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Influence of cellular redox reactions on the structure and function of light harvesting and photosystems

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Photosynthesis enables the conversion of one of the most abundant and free forms of energy, sunlight, into chemical bonds through the utilization of highly tailored protein complexes. These enzymes work in unison to absorb, convert, and transform light into high-energy electrons which are used for various functions important to metabolism and cellular protection. Over the last ~50 years, photosynthetic organisms, such as cyanobacteria, have been adapted and engineered to produce valuable compounds like hydrogen and ethylene, among others. Often this is performed by removing native and/or adding in exogenous energy utilization pathways so that light energy is re-directed towards the synthesis of desired compounds. However, the interplay between primary light capture, conversion reactions, and the downstream electron utilization sinks is not fully understood. Further complicating these strategies are the plethora of compensatory mechanisms that facilitate steady electron flow and the maintenance of photosynthesis under dynamic conditions. This manifests as structural and functional plasticity of the photosynthetic machinery, often seen in modulations of oligomeric compositions or changes in protein-protein interactions and coupling with redox enzymes. Understanding these mechanisms is crucial to biotechnology applications because re-engineering electron utilization sinks has profoundly different effects on the light capture and conversion reactions of photosynthesis. Optimization requires a molecular-level understanding of the functional interrelationships between electron sinks and photosynthetic components that influence photosynthetic efficiencies to realize potential improvements in product yields. Here, we aim to highlight how perturbation of reductive reactions is revealing the functional plasticity in key components of the photosynthetic energy transduction pathway.

KEYWORDS
electron transfer, flavodiiron enzymes, hydrogenase, membranes, photosynthesis, photosystem I, phycobilisomes, plasticity

1 Introduction

Photosynthesis has been studied for centuries, with the concept of two reaction centers working in tandem, in oxygenic photosynthesis, identified in the early 20th century (Baymann et al., 2001). Since then, much has been learned about the structure and function of the individual Photosystem I (PSI) and Photosystem II (PSII) reaction

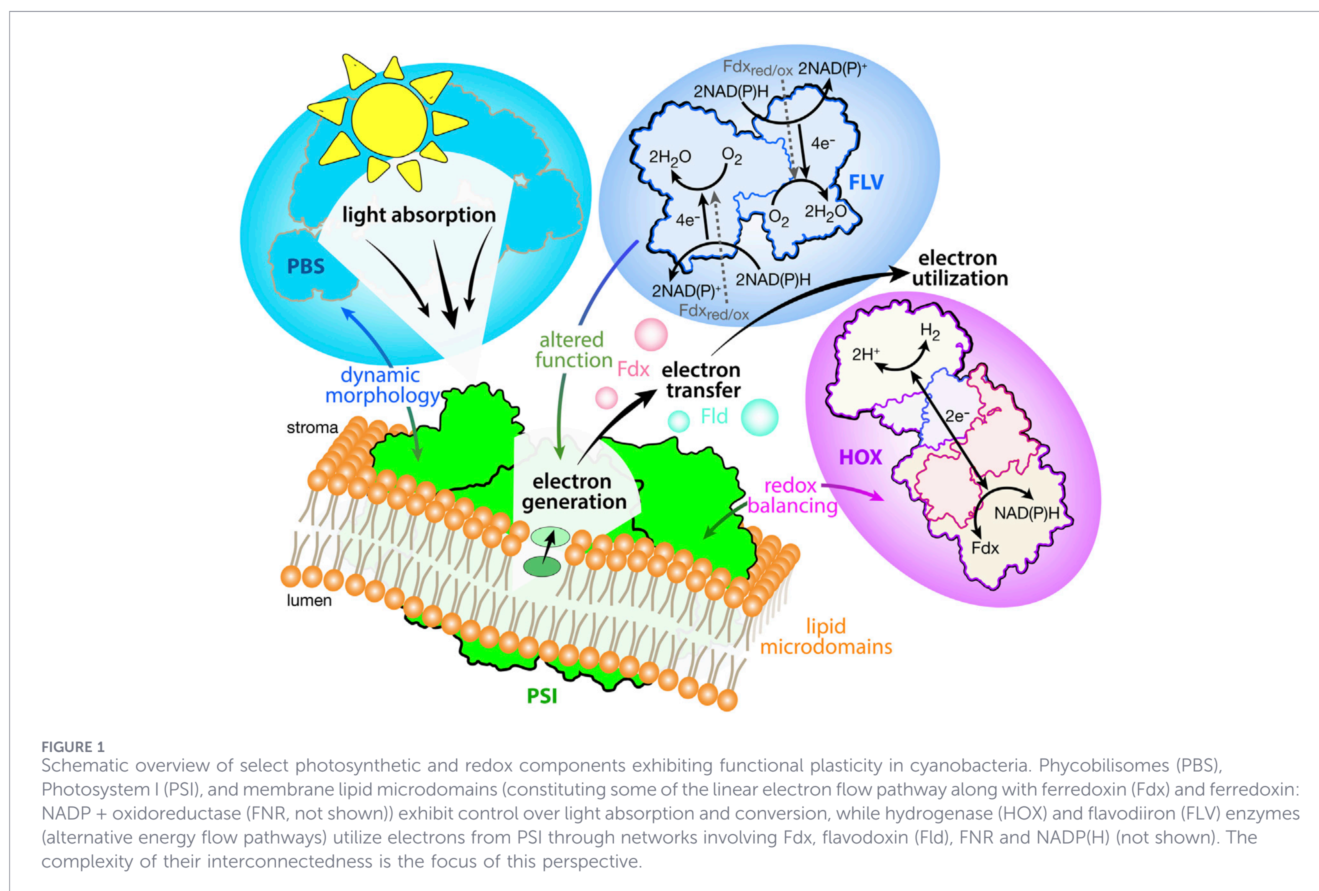

FIGURE 1
Schematic overview of select photosynthetic and redox components exhibiting functional plasticity in cyanobacteria. Phycobilisomes (PBS), Photosystem I (PSI), and membrane lipid microdomains (constituting some of the linear electron flow pathway along with ferredoxin (Fdx) and ferredoxin: NADP + oxidoreductase (FNR, not shown)) exhibit control over light absorption and conversion, while hydrogenase (HOX) and flavodiiron (FLV) enzymes (alternative energy flow pathways) utilize electrons from PSI through networks involving Fdx, flavodoxin (Fld), FNR and NADP(H) (not shown). The complexity of their interconnectedness is the focus of this perspective.

centers as well as their light harvesting antennae and redox partners (Jordan et al., 2001; Netzer-El et al., 2018; Li et al., 2022; Gisriel et al., 2022; Zheng et al., 2021; Kurisu et al., 2003). Absorbed light is directed to the reaction centers by large light harvesting complexes, called phycobilisomes (PBS) in cyanobacteria, converted into electrons by PSII and PSI, and then distributed among a network of reaction pathways that result in production of various metabolites (Figure 1). In addition to these life sustaining reactions, there are alternative energy flow (AEF) pathways that protect the PSII and PSI machinery from redox stress to allow their continued function. In particular, the [NiFe]-hydrogenase (HOX) and flavodiiron (FLV) enzymes relieve excess reductant and participate in the balancing of energy between the electron generating reaction centers and the downstream electron utilization pathways (Jokel et al., 2019). Both HOX (Lupacchini et al., 2025; Lettau et al., 2025a; Ducat et al., 2011) and FLV (Jokel et al., 2019; Santana-Sanchez et al., 2023; Thiel et al., 2019) have been recent targets for engineering approaches aimed at redirecting the excess energy to the production of economically valuable compounds. What is unclear is whether re-engineering these AEF pathways is compensated for by changes in the functional properties of the primary light capture and conversion machinery (Jokel et al., 2019; Thiel et al., 2019; Smolinski et al., 2022; Hubacek et al., 2024; Santos-Merino et al., 2021).

Complicating the highly interdependent nature that exists between electron generating and utilizing pathways is the observation of structural diversity among many of the photosynthetic and AEF components. Here we aim to describe the structural and functional plasticity that is emerging within these pathways and posit their effects on energy transformation in the cyanobacterium *Synechocystis* sp. PCC 6803 (*S.* 6803). Specifically, we describe the understanding of plasticity in four components: the PBS complexes exist in two major forms that differentially associate and transfer excitation energy with specific forms of the reaction centers; the PSI reaction center, which converts photons into high-energy electrons, can be found as a trimer, which is its predominant configuration, or as a monomer, particularly under dynamic environmental conditions; the HOX hydrogenase has been shown to consist of five subunits that catalyze reversible oxidation of molecular hydrogen linked to NAD(P)H and ferredoxin reactivity, as well as a three subunit subcomplex that exhibits diaphorase activity; and finally there are four distinct FLV enzymes that can form either homo- or hetero-dimer pairs (Santana-Sanchez et al., 2019) for linking oxidation of photosynthetic carrier pools to the reduction of O_2 to H_2O. Recent work is revealing unanticipated effects on the primary light capture and conversion processes observed when electron utilization pathways are disrupted. While the field understands much about the biochemistry and biophysics of individual photosynthetic components, an emerging area of research is in understanding how these components can adjust their structural and functional properties to dynamically adapt to changing conditions often experienced in nature.

1.1 Photon capture and conversion

Diversification in reaction center structure and function affect mechanisms of both photon and electron flux, which underpin the absorption and conversion of light energy into chemical bonds. Here we examine these relationships and their potential roles in modulating photosynthetic reactions and reductant pools in response to varying metabolic regimes. Through this analysis, we contend that the functional interplay forms a feedback loop that is pivotal for ensuring the efficacy and efficiency of photosynthesis, as well as in directing energy towards the appropriate metabolic pathways. Furthermore, we describe how diversification may affect the placement and/or interaction of photosynthetic components within the thylakoid membrane. Membrane chemistry and morphology contribute to the formation of discrete, energy-transforming complexes (i.e., super/mega-complexes) (Beckova et al., 2017; Liu et al., 2013; Gao et al., 2016; Zhang et al., 2021), which function to regulate and integrate light capture to photochemical reactions that are fundamental to energy conversion.

1.1.1 Phycobilisomes

Light harvesting in cyanobacteria is primarily facilitated by soluble, supramolecular protein complexes called PBS. PBS range from 3 to 18 MDa and contain thousands of chromophores. They are peripherally bound to thylakoid membranes, so that they can transfer energy to the reaction centers (RCs), PSI and PSII. These energy transfer processes are nearly quantum efficient and occur via both Förster and coherent excitation energy transfer (EET) mechanisms (Sui, 2021). Not only do PBS increase the cross-sectional area of photon capture due to their large sizes, but they also expand the domain of wavelengths absorbed by cyanobacteria due to the covalently bound, linear tetrapyrrole chromophores. These chromophores, or "bilins", absorb around 500–600 nm and give PBSs their brilliant blue color when isolated. The fundamental protein building blocks of PBS are the bilin-bound proteins, called phycobilin proteins (PBPs), and their colorless linkers, which govern PBS assembly and energy modulation (Zhao et al., 2025).

EET efficiency is dictated by the distance and orientation of the chromophores involved. Thus, despite diversity in the supramolecular morphologies of reported PBS structures, precise orientation of the highly conjugated, bilin π-systems underlies all PBS architecture. Large, uninterrupted rows of these π-systems funnel light energy down the PBS antennae towards RCs (Zhao et al., 2025). At the periphery of these antennae, rods made of multimeric disks of PBPs (*e.g.,* phycocyanin, phycoerythrin, and phycoerythrocyanin) are assembled via rod-specific linkers (*e.g.,* CpcC and PecC). These rods are then either linked directly to the thylakoid membrane via the linker CpcL or arranged into a myriad of fanned supramolecular rods that permeate from PBP cores made of allophycocyanin via core-linkers such as CpcG (Watanabe et al., 2023). Several morphologies have been reported for these larger core-rod PBPs, wherein the rods expand either vertically or horizontally. Finally, both the CpcL single-rod PBPs, as well as the massive CpcG PBPs with fanned rods emanating from their PBP cores, complex with PSI and PSII to form the largest categorizable structures in nature, molecular superstructures, deemed "mega-" or "super-complexes" (Domínguez-Martín et al., 2022; Zheng et al., 2023).

In phototrophs, EET networks, electron transport chains, and downstream electron utilization pathways are inextricably connected. Therefore, as the predominant light-capturing antennae in cyanobacteria, PBP modulation is critical to cellular responses to energy fluxes and cellular redox status. Within minutes of altered incident light, cyanobacteria undergo a so-called state transition, wherein EET from PBS to PSI, PSII, or both is adjusted (Calzadilla and Kirilovsky, 2020). For decades, fluorescence studies have shown preferential EET to PSII during state 1 versus EET to PSI during state 2; nevertheless, it is unclear exactly how this EET redistribution occurs. Do state transitions arise primarily from PBS rearrangement between super-complexes, or does excess energy migrate via emergent EET funnels in response to over-reduced PSII within fixed PBS-PSII supercomplexes?

State transitions were first described in red alga over 50 years ago, yet the mechanistic details of these physiological states remain under debate (Bonaventura and Myers, 1969; Murata, 1969). Long-range migration and attachment of PBS to either PSI or PSII was initially proposed, but models in which EET from PBS is modulated via minor structural changes within supercomplexes have recently been suggested. For instance, in the so called "spill over" model, excess EET *spills over* from an attached PBS-PSII supercomplex towards PSI via EET pathways that manifest in response to over-reduced PSII. Importantly, these "spill over" or "PSII quenching" models likely require some detachment and structural change of PBS from PSII during state transitions (Calzadilla and Kirilovsky, 2020). Recent kinetic modelling of time-resolved fluorescence emission spectra suggests that PBS structural changes dictate state transitions within supercomplexes (van Stokkum et al., 2025). Indeed, our lab found evidence of structural alterations in both PSI and CpcL-PBS caused by perturbations in the energy-dissipative oxygen-reduction reaction by knocking out a FLV gene (*flv1*) within *S.* 6803 (Guo et al., 2024), begging the question: what role do single-rod, CpcL-PBS play in cyanobacterial state transitions, if any? Lastly, structural, spectroscopic, and photochemical differences have been reported for both PBS and PSI (*vide infra*) from various cyanobacteria, opening the possibility of several state transition mechanisms across the phylum of cyanobacteria.

Although EET from PBS to both PSI and PSII was corroborated via the isolation of a cyanobacterial PBS-PSI-PSII supercomplex more than a decade ago, high-resolution structural data of this complex has not yet been reported (Liu et al., 2013). Supercomplex structures of CpcL-PBS bound to PSI, as well as CpcG-PBS bound to PSII, have recently been reported, but EET modulation of PBS during state transitions has yet to be investigated structurally (Mao et al., 2026; Zhang et al., 2024). Cryogenic electron tomography (cryo-ET) is a promising approach, but so far, a supercomplex containing PBS, PSI, and PSII has only been reported for a green alga (You et al., 2023). A confounding discovery to the PBS-PSI-PSII supercomplex hypotheses are PSI arrays and photosystem-specific regions in thylakoid membranes (*vida infra*). If PSI and PSII are separated from each other in thylakoid membranes, how could PBS deliver energy to both without migrating? Perhaps super-complexation is dependent on cellular redox status or cyanobacterial species?

To reconcile our current understanding of supercomplexes within cyanobacteria, the difficulties in handling and isolation of superstructures must be overcome. PBSs are delicate complexes that are held together by electrostatic interactions and thus fall apart easily during purification. Similarly, common isolation techniques of PSI and PSII require detergent solubilization, which cause fragile hydrophobic interactions between membrane protein complexes within superstructures to dissociate. Both *in vitro* and *in vivo* chemical-crosslinking strategies have circumvented these issues. Nevertheless, the resultant superstructures are likely too inhomogeneous and flexible for robust single particle analysis via cryogenic electron microscopy. Thus, the structural biology of PBS-PSI-PSII superstructures remains in its infancy, and advances in membrane protein purification (*e.g.,* isolation via nanodiscs) and electron microscopy (*e.g.,* cryoET of thylakoid membranes) will pave the way for our future understanding of state transitions and energy regulation within cyanobacterial supercomplexes. Furthermore, alterations within PBS, PSI, and PSII structures may influence the composition and interactions within supercomplexes, necessitating structural insights for a holistic understanding of Nature's highly efficient EET and its modulation.

1.1.2 Photosystem I and the membrane

The segregation of photosystems in higher plants is well understood; with PSII enriched in the grana and PSI in the stromal lamellae (Kana et al., 2023). More recently, this separation of PSI and PSII into uniformly packed regions has also been observed in the continuous thylakoid membrane architecture of cyanobacteria, which lack specific membrane superstructures such as grana (MacGregor-Chatwin et al., 2017). Further, it has been reported that in cyanobacteria, PSI is localized to the inner thylakoid membrane and PSII/PBS colocalizes toward the outer thylakoid (Kana et al., 2023). The locations of these photosystem-specific regions, as well as the spacing between the protein complexes have been shown to be dynamic under varying light conditions; with PSI regions experiencing greater reorganization relative to the PSII/PBS-rich regions. Specifically, PSI has been observed to exist in a uniform and packed state under continuous light conditions, and are more dispersed throughout the thylakoid when subjected to light-dark periods (Canonico et al., 2020). This heterogenous distribution of photosystems, coupled with the heuristic nature of their reorganization, taking place over minutes to days, suggest that this hierarchical control over spatial proximity and compartmentalization may have functional roles in redox balance between the photosystems, modulating photosynthetic electron transport (Casella et al., 2017). Adding further complexity is the observation of various oligomeric forms of PSI, i.e., as monomers, dimers, trimers and tetramers, in cyanobacteria (Li et al., 2014). However, the implications of PSI oligomeric composition on energy transfer and protein partner interactions are largely unknown as well as how the cooperation with and dependance on membrane architecture contributes to the regulation of PSI structure and function. On the scale of individual PSI complexes, processes governing spatial organization and oligomeric state have recently been observed. In these studies, under times of high and fluctuating light stress, PSI shifts from predominantly trimeric to increased monomeric forms in a mutant background where a downstream electron utilization pathway involving FLV is absent (Smolinski et al., 2022; Smolinski et al., 2025). In addition to these changes in oligomeric state, PSI displays marked changes in photooxidation capacity, spectral properties, pigment composition and an altered PsaL subunit environment (Smolinski et al., 2025). PSI from this strain (*S.* 6803) also exhibited differences in the preference for different forms of PBS (Guo et al., 2024). It is becoming increasingly apparent that there are multiple mechanisms by which phototrophs regulate overexcitation in PSI, including chemical modifications, carotenoid biosynthesis/conversion (Latowski et al., 2011), non-photochemical quenching (van Amerongen and Croce, 2025), and through changes to supramolecular organization and architecture. At present, there are significant knowledge gaps regarding how modifications in the overall architecture of photosystems are initiated or regulated. A deeper understanding of how these spatial and oligomeric adjustments affect and regulate PSI activity will be critical to the advancement of both fundamental and applied efforts.

While much attention has been paid in recent years to the distribution of the photosynthetic machinery within the thylakoid, the distribution of the thylakoid lipids has been largely overlooked. This blindspot arises from our inability to perform lipidomics on targeted areas of the membrane (i.e., in PSI or PSII-rich regions, respectively), and the fact that this lipid profile is lost during detergent isolation of membrane complexes, which yields nearly fully delipidated protein micelles (Brady et al., 2022). Recently, trimeric PSI was isolated from *Thermosynechococcus elongatus* using copolymers, instead of detergents, resulting in nanodiscs that retain an annulus of native thylakoid lipids (Brady et al., 2019). Lipidomic analysis of these nanodiscs, referred to as styrene maleic acid lipid particles (SMALPs), show a distinct lipid profile in the proximal environment of PSI, that differs greatly from the bulk thylakoid membrane composition, mainly being highly enriched in the negatively charged glycerolipid sulfoquinovosyldiacylglycerol (SQDG). This lipid is a minor constituent of the overall thylakoid membrane, accounting for only 15%–20% of the bulk (Kern and Guskov, 2011). In the PSI-SMALPS, which retain nearly 1,300 of the lipids proximal to trimeric PSI, SQDG is the majority lipid, accounting for 62% of the lipid annulus (Brady et al., 2022). On an experimental note, it has been observed that while solubilizing thylakoid membranes with detergents yield all the proteins within the thylakoid, SMA copolymer only seems to target trimeric PSI in cyanobacterial thylakoids (Brady et al., 2019). Further, SQDG was found to spontaneously self-associate into microdomains within Langmuir monolayers, and these SQDG microdomains allow for faster migration of SMA copolymer to the interface and deeper insertion into the acyl region as compared to any other thylakoid lipid (Phan et al., 2020). Taken together, these observations suggest that the thylakoid lipids may also exhibit lateral segregation and the formation of microdomains, which only allow SMA to insert in the region of trimeric PSI. This leaves open a question of whether the lipid environment or larger thylakoid domain is altered when the oligomeric state of PSI is changed and *vice versa*. These thylakoid lipid microdomains may arise from or facilitate the arrangement of photosynthetic machinery within the thylakoid. This hypothesis is supported by numerous studies that suggest the galactolipids, monogalactosyldiacylglycerol (MGDG) and

digalactosyldiacylglycerol (DGDG), which are the majority thylakoid membrane lipids, are not necessary for photosynthesis or growth in *S.* 6803 (Awai et al., 2014). However, the anionic glycerolipids SQDG and phosphatidyl glycerol (PG) are critical to the function of PSII and PSI in oxygenic photosynthesis (Guler et al., 1996).

Maintaining negative membrane potential seems to be essential in oxygenic photosynthesis. It has been shown with knockout mutants across various oxygenic phototrophs that in the absence of SQDG, PG synthesis will increase dramatically, up to 3-5 fold to compensate, leading to partial rescue (Guler et al., 1996). The inverse is also true, leading to the hypothesis that this compensatory mechanism between PG and SQDG may be a strategy to maintain membrane charge and redox balance between the photosystems in times of nutrient deficiency, such as inorganic phosphorus deplete conditions (Benning, 1998). When the biosynthetic pathway for both SQDG and PG are knocked out, growth of cyanobacteria stalls prematurely, underscoring the importance of these anionic glycerolipids in oxygenic photosynthesis (Endo et al., 2016). PG is essential for PSII function and has been found by X-ray crystallography to be at points that may promote flexibility in the protein structure (Jones, 2007), allowing for replacement of core subunits, as well as playing a role in energy transfer (Endo et al., 2016). SQDG can partially rescue these functions under phosphorus limiting conditions, or in PG knockout background, but cannot reverse the phenotype entirely (Nakajima et al., 2018). While PG may be essential to facilitate the replacement of individual subunits, allowing for PSII photoinhibition to be quickly mitigated, PSI does not recover for days following photoinhibition (Sonoike, 2011). This raises the question as to how the activity of PSI is modulated (Hagio et al., 2000; Lima-Melo et al., 2019).

Considering the recent findings cited here, specifically the lateral reorganization of PSI from a uniform array to a dispersed state under changing light conditions (Canonico et al., 2020), and trimeric PSI in cyanobacteria residing within a majority SQDG lipid microdomain (Brady et al., 2022), it's possible that the activity of PSI is relegated via the arrangement of, and the spacing between the individual PSI complexes within the membrane. Further, this arrangement may be facilitated by the presence, or active dissolution, of an SQDG-rich microdomain within the thylakoid membrane. Supporting this hypothesis, it has been shown that photoinhibition of PSI has only been observed in plants at temperatures less than 10 ˚C (Sonoike, 2011). At these low temperatures, membranes become rigid, halting membrane reorganization. This idea of PSI activity modulation being driven by changing the arrangement of the complexes within the membrane is not without precedent. Light scattering, absorption, and overall optical response in the appressed region of chloroplast thylakoids have been shown to be strongly dependent on the concentration of the light harvesting complexes and granal diameter (Capretti et al., 2019). Similar near-field effects may also be at play in modulating PSI energy harvesting, where the architecture and spacing between individual complexes may be a critical regulator of this process. Further investigation into the role of lipid microdomains in this process of membrane remodeling, as it pertains to the PSI-rich region, would help elucidate the mechanisms by which energy transduction and redox balance are maintained between the photosystems.

1.2 Reduction-oxidation (redox) enzyme reactions

The redox enzymes that couple to photosynthetic energy conversion provide a critical link between energy homeostasis and metabolic networks. This is evident in the diversification and plasticity of photon capture and conversion complexes being co-regulated with the expression and activity of redox enzymes. This partnership affords a dynamic response to the constantly changing growth conditions that are supported by an extensive structural and functional heterogeneity of electron utilization enzymes. We show here that there is emerging evidence that the chemistry and capacity of redox enzymes to oxidize reductant pools is critical to the adaptability of photosynthesis for supporting cellular maintenance.

1.2.1 Flavodiiron

The studies on flavodiiron enzymes (FLV) in cyanobacteria have been ongoing for more than 25 years, nevertheless, as new findings emerge, a coherent understanding of the function of FLVs in photosynthesis remains a challenge. FLVs couple the reduction of O_2 to the oxidation of NAD(P)H or reduced ferredoxin pools under conditions of varying light, CO_2, and O_2 levels. Therefore, the presence or absence of FLVs can have profound effects on the function of the primary components, reactions, and processes of photosynthesis.

FLVs are metallo-enzymes that are comprised of a pair of core domains that bind a flavin mononucleotide (FMN) and a non-heme diiron cofactor to catalyze the reduction of either NO to N_2O or O_2 to H_2O. FLVs are widely distributed among microorganisms and include isozymes of significant compositional and structural diversity. Based on the domain and cofactor composition, they are classified into nine groups, designated A through I (Folgosa et al., 2018; Martins et al., 2019), that in addition to a flavin and non-heme diiron binding domains, can incorporate a rubredoxin, NAD(P)H:rubredoxin oxidoreductase or additional flavin binding domains. Both *S.* 6803 and *Anabaena* encode multiple Class C type FLVs, possessing a second flavin binding domain that functions as an NAD(P)H:flavin oxidoreductase (Folgosa et al., 2018; Helman et al., 2003; Vicente et al., 2002) and are subdivided as types 1 and 2 based on diiron cofactor coordination (Borges et al., 2019). There are four FLVs encoded in *S.* 6803 and six in *Anabaena*, that are differentially regulated (Folgosa et al., 2018; Vicente et al., 2002; Gonçalves et al., 2011) and are proposed to have distinct physiological roles.

FLVs purified from *S.* 6803 and *Anabaena* have been shown to catalyze the reduction of O_2, that in combination with the activity of terminal oxidases, leads to a significant consumption of photosynthetic electrons (Helman et al., 2003; Vicente et al., 2002; Brown et al., 2019). Flv1, Flv2 and Flv3 of *S.* 6803 have each demonstrated the use of NAD(P)H as a reductant (Vicente et al., 2002; Brown et al., 2019; Shimakawa et al., 2014). Kinetic studies of Flv1 and Flv3 [identified as *Ss*ATF573 in Vicente et al. (2002)] show that the homodimers have k_{cat} values of 10–10^2 per-second (Brown et al., 2019). Structural models predict a head-to-tail

orientation of monomers with electron transfer likely to occur across the dimer interface (Brown et al., 2019; Zhang et al., 2012). However, how electron transfer in FLVs is controlled to achieve selective four-electron reduction of O_2 to H_2O is a key question to be addressed (Blomberg and Ädelroth, 2024).

Cellular studies of Flv1 and Flv3 (as well as Flv2 and Flv4) suggest that FLVs can function as heterodimers, with indirect evidence suggesting they may couple to ferredoxin(s) (Nikkanen et al., 2025; Sétif et al., 2020), or in the case of Flv2/4, the Q_B site of PSII (Zhang et al., 2012). Rationalizing biochemical function from *in vivo* studies is complicated by the fact that FLV expression is highly co-regulated (i.e., Flv1/3 and Flv2/4). In *S.* 6803, genes for Flv2 (sll0219) and Flv4 (sll0218) form an operon with sll0218. Sll0218 is localized to the thylakoid membrane and is hypothesized to function in stabilization of PSII dimers, which are destabilized in the absence of Flv4 or sll0218 under low (ambient) CO_2 conditions. Clearly FLVs function in cyanobacterial homeostasis, but more work is needed to resolve the biochemical basis for these functions.

The coupling of the oxidoreductase activity of FLVs to the oxidation of photosynthetic carrier pools further contributes to the adaptation of cells to changes in light, CO_2, and nutrient availability. In *S.* 6803, there are distinct modes by which different FLVs contribute to these adaptive responses (Thiel et al., 2019; Santana-Sanchez et al., 2019; Guo et al., 2024; Helman et al., 2003; Gonçalves et al., 2011; Shimakawa et al., 2014; Zhang et al., 2012; Nikkanen et al., 2025; Allahverdiyeva et al., 2011; Bersanini et al., 2013; Bulychev et al., 2018; Elanskaya et al., 2024; Hakkila et al., 2013; Hasunuma et al., 2014; Mustila et al., 2016; Smolinski et al., 2022; Zhang et al., 2009). Examples include a role of Flv2/Flv4 in the photoprotection of PSII and mediating AEF under CO_2 limited growth (Shimakawa et al., 2014). Strains of *S.* 6803 lacking either Flv1 or Flv3, or both, show distinct differences in growth rate, pigment composition, and susceptibility to high-light or low CO_2 conditions. Microarray analysis of the global gene expression profiles for a Flv3 knockout mutant in *S.* 6803 shows significant changes among proteins that function in stress responses, metal homeostasis, and electron flow. This also included downregulation of expression of PSI subunits B, C, D, E, J and L, increases in orange carotenoid protein, and only minimal effects on expression of PSII (Hackenberg et al., 2009). These studies illustrate a complex array of emergent effects on the primary photosynthetic components and reactions from simply altering the expression of a single FLV. This can severely impact the effect of engineering strategies that target the removal or substitution of FLV with other redox enzymes (Santana-Sanchez et al., 2019; Santos-Merino et al., 2021), and points to the need for more fundamental understanding that can be gained from studies of these effects on reaction centers, electron transport components, and redox reaction networks.

1.2.2 HOX [NiFe]-hydrogenase

The cyanobacterial HoxEFUYH [NiFe]-hydrogenase complex is comprised of diaphorase (HoxEFU) and hydrogenase (HoxYH) subcomplexes. These two components can associate to form the full hydrogenase complex, which catalyzes the interconversion of readily available cellular energy in the form of ferredoxins, flavodoxins, and pyridine nucleotides with molecular hydrogen (Tamagnini et al., 2002; Gutekunst et al., 2014; Carrieri et al., 2011; Appel et al., 2022; Artz et al., 2020; Burgstaller et al., 2022). Initial studies have demonstrated that HoxEFUYH can act as an electron valve in cyanobacteria by storing excess electrons in the form of H_2, whereas the bidirectional nature of the hydrogenase affords the ability to uptake electrons from H_2 under oxidizing conditions (Appel et al., 2000; McIntosh et al., 2011). A functional role of HoxEFUYH, beyond H_2 metabolism in redox balancing, is supported by *in vivo* studies demonstrating that HoxEFUYH localizes to the thylakoid membrane and can potentially interface with the NDH-I complex to couple electrons from ferredoxin to the PQ pool (Appel et al., 2022; Burroughs et al., 2014). This is corroborated by HoxH deletion studies that cause effects to metabolism under aerobic conditions while altering the redox state of the PQ pool (Burgstaller et al., 2022). Flexibility of the complex in partitioning electrons under changing conditions is underscored by the functional modularity of the complex. In this regard, the HoxEFU diaphorase subcomplex has been shown to function independently from HoxYH, catalyzing the interconversion of ferredoxins and flavodoxins with NAD(P)(H) (Artz et al., 2020; Eckert et al., 2012; Lauterbach et al., 2011; Palagyi-Meszaro et al., 2009; Lettau et al., 2025b). The HoxEFU subunits share primary sequence homology to NouEFG of Complex I, which contain multiple iron-sulfur clusters and a flavin cofactor for transferring electrons with NAD(H). Variability in the subunit composition of HoxEFU has been observed among other organisms, such as the absence of the HoxE subunit in *Hydrogenophilus thermoluteolus* (Shomura et al., 2017) and incorporation of a non-homologous HoxI subunit in place of HydE in *Cupriavidus necator* (Burgdorf et al., 2005). The growth conditions under which HoxEFU functions, and the extent to which it contributes to energy homeostasis, require further investigation. The structural plasticity of the HOX complex is another example of how redox enzymes can be utilized to regulate redox status of photosynthetic carrier pools under differing energy utilization or growth conditions.

Recent advancements on the mechanistic understanding of reactivity in HoxEFU lend insight as to how substrate binding can influence structural conformation, electron flow, and activity (Lettau et al., 2025a; Artz et al., 2020; Lettau et al., 2025b; Romig et al., 2025; Blahut et al., 2024). Of particular interest is understanding how electron transfer in HoxEFU is regulated at the cofactor level and thus how cofactor properties may be modulated by the local environment, conformational changes, and protein-protein interactions that are likely to change under different growth conditions. HoxEFU contains a total of seven iron-sulfur clusters and one FMN, making it challenging to decipher how electrons are portioned within the complex. Based on the relation of the NAD(P)(H) redox couple to that of ferredoxin, a general model effectively accounts for the observed oxidation or reduction of NAD(P)(H) coupled to different ferredoxins (Artz et al., 2020). More recent biophysical studies have examined how the electronic and magnetic properties of the iron-sulfur cluster and flavin cofactor network are precisely tuned for controlling electron flow (Lettau et al., 2025b; Blahut et al., 2024). Through complementary EPR and electrochemical measurements, we identified a quaternary structure dependent shift in the reduction potential of a [2Fe-2S] cluster in the HoxE subunit, which is adjacent

to a proposed ferredoxin binding site and within electron transfer distance to the NAD(P)H flavin binding site (Blahut et al., 2024). This observation underscores the dynamic structural nature of the complex, and it is hypothesized that conformational gating plays a role in the allosteric control of reactivity based on the presence of substrates. Although the details of this are still unresolved, the observed cooperative reaction kinetics between ferredoxin and NAD(P)+ suggest a possible functional role for higher ordered complexes in managing photosynthetic electron flow. Interestingly, various active HOX subcomplexes, including a HoxEFUYH dimer, have been identified by Blue-Native PAGE and mass spectrometry on crude extracts isolated from *S.* 6803 subjected to oxygen exposure and glutathione treatment (Romig et al., 2025). The exact location of ferredoxin binding to HoxEFU remains to be determined, with several different sites being proposed (Lettau et al., 2025a; Artz et al., 2020; Lettau et al., 2025b). An understanding of how structural interactions can lead to the modulation of multi-electron flow at the cofactor level is essential for future manipulation of this system toward energy applications, such as enabling engineering of photosynthetic pathways.

While progress to date has provided a basis for understanding mechanisms of reactivity through HoxEFU(YH), further mechanistic studies are necessary to elucidate the functional reactive states of both the diaphorase and hydrogenase complexes. Such studies, combining activity measurements with structural modeling and determination, along with elucidation of the thermodynamic landscape, are required to validate models of electron transfer, particularly to support photosynthetic function. Conformational and thermodynamic strategies for modulating the balance of energy carriers are prevalent across homologous [NiFe]-hydrogenases, although their implementation across different systems is diverse (Palagyi-Meszaro et al., 2009; Shomura et al., 2017; Long et al., 2007; Vansuch et al., 2025; Xiao et al., 2025; Preissler et al., 2018). A mechanistic understanding of HoxEFU(YH) reactivity control provides both a deeper understanding of the diversity in [NiFe]-hydrogenases and insight into their differential effects on PSI functionality. Combined knowledge from these observations lay a foundation for future energy applications.

2 Discussion and outlook

There is a rich interplay between RCs and enzyme networks to facilitate the continued conversion of light energy into chemical bonds under dynamic environmental conditions. However, the fundamental mechanisms that regulate and communicate between the electron generation and utilization regimes are not fully elucidated. Recent studies, aiming to redirect energy away from native metabolic pathways, have had profound influence on our understanding of photosynthetic adaptability. One functional partnership between RCs and enzyme networks is the plasticity in PSI structure and PBS interactions with RCs that emerges when FLV proteins are removed. These changes, in turn, affect RC photoexcitation and generation of reducing equivalents. Furthermore, there is an extensive network of ferredoxin and ferredoxin-like proteins in cyanobacteria which act to disperse reducing equivalents among photosynthetic and metabolic networks, and which are highly sensitive to cellular redox status and nutrient and light availability (Cassier-Chauvat and Chauvat, 2014). Thus, the understanding needed to successfully engineer photosynthesis requires addressing knowledge gaps in the various mechanisms that control how components function to allocate electron flow under dynamic energetic circumstances.

Currently, the field is discovering the interdependent relationships that exist between the photon capture and conversion pathways and the electron utilization pathways, and these discoveries point to a need to understand the fundamental mechanisms that govern these feedback loops. Potential signaling candidates likely include the cellular redox status, changes in protein-protein interactions, or changes in pathway kinetics. The redox status of the plastoquinone pool has been broadly implicated in managing electron traffic to prevent various photosynthetic components from becoming over-reduced (Havaux, 2020), which would lead to the generation of reactive oxygen species, damage to photosynthetic machinery, and overall metabolic inefficiencies due to increased cyclic electron flow (where electrons cycle around PSI in a process that generates additional ATP but no NADPH) (Chaux et al., 2015). Similarly, the redox status of the pyridine nucleotide pool is also an important control point between the electron generation and utilization pathways. Alterations in ratios of oxidized and reduced pyridine nucleotides can affect reduction potentials of these substrates, binding affinities with partner proteins, and enzymatic bias. Protein-protein interactions govern how energy and electron transfer pathways function, and are modulated through changes in gene expression, post-translational modifications, or can be disrupted to result in stabilization of functional sub-forms (i.e., PSI oligomeric state, HoxEFU, PBS conformations, long and short forms of FNR, etc.). These sub-forms may act to facilitate changes in other interactions, binding affinities and stoichiometries, and reaction kinetics. Modulating the kinetics of individual steps along redox pathways may also be a key effector of a feedback loop that can be further impacted by cellular redox status and protein-protein interactions. This can be enacted through supramolecular organizations, either super/mega-complexes or segregation within membranes, to co-localize specific components to favor (or disfavor) distinct energy transferring processes. These regulatory mechanisms are also highly intertwined, and basic knowledge about the global regulatory effects of altering electron utilization pathways must be considered to better understand, and predict, the cellular response to engineering and the complex nature of how energy is coupled in cyanobacteria.

Outcomes from the studies discussed here show the wider functional range of photosynthetic components and reveal an evolutionary drive for ‘plasticity’ as a mechanism to retain function and cell viability. These observations underpin a need to investigate the impacts of enzyme deletions on energetically adjacent systems, owing to the reciprocity that has been recently uncovered. As more is learned about the effects of this plasticity on RC and enzyme structure and function, it may challenge us to re-evaluate and develop new definitions of what constitutes functional versus non-functional or damaged components.

Collectively, the work highlighted in this perspective has profound implications on the design and re-engineering of photosynthetic organisms for applications. Expanding our

understanding of the natural variation of RCs is expected to support novel approaches for engineering natural systems and designing synthetic and biohybrid energy-converting complexes. Until the mechanistic diversity of these intertwined pathways is well understood and factored into an engineering strategy, the organism may simply override the desired metabolic outcome by adapting in another manner. Photosynthesis is wonderfully complex in ways that we currently do not fully understand, and more research will only lead to more successful efforts in re-directing function to meet applied goals.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AL: Conceptualization, Writing – original draft, Writing – review and editing. NB: Conceptualization, Writing – original draft, Writing – review and editing. EK: Conceptualization, Writing – original draft, Writing – review and editing. ES-D: Conceptualization, Writing – original draft, Writing – review and editing. MD: Conceptualization, Writing – original draft, Writing – review and editing, Funding acquisition. DM: Funding acquisition, Conceptualization, Writing – original draft, Writing – review and editing. PK: Conceptualization, Funding acquisition, Writing – original draft, Writing – review and editing. CL: Funding acquisition, Conceptualization, Writing – original draft, Writing – review and editing.

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The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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