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Quantitative modeling of energy dissipation in *Arabidopsis thaliana*

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ABSTRACT

In photosynthesis, solar energy is absorbed and converted into chemical energy. Chlorophyll embedded in proteins absorb light and transfer excitation energy to reaction centers where charge separation occurs. However, the solar flux incident on photosynthetic organisms is highly variable, requiring complex feedback systems to regulate the excitation pressure on reaction centers and prevent excess absorbed energy from causing damage. During periods of transient high light, excess absorbed energy is dissipated as heat. This is routinely observed as the quenching of chlorophyll fluorescence, and often broadly referred to as non-photochemical quenching (NPQ). Understanding the mechanisms through which photosynthetic systems dissipate excess energy and regulate excitation pressure in response to variable light conditions requires extensive quantitative modeling of the photosynthetic system and energy dissipation to interpret experimental observations. This review discusses efforts to model energy dissipation, or quenching, in *Arabidopsis thaliana* and their connections to models of regulatory systems that control quenching. We begin with a review of theory used to describe energy transfer and experimental data obtained to construct energy transfer models of the photosynthetic antenna system that underlie the interpretation of chlorophyll fluorescence quenching. Second, experimental evidence leading to proposed molecular mechanisms of quenching and the implications for modeling are discussed. The initial incorporation of depictions of proposed mechanisms into quantitative energy transfer models is reviewed. Finally, the necessity of connecting energy transfer models that include molecular models of quenching mechanisms with regulatory models is discussed.

1. Introduction

Photosynthesis is the process by which organisms absorb sunlight to drive electron transfer and energy storage, but excess sunlight can damage the organism (Blankenship, 2014). The natural fluctuations in light intensity experienced by plants require processes that dissipate energy absorbed in excess of what can be used productively, and that can be rapidly optimized to the light condition (Külheim et al., 2002). Of the two photosystems in higher plants, photoprotection in photosystem II (PSII) has been extensively studied. The suite of dissipative, or photoprotective, mechanisms that protect PSII collectively result in, and are referred to as, non-photochemical quenching (NPQ): the reduction in chlorophyll *a* fluorescence yield due to dissipation of excess excitation by mechanisms other than photochemistry (Demmig-Adams and Adams, 1992; Niyogi, 1999; Ruban, 2016).

NPQ is a broad term encompassing several constituent components often separated into q_E, the rapidly reversible, energy-dependent (pH-dependent) quenching component, and q_I, the slowly reversible component associated with PSII photoinhibition (Krause and Weis, 1991; van Kooten and Snel, 1990; Wraight and Crofts, 1970). Although important in many photosynthetic systems, q_T, a component of NPQ associated with excitation balance between PSI and PSII by altering the relative antenna size, does not contribute significantly in vascular plants, such as *Arabidopsis thaliana*, exposed to high light (Niyogi, 1999). q_E and another related NPQ component termed q_Z (Nilkens et al., 2010) have been the subject of intense study. While there is little consensus surrounding the numerous proposed molecular mechanisms (Duffy and Ruban, 2015) underlying the quenching pathways intrinsic to NPQ in PSII, many elements of the regulation of photoprotection are widely agreed upon (Demmig-Adams et al., 2014). Modeling (Laisk et al., 2009) the proposed mechanisms in the context of the photosynthetic energy transfer network and in the context of the regulatory system provides a powerful way to evaluate whether, and in what way, proposed mechanisms play a role in dissipating energy to protect the photosynthetic solar collection apparatus.

One approach to modeling quenching in the photosynthetic system

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is to construct a model capable of predicting experimental measurements, including, e.g., of the fluorescence lifetimes of the *in vivo* system, from quantum and statistical mechanical first principles, structural and spectroscopic data of individual pigments and pigment protein complexes, and membrane imaging (Amarnath et al., 2016). A model must be capable of appropriate treatment of the absorption of light by antenna (Müh et al., 2010; Müh and Renger, 2012; Renger et al., 2011), the transfer of energy to reaction centers (Bennett et al., 2013), and the charge separation process (Novoderezhkin et al., 2011b) to provide a system in which various mechanisms of quenching can be evaluated. Absorption, energy transfer, and charge separation are fundamentally quantum mechanical in their nature. However, to provide a physically meaningful picture, a model must span length scales from angstroms to hundreds of nanometers. To do so requires multiscale modeling and course graining by making appropriate approximations to simplify much of the quantum dynamical calculations; treating the entire system quantum mechanically is impractical, even for modern supercomputers (Kreisbeck and Aspuru-Guzik, 2016). Fortunately, a number of approximations can be made to allow for a model that contains enough of the quantum mechanical features to adequately represent the system. Even so, an accurate model of the system must still integrate data from numerous areas of photosynthesis, making the building of accurate models challenging.

A second area of study that incorporates modeling is the regulatory function of the plant systems that controls the extent of quenching in the photosynthetic antenna (Zaks et al., 2012). The regulatory system operates on timescales from seconds to the lifespan of the plant, but the timescales of greatest interest for regulating the rapid response include changes in the chemical environment of the thylakoid membrane over timescales of seconds to minutes. Current knowledge indicates that a fundamental trigger for inducing quenching is the formation of a transthylakoid pH gradient that, in turn, activates various proteins that influence the actual quenching (Ruban et al., 2012). One of these is the enzyme violaxanthin de-epoxidase that converts violaxanthin to antheraxanthin and zeaxanthin on a timescale of a few minutes when intrathylakoid pH is low (Jahns et al., 2009). These xanthophylls are important players in the molecular mechanisms of quenching and play a number of roles in the pigment protein complexes that effect the ultrafast dynamics of energy transfer. Chemical regulatory models seek to describe quantitatively how the multiple components contribute to the plant system's regulatory response that controls the quenching.

Important open questions include the importance of various quenching mechanisms identified experimentally, and models of how the biochemical regulatory systems control the activation of potential quenching mechanisms. The dynamic nature of the light incident on plants (Külheim et al., 2002) may imply that various mechanisms could play important roles at different times of day or in different patterns of light variability, suggesting that integrated models of the quenching processes and the regulatory response are key for insight into the potential for optimization (Zhu et al., 2004) of various elements of the quenching mechanisms and regulatory system in order to increase crop yields (Kromdijk et al., 2016) or design biomimetic solar energy devices (Terazono et al., 2011). This review focuses on efforts to model energy dissipation mechanisms using multiscale models that integrate the understanding of structure and function of energy-transfer networks, quenching mechanisms, and chemical regulatory systems that are all necessary for developing the level of understanding and tools required to eventually begin engineering quenching systems.

2. Models of energy transfer for evaluating quenching mechanisms

Upon absorption of a photon by a chlorophyll molecule in the photosynthetic system, the energy absorbed may be transferred to reaction centers where charge separation occurs that drives down-stream chemical reactions. When reaction centers are unable to productively accept the energy absorbed by antenna chlorophyll, the photosynthetic system must dissipate the excess energy to prevent unwanted generation of reactive oxygen species.

Historically, the flow of energy through the system has been described using either "lake" or "puddle" models (Robinson, 1967) that describe transfer within the antenna and to the reaction centers. In a lake model, reaction centers sit embedded in a common pool of antenna; in a puddle model, each reaction center has its own antenna. Intermediate cases were described using a variety of connected unit (Lavorel and Joliot, 1972) and domain models (Den Hollander et al., 1983; Paillotin et al., 1979) to define or model transfer within and between antennas and reaction centers. These types of models still implicitly facilitate the interpretation of many studies of quenching behavior, and provide intuition about the photosynthetic system, but are unsuitable for quantitatively evaluating molecular mechanisms and models of quenching as it is difficult to distinguish between these models with experimental data (Bernhardt and Trissl, 1999).

In order to accurately describe the energy transfer process in a quantitative model, appropriate theories to describe the processes involved as well as information about the parameters of the photosynthetic system are required. The theories and data necessary to develop the parameters have all been areas of intense study, spanning from electronic structure of chlorophyll molecules that serve as the primary molecule used to capture photons in individual pigment-protein complexes to the mesoscopic structure of the photosynthetic membrane. These elements can be integrated into a mathematical description of the energy-transfer network that allows for a quantitative prediction of the behavior of absorbed photons and, in turn, predictions of experimental observables such as the fluorescence lifetimes of a photosynthetic system under varying conditions. The most recent efforts build upon many years of work.

2.1. Models of energy transfer processes

For very simple quantum mechanical systems, such as an isolated atom, all the information necessary to describe the time evolution of the system can be contained in a mathematical operator called the Hamiltonian (Atkins and Friedman, 2011). However, even for systems as simple as a single molecule in solution, much of the information in the Hamiltonian cannot be specified exactly, and therefore describing the time evolution requires a statistical approach. A common approach is to partition the complete description into a system of interest and average over the remaining environment (Mukamel, 1995). To describe energy transfer in pigment-protein complexes of the photosynthetic system, the system of interest commonly includes chlorophyll molecules, or chromophores, where energy in the system is absorbed and can flow towards where charge separation occurs. The environment usually consists of the protein matrix that holds the chromophores and surrounding solvent (van Amerongen et al., 2000).

A fundamental concept used to describe electronic excitations is the exciton, a term describing excitation that may be delocalized, or spread, across more than one molecule due to electronic coupling between the molecules (Scholes and Rumbles, 2006). Although this is applicable to a wide range of semiconductor and molecular systems, excitons in photosynthetic systems delocalize over one or a few chromophores due to differences in the strength of electronic interactions within a chromophore and those between neighboring chromophores. This allows for the construction of a relatively simple quantum mechanical model that treats each chromophore as a "site" where a share of the exciton can be located (Fassioli et al., 2014).

The energy gap between the ground and excited electronic state in a specific sites is referred to as the site energy (Cheng and Fleming, 2009; Hu et al., 2002; Mirkovic et al., 2017; Renger et al., 2001). In an ensemble, similar sites generally exhibit a distribution of energy gaps. When a site is excited, energy is stored in the system. The transfer of excitation between sites can then be described quantitatively using an

appropriate mathematical treatment. Two essential parameters for determining the appropriate model are the electronic coupling, or interaction energy, between chromophores and the coupling to the surrounding protein and solvent environment, or reorganization energy. Together, the site energies and the interaction energies between sites comprise the system Hamiltonian, while the reorganization energy describing the coupling to the environment is contained in the system-environment Hamiltonian. Large and small values of the ratio between the interaction energy and the reorganization energy define two limits of a more complete theory of energy transfer.

In one limit, that of weak interaction energy between chromophores relative to the reorganization energy of the environment, the system can be described by the Förster theory of energy transfer (Förster, 1948) that underlies many measures of distance in biological applications. Förster theory is a perturbative treatment that exploits that the ratio of the interaction energy to the reorganization energy is small and results in a well-defined rate constant to describe the energy transfer. In the opposite limit, with a large interaction energy relative to the reorganization energy, the wave-like quantum nature of energy transfer must be accounted for, as energy moves freely through the system with wave-like coherence. In wave-like transfer, constructive interference of multiple waves determines the location of the energy. As the wave-like coherence decays, the energy stops flowing through the system, transferring the energy from one location to another. In this limit, another perturbative treatment called Redfield theory (Redfield, 1957) can be used to describe the energy transfer and results in a quantum master equation that accounts for the wavelike nature of the energy transfer.

However, in practice, the photosynthetic system is not well described be either limit individually (Ishizaki and Fleming, 2009a) due to the varying distances and energy scales involved. One example is in the simple model photosynthesis pigment protein complex, the Fenna-Matthews-Olson (FMO) complex (Fenna and Matthews, 1975), that has been found to have similar electronic couplings and reorganization energies using a variety of spectroscopic (Brixner et al., 2005; Cho et al., 2005) and structural (Vulto et al., 1998) information. Various methods exist to improve upon the perturbative treatments and extend the quantitative accuracy of the results further from the original cases of the limits and describe multichromophoric systems (Jang et al., 2004, 2002; Scholes et al., 2001; Sumi, 1999; Yang and Fleming, 2002; Zhang et al., 1998). A non-perturbative method that is valid over the full range of values of the parameters is the hierarchy equations of motion (Ishizaki and Fleming, 2009b). Nonperturbative techniques have been successfully applied to small photosynthetic systems (Ishizaki and Fleming, 2009c; Wilkins and Dattani, 2015), but it is not feasible to describe a system large enough to represent the photosynthetic membrane using non-perturbative methods (Strümpfer and Schulten, 2012). A simpler model based firmly on accurate microscopic theory is necessary for understanding the design principles of the photosynthetic system.

A viable approach is to use multiscale modeling to apply appropriate extensions of the perturbative techniques at different length scales. This allows not only for the employment of a tractable computational treatment of the photosynthetic system, but also for an intuitive understanding of the system. Of these extensions of the original Förster and Redfield theories, two are most important for developing models practicable at length scales required to realistically describe the photosynthetic system. These extension are the generalized Förster theory, which accounts for delocalization of the exciton (Jang et al., 2004; Scholes et al., 2001; Sumi, 1999), and modified Redfield theory, which treats only a subset of the couplings to the environment fluctuations perturbative to extend the range of validity (Yang and Fleming, 2002; Zhang et al., 1998). These extensions have been successfully combined in course-grained domain modes of individual higher plant pigment protein complexes (Novoderezhkin et al., 2011a) and supercomplexes (Bennett et al., 2013; Raszewski and Renger, 2008) to predict observed spectra. Coarse graining into domains serves to average over the fast dynamics that require sophisticated treatments to describe accurately and results in a classical rate matrix that accurately describes the longer timescale dynamics most relevant to the fluorescence lifetimes used to study quenching. The latter approach has been validated against non-perturbative methods used to describe portions of the PSII supercomplex (Kreisbeck and Aspuru-Guzik, 2016; Roden et al., 2016). The course-grained model has been extended to the mesoscopic size necessary to realistically describe the observable fluorescence lifetimes of thylakoid membranes or intact leaves used to study quenching (Amarnath et al., 2016). A schematic of the relevant time and length scales of energy transfer processes and decay processes described by the various levels of theory is provided in Fig. 1.

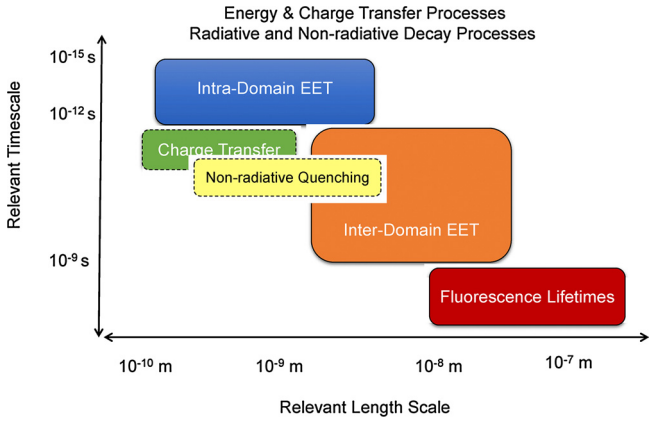

Fig. 1. Semi-quantitative schematic depiction of time and length scales associated with various processes of energy transfer, charge transfer, and decay processes. Overlapping timescales of energy transfer between chlorophylls span rapid intra-domain electronic energy transfer (EET) within domains of closely spaced chlorophylls to long range inter-domain EET between adjacent domains of chlorophylls. Fluorescence decay occurs on the nanosecond timescale, with energy often diffusing many nanometers before charge separation at the reaction center or fluorescence. When quenching sites are active, energy and charge transfer to non-radiative quenching sites are suggested to occur at similar distances from neighboring chlorophyll. Quenching sites dissipate energy through non-radiative decay on timescales much faster than chlorophyll fluorescence.

2.2. Spectroscopic and structural determination of parameters for energy transfer models

In order to employ a model of the energy-transfer process to quantitatively describe fluorescence lifetimes, a number of components are required. Broadly, these fit into two categories: first, composition and arrangement of the pigment-protein complexes in the photosynthetic membrane, and second, a combination of accurate structural models of individual pigment-protein complexes, the complementary system Hamiltonians, and the nature of the system-environment coupling. Membrane organization can be determined via either imaging or statistical mechanical descriptions of the interactions between the pigment-protein complexes in the membrane (Schneider and Geissler, 2013a, 2013b). For the parameters describing the parameters of individual pigment-protein complexes, close combination of the structure determined via either x-ray crystallography, single-particle cryo-electron microscopy, spectroscopic data, and theory are required to determine the full set of parameters. These methods have been co-developed, with each improved iteration of one contribution informing the other's interpretation and analysis.

An example of studies that have focused on the structure-function relationship of an individual pigment-protein complex to inform models applicable to plants such as *A. thaliana* is the light harvesting complex II (LHCII) antenna that has been studied extensively via structural studies (Kühlbrandt, 1988; Kühlbrandt et al., 1994; Kühlbrandt and Wang, 1991; Liu et al., 2004; Standfuss et al., 2005), spectroscopic studies

(Agarwal et al., 2000; Bittner et al., 1995, 1994; Calhoun et al., 2009; Connelly et al., 1997; Eads et al., 1989; Kleima et al., 1997; Kwa et al., 1992; Lewis et al., 2016; Remelli et al., 1999; Rogl and Kühlbrandt, 1999; Salverda et al., 2003; Schlau-Cohen et al., 2009; Visser et al., 1996; Yang et al., 1999), and theoretical treatments (Gradinaru et al., 1998; Gülen et al., 1997; İşeri and Gülen, 2001; Novoderezhkin et al., 2005, 2004, 2003; Trinkunas et al., 1997), resulting in steadily improving determinations of the parameters of the Hamiltonian. Initially, structural determinations of LHCII did not have sufficient resolution to determine chlorophyll site assignments or chlorophyll orientation (Kühlbrandt, 1988; Kühlbrandt and Wang, 1991). Instead, the structures only revealed generic tetrapyrrole rings. Contemporary time-resolved spectroscopic studies demonstrated that various theoretical treatments that assumed only Förster-type energy transfer failed to predict the spectroscopic data from the structural data (Bittner et al., 1995, 1994; Eads et al., 1989; Kwa et al., 1992).

Subsequent crystallography experiments made tentative assignments (Kühlbrandt et al., 1994), and spectroscopic studies attempted to verify them via measurement of chlorophyll *a* to *b* transfer (Connelly et al., 1997; Kleima et al., 1997; Visser et al., 1996). Models attempted to refine assignments and dipole orientations in order to connect the structural and spectroscopic data employing Förster-type transfer with some complications of compartments (Gradinaru et al., 1998; Gülen et al., 1997; Trinkunas et al., 1997). Site directed mutagenesis (modifying individual amino acids near chlorophyll sites to disrupt chlorophyll binding) was used in an attempt to refine the assignments of chlorophyll *a* vs. *b* and the orientation of the Q_y transition dipoles (Remelli et al., 1999; Rogl and Kühlbrandt, 1999; Yang et al., 1999). These studies reported varying results and raised the possibility of mixed chlorophyll *a* or *b* binding sites. Subsequent high resolution crystal structures have largely resolved this controversy. The high resolution structures are able to resolve the C7-formyl group of chlorophyll *b* from the C7-methyl group of chlorophyll *a* and do not observe mixed binding sites (Liu et al., 2004).

Application of photon echo techniques to examine energy transfer in pigment protein complexes overcame significant inhomogeneous broadening, or disorder, and allowed accurate determination of energy transfer rates and evaluation of models (Agarwal et al., 2000; Salverda et al., 2003). Simultaneous fits incorporating these data were performed to evaluate models based on Redfield-type energy transfer (Novoderezhkin et al., 2004, 2003), which resulted in much better fits of the observed data than previous attempts and demonstrated the necessity of a proper treatment of the energy transfer mechanism. However, these efforts still relied on fitting using a mixed site assumption. Subsequent full two-dimensional electronic spectroscopy (Calhoun et al., 2009; Schlau-Cohen et al., 2009) were able to evaluate site energies and couplings directly. Quantum and electrostatic calculations (Novoderezhkin et al., 2005) based on the high resolution crystallographic structures (Liu et al., 2004) were able to resolve many of the inadequacies of previous modeling efforts and compared well to parameters determined from two-dimensional spectra. Continued efforts seek to directly measure energy transfer in space, without the need of a model, through connecting the electronic spectrum to spatial vibrational tags to independently verify the conclusions (Lewis et al., 2016).

In many cases, including LHCII, similarities between different species' pigment protein complexes are exploited to determine complete sets of parameters for the pigment protein complexes. Much of the work has focused on the complexes associated with PSII due to the importance of photoprotection of PSII. One example is the reaction center core, which is well conserved from cyanobacteria to higher plants, thus allowing use of a model determined from cyanobacteria's reaction center core (Raszewski et al., 2008, 2005). The reaction center core includes the reaction center chlorophylls, where charge separation occurs, and that serve as sinks for energy absorbed by and transferred from the antennae. The minor complexes, including CP43, CP47, and CP29, are also described by well-developed models, with spectroscopic and structural data obtained from complexes isolated from spinach (Müh et al., 2012; Pan et al., 2011; Raszewski and Renger, 2008).

3. Mechanistic modeling of quenching

With well-developed models of energy transfer and many of the individual pigment protein complexes parameterized, many of the tools necessary to evaluate mechanistic models of quenching exist. A number of potential mechanisms for the rapidly inducible quenching that protects PSII have been proposed, and it seems likely that no single mechanism dominates the quenching. Broadly, many of the proposed molecular mechanisms involve either interactions between a chlorophyll and a xanthophyll or interactions between a pair of chlorophylls. A current challenge is to incorporate these mechanisms into models of energy migration in pigment-protein complexes.

3.1. Proposed quenching mechanisms

Proposed mechanisms involving xanthophylls are promising due to the short lifetime of the S_1 excited state, which is similar in energy to the Q_y state of chlorophyll. This suggests that energy could be easily transferred from chlorophylls to the xanthophylls and rapidly dissipated. However, the strong coupling between a chlorophyll and xanthophyll can also result in a charge transfer state that is similar in energy to the Q_y state. This finding suggests that a charge transfer and recombination process could also be a viable molecular mechanism for energy dissipation. Study of these mechanisms has resulted in several points of contention – over whether quenching occurs via an energy transfer mechanism, an electron transfer mechanism, or both, which types of xanthophylls are involved, and in which pigment-protein complexes the dissipation occurs. Many of these issues are reviewed by Duffy and Ruban (Duffy and Ruban, 2015) and Jahns and Holzwarth (Jahns and Holzwarth, 2012).

One of the xanthophylls proposed to be involved in the mechanism of quenching is zeaxanthin, which accumulates upon exposure to high light upon two sequential de-epoxidations from violaxanthin and antheraxanthin via the enzyme violaxanthin de-epoxidase. An early proposed mechanism was that de-epoxidation lowered the energy of the S_1 state from above to below chlorophylls' Q_y state, thereby making energy transfer to zeaxanthin favorable and explaining both the observed chemical regulatory behavior and the molecular mechanism (Frank et al., 1997; Frank and Cogdell, 1996). However, it was later found experimentally that the S_1 energies of violaxanthin, antheraxanthin, and zeaxanthin were all below that of chlorophyll, both in solution (Frank et al., 2000; Polívka et al., 1999) and in LHCII (Polívka et al., 2002), necessitating further study.

Calculations of the excited-state energies of a chlorophyll-zeaxanthin dimer and a chlorophyll-violaxanthin dimer using a hybrid of time-dependent density functional theory (TD-DFT) (Runge and Gross, 1984) under the Tamm-Dancoff Approximation (TDA) (Hirata and Head-Gordon, 1999) and the configuration interaction singles (CIS) method (Foresman et al., 1992) suggest that the S_1 state and charge transfer state are both similar in energy to the chlorophyll Q_y state for the zeaxanthin complex, but that only the charge transfer state is similar in energy for the violaxanthin complex (Dreuw et al., 2005, 2003a, 2003b). The relative energies calculated for a single orientation are distance dependent, suggesting that some combination of the proposed mechanisms is possible, depending on details of the protein conformation and fluctuations in the protein matrix. A plot of the energies of zeaxanthin-chlorophyll charge transfer, zeaxanthin S_1, S_2, and chlorophyll *a* Q_y state as a function of separation distance between the chromophores is shown in Fig. 2. Experimental evidence for both possibilities has been reported: The presence of a zeaxanthin radical cation signal was detected experimentally via transient absorption studies and localized to the minor antenna complexes (Ahn et al., 2008; Avenson

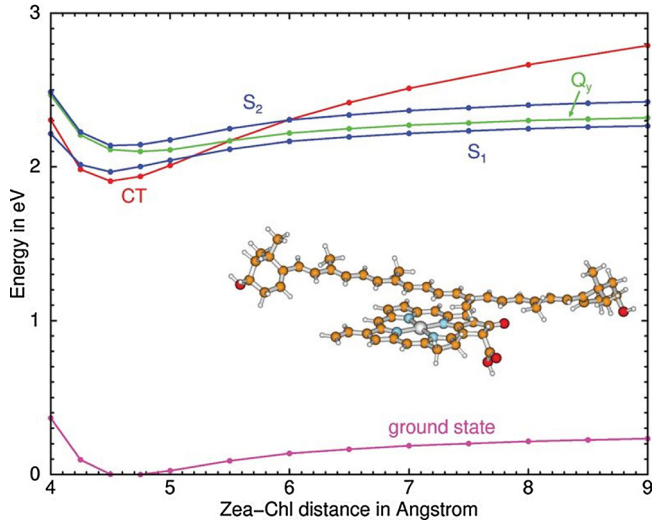

Fig. 2. Potential energies of ground (magenta) and excited states (red, charge transfer states; green chlorophyll *a* excitonic states; blue, zeaxanthin excitonic states) of the zeaxanthin-chlorophyll dimer as a function of separation distances. This figure was originally published in A. Dreuw, G.R. Fleming and M. Head-Gordon, Biochem. Soc. Trans. 33(4):858-862 (2005). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2008; Holt et al., 2005), while direct two photon excitation of the forbidden S_1 state of zeaxanthin indicates excitonic energy transfer between zeaxanthin and chlorophyll molecules (Bode et al., 2009; Holleboom and Walla, 2014).

A second proposed mechanism involves the xanthophyll lutein. Beginning with studies on zeaxanthin-deficient mutants, it has long been proposed that lutein can either play a direct role in the quenching process (Niyogi et al., 1997), or may indirectly contribute to the efficacy of another direct quenching mechanism (Pogson et al., 1998), possibly through a role in the structural organization of LHCII and the PSII antenna size (Lokstein et al., 2002). In isolated LHCII lacking zeaxanthin, the comparison of the kinetics of transient absorption measurements between the quenched and unquenched states support an energy transfer process to a carotenoid S_1 state, similar to the two photon excitation experiments, but since zeaxanthin is not present, the S_1 state is attributed to lutein due to a correspondence between the maximum bleach in the carotenoid triplet spectrum and lutein (Ruban et al., 2007). Additional experiments support the proposal that this is due to a conformational change in LHCII (Ilioaia et al., 2008) that could be moderated by the conversion of violaxanthin to zeaxanthin (Horton et al., 1991; Pascal et al., 2005; Ruban and Johnson, 2010).

In addition to the proposed energy transfer mechanism involving lutein, evidence has also been found for a lutein radical cation signal in mutants of *A. thaliana* lacking zeaxanthin, but overexpressing lutein (Li et al., 2009), as well as in reconstituted minor antenna complexes when zeaxanthin is present (Avenson et al., 2009). This suggests that either lutein can replace zeaxanthin in this radical cation mechanism, that both quenching mechanisms could contribute simultaneously, or that zeaxanthin functions as an allosteric regulator for the lutein charge transfer quenching mechanisms. Evidence of both an energy transfer mechanism and a charge transfer mechanism indicate that lutein can play some role in the molecular mechanism of quenching.

In addition to the proposal that zeaxanthin modulates quenching, first hypothesized to occur via dimer formation and later as a charge transfer and recombination process (Horton et al., 1999), yet another proposed mechanism of quenching involves chlorophyll–chlorophyll interactions in LHCII. Transient absorption data subjected to global target analysis (van Stokkum et al., 2004) found species-associated spectra that do not support energy transfer to a carotenoid such as lutein in quenched LHCII oligomers deficient in zeaxanthin under annihilation-free experimental conditions (Müller et al., 2010). Instead, species-associated spectra are attributed to quenching via a chlorophyll–chlorophyll charge transfer state, in view of enhancement in the far-red portion of the spectra (Miloslavina et al., 2008). Recent work suggests that considering exciton–exciton annihilation, a process by which two excitons combine and then rapidly decay, may be necessary to explain the discrepancies between work that demonstrates chlorophyll-xanthophyll and chlorophyll–chlorophyll interactions as potential quenching mechanisms (van Oort et al., 2018).

Much of the work demonstrating potential molecular mechanisms acknowledges that multiple mechanisms may be present and work in parallel in the intact plant system. Single-molecule experiments provide a way to observe the function of pigment-protein complexes without the heterogeneity inherent to ensemble measurements (Kondo et al., 2017a). Under variable light, algae and mosses possess a pigment-protein complex that is well suited for single molecule fluorescence lifetime experiments called LHCSR (Peers et al., 2009). LHCSR is essential for the quenching response and performs both the regulatory function of sensing pH and the quenching itself (Liguori et al., 2016, 2013). In plants, these functions are distributed between several proteins, making it difficult to ensure that single molecule fluorescence lifetime studies observing two quenching states of LHCII monomers (Schlau-Cohen et al., 2015) are representative of *in vivo* conditions. Single-molecule fluorescence lifetime studies indicate that two distinct quenched states of LHCSR1 exist, with the probability of finding the protein in each state and the transition rate (up to $3.4\,s^{-1}$) influenced independently by the regulatory factors pH and presence of zeaxanthin (Kondo et al., 2017b). A representative schematic of the potential energy surface along two coordinates showing a change in barrier height that would result in an increased transition rate and a change in preferred conformation subject to control by xanthophyll content and pH is shown in Fig. 3.

The rapid rates of transition suggest that the various states are energetically similar and arise from only small conformational changes. Even small changes in orientation and distance could modulate the couplings and energies of different energetically similar excited and charge transfer states in chlorophylls or carotenoids (Dreuw et al., 2005, 2003a, 2003b). Subsequent evidence from similar studies on LHCIIs extracted from various mutant plants emphasizes that the transition rate is influenced by which carotenoid is present in LHCIIs, but the character of the quenched states observed are independent of the carotenoid present (Tutkus et al., 2017), further suggesting that quenching occurs heterogeneously and in agreement with single molecule fluorescence intensity measurements (Krüger et al., 2012). In ensemble measurements, the presence of a particular signal (such as the carotenoid radical cation, carotenoid S_1 excited state absorption, or far-red chlorophyll–chlorophyll charge transfer signals) may indicate that all of these mechanisms are involved in some way. However, addressing the roles they play in the overall plant photosynthetic system − inaccessible to a single molecule experiment − requires integrating information into a quantitative model to effectively evaluate the roles of mechanisms proposed upon observation of characteristic signals.

3.2. Incorporating quenching mechanisms into energy transfer models

Incorporating the mechanisms described in Section 3.1 into energy transfer models of the photosynthetic antenna system and membrane allows an evaluation of how well the proposed mechanism, and the parameters identified from multiple experiments on isolated elements, can reproduce the experimentally observable decrease in fluorescence of the intact photosynthetic membrane. A first step is to accurately determine energies of the S_1 or dimer charge transfer states and their electronic couplings to neighboring chromophores that reflect the molecular configuration and environment within the pigment-protein complex. The rates at which excitons are transferred into a dissipative

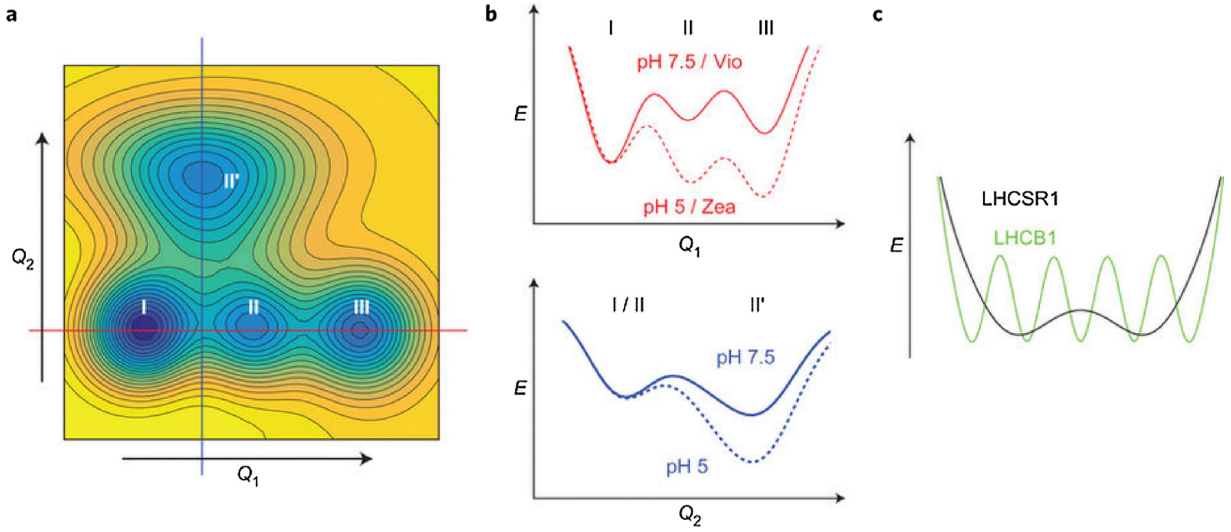

Fig. 3. Representative illustration of the free-energy landscape of LHCSR1, a single protein pH sensor and quenching pigment-protein complex. (a) Contour plot showing three minima as a function of two nuclear coordinates. (b) Cuts along each coordinate displaying the change in surface due to changes in xanthophyll and pH that result in smaller barriers between states and a change in the lowest energy conformation. (c) comparison of barrier heights between conformational states of a non-quenching pigment-protein complex LHCB1. Reprinted by permission of Springer Nature: T. Kondo et al. Nature Chemistry 9(8):772-778 (2017).

state can then be calculated.

Although the energies of the excited states of carotenoids can be calculated reasonably accurately with common methods for electronic structure calculations (Dreuw et al., 2005, 2003a, 2003b), likely to a fortuitous cancellation of errors (Starcke et al., 2006), it is difficult to calculate the charge distributions of the excited states of the carotenoids accurately due to their two-electron character and the strong interactions between electrons (Macernis et al., 2012; Schulten et al., 1976; Starcke et al., 2006). As a result, determining the electronic couplings to neighboring chromophores is difficult. Semi-empirical calculations that take into account the effect of the electron interactions (Macernis et al., 2012) were used to calculate electronic couplings between a specific lutein and the closest adjacent chlorophylls in the structure of LHCII (Liu et al., 2004) and the resulting Förster energy transfer rates in a model of LHCII (Duffy et al., 2013). Fig. 4 shows the lutein and adjacent chlorophylls embedded in the LHCII protein. With the energy of the S_1 state as a fit parameter, the model indicated that the most effective quenching occurred when the energy of the S_1 state was in agreement with the two-photon absorption spectrum (Walla et al., 2001). While an encouraging result, additional study is needed to understand the effects of heterogeneity in the position and orientation

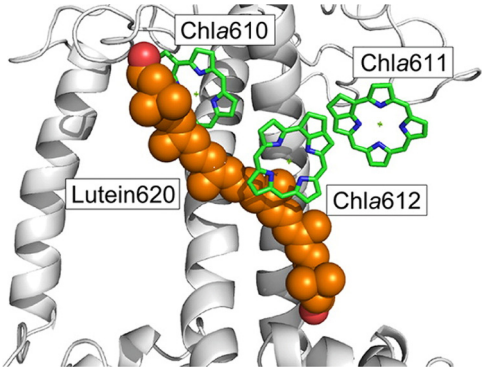

Fig. 4. Structural depiction of a lutein quenching site associated with neighboring chlorophylls in LHCII. Reprinted with permission from Duffy C.D.P, Chmeliov, J, Macernis, M., Sulskus, J. Valkunas, L., Ruban, A.V., 2013, Modelling of Fluorescence Quenching by Lutein in the Plant Light-Harvesting Complex LHCII. J. Phys. Chem. B 117, 10974-10986. Copyright 2013 American Chemical Society.

of lutein to evaluate the role this potential quenching mechanism plays in the plant system and how it might be regulated.

To make predictions of quenched fluorescence lifetimes observed *in vivo*, the quantum mechanical descriptions of energy transfer to quenching sites must be incorporated into larger energy transfer models. The multiscale model of energy transfer at the membrane scale discussed in Section 2.1 (Amarnath et al., 2016) has been developed to include quenching sites located at several of the suggested quenching sites in LHCII (Bennett et al., 2017) and can make predictions of fluorescence lifetimes given various quenching configurations. Changes in experimental fluorescence decay profiles of *A. thaliana* leaves (Sylak-Glassman et al., 2016) are accurately described by changes in a single effective quantity – the exciton diffusion length, L_D. L_D drops from about 50 nm in wild type plants at low light to around 25 nm in the maximally quenched system at high light levels. Conceptually, the L_D is a single variable that serves as the "tap" that controls light harvesting efficiency under conditions of excess light. L_D is a function of the intrinsic rate of quenching at a particular quenching site and the density of quenching sites. The functional dependence can be thought of, in the simplest approximation, as product of the two quantitates. Although different combinations of the intrinsic quenching rate and density of quenching sites can describe the fluorescence snapshot data, they all have the same L_D for a given quenched fluorescence lifetime (Bennett et al., 2017).

One proposed quenching mechanism the coarse grained model evaluates is the decay of the S_1 state of lutein near the terminal emitter of LHCII shown in Fig. 4 (Duffy et al., 2013). The coarse grained model finds a 20 ps non-radiative decay constant for the domain predicts realistic quenched fluorescence lifetimes (Sylak-Glassman et al., 2016) with about 30% of the quenching sites active. On average, an exciton populates the domain for about 3 ps before either energy transfer to another domain or quenching occurs. These values agree with those suggested by semi-empirical calculations of couplings between lutein and adjacent chlorophylls (Duffy et al., 2013) and the probability of the LHCII adopting a quenched conformation determined from single molecule experiments (Krüger et al., 2012). In this parameter regime, the variety of proposed quenching mechanisms all operate in a "weak" limit, regardless of the specific details of the quenching mechanism. In the weak limit, an exciton does not spend much time within a domain before subsequent energy transfer, and therefore will visit multiple active quenching sites before it is likely to be dissipated.

To obtain L_D values that correspond to the highly quenched mutants, additional quenching sites in e.g. minor antenna complexes are required, suggesting that multiple quenching mechanisms work in parallel. Incorporating charge transfer states into exciton models of energy transfer presents another challenge. Exciton models assume that chromophores are locally excited, meaning that site energies and couplings can be calculated from quantum calculations of individual chromophores (Müh et al., 2010; Müh and Renger, 2012; Renger et al., 2011). When charge transfer occurs, this is no longer the case as electron density is transferred between chromophores as well (Dreuw et al., 2005, 2003a, 2003b). One extension of the exciton model uses calculations of the positive and negatively charged states of chromophores in addition to the usual calculations of local excited states to determine charge transfer states' energies and calculate the states' electronic couplings to locally excited states (Li et al., 2017). This method could be applied to begin to incorporate charge-transfer states into models of LHCII and minor antenna complexes to evaluate charge-transfer-based quenching mechanisms.

4. Chemical regulation of quenching

In comparison to the controversy surrounding the molecular mechanisms of quenching, there is relative consensus surrounding major components of the biochemical regulatory processes. It is generally accepted that the rapid induction of the quenching response in *A. thaliana* is triggered by a trans-thylakoid pH gradient that forms in response to high light (Horton et al., 1996) as excitation pressure and charge separation outpace the ATP synthase (Kanazawa and Kramer, 2002). Excessively low pH in the thylakoid lumen protonates the non-pigment-binding PsbS (Li et al., 2004) and violaxanthin deepoxidase (VDE) that converts violaxanthin into zeaxanthin (Hager and Holocher, 1994; Jahns et al., 2009). Double mutants deficient in both PsbS and VDE lack all rapidly reversible q_E (Li et al., 2000). The presence of zeaxanthin, formed by VDE, and under certain conditions lutein (Ruban et al., 2007), allows the protonation-activated PsbS to act in the catalysis of rapid induction and relaxation of quenching (Sylak-Glassman et al., 2014). In addition, the presence of zeaxanthin is also associated with a longer timescale, non-pH-dependent quenching, called q_Z (Nilkens et al., 2010). Zeaxanthin levels and PSII light-harvesting efficiency are significantly and inversely correlated over time scales ranging from minutes to seasons (Adams et al., 2008; Demmig-Adams et al., 2012). The many proposed molecular mechanisms of rapidly reversible quenching attempt to explain the quenching components identified by these regulatory dynamics (Duffy and Ruban, 2015; Jahns and Holzwarth, 2012).

Although there are numerous questions surrounding details of how each of the established components functions, including for example, the mechanism by which PsbS catalyzes the rapid induction of quenching (Daskalakis and Papadatos, 2017; Krishnan et al., 2017; Wilk et al., 2013), many aspects of their chemical kinetics have been measured (Jahns et al., 2009; Kalituho et al., 2007; Takizawa et al., 2007). The resulting kinetics of individual components have been incorporated into a quantitate kinetic model of the interior of the chloroplast with a simple model of the chemical regulation of quenching that predicts how fluorescence lifetimes change in response to changes in light intensity (Zaks et al., 2012). This model is an important tool for connecting the seconds to minutes timescale of the biochemical regulatory dynamics to the ultrafast timescales of energy transfer and quenching mechanisms: a major conclusion was that the pH gradient was insensitive to the presence of quenching. Therefore, subsequent and more sophisticated models of the regulation of quenching can approximate the pH gradient dynamics as an input, greatly simplifying the required details.

In a first attempt to develop a more sophisticated model of the regulation in *A. thaliana*, measurements of ultrafast fluorescence lifetime snapshots resolved on the regulatory timescale and matched to time resolved quantification of xanthophyll pigments were performed

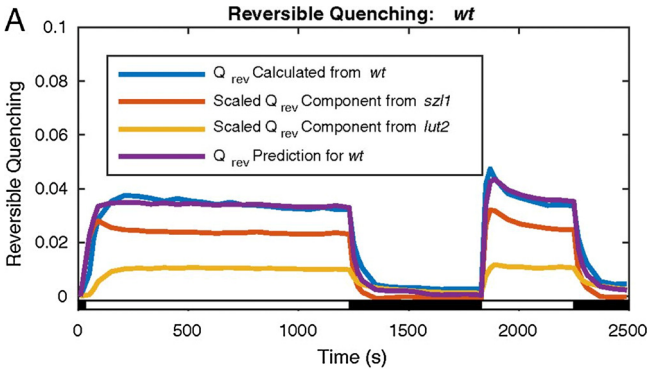

Fig. 5. Analysis of quenching in response to two periods of light and dark acclimation into components isolating the contributions of lutein (red, from *szl1* mutant deficient in zeaxanthin) and zeaxanthin (yellow, from *lut2* mutant deficient in lutein) that require a single common scaling factor to obtain good agreement with wild type (blue, observed; purple, predicted from components). The scaling factor is greater than unity indicates that the wild type is more efficient on a per-molecule basis. Reprinted from Leuenberger et al. PNAS 114(33) E7009-E7017 (2017). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

on intact leaves for a series of mutants deficient in either lutein or zeaxanthin (Leuenberger et al., 2017). In addition to addressing regulatory questions regarding memory effects of the xanthophyll cycle, the resulting kinetic model of regulation allowed the contributions of quenching controlled by different regulatory mechanisms to be quantified. A plot showing individual contributions to the wild type quenching response, formed from mutants deficient in either lutein or zeaxanthin, is shown in Fig. 5. Within an individual mutant, it was found that zeaxanthin was a much more efficient quencher on a per molecule basis. Comparison of the individual components of quenching in wild type, which contains both lutein and zeaxanthin, indicated that the wild type quenching was more efficient on a per xanthophyll basis, than mutants containing just a single xanthophyll. Within an understanding of the exciton diffusion length, discussed in Section 3.2, it is difficult to assess either the origin of or the difference in quenching efficiency between lutein and zeaxanthin, or what results in the gain in efficiency of quenching when both are present: either the intrinsic quenching rate or the effective density of active quenching sites could change. Single molecule fluorescence lifetime studies indicate that multiple quenched states exist for LHCII could all be present simultaneously with different non-radiative lifetimes (Krüger et al., 2012; Schlau-Cohen et al., 2015; Tutkus et al., 2017). Changes in the xanthophyll content could also change conformational behaviors of the pigment-protein complexes, reducing the density of quenching sites (Tutkus et al., 2017).

To quantitatively evaluate how the wild type realizes the observed efficiency gains, further work incorporating molecular models of quenching into models of the thylakoid membrane is necessary. Calculations of energy transfer rates to potential quenching states within single pigment-protein complexes (Duffy et al., 2013) upon substitution of xanthophylls as has been observed experimentally (Li et al., 2009; Lokstein et al., 2002) could indicate if substitution results in the observed discrepancy by changing the transfer or decay rate. However, recent single molecule experiments on monomeric LHCIIs from pigment deficient mutants suggest that xanthophyll deficiencies instead change pigment-protein complex conformational dynamics, and therefore the activation of quenching sites (Tutkus et al., 2017). Integrating these data into coarse grained membrane scale models (Amarnath et al., 2016; Bennett et al., 2017) would be useful for evaluating the effects of xanthophyll deficiency on molecular mechanisms of quenching in addition to the regulation of quenching.

Due to the complexity of the *in vivo* system, it is necessary to employ

regulatory modeling to isolate the contributions of quenching with specific regulatory signatures that suggest distinct molecular mechanisms. For example, in the case of zeaxanthin, multiple quenching processes all depend on zeaxanthin and cannot be isolated with xanthophyll deficient mutants alone (Leuenberger et al., 2017). Upon isolation of the quenching attributable to a particular regulatory signature, the effect of a particular molecular mechanism of quenching on the L_D, and thus the change in fluorescence of an *in vivo* system evaluated with multiscale models, can be evaluated independently of the effect of the xanthophyll as a whole. As regulatory and molecular models of quenching converge, mechanistic connection between regulatory signatures and molecular mechanisms of energy dissipation itself could be achieved through analysis of minimal artificial systems or large scale molecular dynamics simulations.

5. Conclusion

This review discusses the quantitative modeling of energy dissipation, or quenching, in *A. thaliana*. Starting from energy transfer between individual chlorophyll molecules in the antenna, detailed quantum mechanical treatments are necessary at the fastest timescales. However, as time and length scales increase, much of quantum mechanical detail can be approximated into coarse grained models. These coarse-grained models are useful for evaluating proposed molecular mechanisms of quenching in a manner that can predict experimentally observable fluorescence lifetimes. Although evidence suggests a number of different mechanisms of quenching, that seem to occur simultaneously, combining molecular and mechanistic models with regulatory modeling that quantifies of the contributions of components with distinct regulatory signatures provides a path towards evaluating the roles and contributions of proposed mechanisms and to exploring optimization of the regulatory system.

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