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Authors

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Zhang, Jing
Lyu, Qingyang
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Review

Modular configurations of living biomaterials incorporating nano-based artificial mediators and synthetic biology to improve bioelectrocatalytic performance: A review

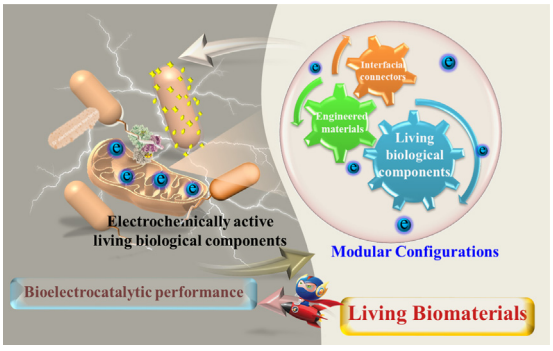
Zheng Chen [a,d,e,*,1], Jing Zhang [d,1], Qingyang Lyu [b], Honghui Wang [d], Xiaoliang Ji [a], Zhiying Yan [b], Fang Chen [e], Randy A. Dahlgren [a,c], Minghua Zhang [a,c]

[a] School of Public Health and Management, Wenzhou Medical University, Wenzhou 325035, People's Republic of China
[b] CAS Key Laboratory of Environmental and Applied Microbiology, Environmental Microbiology Key Laboratory of Sichuan Province, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, People's Republic of China
[c] Department of Land, Air and Water Resources, University of California, Davis, CA 95616, USA
[d] School of Environmental Science & Engineering, Tan Kah Kee College, Xiamen University, Zhangzhou 363105, People's Republic of China
[e] Fujian Provincial Key Lab of Coastal Basin Environment, Fujian Polytechnic Normal University, Fuqing 350300, People's Republic of China

HIGHLIGHTS

- Biomaterials incorporating nano-based mediators and synthetic biology are used to improve bioelectrocatalytic performance.
- Interfacial conductivity is improved through heterojunctions between conductive nanomaterials and EABs.
- Additional electron flux in biohybrids is supplied from illuminated nano-sized semiconductors-derived photoelectrons.
- LBL coating technologies to form core/shell structures are utilized for protecting living biohybrids using.
- Intracellular electron flux of EAB is augmented by synthetic biological modifications of EABs and electroactive biofilms.

GRAPHICAL ABSTRACT



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ABSTRACT

Currently, the industrial application of bioelectrochemical systems (BESs) that are incubated with natural electrochemically active microbes (EABs) is limited due to inefficient extracellular electron transfer (EET) by natural EABs. Notably, recent studies have identified several novel living biomaterials comprising highly efficient electron transfer systems allowing unparalleled proficiency of energy conversion. Introduction of these biomaterials into BESs could fundamentally increase their utilization for a wide range of applications. This review provides a comprehensive assessment of recent advancements in the design of living biomaterials that can be exploited to enhance bioelectrocatalytic performance. Further, modular configurations of abiotic and biotic components promise a powerful enhancement through integration of nano-based artificial mediators and synthetic biology. Herein, recent advancements in BESs are synthesized and assessed, including heterojunctions between conductive nanomaterials and EABs, in-situ hybrid self-assembly of EABs and nano-sized semiconductors, cytoprotection in biohybrids, synthetic biological modifications of EABs and electroactive biofilms. Since living biomaterials comprise a broad range of disciplines, such as molecular

* Corresponding author at: School of Public Health and Management, Wenzhou Medical University, Wenzhou 325035, People's Republic of China.
E-mail address: chenzheng_new@163.com (Z. Chen).
[1] These authors were considered as the co-first authors.

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Photocatalytic
Electroactive biofilms

biology, electrochemistry and material sciences, full integration of technological advances applied in an interdisciplinary framework will greatly enhance/advance the utility and novelty of BESs. Overall, emerging fundamental knowledge concerning living biomaterials provides a powerful opportunity to markedly boost EET efficiency and facilitate the industrial application of BESs to meet global sustainability challenges/goals.

Contents

1. Introduction

The field of BESs involving the harvest of electrons from microbial energy metabolism has made several impressive advances in the past decade (Martinez and Alvarez, 2018). BESs have contributed many scientific and technological applications, including bioremediation of pollutants, bioleaching, renewable and carbon neutral energy production and biosensing (Dong et al., 2020a; Liu et al., 2018). However, inefficient electron transfer at interfaces between EABs and extracellular electrodes often become a bottleneck that limits the widespread application of BESs (Patil et al., 2012; Popat and Torres, 2016). Thus, a paradigm shift is necessary to improve the integration of electron transfer between redox mediators and living biological components, as well as the interfacial connections with EET pathways to foster more efficient charge transfer within traditional BESs. Notably, living biomaterials are an emerging technological solution to this nascent field as they incorporate the adaptive and regenerative properties of living organisms, as well as intriguing advantages of their integration with inorganic catalysts (Tibbitt and Langer, 2017).

Since the majority of natural EET pathways incorporate multi-heme c-type cytochromes (c-cyts) (generally located in the cytoplasmic, periplasmic membranes or pili) (Hernandez and Newman, 2001), charge transport prominently occurs at protein junction sites (Der et al., 2012; Kortemme et al., 2003). Improvements in the understanding of electron-transfer pathways in natural EABs have fueled significant advancements in constructing more biomimetic conduits to connect with extracellular electrodes. To minimize the energy loss in the process of transmembrane electron transfer in EAB cells, research has focused on the design of protein-electrode hybrid interfaces consisting of living biomaterials that enable a close electrical contact and low-energy barrier charge injection (Ha et al., 2021). Although sluggish charge transport resulting from energy loss can be ameliorated through heterogeneous interfacial modifications, challenges from charge diffusion, low electron transfer efficiency to the targeted electrodes and limited electron flux produced from microbial metabolism hinder the efficiency of most traditional BESs (Jensen et al., 2010). Further, optimization of hybrid interfaces has utilized the incorporation of an external platform to supplement electrons. These enhanced designs for hybrid bio-interfaces in biomaterials can greatly increase the electron cascade through supplying additional photoelectrons within BESs (Ding et al., 2019; Dong et al., 2020b; Fang et al., 2020b). Another efficiency-configuration framework aims to promote electron-exporting capability through the use of in-situ modular assemble of nanosized semiconductors and EABs. In living biohybrids incorporating nanosized semiconductors and EABs, photoelectrons are supplied from semiconductors harvesting light energy while further participating in the EAB's respiration process. This refinement adds synergist potential to living biomaterials as each component (abiotic and biotic) contributes its respective advantages while offsetting their corresponding weaknesses.

There are currently no notable examples of economically-viable engineered BESs due to the intrinsic limitations of natural EABs. The lack of sufficient intracellular redox carriers and/or reducing equivalents, as well as protein-cyt c complexes, hinders efficient transmembrane electron transport. This elicits a distinct limitation for natural EABs to initiate efficient electron-exporting capacity for subsequent exploitation in industrial processes (Glaven, 2019; Tefft and TerAvest, 2019; TerAvest and Ajo-Franklin, 2016). However, recent breakthroughs in the use of synthetic biology have allowed scientists to redirect metabolic electron fluxes to external electrodes in a manner that increases power output (Schuergers et al., 2017; TerAvest and Ajo-Franklin, 2016). To optimize extracellular electron transfer, the genetic circuitry of the responsive biological EAB modules must be re-encoded to allow external manipulation of their functions (Ravi et al., 2017). Additionally, the EET efficiency of BESs can be enhanced through the exploitation of cultivated biofilms for use in EABs (Yong et al., 2014b). The habitat provided by electroactive biofilms elicits greater cell density to facilitate direct electron transfer and shorten the diffusion time for soluble mediators to reach the electron acceptors (Luo et al., 2019).

Collectively, modular configurations of living biomaterials harnessing nano-based artificial mediators and synthetic biology have been promoted

as promising strategies to improve the performance and practical/economical application of BESs (Chen et al., 2020b; Roell and Zurbriggen, 2020; Schuergers et al., 2017). In this review, the fundamental principles and advancements were focused on the integration of various nano-based artificial mediators with synthetic biology approaches to design living biomaterials. Meanwhile, the assembly patterns of abiotic and biotic components as well as the long-term stability/efficacy of living biomaterials were highlighted. Overall, this synthesis provides valuable insights for unifying nanomaterial sciences and synthetic biology in the realm of hybrid bioelectronics, and envisions prospects for potential applications of living biomaterials in future industrial applications and global sustainability issues.

2. Conductive nanomaterial–EAB heterojunction complex

2.1. Biointerfacial heterojunction for a single EAB cell with electrically conductive nanomaterials

A large number of electrons produced from intracellular processes of EAB cells participate in the synthesis of reducing substances (e.g., reducing equivalent NADPH) and other intracellular metabolic processes (Hernandez and Newman, 2001). Notably, the path of electron transmission across the cell envelope comprises the inner membrane ⇌ periplasm ⇌ outer membrane pathway (Liu et al., 2018). However, electron escape and sluggish electron-transfer/export persist in the complicated redox environment of the periplasmic space. This contributes to the diversion of intracellular electron flow and a lack of imperative conductive c-cyts via entrapment in the periplasm (Schuetz et al., 2009; Sturm et al., 2015). Accordingly, only a small fraction of the released intracellular electron flow is effectively transferred to the extracellular electrodes (Kumar et al., 2017; Logan et al., 2019). To address this impediment, recent research has advanced the use of a heterojunction consisting of engineered conductive nanomaterials (e.g., nano-magnetite, graphene and carbon nanotubes [CNTs]) for EAB individual cells to effectively ameliorate the adverse cellular activity through enhancement of cellular signaling (Yin and Wu, 2019; Zhang et al., 2018). The selected nanomaterials can be targeted to site-specific cell locations to boost interfacial electrical conductivity, such as (i) the inside envelope of an EAB cell or (ii) the interface between EAB and extracellular electron acceptors (Table 1 and Fig. 1). Fig. 1 profiles improved EET pathways for inside-membrane, biofilm interfaces and membrane-electrode interfaces using conductive nanomaterial heterojunctions and living components. Moreover, Table 1 provides several successful examples and an overview of improved conducting heterojunctions at different interfacial connections using representative conductive nanomaterials.

To improve electron transmission across the envelope of an EAB cell, an appropriate interfacial electronic junction between periplasm and the outer membrane can be achieved through intercalation via in-situ affinity binding or self-assembly methods (Kayser et al., 2018). For instance, the intercalation of palladium (Pd) or gold (Au) nanoparticles (NPs) into the periplasm helps to fill voids between cytochromes (Sun et al., 2010; Wu et al., 2011). Research on the biosynthesis of noble metal NPs demonstrated that Pd and Au NPs display a superior biocompatibility because they can be produced by microbial intracellular synthesis (Ahmad et al., 2003; Omajali et al., 2015). In addition, Pd and Au NPs commonly have a higher electronic conductivity than that of microbial pili (El-Naggar et al., 2008; Wu et al., 2011). Thus, the intercalation of Pd or Au NPs into the periplasm has the potential to greatly improve the conductivity of heterojunctions by filling unblocked conductive areas in the periplasmic space (shown in Fig. 1). Owing to the high recognition of redox proteins and high electrical conductivity by Pd or Au NPs, a rapid outward cellular transfer of electrons can be realized via the natural enzymatic EET pathway.

Table 1
Summary of heterojunction modification strategies targeting different interfacial connections between EAB individual cells and biofilms by conjugating with conductive nanomaterials.

Modification	Nanomaterials	Microorganism	Remarkable results	Ref.
Inside-membrane modification	Zero-valent palladium (Pd) NPs	*Desulfovibrio desulfuricans*	• Pd^0-NPs participated in electron-transport pathways as well as electrocatalysis on electrode surface. • A current increase of more than 232 ± 65 nA was achieved in high Pd^0 loading bio-complex.	Wu et al. (2011)
	Gold (Au) NPs	*G. sulfurreducens*	• Biogenic mineralization of Au-NPs occurred in situ in biofilms. • Current density and substrate removal increased by 44% and by 2.2 times, respectively.	Chen et al. (2018b)
	DSSN +	*S. oneidensis*	• Membrane-spanning conjugated DSSN + enhanced membrane permeability. • A greater than 14% increase in extracellular ferrihydrite reduction occurred in cell-DSSN + interaction.	Sivakumar et al. (2014)
	DSSN +	*E. coli* K-12	• A greater than 4-fold increase of current collection was obtained in cells conjugated with oligoelectrolyte. • 25 mM DSSN + caused an overall increase of charge equivalents on charge-collecting electrode.	Wang et al. (2013a)
Interfacial modification	PPy	*S. oneidensis* MR-1	• PPy coating enhanced cell conductivity and ensured cell viability. • Power density produced by PPy-coated cell was 14.1 time higher than that of wild strain.	Song et al. (2017)
	PEDOT	*P. aeruginosa*	• PEDOT/*P. aeruginosa* composite retained its electroactive redox activity for at least 30 cycles. • More than 90% of biomass was viable in PEDOT film with a thickness greater than 0.5 μm.	Le et al. (2015)
	PDA	*S. xiamenensis*	• More than a 6.1-fold increase in maximum current density occurred in PDA-coated cells. • PDA coating initiated a unique electron transport channel connected by double mediators (PDA and flavin).	Liu et al. (2019)
	CNTs	*S. oneidensis* MR-1	• A complex bound with CNTs and cell-immobilized alginate beads promoted nitrobenzene reduction initiating a shift from intracellular to extracellular processes. • Nitrobenzene reduction efficiency increased by 74%.	(Yan et al., 2014)
	CDs	*S. oneidensis* MR-1	• CD coating contributed to large increases in EET, metabolism, and ATP production. • CD-fed cells increased maximum current value more than 7-fold.	Yang et al. (2020)
	Graphene aerogel/Pt NPs	*S. oneidensis* MR-1	• A 5.3-fold increase of maximum power density was achieved for 3D biohybrids compared to carbon cloth. • Breakthrough created a precedent in 3D biohybrids-equipped MFC by successfully powering an electrical device.	Zhao et al. (2015b)
Biofilm heterojunction	Graphene–CNT	*S. oneidensis*	• A 6-fold increase in current density (120 $\mu A/cm^2$) occurred with hybrid biofilms. • A greater than 15-fold increase of maximum power density (97.9 $\mu W/cm^2$) was obtained with hybrid biofilms.	Zhao et al. (2015a)
	TiO_2@TiN nanocomposite	*S. loihica* PV-4	• Nanocomposite led to a 4.6-fold enhancement in peak current. • A 92.8% increase of power density occurred for biofilms conjugated with a TiO_2@TiN nanocomposite.	(Su et al., 2020)
	GO-PVA	*S. xiamenensis*	• Reaction time for Cr(VI) bioreduction decreased by 39 h when amended with composited biofilms. • Composited biofilms retained outstanding recyclability for more than 10 reaction cycles.	Luo et al. (2019)
	MWCNT@rGO	*S. putrefaciens* CN32	• Maximum power density obtained in MWCNT@rGO/biofilm hybrid was 6 times higher than that of conventional carbon cloth. • Interactions between integrated biofilms and hierarchically porous structure provided a higher EET performance.	Zou et al. (2016)

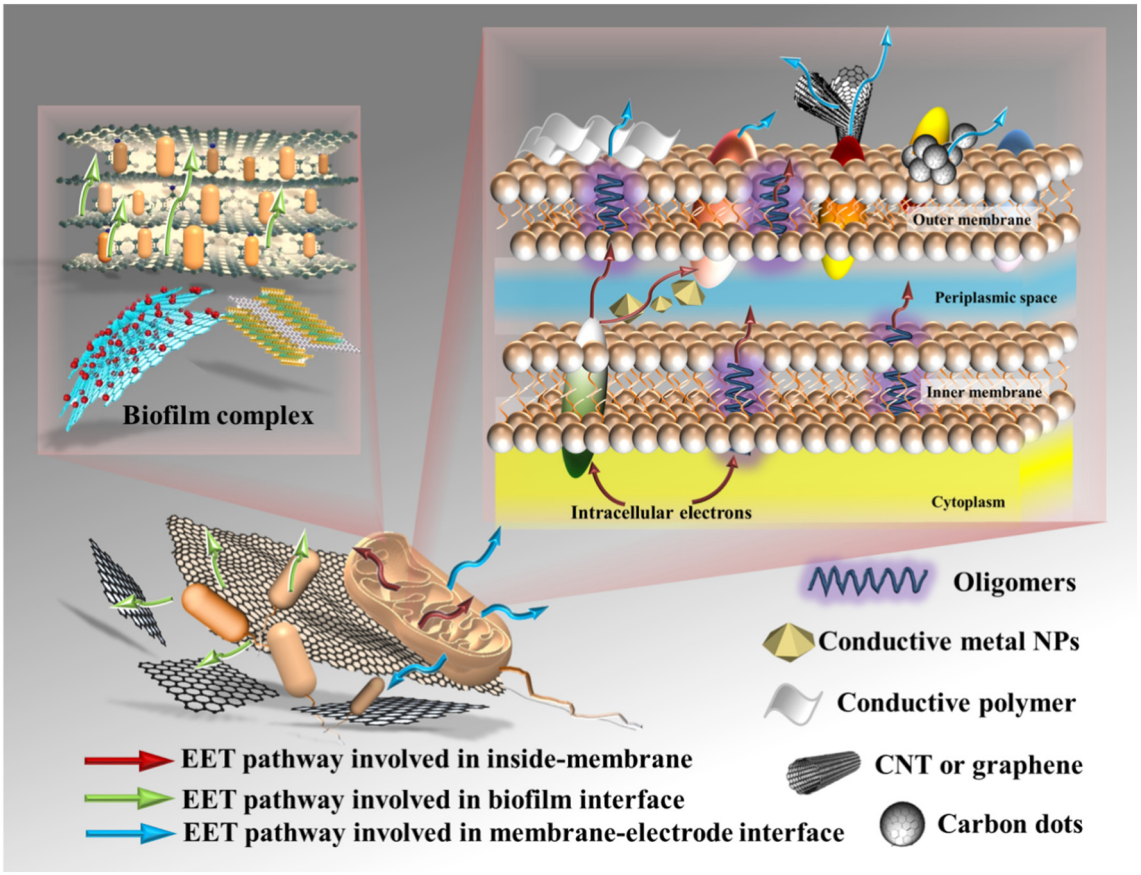

Fig. 1. Conceptual rendering of methods to improve charge transport at the living biomaterials–electrode interface using conductive nanomaterials heterojunctions and living components (individual cells and/or biofilms).

Intercalation of conductive oligomers into the lipid bilayer of the cell envelope can also improve the charge transfer orientation of pristine electrically nonconductive areas where the lipid bilayer and peptidoglycan are densely clustered in the cell envelop (Apetrei et al., 2019; Yang et al., 2008). As a result, oligomers with hydrophobic pendant groups are perpendicularly aligned in cell envelopes and stretched to extracellular interfaces, thereby overcoming physical and electrical impediments within the cell envelope. For example, Sivakumar et al. (2014) documented that assembly of *Shewanella oneidensis* MR-1 and oligoelectrolyte (4,4′-bis (4′-N,N-bis (6″-(*N*, *N*,*N*-trimethyl ammonium)hexyl) amino)-styryl) stilbene tetraiodide (DSSN+, an analogue for specific oligomer) enhanced extracellular reduction of ferrihydrite by a factor of 1.2-fold higher than the DSSN+-free strain. Thus, such optimization and regulation modifications of membrane conductivity and permeability can greatly boost the transmembrane electron transfer process.

Another avenue for increasing electron transport is to improve the orbital mixing between the extracellular electrodes and internal c-cyts responsible for electron transfer at the junction interface. Enhancement of the junction current by shortening the electron transport pathway occurs when a heterojunction complex forms via outward tethering of nanosized artificial mediators to an EAB cell. The specifically tailored structures enable a prompt release of electron flows that were temporarily stranded at the interface between EAB and extracellular electron acceptors. Previous research focused on broadening the channels for charge transfer by doping or coating with conductive polymers on the electrode surface (Table 1), such as with polypyrrole (PPy) (Song et al., 2017), poly(3, 4-ethylenedioxythiophene) (PEDOT) (Le et al., 2015), and polydopamine (PDA) (Liu et al., 2019) nanostructures. For example, Ding et al. (2012) fabricated a vertically aligned polyaniline nanowire array (PANI-NA) as a solid-state mediator to enhance local topological interactions between *Shewanella* and the extracellular electrode surface. More recent advances include in situ formation of highly conductive heterojunctions in an individual EAB cell using electrically conductive carbon-based nanomaterials, such as CNTs, carbon dots [CDs] and graphene sheets (Yazdi et al., 2016; Yong et al., 2014b; Zhou et al., 2015). For instance, Yang et al. (2020) reported augmentation of *S. oneidensis* MR-1 by feeding with CDs for bioelectricity enhancement. In their work, the maximal densities of current and power in the BES incubated with CD-fed *S. oneidensis* MR-1 were 8.3- and 7.5-fold higher than that of the wild strain, respectively (Yang et al., 2020). Treatment with the assembly of CDs enabled *S. oneidensis* MR-1 to generate greater intracellular electron fluxes, higher ATP levels, higher organic substrate utilization and more efficient transmembrane transfer of intracellular electrons (Yang et al., 2020). The effectiveness of carbon-based nanomaterials for interface optimization was attributed to their strong electrical conductivity and ability to enhance EAB adhesion on the surface, thereby increasing the contact between c-cyts and the extracellular electrode (Li et al., 2020c; Yong et al., 2014b).

The combined utilization of different nanomaterials was reported to create multiple benefits for further enhancing BES performance. For instance, hybrid insertion of multi-walled CNT or conductive metal/metal oxide NPs acts as a scaffolding within the graphene skeleton. These structures provide both attachment sites for EAB adhesion in a 3D-skeleton and rapid mass transport (e.g., organic substrates and extracellular electron acceptors) and charge transfer owing to enhanced orbital alignment and contact coupling via graphene connections (Huang et al., 2011; Zhao et al., 2015b; Zou et al., 2016). This reinforcement effect is reflected in the novel living “single cell electron collector” concept, which was exploited by Yu et al. (2020). In their study, microbial mineralization was initially used for in-situ assembly of FeS NPs at intracellular periplasmic space – outer membrane junction sites. Subsequently, in-situ PDA polymerization was used to assemble the extracellular EAB–electrode junction interface. The cellular electron transfer machineries comprising the

biological circuit system were initially separated, but thereafter seamlessly connected to ensure an efficient charge orientation and export of intracellular electrons to extracellular electrodes. Notably, optimization of this "inward-to-outward" hybrid bio-interface achieved record-high interfacial electron transfer efficiency.

2.2. EAB – biofilm heterojunctions of electrically conductive materials

Biofilms formed under natural conditions often develop little biomass resulting in thin deposits, sparse spatial distribution patterns and poor conductivity (Matsukawa and Greenberg, 2004). Accordingly, methods to promote electron transfer at the biofilm-electrode interface are a key consideration. To decrease the "blind areas" (dead ends) where electrons are detained at the biofilm – electrode interface, a successful tactic is to promote formation of a hybrid conductive material – biofilm heterojunction (Yang et al., 2020). Therein, nanomaterials with biocompatibility and high electrical conductivity are used to develop self-sustaining heterojunctions that ensure efficient EET processes. A series of investigations on abiotic/biotic coupling heterojunctions (e.g., nanostructured polymer – biofilms and/or graphene/CNTs – enzymes, Table 1) revealed that overlapping heterojunction structures favored microbial substrate utilization and charge transfer, thereby boosting bio-electricity generation (Lv et al., 2018; Ray et al., 2020; Su et al., 2020; Zhao et al., 2015a). In particular, multiple lines of orbits constructed in these overlapping heterojunction architectures are mostly layer-ordered, multidirectional and highly conductive, thereby favoring the transport of microbial substrates and boosting surface/interface dynamic reactions (Wang et al., 2016; Xie et al., 2015). The improved heterojunction not only enhances cell aggregation and formation of a dense, thick biofilm on the electrode surface, but also induces the reduction of extracellular electron acceptors.

Rouhani et al. (2018) fabricated a hybrid graphene oxide-$CuFe_2O_4$-laccase composite via a covalent bonding method for use in the synthesis of arylsulfonyl benzenediols. SEM and FTIR characterization demonstrated formation of an effective physiochemical connection at this heterojunction complex. Notably, the activity recovery of the immobilized laccase composite retained greater than 80% of its initial activity after 10 reaction cycles (Rouhani et al., 2018). Likewise, Luo et al. (2019) fabricated a unique complex by grafting *Shewanella xiamenensis* biofilms onto graphene oxide/poly (vinyl alcohol) films (denoted as *S. xiamenensis*–GO/PVA complex) to enable Cr(VI) reduction in wastewater. Due to the large specific surface area of GO and favorable biocompatibility of poly(vinyl alcohol), an abundance of *S. xiamenensis* cells developed an ordered architecture based on the layered-skeleton of the GO sheets that orchestrated/arranged cell distribution. The generated biofilm was uniformly stacked and thickened with each subsequent reaction cycle, which ensured a large biofilm buildup to resist extracellular pollutants. The *S. xiamenensis*–GO/PVA complex was effectively used for Cr(VI) bioreduction under aerobic conditions, circumventing many of the limitations experienced under the anaerobic conditions required by most conventional BESs (Li et al., 2019b; Middleton et al., 2003). Moreover, the catalytic efficacy of biofilms for Cr (VI) bioreduction progressively increased in subsequent reaction cycles, with the reaction time of the tenth cycle reduced to 9 h compared to 48 h in the control group (Luo et al., 2019). The ability to recycle the reaction system containing the living heterojunction complexes demonstrates the efficacy for practical/economical, large-scale applications of BESs.

3. Living hybrid composites of self-assembling EAB and photocatalytic semiconductor NPs

3.1. Biohybrids assembled with metal-based semiconductor NPs

In the process of EAB extracellular respiration, the supply of electrons mainly relies on microbial degradation of low-molecular-weight organic substrates to release electrons (Chen et al., 2018c). Conversely, photoelectrons are generated from photoelectron-hole pairs in illuminated semiconductors, accompanied by the capture of oxidizing holes scavenged by reductive sacrificial compounds (like cysteine) to inhibit the recombination of photoelectron-hole pairs (Sakimoto et al., 2016a). Since photoelectrons are highly reductive and their potentials are more negative than that of most biological compounds, the excited photoelectrons from illuminated nano-sized semiconductors are readily accepted by EABs to drive specific reduction processes (Yang et al., 2011b).

Transmittance-based transient absorption and time resolved infrared spectroscopy are able to clearly elucidate the lifetime of charge uptake and discern the pathways of photoexcited electrons directly feeding into membrane-bound proteins in several EAB-semiconductor NP hybrid biomaterials (Kornienko et al., 2016). Photosynthetic living hybrid biomaterials may configure through pairing various host EABs or enzymes (e.g., *Geobacter sulfurreducens*, *Escherichia coli* and catalase) with specific semiconductors (e.g., CdS, TiO_2 and InP NPs) (Cestellos-Blanco et al., 2020; Dong et al., 2020a). This implies that semiconductor NPs featuring large surface areas enable an intimate interaction with EABs contributing to microbial metabolism for enhanced biochemical reactions. For instance, photoelectrons can be transferred to membrane-bound hydrogenase where they utilize H_2 as an intermediate to generate reducing equivalents for microbial central metabolism (Kornienko et al., 2016). Hence, the ability of living hybrid composites to accept/store photoelectrons will contribute additional electron flux/reducing equivalents to desired extracellular reduction processes (Cestellos-Blanco et al., 2020). Promoted by this novel energy utilization pathway, the association of semiconductor NP photocatalysis and microbial EET enables living biomaterials to generate more reducing power, thereby making extracellular reduction more effective and energy efficient. Accordingly, semiconductor NPs give non-photosynthetic bacteria a boost, wherein non-photosynthetic bacteria covered with semiconductor NPs are more efficient in light utilization. These assembled artificial biohybrids show great potential for creating acetic acid, bioplastics and biofuels (Fang et al., 2020b; Gupta et al., 2021; Tremblay et al., 2020).

Fig. 2 illustrates the fine-scale architecture of living biohybrids that are assembled with semiconductor NPs either partially or in their entirety to enhance their function. Nanoparticle-based artificial mediators, such as ZnS, CdS and TiO_2, are representative metal-based semiconductor photocatalysts, which are widely applied to the photodegradation of refractory organic compounds, hydrogen generation by splitting water, and the preparation of hydrocarbon fuels (Collado et al., 2018; Ijaz et al., 2016; Li et al., 2019a; Li et al., 2012; Puentes-Prado et al., 2020). Metal-based semiconductor NPs, featuring high-efficiency, solar/electricity conversion, contribute to building abiotic-biotic hybrid biomaterials that combine the strengths of abiotic catalysis and natural EABs. Thus far, engineered hybrid living materials incorporating EABs and metal oxides/sulfides-based semiconductor NPs have demonstrated applicability in several environmental applications (Cestellos-Blanco et al., 2020; Dong et al., 2020b; Sahoo et al., 2020). For instance, incorporating biocompatible CdS NPs with *Rhodopseudomonas palustris* increased intracellular production of ammonia, and $_L$-amino acids were converted from extracellular inorganic nitrogen gas with the aid of photoelectrons (Wang et al., 2019b). These studies highlight that exploitation of hybrid living materials to harvest light energy in BESs can energetically enhance the conversion of inorganic materials to organic products (such as the synthesis of high value-added organic chemicals and energy products).

Although semiconductor NPs are readily accessible and highly responsive to light irradiation, a major concern is how to construct a reliable hybrid system integrating a flexible conformational structure with sufficient energetic catalysis efficiency to warrant its practical application. In the design of biohybrids, EAB serves as the chassis for the architectural design of the hybrid living biomaterial and provides scaffolding for the immobilization of semiconductor NPs (i.e., key building blocks in biohybrids) (Fig. 2). An ideal combination for structure and function of biohybrid materials requires semiconductor NPs to concurrently possess favorable biocompatibility and photocatalytic properties at a programmed scale. The band gap and spectral wavelength response of the semiconductor photocatalyst are the foremost concerns in the field of photocatalysis (Cheng et al.,

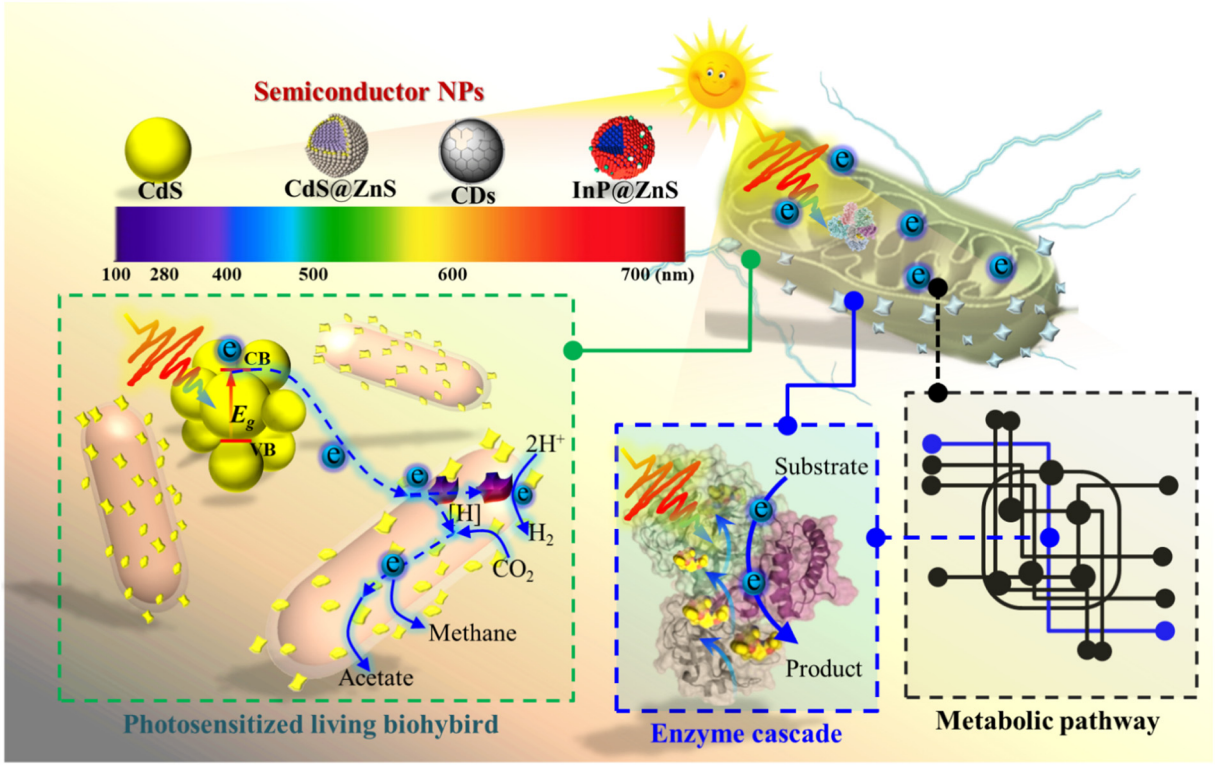

Fig. 2. A schematic representation of living biocatalysts in the form of self-assembling photoelectrochemical semiconductor biohybrids.

2018). Among a variety of metal-based semiconductor photocatalyst NPs, CdS NPs have emerged as a promising semiconductor candidate owing to their biocompatibility with a variety of cellular units (Dong et al., 2020b). In contrast to materials that require UV illumination, CdS NPs have a narrow band gap (~2.4 eV) and provide easier separation of photoelectron-hole pairs under illumination than other semiconductor NPs (like TiO_2 NPs with a wide band gap of 3.2 eV) (Cheng et al., 2018). Additionally, irradiation damage of cellular units in response to visible light for CdS NPs is substantially weaker than for TiO_2 NPs that suffer damage from ultraviolet light (Chen and Mao, 2007).

The majority of past investigations focused on BESs utilizing biohybrids assembled with metal-based semiconductor NPs (Table 2). For instance, Huang et al. (2019) achieved a maximum kinetic rate constant (1.441 h^{-1}) for methyl orange biodecolorization using a CdS NPs-*G. sulfurreducens* living hybrid composite. The composite retained its high catalytic performance even after 4-repeated use cycles. Moreover, Zhang et al. (2020a) employed targeted metabolomics combined with the proteome to probe the Wood-Ljungdahl pathway in CdS NPs-assembled *Moorella thermoacetica* hybrid cells. The presence of CdS NPs under illumination triggered an up-regulated production of enzymes and stimulated the glycolysis and TCA cycles involved in ATP production (Zhang et al., 2020a). Additionally, a layer-by-layer (LBL) deposition that precisely controls shell thickness can be used to build site-specific, core-shell platforms, such as metal-based semiconducting quantum dots (QDs). These QDs promote photoelectron injection more efficiently in living hybrid composites (Ding et al., 2019; Nakamura et al., 2020; Toufanian et al., 2018). Therein, different assembly patterns for core-shells bound with key building blocks can be created to optimize a living hybrid composite's responsiveness to a broad spectrum of wavelengths. This involves the incorporation of different metal-based semiconducting QDs, thereby harnessing pristine living biomaterial with finely tuned bandgap semiconductors to enhance photocatalysis (Ding et al., 2019).

Depending on the host strains and target products, biohybrid outcomes differ among contrasting assembly patterns between metal-based semiconducting core-shell QDs and host strains. For example, a living hybrid composite consisting of CdS@ZnS QDs and *Azotobacter vinelandii* promoted conversion of N_2 to NH_3 under illumination with green wavelengths (Ding et al., 2019); whereas assembly of InP@ZnS QDs with *Cupriavidus necator* allowed production of polyhydroxybutyrate (PHB) by incorporating CO_2 under illumination with red wavelengths (Ding et al., 2019). Thus, selection of specific assembly patterns can be used to fine-tune electron transfer to allow production of both bulk and fine chemicals. Collectively, these findings suggest considerable potential for the use of biohybrids in BES applications. They offer emerging opportunities for applying semiconductor NPs in production of renewable organic products via substrate-free microbial factories using sunlight in scalable industrial processes.

3.2. Biohybrids assembled with carbon-based semiconductor NPs

The ultimate goal for the design of advanced photocatalysts is to achieve green, sustainable and highly efficient materials. Many metal-based semiconductor NPs exhibit desirable photocatalytic capabilities and generate abundant photoelectrons. However, leaching of toxic metals from photocorrosion of biohybrids assembled with metal-based semiconductors NPs may result in environmental pollution (Ding et al., 2019; Huang et al., 2019). Additionally, the wide range of band gaps comprising metal-based semiconductor NPs often rely on high-intensity light sources (e.g., UV-irradiation) for effective excitation, which not only damages living cells (Svitkova et al., 2017), but also limits the practical application of metal-based semiconductor NP-derived biohybrids (Fang et al., 2020b). Thus, it is essential to improve the design of photoactive bio-nano interfaces to achieve the sustainability and efficiency goals of biohybrid-metal semiconductor technologies.

Compared with conventional metal oxide/sulfide semiconductors, metal-free light harvesters commonly exhibit a low toxicity and cost. Several carbon-based materials, such as carbon nitrides (C_3N_4) and CDs with high water solubility, photostability and tunability (with an absorption wavelength > 600 nm), stand out among the most bio-friendly photosensitizers used for photocatalysis (Han et al., 2020; John et al., 2019; Liu et al., 2020a; Zhang and Zhao, 2009). Building upon these advantages, full

Table 2
A representative summary of living hybrid composites used for improving BESs performance.

Nanomaterial/band gap (eV)	Strain/enzyme	Substrates/Products	Remarkable results	Ref.
CdS NPs (2.40)	*G. sulfurreducens*	Methyl orange (MO)/CO_2 + H_2O	• Biohybrid achieved a maximum kinetic rate constant of 1.441 h^{-1} for methyl orange biodecolorization. • Biohybrid retained its high catalytic capacity after four repeated use cycles.	Huang et al. (2019)
CdS nanorods (2.40)	*E. coli*	Glucose/H_2	• Biohybrid displayed increased productions of pyruvate and formate, stimulated hydrogenase activity and elevated ratio of (NAD)H/NAD. • Biohybrid enabled over 120 μmol H_2 generation within 3 h using wastewater and natural sunlight as inputs.	Wang et al. (2017a)
CdS QDs (2.29)	*Moorella thermoacetica*	CO_2/acetate	• CdS QDs under illumination promoted glycolysis and TCA cycles. • Key enzymes involved in WLP and ATP production were upregulated by CdS QDs-illumination treatment.	Zhang et al. (2020a)
CdS NPs (2.41)	*Clostridium autoethanogenum*	CO_2/acetate	• Conversion only relied on the use of photoelectrons from CdS-NPs. • Expression of flavin-binding proteins increased with the activation of genes associated with the WL pathway and energy conservation system.	Jin et al. (2021)
CdS NPs (2.40)	*Methanosarcina barkeri*	CO_2/CH_4	• CH_4 generation (0.19 μmol/h) occurred at a high quantum efficiency (0.34%) comparable to that of plants or algae. • Expression of *mcrA* gene was up-regulated by over 150%.	Ye et al. (2019)
CdS@ZnS QDs (2.31)	*Azotobacter vinelandii*	N_2/NH_3	• Biohybrid sustained its efficacy even under 365-nm UV light excitation. • Biohybrid displayed low total capacitance and charge transport resistance.	Ding et al. (2019)
InP@ZnS QDs (1.42)	*Cupriavidus necator*	CO_2/PHB	• Biohybrid gained desired functionality under illumination with red wavelengths. • PHB production driven by biohybrid was obtained with a high turnover number (10^6–10^8).	Ding et al. (2019)
$CuInS_2$/ZnS QDs (1.79)	*S. oneidensis*	H_2O/H_2	• Unique periplasmic photosensitized biohybrid system enabled a high local expression of hydrogenase. • H_2 generation was 9.6 times higher due to photocatalysis by QDs.	Luo et al. (2021)
g-C_3N_4 (2.70)	*R. eutropha*	CO_2/PHB	• A 1.2-fold increase in PHB production was achieved by a C_3N_4-*R. eutropha* biohybrid even in the absence of an external supply of electron donors. • An augmented level of intracellular NADPH/NADP+ occurred in the C_3N_4- *R. eutropha* biohybrid.	Xu et al. (2019)
g-C_3N_4 (2.70)	Catalase	CO_2 or fructose/PHB	• A C_3N_4-catalase biohybrid achieved a high solar-to-hydrogen efficiency of 3.4%. • Biohybrid promoted heterotrophic bioplastic production by *R. eutropha* from CO_2.	Tremblay et al. (2020)
Single-walled carbon nanotubes (SWCNT) (UR)	*Clostridium ljungdahlii (C.lj.)*	CO_2/acetate	• SWCNT promoted a higher biofilm coverage and improved biofilm electrocatalytic activity. • A high Faradaic efficiency (~91%) for CO_2 reduction occurred at the SWCNT/*C.lj.* hybrid interface.	Li et al. (2021)
Perylene diimide derivative (PDI)/poly (fluorene-*co*-phenylene) (PFP) complex	*M. thermoacetica*	CO_2/acetate	• Positively charged PDI/PFP was intercalated into bacteria membrane, which enables the direct transfer of photoelectrons from PDI/PFP to bacteria. • Efficiency of this organic biohybrid was ~1.6%, which was comparable to reported inorganic biohybrid systems.	Gai et al. (2020)
N, S-doped CDs (NSCDs) (UR)	*S. oneidensis*	Carbon felt-based anode/NSCDs-modified bioanode	• NSCD-modified bioanode had enhanced conductivity and served as a photosensitizer to harvest solar energy. • The NSCD-modified bioelectrode exhibited a 2.6-fold increase in power output compared to raw bioelectrode.	Guo et al. (2019)
Red-emission CDs (RCDs) (2.21)	*S. xiamenensis* (*S.x.*)	*S.x.*-based electrode/RCDs-*S.x.* biohybrid-based electrode	• Increased production of flavins and enhanced conductivity in biohybrid promoted outward export of intracellular electrons. • Illumination of biohybrid electrode lead to a 4.8-fold increase in current density compared to *S.x*-based electrode.	Liu et al. (2020b)
Aspartic acid-based CDs (UR)	L-aspartic acid (AspCDs)/[FeFe] hydrogenase	H_2O/H_2	• Biohybrid achieved an external quantum efficiency of 1.7% at 420 nm under favorable electrostatic conditions. • The stability of biohybrid in the presence of a redox mediator extends to over 1 week.	Holá et al. (2020)

Note: UR = unrecorded in corresponding published article.

exploitations of the intrinsic merits of semiconducting carbon-based materials are expected to improve the performance of multidimensional hybrid biomaterials (Table 2). For example, Liu et al. (2020b) demonstrated that the living hybrid composite comprised of red-emission CDs and *S. xiamenensis* not only enhanced surface and interfacial conductivities between EABs and extracellular electrodes, but also stimulated the production of intracellular flavins to facilitate EET. Further, Yang et al. (2020) substantiated that deposition of CDs on *S. oneidensis* MR-1 cells initiated site-specific interactions with c-cyts and triggered more vigorous metabolism than found in normal cells. As a result, ATP levels increased by 36% compared to the control incubation without CDs.

The opposite charges comprising CDs and membrane-bound proteins facilitate their electrical interactions at the molecular tunnel junction (Chang et al., 2011; Tezcan et al., 2001), and the ligands on the CDs further shorten the electronic gap promoting charge transport, thereby strengthening multiple long-range electron tunneling (Winkler and Gray, 2014). Moreover, a good match of CD size/geometry to the dimensionally active sites of enzymes confers a stronger light-harvesting center in biohybrid systems that can accumulate charge and subsequently transfer electrons (Han et al., 2020). Such intimate assembly properties were verified by Holá et al. (2020) in demonstrating that scalable photocatalytic hydrogen evolution was sustained for more than one week when using a CD-[FeFe] hydrogenase biohybrid as a photosensitizer.

Since the carbon atoms bonding in CDs are strongly sp^2-hybridized and conjugated to form polycyclic structures with different sizes and shapes (Tepliakov et al., 2019), unique CD configurations could be designed to

promote bio-nano interactions and further influence the conformational structure of proteins at the interface. These design modulations offer a favorable association between c-cyts and CDs, while also ensuring that the pathway for electron transfer across the bio-nano binding interface is multi-dimensional. Accordingly, it is plausible to integrate CDs with EABs to enhance microbial metabolism and release more electrons, while also creating multiple avenues for delivery of intracellular electrons.

4. Cytoprotection in biohybrids

4.1. Configuration by coating charged polymers and inorganic materials

Achieving a robust eco-defense capacity for alleviating inhibiting factors is an essential objective for engineering advanced living biomaterials. This concept plays an important role in maintaining the materials' inherent structures and functions in response to environmental stimuli/stress. In living hybrid composites, the living biological component (i.e., EAB and enzyme) is extremely vulnerable and sensitive to the external environment. As the living biological component serves as the "main body" of biohybrids, it is critical to protect the integrity of the biological component. Several other impediments may also emerge in semiconductor NP-assembled biohybrids, such as (1) oxidizing holes containing various types of reactive oxygen species (ROSs) from semiconductor materials that act to suppress microbial metabolism (Dwyer et al., 2009); and (2) the presence of ROSs that hinder the synthesis of terminal products (e.g., organic carbon compounds converted from bioreduction of CO_2 via the Wood–Ljungdahl pathway) (Cestellos-Blanco et al., 2020; Korbecki et al., 2013; Panasyuk et al., 1994). To assure an effective release of photoelectrons, sacrificial agents (such as cysteine) are often added to biohybrid systems to quench holes (Sakimoto et al., 2016b). The resulting demand for commercial sacrificial agents increases the complexity and cost of operating biohybrid systems. Accordingly, the goal/concept of developing "economic and recyclable" new materials is critical to the commercialization of biohybrid production systems. Fig. 3 depicts several cytoprotective strategies using LBL coating technologies in which specific core/shell structures are coated with charged polymers, inorganic materials, hydrogel, metal-organic frameworks (MOFs) and nanozymes. These cytoprotective strategies have been utilized for optimizing and protecting living biohybrid systems, resulting in a series of favorable modification outcomes, such as ROS decomposition, improved mechanical strength, strong adaptability and enhanced thermal stability.

With the rapid development of LBL-based nano-coating technologies (Wu et al., 2015), coating the core/shell of a biohybrid with a charged polymer has been demonstrated to effectively circumvent suppression by ROS (Shchukin et al., 2004; van Dongen et al., 2009). Since the cell surfaces of bacteria are negatively charged (Wilson et al., 2001), coating positively charged polymers on the surface of the bacterial outer membrane offers a protective shield for immobilization of inhibiting compounds (Wei et al., 2018; Yang et al., 2009; Zafar et al., 2019). For instance, biocompatible antioxidant polymeric formulations have attracted interest due to their ROS-scavenging capabilities. Yang et al. (2011a) designed a bulk PDA-coated *Saccharomyces cerevisiae* cell system that efficiently attenuated the detrimental effects induced by foreign lyticase. Furthermore, Wei et al. (2018) employed a LBL coating process that first immersed CdS QDs-*E. coli* hybrid cells with anionic PSS [polyelectrolyte sodium polystyrene sulfonate] and cationic PDADMAC [poly (diallyldimethylammonium chloride)] solutions, and then coated the resulting cells with silicic acid. Thereafter, ROS stress in the biomimetic silica-coated biohybrid cells was

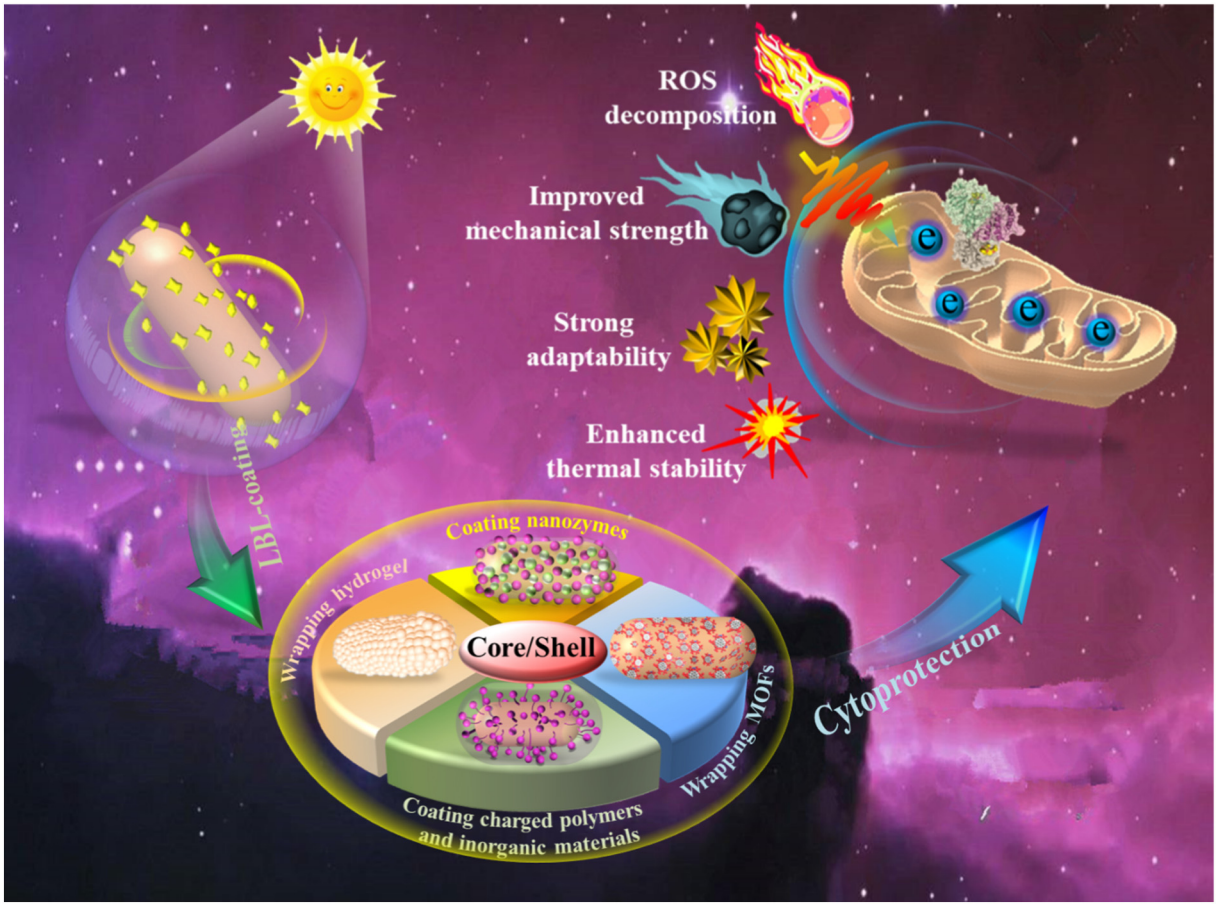

Fig. 3. Cytoprotective strategies utilized for protecting living biohybrids using LBL coating technologies to form core/shell structures with charged polymers, inorganic materials, hydrogel, metal-organic frameworks (MOFs) and nanozymes.

prominently mitigated rendering the biomimetic silicon encapsulated hybrid system effective for hydrogen generation (for 96 h under natural aerobic conditions). Further, to maintain the stable structure and function of hybrid systems, antioxidant polymeric formulations were designed using novel engineered encapsulation platforms, such as molybdenum-based polyoxometalate nanoclusters (Ni et al., 2018), glycol chitosan-coated selenium (Abid et al., 2021) and cerium oxide NPs decorated with polycaprolactone (Jain et al., 2021).

4.2. Encapsulation in hydrogel

In addition to polymer coatings, significant progress has occurred in the design of hydrophilic hydrogel coatings as an effective ROS-scavenger (Chen et al., 2018a; Cheng et al., 2021; Dollinger et al., 2017). The large and complex structural network of hydrophilic hydrogels enables the survival of the encapsulated cells by providing an antioxidant protective layer, even though the biohybrid may be immersed in an environment with high oxidative stress (Chai et al., 2017; Zhang and Khademhosseini, 2017). A representative example of this strategy was reported for enhanced tissue regeneration of diabetic wounds (Zhao et al., 2020). A PVA-based hydrogel, a special ROS-defending system, was established by assembling mupirocin with granulocyte-macrophage colony-stimulating factor to facilitate a cross-linked reaction. Consequently, hydrogel dressing cells formed by LBL coating techniques have the ability to form a compact polymeric shell that provides defensive protection from ROS stress, thereby broadening the environmental applications of living biohybrids. Likewise, the addition of alginate hydrogels into liquid autotrophic media resulted in successful formation of microbeads for cell encapsulation. These microbeads provided an effective shield for photosensitized *M. thermoacetica* cells, but also allowed unencumbered cell proliferation and functioning (Cestellos-Blanco et al., 2019). The protection offered by alginate hydrogels increased conversion of solar-driven CO_2-to-acetate by gold nanocluster-*M. thermoacetica* biohybrids. Structural modification by hydrogels provides beneficial opportunities to protect the structure and function of biohybrids, allowing them to acclimate to more complex and adverse environments. Importantly, additional research examining hydrogel characteristics (e.g., composition, thickness, permeability, etc.) are necessary to optimize the protective systems that hydrogels provide to allow practical scalability of living biohybrids for commercial applications (Kim et al., 2019; Qu et al., 2019).

4.3. Configuration of biohybrids with metal-organic frameworks

Artificial metal-organic frameworks (MOFs) have the ability to serve as a physical barrier to strengthen the robustness of cell membranes and adaptability of cells in biohybrid systems (Shekhah et al., 2011). Beneficial attributes of MOFs include a highly separable topological space, multiple adjustable pores and tunability to target a specific purpose/function. For example, MOFs can be incorporated into living biohybrid composites to act as a physical barrier to resist heat, UV radiation, osmotic pressure and mechanical pressure (Drachuk et al., 2012; Liu et al., 2016; Park et al., 2014). Liang et al. (2017) examined the utility of a living MOF-enzyme complex encapsulated in a unique shell structure to control the adaptive growth of yeast cells. In this case, a zeolitic imidazolate framework-8 was set up as a scaffold for β-galactosidase to fabricate a bioactive porous synthetic shell. Their results demonstrated that a majority of the MOF-coated cells remained active for more than one week, even in a nutrient-deficient environment. Further, a study by Ji et al. (2018) developed a MOF-*M. thermoacetica* hybrid complex in which *M. thermoacetica* was wrapped with a 1–2 nm MOF monolayer (a composite of $Zr_6O_4(OH)_4(BTB)_2(OH)_6(H_2O)_6$) to provide a defense against cellular stress caused by oxidative ROSs. Enclosing the biohybrids within the MOF structure allowed facile reproduction of cells while also protecting the newly generated cells from environmental stressors (mortality of MOF-coated cells was 20% that of the non-MOF control group). Additionally, the electron stream generated from microbial respiration and the photocatalyzed zirconium cluster interface was readily transferred from the porous MOFs to the external electrodes, leading to a doubling of acetate production by CO_2 fixation. Therefore, the formation of microcapsules with nanometer-thick layers of MOF-coatings on individual cells is able to enhance the performance of biohybrids in semiconductors/biological cell systems, while also improving their adaptation/resilience to harsh environmental conditions.

4.4. Configuration of biohybrids with nanozymes

Considering the complicated synthetic processing and high manufacturing cost of MOFs (Zhang and Lin, 2014), their application for protecting biohybrids has been limited. Alternatively, the use of in-situ coatings of defensive enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) has been demonstrated for protecting cells from damage induced by ROS oxidation (Ighodaro and Akinloye, 2018; Jo et al., 2020). These nanozymes exhibit several versatile capabilities, which not only complement the fundamental features of nanomaterials, but also integrate many advantages of natural enzymes (Wang et al., 2019c; Wu et al., 2019). In the process of ROSs scavenging by SOD-mimicking nanozymes, the ROS undergoes a series of decomposition steps: ROS → superoxide → hydrogen peroxide → water + oxygen gas (Wang et al., 2019c). The assembling of nanozymes has sparked considerable interest in recent years as nanozymes require a relatively simple synthesis process and is morphologically stable, as well as being tunable for specific catalytic activities, even under harsh environmental conditions (Golchin et al., 2017; Wang et al., 2020). As a result, several coating strategies have been developed in which biohybrids were encapsulated in a biocompatible, biomimetic nanoreactor that ensures cell viability/function within the "nanozyme capsule". Thus, the prospect of coating biohybrids with nanozymes to resist ROS damage is alluring for manufacturing high-performance living biomaterials.

Artificial nanozymes (e.g., Fe_3O_4, Mn_3O_4, Co_3O_4 and V_2O_5 NPs) are endowed with considerable POD/SOD/CAT-mimicking and redox activities (Wang et al., 2019c; Wu et al., 2019). As a result, ROS radicals generated from semiconductor NPs are likely to be rapidly blocked and caged in a nanoreactor coated with nanozymes, along with an intermediate release of photoelectrons. Figuratively, this nanoreactor acts as a durable/protective habitat to sustain the living attributes of biohybrid composites. The nanozyme coating functions as a durable barrier that is capable of providing protective SOD and CAT compounds to resist ROS attack (Jo et al., 2020; Wang et al., 2019c). For example, Chen et al. (2020a) reported successful formation of a nanoencapsulated living material with an in situ coating of Mn_3O_4 nanozyme on the surface of CdS NPs-*Thiobacillus denitrificans* biohybrids. The nanoencapsulated biohybrid greatly accelerated the decomposition of ROSs, with removal rates for ·OH and H_2O_2 up to 90% and 26%, respectively. Similarly, there was an appreciable acceleration of NO_3^- reduction (28% via photoelectrotrophic denitrification), as well as a decrease in N_2O emission (78%) after Mn_3O_4 nanozyme coating. Hence, the unique properties imparted by nanozyme coatings have excellent prospects as a useful biomimetic antioxidant defensive strategy. The nanozyme coatings provide individual cells with a three dimensional and robust space to maintain their cell viability/functions, while also enhancing cellular metabolism for specific physicochemical manipulations at a single-cell level in a sustainable manner.

Notably, the functions of living biomaterials are strongly dependent on the metabolic activities of EABs and the physicochemical conditions provided by their habitat, which is difficult to sustain in an inhospitable microenvironment for the lifetime of a given living biomaterial. Similar to natural enzymes, nanozymes are inherently sensitive to pH and temperature (Wu et al., 2019). Hence, adverse pH and temperature conditions create limitations for biomaterials consisting of EAB, photocatalysts NPs and nanozymes as their catalytic activities are compromised. In-vitro assays indicated that nanozyme activities are strongly pH dependent, with SOD- and CAT-mimicking activities more suitable for neutral and alkaline conditions, whereas peroxidase-like properties are more appropriate under acidic conditions (He et al., 2018; Liu et al., 2021). Additionally, the optimum temperatures for the nanozymes of peroxidase-mimicking Fe_3O_4 NPs and

glucose oxidase-mimicking AuNPs were 60 °C and 65 °C, respectively (Liu et al., 2021; Vallabani et al., 2017; Xu et al., 2017). Thus, the design of nanozymes must balance both physiological and environmental conditions to optimize the energetics and targeted functions of living biomaterials.

5. Directed evolution of EABs using synthetic biology methods

5.1. Upregulated expression of conductive c-cyts and intracellular redox mediators

EABs are a key component of composited-biomaterials and strongly influence the holistic performance of electron transfer and other biogeochemical functions. Notably, the choice of suitable EABs for use as a living biomaterial framework mostly depends on the availability of their genomic sequences, e.g., *Geobacter* and *Shewanella* (Nguyen et al., 2018). Additionally, model EABs rapidly reproduce and are genetically well characterized, allowing them to efficiently prototype genetic circuits and express foreign biomolecules in a plug-and-play fashion. The expression of proteins responsible for charge transport is critical for determining the efficacy of composited biomaterials. Hence, optimizing promoter–regulator pairs to reduce background activation using genetic editing tools facilitates the directed evolution of EABs toward augmented intracellular electron flux and programmable functionality. The compelling prospects of using synthetic biology tools to design biomolecular and cellular functions (Santos-Merino et al., 2019; TerAvest and Ajo-Franklin, 2016) will allow EABs to become more adaptive and versatile for execution of complex tasks by BESs. Recent advances in genetic manipulation include upregulating the expressions of c-cyts and electrically conductive pili (e-pili) (Fig. 4a), as well as endogenous redox mediators (e.g., flavin and phenazine-like biogenic compounds, Fig. 4b) (Liu et al., 2017; TerAvest and Ajo-Franklin, 2016). These modifications harness more electron-exporting conduits for direct intracellular and extracellular electron transport and shuttling of electrons within living components on a much larger scale. For instance, existing technologies allow the artificial installation of special synthetic electron conduits in EAB cells (Li et al., 2018c; Liu et al., 2017; TerAvest and Ajo-Franklin, 2016). Current and emerging synthetic biology technologies will facilitate the tailoring of EABs to address highly specific physiological functions (Glaven, 2019; TerAvest and Ajo-Franklin, 2016). Therefore, living biomaterials custom-modified by synthetic biology will open numerous possibilities for creating new classes of bio-inspired materials to target specific applications.

In early 2010, a new paradigm for harnessing the synthetic electron conduit in a heterologous host was implemented by heterologously expressing the genes (*mtrC*, *mtrA*, and *mtrB*) encoding for the Mtr pathway of *S. oneidensis* MR-1 in *E. coli* (Jensen et al., 2010). The overexpression created a conduit that routed electrons along a well-defined path from the cell interior to an extracellular acceptor, and ultimately increased the rate of metal oxide reduction by at least 8-fold compared to that of the parental strain. Moreover, the e-pili of *Geobacter metallireducens* were shown to serve as a remarkable electrically conductive material. Tan et al. (2017) heterologously expressed the PilA gene of *G. metallireducens* in *G. sulfurreducens* demonstrating a high yield of pili with exceptional conductivity for long-range EET in the mutant strain. Likewise, Yang et al. (2015) confirmed that the overexpression of native riboflavin by *Bacillus subtilis* in *S. oneidensis* MR-1 conferred enhanced bidirectional EET capability. The newly synthesized flavin conduit enabled the recombinant strain to tightly

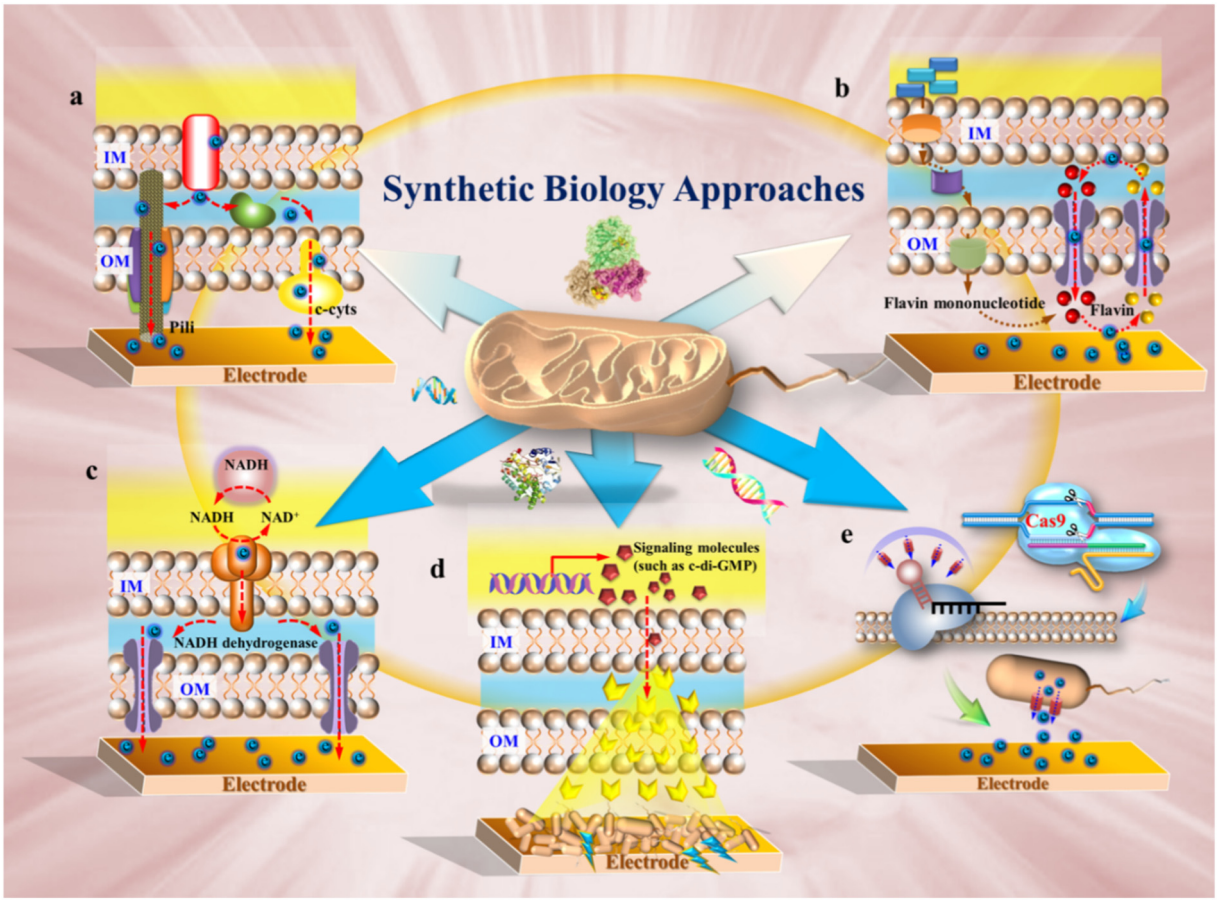

Fig. 4. Schematic representation of synthetic biology approaches for modifying EAB to boost electron production and transfer. The approaches mainly alter the biological components of an individual EAB cell, such as conductive c-cyts (a), intracellular redox mediators (b) and the NADH pool (c). Additional augmentation/formation of biofilms could stimulate cell-to-cell communication using specific quorum-sensing molecules (d). Moreover, improvement of the electron-exporting center in an EAB cell could be achieved using CRISPR-related methodologies (e). (Note: OM and IM labels in this figure refer to the outer membrane and inner membrane, respectively.)

"wire up" to extracellular electrodes resulting in a greater than 15-fold increase in the current density of a microbial fuel cell (MFC) (Yang et al., 2015). Further enhancement of EET processes was accomplished by harnessing collaborative interactions between redox mediators and conductive c-cyts. For example, Min et al. (2017) documented the feasibility of enhancing EET in *S. oneidensis* MR-1 by co-expressing the flavin biosynthesis gene cluster *rib*D-*rib*C-*rib*BA-*rib*E and metal-reducing conduit biosynthesis gene cluster *mtr*C-*mtr*A-*mtr*B. As a consequence, the genetically manipulated strain contributed a 1.1-fold enhancement of the maximum current density for a MFC compared to that (89 mA/m^2) of the wild strain (Min et al., 2017). Hence, incorporation of specific synthesis modules into the living components of EABs generates new conduits to augment electron transfer, thereby benefiting BES applications requiring inward and outward EETs.

5.2. Elevated intracellular reducing equivalents

Enhanced electron fluxes in BESs may also be stimulated through elevating intracellular reducing equivalents in EAB cells, as elevated levels of intracellular reducing equivalents facilitate the outward transport of electrons. The total levels of NADH and NAD^+ and the ratio of NADH/NAD^+ within an EAB cell provide an important measure of intracellular reducing equivalents (Chen et al., 2014). Namely, NADH and NAD^+ are the pivotal cofactors participating in microbial metabolism of organic substrates (Yong et al., 2014a). They serve as important intracellular electron carriers and sources in EET processes. Accordingly, expanding the capacity of the NADH pool provides a novel approach for custom-engineering EABs for the purpose of enhanced EET efficiency.

Previous attempts to increase intracellular reducing equivalents utilized cofactor engineering to manipulate the intracellular NAD ($H/^+$) level (Wang et al., 2017b; Wang et al., 2013b) (Fig. 4c). In a pioneering cofactor engineering study, *E. coli* was modified by heterologously overexpressing NAD^+-dependent formate dehydrogenase from *Candida boidinii* to increase NADH availability (Balzer et al., 2013). The recombinant *E. coli* strain demonstrated faster glucose consumption rates (2 g/L/h) and succinate productivity (2 g/L/h), as well as a lower concentration (0–3 mM) of the reduced byproduct formate (Balzer et al., 2013). This supports the efficacy of introducing appropriate redox partners as an effective strategy for building circuits to support enhanced biocatalytic processes. Subsequent research examined regeneration of intracellular NADH levels by alteration of metabolic fluxes through assembling functional genes in *S. oneidensis* MR-1 (Li et al., 2018b). This modular engineering strategy focusing on central carbon metabolism (i.e., glycolysis, serine/glycine C1 metabolism, pyruvate fermentation pathway and TCA cycle) resulted in 4.3- and 1.2-fold increases in the NADH/NAD^+ ratio and intracellular NADH pool, which contributed to a boost in EET efficiency. Further work by Li et al. (2018b) improved the modular engineering strategy to redirect metabolic fluxes toward NAD^+ biosynthesis by targeting three primary modules, the de novo, salvage and universal biosynthesis modules (Li et al., 2018a). This tailored optimization was effective in increasing intracellular levels of NAD^+, NADH, and NAD ($H/^+$), which further stimulated substrate oxidation and significantly increased the intracellular electron flux. These notable examples highlight the potential for using modular biosynthesis engineering to create more intracellular reducing equivalents by actuating intracellular metabolic processes to increase intracellular electron pools and fluxes.

5.3. Enhanced formation of EAB biofilms

While several studies addressing EET performance focus on single cell dynamics, it is recognized that the coordinated efforts of interacting cells (inter- and intra-species) disproportionately regulate the efficiency of EET. Thus, the incorporation of EAB biofilms is an important avenue to consider in optimizing EET efficiency of BESs (Renslow et al., 2013). This implies that engineering bulk functional biomaterials for use as large-scale EET platforms should emphasize the natural and modified architectures of electroactive biofilms. Formation of aggregated biofilm connections to external electrodes greatly facilitates electron transfer across multiple-scale lengths and decreases energy losses associated with EET processes. Applying genetic circuits within engineered biofilms provides a novel approach for incorporating multiscale patterning into living biomaterial communities. Unlike biofilm heterojunctions tethered with conductive nanomaterials through physical electrostatic adsorption/coatings (Section 2.2), engineered living biomaterials used for large-scale BESs focus on the autonomous architecture of highly adaptive biofilms that are further enhanced by synthetic biology modifications (Fang et al., 2020a). This entails a special "cell-to-cell" communication mechanism in which gene expression is synchronized in response to cell density and thereafter regulates spatial and temporal interactions among bacteria within the consortia (Parsek and Greenberg, 2005). This modulation approach for improving BES efficiency generally uses synthetic biology techniques to elevate intracellular signaling molecules.

Research has substantiated that biofilm formation may be controlled by quorum sensing (QS)-based autoinducers in a unique manner that creates autonomous bacterial communications in colony populations (Dandekar et al., 2012) (Fig. 4d). A well-characterized QS system revealed coordination by acy-homoserine lactone (AHL) molecules among Proteobacteria (Case et al., 2008). Subsequently, Venkataraman et al. (2010) demonstrated that a large shift in phenazine production by *Pseudomonas aeruginosa* PA14 occurred via a QS cascade consisting of autoinducer synthases (LasI and RhlI), which generated a 28-fold greater phenazine concentration than that of the wild strain.

Biofilm formation may also be governed by signaling of several universal bacterial secondary messengers (Boehm et al., 2009). Compelling evidence for the growth and long-term viability of biofilm communities due to promotion by increasing expression of bacterial secondary messengers was demonstrated by Peng et al. (2016). They deleted the *pdeA* gene coding for disruptive phosphodiesterase that degrades cyclic-di-AMP with the aim of increasing the expression of cyclic-di-AMP. The transduction of cyclic di-AMP molecule managers in the signaling network led to preferential bacterial colonization by a *pdeA*-defective *Streptococcus* mutant. Another example by Cheng et al. (2020) demonstrated that the Cr(VI) bioreduction rate was accelerated by at least 3-fold in *S. oneidensis* MR-1 cells by recombinantly over-expressing the gene encoding adenylate cyclase in *Beggiatoa* sp. The modification increased intracellular cyclic adenosine 3′, 5′-monophosphate levels in *S. oneidensis* MR-1 and thickened biofilm communities resulting in enhanced bidirectional EET. Considering the established role of intracellular signaling molecules in underpinning the architecture of biofilms, additional research is warranted to better understand the bacterial intracellular signaling molecules associated with enhanced EET performance.

Herein we focus on a notable example that highlights a recent novel QS-based population-state decision support system developed by Li et al. (2020a). This system intelligently and dynamically reprograms the EET ability of *S. oneidensis* MR-1 based upon population metrics. The smart system is composed of a decision-making unit (with LuxR − AHL complex sensing) and a decision implementation unit (controlled by a responsive system that governs enzymes and pathway genes). The system rebalances the allocation of cellular resources for bacterial growth to ensure subsequent EET enhancement for pollution degradation. Hence, the augmented biofilm formation described in this section responds to the cooperative programmed actions of the living cells with facilitated external intervention or guidance, thereby increasing the functionality and merits of the bulk composited living biomaterials.

5.4. CRISPRi-associated technologies

Impressive advances in genome modification have emerged from the development of CRISPR [Clustered Regularly Interspaced Short Palindromic Repeat Interference] technologies. CRISPR is a remarkable natural immune system and widespread in bacteria and archaea, which provides them with protection against viral infections (Mahmud et al., 2015). With the rapid development of genetic engineering in recent years, CRISPRi

[CRISPR interference]-associated technologies have emerged as an advanced genome-editing tool (Larson et al., 2013). In contrast to traditional genome-editing technologies like ZFE [Zinc Finger Endonuclease] and TALEN [Transcriptional Activator-Like Effector Nuclease], the CRISPR/Cas9 [CRISPR-associated protein 9] system has several superior attributes, such as harboring more facile carrier construction, higher distribution of editable locis, more precise targeting efficiency and simultaneous editing of multiple sites (Javed et al., 2018; Kim, 2016). Owing to these advantages, CRISPR/Cas9 provides a powerful tool for genetic engineering that is able to build novel living-material systems that could perform sophisticated decision-making processes involving multiple inputs and outputs (Fig. 4e). Using CRISPRi-associated technologies, living biomaterials harboring preprogrammed functions to improve EET could be developed by coordinating sophisticated genetic circuitry in the synthetic living components of BESs. Successful application of this technology has been demonstrated in the programing or upgrading of several microorganisms, such as *Shewanella*, *E. coli*, cyanobacteria, *Corynebacterium* and *Actinomycetales* (Cao et al., 2017; Sander and Joung, 2014; Tian et al., 2017; Yao et al., 2016). This initial success in genetic modification of microbial attributes to create functionally-targeted, living biomaterials has further inspired development of genetic tools to improve microbial functional properties, along with bottom-up designs to optimize their use for commercial applications.

Currently, the use of novel engineered organisms to create advanced BESs is still in its infancy, but is destine to create revolutionary breakthroughs. A recent study revealed that a single plasmid CRISPRi system harboring both dCas9 and sgRNA was able to identify the key proteins responsible for the detoxification machinery targeting arsenic (V), vanadium (V) and methyl orange in *Aeromonas hydrophila* through EET processes (Wu et al., 2020). This highlights the potential of CRISPRi as a powerful tool for genome-scale functional screening and mapping of complicated pathways for genes involved in EET. Further, a new strategy of tuning electron fluxes using an engineered CRISPR-ddAsCpf1system was utilized to enhance the EET capacity of *S. oneidensis* MR-1 (Li et al., 2020b). Modifications introduced by the CRISPR-ddAsCpf1 system not only increased the transcriptional levels of the gene regulating $_{L}$-lactate metabolism and EET, but also improved riboflavin production (Li et al., 2020b). These outcomes resulted in the redirection of the electron flux to enhance the bioreduction of methyl orange and hexavalent chromium.

Genome editing techniques based on CRISPR/Cas9 and CRISPRi have also been utilized to modify polyhydroxyalkanoate (PHA) metabolic pathways (Zhang et al., 2020b). Multiple modifications to *E. coli* have been performed to regulate PHA composition and redirect more carbon flux to PHA synthesis. For example, a controllable poly(3-hydroxybutyrate-*co*-4-hydroxybutyrate) biosynthesis from glucose by *E. coli* was manipulated using a CRISPRi system (Lv et al., 2015). Moreover, Jung et al. (2019) modified *E. coli* through simultaneous deletion of four genes related to byproduct formation together with overexpression of *pntAB* to catalyze NADH/NADPH interconversion. This resulted in more PHA storage via increased cell growth and an elevated supply of NADPH. Thus, CRISPR-associated technologies provide several avenues to customize EAB performance for specific attributes/functions, opening up numerous possibilities for optimizing living biomaterial functionalities to flourish in BES applications. Notably, although CRISPRi technology offers researchers several smart options for genetic modification of EABs, several limitations and complications, such as off-target effects, mosaicism and multiple-gene targeting difficulties, need to be overcome to advance its use for future widespread applications (Gaj et al., 2013).

Further, the integration of CRISPR/Cas with other genome components (e.g., specific RNA and proteins) are expected to result in a myriad of advances, including gene editing, gene activation/suppression, plasmid curing and invader defense (Cao et al., 2017; Javed et al., 2018; Li et al., 2020b). From this optimization of technologies, we expect the development of increased EET efficiency for EAB systems, thereby improving their efficacy for multiple applications. The potential to develop "super synthetic biological components" remains an important goal in our quest to sustainably synthesize commercial organic chemicals and energy products in the future.

6. Conclusions and perspectives

This review provides a summary of recent advances in modular configurations of living biomaterials for use in improving bioelectrocatalytic performance through incorporating nano-based artificial mediators and synthetic biology technologies. Design of living biomaterials for use in BESs can be achieved from optimization/integration of living and non-living components using either bottom-up or top-down approaches (Nguyen et al., 2018). Techniques encompass assembly of conductive nano-sized materials, architecture of abiotic/biotic interfacial connectors, and genetic modification of the main living system within the biomaterial (Fig. 5). Heterojunction strategies provide more electron-exporting conduits and optimize the conductive pathways for charge transport across biohybrid composites. Specifically, living biomaterials used in BESs may be enhanced by exploitation of novel engineered biohybrid composites harboring an enlarged electron flux and enhanced EET efficiency. Manufacturing of biohybrids emphasizes fabrication protocols to optimize building of artificial habitat structures and bacterial encapsulation strategies for improving bacterial environmental adaptability (e.g., protection from environmental stressors). Strategies to protect EABs from ROSs are important for retaining the viability/functionality of living biohybrids, such as using various core/shell configurations for cytoprotection. To realize optimum multiscale configurations, from the individual cell to the entire community level of living biomaterials (e.g., biofilms), future work is warranted on architectural designs of principal system components and key accessories of composite biohybrids. To achieve a highly efficient bioelectrocatalytic effect in BESs, bulk engineered-biofilm-derived living biomaterials may enable conventional BESs to operate at the large scale necessary for economically-feasible, industrial applications. Enhanced knowledge of key fabrication methods, biological and physicochemical properties and physiological/ecological interactions are required to further improve BES design and performance.

The increasing availability of living biomaterials has advanced BES development and potential applications at a rapid pace. Considering the critical need for carbon neutrality and mitigation strategies, energy-related applications of biohybrids are expected to contribute to renewable energy generation. Several studies have explored the potential use of biohybrids in solar-to-chemical energy conversion (e.g., artificial fixation of carbon and nitrogen), as well as their utility in the fields of agriculture and nutrition (Su and Ajo-Franklin, 2019; Wang et al., 2019a; Wolfe et al., 2020). Current research on solar energy harvesting using BESs is primarily laboratory based and on a temporal scale of days (Romero et al., 2017), rather than the long-term (years), field-scale studies required to advance the technology to commercial operations. Accordingly, many of the associated technologies required for practical deployment still need to evolve and mature. For instance, the emerging field of biomolecular electronics dictates that orbital tethering at hybrid electrode-protein (e.g., c-cyts) interfaces enables precise electrochemical control over molecular energy levels (Ha et al., 2021). Hence, interface synchronization for highly efficient charge transport at the nanoscale is still required for the fabrication of electrode-protein junctions (Xiang et al., 2016). Further advances in electrode-protein junctions will greatly improve interface coupling via point-site mutations and establish more efficient electrical interactions between the living system and extracellular electrodes. Moreover, artificial coatings of conductive nanomaterials with strong bioaffinity and a porous 3D structure will allow more efficient electron delivery, further contributing to the creation of functionally-engineered, biofilm-based biomaterials (Carrel et al., 2018). Furthermore, investigations addressing the long-term stability and recyclability of biomaterials are warranted to ensure the practical, economic and sustainable use of biomaterials.

With emerging technologies for novel programmable gene editing and gene modulation, especially with the CRISPR and CRISPRi platforms, incorporation of synthetic biology into biohybrid composite systems holds great

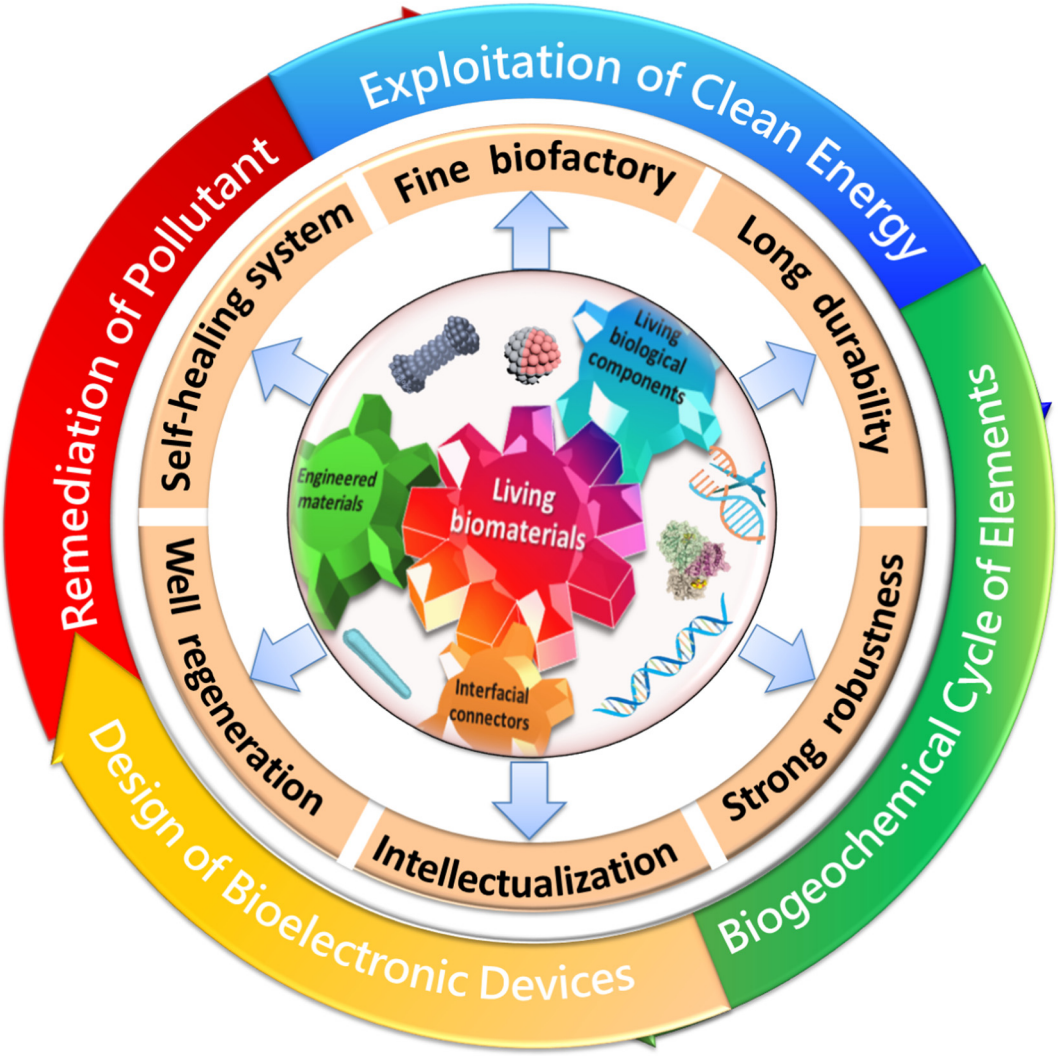

Fig. 5. Overview of the conceptual design framework, optimization targets and future prospects for living biomaterial in BES applications.

promise. These technologies provide elucidation of regulatory genes and metabolic pathways, as well as allowing for genetic-engineering and modular integration of various transcriptional units. The modification of living cells to serve important humanitarian and commercial objectives may allow us to address several of the global sustainability issues we currently face (e.g., food security, clean energy, pollution remediation). Important future research to advance the development and application of BESs include the following considerations. (1) Elucidation of microbial metabolic pathways across a broad spectrum of organic substrates and a decoupling of cellular electron-transport machineries that will allow for the development of more substrates from which to liberate electrons. This is of upmost importance to enhance EET efficiency and ascertain the full potential of the living components. Technological advances in metabolic engineering and synthetic biology offer a viable strategy to assimilate non-conventional substrates or macromolecular organic components that are inherently difficult to metabolize, and also to synthesize biomaterials more efficiently and at a larger scale (e.g., commercial scale). (2) Long-term survival of EABs within BESs is a critical factor determining the ultimate performance of living biomaterials. Development of a self-healing (i.e., self-perpetuating/sustainable), living component as part of the composite biomaterial will provide cytoprotection and sustain the working lifespan even under inhospitable conditions, thereby leading to wider commercialization potential. To improve the resilience of living components or shorten the healing process, a series of strategies could be employed, such as constructing protective shelters (Pungrasmi et al., 2019), introducing anti-desiccation components (Boothby et al., 2017), employing biomineralization relevant pathways (Hao et al., 2022) and engineering nucleating sites (Williams et al., 2017). (3) Although various genome-editing tools demonstrate tremendous capability for modifying microbial cells, only a few genetically modified EABs (e.g., *Geobacter* and *Shewanella*) have been exploited in the creation of living biomaterials. Advances in genomic tools associated with genome sequencing, screening and editing will lead to modification of other microbes, which will further lead to creation of new functional attributes and their incorporation into BESs. (4) Furthermore, employing intracellular protein assemblies will endow EAB cells with an inducible metabolic ability, such as ferritin aggregates and substrate channeling (Behrendorff et al., 2020; Scaletti et al., 2018; Wang et al., 2021). These alterations will potentially induce a unique metabolic regulation giving rise to the production of various value-added bio-byproducts. Thus, there is great potential for the use of synthetic biology technologies to unlock the capabilities of living biological systems in the design of genetic circuitry to functionalize and commercialize the use of BESs to address global sustainability issues (Fig. 5).

Finally, living biomaterials span many research disciplines across the environmental sciences, molecular biology, microbiology, electrochemistry, materials science and engineering continuums. Inspired by the interdisciplinary nature of material fabrication, a systematic amalgamation of multiple modular living and non-living components can be constructed on a large scale to enhance the attractiveness and novelty of living biomaterials. Notably, e-pili display exceptional electrical conductivity, which

enable the long-range electron exchange between microorganisms and their extracellular environment, thereby conferring enhanced conductivity to current-producing biofilms (Sun et al., 2018; Tan et al., 2016). Additionally, nontoxic e-pili can be sustainably produced from renewable feedstocks (Lovley, 2017). The attractive material properties of e-pili confer special attention for practical commercial applications. Thus, the design of new forms, functions and applications for living biomaterials will synergistically develop through an interdisciplinary approach. Additionally, architectural engineering to upscale living biomaterials must address several issues, such as being cost effective, highly precise, multi-functional, adaptable, durable/sustainable, smart and renewable. Moreover, the integration of intelligent machinery into biomaterials will greatly facilitate their commercial applications. It is also necessary to promote the progression of exploration from fundamental studies at present, to the larger proof-of-concept testing stage, and on to final implementation of pilot-scale tests that lead to commercialization. Owing to the synergist benefits of interdisciplinary research, the design and construction of living biomaterials are rapidly overcoming the major obstacles of low efficiency, tunability of function, scalability, tolerance to environmental stressors and economic feasibility. We firmly believe that future living biomaterial systems have the potential to revolutionize several commercial processes while also addressing global sustainability issues. Conceptually, the framework for industrial application will progress from “a tiny microbe” to “a proof-of-concept mesocosm” to “a big super factory”. This will entail an interdisciplinary lead advancement from “a conventional simplex and static material” to “a high-end multiscale, dynamic and controllable living biomaterial” in the future.

CRediT authorship contribution statement

Zheng Chen: Formal analysis, Funding acquisition, Supervision and Writing-original draft. Jing Zhang: Writing-original draft. Qingyang Lyu: Information survey and collection. Honghui Wang: Information survey. Xiaoliang Ji: Information survey. Zhiying Yan: Information collection. Fang Chen: Information collection. Randy A. Dahlgren: Review & Editing. Minghua Zhang: Funding acquisition.

Declaration of competing interest

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

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