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Nanotechnology-assisted liquid crystals-based biosensors: Towards fundamental to advanced applications

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ABSTRACT

Since the discovery of biosensor, continuous efforts are being made to design and develop novel biosensing systems of reduced form factor and high performance. State-of-art biosensing technology is the least component-based and tunable outcome depends on the selection of bio-sensing materials. Among various smart-electro-active nanostructures sensing materials, liquid crystals (LCs) are emerging as a choice of materials to develop efficient biosensor for targeted biomarkers detection. In the modern world of science and technology, LC materials have exhibited significant importance as promising materials in the various display as well as in non-display (optical devices based on LC) applications. Most of the displays currently used and available in the market are based mainly on LC technology. Besides the parent area of electronic displays, advancements have been made to tune the potentials of LC materials properties to develop biosensors of desired performance. Due to easily perturbed by external stimulation and species including bioactive or analytes project LC-based platform suitable for fabricate simple, efficient and cost-effective biosensors. This review article is an effort to describe the advancements in LC and nanotechnology-assisted LC systems for developing an efficient biosensor of tunable performance. The biosensing mechanism associated with nanotechnology-assisted LC-based sensing systems, challenges in the state-of-art technology, and future direction required to develop a LC-based analytical diagnostics tool are also the focus of this report. We believe that this review will serve as a guideline to researchers who aim to fabricate a nanotechnology-assisted LC materials-based biosensor for rapid, cost-effective, selective diagnostics of a targeted disease for health care management.

1. Liquid crystal, a brief background

Liquid crystal (LC) is the intermediate state between highly ordered crystalline solids and isotropic liquids, hence referred as intermediate phases (or mesophases). The LC is a substance that is strongly anisotropic in some of its characteristics as solids and exhibits a definite level of fluidity which is the property of an ordinary liquid (Collings, 2002). Nowadays, there is a great interest in the area of LC based applications due to its sufficiently ordered molecular units. Due to the anisotropy of LCs, they possess birefringence in which light enters the sample and split-up into two parts. Both rays are oppositely-polarized which travel with different velocities and show color effects when observed under polarizing filters (Wu et al., 1984). The salient features of LC materials and state-of-art applications are schematically illustrated in Fig. 1.

Since, due to their orientational elasticity, LC can be self-assembled by itself and thus can preserve topological defect structures which give them a potential for further use in modern display technologies (Salamon et al., 2018). The significant progress has been made recently on a theoretical understanding of electrical properties, contributing to develop advance LC materials (Naemura, 1999). It has also been demonstrated that by changing the polymerization conditions, it is possible to obtain various morphological properties of LCs (Filpo et al., 2008). The observation has been done that approximately one out of 200 organic substances could be assumed to exhibit this kind of mesomorphic properties. Several theories and models of molecular arrangement such as X-ray diffraction, refractive index, thermodynamic, dielectric, spectroscopic, surface tension and proton resonance have been well studied. These mesogenic molecules having birefringent properties are

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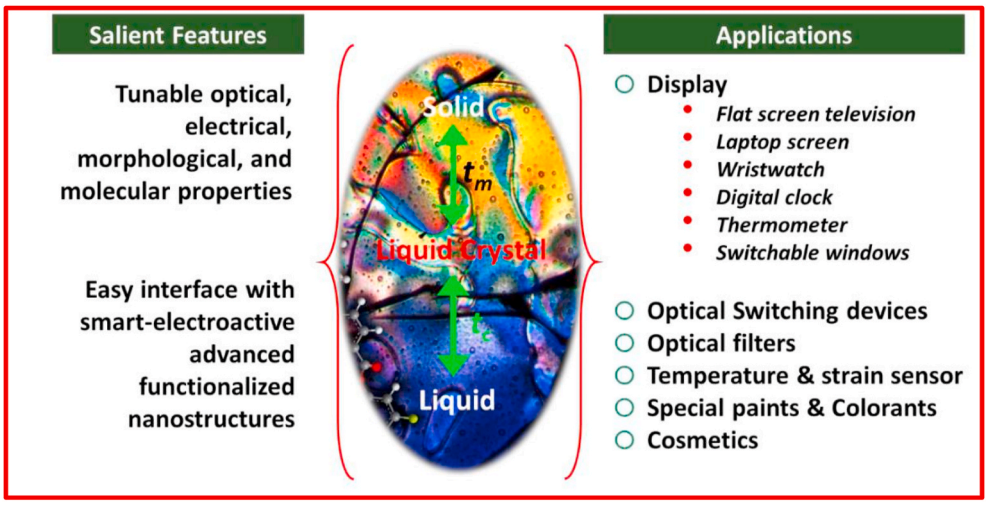

Fig. 1. Schematic illustration of LC-materials along with salient features and their state-of-art applications.

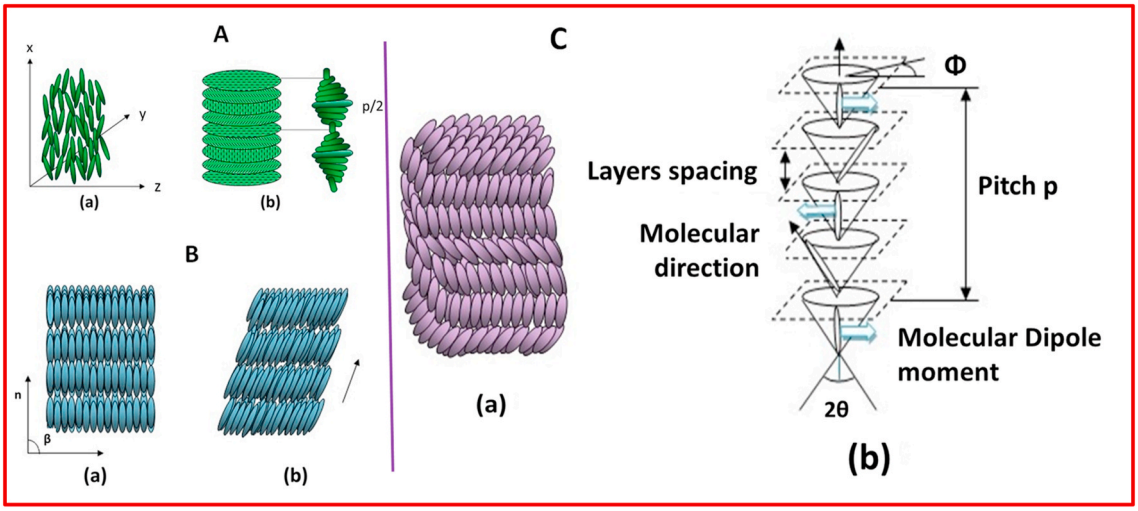

Fig. 2. (A) Molecular structure of (a) nematic and (b) chiral (cholesteric or twisted) nematic LC, (B) Molecular structure of the most commonly used smectic liquid crystal phases; (a) smectic A (Sm A); (b) smectic C (Sm C), (C) Structure of the chiral smectic C phase.

used to detect different analytes and biomolecules also their binding interaction with other molecules as they interrupt the orientation of the director (direction of preferred orientation) and detected via optical appearance (Lee et al., 2015).

It was an Austrian botanist Friedrich Richard Reinitzer who first discovered the LC phase while investigating the derivatives of cholesterol (Hamley, 2007). He observed that at 145.5 °C the clear white cholesterol benzoate melted from powder to a turbid liquid (bright blue-violet color). And when it was heated further up to 178.5 °C, the turbidity vanished, and it turned into a clear liquid (pale blue color). The molecules of LC have long-range orientational ordering (crystalline-like property) but deficiency of short positional ordering (liquid-like property). The color of this mesophase depends on temperature and disappears in the transition by melting but sometimes it endured in the crystalline phase on rapid overcooling. It was German physicist Otto Lehmann who observed the LC material under a polarizing optical microscope (POM) and proposed that they flow like isotropic liquids and possess some optical properties like solids (Kumar, 2011). He named it firstly as 'flowing liquid' and later entitled as 'liquid crystal' (Singh and Dunmur, 2002). It was further improved by French physicist Friedel and the new term was coined as mesomorphous state constructed by the Greek word 'Mezos' means intermediate as LC is the intermediate phase between isotropic liquids and crystalline solids (Ermakov et al., 2016).

There are several ways to classify LC materials, but the most commonly used LC phases are thermotropic and lyotropic (Chandrasekhar, 1992). In the thermotropic class of LC, the transition is given by the definite temperature range between a melting point (T_m) and upper transition temperature (T_c). The transition is repeated reversibly on cooling the isotropic liquid. Lyotropic LCs are the substances in which the LC phase is obtained by dissolving them in solvents over a range of concentrations. Based on molecular features, the LCs are classified as calamitic and discotic LCs. Both Calamitic and discotic LCs can be existed in thermotropic and lyotropic LCs phase (Priestley et al., 1976). Thermotropic LCs are further divided into nematic, smectic, and cholesteric LCs based on the molecular arrangement.

The *nematic LCs* (NLCs) are the most commonly used LCs having a large degree of long-range orientational orderings but lack of long-range translational ordering of molecules (Fig. 2A(a)). The name comes from the Greek word "nema" meaning thread. It is totally different from the liquids as the molecules are oriented in the long molecular direction. In the presence of low electric and magnetic fields the molecules can be easily aligned that is suitable for liquid crystal displays (LCDs) and sensor designing (Popov et al., 2017b). The *cholesteric LCs* or *chiral NLCs,* also a nematic type of LCs composed of doping chirality in it. This type of

LC possesses optically active molecules (Fig. 2A(b)). Therefore, the molecules twist about an axis normal to the long molecular direction and form a helical structure. One of the important properties of cholesteric LCs is its 'pitch' that is the distance between one helical twist of 360° by the director (Soni et al., 2013). These chiral nematic LCs exhibit twisted superstructures and the phenomenon of selective reflection, which plays a key role for designing temperature sensors such as medical thermometers (Hsiao et al., 2015). The cholesteric mesophases having a low pitch (less than 5000 Å) value are referred as blue phases and these exist over small temperature region (Meiboom et al., 1981; Zarin, 2013).

Smectic LCs have a stratified structure but a proper arrangement of molecules within each stratification (Oswald and Pieranski, 2006). The name comes from the Greek word "smegma" which means soap. Molecules in the smectic LCs show a certain degree of orientational order as in NLCs but also tend to align in layers in translational order with well-defined interlayer spacing (Lagerwall and Stebler, 1980). Long molecular axes of molecules make an angle β with normal to this plane. When the director is perpendicular to smectic layers or $\beta = 90^{\circ}$, molecules are said to be smectic A (Sm A) and their centers of gravity show no long-range order within the layers. These molecules are non-chiral and non-polar, described by a 1-D layered structure (quasi-long-range positional order) (Fig. 2B(a)). Over a dozen other distinct smectic modifications have been identified from Sm A to Sm K. The smectic C (Sm C) phase is same as Sm A due to its layered structure, each layer may be considered as a 2-D liquid film but there is no bond orientational or positional order (Fig. 2B(b)).

Chiral Smectic C (Sm C*) is that class of LC in which molecules are inclined at a well-defined orientation in layered structure (Fig. 2C(a)) (Williams and Davis, 1986). The molecules possess spontaneous polarization (P_s) and the property of ferroelectricity therefore they are also known as ferroelectric liquid crystals (FLCs) (Yoshino and Inuishi, 1981). P_s is the most important characteristic of FLCs (George et al., 2012). In the molecules possessing Sm C* phase, the polarization vector is in the molecular layer direction and perpendicular to the long molecular axis. The tilted smectic layers change by a small amount going from layer to layer as illustrated in Fig. 2C(b). The azimuthal angle, ϕ, which is the angle outside the circle of precession, produces helical pattern in LCs and θ is the magnitude of the angle between the molecular director and layer normal. P illustrates the pitch value (i. e. the distance that the director takes to complete one full rotation) (Vij, 2000). The introduction of chirality in the molecules has an impact to exhibit the helical structure (Reddy et al., 2011). Three electro-optical effects exist in the FLC mode which are surface stabilized ferroelectric liquid crystal (SSFLC) effect, deformed helix ferroelectric liquid crystal (DHFLC) effect, and electroclinic liquid crystal effect (Kiselev and Chigrinov, 2014). The detailed study of different possible states of FLC cells has also been discussed (Dijon and Bahadur, 1990).

There is a diverse area of applications of LCs that provide tremendous potential for basic science and technology such as physics, material science, chemistry, space, engineering, biology, food science, and pharmacology, *etc.* (Woltman et al., 2007). Nematics and smectics are widely used in LCDs such as television displays, digital watches, dynamic information billboards mobile phones, laptops, tablets, digital projectors, clocks, pocket calculators, information displays, computer monitors, virtual reality, *etc.* (Vass et al., 1998). The LCD is a visual display instrument with a uniform and flat electronic display panel used as a visual display. With the help of LCs, it creates a visual effect on the screen (Brown, 1973). LCD does not produce light on its own but depends on sunlight or room light to generate images with the aid of LCs. The LCD is made up of two kinds of display grids either a passive matrix or an active matrix display grid. The passive matrix has possessed an arrangement of a set of conductors and the pixels are located at the intersection over the grid. The forwarded current is passing through two conductors for proper luminance of the pixel. While considering an active matrix which is also known as a thin-film transistor (TFT) display, less current is required as a transistor is placed at the junction of each pixel. It includes one data line and the parallel column current line results in the improvement of screen refresh time (Troccoli and Hatalis, 2013). The main use of LC in the display device is due to its ultralow power consumption.

Beyond the realm of displays, LCs can also be used in non-display devices due to their plethora of unique and attractive properties such as memory devices, holography, optical devices like phase-shifting interferometers, LC lasers, tunable filters, optical computing, *etc.* (Sohn et al., 2014). LCs can also be used as a temperature sensor (Algorri et al., 2014). A LC thermometer, temperature strip or plastic strip thermometer is a type of thermometer which uses LC that changes color with temperature (Moreira et al., 2004). Mixtures of LCs are enclosed in distinct partitions and the number of partitions indicates temperatures depending on the amount of heat present. LC can be used as a charge indicator for batteries (Schmidt-Mende et al., 2001). The principle is the same as used by liquid crystalline thermometers. The heat is generated as the electric current is passing through the medium. Thus, the change of the respective orientation of the layers produces a color change. It can also be utilized to detect the poor connections in the circuit.

LCs have a multitude of other uses such as automatic testing of materials. It is used for the envisioning of radiofrequency waves in waveguides (Donisi et al., 2010). Another application of LC is optical imaging. This technique is used for the diagnosis and treatment of different diseases. In this technique, rays are passing through damaged areas such as tumors and fractures which can be shown by the computer attached via a camera (Needleman and a d Dogic, 2017). Ultraviolet and infrared rays are used for the detection of diseases and image appears on the screen. Long chained rigid polymers that orient parallel to each other with very strong intermolecular interaction are used for making helmets and bullets-proof vests. Apart from these applications, there is some remarkable approach in unconventional applications of LCs in metamaterials and photonics, LC-functionalized polymer fibers, sensing, and diagnostics (Dabrowski et al., 2017).

Keeping above-mentioned aspects in view, this review manuscript highlights the possible interaction established between functionalized nanoparticles (NPs) and LC to improve tunable physical properties which enable development of efficient biosensing required for health wellness. The NPs-dispersed LCs have exhibited ground breaking developments in the field of biosciences and medical research to obtained optical and electrical signaling. In the case of biomedical research, NPs supported LCs to exhibit unique optical, electrical, and molecular properties which are absent in pure LCs. Such modifies self-assembled NP-LCs nano-systems are easy to fabricate and tune their performance-based hots (LCs)-guest (NPs) chemistry-based approach. For example, modification and improvement in different physical parameters than the pristine LCs. The ordering of the LCs is reshaped in the form of a fascinating material with some additional enhanced features.

2. LC materials towards biosensor application

The history of the biosensor elucidated in 1962 by Leland C. Clark (known as the father of biosensor) with the evolution of the enzyme electrode (Vadgama, 1981). A biosensor is an analytical device in which a biological response is transformed into a measurable signal (Arora, 2013). The name 'biosensor' signifies that it is a combination of two terms, a bio-element and a sensor element. The bio elements (i.e. enzyme, antibody, lectin, hormone, living cells, tissue, *etc.*) recognize a specific analyte while the work of sensor element (electrical current, electrical potential, thermal or optical signals, *etc.*) is to change the biomolecules into an electrical signal (Turner, 2013). A biosensor aims to give fast, real-time, precise and reliable information related to analytes. The bio element recognizes only a specific analyte to which it is sensitive (Kaushik et al., 2014a, 2014b, 2017; Manickam et al., 2017; Shen and Dierking, 2019, 2014).

There are several combinations of bio element and sensor elements for manufacturing a biosensor which performs different applications.

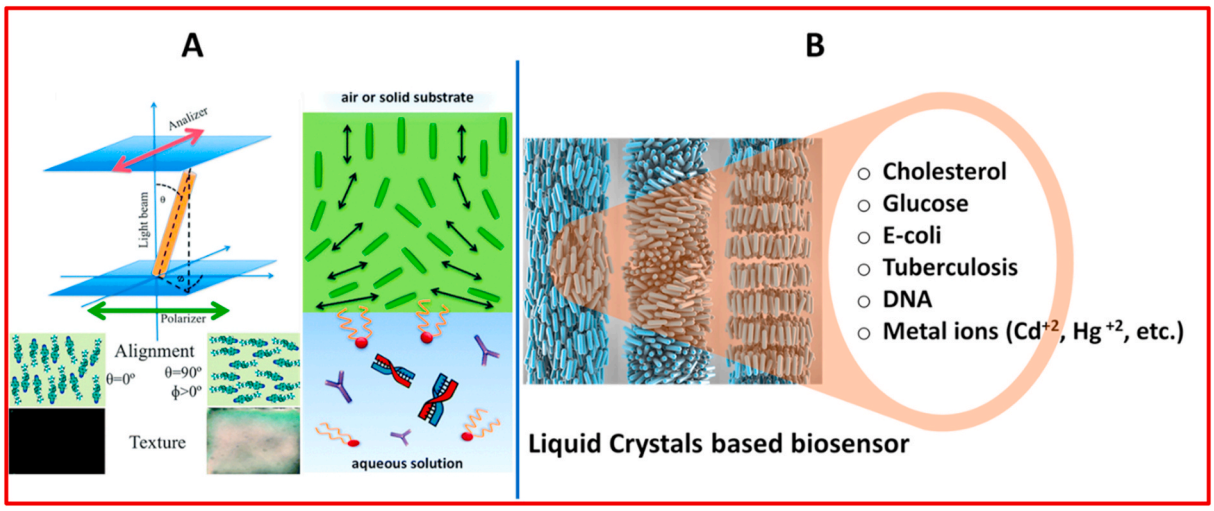

Fig. 3. Illustration of sensing mechanism (A, adopted from Popov et al., 2017b, RSC 2019) and various applications of LC-based biosensors with reference to targeted diseases (B).

Various materials have been utilized to develop a biosensor. However, the complex materials fabrication process, as per biosensor system requirements, made biosensor preparation very challenging. Thus, investigating biosensing materials which can be aligned and fabricate easily are always required (Cruz et al., 2014; Kaushik et al., 2014a, 2014b, 2018; Solanki et al., 2011). Since the reorientation of the director (preferred direction of aligned molecules) has such efficient significances on the optical properties of LC and the director alignment is so sensitive to the chemical and physical surroundings, LCs have been used in biosensors (Kaushik et al., 2018; Tyagi et al., 2014). LC-based biosensors have shown attention because of their novel sensing properties. There is a very exciting development in this field which provides new avenues for open-minded researchers (Dong and Yang, 2013; Madhusudana, 1981).

Apart from conventional biosensors, the LC-based biosensors have made specific attention over the past two decades which possess a broad area of applications due to the high sensitivity of their alignment (Kaushik et al., 2016a, 2016b, 2016c). The schematic showing the detection of various biomolecules through LC material has been highlighted in Fig. 3. In a case, if the light is passed through POM in the same direction of the vertically aligned LC material but block by the polarizer, a dark pattern will be observed. In the presence of an analyte, the alignment become oblique at some angle or parallel, and over the LC materials the incident light is fragmented in two linearly polarized lights in dissimilar director. After combining with the optical anisotropy of LCs, this sensitivity induces a fast, easily visualized response.

The interaction between molecules with surface holds immense importance in executing different cellular activities. The molecules aligned parallel to the surface are known as planar or homogeneous while molecules perpendicular to the surface is called homeotropic alignment (Kaushik et al., 2016a, 2016b, 2016c; Khan et al., 2016). The planar alignment when detected under POM, a bright light was observed by the existence of birefringence whereas no light is detected in case of homeotropic alignment as it does not permit birefringence. The alignment of NLC is totally dependent on the surface topography. Due to surface dependent effects, a small change on the surface in NLC amplifies under polarizing microscopy. Hence, to illustrate the sensitivity with water or air, different textural observations are detected. The response of the sensor can be controlled by changing certain parameters such as depth, anchoring strength and material used (Humar, 2008; Kaushik et al., 2014a, 2014b). The parameters affecting the performance of a LC materials-based biosensor are discussed in the next sections.

3. Parameters affecting LC-based biosensor

3.1. Alignment of LC

For aligning the LC molecules on glass substrates which are coated with a polymer, the rubbing or photo-aligning technique is used. Self-alignment is another concept of homogeneous alignment of the LC molecules without any rubbing technique (Nemoto et al., 2012). The self-alignment process also proves that LC molecules are fixed and orient unidirectional. Apart from this, the other three methods were analyzed one is a plain glass in which there is an inherent directionality to the substrates. Another is a planar alignment process in which the long molecular axis or the director is aligned parallel to the substrate. To achieve this alignment, polyvinyl alcohol (PVA) coated cover slip is used which is rubbed with a velvet cloth in the direction parallel to the directionality of the substrate. And third one is the homeotropic alignment process in which the long axis is perpendicular to the substrate and this can be achieved by using an alignment material such as Lecithin (or that has a long hydrocarbon tail, such as polyimide) to coat the surface of the substrate. This type of alignment is better than the other alignment processes for the detection of different analytes because this gives a good background contrast to deduce the director distortion and appears dark when viewed between cross polarizers. Chen et al. claimed that nematic 5 CB is strongly homeotropically aligned at the LC-air interface (Kasten and Strobl, 1995).

We found dark images for homeotropic alignment glass substrates. When a biomolecule interacts with the surface, anisotropic interaction takes place between the molecules in the surface and the analytes which leads to an orientational arrangement of LC molecules in the layer of the surface. This change turns the dark images to clear bright images (or homeotropic alignment to homogeneous alignment) which could be easily observed through crossed polarizer using POM (Kaushik et al., 2016a, 2016b, 2016c).

3.2. Cell thickness

The cell thickness is measured by the interference fringes from the reflected light having a wavelength in the visible region as the empty cell can be designed as a Fabry-Perot etalon. The differences in the thickness can be accounted for by the different amounts of adhesive used in the construction of the cell. The optical microscopy images of different cell thicknesses without polarizers, with crossed polarizers in the nematic phase, with crossed polarizers on heating through the nematic to isotropic phase transition and with crossed polarizers on

Table 1
A summary of the optical response observed on heating and cooling through the nematic to isotropic phase transition at different cell thicknesses.

Cell thickness	~7.5 μm	~10.0 μm	~12.7 μm	~36.5 μm	~41.8 μm
Nematic phase **Texture**	Dark	Bright gold	Dark	Bright gold	Bright gold
Textures on Heating	Cross defects on gold spots	Cross defects on gold spots	Cross defects on gold spots	Random planar texture	Random planar texture
Textures on Cooling	Random planar texture	Random planar texture (one array shows defect nucleation between gold spots)	Square grid Texture centered on the gold Spots	Random planar texture	Random planar texture
Reflected Intensity on Cooling (A.U.)	0.5 ± 0.4	0.32 ± 0.2	1.05 ± 0.7	0.60 ± 0.01	0.69 ± 0.04

cooling through isotropic to nematic transition have been observed (Cronin, 2011). The reflected intensity of phase transition is given for different cell thicknesses such as 7.5, 10.0, 12.7 and 40.0 μm and filled with 5 CB and an acid terminated self-assembled monolayer (SAM). The aim of using 5 CB as a standard is its well understood physical properties.

From Table 1, it has been concluded that depending on such factors and circumstances, one can detect a thickness of maximum intensity and this idea may be implemented on sensing various biological target molecules (analytes) (Cronin, 2011). The surface interaction for the thin cell is better as compared to the thick cell since most of the molecules are unaffected in the bulk area. So, one can choose thin cells for better intensity and optical images for sensing.

3.3. Anchoring energy

When LC molecules are incarcerated between the cell or glass plates there is an intermolecular interaction between the molecules (Dadivanyan et al., 2012). Due to this, LC molecules change their position and line up in a certain direction depending upon the coated surface. This surface alignment is termed 'Anchoring energy', γ_s. Anchoring energy is a periodic function of azimuthal angle (ϕ) and tilt angle (θ) which defines the surface normal at the surface and given as (Jerome, 1998).

$$\gamma_s(\theta,\gamma) = \sum A_l^m Y_l^m(\theta,\phi) \quad (1)$$

Where $Y_l^m(\theta,\phi)$ is spherical harmonics and A_l^m is coefficients depending on $Y_l^m(\theta,\phi)$.

For biosensors, the most common alignment is homeotropic in which the molecular director is perpendicular to the substrate. The interfaces at which anchoring has done are with crystal surfaces and treated glass substrates. For glass treatment in the case of biosensors, the chemical process is mostly used. In this process, there is a deposition of a layer (surfactant, polymer, inorganic substance, *etc.*). The symmetry of the interfaces (whole surface in case of a thin cell) depends upon the attached biomolecules (Tyagi et al., 2013).

Because of this anchoring energy, there is flatness in the glass which can be used in fabricating biosensor. In the cell filled with twisted NLCs, some areas show an optically uniform texture where the twist energy is comparable with weak surface anchoring, but this cannot be seen in conventional twisted nematic cells (where anchoring energy is strong) (Atherton et al., 2009). Evan et al. showed that if the surface energy is large enough, the elastic energy will be less essential and planar alignment will tend to be observed. The intermolecular elastic energy dominates enough for the substances which have low elastic energy resulting in the perpendicular alignment of the LCs. This idea is useful for sensing mechanisms as one can get a clear optical texture. The surface anchoring possesses a greater effect on reflection intensity than birefringence which is suitable for designing a LC-based biosensor (Evans et al., 1996).

3.4. Transition temperature

The T_c is defined as the temperature required for the transition from liquid crystal to liquid (or vice-versa). It was obtained as a function of density and molecular shape. Since the phase transition involving symmetry change is always sharp and occurs at a distinct temperature, one can easily detect bio-molecules (as they are sustainable at room temperature) needed for our purpose. The shift in this temperature can be observed by comparing it with other thermodynamic quantities such as electric energy or elastic energy. The T_c from Sm C* to Sm A* is an important parameter of the FLCs.

We must choose such types of materials for comparison which T_c in the range of room temperature as all the biomolecules sustain only at room temperature. So, if the T_c of any chosen biomolecules for the substrate is less or greater than room temperature, then it cannot be observed by taking account in case of the biosensor. And one can use another method by doping NPs in LC-based material so that $T_c$occurs nearly the room temperature. And by attaching with biomolecules it began to start responding.

The T_c can be determined by several techniques such as a POM and differential scanning calorimetry (DSC) based on different criteria like structures, microscopic textures, and miscibility rules. Using the light scattering (LS) method, a simple analytical system has been evolved to find out the phase transition temperatures of LCs (Tsuji et al., 2001).The optical response of LC can be detected through polarizing microscopy and thus the phase T_c. A POM is an essential tool for profound observations of LC materials (Dierking, 2003).The phases present in the molecules can be confirmed by changes in the characteristics of the textural patterns. The DSC measurement of T_c of 5 CB/benzene mixture is reported (Kundu et al., 2008). It is cleared in the mixture of 5 CB and benzene that on decreasing the concentration of 4-cyano-4-pentylbiphenyl (5CB) up to 69 wt%, the crystalline-isotropic phase T_c are slightly decreased but at 70%, the T_c abruptly increases to about 27 °C and then decreases to about 15 °C and again increases from 96 to 100 wt % of 5CB. We also used dielectric relaxation spectroscopy to determine T_c in which collective dielectric relaxation processes were observed using an impedance analyzer (Thakur et al., 2003). In this method, we studied the behavior of relaxation frequency as a function of temperature to obtain T_c.

3.5. Helical pitch

The pitch is defined as the distance which takes the director to complete one full rotation in the helix. There are two types of LC which

possess a helical pitch. One of them is chiral NLCs which reflect the light of different wavelengths depending upon the size of the pitch. An optical sensor has been made which is filled with a mixture of toluene and ethanol used as a color tunability with a broad sensing range of 86 °C from −6 °C to 80 °C and high sensitivity of 1.79 nm/°C (Li et al., 2017).

Similarly, the chiral Sm, being a 'chirality phenomenon' has modulated arrangement. In this mesophase, molecules are arranged in layers. Molecules parallel to each other are inclined at an angle with layer normal and form a twisted helix. This results a medium in which the sample of homogeneous alignment acts as a birefringent diffraction grating. The dark and bright lines are observed through POM and the gap between these lines gives the value of the pitch (of the order of several microns) (Biradar et al., 1986).

For the measurement of this helical pitch in Sm C* liquid crystalline material of the homogeneously aligned cell, two methods have been developed either by direct observation of optical fringes (Martinot-lagarde et al., 1981) or laser beam diffraction method. In the homeotropically aligned cell, the Cano method (Kondo et al., 1982) and selective reflection (Różański, 1983) method can be utilized for the helical pitch detection. The fixed helical pitch can be affected by attaching biomolecules and the change can be detected.

3.6. Tilt angle (θ) and spontaneous polarization (P_s)

For the futuristic applications, we can find the responses of the parameters such as θ and P_s. Since these are the basic parameters of FLC, so we can make biosensor based on FLC materials. The molecules of the FLC are tilted in layered form. Thus, there is P_s as the magnitude of the P_s is proportional to the θ. The P_s is defined as there is a polarization in materials even in the absence of an external electric field and quantified by the value of electric dipole moment per unit volume. In the Sm C phase, the tilt does not induce polarization. Whereas in Sm C* phase, the tilt breaks the mirror plane symmetry, the transverse polarization exists as both directions perpendicular to the tilt plane are not identical. The accurate measurement of the θ is very important as it is the primary order parameter of the chiral Sm phase. An optical method based on refracting indices measurement is used for the detection of a θ (Jain et al., 1987). The θ by this method can be observed with an accuracy of ±0.2 °C in the high θ range (20–40 °C).

The $P_s$is the second-order parameter in FLCs. The P_s was determined by applying a triangular wave of a desired frequency and amplitude across the sample cell and the output current was detected through an oscilloscope. The LC material inserted between two conductors can be better shown by a parallel combination of a capacitor, resistor and a polarization arrangement device. Using a triangular waveform has unique advantages as it separates the contribution of a capacitor from impeding with current due to polarization reversal and it is easy to remove the resistive component as this contribution varies linearly with applied voltage. The value of P_s is calculated by numerical integration method computing the area of the remaining polarization current Ip loop by numerical integration method. Suitable lateral substitutions can enhance molecular polarizability which can disrupt molecular packing and the changes can be sensed. Since the parameters of FLCs such as θ and P_s drastically change the molecular arrangement in FLCs, it can be used in sensing techniques.

4. State-of-Art LC-based biosensor

The conventional LC-based biosensing techniques emerged as a promising tool to utilize the property of birefringence and optical anisotropy in LCs. In this direction, the associated sensing mechanism is classified in two categories as 1) LC–aqueous interface sensing and 2) LC–solid interface sensing. The LC–aqueous interface sensor mostly consists of a TEM grid cell over a glass slide coated with some alkylating agents. The LC materials are then filled into the TEM grid mesh and then the surfactants are added to form a SAM at LC-aqueous interface. The sensing process is recorded as a function of changes observed in the orientation of the LC molecules. In case of LC-solid interface, two microscopic LC slides are used at the top and bottom places to form a LC sample cell and with the help of Mylar spacers, a proper spacing is maintained. LC sample is placed inside the LC cell through capillary action by placing a drop of sample at inlet opening followed by assembling different functionalize material and each glass slides.

In recent years, different biosensors have been developed for the detection of different analytes. Among them, the most elegant is LC-based biosensor which is a favorable candidate of the optical biosensor as it possesses unique properties of large birefringence and high sensitivity of the LC molecules (Herminghaus, 1998; Jäntti et al., 2014). The LC biosensors which have discovered up to the date are based only on NLC (Munir et al., 2016). Since NLCs have long-range orientational order and based on alignment change, a wide development of rapid sensors of chemical and biological species has been done.

McCambiley and co-workers have published results relevant to LC biosensor research, comprising the detection of endotoxin. To understand and predict the behavior of confined nematic, theoretical simulations were applied using the phenomenological Landau-de Gennes approach and to control and enhance the efficiency of processing of sensor and to understand the nematic profiles, simulated optical micrographs were matched with experimental results. When the sensor is exposed to air or water distinct optical patterns were observed. Based on changes that occurred in the anchoring strength at the open surface of the sensor, the formational transition observed in the nematic phase. This change was leveraged and used to detect the presence of both a model surfactant and the targeted biomolecule at the open surface (McCamley, 2009).

There are several LCs based biosensor has been discovered for the detection of different analytes (Carlton et al., 2013). A cholesterol oxidase (ChOx) LC-based biosensor is developed for cholesterol detection (Tyagi et al., 2014). The glucose was detected by constructing a glucose biosensor in which a TEM grid filled with 5CB on glass slide (overlaid with octadecyl trichlorosilane) in an aqueous medium coated with poly (acrylicacid-b-4-cynobiphenyl-4-oxyundecylacrylate) (PAA-b-LCP) at the aqueous/5CB interface and immobilizing glucose oxidase (GOx) covalently to the PAA chains (Khan and Park, 2014). There is a biosensor based on the anchoring transitions of LCs at the sodium dodecyl sulfate (SDS)-loaded liquid/aqueous interface for the detection of bile acids (He, 2015). A LC biosensor based on Cd^{2+} has been developed for the detection of cadmium (Deng et al., 2015). In the presence of Cd^{2+} DNA has bent resulting spherical structure (about 2 nm) which disrupted the orientation alignment of LC. For the detection of deoxyribonucleic acid (DNA) molecules, a LC-filled transmission electron microscopy (TEM) grid cell that was coated with the cationic surfactant dodecyl trimethyl ammonium bromide (DTAB), at which the probe of single-stranded DNA (ss DNA) was adsorbed at the LC/aqueous interface (TEMDTAB/DNA), was applied (Khan et al., 2016). The detection of endotoxin has been done through a LC-based biosensor (McCamley, 2009). The detection of organophosphorus nerve agents has been done using liquid crystals E7 assisted on chemically functionalized surfaces (Cadwell et al., 2007). For the detection of mercuric ions in water using amphiphilic dithiocarbonate, a sensor based on LC has been developed (Singh et al., 2016). Kim and co-workers developed an advanced LC-based biosensor to diagnose anti-tuberculosis antibodies (Kim and Jang, 2016). Tuberculosis (TB) is an infectious disease that usually affects the lungs. A recent estimate gives that numerous people developed TB (about 10.4 million) and died from TB (about 1.8 million). For the detection of adenosine triphosphate (ATP), a LC biosensor based on the recombination of split aptamer chip has been developed (Chao et al., 2013). Recently, Yeo et al. fabricated a LC based biosensor for the detection of Ca^{2+} ion in human saliva using 5CB material functionalize with water/5CB interface in the presence of poly (acrylic acid)-b-poly (4-cyanobiphenyl-40-oxyundecylacrylate) (PAA-b-LCP) (Yeo and Park, 2019). Luan and coworkers reviewed the principle, fabrication and

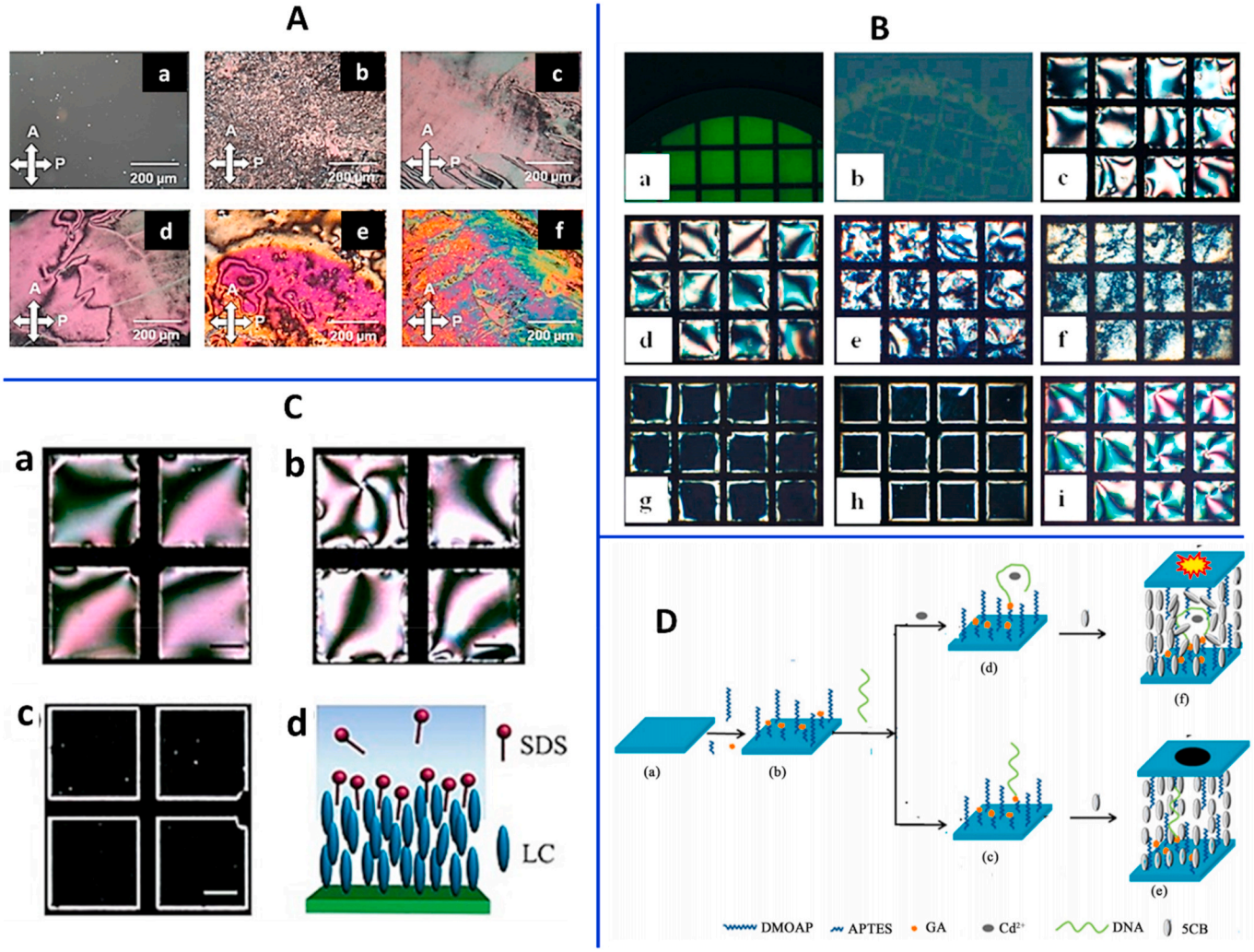

Fig. 4. **(A)** Polarizing optical micrographs showing optical textures of various LC cells geometry of reference cell showing (a) homeotropic alignment (b) enzyme cell; biosensing cell as a function of various cholesterol concentrations (c) 10 mg/dl (d) 50 mg/dl (e) 150 mg/dl and (f) 250 mg/dl, **(B)** TEM grid cells images of (a) immobilized with GOx Rhodamin on PAA-b-LCP (b) filled with a 15.6 μM GOx Rhodamin solution without a PAA-b-LCP coating, POM images of the TEM grid cells under crossed polarizers (c) with a PAA-b-LCP coating without GOx immobilization and NaCl; and (d)–(h) with GOx immobilization on the PAA chains at NaCl concentrations (CNaCls) of 0–2.0 M (i) without a PAA-b-LCP coating at CNaCl = 2 M,**(C)** Polarizing optical microscopic images of LC films in water (a) without SDS and (b)–(c) with SDS of 1.4 and 1.8 mM respectively (d) schematic illustration of LC films and SDS in water,**(D)** Fabrication process of LC biosensing as (a) cleaned glass slide (b) self-assembled DMOAP/APTES by activation with GA (c)–(d) immobilization of DNA in the absence and presence of Cd2+respectively(e)The corresponding 5CB LC molecules fabricated with the DMOAP-coated glass slides (f) 5CB molecules fabricated with slide immobilized with DMOAP/APTMS in the presence of Cd2+Adapted with permission from (Deng et al., 2015; Khan and Park, 2014; He, 2015; Tyagi et al., 2014).

detection techniques of sensing several biological analytes and chemical composites (Luan et al., 2020).

Cholesterol is a wax like substance that is produced in the body by liver but is also found in some nutrients (Michikawa, 2003). It plays a crucial role in the working of every cell and is also needed to produce vitamin D, different hormones and bile acids for digestion. However, the excess of cholesterol (200 mg/dl) in the blood can enhance the risk of hardened arteries, coronary heart disease and even strokes whereas the reduced level of cholesterol is due to malabsorption, wasting syndrome, hypothyroidism, and obstructive jaundice and anemia, *etc.* (Ashen and Blumenthal, 2005). Thus cholesterol detection in blood and food is necessary for detection and treatment. The detection of cholesterol can be done by using cholesterol oxidase (ChOx) LC biosensor which is based on the perturbation of LC orientation. By surface assimilation, a SAM of surfactant (such as DMOAP) and silane (such as APTMS) is developed on a glass plate. Before using the film for biosensing purposes, the cholesterol oxidase should be immobilized on the SAM surface. This biosensing study was carried out on cells in which cholesterol concentrations ranging from 10 mg/dl to 250 mg/dl. The whole mechanism was verified through POM, scanning electron microscope (SEM) and spectrometric techniques. In the case of homeotropic alignment, there is the absence of transmitted light. When ChOx was incorporated, there was a slight transmission of light in the transformation from homeotropic to planar alignment. While the maximum transmission of light was observed in the case of homogeneous alignment caused due to the presence of cholesterol. When the cholesterol concentration was large enough, we observed the extreme contrast is observed in the LC cell, showing that maximum birefringence was achieved. This variation is demonstrated in Fig. 4A using SEM imaging which showed some cup-type structures formation over the cholesterol level. On increasing the concentration of the cholesterol, these structures grow and reveal bulging of the flat surface (Tyagi et al., 2014).

A reliable, fast and proton-sensitive glucose biosensor was constructed by a TEM grid filled with 5CB on an OTS-coated glass substrate by coating with PAA-b-LCP at the water/LC interface and immobilizing GOx on the PAA chains through covalent (Khan and Park, 2014). In this

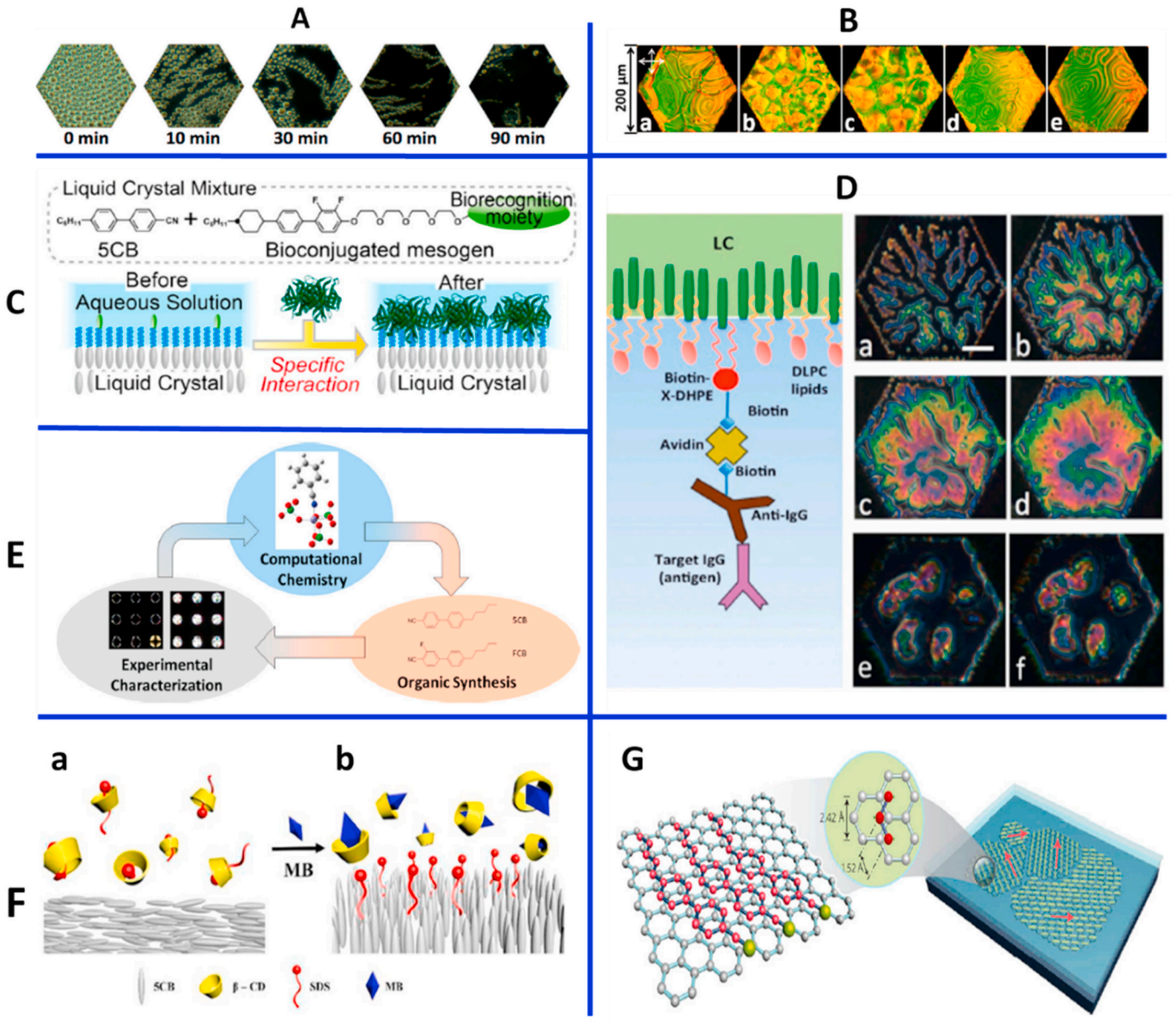

Fig. 5. Toric focal conic domain, formed by hybrid-aligned 8CB film, coverage as a function of time (0–90 min) at 37 °C (A), A 5CB thin film texture coverage with a chiral dopant as a function of water (0–1.89 mM) (B), functionalization of LC for specific binding (C), surface chemistry i.e., biotin-avidin to achieve specific binding with a targeted biomarker (D) and performance of developed immune sensor using biotin-avidin chemistry. This sensor detected 10 mg/mL of antigen as a function of time ranging from 10 to 50 min (D), Computational chemistry-based chemo-responsive design of a LC (E), Host-guest interaction of b-cyclodextrin (CD) and methylene blue as evaluated using MD (F) and exploring orientation of graphene domain in thin film using a LC (G). This figure is adopted from Popov et al. (2017b), MDPI 2019. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

biosensor, the sensitivity of the detection of the small amount of glucose present in the sample is very high. This combined system showed a fast response time, long-term strength and careful diagnosis of glucose against galactose. This biosensor can be utilized in the specific detection of glucose with high sensitivity and activity (Fig. 4B). Apart from LC-based glucose biosensor different other biosensors have been designed for sensitive detection of glucose. A glucose biosensor based on sol-gel immobilization has been developed in which a monolithic silica gel matrix is used for entrapping GOx (Esposito et al., 2011).

Sihui He and co-workers have successfully detected bile acids using LC-based biosensors. Bile acids, an important metabolite, are produced in the liver as the end products of cholesterol metabolism and then discharged into the intestine. Bile acids play an important role in the digestion process and absorption of fats. The concentration of bile acids should be maintained otherwise it causes several intestinal and liver diseases (Sipka and Bruckner, 2014). There are other conventional methods for the detection of bile acids but less popular because of complex and expensive. To overcome such a problem this group developed a low cost, fast detecting biosensor for the detection of bile acids (He, 2015). This sensor is based on the anchoring transitions of LCs at the SDS-laden LC/aqueous interface for the proper diagnosis of bile acids in aqueous solution. The displacement of SDS from the LC/aqueous interface changes the homeotropic-to-planar anchoring transition of the LC at the interface. As the concentration of SDS increases at LC/aqueous interface, the θ decreases and at a critical concentration of SDS, LCs oriented homeotropically which shows as dark appearance under POM (as shown in Fig. 4C).

There is a full elucidation of a biosensor detecting Cd^{2+}. Cd is a heavy metal that can be collected mainly in the liver, lungs, kidney, heart and other parts with the age of more than 20–30 years (Thind, 1972).

Cd^{2+}gets attached with protein containing thiol which changes the structure and function of the protein (Fig. 4D). Some metallic ions (like Zn^{2+}) is relocated from enzyme when its accumulation starts, resulting in disorder in biological processes. These disorders can cause several problems such as kidney failure, reproductive disorders, cancer, *etc*. Therefore, it is interesting to design and develop a fast, high sensitivity and precise technology to detect Cd^{2+} in various fields such as food safety and disease prevention. It is better to take suitable oligonucleotide fragment (a recognition molecule of Cd^{2+}) as it shows better affinity with guanine-rich DNA molecules. Recently, Schwartz used the idea to detect the target DNA by the orientation change of LC molecules due to changes in the conformational arrangement of before and after DNA hybridization. This change can be observed through POM (Deng et al., 2015).

For the diagnosis of DNA molecules, the DTAB-coated E7 (used NLC mixture) in the TEM grid (TEM_{DTAB}) possessed a homeotropic alignment and changed this planar alignment on electrostatic adsorption of the $ssDNA_{probe}$. The$TEM_{DTAB/DNA}$ was further exposed to targeted ssDNA, which resulted in a planar-to-homeotropic transformation of E7 observed under a POM. The detection capability of $TEM_{DTAB/DNA}$biosensor was analyzed with a $ssDNA_{target}$as well as a mismatched ssDNA. The DNA-based biosensor systems have been explored in response to the growing interests in other fields also (i. e. gene analysis, rapid detection of biological analytes, pathogenic bacteria, forensic applications, *etc*.) (Khan et al., 2016).

An advanced sensor based on LC for the detection and diagnosis of sepsis has been developed (McCamley et al., 2007a, 2007b). Sepsis is a severe illness that happens when the body has a huge immune response to bacterial infection (Kumar et al., 2019). This time the released chemicals into the blood which fight against infection produce some inflammation. These results in blood clots and the blood flow become affected. In severe cases, the organs become fail due to lack of proper nutrients and oxygen (Rittirsch et al., 2008). Sometimes, it leads to sepsis shock as the blood pressure drops, and the heart weakens. In the blood of a septic patient, an endotoxin known as lipopolysaccharide (LPS) is present which disrupts the sensor of aligned LC. The bulk LC amplifies these local changes which can be observed through a POM.

Though, in LC-based biosensors, only nematic LCs have been used for several years for their long-range orientational order. But the FLCs which are the latest member of LC family and are well known for their attractive properties such as low threshold voltage, memory effect, P_s, wide viewing angles, better optical contrast, more durability, *etc.* would also be used for highly sensitive and selective LC-based biosensor. It has been reported that FLCs are futuristic materials from biosensing application point of view. Definitely, they are more advantageous than the LC materials used in biosensing applications till date. However, to the best of our knowledge, there is no report in the literature available based on FLC based sensing systems. In fact, considering a LC based biosensor, the LC material is filled in the sample cell at isotropic phase which should be equal to the temperature required for sustaining the bio species. The isotropic phase temperature is very high in case of FLC material which make inappropriate them to be used in sensing. If one can synthesize the FLC having isotropic phase temperature near to the room temperature/ sustainable temperature for biomolecules, then they could be the best for bio-sensing applications. In this direction, researchers/chemists should try to synthesize FLC material, which could have isotropic phase temperature nearly required for biosensing purpose.

5. Nanotechnology enabled LC-based biosensors

This review article suggests the utilization of smart functionalized NPs of desired electrical and optical features that could enhance the sensing capacity of LC-based biosensors. The contribution of LC in sensor development is getting attention of experts to achieve effective diagnostics and environmental nonrioting (Popov et al., 2018). The easy alignment of LC and further controlled polarization vial optimization stimulation of temperature helps to get the desired phase which is useful for developing sensitive sensors (Popov et al., 2018). In such situations, the final optical signal will be of high amplification needed for accurate detection using spectrophotometers. For example, 8CB (4-cyano-4'-octylbiphenyl) exhibited a controlled phase change as a function of time (0–90 min) due to the formation of a hybrid alignment as illustrated in Fig. 5A (Popov, 2015). A LC can be turned into a chiral phase via doping of an appropriate surfactant, for example, SDS (Fig. 5B) which changed the pitch of periodic texture (Popov et al., 2017a). Such a platform is very useful for sensing the chirality of various biomolecules. Besides, the surface functionality is emerging as another approach to design and develop sensitive LC-based biosensors for selective detection of a targeted biomolecule. Due to desired functionality, and biorecognition molecule, for example, amphiphilic mesogens can be bind with a LC material. Surface chemistry-based such approaches make transition alignment very easy resulting in selective detection of targeted marker (Fig. 5C) (Eimura et al., 2016).

Besides surface modification, specific biomolecule can be attached with LC via a cross-linker, for example, EDC-NHS and biotin-avidin chemistry (Fig. 5D) (Popov et al., 2017b), an adopted approach to generate functionality which allows binding with a biorecognition element such as DNA, antibody, *etc.* to detect targeted biomarker at a low level and in a wide range. In order to develop a sensor that has clinical relevance, the optimization of a LC structure, alignment, effect of stimulation, final expected properties are crucial. Despite experimental approaches, the introduction of computational science is increasing significantly. This approach helps to optimized synthesis routes, understand predictions, maximize chances of success, and assess risk factors. The optimized LC materials are known to exhibit desired properties such as chemo-responsive as illustrated in Fig. 5E (Szilvási et al., 2017). Besides computational chemistry, molecular dynamics (MD)-based calculation is also in practice to optimize the physical properties of a LC system in an environment. Considering every factor during simulation, MD will simplify the structures of material for example binding/non-binding sites, according to the targeted application and environment. In order to make a sensor, MD will reveal the organization of a LC thin film at the interface with substrate or biomolecules, as illustrated in Fig. 5F (Liu et al., 2017).

The outcomes of LC-based sensing systems are well-adopted with the scope of developing more advanced and efficient structures. These next-generation LC sensing materials will be more affordable, sensitive, and adoptable, special considering wearable sensing system development. Such of targeted future plan of LC-based sensors raised the demand for the introduction of nanotechnology in the science of developing LC-based smart and efficient sensor needed for selective diagnostics and sensitive environmental monitoring (Kaushik and Chandra, 2016).

The self-assembly of NPs in LC phase improve various aspects of biological sensors and drug delivery. There are four groups of NPs including ferroelectric, metal, semiconductor and carbon adopted to improve the characteristics of host LC material (Joshi et al., 2010; Lapanik et al., 2012; Lisetski et al., 2009; Singh et al., 2014). The ferroelectric NP plays a significant role in LC via increasing the order parameter due to the interaction between P_s of the NP with the elastic forces of the LC (Li et al., 2006). One of such exciting research was performed using 1 or 2D anisotropic NPs in lyotropic LC to achieve self-assembly (Kato et al., 2006). Based on observed improved characteristics, this soft matter leads with more advanced and improved medical technique to detect immune related bio-actives related with several types of diseases threatening mankind (Shen and Dierking, 2019). Various reports have explained the improvement of disruption of LC inclination in the presence of NPs which leads to the simple and amplified detection of a targeted marker using NP-assisted LC based sensors (Choudhary et al., 2018; Hartono et al., 2009; Liao et al., 2011; Tan et al., 2010; Wei and Jang, 2017; Yang et al., 2012; Zhao et al., 2015). Recently, Wei et al. utilized nickel (Ni) NPs to disperse in LC for

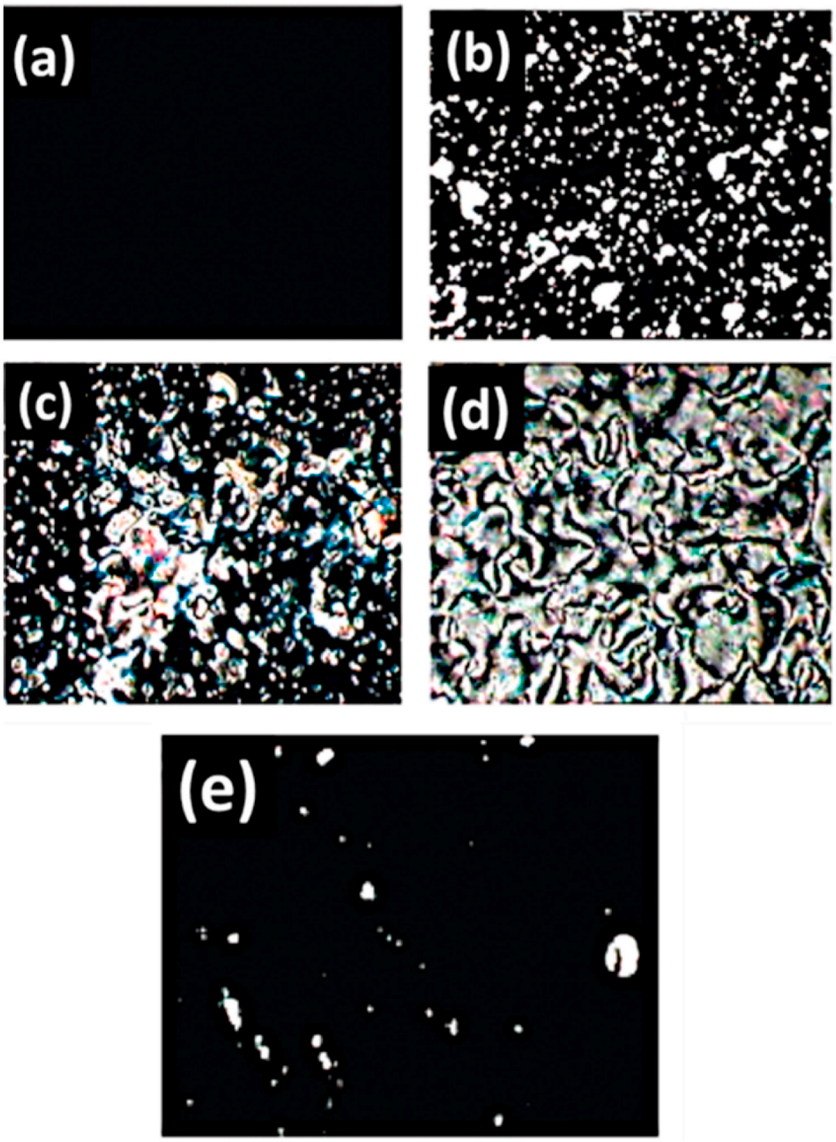

Fig. 6. Optical images of LC cells based on DNA functionalized AuNPs. Complementary target DNA at concentrations of (A) 0; (B) 0.1 pM; (C)1 pM; (D) 10 pM; and the two-base mismatched DNA at a concentration of (E) 10 pM. Adapted with permission from Yang et al. (2012).

an easy visualization of the enzymatic activities between cholylglycine hydrolase (CGH) and cholylglycine (CG) (Wei and Jang, 2017). Thus, generated uniform homeotropic alignment in LC through Ni NPs could be disrupted through the immobilization of CG on CGH layer.

Nanotechnology will introduce surface-functionalized structures of nanoscale which exhibit desired shape, size, morphology, surface charge, and intrinsic properties like optical, electrical, magnetic and molecular (Kaushik et al., 2014a, 2014b, 2016a, 2016b, 2017, 2018; Kaushik and Mujawar, 2018; Solanki et al., 2011; Tiwari et al., 2019). Due to small size, these nano-structures/systems can easily mix and align with a LC to generate a new phase or class of material i.e., hybrid composites. This kind of new sensing material will exhibit novel properties that are absent in precursors i.e. LC and selected nanostructure. NPs enhance the local orientational order parameters of LCs and thus the biological entity easily binds to the surface of the LCs (Choudhary et al., 2018). This concept would further help in improving the detection efficiency, compatibility and selectivity of different recent diseases such as cancer *etc.* (Vallamkondu et al., 2018). Some other methods such as Photonic Immobilization Technique for the antibody functionalization on electrodes can be incorporated in LC that will promote further development of detection of a variety of analytes. This technique will be helpful for sensing light molecules and provide flexibility and portability as well as quick response (Funari et al., 2013, 2015). The hybrid system of a LC and nanostructure can be controlled easily to achieve desired optical, electrical, and magnetic properties which are useful to develop a sensor of high sensitivity, wide detection range, low detection range, and high stability. Due to manageable features, nanotechnology-assisted LC-based biosensor can be a system of choice to develop miniaturized sensing systems needed for a point-of-care (POC) application.

In this direction, efforts have been made to explore the interaction of LC and nanostructure such as carbon nanostructures, molybdenum diselenide, and tungsten diselenide. For example, LC has been explored to understand the alignment of the 2D graphene sheet (Fig. 5G) via imaging the birefringence of a nematic LC due to strong π-stacking interaction (Kim et al., 2011).

The alignment of LC molecules is highly influenced by surface effects. Thus, a small change of the surface leads to the LC molecules to be oriented in a different direction and thus gives some transmitted light intensity through LC cell when observed under POM. At first, the substrate is chemically functionalized on a plain glass surface. In this process there is no light passes through the sample cell. The glass slide is then incorporated with enzymes of the targeted diseases. The slight

Table 2
Performance of LC-based biosensors.

S. No.	Sensing platform	Sensing parameters	Remarks	References
1.	SAM (surfactant) = sodium dodecyl sulfate DT = polarizing microscopy TA = endotoxin	DR = 1ng/ml-1 mg/ml DL = 1 ng/ml	label-free detection, no complex binding process	Maureen K. McCamley (2009)
2.	SAM (surfactant) = dodecyltrimethylammonium bromide (DTAB) DT = polarizing optical microscopy IB = single-stranded deoxyribonucleic acid probe (ssDNAprobe) TA 8= DNA	DR ≥ 0.05 nM DL = 0.05 nM	label-free detection of specific pathogen DNA.	Mashooq Khan et al. (2016)
3.	SAM = dimethyloctadecyl [3-(trimethoxysilyl)propyl]ammonium chloride (DMOAP) and (3-Aminopropyl)trimethoxy-silane (APTMS) DT = polarizing optical microscopy IB = cholesterol oxidase TA = cholesterol	DR = 10–250 mg/dl DL = 10 mg/dl	simple detection, direct transduction, high sensitivity, and low-cost.	MuktaTyagi et al. (2014)
4.	SAM (coating) = poly (acrylicacid-b-4-cynobiphenyl-4-oxyundecylacrylate) (PAA-b-LCP) DT = polarized optical microscopy IB = glucose oxidase TA = glucose	DR = 0.02–2 mM DL = 0.02 mM	Low production cost and easy detection through the naked eye	Mashooq Khan and Soo-Young Park (2014)
5.	SAM = N, N-dimethyl-N-octadecyl-3-aminopropyltrimethoxysilyl chloride (DMOAP) and (3-aminopropyl) triethoxysilane (3-APTES) DT = polarizing microscope IB = DNA TA = Cd^{2+}	DR = 0.1–1 nM DL = 0.1 nM	high specificity and sensitivity	Shixiong Deng et al. (2015)
6.	SAM = carboxylic acid DT = naked eye IB = metal perchlorate salts TA = organophosphorous nerve agents sarin (GB), soman (GD), tabun (GA) and VX	GB = 2.25×10^4 mg/m^3 GD = 2.060×10^3 mg/m^3 GA = 5.60×10^2 mg/m^3, VX = 1.6 mg/m^3	simpler and less expensive	Katie D. Cadwell et al. (2007)
7.	SAM (coated) = octadecyltrichlorosilane (OTS) DT = polarized light microscope IB = TEM grid TA = mercuric ions (Hg^{2+})	DR ≥ 0.5 μm DL = 0.5 μm	fast, precise and selective detection of metal ions with a very low detection limit	Sachin Kumar Singh et al. (2016)
8.	SAM = poly (urethane acrylate)-coated silica substrates into 1 mMethanolic solution consisting of 0.5 mMmercaptoundecanoic acid and 0.5 mMdecanethiol DT = Polarization Light Microscope, Ellipsometry, Atomic Force Microscopy IB = tuberculous antigen ESAT-6 TA = tuberculosis	0.015–15 μg/mL	label-free detection of anti-tuberculosis antibodies	Hyeong Jin Kim et al. (2015)
9.	SAM = triethoxysilylbutyraldehyde/N,N-dimethyl-N-octadecyl (3-aminopropyl) trimethoxysilyl chloride (TEA/DMOAP) DT = polarized optical microscopy IB = single-strand ATP aptamer TA = adenosine triphosphate	DR ≥ 10 nmol/L DL = 10 nmol/L	simple and sensitive detection	Zhaoyang Wu et al. (2013)

Abbreviations: IM, immobilizing matrix; DT, detection techniques; DR, detection range; DL, detection limit; RT, response time; IB, immobilizing biomolecule; TA, target analyte.

transmission of light is detected through the sample cell when observed under POM. With addition of this, when finally, the surface is integrated with NPs, the light can be observed with maximum intensity as incident after passing through the LC materials (Liao et al., 2012).

Firstly, Liu and co-workers state a simple LC-NPs assisted approach for the highly sensitive detection of DNA by using Gold NPs (AuNPs) (Liu and Lu, 2003). When the AuNPs interact with DNA strands, there is a significant change in the surface density of DNA strands and amplification in interruption of thin LC layers takes place which results in the homeotropic-to-tilted transition of the LC molecules and optical textures are observed rather than the dark background. It provides high selectivity and a significantly lower detection limit of 0.1 pM (Fig. 6). The variation of the birefringent domain with the concentration of targeted DNA is also given (Yang et al., 2012).

Further to detect L-tyrosine (Tyr), an amino acid that is used by cells to synthesize proteins, a LC-based biosensor has been reported (Li et al., 2015). The activity of Tyr directly controls the melanin's absorption (absorbent of light and save the skin cells from UVB radiation, lowering the risk of cancer), which can be used to treat a different congenital disorder such as albinism. Thus, Tyr detection is very important (Roufs, 1990). As the concentration of the Tyr increases the birefringent texture in the optical images was amplified, showing the huge production of l-DOPA (L-3,4-dihydroxyphenylalanine) to form large-size AuNPs which change the surface topology of LC cells and induced a homeotropic-to-tiled transition of the LC molecules. Thus, a LC biosensor based on the catalyzed enhancement of AuNPs for the Tyr detection is designed and achieved by the birefringent characteristic of LC under crossed polarizers. This biosensor works properly, especially at low Tyr concentration.

A LC biosensor based on the enzymatic growth of AuNPs has been fabricated for the detection of acetylcholine (ACh) which is an organic substance that controls the functions (in the brain and body) of human as well as animals as a neurotransmitter and acetylcholinesterase (AChE) inhibitor (McGeer and McGeer, 1973). When different concentrations of ACh is added to the AuNPs growth solution, the optical images of birefringent texture decrease with increase in the ACh

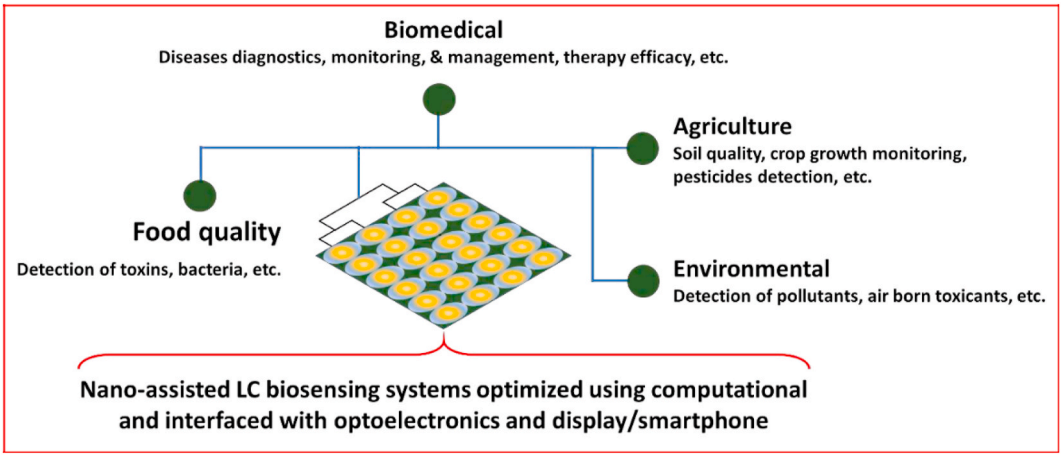

Fig. 7. Prospects of nanotechnology assisted LC-based biosensing systems optimized using computational chemistry, molecular dynamics, and opto-electronics.

concentration from 0.015 to 1.5 mmol/L (Liao et al., 2012).

A novel LC-based sensor based on nickel nanosphere (NiNS) for the detection of thrombin was manufactured (Maragoudakis and Tsopanoglou, 2019). The homeotropic alignment of 5CB was easily obtained by doping NiNSs. A sandwiched system of aptamer-functionalized AuNPs was fabricated which made the strand-like aptamers enhance the disruption of the LC orientation results in the orientational transition in LCs. This transition can easily be visualized, and 0.1–100 nM concentrations of thrombin were detected. Depending on the ratio of the area of bright images of LC to the whole sample we can find the quantitative concentration of thrombin (Zhao et al., 2015).

6. Viewpoint

The main idea of developing biosensor emerged form demand of managing a better health care. It can be used in instant remedial action to provide a better estimation of the metabolic state of a patient. Due to its small size, it can be handled easily (McCamley et al., 2007a, 2007b). LC-based biosensors are of low cost and thus can further used for the detection of different diseases and metabolites such as diabetes, cancer, stroke, multiple sclerosis, heart rate, body temperature, blood pressure, *etc*. The performance of LC-based biosensors reports in the literature is summarized in Table 2. Biosensors are successfully used for the quantitative estimation of several biologically important substances in body fluids such as glucose, cholesterol, urea, endotoxin, DNA molecules, cadmium, bile acids, TB, ATP, *etc*.

Apart from the applications in clinical diagnosis and biomedicine area, LC-based biosensor can be used in pharmaceutical (estimation of drug residues in food, such as antibiotics and growth promoters, drug recognition and assessment of biological activity of newly compounds), fermentation control and analysis of food and drink, industrial effluent control, pollution control and examine of mining, industrial and toxic gases as well as military applications. Numerous LC biosensor techniques have been reported that allow researchers to better study the structure and interface phenomena (Rogers, 2000). Thus, biosensor technology possesses an enormous potential and provides revolutionize analysis and control of biological systems.

7. Conclusions and prospects

Different types of LC-based biosensing approaches, sensing techniques, various display, and non-display applications of LCs have been described in this report. The molecular reorientation process in the presence of an external electric field plays an important role in sensing techniques. The effect of nanomaterials on the sensing properties of LCs has been observed. In recent years with modern nanotechnology, the fabrication of novel NPs with LCs has been improved the sensing properties. The current and future research efforts promise to further expand our knowledge in the field of LCs sensor devices and will likely contribute to the identification of several new diseases.

Table 3
Applications of liquid crystals-based biosensors for efficient diagnostics for health wellness.

Field	Targeted Applications
Healthcare	Targeted biomarker detection
	Disease monitoring
	Affordable Diagnostics
	POC application
	Therapy efficacy assessment
	Personalized diseases management
Agriculture	Soil quality assessment
	Pesticides detection
	Crop growth management
Environmental	Detection of pollutants
	Air born toxicants
	Water quality assessment
Food quality	Detection of food borne toxins
	Detection of food borne bacteria
	Food safety and storage management

The outcomes of this report provide fundamental insights into the origins of anchoring transitions which reveals a wide range of dynamic phenomena exhibited by LCs with reference to targeted analytes. These LC-based sensors could abruptly change surface topography of the substrate and a homogeneous-to-homeotropic orientational transition results in an optical signal which is observed by naked eyes. The quantitative observations of optical images under POM further confirm the sensing mechanism. This type of sensing technique has been successfully utilized for the detection of enzymatic/protein interactions or various ligand-receptor interactions. It can also be used to probe directly at different interfaces such as liquid-liquid interface, oil-water interface *etc*.

The FLCs based biosensor as an attractive optical material due to its fast-electro-optic response and surface stabilized biostability which is very sensitive to alignment conditions (Clark and Lagerwall, 1980). By applying a high-frequency ac electric field, the ac field-stabilization effect stabilizes the switched state of FLC with negative dielectric anisotropy (Ozaki et al., 1987; Pesant et al., 1985; Umeda et al., 1988). The FLC compounds having small P_s and low rotational viscosity (η) possess a larger ac field-stabilization effect than those compounds with large P_s, and high η under the same dielectric torque condition. Therefore, FLCs can be used for a faster response. Therefore, this type of LC may provide new avenues for open-minded researchers for exciting research in the

biosensor and other applications.

Many conventional *in vitro* diagnostics for infectious diseases (HIV/AIDS, hepatitis B, measles, tuberculosis, *etc*.) are time-consuming, expensive and less efficient in accuracy and precision. In the proposed FLC based biosensor, it would be easily detected due to their P_s and θ. Most of POC applications in the real-world require label-free optical biosensors which need the precise alignment of the light coupling to the sensitive area which can be done by this proposed biosensor. The NPs-assisted LC-based biosensor can be further explored in different arena of life such as biomedical, agriculture, environmental as depicted in Fig. 7. Keeping advancements and capabilities into considerable, LC-based nano-systems can be utilized for the efficient biosensing of severe acute respiratory syndrome coronavirus 2 (SRS-CoV-2) selectively, rapidly, and at low level. Such sensing competences are required to manage recent COVID-19 pandemic outbreak (Mujawar et al., 2020; Paliwal et al., 2020).

Nanotechnology-assisted LC-based advanced biosensors can potentially be applied for diseases diagnostics at early stage, even at POC application, required for a better access of health care. Keeping scope, demand, and prospects in view, such of effective and efficient biosensors project various versatile futuristic applications as summarized in Table 3.

Overall, the results of many scientific researches suggest many principles based on LC interfaces which might be used for designing of highly specific biosensors based on stimuli-responsive materials. The expected success in this area also depends on the techniques used in immobilization methods, selection of enzymes, and target molecules. Various strategies based on smart nanostructures would be useful for improving the sensing performance of LC biosensor, mainly low detection of limit and high sensitivity. Besides, such of sensing system are cost-effective due to easy fabrication without need to expensive laboratory set-up, need of low operational power, and no batch-to-batch response variation exhibit repeatable and reproducible sensing outcomes. This report summarized strategies and mechanisms involved in developing portable LC based biosensors for label-free detection of a targeted analyte at a low level. Authors are determined to explore such sensor for diseases diagnostics, and food safety, and fighting against epidemics. We believe that due to desired sensing performance, nano-enabled LCs-biosensors can potentially be applied for detecting any biological molecules.

Declaration of competing interest

There are no conflicts of interest declared by the authors.

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