

# Evidence for Correlated Static Disorder in the Fenna-Matthews-Olson Complex

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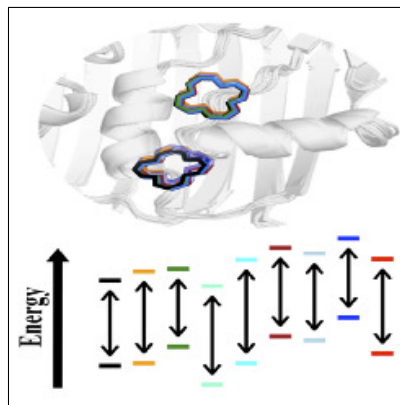
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## Abstract

Observation of excitonic quantum beats in photosynthetic antennae has prompted wide debate regarding the function of excitonic coherence in pigment-protein complexes. Much of this work focuses on the interactions of excitons with the femto- to picosecond dynamical fluctuations of their environment. However, in experiments these effects can be masked by static disorder of the excited state energies across ensembles, whose microscopic origins are challenging to predict. Here, the excited state properties of  $\sim 2000$  atom clusters of the Fenna-Matthews-Olson complex are simulated using a unique combination of linear-scaling density functional theory and constrained geometric dynamics. While slow, large amplitude protein motion leads to large variations in the  $Q_y$  transitions of two pigments, we identify pigment-protein correlations that greatly reduce variations in the energy gap across the ensemble, which is consistent with experimental observations of suppressed inhomogeneous dephasing of quantum beats.

## Graphical TOC Entry



Green sulfur bacteria (GSB) have evolved a diverse range of pigment-protein complexes (PPCs) to perform the crucial photosynthetic light reactions that power their lifecycles. They are the sole host of the trimeric Fenna-Matthews-Olson (FMO) complex, whose robust optoelectronic structure over its conformational ensemble we shall reveal by combining large-scale electronic structure methods and simulations of slow conformational motion. As shown in Figure 1, each monomer of the FMO complex positions eight bacteriochlorophyll *a* molecules (pigments) with sub-nm precision, using local protein interactions to tune the individual pigment energies to facilitate excitonic energy transfer (EET) from the giant chlorosome antenna to the reaction center (RC).<sup>1-3</sup> Rigidly coordinated Forster (dipole-dipole) coupling leads to coherently delocalized excited states spanning roughly 1 to 3 pigments, and spatially directed EET is then driven by energetic relaxation to the lowest energy state localized around pigment 3, the closest site to the RC.<sup>4-6</sup>

Ultrafast optical experiments, particularly two-dimensional electronic spectroscopy (2DES), have verified the existence of delocalized excitons and the efficient relaxation pathways that are driven by dissipative pigment and protein vibrations with fs-to-ps periods. Unexpectedly, long-lasting ( $> 2$  ps at 77 K) oscillatory signals were also observed in early 2DES experiments, and their assignment to robust excitonic superposition states has raised great debate about the longevity and possible role of electronic coherence in PPCs, particularly given the short ( $< 100$  fs) optical dephasing times of individual excitons.<sup>7-10</sup> The main source of dissipation and homogenous dephasing in PPCs is the relatively weak coupling of excitons to fast fluctuations of intramolecular and protein motions (typical net reorganization energy  $\sim 35$  cm<sup>-1</sup>), and many theoretical studies have tackled the problem of how the frequency distribution and coupling strength of exciton-environment interactions may impact the lifetime of excitonic superposition states and their role – if any – in the function of antenna complexes and reaction centers.<sup>5,8-15</sup>

In this work, we do not consider these ultrafast dynamics and the implications of quantum dynamics, focusing instead on another long-standing issue of direct relevance for experiments

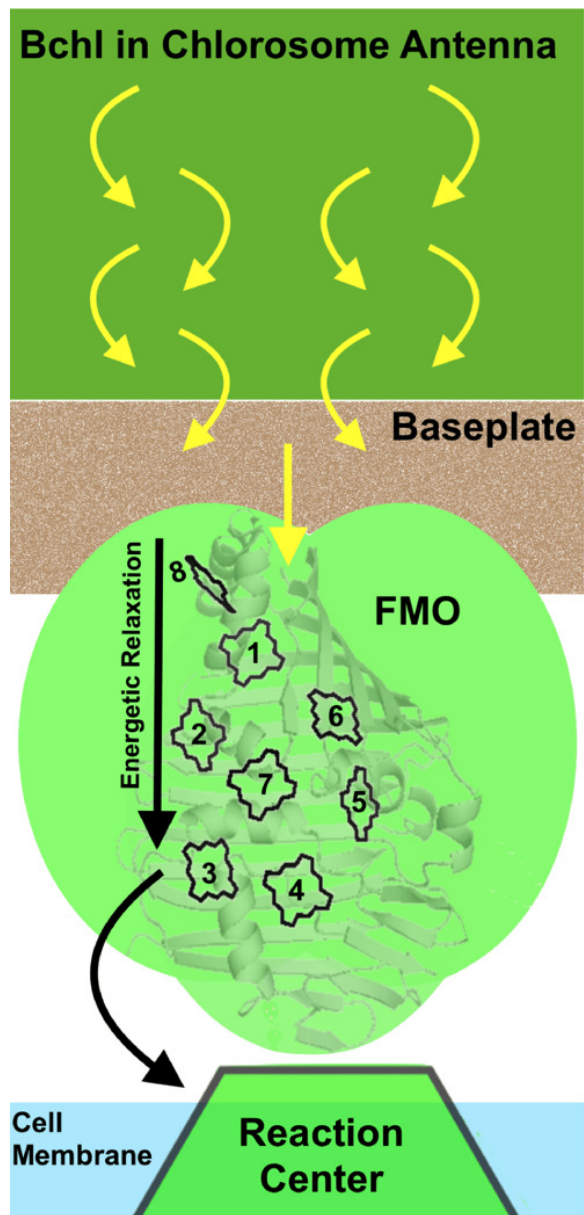


Figure 1: Light absorbed by pigment molecules in the chlorosome is driven by dissipative exciton transfer through bacteriochlorophyll (Bchl) pigments in the FMO complex to the photosynthetic reaction center where it is used to drive charge separation.

on PPCs, for which the necessary computational techniques have only recently become available; that is, the problem of static disorder. Slow (ms- $\mu$ s) structural dynamics play a crucial role in ensemble experiments, as they generate the conformational ensemble of protein structures probed in ultrafast experiments. Due to strong tuning of excited state energies by the protein scaffold, ultrafast experiments do not time-resolve this motion and instead see a snapshot of the ensemble, characterized by a “static” energetic disorder distribution that leads to inhomogeneous optical dephasing in 2DES.<sup>16</sup> In many models of the optical responses of PPCs, this energetic disorder, which contributes to spectra in a completely independent way to homogeneous/ultrafast processes, is often assumed to act independently on each pigment (uncorrelated disorder). This implies that the energy gaps between excitonic transitions are also randomized across the ensemble, leading to rapid inhomogeneous dephasing of excited state superpositions. The observation of quantum beats therefore requires close consideration of static disorder and, importantly, positive inter-pigment correlations in energetic disorder have been suggested, phenomenologically, to greatly reduce the inhomogeneous dephasing of excitonic coherence by maintaining the energy gaps between excited states.<sup>17,18</sup>

Motivating this even further, correlations in static disorder have also been introduced to make sense of nonlinear optical experiments in a range of PPCs, such as ensembles of the B820 dimer and light harvesting (LH) complex II.<sup>17,19</sup> These studies, based on methods that are extremely sensitive to disorder properties, such as three-pulse echo peak shift, all highlight that simple, uncorrelated disorder fails as a model for excitonic energy disorder, and further suggest that the protein scaffold is responsible for coordinating energy shifts in each realization of the ensemble, and hence across the ensemble. Ishizaki and Fleming have also suggested that inhomogeneous disorder may even provide the fundamental limit for the observation of coherence in photosynthetic systems, where each individual realization could show coherent dynamics that are even longer than 2 ps.<sup>20</sup>

Functionally, static correlations imply the maintenance of energetic structure across the ensemble, potentially offering much desired reliability to these self-assembling systems of

excitonic wires. Recently, Fidler et al. have presented further experimental 2DES evidence for such correlated disorder in the FMO complex.<sup>13</sup> They observed that the quantum beat frequencies, which are set by the differences in energy of the lowest excitonic states, do not change across the ensemble of FMO structures, even though the mean energy of their excited states varies appreciably (seen as optical inhomogeneous dephasing). In another complex (LHII), energy gaps were shown to vary significantly across the ensemble, and only very weak, rapidly damped ( $< 170$  fs) quantum beating has been observed in this system.<sup>13</sup> Although apparent correlation effects due to vibrational coherences in the 2DES signal cannot yet be ruled out, there is clearly an urgent need to investigate static disorder properties in order to address the many other aspects of PPC exciton dynamics that are being debated on the basis of results taken from ensemble experiments. However, exploring the mechanisms behind this in atomistic detail has so far proved extremely challenging.

Interestingly, spatial correlations amongst the fast fs-ps dephasing environments acting on the pigments were also suggested to reduce the homogeneous dephasing of excitons, albeit with the undesirable side effect of suppressing energy transport.<sup>11,12</sup> All-atom molecular dynamics (MD) simulations with quantum mechanical (QM) excited state calculations have been used to investigate this idea, but no evidence for spatially correlated site-energy fluctuations have been observed amongst the fast molecular fluctuations accessible to these methods.<sup>14,15</sup> One reason for the difficulty in observing these correlations may be the mismatch between the ground state molecular mechanical and QM potential energy surfaces, which is problematic when post-processing MD trajectories with QM excited state calculations. Contributions to the site energies caused by high frequency intramolecular pigment vibrations are significantly over-estimated and may mask any underlying correlations.<sup>21-24</sup> Indeed, Wang et al.<sup>24</sup> have recently demonstrated that correlations between pigment site energies in the FMO complex are much stronger when the high frequency component of the site energy variations is filtered out (as is done in the ‘charge density coupling’ (CDC) approach<sup>3</sup> introduced by Renger and co-workers). However, these CDC simulations were

performed on sub-nanosecond time scales, which motivates the question as to whether such correlations persist during conformational dynamics that are more relevant to static disorder. Normal mode analysis (NMA) can be employed to overcome the sampling limitations of MD simulations and to compute the low-frequency portion of the protein’s spectral density, but the breakdown of the harmonic approximation at low frequencies has been highlighted by Renger et al. and suggests that the impact of very soft, slow conformational motions can only be accounted for phenomenologically by NMA.<sup>22</sup>

In order to overcome the time scale problem in MD simulations, we have performed constrained geometric simulations of the entire FMO trimer.<sup>25</sup> This technique identifies geometric constraints related to bond lengths and angles, hydrophobic interactions and hydrogen bonds. Using the pebble game algorithm,<sup>26</sup> these constraints are used to determine flexible and rigid regions in the pigment-protein framework, thus substantially reducing the number of degrees of freedom to be explored and enabling examination of large-amplitude anharmonic motion, whilst retaining the bonding and non-covalent interaction networks identified in the crystal structure<sup>27–29</sup> (Supporting Information S1.1). This efficiency does come with the approximation that no constraints are formed or broken during the generation of the ensemble, and with the neglect of long-ranged electrostatic interactions and hydration (except for a number of explicitly included water molecules). Yet even with these approximations, the consistency of the motions explored by constrained geometric simulation with those explored by more computationally intensive MD and, more importantly, experiment has been well-established,<sup>30–32</sup> which indicates that dynamics of the native state emerge naturally from a simple network of contacts. It should be noted that, unlike MD, constrained geometric simulation does not give access to a characteristic time scale for the formation of individual conformations. However, its ability to explore large amplitudes of motion in enzymes<sup>31,33</sup> and gating mechanisms in ion channels<sup>34,35</sup> highlights the ability of this technique to investigate functionally relevant motion on timescales that would generate essentially static disorder in an optical experiment. An added benefit of this technique is that the intra-pigment bonds

and angles are fixed, and hence this high frequency component is filtered out, allowing us to report only the inter-molecular (and low frequency intra-molecular) contributions to the pigment site energies that contribute to static disorder.

Using constrained geometric simulation, we have previously identified a range of highly-correlated large amplitude motions between structural elements, including between pigments 3 and 4, and have shown that the excitonic couplings of the conformal ensemble show an extremely low variance ( $< 5\%$ ).<sup>25</sup> However, the complex interplay of long-range electrostatic and local pigment-protein interactions that determine pigment site energies means that correlated energetic disorder does not necessarily follow from the observed spatial correlations in structural motion.<sup>36</sup> Thus, in what follows, we perform principal component analysis of our conformal ensemble to determine the large amplitude motion of the entire FMO complex, and perform fully quantum mechanical calculations of  $\sim 2000$  atom clusters of the PPC to determine site energy variations from first principles (Supporting Information S1).

We begin by performing an additional all-atom constrained geometric simulation whereby the PPC undergoes random motion augmented by a bias along the first principal component (PC1) eigenvector. In this manner, the system explores the available conformational space along the proposed large-amplitude mode, whilst being restricted to physically-meaningful structures by the covalent and non-bonded constraints identified in the crystal structure. The pattern of displacement described by the PC1 for the FMO complex is depicted in Figure 2. The largest displacements in PC1 are centered around  $\alpha$ -helices 7 and 8 – two structural elements that have been shown to be important in creating the excitonic energy funnel leading to pigments 3 (the energy sink) and 4.<sup>37-39</sup> As pigments 3 and 4 are also the primary participants in the two lowest energy excitons that show long-lasting quantum beats in 2DES spectroscopy, we focus our investigation on the motion and site energies of pigments 3 and 4 and the surrounding protein environment.<sup>13</sup>

From this biased constrained geometric simulation, we have selected eight conformations along the trajectory and computed the site energies of the pigments in each conformation



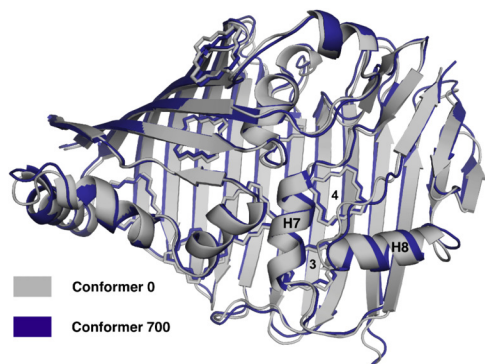


Figure 2: The FMO complex crystal structure (conformer 0) is biased along PC1, from which we select eight snapshots. Above we have displayed the limits of the PC1 motion, highlighting  $\alpha$ -helices that play an important role in determining the energetic landscape for pigments 3 and 4.

with the ONETEP linear-scaling density functional theory (DFT) software suite.<sup>40</sup> Details and validation of the excited state DFT methodology are given in section S1 of the Supporting Information and elsewhere but, in brief, a  $\sim 2000$ -atom cluster centered on the pigment of interest and containing all protein residues, water molecules and pigments within  $15 \text{ \AA}$  is extracted from the full PPC conformer and simulated in its entirety using DFT with in situ optimized local orbitals that describe both occupied and low-lying unoccupied electronic states.<sup>38,41,42</sup> These methods have been shown to result in root-mean-square errors of just  $47 \text{ cm}^{-1}$  between computed (relative) site energies and those fit to optical spectra when applied to the FMO x-ray crystal structure.<sup>38</sup>

The variation in the site energies of the eight PC1 conformers is summarized in Figure 3. The average site energies of pigments 3 and 4 along PC1 are  $12,210 \text{ cm}^{-1}$  and  $12,513 \text{ cm}^{-1}$ , respectively, and site 3 remains the energy sink in all conformations. These average values are in good overall agreement with previous calculations. For example, Adolphs et al. computed values of  $12,190 \text{ cm}^{-1}$  and  $12,380 \text{ cm}^{-1}$  using a genetic fit to the experimental optical spectra and  $12,195 \text{ cm}^{-1}$  and  $12,395 \text{ cm}^{-1}$  using a classical, structure-based Poisson-Boltzmann approach built on phenomenological point charge distributions.<sup>3,39</sup>

Turning to energy variations over the entire PC trajectory, we find large standard devia-

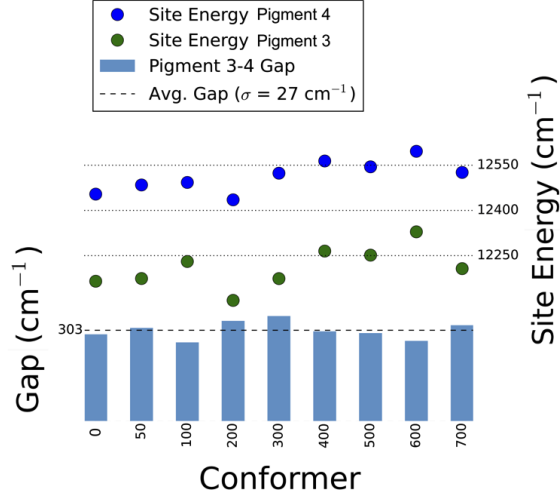


Figure 3: Eight conformers were selected from the all-atom biased PC1 simulation and the site energies of pigments 3 and 4 were calculated using ONETEP (green/blue dots). The difference in the site energies (gap) between pigments 3 and 4 is calculated for each conformer (bars).

tions in the observed site energies of pigments 3 and 4 of  $67 \text{ cm}^{-1}$  and  $52 \text{ cm}^{-1}$ , respectively, corresponding to a full-width at half maximum (FWHM) of  $158 \text{ cm}^{-1}$  and  $122 \text{ cm}^{-1}$  for a Gaussian site-energy distribution. Encouragingly, these values are only slightly higher than the assumed or fitted theoretical literature values for the site energy disorder/inhomogeneous broadening of the lowest energy sites ( $50\text{--}100 \text{ cm}^{-1}$ ).<sup>5,22,43,44</sup> If these variations of the site energies were uncorrelated and Gaussian, we would expect variations of the energy gap between sites 3 and 4 of around  $85 \text{ cm}^{-1}$ . Such energy gap variations, which exceed the excitonic coupling strength of the pigments ( $\sim 50 \text{ cm}^{-1}$ ), would lead to extremely rapid inhomogeneous dephasing of inter-exciton coherences, faster in fact than the optical inhomogeneous dephasing times.<sup>3,25</sup> However, as can be seen in Figure 3, the environment-induced site energy fluctuations maintain a remarkably homogeneous energy gap ( $303 \pm 27 \text{ cm}^{-1}$ ) across different realizations of the structural ensemble, in spite of the much larger variances of the individual site energies. As is strikingly evident to the eye in Figure 3, this arises from very strong correlation ( $R = 0.91$ ) of the site energies along complex, non-monotonic trajectories, which could not arise in a normal mode analysis, and suggests the occurrence of qualitative

changes in the local environment of the pigments during the motion.

This is the key finding of this paper, which establishes the hitherto conjectured correlation of site energy disorder due to slow conformational motion and supports the experimental observable of correlated disorder.<sup>13</sup> Quantitatively, we note that the bare scale of energy gap disorder is smaller than predictions of the excitonic coupling between these sites, suggesting that the suppressed disorder does not destabilize the formation of delocalized low-energy excitons. Our determination of the variance of the mean transition energy is, we believe, the first ab initio estimate of the magnitude of the optical dephasing strength, and could be used in future modeling and/or for deconvolution of optical spectra.<sup>5,25</sup> We now analyze the underlying PC1 motion to determine the physical mechanisms behind a) the relatively large fluctuations in individual site energies, and b) the very low static disorder in the site energy differences. It is very difficult to break down the protein’s influence on the quantum mechanical site energies and so, in what follows, we perform a correlation analysis to determine which structural elements drive and/or correlate the site energy shifts.

First, hydrogen bond donors have been shown to cause a substantial red-shift of the pigments’ site energies and make an important contribution in maintaining the energy funnel and, critically, the energy sink at pigment 3.<sup>3</sup> However, these hydrogen bonds have relatively stable energies, measured to be around 3–8 kT, and they remain rigid in the constraints-based dynamics used here. As their influence is short range, this suggests negligible changes to the energy gaps between the pigments under slow conformational motion.

Next, we consider the impact of larger secondary structure elements on the site energies of the two pigments. In particular, alignment of the electric fields of the  $\alpha$ -helix dipoles with the difference in charge density between the excited state and the ground state of the pigments causes a red shift in their site energy of around 200  $\text{cm}^{-1}$ .<sup>3,39</sup> These shifts are the largest single contributions to the establishment of pigment 3 as the energy sink. Resulting from a dipolar interaction, the magnitude of the red-shift is likely to be sensitive to the distances between the pigments and these  $\alpha$ -helices. To study the relationship between the

pigments and their environment along the PC1 trajectory we employ a cross-correlation analysis (Supporting Information S1.4). This analysis uncovers a high positive correlation in the motion of the pigments and the residues of  $\alpha$ -helix 7 (Figure 4, left). Similar to the behavior of the pigment-protein hydrogen bonds, this strong positive correlation indicates that pigments 3, 4 and  $\alpha$ -helix 7 move together as a single unit, which preserves the energy shifts on these sites from this  $\alpha$ -helix. On the other hand, we find low correlations between the negative end of  $\alpha$ -helix 8 (V349–K354) and the pigments, indicating a reasonably high variation in the distances between pigments 3 and 4 and the negative dipole of  $\alpha$ -helix 8 (0.8 and 0.7 Å, respectively). However, these two  $\alpha$ -helix-pigment distances are additionally found to be well correlated with each other ( $R = 0.8$ ), suggesting that  $\alpha$ -helix 8 motion can lead to substantial shifts in the pigment energies without changing their relative energy gap, as we have found in our quantum mechanical simulations. The 16 strongest correlations between the pigment-residue distances and the pigment site energies (Figure 4, right) are found to involve residues that are located at the negative end of  $\alpha$ -helix 8, as well as in nearby loops and the clam shell. There is a particularly strong correlation between the V349–pigment 4 separation and the site energies of the pigments 3 ( $E_m(\text{B3})$ ) and pigment 4 ( $E_m(\text{B4})$ ), reinforcing the idea that the pigment’s proximity to  $\alpha$ -helix 8 is a key contributor to the site energy variation observed in Figure 3. We reiterate that the constrained geometric simulations used to produce the ensemble of structures does not allow us to assign a time scale to the investigated dynamics. Nevertheless, the observation that the site energy shifts are correlated with the motion of large secondary structure elements indicates that the studied regime is relevant to static disorder.

In summary, we have introduced a unique combination of methods; namely large-scale quantum mechanics for the description of excited states in molecular systems with constrained geometric dynamics simulations for the exploration of conformal space. We have found that large secondary structure motions in the FMO complex are the root cause of site energy fluctuations in our generated structures, which we find to be significantly larger than

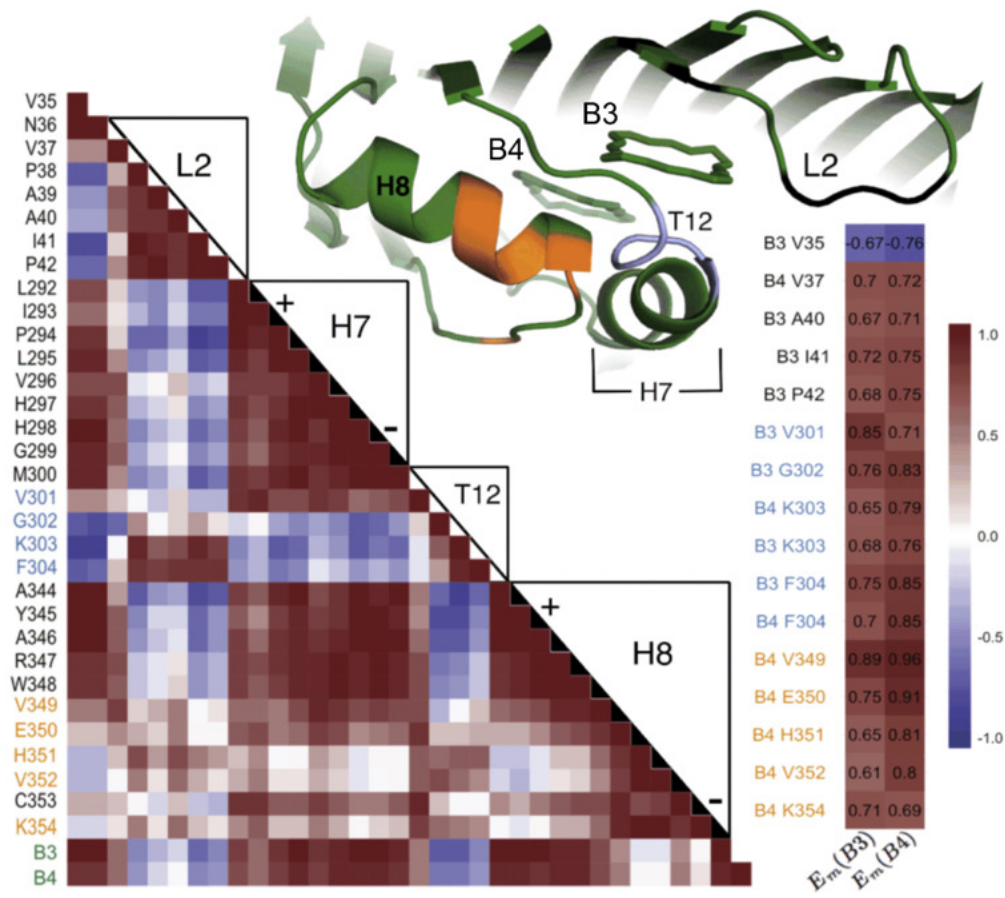


Figure 4: Cross correlation analysis (left) between the motion of the pigments (B3, B4) and nearby protein structures in the PPC snapshots generated along PC1. The correlation coefficient (right) has been calculated between the pigment site energy fluctuations and the distance connecting the center of mass of the pigment with the  $C_\alpha$  atoms in the environment. We display the top correlations found when considering all the distances in the system, with colored labels corresponding to colored section of the protein model (above). The residues found to have the greatest influence on the site energy fluctuations are in  $\alpha$ -helix 8, turn 12 and loop 2.

the reorganization energy of rapid fs-to-ps fluctuations that determine energy relaxation ( $\sim 35 \text{ cm}^{-1}$ ). However, this first theoretical observation of correlated site energy static disorder reveals how the FMO complex may be able to protect its ensemble excitonic structure from large energy fluctuations by mechanically constraining the protein's unavoidable low-energy fluctuations to motions that do not alter interpigment energy gaps. The ability to predict how transition energies change under very slow conformational motion opens the way for a detailed and realistic exploration of the potential functional impact of energetic disorder on the optoelectronics of PPCs, including the critical links between slow conformational dynamics and photoexcitations in processes such as non-photochemical quenching, fluorescence blinking dynamics and charge transfer in reaction centers.<sup>45-48</sup>

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## Supporting Information Available

Computational methods, including constrained geometric simulations, principal component analysis, large-scale DFT calculations and statistical analysis. ONETEP software input files. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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