Recent Progress of Protein-Based Data Storage and Neuromorphic Devices

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By virtue of energy efficiency, high speed, and parallelism, brain-inspired neuromorphic computing is a promising technology to overcome the von Neumann bottleneck and capable of processing massive sophisticated tasks in the background of big data. The abilities of perceiving and reacting to events in artificial neuromorphic systems allow us to build the communicative electronic–biological interfaces to get closer to electronic life. Protein materials offer great application potentials in such a system due to their sustainability, low cost, controllable hierarchical structure, intrinsic biocompatibility, and biodegradability. Herein, a timely review of the development of protein-based memories for data storage and neuromorphic computing is provided. Proteins’ unique mechanical, electronic, optical properties, and their broad applications are discussed. Then, the progress of protein-based two-terminal memristor and three-terminal transistor-type memory is reviewed, and their applications for data storage, logic circuit, and neuromorphic computing are introduced. Finally, the major challenges and outlook toward the future developing directions of protein-based computing systems are pointed out.

1. Introduction

The advent of the era of big data has led to great demand in exploring revolutionary data-processing technologies. However, the computing capabilities of systems based on von Neumann architecture seem to be reaching a plateau, mainly due to the performance gap between the data-processing units and data-storage units (the memory wall).[1,2] Some new devices and computing schemes are proposed to solve the von Neumann bottleneck. One promising strategy is in-memory computing, the core idea of which is to eliminate the physical distance between computing and data storage, so computation is conducted exactly at where the data are generated and stored.[3–5] In recent years, the in-memory computational memory devices have been applied in the hardware neuromorphic computing area, working as neuromorphic units. Neuromorphic computing is a human brain-inspired model, mimicking the way of information processing in networks of neurons and synapses.[6–14] Synaptic plasticity, the capability to change the connection strength between two neurons, is the most crucial feature of synapse. This characteristic can be simulated by modulating the conductance of artificial synapse devices when applying external electrical stimuli. Artificial neurons can fire, responding to the electrical stimuli, and emulate basic functions of the biological neurons, such as threshold-driven spiking, refractory period, and so on.[15–26] The designed interaction of these two neuromorphic units could build a neuromorphic system with high parallelism, low consumption, and high efficiency, which is capable of breaking through the energy and throughput restrictions of current computing architectures and even realizing artificial intelligence.[27–30]

Two-terminal memristors and three-terminal field-effect transistor (FET)-based memories, which match the in-memory computing idea, have been reported as neuromorphic devices. To develop high-performance neuromorphic devices, one of the biggest challenges is choosing the optimum material.[31–33] Up to now, various materials have been explored as the active
components of neuromorphic electronics, including oxide, perovskites, quantum dots (QDs), polymers, biomaterials, phase change materials, 2D materials, etc.\textsuperscript{[34–42]} Although some of these materials may exhibit better performance, in the long term, many fabrication methods and prepared devices are not sustainable, which could result in electronic wastes with nondegradable and toxic components.\textsuperscript{[33,44]} In addition, the pursuit for wearable and implantable electronics has promoted the development of flexible and stretchable neuromorphic electronics that can be applied in health monitoring, biological–electronic interfaces, and biomedical diagnosis and therapy.\textsuperscript{[45–47]} Meanwhile, higher requests are put forward to corresponding materials, like biocompatibility and biodegradability. These flexible devices are crucial for constructing soft e-systems which can bring us closer to future intelligent electronic systems and improve our living level.

Naturally biological materials can offer a promising platform for applications of “green” neuromorphic devices due to their intrinsic sustainability, bioresorbability, biocompatibility, and biodegradability. For few decades, biological nanomaterials have been explored as alluring building blocks of bioelectronics. Proton, electron, and hole transport behaviors in biomaterials enable their applications in solid-state devices, such as FETs, memristor, diodes, solar cells, and organic display devices.\textsuperscript{[41,48–59]} Multifunctional biomaterials can be obtained via modifying functional groups, reconstructing hierarchical structures, and changing morphology, which allow optimizing their usage in diverse fields. Proteins, as one kind of representative biomaterials, have evolved in nature over millions of years. They are an essential part of cells, tissues, and many chemical reactions. Protein is composed of coiled and folded polypeptide chains after the dehydration condensation of amino acids, forming a certain spatial structure. The diverse and complicated structures endow proteins excellent electrical, optical, mechanical, chemical, and electromagnetic properties.\textsuperscript{[53–58]} Therefore, proteins are of particular interest, considering their tailorable properties for broad applications. Some proteins such as silk fibroin (SF), ferritin, keratin, and collagen have been developed as data storage memory devices and neuromorphic devices.\textsuperscript{[59–101]}

Herein, we summarize the advancements of data-storage devices and neuromorphic units based on protein materials. We begin with a discussion of the unique properties of proteins, which highlights the superiority of proteins in electronics. Then, protein-based memristors, FET-based memory, molecular devices, and neuromorphic devices are explained in detail. We review recent developments of proteins-based storage memory and neuromorphic devices to analyze and compare their progresses and deficiencies. Finally, we will present the major challenges that have to be settled and anticipated for future realistic applications of proteins-based neuromorphic devices.

2. Unique Properties of Proteins for Data Storage

Proteins are one of the representative products of natural wisdom with sophisticated hierarchical structures. Their diverse functions range from catalysis in chemical reactions to immunity protection, from correct expression of genetic information to providing energy. Usually, natural proteins exhibit combined merits such as renewability, high abundance, nontoxicity, biocompatibility, and biodegradability. As the development of material research and engineering, proteins can be manipulated for various structures and formats by biotechnological strategies and chemical strategies, which offer their great application potential in a variety of fields such as synthetic biology and bioelectronics.\textsuperscript{[104–106]}

In the field of data storage, memory devices have at least two distinguishable states with different physical or chemical features which can be detected and transformed into quantifiable and treatable electrical signals. The complicated memory unit can be defined by its material and architecture. Basically, the memory mechanisms include charge-trapping/detrapping, tunneling effect, formation/annihilation of conductive filaments, charge transfer, etc. Proteins can play different roles in memory devices due to their marvelous multifunctionalities and superior maneuverability, meeting the diverse requirements for data-storage systems. For example, metalloproteins contain metal ions which work as redox centers to store/release electrons.\textsuperscript{[71]} The protein molecules in two redox states allow memory devices exhibiting binary conductance states. The metalloproteins can be tuned by doping various metal ions with different redox potentials toward multilevel data storage. Some proteins without metal ions could act as the biopolymer matrix to enhance the stability of doped active units. Usually, in conductive filament devices, the uncontrollable growth of filaments results in the fluctuation of the device’s operation voltage and the inferior reliability and instability could hinder their further applications. Inspired by the concept of catalysis, protein nanowires of the bacterium \textit{G. sulfurreducens}, which are known for their ability to facilitate metal reduction, have been introduced into conductive filament devices to catalyze the formation of filaments.\textsuperscript{[107]} The operation voltage of the protein nanowire device has reached the millivolt level with prominent stability. Not only being used as the active component in memory devices, but also proteins can serve as dissoluble and resorbable substrates for bioelectronics. Silk, the most representative protein, has offered immense potential for the applications of implantable biointegrated circuits, as the silk film enables conformal and noninvasive contact with the curved surfaces and controllable biodegradability rate. Proteins can be applied in biosensors because of their high specificity. It would be fascinating to couple the functions of sensing and data storage in a single protein-based unit through elaborate device designing. The demands for memory devices vary from applications to working conditions, which put forward higher requirements to the applied materials. Protein molecules have alterable structures with high precision and complexity which can be designed via advanced technologies such as genetic engineering, recombinant DNA technique, meso-functionalization, and so forth. Fully understanding the relationship between proteins’ hierarchical structures and device properties could offer researchers targeted properties for specific applications.

According to the earlier introduction, proteins have a great deal of advantages for the application of memory devices, by virtue of their unrivaled mechanical, electronic, chemical, and optical properties. We believe protein material could be crucial building blocks in data storage, logic circuit, neuromorphic computing, and even artificial intelligence (Figure 1). Their superior properties bring more optional multifunctionalities...
into traditional electronic devices. Protein-based neuromorphic units possess both functional and component similarities to biological counterparts, enabling the fabrication of naturally communicative electronic–biological interfaces.

3. Protein-Based Memristors for Data Storage

The theory of memristor (the abbreviation of memory resistor) proposed by Chua was successfully linked to an experiment by Strukov et al.\cite{108} A typical memristor has a two-terminal metal–insulator–metal (MIM) structure, in which the resistance changes as a function of the operation history of electrical stimulus. The external electrical inputs could result in material reconfiguration in the storage layer, thereby changing the physical properties which reflect in the form of resistance. The concept of the memristor has been extended to recent cutting-edge memory technologies, including ferroelectric random access memory (FeRAM), phase change memory (PCM), resistive random access memory (RRAM), and so forth.\cite{1,109} The memristor is capable of performing the storage and calculation of information in the same place. The unique working mechanism and simple structure qualify memristors as unique promising building blocks of digital and logic circuits, analog circuits, and neuromorphic application. Numerous studies on memristors have proven the superiorities of memristors, such as ultralow power consumption,\cite{110} fast switching speed,\cite{111} long retention,\cite{112} and excellent cycle endurance.\cite{113} Such memristive devices could fasten the development of an innovative data-processing system, which is an urgent need in the background of big-data era and internet of things. In future, memristive technology can be applied in three main fields, including on-chip memory and storage, in-memory computing, and biologically inspired computing.\cite{1}

Current–voltage (I–V) hysteresis characteristic is a distinctive fingerprint of memristors. The alteration of resistance in memristors can be abrupt or gradual in different material systems, corresponding to the digital and analog features, respectively (Figure 2). In general, digital (binary) memristors can be applied in mass data storage and logic circuits, whereas analog memristors with continuously tunable resistance states are ideally suited for realizing hardware artificial neural networks.\cite{109} In this section, we will review the works over the past decades of protein-based memristors for information storage. The following discussion would be classified by proteins’ categories.

3.1. Silk Protein-Based Memristor

Silk produced by Bombyx mori (silkworm) is one of the representative biomaterials for a wide range of biotechnology applications, such as biomedical diagnostics, tissue engineering, and so forth.\cite{114} Natural silk mainly contains two proteins, SF that comprises repetitive amino acid sequences and sericin that connects fibroin chains. On the demand of prospective
biocompatible, biodegradable, and implantable electronics for data storage and sensing systems, SF attracts great attention and exhibits tremendous potential due to its biocompatibility, optical transparency, abundance, ultralight weight, flexibility, superior mechanics, and so forth.

Up to now, lots of studies with respect to SF-based memristive devices have been undertaken, where silk protein is used as the active layer. Hota et al. reported the first memristor utilizing pure SF as the switching layer. Bipolar memristive characteristics have been observed, and the resistance switching mechanism was the different conductivity between the oxidation and reduction state of SF when under opposite external bias, which was confirmed by cyclic voltammetry tests. Soon afterward, by introducing gold nanoparticles (Au NPs) into the SF matrix, a transparent and flexible RRAM memory was achieved with improved performance in the operating voltage and current ON/OFF ratio by Gogurla et al. The improvement was described as the synergy of negatively charged Au NPs and positively charged oxidized SF chains, which enhanced the conductive path in the switching layer. A series of studies have been achieved by Chen et al. in Nanyang Technological University, concerning RRAM memories based on SF. Chen’s group reported the first programmable memristor based on SF which could exhibit both memory resistive switching (memory RS, nonvolatile, high resistance state [HRS] and low resistance state [LRS] can retain without external bias) and threshold RS (volatile, only HRS is stable in the absence of external bias) via modulating the compliance current (CC) in the set process. A higher CC (>100 μA) corresponded to the memory RS mode whereas the lower one (<10 μA) triggered the threshold RS mode (Figure 3a–c). In addition, the RS effect could be subdivided into reversible RS and the write-once-read-many-times (WORM) mode which were also achieved in this single device. The excellent retention time (>10⁴ s) and selectivity (>10⁷) have promised SF-based RRAM for practical data-storage applications in future and the configurable mode may offer researchers new ideas to expand its application (e.g., the threshold RS device can act as a selector to solve the notorious sneak path problem in high-density data-storage system with cross-bar architecture). Functional RRAM devices with SF used as the active layer and supportive substrate simultaneously were demonstrated by the same group in 2016. A physically transient RRAM with fibroin (substrate)/Au/Mg/fibroin (switching layer)/Mg structure was fabricated, showing reasonable bipolar memory characteristics with ON/OFF ratio of 10² and retention time of more than 10⁷ s (Figure 3d). The devices could be disintegrated when immersed in deionized (DI) water or PBS after 2 h, and the dissolution mechanisms were related to hydrolysis and proteolytic degradation, as shown in Figure 3e. The controllable decomposition time avoids the secondary surgical operation of the implantable and diagnostic electronics based on SF substrate. The later-reported ultralightweight memristor’s structure was fibroin (substrate)/Au/fibroin (switching layer)/Ag and the devices’ per area mass was only 0.4 mg cm⁻², which was far lighter than traditional silicon substrate or office paper (Figure 3f,g). Further studies are inevitable to combine these functions in an individual SF-based device to pave the way toward the expected biocompatible, ecofriendly, implantable, and secure electronics.

To endow SF-based memory multifunctions, light is introduced as another controllable stimulus besides electrical operation. Lv et al. reported a photonic biomemory device based on the carbon dots (CDs)–silk composite in which the CDs played a significant role for their superior optical properties, biocompatibility, and inexpensive cost. Figure 4a) The characteristics of memory devices with various top electrodes (Al, Au, and Ag) were systematically studied (Figure 4b). The memories with Al and Au electrodes represented WORM characteristics, which was evidence to be charge trapping/detrapping by means of Kelvin probe force microscopy (KPFM), whereas the Ag-based memory showed reversible RS characteristics, which were evidenced to be the formation and dissolution of the Ag conductive filament via scanning electron microscopy (SEM) and energy-dispersive spectroscopy (EDS), as shown in Figure 4d–g. The decreasing set voltage and LRS current have been observed under UV illumination because of the adjustment of the charge-trapping capacity of CDs (Figure 4b,c). To obtain high-density data-storage systems, multilevel storage may offer a new way to overcome the scaling difficulty. Murgunde et al. fabricated a multilevel bistable RRAM based on the heterojunctions of CdSe NPs and SF. The observed multistep switching was attributed to multiple charge-trapping states within the composite. Thanks to the intrinsic flexibility, biocompatibility, and tunable biodegradability of silk, Sun and colleagues realized a hybrid silk device for electrical and optical information encryption and decryption. The prepatterned silk worked as the
multichromatic diffractive optical element (MC DOE) substrate and then the silk memristor was fabricated onto the silk DOE substrate. The encryption information and the decryption key were stored in the DOE and silk memristor, respectively. The initial diffractive pattern was random. Only when degrading the MC-DOEs in a correct fashion, according to the electrical message in the silk memristor, the true information can be read. Otherwise the MC-DOEs would degrade in a wrong way and the information would be destructed. This electrical–optical encryption and decryption strategy really expands the silk memristor’s applications in information concealment, reappearance, and destruction.

3.2. Ferritin-Based Memristor

Ferritin, another representative biomolecule, is a spherical metalloprotein with \( \approx 12 \text{ nm} \) diameter, which comprises a shell with \( \approx 2 \text{ nm} \) thickness and an iron-storage cavity with \( \approx 8 \text{ nm} \) diameter. Because of its high stability in severe circumstances, the vacant cavity of ferritin was exploited as a nanoreactor to crystallize various nanomaterials by biomineralization in the early period. Uraoka and coworkers embedded dispersed Pt NPs, which were synthesized in the ferritin cavity into the active layer of RRAM to constrain the electric field and thereby confine the conductive paths.\(^{[120]}\) A stable unipolar RS memory was obtained with less fluctuation in memory properties compared with the devices without incorporating Pt NPs, and even the forming voltage and LRS resistance could be tunable by the density of Pt NPs. It is a significant start of applying ferritin in the field of data-storage memories.

The first memristor utilizing ferritin as the switching layer was reported by Cho et al. Researchers used layer-by-layer (LBL) assembly technology to fabricate (poly allylamine hydrochloride [PAH]–ferritin) multilayer-based nonvolatile bipolar RRAM devices (Figure 5a).\(^{[78]}\) The charge trap/release of the \( \text{Fe}^{3+}/\text{Fe}^{2+} \) pair led to the conductance switching behavior, which was proved by KPFM. Chen and coworkers reported a ferritin-based nanodevice, consisting of a \( \approx 12 \text{ nm} \)-modified nanogap...
through the on-wire lithography (OWL) technique. Ferritin was chemically immobilized in the nanogap to bridge two Pt microelectrodes (Figure 5b). The invertible switching mechanism was explained as the ferric and ferrous redox couples in the core of ferritin, responding to opposite applied voltages, have different electron transfer abilities. The subsequent study in 2014 by the same group focused on the controllability of devices. With the identical nanodevice structure, the Archaeoglobus fulgidus ferritin (AfFtn) with tunable iron loading capacity was fixed in the precise nanogap. A larger ON/OFF current ratio was achieved via increasing the amount of iron inside the AfFtn (Figure 5c). The yield of the effective devices was only ≈11% and more explorations upon improving the stability and availability of the biomolecular nanodevice are needed in future. The molecular manipulation perhaps opens up the bioengineering approach to modulate the performance of biomemristors. Zhang et al. demonstrated a ferritin-based biomemristor in which the threshold RS mode (≤5 μA) and memory RS mode (>100 μA) coexisted by adjusting the preset CC (Figure 5d). In consideration of the inert Pt electrodes, the conductive filaments were speculated to be composed of iron ions, which were probed by conductive atomic force microscopy (CAFM).
3.3. Albumen-Based Memristor

Apart from SF and ferritin, egg albumen (EA) nowadays is also a promising biomaterial which could keep pace with demands of next-generation nonvolatile memory devices because of its fabulous biocompatibility, biodegradability, flexibility, and affordable costs. EA is composed of about 10% proteins (such as albumins, mucoproteins, and globulins) and 90% water. These macromolecules are easily denatured after applying heat on them.

Chen et al. fabricated a biomemristor with RS characteristics utilizing dry-cured and thermal-baked EA as the functional layer, as shown in Figure 5e. Two distinguishable RS of thermal-denatured EA were observed for retention time ($>10^4$ s) and endurance cycles ($>500$) after applying writing/erasing operations of 3.6 and $-0.55$ V, respectively, indicating excellent stability of the memory devices. In addition, in contrast to dry-cured devices, the proteins after heat treatment conducted a much narrower HRS, SET voltage ($V_{SET}$), and RESET voltage ($V_{RESET}$) distribution variations. Based on the electrical and morphological characterization, the authors interpreted that the denatured proteins minimized the probability of scattered oxygen atoms, which was beneficial for the migration of oxygen atoms and consequently, leading to a fantastic LRS/HRS ambipolar performance (Figure 5f).

He et al. combined EA and dissolvable Mg and W electrodes to manufacture water-soluble memristors. A $4 \times 4$ crossbar architecture was fabricated, showing bipolar switching property with a superior dependability and stability. During the forming process of disulfide and peptide bonds, water molecules, electrons, and holes were produced, whereafter a network of 3D cross-linked proteins was constructed. The author and his coworkers revealed that the switching phenomenon was ascribed to the conductive filament generated by the redox reactions between Fe$^{3+}$ and Fe$^{2+}$. As shown in Figure 5g, a time sequence of optical images showed the dissolving course of the cross-bar structure while surrounded by DI water.

Recently, Zhou et al. fabricated an ultraflexible EA memristor array to obtain multifunctional logic gate including "AND," "OR," and "NOT" operations. It is worth noting that both the active layer and the flexible substrate were made of EA by...
physical and chemical treatment. By applying three individual signals (including two distinct electric pulses and a broad-band light pulse) on the memristor simultaneously or independently, the logic state can be transformed easily among the three basic logic operations. Only under the LRS can the logic blocks be promising to construct. Ulteriorly, a trap/release physical mechanism was proposed to demonstrate this phenomenon. When the device was in the HRS state, the proportion of trapped sites was comparatively low, whereas when it entered the LRS state, generally, the injected carriers were captured until the trap sites were suffused. Therefore, a logic state of “1” can be straightly gained due to the hopping conduction and releasing-charges processes as the output current exceeded 5.0 mA under light illumination (Figure 5h).

3.4. Other Protein-Based Memristors

Besides the representative proteins, some other proteins are deployed in the construction of memristors. Ground on the LBL assembly technique mentioned above, Cho’s team explored some proteins (catalase protein and lysozyme protein) for the fabrication of RRAM devices, and typical RS characteristics were achieved successfully with tunable performance by molecular manipulation, which broadened the range of valid biomaterials for memristors.[123,124] Sericin, a byproduct of silk processing, was used as the building block of RRAM by Chen’s group and a nonvolatile multilevel biomemory was obtained at different CC with the charge-trapping/release mechanism.[89] This study confirms the feasibility of the discarded byproduct of natural materials in the field of value-added electronics, whereas further researches are needed to improve the stability of devices. Hexa-His-tagged recombinant molecular chaperone DnaJ (rDnaJ), a heat-denatured protein, was exploited as the active layer by Lee and coworkers and a bio-memristor was fabricated with tailoring the cupric ion chelating properties (Figure 6a).[92] The performance of the memory was highly affected by the metal ions’ affinity of amino acid residues in rDnaJ protein layer, which was mediated by the protonation/deprotonation degree of the imidazole group of histidine residues in different pH conditions (Figure 6b,c). The optimal performance of devices was obtained at pH 6 with an extremely low operation voltage ($V_{\text{SET}} \approx 0.12 \text{ V}$, $V_{\text{RESET}} \approx -0.08 \text{ V}$), remarkable uniformity, large selectivity ($>10^8$), and excellent retention time ($>10^6$ s). Cyclic voltammetry and CAFM tests were conducted and revealed the relationship between metal ion chelation and the degree of protonation at various pH conditions successfully. It is noteworthy that Lee et al. have investigated how the recombinant protein with genetically engineered properties affects the device’s properties. Recombinant DNA technology has contributed to significant achievements in some specific areas.[125] However, there are very limited numbers of researches concerning how to modulate the device performance by reconstructing recombinant proteins in this area. In our opinions, there might be some factors hindering the exploration of the modulated device properties by recombinant DNA technology. First, the recombinant DNA technique is suitable for precise structural modulation of protein molecules, but more operation complexity and limitation of large-scale device fabrication may exist. The recombinant DNA technique is more often utilized in therapeutic products, diagnosis, and energy applications, so how to apply such advanced and complicated technology into the field of data storage still needs deeper interdisciplinary communication. Second, the recombinant DNA technique for the modification of a protein structure is difficult to apply in some kinds of metalloproteins.[126] Third, the anticipated properties of recombinant proteins might change in the traditional device fabrication process due to unexpected

![Figure 6. a) 3D schematic of the rDnaJ memristive device arrays. b) The distributions of set and reset voltages corresponding to different pH of the buffer used to form the active layer. c) Cumulative histogram of current in rDnaJ devices with different processing conditions. a–c) Reproduced with permission.[92] Copyright 2018, American Chemical Society. d) I–V properties in room temperature and 358 K. e) Logical functions of “NAND” and “NOR” in room temperature and 358 K, respectively. d,e) Reproduced with permission.[90] Copyright 2019, American Chemical Society.](https://www.advancedsciencenews.com)
structural changes. Corresponding nanotechnologies still have to be developed. At last, fully understanding the relationship between hierarchical structures and device properties is essential for more advanced materials and device designing. Further investigations are required to develop a designing strategy: from genetic engineering to target device functions. Thermal effect could affect the molecule of proteins, which represents the feasibility of constructing a protein-based thermoresponsive memristor. Sun’s group reported a thermoresponsive memory based on soya proteins. The as-fabricated device exhibited tristable states “WORM times” characteristic at room temperature and switched to the binary WORM memory mode when heated to 358 K (Figure 6d). At room temperature, two −1.6 V pulse signals with 2 ms width are needed to set the output current below 10⁻⁷ A (defined as “0”), but only one or no input signal would result in output current higher than 10⁻⁷ A (defined as “1”), which realized the function of “NAND” logic gate. At 358 K, the current is higher than 10⁻⁷ A, only when neither of input pulses (−3 V, width of 2 ms) was used, which corresponded to the “NOR” logic gate. The “NAND” and “NOR” logic gate functions can be tuned by the temperature in this soya protein RRAM (Figure 6e). The molecular structural change under electrical stimulus and heating affected the charge transport channels, thereby resulting in the transformation of memory switching characteristics. Moreover, the degradable device demonstration was performed based on dissoluble Mg electrode and gelatin substrate.

Table 1 shows the basic performance parameters from some representative works about protein-based memristors. There is still a large performance gap between protein-based devices and inorganic counterparts. Various proteins have been applied as the active layers of memristors, and different device mechanisms have been proposed to explain the memory effects, such as charge trapping/detrapping, redox reactions, formation/rupture of metal filaments, etc. At present, there is not yet clear consensus upon the underlying mechanisms of protein memristors among various research groups. A clear understanding of the physical mechanism could enable better performance optimization. Meanwhile, the exploration of the new functions is equally important, by which we can have a profound insight into how the devices work and have better prioritization schemes.

Table 1. Representative parameters of protein-based memristors.

| Materials   | Device structure            | V_SET [V] | V_RESET [V] | ON/OFF ratio | Cycles | Retention time [s] | Ref |
|-------------|-----------------------------|-----------|-------------|--------------|--------|--------------------|-----|
| Azurin      | Al/Azurin/ITO/PET           | 8.0       | 8.0         | 3            | ≈500   | 10³                | [73]|
|             | Azurin/CdSe–ZnS/Au          | 1.5       | 0.5         | 1000         | ≈50    | –                  | [74]|
| EA          | Al/EA/ITO/Class             | −0.55     | −0.8        | >10³         | 500    | >10⁴              | [72]|
|             | Mg/EA/W                     | 1.0       | −0.8        | ≈10³         | 120    | >10⁴              | [75]|
|             | Ag/10% H₂O₂-EA/ITO/PET      | From 1.7 to 4.2 | From −1.5 to −2.0 | >10⁴ | ≈900 | >10⁴              | [63]|
|             | Ag/EA/ITO/PET               | 0.6       | −0.7        | ≈10³         | 50     | 10⁴               | [64]|
|             | Al/AE/Au:SiO₂/ITO/PEN       | −1.0      | 3.3         | >10²         | >10⁴  | >10⁴              | [76]|
|             | Au/EA/Au                    | <2        | >−1.5       | ≈10⁴         | –      | >10⁴              | [77]|
| Ferritin    | Ag/PAH/Ferritin/Pt/Ti       | −1.5      | 1.5         | ≈10³         | 300    | >10⁴              | [78]|
|             | Pt/Ferritin/Pt              | 0.5–2.2   | From −0.16 to −1.1 | >10³ | 70 | >6 × 10⁴         | [71]|
|             | Al/Silk/ITO                 | 10.4      | −11.5       | 10           | 120    | >9 × 10⁴          | [79]|
|             | Ag/Fibroin/Au               | 2.5       | –           | >10⁴         | –      | >10⁴              | [69]|
| SF          | Mg/ZnO/W/SF                 | From −1 to −0.55 | From 1.3 to 1.8 | 10⁵ | 140 | >10⁴              | [80]|
|             | Ag/SF-CDs/ITO               | 0.3       | −0.9        | 10⁴          | 10⁶    | >1.4 × 10⁴        | [81]|
|             | Ag/SF-AgNCS@85A/ITO         | 0.3       | −0.18       | 10⁵          | 10⁶    | >1.4 × 10⁴        | [82]|
| Gelatin     | Al/Gelatin/ITO              | −0.7      | 2.4         | >10³         | >120   | >10⁴              | [83]|
|             | ITO/Al-chelated gelatin /ITO| −0.49     | 2.34        | >10⁴         | 60     | >10³              | [84]|
|             | Mg/Gelatin/W                | 4.0       | −4.5        | >10⁴         | 75     | >10⁴              | [85]|
|             | Al/Silver-embedded gelatin /ITO| −1.2 | 2.1         | >10³         | –      | >10 days          | [86]|
|             | Al/Gelatin composite/Al/paper| From −3.5 to −2.9 | From 3.8 to 4.2 | >10³ | 18 | ≈7 weeks          | [87]|
| Keratin     | Ag/Keratin/FTO              | 1.5 V     | −1.0        | >10³         | 10⁶    | >10⁴              | [88]|
| Sericin     | Ag/Sericin/Au               | From 1 to 2.5 | From −0.35 to −0.8 | 10⁶ | 21 | >10⁴              | [89]|
| Soy protein | Mg/Soya protein/ITO         | –         | −1.0        | >10³         | –      | >10⁴              | [90]|
| DNA         | Au/CuO–DNA–Al/Au            | 2.25      | −2.25       | 100          | 500    | >10⁴              | [91]|
| rDnaJ protein | Cu/DnaJ/Pt                 | 0.12      | −0.08       | >10⁴         | 10⁶    | >10⁴              | [92]|
| S-layer protein | Al/Slp/ITO/PET             | 1.5       | −1.5        | 6.2          | 500    | >4 × 10⁴          | [93]|
4. Protein-Based Transistor-Type Memory

To meet the demand of data storage in electronic era, some three-terminal memory devices derived from traditional FET architecture have been proposed such as charge-trapping flash memory, floating gate (FG) flash memory, electrolyte-gated transistor, etc.\[9,127–133] Among these devices, FG flash memory shows great commercial value in flash drives and solid-state drives. Figure 7 shows the basic operating mechanism of FET and FG flash memory. Briefly, the electrical voltage applied in the gate electrode of FET modulates the conductance of the semiconductor channel, thereby controlling the ON and OFF stages of devices. The insertion of the tunneling dielectric and FG layer in the transistor structure forms a standard FG flash memory cell. Under programming voltage, charges would tunnel from the channel area to the FG layer and be trapped. The charging FG directly affects the conductivity of the channel and results in a shift of the transfer curve and corresponding alteration of the threshold voltage, which define the programmed state. In contrast, the opposite voltage would release the trapped charges in the FG layer and the transfer curve recovers to the original state, which is termed “erasing operation.” Reversible switching between two states in FG memory device promises its application in the digital circuit, and the distinguishable programmed state and original state can correspond to the “1” and “0” states, respectively. In addition to digital-type devices, analog-type flash memories with a consecutively changed threshold voltage have been extensively studied for neuromorphic computing. In this part, we review the recent works on protein-based flash memory for data storage. According to the building blocks in flash memory, the discussion is classified into four parts: charge-trapping layer, dielectric layer, semiconductor layer, and biotemplate.

4.1. Charge-Trapping Layer

Cho and coworkers introduced the LBL assembly technique and constructed the PAH/ferritin NP multilayers working as the charge-storage element in nano-FG flash memory (Figure 8a).\[94] Large memory window (20 V) and program/erase current ratio (10^4) were observed, due to the conducting channel affected by the charge trap/release of redox Fe^{III}/Fe^{II} couples in ferritin. However, the PAH/apoferritin NP multilayer-based device also showed transistor memory characteristics but with unstable retention and a small memory window, which might originate from the inferior charge property of amino acid residues in the protein shell. With the utilization of high-k Al_{2}O_{3} as the gate dielectric and poly(ethylene naphthalate) (PEN) as the substrate, they further fabricated the flexible organic FET (OFET) devices allowing low voltage operation (Figure 8b). Lee and coworkers demonstrated a nonvolatile OFET flash memory using myoglobin as the charge-trapping layer, and favorable memory window (≈11 V) and carrier mobility (0.0574 cm^2 V^{-1} s^{-1}) were obtained. Redox active sites in the heme structure were capable of trapping/releasing charges from/into the semiconducting channel under different gate biases, which resulted in a proper memory window, whereas the organic rings around the metal ions acted as the tunneling dielectric.\[95]

Alpha- synuclein (αS) molecules were applied to envelop Au NPs to form uniform αS–Au NPs conjugate monolayers, which served as nanoscale charge-trapping centers of the OFET, and obvious hysteresis in transfer and output curves under the dual-sweeping mode were observed (Figure 8c).\[96] Memory window, threshold voltage, retention time, and magnitude of current could be mediated precisely by the density and size of NPs (Figure 8d,e). The erasable/rewritable memory characteristic was indeed ascribed to the charge-trapping capacity of Au NPs, and the αS encapsulation functioned as the tunneling
insulator as well as the disperser/absorbent. A subsequent study by the same group was aimed at investigating the adhesion property of αS onto the surface of a few versatile substrates and a flexible flash memory utilizing αS–Au NPs as nano-FG was explored. These studies open up a new vista for utilizing programmable proteins as pluripotent components in bioelectronics.

4.2. Dielectric Layer

Hwang and coworkers used the SF thin film as the dielectric layer to produce a flexible OFET on poly (ethylene terephthalate) (PET) with outstanding peculiarity such as an ultrahigh mobility of 23.2 cm² V⁻¹ s⁻¹ and a low operating voltage of −3 V. Tiny hysteresis in the transfer curve represented that only few charge-trapping sites existed near the pentacene/SF interface, so low interface scattering was ensured which partially contributed to high mobility. Grazing incidence X-ray diffraction (GIXRD) was used to investigate the crystal quality of pentacene deposited on SF and SiO₂. At a small thickness (Figure 8f) and large thickness (>30 nm, Figure 8g), the pentacene orthorhombic phase and thin-film phase served as the primary channel for carrier transport, respectively. According to the GIXRD measurements, with deposition thicknesses of 25 and 70 nm, the amount of both orthorhombic and thin-film phases of pentacene on SF was obviously higher than that on SiO₂, which indicated that the preferred formation of crystalline pentacene occurred on SF thin film with the reduced amorphous phase of pentacene compared with that prepared on SiO₂ dielectric. An extraordinary improvement of mobility through replacing SiO₂ (0.22 cm² V⁻¹ s⁻¹) by the SF thin film exhibits the great potential of SF for optimizing the performance of OFET. Chicken albumen extracted from egg white showed its potential to be a decent dielectric material with a high dielectric constant (5.3–6.1) in Wen’s study. Thermal processes induced the formation of disulfide bonds between proteins, which promised the smooth and dense albumen film,
together with low gate leakage current. Both p-type (pentacene) and n-type (C60) transistors based on albumen dielectric were prepared and applied to make complementary inverters, whose gain reached 15.3 and 20 when \( V_{GD} \) was 15 and 20 V, respectively.

The internal structures of protein dielectrics, which vary in different work circumstances or treatment methods, have considerable impact on the characteristics of the semiconducting layer and in turn the performance of the OFET. Some groups have investigated how the external environmental conditions affect the performance of protein transistors, trying to obtain the optimized properties.\(^{[137-139]}\) It is feasible to gain the highest device performance via adjusting the structures of biodielectrics in OFETs regarding specific semiconductors, but at the same time preventing the unexpected structural changes in different environments is an inevitable problem that has to be settled.

Hysteresis in OFETs is common because of charge trapping, polarization, or other complicated effects in organic dielectric layers. A smaller hysteresis represents a better semiconductor/dielectric interface with fewer impurities, confirming the OFET devices operating as standard transistors. Nevertheless, making good use of this effect could endow the nonvolatility characteristic of OFETs to work as data-storage memories. Yoon’s group demonstrated a nonvolatile OFET consisting of albumen as dielectric layer and In–Ga–Zn–O (IGZO) as the semiconducting layer.\(^{[140]}\) A high current ON/OFF ratio of \( \approx 1.1 \times 10^6 \) and mobility of 11.5 cm\(^2\) V\(^{-1}\) s\(^{-1}\) were obtained and obvious hysteresis was observed in transfer characteristics in the double sweeping mode with a memory window of 11.8 V. No distinct degradation of the device performance occurred when under bending condition and on the synthetic paper substrate. The bistable property was generated by the switching behavior of remnant polarization in albumen. Although there are some problems such as inferior retention and low yield (\( \approx 50\% \)), this novel characteristic is inspiring enough for researchers to exploit the nonvolatile application.

Recently, it was reported that a heme protein (cytochrome c, Cyt c) embedded in poly(vinyl alcohol) (PVA) dielectric greatly improved the OFET’s stability and retention characteristic.\(^{[98]}\) The PVA:Cyt c OFET could maintain outstanding hysteresis features after 10 000 cycles even at a high-temperature condition. The superior performance resulted from the fact that PVA chains were immobilized by the interactions with Cyt c nanospheres, which indicates the proteins have the capability to work as not only the dielectric layer but also the adjusting element for OFETs. Wu and coworkers demonstrated a chicken albumen dielectric-based coplanar FET, which can be tuned from the depletion mode to enhancement mode via tuning the thickness of the channels or applying positive voltage to another gate. It supports a new view for controlling the transistor mode, but detailed studies such as how the distance between two gates could influence the tunable threshold are still needed.\(^{[141]}\)

### 4.3. Semiconductor Layer

Back in 2004, researchers focused on utilizing protein molecules into nanoelectronics. Rinaldi et al. fabricated a biotransistor in which the azurin interconnected source and drain electrodes as the semiconductor.\(^{[142]}\) Via chemical surface treatment, azurin was immobilized in the gap between two Au electrodes and the schematic structure is shown in Figure 9a. From the output characteristics as a function of gate bias, the device behaved as a classic ambipolar transistor. Nevertheless, asymmetric curves were observed in the opposite \( V_{DS} \) region as in the azurin deposition process, internal dipole generated in the oriented protein film would offer the preferred conducting path for carriers and thereby affect the conduction channel in the opposite electric field. In the transfer curve, with increased gate voltage, the \( I_{DS} \) enhanced first but decreased gradually after \( V_{GS} \) reached a specific value (\( \approx 1.1 \) V); so, a peak shape was observed. From the electronic perspective, the resonance in the transfer curve represented a conversion from the n-type transistor (rising part of \( I_{DS} \)) to p-type transistor (reducing part of \( I_{DS} \)). This peculiar property allowed the integration of both conducting types in an individual biotransistor and especially electrical operation in the unilateral voltage region. The proposed conduction mechanism was electrons hopping between Cu redox centers in azurin (\( Cu^{2+} + e^- \rightarrow Cu^{+} \)), which was confirmed by the inferior conducting properties of the transistor based on azurin without metal atoms (Apo-azurin) or azurin whose Cu atoms were replaced by Zn atoms (Zn–azurin), as no metal redox sites exist in apo-azurin, whereas Zn has only one oxide state, Zn\(^{2+}\). The valid explanation for the resonance in transfer characteristics and actual application of device’s type transformation weren’t accomplished in their researches, and the problems of aging and reproducibility of devices were left to be settled. If the stability and endurance of the azurin-based transistors can be guaranteed, the characteristic of the controllable modulation of currents may contribute to hardware neuromorphic computing. Furthermore, it is inspiring to discover the inherent mechanism behind the devices to explore the unexpected functionalities with which proteins could endow the electronic devices.

Protonic transportation plays a crucial part in signaling in biology and has been applied in diverse devices including transistors, batteries, sensors, and so forth, which is expected to bridge the biological systems and traditional electronics for future bioelectronics. Proteins with proton conduction, which are applied as a passive layer (dielectric) in the last section, are reported as the semiconducting layer of protonic transistors in some literatures. Gorodetsky and coworkers have undertaken a range of studies toward the protonic transistors based on reflectin extracted from cephalopods. In 2014, they systematically investigated the proton-conducting characteristics of Doryteuthis pealeei reflectin A1 (D. pealeei reflectin A1), which was used as the semiconducting layer in the protein-based protonic transistor for the first time (Figure 9b).\(^{[143]}\) As shown in Figure 9c, the curves obtained from electrochemical impedance spectroscopy (EIS) and kinetic isotope effect measurements were the fingerprints of protonic conductors, which corroborated the protonic conducting property of the reflectin film scrupulously. Thereafter, the electrical properties of the reflectin film in different humidity conditions were analyzed, in which palladium hydride was served as two-terminal electrodes for its facilitation of proton injection. A higher current level was observed with elevated relative humidity due to more protons produced via hydration, and small hysteresis might be caused by the impurified reflectin/SiO\(_2\) interface. Reflectin with targeted mutation and disordered amino acid sequence exhibited lower conductance.
compared with the wild type, indicating that carboxylic acid and unique structural sequence were the keys for proton conducting. The output curves of three-terminal protonic transistors under varying gate voltages revealed that a negative $V_{GS}$ induced protonic accumulation in the conducting channel which increased the current level while opposite $V_{GS}$ caused protonic depletion and diminished conductance, which coincided with the behaviors of traditional FETs (Figure 9d,e). The obtained mobility of $\approx 7.3 \times 10^{-3} \text{cm}^2 \text{V}^{-1} \text{s}^{-1}$ was similar to the value of reported protonic transistors. The merits of protein in this finding, including structural modification and adjustable characteristics, may reform the protocols of protonic biotransistors. The optimization of current ON/OFF ratio was conducted through reducing the thickness of the reflectin film in 2015.\[144\] Besides reflectin A1, Gorodetsky et al. investigated D. pealeii reflectin A2 isoform to testify the feasibility of protonic transistors relying on multiple D. pealeii reflectin isoforms, and they showed improvement in the fabrication technique to balance the purity and yield.\[145\]

Interestingly, by introducing the photoacid hydrosulpyrene-1,3,6-trisulfonic acid (HPTS) into the reflectin A1 film, light acted as another stimulus to modulate the electrical properties of protonic transistors.\[70\] Under blue light illumination, HPTS molecules were in excited states and acted as dopants releasing free protons, so a higher current level was obtained. HPTS molecules in ground states would not contribute protons into the conducting channel without light illumination, as shown in Figure 9f–h. The modulation of electrical characteristics by two independent exogenous stimuli (light and electricity) was achieved via doping methodology, which endows extra functionality to protein-based protonic transistors.

4.4. Biotemplate

Nano-FG flash memories based on NPs are under extensive investigation due to their superiorities over traditional flash...
memories, including improved retention property because of the Coulomb blockade effect, quantum confinement, and lessened charge leakage. Nevertheless, it is challenging to fabricate uniform high-density nanodot arrays depending on traditional technologies such as physical/chemical vapor deposition (PVD/CVD). Biomimeticization based on the cage-shaped biotemplate, which has broader applications in the field of FG flash memories than memristors, acts as a reliable method to primarily solve the problems of ununiform distribution and heterogeneous sizes. The first floating nanodot gate transistor produced by such a biological process with memory characteristics was demonstrated by Yukiharu Uraoka’s team in 2006 and hitherto they have reported a series of studies concerning nanodot FG flash memories on the basis of biomimeticization.\(^{\text{146}}\)

In 2008, they utilized ferritin protein as the synthesizer and self-assembly template to fabricate homogeneous high-density (\(6.5 \times 10^{13} \text{ cm}^{-2}\)) cobalt oxide (Co\(_3\)O\(_4\)) nanodot arrays with an average size of \(6.6 \pm 0.5 \text{ nm} \) embedded in the SiO\(_2\) layer, which worked as the charge confinement entities. Of particular note was that the Co\(_3\)O\(_4\) nanodots were partially reduced to the metal state (Co) which served as the potential well for better charge retention, as shown in Figure 9ij.\(^{\text{99}}\) A clockwise hysteresis can be observed in the transfer curve with a memory window of 3.4 V, when gate voltage swept in \(\pm 6 \text{ V} \) region (Figure 9k). The excellent durability, large charge capacity, and robust retention of devices were the result of comprehensive factors including uniformity, well dispersion, high density of Co\(_3\)O\(_4\) nanodots, and the enhanced charge restriction in Co\(_3\)O\(_4\)/Co composites. In 2015, this team reported a V-groove junctionless FET with an ultrashort channel (\(=3.6 \text{ nm} \)) in which FeO\(_x\) NPs biomimeralized by ferritin were buried in the V-groove as nano-FG.\(^{100}\) The nearly full coverage in the Si channel via FeO\(_x\) NPs caused strong electrical interaction between them, and therefore NPs in such structures had a greater impact on channel conductance than normal floating nanodot flash memory, which accounted for a larger memory window (\(\approx 3.3 \text{ V} \pm 4 \text{ V} \) sweeping region). Table 2 shows the ON/OFF ratio, cycle number, retention time, memory window, and mobility parameters from some representative works about protein-based transistor-type memories. Proteins can play different roles in transistor-type memory devices, implying their superior versatility. Giving full play to these advantages of proteins could bring novel multifunctionalities and higher manipulation to traditional transistor-type memory devices.

### 5. Nanoscale Molecule Device

Due to the physical and technical limitations of silicon-based devices, some new concepts have been proposed for future low-consumption and small-sized memory devices. One approach is utilizing single or a few molecules to perform electronic function. The molecular electronic device exhibits specific electrical characteristics in different molecular redox states, which correspond to the bits in digital circuits.

Porath and colleagues reported a nanoscale built-in memory and a ternary logic multiplier based on a silicon NP embedded in the cavity of a circular boiling-stable protein (SP1), as shown in Figure 10a.\(^{\text{147}}\) The silicon NP could store the injected charges whereas the SP1 protein acted as the isolation shell to prevent the leakage of charges. CAFM was used to control the injecting and withdrawing of charges from the probe tip, and electrostatic force microscopy (EFM) was conducted to detect the state. This hybrid nanoscale memory exhibited excellent stability in consecutive set–reset operations, as shown in Figure 10b. In this work, SP1 protein only worked as the isolation element because of its stability, but for the redox-active proteins, they are capable of acting as the core role of the molecular electronic memory.

A hybrid material containing recombinant azurin and CdSe–ZnS QDs was applied to fabricate a nanoscale binary RRAM. The electrical characteristics were measured by applying the voltage from the STM conductive tip, where the Au substrate was grounded (Figure 10c), and two distinct conductivity states can be observed during voltage sweeping (Figure 10d).\(^{\text{148}}\) The conductivity switching behavior was attributed to the charge transfer between CdSe–ZnS QDs and azurin under the electric field. In this research, azurin was modified to introduce cysteine groups via site-directed mutagenesis, which enabled recombinant proteins to anchor the Au substrate by covalent bonding directly; there was no need for an additional linker material.

| Materials       | Component | Cycles | On/Off ratio | Memory window [V] | Retention time [s] | Mobility [cm\(^2\) V\(^{-1}\) s\(^{-1}\)] | Ref |
|-----------------|-----------|--------|--------------|-------------------|-------------------|---------------------------------|-----|
| Ferritin        | CR layer  | 300    | \(10^4\)     | >20               | \(>10^4\)         | 0.013                           | [94]|
| Myoglobin       | CR layer  | 100    | \(10^4–10^5\)| 11                | 500               | 0.0574                          | [95]|
| αS              | CR layer  | 7      | –             | 65                | \(10^5–10^7\)     | –                               | [96]|
| SF              | CR layer  | 500    | –             | 16.8              | \(7 \times 10^6\) | –                               | [103]|
| EA              | Dielectric| –      | \(\approx1.1 \times 10^6\)| 11.8              | \(4 \times 10^4\)  | 11.5                            | [68]|
| SF              | Dielectric| –      | –             | 9.8               | 150               | –                               | [97]|
| EA              | Dielectric| –      | –             | 4                 | –                 | –                               | [102]|
| Keratin         | Dielectric| –      | \(1.1 \times 10^4\)| –                 | –                 | 0.35                            | [62]|
| Cyt c           | Dielectric| \(10^4\)| \(10^5\)     | 5.86              | –                 | \(1.9 \times 10^{-1}\)          | [98]|
| Ferritin        | Bio-template| \(10^3\)| \(10^3\)     | 3.3               | \(>10^4\)         | –                               | [99]|
| Ferritin        | Biotemplate| \(10^6\)| –             | 5.7               | \(>10^4\)         | –                               | [100]|
| Chaperonin      | Biotemplate| \(>10^3\)| –             | –                 | \(>10^4\)         | –                               | [101]|

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**Table 2.** Performance comparison of protein-based transistor-type memory.
The recombinant DNA technique mainly dealt with the problem of immobilization rather than modulating device performance. Usually there are only two redox states in a single protein, some strategies have been taken for improving the data-storage density. Incorporating different redox-active molecules with separated potentials is a feasible way for realizing multistate functionality. Choi and coworkers adopted a recombinant azurin/cytochrome c hybrid layer to fabricate a nanoscale-multilevel biomemory device.[149] They investigated the electrochemical characteristics of the heterolayer on Au surface by cyclic voltammetry and open-circuit potential (Figure 10e). Open-circuit potential amperometry technique was conducted for showing memory switching for writing, reading, and erasing operations. The electron transfer in the recombinant azurin/cytochrome c layer resulted in four different charging states, i.e., multistate storage. This work verified the feasibility of protein-based molecular electronics with functions of multilevel storage, low consumption, and robustness. Although many problems remain to be solved, such as large-scale operating scheme, device reproducibility, and integration technology, a single electrochemical protein has great potential to realize molecular storage technology and even molecular computing.

6. Protein-Based Electronics for Brain-Inspired Computing

The human pursuit of intelligent machines has never ceased throughout human history. Especially in this electronic era, a large number of complicated tasks and data have to be processed efficiently, which increases people’s desire for building a brain-inspired computing system that works like a human brain with high-performance computing and energy efficiency. The developments of neuroscience and the semiconductor industry in the past decades have pushed the research progress of mimicking biological functions in the filed of electronics. After the concept of “neuromorphic computing” proposed by Mead in, researchers have made efforts in achieving artificial neural and synaptic circuits with complementary metal-oxide-semiconductor (CMOS) technology.[150] However, due to von Neumann bottleneck, CMOS-based neural networks have no inherent on-chip hardware learning ability, which must be realized through software programming. In addition, the energy consumption, scale ability, and calculating efficiency of such a neuromorphic network are far from those of a biological human brain.

The emergence of two- and three-terminal memristive devices with novel structures and mechanisms boosts the advancement of neuromorphic units and brings the development of neuromorphic systems to a new stage. Such new devices in neuromorphic circuits which can simulate the basic biological functions are referred to as neuromorphic devices. Neuromorphic (artificial) synapse and neuron are two basic units in the neuromorphic system, mimicking biological synaptic plasticity and neural functions, respectively. Biological synapse is made of a presynaptic membrane, postsynaptic membrane, and cleft. Synapses are in charge of information transmission between neurons with tunable synaptic weight that controls the connection strength. This synaptic plasticity is the most crucial characteristic of
synapses. Basic synaptic functions include short-term plasticity (STP), long-term plasticity (LTP), spike rate-dependent plasticity (SRDP), and spike time-dependent plasticity (STDP), which have been simulated in the single memristive device. Biological neuron consists of cell body, axon, and dendrites. Information in the form of spikes is transmitted from dendrites to the cell body and then away through the axons to the next neuron. Briefly speaking, a neuron can receive and integrate information obtained from other neurons, encode the information, and generate spikes to further transmission. Basic requirements for neuromorphic neuron are accumulating and firing, and some higher-level biological details are needed in specific neural models.\[131,132\]

At present, how to emulate the synaptic functions is still the primary focus in the neuromorphic field. In the two-terminal artificial synapse, the external electrical stimuli as presynaptic spikes are applied on the top electrode (presynaptic membrane) and the bottom electrode works as the postsynaptic membrane. The material reconfiguration in the active layer between the top and bottom electrode can accurately represent synaptic plasticity characteristics, where ion redistribution is similar to the influx of ions and neurotransmitters, and synaptic weight is represented by the tunable conductance state. In neuromorphic networks, analog memristors could update the synaptic weights to store data and process input information at the same time-place, and the memristor crossbar array could finish matrix-vector multiplication with high parallelism and efficiency, according to Ohm’s law and Kirchhoff’s law. This computing architecture outperforms than von Neumann architecture in massive computing tasks such as pattern recognition and sound localization. In the three-terminal structure, i.e., transistor-based memory, the gate electrode is regarded as presynapse, and the conductance of the semiconductor channel, which can be modulated, is equivalent to synaptic weight controlling signal conveying. Compared with the two-terminal artificial synapse, the transistor-type synapse enables the simultaneous operation of signal transmission and weight modulation, which is closer to the biologically temporal additive feature in information transmission. Moreover, three-terminal devices have more flexibility in geometry (semiconductor memory, multigate flash memory, etc.). Various stimuli such as pressure, light, gas, and heat are feasible to be introduced into such device configurations, which allow the implementation of more complicated biological functions. Besides emulation of synaptic functions, some artificial neuron memristors and transistors have been reported to be applied in different neuron models.\[133\]

There are many assessing parameters for artificial devices, such as resistance state stability, energy consumption, operation speed, endurance, weight updating linearity, etc. It is still challenging to optimize all the properties in a single neuromorphic device. A large number of studies have been undertaken to realize performance optimizing on the oxide-based device, but exploitation of the novel functional neuromorphic device is equally important. The discovery of new effects and mechanisms may help us create innovative units or even architectures which can radically improve the performances. In this section, we summarize and analyze recent works on protein-based neuromorphic devices. Various advantages of proteins bring more maneuverability and functionalities into the neuromorphic device, giving researchers more inspiration to design an innovative biological–electronic information communicative interface.

6.1. Two-Terminal Architecture

To build the direct communication of artificial neuron (synapse) and biological neuron (synapse), how to realize the biovoltage operation is an urgent need to be addressed. As protein nanowires of bacterium G. sulfurreducens are known for their ability to speed the metal reduction in a biological environment, Fu et al. introduced these protein nanowires into memristors to facilitate the filament formation, thereby reducing the switching voltage.\[107\] They successfully constructed a highly stable diffusive memristor, which can be operated at the biological voltages (40–100 mV, Figure 11a–c). The protein nanowires were believed to play the critical part in lowering the operation voltage according to the statistics of electroforming voltage in protein-nanowire devices. A right shift in the reduction peak in cyclic voltammetry measurements proved that the protein nanowires could really facilitate $\text{Ag}^+$ cathodic reduction (Figure 11d). The protein-nanowire memristor naturally works as an artificial neuron with integration, threshold, and self-recovery functions, especially for its biovoltage characteristic. More pulses are needed for the lower-frequency EPSC spiking, which were emulated by a single protein-nanowire memristor, as shown in Figure 11e. In addition, the tunable conductance of protein-nanowire memristors has mimicked synaptic plasticity, which enabled the realization of frequency-dependent pair pulse facilitation (PPF) and pair pulse depression (PPD) (Figure 11f). The authors proposed biosensing signal demonstration based on an integrate-and-fire neuron circuit for monitoring the heart rate. The heart rate was connected with the input signal’s frequency, and only an abnormally high heart rate could result in neuron firing, and the biovoltage artificial neuron circuit worked as an on-site health monitor (Figure 11g,h). The catalytic strategy greatly reduces energy consumption in a spiking event similar with a biological neuron/synapse, which significantly promotes the development of low-power neuromorphic computing. Moreover, the intrinsic biocompatibility and biodegradability of protein nanowires offer the probability for realizing biological–electronic interfaces. This optimizing concept for modulating the operation voltage may have a broader application in different kinds of memristors.

Lee and coworkers reported a transparent and flexible memristor to emulate the synapse, in which collagen extracted from fish skin served as the dielectric layer.\[61\] In this study, Mg and ITO electrodes emulated the presynaptic and postsynaptic layer, respectively, whereas the magnesium ions and collagen film acted as the synaptic cleft and neurotransmitters. The gradual conductance alteration depending on the successive sweeping voltage exactly matched the variable synaptic weight, responding to potentiated or depressed stimulus, as shown in Figure 11i. Fundamental biological synaptic characteristics involving excitatory postsynaptic current (EPSC), potentiation and depression (Figure 11j), PPF, SRDP, and STDP were emulated successfully in this artificial synapse, and the mechanism of the analog memory characteristic was ascribed to the accumulative modulation of $\text{Mg}^{2+}$ concentration in the collagen film according to the bias. Yan et al. utilized EA memristors to build an artificial
synapse for constructing a brain-inspired neuromorphic system.\cite{154} By modulating distinct pulse amplitudes, PPF to PPD switching can be measured which corresponded to the deactivation of the voltage-susceptive Ca$^{2+}$ channels in biologic synapses. Moreover, they observed STP-to-LTP transition as this behavior was dependent on pulse amplitudes as well. The forgetting rate exhibited positive correlations with the pulse frequencies and the consecutive number of pulses, enabling the devices to mimic synapses for in-memory computing and conduct sophisticated projects.

Hybrid nanocomposites based on QDs and an organic medium, which can improve charge storage property, are effective switching layers in synaptic memristors. An artificial synapse device based on chicken EA, graphene QD nanocomposites, was reported recently.\cite{155} The conductance gradually decreased in consecutive positive and negative voltage sweeping, indicative of the ability to mimic synaptic plasticity. However, the conductance can’t be modulated to a higher level according to the experiment results, which would limit its emulation of PPF. In addition, the introduction of graphene QDs may endow the memristor a photoresponsive property, but this part is not mentioned and still needed for deeper investigation.

SF can be functionalized by doping some functional elements, such as metal nanoclusters (NCs), QDs, or nanocomposites. However, direct incorporation might jeopardize the protein molecular networks, so a soft medium which can make good connection between functional NPs and the protein network is a considerable factor in the functionalizing process. As wool keratin (WK) molecules were reported to synergistically interact with the SF network, Liu and coworkers used WK as the mediating nanocage which contained functional Au NCs, and Figure 12a shows the atomic force microscopy (AFM) and transmission electron microscopy (TEM) images of WK@Au NCs–SF-based memristors.\cite{156} Compared with neat SF-based memristors, WK@Au NCs–SF-based memristors exhibited more uniform $I$–$V$ curves and narrower parameter distribution, confirming their more stable properties than the neat SF devices. Apart from the greater stability, the average SET/RESET voltage of WK@Au NCs–SF devices (0.3 V, $-0.3$ V) is much smaller than that of the neat SF devices (1.5 V, $-1$ V), representing the lower power consumption of the mesoscopic-functional memristor. The conductance of WK@Au NCs–SF devices can be modulated through consecutive DC voltage sweeping (Figure 12b) and pulse stimulation, which correspond to the biosynaptic weight change.
According to the Hebbian learning rules, the STDP function, which is dependent on the time difference between pre- and post-synaptic spikes, was emulated in this WK@Au NCs–SF device (Figure 12c). In 2019, the same group adopted the mesoscopic reconstruction strategy to further improve the performance of silk-based memristors.[82] They introduced Ag NCs@bovine serum albumin (BSA) into SF as electronic potential wells, which attract metal cations and speed up the migration of cations (Figure 12d,e). The low potential paths interconnecting the Ag NCs@BSA facilitate the uniform formation of conductive filaments, thereby endowing the as-fabricated devices’ superior properties, including fast switching speed (10 ns), low operation voltage ($V_{\text{SET}} \approx 0.3 \text{ V}$, $V_{\text{RESET}} \approx -0.18 \text{ V}$), narrow distribution of switching parameters, and high ON/OFF ratio ($\approx 10^5$). Furthermore, some basic biological synaptic functions had been mimicked based on the Ag NCs@BSA-functionalized SF memristors, as shown in Figure 12f-i. Mesofunctionalization is a promising strategy to reconstruct the SF with different functions to meet specific requirements in electronics and optoelectronics.

6.2. Three-Terminal Architecture

In Wan’s research, chicken albumen was used as the dielectric layer, and the mechanism was explained thoroughly and in detail.[102] Proton conductivity and hydrophilicity were the keys to obtain the hysteresis property so they dried the albumen films in ambient environment instead of annealing at a high temperature to avoid irreversible thermal denaturation and reduction of ionic conductivity. With an MIM structure (IZO/albumen/ITO), the results of EIS proved the hydrated albumen as an ion conductor, in which the interaction between H$_2$O and the amino acid generated (CH$_2$)$_2$—COO— chains and H$^+$ (H$_3$O$^+$). When under a high external bias, the proton migration formed the electric-double-layer (EDL) capacitor, and proton penetration into IZO caused the surface hydrogenation and invertible electrochemical reaction in the IZO/albumen interface, which increased the channel conductance of IZO ($\ Figure 13$). They fabricated an OFET with two extra in-plane gates, and a hysteresis window of 4 V was observed in the transfer curves. The flow of protons could modulate the channel conductance of IZO under bias, which was similar to the behavior of neurotransmitters in tuning the synaptic weight, and ITO was regarded as a presynaptic terminal while IZO between source and drain electrodes was taken as a postsynaptic terminal in such a situation. Temporal (PPF, dynamic filtering, from STP to LTP,) and spatial (EPSC summation, shunting inhibition) synaptic functions were mimicked by this transistor successfully, as shown in Figure 13b–d. Hygroscopicity of keratin can enhance the interaction between water and amino groups to generate mobile protons, so keratin behaves as an EDL-structured capacitor similar to albumen when under external bias. Leong and coworkers...
utilized keratin dielectric to fabricate a p-channel transistor synapse.\cite{62} Mobile protons migrated and accumulated at the gate/dielectric interface under negative gate bias, which induced the increase of holes (i.e., the device’s conductance) in the channel at semiconductor/dielectric interface (Figure 13e). Based on the adjustable conductance, some synaptic behaviors were realized, as shown in Figure 13f,g. In addition, they constructed the flexible biodegradable transistor consisting of keratin dielectric and keratin protein substrate, which dissolved in alkaline ammonium hydroxide solution after 7 days.

Lv et al. fabricated an artificial photoelectronic synapse with FET architecture in which hybrid CD\textsubscript{s}/silk protein worked as the charge-trapping layer (Figure 13h).\cite{103} In this research, UV light pulse (365 nm, 0.15 mW cm\textsuperscript{-2}, 5 s) enabled prominent increase of $I_{DS}$ to obtain a memory window of $\approx$15.2 V, so optical writing and electrical erasing operations were conducted, highlighting the fast programming speed (Figure 13i). $V_{th}$ increased from $-9.8$ to 5.1 V as light intensity ranged from 0 to 0.15 mW cm\textsuperscript{-2} and in addition, the current level could be accumulatively mediated via a successive light pulse stimulus.
exhibiting the multibit storage property (Figure 13j). The different retention of photo-programmed current with varying illumination intensity signified the concomitant volatile and nonvolatile features, which exactly resembled the STP and LTP in neuroplasticity. The controllability of conductance through UV light and electrical pulses imitated some synaptic functions involving PPD, PPF, and STP to LTP (Figure 13k,l). Moreover, the protein synapses were applied in the simulation of pattern recognition (Figure 13m). The proposed mechanism manifested by comprehensive AFM measurements was that the photoexcited electron–hole couples would separate and the photogenerated electrons were trapped into CDs whereas the photogenerated holes would accumulate in the semiconducting channel at the pentacene/CD–silk interface, affecting conductance. The light intensity-dependent electron storage capacity of CDs elucidated that a longer time was needed for charge recombination with stronger light intensity, accounting for the transition from volatile to the nonvolatile regime. Silk protein acted as a 3D matrix for CDs to promote the charge-trapping stability and endurance of the device.

7. Conclusion and Outlook

In this Review, we have summarized and analyzed the studies of protein-enabled memory devices for data storage and neuromorphic applications in the past decades. Our discussions revolve around proteins as different functional components in two- and three-terminal memory devices for the applications of data storage and neuromorphic computing. In light of the rich advantages in optics, electronics, and mechanics, proteins have emerged as novel building blocks in bioelectronics. The introduction of proteins broadens the functionalities of memory devices, including flexibility, biodegradability, biocompatibility, and so forth, which contribute to the flourishing development of smart implantable and wearable bioelectronics. Especially in the background of the electronic era, protein-based devices are crucial to meet the demand of massive data-storage and bioplastable neuromorphic systems, toward the development of sustainable green electronics. Despite recent advancements, the development of protein-based memory is still at a preliminary stage, and there are certain primary and technical challenges that have to be addressed. The following development directions of protein-based memory devices mainly include the following aspects. First, as the internal structure of proteins might change in different humidities or temperatures, it is necessary to adopt specific encapsulation techniques and improve the stability of protein molecules in different working conditions. However, if the structural changes could reflect in electric signals, grasping their correspondence could enable the fabrication of functional sensor-like memory devices which are sensitive to the environment. Second, not fully compatible to traditional photolithography is a considerable obstacle for forming designed micro/nanostructured protein patterns. For example, toxic organic solvents in traditional photolithography could destroy the integrity of the proteins. Micro/nanopatterning is crucial to realize high-density and high-resolution memory arrays. A few methods such as the “protein photosresist” or a combination of soft and hard masks may provide the opportunity to totally overcome this challenge, but how to maintain the basic electric performances in special fabrication technologies needs deeper studies. Third, the performance of protein-based memory devices, such as endurance, stability, operation speed, and power consumption, is still not up to that of inorganic counterparts. On the one hand, although some devices are reported to possess certain outstanding performances such as ultrafast switching or ultralow power consumption, it is still challenging to combine all the superior properties in a single device. On the other hand, protein-based memory devices should not be regarded as the total replacement for the traditional devices, as there is still a performance gap between them and inorganic counterparts. Instead, protein-based memory devices should be regarded as the extended functional devices in specific applications where they could outperform traditional devices by virtue of some intriguing properties (biocompatibility, biodegradability, etc.) Fourth, the operation mechanisms behind the protein-based memory devices are controversial. Further mechanism investigations have to be undertaken to have a profound insight into materials and devices design. At present, there is not yet clear consensus upon the underlying mechanisms of protein memory devices among various research groups, which is mainly due to diverse device structures, materials, and interface in different physical systems. Protein molecules have alterable structures with high precision and complexity. Fully understanding the relationship between hierarchical structures and device properties could offer researchers to make advanced designs toward targeted properties for specific applications. In the future, we can design a novel device more purposefully based on the fundamental understanding of the physical mechanism. Finally, most studies stay at the device level. If the aforementioned challenges can be overcome, we should think more about how to develop ways of integration, appropriate algorithms, and novel architectures for “protein” neuromorphic computing.

In the long term, these protein materials are anticipated to have a revolutionary impact on our daily lives. We believe protein-based memory devices must play an essential part in neuromorphic computing systems. Such a biocompatible advanced processing system can help the development of implantable bioelectronics and communicative electronic–biological interfaces for versatile applications. This needs us to strengthen the multidisciplinary connection, including materials science, biology, medicine, physics, etc., and the dream of truly electronic life is not that far.

Acknowledgements

The authors acknowledge grants from National Natural Science Foundation of China (grant no. 61974093), Guangdong Province Special Support Plan for High-Level Talents (grant no. 2017TQ04X082), Guangdong Provincial Department of Science and Technology (grant no. 2018B030306028), the Science and Technology Innovation Commission of Shenzhen (grant nos. JCYJ20180507182042530 and JCYJ20180507182000722), and NTUT-SZU Joint Research Program and the Natural Science Foundation of SZU.

Conflict of Interest

The authors declare no conflict of interest.
Keywords
bioelectronics, flash memories, memristors, neuromorphic computing, protein materials
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