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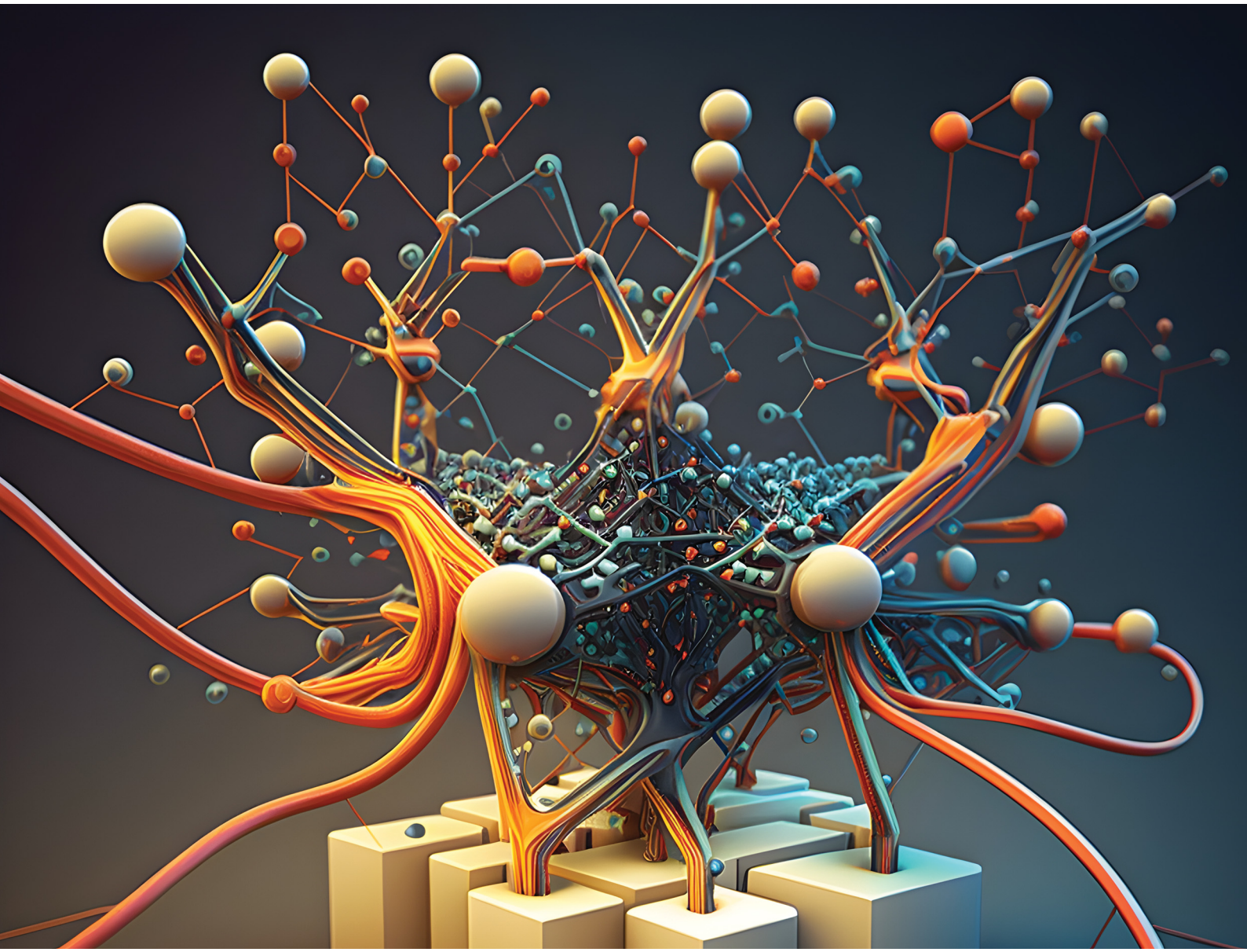

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REVIEW ARTICLE

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REVIEW

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Control of charge transport in electronically active systems towards integrated biomolecular circuits (IbC)

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The miniaturization of traditional silicon-based electronics will soon reach its limitation as quantum tunneling and heat become serious problems at the several-nanometer scale. Crafting integrated circuits *via* self-assembly of electronically active molecules using a "bottom-up" paradigm provides a potential solution to these technological challenges. In particular, integrated biomolecular circuits (IbC) offer promising advantages to achieve this goal, as nature offers countless examples of functionalities entailed by self-assembly and examples of controlling charge transport at the molecular level within the self-assembled structures. To this end, the review summarizes the progress in understanding how charge transport is regulated in biosystems and the key redox-active amino acids that enable the charge transport. In addition, charge transport mechanisms at different length scales are also reviewed, offering key insights for controlling charge transport in IbC in the future.

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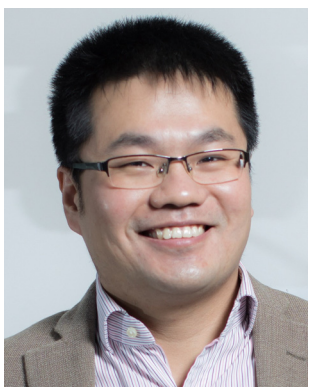


Bo Li

Dr. Bo Li is currently an assistant professor in the Department of Mechanical Engineering, Kennesaw State University, USA. He received his PhD in Materials Science and Engineering from Georgia Institute of Technology in 2015. From 2015 to 2020, he was a postdoctoral fellow at the University of Illinois at Urbana-Champaign. His research aims to develop self-assembled electronically active biomaterials for artificial intelligence and next generation electronics, including (a) understanding the charge transport in the self-assembled systems and (b) controlling the self-assembly under non-equilibrium conditions. His research directly addresses these fundamental scientific issues by leveraging a unique set of skills in innovative materials synthesis and characterization.

1. Introduction

Society is facing a technological revolution in information processing and data storage applications. As Moore's law has been violated since 2016,[1] the miniaturization of traditional silicon-based electronics will soon reach its limitation as quantum tunneling and heat become serious problems at the several-nanometer scale and the increase in manufacture cost also creates a huge economic barrier.[2] To this end, crafting integrated circuits *via* self-assembly of electronically active molecules using a "bottom-up" paradigm provides a promising solution to these technological challenges.[3,4]

In 2000, Whitesides proposed a 3D self-assembled light-emitting diode (LED) network formed by millimeter-scale polyhedra, with surfaces patterned with solder dots, wires, and LEDs (Fig. 1a),[5] hoping that when the size of an individual electronic element decreases, a more complex self-assembled electronic system will be crafted in the future. To date, more than two decades have passed witnessing remarkable progress in nanotechnology and nanomaterials, especially with significant advances in single molecule electronics such as molecular logic gates,[6] molecular diodes[7] and molecular photoswitchs.[8] To some degree, the miniaturization of electronic components has been achieved down to the molecular scale. Nevertheless, the implementation of self-assembled molecular electronics and, more critically, the development of integrated molecular circuits remain elusive objectives.

Overall, there are two fundamental challenges: (1) the ability to manipulate charge transport in the self-assembled

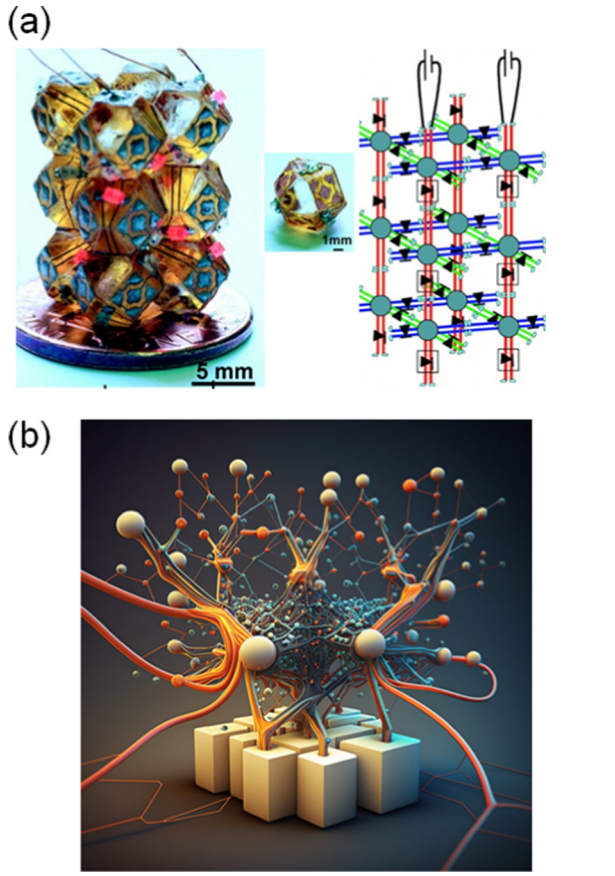


Fig. 1 (a) Photo of 3D self-assembled light-emitting diode (LED) networks. Reproduced with permission from ref. 5, Copyright © 2000, The American Association for the Advancement of Science. (b) Schematic illustration of 3D self-assembled circuits.

electronically active molecular systems and (2) the ability to program and precisely control the self-assembly behavior of molecules *via* multiple levels of hierarchies. A comprehensive understanding of charge transport control in self-assembled molecular systems is essential for identifying the ideal self-assembled structure. To this end, in this review, we will focus on recent progress regarding challenge (1).

Why to use biomolecules for integrated molecular circuits? Biomolecules are the ideal candidate for the design of integrated molecular circuits due to their great potential to address critical challenges in this field. The major advantage of using biomolecules is that nature has provided a wealth of knowledge that can be leveraged to tackle the two challenges. First, self-assembly is a ubiquitous process in biology and plays a critical role in the formation of complex biological structures that are crucial to cellular function.[9–16] In fact, molecular self-assembly is increasingly important for the development of biomaterials due to its ability to construct materials with a high degree of precision and complexity.[17] The integration of order and dynamics through molecular self-assembly enables the achievement of various functions such as stimuli-responsiveness, adaptation, recognition, transport, and catalysis,[18–21] making it a promising platform for the fabrication of integrated molecular circuits. Second, charge transport plays a crucial role in enabling cellular metabolism and supporting life.[22] Nature has evolved a range of bioenergetic systems that control charge transport at the single-molecule level, offering a blueprint for utilizing self-assembly to manipulate charge transport.[23–30] Notably, unlike integrated circuits in semiconductor chips in which transistors must be fabricated in fixed periodic patterns, the integrated biomolecular circuits (IbC) could be flexible and dynamic in a solution environment (Fig. 1b as an example). In nature, an excellent example of efficient information processing and data storage is provided by the complex central neural networks of the brain.

In this review, we will first use a photosystem as an example to briefly discuss how charge transport is controlled in an electronically active biosystem in Section 2. In tandem, we emphasize the redox-active amino acids (RAAs) that are responsible for charge transport in biosystems in Section 3. We hope that these two sections can provide general ideas on how to utilize biomolecules to control charge transport at the molecular scale *via* the assistance of RAAs. In Section 4, we summarize recent advances in the modulation of charge transport within synthetic bio- or bio-hybrid molecules. Notably, this review is primarily centered on charge transport at the single molecular level, and therefore, any reference regarding the electronic properties of molecular films or self-assembled bulk materials will not be included in this review. By incorporating the charge transport in both biological systems and synthetic biomolecules from Sections 2 to 4, we present a comprehensive theoretical framework for understanding the mechanisms of charge transport across different length scales in Section 5, which serves as a fundamental and essential prerequisite for designing integrated biomolecular circuits. At the end of this review, the remaining critical questions and outlook are provided.

2. Biosystems with controlled charge transport: photosystem II (PSII) as an example

We will limit the discussion in this section to how charge transfer is mediated, facilitated and controlled in photosynthesis, drawing from the vast knowledge and experience gained through billions of years of evolution.[31–39] Admittedly, to date, we are still far from fully understanding the charge transport mechanisms in biosystems. However, remarkable advances have been made in recent years in understanding the key factors that the biosystems use to enable charge transport, which shed light on design rules for new electronically active biomaterials. In particular, the design principles for long-range charge transport in IbC can be inspired by those electronically active biosystems.

Oxygenic photosynthesis is the most popular model system for studying the charge transport in biosystems, which converts solar energy into chemical energy on Earth *via* four multi-subunit membrane-bound protein complexes, namely photosystem I (PS I), photosystem II (PS II), the cytochrome b6f complex, and F-ATPase.[40] Amazingly, the charge transfer in this biosystem

is of very high efficiency. PS I exhibits the most negative redox potential, determining the overall enthalpy of living systems.[41] In parallel, PS II generates an oxidizing agent with a sufficiently high redox potential to oxidize H_2O.[42] Notably, PS II is the primary system involved in electron transfer through its diverse protein complexes,[43] and has been widely studied for understanding electron transfer mechanisms. The structures of PS II allow the determination of important parameters such as distance and local solution environment, which are critical for exploring the factors that control electron transfer rates, which can be measured using biochemistry, molecular genetics and ultra-fast spectroscopic techniques.[44]

Light-induced oxidation of water takes place within photosystem II, located at one end of the chain, initiating the oxidation of water and subsequent electron transfer along the electron transport chain.[45] As shown in Fig. 2, upon absorption of a photon, P680 in the reaction center of PSII undergoes excitation to its higher energy state, P680*. This excited state is quickly transferred to a nearby electron acceptor, pheophytin, within a time scale of few picoseconds. The primary electron acceptor, plastoquinone A (Q_A), accepts the electron from pheophytin within 200–400 ps and transfers it to the secondary electron acceptor, plastoquinone B (Q_B), in 200 ms. Q_B undergoes two successive reductions by Q_A, resulting in the conversion of Q_B to plastoquinol, consequently replaced by a new plastoquinone. In order to complete this process, the positive charge or "hole" on $P680^+$ must be transferred to the manganese cluster *via* a redox-active tyrosine residue, Y_Z, which is responsible for oxidizing water to oxygen (O_2), involving 5 different oxidation states of the manganese cluster (Mn cluster), known as S-states, with requirement of the absorption of four photons and the reduction of 2 Q_B plastoquinones. As a result, protons are translocated into the thylakoid lumen, resulting in the formation of reactive oxygen species.[46,47] Notably, a tyrosine residue Y_Z is believed to be the transfer electrons from the water splitting Mn complex to the central chlorophyll radical P680+ (Figure) through a proton-coupled electron transfer (PCET) process, which has been extensively investigated in recent years.[48] As there exists a body of well-regarded review articles on the PCET mechanism available elsewhere,[49–52] it will not be discussed in this review. As electron tunneling in a single molecule is always distance dependent, the geometry of crucial redox cofactors and dimensions of the PSII complex are of crucial importance to enable efficient charge transport, which are tuned by hydrogen bond lengths.[53]

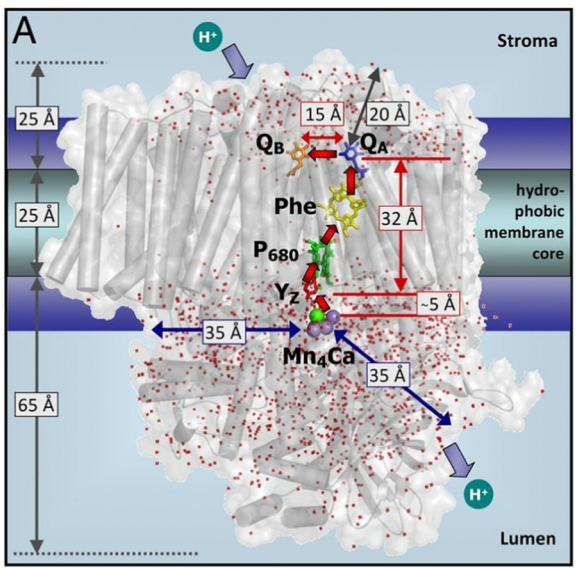


Fig. 2 Structural illustration of Photosystem II. Red arrows connect redox cofactors in the electron transport chain, including the primary electron donor (P680), the primary pheophytin acceptor (Phe), the primary (Q_A) and secondary (Q_B) quinone acceptors, and, at the electron donor side, a redox-active tyrosine (Y_Z) and the Mn complex. Reproduced with permission from ref. 45, Copyright © 2023 National Academy of Science.

Photosystems are an ideal example for demonstrating charge transport mechanisms in biosystems which involve two key charge transport strategies: (a) single-step/multi-step tunneling with charge transport distance in the nanometer scale and (b) diffusive charge transport for much longer distances. In diffusive charge transport, mobile electron carriers are required to travel several hundreds of nanometers to close the photosynthetic electron transport distance between PSII and PSI in thylakoid membranes, which is achieved by the diffusion of hydrophobic plastoquinone between PSII and the cyt b6f complex and by the diffusion of small blue copper protein plastocyanin between the cyt b6f complex and PSI.[54]

In this section, we limit the discussion on PS II, rather than including other electronically active biosystems such as the electron transfer systems in mitochondria. One reason is that that many electronically active biosystems utilize similar charge transport mechanisms as oxygenic photosynthesis, relying on redox-active machines to control and facilitate long-distance charge transport, while involving redox-active amino acids for long-range charge transport *via* a hopping mechanism. In addition, the purpose of this section is to gain insights on how to control charge transport in self-assembled biosystems towards designing IbC. However, it is not feasible to copy the protein complexes from biosystems to implement in the IbC design, due to difficulties in manipulating their conformation and engineering locations of the redox-active amino acids within them. Furthermore, we are still not clear about which amino acids in those protein complexes are not responsible for controlling charge transport and can be removed without changing the overall charge transport behavior. However, we eventually have to explore alternative approaches by designing redox-active centers in electronically active bio- or bio-hybrid materials that meet specific requirements of IbC.

3. Key redox-active amino acids

Seventy years ago, Michaelis highlighted the importance of bringing redox-active amino acids together for designing an oxidoreductase protein,[55] noting that the transfer of electrons between redox prosthetic groups took place one electron at a time. Since then, redox-active amino acids (RAAs) have been

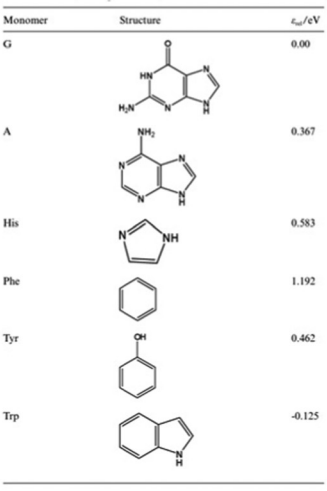
recognized as the key factors that drive electron transfer in biosystems, enabling life on Earth and its emergence. In particular, RAAs act as the ''stepping stones'' to orchestrate electron hopping and, therefore, entails long-range charge transport in electronically active biosystems. To this end, understanding charge transport *via* amino acids is critically important for designed IbC.[56] Electron flow within biological structures often requires the rapid movement of charges over long molecular distances, typically within the submillisecond range. Kinetics modeling indicates that the rates of charge-transfer reactions can be significantly improved through hopping.[57,58] Electron hopping entails efficient and rapid charge transfer across significant distances with minimal loss of free energy. This involves the utilization of redox-active amino acid side chains as intermediate donors or acceptors rather than tunneling bridges,[59] which facilitate the transfer of electrons between reactants.[60–62] Most of the redox-active amino acids have aromatic side chains to facilitate electron transfer.[63] The common structures that are observed in electron transfer (ET) in biosystems are: guanine (G), adenine (A), histidine (His), phenylalanine (Phe), tyrosine (Tyr), and tryptophan (Trp), with the relative energy of the radical cation states shown in Fig. 3a. It is noteworthy that only Phe, Tyr, and Trp are aromatic structures in the strict sense. The inherent redox properties of natural nucleobases and RAAs facilitate ET between these sites within protein–nucleic acid complexes.[64] However, DFT simulation indicates that π stacking of nucleobases and aromatic amino acids is not necessary for effective ET.[64]

The hopping mechanism requires one or more relay stations, which can transiently carry electrons or holes. The *ab initio* calculations showed that the relay stations can lower the local ionization energies to capture electron holes efficiently, which might be easily formed and broken due to their appropriate binding energies.[65] Electronic conductance of a protein is maximized when electrons are injected at the redox potential of the protein.[66] Fig. 3b summarized the binding energies and ionization energies from each different amino acid such as tryptophan (W), tyrosine (Y), cysteine (C), methionine (M), phenylalanine (F) and histidine (H) with their distance differences from each relay.[65] Extensive research has been conducted on the electron transfer properties of amino acids, such as proline and tryptophan. Tryptophan, in particular, has been the subject of many studies, including those investigating its role in cytochromes. When tyrosine and tryptophan are combined, they can interact with proteins both externally and within a folded protein, creating a tunnel for electrons to pass *via* a hopping mechanism, which has been explained by PCET.

3.1 Tryptophan

Tryptophan (Trp or W) is essential for electron transport (ET), especially long range ET, in various biological processes such as photosensing, DNA repair and photosynthesis,[67] serving as an effective hopping site in long range ET. For example, in conjugates of cytochrome P450 constructed from Bacillus megaterium (CYP102A1) with surface-bound Ru-photosensitizers, a two-step hopping through an intervening tryptophan radical that lies in the path between Ru and heme was observed during the heme oxidation. Long-range hopping through oxidized radicals of tryptophan and tyrosine has also been demonstrated in synthetic constructs of blue copper protein *Pseudomonas aeruginosa* azurin.[68] In addition, an intervening tryptophan residue was found to facilitate ET between distant metal redox centers in a mutant *Pseudomonas aeruginosa* azurin, based on transient optical and infrared spectroscopic experiments.[37] Tryptophan-accelerated Cu^{I} oxidation by a photoexcited Re^{I}-diimine on a β strand occurs rapidly within a few nanoseconds, two orders of magnitude greater than the rate of single-step electron tunneling over a donor–acceptor distance of 19 angstroms.

(a)



(b)

B3LYP	WMW	FMH	FMY	FMF	YCY	FCY	FCF
d_{short} (Å)	3.56/3.56	3.34/3.03	3.22/3.34	3.20/3.16	3.43/3.55	3.26/3.34	3.16/3.15
BE (kcal/mol)	10.9	6.2	5.8	8.1	10.9	6.6	10.2
IE_v (eV)	6.46	6.66	6.75	6.86	6.98	6.99	7.04
ΔIE_v (eV)	0.53	0.41	0.48	0.56	0.50	0.43	0.67
B3LYP	**FFC**	**FFM**	**FWM**	**FYM**	**HFC**	**YFC**	**YFM**
d_{short} (Å)	3.31/3.28	3.42/3.18	3.71/3.25	3.50/3.38	3.29/3.37	3.38/3.46	3.49/3.49
BE (kcal/mol)	7.0	12.0	6.5	8.5	5.1	4.6	8.2
IE_v (eV)	7.29	7.07	6.39	6.91	7.07	7.16	7.00
ΔIE_v (eV)	1.51	1.63	0.76	1.25	1.44	1.00	1.16

Fig. 3 (a) The relative energy of the radical cation states compared to G^+. Reproduced with permission from ref. 64, Copyright © 2010 The Royal Society of Chemistry. (b) Shortest Distances (d_{short}), Binding Energies (BEs), Vertical Ionization Energies (IE_vs) and Decreasing Values (ΔIE_vs) for different RAA complexes. Reproduced with permission from ref. 65, Copyright © 2015 American Chemical Society.

As a hopping site, the position of tryptophan in proteins plays a crucial role in ET processes. A series of linear oligoalanine peptides with a single tryptophan substitution at different positions were designed.[69] Adding a single Trp to 6-Ala peptide added a HOMO (Highest Occupied Molecular Orbital) level with 1–2 eV above that of the homo-Ala peptide and resulted in a marked reduction in the effective energy barrier (of ~1 eV) for electron tunneling. In addition, two closely spaced (3 to 4 Å) intervening tryptophans in a modified azurin resulted in a significant acceleration of long-range ET from CuI to the photoexcited sensitizer.[70] In a related work, an increase of ET rate has been noticed by replacing a surface exposed leucine located in the vicinity of the heme pocket with tryptophan in tobacco peroxidase.[71] The observed ET enhancement facilitated by tryptophan suggests that deliberate manipulation of the quantity and location of tryptophan within biomaterials could substantially impact their charge transport properties, which in turn provides a promising design approach for developing biomaterials that can be utilized in bioelectronics and biosensor applications.

Moreover, synthetic *Pseudomonas aeruginosa* azurin constructs containing multiple closely spaced Trp (or Tyr) showed that multi-step hopping confers a ~9000-fold advantage over single-step tunneling, which could support high potential hole transport across distances of 30 Å or more.[72] It is also noteworthy that, in the structures of redox enzymes, especially those involved in reactions with oxygen, Trp and Tyr residues are commonly separated by ≤5 Å.[73–76] These chains may serve as protective antioxidants by neutralizing highly oxidizing intermediates in cases where the reactions with intended substrates are disrupted.[77] Another example of a Trp "wire" for long range charge transport is demonstrated in new mutants of cytochrome *c* peroxidase (CcP), in which oxidizing equivalents were transported from the heme to the protein surface *via* such Trp "wire".[78]

In addition, a chain of conserved tryptophan residues was found to be responsible for the irradiation of cryptochrome (CRY), a broadly represented group of photosensors, which yielded reduction of an oxidized flavin cofactor. The substitutions of four key Trp residues in CRY to redox-active tyrosine and redox-inactive phenylalanine changed the light sensitivity of CRY photoreduction. In hydrolases, tryptophan residues for the repair of oxidative stress are often present in the form of long chains, whereas in oxidoreductases, they may be found in just a few chains. Proteins that feature chains of redox-active tyrosine and tryptophan residues can provide protection against protein damage by transferring oxidizing equivalents away from critical active site regions and directing them towards surface sites for scavenging.[73] Furthermore, ET from tryptophan (Trp) to heme in ferrous myoglobins was proved by ultrafast UV spectroscopy, showing the generality of Trp–porphyrin electron transfer events in heme proteins.[79]

3.2 Tyrosine

Similar to tryptophan, tyrosine (Y) is also an important redox-active amino acid in crucial physiological processes in biological systems and influences electron transfer by losing an electron to a suitable electron acceptor. The reaction can be facilitated by excitation of the acceptor using a photosensitizer.[80] In addition, PCET with tyrosine is found to be critical for various biofunctionalities. Electron hopping often utilizes tyrosine as a high potential intermediate to allow long-distance biological electron transfer, which has been observed in redox machines in photosynthesis and ribonucleotide reductase.

Tyrosine radicals are vital to ET in photosynthesis. In oxygenic photosynthesis, Photosystem II (PSII) utilizes sunlight to facilitate the catalytic oxidation of water and the reduction of plastoquinone. Two redox-active tyrosine residues, Y_Z and Y_D, participate in intricate electron transfer pathways during this process, but with different roles.[81] Y_Z is a fast electron donor that mediates ET between an oxygen-evolving complex and primary chlorophyll (chl) donor, which requires oxygen evolution.[82] Y_D is a slow auxiliary donor to the primary donor, P680, and contributes to the assembly of an oxygen-evolving complex.[83,84] Y_Z and Y_D are extensively studied due to the ability to measure tyrosine oxidation and reduction with nanosecond time resolution from liquid helium to room temperature, along with site-directed mutagenesis and the abundance and purity of PS II preparations.[85] In addition, photosynthetic organisms generate a highly oxidizing chlorophyll complex ($P680^{\bullet+}$). Reduction of this complex occurs through a pathway of electron transfer involving an electron transfer relay comprising a tyrosine (Y)–histidine (H) complex.[86,87] Tyrosine undergoes a PCET process in native proteins which are normally hydrogen bonded to neighbouring amino acids and water molecules, thereby facilitating fast reactions by providing proton acceptors in close proximity.[88] To probe the short lifetime of tyrosyl radical intermediates, transient absorption spectroscopy is used.[89]

Importantly, the ET *via* tyrosine often involves the participation of tryptophan and other redox-active amino acids. For example, the co-occurrence of tryptophan and tyrosine are commonly observed in high-potential charge transport processes, and with greater-than-average frequency in O_2- and H_2O_2-reactive enzymes.[68,90] ET from tyrosine to the tryptophyl radical was observed to have a relatively high rate in neutral environments. It is postulated that this reaction occurs *via* a series of sequential steps, including proton transfer from tyrosine to a tryptophyl radical followed by electron transfer.[91] Intra-amino acid electron transfer from tyrosine to tryptophanyl radicals is an essential step in the process leading to the active form of photolyase.[92] Similar to tryptophan, the pH level also affects the rate constant of tyrosine. The efficiency of long-range electron transfer was enhanced when in an oxidized state. Tryptophan and tyrosine are often studied together in experiments. Between pH 6 and 10, W was also found to oxidize Y and the intramolecular charge transfer rate increases as the pH is lowered over the range $6 > pH > 2$.[93] Under conditions of limited Fe^{2+} availability, a comparable reaction may occur during the assembly of the tyrosyl radical-diiron(III) cofactor of *E. coli* ribonucleotide reductase enzyme. Charge transfer between tyrosine and histidine is also common. In PS II, the transfer of electrons from the manganese-containing oxygen evolving complex (OEC) to the oxidized primary electron-donor

chlorophyll P680$^{\bullet+}$ occurs *via* a proton-coupled electron transfer process mediated by a tyrosine–histidine pair.[94]

To facilitate ET, tyrosine residues must interact closely with enzymes to enable their activation for redox reactions. These activated tyrosine residues can then be transported within the protein for participation in protein electron transfer.[95] The transfer of iron in human serum is a regulated process involving the sequential movement of iron from ferroportin to Cp (*i.e.*, ceruloplasmin, a multi-copper oxidase) and then to transferrin. In this process, a tyrosine residue present in Cp acts as a gate to prevent the formation of reactive oxygen species (ROS) when the delivery of Fe^{2+} becomes dysregulated.[96]

3.3 Histidine and cysteine

The nitrogen functional group in histidine (H) makes it have slightly different roles in charge transfer in biosystems, serving as a mediator to provide a redox relay for proton-coupled electron transfer both in biosystems and in the lab.[97] Inspired by the histidine–tyrosine pair, artificial redox relays entailed by benzimidazole–phenol dyads were proposed, with the benzimidazole models histidine and the phenol models tyrosine. By electrochemically oxidizing the phenol group in these artificial relays, a concerted two-proton transfer process was observed, as predicted.[98] These findings shed light on the mechanisms underlying proton-coupled electron transfer in natural systems and may have important implications for the design of new synthetic materials with enhanced electron transfer capabilities.

Cysteine (C) is an amino acid that contains a thiol group, which makes it a relatively uncommon molecule in electron transport. Despite this, cysteine is known to play an important role in the electron transfer processes observed in various diseases, including cancer and diabetes. In particular, cysteine is used as an antioxidant in the fluids of the body, where it can help protect against oxidative damage caused by reactive oxygen species. As a result, cysteine has become a major focus of research in the field of disease biology, with many studies seeking to elucidate the molecular mechanisms underlying its activity in various pathological studies.[99] Aromatic sulfur compounds, such as hydrogen sulfide, methanethiol, and dimethyl sulfide, have been employed to investigate how cysteine influences proton-coupled electron transfer in various complexes.[100]

4. Proposed charge transport mechanisms at different length scales

To date, three distinct electron transport mechanisms have been discovered in biosystems: electron tunneling (~2 m),[101–106] multi-step tunneling (*i.e.*, hopping) (2–10 nm)[107] and ionic diffusion (from hundreds nm to μm),[45] as shown in Fig. 4a and b. Single-step tunneling is limited within several nanometers and the current can drop by a factor of $\sim 10^8$ beyond 2 nm.[108] In contrast, for charge transport with a longer distance, hopping is required. However, the switching from tunneling to hopping remains unclear. Moreover, there have been reports on longer electron transport distances for tunneling (>2 nm) and hopping (>10 nm),[107] leading to a question on whether there exist limited distances for the two electrons. In addition, electron transport could be attributed to the combination of all three mechanisms at distances of 2–10 nm, which has yet to be explored.

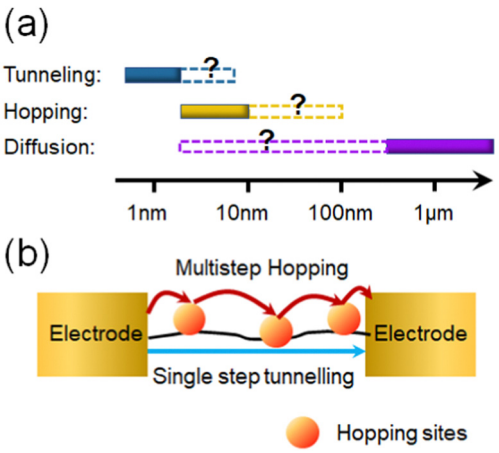


Fig. 4 (a) Electron transport mechanism in biosystems. (b) Schematic illustration of single step electron tunneling (lower pathway) and multi-step tunneling (*i.e.*, hopping) (upper pathway) *via* redox active groups serving as an effective hopping site.

4.1 Short range charge transport

For tunneling (typically <2 nm),[107] an electron crosses the molecule in a single step without appreciable residence time on it. In ballistic electron transfer, the electron transmission probability is 100%, yielding a distance-independent conductance of $G_0 = 2e^2/h$ (*i.e.*, quantum conductance) for electron tunneling, where e is the charge of one electron and h is the Planck constant. However, the quantum conductance has only been experimentally observed in a single chain of metal atoms, such as gold.[109] For electron transfer between two metal electrodes through a non-metal molecule *via* single step tunneling, the transmission probability is much lower than 100%. In addition, exponential decay of conductance as a function of distance is observed.[110] In the tunneling regime, according to Simmons theory,[111] molecule conductance follows $G = G_0 e^{-\beta L}$ (where β is the decay constant). The decay constant is the key parameter that determines the tunneling conductance and is varied by the energy barrier height (*i.e.*, φ) between the electrodes and molecules at low bias $\left(\beta = \frac{2\sqrt{2m\varphi}}{\hbar}\right)$.[112]

On the other hand, the electron tunnelling between two unbound redox centers in a solution environment is usually referred to as a superexchange process, which is explicable by Marcus theory.[113] The electron tunneling arises from the coupling of the electron wavefunctions between the donor and acceptor, with an exponential decay in the electron tunnelling rate with distance through insulating proteins.[33] Importantly, as Marcus Theory emphasized on biological redox reactions, a term named reorganization energy λ was also introduced. The impact of types of amino acids and their conformations on

superexchange pathways could be included for theoretical calculation. More importantly, the solvent effect on charge transfer rate is also included in the terms of reorganization energy λ in Marcus theory.[114] Previous theoretical and experimental studies have suggested that λ is proportional to either Pekar factor or Lippert-Mataga factor,[115] which are dependent on the high-frequency and static dielectric constants.[116] In contrast, the solvent effect was not considered in electron tunneling in the metal–molecule–metal configuration as discussed above. Indeed, it was found that the single molecule conductance is only slightly affected by changes in the solvent in metal–molecule–metal configuration.[117] Furthermore, direct measurement of single molecule conductance of benzenediamine in organic solvent showed that the charge transfer is correlated to neither the dielectric constant nor the dipole moment of the solvent.[118]

4.2 Long range charge transport

Studies of kinetics have revealed that electron tunneling through proteins covers a distance up to approximately 2.5 nm.[101] Electron tunneling distances measured *via* the scanning tunneling microscopy break junction method (STM-BJ) and the mechanically controllable break junction (MC-BJ) show a comparable range, roughly below 2 nm.[102–106] For charge transport with longer distance, multi-step tunneling (*i.e.*, hopping) is required, which involves multiple redox centers as the hopping sites. Interestingly, electrical resistance measurement of long conjugated molecular wires (conjugated oligophenylene imine, OPI) showed that there existed a "critical length", roughly 4 nm, above which the electron transport mechanism switched from tunneling to hopping, even with the same type of molecules.[119,120] More importantly, the site-specific distribution only had a small effect on tunneling conductance, but, in contrast, greatly affected the hopping conductance.[119] Similar tunneling to hopping transition was also observed at around 3 nm in oligo(aryleneethynylene) (OAE) derivatives of up to 6 nm,[121] as well as other systems (Fig. 5).[122–124] These results indicate that the arrangement of redox centers might only be an effective strategy for long range charge transport (>4 nm). It is noteworthy that the conductance of a self-assembled molecular film was significantly enhanced by incorporation of metal centers as the hopping sites with electron traveling distance above 10 nm.[125]

In contrast to electron tunneling, hopping is less length dependent, or sometimes even length independent. More importantly, the hopping mechanism exhibits a strong temperature dependency, which could originate from Arrhenius-type thermal activation explained in Marcus theory.[126–128] As discussed in Sections 2 and 3, long range charge transport *via* hopping is commonly observed in biosystems, in which redox-active centers (*e.g.*, RAAs) serve as hopping sites.[129,130] Tyrosine and tryptophan have redox potentials of around 1 V *versus* the Normal Hydrogen Electrode (NHE) and histidine has those of 1.17 V, making them suitable for facilitating electron hopping.[131–134] Despite the considerable amount of research on electron transfer rates through hopping in biological systems

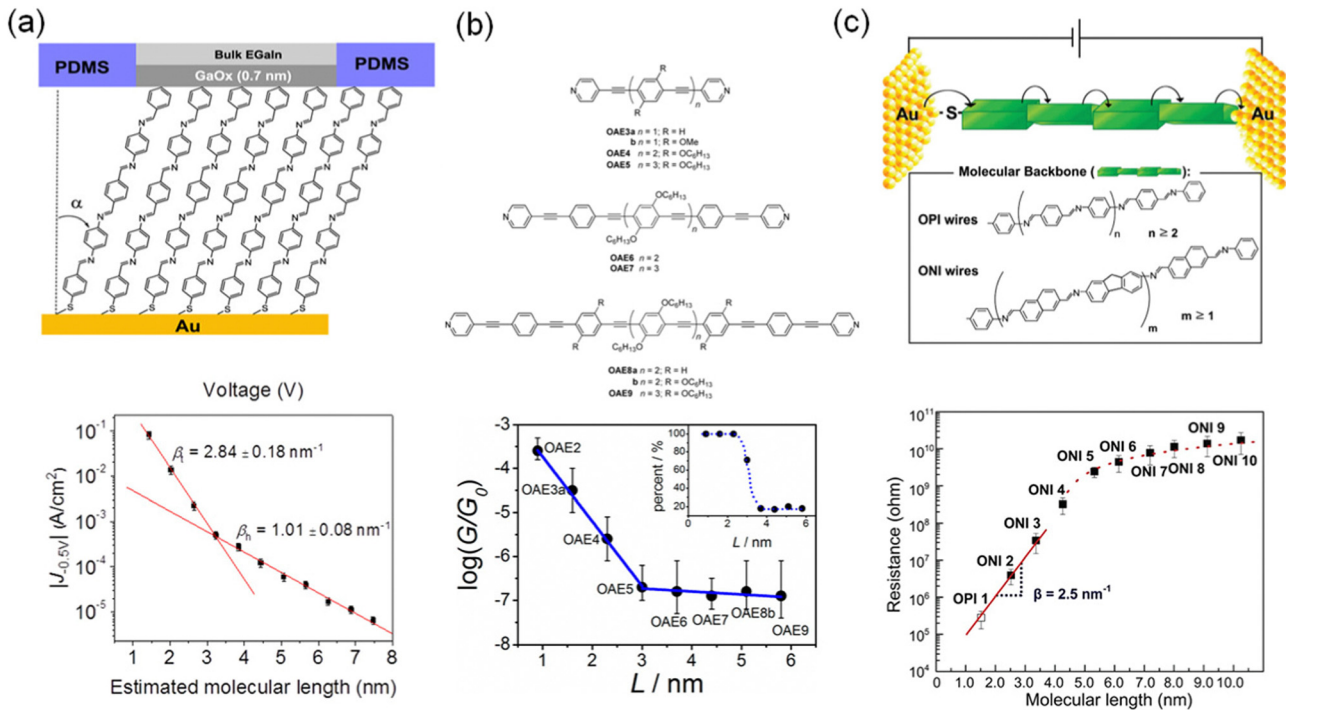


Fig. 5 Tunnelling to hopping transition observed in various conjugated molecular systems (a) oligophenylene imine, OPI. Reproduced with permission from ref. 120, Copyright © 2016 American Chemical Society; (b) oligo(aryleneethynylene), OAE. Reproduced with permission from ref. 121, Copyright © 2013 American Chemical Society; (c) oligonaphthalenefluorene imine, ONI. Reproduced with permission from ref. 124, Copyright © 2010 American Chemical Society.

measured by time-resolved spectroscopy, the relationship between conductance/resistance and distance has been rarely obtained, due to the difficulty of applying an external electrical field to the redox-active molecules using electrodes.[135]

4.3 Beyond long range charge transport

A practical solution for long range charge transport beyond a "wire-like" multi-step hopping mechanism is by ionic charge transport in solution, which relies on the diffusion of charge carriers that can be modulated by concentration gradient, temperature, and activation energy for diffusion.[136,137] Ionic charge transport is basically the reason why you get an electric shock when electricity touches water. Clearly, the charge transport distance can easily surpass the nanometer scale and reach even the meter scale, which is sufficient for long range charge transport in any type of IbC.

Ionic charge transport has been widely used for change transport above the nanometer scale (*e.g.*, >100 nm) in biosystems. The efficient ionic charge transport is often facilitated by confining and directing the transport in specific ion channels. A well-known example is the signal (*i.e.*, action potentials) transport in neutral systems by the movement of ions through ion channels that results in voltage changes, with traveling distances as much as one meter within milliseconds.[138] In photosynthesis, mobile electron carriers are required to travel several hundreds of nanometers to close the photosynthetic electron transport distance between PSII and PSI in thylakoid membranes, which is achieved by the diffusion of hydrophobic plastoquinone between PSII and the cyt b6f complex and by the diffusion of small blue copper protein plastocyanin between the cyt b6f complex and PSI.[54]

Unquestionably, at the millimeter scale and beyond, neither single step nor multi-step electron tunneling (*i.e.*, tunneling and hopping) is an option for charge transport, due to the significant conductance decay at such long distances, and charges have to be transported by diffusion of mobile charge carriers. However, at much shorter distances, (*e.g.*, <10 nm) to distinguish and determine the main charge transport mechanism becomes challenging. Or both mechanisms could contribute to short range charge transport *via* redox-active groups. Recently, Sato *et al.* proposed a diffusion-cooperative model to elucidate the charge transport mechanism in nonconjugated redox-active polymers in the presence of electrolytes (Fig. 6a).[139] Besides electron hopping, the Brownian motion of redox centers bound to the redox-active polymers was found to contribute to the charge transport in a diffusive manner. Recently, such diffusion assisted charge transport has been observed in a percolating network of open-shell sites in nonconjugated radical polymer film (Fig. 6b).[140] When the polymer film was heated above the glass transition temperature and cooled back down into the glassy state, conductivity comparable with chemically doped conducting polymers was achieved. With the capability to transport charge in the solid state, diffusion assisted charge transport has been applied to the fabrication of redox-active polymer based redox flow batteries.[141]

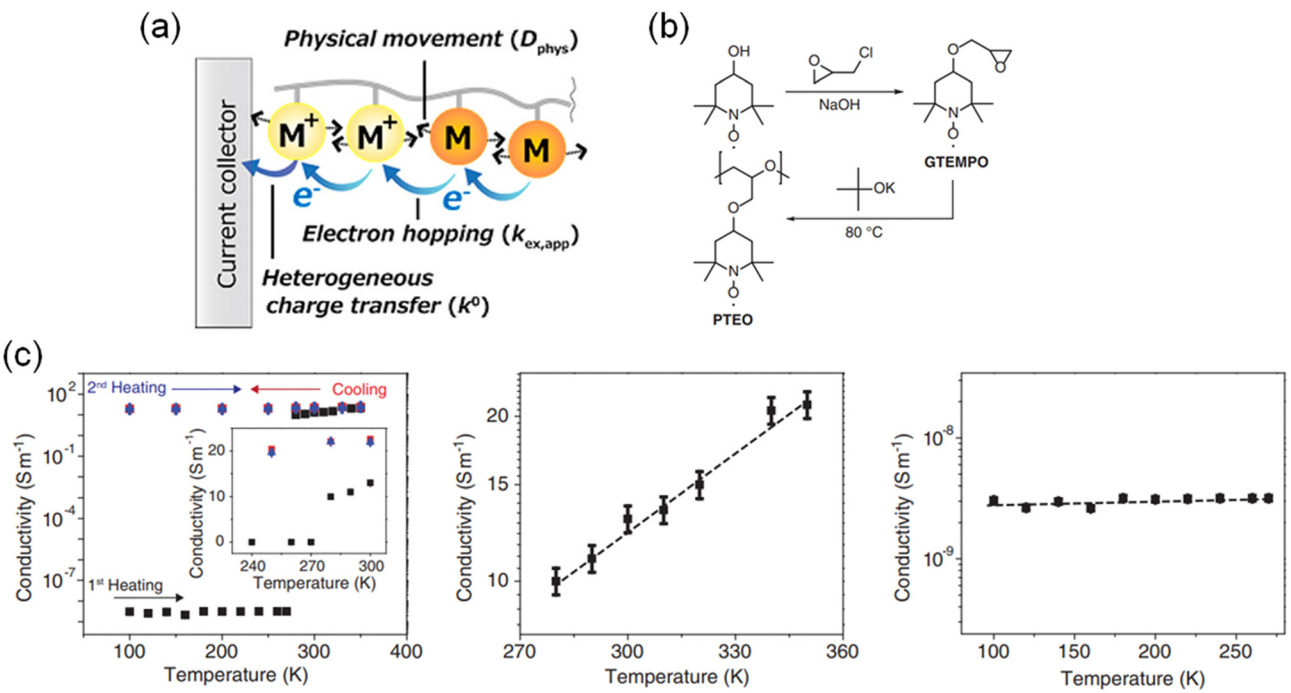


Fig. 6 (a) Scheme for electron transport in a diffusion-cooperative model *via* a redox-active nonconjugated polymer. Reproduced with permission from ref. 139, Copyright © 2018 American Chemical Society. (b) An example of a nonconjugated radical polymer, poly(4-glycidyloxy-2,2,6,6-tetramethylpiperidine-1-oxyl) (PTEO), with high electrical conductivity enabled by a percolating network of open-shell sites as redox centres. (c) Electrical conductivity as a function of temperature for PTEO. Reproduced with permission from ref. 140, Copyright © 2018, The American Association for the Advancement of Science.

5. Conclusions and outlook

Key questions to be addressed:

1. Can a molecular transistor gate be controlled individually in IbC? To control charge transport not only refers to changing the current flow directions in self-assembled systems, but also means the ability to tune the molecular conductance, and ideally, to turn on/off the current at will. One example is to change the 0/1 status of a molecular transistor individually within the integrated molecular circuits. To apply the gate field effectively, the gate molecule must be within a distance comparable to the size of a molecule. However, this is yet to be achieved.[108] Currently, an alternative approach is to apply an electrochemical gate to the entire solution.[142–146] While this approach is suitable for examining the electronic characteristics of a molecular transistor and exploring nanoelectrochemistry and interfacial electrochemistry,[147] it lacks the ability to regulate individual transistors within integrated molecular circuits. Maybe designing a redox-active chain like in biosystems will provide possible solutions for individual control of molecular electronic components in the future.

2. Is it required to "wire" all the molecular electronic components in IbC? Even though molecular electronical elements have been extensively explored in recent decades, a basic prototype of self-assembled IbC has yet to be crafted in the lab. While the molecular electronical elements seem to be ready for integration, how to integrate them *via* molecular conducting wires in an organized structure becomes the key bottleneck. A fundamental question to ask before wiring the molecular electronical elements is: do we really need to wire them? While electron tunneling is what we are always trying to avoid in semiconductor chip fabrication, it is the governing charge transport mechanism at the molecular scale and, therefore, in IbC. It is known that there is an exponential decay in electron tunnelling between two redox centers.[148] If the two redox centers are covalently bonded, the tunneling rate ($\beta \approx 0.9$ Å) is much faster than tunnelling through vacuum ($\beta \approx 2.8$ Å).[33] It was even found that the single molecular conductance could reach 70% of the quantum conductance when a ferrocene-based organometallic molecular wire was used.[149] In short, for electron tunneling, a molecular wire assists it, rather than enables it. To this end, it is possible for two molecular electronic elements to work together to enable the desired function by simply putting them close to each other, *via* interactions such as electrostatic interactions, van der Waals forces, and hydrogen bonding.

3. Can DNA origami deliver its promise in self-assembled molecular electronics? DNA origami has shown the greatest promise to date. It has shown capability for the construction of complex nanostructures with molecular precision. DNA origami can be programmed using staple sequences, allowing for computer-aided design and universal synthesis protocols.[150] This programmability makes DNA origami a user-friendly technology. DNA origami synthesis achieves a higher yield and robustness, due to the high cooperativity of scaffold-staple interactions during origami folding. Since the initial demonstration of 2D "smiley faces", DNA origami has progressed to synthesize virtually any arbitrary shape with user-defined asymmetry, cavities, or curvatures. However, long-range charge transport in DNA is still challenging.[151] In this regard, the combination of DNA origami and conductive molecules including redox-active proteins could be a potential solution. For example, DNA origami can be used as scaffolds for assembling and organizing conductive molecules thanks to the versatility to chemical modification along DNA stands. In this context, complex molecular circuits could be crafted.

In this review we focus on the control of charge transport in self-assembled systems, including both biosystems in nature which we can learn from, but also synthetic molecular systems, aiming to provide insights for solving challenge (1). However, to realize integrated biomolecular circuits, both challenge (1) and (2) need to be addressed. To solve challenge (2) requires huge progress in the field of self-assembly. To date, precise control over the self-assembled conformation is yet to be achieved. In biosystems, all the electronically active protein complexes are formed *via* four levels of hierarchies with increasing complexity: primary structure, secondary structure, tertiary structure, and quaternary structure. In contrast, recent progress in artificial self-assembled materials (*e.g.*, supramolecular assembly) only allows for limited control of secondary structure (*e.g.*, β sheet formation and 1D assembly), by engineering non-covalent bonding and varying thermal dynamic conditions.[152–162]

Conflicts of interest

There are no conflicts to declare.

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