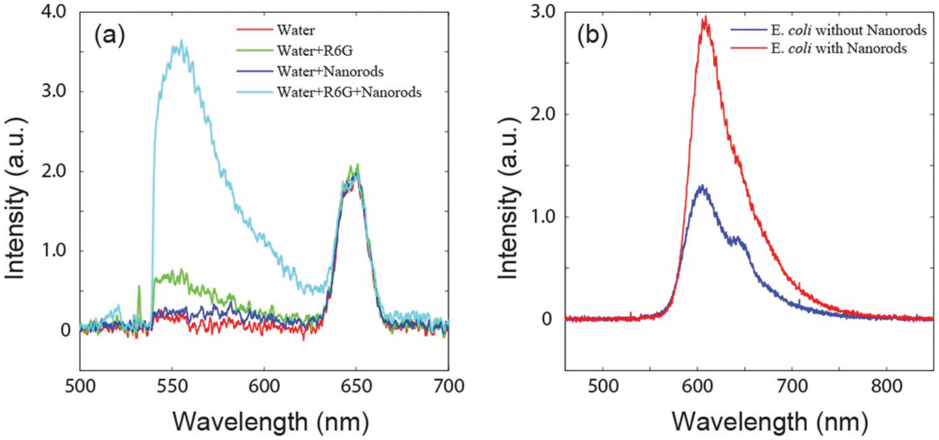

Figure 8. (a) Measured emission spectra of four different samples for direct comparisons. The emission peak at 560 nm corresponds to the R6G fluorescence, which is enhanced by adding gold nanorods (with average length 100 nm and diameter 50 nm) in the suspension to achieve nonlinear self-trapping of light, and the one at around 650 nm corresponds to the Raman signal of water. (b) Measured fluorescence enhancement of E. *coli* bacterial suspensions due to nonlinear self-guiding of light after adding gold nanorods.

living cells (especially in RBC suspensions) hint to the possibility of using these findings in predicting and diagnosing blood related disorders like sepsis and malaria. These results also open the way towards the controllable transportation of particles which can be important in drug delivery and photodynamic therapy [41,62,69,71]. Additionally, the distinct nonlinear behavior observed due to bursts of RBCs may prove to be useful for the detection of free Hb concentrations using nonlinear optics, which could in turn help in screening blood bags before transfusion [22,72,73].

Indeed, the ability to focus light through strongly scattering media such as bacterial suspensions or blood may thus prove a significant step towards the creation of enhanced non-invasive *in vivo* imaging and sensing technologies in both visible and NIR regimes. As an example, we present in Figure 8 our recent preliminary experimental results showing fluorescence enhancement in colloidal suspensions by adding Rhodamine 6G (R6G) fluorescent dye molecules. As a proof of principle, we mixed a very low concentration (0.2 nM) of R6G with a colloidal suspension of gold nanorods in a 3 cm-long sample, and observed more than 15-fold enhancement in fluorescent signal due to the nonlinear self-action of the probe beam (λ = 532 nm). As seen in Figure 8(a), the emission peak at 560 nm corresponding to the R6G fluorescence is enhanced by adding gold nanorods in the suspension to achieve nonlinear self-trapping of light. Such enhancement is also obtained in a biological suspension of low-concentration E. *coli* cells in transmittance-type volume detection settings due to the formation of plasmonic resonant solitons (Figure 8(b)). The fluorescence is possibly increased by two mechanisms: the first comes from plasmonic resonance enhancement in randomly distributed gold nanorods located inside the suspensions; the second comes from nonlinear guiding of light from plasmonic resonant solitons. Interestingly, self-induced soliton-like waveguides formed in a colloidal suspension could also help in guiding the fluorescent signal out of the suspension thus increasing the signal to noise ratio for improved detection. Such nonlinear enhancement may therefore be employed for detecting faint signals in biological suspensions that would be otherwise hardly detectable. This certainly merits further research, as important directions for real-time chip-based optical detection of small volumes and to enable multiplexing by incorporating various optical sensing modalities (fluorescence and Raman spectroscopy) to provide better sensitivity and distinct chemical specificity.

Summary and outlook

Although theoretical and experimental studies in nonlinear optics with soft condensed matter started way back in the late 1960s, a renewed interdisciplinary interest emerged in many branches of sciences, including material sciences, optofluidics, optohydrodynamics, biophotonics and life sciences. The nonlinear light-matter interaction has been noted for colloidal suspensions to organize particles into equilibrium positions due optical forces and beam pressure, which helps in optically controlled self-assembly. With new developments in nonlinear synthetic materials including smart polymers, advanced liquid crystals, as well as metamaterials, the subject of nonlinear soft matter is positioned itself at one of the frontiers of optics and biophotonics. More recently, it has been demonstrated that nonlinear responses are not just limited to stiff particles or materials but can also be extended to living cells and bio-soft matter. In this review, we only provided a brief summary of our recent work on nonlinear biological suspensions, which by no means is complete. We discussed the optical forces contributing to the nonlinear response and associated experimental observations. To explain the formation of ‘biological’ optical waveguides, nonlinear Schrödinger equation-based simulations illustrated that a nonlocal nonlinearity mediated by the combined optical (gradient and forward scattering) forces plays a major role for guiding the living cells in bio-suspensions. In this growing paradigm of nonlinear optics, applications towards beam guidance, particle transport and the enhancement of fluorescence detection are also briefly described. These approaches would expose exciting new avenues towards the development of plasmonic devices, optical switches, biocompatible optical components and nano-sensors. The investigations on bio-soft matter could also offer new perspectives to develop diagnostic tools and associated laser treatment therapies. In particular, the studies on RBCs could provide a diagnostic tool to identify modifications or defects in the morphological features of cells, a characteristic commonly observed in several diseases such as sickle cell anemia or malaria. Significant challenges need to be overcome for the development of practical biomedical devices such as laser power optimization. Nevertheless, we expect that these findings may stimulate a broad interdisciplinary interest in future research, and may herald new techniques for overcoming scattering loss in the soft-matter optofluidic and deep tissue imaging, as well as for various biomedical applications.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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