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Optoelectrical microfluidics as a promising tool in biology

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Noncontact robotic particle grippers with trapping, manipulation, and release functions are highly desired in cell biology and microfluidics. Optoelectric techniques combine optical and electrokinetic effects to create thousands of such individually addressable traps. By projecting reconfigurable light patterns, these techniques can concentrate molecules, as well as manipulate, sort, and electroporate cells in a programmable manner. We describe the underlying physical mechanisms and discuss applications in biology and future prospects of these devices.

Optoelectrical techniques: fusion of optics, electrokinetics, and microfluidics

Microfluidics is ushering a new era in drug discovery [1], biological analysis, and point-of-care diagnostics [2,3]. By performing desired analysis in picoliter to nanoliter volumes at high throughput, microfluidic devices outperform some of the conventional benchtop technologies. However, these advantages come with the added complexity of particle manipulation in a microscale environment. Trapping, sorting, and transport of biological entities such as cells, beads, nucleic acids, and proteins are some of the fundamental operational requirements for realization of microfluidic platforms. As a result, since the inception of microfluidics, various techniques have been proposed for controlled manipulation of particles. Optical tweezers (see Glossary [4] and alternating current (AC) electrokinetics [5,6] are some of the key particle manipulation methods; however, these techniques either lack resolution or high throughput [7]. Opto-electrofluidics combines optical and electrokinetic effects to yield high resolution, high throughput, and programmable manipulation. By controlling the movement of particles via optical patterns, optoelectrical techniques can simultaneously trap and sort thousands of particles. The optical patterns can be designed and reconfigured using a computer program, allowing automated individual addressing of particles.

Fundamentally, optoelectrical techniques inherit the strengths of both optical tweezers and electrokinetic methods. Optical tweezers utilize focused laser beams for trapping microparticles. They can provide on-demand, high-resolution manipulation and sorting of particles [8]. As a result, optical tweezers have been widely used in single-cell studies [9] and mechanical characterization of single molecules [10]. However, optical tweezers require a high laser intensity and have low throughput. The throughput issue can be partially addressed by multiplexing a single laser beam in multiple traps with a spatial light modulator, but each optical trap requires laser power of the order of 1 mW, resulting in the need for a very large amount of power for the input beam [11]. Recently, researchers have demonstrated parallel trapping of micro- and nanoparticles with low optical intensities using plasmonics-based optical trapping systems [12,13]. These techniques require plasmonic nanostructures, such as an array of gold or silver nanodisks on the substrate surface, which are expensive to fabricate. Moreover, in the case of plasmonic tweezers, the trapping force can only be experienced within a few nanometers from the nanostructure. Hence, distant particles cannot be efficiently trapped.

AC electrokinetics utilizes effects induced by an electrical field achieved via microelectrodes for particle manipulation. In contrast to conventional optical tweezers, electrokinetic techniques have high throughput, but suffer from a requirement of labor-intensive microfabrication.

Glossary

AC electrokinetics: effects induced by an alternating-current (AC) electric field that can cause migration of particles or fluid flow in a microfluidic environment.

Biological microbeam: micrometer-sized beam used to irradiate cells with precise doses of radiation.

Digital micromirror display (DMD): array of micromirrors that allows projection of computer-generated patterns on a substrate through a microscope objective lens. These optical patterns can be dynamically configured for manipulation of particles.

Electrohydrodynamic (EHD) force: particle–particle attraction and particle–electrode repulsion due to local flow around particles.

Electroporation: permeabilization of cellular membranes under the action of an external electric field. It is typically used to inject foreign molecules into cells.

Electrowetting: change in contact angle of a liquid droplet on a solid substrate in the presence of an electric field.

Ionic double layer: presence of excess ions at an electrolyte-substrate interface. It consists of a fixed layer of ions, adsorbed on the surface, surrounded by a free (diffuse) layer of ions.

Optical tweezers: use of focused laser beams for trapping of microparticles. Optical tweezers require the laser to be focused using an objective lens with a high numerical aperture (NA). The trapped particles can be precisely manipulated by either optically steering the laser beam or translating the microscope stage.

Optoelectrical techniques: methods in which electrokinetic effects are optically actuated and thus allow particle manipulation with illumination.

Photoconductors: materials that become electrically conductive by absorbing electromagnetic radiation.

Plasmonic nanostructures: subwavelength metal nanostructures such as silver or gold nanodisks. These features can concentrate an incident beam into highly localized optical fields in which nano- and microparticles can be trapped.
Moreover, particle collection is spatially restricted to regions predefined by the microelectrode geometry that remain invariant once the device is fabricated. Optoelectronic techniques leverage the high resolution and flexibility of optical tweezers with the selectivity and high throughput of electrophoretic techniques. In optoelectronic techniques, optical control of electrophoretic forces can be accomplished in two ways, as exemplified by two key optoelectric platforms. Optoelectronic tweezers (OET) modulate the conductivity of the substrate using optical patterns [7], whereas rapid electrophoretic patterning (REP) changes the electrical properties of the medium [14–16]. This review provides a brief introduction to the physical mechanisms of OET and REP, and discusses their applications in biology.

**Optoelectronic Tweezers**

In OET, a spatially varying electric field is created by optical illumination on a photoconductor substrate. This nonuniform electric field results in dielectrophoresis (DEP) (Box 1), AC electroosmosis (ACEO) (Box 2), and electrothermal flow (Box 3), which help in trapping particles and macromolecules on the substrate surface [17–19]. In conventional AC electrokinetic devices, DEP is generally facilitated by microfabricated electrode geometries. Microwell devices with embedded DEP electrodes have been used for cell trapping [20,21], sorting [22–24], and electrophoresis [25]. Despite numerous applications, electrode-based DEP lacks flexibility of manipulation because of the fixed electrode patterns. This problem can be partially addressed by integrating a large number of individually addressable DEP electrodes on a chip [26–28], but the high cost of fabrication makes this less attractive for disposable applications. In addition, on-chip control circuitry puts an upper limit on the trap density. OET overcomes these limitations by creating reconfigurable virtual electrodes on a photoconductor surface.

An OET setup consists of a transparent glass slide coated with indium tin oxide (ITO), a photoconductor substrate, a spacer, a digital micromirror display (DMD), and a microscope (Figure 1A). The photoconductor substrate is made of layers of ITO, doped n+ hydrogenated amorphous silicon (a-Si:H), undoped a-Si:H, and silicon nitride on the glass surface [7]. The DMD consists of an array of micromirrors that allow projection of computer-generated patterns on the photoconductor substrate. Both the ITO electrode and the photoconductor are separated by a spacer of suitable thickness (~100 μm). A colloidal solution is provided between the two substrates, and an AC electric field is applied through a function generator. Depending on the intensity of the illumination, the a-Si:H layer exhibits variable conductivity. In the ‘dark state’, a high voltage drop occurs across the a-Si:H layer, resulting in a very low electric field in the liquid medium. By contrast, when the photoconductor surface is illuminated with sufficient light intensity, the conductivity of the illuminated region increases by few orders of magnitude because of light-induced generation of charge carriers. In this ‘bright state’, most of the voltage drop occurs through the liquid layer, giving rise to a spatially varying electric field between the ITO surface and the virtual electrode.

**Box 1. Dielectrophoresis**

Under the action of an electric field, a colloidal particle undergoes polarization, resulting in a net induced dipole moment in the particle. If the electric field is nonuniform, forces on the two poles of the induced dipole become unequal and the particle experiences a net force, known as the DEP force. For a homogeneous dielectric particle, the time-averaged DEP force is described by

\[
F_{\text{DEP}} = \frac{1}{2} \text{Re}(\vec{\rho} \cdot \nabla) E^* 
\]

where \(\vec{\rho}\) is the effective dipole moment of the particle and \(E^*\) is the complex conjugate of the harmonic electric field. The symbols \(\text{Re}\) and \(\nabla\) denote the real part of the expression and the gradient operator, respectively. For a spherical particle, Equation 1 reduces to

\[
F_{\text{DEP}} = 2\pi \varepsilon_0 \varepsilon_r (f_{\text{per}}) \nabla \cdot (\varepsilon_{\text{ref}} E_{\text{ref}})^2
\]

where \(\varepsilon_0\) is the electrical permittivity of the medium, \(\varepsilon_r\) is the particle radius, and \(\varepsilon_{\text{ref}}\) is the root mean square of the electric field strength. \(\text{Re}(\vec{\rho})\) is the real component of the Clausius-Mossotti (C-M) factor, which can be evaluated as

\[
f_{\text{per}} = \frac{f_p - f_m}{f_p + 2f_m}
\]

where \(f_p\) and \(f_m\) are the complex permittivity of the particle and the medium, respectively.

\[
f_p = \frac{\varepsilon_p - \varepsilon_0}{\varepsilon_p + 2\varepsilon_0}, f_m = \frac{\varepsilon_m - \varepsilon_0}{\varepsilon_m + 2\varepsilon_0}
\]

where \(\varepsilon_0\) is the conductivity of the medium and \(\varepsilon_p\) and \(\varepsilon_m\) are the permittivity and conductivity of the particle, respectively. \(\omega\) is the circular frequency of the electric field. The modulus of the C-M factor depends on the frequency of the electric field. At low AC frequencies, the real component of the C-M factor is given by \(\varepsilon_{\text{per}} = \varepsilon_p\), and at high AC frequencies it is given by \(\varepsilon_{\text{per}} = \varepsilon_p - 2\varepsilon_m\). If the C-M factor is positive, particles are pulled toward the region of the high electric field strength by a positive DEP force, and vice versa. Because the C-M factor is frequency-dependent, the DEP force also shows frequency dispersion. The above analysis of the C-M factor is valid for a homogeneous particle, such as a latex sphere. However, for a nonhomogeneous particle (e.g., a biological cell), the complex permittivity of the particle is estimated using a multishell model. For more discussion on multishell models, readers are referred to the work of Morgan and Green [6].

Using optical patterns, virtual electrodes can be dynamically created in a reconfigurable manner. Owing to high photoconductance gain, very low optical intensity (10^4 W/m^2) from an incoherent light source is sufficient for activation of a virtual electrode. A low-power laser beam coupled to a DMD [7], pixels of a liquid crystal display [29,30], or a computer projector [31,32] is sufficient for the creation of thousands of OET traps.

**Alternative Photocoordinators**

Apart from a-Si:H, researchers have used bulk-heterojunction polymers (BHJs) [33], titanium oxide phthalocyanine (TiOCP) [34,35], and oxide crystals [36–39] as photocoordinators in OET devices. Wang et al. proposed use of a BHJ polymer, a mixture of regioregular poly(3-hexylthiophene) and [6,6]-phenyl C61-butyric acid methyl ester (P3HT:PCBM), in OET devices [33]. P3HT:PCBM-based devices can achieve similar trapping force to a-Si:H-based devices, but considerable chemical handling and thermal deposition are required for their fabrication. Using TiOCP, a photoconductive surface can be prepared in a single spin-coating step, but the stability over an extended period of time must still be investigated [34]. Oxide crystals, such as Fe-doped lithium niobate and bismuth silicon oxide, display
Box 2. AC electroosmosis

An electrode surface generally has a net charge. When the electrode is placed in contact with an ionic solution, counterions from the bulk of the electrolyte solution are attracted to the electrode surface. This leads to an electric double layer between the surface and the electrolyte. The diffuse region of the double layer consists of excess charge density of counterions. Under the action of a tangential electric field, these excess counterions experience a net electrostatic force. As a result, the ions move, generating a flow along with their movement. The time-averaged ACEO flow velocity is given by [6]

\[ u_a = \frac{1}{2} Re \frac{\alpha q_{oa} E}{\eta} \]

where \( \alpha \) is the charge density in the double layer, \( \lambda_d \) is the Debye length, \( E^* \) is the complex conjugate of the tangential electric field, and \( \eta \) is the viscosity of the medium. Depending on the conductivity of the electrolyte, ACEO flow velocity can be negligibly small at very low and high electric field frequencies, and reaches a peak at an intermediate frequency. In an OET chip, the presence of a nonuniform electric field results in an ACEO vortex below 1 kHz (Figure 1).

![Figure 1](image)

Figure 1. Illustration of ACEO in an OET device. (A) A tangential electric field present in the OET generates an electroosmotic-flow-driven vortex pattern around the illumination site. Adapted with permission from [16]. (B) Vortex fluid flow map. Close to the electrode surface, a stagnation zone (shown in the inset) exists in the eye of the toroidal vortex, where particles and macromolecules can be trapped. Reproduced, with permission, from [16].

Rapid electrokinetic patterning

REP is a noninvasive technique involving simultaneous application of a uniform AC electric field and an optical laser for manipulation of a diverse set of colloids [14,40,41].

In the REP chip, two ITO-coated transparent glass plates are separated by a suitable spacer (~100 μm) to create a microfluidic channel (Figure 1B). The laser spot creates thermal gradients that couple with the applied electric field to produce a toroidal electrothermal vortex (Box 3). The electrothermal vortex exerts a hydrodynamic drag force on the particles and transports them close to the electrode surface. Particles are then trapped by electro-particle interactions at the illuminated sites. The accumulated particles can be rapidly translated either by controlling the laser location with a spatial light modulator or by moving the translation stage. When the laser is turned off, the electrothermal flow stops and the particles are immediately scattered on the electrode surface [42].

Particle trapping in REP is governed by a delicate balance of several electrokinetic and electrohydrodynamic (EHD) forces (Figure 2) [43,44]. In an REP chip, particles experience four forces: dipole–dipole repulsion (F_{particle–particle}), particle–electrode attraction (F_{particle–electrode}), electrothermal-flow-induced drag force (F_{EHD–fluid}), and particle–particle attraction (F_{EHD–EHD}) because of EHD flow around the polarized particles induced by interaction between the applied electric field and the ionic double layer of particles and an electrode [45,46]. The EHD force and the electrothermal-flow-induced drag force depend on the AC frequency. Hence, at a certain electrical frequency, the forces balance each other and particles aggregate. Depending on the dielectric properties, shape,
and size of the particles, there exists a critical minimum frequency \( f_{c} \) above which particles cannot be held in a REP trap \([40,41,43,47]\). The particle cluster becomes unstable as the applied AC frequency approaches the critical frequency. At higher frequencies, particles are swept away from the cluster by a strong electrothermal flow. Hence, particles can be sorted on the basis of their material properties and size \([40,41,47]\).

### Applications in biology

#### Cell trapping

The ability to handle single biological cells is important in the study of in vitro fertilization, cell–cell interactions, cell sorting, cell transfection, and tissue engineering. OET can achieve parallel manipulation of many thousands of cells with single-cell resolution (Figure S1 in the supplementary material online). Hence, OET has been used for trapping and manipulation of HeLa cells \([48–53]\), human B cells \([7]\), murine red and white blood cells \([30,54,55]\), delicate human liver cells (HepG2) \([34]\), porcine oocytes \([56]\), human sperm cells \([57]\), oral and prostate cancer cells \([58,59]\), fibrosarcoma cells \([60]\), and protozoan cells \([61]\).

Recently, Neale et al. proposed the use of OET devices for measurement of the relative stiffness of cells \([54]\). In an OET device, nonspherical cells are aligned and stretched in the direction of the electric field. Neale et al. observed that healthy mouse erythrocytes can undergo a change of \(\sim 10\%\) in cell diameter due to stretching, which can be used as an indicator of the relative cell stiffness. Single-particle control by OET can also be exploited in bottom-up tissue engineering. Lin et al. used an OET platform to replicate the cell distribution in articular cartilage tissue \([62]\). Alginate microbeads containing chondrocyte cells at three different cell densities \((2.4 \times 10^{5}, 1.0 \times 10^{6}, \text{and } 7.7 \times 10^{6} \text{ cells/ml})\) were sorted and organized using OET to form a cell sheet to replicate the cell distribution in superficial, transitional, and radial zones of the tissue. OET has also been used for cell trapping in microdroplets \([63]\). Droplets provide an isolated environment for storing biological and
chemical entities. Valley et al. combined OET with an electrowetting platform in which an electrically induced gradient in surface energy is used to induce droplet motion [52]. Cells were forced into static droplets using OET traps, whereas droplet operations such as merging and splitting were achieved by electrowetting.

OET can be integrated with various techniques to hold particles in place while they are being investigated or treated. A good example is a biological microbeam, which is a micrometer-sized beam that can be used to expose cells to exact doses of radiation. Grad et al. incorporated OET in a microbeam for maintaining precise positions for nonadherent cells during UV-microspot irradiation [60]. In another application, Chuang et al. used an OET platform for temporary immobilization and subsequent laser surgery of Caenorhabditis elegans worms [64]. Instead of relying on electrokinetic forces, they utilized the rapid joule heating effect to reversibly knock down worms by heat. In an OET device, if the conductivity of the medium is high (~1 S/m), then the region under the action of the electric field can be rapidly heated via joule heating. By projecting illumination, Chuang et al. dynamically created and maintained such heated regions in the knockdown temperature range of C. elegans (31–37°C).

Similar to OET, REP has been used for manipulation of biological samples. Kwon et al. used REP for aggregation and patterning of the Gram-negative, rod-shaped bacterium Shewanella oneidensis MR-1 (Figure S2 in the supplementary material online) [47]. A population of ~700 MR-1 bacteria (each ~1 μm in diameter and ~2–3 μm in length) was rapidly concentrated on the electrode surface (~0.73 s) using a tightly focused laser spot. The authors also used DMD to create two distinct laser spots that allowed simultaneous concentration at two different locations.

Cell sorting

Cell sorting is one of the most fundamental operations in biological research. Many conventional sorting methods require cell labeling with a fluorescent tag or attachment of magnetic beads [22]. These probes can potentially affect cell behavior; for example, the therapeutic potential of stem cells can be affected by such probes [65,66]. Because electrokinetic methods rely on physical and dielectric properties of the cells and media, cells can be noninvasively sorted on the basis of their phenotype without any labeling.

Using OET, Chiu et al. demonstrated separation of live human B cells from dead cells [7]. For separation, cells were dispersed in an isotonic buffer of low conductivity (10 mM). Owing to the presence of an ion differential across the membrane, live cells remain more conductive than permeable dead cells. This difference in conductivity is exploited for separation. Live cells experience positive DEP and move toward the bright areas, whereas dead cells undergo negative DEP and are repelled from the illuminated sites (Figure S3 in the supplementary material online). Based on a similar concept, OET devices have been used for viable cell selection in the area of in vitro fertilization. OET has been utilized for optimal quality selection of mouse embryos [67], separation of normal and abnormal porcine oocytes [56], and separation of nonmotile viable human sperm cells from dead sperm [57,68]. Huang et al. used OET for separation of cancer cells from leukocytes in a continuous-flow system [69].

In contrast to OET, cell separations with REP have only recently been demonstrated. Kwon et al. used REP to separate two different microorganisms on the basis of their size [47]. Saccharomyces cerevisiae, which is a unicellular spherical fungus (~5 μm in diameter), and Staphylococcus aureus, which is a Gram-positive spherical bacterium (~1 μm in diameter), were separated by changing the AC frequency from 17.5 to 38.9 kHz. This resulted in removal of S. cerevisiae from the cluster, whereas S. aureus was still held in the trap (Figure S4 in the supplementary material online) [47].

Electroporation

When a cell is exposed to an external electric field, a transmembrane potential (TMP) is induced across the membrane. If the TMP is lower than a threshold value (0.2–1.5 V), then, depending on the pulse duration, electroporation can be reversible and pores may reseal [70]. Reversible electroporation is used to introduce foreign molecules such as DNA, proteins, and drugs into the cell interior. Existing electroporation methods work in bulk on a large number of cells [25]. Using OET, a single cell can be selectively electroporated while leaving other nonilluminated cells unaffected on the substrate. Valley et al. demonstrated propidium iodide uptake in selected HeLa cells [48] by applying an electroporation bias of 1.5 kV/cm across the chip. A few selected cells were exposed to illumination, which resulted in a strong electric field around them that caused electroporation [48]. If the electric field strength exceeds a threshold value, then cell lysis can also be achieved in the same OET set-up. Lin and Lee used this concept to demonstrate cell lysis of fibroblasts and oral cancer cells [58,59].

Concentration of molecules

OET can trap biological entities over a vast range of length scales. In addition to trapping cells and microparticles, OET has been used for trapping of molecules [18,71,72] and nanoparticles [73–76]. Depending on the AC frequency, the nonuniform electric field present in OET devices can cause both DEP and ACEO. DEP forces scale with particle volume, which is negligible for macromolecules and nanoparticles. A better option for trapping of molecules is to utilize the toroidal vortex generated by ACEO at low electrical frequencies. Chiu et al. used light-activated ACEO for rapid concentration of lambda phage DNA molecules [18]. Hwang and Park investigated the effect of electrical frequency on the molecular concentration of fluorescein isothiocyanate (FITC)-tagged dextran molecules [72]. They showed that the fluorescence intensity reaches a maximum at ~1 kHz and then decreases as the frequency is increased.

Advantages and disadvantages of OET and REP

OET has some unique advantages over REP and optical tweezers. OET does not require a high-intensity laser beam, so the likelihood of photodamage is minimized [4]. Unlike optical trapping and REP, OET does not require focusing of the light beam using objective lenses with a
high numerical aperture (NA). Therefore, OET manipulation is possible over an area two orders of magnitude larger by using low-NA objective lenses. Huang et al. recently improved the technique by combining OET with lens-free holographic microscopy [53]. They demonstrated automated manipulations over an area of 240 mm², which is 100 times larger than for a conventional OET system integrated in a lens-based microscope. Operationally, OET is a more versatile platform than REP, but it is easier to fabricate an REP chip than an OET device. An REP chip is primarily made of ITO-coated glass, which is readily available on the market, whereas OET devices are made of a photconductor that is not only commercially unavailable but also requires a careful fabrication process. However, photconductor surfaces for OET devices could eventually be mass-produced for a fraction of a dollar per device [77]. REP experiments also benefit from access to readily available infrastructure that is already present in many research laboratories in the form of an optical trapping setup.

In contrast to optical trapping, which can only trap a few particles, REP and OET can concentrate hundreds of particles and move them rapidly on the substrate. REP and OET can also easily trap nanoparticles with the same substrate as used for larger particles, whereas optical tweezers require a nanostructured substrate. In summary, optoelectric techniques exploit optical and electrokinetic mechanisms to achieve unparalleled advantages in manipulation. However, reliance on electrokinetic mechanisms also exposes these techniques to the disadvantages of electrokinetic methods. For example, OET platforms require suspension of cells in low-conductivity media (<0.1 S/m) [75], which is nonphysiological. Low-conductivity solutions can cause undue cellular stress and irreversible damage to cells over time [78,79]. Hsu et al. addressed this limitation by using a phototransistor-based OET device (Ph-OET) [51]. In this device, instead of the a-Si layer, bipolar junction transistors were used as the photoductor. Because the photocoercivity is two orders of magnitude higher, the Ph-OET platform facilitates cell manipulation in commonly used solutions that are more physiological, such as Dulbecco’s modified Eagle medium and phosphate-buffered saline [51]. Nevertheless, labor-intensive and expensive fabrication processes limit widespread use of these devices.

Nonspecific adhesion of cells to the electrode surface is another common problem associated with optoelectric platforms. In conventional OET, DEP forces bring particles very close to the electrode surface, where permanent adhesion can occur because of various particle-electrode interactions such as electrostatic and van der Waals forces. The cell-electrode adherent forces can be in the range of nanonewtons, whereas manipulation forces in OET are of the order of piconewtons [50]. Therefore, large adherent cells cannot be effectively manipulated by conventional OET devices, but solutions are available. Lau et al. proposed the use of antifouling coatings, such as bovine serum albumin and poly(ethylene glycol) (PEG) on the photoductor surface to prevent cell adhesion. The PEG coating was very effective in preventing cell adhesion. In another approach, Hwang et al. proposed an OET device made of two photocoherent substrates [80]. In this configuration, particles experience a DEP force from each surface, resulting in particle suspension between the surfaces. Even though this method lowers the probability of adhesion, optical imaging through the photoductor surface results in less clear optical images.

Concluding remarks and future perspectives
Optoelectric techniques are established as highly flexible tools for the manipulation of cells, molecules, and nanoparticles. OET has attracted considerable attention since their invention. As a result, OET trapping mechanisms are still well understood. More research effort in REP is still needed to develop a quantitative understanding of the delicate balance of forces that lead to particle trapping. A greater theoretical understanding of the trapping mechanism will improve the predictability of trapping and make it possible to use the REP platform for mechanical and biophysical characterization of cells and molecules [41]. At present, particles are sorted in batch mode when using REP. Development of a continuous particle sorter will be an important contribution. Use of a high-conductivity medium is an important requirement for long-term biological applications. However, REP has not yet been tested with such solutions. This presents another opportunity for advancement.

In conclusion, optoelectric techniques have almost passed through the phase of technology development. It is now time for application-driven research in biology and medicine to propel these techniques to the next level. The glaring gap in applications makes this review highly pertinent. Our aim in describing these devices is to attract researchers in biology and medicine to use these platforms for novel applications.

Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tibtech.2014.06.002.

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