Biomaterials 314 (2025) 122861

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Natural biomaterials for sustainable flexible neuromorphic devices

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ARTICLE INFO

Keywords:
Neuromorphic electronics
Natural biomaterials
Flexibility
Biocompatibility
Biodegradability

ABSTRACT

Neuromorphic electronics use neural models in hardware to emulate brain-like behavior, and provide power-efficient, extremely compact, and massively-parallel processing, so they are ideal candidates for next-generation information-processing units. However, traditional rigid neuromorphic devices are limited by their unavoidable mechanical and geometrical mismatch with human tissues or organs. At the same time, the rapid development of these electronic devices has generated a large amount of electronic waste, thereby causing severe ecological problems. Natural biomaterials have mechanical properties compatible with biological tissues, and are environmentally benign, ultra-thin, and lightweight, so use of these materials can address these limitations and be used to create next-generation sustainable flexible neuromorphic electronics. Here, we explore the advantages of natural biomaterials in simulating synaptic behavior of sustainable neuromorphic devices. We present the flexibility, biocompatibility, and biodegradability of these neuromorphic devices, and consider the potential applicability of these properties in wearable and implantable bioelectronics. Finally, we consider the challenges of device fabrication and neuromorphic system integration by natural biomaterials, then suggest future research directions.

1. Introduction

The computing capacity of von Neumann computers has grown exponentially with the advancement of complementary metal-oxide-semiconductor (CMOS) technology and the continual downsizing in transistor size [1]. However, as physical limits are approached, relying solely on device scaling becomes insufficient for continued increase in processing speed. In contrast, a vertebrate brain operates in a massively parallel manner through a network of densely interconnected neurons; this structure has significant advantages in energy efficiency and processing speed [2]. It can process multiple complex tasks with ultralow energy consumption, particularly when processing unstructured data in real time [3].

To process large-scale complex data, neuromorphic electronics that emulate biological neural functions has been proposed [4]. In biological neural systems, synapses are critical components that enable neurons to simultaneously perform communication, computation, and memory functions, and thereby overcome the von Neumann bottleneck. The von Neumann architecture separates storage and processing units, so the transfer of data from storage to processor imposes a limit to the computing speed [5,6]. Therefore, endowing electrical devices with synaptic behaviors is crucial advancement for neuromorphic electronics.

The rapid development of wearable and implantable bioelectronics has presented prospects for use of neuromorphic electronics in biomedical applications. Many researchers are attempting to integrate neuromorphic devices with biological tissues to emulate and accelerate neural signal transmission and processing within organisms [7–11]. These devices are expected to be applied in health monitoring, bioelectronic interfaces, and biomedical diagnosis and treatment. However, traditional rigid devices do not readily conform to human skin or organs while transmitting neural signal on the body, so motion of the organism can cause artifacts and reduce measurement accuracy [12]. To overcome these limitations, the design of neuromorphic devices emphasizes flexibility, biocompatibility, and light weight [13]. These requirements have promoted the development of flexible neuromorphic devices, and thereby allows them to integrate conformably with the human body

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https://doi.org/10.1016/j.biomaterials.2024.122861
Received 3 June 2024; Received in revised form 10 September 2024; Accepted 26 September 2024
Available online 3 October 2024

[14]. This integration minimizes interference with biological systems, and thereby enables high-quality signal acquisition and processing [15]. Furthermore, flexible neuromorphic devices are promising in implantable electronics, particularly because good tissue conformability, low invasiveness, and imperceptibility make them highly suitable for long-term implantation [16]. These devices can precisely interface with neural tissues to modulate or repair abnormal neural signals, and therefore may aid in treatment of neurodegenerative diseases [17].

The development of these technologies has provided revolutionary solutions for the advancement of biomedical applications, but many fabrication processes and devices are unsustainable, so their use may lead to depletion of non-renewable resources and generation of electronic waste that contains toxic components or non-degradable materials [18]. Although emerging flexible electronic devices are expected to reduce the weight, their complex recycling processes pose new challenges [19]. Therefore, bioelectronic devices should be entirely or almost entirely fabricated by components obtained from sustainable sources through green processes, allowing these components to either be recycled into value-added products or biodegrade at the end of their useful life without any negative impact on the environment.

Natural biomaterials have offered attractive building blocks for developing sustainable bioelectronic devices due to natural abundance, renewability, and biodegradability [20]. For instance, biomaterials-based memristive devices, with their complex multilayer structures and multifunctionality of functional groups, offer significant advantages in mimicking synaptic behavior and demonstrate considerable importance and practical application value in the domains of data processing and computing systems, neuromorphic sensory perception systems, and artificial intelligence [21–24]. In addition, the biocompatible, flexible, ultra-thin, and light-weight traits of biomaterials enable them to demonstrate potential in wearable and implantable neuromorphic electronics for neuro-robots, neuroprostheses, and smart medicine [25,26]. These applications typically require neuromorphic devices to have high mechanical flexibility to seamlessly interface with biological tissues, and must ensure biocompatibility and unobtrusiveness to minimize allergic or inflammatory responses [27,28]. Although reports on related applications are still limited, artificial synapses that use biomaterials hold significant potential in sustainable, flexible neuromorphic electronics and are expected to play a crucial role in wearable and implantable biomedical applications.

This review is divided into four parts (Fig. 1). The first part covers recent progress in the design of sustainable flexible neuromorphic devices that apply natural biomaterials, detailing their sources, chemical structures, solubility, mechanical properties, and charge-transfer characteristics of biomaterials. The second part presents operating principles for applying biomaterials in neuromorphic devices. The third part discuss the advantages of artificial synapses that use biomaterials, including mechanical flexibility, biocompatibility, and biodegradability. The fourth part considers future development prospects of neuromorphic devices that use biomaterials, and discusses the major challenges that must be overcome to achieve practical application in sustainable flexible electronics.

2. Natural biomaterial sources and types

Natural biomaterials are extracted from animals, plants, or microbes. Evolution has produced biomaterials that have efficient structures and functions, one of which is charge transport. This phenomenon is required in electronic devices. The use of biomaterials has greatly increased the biocompatibility, biodegradability, and flexibility of electronic devices, has advanced the development of sustainable neuromorphic devices and expanded their potential applications toward

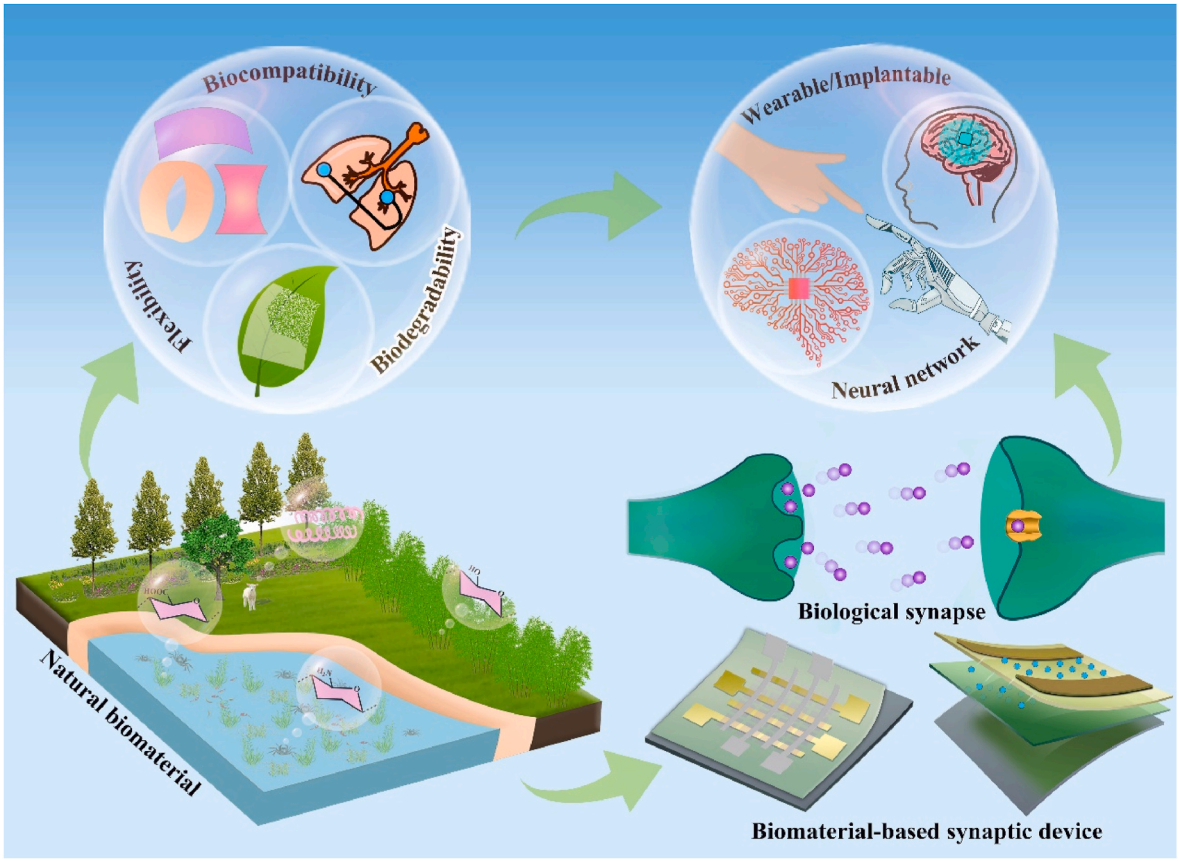

Fig. 1. Schematic diagram showing the fundamental properties of natural biomaterials, and their application potential in sustainable flexible neuromorphic electronics.

wearable and implantable electronics. In this chapter, we review the sources, chemical structures, and charge-transport properties of natural polymers, then explore their uses within neuromorphic devices.

2.1. Polysaccharides

A polysaccharide is a large carbohydrate molecule that consists of multiple monosaccharide units linked together by glycosidic bonds. Polysaccharide molecules possess a variety of functional groups, including carboxyl (-COOH), hydroxyl (-OH), and amino (-NH_2) [29]. They endow polysaccharides with good water solubility, proton conductivity, and a tendency to react with metal ions [30–32]. Considering the types and charge characteristics of these groups, polysaccharides can be categorized as cationic, anionic, or neutral [33,34].

Cationic polysaccharides are a type of carbohydrate that bear positively-charged groups. Chitosan is the only naturally-existing

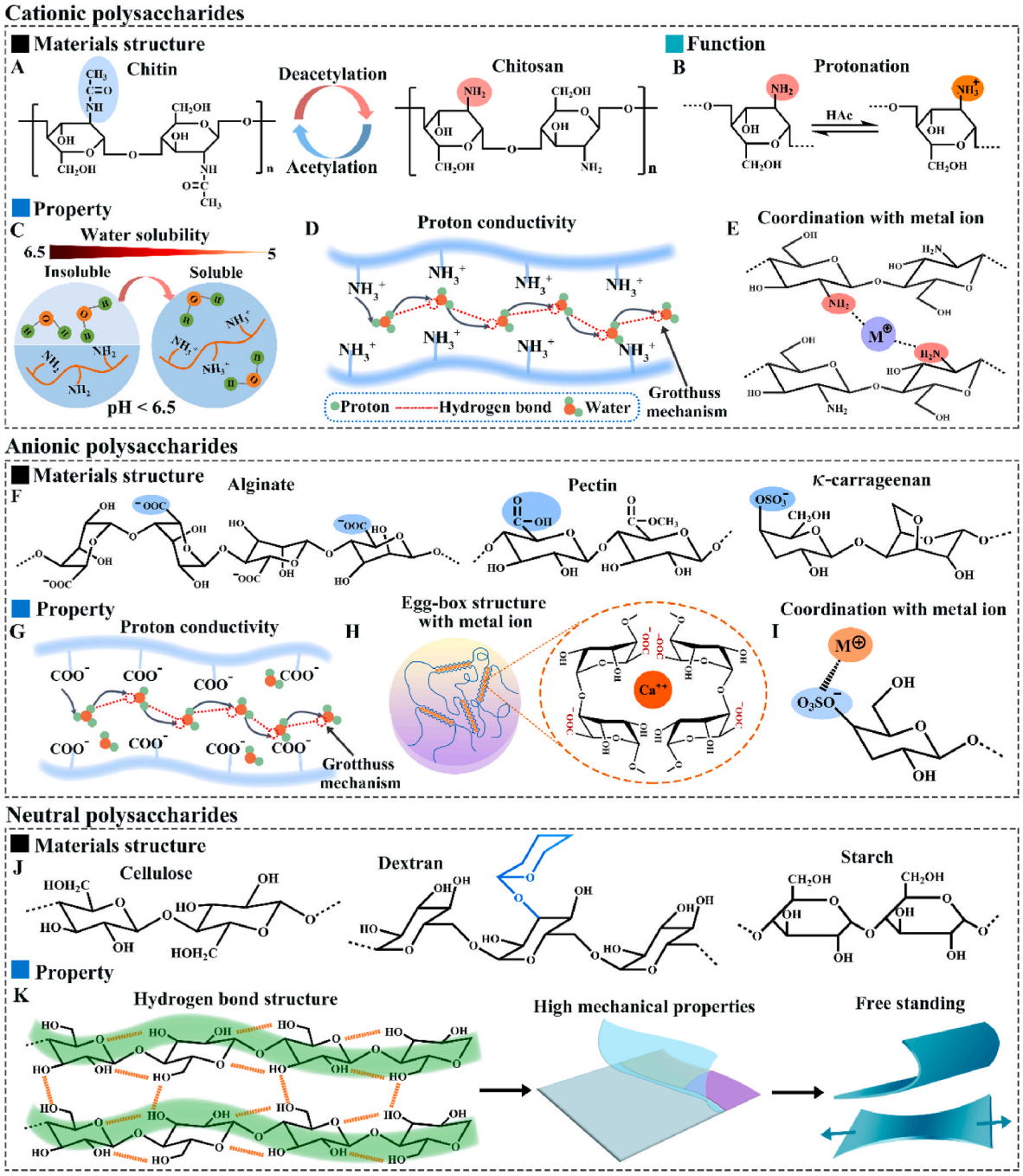

Fig. 2. Structure and properties of different kinds of polysaccharides. A) Schematic representation of the deacetylation process and chemical structure of chitosan, with changes in functional groups indicated by blue and red circles. B) Protonation and deprotonation of chitosan, with changes in functional groups indicated by red and orange circles. C) Mechanism of water solubility of chitosan. D) Grotthuss mechanism for proton conduction along hydrogen bonds formed by water and polar groups of chitosan. E) Chelation mechanism of chitosan with metal ion. F) Chemical structure of anionic polysaccharides. G) Grotthuss mechanism for proton conduction along hydrogen bonds formed by water and polar groups of anionic polysaccharides. H) Scheme of "Egg-box" structure in alginate hydrogel crosslinked with calcium ions. Orange circles represent cations. I) Chelation mechanism of carrageenan with metal ion. Orange circles represent cations. J) Chemical structure of neutral polysaccharides. Blue functional groups represent branched chains. K) Schematic diagram of the hydrogen-bond structure and mechanical properties of cellulose. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

cationic polysaccharide, and has been the subject of extensive research [35]. Chitosan is a long linear polymer composed of D-glucosamine and N-acetyl-D-glucosamine units, and is primarily prepared by alkaline deacetylation of chitin extracted from the shells of crustaceans and insects (Fig. 2A). It bears free amino groups (-NH_2), is weakly alkaline, and generally insoluble in water or organic solvents. However, in dilute aqueous acidic solution (pH < 6.5), these amino groups are protonated to (-NH_3^+), and the chitosan thus becomes soluble in aqueous acidic solution (Fig. 2B and C) [36], because the protonated cations destroy the hydrogen bonds between adjacent chitosan molecules [37].

Chitosan has high proton conductivity. When treated using acetic acid, the chitosan molecules undergo protonation, with protons (H^+) dissociating from the acetic acid and binding to the free amino groups in the backbone of chitosan (-NH_2 + HAc ↔ -NH_3^+ + Ac^-) (Fig. 2B) [38]. Meanwhile, water molecules adsorbed on the chitosan chain can form hydrogen bonds, which provide pathways for transfer of protons from amino groups to water molecules (-NH_3^+ + H_2O ↔ -NH_2 + H_3O^+) [39]. The protons released from protonated amino groups can move through the hydrogen-bond network of hydrated molecules by proton jumping (i.e., the Grotthuss mechanism, Fig. 2D) [40]. Therefore, chitosan conducts protons but insulates electrons, and thus has been widely used in the gate-insulating layers of synaptic transistors. The high proton conductivity of chitosan is particularly suitable for synaptic transistors, because it can modulate synaptic properties by exploiting the electrostatic effect of protons, and thereby provide significant advantages for synaptic transistors that have low operating voltages [41–44]. The amino groups in chitosan react strongly with metal ions, and are therefore particularly effective in the active layers of memristors (Fig. 2E). The lone pair electrons in the nitrogen atoms of amino groups can react with metal cations, so these amino groups can adsorb metal cations by chelation; this process has been exploited in synaptic devices that use resistive switching behavior [45].

Anionic polysaccharides are long-chain carbohydrates that carry negative charges. These negative charges result primarily from uronic acids or other acidic functional groups such as carboxyl groups (-COO^-) and sulfate groups (-SO_4^{2-}) on the polysaccharide chains (Fig. 2F) [34]. Anionic polysaccharides extracted from seaweeds (alginate, κ-carrageenan) and plant cell walls (pectin) have demonstrated diverse functionalities in artificial synapses [46,47]. Due to the presence of negatively-charged groups, anionic polysaccharides can easily form stable interactions with surrounding water molecules in humid environments. These stable interactions facilitate efficient proton transfer through the hydrogen-bond network formed by water molecules (Fig. 2G). This process endows anionic polysaccharides with excellent water solubility and proton conductivity [35,48,49]. Due to the strong proton/electron coupling effect, anionic polysaccharides have shown application potential in the gate dielectric layer of neuromorphic devices [50].

Anionic polysaccharides can also interact with metal ions to form three-dimensional network hydrogels that have excellent mechanical properties. Taking alginate as an example, under the influence of divalent cations such as calcium ions (Ca^{2+}), the carboxylic acid groups in α-L-guluronic acid of adjacent polymer chains of alginate interact with Ca^{2+} to form a stable egg-box structure hydrogel (Fig. 2H) [51–53]. The hydrogel structure has high mechanical strength, so anionic polysaccharide film can serve as both the gate-dielectric layer and the mechanical support substrate, and essentially act as free-standing gate insulators for the synaptic devices [54,55]. Metal ions can also migrate by interactions with the functional groups of anionic polysaccharides, such as carboxyl or sulfate groups, which have negative charges that can form stable coordination bonds with metal ions (Fig. 2I). Therefore, anionic polysaccharides can be used as ion-conducting media in memristors.

Neutral polysaccharides extracted from plants are uncharged carbohydrates such as cellulose, dextran, and starch (Fig. 2J) [34]. The solubility of neutral polysaccharides in water is highly related to their molecular structure. Hydrogen bonding has a strong effect on the structure and stability of aggregates of polysaccharide molecules, and strongly influences their solubility in water. Linear polysaccharide molecules tend to form tightly-packed structures due to hydrogen bonding, and therefore have low solubility in water. For example, cellulose is a linear polysaccharide in which strong hydrogen bonding between molecules contributes to a highly-ordered structure, which is almost insoluble in water [56]. In contrast, branched polysaccharides such as dextran have a loose molecular arrangement, which reduces crystallinity and thereby increases solubility. Moreover, functional groups (-OH) within a neutral polysaccharide molecular chain are difficult to dissociate into ions, and therefore do not contribute additional mobile ions in aqueous solutions; therefore, neutral polysaccharides have relatively low electrical conductivity, especially low proton conductivity [57,58]. Neutral polysaccharides have weaker metal-chelating abilities than charged polysaccharides. The difference occurs because neutral polysaccharides lack charged functional groups that can effectively form stable complexes with metal ions. Neutral polysaccharides interact with metal ions primarily via non-charged functional groups such as hydroxyl, so the complexes typically have lower energy stability than complexes of charged polysaccharides [59].

Neutral polysaccharides can have useful mechanical properties. For instance, the theoretical Young's modulus of crystalline cellulose can reach about 100–200 GPa, and its tensile strength is about 4.9–7.5 GPa, which is higher than most metals, alloys, and synthetic polymers [60]. This mechanical strength partly originates from the dense hydroxyl groups on the cellulose molecular chains, which form tight intermolecular and intramolecular networks by hydrogen bonding (Fig. 2K). These hydrogen bond networks also offer physical entanglements, which contribute to toughening the material [61]. Therefore, due to these properties, neutral polysaccharides have demonstrated potential applications in flexible neuromorphic devices, particularly as ultrathin free-standing substrates.

2.2. Proteins

Proteins are complex biomolecules composed of amino acids linked by peptide bonds (Fig. 3A). Proteins have a linear arrangement of amino acids, but interactions among them induce folding and torsion reactions that yield complex three-dimensional shapes, which endow proteins with a high functional diversity (Fig. 3B) [62]. Considering structures and functions, proteins can be largely classified into fibrous and globular types [63].

Fibrous proteins are structural components, which have the main function of providing structural support and strength [64]. They have specific repeating structures that help them form sturdy constructs. Most fibrous proteins have amino-acid sequences and secondary structures that tight packing into stable fibrous structures; as a result, most are insoluble in water [65]. Common fibrous proteins include silk fibroin, keratin, and collagen (Fig. 3C) [66–68].

Silk fibroin is highly regarded for its exceptional mechanical strength and mechanical flexibility, which are comparable to the strongest synthetic fibers. Silk fibroin is composed of two main repetitive structures: a light chain (L) polypeptide and a heavy chain (H) polypeptide (Fig. 3C) [69–75]. Silk fibroin contains abundant beta (β)-sheet structures composed of hydrophobic amino acids (Fig. 3D). A strong hydrogen bond network develops in the β-sheet nanocrystals, and endows it with high mechanical strength and durability. Moreover, the β-structure of silk fibroin is highly related to its electrical properties. For instance, the dielectric properties of novel silk fibroins prepared by the polymerization reaction of silk fibroin and 2-isocyanatoethyl methacrylate has been greatly improved [76]. The improvement in dielectric performance is due to the changes in molecular structure. During the polymerization process, the molecular structure of silk fibroin changes, leading to the formation of more β-sheet and β-turn structures. These structures form a

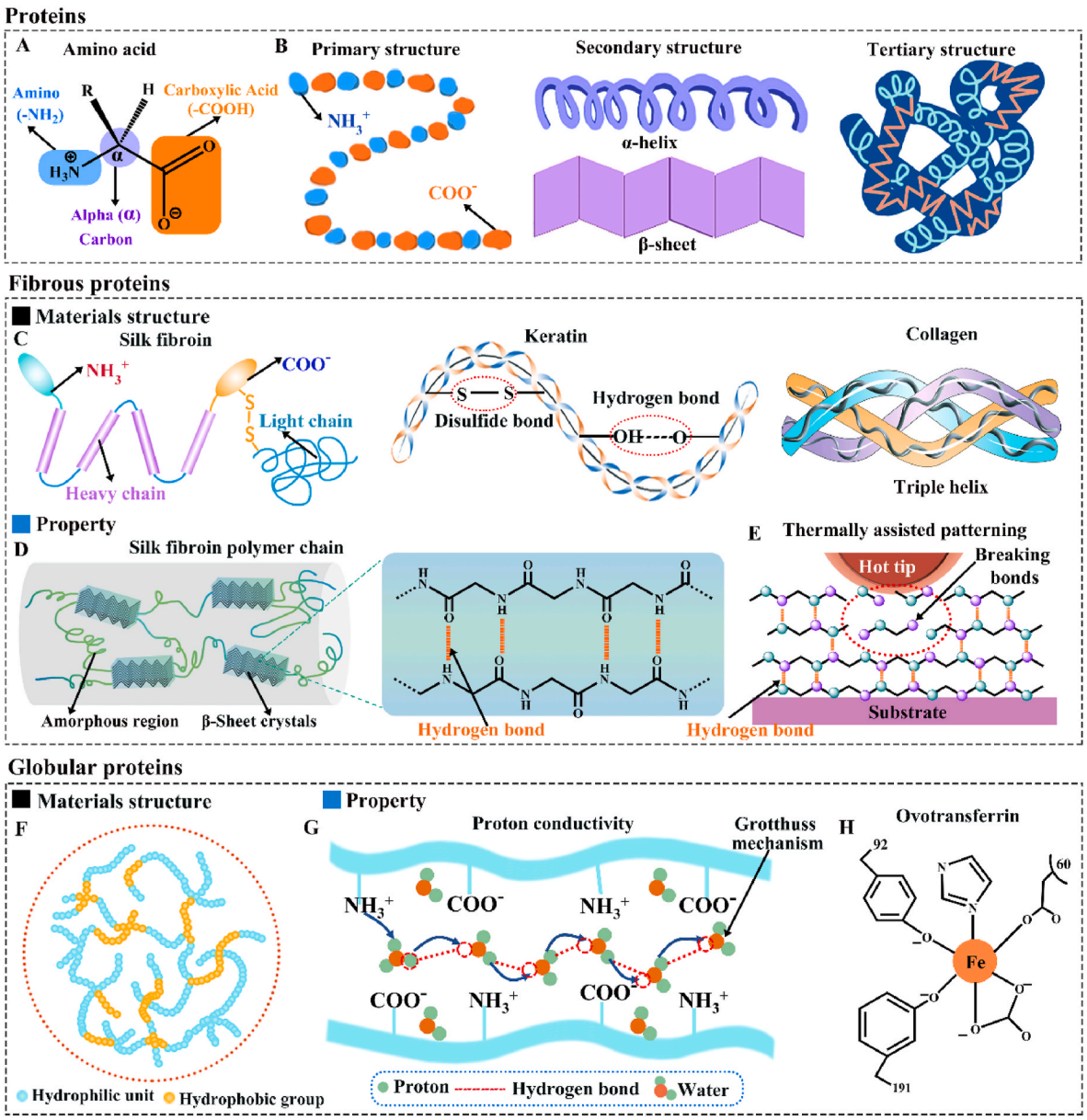

Fig. 3. Structure and properties of different kinds of proteins. A) Basic structure of amino acids, which consists of a central alpha (α) carbon atom bonded to an amino group (NH_2), a carboxyl group (COOH), and a hydrogen atom. B) Levels of protein structure. C) Schematic representation of the structures of different kinds of fibrous proteins. D) Schematic representation of silk fibroin chains containing both crystalline and amorphous domains. E) Schematic diagram of thermal scanning probe lithography patterning silk fibroin. F) Schematic diagram of three-dimensional structure of globular protein, with blue and orange representing hydrophilic and hydrophobic fragments respectively. G) Grotthuss mechanism for proton conduction along hydrogen bonds formed by water and polar groups of albumen. H) Hydrogen-bonding network near Fe binding sites of the N-terminal lobe of ovotransferrin. The orange circles represent iron element. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

strong hydrogen bond network within the material, thereby increasing the dielectric properties. Silk fibroin also includes non-crystalline regions that enable deformation without fracturing under stress [77,78]. The excellent mechanical strength and flexibility of silk fibroin, combined with its natural insulating properties, demonstrate potential in the design and fabrication of ultra-lightweight flexible memristors, both as active layers and as free-standing substrates [79,80]. Additionally, silk fibroin has a sensitive thermal response, and therefore can be precisely patterned using mask-less thermal scanning probe lithography (Fig. 3E) [81]. β-sheet crystallites in silk fibroin melt at 292–351 °C. Melting disrupts the hydrogen bonds that stabilize its secondary structure, so the silk fibroin changes from crystalline to amorphous; concurrently, its water solubility increases significantly. After the thermal patterning process, the film is immersed in deionized water, which dissolves the thermally-altered regions of the silk fibroin, to yield the desired pattern [82]. This thermally-assisted patterning of silk fibroin demonstrates its potential applications in high-density neuromorphic devices.

Globular proteins are composed of folded amino acid chains that are therefore tightly packed. The folding patterns are much more complex than those of fibrous proteins, enabling globular proteins can perform a wider range of functions than fibrous proteins [83]. In aqueous environments, the hydrophilic amino acid chains in tertiary structure are usually exposed on the outside and hydrophobic residues are exposed on the inside (Fig. 3F). Because of this structural arrangement, most globular proteins have good solubility in water [84]. Egg white (albumen) is an excellent natural source of globular proteins. It is primarily composed of water (88 %) and protein (11 %) [85]. Most proteins in albumen are globular, and their spatial structure is stabilized by non-covalent

interactions such as hydrogen bonds, van der Waals forces, and ionic bonds [86]. The formation or breaking of these bonds involves migration of molecules, electrons, and hydrogen atoms; this freedom of movement is advantageous in neuromorphic devices.

Albumen films are conductive to protons but insulate against electrons, and are therefore good gate dielectric materials for synaptic transistors. Albumen contains abundant hydrophilic functional groups, such as carboxyl (-COOH), amino (-NH_2) [87]. These functional groups can interact with water molecules, thereby facilitating the movement of protons in a hydrated state (Fig. 3G) [88–90]. Also, albumen contains trace amounts of metal ions, including iron (Fe), sodium (Na), and potassium (K). They can participate in redox reactions under external electric field, such as the oxidation ($Fe \rightarrow Fe^{3+} + 3e^-$) and reduction ($Fe^{3+} + 3e^- \rightarrow Fe$) of Fe in ovotransferrin (Fig. 3H). The resultant changes in resistance make albumen suitable as active layer materials for two-terminal synaptic devices, even those that have inert-metal electrodes.

2.3. Other biomaterials

Chlorophyll is an organic pigment and semiconductor [91]. It is chemically stable and abundant [92,93]. Chlorophyll molecules can absorb light energy and convert it to chemical energy. This capability is attributed to its heterocyclic chemical structure surrounding a central magnesium ion (Mg^{2+}). Because of this structure, absorbed light excites electrons from the ground state to higher energy levels, and thereby enable the electron-transfer process of photosynthesis [94,95]. These properties of chlorophyll endow it with application potential in optoelectronic synaptic devices. For instance, photoelectrical synaptic transistors sensitized with chlorophyll achieve an ultrahigh gain with rapid responsiveness [92]. These characteristics suggest that chlorophyll-sensitized photoelectrical synaptic transistors may have applications potential in neuromorphic visual systems [96].

Lignin is a major component of wood, and one of the most abundant polymers in nature [97]. It is an amorphous aromatic polymer composed of three phenylpropane units [98–100]. Lignin also bears abundant functional groups, including hydroxyl, methoxy, ether, and carboxyl [101]. When lignin is heated to a temperature from 200 to 1000 °C, it undergoes pyrolysis, which drives off most of the functional groups leaves an amorphous carbon matrix or graphitic structure [102–105]. These resulting structures have significantly different electrical properties than lignin. They have excellent electrical conductivity, so they have been applied in active channel layers of neuromorphic devices.

Other natural biomaterials that are considered for use in neuromorphic electronics include wheat flour, blood, anthocyanin, papaya peel, guar gum, membrane proteins, honey, hyaluronic acid, DNA, silibinin, lotus root, and lactalbumin bilayer [106–118]. They have tailorable chemical composition and mechanical properties, and are abundant, biodegradable, biocompatible, and anti-microbial. Use of natural biomaterials increases the functionality of artificial synapses and is a sustainable approach that uses renewable resources. They constitute resources for use in development of wearable and implantable neuromorphic systems.

3. Emulation of biological synapses using biomaterials

3.1. Emulation of biological synaptic behaviors

With the rapid advancement of artificial intelligence, the use of neuromorphic electronics is increasingly being considered. This field is dedicated to developing synapse-like devices to simulate synaptic plasticity and functions of brain [119]. A human brain is a sophisticated system composed of around 10^{12} neurons, each connected to thousands of other neurons via synapses. The connection strength ('synaptic weight') between two neurons depends on the recent activity history of the synapse (Fig. 4A) [120]. Synaptic plasticity is a biological process in which synaptic activity leads to changes in synaptic weight; in the brain these changes constitute the basis of learning and memory [121]. Considering duration, synaptic plasticity can be categorized as short-term or long-term (Fig. 4B).

Short-term plasticity leads to changes in synaptic weight that can last from milliseconds to minutes, including short-term potentiation (STP), short-term depression (STD). When two consecutive stimuli (voltage 'spikes') are applied to a synapse, the excitatory postsynaptic current (EPSC) amplitude in response to the second stimuli can be increased (paired-pulse facilitation, PPF) or decreased (paired-pulse depression, PPD) compared to the response to the first one (Fig. 4C); these phenomena are essential forms of short-term plasticity [122]. Short-term plasticity can rapidly change synaptic weights, so synapses can act as filters by strengthening or depressing synaptic transmission efficiency. Long-term plasticity refers to changes in synaptic weight that can last for hours or even longer [123]. Long-term plasticity can be divided into long-term potentiation (LTP) and long-term depression (LTD), which are regarded as essential to learning and memory (Fig. 4D). Repeated or frequent neural stimulation can induce a transition from short-term to long-term plasticity.

The concept of synaptic plasticity is influenced by Hebb's rules. Spike-timing-dependent plasticity (STDP) is one of the most well-known Hebbian learning rules; it describes the dependence of synaptic weights on the temporal order of presynaptic and postsynaptic spikes (Fig. 4E) [124]. Synaptic weights can also be influenced by spike rate (spike-rate-dependent plasticity, SRDP), spike number (spike-number-dependent plasticity, SNDP), and spike voltage (spike-voltage-dependent plasticity, SVDP).

Spatiotemporal integration is another important process in emulation of biological synapses, and involves signal integration in spatial and temporal sequences (Fig. 4F) [125]. This integration allows neurons to extract information from multiple input terminals and adjust their responses according to the spatiotemporal patterns in this information [126]. In neuromorphic devices, spatiotemporal integration generates specific responses by considering the spatial position of the input signals, and the intervals between them; this response emulates the information-processing mechanisms of neural networks. Therefore, the development of artificial synapses that emulate biological synapses has become an important direction in neuromorphic devices.

3.2. Mechanism

Biomaterials are biocompatible, biodegradable, mechanically flexible, and lightweight, so they are promising materials for fabrication of sustainable flexible electronics. The library of natural biomaterials includes polysaccharides, proteins, various plants, and their derivatives. These materials exhibit unique chemical and carrier transport properties, such as chelation with metal ions and excellent proton conductivity, providing an effective pathway for the construction of efficient and reliable sustainable flexible artificial synapses.

In this section, we summarize the working mechanisms of artificial synapses that use biomaterials, dividing them into memristors and synaptic transistors. Several mechanisms have been proposed to explain the resistance switching behavior in typical memristors. These mechanisms include ion migration, charge trapping, phase transition, and redox mechanism [127–130]. However, the inherent properties of natural biomaterials dictate that they contain abundant functional groups and complex multilayered structures instead of strict physical band structures. Therefore, the mechanisms of biomaterial-based memristors primarily involve the formation and rupture of conductive filaments or the trapping and detrapping of charges (Fig. 4G). Biomaterial-based synaptic transistors primarily include electrical synaptic transistors and photo-synaptic transistors, with their working mechanisms involving electrochemical reactions and the trapping and detrapping of photo-generated charges (Fig. 4H).

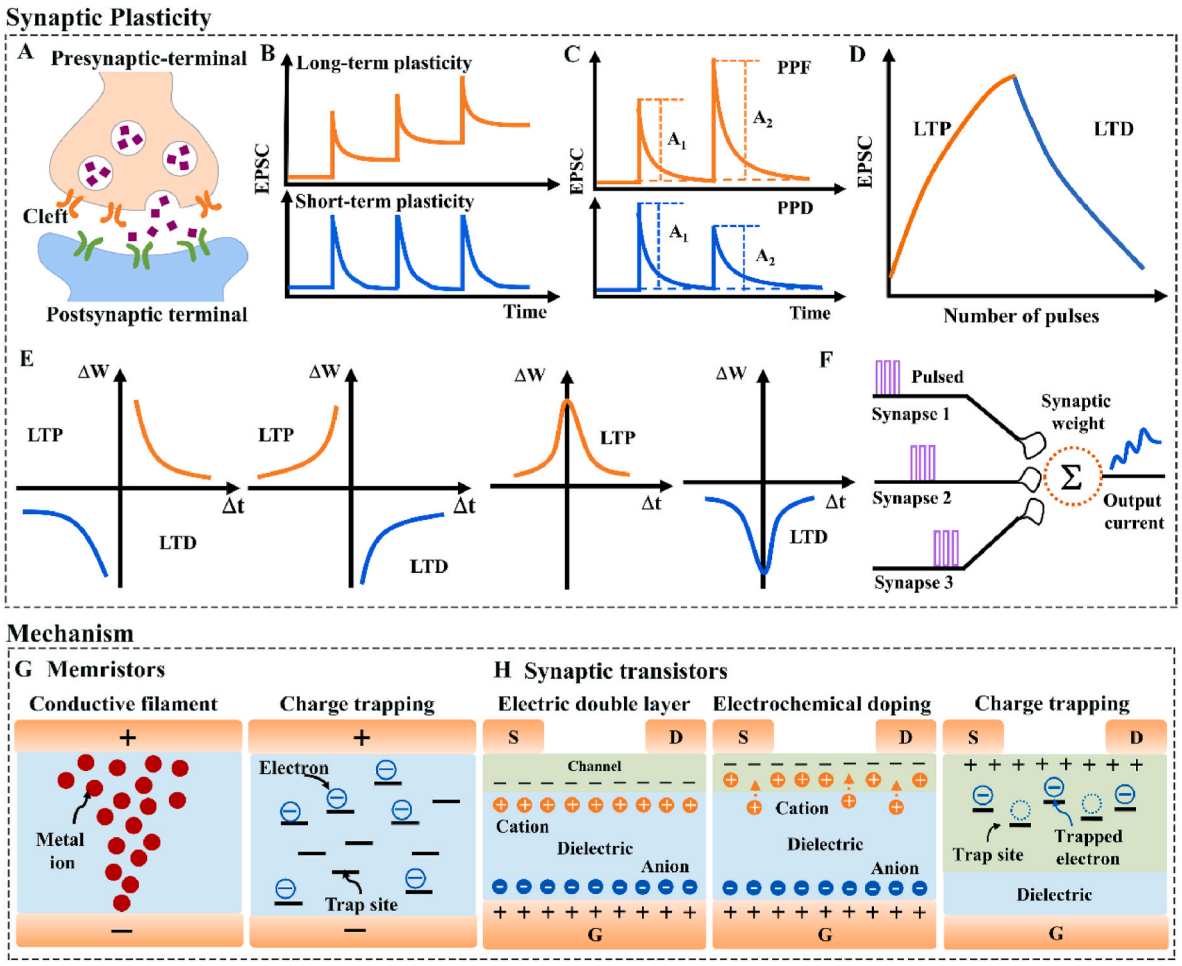

Fig. 4. Synaptic plasticity and mechanism of biomaterial synapses. A) Schematic of a biological synapse. B) Long-term plasticity (orange) and Short-term plasticity (blue) of the artificial synapses. C) PPF (orange) and PPD (blue) of the artificial synapses. D) LTP (orange) and LTD (blue) of the artificial synapses. E) Schematic diagram of STDP according to the relative timing of pre-and post-synaptic pulse. F) Schematic diagram of spatial summation with different time intervals of input pulses. G) Mechanisms of biomaterials-based memristors: conductive filament and charge trapping. H) Mechanisms of biomaterials-based synaptic transistors: electrochemical reaction, electrochemical doping, and charge trapping. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2.1. *Memristors*

3.2.1.1. Conductive filament. Growth and rupture of conductive filaments enable resistive switching characteristics of memristors. The processes involve migration of metal ions and redox reactions to form conductive filaments. Under an electric field, the active metal electrode is oxidized, and releases metal ions that migrate to the opposite electrode, where are reduced; the resulting metal atoms form nanoparticle clusters that assemble to form metallic filaments. When they span the space between electrodes, the filaments cause a transition into a low-resistance state (LRS); this is called the "set" process. Conversely, application of reverse voltage disrupts the metallic bridges by Joule heating effect or electrochemical oxidation, so the device reverts to a high-resistance state (HRS); this is the "reset" process. This mechanism enables precise control over the migration of metal ions and the formation and rupture of conductive filaments, and therefore provides an effective approach for constructing efficient and reliable artificial synapses.

Biomaterials bear abundant polar functional groups such as carboxyl (-COOH), amino (-NH_2), hydroxyl (-OH), and thiol (-SO_4^{2-}). They can react with metal ions to promote formation of conductive filaments. ι-Carrageenan (ι-car), an anionic polysaccharide biopolymer, has successfully simulated synaptic behaviors such as STP, PPF, and the transition from STP to LTP in memristors that have an Ag/ι-car/Pt sandwich structure [131]. ι-car is an ionic conductor through which metal ions can migrate. It contains functional groups such as -SO_4^{2-}, C–O–C and C–O–H that can interact with metal ions, and thereby facilitate and control their migration. A similar resistive switching mechanism also occurs in biomaterials such as chitosan and cellulose.

The switching behavior of chitosan is closely related to the interaction between active metal ions and the films. In chitosan molecules, the amino group can provide pairs of free electrons, so it is the primary active group in the reaction. Amino groups bind with metal ions to form stable complexes in weakly acidic solutions. These complexes stabilize the metal ions, and thereby facilitate formation of conductive filaments [132]. Cellulose is a neutral polysaccharide, and its resistive switching behavior is a result of molecular structure and functional groups. Cellulose molecules contain C–O–C and C–O–H groups, which can interact with metal ions, and thereby facilitate their migration. Although cellulose has weaker metal-chelating capabilities than polysaccharides that bear cations and anions, its surface is a porous network structure that can facilitate penetration and diffusion of metal ions [133–135]. Corn starch is also a neutral polysaccharide with three hydroxyl groups (C–OH) and one C–O–C bond in each of its glucose monomer units. The oxygen atoms in these highly polar groups can strongly interact with metal ions to facilitate the conduction of cations [136].

The diverse functional groups in biomaterials can effectively

promote formation of conductive filaments. However, the stochastic motion of metal ions for forming filaments can cause abrupt current change, which lead to asymmetry and nonlinearity in weight updates, and to decreased device reliability. To address this problem, optimization strategies should focus on regulating the dimensions of filament growth or on suppressing multifilament formation. For instance, by doping $AgNO_3$ into ι-car, the asymmetry, linearity, and repeatability ($\sim 10^4$) of the device can be significantly improved [137]. This phenomenon occurs because doping by $AgNO_3$ ensures uniform distribution of Ag ions within the material, and thereby enables precise control of the number and thickness of Ag filaments. This control effectively reduces the formation of multiple conductive paths and eliminates uneven Joule heating, and thereby prevents excessive heat concentration in localized areas of the device, and thus ensures that the conducted current is uniform and stable. Moreover, doping CuO nanoparticles into egg albumen leads to more stable and easily formed silver atom channels. CuO nanoparticles facilitate electrochemical metallization by modulating the electric field in the active layer, making it easier for silver atoms to be injected into the active layer under a lower electric field. Therefore, compared to devices without CuO doping, the doping of CuO nanoparticles effectively enhances the conductivity and stability of the device through increased electrochemical metallization [138].

The stochastic nature of the formation and rupture of conductive filaments results in significant differences between cycles and among devices. This variability reduces their uniformity and reliability. One solution is to use specially-designed electrodes to locally strengthen the electric field and thus enable precise control of the formation of conductive filaments [139,140]. Silk fibroin is thermally patternable and has excellent dielectric strength, mechanical flexibility, and chemical stability. An Ag/silk fibroin/Au memristor with customized nanocone electrodes was realized by thermal scanning probe lithography (t-SPL) technology to exploit these characteristics. The thermally responsive characteristic of silk fibroin allows for the patterning of a nanocone array on demand by using a nanoscale heated probe; this method has provided resolution finer than 20 nm. This approach significantly reduces variability between cycles and devices; it also achieves small operating voltage (0.5 V) and current (100 nA), ultra-fast switching (<100 ns), and large on/off ratio (10^4) [141]. In addition, due to its light weight and flexibility, silk fibroin was used both as the memristive active layer and the substrate, and achieved an ultra-light weight of only 0.4 mg cm^{-2}, which can be supported by a human hair [142].

Design of sustainable neuromorphic devices has used biomaterials such as albumen enriched with metal ions, and lignin with high carbon content. The devices have demonstrated significant value in synaptic devices that exploit non-active electrode conductive filaments. For example, an artificial synapse that had W/egg albumen/ITO/PET structure exhibited threshold switching behavior and simulated synaptic functions such as EPSC, STP, LTP, and the transition between STP and LTP [143]. Unlike conventional resistive switching, the resistance changes in egg albumen are primarily caused by threshold phenomenon that result from migration of a limited number of metal ions. Egg albumen contains trace amounts of metals such as Fe, Na, and K. Under an electric field, they are oxidized to ions (e.g., $Fe \rightarrow Fe^{3+} + 3e^{-}$) and migrate to the ITO bottom electrode, where they are reduced again to Fe, and form conductive filaments, so the LRS is established. As the voltage increases, if the supply of metallic ions in the albumen is insufficient, the iron atoms in the filament oxidize, so the filaments rupture and the HRS is restored; this response yields the threshold switching phenomenon.

Lignin biopolymers can demonstrate resistance switching that is induced by carbon-rich filaments. An artificial synapse that used memristors that had the structure Au/lignin/ITO/PET demonstrated the basic functions of neural synapses, including LTP, LTD, SRDP, and the transition from STP to LTP [104]. This phenomenon is attributed to the high carbon content of lignin, which heat can transform to amorphous or graphitic structure, and thereby change the electrical conductivity of lignin [144].

3.2.1.2. Charge trapping/detrapping. Resistance switching behavior by charge trapping/detrapping is entirely dependent on purely electronic mechanisms. In these devices, electrons move along isotropic pathways in three-dimensional space; this phenomenon ensures high device uniformity. The charge trapping/detrapping mechanism primarily involves three types of traps: interface traps between the electrode and the active layer, vacancy or defect traps within the active layer, and traps that are induced by doping with nanostructures.

Interface traps are located at the interface between the metal and the active layer. In devices in which interface traps are dominant, voltage stress can cause carriers from the electrodes to be captured or released by trap sites. This process causes changes in the height of Schottky barrier and leads to the switching of device resistive. Active-layer traps are defects in the active layer. In devices in which active-layer traps are dominant, voltage stress causes them capture or release carriers. These processes change the distribution of trap energy levels, and thereby result in the resistive switching behavior. However, trap sites within the active layer are usually "atom-level" and randomly distributed, so electron transport is nonuniform [145,146]. By introducing nanostructures into the active layer, the number and distribution of traps can be adjusted to become distributed in layers, and thereby improve the uniformity of electron transport. To explain the resistive switching behavior of devices dominated by randomly and layered traps, several models, such as trap-controlled space charge limited current (SCLC) and trap-assisted tunneling have been applied [147,148].

Numerous research groups have demonstrated the synaptic devices that use biomaterials and exploit the charge trapping/detrapping mechanism [109,149–151]. Collagen has a triple helix structure formed by self-assembly of three polypeptide strands [152]. These helical structures provide a pathway for charge trapping/detrapping [153]. A flexible synaptic device that has the structure Mg/collagen/ITO can simulate various synaptic behaviors by exploiting the charge trapping/detrapping, including EPSC, PPF, STDP, and SRDP [149]. This device can operate stably even when bent. The conduction mechanism of synaptic devices that use collagen is primarily controlled by SCLC and Ohmic conduction. The SCLC phenomenon is caused by charge carriers being trapped in defects within the collagen structure; these defects are located below the conduction band. Ohmic conduction occurs at low bias because the electric field across the device is insufficient. The consistency of synaptic devices that exploit charge trapping/detrapping can be increased by introducing nanoparticles into biomaterials. For instance, incorporating gold nanoparticles (Au NPs) into agarose can achieve reliable resistive switching characteristics, excellent retention for 10^5 s under 80 °C, low energy consumption for the LTP (64.4 pJ/event) and LTD (164.4 pJ/event), and maintain LTP/LTD characteristics for up to 5000 bending cycles [150]. These improvements occur because Au NPs have superior electron-trapping properties, which can stabilize retention of the resistive state.

3.2.2. Synaptic transistors

3.2.2.1. Electrochemical reaction. Synaptic transistors that use natural biomaterials exploit formation of an electric-double-layer (EDL) by accumulated protons or ions, to electrostatically modulate the channel conductance to implement synaptic characteristics of the device [154]. These synaptic transistors typically have a dielectric layer composed of natural biomaterial sandwiched between the gate electrode and channel layer with source/drain electrodes on both sides; in this structure, the EDL forms at the interface between the dielectric layer and the channel layer, and can directly modulate the channel conductance.

When an n-type semiconductor is used as the channel layer, application of a positive gate voltage drives protons inside the natural biomaterial layer toward the channel layer, where they accumulate at its

interface with the biomaterial. The accumulated protons form an EDL, which attracts electron carriers in the n-type semiconductor to the interface and electrostatically increases the conductance of the channel. After removal of applied voltage, protons drift back to their equilibrium distribution due to the concentration gradient, so the channel conductance decreases to its initial state. This process results in excitation and rapid decay of the device current, and emulates STP behavior of biological synapse. Furthermore, if the voltage amplitude or frequency is high enough, migrated protons penetrate the channel layer; this phenomenon induces a non-volatile change to the channel conductance, so emulates LTP behavior of biological synapse.

For effective implementation of synaptic characteristics by using an EDL, biomaterials that possess numerous mobile protons and have high proton conductivity are preferred. Abundant protons can form a high capacitance in the EDL and thereby facilitate modulation of channel conductance. High proton conductivity allows the EDL to form at low operating voltage, and thereby achieves low power consumption, which is a critical requirement in neuromorphic devices [155]. For instance, a transistor that uses egg albumen, which has high proton conductivity, has successfully demonstrated synaptic characteristics, such as PPF, STP to LTP transition, and spatiotemporal integration [90,156]. The device consists of egg albumen as gate dielectric layer, IZO channel layer with source/drain electrodes on the top, and ITO gate electrode at the bottom. In this device, the egg albumen has low conductivity for electrons, but high conductivity for protons as a result of bearing various hydrophilic functional groups, which interact with water molecules and facilitate the Grotthuss mechanism. Under positive voltage bias, protons in egg albumen migrate to the channel interface, where they form an EDL, and thus impart synaptic characteristics to the device.

Anionic polysaccharides and cationic polysaccharides have abundant protons and high proton conductivity, and therefore have been used in synaptic transistors that exploit electrochemical reactions [157–163]. One such synaptic transistor uses pectin, an anionic polysaccharide, and achieved low operating voltage of 20 mV, which is even lower than that of biological synapses (~100 mV) [158]. The low operating voltage of the synaptic transistor is a consequence of the high number of carboxyl groups in pectin, which interact with water molecules to yield abundant interior protons. As a result, the capacitance of EDL is high during operation, so channel conductance is easily modulated. A synaptic transistor composed of chitosan achieved the highest EDL capacitance of ~9.8 μF cm^{-2}; it was primarily attributed to the abundant protons generated during protonation of amino groups, and to formation of hydrogen-bond networks among hydrated chitosan molecules [160]. These networks promote proton conductivity, and thereby help to modulate the channel conductance to implement synaptic characteristics.

The high proton conductivity of these biomaterials enables fabrication of in-plane-gate structure without an additional conductive layer; this trait is advantageous for constructing multi-gate synaptic transistors that resemble natural neurons, which have multiple dendrites [90,159,162,163]. The conventional in-plane-gate structure modulates the channel conductance by two steps: applied gate voltage couples to the conductive layer; then the conductive layer couples to the channel, i.e., the gate bias is coupled through two capacitors in series. However, high proton conductivity provides high lateral capacitance between the in-plane-gate and the channel, so the gate bias can directly modulate the channel without coupling to the conductive layer [164].

Neutral polysaccharides acquire protons by self-dissociation of absorbed moisture, because their uncharged and strong hydrogen bonding from tightly packed molecular structure inhibits the dissociation of protons in itself; this mechanism is unlike those in charged polysaccharides, which can acquire protons from interaction between residual water molecules inside the polymer layer, and charged functional groups [56]. Acquisition of protons by dissociation of water in neutral polysaccharides yields fewer mobile protons and low proton transport capabilities than charged polysaccharides, and hinders implementation of synaptic characteristics in transistors that use neutral polysaccharides. To solve this problem, modification of neutral polysaccharides has been evaluated.

One method is to increase the water content in neutral polysaccharides by raising the relative humidity (RH) [158,165,166]; the additional water molecules increase the number of free protons and strengthen the hydrogen bond network. In a dextran synaptic transistor, this method increased the amplitude of EPSC on by 72.7 % as RH was increased from 30 % to 50 % [165]. Another method is to convert the functional groups in neutral polysaccharides. Cellulose on which hydroxymethyl groups had been converted to sodium carboxylates was used in a synaptic transistor and successfully implemented synaptic characteristics [167]. In this converted cellulose, not only protons from absorbed moisture but also sodium ions can move after dissociating from carboxylic groups under external electric field and form an electrical double layer, which facilitates modulation of channel conductance to achieve synaptic characteristics.

3.2.2.2. Charge trapping and detrapping. Synaptic characteristics implemented by the charge trapping/detrapping mechanism exploit a change of channel conductance, due to the electrostatic gating effect of trapped charges in trap sites such as defects and interfaces. Most synaptic transistors that use biomaterials exploit charge trapping/detrapping as a mechanism are mostly photonic synapses, which use light as a stimulus. These devices have an active layer composed of a photo-responsive biomaterial combined with a semiconductor that provides photoexcited charges and that has trap sites within it and at the interface between the active layer and the dielectric layer. Under illumination, electron-hole pairs are generated in the active layer by photoexcitation. At the same time, one type of charge can separate from the pair and become trapped at these defects, while the other type of charge can act as additional charge carriers in the channel. The trapped charges create an additional internal electric field, which attracts oppositely-charged carriers, and thereby increases the channel conductance. After illumination, the trapped charges escape from trap sites electron-hole pairs recombine, so the channel conductance decreases. As a result, the device current decays, similar to the behavior of a biological synapse. Increase in the intensity, frequency, or number of optical pulses raises the density of charges trapped in the deep trapping sites, so the time to release the trapped charges increases; this phenomenon causes long-term synaptic plasticity.

The synaptic plasticity induced by charge trapping/detrapping can be influenced by the density of defects in the active layer [168,169]. Therefore, fabricating an active layer with materials that include abundant defects may improve the synaptic memory behavior of the device. For example, chlorophyll blended with poly[2,5-bis(2-octyldodecyl)pyrrolo[3,4-*c*]pyrrole-1,4(2H,5H)-dione-3,6-diyl)-alt-(2,2′; 5′,2″; 5″,2‴-quaterthiophen-5,5‴-diyl)] (PDPP4T) retained synaptic memory for more than 20 s even under operating voltage low as 10^{-5} V [170]. An organic field effect transistor that used only PDPP4T did not show synaptic characteristics, but chlorophyll-added transistor achieved synaptic characteristics, due to the defects in chlorophyll itself and at the interface created by phase separation between chlorophyll and PDPP4T. Moreover, blending of chlorophyll with single-walled carbon nanotubes realized synaptic behaviors that consume energy of only 17.5 fJ [95]. This approach has been used to demonstrate synaptic transistors that use photo-responsive natural biomaterials in which charge trapping/detrapping occurs. These devices can perceive information transmitted using the light, then process the information using synaptic behavior. This ability gives them potential to mimic the operation of a human visual system. Because of this enhancement in synaptic memory behavior by using charge trapping/detrapping as a mechanism, along with the advantages of using natural biomaterials such as biocompatibility, these synaptic devices may be useful in developing artificial retinas.

4. Characteristics of artificial synapses that use biomaterials

Neuromorphic devices have potential applications as neural prostheses, wearable and implantable biomedical systems. Accordingly, they must interact appropriately when they integrate with a living body. Thus, construction of artificial synapses should consider the interface between electronic devices and biological systems, such as the skin, and the tissues of organs. Moreover, considering the harm on the environment caused by electronic waste, neuromorphic devices for use as future flexible and sustainable applications in next-generation computing devices, should be also ecologically benign. Natural biomaterials meet these requirements, due to biocompatibility, mechanical flexibility, and biodegradability. In this section, we review these characteristics granted by biomaterials to artificial synapses, with focus on structural features and functional groups.

4.1. Biocompatibility

For bioelectronic interfaces and biomedical applications, neuromorphic devices are applied to the surface of a biological systems without causing immune responses or damaging or killing cells and tissues near the point of attachment. Development of biocompatible artificial synapses is still in its initial stages, so most studies have been conducted *in vitro*, usually using devices immersed in cell-culture medium that simulates physiological conditions [109,158,165,166,168,171]. This approach helps to avoid ethical restrictions and minimizes the costs, so preliminary evaluation of biocompatibility can be conducted at the laboratory level. The main cause that degrades biocompatibility is cytotoxicity [172]. Natural biomaterials tend to have low toxicity and have an ability to support cell proliferation and differentiation; therefore, the development of artificial synapses that use natural biomaterials could be the key to solving this problem [173].

In vitro cell viability testing is an effective method to evaluate the biocompatibility of artificial synapses that use biomaterials. For example, the biotoxicity of an eco-friendly synaptic phototransistor is assessed using the single-celled organism paramecium [168], which is extremely sensitive to the environment and can be killed by substances that are even slightly toxic. The transistor included natural biomaterials,

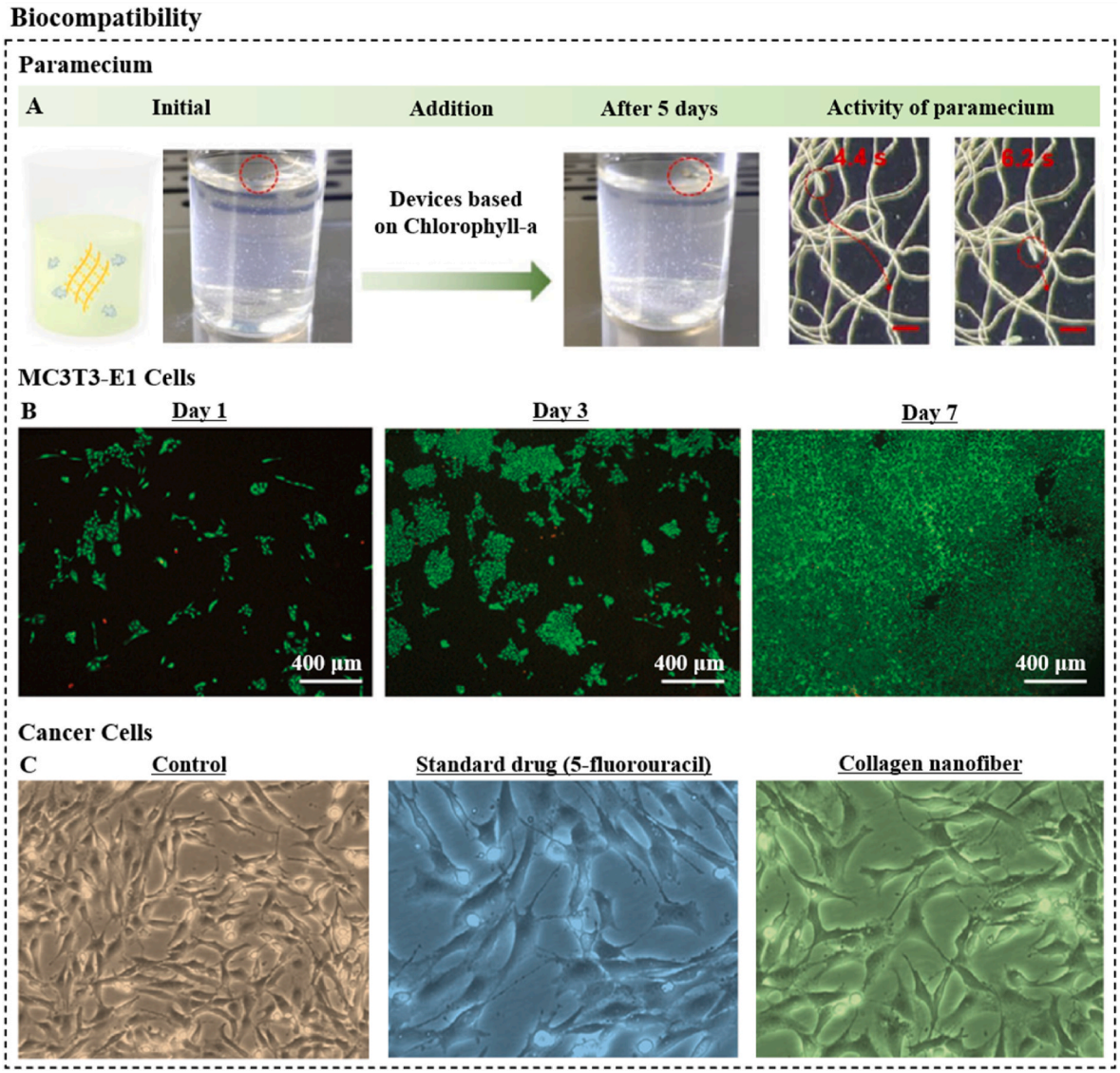

Fig. 5. *In vitro* tests to evaluate biocompatibility of synaptic devices. A) Observation on paramecium activity with device immersed in the cell culture. Reproduced with permission from Ref. [168]. Copyright 2022, The Authors. Published by Springer Nature. B) Proliferation of MC3T3-E1 cells with device. Reproduced with permission from Ref. [166]. Copyright 2020, The Royal Society of Chemistry. C) Evaluation of anticancer activity of collagen nanofiber-based synaptic device compared to the control group and the standard drug (5-fluorouracil). Reproduced with permission from Ref. [171]. Copyright 2024, Wiley-VCH.

i.e., cellulose nanopaper as the dielectric/substrate and natural chlorophyll-a as the photoactive material. The device was placed in the culture medium to assess their effect on paramecium activity, compared to another treatment that did not include the device. In both treatments, the paramecia survived for 5 d (Fig. 5A). Even after 10 d, most of the paramecia in both groups remained alive. This result demonstrates the biocompatibility of the device that uses cellulose and chlorophyll-a.

MC3T3-E1 cells derived from mouse-calvaria cells are also used to test the biocompatibility of natural artificial synapses that use biomaterials [174]. These cells are widely used as reference material for evaluating the biological response of the device according to International Organization for Standardization (ISO) 10993–12. Passing the cytotoxicity test following the protocols of the ISO 10993–5 indicates that the device could be used as a medical device [175,176]. *In vitro* cell viability test was conducted using MC3T3-E1 cells to evaluate the potential of a synaptic device that uses dextran, for implantable applications [166]. The device was immersed in cell-culture solution, and percentage cell survival was quantified after 1, 2, 3, or 7 d. The cells not only survived but continued to proliferate even after 7 d, with almost no cell necrosis (Fig. 5B); thus, dextran endowed the device with biocompatibility that makes it suitable for implantable neuromorphic electronics.

Furthermore, a device that shows anticancer activity is advantageous for long-term implantable devices, because prolonged implantation might cause mutation of normal cells to cancer cells [177]. Therefore, the anticancer activity of natural biomaterial has also been investigated. Synaptic memristors that used synthetically-produced collagen nanofibers as the switching layer were soaked in a cell culture of a widely-used cancer cell line MCF-7 to observe the potential effects of the devices on the vitality of the cancer cells (Fig. 5C) [171]. Collagen nanofibers demonstrated moderate anticancer activity compared to standard drug (5-fluorouracil); cancer cell numbers decreased to 50 %

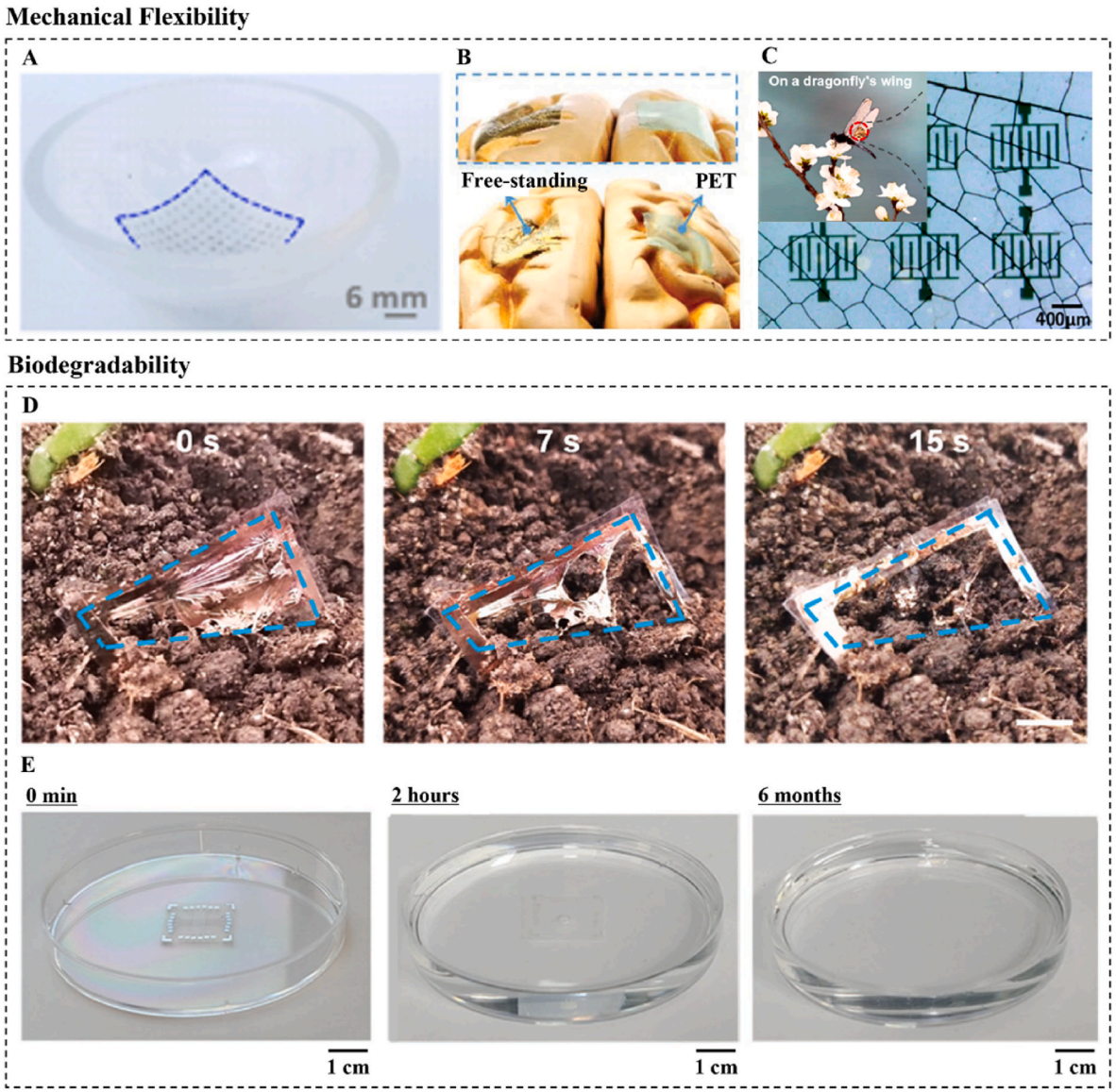

Fig. 6. Demonstration of mechanical flexibility and biodegradability of synaptic devices that use biomaterial. A) Integration of the free-standing synaptic device inside the concave hemispherical surface. Reproduced with permission from Ref. [178]. Copyright 2022. Published by Elsevier. B) Conformal integration of free-standing synaptic device on brain replica (left), compared to device fabricated on PET substrate (right). Reproduced with permission from Ref. [165]. Copyright 2020, Wiley-VCH. C) Conformal attachment of the ultrathin and light-weighted synaptic device on a dragonfly's wing. Reproduced with permission from Ref. [158]. Copyright 2021, American Chemical Society. D) Rapid degradation of the synaptic device on the ground under dripping water. Reproduced with permission from Ref. [166]. Copyright 2020, The Royal Society of Chemistry. E) Gradual degradation of the synaptic device in PBS solution (pH 7.4). Reproduced with permission from Ref. [108]. Copyright 2021, Wiley-VCH.

after 24 h, and to ~10 % within 48 h. The number of cells also decreased to ~60 % as the concentration of collagen nanofibers increased. In this experiment, collagen nanofibers are consumed by the cancer cells as they act similar to nutrients that are contained in normal cells and that cancer cells need for growth, but when cancer cells consume the collagen nanofibers, they hinder growth of the cells.

4.2. Mechanical flexibility

Bio-signal sensing and prosthetic applications require neuromorphic devices that can integrate conformally with the living body, to achieve highly-sensitive detection of bio-signals, and to reduce the risk of delamination despite the body's movement. Moreover, while integrated on the living body, the device must not pose risk of inflammation or discomfort associated with mechanical mismatch between the device and the tissues. Therefore, mechanical flexibility is a necessary property of neuromorphic devices for these applications. Natural biomaterials are ideal candidates to meet this requirement, due to their excellent mechanical strength and resistance to tearing when deformed. These materials can serve as functional layers that impart electronic properties, and can provide structural support, and thereby enable fabrication of ultra-thin and ultra-flexible free-standing devices.

Artificial synapses that use biomaterial can be given superb mechanical flexibility by fabricating a free-standing device on a dielectric layer composed of a natural biomaterial. For instance, substrate-free optoelectronic synaptic transistors utilizing a natural acidic polyelectrolyte derived from orange-peel pectin, has been intimately integrated to the curved surface of a concave hemisphere (Fig. 6A) [178]. The radius of curvature is even smaller than that of a human cornea, so the device can be easily integrated in a human eyeball, and may be applicable to smart lenses. The polyelectrolyte of orange peel gel solidified due to formation of hydrogen bonds between free carboxyl groups and between hydroxyl groups, so the pectin can serve both as a gate dielectric layer and as a mechanical support layer [179,180]. This solid polyelectrolyte enables physical deformation without affecting the functions of the device [178]. The result indicates that pectin may have uses in in artificial synapses for smart wearable electronics.

Decreasing the thickness of the dielectric layer increases flexibility and reduces weight, so the device may even conformally integrate to a wrinkled surface. For instance, free-standing synaptic transistors that used dextran, and that were only 309 nm thick and weighed only 0.6 g m^{-2} have been successfully integrated to the wrinkled surface of a brain replica [165]. The device demonstrates the increased potential for applications as prosthetic neural interfaces, compared to planar devices fabricated on PET (Fig. 6B). The device was also attached to a glass rod that had a radius similar to that of an arteriole, and thus has potential for applications in health-monitoring of the vascular system. In this research, the high hydrophilicity due to branches of hydroxyl groups and mechanical robustness owing to intermolecular cross-linking of dextran chains by hydrogen bonding allow formation of an ultra-thin dielectric layer; the hydrophilic dextran solution was deposited as ultra-thin film by spin-coating on a hydrophobic substrate, then peeled off for use as a free-standing device [181–184]. Although the device is ultra-thin, the mechanical robustness of dextran enables the film to be untorn and just crumple to mechanical stress; this trait makes dextran suitable for use in health monitoring devices that can integrate conformally with a living body. In addition, the extreme thinness and extremely light weight of these devices enables them to even integrate with floating dandelion seeds and dragonfly's wing without interrupting their flight (Fig. 6C) [158,165]. These results could be useful in smart environment-monitoring systems, that could cover a wide terrain by dispersing naturally with the help of living organisms.

4.3. Biodegradability

To reduce accumulation of electronic wastes, neuromorphic devices must degrade quickly in the environment and cause no harm to either human or nature. Degradation of biodegradable neuromorphic devices usually uses a dissolution method, which requires appropriate solvents such as water and acids or bases to facilitate hydrolysis and oxidation reactions. These reactions result in small and harmless fragments such as carbon dioxide, methane, and basic elements, which are further degraded by oxidation and microbial enzymatic processes [185]. Thus, development of sustainable neuromorphic devices requires appropriate choice of biodegradable materials. Biomaterials have chemical structures conducive to enzymatic degradation, and therefore provide promising candidates for materials to increase the biodegradability of the devices.

In the initial stages of developing biodegradable artificial synapses, the devices degraded only partially; the bottom electrodes and the substrate remained. To demonstrate degradation in water, the devices were fabricated using water-soluble natural biomaterials used as the dielectric layer on an insoluble bottom electrode-patterned substrate. Only the upper side of top electrode and biomaterial dissolved, but the transparent bottom electrode (indium tin oxide) and the substrate remained [160,163,186,187]. For instance, in a flexible biomemristor fabricated using collagen electrolyte and Mg electrodes, both the Mg top electrode and collagen completely dissolved in water via hydrolysis after dropping water on the device, while the indium tin oxide bottom electrode and polyethylene terephthalate substrate remained undissolved [188].

To achieve full degradation of the device in water, further research evaluated use of substrate-free devices that use water-soluble biomaterial as a mechanical support layer [95,158,165,166,189]. The structure of these devices adheres to the dielectric layer of a biomaterial, so the device can degrade fully in water as the biomaterial dissolves. For example, synaptic transistors that used a dielectric layer composed of dextran was evaluated under dripping water [166]. The device completely disappeared within 15 s without leaving any pollutants (Fig. 6D). This fast degradation is due to abundant hydroxyl groups (-OH) in dextran molecules forming hydrogen bonds with water molecules. The strong hydrogen bonding of dextran helps disruption of the hydrogen bond network between water molecules, and thereby facilitates hydration and dissolution of dextran molecules. Moreover, the stretchable artificial optoelectronic synaptic device fabricated from the ionic gelatin heterojunction can be completely dissolved within 5 min when submerged in hot water at 60 °C [190]. The entire device can rapidly and harmlessly biodegrade in water because its components, including gelatin, glycerol, choline chloride, and photothermal polydopamine nanoparticles, are all naturally biodegradable materials [191]. In addition to rapid biodegradability, the gelatin-based gel also exhibits self-healing capabilities along with adjustable elasticity. After complete cleavage, the device can be fully repaired within 1 min, primarily due to non-covalent interactions between different molecular chains. Therefore, nature biomaterials, with their excellent biodegradability and elasticity (Table 1), are promising materials for developing sustainable, flexible neuromorphic applications.

For implants, biodegradable devices have benefits, because they are naturally resorbed by living body as they dissolve. This phenomenon eliminates the need for surgery to removing the device after it stops functioning. Natural biomaterials have advantages over conventional biomedical materials primarily due to excellent biocompatibility, and tailorable degradability owing to the modifiable functional groups [192,193]. Consequently, artificial synapses that use biomaterials to attain biodegradability in circumstances similar to the inside of a living body have been presented. Synaptic memristors that used hyaluronic acid (HA) was evaluated in phosphate-buffered saline solution (pH 7.4), which is similar to fluids inside the human body, and is commonly used solvent in biological research [108]. HA is an anionic polysaccharide; this group is a main component of the extracellular matrix in connective tissue. HA has high hydrophilicity similar to those of other anionic polysaccharides, and contributes significantly to cell proliferation and

Table 1
Degradation time of natural biomaterial-based synaptic devices.

Natural biomaterial[a]	Type	Device structure	Materials		Solvent for degradation[b]	Complete degradation[c]	Degradation time	Thickness[e]	Reference
			M: TE/BE T: S&D/ SC/G	Substrate					
Chitosan	Cationic Polysaccharide	T	ITO/ITO/ ITO	PET	DI water	○	15 min	–	[160]
Chitosan/C_3N_4	Cationic Polysaccharide	T	Al/IZO/ ITO	Glass	DI water	X	10 min	–	[163]
Collagen	Fibrous Protein	M	Mg/ITO	PET	DI water	X	5 min	–	[188]
Dextran	Neutral Polysaccharide	T	Au/DNTT/ Au	Free-standing	DI water	○	15 s	200 nm	[166]
Gelatin	Fibrous Protein	T	Al/IGZO/Si	Si substrate	DI water	X	10 min	–	[191]
Gelatin	Fibrous Protein	–	–	–	DI water	○	5 min	–	[190]
Hyaluronic acid	Anionic Polysaccharide	M	Mg/W	PHB92/ PHV8	PBS solution	○	1 min	–	[108]
Pectin	Anionic Polysaccharide	T	Au/DNTT/ Au	Free-standing	DI water	○	100 s	644 nm	[158]
Pullulan	Neutral Polysaccharide	T	Au/C8-BTBT /PEDOT: PSS	Free-standing	DI water	○	30 s	493 nm	[189]
Starch	Neutral Polysaccharide	T	ITO/ITO/ ITO	Glass	DI water	X	60 s	–	[186]
Silibinin	Other biomaterial	M	Mg/W	PHB/PHV	PBS solution	○	2 h	–	[109]
Silk fibroin	Protein	M	Ag/ITO	ITO	Papain solution[d]	X	10 min	–	[187]

Abbreviation: M: Memristor; **T**: Transistor; **TE**: Top electrode; **BE**: Bottom electrode; **S&D**: Source and drain electrodes; **SC**: Semiconductor; **G**: Gate electrode; **DNTT**: Dinaphtho[2,3-b:20,30-f]thieno[3,2-*b*]-thiophene; **IGZO**: Indium Gallium Zinc Oxide; **C8-BTBT**: 2,7-dioctyl [1]benzothieno[3,2-b] [1]benzothiophene; **PET**: Polyethylene terephthalate; **PHB**: Polyhydroxybutyrate; **PHV**: Polyhydroxyvalerate; **PEN**: Polyethylene naphtholate.

[a] Natural biomaterials are used for gate dielectric in transistor structure and active layer for memristor structure.

[b] Solvent for degradation indicates solvent used for degradation test of natural biomaterial-based synaptic devices.

[c] Complete degradation indicates the entire device degraded including the electrodes and substrate.

[d] Papain solution is a protease resembling mammalian lysosomal enzymes, which breaks down protein into smaller polypeptides and eventually amino acids, making it easily absorbed or metabolized in the living body.

[e] Thickness value of the entire device that achieved complete degradation are presented.

migration, and therefore can grant biocompatibility and biodegradability to the device [194]. The device was immersed in PBS solution; due to hydrolysis in the solution, both HA switching layer and magnesium top electrodes degraded within 1 min, the tungsten bottom electrodes degraded after 2 h, and the entire device including substrate dissolved within 6 months (Fig. 6E). [195–197]. A device that used HA as a switching layer obtained synaptic behavior, was mechanically flexible and biocompatible, and therefore suitable to communicate with a living body; it was also biodegradable. These traits demonstrate its potential for use in implantable neuromorphic electronics for biomedical applications.

5. Conclusion and perspective

This review has summarized recent progress in development of neuromorphic devices that exploit biomaterials, with focus on the advantages of these materials in implementing artificial synapses. The neuromorphic devices based on natural biomaterials have emerged not only as a research topic of interests but also an area of far-reaching societal impacts. Effectively fabricating and integrating biomaterial-based artificial synapses with controllable and desirable properties will provide significant opportunities for the sustainable development of next-generation wearable and implantable biomedical technologies. These devices have the potential to revolutionize brain-machine interfaces, neuroprostheses, and other neural implant technologies by mimicking the complex functions of biological synapses in the human brain. When designing bio-hybrid neuromorphic systems, careful consideration must be given to the mechanical compatibility between the devices and human skin or organs. The use of biomaterials has expanded the functionality of neuromorphic devices, including flexibility, biodegradability, and biocompatibility, and has thus greatly promoted their potential for use as materials in wearable and implantable biomedical electronics (Fig. 7A and B).

Recently, significant attempts have successfully integrated biomaterial-based neuromorphic devices with biological components at the system level, establishing a link between artificial sensory nerves and biological interfaces. For instance, integrating active sensors and memristors made from protein nanowires yields wearable, self-powered neuromorphic interface that can intelligently interpret biologically relevant stimuli and issue warning signals in response to abnormal respiratory rates (Fig. 7C) [198]. The resulting neuromorphic interface closely resembles biological interfaces, where sensory organelles and processing neurons share the unitary signal, thereby offering the efficiency of rapid decision-making. Moreover, an *in vitro* monitoring system for hyperglycemia and hyperlipidemia can be developed by integrating blood-based biomemristor with logic circuits [111]. Biomaterial-based neuromorphic devices also have great potential in the treatment of neurological disorders. To diagnose and treat neurological disorders, neuromorphic devices need to be implanted into the body and connected to nerves. However, the major challenges in implantation include the potential toxicity of the materials and the need for an additional procedure to remove the device after treatment. Neuromorphic devices constructed with biomaterials brings multiple advantages in terms of biocompatibility, biodegradability, and tissue compliance. These devices can seamlessly integrate with biological tissues or organs and emulate event-driven synaptic signal transmission in biological peripheral nerves, thereby promoting the development of applications such as implantable neural links. The design of implantable electrodes presents another significant challenge. These electrodes should be highly biocompatible, mechanically flexible, and miniaturized. Currently, metals, carbon nanomaterials, conductive polymers, and hydrogels have been investigated. Among them, hydrogels, with

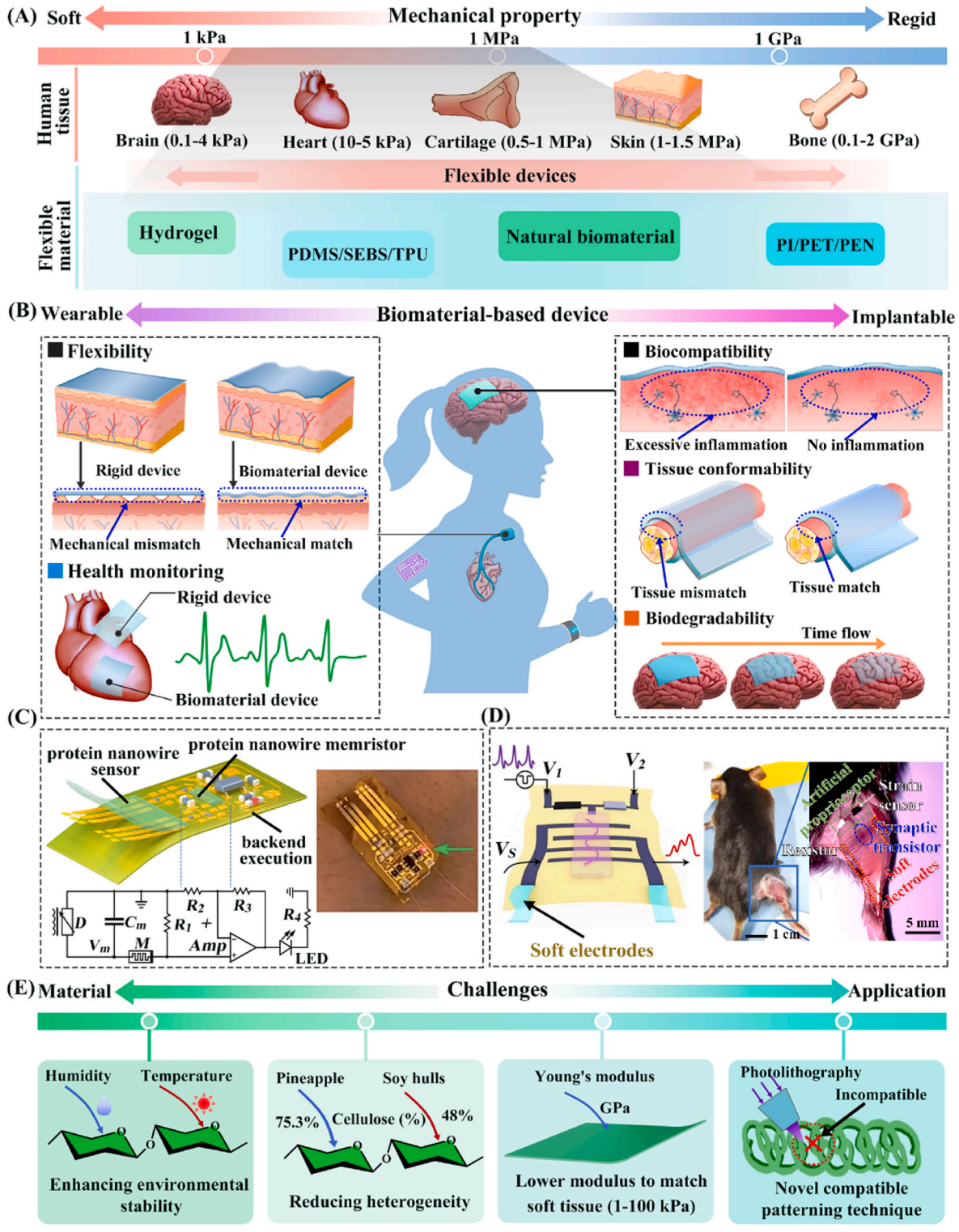

Fig. 7. Potential applications and future development directions of biomaterial-based neuromorphic devices. A) Mechanical properties of human tissues compared to flexible materials used in devices. The PET, PI, PDMS, SEBS, TPU, and PEN refer to polyethylene terephthalate, polyimide, polydimethylsiloxane, styrene-ethylene-butylene-styrene, thermoplastic polyurethane, and polyethylene naphthalate, respectively. B) Advantages of biomaterial-based neuromorphic devices in wearable and implantable applications. C) Schematic and circuit diagram of integrated wearable neuromorphic interface using protein nanowires. Reproduced with permission from Ref. [198]. Copyright 2021, The Authors. Published by Springer Nature. D) Schematic of a neuromorphic system demonstrating soft neural interfaces for controlling body movements, including an in vivo application with a mouse model. Reproduced with permission from Ref. [200]. Copyright 2022, The Authors, under exclusive license to Springer Nature Limited. E) Key challenges and solutions for biomaterial neuromorphic devices.

inherent hydrophilicity, biocompatibility, and mechanical flexibility, are considered the most promising in neural interfaces [199]. For instance, an organic synaptic transistors fabricated with hydrogel PEDOT:PSS electrodes have been successfully applied to stretchable neuromorphic efferent nerves (Fig. 7D) [200]. These neuromorphic efferent nerves can bypass broken electrophysiological signal path and redirect electrophysiological signals through soft neural interfaces and stretchable electronic systems, allowing for the control of body movement in mouse models with neurological motor disorders. Additionally, biomaterials show considerable potential for use in implantable electrodes. For example, composite transparent electrodes made from silver nanowires and biomaterial propolis demonstrate excellent mechanical and thermal stability, as well as environmental adaptability [201].

Although various biomaterials have been developed and widely used as components of biomedical implants, including sensors, triboelectric devices, and actuators [202–204], biomaterial-based neuromorphic devices are still in the proof-of-concept stage and have not yet undergone practical testing in implantable neural systems. Therefore, several key problems and challenges related to flexible biomaterial-based neuromorphic systems remain to be addressed, as discussed below (Fig. 7E).

To advance the design of neuromorphic systems for biomedical applications, long-term stable natural biomaterial must be developed. In many cases, the internal structure of biomaterials is highly sensitive to environmental humidity or temperature, so their functionality and efficiency can be affected by environmental changes. For instance, the conductivity of chitosan can change by two orders of magnitude relative humidity range, i.e., increasing from $\sim 3 \times 10^{-6}$ S cm^{-1} at 55 % to $\sim 1 \times 10^{-4}$ S cm^{-1} at 75 %. The conductivity of collagen can change by six orders of magnitude as the water content increases from 8 % to 40 % [205]. Although the hydration of biomaterials can increase proton conductivity, this instability of conductivity caused by environmental humidity can affect device functionality, such as making synaptic weight updates unpredictable. At the same time, this instability can lead to swelling and potential failure at the interface with electrodes or other functional electronic components; these changes also affect device reliability and durability. Therefore, to ensure the safety and reliability of neuromorphic devices that use biomaterials, efficient and reliable packaging methods must be developed isolate the components from the effects of ambient humidity and temperature.

Device-to-device variability must be reduced. Natural biomaterials can be heterogeneous when they originate from different species or even when they originate from the same organism. For instance, cellulose extracted from cotton has high tensile strength and thermal stability, whereas cellulose derived from bamboo degrades easily at low temperatures; the difference in traits is primarily due to differences in the crystalline content of the cellulose [206]. Various pre-treatment and post-treatment strategies have been proposed to modulate heterogeneity. Pre-treatment can effectively improve the quality and molecular weight uniformity of biomaterials, and thereby reduce batch-to-batch differences. Post-treatment techniques are intended to improve the mechanical and electrical properties of materials, and thereby to ensure that materials from different batches have consistent responses. However, application of these technologies in commercial-scale production is still limited. Therefore, to achieve predictability and uniformity in biomaterials, more-advanced processing technologies must be developed.

Integrating natural biomaterials effectively into neuromorphic electronic systems is another key challenge. Practical applications of neuromorphic devices require nanoscale fabrication with high precision and uniformity, so lithography techniques for high-resolution patterning must be used for these systems. However, many biomaterials are incompatible with traditional photolithography, because it uses organic solvents and ultraviolet light, which can damage the structure and functionality of biomaterials. Therefore, to accommodate the sensitivity of biomaterials and ensure their biocompatibility, new fabrication technologies must be developed. Recently, several unconventional soft-lithography techniques have been developed that can precisely pattern biomaterial without causing damage; these methods may enable stable and reliable integration of neuromorphic electronics that use biomaterials. However, relatively few studies have considered these technologies, and their compatibility with biological tissues requires testing and validation.

Finally, during the long-term wearable and implantation, neuromorphic devices must not become separated from biological tissues by repeated cycles of strain and stress. Therefore, neuromorphic devices must be developed that are imperceptible and have minimal effect on the host matrix such as skin or organs. Currently, the Young's modulus of biomaterials is generally at the gigapascal level, which is far higher than the Young's modulus of human soft tissues and brain (1–10 kPa) [207]. Hydrogelation of biomaterials is one method to reduce material hardness to better mimic the physical properties of soft tissues. For instance, the Young's modulus of hydrogel made from collagens can be reduced to 20–200 MPa [208]. However, the hydrogelation process typically reduced mechanical strength. Therefore, to meet the stringent standards of biomedical applications, hydrogels must be developed to have both low Young's modulus and excellent mechanical properties.

Overall, the devices that use natural biomaterial will be important in sustainable flexible neuromorphic electronics. These biocompatible and biodegradable electronics will significantly facilitate the development of wearable and implantable bioelectronic interfaces, and may offer new directions for biomedical monitoring and clinical applications in neuroscience, and are expected to have a revolutionary effect on scientific progress and sustainable development.

CRediT authorship contribution statement

Yanfei Zhao: Writing – original draft, Visualization. **Seungbeom Lee:** Writing – original draft, Visualization. **Tingyu Long:** Writing – original draft. **Hea-Lim Park:** Writing – original draft, Supervision, Project administration. **Tae-Woo Lee:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grants funded by Korea government (MSIT). (grant numbers: 2022M3C1A3081211 and RS-2024-00416938).

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