Successes & challenges in the atomistic modeling of light-harvesting and its photoregulation

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Abstract

Light-harvesting is a crucial step of photosynthesis. Its mechanisms and related energetics have been revealed by a combination of experimental investigations and theoretical modeling. The success of theoretical modeling is largely due to the application of atomistic descriptions combining quantum chemistry, classical models and molecular dynamics techniques. Besides the important achievements obtained so far, a complete and quantitative understanding of how the many different light-harvesting complexes exploit their structural specificity is still missing. Moreover, many questions remain unanswered regarding the mechanisms through which light-harvesting is regulated in response to variable light conditions. Here we show that, in both fields, a major role will be played once more by atomistic descriptions, possibly generalized to tackle the numerous time and space scales on which the regulation takes place: going from the ultrafast electronic excitation of the multichromophoric aggregate, through the subsequent conformational changes in the embedding protein, up to the interaction between proteins.

1. Introduction

The basic photosynthetic architecture consists of pigment-protein complexes (also called Light Harvesting, LH, or *antenna*, complexes) that harvest solar energy, and reaction centers (RC) that convert the absorbed energy into stable separated charges. Both the LH process and the following charge separation are extremely rapid events with high quantum efficiency. Such an efficiency, however, is only achieved at specific light conditions. All photosynthetic organisms in fact, need to regulate the LH process to balance the input of light energy and to avoid light-induced damage [1, 2, 3, 4, 5].

Because of their importance in the photosynthetic machinery, LH complexes have been largely studied with theoretical models and simulated with computational methods [6, 7, 8, 9].

Looking back at the first attempts of computer simulation of the antenna complexes and comparing them with the most recent ones, it is evident that a breakthrough has been represented by the introduction of atomistic descriptions. In fact, earlier attempts at modeling antenna complexes have been characterized by empirical approaches, whereby a fit to spectroscopic information was directly used to extract the key electronic parameters, such as exciton couplings [10, 11, 12], site energies [13], and spectral densities [14]. Atomistic modeling has allowed gaining independent estimates of these parameters [8], thereby laying the groundwork for the microscopic simulation of energy transfer dynamics and time-resolved spectroscopy. This progress has been made possible thanks to the availability of accurate structural data of the complexes, which have revealed the atomistic details not only of the protein, but also of the embedded multichromophoric aggregate responsible for absorbing and harvesting light [15]. The success of this interplay between structural data and atomistic models has been further amplified by the advent of new and more powerful spectroscopic techniques that can follow the dynamics of energy/charge transfers with a femtosecond resolution and reveal the multidimensionality of the transfer pathways with sub-nanometric resolution [16, 17, 18, 19]. In particular, the relatively recent development of two-dimensional electronic spectroscopy (2DES) has provided a new and more incisive tool for studying energy transfer pathways in the extremely complicated LH systems, where one-dimensional techniques commonly fail in achieving a clear picture because they cannot disentangle the plethora of overlapping signals [20, 21, 22, 23].

The continuously increasing number of time- and space-resolved data has further pushed the atomistic modeling towards descriptions of increasing accuracy and completeness. Along this line, a very important role has been played (and still is) by multiscale approaches combining quantum chemistry and classical models [24, 25, 26]. This combination in fact has allowed to simulate the multichromophoric aggregates in the presence of the effects of the composite environment, formed by the protein, possibly a membrane, and the solvent [27]. As a matter of fact, it is now unanimously accepted that the protein does not only represent

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the scaffold needed to keep the pigments in the optimal configuration. Indeed, the electrostatic and polarization effects of the protein (and the solvent) acting at molecular scale on the pigments are the ones that determine their electronic response to light and modulate their interactions, thus directly controlling the excitonic nature of the aggregate. It is in fact the presence of coupled excitations among different pigments (the "excitons") which makes the energy transfer in LH complexes so unique. More recently, another fundamental role of the protein has been revealed, namely its dynamics, both in terms of thermal fluctuations and conformational changes, which have been suggested to represent the secret for combining efficiency and robustness. Initially, this multiscale nature of the LH process, where the ultrafast electronic processes localized on the multichromophoric aggregate are coupled to the much slower dynamics of the protein, represented a challenge for the simulations, and approximations had to be introduced in order to cope with such a complexity. In some cases the modeling was applied to simplified systems made of a reduced number of pigments and/or neglecting the embedding protein. Even when the realism was increased so to simulate the complete embedded multichromophoric aggregate, a single, rigid, structure was often considered thus neglecting any possible effect due to thermal fluctuations. During the years, most of these approximations have been overcome thanks to the progress in both multiscale models and computational techniques. For example, nowadays, it is possible to simulate the real antenna complex embedded in a lipid membrane, also accounting for thermal fluctuations through molecular dynamics (MD) techniques [28, 29, 30, 31].

All these progresses have clearly enhanced the accuracy of the simulations and their predictive character. Some important limitations are still present, and they still prevent a complete and general understanding of the LH process. In particular, only very recently, atomistic simulations have been applied to studying how the LH process responds to different light conditions so to avoid that the excess of absorbed energy leads to an overload of the RC capacity [2]. This is indeed a very important aspect, because if this overload happens, not only a sensible reduction of the photosynthetic efficiency is seen but undesirable processes could also take place finally leading to dramatic damages of the photosynthetic apparatus. In oxygenic photosynthesis in particular, an accumulation of excited pigments that can no longer release their excess of energy to the RC can transform into triplets and, by interaction with triplet oxygen, can cause the formation of highly reactive singlet oxygen. To avoid such events, triplets need to be rapidly quenched, and this is generally realized through triplet energy transfer to carotenoid pigments which finally dissipate the energy through harmless heat. However, the various photosynthetic organisms have also developed mechanisms that prevent the accumulation of excess energy around the RC. This is mostly achieved through the so-called nonphotochemical quench-

ing (NPQ), namely the de-excitation of the excited pigments, which results in the thermal dissipation of absorbed light energy [32, 33]. As a matter of fact, NPQ is a general term that encompasses multiple processes with different underlying mechanisms, which have not yet been fully understood [4, 5].

In this review, we summarize the state-of-the-art of the atomistic modeling of LH complexes and individuate the challenges that still have to be faced to reach an accurate and complete simulation of the light-harvesting and its regulation to different light conditions.

2. The atomistic modeling and its successes

LH complexes are multichromophoric complexes whose excitations are delocalized over different pigments. Examples of multichromophoric aggregates in selected LH complexes from bacteria (FMO, LH2), algae (PCP, PE545) and plants (LHCII) are shown in Fig. 1, where the families of involved pigments (namely (bacterio)chlorophylls, carotenoids and phycobilins) is also reported. From the figure, the differences in the chemical nature of the pigments, but also in their 3D arrangement, come out clearly. It is exactly the combination of these two elements which makes each LH complex unique. Necessarily, this uniqueness requires a modeling strategy general enough to be applied to very different systems, but tunable enough to adapt to the specificities of each individual case. The main aspects of this kind of modeling are summarized in the following three subsections.

2.1. The excitonic Hamiltonian

A description that treats the whole multichromophoric aggregate at a quantum mechanical (QM) level is usually neither feasible nor convenient, so alternative approximated strategies have been devised. A very popular and sensible strategy is to resort to an excitonic approach. Within this framework, the excitations of the whole multichromophoric aggregate (from now on called "excitons") can be written as linear combinations of excitations localized on individual pigments. If we assume, for the sake of simplicity, that each pigment contributes with just one excitation, the resulting excitonic Hamiltonian becomes:

$$\hat{\mathcal{H}}_{\text{ex}} = \sum_i \mathcal{E}_i \left| i \right\rangle \left\langle i \right| + \sum_{i \neq j} V_{ij} \left| i \right\rangle \left\langle j \right| \tag{1}$$

with the sum running over all the pigments, $\mathcal{E}_i$ being the excitation energy of the state localized at pigment i (site energy) and V_{ij} being the electronic coupling between the excitations of pigments i and j. The eigenstates and eigenvalues of such Hamiltonian will correspond to the coefficients of the expansion of the excitons on the local basis and the exciton energies, respectively. Using the exciton coefficients, all other properties of the excitons (e.g. excitonic dipole moment) can also be obtained, as linear combinations of the properties of the locally excited states.
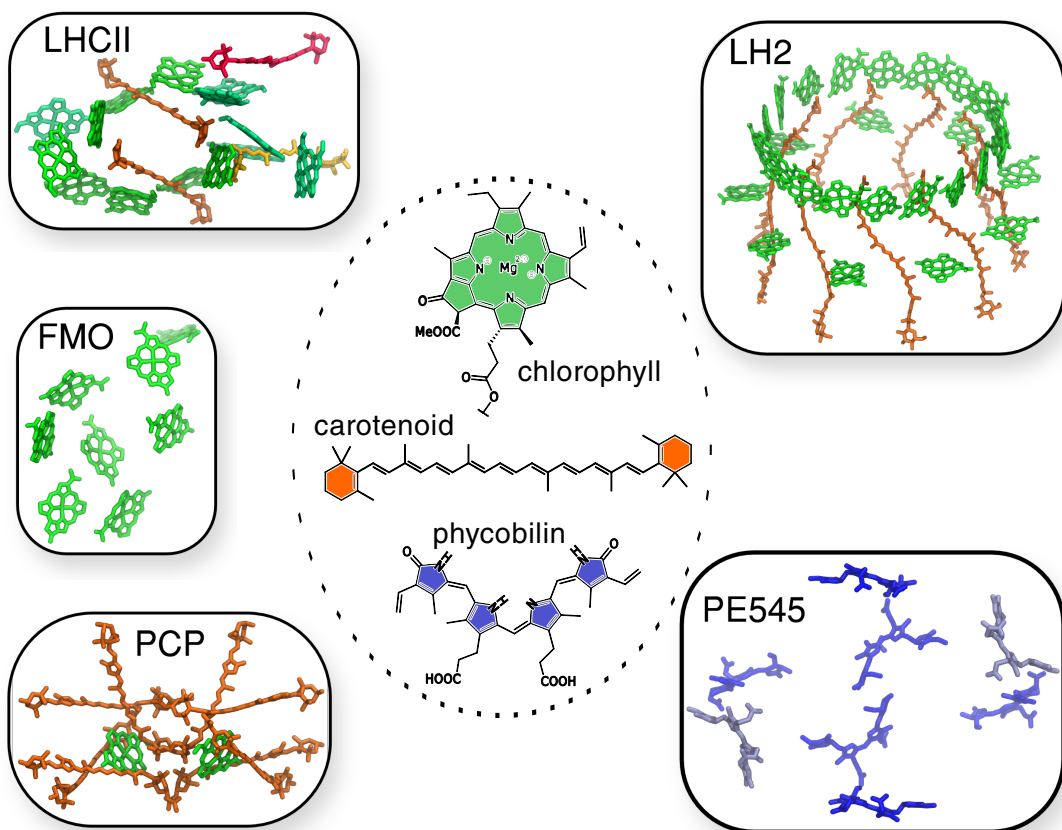
Figure 1: Examples of multichromophoric aggregates as found in different LH complexes. Starting from the left upper corner we see the major LH complex of plants LHCII (here represented in its monomeric form), the LH2 from *Rhodoblastus acidophilus* (purple non-sulfur bacteria), the phycoerythrin 545 (PE545) antenna of *Rhodomonas sp.* (marine algae), the peridinin–chlorophyll a–protein (PCP) from *Amphidinium carterae* (oceanic plankton) and the Fenna–Matthews–Olson (FMO) complex of *Prosthecochloris aestuarii* (green sulfur bacteria). In the central ellipse a schematic representation of the different types of pigments is reported; namely (bacterio)chlorophylls, carotenoids and bilins.

The ingredients of $\hat{\mathcal{H}}_{ex}$, namely site energies and couplings, have different roles in determining the exciton structure and optical properties of LH complexes, depending on the pigment composition of the complex, and on the arrangement and packing of pigments (See Figure 1). In closely packed aggregates (such as LH2), the large coupling values mainly determine the overall exciton structure, whereas in other aggregates (such as FMO) the site energies contribute to tuning the exciton composition and the overall energy ladder.

To properly describe excitations in individual pigments an excited-state QM method is needed, but, at the same time, the protein and the environment play an important role in the process, so their effect must be included as well. The most efficient way to do that is to employ a multiscale approach in which the pigments are treated with the selected QM method, while the effect of the remainder is described by the means of a classical method.

For what concerns the QM methods, a specific issue of LH pigments is their large dimension and high conjugation. These two characteristics together largely limit the possible choices. Often, a good compromise between

feasibility and accuracy has been found in semi-empirical methods, possibly combined with configuration interaction (CI) descriptions [34]. These approaches have been mostly used in earlier applications [35] but they are still used [36, 37]. In most cases, however, the semiempirical approaches have been replaced by time dependent density functional theory (TD-DFT) [38]. TD-DFT has in fact shown to represent a valid approach for most of the LH complexes even if the well-known weaknesses of such an approach can have an impact also for some specific cases of LH complexes. In particular, we recall here the difficulty of DFT in accurately describe CT states and the impossibility of its TD formulation to describe excitations characterized by a strong multiconfigurational character. The former problem has been largely reduced by introducing long-range corrected functionals while the latter has been faced by using the multi-reference extension of DFT also known as MRCI-DFT [39]. In particular, MRCI-DFT has shown to be a very promising approach to describe LH carotenoids as it can describe with the same level of accuracy all their lowest states even if they present a very different multiconfigurational character [40]. As a matter

of fact, more accurate QM methods have been also used for LH complexes, mostly as benchmarks for less expensive methods [41, 42], even though some direct applications have also been presented. In particular, we quote here the complete active space methods in combination with perturbation theory (CAS-PT2) used for bacteriochlorophylls and carotenoids of LH2 [43, 44], the approximate second-order coupled cluster (CC2) and the algebraic diagrammatic construction through second-order (ADC(2)) methods used for dimers and larger clusters of (bacterio)chlorophylls [45, 46], and the Bethe-Salpeter equation and the GW approximation (BSE/GW) used for phycoerythrobilins of PE545 [47].

Regarding the classical models for describing the environment, in the literature different approaches have been used to describe LH complexes. For the sake of clarity they will be classified in two main categories: continuum or discrete approaches. In the application of continuum models, the protein and the embedding environment (membrane and/or solvent) lose their atomistic nature and they are replaced by an effective dielectric medium. This loss of realism is however counterbalanced by the fact that this model allows to include electrostatic and mutual polarization effects with the QM subsystem at almost no additional computational cost. Two are the continuum approaches which have been more largely used to describe LH complexes, namely the Polarizable Continuum Model (PCM) [48] and the electrostatic shift approach (also known as the Poisson-Boltzmann/quantum chemical, PB/QC approach) [7].

Within the framework of discrete models, instead, the atomistic description of the environment is maintained, introducing a purely classical approach based on molecular mechanics (MM) force fields (FF). QM/MM methods have been extensively used to compute site energies in a large variety of LH complexes; in these applications the QM pigments feel the presence of the protein and the environment as a distribution of point atomic charges (this method is commonly called "Electrostatic embedding" QM/MM). A more realistic extension of QM/MM methods has been proposed and applied to LH complexes supplementing the point charges with atomic polarizabilities: in such a way mutual polarization effects between the QM and the MM subsystems are included together with electrostatics (this approach is commonly known as "polarizable embedding" QM/MM or QM/MMPol) [49]. Another approach still based on a discrete environment has also been used in the context of LH complexes, namely the so-called frozen density embedding (FDE) [50, 51]. This method goes beyond the classical description of the environment; the system is now divided into fragments, each of whom is described at QM level including the potential from the other "frozen" fragments [52].

The other ingredient required to build the excitonic Hamiltonian of Eq. (1) is represented by the couplings between different singly excited states $|i\rangle$. In general, the couplings can be decomposed into three terms: a Coulomb interaction between the transition densities localized on the individual pigments V^{Coul}, a term due to orbital overlap V^{ovlp} and a term due to electronic exchange V^{exch}. The latter two terms decay exponentially with the pigment–pigment distance, therefore usually computing just the first term is a good approximation, at least for the most common case of bright singlet excitations, namely

$$V_{ij} \simeq V_{ij}^{\mathrm{Coul}} = \iint \frac{\rho_i^{\mathrm{tr}}(\boldsymbol{r})\rho_j^{\mathrm{tr}}(\boldsymbol{r'})}{|\boldsymbol{r} - \boldsymbol{r'}|}\,\mathrm{d}^3 r\,\mathrm{d}^3 r' \qquad (2)$$

where ρ^{tr} are the transition densities of the two coupled pigments.

During the years, several strategies have been proposed to compute V_{ij}^{Coul}. In the point dipole approximation (PDA), the transition density is approximated as a transition dipole $\boldsymbol{\mu}^{\mathrm{tr}}$ so that the integral of Eq. (2) is replaced by a dipole–dipole interaction:

$$V_{ij}^{\mathrm{Coul}} = |\boldsymbol{\mu}_i^{\mathrm{tr}}||\boldsymbol{\mu}_j^{\mathrm{tr}}|\frac{\kappa}{R_{ij}^3}$$
$$\kappa = \hat{\boldsymbol{\mu}}_i^{\mathrm{tr}} \cdot \hat{\boldsymbol{\mu}}_j^{\mathrm{tr}} - 3(\hat{\boldsymbol{\mu}}_i^{\mathrm{tr}} \cdot \hat{\boldsymbol{R}}_{ij})(\hat{\boldsymbol{\mu}}_j^{\mathrm{tr}} \cdot \hat{\boldsymbol{R}}_{ij}) \qquad (3)$$

where the hat indicates the unit vector and R_{ij} the interpigment distance.

Even though this approach is known to break down at close interpigment separations, it still remains useful to provide an interpretation of the couplings in terms of pigment–pigment distance R_{ij} and mutual orientation (expressed by κ). Another popular strategy, more accurate than the PDA, is to map the transition density to atom-centered transition charges; this strategy is known as "transition monopole approximation" (TMA) [53]. The charges can be found either by Mülliken population analysis [54, 55] or by fitting the transition potential (TrEsp) [56]. A more expensive way to compute the coupling is to solve the integral of Eq. (2) with a numerical quadrature over a cubic grid (the method is also known as "Transition Density Cube", TDC) [57, 58]. The most general and accurate approach for computing the Coulomb integral (2) has been proposed more recently and it is based on an atomic orbital expansion of the transition densities [59]. The method has also the advantage to be extremely general, as it can use transition densities obtained from any QM method [41, 60].

A completely different strategy to obtain the couplings is by the means of diabatization schemes, in which the QM calculation is done directly on pigment dimers and then the resulting excited states are localized onto the individual pigments, thus getting both the site energies and the corresponding couplings [61]. In this approach the computational cost is higher as the system comprises two pigments; however, an important advantage is that it accounts also for V^{exch} and V^{ovlp}, whereas for the all the other strategies, these terms must be added separately to the Coulomb one [62].

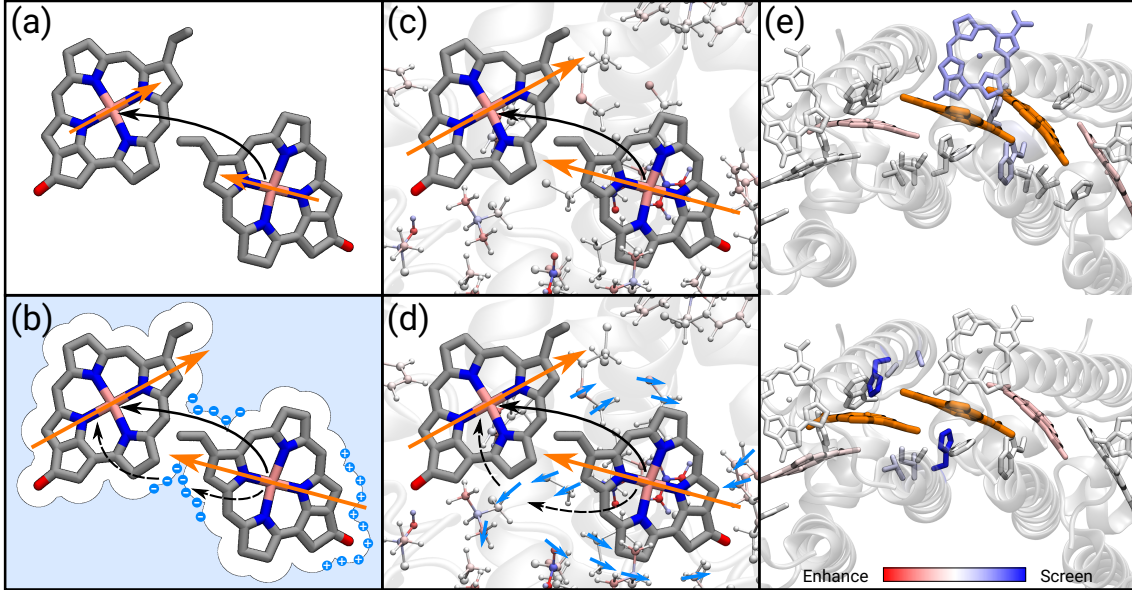The couplings can be largely affected by the protein/solvent through two mechanisms [64]: implicitly,

Figure 2: (a) Electronic coupling computed *in vacuo*. The interaction is between the two transition dipoles. (b) Electronic coupling computed in a polarizable continuum scheme. The transition dipoles are enhanced by the environment and, in addition to the dipole–dipole interaction (solid arrow), there is an interaction through the environment (dashed arrows). (c) Electronic coupling computed in a MM electrostatic embedding. The transition dipoles are enhanced by the environment, but there is no screening effect. (d) Electronic coupling computed in a MM polarizable embedding (MMPol). The transition dipoles are enhanced and there is a interaction through the environment. (e) Effect of the polarizable environment on two non equivalent electronic coupling of the LH2 (blue: screening, red: enhancing) [63]. Note how the histidines coordinating the BChls reduce the second coupling while they do not affect the first.

through their effect on transition densities of the two interacting pigments, and explicitly, by screening the Coulomb interaction between the two transitions (Fig. 2). Whereas all the classical descriptions of the environment proposed so far account for the implicit contribution, only the polarizable models can account for the explicit one.

Historically, the screening effect has been included in simple coupling models like PDA and TMA through a $1/\epsilon_{\text{eff}}$ scaling factor [65], where ϵ_{eff} is a effective dielectric permittivity of the composite (protein and solvent) environment. In more accurate versions of continuum models, instead, both implicit and explicit effects are automatically included though the polarizable nature of the model [62, 59]. Also within the TrEsp approach, the environment effect on the coupling is accounted for through a Poisson-Boltzmann description leading to the so called Poisson-TrEsp [7]. Up to now, however, the most general way to include the full effect of the environment in the couplings has been proposed within the QM/MMPol scheme [49]. Within such framework, in fact, both electrostatic and polarization effects are included still keeping an atomistic description of the protein (and the solvent). This polarizable and atomistic formulation, when combined with a correct sampling through Molecular Dynamics (*vide infra*), allows an accurate description of the heterogeneous nature of the protein [30]. Continuum models, by implicitly taking into account the statistical sampling, generally lead to good results for isotropic environments, but clearly show limitations in heterogeneous and composite systems such as those embedding the LH pigments (see panel b-d of Fig. 2).

2.2. Structures & Dynamics

As soon as atomistic structures of LH complexes became available, several research groups exploited them to simulate the spectroscopic properties and the energy transfer processes of LH complexes [66, 57, 12, 67, 7, 68]. These first models were based on a *static* picture and therefore temperature effects were not explicitly taken into account, but introduced into the model parametrically through some simplified models or using experimental data. As already pointed out in the Introduction, the thermal fluctuations and the dynamics of the biological matrix are in fact of paramount importance and they cannot be simply neglected in the computational simulation of LH complexes. The effect of thermal fluctuations on site energies and couplings can be smaller or greater depending on the flexibility of the pigments and of the protein scaffold, as well as on the different pigment packing observed across LH complexes (See Figure 1).

This initial static picture has been more recently supplemented by an explicitly dynamic one. This has been made possible by the use of MD techniques. The introduction of MD simulations has paved the way to a different and more realistic description of LH complexes through the inclusion of thermal fluctuations. One of the main advantages of this dynamic description is that the coupling between the structural fluctuations of the system and the

excitonic properties of the multichromophoric aggregate is now directly extracted from the atomistic simulations (*vide infra*). A qualitative representation of the time scales of different motions in LH complexes and their description through MD is given in Fig. 3.

Due to the need to calculate forces for all atoms of very large systems at each time step of the trajectory, the MD approach has an intrinsic high cost that imposes the use of cheap MM force fields (FF), instead of costly QM models. The quality of the MD results thus relies on the accuracy of the force fields used. For proteins, FFs have now reached a high level of accuracy and reliability; however this is not the case for the LH pigments. During the years, FFs for the different LH pigments have been proposed in different parametrization frameworks mostly based on the fitting of QM data [28, 69, 70, 71, 72, 73, 74]. This approach has proven successful in some aspects, but has also shown some limitations, which will be better analyzed in the following section.

As said, the most common application of MD in studies of LH complexes is to achieve a proper structural sampling of the LH complex (and its environment) at the selected temperature (See Fig. 3). In other words, MD trajectories are used to generate an *ensemble* of configurations of the whole system to be further used in (embedded) QM calculations.

An interesting application of this strategy was to explain the observed temperature effects in the spectroscopic properties and the energy transfer rates of LH complexes. In particular, some of the present authors, using a room temperature MD simulation of LH2 embedded in a lipid membrane, combined with TD-DFT/MMPol calculations, succeeded in reproducing the observed blue-energy shift in the low-energy signal in the absorption and circular dichroism spectra of LH2 when moving from very low to room temperature [31]. This approach was further extended to reproduce the faster energy transfer observed at room temperature in the complex by combing the excitonic parameters obtained along the MD trajectory with a modified Redfield description of the energy transfer dynamics [43].

In addition to correctly accounting for thermal fluctuations, the MD strategy has also been employed to investigate correlated energy fluctuations in LH complexes. In fact, some experimental works initially suggested that long-range correlation of pigment motions could play a role in the observation of long-lasting quantum coherence effects [75, 76]. Several groups exploited the atomistic detail provided by MD simulations to verify this hypothesis. In particular, MD trajectories were combined with an excitonic approach in the study of LH2 and FMO systems by Kleinekathöfer and collaborators [77, 78], and in the study of PE545 by one of the present authors and collaborators [37]. All these studies agreed in finding that long-range correlation effects in pigment motions, site energies and couplings were negligible.

From these few examples it should be clear that moving from the static, crystal-based, description to the one coming from a MD trajectory offers a much richer picture of the LH complexes and their properties. In addition, the use of MD simulations also helps in improving the accuracy of the QM calculations. Often, crystal structures present slightly inaccurate arrangements of the protein residues close to the pigments, or of the pigments themselves. As a result, the multiscale QM/classical calculations performed on such structures can lead to artifacts [79, 80, 81]. This is particularly true for the site energies, which are very sensitive to the pigment internal geometry and to specific interactions with the environment, such as H-bonds. In fact, the resolution of protein X-ray structures is not sufficient to accurately determine intramolecular bond lengths, on which the pigments' excitation energies are strongly dependent. On the contrary, MD models, combined with the same level of QM theory, are able to correctly represent the spectroscopic properties of the systems [31, 81, 80]. To give an example of the improvement that an MD based approach can achieve with respect to crystal structures, we show in Figure 4 how the crystal structure biases can impact the spectral description of the minor LH complex CP29 [80]. It has to be noted that hydrogen atoms are not resolved in LH complexes' crystal structures, thus creating additional uncertainty in the direction of hydrogen bonds or in the protonation of titratable residues.[82, 7]

Finally, MD can give a direct access to vibrational modes. The latter are extremely sensitive to the exact shape of the potential energy surface used for representing the system and therefore the selection of an appropriate force field is crucial in order to get accurate and physically sound results. More details on this aspect are presented and discussed in the next section.

2.3. Spectral density & disorder

A fundamental ingredient for simulating spectroscopic properties and exciton dynamics of LH complexes is the coupling of the electronic excitations to the nuclear motion, which determines both the energy transfer properties and the optical line shapes.

A widely used formalism to include the coupling to vibrations is based on the spectral density (SD) of the exciton-phonon coupling ($J(\omega)$) [83, 84], which quantifies the frequency-dependent coupling between excitons and nuclear degrees of freedom. The spectral density $J(\omega)$ describes the density distribution of vibrational modes weighted for the strength of their coupling with the excitation.

The coupling of site energies to internal vibrations of the pigments gives rise to sharp peaks in the SD located at the normal-mode frequencies of the pigment [85], whereas the coupling to the quasi-continuum of protein fluctuations and solvent reorientation gives a smooth background. By integrating the SD over the frequency range one can also have access to the reorganization energy λ.

Atomistic strategies to estimate the SD of a pigment in LH complexes have mainly relied on the calculation of its
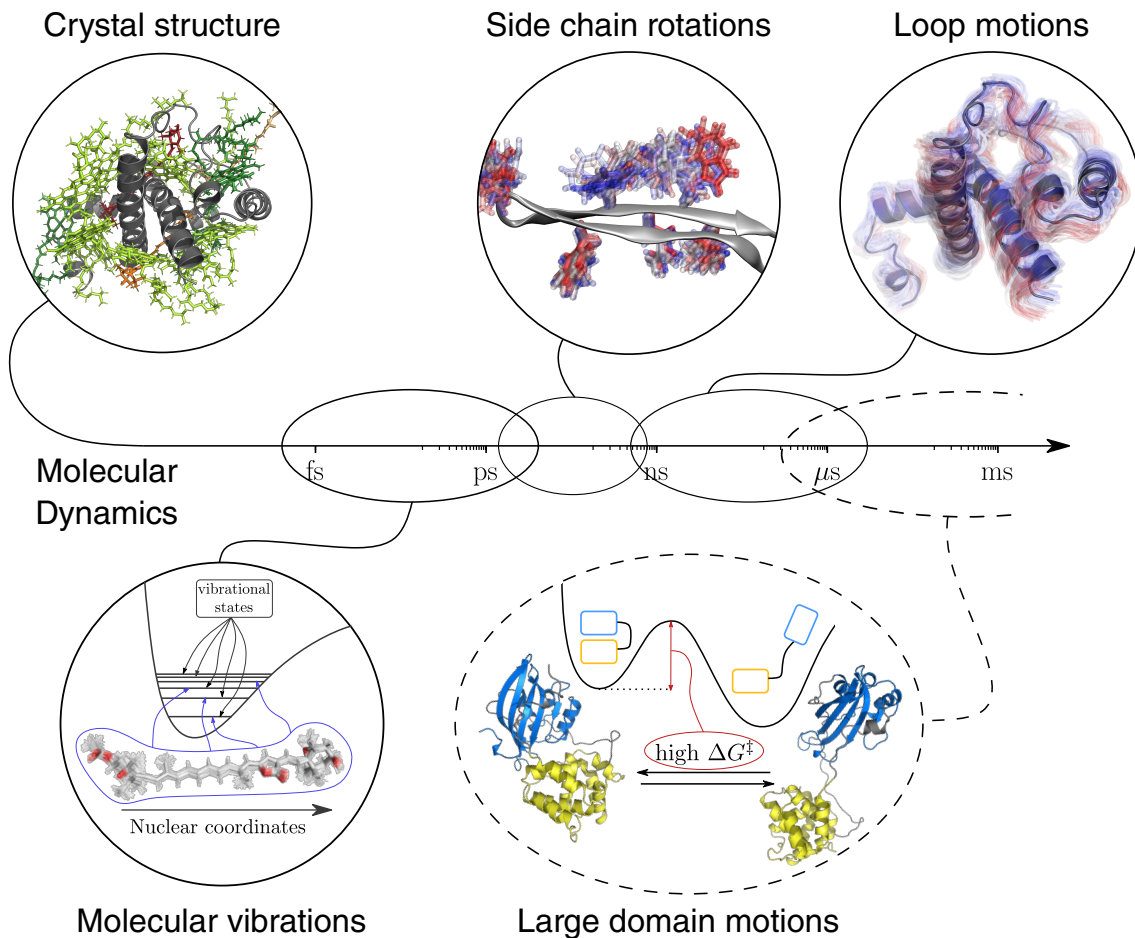
Figure 3: Qualitative representation of the information gained from molecular dynamics on different timescales. Routine MD simulations allow sampling of internal vibrations of the pigments and structural fluctuations of the embedding protein (side chain rotations and loop motions). On the contrary, large domain motions and conformational changes are still out of reach for conventional MD techniques.

site energy fluctuations $\Delta\mathcal{E}$ along a classical MD trajectory. The corresponding autocorrelation function can be Fourier transformed to obtain the SD $J(\omega)$ [84].

From a practical point of view, site energy fluctuations can be computed by evaluating the site energies along snapshots of the MD trajectory [84]. Such trajectories have been mainly obtained using classical MD simulations based on MM force-fields [86, 87, 29], which can treat the dimensions of light-harvesting complexes for the required time scales. The site energies, on the other hand, can be evaluated using a quantum mechanical approach coupled to a MM description of the environment, as detailed in Section 2.1.

The trajectory-based method allows computing the coupling of the excitation to both the internal vibrations of the pigments and the structural fluctuations of the protein and the environment. However, its practical applicability requires a large number of calculations to sample fluctuations across several time scales [84, 87, 29]. For this reason, several studies employed semiempirical QM methods to contain the computational cost of site energy evalua-

tions [88].

As already anticipated in the previous section, another striking limitation of the trajectory-based approach when using MM force fields is the accuracy. While protein force fields are rather accurate in describing the structural fluctuations of the peptide environment, they are not optimized to faithfully reproduce the internal coordinates of the pigments. As a result, the energy fluctuations estimated on such MM potentials can be exaggerated, leading to a systematic overestimation of the SD intensities [89], or to an inaccurate distribution of SD intensities along the frequency spectrum [85, 90, 91]. It has been shown that the MD-based approach is very sensitive to the parameters of the force field, whereas the details of the QM method for excited-state calculations are less important [87, 36].

In order to overcome the limitation of MM-based MD, a normal-mode analysis (NMA) approach has been proposed [85, 90]. Such an approach computes the harmonic normal modes of the pigment in a frozen protein environment, and their linear coupling to the excitation using QM/MM methods. By computing the equilibrium geome-
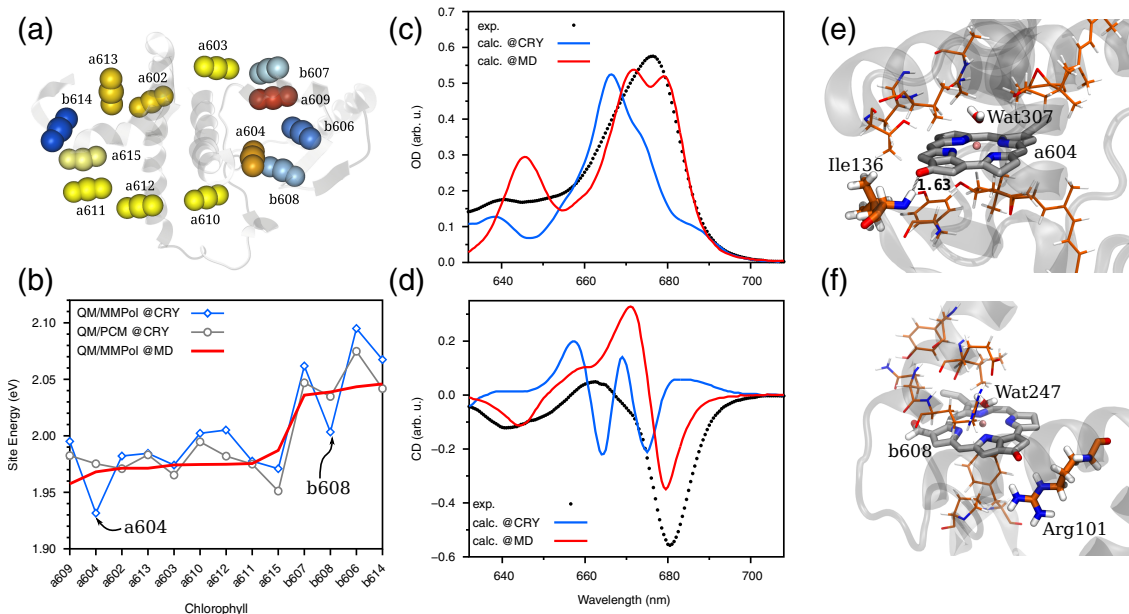
Figure 4: Comparison of crystal (@CRY) and MD-based (@MD) quantum chemical calculations of the site energies of CP29 [80]. (a) Arrangement of *Chl a* pigments in the protein scaffold. (b) Comparison of site energies computed with QM/MMPol along the MD (red line) and on the crystal structure (blue diamonds), showing that Chls *a604* and *b608* are unphysically red-shifted in the crystal description. The corresponding absorption (c) and circular dichroism (d) spectra show that the crystal description is rather inaccurate. (e,f) Representation of the local environment of (e) Chl *a604* and (f) Chl *b608*, highlighting the closest residues. Note the very short H-bond between Chl *a604* and *Ile136*.

try and frequencies of the chromophore at a QM level, the NMA approach circumvents the inaccuracies of the force-field description. Moreover, it allows computing the SD using only the crystal structure of the complex. On the other hand, this method does not account for protein fluctuations, whose effect has still to be included *a posteriori*, for example with a simplified atomic charge scheme [85] or with a phenomenological approach [43, 92].

Several groups have sought to overcome the force-field issue and to refine the MD sampling of nuclear fluctuations, for example, by computing the trajectories using multiscale QM/MM molecular dynamics [93, 94, 95, 96], which combines the ability of MD to account for the environment with the accuracy of the quantum chemical potentials. Another way to refine the MD description, keeping the computational cost adequately low, is by developing ad-hoc force-fields for the pigments, specifically aimed at reproducing excitation properties, [72, 73] or by using potentials interpolated from quantum chemical data [91, 97].

In addition to the evaluation of the SD, and the coupling to finite-frequency dynamic disorder that gives rise to homogeneous broadening, also inhomogeneous broadening has to be included in the simulation of spectra. The latter comes from static disorder, which can be understood as energetic disorder coming from slow large-scale motions of the environment, for example protein conformational changes. Static disorder has been often modeled phenomenologically, by assigning random shifts in site energies [7, 80, 66, 12]. In principle, disorder could be extracted from uncorrelated snapshots in a MD trajectory. However, site energies computed along a MD trajectory contain both static and dynamic disorder contributions, which are not trivial to disentangle. A possibility is to only compute the environment shift fluctuations and treat them as static [31]. Another possibility is to average energy fluctuations in different timescales, keeping only the sufficiently slow fluctuations as static disorder [97, 98].

The spectral densities, together with the exciton Hamiltonian elements, are the main ingredients to compute the optical spectra of a LH complex and especially the exciton dynamics. The "recipes" differ in how the interaction between the excitons and vibrations is treated. It is customary to divide the total Hamiltonian of the complex into an excitonic part and a vibrational part, plus their interaction [7]:

$$\hat{\mathcal{H}}_{\text{LHC}} = \hat{\mathcal{H}}_{\text{ex}} + \hat{\mathcal{H}}_{\text{vib}} + \hat{\mathcal{H}}_{\text{ex-vib}} \tag{4}$$

where $\hat{\mathcal{H}}_{\text{ex}}$ is the exciton Hamiltonian defined in Eq. (1), which is treated as the "system". While the shape of the optical spectra is determined by the entire Hamiltonian, the overall positions and intensities of absorption bands is mainly given by the excitonic part $\hat{\mathcal{H}}_{\text{ex}}$. Thus, the easiest approximate way to compute the absorption spectra is to broaden each exciton transition with some phenomenological lineshape, which can be Gaussian or Lorentzian, to generically account for disorder effects [81, 50]. A more refined strategy is to employ the energetic disorder estimated through MD simulations, by averaging the optical spectra

on several configurations sampled by the MD, even though this requires a separation of static and dynamic disorder contributions [31].

The effect of exciton-vibrational coupling in the optical spectra of LHCs is seen in the homogeneous line shape, and depends on the degree of delocalization of exciton states [7]. Exciton delocalization tends to dampen the broadening effect of exciton-vibrational coupling, and vice-versa. Treating exactly both the excitonic Hamiltonian and the exciton-vibrational interaction is still an open challenge, intimately related to the description of exciton dynamics [7, 99]. Numerically exact methods, such as the hierarchical equations of motion (HEOM) approach [100, 101], are still computationally expensive, and suffer some limitations in the functional form of the spectral density [101]. On the other hand, useful approximate theories have been recently developed, which are able to recover the main features of the exact theories [99, 102].

3. Challenges & possible solutions

In the previous section we have reported an overview of the state-of-the-art of atomistic models applied to the description of LH complexes. However, as anticipated in the Introduction, there are important aspects that still need to be improved in order to achieve both a better accuracy and a more complete picture. In Fig. 5 we propose a list of main issues that need to be further developed in the next future: all of them are briefly described here below.

3.1. The LH function

As reported in the previous section, most of the applications of atomistic models to LH complexes have used an excitonic formulation to describe the multichromophoric aggregate, possibly combined with a classical model for including the effect of the composite biological environment. These excitonic models have proven very general, e.g. they have been applied to very different systems, and in most cases they have shown to give very accurate descriptions. However, there are cases where important flaws have been observed.

For example, in LH complexes presenting closely packed chromophoric units, collective excitations of the complex may also present some charge transfer (CT) character between the pigments. Indeed, the involvement of charge-transfer states in the LH2 complex has been proven both experimentally [103, 104, 105, 106, 107] and computationally [66, 108, 109, 31, 63, 98] and it is not unlikely that similar situations could arise also in other LH complexes. When CT states play a role, writing the excitons as linear combinations of local excitations only, as normally done in the exciton model, is no longer sufficient. Thus, the model Hamiltonian from Eq. (1) must be extended with CT states and two additional ingredients are required: the energies of CT states and their coupling with locally excited states. As CT states are optically dark, their energies are difficult to obtain experimentally. In addition,

CT couplings cannot be recast into approximate expressions, unlike exciton couplings. These further difficulties with respect to local excitations still make the inclusion of CT effects rather limited in the simulation of LH complexes and in most cases empirical models, which use ad-hoc parameters for describing CT states, have been used [13, 107]. Only recently some approaches based on quantum chemical models have been proposed [109, 63]. These methods have allowed to investigate the role of CT in the unexpected broadening of the low-energy band in LH2 [98] and in the spectral shift observed in the different forms of LH2 obtained at high and low-light conditions [63]. These examples, even though still limited, seem to show that CT states can indeed play a role in the LH complexes, not only through a minor effect on the spectral properties. It is therefore extremely important that the atomistic descriptions accurately include their effect in a more systematic way. Moreover, as CT states are expected to be extremely sensitive to electric fields and polarization effects, these investigation will necessarily be coupled to an accurate model for the environment.

As already mentioned in the previous section, the accuracy of a QM description of the LH pigments is strictly related to the quality of the underlying geometrical structure. Unfortunately, it is now understood that standard MM force fields are not sufficiently accurate to describe the internal structures of the pigments, especially when the latter are very flexible molecules such as bilins and carotenoids [110, 72, 73]. To overcome this limitation, several strategies have been explored. Structures extracted from the MD can be refined through a geometry optimization at the QM/MM level of the pigments, keeping the environment frozen in its configuration following from the MD trajectory. This strategy should allow to locate "inherent structures" of the pigments in the protein, that is, the accessible local minima in the pigment potential energy surface [111]. This method requires, however, a large number of QM/MM optimizations whose cost is not negligible compared to the cost of sampling structures. Moreover, the tightly packed arrangement of pigments in some LH complexes can prevent a simple application of the method, because the structure of one pigment can affect the other close-by pigments in a non negligible way, implying that an iterative, and extremely costly, procedure should be applied.

A promising route to systematically improve the internal structure description achieved through MM FFs is to specifically target their parametrization to reproduce the excitation properties of the pigments [72, 73]. By using QM calculations of excitation energies in the fitting, it is possible to derive optimal force field parameters that give excitation energy fluctuations in the same range as *ab initio* MD [73]. A further step along this line is to overcome completely the functional form of standard MM force fields and use interpolation schemes to accurately reproduce a reference QM potential [91].

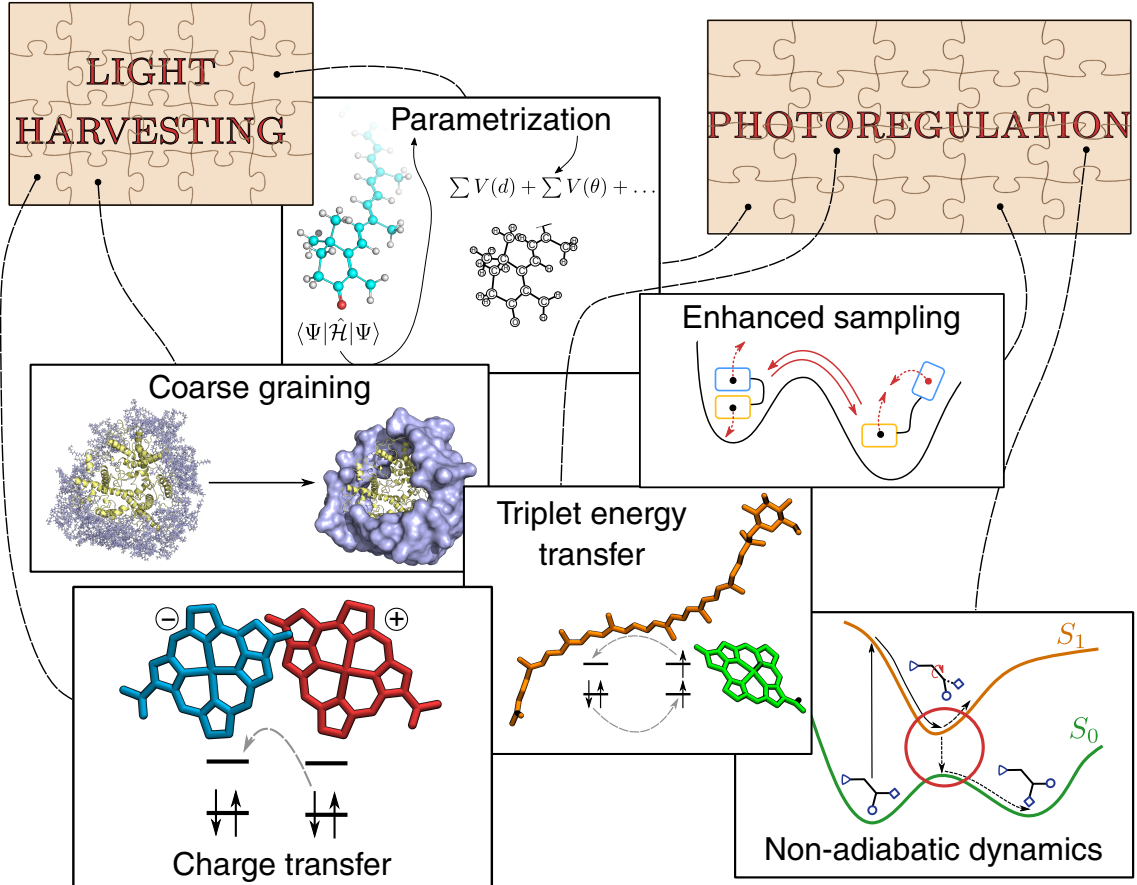Even once a proper excitonic Hamiltonian (possibly ex-

Figure 5: Solving the complex puzzle of light harvesting and its regulation will require new methodologies. These will be used to reduce the cost associated with the calculations (e.g. through novel force fields and coarse grain descriptions), introduce new effects into existent models (e.g. charge transfer effects and TET) or overcome limitations that are inherent to currently used methodologies (e.g. non adiabatic dynamics to overcome the Born Oppenheimer approximation, enhanced sampling to escape from "free energy traps").

tended to CT) has been defined, and a correct description of geometrical fluctuations have been achieved through MD based on optimized FF, important challenges still remain. An accurate modelling of exciton dynamics in LH complexes in fact has to take into account that different types of interactions, namely the exciton couplings in $\hat{\mathcal{H}}_{ex}$ and the exciton-vibrational coupling $\hat{\mathcal{H}}_{ex\text{-}vib}$, have similar magnitude, which somewhat hinders the use of the most common perturbative theories [112, 113, 114]. When dealing with linear spectroscopy, perturbative theories are often sufficient to describe spectra for the range of coupling strengths usually found in LH complexes [102, 99, 11]. On the other hand, if one is interested in describing energy transfer dynamics and its effect on nonlinear spectroscopy, the quality of the quantum dynamics theory becomes a compelling issue. This is particularly important when considering the relaxation of low-lying states into self-trapped exciton states, also known as dynamic localization [7, 11]. Self-trapping of excitons can be even more pronounced when CT states mix with exciton states, owing to the large exciton-phonon coupling of CT states [10, 98]. Therefore, when CT states are present, perturba-

tive theories will not be able to describe the fluorescence properties of self-trapped excitons [98]. Numerically exact theories such as HEOM can in principle describe all orders of the exciton-vibrational coupling, and HEOM has been employed also to describe dynamic localization in mixed exciton-CT states [13]. HEOM can thus provide a useful benchmark for simpler theories [11], but, as mentioned above, there are some limits in the form of exciton-vibrational coupling that HEOM can describe [101, 96]. Recently, trajectory-based mixed quantum-classical methods have been explored for the treatment of exciton dynamics in LH complexes [115, 116, 117]. Such methods abandon the quantum description of the vibrational Hamiltonian $\hat{\mathcal{H}}_{vib}$, but, on the other hand, can treat the nuclear fluctuations with atomistic precision, without assuming the harmonic oscillator model for the vibrational motion, or to explicitly compute spectral densities [117].

3.2. From the LH function to its photoregulation

As reported in the Introduction, the light-harvesting machinery needs to self-regulate in order to cope with variable light-conditions. Excess light can in fact be dangerous

because it can cause photo-oxidative damage and decrease the efficiency of photosynthesis because of photoinhibition. Photosynthetic organisms have evolved many photoprotective mechanisms which, among the others, include quenching of singlet and triplet excited states of pigments.

In particular, photoprotection in oxygenic photosynthesis involves quenching of chlorophyll triplets by carotenoid molecules [118, 119], through triplet energy transfer (TET). Unlike singlet energy transfer, which involves the Coulomb-like couplings presented in the previous section, TET is understood within Dexter's exchange interaction, which involves wavefunction overlap between the coupled pigments. Investigating the role of TET in photoprotection is thus more complicated, as the relevant coupling term cannot be expressed with the approximation presented in the previous section. Atomistic investigations of TET in photoprotection [120, 121] have thus employed quantum chemical methods, in conjunction to a diabatization scheme called Fragment Spin Difference [122] to compute the TET coupling. One of the main findings of these atomistic simulations is that TET rates can be strongly enhanced by geometrical fluctuations [121], due to the steep distance dependence of Dexter's mechanism. Only by combining an MD simulation with a multiscale QM/MMPol description of the TET couplings, it was possible to show that in the minor LH complex of plants (CP29) the triplet quenching times is reduced in the sub-nanosecond scale if thermal fluctuations are included in the model. These findings add a new perspective for the interpretation of the photoprotection function and its relation with structural motions of the LH complexes which deserve further computational and experimental investigation.

The quenching of the triplets cannot be the only mechanism into play to avoid photodamage/photoinhibition. In fact, as reported in the Introduction, many different mechanisms have been identified which finally allow LH to optimally self-regulate according to the light conditions. Commonly, NPQ is used as a collective name to indicate such set of different mechanisms and processes. Due to its complex and composite nature, NPQ has been investigated in detail only in the last few decades using cutting edge spectroscopic, biological and structural techniques [19, 123, 124, 125] Particular attention has been so far devoted to the study of higher plants and cyanobacteria. In plants, a series of competing regulatory mechanisms has been partially elucidated [5]. They probably involve allosteric changes in the LHCII and aggregation of the antenna complexes in the membrane. Up to now, however, it is still not clear which is the pigment that performs the actual fluorescence quenching and the atomistic detail of the potential allosteric change [126]. In cyanobacteria, instead, NPQ uses a very different strategy, which is mediated by a small carotenoid binding protein called *Orange Carotenoid Protein* (OCP). OCP is able to interconvert from a resting "orange" form to a light-activated "red" one which finally interacts with the LH supercomplex of cyanobacteria (called PBS) quenching its fluorescence [127]. In the last ten years, a large experimental effort was devoted to the understanding of the interconversion mechanism of OCP, and it is now clear that the interconversion is associated with the dissociation of the two sub-domains of the protein [128] and to a displacement of the carotenoid in the polypeptide [129]. Up to now, despite substantial effort [124, 125, 130], it is still unclear which is the exact sequence of events that finally lead to the dramatic structural rearrangement of the pigment and the embedding protein, and which is the photochemical trigger of the interconversion.

Only few research groups have investigated these phenomena using atomistic models. In particular, Duffy and coworkers have extensively studied carotenoid-mediated quenching mechanisms using semiempirical QM methods [131, 132]. They have also combined the same approach with MD trajectories for investigating the role of the protein dynamics in the quenching of the excited chlorophylls by energy transfer to carotenoids in major and minor LH complexes of plants [133]. Still using classical MD, Croce and coworkers suggested that NPQ in LHCII is probably connected to some conformational changes in the system structure [134]. Finally, Papadatos *et al.* used MD trajectories to asses the role of pH variation and of the xanthophyll cycle on the NPQ of LHCII [135, 136]. To the best of our knowledge, NPQ in cyanobacteria, instead, has never been studied with atomistic computational techniques.

From these first attempts, it came out clearly that the atomistic study of NPQ encounters both the problems emerged in the study of the light-harvesting process and new challenges, linked to the intervention of photochemical reactions triggering longer time scale phenomena, such as structural rearrangement and protein-protein interactions. Such problems can hardly be tackled with the techniques presented so far.

First of all, in order to specifically describe a photochemistry that may involve various electronic states requires to introduce a non-adiabatic dynamics of the (interacting) pigments. Due to the large dimensions of LH pigments, approaches based on a classical description of the nuclei, namely the mixed quantum classical non-adiabatic molecular dynamics [137, 138], appear to be the most promising strategy: within this context the nuclei are still propagated according to the Newton's equation, but the electronic degrees of freedom are propagated according to the time-depending Schrödinger equation. These schemes have been already coupled to a nonpolarizable MM description of the environment, to perform photochemistry of molecules embedded in biological matrices [139], but their extension to polarizable embeddings is still missing. The presence of a responsive environment could lead to non-negligible effects both in the potential energy surfaces of the involved electronic states, and in the subsequent non-adiabatic dynamics.

Moving to the large-scale motions that these photochemical events induce in the embedding protein, other numerical and computational problems appear. As a mat-

ter of fact, even with the most advanced hardware, it is not possible to simulate more than a few μs of classical MD on a system as large as a solvated LH complex. To address this general problem, different techniques, called *enhanced sampling* methods, have been developed and used to address conformational, folding and allosteric problems in both protein and other biological structures [140, 141, 142]. It is our opinion that, in order to push beyond our current limit in the atomistic simulation of the full spectrum of functions of LH systems, such methods should be adopted and possibly refined to match the specific needs of the complex problem under analysis. Moreover, other aspects of NPQ, related to molecular recognition and protein aggregation, are probably better addressed by other, even more approximate methods, such as docking [143], or coarse-grain models [144] together with more sophisticated tools for MD analysis [145].

4. Conclusions

The atomistic modeling of photosynthetic light-harvesting represents a real challenge due to the composite character of the involved systems, their very large dimensions, the strong interactions among all the different parts and the importance of the coupling among all the dynamics. In this review, we have summarized the remarkable progress achieved in the last years and the insights they have lead in our understanding of LH complexes. Now, however, a step further has to be made, to reveal the delicate interplay of different mechanisms that regulate the efficiency of light-harvesting together with its robustness with respect to changes in the external conditions. In this review we have suggested that this development will be represented by our ability to design new computational strategies, suitable for simulating the dynamics of the real composite system, taking into account all the scales of the different parts in a coherent formulation. This is an extremely challenging goal which requires combining and integrating new theoretical models with new computational algorithms and new tools for the analyses of the simulations. The scenario is not fully predictable but for sure a major role will still be played by smarter and more performing integrations of classical and quantum chemical dynamic approaches possibly in combination with machine learning techniques which will allow an unexpensive determination of excitation energies, forces and couplings [146, 147].

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