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REVIEW

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Natural biopolymers as proton conductors in bioelectronics

Manping Jia[1] | Jinhwan Kim[1] | Tiffany Nguyen[1,2] | Thi Duong[1,3] | Marco Rolandi[1]

[1]Department of Electrical and Computer Engineering, University of California Santa Cruz, Santa Cruz, California, USA

[2]Department of Biomedical Engineering, California State University Long Beach, Long Beach, California, USA

[3]Department of Mechanical and Aerospace Engineering, The Henry Samueli School of Engineering, University of California, Irvine, California, USA

Correspondence
Marco Rolandi, Department of Electrical and Computer Engineering, University of California Santa Cruz, Santa Cruz, CA 95064, USA.
Email: mrolandi@ucsc.edu

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Abstract

Bioelectronic devices sense or deliver information at the interface between living systems and electronics by converting biological signals into electronic signals and vice-versa. Biological signals are typically carried by ions and small molecules. As such, ion conducting materials are ideal candidates in bioelectronics for an optimal interface. Among these materials, ion conducting polymers that are able to uptake water are particularly interesting because, in addition to ionic conductivity, their mechanical properties can closely match the ones of living tissue. In this review, we focus on a specific subset of ion-conducting polymers: proton (H^+) conductors that are naturally derived. We first provide a brief introduction of the proton conduction mechanism, and then outline the chemical structure and properties of representative proton-conducting natural biopolymers: polysaccharides (chitosan and glycosaminoglycans), peptides and proteins, and melanin. We then highlight examples of using these biopolymers in bioelectronic devices. We conclude with current challenges and future prospects for broader use of natural biopolymers as proton conductors in bioelectronics and potential translational applications.

KEYWORDS
bioelectronics, chitosan, iontronics, melanin, reflectin

1 | INTRODUCTION

Bioelectronics merges electronic devices and biological systems by sensing and controlling biological processes.[1–5] The discovery of bioelectricity by Galvani in the 1780s can be considered the birth of bioelectronics.[6] Galvani showed that connecting frog legs with metals resulted in twitching of the leg muscles.[7] This discovery paved the path to several more on the role of electricity in biological processes.[7] Bioelectronic devices have now found use in clinical settings including the cardiac pacemaker,[8] implants for deep brain stimulation,[9] cochlear implants to restore auditory functions,[10–14] and implants for vagus nerve stimulation in the treatment of inflammation.[15,16] The experiments of Galvani also created interest in the role of bioelectricity and membrane potential in the development of cells and cell systems.[17,18]

In biological systems, signals are carried mostly by ions and small molecules, not electrons and holes as in electronic semiconductor devices.[19] These ions have much higher conductivity in water-rich biological tissue than electrons or holes and are involved in most physiological processes, such as muscle contraction, neuronal signaling, and metabolism.[20,21] Thus, an increasing amount of research involves the investigation of ion-conducting bioelectronic devices.[4,22–24] In these devices, ion conducting materials, such as conducting polymers and hydrogels, have potential in bridging the gap between electronic devices and biological systems.[25–34] Among ions, protons play a fundamental role in many physiological processes, including the synthesis of adenosine triphosphate (ATP),[35] enzyme activity,[36] and gene expression.[37] Much work has been dedicated to proton conducting polymers for energy applications.[38] The study of proton conducting bioelectronic devices is relatively more recent.[39–45]

In this review, we discuss three types of natural biopolymers and their applications in bioelectronic devices as proton conductors (Figure 1). We discuss polysaccharides (chitosan and

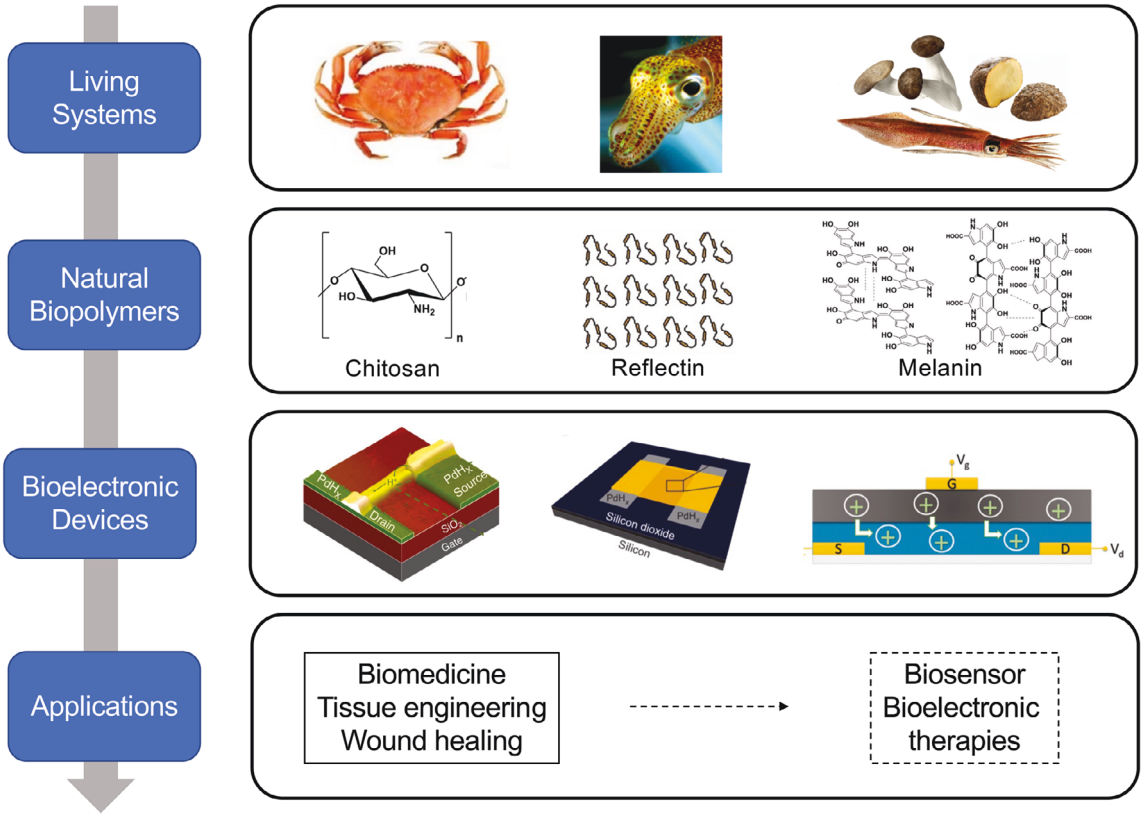

FIGURE 1 Natural biopolymers discussed in this work as proton conductors in bioelectronic devices and their potential in bioelectronic therapies. Reproduced from Ruiz and Corrales,[46] Open access. Reproduced from Zhong *et al.*,[47] under the permission of Nature. Reproduced from Ordinario *et al.*,[42] under the permission of Nature. Reproduced from Sheliakina *et al.*,[48] under the permissions of Creative Commons Attribution 3.0 International License: https://creativecommons.org/licenses/by/3.0/

glycosaminoglycans [GAGs]), peptides and proteins, and the pigment melanin.[49–51] First, we start with a brief description of the proton conduction mechanism. Then we discuss the proton conduction of each natural biopolymer and their derivatives, and we provide insights on how to tune the proton conductivity. Finally, we highlight excerpts from selected examples of their applications in bioelectronic devices.

2 | PROTON CONDUCTION

Most systems that contain water and water itself are able to conduct ions and protons.[52] In water and hydrated systems, H^+ have higher mobility than other ions, and this higher mobility cannot be accounted for by simply considering the effects of ionic radius and mass on their diffusion coefficient and mobility.[53] Most ions follow center of mass diffusion, which can be described by the general ionic conductivity Equation (1) together with the Einstein relationship (2), as shown in Equation (3).

$$\sigma = nq\mu \tag{1}$$

$$\mu = \frac{D}{k_B T} \tag{2}$$

$$\sigma = n\frac{Dq}{k_B T} \tag{3}$$

where n is the charge density, q is the fundamental charge, μ is the mobility, D is the diffusion coefficient, T is the temperature, and k_B is Boltzmann's constant. Like other ions, protons can also follow a version of the mass diffusion, called the vehicle mechanism.[52] In the vehicle mechanism, H^+ diffuse in the form of hydrated proton aggregates, such as the hydronium ion (H_3O^+), the Zundel ion ($H_5O_2^+$), and the Eigen ion ($H_9O_4^+$), which move through aqueous channels as a single entity.[52,54] In hydrogen bonded systems, such as water, H^+ follow the Grotthuss mechanism, which results in higher mobility.[53] In the Grotthuss mechanism, H^+ move faster because they quickly transfer along a network of hydrogen bonds—a proton wire[55]—via tunneling or hopping (Figure 2A).[53] The translocation of a proton along the proton wire creates a Bjerrum D orientation defect in the water chain, which needs to rotate itself to accept another proton.[57,58] Thus the dynamics in the Grotthuss mechanism are often referred to as "hop and turn." Similarly to the transfer of H^+, hydroxyl ions (OH^-) can also transfer along a proton wire in the form of proton holes (Figure 2B).[59]

In this scenario, proton conduction can be qualitatively described using the same description used for electrons and holes "hopping" in

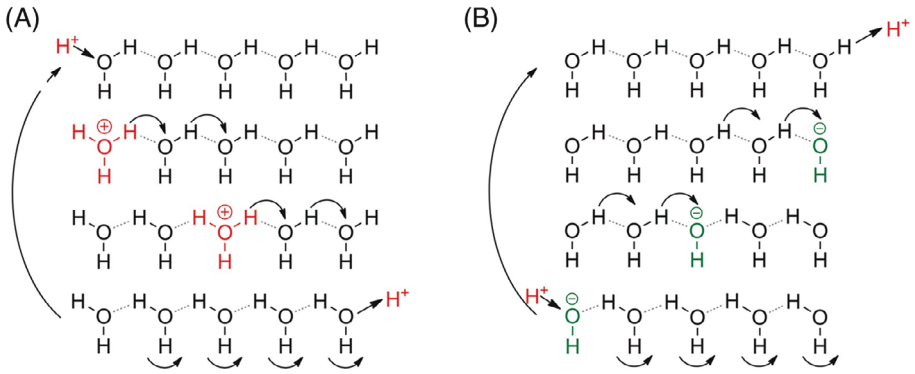

FIGURE 2 A, Grotthuss mechanism for the conduction of H^+ as hydronium ion along proton wires. B, An equivalent mechanism for OH^- conductivity as proton hole along proton wire. Reproduced from Deng *et al*.,[56] with permission from Nature

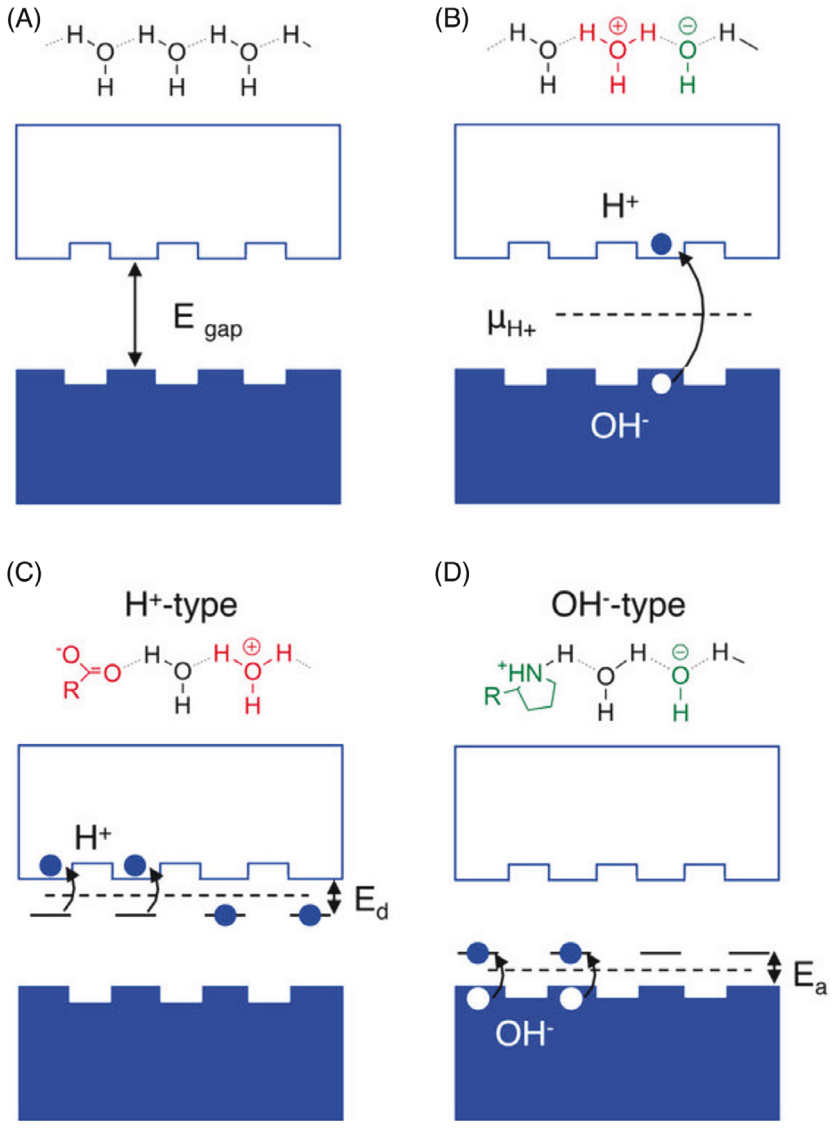

FIGURE 3 Energy diagram representation of conduction in hydrogen bonded proton wire. A, A wire with no H^+ or OH^- defect does not conduct. B, For an intrinsic proton wire, the protochemical potential μ_{H+}H1 is in the middle of the bandgap. C, An acid donates a H^+ into the conduction band of a proton wire to yield a H^+-type protonic conductor. D, A base accepts a H^+ to create a OH^- (proton hole) in the valence band of a proton wire to yield a OH^--type protonic conductor,[56] with permission from Nature

amorphous in semiconductors with H^+ are distributed between a "valence band" and a "conduction band" (Figure 3A). Even when a proton is in the "conduction band," it still needs to overcome a structure dependent potential barrier, which is typically comparable to the energy required to break a hydrogen bond (~0.1 eV) in the second solvation shell.[59–61] Similarly to semiconductor, an intrinsic proton wire does not conduct until a H^+ and OH^- pair is created. The energy required to create H+ and OH− pair in the proton wire is derived from the Gibbs Helmholtz equation and the dissociation constant of water (K_w) as:

$$E_{gap} = \Delta G^{0\prime} = -k_B T ln K_w = 0.83\,eV \quad (4)$$

this value is similar to the activation energy measured in proton conducting biopolymers.[62] To increase the conductivity of a proton wire, H^+ and OH^- dopants can be added with acidic and basic functionalities in the hydrogen bond network. In this case, we can substitute K_w with K_a (acid dissociation constant) or K_b (base dissociation constant) to in Equation (4) to find the activation energy (Figure 3C,D).[63,64]

3 | NATURAL BIOPOLYMERS AS PROTON CONDUCTORS

Natural biopolymers are naturally derived materials, including polynucleotides, polypeptides, and polysaccharides. They are biocompatible, biodegradable and environmentally friendly, naturally abundant, sustainable, and have multiple reactive sites for chemical modification.[65] Here, biocompatibility indicates the interaction between living systems and materials without side effects, such as toxicity, injury, or inappropriate systemic effects.[66] Natural biopolymers have been widely utilized in pharmaceuticals,[50,67] tissue engineering,[68] wound healing, and enzyme immobilization in biosensors for decades.[69] Examples include collagen, keratin, chitosan, and proteins. In this section, we are interested in natural biopolymers functioning as proton conductors in bioelectronic devices: Polysaccharides (chitosan, GAGs), proteins and peptides, and the pigment melanin.[49–51]

3.1 | Polysaccharides

Polysaccharides are naturally abundant and key components in bio-based materials for medical devices and pharmaceuticals.[70,71] The preparation and characterization of polysaccharides have been well described in the literature.[72] In this review, we primarily focus on the proton-conducting properties of polysaccharides with chitosan and GAGs as representatives.

3.1.1 | Chitosan

Chitin is the second most abundant polysaccharide in nature behind cellulose, and chitosan is the most common derivate (Figure 4).[74] Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine (Figure 4A).[46,75] The degree of deacetylation of chitosan describes the molar percentage of glucosamine monomeric units and varies from 0 (chitin) to 100 (fully deacetylated chitin or chitosan).[76] Chitosan forms inter and intra- molecular hydrogen bonds in the hydrated state and subsequently ionic complexes with anionic species,

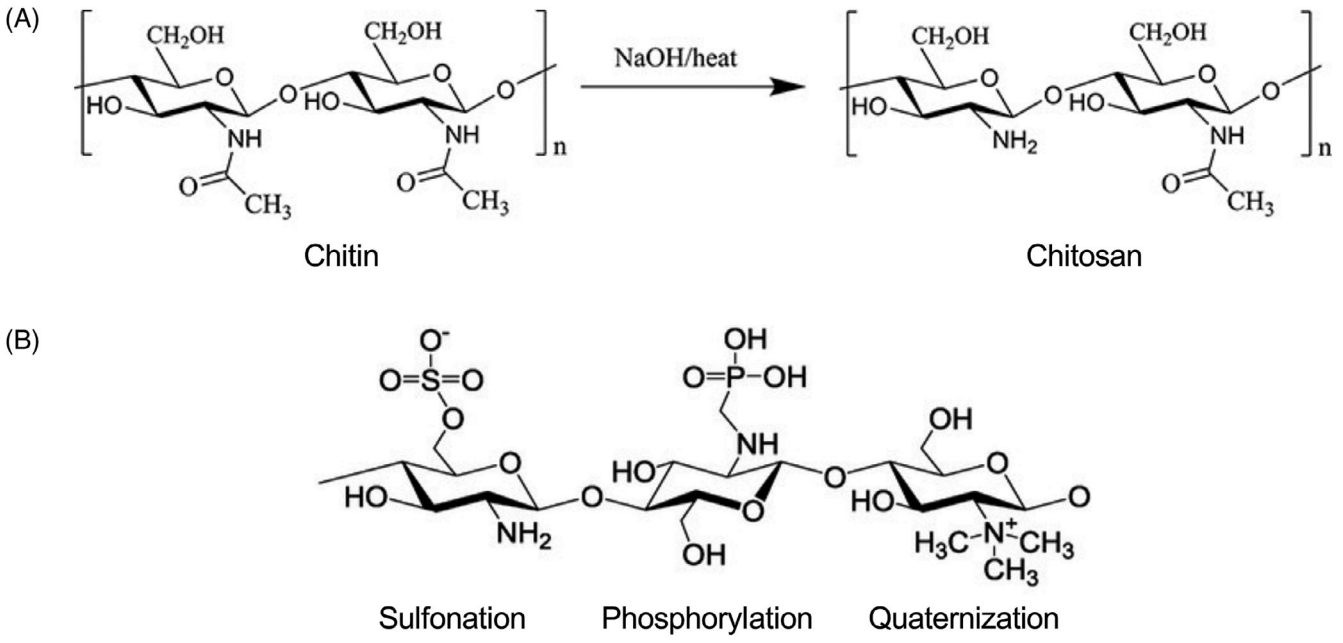

FIGURE 4 A, Chitin deacetylation process to produce chitosan. Reproduced from Ruiz and Corrales,[46] Open access. B, The chemical modification methods to improve the proton conductivity of chitosan. Reproduced from Amdursky *et al*.,[73] under the permission of Wiley

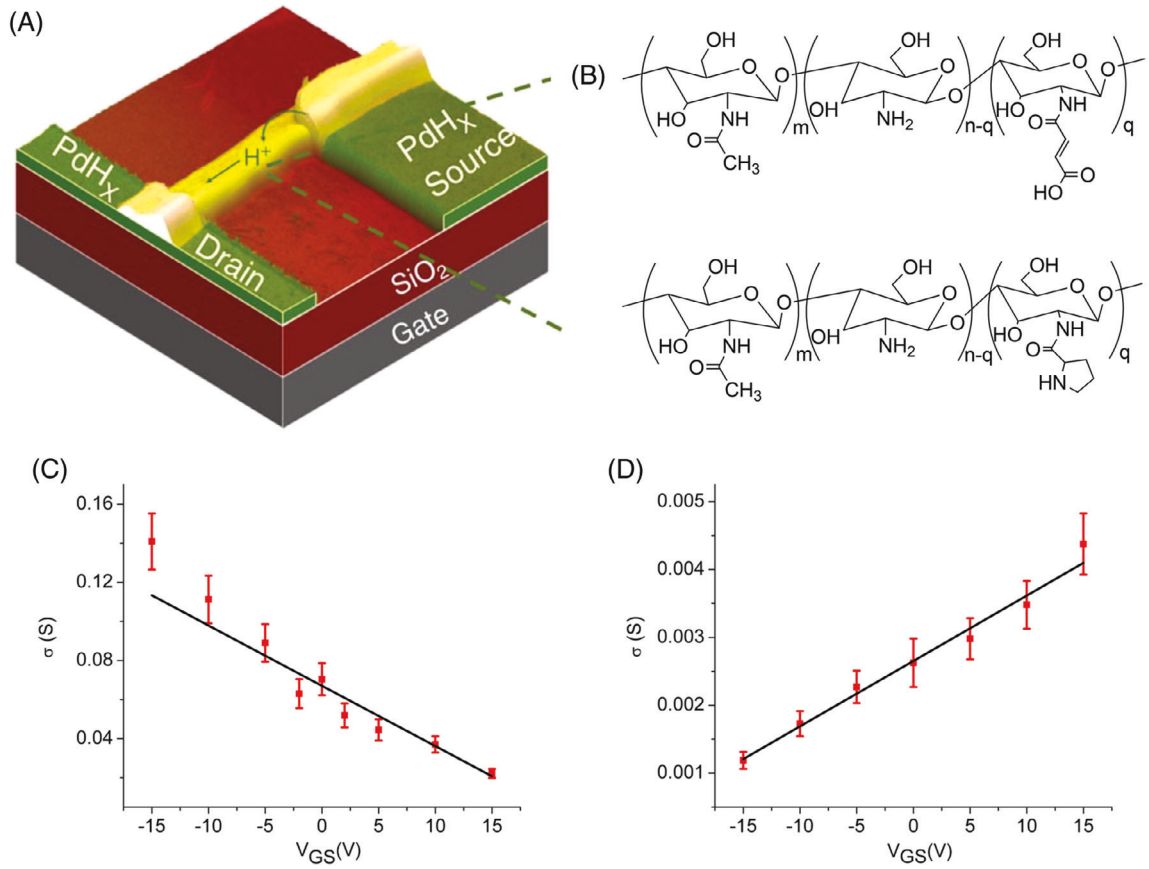

FIGURE 5 A, Schematic of bottom contact back-gated H^+ FET with PdH_x as the source and drain electrodes connected by maleic-chitosan as the channel (yellow). Reproduced from Zhong *et al*.,[47] under the permission of Nature. B, Molecular structure of maleic-chitosan (top) and proline-chitosan (bottom). C, Plot of channel conductivity as a function of V_{gs}. Reproduced from Deng *et al*.,[56] under the permission of Nature

such as lipids, DNA, and some negatively charged synthetic polymers, such as poly (acrylic acid).[77] Chitosan is a good scaffold for interfacing biological system and electronic devices, especially for immobilization of enzymes in biosensors,[78,79] tissue engineering,[80,81] controlled release systems,[82,83] gene carriers,[83] and wound healing.[84,85] In electrical stimulation based bioelectronic devices, chitosan is mixed with carbon nanomaterials or conducting polymers to form highly conductive composites.[86–88]

In acidic media, the protonation of the $—NH_2$ group at the C-2 position of the D-glucosamine repeat unit makes chitosan a polyelectrolyte that is able to support a proton wire when hydrated.[46,89]The Chitosan and its proton conductivity have been investigated for applications in fuel cells and batteries.[90] approaches to improve the proton conductivity of chitosan developed in these applications are highly applicable to bioelectronic devices. Here we discuss two main factors that affect the intrinsic chitosan proton conductivity: (a) hydrophilicity, and (b) charge density. These can be adjusted through molecular weight and the degree of deacetylation.[91] Hydrophilicity controls the amount of water available for proton transport. The amount of water absorbed, or swelling index, is inversely proportional to the crystallinity of the polymer, which in turn is affected by molecular weight—higher molecular weight corresponds to lower crystallinity. The proton current in hydrated chitosan is attributed to protons bonded with the amino groups in the chitosan backbone, so more amino groups in highly deacetylated chitosan (charge density) result in higher proton conductivity. The degree of deacetylation affects both the hydrophilicity and charge density, however. Chitosan with a higher degree of deacetylation has more amino groups and mobile charges, but also has higher polymer crystallinity and therefore absorbs less water. As a result, chitosan with a very high degree of deacetylation slightly lower protonic conductivity than chitosan that is highly, but not fully, deacetylated.[91]

To increase chitosan proton conductivity, acidic groups are added to chitosan via sulfonation, phosphorylation, and quaternization (Figure 4B).[73,74,92] Cui *et al*.[93] prepared chitosan sulfate membranes by grafting chitosan monomers with sulfonic groups resulting in a 4-fold improvement in protonic conductivity. Phosphorylation introduces phosphonic acid or phosphonate groups on amino groups of chitosan. The strong interaction between phosphoryl groups and water enhances the solubility of chitosan, which improves the hydrophilicity and proton conductivity.[94,95] In addition, phosphorylated chitosan has more ionic clusters and cation transfer pathways, resulting in higher proton exchange capacity and proton conductivity.[96,97] Bui *et al*. reported that the ionic conductivity of quaternized

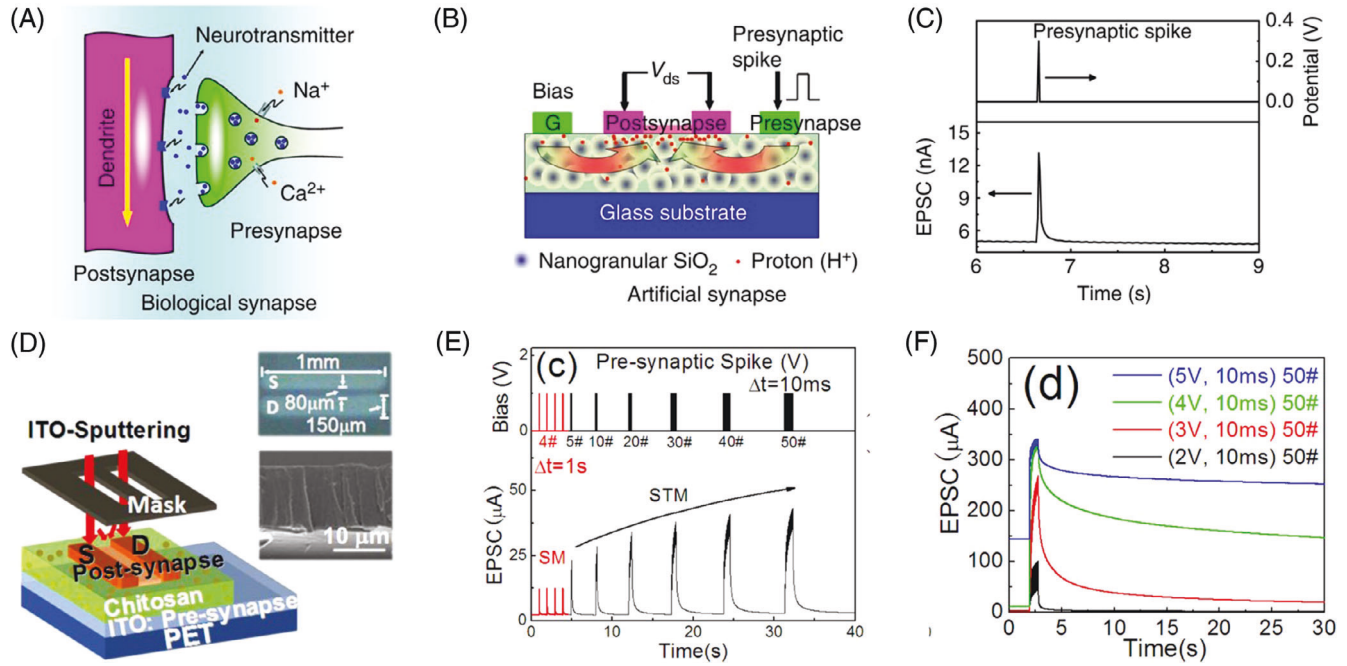

FIGURE 6 A, Biological synapse. B, Schematic structure of the coplanar-gate chitosan gating synaptic transistor. C, EPSC behavior triggered by a presynaptic spike ($V_g = 0.3$ V, 10 ms) with $V_{ds} = 0.5$ V. Reproduced from Zhu *et al*.,[103] under the permission of Nature. D, Schematic of a chitosan-gated flexible ITO synapse transistor. E, EPSC responses on presynaptic spikes ($V_g = 1.0$ V, 10 ms, $V_{ds} = 0.5$ V) with different spike numbers. F, EPSC responses on presynaptic spikes with different spike amplitudes ranged from 2 to 5 V. The EPSC responses demonstrate transition from STM to LTM. Reproduced from Yu *et al*.,[104] under the permission of ACS publication group

chitosan increases with the increment of quaternization degree.[98] Except the addition of acidic groups, the degree of crosslinking can also increase the proton conductivity of chitosan up to one order of magnitude due to the reduced crystallinity and improved water uptake.[99]

With the development of ion-conducting bioelectronics, chitosan and its derivatives can be used as proton conductor in field-effect transistor (FET)[47,56] and neuromorphic systems, such as artificial synapse, resistors, and memristors.[100,101] For example, our group has developed H^+ and OH^- type FETs using maleic-chitosan (poly (β-[1,4]-*N*-maleoyl-D-glucosamine)) and proline-chitosan (poly (β-[1,4]-*N*-proline-D-glucosamine)) as the channel between source and drain electrodes (Figure 5A,B).[47,56] Maleic-chitosan and proline-chitosan have hydrophilic groups that participate in hydrogen bonding with water and form proton wires that are doped by the acidic maleic group (H^+) and by the basic proline group (OH^-). In comparison, the proton conductivity in chitosan without maleic groups or proline-groups is significantly lower.[102] The gate voltage, $V_{GS,}$ allows to modulate the charge carrier density in the FET channel. For maleic chitosan, the channel contains excess H^+ and V_{GS} with a negative value increases the charge carrier density of H^+ in the channel thus increasing the overall conductivity (σ) (Figure 5C). For proline chitosan, the channel in turns contains excess OH^- and thus a positive value of V_{GS} increases σ (Figure 5D).

In 2018, Zhou *et al*. have used chitosan as a gate dielectric to create and artificial synapses with learning ability (Figure 6).[104] Protons accumulate at the chitosan/channel interface at positive gate bias, resulting in the formation of an electric-double-layer and increase of the source-drain current, whereas protons move to chitosan/gate interface depleting ITO channel and decrease source-drain current. The authors show that the transistor is able to mimic the transitions from sensory memory to short term memory (Figure 6E), and short-term memory to long term memory (Figure 6F), demonstrating a "multistore model" brain memory. Artificial synapses have the potential to be integrated with other bioelectronic components, such as sensors and oscillators to achieve neurorobotics and neuroprosthetics.[105] More research work in this field are highlighted in these reviews.[106–109]

3.1.2 | Glycosaminoglycans

GAGs are major components of the extracellular matrix in animal tissues with critical functions in cell growth, differentiation, morphogenesis, migration, and bacteria/viral infections.[110,111] GAGs play an important role in regulating hydration and water homeostasis by forming with water a gel-like matrix.[110,112] GAGs have been widely used in biomedicine as anticoagulants,[113,114] antitumor[115–117] anti-inflammation,[118] as well as wound healing[119–121] and tissue engineering.[50] The most common GAGs are keratan sulfate, hyaluronic acid, heparan sulfate, and chondroitin sulfate A, and dermatan sulfate (Figure 7). These GAGs are long, linear heteropolysaccharide chains composed of repeating disaccharide units with acid groups. These GAGs contain acidic groups that can bind to positively charged amino

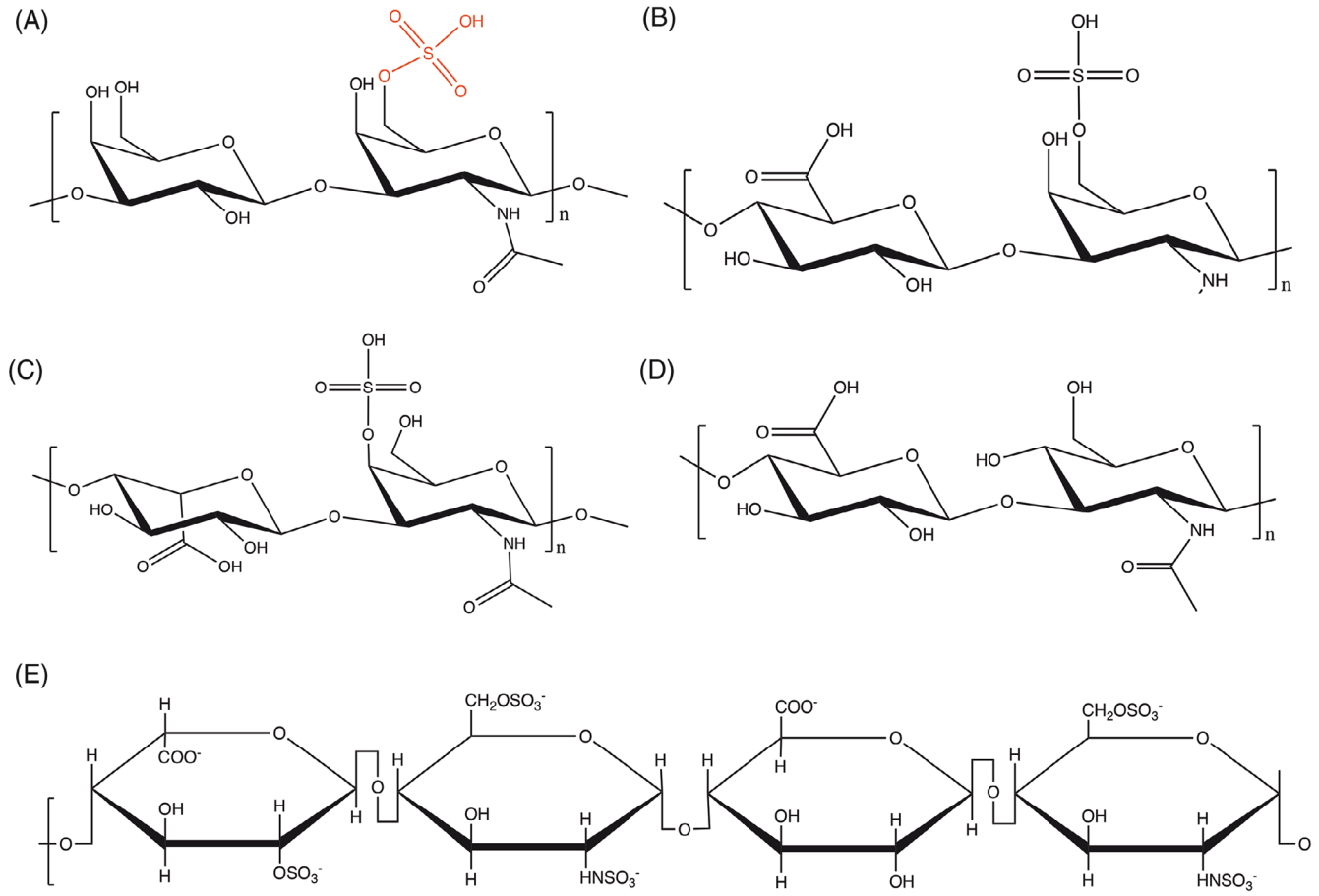

FIGURE 7 Chemical structure of A, keratan sulfate; B, chondroitin sulfate A; C, dermatan sulfate; D, hyaluronic acid; E, heparan sulfate

acid residues and also support the formation of proton wires for proton conduction to occur.[122]

We have previously demonstrated that the jelly found in the Ampullae of Lorenzini (AoL), the electron sensing organs that allow sharks and skates to detect their prey, is an excellent proton conductor and it likely contains keratan sulfate (Figure 8A Top). The proton conductivity of the jelly in the AoL is 2 ± 1 mS cm^{-1} (Figure 8B-E).[123] This conductivity is only one order of magnitude lower than the proton conductivity of Nafion (28 ± 14 mS cm^{-1}) measured with the same geometry.

We speculated that the hydrophilic groups of keratan sulfate induce water organization in the AoL jelly into hydrogen bond chains, allowing proton conduction according to the Grotthuss mechanism, and their sulfate groups effectively dope the proton wires of H^+ with a mechanism similar to Nafion. Following this hypothesis, we further characterized the proton conductivity of purified keratan sulfate from bovine cornea to be 0.5 ± 0.1 mS cm^{-1}. This value is consistent with the one for AoL jelly especially considering that the two biopolymers come from different sources.[124] We compared the keratan sulfate protonic conductivity to other GAGs and we found that most of them are proton conductors and that keratan sulfate has the highest value for proton conductivity among them.[124] Furthermore, Amemiya and co-workers did the first structural study on AoL gel to decode the influence of various polysaccharides and proteins on their proton conduction.[125] By measuring the proton conductivity properties of the gel before and after digestion with proteolytic enzymes, they discovered the removal of proteins did not diminish proton conductivity.

Recent, work has focused on increasing GAGs' proton conductivity while maintaining their biocompatibility. For example, Bermudez *et al.* reported a proton conducting electrolyte composed of chondroitin sulfate and citric acid.[126] Citric acid acts as a cross-linker interacting with the anionic groups in chondroitin sulfate. This interaction decreases the pH from 6 to 2.1, increasing the concentration of H^+, and thus increases the proton conductivity. By tuning the ratio of chondroitin sulfate and citric acid, the proton conductivity of the chondroitin sulfate and citric acid composites increases one order of magnitude compared to that of chondroitin sulfate alone. Interestingly, the proton conductivity does not always increase by adding citric acid despite the fact that adding citric acid increases H^+ concentration. This is because adding citric acid also affects the polymer structure causing phase separation, which in turn may result in the creating of a smaller number of proton wires. GAGs have been widely researched in biomedicine and they have good untapped potential in bioelectronics.[127]

3.2 | Peptides and proteins

Peptides and proteins are important cell components and carry out many cellular functions, such as enzymatic activity, transmembrane

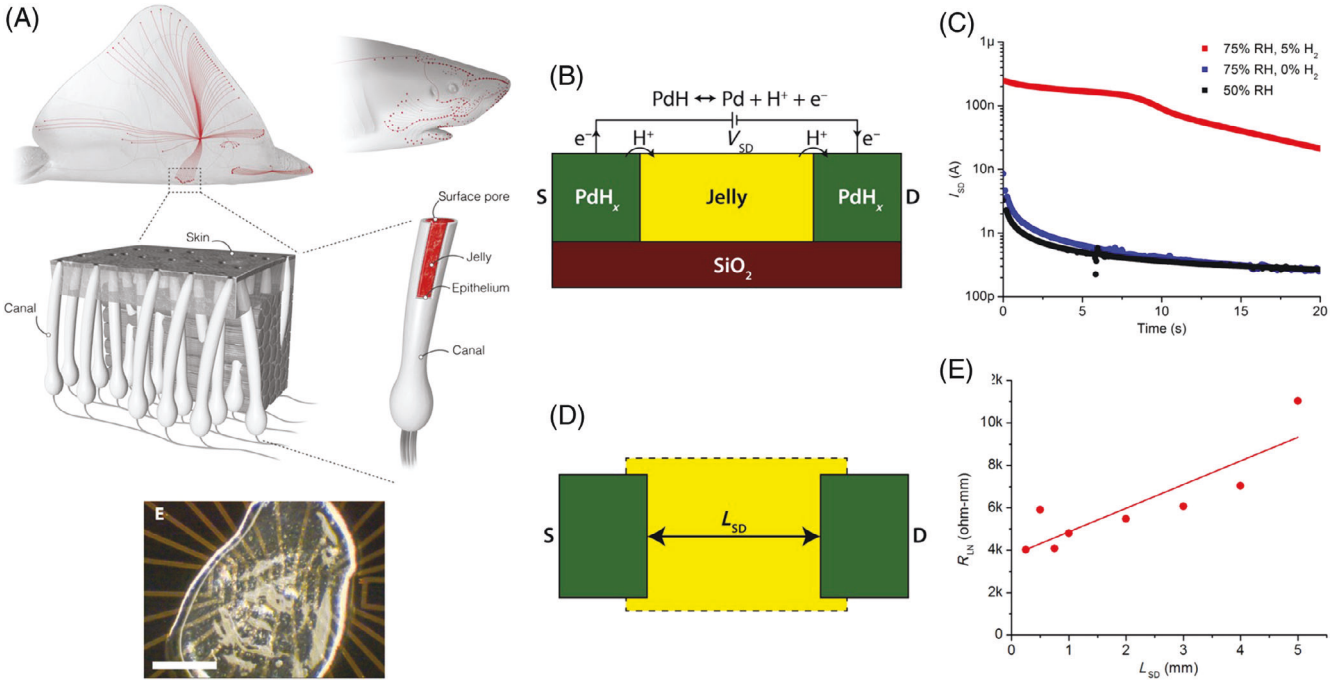

FIGURE 8 A, Skates and sharks locate their prey by detecting the weak electric fields naturally generated by biomechanical activity with a network of electrosensory organs called the AoL (Top). A sample of the AoL jelly on an electrical device (Bottom). Scale bar, 0.5 mm. B, Palladium hydride (PdH_x) contacts that convert H^+ flow into measurable e^-. C, Transient response to a 1 V applied signal in AoL jelly. D, Transmission line measurement (TLM) geometry. Varying the distance between source and drain (L_{SD}) distinguishes between the fixed PdH-jelly interface resistance and the varying bulk resistance. E, R_{LN} as a function of L_{SD}. A linear fit gives a bulk material proton conductivity of 2 ± 1 mS cm^{-1}. Reproduced from Josberger *et al*.,[123] under the permission of Science Advances

channel transport, and signal transduction.[128–130] Peptides and proteins are made from amino acid chains linked by peptide bonds, and proteins tend to be larger and are typically made by more than 50 amino acids.[131,132] Here, we will review proteins and peptides in the context of proton conducting bioelectronics.[42]

Early investigation on the conductivity of proteins in the 1960s mainly focused on globular and fibrous proteins.[133,134] Murphy showed that the water content of some proteins, such silk and wool, is essential contributor to their conductivity.[134] In the 1970s, Bardelmeyer also reported that the conductivity of collagen increased from 10^{-11} S cm^{-1} at low water content (8.5%) to 10^{-3} S cm^{-1} at saturation, and the activation energy for conduction decreased from 1.15 to 0.31 eV.[62] The activation energy shows a linear relationship with water content but with different slopes under and above 50% water content.[135] Despite this early progress, there has been relatively little work on proton conducting proteins until recently.

Pioneering work by Gorodetsky and co-workers showed bulk proton conductivity of a drop-casted reflectin film, a structural protein found in reflective tissues of the squid *Euprymna scolopes* in 2004.[42,136] The authors postulated that with the amphipathic structure, the hydrated reflectin films are segregated into distinct hydrophobic regions and proton-conducting hydrophilic water channels, which is analogous to that reported for the sulfonated fluoropolymers Nafion (Figure 9A).[42] The proton conductivity is measured using electrochemical impedance spectroscopy (EIS), and the distinct isotope effect confirmed that protons are charge carriers in reflectin (Figure 9B). Using mutagenesis studies, they found that amino acid side chains and their sequence are critical to protonic conductivity (Figure 9C).[137] That is, the absence of amino acid side chains decreases the protonic conductivity by one order of magnitude with similar water uptake, such as the scrambled sequence (Figure 9D). It is worth noting that reflectin is simple to produce in high purity and yield as a solid-state thin-film proton conductor, and shows remarkably robust and chemical stability when integrated into proton transistors.[42] In additional work, the authors showed a facile approach to add photochemical dopants into the reflectin channel to create a transistor that can be controlled by two independent stimuli: applied voltage and light.[138]

Recently,[139] Demirel *et al*. investigated the effects of tandem repetition on bulk proton conductivity in a family of highly stretchable and self-healing proteins inspired from squid ring teeth (Figure 10A).[139,141] The proton conductivity scaled linearly with respect to tandem repetition numbers, and reached up to 3.5 mS cm^{-1}, which is the highest reported value among biological materials. Impressively, these tandem-repeat proteins are not only highly stretchable (~300%) and self-healing, but also maintain proton conductivity after recovery (Figure 10B). This property makes them good candidates for soft and stretchable bioelectronic devices.

Stevens *et al*.[142] reported an electrospun mat composed of an inexpensive and commercially available protein, bovine serum albumin

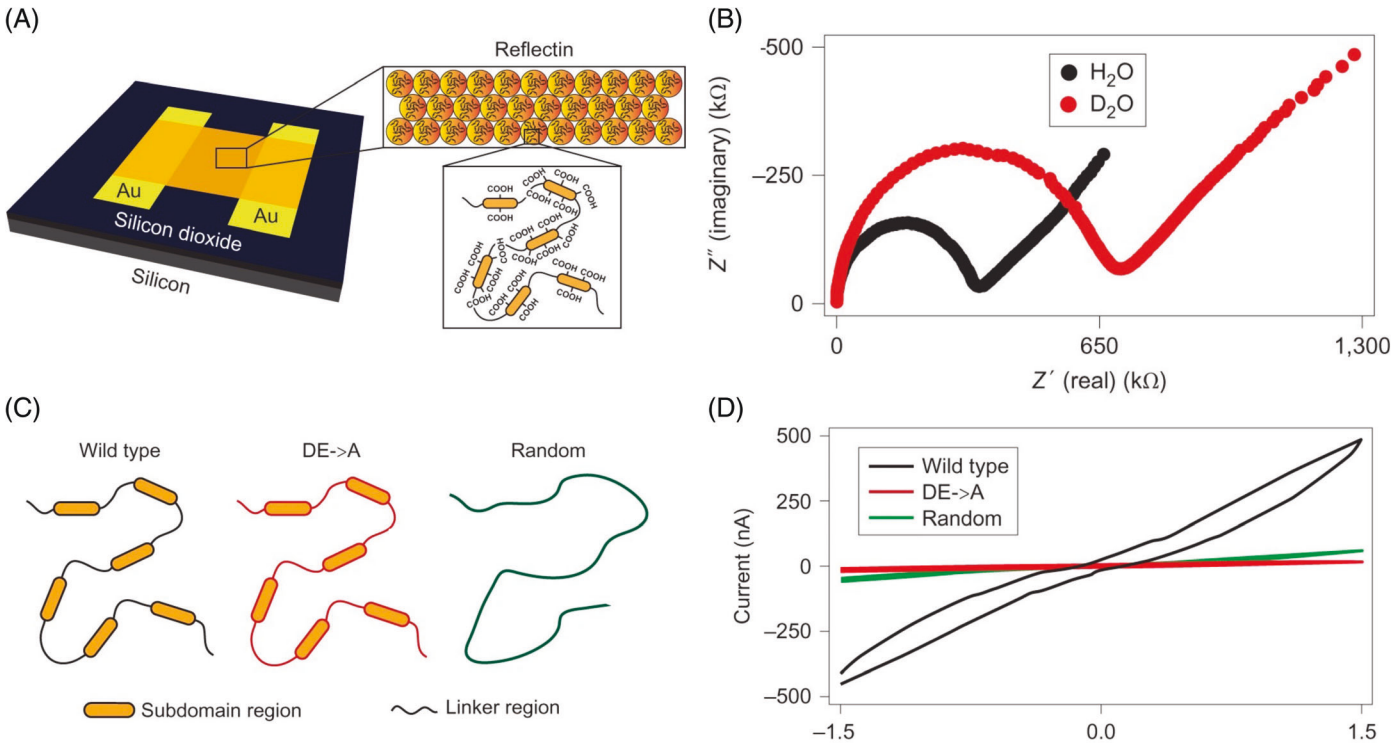

FIGURE 9 A, Schematic of a two-terminal device in which a reflectin protein film bridged two gold electrodes. B, A typical Nyquist plot for a reflectin-bridged two-terminal device in the presence of water vapor (black) and in the presence of deuterium oxide vapor (red), both at an RH of 90%. C, Cartoon of the primary structures of wild-type reflectin (left), the DE-A mutant (center), and the Random mutant (right). D, The current for the mutants decreases relative to that for the wild-type protein. Reproduced from Ordinario *et al.*,[42] under the permission of Nature

(BSA), with a fibrillar structure. While hydrated, the brittle fibers absorb water in a sponge-like manner reducing the spacing between individual fibrils. This free-standing mat can transport protons over millimeter length-scales, suggesting that oxo-amino-acids play a major role in the translocation of protons via an "over-the-barrier" hopping mechanism. BSA mats are biocompatible and highly robust in a variety of organic solvents and acids, but the proton conductivity still needs improvement before it can be used in bioelectronic devices.

Peptide molecules have been used as a bridge in molecular junctions in order to rationalize the effects of amino acid side chains, amide backbone, and structural conformation on electrode transfer. The tendency of peptides to form fibrils and nanotubes motivates the investigation of proton transport in the fibrous films.[143–145] Ashkenasy and co-workers showed hybrid electron and proton transport in peptides filaments self-assembled from amyloid-β derived peptide molecules.[143] Both electrons and protons contribute to the conductivity, with a current ratio of 1:2 respectively at low humidity, and with proton transport dominating the conduction at high humidity. They further investigated the influence of peptide folding state on the proton conductivity and designed high-performance proton conductor by modifying the basic sequence of self-assembling peptides.[144] Aromatic stacking of peptide side chains were found to promote long-range peptide self-assembly, and hence the proton conductivity. This effect is more prominent in dehydrated assemblies. In high humidity case, the uptake of water become more dominant in determining the conductivity, so carboxylic acid side chains are more effective to donate proton charge carriers.

Inspired by the fact that proton conduction can be introduced to polysaccharides by adding acidic and basic side chains,[47] Ashkenasy and co-workers also used a family of linear self-assembling amyloid β (Aβ) peptide to study the effect of the acidic (glutamic acid, Aβ-E), basic (lysine, Aβ-K), or amino acid (glutamine, Aβ-Q) in the side chain on the proton conduction of peptides (Figure 10C).[140] The resistance of all three samples is inversely proportional to the relative humidity (Figure 10D). Aβ-Q shows much higher resistance under the entire relative humidity range, indicating the critical role of acidic and basic side chains in promoting protonic conduction. Moreover, the self-doping process is significantly more effective for acidic side chains than basic ones, so the H^+ concentration in Aβ-E is one order of magnitude higher than OH^- in Aβ-K, resulting in lower resistance of Aβ-E. More recently, Ashkenasy and co-workers reported self-assembled octa-D, L-α-peptide nanotubes with amine side chains that showed proton conductivity in the range of 0.3 mS cm^{-2}, which is within the same order of magnitude as that of Nafion ultrathin films.[145] Nam and co-workers reported a short tyrosine-rich peptide and manganese oxide hybrid film that showed enhanced proton conductivity (~18.6 mS cm^{-1}) by synergistic effect, which suggests that hybrid composites can also be a promising method for designing protein-based ionic conductors with high conductivity.[146]

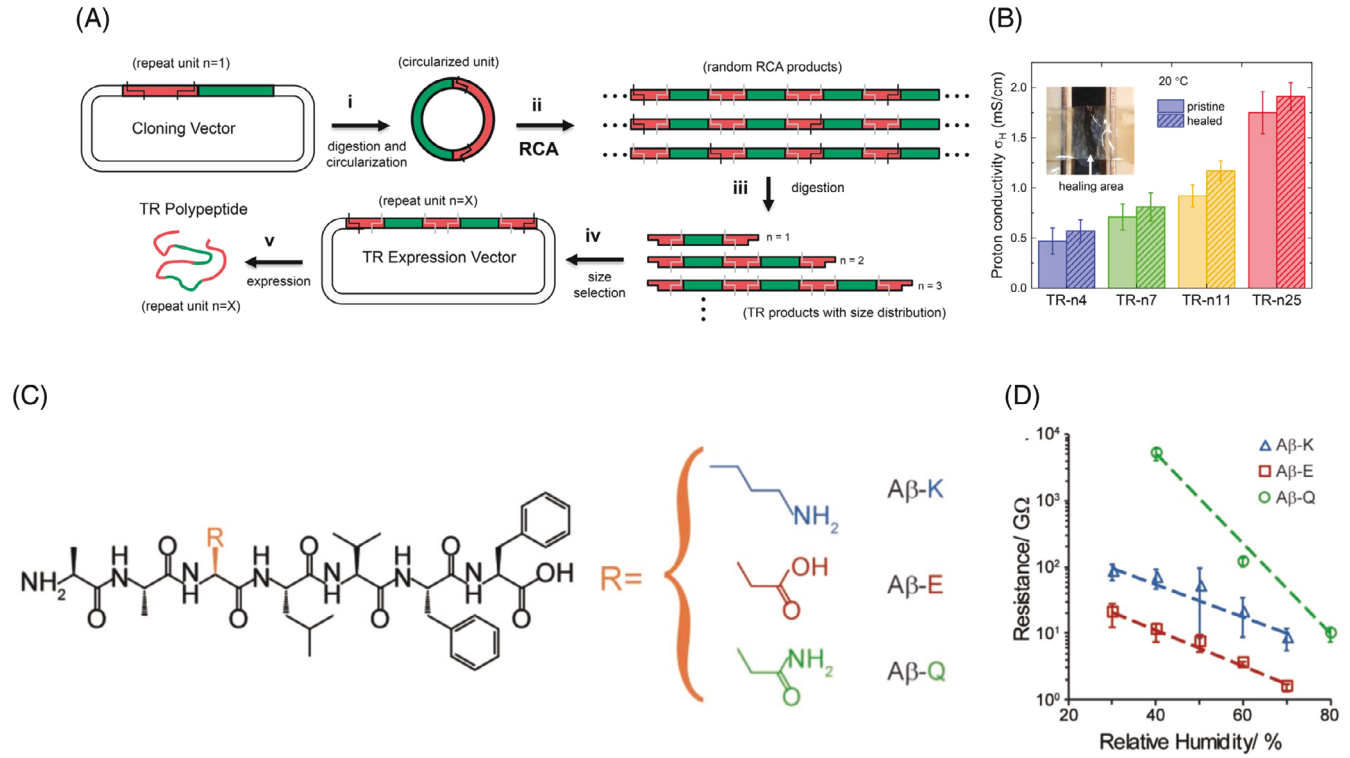

FIGURE 10 A, Tandem repeat construct: the PD-RCA workflow. B, Proton conductivity comparison of self-healed and pristine TR-films. Inset shows the optical images of self-healing in a TR-n11 film.[139] Copyright 2018, published by ACS publication group. C, Chemical structure of the studied peptides. R represents side chain of lysine (K) for Aβ-K, glutamic acid (E) for Aβ-E, and glutamine (Q) for Aβ-Q. D, Resistance of different peptides at different humidity. Reproduced from Silberbush *et al.*,[140] under the permission of Wiley

The modification methods on proteins and peptides show the possibility to use peptides as building blocks for the preparation of bioinspired supramolecular proton conducting polymers. Although the proton conductivity of proteins and peptides is relatively lower than conventional conducting materials, they also have unique advantages such as biocompatibility, highly tunable structure, and physicochemical properties. Much research efforts have been devoted to making bulk proteins and peptides with popular fabrication methods, such as spin-coating, inkjet-print,[147] studying the corresponding characteristic and applications in bioelectronic devices.[146,148]

3.3 | Melanin

Melanin refers to naturally occurring dark pigmentary macromolecules. Sources of melanin includes including animals (mammal tissues, insect exoskeletons, cephalopod ink sacs), plants, fungi, and bacteria (Figure 1).[149] Based on the structure and monomer precursor, natural melanin can be classified into five types: eumelanin, pheomelanin, neuromelanin, allomelanin, and pyomelanin. There are also synthetic melanin-like polymers, such as poly dopamine.[51] Among melanin, archetypal melanin (also referred to as "eumelanin") is the most common type and the major component in human skin pigment. Eumelanin consists of 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) monomers and their redox forms. These monomers form oligomers and subsequently melanin polymers with globular or rod-like structures. These structures are driven by pi-pi stacking or hydrogen bonding, respectively (Figure 1).[150]

In the 1970s, the electrical conductivity of melanin was discovered and melanin was considered to be the first naturally occurring amorphous organic semiconductor.[151,152] Although melanin's hydration-dependent conductance has been described for years with the amorphous semiconductor model, landmark work performed by Meredith and co-workers demonstrated that melanin is an electronic-ionic hybrid conductor and protons dominate conductivity at high humidity.[150] The origin of the proton conductivity is a local redox reaction called comproportionation, in which two quinone moieties with different oxidative states react together with adsorbed water to form an intermediate oxidative state and release protons (Figure 11A).[150] Following Grotthuss mechanism, the released protons "hop" through the hydrogen-bonded water network with mobility as high as 10^{-3} cm^2 V^{-1} s^{-1}, which is close to the typical mobility of an electronic hole in a disordered molecular semiconductor. This similarity in mobility between protons and electronic hole has led many researchers to consider melanin as a p-type amorphous semiconductor before this study.[51,150,152,153] Furthermore, Meredith provided supportive evidence for the comproportionation conductivity model and the ionic-electronic behavior of melanin using D_2O as a probe.[154]

Santato and co-workers studied the conduction of thin film melanin by current-voltage (I-V) measurements, transient current

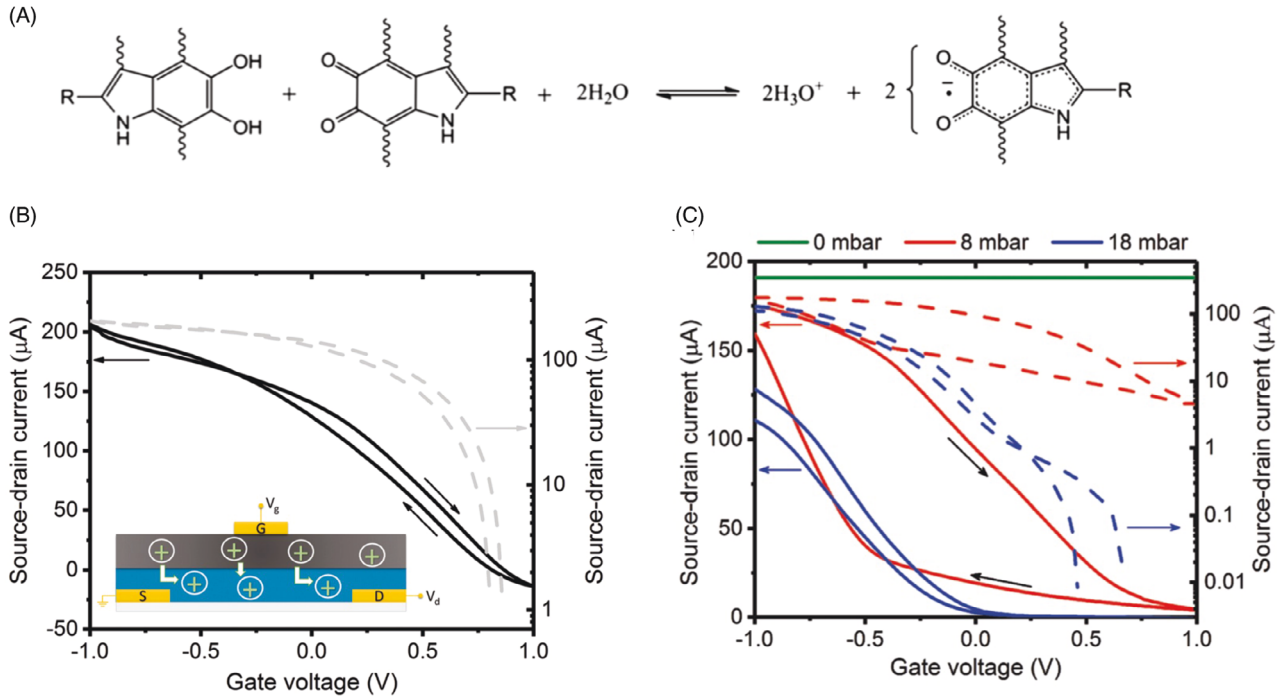

FIGURE 11 A, Melanin molecular structure and the comproportionation reaction. B, Transistor transfer characteristic of an all-solid-state OECT. Inset shows schematic in which blue corresponds to PEDOT:PSS channel and dark gray to the melanin gate and S, D, G are the source, drain and gate electrodes. Protons injection from the melanin de-dope the PEDOT:PSS channel reducing the source-drain current. C, Transistor transfer characteristic of OECT at different hydration status. Reproduced with permission. Reproduced from Sheliakina *et al*.,[48] under the permissions of Creative Commons Attribution 3.0 International License: https://creativecommons.org/licenses/by/3.0/

TABLE 1 Proton conductivity of natural biopolymers

Category	Materials	Conductivity (mS cm^{-1})	Application	Reference
Polysaccharide	Chitosan	1.1	Biosensor	[163,164]
	Maleic chitosan	0.50 ± 0.11	H^+-FET (field effect transistor)	[47]
	Proline chitosan	0.03		[165]
	AoL jelly	2 ± 1	-	[123]
	Keratan sulfate	0.5 ± 0.1	-	[124]
Peptide and protein	Reflectin	0.1	Protein-based protonic transistors	[42]
	Tandem repetition proteins	3.5	-	[139]
	Tyrosine-rich peptide	18.6	-	[146]
Melanin	Eumelanin	1.0×10^{-2}	OECT	[48,158]
	DOPA-melanin pellet	1.0	-	[155]

measurement with proton-transparent electrodes (Pd), and EIS measurement. From these studies, the conductivity of melanin is between 10^{-4} and 10^{-3} S cm^{-1} over micrometric distances and mostly attributed to proton conduction and electrochemical processes at high hydration levels.[155] Eom *et al*. created composite films of tightly packed melanin nanoparticle clusters in a polyvinyl alcohol matrix, achieving conductivity up to 1.17 ± 0.13 S cm^{-1}.[156] Melanin's hybrid conductivity of protons and electrons is believed to be highly influenced by the complex chemical disorder levels and structure of melanin, and residual electron conduction originates from the conjugation of melanin's polymer backbone, which allows for the flow of delocalized electrons.[51] However, some disagreement remains over the dominant conduction mechanism of melanin being protonic or electronic, and melanin's structure has yet to be completely understood.[157–159] Applications of melanin include tissue engineering, supercapacitors, energy storage devices,[160] and humidity sensor.[161]

Among these applications, Meredith *et al*. recently created a solid-state OECT using melanin as the transducer between ionic

signals and electric signals (Figure 11A).[48] In this work, PEDOT:PSS connects the source and drain electrodes, and melanin acts as the proton-injecting top gate in the electrochemical transistor (the inset of Figure 11B).For negative and zero gate voltage, the transistor is in the on state. While for a positive gate voltage (<1.0 V), protons in the melanin layer were injected into the PEDOT:PSS layer and turned the transistor to the "off" state. In Figure 11C, by adjusting the humidity of the environment (0 mbar water vapor pressure—dry, 8 mbar—low hydration, 18 mbar—high hydration) the authors further verified that (a) there is no transistor behavior when the gate is dry; (b) the transistor characteristics are recovered at low hydration status; (c) the "turn off" voltage decreases significantly at high hydration status (0.2 V) compared to low hydration status (1.0 V); (d) the on/off ratio increases from ~20 at low hydration status to $>10^4$ at high hydration status. These observations are consistent with melanin being the source of protons to gate the PEDOT:PSS OECT channel.

Recently, the Meredith group chelated the transition metal ion Cu (II) into melanin to enhance and control melanin's proton conductivity and the performance as a transducing material in OECTs.[162] The authors proposed that the generation of semiquinone radicals from the comproportionation reaction increases the reduction of Cu(II) along with the formation of quinone reactants, which in turn feedback into the comproportionation reaction to generate more free protons. Thus, the free proton concentration and proton conductivity of melanin are adjustable with controlled Cu upon hydration. The Cu (II)-melanin film was incorporated into OECTs, whose ON/OFF ratio and transconductance are approximately twice higher than that using only melanin.

4 | CONCLUSION AND PERSPECTIVES

Natural biopolymers have unique features that make them promising candidate in bioelectronic devices, such as good biocompatibility/biodegradability, abundance, sustainability, and a high level of structural complexity that is difficult to match using synthetic materials. In this review, we highlighted several natural biopolymers that are proton conductors and recent advances in their applications in bioelectronic devices (Table 1).

We summarized these advances and we hope to bring insight into how proton conducting biopolymers may be added to the bioelectronics toolbox for novel functionality. Despite the benefits of natural biopolymers, several major challenges still remain in integrating biopolymers with the bioelectronic devices. First, as the size of bioelectronic devices becomes smaller, the importance of the fine patterns required is expected to increase.[166,167] However, traditional photolithography techniques tend to damage natural biopolymers and their original structure and functionality. Alternatively, soft lithography is becoming a popular method for producing fine patterns on biopolymer surfaces, including (a) micro-contact printing; (b) replica molding for fabrication of microfluidic devices in poly(dimethyl siloxane), and of nanostructures in polyurethane or epoxy; and (c) solvent-assisted micro-molding of nanostructures in poly(methyl methacrylate).[65,168–170] However, soft lithography also faces several limitations such as (a) requirement for uniform surfaces[171]; (b) requirement for homogeneous ink using plasticizers[172]; (c) the increase in the possibility of contamination[173]; (d) expensive semiconductor equipment.

Second, natural biopolymers are heterogeneous when they are sourced from different species and even when they are sourced from the same organism. This heterogeneity is a problem for reliable and scalable manufacturing. Third, biopolymers become hydrated in aqueous environments, which is good for protonic conducting and biocompatibility, but also results in swelling and potential failure at the interface with other functional electronic components.

By addressing the current limitations and developing novel fabrication strategies, research on natural biopolymers in bioelectronics is expected to result in a wider range of applications. Indeed, we believe they have the potential to be developed into practical tools for the diagnosis and treatment of medical conditions. In summary, this review aims to draw attention to the emerging interdisciplinary research in proton conducting biopolymers in bioelectronics and thus help bridge the gap between materials science and bioelectronic devices. Specifically encouraging engineers to view biopolymers from a device perspective and materials scientists to view devices from a materials design perspective to spur innovation.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in all of the cited references.

ORCID

Manping Jia https://orcid.org/0000-0001-7299-6220
Marco Rolandi https://orcid.org/0000-0001-7898-2479

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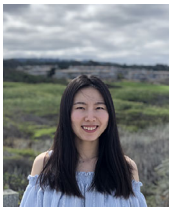
AUTHOR BIOGRAPHIES



Manping Jia is a PhD candidate in the Department of Electrical and Computer Engineering at the University of California, Santa Cruz (United States). Her research is focused on developing ion-conducting materials and bioelectronic devices for the purpose of actuating and sensing physiological processes. She received her BS and MS in Materials Science and Engineering from the University of Science and Technology Beijing (China) in 2014 and 2017, respectively.

Jinhwan Kim received his BSc degree in Biomedical Engineering from Yonsei University (South Korea) in 2016, and his MSc and PhD degrees from Gwangju Institute of Science and Technology in 2018 and 2021, respectively. Since 2021, he has been working as postdoctoral researcher at the University of California Santa Cruz (Santa Cruz, USA). His research interests include bioelectronic device and micro/nano sensor fabrication and application.

Prof Marco Rolandi is professor and chair in the Department of Electrical and Computer Engineering at the University of California, Santa Cruz (United States). His research focuses on biomaterials and bioelectronic devices for biological control applied to synthetic biology and tissue regeneration. Prior to joining the University of California, Santa Cruz, Marco was an associate professor of Materials Science and Engineering at the University of Washington (United States).

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