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Biosensors and Bioelectronics Open Access

Sun Q, et al. Biosens Bioelectron Open Acc: BBOA-137.
DOI: 10.29011/ 2577-2260. 100037

Review Article

Electronic Biomaterials Towards Flexible Sensors: A Review

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Citation: Sun Q, Qian B, Uto k, Chen J, Liu X, et al. (2018) Electronic Biomaterials Towards Flexible Sensors: A Review. Biosens Bioelectron Open Acc: BBOA-137. DOI: 10.29011/ 2577-2260. 100037

Received Date: 25 May, 2018; **Accepted Date:** 04 June, 2018; **Published Date:** 11 June, 2018

Abstract

Biomaterials have gained increasing attention in fabrication of a variety of flexible electronics due to their tunable solubility, robust mechanical property, multi-active binding sites, and excellent biocompatible and biodegradable characterization as well. Here, we review the recent progress of bio-based materials in flexible sensors, mainly describe nature biomaterials (silk fibroin and cellulose) and conventional chemical-synthesized biomaterials as well as their applications in health monitors, biosensor, Human-Machine Interactions (HMIs) and more, and highlight the current opportunities and challenges that lay ahead in mounting numbers of academia and industry. Thus, we expect this review could contribute to unveiling the potentials of developing outstanding and eco-friendly sensors with biomaterials by utilization of printing techniques.

Keywords: Biocompatibility; Biodegradability; Biomaterials; Biosensor; Flexible Electronics

Introduction

Flexible wearable electronic devices which can tolerate or withstand the stretching or bending forces, or other large deformation have been widely investigated in past decades [1]. The flexible, extensible electronic device normally consists of traditional rigid board systems and stretchable materials: the former typically shows good mechanical properties and the lateral can be stretched like a rubber band [2] and folded like paper [3]. Particularly, the ever-growing demands for flexible electronic devices will dedicate to a rapid population growth. Hence, the disposal of abandoned electronic devices has already received considerable concerns around the globe in recent years, which may cause adverse impact on the environment. However, majority of previous developed electronic devices that are made up of non-biodegradable raw materials, like some plastics, cannot meet the trend of frequent updating of consumer electronics. Therefore, intensive studies are striving to challenge with this issue.

With the rapid development in electronic biomaterials and the relevant manufacturing techniques, researchers tend to combine bio-based materials with flexible electronic devices for sustainable development. The flexible sensor, one of the most essential parts of flexible electronics has its potential applications in monitoring human and robot motion [4-6] and personal healthcare [7,8], detecting overall hygiene in the food system [9] as well as analyzing pesticide residues and toxic substances [10]. Furthermore, strategies to construct bio-based sensors with high mechanical durability, high sensitivity to deformations and responsive conductivity are also well addressed in numbers of published works.

Herein, we focus on the work of predecessors who committed to research biomaterials and bio-based sensors. First, we summarize various biomaterials ranging from natural to conventional chemical-synthesized biomaterials, and introduce fundamental processing properties of biomaterials and their great potential for bio-based sensors. Then, we highlight several applications with the example of respective biomaterials in individual healthcare, wellness pressure, sensing-based Electronic skin (E-skin), biomedical diagnosis, food safety and environment governance. Finally, the future perspectives of bio-based sensors and the technological issues involved in applying biomaterials and practical devices are discussed and prospected with the hope to improve the development and application of biomaterial-based sensors in our daily life.

Biomaterials

Biomaterials, also known as bio-based materials are produced from renewable resources. Specifically, those biomaterials are made from raw materials such as cereals [11], legumes [12], straw [13], bamboo powder [14] and other raw materials through biosynthesis, bioprocessing and biological refining process. Besides that, biomaterials also include bio-based plastics and fibers, sugar engineering products, and bio-based rubber made from biomass thermoplastic processing, which are degradable when exposed to microorganisms, carbon dioxide (aerobic) processes, methane (anaerobic processes), or water (aerobic and anaerobic processes). Polymer materials play irreplaceable role in human daily life. Even though, except natural rubber and few other materials, most polymer materials are highly dependent on fossil resource (mainly oil and coal), which have induced lots of problems on environmental pollution, human health issues and destruction of the entire eco-environment. To bring a significant reduction in greenhouse gas emissions and saving of fossil energy, sustainable and eco-friendly polymers have become increasingly important. Many efforts have been taken to fabricate various biodegradable materials from bio-based chemicals.

Here, the silk fibroin with nanofibers and cellulose with nanofibers and nanocrystals, as well as polylactic acid and polyurethane that could be fabricated into nanostructures are highlighted to describe the recent progress and novel application of biomaterials in flexible electronics, such as the artificial skin, flexible displays, biosensors and so on.

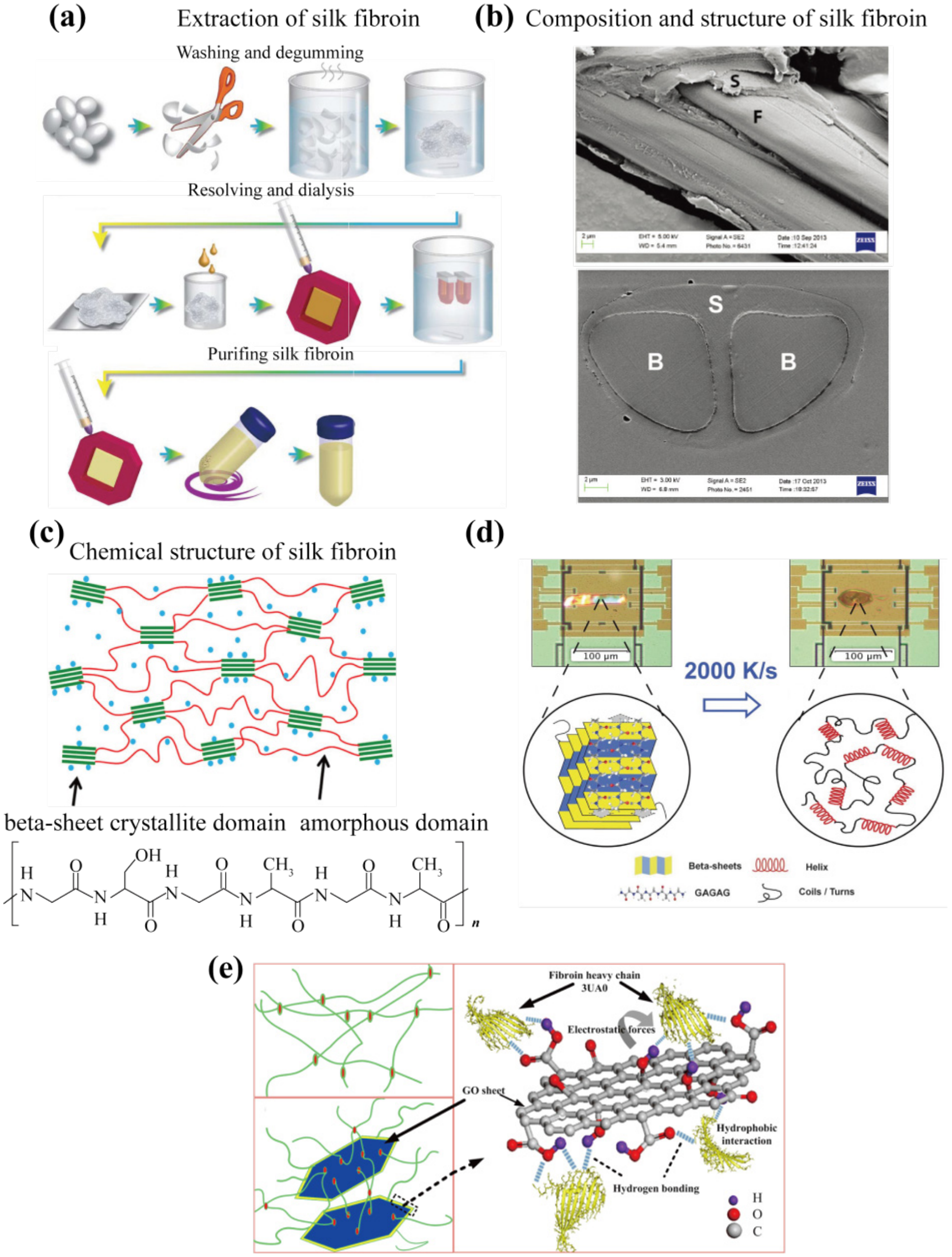
Natural Biomaterials

Natural biomaterials possess outstanding advantages for high-performance and functional electronic devices on the account of their renewable, biocompatible, biodegradable and excellent mechanical properties, as well as multiple reactive sites for modulating novel functions. They have been bringing huge benefits to mankind in the aim of improving the hygiene, health and life conditions. The widespread applications of natural biomaterials have spread to the tissue regeneration [15], drug delivery system [16], implants, enzyme immobilization [17], wound dressings [18], sensing [19] and electrical devices [20]. Recently, the applications of natural biomaterials in the flexible electric devices have been research hotspot [21]. The ease processing of natural biomaterials with promising structures and forms (such as optical films and hydrogels), as well as adaptable performance make them potential in organic, electrical or ionic conductivities by incorporating with highly conductive materials or structure alteration via chemical modification. Here, we highlight two kinds of biomaterials which have gained lots of interests in the fields of flexible electronic devices: protein (silk fibroin), and polysaccharides (cellulose).

Silk Fibroin

Silks are nature fibrous proteins existing in the glands of some arthropods, such as silkworms, spiders, scorpions, mites and bees. In recent years, silk from *Bombyx mori* (silkworm) has been widely studied due to its high yield [22], excellent tensile strength (0.5~1.3 GPa) and toughness (6×10^4~16×10^4 J/kg) [23], predominant biocompatibility, tunable biodegradability, and ease of processing [24]. These predominant characterizations give silk proteins versatile applications in biological fields, including tissue engineering [22,25-26], wound healing [27,28], and drug delivery [29,30]. Silk fibroin (SF) (≈75 wt%) and sericin (≈25 wt%) are the two major proteins of silk [31]. As shown in figure 1 (a and b), SF protein is located at the corner of the silk fiber surrounded by the sericin proteins which could be removed by a thermo-chemical treatment (degumming) [32]. SF is a natural fibrous protein composed of a heavy and a light chain that are linked together by a disulfide bond, as well as a 25 kDa glycoprotein (P25) non-covalently linked to these chains [33,34]. The hydrophobic domains of heavy chains containing repeated Gly-X (X being Ala, Ser, Thr, Val) form anti-parallel β-sheets, while the L-chain is hydrophilic in nature and relatively elastic [22] (Figure 1c). Under high thermal treatment, these crystal β-sheets could be reversed to random coils [35] (Figure 1d). Besides that, the crystal β-sheets structures of SF protein could be improved by water vapor annealing to increase its water insolubility which could be controlled under different annealing times and temperatures [36]. The controllable structures of SF proteins by thermal treatment makes it possible to modify their degradation rates, enzyme/drug release ratios, and hydrophilic/hydrophobic properties.

Besides that, SF proteins properties could also be modulated by incorporating with other conductive materials. Graphene Oxide (GO) with abundant oxygen functional groups (hydroxyl and carbonyl groups) could form intermolecular hydrogen bonds with SF by interacting with the hydrophilic blocks of amphiphilic SF, which increased the mechanical, biological and conductive properties [37] (Figure 1e). Similarly, carbon nanotube could also improve both the mechanical properties and conductivities of SF proteins by increasing the β-sheets structures of SF [38]. Except the adaptable structure, mechanical and conductive properties, SF could be prepared into various formats, such as the porous scaffolds, hydrogels, optical transparent film, and fibers, which make it an excellent candidate in flexible electronic sensors. Furthermore, SF accesses to the third generation of biosensor because of good water solubility to avoid the usage of reagents and ease immobilization of enzymes in SF films [39], which make it potential for solution-processed electronics [40-42]. Therefore, SF is a very promising candidate for the flexible electronic devices due to its excellent biological and adaptable electrical properties.



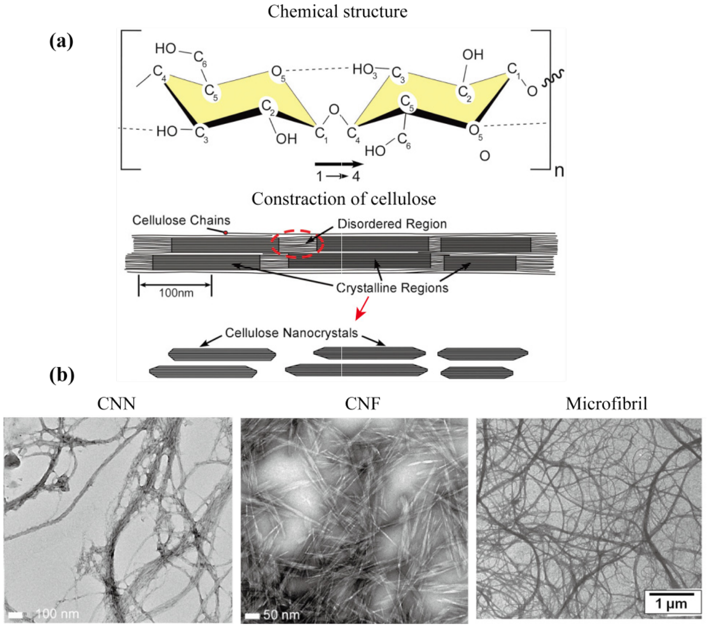
Figures 1(a-e): The detailed information about the SF proteins: **(a)** The degumming process to extract pure SF protein from silk [43]; **(b)** The distribution of SF and sericin in silk fibers [44]; **(c)** The chemical structure of SF [45,46]; **(d)** The revisable structure changes of β-sheets and random coils under high thermal treatment [35]; **(e)** The chemical bonding between SF and GO [37].

Cellulose

Cellulose is a polysaccharide widely existed in the nature environment, such as the cotton, wood, cereal, fiber, and bacteria, composited by hundreds to thousands of ringed glucose molecules through β-1, 4 glucosidic bonds [47]. As shown in figure 2a, the liner configuration of cellulose chains is formed due to the chemical interactions between hydroxyl group and oxygen's of adjacent ring molecules, which stabilize the linkages and form the parallel linear nanofibers. The cellulose chains are formed by amorphous-like (disordered) and crystalline (highly ordered) regions which are used to form the cellulose nanocrystals. The cellulose could be divided into three layer from the view of structure: 1) the formation of cellulose crystals with the diameter of few Å assembled by glucose macromolecular chains; 2) supramolecular layer further formed by above cellulose crystals with the sizes from 4 nm to 1 μm; 3) fiber bundles constructed by above nanofibers; and finally, the fiber bundles together with the amorphous molecules composite the fibrous cellulose in a self-assemble way.

Currently, nanocellulose could be obtained through mechanical, oxidation, and hydrolysis methods [48]; and based on different preparation methods, two kinds of nanocellulose with different morphologies and chemical groups could be formed: Cellulose Nanofibrils (CNFs) and Nanocrystals (CNNs), as shown in figure 2b. CNF is produced by mechanical methods with high shearing following homogenization at high pressure. CNF is a network structure formed by the fibrils with length in micrometer and width in nanometer [49], containing both crystalline and amorphous regions. After removing the amorphous regions via acid hydrolysis, CNN could be formed with highly crystalline structures. In addition, the cellulose microfibrils could also be prepared by biosynthesis which is a multistep process depending on the organism producing the cellulose. Detailed preparation methods could be found in previous work of Brown [50], and Saxena and Brown [51].

Cellulose fiber is a naturally renewable resource, which has been widely applied in the flexible and transparent bioelectronics due to its robust mechanical property, biocompatibility, and biodegradability, as well as high surface area, low thermal expansion, and good flexibility. In addition, as the carrier materials or skeleton supporting materials, the properties of cellulose fiber could be altered and expanded through combining with conductive composites via in-situ polymerization or filtering, such as combing with carbon nanotube and graphene for the flexible electrodes, metal oxide for the photovoltaic materials and solar cells, as well as conducting polymers for the electrochemical sensors, and so on. Therefore, with outstanding mechanical, biocompatible, flexible and adaptable conductive properties, cellulose could bridge the world between nature biomaterials and flexible bioelectronics.



Figures 2(a, b): The introduction of cellulose: **(a)** The chemical structure and construction of cellulose [47]; **(b)** The morphology of cellulose nanofibrils, nanocystals, [52] and microfibrils [47].

Conventional Chemical-Synthesized Biomaterials

The first generation of bio-based polymers focused on deriving polymers from agricultural feedstock's such as corn, potatoes, and other carbohydrate feedstock's. Natural biopolymers are the other class of biomaterials, such as proteins, nucleic acids, and polysaccharides (collagen, chitosan, etc.) [53]. In addition, biodegradable polymers can be produced by chemical synthesis [54], such as Polylactic Acid (PLA), Polyurethanes (PUs) and Polyhydroxyalkanoates (PHAs).

Polylactic Acid

The original materials of PLA mainly including corn, soybeans, beets, potatoes and other biological materials which are made of starch and sugar. One of the most important raw materials is corn, so PLA resin is also known as "Corn Resin". Based on different optical rotation, PLA has three typical optical isomeric forms: optically active and crystalline form (poly (L-lactide) (Poly (L-Lactic Acid) (PLLA)) and poly (D-lactide) (Poly (D-Lactic Acid)) (PDLA)), optically inactive and amorphous poly (DL-lactide) (Poly (DL-Lactic Acid)) (PDLLA). Thereinto, the synthesis, recycling, and degradation of PLLA are shown in figure 3 [55]. PLA is nowadays economically competitive and has been widely used in many day-to-day applications, mainly used in food packing [56] on the account of its outstanding advantages: ease of processing, superior transparency and environmentally benign characteristics. Furthermore, oriented PLLA materials have piezoelectric properties [57], and the piezoelectric constants of PLLA increase with the draw ratio and reach maximum at a draw ratio of around 4~5 [58], which make PLLA a good candidate for piezoelectric sensors.

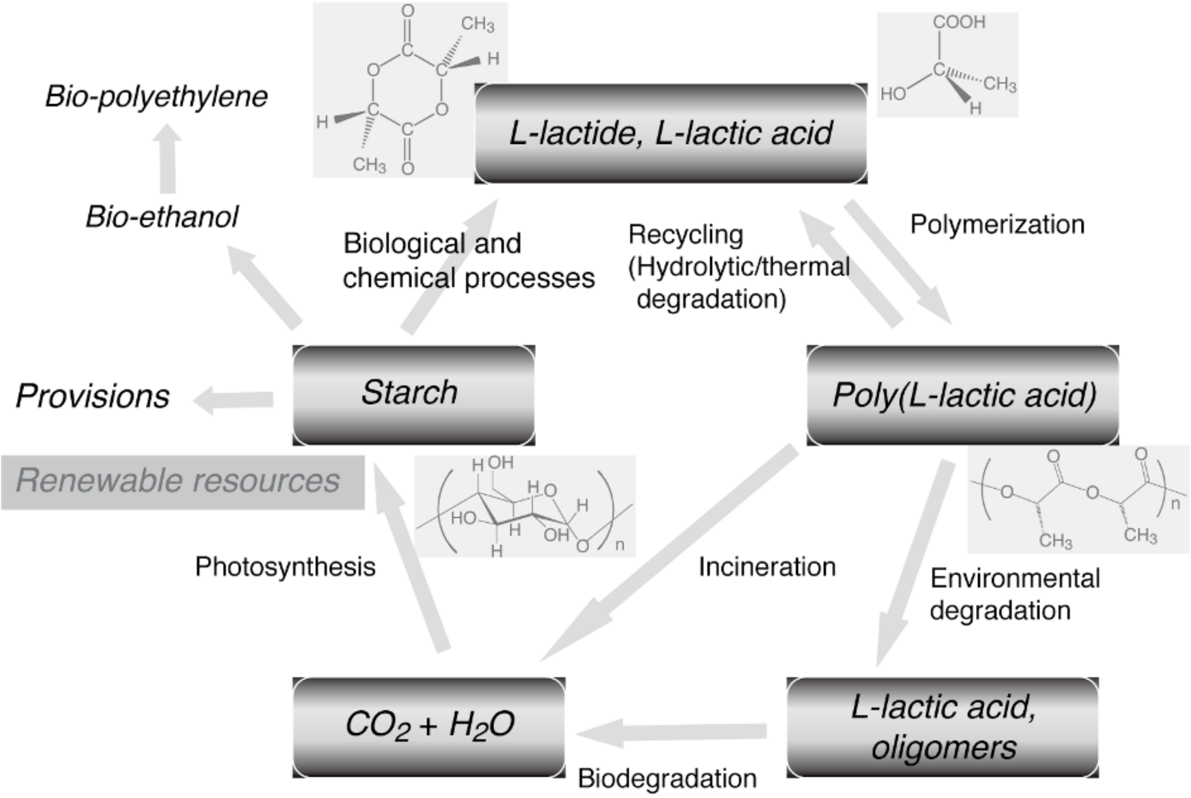


Figure 3: Synthesis, recycling, and degradation of PLLA [55].

Polyurethanes

Polyurethane (PU) refers to a type of polymer which contains a urethane feature unit in the main chain. PU is a block copolymer obtained by a stepwise addition reaction of isocyanate (NCO) and active hydrogen groups [59], followed by chain extension and cross-linking. By changing the proportion of raw materials and the ratio of active hydrogen to NCO, properties of PU can be adjusted within a wide range: from soft sponges to elastomers, coatings to sealants, and shoe soles to elastic fibers. In particular, polyurethane (PU)-based materials have been used in different forms, such as in thermoplastic polyurethane (TPU), PU sponges, and PU yarn [60]. They are known for the favorable tensile properties and thus appropriate for preparing strain or pressure sensors [61]. The sensors based on the above-mentioned materials can demonstrate high stretch ability, little hysteresis, and long-term durability.

Polyhydroxyalkanoates

Polyhydroxyalkanoates (PHAs) are a family of polyesters produced by bacterial fermentation with the potential to replace conventional hydrocarbon-based polymers, so they are thermoplastic, biodegradable, biocompatible, and nontoxic [62] The most common PHAs are Poly-B-Hydroxybutyrate (PHB), Hydroxybutyrate Copolyester (PHBV), Poly(3-Hydroxybutyrate-Co-3-Hydroxyhexanoate) (PHBH), and Poly(3-Hydroxybutyrate-Co-4-Hydroxybutyrate) (P34HB) [63]. PHB, a typical representation of PHAs, has excellent performances of biodegradable, biocompatible and piezoelectric property, except the poor physical properties which make it hard to be applied due to the difficulties in the plastic processing. PHBV is the second generation of PHAs, owning much weaker crystallinity and hardness, but stronger strength and toughness compared with PHB. PHBH is a copolymer composed of short and medium-long chains, which has much improved mechanical properties, compared with PHB and PHBV [64]. As the third generation of PHAs, P34HB is synthesized by *Alcaligenes eutropha* in a sufficient nitrogen atmosphere and a culture medium containing 4-hydroxybutyric acid, 1,4-butanediol/butyrolactone [65]. The presence of 4-hydroxybutyrate increases the flexibility of P34HB due to the reduced crystallinity, making it possible to be molded on conventional plastics processing equipment. Therefore, the advantages of PHAs in biodegradability, biocompatibility and flexibility make them candidates in the application of flexible sensors.

The Composites of Conventional Biomaterials

Nowadays, massive efforts have been devoted to investigate the synthesis and properties of biodegradable copolymers. Through compounding with other dicarboxylic acids or diols, mechanical properties of these biomaterials can be improved in a large scale, which is promising for the application of flexible sensors. PLA mechanical performance could be substantially improved by melt blending with high crystalline isotactic PHB. Besides that, the process ability and thermal stability of PLA/PHB blends can be improved by plasticization through adding micro-/nanoparticles. Furthermore, the fillers (such as catechin) [66], and nanofillers (such as nanocellulose and Organically Modified Nanoclay (OMMT)) [67] could enhance the interfacial adhesion in the blend, leading to more homogeneous material in the final blend composites. Arrieta et al. [68] pointed out that the mechanical performance of PLA/PHB blend matrix has been reinforced through combination with Cellulose Nanocrystals (CNC) and functionalized CNC by means of a surfactant (CNC-s). Jandas et al. [69] further improved the flexibility of PLA-PHB by grafting of Maleic Anhydride (MA) in a reactive extrusion approach. The optimum flexibility of PLA/PHB/MA blends was reached more than 500% by grafting 7 wt% of MA. In addition, blending of PLA with PBS is an effective way to fine tune PLA brittleness. Supthanyakul et al. [70] proposed a simple triblock copolymer for improving the mechanical PLA/PBS blend. The addition of plasticizers is another way to overcome the brittle nature of PLA and improve its flexibility [71]. Fortunati et al. [72] added the Isosorbide Diester (ISE) plasticizer to PLA and PBS substrates, suggesting that ISE at 15 wt% represents the best choice to produce PLA/PBS plasticized blend films. Therefore, the mechanical properties of the conventional biomaterials could be improved through blending with other biomaterials, promising to be applied in the flexible sensors.

Biomaterials Based Sensors

A sensor is a transducer which senses or detects some characteristics of environment, human activity and food safety and so on [73]. Electronics with flexible, stretchable, and wearable features have risen exponentially to be next-generation electronics [74]. Conventional strain-sensing platforms based on semiconductors and metal foils could not fulfill the requirements of wearable strain sensors because of their rigidity, low resolution, and low sensing range (usually<5%) [75]. Various efforts have been made to develop flexible and wearable strain sensors by using nanomaterials as sensing elements coupled with elastic polymers as flexible, stretchable, and durable support materials. Nanomaterials, such as silicon nanoribbons [76], metal nanoparticles [77] or nanowires, and low-dimensional carbons (such as Carbon Nanotubes (CNTs), graphene, and carbon blacks) have been employed to improve the performance of flexible electronics. In addition, to avoid the decomposition problem by using the traditional plastics, biomaterials are chosen according to their robust mechanical property, biodegradability, biocompatibility and eco-friendly [78]. In this part, SF and cellulose, as well as PLA and PU are respectively chosen as the representatives to explain application of the nature biomaterials and chemical-synthesized biomaterials based flexible electronics in improving the quality of human life and progressing of eco-friendly development.

Silk Fibroin-Based Flexible Sensor

SF films provide an effective and attracting platform for the development of the bio-electronics with high biocompatibility and biodegradability, due to their compact and safe contact with the curved surfaces of tissues and organs. In addition, the robust mechanical properties, adaptable protein structures and excellent optical properties make SF a competitive candidate for the construction and application of flexible sensors, as it enables the elastic deformation/folding, programmable dissolution/biodegradation, and versatile processing at ambient conditions. Therefore, SF as an efficient medium has a widespread promotion in implantable devices, biosensor, and E-skin for electronic components transmission to the surfaces of various organs to get desirable functionality and conformal deformations with the organs. In this review, we mainly focus on new progress of SF in recent few years. To get further detailed information about the application of SF on flexible food sensor or various kinds of electronics, please refer published reviews [79-81].

Optical diffraction-based biosensors are especially attractive in labeled and label-free bio-sensing on the account of the various diffraction efficiencies which depend on the bonding of chemical or biological molecular on a diffraction grating under a certain wavelength and detection angle, no matter with the fluctuations or damping of the probe lasers [82]. Zhou et al. [83] reported a set of bioactive Diffractive Optical Elements (DOEs) fabricated by functionalized SF film for optical diffraction-based sensing applications through modulating critical design sizes and facile water vapor annealing times (Figure 4a). The results showed that 2 μm of the critical size of SF-DOEs owned a highest Signal-to-Noise Ratio (SNR), meaning a much stronger optical signal. Through controlling the annealing time, the surface structure of SF-DOEs could be altered: the longer annealing time treatment, the longer degradation time due to the increased crystalline levels within the protein matrix. In addition, SF-DOEs showed excellent sensing activities: excellent optical qualities as sensitizing agents, precisely adjusted biological concealment via regulating the secondary conformation, hydration sensing, drug release monitoring upon degradation, and therapeutic treatment as well.

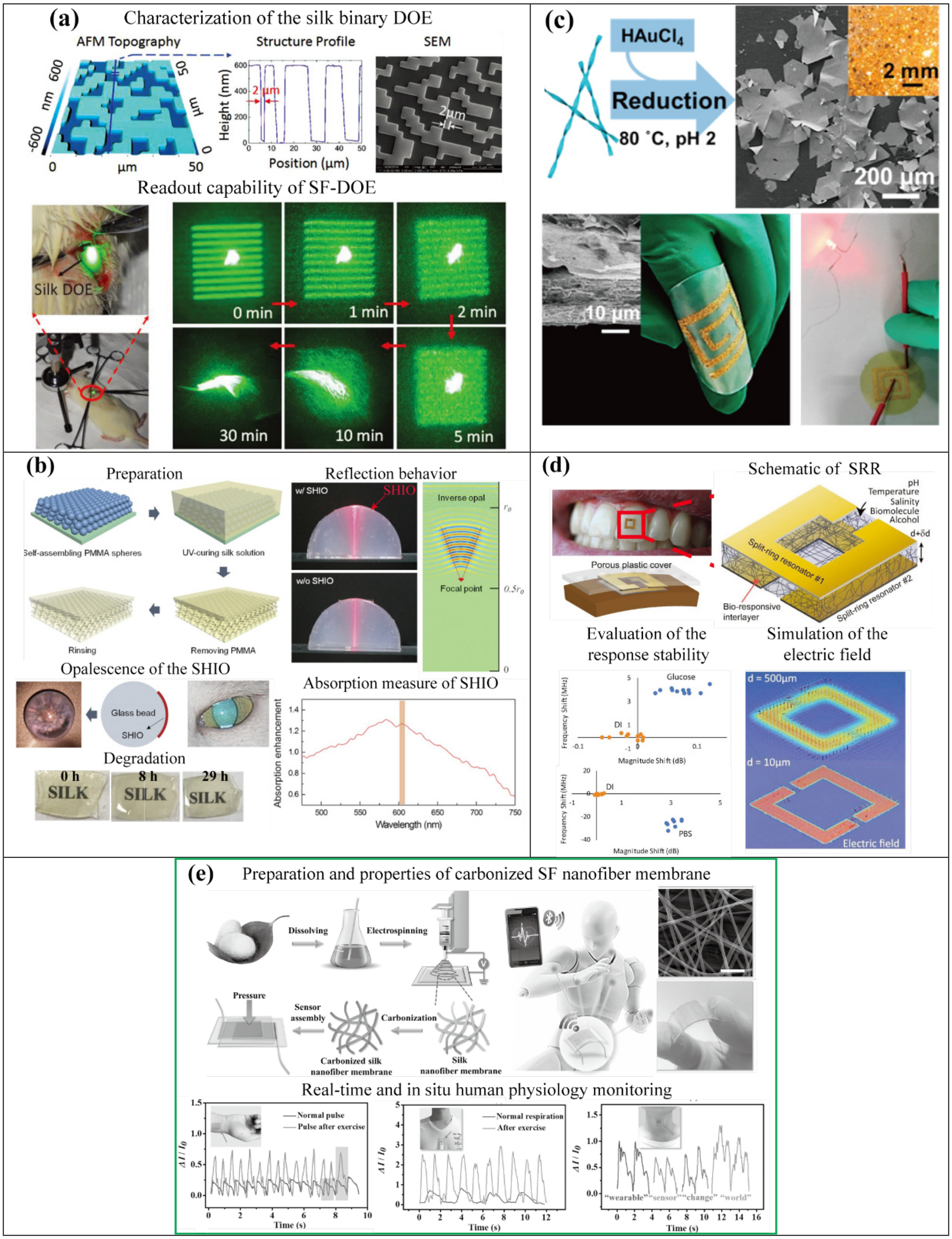
In this work, a new class of transient optical devices were reported, which was safe to human and eco-friendly. In addition, Min et al. [84] introduced Three-Dimensional Photonic Crystals (3D PhCs) (also known as opals) of silk hydrogen film with the deformable, durable and biodegradable properties (Figure 4b). The opals are prepared by self-assembly of colloidal crystals and their derivatives with a wide application in colorimetric sensors, photonic pigments, and full-color displays [85-87]. SF molecules were photo-cross linked with stilbene chromophore under short-wavelength UV exposure into the Silk Inverse Hydrogel Opals (SHIO) with porous structures. when weights were loaded to expose uniform pressure onto the SHIO, the reflection peak showed blue shifts due to the reduction of the interplanar space, which could be used to sense the Intraocular Pressure (IOP). In addition, when conformably loading the SHIO on an agarose gel hemisphere to mimic the human eye, the SHIO functioned like a concave mirror to reflect the red laser beam, which was expected to be an artificial tapetum to help improve human night vision. Furthermore, the UV-light cross linking decreased the degradation of SHIO, leading to long-term degradation of implantable devices.

To improve the mechanical and conductive properties of SF to widen its applications in flexible electronics, the synthetic or natural polymers were added, such as GO, nanotube, and PEDOT: PSS [88-92]. Lv et al. [93] prepared one kind of SF fibrous film hybridized with Kevlar nanofibrils through a biomimetic nanofibrous strategy (Figure 4c). The adding of Kevlar nanofibrils improved the mechanical properties of SF film, two times higher than the pure SF films, due to the reinforcing effect of Kevlar nanofibrils and the increasing content of silk β-sheets. Furthermore, the Au single-crystal microflakes synthesized with the support of SF nanofibrils were patterned on the SF/Kevlar-nanofibrils membrane, showing excellent mechanical flexibilities, even being twisted, bended or wrapped without any clear conductivity decay. Ma et al. [94] introduced a novel and highly conductive reduced GO/SF film (biopaper) with a large area (hundreds of cm^2) produced by printable GO/SF (98/2, w/w) solution via seriography. This kind of biopaper generated a 10^6 increase in conductivity (up to 10^4 S/m). Besides that, it showed excellent mechanical and flexible properties: no mechanical weak interfaces between dissimilar materials and unimpaired functionality of GO/SF microcircuits even after thousands of punitive folding cycles and chemical attack by harsh solvents. This novel approach upon low-cost and portable solution for printable and uniform micrometer-scale conductive circuits is potential to be used as wearable health monitors, E-skin, conformable displays and flexible biosensors.

Besides that, wearable devices are essentially tiny computers with the capabilities of sensing, processing, storage and communications, which have emerged as powerful tools for individual healthcare and wellness. Tseng et al. [95] developed a novel trilayer wearable sensor (Figure 4d) which could be mounted on the tooth enamel for the detection of foods during human ingestion. This wearable sensor was constructed based on a conformal Radiofrequency (RF) construct (an active layer encapsulated between two reverse-facing split ring resonators). On one hand, silk film was located as the outer layer due to its biocompatibility, controllable ability of absorption and swelling to different thickness, and penetrable ability by biomolecules, as well as adaptable transport properties by altering the conformation of SF proteins. On the other hand, silk film was also acted as the active layer for *in vitro/vivo* responses to solvents with varying degrees of ionic strength, glucose concentration, and solvent concentrations. The *in vitro* and *in vivo* results both showed good responses, high sensitivities, and outstanding repeatability and stability. The RF wearable sensor provides a new insight to the application of SF-based biosensors in various environments and allows distributed and multiplexed sensing via the additional responsive interlayer.

Furthermore, flexible and stretchable artificial E-skin has been eye-catching due to its great prospects in the application of wearable electronics and smart Human-Machine Interaction (HMI). The pressure sensing-based E-skin has been wildly used in the health monitoring, smart robots and disease diagnostics [96-99]. Wang et al. [100] reported one flexible piezoresistive pressure sensors with the carbonized SF nanofiber membrane (CSilkNM) as the active materials to construct the skin-like pressure sensor (figure 4e) with high sensitivity (34.47 k/Pa), low detection limit (0.8 Pa), short response time (<16.7 ms) and very high durability (>10000 cycles). When adhered on human skin to detect the human physiological signals and delicately collect physical signals, it showed high sensitive and effective responses based on the different organs of humans.

Expect above applications, SF also has been used in the implantable sensor as a stiff support that enables insertion in mouse brain tissues [101], memristive device with bipolar resistive switching ratio of 10^4 and programmable device lifetime characteristics [102], and biosensor for the detection of Nitric Oxide (NO) at nanomolar levels [39], as well as bio-triboelectric generator generating a high voltage with large surface area [103]. Therefore, advances in SF-based flexible electronics would open new avenues for employing biomaterials (nature or synthesized biopolymers) in the design and integration of high-performance and high-biocompatibility electronics for future applications in biosensors, wearable sensor, E-skins, and biomedical diagnosis.



Figures 4(a-e): The application of SF in the flexible bioelectronics: **(a)** Functional SF films for the application of optical diffraction based biosensors with read-out capability [83]; **(b)** Deformable and conformal SF hydrogel film as the inverse opals with the potential to improve the night vision of human with longer degradation time without affecting the visibility (even after 29 h) [84]; **(c)** Functional SF nanofibrous membrane as the substrate and electrode of the flexible electronics [93]; **(d)** SF-based functional trilayer SRR sensor for tooth-mounted and wireless monitoring of the oral cavity and food consumption with high sensitivities and performances [95]; **(e)** Carbonized SF nanofiber member for the application as flexible, transparent and sensitive E-skin which could sense the tiny vibration of human organs [100].

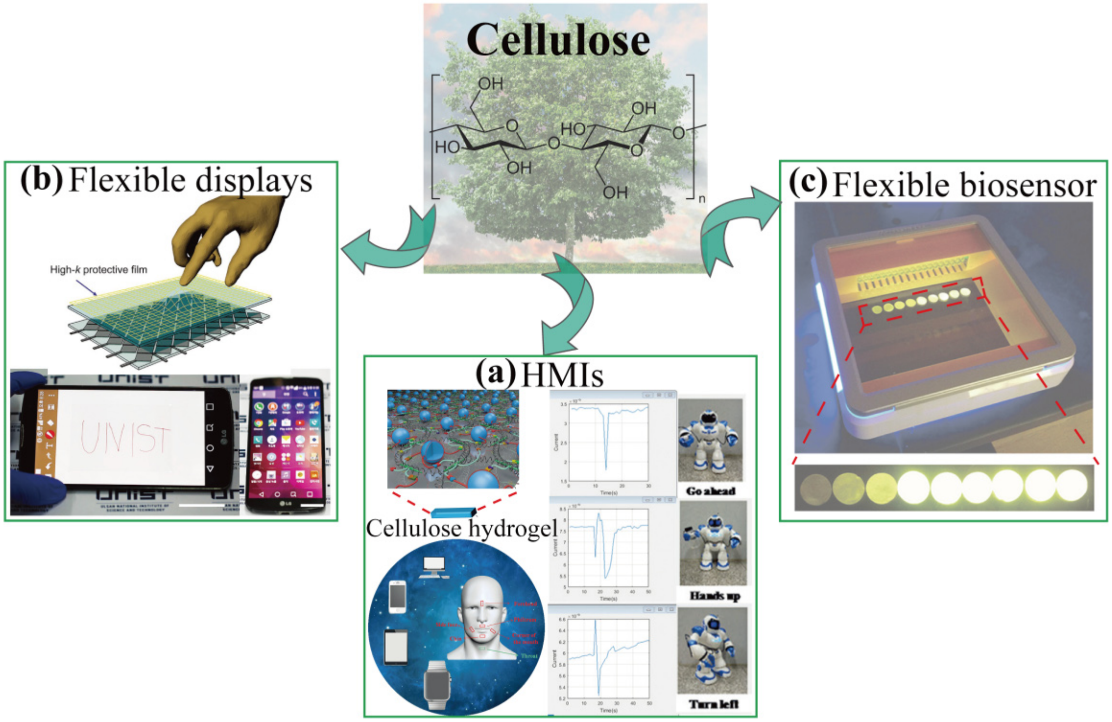
Cellulose-Based Flexible Sensor

Cellulose as a natural biomaterial has been widely applied to flexible sensors due to its eco-friendly, easy woven to films, large surface areas, excellent mechanical and alterable conductive properties. To alter the conductivity and mechanical properties of flexible biosensor, some conductive materials are combined based on the various applications, such as nanotube, graphene oxide, metals and semi-conductive polymers. Flexible strain sensors could be divided into resistive-type, capacitive-type and piezoelectricity-based sensors, which transduce mechanical deformations into electrical signals [104]. Importantly, materials for flexible stain sensors should offer outstanding and stable mechanical and electrical properties due to repeated tensile and compressive strains [104,105]. Flexible stain sensors have gained growing applications in various aspects, such as HMI for signal collection of bio-mechanical movements [106-109], virtual reality devices [110,111], and smart living [112]. To overcome the disadvantages of some flexible sensors with weak response reliability and mechanical stability, Cao et al. [113] firstly reported one self-healing hydrogen stain sensor for HMIs with especially sensitive, stable and spontaneous self-healing capability at ambient temperature without any other stimulus (Figure 5a). With the inspiration by the multiple hydrogen bonding connection of Deoxyribonucleic Acid (DNA), the hydrogen stain sensor was constructed by layer-by-layer method, in which Carboxyl Cellulose Nanocrystals (C-CNC) was employed not only to construct supramolecular multiple hydrogen bonding network with chitosan-decorated Epoxy Natural Rubber (ENR) latex, but also a three-dimensional nanostructured conductive network with Carbon Nanotube (CNT).

The results showed that the strain sensor could detect the signals with a low stain detection limit of 0.2%, fast (only 15 s) and repeatable self-healing ability. Furthermore, when detecting tiny human motions and HMI, it showed highly distinguishable and reliable signals of human motions, and bright prospect in controlling robot to improve the real-time speaking of the mute. However, when the stain increased from 0 to 10%, cracks appeared in the interconnected conductive network, leading to the significant decrease in current signals and enhanced signal intensities. Therefore, to realize the application of the stain sensor on recording both tiny and strenuous human motion, more work on improving stability of the conductive network should be carried on. In addition, silver nanofiber was added to construct a cellulose-silver nanofiber hybrid film with high conductivity, robust mechanical, thermally stable and transparent property [114]. The hybrid film could response upon the multi-touch of human fingers (Figure 5b), showing the potential to be the cover layer of flexible Touchscreen Panels (TSPs) in smart watches, wrist bands, smart glasses, and fitness or medical monitors without affecting touch performance. Furthermore, Cheng et al. [115] introduced one flexible cellulose-based sponge with multifunction, which could be a flexible stain sensor via responding the press and resistance, as well as a Thermoelectric (TE) material for the self-powering by utilizing the temperature differences between the body and environment, showing the potential application in artificial intelligence products or remote medical monitoring devices. Meanwhile, Rajala et al. [116] also displayed the excellent property of cellulose as a piezoelectric sensor material.

Moreover, cellulose has also got lots of attention in the application of flexible biosensors. Derikvand et al. [117] prepared a new fluorogenic esterase biosensor (Figure 5c) in a chemo-enzymatic approach to activate the cellulose substrate, which broadens the application to cellulose papers, gauzes, and hydrogels. In addition, to predict some complications after Subarachnoid Hemorrhage (SAH), Kim et al. [118] explored a novel label-free cellulose Surface-Enhanced Raman Spectroscopy (SERS) biosensor with the Gold Nanoparticle (AuNP) which enhanced localized surface Plasmon Resonance (LSPR). The cellulose biosensor performed low detection limitation and high reproducibility, potential to be expanded to various neurosurgical diagnoses. In addition, a recyclable pH biosensor formed by cellulose could be used for human health monitoring based on the visual color changes against each pH [119]. Except on the health monitoring and protection of human, cellulose biosensor has also been used in food and environment detection [120-124].

In a conclusion, cellulose-based flexible electronics display lots of benefits to not only human health monitoring, but foods and environmental detection and governance, which promoted the progress of medical hygiene, health monitoring, food safety and environment governance.



Figures 5(a-c): The main applications of cellulose in **(a)** HMIs [113] **(b)** flexible displays [114], and **(c)** biosensors for fluorogenic esterase detection [117].

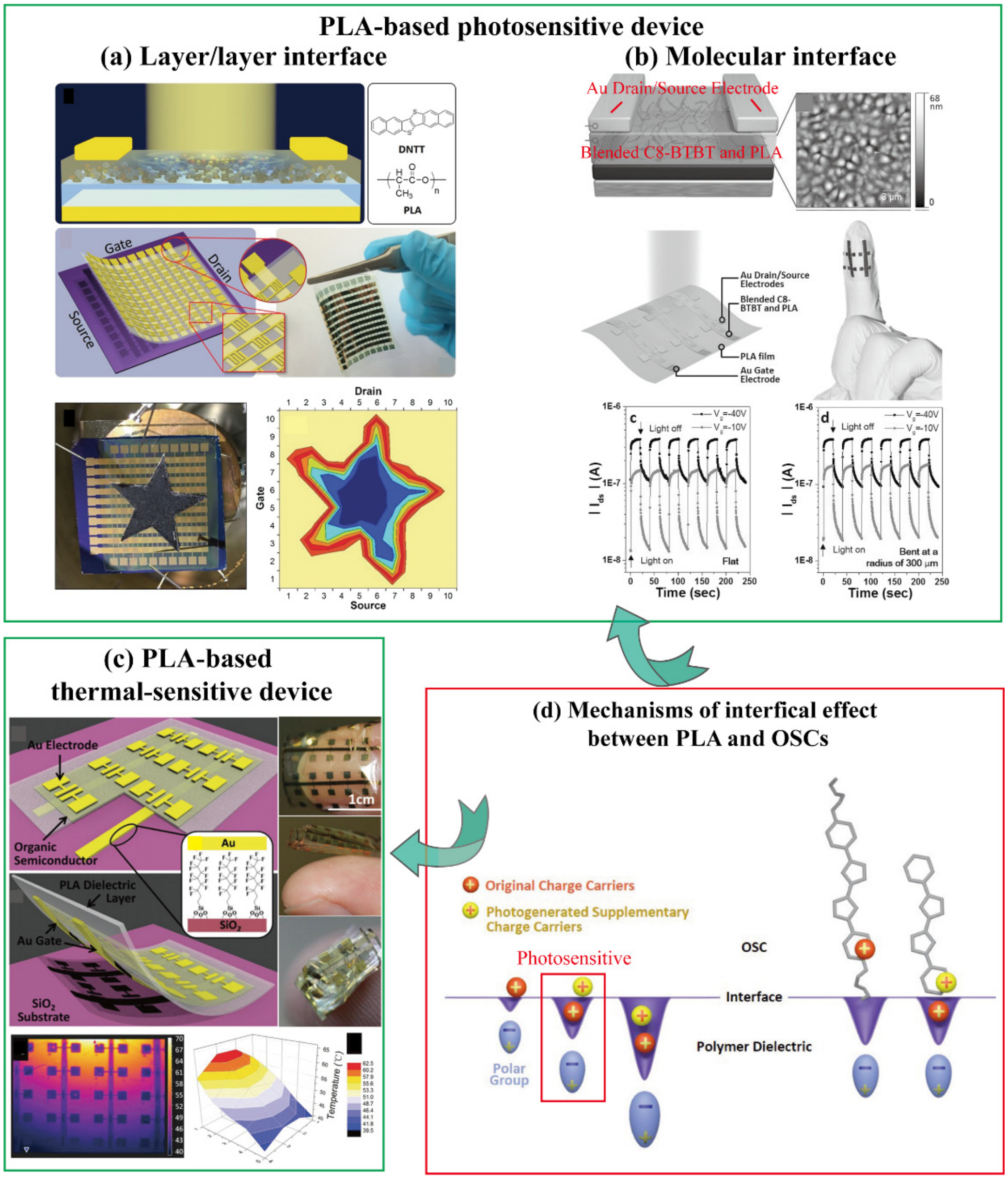
Conventional Chemical-Synthetic Biomaterials-Based Sensors

Recent advances in bio-nanotechnology have increased the demand for conductive, dielectric as well as other functional biopolymer nanocomposites. To become electrically conductive, polymers should possess conjugated p-bonds along their backbone, which loosely hold electrons and allow relatively easier delocalization of electrons [125]. Flexible polymer-based dielectric materials that are used to store dielectric energy have widely been used in modern electronics and electric power systems, due to their relatively high energy density, light weight and low cost. Here, the PLA and PU based flexible electrics are highlighted to illustrate the novel applications of conventional biomaterials.

PLA-Based Flexible Sensor

PLA has been widely used in the flexible sensors due to the polar groups in PLA molecules which induce the charge trapping effect and thus enhance photo- and thermal-sensitivity. Chu et al. [126] fabricated one Organic Phototransistor (OPT) using PLA as the gate dielectric material (Figure 6a), in which the charge trapping effect at the organic semiconductor/dielectric interface induced by the polar groups of PLA leads to reduced drain current of the device when in the dark. To verify the photosensitivity, the PLA-based OPT was incorporated into a 10×10 array to sense a star object. The result displayed a similar pattern as the star object, indicating PLA-based OPT suitable for the optoelectronic applications. Similarly, one printable and flexible OPT was prepared through blending PLA with a common soluble organic semiconductor 2,7-dioctyl[1]-benzothieno[3,2-b][1]benzothiophene (C8-BTBT) [127] (Figure 6b). The sensitivity of the blended-OPT was improved due to the occurrence of the interfacial trapping effects at the molecular interfaces of C8-BTBT and PLA. Besides that, even under bending conditions, the photosensitivity was not affected, indicating the excellent flexibility of the device. Except on the application in the photosensitive devices, temperature sensing of PLA has also been studied [128]. In this case, a three-arm stereocomplex PLA (tascPLA) was employed as dielectric and substrate materials, which increased the thermal stability of the flexible electronics. Moreover, the PLA-based flexible electronics was successfully applied to the skin-like temperature sensor (Figure 6c). Therefore, combining with its transparency, degradability, and biocompatibility, the PLA-based flexible thermal electronics could be used as environment friendly electronics, implantable medical devices, and artificial skin.

To further understand the mechanism of the photosensing property induced by the interfacial effect between the organic semiconductors and dielectric polymers, Wu et al. [129] prepared several organic transistors including PLA-based transistor, in which PLA was one of the dielectric polymers to construct an organic semiconductor/dielectric interface. As shown in figure 6d, the charge carrier transportation rate was reduced because the charge carriers in the conducting channels was shallowly trapped by the functional groups of polymer dielectrics. Besides that, long OSC side chains and low polarity of polymer functional group induced weak shallow traps on the devices interfaces. However, only the traps with appropriate energy levels could lead to an obvious photosensitive μ change for the OFET, as indicated by the red rectangle. In a conclusion, the energy from the thermal- /photo- resources were stored by the semi-conductor from the dielectrics by shallow trap or long trap, but only suitable trap could generate the sensitives because the absorbed energy should be released from the semi-conductors in the form of thermal-/photo- energy. Therefore, PLA-based photo- and thermal-sensitive sensor was successfully fabricated due to the proper shallow traps between the interface of PLA and OSCs.

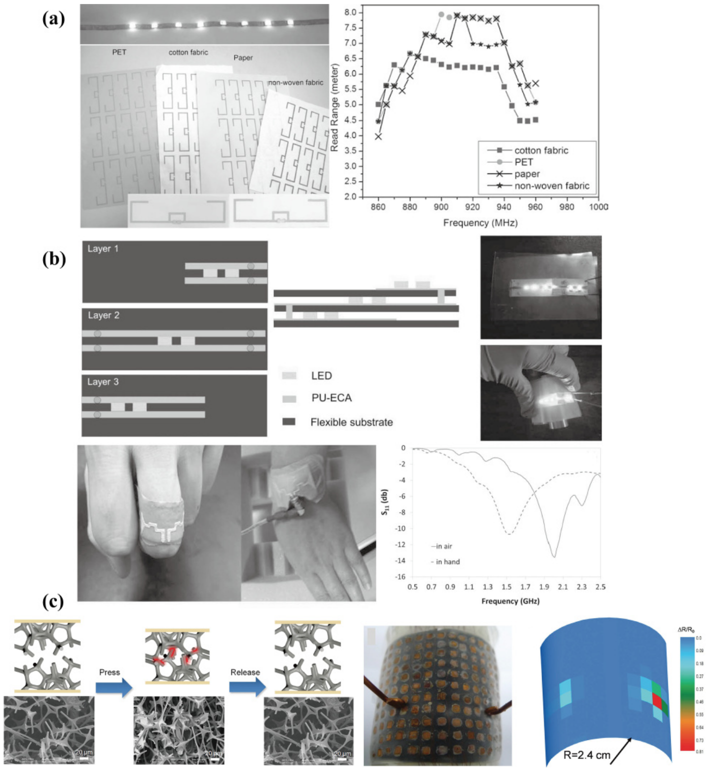


Figures 6(a-d): The application of PLA in flexible photo [126,127] and thermal-sensitive [128] electronics and the relative mechanisms [129] of interfacial effect between PLA and OSCs.

PU-Based Flexible Sensor

For the fabrication of flexible sensors, the traditional printed circuits and electrical interconnects are made from copper foils and Sn/Pb solders [130], which have lots of feedbacks, such as high processing temperature and cost and low fabrication speed. However, Isotropically Conductive Adhesives (ICAs) show huge promise in replacing the above materials. ICAs, composed by polymer and electrically conductive fillers could be processed under low temperature, and compatible with traditional printing methods. PUs have been widely applied in the composite of ICAs due to excellent biocompatibility, robust mechanical property, energy-economic, and eco-friendly. Yang et al. [131] fabricated one Water-Based ICAs (WBICAs) using water-based aliphatic PU resin dispersant and micro-silver flasks, which showed a high conductivity (8×10^{-5} Ω cm) and long stability (at least 1440 h during 85°C/85% RH aging)). Besides that, the WBICA printed circuit with Light Emitting Diode (LED) and Radio Frequency Identification (RFID) antennas showed its excellent conductivity and easy processing on different flexible substrates (Figure 7a), which made it possible to construct green and low-cost flexible electronics. Based on this, Poly (Ethylene Glycol) (PEG) was added as a curing agent of PU and reducing agent to reduce silver carboxylate and generate silver nanoparticles that could improve the conductivity [132]. The PU-based Electrically Conductive Adhesive (ECA) performed a higher conductivity ($\approx1.0\times10^{-5}$ Ω cm) which kept maintained even bending, rolling, and compressing.

In addition, it showed good adhesions to various flexible substrates and facile processing. Therefore, the PU-ECA could be applied in the flip-chip, three-dimensional integration, and wearable radio-frequency devices (Figure 7b). Except that, PU sponge could also act as a piezoresistive sensor due to its outstanding mechanical property. Yao et al. [133] introduced a flexible and sensitive PU microporous sponge coated by Reduced Graphene Oxide (RGO) nanosheets as conductive layer (Figure 7c). The PU-RGO sponge performed high pressure sensitivity, long cycling stability (over 10000 cycles) together with large-scale fabrication of the pressure sensors, which make PU-RGO sponge a promising low-cost E-skin. In addition, Multiwall Carbon Nanotubes (MWNTs) [134] and RGO [135] were also added to improve the conductivity and mechanical property of PU-based electronics, expanding its application in flexible electronics.

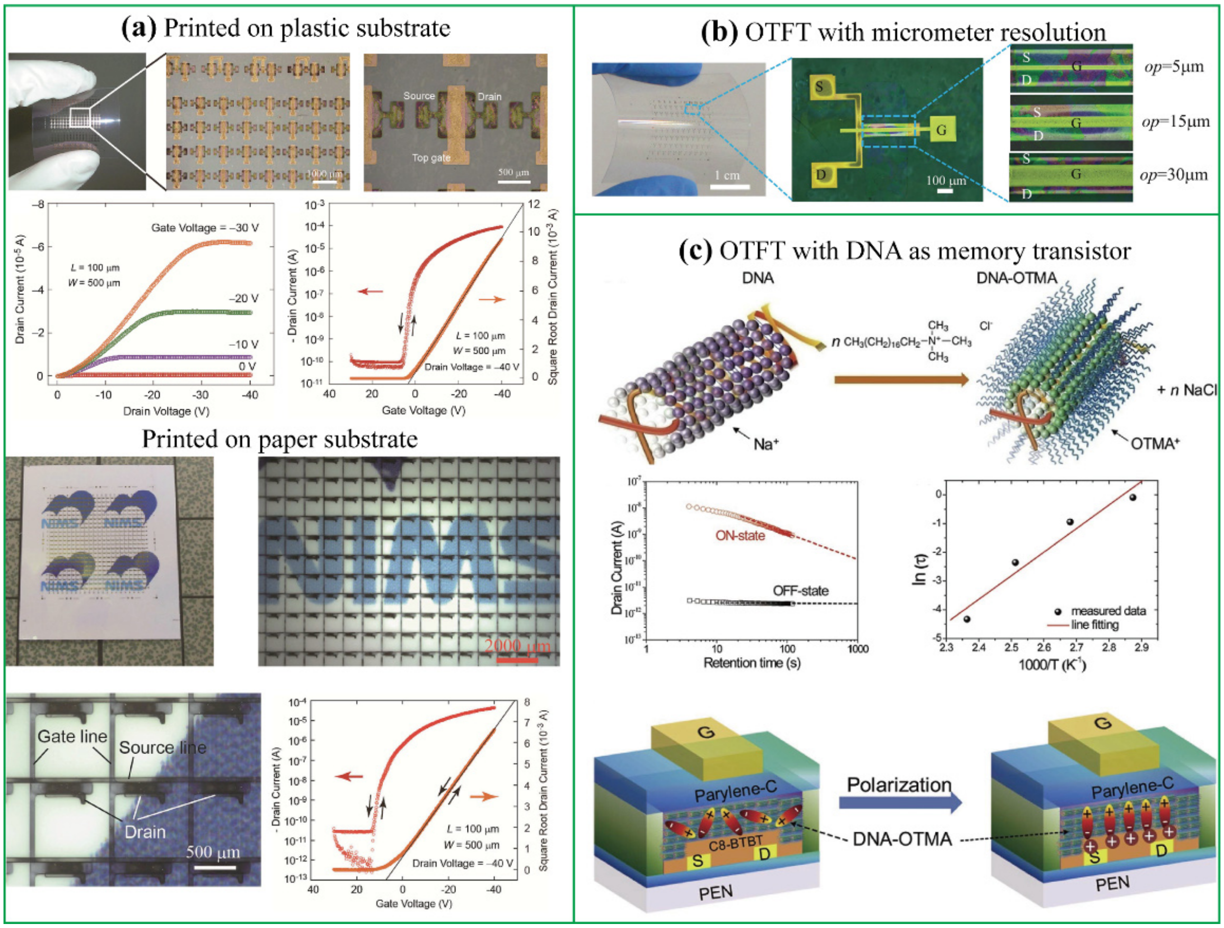


Figures 7(a-c): The application of PU in the flexible electronics: **(a)** The PU-based WBICAs was used for printed circuit with LED and RFID on different substrates [131]; **(b)** PEG blended PU-ECA for printed flexible circuits with LED and E-skin [132]; **(c)** Microporous RGO-PU sponge as piezo resistive sensor for the application as E-skin [133].

Room-Temperature Printing of DNA-Based Flexible Memory

Recently, a tremendous progress has been made on the development of printable electronics with mechanically flexible substrates, which performance well with high conductivity and reproducibility. Compared with the traditional fabrication of electronics, printable electronics have become urgent social needs due to the advantages of low-cost, large-area fabrication, time-saving, and eco-friendly. Printing electronics on flexible substrates is potential to develop flexible displays, sensors, E-skin, and others [136]. However, high process temperatures (>150°C) are typically used for printed electronics, which limits the use of common flexible substrates due to the distortion caused by heat [40]. Minari, Kanehara and Liu et al. have accumulated lots of experience on the printable electronics fabrication at Room Temperature (RT) with high conductivity, resolution, and reproducibility. Organic Thin-Film Transistors (OTFTs) were printed with π-junction gold Nanoparticle (NP) ink on flexible substrates and exhibited average field-effect mobilities of 7.9 and 2.5 $cm^2/V/s$ on plastic and paper substrates, respectively (Figure 8a) [40]. It suggests that RT printing is potential to be applied in a large scale of thin-film electronic devices, such as light-emitting devices and photovoltaic cells. Based on this, much advanced OTFTs were fabricated with 1-micrometer resolution by printing methods at RT (figure 8b) [42]. In the fabrication of the OTFTs, spontaneous patterning of narrow lines and gaps (down to 1 μm) of Au nanopartilces, as well as discrete organic semiconducting thin films, were achieved via forming sharply defined wettability contrast by the Parallel Vacuum Ultraviolet (PVUV) system, which is promising for fully solution-processed, large-area, and high-resolution flexible devices. Recently, flexible electronics were combined with DNA to fabricate non-volatile memory transistors that displayed high performance in the hole mobility and memory window (Figure 8c) [137], which indicates that OTFTs are competitive candidates to combine with biomaterials for various applications. Therefore, RT-printing process opens a new way to fabricate electronics on a large scale of flexible substrates, expending the application of flexible electronics in various fields, such as artificial skin, flexible display and biosensors via combining with biomaterials.

In a conclusion, we introduced the novel application of traditional chemical-synthesized biomaterials with the examples of PLA, PU, NPs and DNA which have been widely applied in industrial products and daily life. Due to the excellent mechanical property and biocompatibility, new application of them in flexible electronics have been explored, which give us inspiration that exploring and studying the traditional biomaterials would bring lots of research interests and novel applications in flexible electronics to make our life much convenient and smarter.



Figures 8(a-c): The application of printable electronics on flexible substrates as OTFTs: **(a)** RT-printing of OTFTs on the plastic and paper substrate [40]; **(b)** Advanced OTFT fabricated at RT with 1-micrometer resolution [42]; **(c)** RT-printing OTFT combined with DNA as the memory transistor [137].

Citation: Sun Q, Qian B, Uto k, Chen J, Liu X, et al. (2018) Electronic Biomaterials Towards Flexible Sensors: A Review. Biosens Bioelectron Open Acc: BBOA-137. DOI: 10.29011/ 2577-2260. 100037

Conclusions and Outlooks

Natural biomaterials with good biocompatibility such as SF, cellulose, starch, chitin are abundant in nature. Most of these molecules contain number of bioactive sites, such as hydroxyl groups and other polar groups, which improve their molecular modification and thus alter their properties based on different requests for the flexible electronics. Due to direct extraction from nature materials, the preparation process is much easy and low-cost. Moreover, chemical structures of chemical-synthesized biomaterials can be designed by starting from chemical molecules through simple physical and chemical modifications with a wide range of properties aiming at the application in flexible electronics. Besides that, conventional chemical-synthesized biomaterials could be mass-produced with good reproducibility through controlling the reaction conditions. Compared with petroleum-based materials, the biggest advantage of biomaterials is their capability of degradation in the environment, which allows for the sustainable development of flexible electronics. In this review, several representative biomaterials are introduced from the view of novel applications in biosensor, flexible displays, wearable devices, and others. Following that, the RT-printing processes for large-scale flexible OTFTs are discussed with high performance and new application in memory transistors by combining with DNA. Therefore, biomaterials exhibit specific advantages on the development and application of eco-friendly flexible bioelectronics.

In addition to satisfying the basic monitoring function, it is now possible to give the sensor with intelligent functions, such as the ability of self-healing when damaged, thereby enabling to realize long lifetime devices. Stimuli-responsive materials with sophisticated controllable shape-changing behaviors are also highly desirable in fabrication of smart sensors, which will devote to the development of electronic medical and health-care devices. However, some additives, such as GO, gold and silver nanomaterials are used to improve the mechanical properties of flexible electronics, which will cause the environmental stresses due to the weak degradation. Based on this issue, some measurements should be taken, such as the recycle of these materials and improvement of the usage lifetime of flexible electronics, and so on. Furthermore, even though completely degradable materials have made great strides as well, they are still not fully converted in industrial composting plants, which have seriously affected the sensitive waste management system. Therefore, E-waste must be carefully managed before it falls into an irreversible pollution matter. Besides raising the awareness of consumers to take the initiative to recycle, purchasing alternatives to traditional devices is also crucial. The usage of biomaterials would still bring different social values by promoting the development of plastics. Except that, it is also necessary to explore the adaptability of the degradation time of the various component materials in the device.

Another important consideration to note is the reliability of these bio-degradable materials under operational stress such as heating for prolonged use, UV exposure to the Sun, environmental temperature and humidity for detection stability, as well as cyclical mechanical deformation. Except above mentioned, the preparation technology of flexible electronics should be improved and widen as well. RT-printing methods are promising to be applied for construction of flexible electronics with sophisticated and multi-functional patterns. Meanwhile, device areas ranging from small (centimeter squares) up to large (meter squares) could be also achieved. In a conclusion, for the sustainable development of eco-friendly flexible electronics, more and more novel and functional biomaterials should be discovered and studied. Except that, the functions, properties and fabrication methods of biomaterials-based flexible electronics should be explored and improved, such as by combining with internet of things or mimicking the human nerve systems for the development of precision medicine, neurorobotics, neuroprosthetics and Artificial Intelligence (AI), and so on.

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