Dynamic protein conformations preferentially drive energy transfer along the active chain of the photosystem II reaction centre

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One longstanding puzzle concerning photosystem II, a core component of photosynthesis, is that only one of the two symmetric branches in its reaction centre is active in electron transfer. To investigate the effect of the photosystem II environment on the preferential selection of the energy transfer pathway (a prerequisite for electron transfer), we have constructed an exciton model via extensive molecular dynamics simulations and quantum mechanics/molecular mechanics calculations based on a recent X-ray structure. Our results suggest that it is essential to take into account an ensemble of protein conformations to accurately compute the site energies. We identify the cofactor CLA606 of active chain as the most probable site for the energy excitation. We further pinpoint a number of charged protein residues that collectively lower the CLA606 site energy. Our work provides insights into the understanding of molecular mechanisms of the core machinery of the green-plant photosynthesis.
Photosynthesis provides the foundation for life by converting sunlight into biochemical energy. By catalysing the oxidation of water to molecular oxygen, the photosystem II (PSII) is a crucial component for photosynthesis. The PSII is a membrane-bound protein–cofactor complex that contains the antenna complex and reaction centre (RC). Sunlight is first captured by the antenna system and then the excitation energy is trapped in the PSII RC, leading to charge separation and electron transfer with the aid of cofactors, and finally resulting in the production of molecular oxygen.

A fascinating fact concerning the PSII is that cofactors are arranged in two branches with a C2 symmetry, but half of them (one complete branch) are not involved in the primary electron transfer from water to plastoquinone. Due to this, the underlying C2 branches are termed: active and inactive chains, according to their contributions to the primary electron transfer. Starting from a pair of chlorophyll a (CLA) molecules, each branch contains in order: one accessory CLA, one pheophytin (PHO), one plastocyanin (PL9), and one plastoquinone-9 (PL9). A bicarbonate ion (BCT) branch contains in order: one accessory CLA, one pheophytin, one chlorophyll a, and another bicarbonate ion.

Understanding how the excitation energy is trapped and transferred in the PSII RC is an essential prerequisite to understand the subsequent preferential electron transfer pathway. Extensive experimental and theoretical studies have attempted to identify the underlying functional states during these processes.

Optical spectroscopy is a powerful tool to study the electron and energy transfer processes. However, for PSII, the optical bands of different cofactors are largely overlapped. To overcome this problem, researchers have employed low-temperature optical difference spectroscopy and site-directed mutagenesis of amino acids surrounding the cofactors. For example, a mutation of D1-Thr179 (the amino acid spatially close to CLA607 in the inactive chain) is not superfluous, but to protect the RC from photodamage under high light intensity or the green-shift effect. The protection mechanism is achieved by a low quantum yield electron loop with the help of nearby cytochrome b559 and β-carotene (BCR). Optical spectroscopy studies have shown that CLA606 is the most probable site for the energy trap, because it has the highest site energy after 15 ns (Supplementary Fig. 1a,b and Supplementary Methods).

Further validations of MD simulations against other properties are based on the conformations from the last 5 ns of those independent 20 ns simulations. The crystal structure of PSII at 1.9 Å resolution (Protein Data Bank (PDB) 1D: 3ARC) has identified all axial ligands of CLAs. Seven of them are water molecules and others are amino acids (Supplementary Table 1). In this work, the distance between the Mg atom of each CLA and its coordinated ligand atom evaluated from our MD simulations.

Results

Validation of MD simulations. The PSII complex (see Fig. 1) in our MD simulations is stable from the perspective of various structural analyses. The root mean square deviations (r.m.s.d.) of the protein carbon-α atoms relative to the crystal structure are 1.25 and 0.5 Å for 300 and 77 K, respectively (see Fig. 2a). Overall, stable conformations are observed for all the cofactors in the PSII complex, including CLA, PHO, PL9, BCR, BCT, haem b (HEM) and the oxygen-evolving complex (OEC) (see Fig. 2a). For individual cofactors in the RC at 300 K, the r.m.s.d. is below 1.5 Å, except for CLA610, CLA611 and CLA607, which have slightly larger r.m.s.d. (2.0–3.0 Å) (see Fig. 2a). The higher flexibility of these three cofactors may be due to their less-compact protein environment, especially in the tail regions (see Fig. 1b for their locations in the RC). At 77 K, all the cofactors in the RC are very stable (with r.m.s.d. < 1.0 Å). We perform five independent simulations at both 300 and 77 K and each resulting r.m.s.d. curve reach a plateau after 15 ns (Supplementary Fig. 1). To confirm that the system has reached equilibrium, we extended two 300 K simulations to 100 ns, which confirmed that the r.m.s.d. of protein and cofactors in these 100 ns simulations mostly remain a plateau after 15 ns (Supplementary Fig. 1a,b and Supplementary Methods).

Further validations of MD simulations against other properties are based on the conformations from the last 5 ns of those independent 20 ns simulations. The crystal structure of PSII at 1.9 Å resolution (Protein Data Bank (PDB) 1D: 3ARC) has identified all axial ligands of CLAs. Seven of them are water molecules and others are amino acids (Supplementary Table 1). In this work, the distance between the Mg atom of each CLA and its coordinated ligand atom evaluated from our MD simulations satisfactorily reproduces that of the crystal structure, with
discrepancies being all <0.15 Å (see Fig. 2b). In the crystal structure, there are four hydrogen bonds around CLA606 and only three around CLA607 (see Fig. 2c), our MD simulations also reproduce this property (see Fig. 2d). With the above validations of MD simulations against the crystal structure, we calculated the site energies of cofactors based on our MD conformations to elucidate the molecular mechanism for the unidirectional energy transfer processes.

The dynamic environment enables selection of the active chain. The C2-symmetric arrangement of cofactors alone cannot explain the pathway selectivity. Therefore, we hypothesized that the dynamics of the PSII environment might play a determinant role in this mechanism. We calculated the site energies of cofactors in the PSII complex with respect to the results in vacuum, using both the static crystal structure and an ensemble of MD conformations (Methods and Supplementary Methods). Figure 3a reports the calculated site energies of cofactors from the MD conformations of the PSII complex versus those in vacuum at 300 K. While the site energies for CLAs are all comparable in vacuum, the addition of the PSII protein complex allows differentiating them. The site energies of two PHOs, which are substantially lower in vacuum, become comparable with or even higher than those of CLAs in the PSII complex. As shown in Fig. 3b, the effect of PSII complex on the site energies of cofactors in terms of their differences from the vacuum values is comparable at low temperature (77 K) and room temperature (300 K). The most significant effect is observed on CLA606, whose site energy has been greatly reduced by the PSII complex (Fig. 3a,b, Supplementary Tables 2 and 3). The averaged site energy of CLA606 over an ensemble of MD conformations is the lowest one among all the cofactors in the RC. This result is consistent with previous studies7,16–19,25, where the site energies were obtained by fitting to experimental spectra. In sharp contrast, the PSII complex has nearly zero effect on the site energy of the inactive chain counterpart CLA607. The aforementioned distinct PSII effects on the site energies of these two accessory CLAs differentiate the two chains.

X-ray structure alone fails to explain the pathway preference. Figure 3c highlights the fact that the crystal structure alone is insufficient to explain the energy transfer pathway selectivity. In particular, two PSII monomers (M1 and M2) in the crystal structure exhibit inconsistent relative site energies of cofactor pairs. For example, $E_{\text{CLA611}} > E_{\text{CLA610}}$ in M1, while $E_{\text{CLA611}} < E_{\text{CLA610}}$ in M2. The discrepancies between the two monomers are eliminated when an ensemble of conformations is considered (see Fig. 3d). Thus it is essential to include an ensemble, rather
Figure 2 | MD simulations preserve important protein–cofactor interactions. (a) r.m.s.d. with respect to the crystal structure (PDB ID: 3ARC) for various components of the system are calculated based on MD simulations at 300 and 77 K. The r.m.s.d. of the protein and cofactors (located in the electron transfer chains) are computed based on Cα and heavy atoms, respectively. (b) The deviation from the crystal structure of the distance between the Mg in CLA and its coordinated atom. (c) Hydrogen bonds that CLA606 and CLA607 can form with the protein residues in the crystal structure. (d) The fraction of time that an individual hydrogen bond as shown in c is formed in the MD simulations.

Figure 3 | PSII complex reduces site energy of the active chain cofactor CLA606. (a) Site energies of the eight cofactors calculated in vacuum and in PSII are compared at 300 K. (b) The site energy shift due to the PSII complex ($\Delta E = E_{\text{PSII}} - E_{\text{vacuum}}$) are displayed for the static crystal structures (light grey), 300 K MD simulations (dark grey) and 77 K MD simulations (white stripes). (c) Site energy differences between pairs of cofactors located in the active (D1) and inactive (D2) branches are compared for two monomers (M1 and M2) in the crystal structure. (d) The same as in c, except that the results for 300 K MD simulations are shown.
than a single static snapshot, to identify the site energy difference between active and inactive chains. Further comparisons between two chains also show that the site energies of all three CLAs in the active chains are lower than their counterparts in the inactive chain. Among them, the largest difference is between accessory CLA606 and CLA607. We have thus concluded that an ensemble of PSII complex conformations energetically favour the excitation of the cofactors, particularly CLA606 in the active chain over its counterpart in the inactive chain. This further results in a preferential pathway selection for energy excitation of the active chain.

The active chain cofactor CLA606 is the energy trap. In addition to the excitation of individual cofactor, we construct an exciton model to consider coupling between different cofactors during excitation. Our exciton model shows that the most probable site (30%) for excitation is CLA606 in the active chain at 300 K, indicating that this cofactor serves as an energy trap (see Fig. 4). This is in agreement with our previous observation that CLA606 has the lowest site energy among all the RC cofactors. As the temperature decreases from 300 to 77 K, the probability for the energy excitation of CLA606 increases from 30 to 70% (Fig. 4 and Supplementary Fig. 2). This observation is also consistent with previous experimental spectroscopy studies, which suggested that the excitation probability of CLA606 is 30 and 80% at 300 and 5 K, respectively. Further investigation shows that the decrease in the excitation probability of CLA606 with the increase in the temperature is due to the larger contributions from the high-energy exciton states (see Methods for details). We also find that the effective site energies (and their

Figure 4 | CLA606 is the most probable site for the excitation in the RC. (a) Probability of each cofactor in the local excited states at 300 K revealed by the exciton model. The probabilities ($P_m$) are calculated as weighed sum of each cofactor's contributions to all the excited states (M) obtained by the exciton model (see equation 2). (b) Exciton matrix (unit: meV) built from 300 K MD simulations. The diagonal terms are the average site energies for the cofactors and the off-diagonal terms correspond to the strengths of the coupling. (c) Comparison between the excitation probabilities of the cofactors at 300 K (dark grey) and those at 77 K (white stripes).
Protein residues collectively lower CLA606’s site energy. As discussed above, we found that the PSII complex is essential for selecting the preferential energy transfer pathway by means of reducing the site energy of CLA606. In this section, we further examine the PSII complex to identify which components have the largest contributions to lower the site energy of CLA606. We studied individually the effects of waters, cofactors and protein components. While the former two have little effect on the site energies, we find that the protein environment reduces the site energy of CLA606 by 0.036 and 0.0 eV at 300 and 77 K respectively, but has almost no effect on CLA607 (see Fig. 5 and Table 1). Remarkably, we found that the charged amino acids contribute most to lowering the excitation energy of CLA606 (see Table 1). We performed single mutant calculations and pinpoint seven critical charged amino acids with each contributing over 0.0035 eV to reducing the site energy of CLA606 (see Fig. 6a,b). Other charged amino acids have negligible effect. In summary, the seven charged amino acids depicted in Fig. 6 work collectively to lower the excitation energy of CLA606. Interestingly, these charged residues are highly conserved among different species (see Fig. 6c) and some of them (Glu329, Glu189, Asp170) have been previously identified to have a role in differentiating the cofactor reox potentials of the two chains. Previous site-directed mutagenesis experiments revealed that the mutation of Thr179 to the charged glutamic acid (Glu) leads to a blue shift of ~1 nm in the absorption difference spectrum due to the alteration in the excitation energy of CLA606 (refs 31,32). Our calculations also show that this mutation can raise the average site energy of CLA606 by ~0.0047 eV (refs 31,32), for which a crystal structure has not yet been reported. Therefore, it is reasonable to conclude that some site energy values from our calculations deviate from previous theoretical analysis based on available experimental spectra (see ‘Site energy calculations’ section in Supplementary Methods). On the basis of these observations, we conclude that CLA606 always has the lowest excitation energy with the presence or absence of the core antenna, while the transition energies of other cofactors are more system-size dependent.

Methods

Model preparation. The crystal structure (PDB ID: 3ARC) at 1.9 Å resolution was used to build up the system for MD simulations. First, we removed the exogenous molecules of diglyceride, alkyl chains, detergents and glycerol. Then, the ‘what if’ suite was used to add the missing lateral chains. The protonation states of His, Asp, Glu, Arg and Lys were automatically determined by Gromacs 4.5 (ref. 53). For those His residues in coordination with HEM or CLA, we have manually set their protonation states to maintain the coordination. The PSII complex was inserted into pre-equilibrated lipid bilayers composed of a single-component 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) to mimic the natural thylakoid membrane (Supplementary Methods). The system was then neutralized by adding 92 sodium ions and solvated in a water box containing 139,935 TIP3P water molecules. Our simulation box (264.3 Å × 165.2 Å × 145.0 Å) contains 578,609 atoms in total (see Fig. 1a).

Table 1 | The effect of protein residues on site energies of CLA606 and CLA607.

| Temperature | Cofactors | Site energies* in different environments |
|-------------|-----------|------------------------------------------|
|              | Protein   | Charged residues | Neutral residues |
| 300 K        | CLA606    | −0.036               | −0.0252           | −0.0093 |
|              | CLA607    | −0.0092             | −0.0046           | −0.0047 |
| 77 K         | CLA606    | −0.0046             | 0.024             | −0.0154 |
|              | CLA607    | −0.0109             | −0.0062           | −0.0033 |

Table 1. The effect of protein residues on site energies of CLA606 and CLA607.

Discussion

To investigate the effect of the PSII environment on the pathway selection of energy transfer in RC, we have constructed an exciton model (Fig. 4b and Supplementary Fig. 2b) on the basis of MD simulations in explicit solvent and extensive QM/MM calculations. From the detailed analysis of the site energy calculations based on the whole PSII complex, we have found that the protein environment determines the difference in probability of energy excitation between the active and inactive chains. In addition, the static protein environment captured by the X-ray crystallography is insufficient to explain the preference of energy excitation along the active chain. It is essential to consider the PSII protein’s structural ensemble to compute accurately the excitation probabilities of its cofactors. We have also observed that CLA606 is the site of energy trap in the PSII complex and may further initiate the charge separation at this site, as has been observed by previous experimental studies. Finally, we have identified a small number of charged protein residues in the vicinity of CLA606 collectively lowering its excitation energy.

Interestingly, we noticed that the site energies are sensitive to the system complexity. Our simulations and calculations are performed for the whole PSII complex (based on the most detailed crystal structure available), while previously reported experimental spectra were acquired based on minimal scaffold PSII (denoted also as D1-D2-cyt559)12–15,20, for which a crystal structure has not yet been reported. Therefore, it is reasonable to conclude that some site energy values from our calculations deviate from previous theoretical analysis based on available experimental spectra (see ‘Site energy calculations’ section in Supplementary Methods). On the basis of these observations, we conclude that CLA606 always has the lowest excitation energy with the presence or absence of the core antenna, while the transition energies of other cofactors are more system-size dependent.
Figure 6 | Several conserved residues collectively reduce the site energy of CLA606. (a) Charged residues (red: positive-charged; blue: negative-charged) can reduce the site energy of CLA606 over 0.0035 eV individually. The tail of CLA606 is omitted in the figure for clarity. (b) Site energies of CLA606 on seven single mutations are shown. The collective mutations of all these seven residues dramatically increase CLA606’s site energy to almost the same value as its counterpart cofactor (CLA607) in the inactive chain. The wild-type site energies for both CLA606 and CLA607 are also displayed for reference. (c) These seven residues are highly conserved among different species. The sequence alignment was performed with the ClustalW2 program68,69.

| P. patens | L. japonicas | C. reinhardtii | G. theta | T. vulcanus |
|-----------|--------------|----------------|---------|------------|
| R170      | R129         | R27            | E333    | D170       |

| Site energy (eV) | Site energy (eV) | Site energy (eV) | Site energy (eV) | Site energy (eV) |
|------------------|------------------|------------------|------------------|------------------|
| 1.55             | 1.56             | 1.57             | 1.58             | 1.59             |

MD simulations. We first performed a 10,000-step energy minimization with the steepest descent algorithm66 by freezing the PSII complex. The whole system was further energy minimized in another 5,000 steps. Next, the system was simulated with position restrained on all the heavy atoms of the PSII complex with a force constant of 10 kJ mol$^{-1}$ Å$^{-2}$ under NVT ensemble ($T = 300$ K), followed by another 10 ns simulation under NPT ensemble ($T = 300$ K and $P = 1$ bar). The final configuration from the position-restrained simulation was used to initiate five independent 20 ns production of NPT ($T = 300$ K and $P = 1$ bar) simulations with temperature annealing from 300 to 500 K in the first 1 ns and different initial velocities (see Supplementary Methods for the simulating parameters). To study the properties at low temperatures, similar procedures and parameters were used to perform another round of MD simulations at 77 K. Following a similar procedure, we also simulated the Thr179Glu mutant (Supplementary Methods). All the MD simulations were performed using Gromacs 4.5 (ref. 53).

Calculation of site energies and coupling strength. The Zerner’s Intermediate Neglect of Differential Orbital with parameters for Spectroscopic properties (ZINDO/S)22,64 method (implemented in the ORCA code67) was adopted to calculate the energy gap between the ground state and the first excited state ($Q_0$ state) of the cofactor. The last 5 ns of MD simulations was used for the analysis (with a total of 1,250 conformations). For each conformation, we have performed site energy calculation in vacuum, PSII environment and various components of the PSII environment separately (for example, protein, cofactors, waters, charged residues and neutral residues). To account for the environmental effects on the site energy calculations, we have adopted a QM/MM method by treating the cofactors quantum mechanically while the environment as point charges. In particular, we have included atoms within 22 Å of the cofactor and treated them as the point charges. In this study, we only considered the excitation energy calculated by the TrEsp method22,45 to determine the coupling strength between pairs of cofactors, in which the transition density of one cofactor was described by the atomic transition density calculated by the TrEsp method22,45. By diagonalizing the Hamiltonian, the effective Hamiltonian, with the diagonal elements describing the site energies of the cofactors calculated by the TrEsp method22,45. The off-diagonal terms denoting the coupling strength between the cofactors calculated by the TrEsp method22,45. By diagonalizing the Hamiltonian, the energies of the excited states were given by the eigenvalues of the Hamiltonian and the components of the corresponding normalized eigenvectors denoted the contributions of each cofactor to the respective excited state. The probability of excitation on the cofactor $m$ was calculated as:

$$P_m = \sum_M \left| \langle M | \psi_m^{(2)} \rangle \right|^2$$

where $\langle M |$ denotes the coordinates of the $j$th atom of the cofactor $m$ with the transition charge $q(j)$, while $R_j$ indicates the coordinates of the $j$th atom of the other cofactor $n$ with the transition charge $q(j)$. $f$ is a distance-dependent factor to account for the solvent effect on the electronic coupling$^{42,43}$, with

$f = 2.68 \times \exp(-0.27 \times d) + 0.54$ for two molecules separated by distance $d$ (Supplementary Fig. 7 and Supplementary Table 5,6; see ‘Coupling strength calculations’ section in Supplementary Methods for more details).

Exciton model and equilibrium populations. The system was described by an effective Hamiltonian, with the diagonal elements describing the site energies of the cofactors and the off-diagonal terms denoting the coupling strength between the cofactors calculated by the TrEsp method22,45. By diagonalizing the Hamiltonian, the energies of the excited states were given by the eigenvalues of the Hamiltonian and the components of the corresponding normalized eigenvectors denoted the contributions of each cofactor to the respective excited state. The probability of excitation on the cofactor $m$ was calculated as:

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$f = 2.68 \times \exp(-0.27 \times d) + 0.54$ for two molecules separated by distance $d$ (Supplementary Fig. 7 and Supplementary Table 5,6; see ‘Coupling strength calculations’ section in Supplementary Methods for more details).
where $f(M)$ is the Boltzmann factor for the exciton state $M$ and $c_{m}^{M}$ is the contribution of the cofactor m to the exciton state $M$. When the temperature increases, $f(M)$ becomes larger, and exciton states with higher energies will have substantially more contributions to the excitation. Since these exciton states contain a more uniform contribution from various cofactors, it will result in a more flat distribution of excitation probabilities at higher temperature.

**Sequence alignment**. We have performed the similarity search of the D1 subunit sequence using the Basic Local Alignment Search Tool (BLAST) program, followed by the multiple sequence alignment by the ClustalW2 program.6,8

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Acknowledgements
We would like to acknowledge the National Science Foundation of China (No. 21033008 to Y.J.Y. and No. 21273188 to X.H.). X.H. acknowledges National Basic Research Program of China (973 program 2013CB834703), and Hong Kong Research Grants Council (610111, 609813, T13-607/12R and AoE/M-09/12). Computing resources were provided by the Shenzhen Supercomputing Centre. We would also like to acknowledge Dr Yifan Song for useful discussions on the MCCE calculations.

Author contributions
L.Z., D.-A.S., Y.J.Y. and X.H. conceived and designed the experiments. L.Z. performed the experiments. L.Z. and H.Z. analysed the data. L.Z., D.-A.S., A.Y., Y.J.Y. and X.H. wrote the paper.

Additional information
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Competing financial interests: The authors declare no competing financial interests.

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How to cite this article: Zhang, L. et al. Dynamic protein conformations preferentially drive energy transfer along active chain of the photosystem II reaction centre. Nat. Commun. 5:4170 doi: 10.1038/ncomms5170 (2014).

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