Charge transport at the protein-electrode interface in the emerging field of BioMolecular Electronics

Tracy Q. Ha[‡a], Inco J. Planje[‡*a], Jhanelle R. G. White[a], Albert C. Aragonès[b], Ismael Díez-Pérez[*a]

[a] *King's College London, United Kingdom*
[b] *Max Planck Institute for Polymer Research, Mainz, Germany*

Abstract

The emerging field of BioMolecular Electronics aims to unveil the charge transport characteristics of biomolecules with two primary outcomes envisioned. The first is to use nature's efficient charge transport mechanisms as an inspiration to build the next generation of hybrid bioelectronic devices towards a more sustainable, biocompatible, and efficient technology. The second is to understand this ubiquitous physicochemical process in life, exploited in many fundamental biological processes such as cell signalling, respiration, photosynthesis, or enzymatic catalysis, leading us to a better understanding of disease mechanisms connected to charge diffusion. Extracting electrical signatures from a protein requires optimised methods for tethering the molecules to an electrode surface, where it is advantageous to have precise electrochemical control over the energy levels of the hybrid protein-electrode interface. Here, we review recent progress towards understanding the charge transport mechanisms through protein-electrode-protein junctions, which has led to the rapid development of the new BioMolecular Electronics field. The field has brought a new vision into the molecular electronics realm, where complex supramolecular structures such as proteins can efficiently transport charge over long distances when placed in a hybrid bioelectronic device. Such anomalous long-range charge transport mech-

[‡]These authors contributed equally.
[*]Corresponding author, email inco.planje@kcl.ac.uk
[*]Corresponding author, email ismael.diez_perez@kcl.ac.uk

anisms acutely depend on specific chemical modifications of the supramolecular protein structure and on the precisely engineered protein-electrode chemical interactions. Key areas to explore in more detail are parameters like protein stiffness (dynamics) and intrinsic electrostatic charge, and how these influence the transport pathways and mechanisms in such hybrid devices.

Keywords: BioMolecular Electronics, single-protein junctions, protein films, electron transport, electron transfer, electrode surface, bio-engineering, coupling, hybridisation, protein-electrode interface, contacts, STM, STM-BJ

Proteins are vital charge mediators in nature [1, 2]. Although the amino acid building blocks are mostly insulating [3], folded proteins have remarkable long-range charge transfer properties [4]. Proteins fulfil many critical functions in cellular processes governed by electron movement, such as respiration [5], photosynthesis [6], and enzyme catalysis [7]. The field of BioMolecular Electronics studies the charge transport properties of proteins and other biomolecules with two main objectives. The first is to design and build the next generation of hybrid bioelectronic interfaces towards more efficient and biocompatible electronic devices. The second is to enhance our understanding of medicinal chemistry by pinpointing the chemical interactions that lead to biological electron transport. As an example of the latter, the mitochondrial electron transport chain has been identified as a critical ingredient in the bioenergetics during cancer cell metastasis [8]. Both the above aims involve understanding and manipulating nature's efficient bioelectricity, with a prominent example being the outstanding bacterial circuitry based on multi heme cytochrome wires [9]. The field outcomes foresee societal impact like, for instance, on highly applied technological fields designing bio-compatible and non-invasive bioelectrical sensors for point of care detection of analytes in the body.

The majority of (electronic) studies on proteins to date have focused on solution-based electron transfer and catalytic properties [10, 11, 12, 13]. An excellent overview of the electrochemical characterisation of surface-bound proteins can be found elsewhere [14]. Pioneering work using surface-probe techniques and electrochemistry focused on the details of the protein-electrode interface [15, 16, 17]. To further advance this field, a key focus area is to study the properties beyond the bulk average, to gain insight into the details outlined above. To achieve this aim, we can decrease the number of proteins under investigation by introducing a second "small" electrode, which serves as the top contact for a group of proteins down to even a single protein. These electrode-protein-electrode configurations have been reviewed in detail [13, 18, 19].

Our focus here is to review the latest experimental developments on designing the protein-electrode interfaces, highlighting their essential role on the re-

sulting charge transport mechanisms through these nanoelectronic protein junctions. We start with a brief overview of experimental techniques for the fabrication of electrode-protein-electrode junctions. Next, we discuss these junctions using an energy-level framework, in which two crucial parameters dominate the final transport properties of the junction. The first is the offset (or alignment) between the energy levels of the protein and those of the electrodes (Protein energy levels). The second is the extent of orbital mixing (i.e. hybridisation) between the orbitals of the protein and the electrodes at the interface (Bioengineering the protein-electrode interface). We then discuss the still largely unanswered question of how electrons flow through biomolecules over long distances. Finally, we summarise our discussion and share some prospects for what will surely be the next, fascinating few years of rapid development of the BioMolecular Electronics field.

Tools to study protein charge transport

The metal-molecule-metal configuration has been used extensively to study charge transport in a wide variety of synthetic organic molecules in the field of molecular electronics [20]. Experimental methods to create nanoscale electronic junctions have been discussed in great detail by Xiang *et al.* [21]. Depending on the technique, these junctions consist of a (mono)layer of molecules, often referred to as ensemble junctions, or just a few (or even single) molecules. Here, we highlight a few approaches that have been successfully used to measure the charge transport properties of proteins.

Ensemble protein junctions

The liquid metal junction using a mercury drop has been around for a long time [22]. Recently, Nakamaru *et al.* used it to measure the light-dependent electrical properties of cytochrome c [23], see Figure 1A. They found that these protein junctions behave as efficient light-sensitive photoconductors and hence can act as photoelectrochemical switches. Chiechi *et al.* later developed a more

robust version exploiting non-Newtonian eutectic gallium-indium (EGaIn) [24]. An example is given in Figure 1B, where a layer of ferritin molecules is trapped between a gold bottom electrode and the eutectic drop, see The enigma of charge transport mechanisms in proteins for further details.

Electrophoretically produced gold nanowire-based junctions have successfully been exploited to study charge transport in nanoscale protein ensembles, see Figure 1C. This method relies on forming self-assembled monolayers of proteins, after which gold nanowires are electrophoretically deposited on top to function as the second electrode [25]*. Figure 1D shows how the probe of an atomic force microscope can be used to form protein junctions when coated with a conductive material. This probe then serves as the top electrode to contact a small area of a protein layer, or even individual proteins depending upon sample preparation conditions. Here, a laser is deflected off the micro-cantilever to measure the force and current of the junction simultaneously [26].

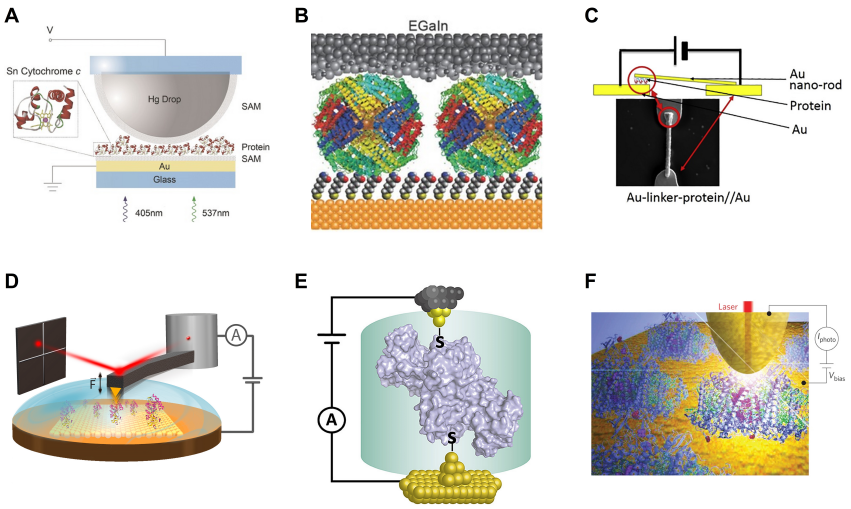

Figure 1: **Experimental techniques in the field of BioMolecular Electronics.** (A) A monolayer of proteins self-assembled onto a gold electrode using a mercury-drop as the top electrode. Reprinted with permission from reference [23]. (B) Ensemble protein junction using eutectic gallium-indium. Reprinted with permission from reference [27]. (C) Ensemble protein junction using a suspended gold nanowire as the top electrode contact. Reprinted with permission from reference [25]*. (D) Atomic force microscopy using a conductive probe to measure the current and force of a protein junction simultaneously. (E) A single-protein junction using the electrodes of a scanning tunnelling microscope. Reprinted with permission from reference [28]**. (F) Scanning near-field optical microscopy for the measurement of individual protein photocurrents. Reprinted with permission from reference [29].

Single-protein junctions

Scanning tunnelling microscopy (STM) is a crucial method for studying single-protein charge transport behaviour. Artes *et al.* have used STM-based single-protein junctions extensively to study the redox-related charge transport properties of single azurin proteins [30]. In particular, they reported the first single-protein junction example using the dynamic STM break-junction technique [31]**, showing unexpectedly large conductance values. Moreover, such single-protein devices displayed a particular electrochemically enhanced transport behaviour supported by the redox properties of the protein [32]. They also

demonstrated controlled redox switching using an electrochemical STM (EC-STM) setup [33].

Zhuang *et al.* recently used the same STM-based single-protein approach to study the dynamics of an enzyme [28]**, see Figure 1E. Their results show that the presence of NAD co-enzyme, responsible for the enzyme activity, results in a structure-induced reduction of the electron transport pathway. This structural change leads to an increase in the junction current, thus suggesting a relationship between charge transport and enzymatic activity. Zhang *et al.* also reported on the activity of enzymes in a single-protein junction, which they monitored directly using the electrical current of the STM [34]**. They showed that large current fluctuations result from changes in the electrical coupling due to structural changes in the protein matrix, yielding information on the enzyme activity of the polymerase.

Using a different approach, Gerster *et al.* used scanning near-field optical microscopy to measure the photocurrent of a covalently bound single photosynthetic protein [29], illustrated in Figure 1F. These examples set the stage for integrating the enzyme-electrode interface in the design of hybrid bioelectronics. They also highlight the importance of the protein-electrode interface alignment and hybridisation in the energy-level picture mentioned in the introduction, which we will explore in the following two sections.

Protein energy levels

The molecular energy levels of a (redox) protein dictate the electron transmission through a biomolecular junction. Particularly important is the position of these energy levels with respect to the Fermi energy (E_F) of the contacting electrodes. Precise control over the relative position of these energy levels using a gating electrode is a key tool for studying the details of the transport mechanisms in biomolecular junctions, see Figure 2A. In this example, at gate potentials away from the protein redox midpoint (both at -0.4 V and +0.2 V versus an AgCl reference electrode), the junction current is relatively low. This

low current stems from the relatively large offset in energy between the low-lying protein redox level and the electrode Fermi levels, thus imposing an off-resonant tunnelling scenario. In contrast, the junction current is at a maximum when this redox energy level is aligned with E_F, at a gate potential close to the protein redox midpoint of -0.1 V vs AgCl.

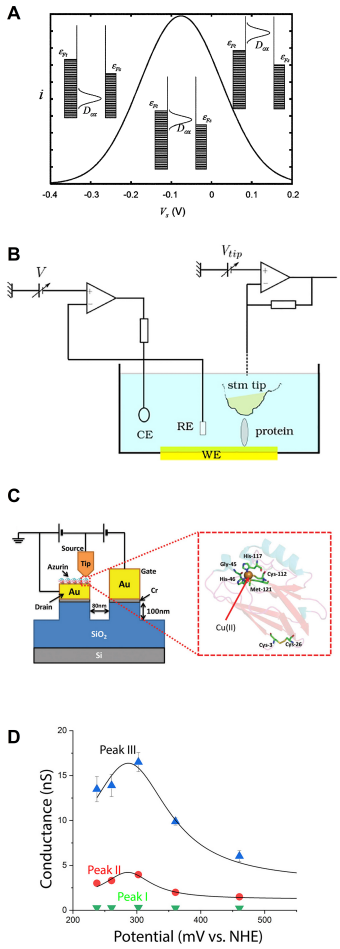

Figure 2: **The energy levels of the protein can be aligned to the Fermi level of the electrodes using an electrochemical gate.** (A) An energy-level framework of the gating effect. The applied gate voltage shifts the energy levels of the protein into and out of resonance, enhancing the junction conductance at the resonant potential. Reprinted with permission from reference [35]. (B) Schematic setup of an electrochemical scanning tunnelling microscope. Reprinted with permission from reference [36]. (C) A solid-state protein ensemble junction, with a conducting probe atomic force microscope used as a gating electrode. Reprinted with permission from reference [37]. (D) The conductance of streptavidin depends on the electrochemical cell potential. Reprinted with permission from reference [38]**.

The EC-STM provides an efficient gating method [39], allowing precise control over the relative position of the protein-electrode energy levels, see Figure 2B. An electrochemical functionality is added to the standard STM setup using a bipotentiostat configuration. Using this setup, one has precise control over the electrochemical potential of the substrate and the STM tip independently. In turn, this control allows for probing the relevant (non)redox molecular energy levels, from which a picture can be drawn that highlights the chemical electron pathways in a protein supramolecular structure. Nongjian Tao first demonstrated such control using a redox metalloporphyrin bound to an atomically flat electrode [40]. It was first used in a single-protein configuration by Alessandrini *et al.* who reported a redox-dependent tunnelling current for individual azurin proteins bound to a gold surface [41].

Kayser *et al.* recently reported a different approach using a solid-state side-gated transistor configuration combined with conducting probe atomic force microscope [37], as shown in Figure 2C. They combined their gating experiment with a variation in the work function of their substrates to map out the resonance positions of different azurin-based junctions. Zhang *et al.* took a different approach and measured the charge transport characteristics of proteins that have no redox activity, see Figure 2D. They used a combination of rest potentials and different electrode materials (also making use of differences in metal work functions), where they found peculiar resonance peaks in streptavidin, immunoglobulin E, and Φ29 polymerase, despite their lack of metal redox centres [38]**. The latter suggested the critical role of aromatic amino acids in a protein backbone, which might act as effective electron pathways across the protein structure.

Bioengineering the protein-electrode interface

As discussed above, the efficiency of charge transport through (bio)molecular junctions strongly depends on both the alignment and coupling of the energy levels at the molecule-electrode interface. This complex problem has been

thoroughly studied in simpler molecular junctions using synthetic molecules [42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52]. The optimisation of the electrical contact, i.e., finding ways for low energy barrier charge injection, in a hybrid protein-electrode interface is critical in the observed final electrical characteristics of the protein junction. One of the major issues in nano-biotechnology is to reach protein-compatible designs for this integration.

Figure 3A illustrates a Lorentzian function of frontier molecular orbitals in a molecular junction relative to the band energies of the metal, E_F. The magnitude of electron transmission increases with increasing hybridisation (i.e., the degree of orbital mixing) of the energy levels of the protein and the electrode. The hybridisation refers to the chemical mixing between energy levels of the proteins and the metal electrode surface. It is often referred to as the degree of protein-electrode coupling. A better (chemical) coupling broadens the Lorentzian curve (Γ) and increases the area under the curve, typically resulting in higher electron transmission. Crucially, the hybridisation can be controlled by appropriate and specific chemical modifications to both the electrodes and the proteins under investigation. A delicate balance between high hybridisation (high transmission) and protein folding preservation is at the heart of the protein-electrode interface design.

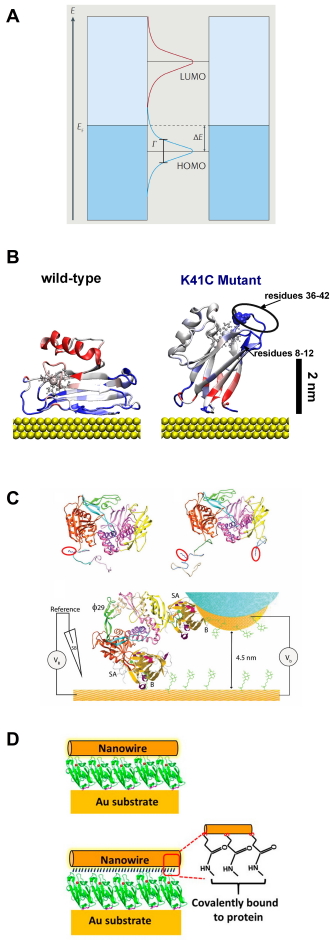

Figure 3: **The (chemical) details at the protein-electrode interface strongly influence the efficiency of charge transport.** (A) A Lorentzian plot of the transmission function plotted against energy, which shows the conductance of hybridised molecular orbitals of a single molecule relative to the band energies of a metal. Reprinted with permission from reference [51]. (B) A molecular dynamics simulation to investigate the effect of point mutagenesis on the orientation of a protein. Reprinted with permission from reference [53]*. (C) Top: Φ29 polymerase with one (left) or two (right) specific lysine contacts. Bottom: Streptavadin immobilised on electrodes via thiolated biotin anchoring groups, which encloses a Φ29 polymerase. Reprinted with permission from reference [34]**. (D) An ensemble of proteins trapped between a gold substrate and a gold nanowire. Reprinted with permission from reference [54]**.

Pioneering work by Ulstrup *et al.* has contributed significantly towards enhancing the protein-electrode coupling. They showed that azurin molecules adsorbed onto gold electrodes yield a stable, functional monolayer, either directly through surface cysteine residues [15] or via alkanethiol monolayers [55], both displaying controllable levels of coupling of the redox centre with the surface electrode. Several contributions towards the design of hybrid bio-interfaces expanded on these pioneering reports. Examples include further electrode surface modification with monolayers of a variety of functional groups [56, 57, 58, 59, 60, 61], bioengineering contacts [58, 61, 62], and the use of chemically linked redox mediators and relays [56, 63]. These methods aim to improve orientation, stability, and establish electrical interactions between the redox cofactor and the electrodes.

A different approach to enhance the interface coupling is to introduce chemical modifications to (the surface of) the protein amino acid matrix, via point-site mutations. In such a case, the highly cooperative nature of the protein folding structure can simultaneously affect the protein-electrode coupling and the electron pathways inside the protein backbone, ultimately dictating the charge transport characteristics of the protein junction. Ruiz *et al.* showed that a single point-site mutation at the natural protein docking area in a copper-azurin junction switches the charge transport mechanisms from the redox-enhanced current in the wild-type to an off-resonant one in the mutated variant [64]**. A follow-up theoretical analysis of the latter reveals that such modifications might control the orientation at the protein-interface [53]*, as depicted in Figure 3B.

Zhang *et al.* have bioengineered specific contacts to a Φ29 polymerase protein [34]**. Figure 3C shows the modified protein in the top, either with a single thiolated contact, or two of these specific anchoring units. In the bottom part, streptavidin is tethered to gold electrodes using these thiolated biotin groups. A higher junction conductance is measured when two specific contacts are used, attributed to the result of biotin-binding into a deeper pocket of the streptavidin. In turn, this configuration provides a more efficient injection of charge carriers into the hydrophobic interior of the protein. Using specific contacts to modify

electrodes also eliminates unpredictable orientations of proteins at the interface that yield protein junctions with low electrical activity.

Using the gold-nanowire method, Fereiro *et al.* showed how the coupling strength of the chemical linkers can act as a switch between different electron transport mechanisms through a protein layer [54]**, see Figure 3D. Similarly, the same group reported the immobilisation of cytochrome c using the surface-exposed cysteine 104 residue that binds covalently to gold electrodes, forming an oriented, robust monolayer that allows for electron transport at room and cryogenic temperatures [65]*. Mukhopadhyay *et al.* report the reproducibility of current densities of three different proteins on SAM modified electrodes within six types of junction configurations performed in different laboratories across the world [25]*. The study concludes that the protein-electrode interface can dominate the efficiency of electron transport without altering the mechanism.

The enigma of charge transport mechanisms in proteins

Understanding the mechanisms of charge transport in biomolecular entities is inherently embedded in the aims of BioMolecular Electronics, as outlined in the introduction. In electronic junctions of relatively simple organic molecules, the transport mechanisms are mainly influenced by the length of the tunnelling barrier (defined by the molecular length), and the temperature [66]. Shorter molecules mostly display off-resonance tunnelling, where the transport is not affected by the surrounding temperature, while longer molecules tend to display a thermally-activated hopping mechanism. This effect is illustrated in Figure 4A. The tunnelling current depends exponentially on the width of the barrier (represented by the molecular length), whereas the length dependence is negligibly small in the hopping mechanism.

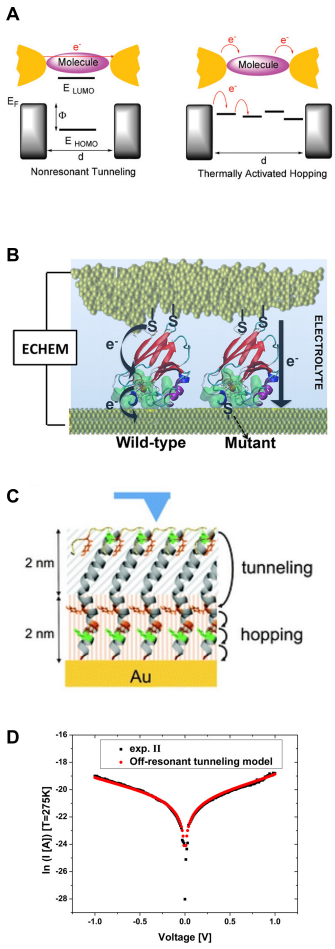

Figure 4: **Anomalous thermally-independent long-range electron charge transport is the dominant mechanism in biomolecular junctions.** (A) Schematic representation of non-resonant tunnelling (left) and thermally activated hopping (right). Reprinted with permission from reference [67]. (B) Mutagenesis of azurin molecules changes the transport mechanisms from sequential tunnelling to fully coherent tunnelling. Reprinted with permission from reference [64]**. (C) Self-assembled monolayers of thiolated protein nanowires from *Geobacter sulfurreducens* demonstrate a hybrid mechanism along different parts of the amino acid chain. Reprinted with permission from reference [68]. (D) Theoretical models reveal that the mechanism strongly depends on the redox-active metal centre in azurin junctions. Reprinted with permission from reference [69].

However, in biomolecular junctions, the transport mechanisms do not align with either of the two scenarios above. Instead, an anomalous temperature-independent long-range transport mechanism prevails in most protein junctions consisting of wild-type proteins [64]** [70]*. Although the details of the mechanisms are still unknown, several hypotheses revolve around particular "energy state-assisted" tunnelling processes such as a sequential two-step tunnelling with partial structure relaxation [71], or a "flickering" mechanism describing a form of "efficient hopping" assisted by the particularities of the protein dynamics [72]. Whichever mechanism, they strongly depend on complex factors, such as the protein supramolecular structure and its conformation in the nanoscale gap. Kumar *et al.* showed how the charge transport mechanism in monolayers of ferritin molecules depends on the iron content of the molecules [27]. Similarly, Garg *et al.* found that the presence of heme chains within the protein structure as characteristic in multi heme cytochrome systems boosts conduction efficiency by several orders of magnitude [73].

Likewise, Ruiz *et al.* reported that by exchanging the natural lysine at the 41 position for an additional cysteine [64]**, the mechanism of charge transport changed from two-step sequential tunnelling to off-resonant tunnelling, where the redox energy state "vanishes" from the electron pathway, see Figure 4B. Similar outer protein mutations have been used to control the orientation of the protein junction, which, in turn, dictates the final electron pathway [74]. Cosert *et al.* took this approach to functionalise protein nanowires from *Geobacter sulfurreducens* and used these to form self-assembled monolayers on gold substrates, see Figure 4C. They showed that tunnelling prevails in the top part of the layer, where no aromatic residues are present, whereas hopping takes over in the presence of such aromatic rings in the bottom part of the layer [68].

Despite significant challenges in theoretical modelling of charge transport through large, complex molecules such as proteins, Valianti *et al.* reported fitted trends through several azurin junctions [69], see Figure 4D. They found that the copper centre in azurin seems responsible for the efficient long-range charge transport characteristics. Romero-Muñiz *et al.* pioneered the first calculation

of an entire protein electronic structure [75], concluding that the oxygen-based state distributed throughout the protein core might also be involved in the long-range transport displayed in these systems. The same authors recently reported calculations of Landauer coherent transport through a single-protein junction that highlights the limitations of a pure off-resonant tunnelling mechanism in describing charge transport in such complex junctions and pointing to other possible missing ingredients [76]. In this vein, Papp *et al.* recently showed that decoherence could be a critical parameter for efficient biological transport [77]. This decoherence results from strong coupling in vibrational states of the protein supramolecular structure. These theoretical reports, and others beyond the scope of this review, highlight the gaps in our current understanding of the detailed charge transport mechanism through proteins and other biomolecules.

Conclusions and outlook

In this review, we have summarised recent progress in the field of BioMolecular Electronics, with a specific focus on the main mechanistic features that are characteristic in the charge transport across protein nanoelectronic junctions. The results obtained so far indicate that in a metal-protein-metal junction, the final charge transport properties are dominated by the relative position of energy states and their hybridisation between protein and electrode. Energy-level gating and chemical engineering of the protein-electrode interface in protein junctions have been pivotal in understanding such complex processes. We anticipate that they will continue evolving in the years to come. Overall, an anomalous thermally-independent long-range charge transport mechanism is prevalent in most wild-type proteins. When specific point-site mutations are introduced to the amino acid matrix, this efficient mechanism often breaks down, indicating the crucial role of the supramolecular protein structure. Likewise, the details of the protein-electrode chemical interactions dictate the efficiency of charge injection into the protein core and yields valuable information on how nature solves this fundamental physicochemical process. In the following years, we

shall see exciting developments in device architectures, which will hopefully propel our understanding of all the remaining open questions in this newly born BioMolecular Electronics field. We believe that understanding the principles of bioelectricity is crucial for laying the foundations of a future hybrid bioelectronic technology.

Acknowledgements

We thank the European Research Commission for funding under Consolidator Grant (CoG), PE5, ERC-2017-COG. We also want to thank Professors Stuart Lindsay and David Cahen for the many, invaluable discussions on protein junctions we have had over the years.

CRediT author statement

Tracy Q. Ha performed writing - original draft, conceptualisation, and editing. Inco J. Planje performed writing - original draft, conceptualisation, reviewing, and editing. Jhanelle R. G. White performed writing - editing. Albert C. Aragonès performed writing - reviewing, and editing. Ismael Díez-Pérez acquired funding, carried out supervision, and performed writing - reviewing and editing.

Declaration of interest

None

References

[1] D. Beratan, J. Onuchic, Winkler, H. Gray, Electron-tunneling pathways in proteins, Science 258 (5089) (1992) 1740–1741. doi:10.1126/science.1334572.
URL https://www.sciencemag.org/lookup/doi/10.1126/science.1334572

[2] C. C. Page, C. C. Moser, X. Chen, P. L. Dutton, Natural engineering principles of electron tunnelling in biological oxidation–reduction, Nature 402 (6757) (1999) 47–52. doi:10.1038/46972.
URL http://www.nature.com/articles/46972

[3] L. Scullion, T. Doneux, L. Bouffier, D. G. Fernig, S. J. Higgins, D. Bethell, R. J. Nichols, Large conductance changes in peptide single molecule junctions controlled by pH, Journal of Physical Chemistry C 115 (16) (2011) 8361–8368. doi:10.1021/jp201222b.
URL https://pubs.acs.org/doi/10.1021/jp201222b

[4] M. Cordes, B. Giese, Electron transfer in peptides and proteins, Chemical Society Reviews 38 (4) (2009) 892. doi:10.1039/b805743p.
URL http://xlink.rsc.org/?DOI=b805743p

[5] G. T. Babcock, M. Wikström, Oxygen activation and the conservation of energy in cell respiration, Nature 356 (6367) (1992) 301–309. doi:10.1038/356301a0.
URL http://www.nature.com/articles/356301a0

[6] D. J. Vinyard, G. M. Ananyev, G. Charles Dismukes, Photosystem II: The Reaction Center of Oxygenic Photosynthesis, Annual Review of Biochemistry 82 (1) (2013) 577–606. doi:10.1146/annurev-biochem-070511-100425.
URL http://www.annualreviews.org/doi/10.1146/annurev-biochem-070511-100425

[7] J. Stubbe, W. A. van der Donk, Protein Radicals in Enzyme Catalysis, Chemical Reviews 98 (2) (1998) 705–762. doi:10.1021/cr9400875.
URL https://pubs.acs.org/doi/10.1021/cr9400875

[8] F. Urra, B. Weiss-López, R. Araya-Maturana, Determinants of Anti-Cancer Effect of Mitochondrial Electron Transport Chain Inhibitors: Bioenergetic Profile and Metabolic Flexibility of Cancer

Cells, Current Pharmaceutical Design 22 (39) (2016) 5998–6008. doi:10.2174/1381612822666160719122626.
URL http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1381-6128&volume=22&issue=39&spage=5998

[9] S. Xu, A. Barrozo, L. M. Tender, A. I. Krylov, M. Y. El-Naggar, Multiheme Cytochrome Mediated Redox Conduction through Shewanella oneidensis MR-1 Cells, Journal of the American Chemical Society 140 (32) (2018) 10085–10089. doi:10.1021/jacs.8b05104.
URL https://pubs.acs.org/doi/10.1021/jacs.8b05104

[10] R. A. Marcus, Chemical and Electrochemical Electron-Transfer Theory, Annual Review of Physical Chemistry 15 (1) (1964) 155–196. doi:10.1146/annurev.pc.15.100164.001103.
URL http://www.annualreviews.org/doi/10.1146/annurev.pc.15.100164.001103

[11] C. C. Moser, J. M. Keske, K. Warncke, R. S. Farid, P. L. Dutton, Nature of biological electron transfer, Nature 355 (6363) (1992) 796–802. doi:10.1038/355796a0.
URL http://www.nature.com/articles/355796a0

[12] H. B. Gray, J. R. Winkler, Long-range electron transfer, Proceedings of the National Academy of Sciences of the United States of America 102 (10) (2005) 3534–3539. doi:10.1073/pnas.0408029102.
URL http://www.pnas.org/cgi/doi/10.1073/pnas.0408029102

[13] C. D. Bostick, S. Mukhopadhyay, I. Pecht, M. Sheves, D. Cahen, D. Lederman, Protein bioelectronics: a review of what we do and do not know, Reports on Progress in Physics 81 (2) (2018) 026601. doi:10.1088/1361-6633/aa85f2.
URL http://stacks.iop.org/0034-4885/81/i=2/a=026601?key=crossref.ec73b13b9a6ad598d883add951b9746ahttps://iopscience.iop.org/article/10.1088/1361-6633/aa85f2

[14] P. N. Bartlett, Bioelectrochemistry: Fundamentals, Experimental Techniques and Applications, John Wiley & Sons, Ltd, Chichester, UK, 2008. doi:10.1002/9780470753842.
URL http://doi.wiley.com/10.1002/9780470753842

[15] Q. Chi, J. Zhang, J. U. Nielsen, E. P. Friis, I. Chorkendorff, G. W. Canters, J. E. T. Andersen, J. Ulstrup, Molecular Monolayers and Interfacial Electron Transfer of Pseudomonas aeruginosa Azurin on Au(111), Journal of the American Chemical Society 122 (17) (2000) 4047–4055. doi:10.1021/ja993174t.
URL https://pubs.acs.org/doi/10.1021/ja993174t

[16] P. Facci, D. Alliata, S. Cannistraro, Potential-induced resonant tunneling through a redox metalloprotein investigated by electrochemical scanning probe microscopy, Ultramicroscopy 89 (4) (2001) 291–298. doi:10.1016/S0304-3991(01)00093-6.
URL https://linkinghub.elsevier.com/retrieve/pii/S0304399101000936

[17] R. Rinaldi, A. Biasco, G. Maruccio, V. Arima, P. Visconti, R. Cingolani, P. Facci, F. De Rienzo, R. Di Felice, E. Molinari, M. Ph. Verbeet, G. W. Canters, Electronic rectification in protein devices, Applied Physics Letters 82 (3) (2003) 472–474. doi:10.1063/1.1530748.
URL http://aip.scitation.org/doi/10.1063/1.1530748

[18] J. M. A. Vivancos, J. Hihath, I. Díez-Pérez, Biomolecular electronics, in: I. Bâldea (Ed.), Molecular Electronics: An Experimental and Theoretical Approach, Pan Stanford Publishing, 2016, Ch. Biomolecul, pp. 281–323.

[19] S. Lindsay, Ubiquitous Electron Transport in Non-Electron Transfer Proteins, Life 10 (5) (2020) 72. doi:10.3390/life10050072.
URL https://www.mdpi.com/2075-1729/10/5/72

[20] J. C. Cuevas, E. Scheer, Molecular Electronics, Vol. 1 of World Scientific Series in Nanoscience and Nanotechnology, WORLD SCIENTIFIC, 2010.

doi:10.1142/7434.
URL https://www.worldscientific.com/worldscibooks/10.1142/7434

[21] D. Xiang, X. Wang, C. Jia, T. Lee, X. Guo, Molecular-Scale Electronics: From Concept to Function, Chemical Reviews 116 (7) (2016) 4318–4440. doi:10.1021/acs.chemrev.5b00680.
URL http://dx.doi.org/10.1021/acs.chemrev.5b00680http://pubs.acs.org/doi/10.1021/acs.chemrev.5b00680

[22] K. Slowinski, H. K. Fong, M. Majda, Mercury-mercury tunneling junctions. 1. Electron tunneling across symmetric and asymmetric alkanethiolate bilayers, Journal of the American Chemical Society 121 (31) (1999) 7257–7261. doi:10.1021/ja991613i.
URL https://pubs.acs.org/doi/10.1021/ja991613i

[23] S. Nakamaru, F. Scholz, W. E. Ford, Y. Goto, F. von Wrochem, Photoswitchable Sn-Cyt c Solid-State Devices, Advanced Materials 29 (22) (2017) 1605924. doi:10.1002/adma.201605924.
URL http://doi.wiley.com/10.1002/adma.201605924

[24] R. C. Chiechi, E. A. Weiss, M. D. Dickey, G. M. Whitesides, Eutectic Gallium–Indium (EGaIn): A Moldable Liquid Metal for Electrical Characterization of Self-Assembled Monolayers, Angewandte Chemie International Edition 47 (1) (2008) 142–144. doi:10.1002/anie.200703642.
URL http://doi.wiley.com/10.1002/anie.200703642

[25] S. Mukhopadhyay, S. K. Karuppannan, C. Guo, J. A. Fereiro, A. Bergren, V. Mukundan, X. Qiu, O. E. Castañeda Ocampo, X. Chen, R. C. Chiechi, R. McCreery, I. Pecht, M. Sheves, R. R. Pasula, S. Lim, C. A. Nijhuis, A. Vilan, D. Cahen, Solid-State Protein Junctions: Cross-Laboratory Study Shows Preservation of Mechanism at Varying Electronic Coupling, iScience 23 (5). doi:10.1016/j.isci.2020.101099.

[26] A. Alessandrini, P. Facci, AFM: a versatile tool in biophysics, Measurement Science and Technology 16 (6) (2005) R65–R92. doi:10.1088/0957-0233/16/6/R01.
URL https://iopscience.iop.org/article/10.1088/0957-0233/16/6/R01

[27] K. S. Kumar, R. R. Pasula, S. Lim, C. A. Nijhuis, Long-Range Tunneling Processes across Ferritin-Based Junctions, Advanced Materials 28 (9) (2016) 1824–1830. doi:10.1002/adma.201504402.
URL http://doi.wiley.com/10.1002/adma.201504402

[28] X. Zhuang, A. Zhang, S. Qiu, C. Tang, S. Zhao, H. Li, Y. Zhang, Y. Wang, B. Wang, B. Fang, W. Hong, Coenzyme coupling boosts charge transport through single bioactive enzyme junctions, ISCIENCE (2020) 101001doi:10.1016/j.isci.2020.101001.
URL https://doi.org/10.1016/j.isci.2020.101001

[29] D. Gerster, J. Reichert, H. Bi, J. V. Barth, S. M. Kaniber, A. W. Holleitner, I. Visoly-Fisher, S. Sergani, I. Carmeli, Photocurrent of a single photosynthetic protein, Nature Nanotechnology 7 (10) (2012) 673–676. doi:10.1038/nnano.2012.165.
URL http://www.nature.com/articles/nnano.2012.165

[30] J. M. Artés, I. Díez-Pérez, F. Sanz, P. Gorostiza, Direct Measurement of Electron Transfer Distance Decay Constants of Single Redox Proteins by Electrochemical Tunneling Spectroscopy, ACS Nano 5 (3) (2011) 2060–2066. doi:10.1021/nn103236e.
URL https://pubs.acs.org/doi/10.1021/nn103236e

[31] J. M. Artés, I. Díez-Pérez, P. Gorostiza, Transistor-like Behavior of Single Metalloprotein Junctions, Nano Letters 12 (6) (2012) 2679–2684. doi:10.1021/nl2028969.
URL https://pubs.acs.org/doi/10.1021/nl2028969

[32] J. M. Artés, M. López-Martínez, A. Giraudet, I. Díez-Pérez, F. Sanz, P. Gorostiza, Current–Voltage Characteristics and Transition Voltage Spectroscopy of Individual Redox Proteins, Journal of the American Chemical Society 134 (50) (2012) 20218–20221. doi:10.1021/ja3080242.
URL https://pubs.acs.org/doi/10.1021/ja3080242

[33] J. M. Artés, M. López-Martínez, I. Díez-Pérez, F. Sanz, P. Gorostiza, Conductance Switching in Single Wired Redox Proteins, Small 10 (13) (2014) 2537–2541. doi:10.1002/smll.201303753.
URL http://doi.wiley.com/10.1002/smll.201303753

[34] B. Zhang, H. Deng, S. Mukherjee, W. Song, X. Wang, S. Lindsay, Engineering an Enzyme for Direct Electrical Monitoring of Activity, ACS Nano 14 (2) (2020) 1360–1368. doi:10.1021/acsnano.9b06875.

[35] A. Alessandrini, S. Corni, P. Facci, Unravelling single metalloprotein electron transfer by scanning probe techniques, Physical Chemistry Chemical Physics 8 (38) (2006) 4383. doi:10.1039/b607021c.
URL http://xlink.rsc.org/?DOI=b607021c

[36] M. Elliott, High-resolution electrochemical STM of redox metalloproteins, Current Opinion in Electrochemistry 4 (1) (2017) 152–158. doi:10.1016/j.coelec.2017.08.007.
URL https://linkinghub.elsevier.com/retrieve/pii/S2451910317301199

[37] B. Kayser, J. A. Fereiro, C. Guo, S. R. Cohen, M. Sheves, I. Pecht, D. Cahen, Transistor configuration yields energy level control in protein-based junctions, Nanoscale 10 (46) (2018) 21712–21720. doi:10.1039/c8nr06627b.

[38] B. Zhang, W. Song, J. Brown, R. Nemanich, S. Lindsay, Electronic Conductance Resonance in Non-Redox-Active Proteins, Journal of the American Chemical Society 142 (13) (2020) 6432–6438. doi:10.1021/jacs.0c01805.

[39] S. Guo, J. M. Artés, I. Díez-Pérez, Electrochemically-gated single-molecule electrical devices, Electrochimica Acta 110 (2013) 741–753. doi:10.1016/j.electacta.2013.03.146.
URL http://dx.doi.org/10.1016/j.electacta.2013.03.146https://linkinghub.elsevier.com/retrieve/pii/S0013468613005690

[40] N. J. Tao, Probing potential-tuned resonant tunneling through redox molecules with scanning tunneling microscopy, Physical Review Letters 76 (21) (1996) 4066–4069. doi:10.1103/PhysRevLett.76.4066.
URL https://link.aps.org/doi/10.1103/PhysRevLett.76.4066

[41] A. Alessandrini, M. Salerno, S. Frabboni, P. Facci, Single-metalloprotein wet biotransistor, Applied Physics Letters 86 (13) (2005) 1–3. doi:10.1063/1.1896087.

[42] Y. Selzer, A. Salomon, D. Cahen, Effect of Molecule-Metal Electronic Coupling on Through-Bond Hole Tunneling across Metal-Organic Monolayer-Semiconductor Junctions, Journal of the American Chemical Society 124 (12) (2002) 2886–2887. doi:10.1021/ja0177511.
URL https://pubs.acs.org/doi/10.1021/ja0177511

[43] J. Taylor, M. Brandbyge, K. Stokbro, Theory of Rectification in Tour Wires: The Role of Electrode Coupling, Physical Review Letters 89 (13) (2002) 138301. doi:10.1103/PhysRevLett.89.138301.
URL https://link.aps.org/doi/10.1103/PhysRevLett.89.138301

[44] J. M. Beebe, V. B. Engelkes, L. L. Miller, C. D. Frisbie, Contact resistance in metal-molecule-metal junctions based on aliphatic SAMs: Effects of surface linker and metal work function, Journal of the American Chemical Society 124 (38) (2002) 11268–11269. doi:10.1021/ja0268332.
URL https://pubs.acs.org/doi/10.1021/ja0268332

[45] X. Li, J. He, J. Hihath, B. Xu, S. M. Lindsay, N. Tao, Conductance of Single Alkanedithiols: Conduction Mechanism and Effect of Molecule-Electrode

Contacts, Journal of the American Chemical Society 128 (6) (2006) 2135–2141. doi:10.1021/ja057316x.
URL https://pubs.acs.org/doi/10.1021/ja057316x

[46] Y. S. Park, A. C. Whalley, M. Kamenetska, M. L. Steigerwald, M. S. Hybertsen, C. Nuckolls, L. Venkataraman, Contact Chemistry and Single-Molecule Conductance: A Comparison of Phosphines, Methyl Sulfides, and Amines, Journal of the American Chemical Society 129 (51) (2007) 15768–15769. doi:10.1021/ja0773857.
URL https://pubs.acs.org/doi/10.1021/ja0773857

[47] J. A. Malen, P. Doak, K. Baheti, T. Don Tilley, R. A. Segalman, A. Majumdar, Identifying the length dependence of orbital alignment and contact coupling in molecular heterojunctions, Nano Letters 9 (3) (2009) 1164–1169. doi:10.1021/nl803814f.
URL https://pubs.acs.org/doi/10.1021/nl803814f

[48] Z.-L. Cheng, R. Skouta, H. Vazquez, J. R. Widawsky, S. Schneebeli, W. Chen, M. S. Hybertsen, R. Breslow, L. Venkataraman, In situ formation of highly conducting covalent Au-C contacts for single-molecule junctions., Nature nanotechnology 6 (6) (2011) 353–357. doi:10.1038/nnano.2011.66.
URL http://dx.doi.org/10.1038/nnano.2011.66

[49] I. Diez-Perez, J. Hihath, T. Hines, Z. S. Wang, G. Zhou, K. Müllen, N. Tao, Controlling single-molecule conductance through lateral coupling of ϕ orbitals, Nature Nanotechnology 6 (4) (2011) 226–231. doi:10.1038/nnano.2011.20.
URL http://www.nature.com/articles/nnano.2011.20

[50] J. S. Meisner, S. Ahn, S. V. Aradhya, M. Krikorian, R. Parameswaran, M. Steigerwald, L. Venkataraman, C. Nuckolls, Importance of Direct Metal-π Coupling in Electronic Transport Through Conjugated Single-Molecule Junctions, Journal of the American Chemical Society 134 (50) (2012)

20440–20445. doi:10.1021/ja308626m.
URL https://pubs.acs.org/doi/10.1021/ja308626m

[51] T. A. Su, M. Neupane, M. L. Steigerwald, L. Venkataraman, C. Nuckolls, Chemical principles of single-molecule electronics, Nature Reviews Materials 1 (3) (2016) 16002. doi:10.1038/natrevmats.2016.2.
URL http://www.nature.com/articles/natrevmats20162

[52] B. Zhang, W. Song, P. Pang, H. Lai, Q. Chen, P. Zhang, S. Lindsay, Role of contacts in long-range protein conductance, Proceedings of the National Academy of Sciences of the United States of America 116 (13) (2019) 5886–5891. doi:10.1073/pnas.1819674116.

[53] Ortega, Vilhena, Zotti, Díez-Pérez, Cuevas, Pérez, Tuning Structure and Dynamics of Blue Copper Azurin Junctions via Single Amino-Acid Mutations, Biomolecules 9 (10) (2019) 611. doi:10.3390/biom9100611.
URL https://www.mdpi.com/2218-273X/9/10/611

[54] J. A. Fereiro, G. Porat, T. Bendikov, I. Pecht, M. Sheves, D. Cahen, Protein Electronics: Chemical Modulation of Contacts Control Energy Level Alignment in Gold-Azurin-Gold Junctions, Journal of the American Chemical Society 140 (41) (2018) 13317–13326. doi:10.1021/jacs.8b07742.
URL https://pubs.acs.org/doi/10.1021/jacs.8b07742

[55] Q. Chi, J. Zhang, J. E. T. Andersen, J. Ulstrup, Ordered Assembly and Controlled Electron Transfer of the Blue Copper Protein Azurin at Gold (111) Single-Crystal Substrates, The Journal of Physical Chemistry B 105 (20) (2001) 4669–4679. doi:10.1021/jp0105589.
URL https://pubs.acs.org/doi/10.1021/jp0105589

[56] I. Willner, E. Katz, A. Riklin, R. Kasher, Mediated Electron-Transfer in Glutathione-Reductase Organized in Self-Assembled Monolayers on Au Electrodes, Journal of the American Chemical Society 114 (27) (1992) 10965–10966. doi:DOI10.1021/ja00053a045.
URL https://pubs.acs.org/doi/pdfplus/10.1021/ja00053a045

[57] R. Das, P. J. Kiley, M. Segal, J. Norville, A. A. Yu, L. Wang, S. A. Trammell, L. E. Reddick, R. Kumar, F. Stellacci, N. Lebedev, J. Schnur, B. D. Bruce, S. Zhang, M. Baldo, Integration of Photosynthetic Protein Molecular Complexes in Solid-State Electronic Devices, Nano Letters 4 (6) (2004) 1079–1083. doi:10.1021/nl049579f.
URL https://pubs.acs.org/doi/10.1021/nl049579f

[58] K. Ataka, B. Richter, J. Heberle, Orientational Control of the Physiological Reaction of Cytochrome c Oxidase Tethered to a Gold Electrode, The Journal of Physical Chemistry B 110 (18) (2006) 9339–9347. doi:10.1021/jp0534131.
URL https://pubs.acs.org/doi/10.1021/jp0534131

[59] C. F. Blanford, R. S. Heath, F. A. Armstrong, A stable electrode for high-potential, electrocatalytic O2 reduction based on rational attachment of a blue copper oxidase to a graphite surface, Chemical Communications (17) (2007) 1710. doi:10.1039/b703114a.
URL http://xlink.rsc.org/?DOI=b703114a

[60] M. Kondo, Y. Nakamura, K. Fujii, M. Nagata, Y. Suemori, T. Dewa, K. Iida, A. T. Gardiner, R. J. Cogdell, M. Nango, Self-Assembled Monolayer of Light-Harvesting Core Complexes from Photosynthetic Bacteria on a Gold Electrode Modified with Alkanethiols, Biomacromolecules 8 (8) (2007) 2457–2463. doi:10.1021/bm070352z.
URL https://pubs.acs.org/doi/10.1021/bm070352z

[61] M. Kondo, K. Iida, T. Dewa, H. Tanaka, T. Ogawa, S. Nagashima, K. V. P. Nagashima, K. Shimada, H. Hashimoto, A. T. Gardiner, R. J. Cogdell, M. Nango, Photocurrent and Electronic Activities of Oriented-His-Tagged Photosynthetic Light-Harvesting/Reaction Center Core Complexes Assembled onto a Gold Electrode, Biomacromolecules 13 (2) (2012) 432–438. doi:10.1021/bm201457s.
URL https://pubs.acs.org/doi/10.1021/bm201457s

[62] S. A. Trammell, A. Spano, R. Price, N. Lebedev, Effect of protein orientation on electron transfer between photosynthetic reaction centers and carbon electrodes, Biosensors and Bioelectronics 21 (7) (2006) 1023–1028. doi:10.1016/j.bios.2005.03.015.
URL https://linkinghub.elsevier.com/retrieve/pii/S0956566305000990

[63] M. Zayats, E. Katz, R. Baron, I. Willner, Reconstitution of apo-glucose dehydrogenase on pyrroloquinoline quinone-functionalized Au nanoparticles yields an electrically contacted biocatalyst, Journal of the American Chemical Society 127 (35) (2005) 12400–12406. doi:10.1021/ja052841h.

[64] M. P. Ruiz, A. C. Aragonès, N. Camarero, J. G. Vilhena, M. Ortega, L. A. Zotti, R. Pérez, J. C. Cuevas, P. Gorostiza, I. Díez-Pérez, Bioengineering a Single-Protein Junction, Journal of the American Chemical Society 139 (43) (2017) 15337–15346. doi:10.1021/jacs.7b06130.
URL https://pubs.acs.org/doi/10.1021/jacs.7b06130

[65] J. A. Fereiro, B. Kayser, C. Romero-Muñiz, A. Vilan, D. A. Dolgikh, R. V. Chertkova, J. C. Cuevas, L. A. Zotti, I. Pecht, M. Sheves, D. Cahen, A Solid-State Protein Junction Serves as a Bias-Induced Current Switch, Angewandte Chemie International Edition 58 (34) (2019) 11852–11859. doi:10.1002/anie.201906032.
URL https://onlinelibrary.wiley.com/doi/abs/10.1002/anie.201906032

[66] S. H. Choi, B. S. Kim, C. D. Frisbie, Electrical resistance of long conjugated molecular wires, Science 320 (5882) (2008) 1482–1486. doi:10.1126/science.1156538.
URL http://www.sciencemag.org/cgi/doi/10.1126/science.1156538

[67] S. Rigaut, Metal complexes in molecular junctions, Dalton Transactions 42 (45) (2013) 15859–15863. doi:10.1039/c3dt51487k.
URL http://xlink.rsc.org/?DOI=c3dt51487k

[68] K. M. Cosert, R. J. Steidl, A. Castro-Forero, R. M. Worden, G. Reguera, Electronic characterization of Geobacter sulfurreducens pilins in self-assembled monolayers unmasks tunnelling and hopping conduction pathways, Physical Chemistry Chemical Physics 19 (18) (2017) 11163–11172. doi:10.1039/C7CP00885F.
URL http://xlink.rsc.org/?DOI=C7CP00885F

[69] S. Valianti, J.-C. Cuevas, S. S. Skourtis, Charge-Transport Mechanisms in Azurin-Based Monolayer Junctions, The Journal of Physical Chemistry C 123 (10) (2019) 5907–5922. doi:10.1021/acs.jpcc.9b00135.
URL https://pubs.acs.org/doi/10.1021/acs.jpcc.9b00135

[70] B. Kayser, J. A. Fereiro, R. Bhattacharyya, S. R. Cohen, A. Vilan, I. Pecht, M. Sheves, D. Cahen, Solid-State Electron Transport via the Protein Azurin is Temperature-Independent Down to 4 K, The Journal of Physical Chemistry Letters 11 (1) (2020) 144–151. doi:10.1021/acs.jpclett.9b03120.
URL https://pubs.acs.org/doi/10.1021/acs.jpclett.9b03120

[71] A. M. Kuznetsov, J. Ulstrup, Mechanisms of in Situ Scanning Tunnelling Microscopy of Organized Redox Molecular Assemblies, Journal of Physical Chemistry A 104 (49) (2000) 11531–11540. doi:10.1021/jp993635x.
URL https://pubs.acs.org/doi/10.1021/jp993635x

[72] Y. Zhang, C. Liu, A. Balaeff, S. S. Skourtis, D. N. Beratan, Biological charge transfer via flickering resonance, Proceedings of the National Academy of Sciences 111 (28) (2014) 10049–10054. doi:10.1073/pnas.1316519111.
URL http://www.pnas.org/cgi/doi/10.1073/pnas.1316519111

[73] K. Garg, M. Ghosh, T. Eliash, J. H. van Wonderen, J. N. Butt, L. Shi, X. Jiang, F. Zdenek, J. Blumberger, I. Pecht, M. Sheves, D. Cahen, Direct evidence for heme-assisted solid-state electronic conduction in multi-heme c -type cytochromes, Chemical Science 9 (37) (2018) 7304–7310. doi:

10.1039/C8SC01716F.
URL http://xlink.rsc.org/?DOI=C8SC01716F

[74] E. A. Della Pia, J. E. Macdonald, M. Elliott, D. D. Jones, Direct Binding of a Redox Protein for Single-Molecule Electron Transfer Measurements, Small 8 (15) (2012) 2341–2344. doi:10.1002/smll.201102416.
URL http://doi.wiley.com/10.1002/smll.201102416

[75] C. Romero-Muñiz, M. Ortega, J. G. Vilhena, I. Díez-Pérez, J. C. Cuevas, R. Pérez, L. A. Zotti, Ab initio electronic structure calculations of entire blue copper azurins, Physical Chemistry Chemical Physics 20 (48) (2018) 30392–30402. doi:10.1039/c8cp06862c.
URL http://xlink.rsc.org/?DOI=C8CP06862C

[76] C. Romero-Muñiz, M. Ortega, J. G. Vilhena, I. Díez-Pérez, R. Pérez, J. C. Cuevas, L. A. Zotti, Can Electron Transport through a Blue-Copper Azurin Be Coherent? An Ab Initio Study, The Journal of Physical Chemistry C 125 (3) (2021) 1693–1702. doi:10.1021/acs.jpcc.0c09364.
URL https://pubs.acs.org/doi/10.1021/acs.jpcc.0c09364

[77] E. Papp, D. P. Jelenfi, M. T. Veszeli, G. Vattay, A Landauer Formula for Bioelectronic Applications, Biomolecules 9 (10) (2019) 599. doi:10.3390/biom9100599.
URL https://www.mdpi.com/2218-273X/9/10/599

For TOC only