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Structural Basis for Allosteric Regulation in the Major Antenna Trimer of Photosystem II

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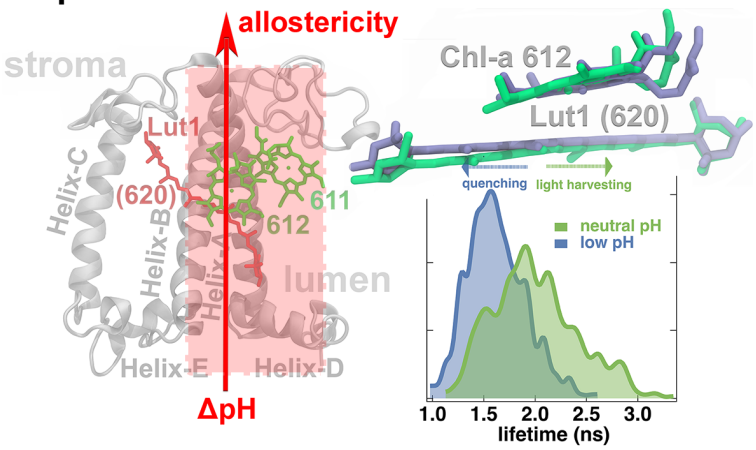
Abstract

The allosteric regulation of protein function proves important in many life-sustaining processes. In plant photosynthesis, LHCII, the major antenna complex of Photosystem II, employs a delicate switch between light harvesting and photoprotective modes. The switch is triggered by an enlarged pH gradient (ΔpH) across the thylakoid membranes. Using molecular simulations and quantum calculations, we show that ΔpH can tune the light-harvesting potential of the antenna via allosteric regulation of the excitonic coupling in chlorophyll – carotenoid pairs. To this end, we propose how the LHCII excited state lifetime is coupled to the environmental conditions. In line with experimental findings, our theoretical model provides crucial evidence towards the elucidation of the photoprotective switch of higher plants at an all-atom resolution.

allosteric regulation; light harvesting complex; photoprotection; non-photochemical quenching; energy transfer; carotenoids; molecular modeling; pigments

Graphical Abstract



INTRODUCTION

Insight into the allosteric regulation of protein dynamics provides a crucial step for the unravelling of the structure-function relation. The Light Harvesting Complexes (LHCII), or antenna, of Photosystem II (PSII) provide an ideal case study for such regulation.[1-2] They embed pigments like chlorophylls (Chl) and carotenoids (Car) within the thylakoid membranes of higher plants. The Chl-Car orientations are fine-tuned for the optimal yield under low light. However, in high or fluctuating light conditions, the antenna proteins activate a down regulatory mechanism termed Non-Photochemical Quenching (NPQ) of Chl fluorescence.[3] Insight into NPQ can potentially lead to artificial and more efficient solar energy harvesting,[4] or the increase of crop yields.[4-5] Herein we provide insights into the exact protein scaffold dynamics that lead to quenching. At the same time, we probe the identity and location of potential quenchers associated with the dynamics. We try to answer some of the open questions concerning the atomic details of NPQ, and discuss the protein domains that at least partially, can control NPQ. Despite extensive experimental and computational studies, it is agreed so far only that the quenching site lies within the LHCII. The latter includes the major trimers (Lhcb1-3) and the minor monomers: CP29 (Lhcb4), CP26 (Lhcb5) and CP24 (Lhcb6).[6] The major energy-dependent quenching (qE) component of NPQ is triggered by an enlarged proton gradient (ΔpH) across the thylakoid membranes. The gradient is built up due to the lumen acidification in bright light (low lumenal pH ~ 5.5).[7] This leads to concealed conformational changes within the antenna that affect inter-pigment interactions.[8-9] Potential quenching sites in the antenna include mainly Chl-Car pairs. Specifically, lutein-620 (Lut1) could quench the excess excitonic energy of the terminal emitter site of LHCII (Chl-a 611, 612). Chl-a 611/ 612 is the excitonic pair with the strongest inter-pigment coupling in the crystal structure and a gate for the transfer of energy to the minor CP29 and the PSII core. [10-14] Energy transfer is possible between the lowest Q_y singlet state of Chl-a 612 and the carotenoid Lut1 dark states (S1, S*).[15-19] The short-lived S_1 state has a lifetime of 10-25ps.[20-21] In the photoprotective mode, the S_1 state can become an energy sink. Moreover, lutein-621 (Lut2) is found close to the Chl 602/ 603 pair and could also undertake the role of the energy sink to support or replace the role of Lut1. Charge transfer (CT) states in Chl-Car pigment pairs have also been proposed as energy sinks with the involvement of Lut or zeaxanthin (Zea) cation radicals. The latter quenching pairs are possibly formed via the accumulation of Zea close to Chls when the antenna interacts with the PSII subunit S (PsbS) under photoprotection.[21] Alternatively, chlorophyll dimers[22] can act as quenchers via CT states. Herein we provide strong indications for the missing link between pH gradient, antenna conformations, excitonic couplings in Chl-Car pairs and NPQ. Accumulating evidence[15-18, 20, 23] has identified the Chl-a 611/ 612/ Lut1 triad (**Fig. 1A-B**) that potentially can exert considerable fluctuations associated with photoprotection.[17-18, 20-21, 24] Based on experimental data, the Q_y-S_1 energy transfer is supported by the proposed "*eco-*

nomic" NPQ model, where excitonic energy is partly captured in traps, while a sufficient amount reaches the open reaction centers to support life.[25] Our working hypothesis is that conformational changes within the LHCII scaffold, that are associated with NPQ factors, e.g., low lumenal pH leading to an enlarged ΔpH, should be 'transferred' to the pigments, and alter the inter-pigment dynamics. This should guide the transition from the light-harvesting to the photoprotective mode. Although conformational changes imply the existence of allosteric pathways, these remained so far elusive.[26] Our main goal, herein, is thus to identify these allosteric pathways, associated with the photoprotective switch under NPQ conditions.

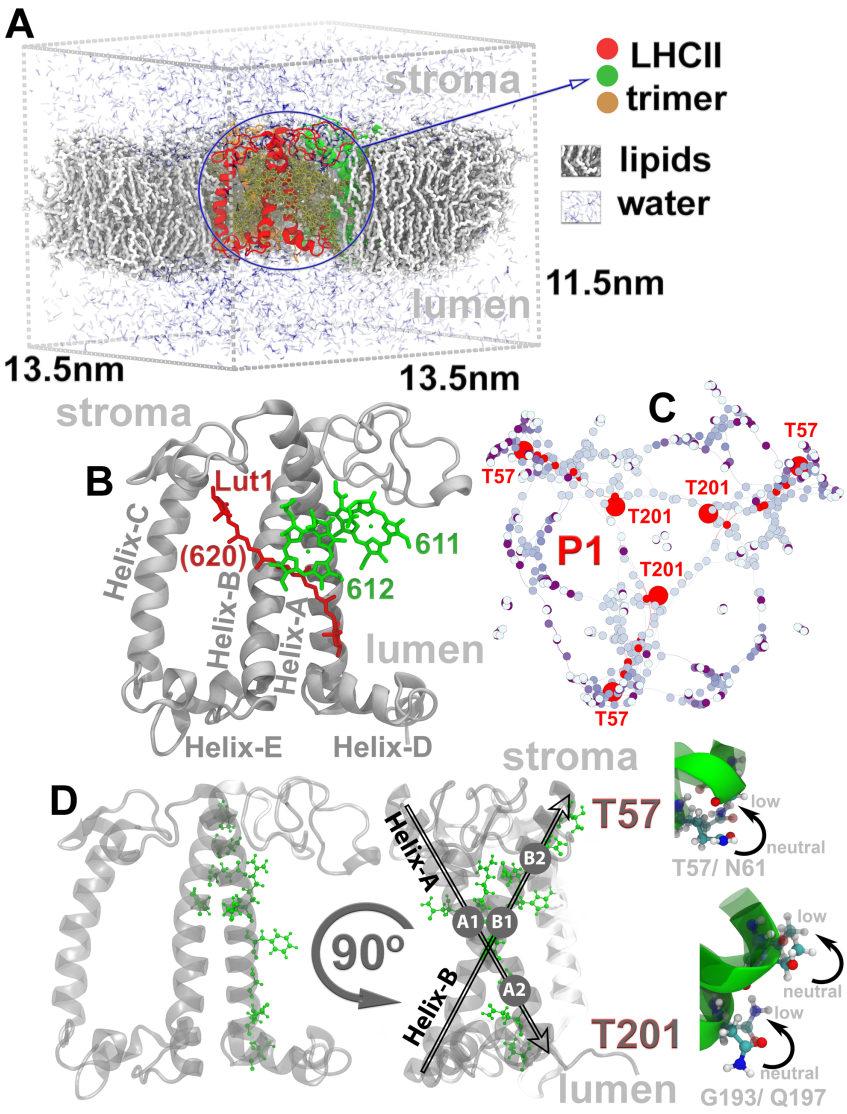


Figure 1. The major light harvesting antenna models

(A) The LHCII trimer embedded within a hydrated lipid bilayer membrane. The trimer is depicted in red, green and brown cartoons, the membrane in white-grey licorice and waters in

white-blue lines. The unit cell dimensions are shown for reference. (B) A LHCII monomer depicted in gray cartoon. The terminal emitter site (Chls-a 611, 612) is shown in green and the lutein (Lut1) carotenoid adjacent to the terminal emitter in red. All helices are indicated for reference. (C) The trimer crystal structure (chains C, E H) in graph theory representation.[27] Nodes (residues) are shown in circles while the large red cycles correspond to the residues Thr-201 (lumen) and Thr-57 (stroma). The blue coloring gradient is used to identify closely (dark), or loosely (light) interacting nodes. The shortest pathways between T201 and T57 in each monomer are depicted by red circles (P1). (D) Residues of the shortest pathway that connect T201 and T57 within the chain C crystal structure are depicted by green balls and sticks. The dihedral angle (A2-A1–B1-B2) is formed by helices A and B. The conformations of T57-N61 and G193-Q197 are highlighted for the neutral and the low lumenal pH states. The black solid arrows indicate the conformational transitions associated with the change from neutral to low lumenal pH.

RESULTS

The light harvesting antenna models

In the present study, we have assembled a major LHCII trimer model (chains C, E, H)[10] which is embedded in a fully hydrated lipid bilayer membrane (**Fig. 1A**). Two different initial states of the trimer are considered mimicking (**i**) low Δp**H** (neutral lumenal pH, light-harvesting mode) and (**ii**) enlarged ΔpH (lower lumenal pH, NPQ mode).[28] Based on published protocols,[29-30] the models of ~221k atoms are relaxed and equilibrated prior to the production runs (*details for the protocols are provided in the Supplemental Information*, SI). These various models probed can give insight into the conformations of the trimer at the different states. We note that the protonations at the protein lumenal sites for the enlarged ΔpH case, implicitly take into account possible effects from LHCII aggregation, from the interactions with the photoprotective PsbS protein, or from the association of Zea carotenoids,[3] that could increase the pKa values of lumen-exposed residues (*please refer also to the* SI)[29-30].

The allostericity within the antenna

At the different pH states and sampled over the 3.0μs-long unbiased simulations, the first three eigenvectors reproduce between 40-45% of the total protein motion in Principal Component (PCA) or Essential Motion Analysis.[31] For the low lumenal pH model, the PCA eigenvalues decay twice faster than those for the neutral lumenal pH state. This finding indicates that at neutral pH the trimer samples a broader phase space. The above suggests that (de)protonations at the lumenal site are sensed across the protein scaffold. How are these changes at the lumenal site, induced by ΔpH, propagated across the protein scaffold? Given also the important role of the N-terminus in regulating inter-pigment orienta-

tions,[23] a connection to the effects of pH at the lumenal side with its consequences across the scaffold is so far lacking.

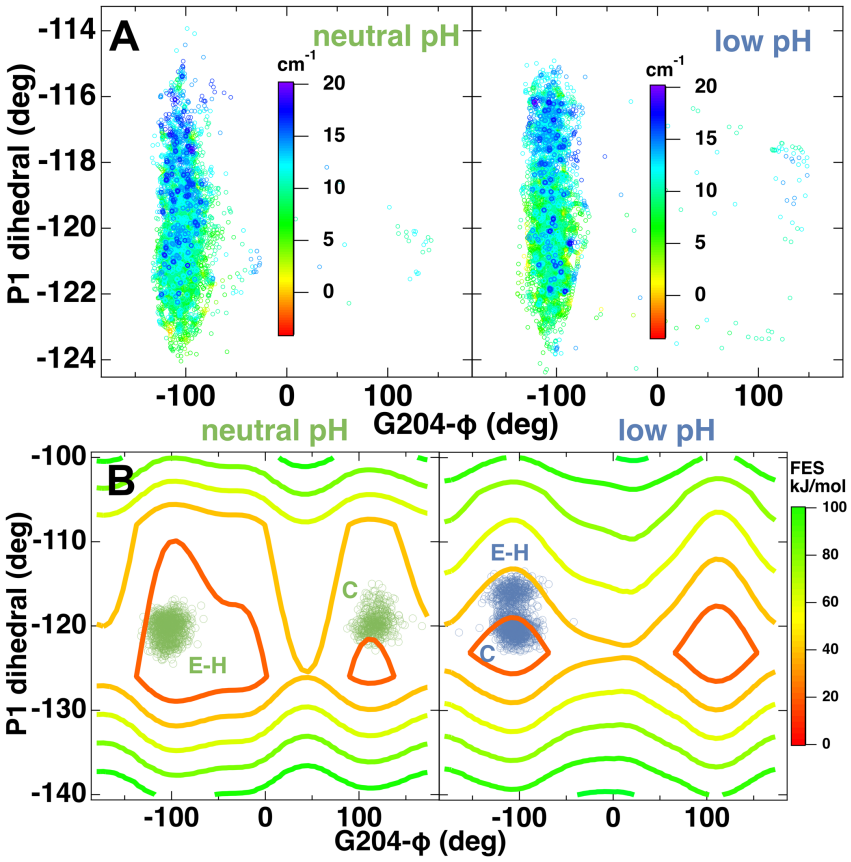


Figure 2. The major light harvesting antenna dynamics
(A) The excitonic couplings between Chl-a 612 and Lut1 for the neutral and low lumenal pH states. (B) The FES along the CV space defined by the P1 dihedral angle (A2-A1–B1-B2, refer to Fig. 1D) and the G204 ϕ-torsional at the start of helix-D. In addition, the point clouds refer to two 0.5μs-long unbiased trajectories with starting structures at the FES minima at neutral (green) and low (blue) lumenal pH. The point clouds belonging to chains C, E and H clouds are designated by the respective letters. A coloring scheme is provided for the free energy contour plots from zero (red) to 100 kJ/mol (green).

A LHCII monomer (chain C)[10] is depicted in **Fig. 1B** together with its key structural features. An allosteric pathway that connects the lumen (helix-D, C-terminus) to the stromal side (N-terminus) is revealed by a graph-theoretical approach for the trimer (for more details *please refer to the SI*). The resulting protein graph is shown in **Fig. 1C**. Perturbations at one residue can create long-range allosteric effects by their propagation through the network.

The residues along the shortest pathway[32] from the stromal (Thr-57, T57) to the lumenal side (Thr-201, T201) were also evaluated for the trimer, based on the crystal structure.[10] We note that the crystal structure is known to refer to a quenched state.[23, 33] The common shortest pathway is along Thr-57, Asn-61, Glu-65, Arg-185, Phe-189, Gly-193, Gln-197 and Thr-201 (**Fig. 1D**). This pathway, termed P1 hereafter, actually involves parts of helices A/ B. It is lambda shaped (**Λ**) and can be characterized by a P1 dihedral angle (**A2-A1–B1-B2**) as shown in **Fig. 1D**. The points A1 and B1 represent the center of masses (CoMs) of the Ca atoms in helices A and B, respectively. Moreover, points A2 and B2 represent the CoMs of only those Ca atoms below and above the crossing of helices A and B, respectively. The P1 dihedral defined using these four CoMs refers to the interhelical crossing angle between helices A and B.[34] Changes for the P1 pathway both at the lumenal and the stromal side associated with the transition from neutral to low lumenal pH can be revealed by visual inspection. At low lumenal pH there is a strengthening of the hydrogen bonds Thr-57…Asn-61 and Gly-193…Gln-197 (**Fig. 1D**). The residue Gln-197 has been proposed earlier to be involved in the orientational changes affecting Lut1 (**Fig. 1B**) at NPQ conditions as it forms an hydrogen bonding interaction connecting helix-D to Lut1.[35] Compared to the neutral pH state, more hydrogen bonds have been found at the low lumenal pH conformation. Thus, these additional hydrogen bonds are part of the P1 properties. It is obvious that pH dependent conformational changes along the P1 pathway and helix-D can affect the inner structure of the LHCII (**Fig. 1C-D**). This movement seems to be a crucial ingredient for the formation of a quencher.[26] Thus, ΔpH can also be sensed at the N-terminus site[23] as the changes propagate across the protein scaffold.

Inter-pigment excitonic couplings

Fig. 2A presents the excitonic couplings for the Chl-a 612/ Lut1 pair (shown in **Fig. 1B**) for the neutral and the low lumenal pH states. These plots show data averaged over the monomers within each major LHCII trimer and over the two 1.5μs-long unbiased Molecular Dynamics (MD) trajectories. The couplings are presented in the space of the P1 dihedral angle and the deflection of helix-D towards the inner structure of LHCII. This plasticity of helix-D at NPQ conditions,[36-37] points to different conformations of the ϕ torsional angle of Gly-204 (G204) at the start of helix-D.[36-37] Clear variations in the calculated Chl-a 612/ Lut1 couplings between the neutral and low lumenal pH state are visible along the P1 dihedral. More importantly, although in the trajectories we observe an inadequate sampling of the helix-D conformation especially for the positive G204-ϕ values, both the P1 dihedral and the helix-D location seem to control the Chl-a/ Lut1 excitonic couplings for the unbiased MD simulations. Lower Chl-a 612/ Lut1 coupling values are associated with more negative P1 dihedral angles while stronger couplings are connected with less negative P1 angles. The latter conformations thus can lead to the quenched mode (NPQ).

A soft switch between light harvesting and photoprotection

To enhance the sampling of the conformations within the Collective Variable (CV) space defined by the P1 dihedral angle and more importantly the helix-D conformation,[35-36] we have employed the well-tempered metadynamics (WT-metaD)[38-39] approach for both the low ΔpH (neutral lumenal pH), and the enlarged ΔpH states (low lumenal pH).[38-42] For details, *please refer to the SI*. In **Fig. 2B**, we show the calculated Free Energy Surfaces (FES) over the CV space for the chain C monomer. We have to note that the FES should be considered only qualitatively. The simulation time (0.2μs) is rather short and despite indications for convergence (*please refer to* the SI), the convergence for all monomers of the trimer would need unreasonably high computational cost. This would not add to our goal that is simply to show thermally accessible conformational changes in the P1/ helix-D domains that can affect inter-pigment dynamics. We have performed additionally two 0.5μs-long unbiased simulations started roughly at selected FES minima (**Fig. 2B**). As can be seen in **Fig. 2B**, the chains C, E and H sample different parts of the CV space, based on the respective point clouds. Qualitatively, the FES minima and the point clouds are in reasonable agreement, while any small disagreements between FES and unbiased simulations, can be attributed to not fully converged FES, or the choice of chain C only monomer within the trimer for biased sampling. Although certainly high-energy regions of the CV space are inaccessible due to the very high energies, the conformational diversity of the three LHCII chains is an advantage we can exploit to explain also the inter-pigment couplings. The TrESP (transition charge from electrostatic potential) method[19, 43-45] has been employed to calculate the Chl-a 612/ Lut1 associated couplings at low and neutral lumenal pH. These are cumulatively shown in **Fig. 3A** and indicate a soft switch.

Shown in **Fig 3B** are the conformations of the Chl-a 612/ Lut1 pair (inset) and the associated protein scaffold changes at P1 dihedral/ G204-ϕ torsional values of -123°/ -100° (light-harvesting mode, green) and -115°/-100^0 (quenched, blue). Differences in the orientations within the pigment pair can clearly be observed. The structure that supposedly belongs to the quenched state shows an orientation of the pigments with the chlorin ring parallel to the Lut1 middle conjugation plane (increased coupling leading to a quenched state). In the other structure the pigments deviate from the parallel orientation (lower coupling leading to less quenching). The simulations indicate transitions between a compact and looser Chl-Car pigment arrangement that is guided by the protein scaffold. The closer packing should be avoided in the light-harvesting mode by a different P1 dihedral angle and a relaxed helix-D conformation.[36-37] We note that the crystal structure of LHCII from spinach,[10] exerts P1/ G204-ϕ values of -118.5^0 and -97.0^0, respectively, which fall within the quenched (blue) region of the CV phase space in **Fig. 3A**.

The amount of energy that Lut1 can quench from the Chl pool thus should be related mainly (a) to the Chl-a 612/ Lut1 orientation and/or (b) to the distance between these pigments. These features can be quantitatively described by the k^2 orientation factor[46-47] and the inter-pigment distance. In **Fig. 3C**, we depict the distributions of these features for the different LHCII states-chains. The k^2 factor is calculated based on the orientations of the donor and acceptor transition dipole moments, as $k^2 = (\sin\Theta_D * \sin\Theta_A * \cos\Phi - 2 * \cos\Theta_D * \cos\Theta_A)^2$, where Φ denotes the angle between the planes containing the two transition dipoles (ND-NB-C15-C35 atoms). Furthermore, Θ_D (C15-NB-ND) and Θ_A (NB-C15-C35) are the angles between the donor or acceptor transition dipoles and the vector joining the donor and acceptor, respectively (**Fig. 3D**).[19, 23] The distance between the pigments is defined as the distance between the CoM of the C15-C35 and the NB-ND atom pairs (**Fig. 3D**).[19, 23]

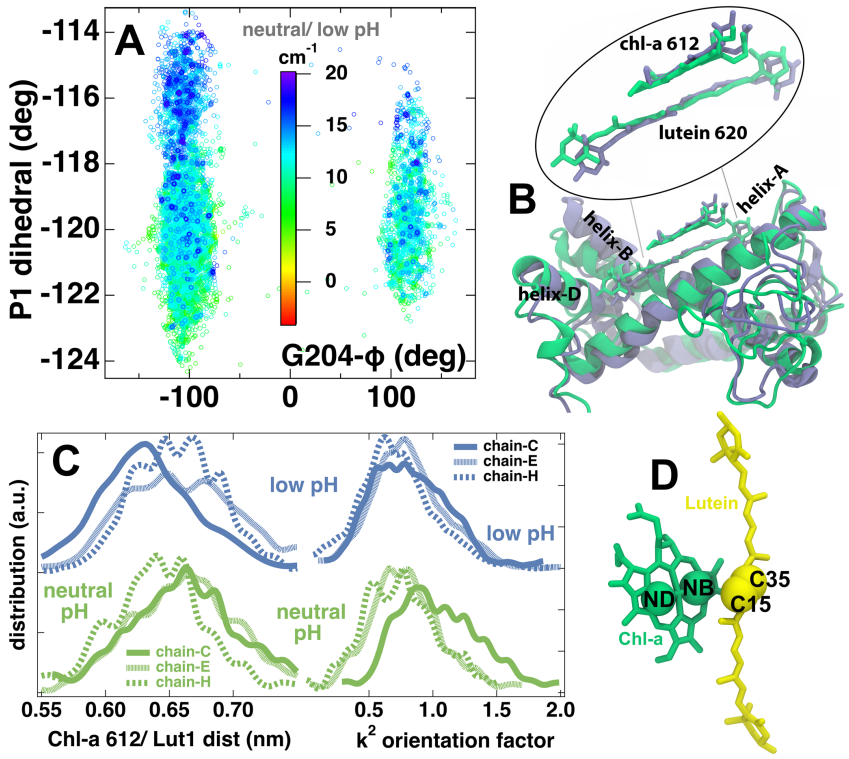


Figure 3. A soft switch for the major light harvesting antenna

(A) The excitonic couplings for the Chl-a 612/ Lut1 pair within the chain C monomer. The coupling values are described using a colour scheme from red (zero) to dark blue (20 in cm^{-1}). Data from both pH states shown jointly in the same grph. (B) The orientations of the Chl-a 612/ Lut1 (inset) and the protein scaffold at the assumed light-harvesting (green) and quenched (blue) modes. (C) The dependence of the Chl-a 612/ Lut1 excitonic couplings on the distance (dist) and k^2 orientation factors of the pigment pair Chl-a 612/ Lut1 for the neu-

tral (green) and low lumenal pH (blue) states. (D) The atoms that define the orientation factor k^2 are shown for reference.

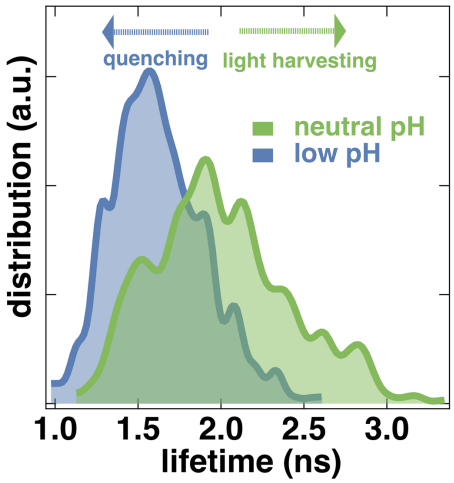


Figure 4. The excited state lifetimes for the neutral (green) and low (blue) lumenal pH state of LHCII.

The defining factor of the excitonic coupling values sampled herein, seems to be the lumenal pH, or rather more accurately, the protonations at the lumenal side. For the low lumenal pH state, the Chl-a 612/ Lut1 pairs are 'locked' in the quenched (high excitonic coupling) states, that is not dependent on the k^2 factor, but rather on the inter-pigment distance, whereas for the neutral lumenal pH state, the k^2 factor and the inter-pigment distance seem to co-regulate these excitonic couplings. This regulation can be made possible by the P1 pathway and the helix-D conformation, that acts as a soft switch in our models. The Chl-a 612/ Lut1 orientational control is possible, as the P1 dihedral angle depends on the angle between helices A/B and Chl-a 612 is coordinated to Asn-183 of helix-A, while Lut1 is hydrogen bonded to helix-D (Gln-197). The TrESP excitonic couplings (**Fig. 3A**) can be translated into excited state lifetimes for the major LHCII[20] and are shown in **Fig. 4**. The details of the lifetime calculations are given in the SI. The lifetime calculations do not indicate a hard, but a rather *soft switch* from a totally unquenched to a quenched state. We therefore computed instantaneous pseudo mean excitation lifetimes (for convenience termed 'lifetimes') which nevertheless are a robust indication of the impact of allostericity in changing the Chl-a 612/ Lut1 interactions and the overall function of the trimer. Based on our sampling herein, there is a 25% reduction in the excited state lifetimes when we transition from the neutral to the enlarged ΔpH state (low lumenal pH) of the trimer. The latter seems to depend on the P1 dihedral angle and the helix-D conformation. Additional mechanisms might be in place that can co-regulate the NPQ response, e.g., a tuning of the energy levels of the involved or other chlorophylls and carotenoids.

DISCUSSION

In detail, we have provided important atomic level insights into the allostericity within LHCII. This allostericity is a crucial ingredient for future experimental and computational studies. Subtle environmental changes could have strong effects on the equilibration of energy within LHCII. To prove our point, we have provided a complete pathway from the enlarged pH gradient across the thylakoid membrane to quenching at the terminal emitter sites. Our work illustrates that the lifetime of the complex is can be coupled to the environmental conditions via allosteric regulation of the coupling in the Chl-a 612/ Lut1 pair. The differences between the LHCII states, in terms of inter-pigment couplings and lifetimes, are relatively small (25%). However, more elaborate methods for calculating such parameters alongside an accurate description of the pigment site energies and their spectral densities,[48] could significantly enhance such differences, e.g., by (de)tuning on the involved energy levels. A calculation of the latter, however, proves rather tricky because of the complex electronic structure of lutein and is computationally extremely expensive for the system under study. Nevertheless, the presented strong atomistic evidence fits well with the established NPQ literature, where the lumenal pH controls excited state lifetimes of the Chl pigments. It is possible that protonations of the LHCII lumenal exposed residues at low pH, are controlled by the state of aggregation, the formation of LHCII-PsbS complexes, or the interaction with zeaxanthin at NPQ conditions.[3] Such interactions are implicitly taken into account through the chosen protonation states of the isolated complexes at the lumenal side. It could also be that inter-pigment couplings, other than within the Chl-a 612/ Lut1 pair, at least partially, affect the lifetimes of the LHCII trimer. Nevertheless, we have provided key molecular insight into important conformational transitions of LHCII, i.e., the switching from a light-harvesting to a partly quenching mode, that might be important for a plethora of systems and the respective inter-pigment dynamics. This study hopefully will stimulate further theoretical as well experimental work unravelling all details of the NPQ mechanism. Specifically, this work also forms the basis for explicitly probing the potential role of PsbS in inducing a quenching conformation of LHCII trimers within the proposed LHCII-PsbS complexes.[49] Increased levels of PsbS have been associated with increased crop yields.[4]

CONCLUSION

Proteins exert their function within well-orchestrated and controlled schemes that include many macrostates. In several cases, allostericity plays a major role for the switch between these states. The major photosynthetic antenna, of higher plants, is very efficient in harvesting the light energy even under low light conditions for survival. However, under excess light, it is able to switch to a quenched mode that safely dissipates the excess energy as heat. This switching results in a major drawback for the photosynthetic process, as the re-

covery from the quenched state is relatively slow and exerts a negative impact on crop yields.[4] The elucidation of the quenching mechanism is still a matter of considerable debate in the on-going scientific research. Herein, we have employed all-atom molecular dynamics simulations and identify the domains of the photosynthetic antenna that can respond to environmental stimuli via allosteric regulation. The fundamental insight that we obtain into key conformational switches within the protein scaffold (helix A/B interhelical crossing angle and helix-D) can be used in future studies to efficiently custom-build the recovery from the quenched state.

COMPUTATIONAL METHODS

The LHCII dynamics at equilibrium are firstly monitored, at all-atom resolution, at neutral and low lumenal pH, by two classical MD trajectories 1.5μs each. Secondly, two enhanced sampling WT-metaD[38-40] trajectories for the neutral/ low pH states (0.2μs each) have been produced along with two associated 0.5μs-long unbiased MD trajectories initiated at the minima of the calculated FES. For details *please refer to the SI*.

The excitonic couplings between Chl-a 612/ Lut1 have been calculated directly along the MD trajectories using the standard TrESP method.[43-45] The transition charges for Chl-a and Lut have been taken from recently reported RASSCF calculations where most of the active space orbitals have C_{2h} symmetry yielding a very low transition dipole moment for the dark state of the Lut molecule.[38] Different quantum chemical approaches to obtain transition charges for Chl and Lut molecules are discussed in Ref.[19] In the original TrESP procedure, the transition charges are rescaled to reproduce the experimental *in vacuo* transition dipole moments. This rescaling is not easily possible for the optically forbidden Lut transition while the RASSCF calculations already yield a rather low oscillator strength.[43] Thus, the Lut transition charges have been adopted in an unscaled way. Moreover, the resulting coupling values are quite reasonable as the typical values of 10-20 cm^{-1} are in line with the weak interactions arising from the optically forbidden nature of the carotenoid transition.[17, 50] For simplicity, dielectric effects on the inter-pigment couplings are neglected in this study since we are mainly interested in relative effects.

SUPPLEMENTAL INFORMATION

Supplemental Information includes the sections: 1. Classical Molecular Dynamics Methods, 2. Enhanced and bias sampling, 3. The graph theory framework, 4. TrESP coupling calculations, 5. Calculation of LHCII excitation lifetimes, one figure and one table.

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AUTHOR CONTRIBUTIONS

V.D. designed, performed the MD simulations, analyzed the data, and wrote the paper. S.M. and U.K. contributed to the calculations and analysis of the Chl-a/ Lut1 excitonic couplings. C.L.H and C.D.P.D developed the coarse-grained model and calculated the reported lifetimes based on the couplings. S.T. contributed to the setup of the LHCII models. All authors discussed the results, commented on the manuscript and contributed to the writing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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