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Theoretical characterization of electronic states in interacting chemical systems

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In this article we characterize, by means of the perturbed matrix method, the response of the electronic states of a chemical system to the perturbing environment. In the theory section we describe in detail the basic derivations and implications of the method, extending its theoretical framework to treat possible excitonic effects, and we show how to characterize the perturbed electronic states. Finally, by using a set of chemical systems interacting with complex atomic-molecular environments, we describe the nature and general features of the electronic state mixing and transitions as caused by atomic and molecular interactions. © *2009 American Institute of Physics*. [DOI: 10.1063/1.3080887]

I. INTRODUCTION

The computational methodologies nowadays available are able to provide extremely accurate information on the electronic structure, and hence on the photoexcitation, of an isolated molecule. Unfortunately, there are still many difficulties in modeling electronic states in condensed phase,[1] and the nature of quantum state mixing and transitions in a chemical system interacting with its perturbing environment is still elusive. The inclusion of the electronic degrees of freedom (necessary for studying an electronic process) into a simulation of a large number of molecules (necessary for a reliable modeling of condensed phase) is in fact still challenging in the computational and theoretical points of view. In this context we have recently proposed a theoretical-computational approach, the perturbed matrix method (PMM),[2,3] whose main feature is the possibility of explicitly evaluating the coupling between the electronic states of a chemical system and the fluctuating perturbation exerted by its complex (semiclassical) atomic-molecular environment. The underlying philosophy of PMM is essentially in line with all the currently employed quantum-mechanics/molecular-mechanics (QM/MM) procedures.[4,5] In other words, a portion of a complex molecular system hereafter called quantum center (QC), e.g., a solute, a part of a biomacromolecule, a molecular cluster, etc., is treated quantum mechanically (i.e., we explicitly consider its electronic wave functions) with the rest of the system, e.g., the solvent and/or the protein, acting as a perturbation. It is worth to note that within the available QM/MM methods different basic procedures are utilized: A major group[6] includes the use of an available set of QC-environment configurations which hence provides the structures for possibly high-level electronic-structure standard quantum-chemical calculations. Such an approach may ensure an excellent description of the perturbed electronic states but requires high computational costs, implying the use of a limited number of configurations, hence making it difficult to obtain statistical mechanically reliable electronic properties, i.e., insufficient phase-space sampling. A more recent approach[7,8] is based on the use of a classical molecular dynamics (MD) simulation where the QC energy and QC-environment interaction are obtained by quantum-chemical calculations, introduced "on the fly" in the time propagation procedure. Such an approach, providing in principle the dynamics of the perturbed electronic states within the Born–Oppenheimer approximation, suffers from high computational costs which typically require the use of a certain number of approximations and allow relatively short simulations, order of picoseconds for condensed phase systems, hence providing a poor phase-space sampling. The novelty in PMM is the way in which the environment perturbation is dynamically coupled with the QC, specifically designed to ensure a reasonably high-level electronic-structure calculations and extended phase-space sampling by using long time-scale classical (empirical) MD simulations and expansion of the perturbation operator. Hence, once an extended MD trajectory is available, we may reconstruct in detail the QC perturbation pattern due to the environment atomic interactions (i.e., the perturbing electric field) and, in turn, to obtain the perturbed QC electronic states via diagonalization of the QC (perturbed) Hamiltonian matrix (i.e., the matrix expressing the Hamiltonian operator).

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When the MD atomistic force field used is reliable and accurate to provide the statistical mechanics of the molecular system considered, the outlined procedure is not only very efficient, allowing the evaluation of QC quantum states and properties for a large number of phase-space positions, but it also guarantees a coherent and balanced description of QC-environment interaction as the same level of theory is used to describe both QC and environment atoms in the MD simulation.

In a number of recent applications carried out both on large biomolecular systems[9–14] and small solutes in solution,[15–19] PMM has actually revealed to be a rather reliable computational tool for modeling spectroscopic (absorption) processes and chemical reactions in condensed phase. In particular, in one of these papers[19] we were able to reproduce the density-temperature dependence of liquid water (electronic) spectra by utilizing a single water molecule as QC, thus showing that PMM calculations based on a small chemically stable QC interacting with a semiclassical atomic-molecular environment may capture the essential physics of the process. Such remarkable results point out the major role of (classical) electrostatic interactions, indicating that relatively simple PMM applications may provide a reliable and accurate description of the perturbed electronic wave functions in complex systems of chemical-biochemical interest.

In order to provide deeper insights into such a matter we address in this article via PMM the problem of the nature of electronic state mixing and transitions as caused by the fluctuating perturbation due to atomic-molecular motions. In the theory section we describe thoroughly the basic derivations and physical implications of PMM, extending its theoretical framework to treat possible excitonic effects in clusters of chromophores embedded into a semiclassical atomic-molecular environment, and we show how to use PMM results in order to characterize the nature and (statistical) properties of the QC perturbed quantum states as emerging from the QC-environment interaction. Finally, in the results section, by using PMM calculations on relevant chemical-biochemical complex systems previously investigated,[11,16,20] we characterize in detail the behavior of perturbed electronic states, unveiling their statistical inherent nature.

II. THEORY

The main body of the theoretical basis of PMM is widely described in our previous articles.[2,3,15,17,21] In this section we describe more thoroughly the basic derivations and physical implications of PMM, extending its theoretical framework to model excitonic effects in multichromophore systems. Finally, we show how to use statistical analysis of PMM results in the electronic state space in order to characterize the nature of QC perturbed quantum states.

A. Basic derivations

Defining with $\boldsymbol{r}_n$ the nuclear coordinates of the QC and $\boldsymbol{x}$ the coordinates of the atoms providing the (classical) perturbing field we can write the overall (electronic[22]) Hamiltonian operator ($\hat{\mathcal{H}}$) as

$$\hat{\mathcal{H}}(\boldsymbol{r}_n,\boldsymbol{x}) = \hat{H}^0(\boldsymbol{r}_n) + \hat{V}_{\mathrm{QC},e}(\boldsymbol{r}_n,\boldsymbol{x}) + \hat{\mathcal{H}}_e^0(\boldsymbol{x}), \tag{1}$$

where $\hat{H}^0$ is the Hamiltonian operator of the isolated QC, $\hat{V}_{\mathrm{QC},e}$ is the QC-environment interaction operator, and $\hat{\mathcal{H}}_e^0$ is the Hamiltonian operator of the environment (excluding the QC-environment interaction). For each $\boldsymbol{r}_n,\boldsymbol{x}$ configuration we always assume that the overall electronic state Ψ_T may be expressed as the product of a QC state Φ and an environment state Ψ_e, that is, $\Psi_T \cong \Phi\Psi_e$. Such an assumption can be considered as an excellent approximation as long as QC and environment electrons may be well distinguished and treated as belonging to different physical systems, as usual if no chemical reaction or too close interaction between QC and environment atoms is considered. If we further assume that for any QC excitation the environment ground state is virtually the same we have for any overall state with only the QC excited

$$\hat{\mathcal{H}}\Psi_{T,n} = \mathcal{H}_n\Psi_{T,n}, \tag{2}$$

$$\Psi_{T,n} = \Phi_n\Psi_{e,0}, \tag{3}$$

clearly implying

$$\hat{\mathcal{H}}_{\Psi_{e,0}}\Phi_n = \mathcal{H}_n\Phi_n, \tag{4}$$

$$\hat{\mathcal{H}}_{\Psi_{e,0}} = \langle\Psi_{e,0}|\hat{\mathcal{H}}|\Psi_{e,0}\rangle, \tag{5}$$

with $\mathcal{H}_n$ the overall (electronic) Hamiltonian eigenvalue. Moreover, from the definition of the Hamiltonian operator we have

$$\hat{\mathcal{H}}_{\Psi_{e,0}} = \hat{H}^0 + \hat{V}_{\Psi_{e,0}} + \mathcal{H}_{e,0}, \tag{6}$$

$$\hat{V}_{\Psi_{e,0}} = \langle\Psi_{e,0}|\hat{V}_{\mathrm{QC},e}|\Psi_{e,0}\rangle, \tag{7}$$

$$\mathcal{H}_{e,0} = \langle\Psi_{e,0}|\hat{\mathcal{H}}_e^0|\Psi_{e,0}\rangle. \tag{8}$$

We may proceed further by noting that $\hat{V}_{\Psi_{e,0}}$ corresponds to the QC perturbation due to the environment charge distribution as provided by $\Psi_{e,0}$ (i.e., the environment perturbed ground state). Hence, separating the term due to the environment atomic charges $\hat{V}^{\mathrm{ac}}_{\Psi_{e,0}}$ from the higher order terms, expressed by $\Delta\hat{V}_{\Psi_{e,0}}$, we obtain

$$\hat{\mathcal{H}}_{\Psi_{e,0}} = \hat{H}^0 + \hat{V}^{\mathrm{ac}}_{\Psi_{e,0}} + \Delta\hat{V}_{\Psi_{e,0}} + \mathcal{H}_{e,0}, \tag{9}$$

providing the corresponding expression in matrix notation,

$$\tilde{\mathcal{H}}_{\Psi_{e,0}} = \tilde{H}^0 + \tilde{V}^{\mathrm{ac}}_{\Psi_{e,0}} + \Delta\tilde{V}_{\Psi_{e,0}} + \mathcal{H}_{e,0}\tilde{I}, \tag{10}$$

where we use the QC unperturbed basis set (Φ^0) to express all the matrices (i.e., the unperturbed QC Hamiltonian matrix $\tilde{H}^0$ is diagonal). We may further develop the obtained expression of the operator by considering that for a QC interacting with a set of point charges, the atomic charges, atomic pair dispersion interaction, and short-range repulsion are not present and therefore, assuming $\Delta\tilde{V}_{\Psi_{e,0}} \cong \Delta V_{\Psi_{e,0}}\tilde{I}$ (i.e., the eigenvectors of $\tilde{\mathcal{H}}_{\Psi_{e,0}}$ coincide with the eigenvectors of $\tilde{H}^0 + \tilde{V}^{\mathrm{ac}}_{\Psi_{e,0}}$), we can write

$$\tilde{\mathcal{H}}_{\Psi_{e,0}} \cong \tilde{H}^0 + \tilde{V}^{\mathrm{ac}}_{\Psi_{e,0}} + (\Delta V_{\Psi_{e,0}} + \mathcal{H}_{e,0})\tilde{I} \cong \tilde{H}^0 + \tilde{V}^{\mathrm{ac}}_{\Psi_{e,0}} + (\mathcal{U}'_{\mathrm{env}} + \mathcal{U}'_{D,R})\tilde{I}, \tag{11}$$

where in the approximation used $\Delta V_{\Psi_{e,0}} + \mathcal{H}_{e,0} \cong \mathcal{U}'_{\mathrm{env}} + \mathcal{U}'_{D,R}$, the term $\mathcal{U}'_{\mathrm{env}}$ is the environment potential energy (excluding all the semiclassical interactions with the QC), and $\mathcal{U}'_{D,R}$ is the QC-environment atomic pair dispersion-repulsion interaction term as provided by the atomic force field utilized in the MD simulations (note that the interaction potential $\Delta V_{\Psi_{e,0}}$ is not in general equivalent to the dispersion-repulsion interaction term as in $\mathcal{U}'_{D,R}$ intramolecular relaxation energies may be involved). Finally, expanding $\tilde{V}^{\mathrm{ac}}_{\Psi_{e,0}}$ via QC multipoles and approximating all the terms from the quadrupoles by a short-range potential matrix term (i.e., $\Delta V^{\mathrm{ac}}_{\Psi_{e,0}}\tilde{I}$), we obtain[3,15,17,21]

$$\begin{aligned}\tilde{H} &= \tilde{\mathcal{H}}_{\Psi_{e,0}}(\boldsymbol{r}_n,\boldsymbol{x}) - \mathcal{U}'_{\mathrm{env}}\tilde{I}\\ &= \tilde{H}^0(\boldsymbol{r}_n) + \tilde{V}(\boldsymbol{r}_n,\boldsymbol{x})\\ &\cong \tilde{H}^0(\boldsymbol{r}_n) + q_T\mathcal{V}(\boldsymbol{r}_0,\boldsymbol{x})\tilde{I} + \tilde{Z}_1(\boldsymbol{E}(\boldsymbol{r}_0,\boldsymbol{x}),\boldsymbol{r}_n) + \Delta V(\boldsymbol{r}_n,\boldsymbol{x})\tilde{I},\end{aligned} \tag{12}$$

where q_T is the QC total charge, $\mathcal{V}(\boldsymbol{r}_0,\boldsymbol{x})$ and $\boldsymbol{E}(\boldsymbol{r}_0,\boldsymbol{x})$ are the (perturbing) electric potential and electric field, as provided by the environment atomic charges, at a given QC $\boldsymbol{r}_0$ position (typically the mass or geometry center), $\tilde{Z}_1(\boldsymbol{E},\boldsymbol{r}_n)$ is the perturbation energy matrix explicitly given by $[\tilde{Z}_1]_{l,l'} = -\boldsymbol{E}\cdot\langle\Phi^0_l|\hat{\boldsymbol{\mu}}|\Phi^0_{l'}\rangle$ with $\hat{\boldsymbol{\mu}}$ the dipole operator, and $\Delta V(\boldsymbol{r}_n,\boldsymbol{x}) = \Delta V^{\mathrm{ac}}_{\Psi_{e,0}} + \mathcal{U}'_{DR}$ approximates all the higher order terms as a short-range potential (in the case the QC is a subpart of a molecule ΔV may also include an additive constant corresponding to a possible reference energy shift). Equation (12) expressing the QC perturbed Hamiltonian matrix $\tilde{H}$ and providing the usual PMM expression for a QC interacting with a semiclassical atomic-molecular environment may be equivalently expressed in the typical operator notation

$$\hat{H} = \hat{H}^0 + \hat{V} \cong \hat{H}^0 + q_T\mathcal{V} - \boldsymbol{E}\cdot\hat{\boldsymbol{\mu}} + \Delta V, \tag{13}$$

with the perturbation operator $\hat{V}$ physically corresponding to the perturbation due to the ground state environment atomic-molecular field acting on the QC. The eigenvectors of $\tilde{H}$, i.e., the eigenstates of $\hat{H}$, can be therefore used to obtain the perturbed QC electronic properties for each QC perturbed state. It must be remarked that Eqs. (12) and (13), relying on the approximation that the perturbation operator may be truncated at the dipolar term including implicitly all the higher order terms within a short-range potential independent of the electronic states, might be not accurate at close QC-environment interaction range where explicit higher order terms or distributed multipolar operators may be needed.[23] However, when we can disregard, as usual, highly excited electronic states in the Hamiltonian matrix (i.e., we are interested in the perturbed ground and first excited states) the approximation utilized in Eqs. (12) and (13) is typically rather accurate and, moreover, inclusion of explicit higher order multipolar terms, although in principle possible,[3,17] would require the use of rather inaccurate unperturbed (transition) multipoles, resulting in a poor PMM quality.

B. Extension to interacting chromophores

The relations derived in the previous subsection may be used to treat any quantum process of a chemical system (the QC) embedded into a semiclassical environment (i.e., we may assume factorization of the overall wave function and invariance of the environment electronic ground state for QC state transitions). In case we deal with a set of N interacting chromophores (N QCs) embedded in a semiclassical molecular environment, it is clear that we must take into account the possible excitation coupling occurring between QCs, partly breaking the previous approximations. In such a case we can still assume that the overall electronic ground state may be defined by the product of QCs and environment ground states (i.e., $\Psi_{T,0} = \Psi_{e,0}\Pi^N_{l=1}\Phi_{l,0}$). However, excited state factorization and QC independent excitations cannot be simply assumed. We may extend our previous results to treat such a condition by considering the perturbed Hamiltonian operator for all the N QCs,

$$\hat{H} = \sum_{l=1}^{N}(\hat{H}^0_l + \hat{V}_l) + \frac{1}{2}\sum_{l}\sum_{l'\neq l}\hat{V}_{l,l'}, \tag{14}$$

with $\hat{H}^0_l$ and $\hat{V}_l$ the lth QC unperturbed Hamiltonian and (environment) perturbation operators, as defined in Eq. (13) of the previous subsection, and $\hat{V}_{l,l'}$ the $1,1'$ QC interaction operator providing the QC mutual perturbation. We may introduce a new lth QC Hamiltonian operator $\hat{H}_l$ as defined by

$$\hat{H}_l = \hat{H}^0_l + \hat{V}_l + \sum_{l'\neq l}\langle\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l',0}\rangle, \tag{15}$$

with the corresponding matrix expression (utilizing again the QC unperturbed basis set and derivations/approximations to expand $\langle\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l',0}\rangle$ similar to the ones described in the previous subsection) given by

$$\tilde{H}_l \cong \tilde{H}^0_l + q_{T,l}\mathcal{V}_l\tilde{I} + \tilde{Z}_{1,l} + \Delta V_l\tilde{I}, \tag{16}$$

where $\mathcal{V}_l$, $\tilde{Z}_{1,l}$, and ΔV_l now include the contributions due to all the $1,1'$ QC interactions (i.e., the effects of the other QCs perturbing electric field, as obtained when they are in their ground states, are included into the perturbation). The eigenstates of such Hamiltonian operators, expressed by the eigenvectors of the corresponding Hamiltonian matrices, furnish a complete basis set to express the (perturbed) Hamiltonian matrix $\tilde{H}$ for the N interacting chromophores (corresponding to the $\hat{H}$ operator). In fact, defining with $\Phi_{k,p}$ the pth eigenstate of the kth QC Hamiltonian operator $\hat{H}_k$ [Eq. (15)] [corresponding to the pth eigenvector of $\tilde{H}_k$, Eq. (16)] and considering no more than a single excited QC in each reference state, we may define the reference basis set of the N QCs via the ground state $\Psi^{\mathrm{ref}}_0 = \Pi_l\Phi_{l,0}$ and the excited states $\Psi^{\mathrm{ref}}_{k,p}$

$=\Phi_{k,p}\Pi_{l\neq k}\Phi_{l,0}$ $(k=1,N\ \ p>0)$, providing the Hamiltonian matrix elements

$$
\begin{aligned}
[\widetilde{H}]_{\Psi_0^{\mathrm{ref}},\Psi_0^{\mathrm{ref}}} &= \langle \Pi_l\Phi_{l,0}|\hat{H}|\Pi_l\Phi_{l,0}\rangle \\
&= \langle \Pi_l\Phi_{l,0}|\sum_{l'}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \sum_{l''\neq l'}\hat{V}_{l',l''}\right] \\
&\quad - \frac{1}{2}\sum_{l'}\sum_{l''\neq l'}\hat{V}_{l',l''}|\Pi_l\Phi_{l,0}\rangle \\
&= \sum_l \langle\Phi_{l,0}|\hat{H}_l|\Phi_{l,0}\rangle \\
&\quad - \frac{1}{2}\sum_l\sum_{l'\neq l}\langle\Phi_{l,0}\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l,0}\Phi_{l',0}\rangle,
\end{aligned}
\tag{17}
$$

$$
\begin{aligned}
[\widetilde{H}]_{\Psi_0^{\mathrm{ref}},\Psi_{k,p}^{\mathrm{ref}}} &= [\widetilde{H}]^*_{\Psi_{k,p}^{\mathrm{ref}},\Psi_0^{\mathrm{ref}}} \\
&= \langle\Phi_{k,0}\Pi_{l\neq k}\Phi_{l,0}|\hat{H}|\Phi_{k,p}\Pi_{l\neq k}\Phi_{l,0}\rangle \\
&= \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \frac{1}{2}\sum_{l''\neq k,l'}\hat{V}_{l',l''}\right] \\
&\quad \times|\Pi_{l\neq k}\Phi_{l,0}\rangle\langle\Phi_{k,0}|\Phi_{k,p}\rangle + \langle\Phi_{k,0}|\hat{H}^0_k + \hat{V}_k \\
&\quad + \sum_{l'\neq k}\langle\Phi_{l',0}|\hat{V}_{k,l'}|\Phi_{l',0}\rangle|\Phi_{k,p}\rangle \\
&= \langle\Phi_{k,0}|\hat{H}_k|\Phi_{k,p}\rangle = 0,
\end{aligned}
\tag{18}
$$

with clearly $\langle\Phi_{l,0}|\hat{H}_l|\Phi_{l,0}\rangle=\varepsilon_{l,0}$ the ground state eigenvalue of $\widetilde{H}_l$ and, from the definition of the eigenfunctions Φ,

$$\langle\Phi_{k,0}|\Phi_{k,p}\rangle = 0, \tag{19}$$

$$\langle\Phi_{k,0}|\hat{H}_k|\Phi_{k,p}\rangle = \varepsilon_{k,p}\langle\Phi_{k,0}|\Phi_{k,p}\rangle = \varepsilon_{k,0}\langle\Phi_{k,0}|\Phi_{k,p}\rangle = 0. \tag{20}$$

Note that the result obtained in Eq. (18), i.e., $[\widetilde{H}]_{\Psi_0^{\mathrm{ref}},\Psi_{k,p}^{\mathrm{ref}}} = [\widetilde{H}]_{\Psi_{k,p}^{\mathrm{ref}},\Psi_0^{\mathrm{ref}}}=0$, is consistent with the assumption that the actual N QCs ground state Ψ_0 is given by the product of the QCs ground states, i.e., $\Psi_0=\Psi_0^{\mathrm{ref}}$ and therefore $\Psi_{T,0}=\Psi_0^{\mathrm{ref}}\Psi_{e,0}$.

The other Hamiltonian matrix elements

$$[\widetilde{H}]_{\Psi_{k,p}^{\mathrm{ref}},\Psi_{k',p'}^{\mathrm{ref}}} = \langle\Phi_{k,p}\Pi_{l\neq k}\Phi_{l,0}|\hat{H}|\Phi_{k',p'}\Pi_{l\neq k'}\Phi_{l,0}\rangle \tag{21}$$

can be easily obtained when considering the two possible cases $k=k'$ and $k\neq k'$. For the former case $(k=k')$ we may write

$$
\begin{aligned}
[\widetilde{H}]_{\Psi_{k,p}^{\mathrm{ref}},\Psi_{k,p'}^{\mathrm{ref}}} &= \langle\Phi_{k,p}\Pi_{l\neq k}\Phi_{l,0}|\hat{H}|\Phi_{k,p'}\Pi_{l\neq k}\Phi_{l,0}\rangle \\
&= \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \frac{1}{2}\sum_{l''\neq k,l'}\hat{V}_{l',l''}\right]|\Pi_{l\neq k}\Phi_{l,0}\rangle\langle\Phi_{k,p}|\Phi_{k,p'}\rangle + \langle\Phi_{k,p}|\hat{H}^0_k + \hat{V}_k + \sum_{l'\neq k}\langle\Phi_{l',0}|\hat{V}_{k,l'}\ \Phi_{l',0}\rangle|\Phi_{k,p'}\rangle \\
&= \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \frac{1}{2}\sum_{l''\neq k,l'}\hat{V}_{l',l''}\right]|\Pi_{l\neq k}\Phi_{l,0}\rangle\langle\Phi_{k,p}|\Phi_{k,p'}\rangle + \langle\Phi_{k,p}|\hat{H}_k|\Phi_{k,p'}\rangle,
\end{aligned}
\tag{22}
$$

providing $[\widetilde{H}]_{\Psi_{k,p}^{\mathrm{ref}},\Psi_{k,p'}^{\mathrm{ref}}}=0$ when $p\neq p'$ and

$$
\begin{aligned}
[\widetilde{H}]_{\Psi_{k,p}^{\mathrm{ref}},\Psi_{k,p}^{\mathrm{ref}}} &= \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \sum_{l''\neq k,l'}\hat{V}_{l',l''} - \frac{1}{2}\sum_{l''\neq k,l'}\hat{V}_{l',l''}\right]|\Pi_{l\neq k}\Phi_{l,0}\rangle + \varepsilon_{k,p} \\
&= \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}\left[\hat{H}^0_{l'} + \hat{V}_{l'} + \sum_{l''\neq k,l'}\hat{V}_{l',l''} - \frac{1}{2}\sum_{l''\neq k,l'}\hat{V}_{l',l''}\right]|\Pi_{l\neq k}\Phi_{l,0}\rangle + \varepsilon_{k,p} \\
&\quad + \langle\Pi_{l\neq k}\Phi_{l,0}|\sum_{l'\neq k}[\langle\Phi_{k,0}|\hat{V}_{l',k}|\Phi_{k,0}\rangle - \langle\Phi_{k,0}|\hat{V}_{l',k}|\Phi_{k,0}\rangle]|\Pi_{l\neq k}\Phi_{l,0}\rangle \\
&= \sum_{l\neq k}\langle\Phi_{l,0}|\hat{H}_l|\Phi_{l,0}\rangle - \frac{1}{2}\sum_l\sum_{l'\neq l}\langle\Phi_{l,0}\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l,0}\Phi_{l',0}\rangle + \varepsilon_{k,p} \\
&= \sum_l \varepsilon_{l,0} - \frac{1}{2}\sum_l\sum_{l'\neq l}\langle\Phi_{l,0}\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l,0}\Phi_{l',0}\rangle + \varepsilon_{k,p} - \varepsilon_{k,0}
\end{aligned}
\tag{23}
$$

for $p=p'$.

Finally, in the case $k\neq k'$ we obtain

$$\begin{aligned}[\tilde{H}]_{\Psi^{\mathrm{ref}}_{k,p},\Psi^{\mathrm{ref}}_{k',p'}} &= \langle \Phi_{k,p}\Pi_{l\neq k}\Phi_{l,0}|\hat{H}|\Phi_{k',p'}\Pi_{l\neq k'}\Phi_{l,0}\rangle \\ &= \langle \Pi_{l\neq k,k'}\Phi_{l,0}|\sum_{l'\neq k,k'}\left[\hat{H}^0_{l'}+\hat{V}_{l'}+\frac{1}{2}\sum_{l''\neq l',k,k'}\hat{V}_{l',l''}\right]|\Pi_{l\neq k,k'}\Phi_{l,0}\rangle\langle\Phi_{k,p}|\Phi_{k,0}\rangle\langle\Phi_{k',0}|\Phi_{k',p'}\rangle + \langle\Phi_{k,p}|\hat{H}^0_k+\hat{V}_k \\ &\quad + \sum_{l'\neq k,k'}\langle\Phi_{l',0}|\hat{V}_{k,l'}|\Phi_{l',0}\rangle|\Phi_{k,0}\rangle\langle\Phi_{k',0}|\Phi_{k',p'}\rangle + \langle\Phi_{k',0}|\hat{H}^0_{k'}+\hat{V}_{k'} \\ &\quad + \sum_{l'\neq k,k'}\langle\Phi_{l',0}|\hat{V}_{k',l'}|\Phi_{l',0}\rangle|\Phi_{k',p'}\rangle\langle\Phi_{k,p}|\Phi_{k,0}\rangle + \langle\Phi_{k,p}\Phi_{k',0}|\hat{V}_{k,k'}|\Phi_{k,0}\Phi_{k',p'}\rangle \\ &= \langle\Phi_{k,p}\Phi_{k',0}|\hat{V}_{k,k'}|\Phi_{k,0}\Phi_{k',p'}\rangle. \end{aligned} \tag{24}$$

It is worth to note that in all the diagonal elements we have the term $\varepsilon_0=\Sigma_l\varepsilon_{l,0}-\frac{1}{2}\Sigma_l\Sigma_{l'\neq l}\langle\Phi_{l,0}\Phi_{l',0}|\hat{V}_{l,l'}|\Phi_{l,0}\Phi_{l',0}\rangle$ corresponding to the interacting chromophores ground state energy, i.e., the ground state eigenvalue of $\tilde{H}$, hence implying that

$$\tilde{H}=\varepsilon_0\tilde{I}+\Delta\tilde{H}, \tag{25}$$

where $\tilde{I}$ is the identity matrix and $\Delta\tilde{H}$ (excitation matrix) has clearly the first row and column defined by null elements with its diagonal elements (beyond the null ground state one) given by $\varepsilon_{k,p}-\varepsilon_{k,0}$ and its off-diagonal elements identical to the ones of $\tilde{H}$. From the last equation it is evident that the excitation matrix provides the eigenvectors of $\tilde{H}$ with eigenvalues ($\Delta\varepsilon_i$) corresponding to the excitation energies, i.e., $\Delta\varepsilon_i=\varepsilon_i-\varepsilon_0$ where ε_i is the ith eigenvalue of $\tilde{H}$. Furthermore, we may explicitly express (in a.u.) the nonzero off-diagonal elements of $\Delta\tilde{H}$ via multipolar expansion (truncated at the dipolar terms) of the chromophore interaction operator

$$\begin{aligned}\hat{V}_{k,k'} &\cong \frac{q_{T,k}q_{T,k'}}{R_{k,k'}}+\frac{q_{T,k}\hat{\boldsymbol{\mu}}_{k'}\cdot\boldsymbol{R}_{k,k'}}{R^3_{k,k'}}-\frac{q_{T,k'}\hat{\boldsymbol{\mu}}_{k}\cdot\boldsymbol{R}_{k,k'}}{R^3_{k,k'}} \\ &\quad +\frac{\hat{\boldsymbol{\mu}}_k\cdot\hat{\boldsymbol{\mu}}_{k'}}{R^3_{k,k'}}-3\frac{\hat{\boldsymbol{\mu}}_{k'}\cdot\boldsymbol{R}_{k,k'}\hat{\boldsymbol{\mu}}_k\cdot\boldsymbol{R}_{k,k'}}{R^5_{k,k'}},\end{aligned}$$

with $\hat{\boldsymbol{\mu}}_k$ the kth chromphore dipole operator and $\boldsymbol{R}_{k,k'}$ the k' to k chromophore displacement vector defined by the corresponding chromophore origins (typically the centers of mass or geometry), providing

$$\begin{aligned}&\langle\Phi_{k,p}\Phi_{k',0}|\hat{V}_{k,k'}|\Phi_{k,0}\Phi_{k',p'}\rangle \\ &\quad\cong\frac{\langle\Phi_{k,p}|\hat{\boldsymbol{\mu}}_k|\Phi_{k,0}\rangle\cdot\langle\Phi_{k',0}|\hat{\boldsymbol{\mu}}_{k'}|\Phi_{k',p'}\rangle}{R^3_{k,k'}} \\ &\quad\quad -3\frac{\langle\Phi_{k',0}|\hat{\boldsymbol{\mu}}_{k'}|\Phi_{k',p'}\rangle\cdot\boldsymbol{R}_{k,k'}\langle\Phi_{k,p}|\hat{\boldsymbol{\mu}}_k|\Phi_{k,0}\rangle\cdot\boldsymbol{R}_{k,k'}}{R^5_{k,k'}}.\end{aligned}$$

The obtained relations, expressing the Hamiltonian matrix, point out that the only nonzero off-diagonal elements possible are those associated with the case $k\neq k'$ corresponding to the $\langle\Phi_{k,p}\Phi_{k',0}|\hat{V}_{k,k'}|\Phi_{k,0}\Phi_{k',p'}\rangle$ terms, involving inner products of the chromophores perturbed transition dipoles. It is therefore evident that only when such terms are nonnegligible compared to the diagonal elements may we have excitonic effects, i.e., the excited states are linear combinations of the reference excited states; otherwise the excitation matrix and thus the Hamiltonian matrix are virtually diagonal, hence providing that the reference basis set coincides with the N chromophores electronic eigenstates, i.e., independent chromophore excitations, thus properly described by single QC PMM calculations (see previous subsection). It is worth to note that similarly to the single chromophore perturbation operator, for the chromophore interaction operators we used the approximation that all the multipolar terms beyond the dipolar ones are implicitly included within a short-range potential independent of the electronic states, and hence in the elements of $\Delta\tilde{H}$ such terms may be neglected.

Using the same reference basis set we may obtain the dipole matrix elements from the definition of the N QC dipole operator $\hat{\boldsymbol{\mu}}$,

$$\hat{\boldsymbol{\mu}}=\sum_l\hat{\boldsymbol{\mu}}_l+\sum_l q_{T,l}\boldsymbol{R}_l \tag{26}$$

($\hat{\boldsymbol{\mu}}_l$ is the lth chromophore dipole operator with respect to the lth chromophore origin and $\boldsymbol{R}_l$ the vector radius defining the lth origin position in the laboratory reference of frame), providing

$$\langle\Psi^{\mathrm{ref}}_0|\hat{\boldsymbol{\mu}}|\Psi^{\mathrm{ref}}_0\rangle=\sum_l\langle\Phi_{l,0}|\hat{\boldsymbol{\mu}}_l|\Phi_{l,0}\rangle+\sum_l q_{T,l}\boldsymbol{R}_l, \tag{27}$$

$$\langle\Psi^{\mathrm{ref}}_0|\hat{\boldsymbol{\mu}}|\Psi^{\mathrm{ref}}_{k,p}\rangle=\langle\Phi_{k,0}|\hat{\boldsymbol{\mu}}_k|\Phi_{k,p}\rangle, \tag{28}$$

$$\begin{aligned}\langle\Psi^{\mathrm{ref}}_{k,p}|\hat{\boldsymbol{\mu}}|\Psi^{\mathrm{ref}}_{k,p'}\rangle&=\sum_{l\neq k}\langle\Phi_{l,0}|\hat{\boldsymbol{\mu}}_l|\Phi_{l,0}\rangle\langle\Phi_{k,p}|\Phi_{k,p'}\rangle \\ &\quad+\langle\Phi_{k,p}|\hat{\boldsymbol{\mu}}_k|\Phi_{k,p'}\rangle \\ &\quad+\langle\Phi_{k,p}|\Phi_{k,p'}\rangle\sum_l q_{T,l}\boldsymbol{R}_l,\end{aligned} \tag{29}$$

$$\langle\Psi^{\mathrm{ref}}_{k,p}|\hat{\boldsymbol{\mu}}|\Psi^{\mathrm{ref}}_{k',p'}\rangle=0, \tag{30}$$

with clearly $k\neq k'$ in the last equation.

TABLE I. Water dimer first ($\Delta E_{\mathrm{exc},1}$) and second ($\Delta E_{\mathrm{exc},2}$) excitation energy shifts with respect to the unperturbed monomer first excitation energy as a function of intermolecular hydrogen-oxygen distance (see Sec. III for computational details). In the table we also report the absolute values of the dimer first (Proj. 1st exc. state) and second (Proj. 2nd exc. state) excited state projections along the monomers first (perturbed) excited state. From the table it is clear that for all the intermolecular distances the first two dimer excited states are equivalent to monomer first excitation, with hence no relevant excitonic effects. Note that even in the dimer global energy minimum ($R_{\mathrm{OH}}=0.197$ nm, where intermonomer electronic exchange may be relevant) our results are in reasonable agreement with high-level *ab initio* calculations (Refs. 24 and 25) on water dimer.

R_{OH} (nm)	$\Delta E_{\mathrm{exc},1}$ (eV)	$\Delta E_{\mathrm{exc},2}$ (eV)	Proj. 1st exc. state	Proj. 2nd exc. state
0.197	0.14	0.25	0.9999	0.9999
0.210	0.09	0.09	0.9990	0.9990
0.510	0.03	0.03	0.9997	0.9997
1.000	0.00	0.00	1.0000	1.0000

C. Statistical characterization of perturbed electronic states

In this subsection we describe how to characterize the perturbed QC electronic states as obtained by PMM, limiting our attention to single chromophore systems, i.e., we consider a single QC embedded into a semiclassical atomic-molecular environment. Note that such a condition, equivalent to the multi-QC system with a virtually diagonal overall Hamiltonian matrix, i.e., $\Psi_n \cong \Psi_n^{\mathrm{ref}}$, is usually an excellent general approximation as for most molecular systems $\langle \Phi_{k,p}\Phi_{k',0}|\hat{V}_{k,k'}|\Phi_{k,0}\Phi_{k',p'}\rangle \cong 0$, at least when compared to the diagonal elements (see, for example, Table I). However, extension of this analysis to the more complex multiple-chromophore case is relatively straightforward and, for the sake of simplicity, will be addressed in future publications specifically dealing with excitonic systems.

If a MD simulation, or more generally a configurational space sampling, is carried out a "sequence" of $\boldsymbol{E}$ and $\mathcal{V}$ is produced. Hence, the diagonalization of $\tilde{H}(\boldsymbol{r}_n,\boldsymbol{x})$ carried out along such a configurational sampling will produce a "trajectory" of perturbed eigenvalues (ε_i) and eigenvectors ($\boldsymbol{c}_i$) of the QC and, therefore, of whatever perturbed electronic property. Each perturbed QC electronic state, given by the corresponding Hamiltonian eigenvector, will then be defined by a trajectory in the electronic state space, i.e., the space defined by the electronic unperturbed Hamiltonian basis set, providing a statistical distribution of the Hamiltonian eigenvector fluctuations (note that given the orthonormality of Hamiltonian eigenvectors such a distribution is due to the rotational fluctuations of a unit vector). By performing principle-component analysis on each Hamiltonian eigenvector trajectory, we may identify the subspace of the electronic state space where the eigenvector is mainly confined. This is accomplished by constructing and diagonalizing the correlation matrix for the ith Hamiltonian eigenvector $\tilde{C}_i=\langle \boldsymbol{c}_i\boldsymbol{c}_i^{*T}\rangle$ where the angular brackets represent averaging over the trajectory distribution. The eigenvectors $\boldsymbol{\eta}_{l,i}$ of $\tilde{C}_i$ correspond to directions in the electronic state space maximizing/minimizing the Hamiltonian eigenvector mean square projection, expressed for each eigenvector by the corresponding eigenvalue, i.e., $\lambda_{l,i}=\langle|\boldsymbol{\eta}_{l,i}^{*T}\boldsymbol{c}_i|^2\rangle$ with clearly (orthonormality of electronic states) $\Sigma_l\lambda_{l,i}=1$. The eigenvalue spectrum will then furnish the characterization of each perturbed Hamiltonian state in terms of essential eigenvectors to be used (essential subspace) to describe satisfactorily all the rotational fluctuations of the unit vector representing the perturbed electronic state. Hamiltonian states providing an eigenvalue spectrum with only one eigenvalue significantly different from zero correspond to virtually static perturbed electronic states which may be described by a single (time independent) unit vector, i.e., the perturbed state may be rotated with respect to the corresponding unperturbed one but no rotational fluctuations are present. For Hamiltonian states characterized instead by more nonzero eigenvalues the rotational fluctuations are present and hence they cannot be described by a single static unit vector but rather by a distribution in the essential subspace (the subspace of the electronic state space defined by the eigenvectors with nonzero eigenvalues).

III. COMPUTATIONAL METHODS

Details of the quantum-chemical calculations and MD simulations, carried out on the investigated systems, can be found in the cited literature. Hence we report in this article only some relevant information. For the unperturbed states of water we utilized complete active space self-consistent field including 8 electrons in 12 orbitals in conjunction with the 6-311++G(d,p) atomic basis set. These unperturbed calculations were used for both the water dimer and liquid water. In the latter case we performed MD simulation at 300 K using a cubic box with 256 single point charge (SPC) water molecules[26] at a density of 55.32 mol/l. For dimer calculations we utilized the global energy minimum and a set of dimer structures as provided by moving apart both water molecules in their (optimized) monomer geometries. In the case of the electron transfer in Cu–Zn superoxide dismutase (CuZnSOD), we carried out B3LYP calculations on the QC defined by Cu atom bound to superoxide anion and four histidines. Then configuration interaction calculation with single and double excitations using the B3LYP eigenvectors were performed for evaluating the unperturbed states using a mixed basis set consisting of 3-21g for all the atoms with the exception of Cu and superoxide anion for which the 6-31+G(d) basis set was used. For the MD simulation CuZnSOD was immersed in a box of 10 372 SPC water molecules and 9 sodium ions and the simulation was extended for 14 ns at 300 K. For unperturbed states of uracil we carried out linear response calculations based on coupled cluster with the inclusion of the single and double excitations with Dunning's triple zeta basis set. As far as MD simulations are concerned uracil was put at the center of a box consisting of 513 TIP3P water molecules[27] and simulated for 4 ns.

In all of the above MD simulations, carried out in the *NVT* ground state ensemble, we used the GROMACS software package[28] modified to use the isokinetic temperature coupling[29] and to apply rototranslational constraints to the

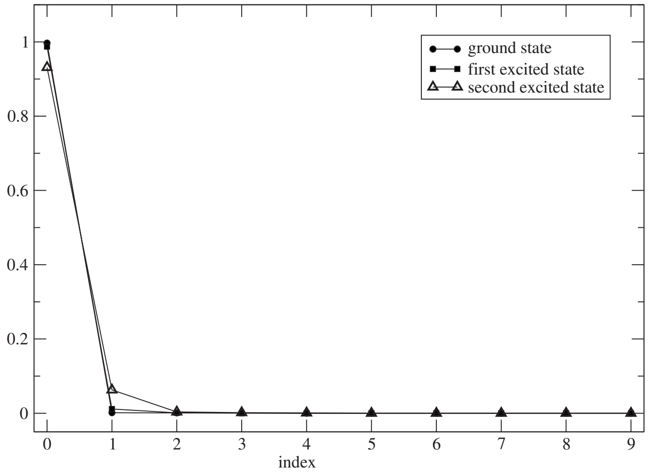

FIG. 1. Principle-component eigenvalues for water perturbed ground state and first two excited states.

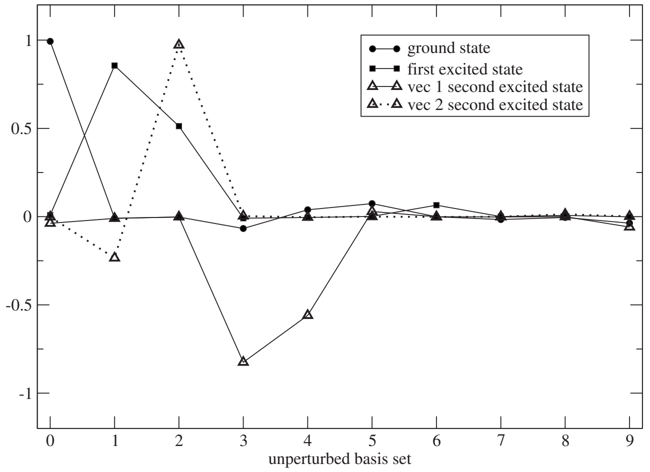

FIG. 2. Relevant principle-component eigenvectors for water perturbed ground state and first two excited states. Note that we use the unperturbed electronic states as basis set.

solute.[30] The long-range electrostatics was calculated using the particle mesh Ewald method.[31]

IV. RESULTS AND DISCUSSION

In this section we show the results obtained by using three different systems of increasing complexity, defined by a chromophore embedded in a semiclassical molecular system: A water molecule in liquid water,[16] aqueous uracil,[20] and solvated CuZnSOD (Ref. 11) considering as QC the enzyme reactive center for the electron transfer step of the reaction. In this paper we always consider a single QC, hence neglecting excitonic coupling, as for usual condensed phase systems chromophore interaction effects do not seem relevant[11,16,19,20] (as an instructive prototypical example we show in Table I the main features of the water dimer at different intermolecular distances as obtained by considering two interacting QCs, see theory section, clearly indicating that no relevant excitonic effects are present). Note that for the sake of simplicity we limited our analysis to the QC perturbed ground and first two excited electronic states considering only ground state (statistical) ensembles, i.e., all the MD simulations were carried out in the electronic ground state of the overall system.

A. Liquid water

In Fig. 1 we show the principle-component eigenvalues for the perturbed ground and first two excited states of the water molecule. From the figure it is evident that for both the ground state and first excited state a single principle-component eigenvector may fully describe their behavior, while for the second excited state two principle-component eigenvectors must be used (principle-component eigenvectors associated with null eigenvalues correspond to a subspace orthogonal to the electronic state considered). By expressing in the unperturbed (electronic) basis set the relevant principle-component eigenvectors of each perturbed electronic state (Fig. 2), it is clear that the perturbed ground state virtually coincides with the unperturbed one, the perturbed first excited state is rotated with respect to the corresponding unperturbed state in the plane defined by the first two unperturbed excited states, and, most interesting, the perturbed second excited state is confined within a plane obtained by mixing the first four unperturbed excited states. It is worth to note that perturbed electronic states which are described by two or more principle-component eigenvectors necessarily correspond to a rotational distribution of a unit vector. This is shown in Fig. 3 where it is reported the distribution of the projections of the perturbed second excited state on the plane defined by its two relevant principle-component eigenvectors. The figure clearly shows that water-water interactions cause the second excited state to rotate in the plane, according to a characteristic distribution.

These results provide a clear indication that perturbed electronic states may be divided into three groups: Electronic states which virtually coincide with their corresponding unperturbed states, with hence only first order perturbation energy effects (electronic ground states are typically fitting in this group); electronic states which may still be described by a single unit vector in the electronic state space, but such a vector does not coincide with the corresponding unperturbed

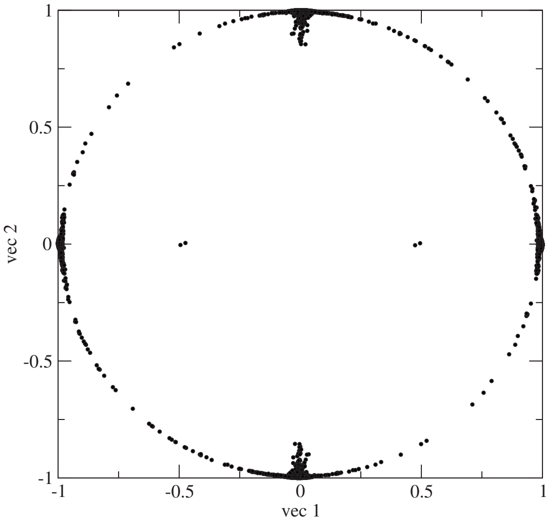

FIG. 3. Projection distribution of water perturbed second excited state onto the plane defined by its two relevant principle-component eigenvectors.

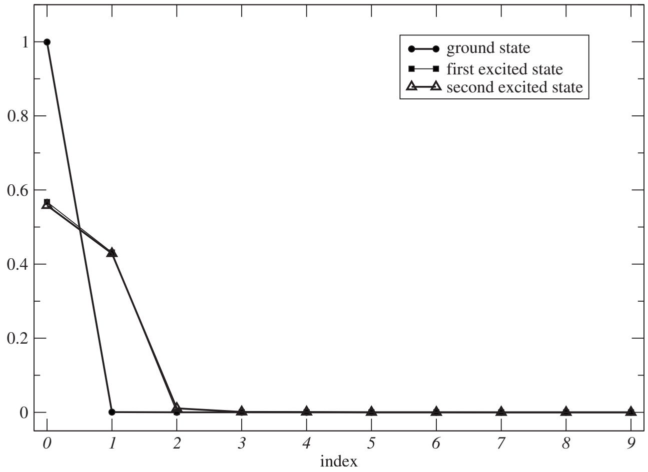

FIG. 4. Principle-component eigenvalues for aqueous uracil perturbed ground state and first two excited states.

state, i.e., "static" mixture of unperturbed states; electronic states oscillating within a given subspace, defined by two or more principle-component eigenvectors, which hence must be thought as rotational distributions in the subspace, i.e., "dynamic" mixture of unperturbed states.

B. Aqueous uracil

Figures 4 and 5, equivalent to Figs. 1 and 2 for liquid water, clearly indicate that also in this case the perturbed electronic ground state is virtually identical to the unperturbed one but show that both perturbed excited states must be considered as dynamic mixtures in the plane defined by the first two unperturbed excited states, i.e., the two relevant principle-component eigenvectors of both perturbed excited states are defined in such a plane. Again, when considering the projection distributions of both perturbed excited states onto their principle-component eigenvector planes (see Fig. 6) the dynamic mixing is evidenced, pointing out for the second excited state even the presence of a few rotational fluctuations orthogonal to the plane as indicated by the low radial probability density corresponding to projections along the third principle-component eigenvector. Such data indicate the complexity of aqueous uracil electronic excitations (as a result of the fluctuating uracil-water interactions) and suggest a possible subtle electronic interplay in nucleic acid molecules.

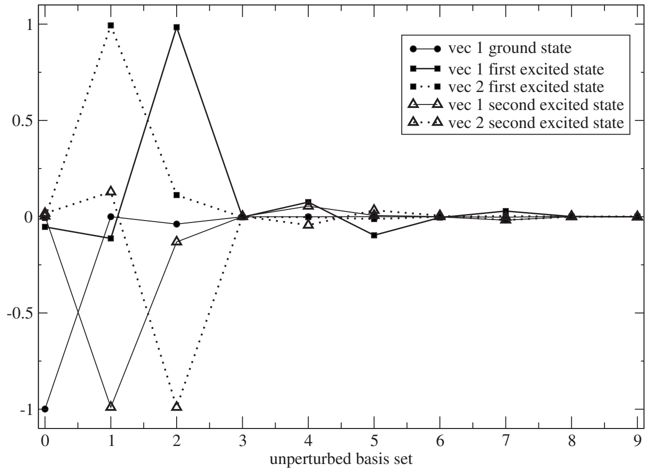

FIG. 5. Relevant principle-component eigenvectors for aqueous uracil perturbed ground state and first two excited states. Note that we use the unperturbed electronic states as basis set.

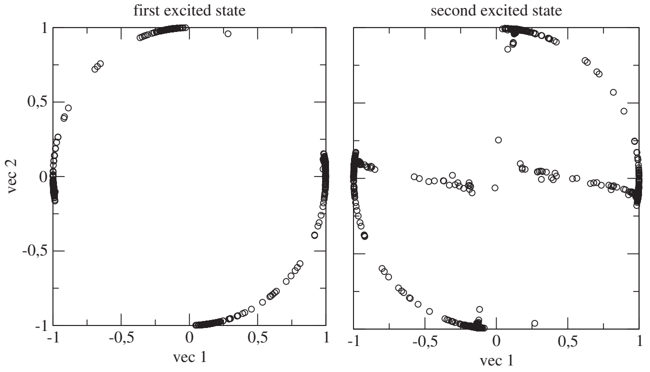

FIG. 6. Projection distributions of aqueous uracil perturbed first and second excited states onto the planes defined by their two relevant principle-component eigenvectors.

C. Reactive center in CuZnSOD

In the case of the reactive center in CuZnSOD, we consider the chemical condition (i.e., position along the reaction coordinates) providing the electron transfer in the solvated protein[11] (note that for the isolated reactive center calculations show that no electron transfer may occur). Figure 7, equivalent to Figs. 1 and 4 of the previous systems, clearly indicates that in this case the perturbed ground state as well as the perturbed first two excited states are defined by a single principle-component eigenvector. Interestingly, Fig. 8 (equivalent to Figs. 2 and 5 of the previous systems) shows that all these three perturbed electronic states are actually rotated with respect to the corresponding unperturbed states (i.e., static mixtures of unperturbed states): The perturbed ground state corresponds exactly to the unperturbed first excited state and the two perturbed excited states are linear combinations of the unperturbed ground and second excited states. The remarkable exchange between (unperturbed)

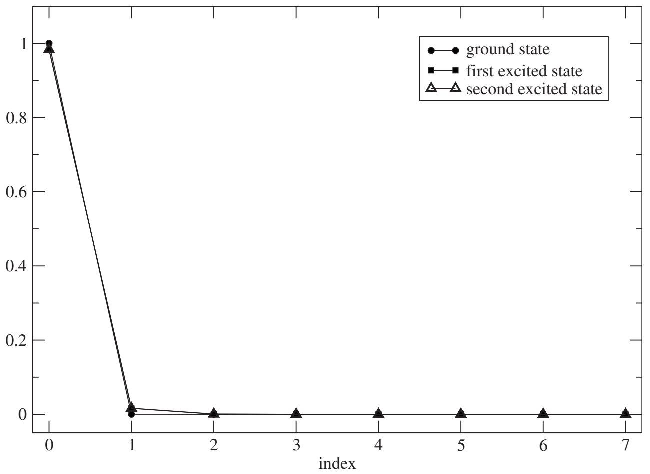

FIG. 7. Principle-component eigenvalues for CuZnSOD reactive center perturbed ground state and first two excited states.

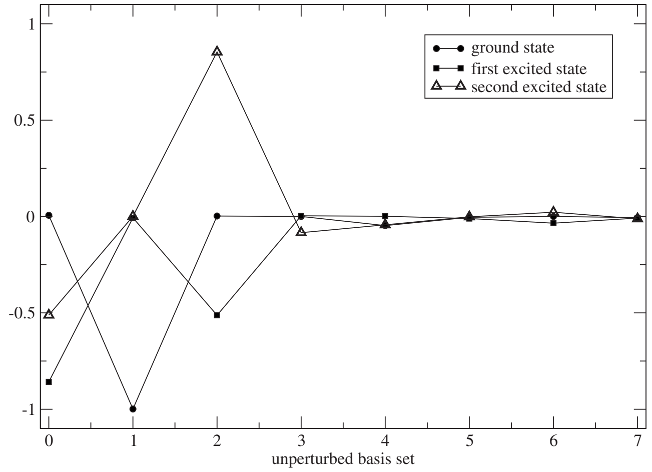

FIG. 8. Relevant principle-component eigenvectors for CuZnSOD reactive center perturbed ground state and first two excited states. Note that we use the unperturbed electronic states as basis set.

ground state and first excited state, induced by the perturbing field of the protein-solvent environment and clearly responsible for the efficient electron transfer, is probably rather peculiar of reactive centers in redox proteins.

V. CONCLUSIONS

In this paper we provide a general detailed description of the theoretical basis of PMM, deriving and discussing more thoroughly than in previous papers its physical implications and assumptions, and show how to characterize the obtained perturbed electronic states via statistical analysis. In the theory section, we also extend PMM theoretical framework to treat excitonic effects in chromophore clusters via explicit modeling of the excitation coupling process. Such excitation coupling effects, although may be often neglected (see theory section), are of great interest in the study of relevant biochemical-biophysical systems (e.g., DNA molecules) where nearby chromophores may modulate their excitations via reciprocal interaction.

Finally, by using a set of chemical-biochemical systems previously investigated,[11,16,20] we characterize in detail the nature of perturbed electronic states, showing that QC-environment interaction causes relevant state mixing and transitions which may even lead to fluctuations of the perturbed state in a given subspace. From the results it clearly emerges a complex repertoire of perturbation effects that we may essentially group into three main features: Perturbed electronic states which virtually coincide with their corresponding unperturbed states, with hence only first order perturbation energy effects (electronic ground states are typically fitting in this group); perturbed electronic states which may still be described by a single unit vector in the electronic state space, but such a vector does not coincide with the corresponding unperturbed state, i.e., static mixture of unperturbed states; perturbed electronic states oscillating within a given subspace which hence must be thought as rotational distributions in the subspace rather than a single unit vector, i.e., dynamic mixture of unperturbed states. The remarkable coupling between electronic states and atomic-molecular motions evidenced, ruling out the possibility of a general simple correspondence between perturbed and unperturbed states, unveils the inherent statistical nature of quantum states in interacting chemical systems and sheds light on the emerging electronic-structural interplay occurring in complex molecular systems such as liquids and biomacromolecules.

[1] D. C. Clary, Science **314**, 265 (2006).
[2] M. Aschi, R. Spezia, A. Di Nola, and A. Amadei, Chem. Phys. Lett. **344**, 374 (2001).
[3] R. Spezia, M. Aschi, A. Di Nola, and A. Amadei, Chem. Phys. Lett. **365**, 450 (2002).
[4] H. Lin and D. G. Truhlar, Theor. Chem. Acc. **117**, 185 (2007).
[5] K. M. Merz, Jr., *Applications of QM/MM Methods to Biomacromolecules*, Encyclopedia of Computational Chemistry Vol. 4, edited by K. M. Merz, Jr. (John Wiley & Sons, Ltd., Chichester, 1998), pp. 2330–2343.
[6] R. Rivelino, B. J. Costa Cabral, and K. Coutinho, Chem. Phys. Lett. **407**, 13 (2005).
[7] G. Brancato, N. Rega, and V. Barone, Chem. Phys. Lett. **453**, 202 (2008).
[8] S. Komin, C. Gossens, I. Tavernelli, U. Rothlisberger, and D. Sebastiani, J. Phys. Chem. B **111**, 5225 (2007).
[9] R. Spezia, M. Aschi, A. Di Nola, M. Di Valentin, D. Carbonera, and A. Amadei, Biophys. J. **84**, 2805 (2003).
[10] M. Aschi, C. Zazza, R. Spezia, C. Bossa, A. Di Nola, M. Paci, and A. Amadei, J. Comput. Chem. **25**, 974 (2004).
[11] M. D'Alessandro, M. Aschi, M. Paci, A. Di Nola, and A. Amadei, J. Phys. Chem. B **108**, 16255 (2004).
[12] A. Amadei, M. D'Alessandro, M. Paci, A. Di Nola, and M. Aschi, J. Phys. Chem. B **110**, 7538 (2006).
[13] A. Amadei, M. D'Abramo, I. Daidone, M. D'Alessandro, A. Di Nola, and M. Aschi, Theor. Chem. Acc. **117**, 637 (2007).
[14] M. Anselmi, M. Aschi, A. Di Nola, and A. Amadei, Biophys. J. **92**, 3442 (2007).
[15] A. Amadei, M. D'Abramo, C. Zazza, and M. Aschi, Chem. Phys. Lett. **381**, 187 (2003).
[16] M. Aschi, M. D'Abramo, C. Di Teodoro, A. Di Nola, and A. Amadei, ChemPhysChem **6**, 53 (2005).
[17] A. Amadei, F. Marinelli, M. D'Abramo, M. D'Alessandro, M. Anselmi, A. Di Nola, and M. Aschi, J. Chem. Phys. **122**, 124506 (2005).
[18] M. Aschi, M. D'Abramo, F. Ramondo, I. Daidone, M. D'Alessandro, A. Di Nola, and A. Amadei, J. Phys. Org. Chem. **19**, 518 (2006).
[19] M. D'Abramo, A. Di Nola, M. Aschi, and A. Amadei, J. Chem. Phys. **128**, 021103 (2008).
[20] C. Zazza, A. Amadei, N. Sanna, A. Grandi, G. Chillemi, A. Di Nola, and M. Aschi, Phys. Chem. Chem. Phys. **8**, 1385 (2006).
[21] A. Amadei, M. D'Alessandro, and M. Aschi, J. Phys. Chem. B **108**, 16250 (2004).
[22] With electronic Hamiltonian we mean, as usual, the total electronic energy operator including the nuclear-nuclear interactions.
[23] A. J. Stone, *The Theory of Intermolecular Forces* (Clarendon, Oxford, 2002).
[24] J. N. Harvey, J. O. Jung, and R. B. Gerber, J. Chem. Phys. **109**, 8747 (1998).
[25] G. Avila, G. J. Kroes, and M. C. van Hemert, J. Chem. Phys. **128**, 144313 (2008).
[26] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans, *Intermolecular Forces*, edited by B. Pullmann (Reidel, Dordrecht, 1981), pp. 331–342.
[27] W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. **79**, 926 (1983).
[28] D. van der Spoel, R. van Drunen, and H. J. C. Berendsen, Groningen machine for chemical simulations, Department of Biophysical Chemistry, BIOSON Research Institute, Nijenborgh 4 NL-9717 AG Groningen, 1994 (e-mail to gromacs@chem.rug.nl).
[29] D. J. Evans and P. T. Cummings, Mol. Phys. **72**, 893 (1991).
[30] A. Amadei, G. Chillemi, M. A. Ceruso, A. Grottesi, and A. Di Nola, J. Chem. Phys. **112**, 9 (2000).
[31] T. A. Darden, D. M. York, and L. G. Pedersen, J. Chem. Phys. **98**, 10089 (1993).