

Simple minimum principle to derive a quantum-mechanical/molecular-mechanical method

Koji Yasuda^{a)} and Daisuke Yamaki

Graduate School of Information Science, Nagoya University, Chikusa-ku, Nagoya 464-8601, Japan

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We propose a minimum principle to derive a QM/MM (quantum-mechanical/molecular-mechanical) method from the first principle. We approximate the Hamiltonian of a spectator substituent as the structure-dependent effective Hamiltonian in a least-squares sense. This effective Hamiltonian is expanded with the orthogonal operator set called the normal-ordered product. We determine the structure-dependent energy that corresponds to the classical MM energy and the extra one-electron potential that takes account of the interface effects. This QM/MM method is free from the double-counting problem and the artificial truncation of the localized molecular orbitals. As a numerical example we determine the one-electron effective Hamiltonian of the methyl group. This effective Hamiltonian is applied to the ethane and $\text{CH}_3\text{CH}_2\text{X}$ molecules ($\text{X}=\text{CH}_3, \text{NH}_2, \text{OH}, \text{F}, \text{COOH}, \text{NH}_3^+, \text{OH}_2^+, \text{and } \text{COO}^-$). It reproduced the relative energies, potential energy curves, and the Mulliken populations of the all-electron calculations fairly well. © 2004 American Institute of Physics. [DOI: 10.1063/1.1772354]

I. INTRODUCTION

Despite the steady progress of the electronic structure theory and the rapid increase of the available computer resources the theoretical investigation of macromolecules, for example the enzyme reaction, may be still formidable today even by the fastest computer. Typical enzymes are large proteins whose active sites often have the transition metals of various oxidation states. The determination of the total energies, the stable structures, and the free energies by the molecular dynamic (MD) simulations are often required, but no single theoretical method can do all of them. Molecular mechanics (MM) and the semiempirical methods are suitable for MD simulation because of their low computational costs, but they are hard to apply to general chemical species and spin states, as well as the transition states of chemical reactions. The *ab initio* methods are systematically improvable and the high-level methods that take account of the electron correlations describe the reaction energies very accurately, but owing to the heavy computational demands the long-time MD simulation is hopeless even by the linear scaling method, in which the net computational cost is proportional to the system size.

It is common knowledge that only a limited number of electrons in an enzyme actually take part in the chemical reaction; others just stay as spectators. Hence it is natural to divide the whole enzyme into the active and the inactive parts, to assume the transferability of the chemical properties of the inactive part, and to apply the expensive *ab initio* method to the active part alone. Such active-inactive separation has a long history, and the most successful example is the effective core potential (ECP).¹⁻⁵ Recently this topic attracts renewed attention as the hybrid method, called the

QM/MM (quantum-mechanical/molecular-mechanical) method.⁶⁻¹⁶ This is the only practical method at present to investigate the enzyme reaction. It treats the active site by the *ab initio* method while the rest large inactive part by the MM method. QM/MM method was successfully applied to the intermolecular interactions. However when applying it to an enzyme reaction it still has a problem for the consistent treatment of the interface between the quantum and the classical subsystems. The typical example is the double-counting of the energy.

One of the reasons is that there are no satisfactory theory of the QM/MM method. Some QM/MM methods were derived with the assumption that the total wave function is the product of the active and the inactive wave functions (separable ansatz¹). It is useless for the interface problem because it implies no interactions between the active and the inactive parts. Other QM/MM methods were derived empirically as the practical models for the real systems, and are difficult to improve systematically. What we really need is the simple assumption based on the firm ground of the many-electron theory, which automatically leads us to a QM/MM method. In this paper we propose such a minimum principle. We will determine the effective Hamiltonian that approximates the *ab initio* Hamiltonian in a least-squares sense, under the condition that it contains no electronic operators of the spectator substituents. The organization of this paper is as follows. In Sec. II we will summarize the famous QM/MM methods and point out their problems. In Sec. III based on the minimum principle we will derive the QM/MM method theoretically. In Sec. IV some numerical results will be presented.

II. COMPARISON OF THE QM/MM METHODS

In this section we summarize some famous QM/MM methods and point out some of their problems. Most theoret-

^{a)}Electronic mail: yasudak@info.human.nagoya-u.ac.jp

ical analyses on the QM/MM method are based on the separable ansatz by McWeeny and Kleiner, and Huzinaga and Cantu.¹

$$\Psi_{\text{tot}} = A(\Psi_A \Psi_I). \quad (1)$$

Total wave-function Ψ_{tot} is assumed to be the antisymmetrized product of the wave functions of the active (A) and the inactive (I) parts. Strictly speaking no subsystem can be described by the wave function. Rather it is described by the statistical (or the density) operator.¹⁷ Transferrability implies that the active part has little influence on the inactive wave function Ψ_I . This ansatz is too strong to investigate the interface problem, because it holds only when there is no interaction between the active and the inactive subsystems. The separable ansatz is less useful for the intramolecular separation, where the intersystem interaction is stronger, than in the core-valence and the intermolecular separations.

Usually the inactive wave-function Ψ_I is assumed to be a Slater determinant of the frozen orbitals. These orbitals add the following three contributions to the Hamiltonian of the active part: (i) frozen orbital energy; (ii) Coulomb and exchange potential from the inactive electrons; and (iii) the auxiliary potential to prevent the collapse of the active electrons to the frozen orbitals. They are the same as the usual ECPs, except for the following differences: (i) Frozen orbital energy and the Coulomb and exchange potential depend on the structure. When we replace some part of them with the classical MM energy and the classical electrostatic interactions, it is difficult to avoid the so-called double-counting problem; (ii) since the Coulomb and exchange potential is not spherical, the fitting to some simple one-electron potential is more difficult; and (iii) the active and the inactive localized molecular orbitals (LMOs) have overlap regions in space to maintain the orthogonality (the orthogonalization tail). We should truncate these tails to make the basis functions compact.

One of the famous QM/MM methods is the local self-consistent field (LSCF).⁶⁻⁹ This method faithfully realizes the separable ansatz. LSCF transfers the frozen orbitals representing the spectator substituents from some simple model. The orthogonalization tails of the frozen orbitals are simply truncated. Contributions to the energy and the Fock operator from the neighbors are evaluated exactly with these frozen orbitals. Active orbitals in the quantum subsystem are explicitly orthogonalized to the frozen orbitals. The quantum and the classical subsystems are connected with the localized σ -bond, which is determined with a certain model. The prime difficulty of LSCF is the charge neutrality. In Fig. 1(b), three localized C–C bonds in the real system are replaced with three model LMOs, in which six electrons occupy. In order to ensure the charge neutrality we must distribute +3 positive charges, but separable ansatz itself provides no recipe. Other shortcomings of LSCF are that (i) it needs additional two-electron integrals for inactive parts, (ii) the truncation of LMO is not elegant, and (iii) the structure optimization needs a complicated program.

Another famous QM/MM method, the link atom method,¹⁰ first cut a σ -bond to make a molecule into two fragments. The free valency on the first fragment is capped

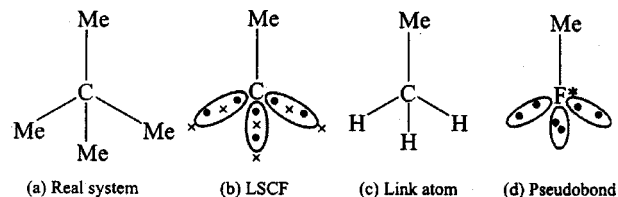


FIG. 1. Comparison of the quantum subsystems in the various QM/MM methods. Me denotes CH_3 group. LSCF method replaces three localized C–C σ -bonding orbitals with the predetermined localized MOs. In order to satisfy charge neutrality usually +0.5 positive charges are placed at the three carbon atoms and at the bond centers (cross positions). Pseudobond method replaces the central carbon atom with the modified fluorine atom.

with hydrogen atoms and this model system is treated by the *ab initio* method, while the rest substituents are treated by the MM method [Fig. 1(c)]. The ground-state wave function at the most stable structure is given by minimizing the expectation value of the QM/MM Hamiltonian

$$H = H_{\text{QM}} + H_{\text{MM}} + H_{\text{QM/MM}}. \quad (2)$$

H_{QM} is the *ab initio* Hamiltonian or usually the Fock operator of the model molecule while H_{MM} is the MM energy of the rest substituents. QM/MM interaction $H_{\text{QM/MM}}$ consists of the electrostatic and the van der Waals interactions between QM and MM atoms, and the bond energy term between QM and MM atoms. Sometimes this simple link atom method is as accurate as more elaborated LSCF method.

This link atom method has the following problems: (i) It is not evident how to determine the position of the extra link atom. Usually the position is either optimized to give the minimum energy or the bond length of the link atom is assumed to be a simple linear function of the bond length replaced; (ii) the interaction between the link atoms and MM atoms; at first sight link atoms should not interact with MM atoms, because they do not exist in the real molecule. Such artificial interaction may be unusually large, because the link atom is often very close to the MM atom. However previous research by Reuter *et al.*¹¹ showed that the neglect of this interaction leads to the unusual bond polarization, because electrons feel very different electrostatic potential on the link atom and the QM atom; and (iii) double counting issue; it is not evident that this method counts the energy of the QM-MM bond once and only once, because we can describe it by either the QM or MM method. It implies that the true QM/MM Hamiltonian should be much more complicated than those used today.

In order to avoid the position problem of the link atom, free valency is sometimes capped with the pseudohalogen, that has the similar electronic effects as the carbon atom. In the pseudobond method by Zhang, Lee, and Yang¹² fluorine atom is modified with ECP to give the similar potential surface and the charge distribution to the saturated carbon atom [Fig. 1(d)]. Their simple ECP works well except for the following shortcomings. The shape of the lone pair does not necessary resemble the real LMO. In particular the direction of the lone pair does not necessary follow the bond replaced. Also it introduces the same number of the extra electrons as the methyl group.

Dilabio, Hurley, and Christiansen reported the practically important attempt¹³ to make a one-electron pseudoatom for sp^3 carbon atom, called the quantum capping potential (QCP). They successfully reproduced the relative energies for the structure change of the quantum subsystems. However QCP became less accurate as the structure of the interface changes, because the exchange repulsion was not accurately reproduced. Another important generalization is the effective group potential (EGP) by Poteau *et al.*,¹⁴ which places ECPs on many centers. This additional flexibility enables us to express the exchange repulsion efficiently. To determine these ECPs they minimized the error of the Fock operator in the least-squares sense, as proposed in Ref. 18. They successfully replaced the SiH_3 group with one-electron EGP. Unfortunately their procedure to determine EGP is specific for the mean-field approximation and rather complicated. Additional elaboration is necessary to connect seamlessly their potential to the usual MM energy.

III. LEAST-SQUARES APPROXIMATION OF THE HAMILTONIAN

In this section we propose a minimum principle to derive a QM/MM method theoretically. Assuming that the basis functions (atomic orbitals, AOs) are on the nuclei as usual, we divide the nuclei and the basis functions as the quantum (Q), classical (C), and the interface (I) subsystems. We require that the QM/MM effective Hamiltonian H' has the following properties: (i) The classical subsystem has no basis functions, while it may have some one-electron potentials like point charges and ECPs and (ii) it should be transferable; the same effective Hamiltonian representing a some classical subsystem can be used with various quantum subsystems. Thus the transferable part of the QM/MM Hamiltonian $H'_{\text{I+C}}$ should be derived from the classical and the interface part of the *ab initio* Hamiltonian $H_{\text{I+C}}$ (these subsystems are abbreviated to I+C). Under these assumptions we search for the best hermitian effective Hamiltonian H' which approximates the *ab initio* Hamiltonian H by minimizing the error L .

$$L = \langle \Psi | (H - H')^2 | \Psi \rangle \quad (3a)$$

$$= \langle \Psi | (H_{\text{I+C}} - H'_{\text{I+C}})^2 | \Psi \rangle \quad (3b)$$

$|\Psi\rangle$ is an exact (or an approximate) wave function of either H or H' . When L reaches the minimum of zero the equality $H|\Psi\rangle = H'|\Psi\rangle$ holds, because L is the square-norm of the vector $(H - H')|\Psi\rangle$. Now suppose that $|\Psi\rangle$ is an exact wave function of H with energy E . Then H' shares this eigenvalue and the wave function with H , and hence we can use the effective Hamiltonian H' instead of the real *ab initio* Hamiltonian for this state. Thus we have the theorem.

Theorem 1: If $\langle \Psi | (H - H')^2 | \Psi \rangle = 0$ and $H|\Psi\rangle = E|\Psi\rangle$, then $H'|\Psi\rangle = E|\Psi\rangle$. Note that this theorem holds even for each excited state.¹⁹ Strictly speaking the minimums of the Eqs. (3a) and (3b) may differ, because of the interaction between the quantum and the classical subsystems and the incomplete transferability. Such difference of course decreases as we choose larger interface.

Usual QM/MM methods replace the Hamiltonian of the classical subsystem with the MM Hamiltonian, that is the

ground-state potential energy function. Similarly we choose an arbitrary additive constant of the effective Hamiltonian as a function of the nuclear coordinates of the classical and the interface subsystems. The electronic effects of the interface are expressed by the additional hermitian operator $\sum_i r_i u_i$. The linear parameters r_i , such as the one-electron AO integrals or the ECP coefficients as well as the additive energy constant, are determined by minimizing the error L .

For later use we introduce the orthonormal orbital $\varphi_i(r)$ of the subsystem I+C. We used the natural orbitals (NOs), the eigenfunctions of the first-order reduced density matrix (1-RDM)²⁰ of this subsystem. This partial 1-RDM γ in AO basis is just the submatrix of the whole 1-RDM γ_{total} in AO basis.

$$\gamma_{\text{total}}(r', r) = \sum_{kl}^{\text{Q+I+C}} \gamma_l^k \chi_k(r) \chi_l(r'), \quad (4a)$$

$$\gamma(r', r) = \sum_{kl}^{\text{I+C}} \gamma_l^k \chi_k(r) \chi_l(r'). \quad (4b)$$

$\chi_k(r)$ is the k -th AO. The sums in Eqs. (4a) and (4b) run over all the AOs and the AOs on the classical and the interface subsystems, respectively. Partial n -RDM of the subsystem I+C can be defined similarly. The eigenfunction of Eq. (4b) is

$$\varphi_i(r) = \sum_k^{\text{I+C}} C_k^{(i)} \chi_k(r), \quad (5)$$

where $C_k^{(i)}$ is the AO coefficient of the i -th NO. We denote the corresponding eigenvalue n_i . The natural spin orbital, which is the direct product of $\varphi_i(r)$ and the spin function, defines the creation operator $a_{i\sigma}^\dagger$. We define the following creation and the displacement operators as usual:

$$\chi_{k\sigma}^\dagger = \sum_i C_k^{(i)} a_{i\sigma}^\dagger,$$

$$a_j^i = \sum_\sigma a_{i\sigma}^\dagger a_{j\sigma},$$

$$a_{kl}^{ij} = \sum_{\sigma\tau} a_{i\sigma}^\dagger a_{j\tau}^\dagger a_{l\tau} a_{k\sigma},$$

$$\chi_j^i = \sum_\sigma \chi_{i\sigma}^\dagger \chi_{j\sigma},$$

$$\chi_{kl}^{ij} = \sum_{\sigma\tau} \chi_{i\sigma}^\dagger \chi_{j\tau}^\dagger \chi_{l\tau} \chi_{k\sigma}.$$

The Hamiltonian of the fragment I+C is given as

$$H_{\text{I+C}} = \sum_{ij}^{\text{I+C}} v_j^i \chi_j^i + \frac{1}{2} \sum_{ijkl}^{\text{I+C}} w_{kl}^{ij} \chi_{kl}^{ij} + E_{\text{nuc}}, \quad (6)$$

where v , w , and E_{nuc} are the one-, and two-electron AO integrals, and the nuclear repulsion energy of the subsystem I+C, respectively.

A. Normal ordered products

The error of Eq. (3b) can be written compactly with the inner product of operators defined as

$$(A|B) = \langle \Psi | A^\dagger B | \Psi \rangle, \quad (7)$$

$$L = (H_{I+C} - H'_{I+C} | H_{I+C} - H'_{I+C}).$$

The inner product of operators is the expectation value of the operator product, and the inner product with the constant 1 is the expectation value of the operator itself. We expand the effective Hamiltonian with the orthogonal operators, called the generalized normal-ordered product (N -product) of Kutzelnigg and Mukherjee.²¹

$$N(a_j^i) = a_j^i - \langle a_j^i \rangle, \quad (8a)$$

$$N(a_{kl}^{ij}) = a_{kl}^{ij} - \langle a_k^i \rangle a_l^j - \langle a_l^j \rangle a_k^i + \frac{1}{2} \langle a_l^i \rangle a_k^j + \frac{1}{2} \langle a_k^j \rangle a_l^i + \langle a_k^i \rangle \langle a_l^j \rangle - \frac{1}{2} \langle a_l^i \rangle \langle a_k^j \rangle. \quad (8b)$$

Expectation value is calculated with Ψ , $\langle A \rangle = \langle \Psi | A | \Psi \rangle$. Usually the N -product is defined so that the expectation value with respect to a Slater determinant is zero. Kutzelnigg and Mukherjee extended it so that we can take any wave functions as vacuum. The structure of this N -product is the direct consequence of the cumulant expansion of RDMs.²²

When the total wave function is a Slater determinant, the effective Hamiltonian becomes very simple. The story is the same when the total wave function is the product of the complicated function $|\Psi_Q\rangle$ of the quantum subsystem and a Slater determinant $|\Psi\rangle$, because the function $|\Psi_Q\rangle$ has no effects on the partial RDMs of the subsystem I+C. Thus it covers most of the important chemical situations, including bond breaking processes within the quantum subsystem. Note we do not have to assume that LMOs of the subsystem I+C can be expanded with AOs on the same subsystem alone. Because of the orthogonalization tail it is generally impossible to expand LMOs of the active (inactive) subsystem with AOs on the same subsystem alone. It is one of the problems in the separable wave-function approach. On the other hand in our approach AOs are used to define each subsystem and the truncation of the orthogonalization tail is avoided by the least-squares error minimization. The price to pay is that our subsystem has no good wave function as Ψ_I in Eq. (1) and we have to use the statistical operator to describe the electronic state.

Under our assumption the partial n -RDM of the subsystem I+C is the antisymmetrized product of the partial 1-RDM, for example the partial 2- and 3-RDMs become

$$\Gamma_{kl}^{(2)ij} = \frac{1}{2} \gamma_k^i \gamma_l^j - \frac{1}{4} \gamma_l^i \gamma_k^j, \quad (9a)$$

$$\Gamma_{lmn}^{(3)ijk} = \frac{1}{6} \gamma_l^i \gamma_m^j \gamma_n^k - \frac{1}{12} (\gamma_l^i \gamma_m^j \gamma_n^k + \gamma_l^j \gamma_m^i \gamma_n^k + \gamma_l^i \gamma_m^k \gamma_n^j + \gamma_l^j \gamma_m^k \gamma_n^i) + \frac{1}{24} (\gamma_l^i \gamma_m^k \gamma_n^j + \gamma_l^j \gamma_m^i \gamma_n^k). \quad (9b)$$

This is because that the total n -RDM also satisfies the same hierarchy²⁰ and that the partial n -RDM is the submatrix of the total n -RDM. Eqs. (9) hold not only for RDMs of a Slater determinant but also for RDMs of a noninteracting, finite-temperature canonical ensemble. By using Eqs. (9) any

inner product of operators can be written with 1-RDM, because it is the expectation value of the operator product. It is also straightforward (but tedious) to show that the inner products between these N -products are

$$(1|N(a_j^i)) = (1|N(a_{kl}^{ij})) = (N(a_n^m)|N(a_{kl}^{ij})) = 0, \quad (10a)$$

$$(N(a_j^i)|N(a_{j'}^{i'})) = \frac{1}{2} n_j (2 - n_i) \delta_{jj'} \delta_{ii'}, \quad (10b)$$

$$\begin{aligned} (N(a_{kl}^{ij})|N(a_{k'l'}^{i'j'})) \\ = \frac{1}{8} n_k n_l (2 - n_i) (2 - n_j) (2 \delta_{ii'} \delta_{jj'} \delta_{kk'} \delta_{ll'} \\ + 2 \delta_{ij'} \delta_{j'i'} \delta_{kl'} \delta_{l'k'} - \delta_{ii'} \delta_{j'j'} \delta_{kl'} \delta_{l'k'} \\ - \delta_{ij'} \delta_{j'i'} \delta_{kk'} \delta_{ll'}). \end{aligned} \quad (10c)$$

Because of the hierarchy Eqs. (9) the expectation values of the N -products are zero and the N -products of different ranks are orthogonal to each other. The reader can verify them easily when φ_i coincide with the Hartree-Fock orbitals of Ψ . The important fact is that the N -product has a simple properties Eqs. (10) even if we define the creation and the annihilation operators with the natural orbitals of the subsystem. Note that since the natural orbital of the subsystem differs from the Hartree-Fock orbital n_i satisfies the inequality $0 < n_i < 2$. When we assume that LMOs of the subsystem I+C can be expanded with AOs on the same subsystem n_i become either 0 or 1, and hence our procedure is evidently an extension of the separable ansatz. This new property is the key ingredient of the present QM/MM method.

B. Local self-consistent field

In this section we derive the local SCF⁶⁻⁹ with our minimization principle. We decompose the *ab initio* Hamiltonian of the isolated fragment I+C as the sum of the N -products.

$$H_{I+C} = H_0 + H_1 + H_2, \quad (11a)$$

$$H_0 = \sum_{ij}^{I+C} v_j^i \langle \chi_j^i \rangle + \frac{1}{2} \sum_{ijkl}^{I+C} w_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle + E_{\text{nuc}}, \quad (11b)$$

$$H_1 = \sum_{ij}^{I+C} f_j^i N(\chi_j^i), \quad (11c)$$

$$H_2 = \frac{1}{2} \sum_{ijkl}^{I+C} w_{kl}^{ij} N(\chi_{kl}^{ij}), \quad (11d)$$

$$f_j^i = v_j^i + \sum_{kl}^{I+C} \left(w_{jl}^{ik} - \frac{1}{2} w_{ji}^{kl} \right) \langle \chi_{kl}^i \rangle.$$

E_{nuc} is the nuclear repulsion energy of the subsystem I+C. The generalized Fock operator f appears as the result of the N -product decomposition. Similarly we decompose the effective Hamiltonian H'_{I+C} as

$$H'_{I+C} = H'_0 + H'_1 + H'_2, \quad (12a)$$

$$H'_0 = \sum_{ij}^I \tilde{f}_j^i \langle \chi_j^i \rangle - \frac{1}{2} \sum_{ijkl}^I \tilde{w}_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle + E'_{\text{nuc}} + E_{\text{bond}}, \quad (12b)$$

$$H'_1 = \sum_{ij}^I \tilde{f}_j^i N(\chi_j^i), \quad (12c)$$

$$H'_2 = \frac{1}{2} \sum_{ijkl}^I \tilde{w}_{kl}^{ij} N(\chi_{kl}^{ij}). \quad (12d)$$

E'_{nuc} and E_{bond} are the nuclear and the point charge repulsion energy and an unknown function of the nuclear coordinates of the subsystem I+C, respectively. Because of the orthogonality of the N -product the error becomes $L = \sum_{i=0}^2 \langle \Psi | (H'_i - H_i)^2 | \Psi \rangle$ and we can search for the zero-, one- and two-electron parts of the effective Hamiltonian separately. The best parameter E_{bond} is the solution of $H'_0 = H_0$.

$$E_{\text{bond}} = E_{\text{nuc}} - E'_{\text{nuc}} - \sum_{ij}^I \tilde{f}_j^i \langle \chi_j^i \rangle + \sum_{ij}^{\text{I+C}} f_j^i \langle \chi_j^i \rangle + \frac{1}{2} \sum_{ijkl}^I \tilde{w}_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle - \frac{1}{2} \sum_{ijkl}^{\text{I+C}} w_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle. \quad (13)$$

The AO integrals of the effective Fock operator \tilde{f} that minimize the error $\langle \Psi | (H'_1 - H_1)^2 | \Psi \rangle$ are the solution of the system of linear equations.

$$\sum_{ij}^I (N(\chi_j^{i'}) | N(\chi_j^i)) \tilde{f}_j^i = \sum_{ij}^{\text{I+C}} (N(\chi_j^{i'}) | N(\chi_j^i)) f_j^i. \quad (14)$$

Indices i and j run over AOs on the subsystem I+C in the right-hand side, while in the left-hand side they run only over AOs on the interface. The equation for the effective two-electron integrals is given similarly.

These equations reproduce the LSCF (or the equivalent method) if we keep the localized σ -bonds called the frozen orbitals as the only AOs in the subsystem I+C. Our derivation is superior to the previous one in the following aspects: (i) We can also determine the best neutralizing positive charges by the error minimization; (ii) LSCF was derived from the separable ansatz while in the present approach such strong assumption was used at the very end of the derivation. Orbitals play lesser role and the extension of LSCF is easier to the correlated wave function or to the systems inherently delocalized in nature such as π electrons; (iii) MM energy expression naturally appears in the effective H' and we can avoid the empirical adjustment of the MM parameters;⁹ (iv) we can also avoid the double counting of the energy automatically by the orthogonal N -product decomposition and the least square procedure; and (v) truncation of LMO tail is not necessary.

C. ECP expansion of the effective Hamiltonian

Practically it is convenient to express the extra potential in the effective H' that takes account of the interface effects with some simple operators, like the point charges and ECPs. In this section we determine the best ECP as well as the best MM energy expression by the error minimization of the effective H' . Similarly to the previous section we decompose the effective H' in each rank of the N -product.

$$H'_{\text{I+C}} = H'_0 + H'_1 + H'_2, \quad (15a)$$

$$H'_0 = \langle f' \rangle + \sum_i r_i \langle u_i \rangle - \frac{1}{2} \sum_{ijkl}^I w_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle + E'_{\text{nuc}} + E_{\text{bond}}, \quad (15b)$$

$$H'_1 = N \left(f' + \sum_i r_i u_i \right), \quad (15c)$$

$$H'_2 = \frac{1}{2} \sum_{ijkl}^I w_{kl}^{ij} N(\chi_{kl}^{ij}). \quad (15d)$$

For simplicity we assume that the effective two-electron AO integrals are the same as the usual *ab initio* ones. The extra part of H'_1 is expanded with potentials u_i . The effective Fock operator f' consists of the kinetic energy, the electrostatic potential from the atoms in the classical subsystem, the attraction from the nuclei on the interface, and the Coulomb and exchange potential from the interface

$$\sum_{kl}^I \left(w_{jl}^{ik} - \frac{1}{2} w_{jl}^{ki} \right) \langle \chi_{kl}^i \rangle. \quad (16)$$

The error of H'_1 is

$$\begin{aligned} \langle \Psi | (H'_1 - H_1)^2 | \Psi \rangle &= \sum_{ij} r_i r_j (N(u_i) | N(u_j)) \\ &+ 2 \sum_i r_i (N(\delta f) | N(u_i)) \\ &+ (N(\delta f) | N(\delta f)), \end{aligned} \quad (17)$$

$$\delta f = f' - f.$$

The best parameters r_i that minimize Eq. (17) are the solution of the following system of linear equations:

$$\sum_j (N(u_i) | N(u_j)) r_j = -(N(\delta f) | N(u_i)). \quad (18)$$

Since these equations depend on the molecular geometry, we have different systems of linear equations for each geometry. Assuming that r_i is independent of the structure, this overdetermined system of linear equations is solved by the singular value decomposition method. The best parameter E_{bond} is the solution of $H'_0 = H_0$.

$$\begin{aligned} E_{\text{bond}} &= E_{\text{nuc}} - E'_{\text{nuc}} + \langle f - f' \rangle + \frac{1}{2} \sum_{ijkl}^I w_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle \\ &- \frac{1}{2} \sum_{ijkl}^{\text{I+C}} w_{kl}^{ij} \langle \chi_{kl}^{ij} \rangle - \sum_i r_i \langle u_i \rangle. \end{aligned} \quad (19)$$

We later express E_{bond} as a simple analytical function of the nuclear coordinates of the subsystem I+C like MM energy.

One notices that this method is a generalization and the rigorous formulation of the pseudobond and the EGP methods. In the previous section we reproduced LSCF. Thus our minimum principle unifies the pseudobond, EGP, and LSCF. The important advantage of the present derivation is the transparent formulation; both ECP and MM energy are determined simultaneously by minimizing the error of the ef-

fective Hamiltonian. The convergence to the exact ground-state wave function is ensured by Theorem 1. Selection of the best parameter is much simpler than that in the pseudobond or the EGP method. The former needs some trial and error to minimize the nonlinear objective function. Moreover this objective function is somewhat arbitrary. The EGP method is closely tied to the independent-particle model and it involves the complicated multistep procedure. On the other hand our method tries to approximate the Hamiltonian itself, and the parameters are the solution of the well-defined, simple linear equation.

D. Elimination of inert electrons

It is sometimes necessary to eliminate the inert electrons explicitly that occupy the distant LMOs from the quantum subsystem. We eliminate these LMOs by the particle-hole transformation, a generalization of the shift operator technique¹ for LMOs. The next theorem gives the basis of this elimination.

Theorem 2: If $|\Phi\rangle = \prod_{k=1}^N \prod_{\sigma} a_{k\sigma}^{\dagger} |0\rangle$ is the ground-state Hartree–Fock solution of the two-body Hamiltonian $H(E_{\text{nuc}}, v, w)$,

$$H(E_{\text{nuc}}, v, w) = \sum_{ij} v_j^i a_j^i + \frac{1}{2} \sum_{ijkl} w_{kl}^{ij} a_{kl}^{ij} + E_{\text{nuc}}, \quad (20)$$

the wave function $|\tilde{\Phi}\rangle = \prod_{k=1}^M \prod_{\sigma} a_{k\sigma}^{\dagger} |0\rangle$ becomes the ground-state Hartree–Fock solution of another two-body Hamiltonian $\tilde{H} = H(\tilde{E}_{\text{nuc}}, \tilde{v}, \tilde{w})$ with the same energy, where $M < N$ and

$$\tilde{E}_{\text{nuc}} = E_{\text{nuc}} + 2 \sum_{k=M+1}^N v_k^k + \sum_{k,l=M+1}^N (2w_{kl}^{kl} - w_{kl}^{lk}), \quad (21a)$$

$$\tilde{v}_j^i = \left\{ v_j^i + \sum_{k=M+1}^N (2w_{jk}^{ik} - w_{jk}^{ki}) \right\} s_j^i, \quad (21b)$$

$$\tilde{w}_{kl}^{ij} = s_k^i s_l^j \{ w_{kl}^{ij} |s_j^i| + w_{kj}^{il} (|s_j^i| - 1) \}. \quad (21c)$$

$$s_j^i = +1 \quad (1 \leq j, i \leq M),$$

$$= -1 \quad (M+1 \leq j, i \leq N),$$

$$= 0 \quad (\text{otherwise}).$$

Proof will be presented in Appendix A. This theorem states that two different Hamiltonians, H and \tilde{H} , share the same ground-state Hartree–Fock energy. In contrast to LSCF we do not have to impose the orthogonal constraints to the eliminated LMOs. All we have to do is to replace (E_{nuc}, v, w) with $(\tilde{E}_{\text{nuc}}, \tilde{v}, \tilde{w})$ in the Hamiltonian. When the eliminated orbitals are the canonical Hartree–Fock MOs, it reduces to Huzinaga's shift operator technique.¹ We can derive the effective Hamiltonian which approximates this transformed Hamiltonian.

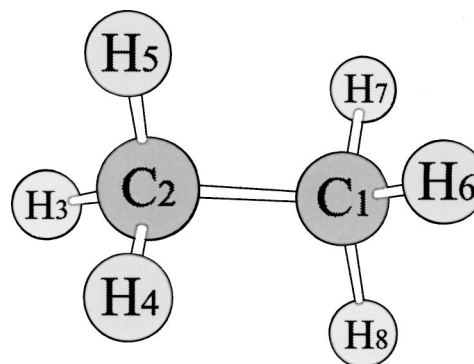


FIG. 2. Structure of ethane, showing the element numbering.

IV. NUMERICAL RESULTS

We applied this ECP expansion to ethane C_2H_6 to derive the one-electron effective Hamiltonian for methyl group; i.e., we tried to express the methyl group as a one-electron substituent. We assigned nuclei H_6 , H_7 , and H_8 as classical and other nuclei as interface (Fig. 2). STO3G basis functions²³ were used for C_1 , H_6 , H_7 , and H_8 , while 3-21G basis functions²³ were used for other atoms. We replaced $1s$ core electrons of C_1 with ECP in Ref. 13 and calculated the canonical Hartree–Fock orbitals. The occupied orbitals were localized with the Boys procedure. Three σ -bonding orbitals of $\text{C}_1 - \text{H}_\alpha$ ($\alpha = 6, 7, 8$) were eliminated with the particle-hole transformation to get the equivalent Hamiltonian and the Hartree–Fock wave function. We approximated this Hamiltonian without using the basis functions on H_6 , H_7 , and H_8 and by adding ECPs

$$U(r) = U_L(r) + \sum_{l=0}^{L-1} \sum_{m=-l}^l \{U_l(r) - U_L(r)\} |l, m\rangle \langle l, m|, \quad (22)$$

$$U_l(r) = r^{-2} \sum_i C_{li} r^{n_{li}} \exp(-\zeta_{li} r^2),$$

on C_1 and C_2 . $|l, m\rangle$ is the usual spherical harmonics. To determine the linear coefficients C_{li} in Eq. (22) a set of linear Eqs. (18) was solved by the singular value decomposition method for the selected structures. The same exponents n_{li} and ζ_{li} as Ref. 13 were used. We also calculated E_{bond} of Eq. (19). All the geometries were optimized with the restricted Hartree–Fock method and 6-31G** basis set. To make the whole molecule neutral the nuclear charges of C_1 and H_α ($\alpha = 6, 7, 8$) of the effective H' were changed to 1 and 0, respectively. Thus ethane becomes ten-electron system.

We also performed the link atom and the pseudobond calculations for comparison. In the link atom method bond length between the interface carbon and the capping hydrogen was rescaled by a factor of $0.711 = 1.091/1.536$, which is a typical ratio of C–C and C–H bond lengths, and STO3G basis set was used for this hydrogen. The 3-21G basis set was used for the pseudobond calculations. It contains the same number of the electrons as the real ethane.

TABLE I. Gaussian expansion of a one-electron effective potential for methyl group.

Atom	Type	n	ζ	QCP1 ^a	QCP4 ^a	Present
C ₁	p	1	8.14	-0.86	-0.86	5.7873
		1	1.29	-2.60	-3.56	-3.4766
		2	1.072	...	1064.0	-21.5476
		2	1.046	...	-2128.0	...
	$s-p$	2	1.02	...	1064.0	19.0217
		0	10.16	5.90	5.90	-0.1660
		1	2.56	-7.30	-7.30	-7.5724
C ₂	p	2	3.62	26.11	26.11	49.1188
		1	8.00	0.9129
	$s-p$	1	8.00	0.9163

^aReference 13.

Table I summarizes our ECP and QCPs by Dilabio *et al.*¹³ While QCP4 has large alternant coefficients to represent the Pauli repulsion, our ECP has rather small coefficients. Another important difference is that QCPs are spheri-

cally symmetric while our ECP is not, because the constant E_{bond} depends on the structure and both carbon atoms have potentials. We found that near the equilibrium geometry structure-dependence of E_{bond} is accurately expressed as

$$\begin{aligned}
 E'_{\text{nuc}} = & (17.5259 + 0.2332R_{C_1C_2})\exp(-3.0043R_{C_1C_2}) + \sum_{\alpha=6}^8 (-1.7589R_{C_1H_\alpha} + 0.7933R_{C_1H_\alpha}^2) \\
 & + 1.271 \times 10^{-2}(R_{C_2H_3} + R_{C_2H_4} + R_{C_2H_5}) - 2.275 \times 10^{-1}(\theta_{H_6C_1C_2} + \theta_{H_7C_1C_2} + \theta_{H_8C_1C_2}) \\
 & - 1.643 \times 10^{-1}(\theta_{H_6C_1H_7} + \theta_{H_7C_1H_8} + \theta_{H_8C_1H_6}) - 2.25 \times 10^{-2}(\theta_{H_3C_2C_1} + \theta_{H_4C_2C_1} + \theta_{H_5C_2C_1}) \\
 & - 1.09 \times 10^{-2}(\theta_{H_3C_2H_4} + \theta_{H_4C_2H_5} + \theta_{H_5C_2H_3}) + 2.51 \times 10^{-2} \cos(3\phi_{H_6C_1C_2H_3}) - 1.2664.
 \end{aligned} \quad (23)$$

Energy, bond lengths, and angles are in atomic units, angstrom, and radian, respectively. ECP parameters in Table I and Eq. (23) constitute our final effective Hamiltonian of methyl group.

Table II compares the minimum positions and the second derivatives (curvatures) of the potential energy curves of ethane calculated with these ECPs. As shown in this table our effective Hamiltonian reproduced these structural param-

eters very well. It has no systematic deviation of the length R_{CC} observed in QCP1, and the angle θ_{CCH} observed in QCP4. Link atom and the pseudobond methods both successfully reproduced the stable structures, especially bond lengths. One reason of the structural agreement is that they were determined to reproduce the structure of ethane itself. On the other hand the curvature of the potential energy curve, which was not used as the training set, was not well

TABLE II. Errors of structural parameters and the Mulliken populations for ethane. Bond lengths and angles are in angstrom and degrees, respectively. R'' and θ'' indicate the errors in percentage of the second derivatives with respect to the bond lengths and angles, respectively. C₁, C₂(s), and C₂(p) indicate the negative of the net charges on the terminal methyl group, and s and p AO populations on carbon 2, respectively. Numbers in the square brackets indicate powers of ten.

	RHF	QCP1	QCP4	Link atom	Pseudobond	Present
Errors of the structural parameters						
$R_{C_1C_2}$	1.543	... ^a	0.137	0.002	0.016	-0.033
$R''_{C_1C_2}$	0.931	-46.50	-49.11	-27.38	39.19	-6.99
$R_{C_2H_6}$	1.084	8.83[-3]	1.15[-3]	-1.98[-3]	4.74[-3]	-3.00[-5]
$R''_{C_2H_6}$	4.096	-6.31	-1.40	1.69	-3.90	-0.87
$\theta_{C_1C_2H_6}$	110.864	1.801	-2.865	-1.123	1.191	-1.380
$\theta''_{C_1C_2H_6}$	2.996[-4]	-0.74	-26.98	-6.57	9.71	-5.68
Errors of the Mulliken populations						
C ₁	0	-0.20	0.02	-0.12	-0.01	0.16
C ₂ (s)	3.46	0.03	-0.03	-0.04	-0.03	-0.07
C ₂ (p)	3.14	0.12	-0.12	0.17	-0.10	-0.18

^aPredicted C-C bond length was shorter than 0.5 Å.

TABLE III. Errors of the relative energies and the Mulliken populations for $\text{CH}_3\text{CH}_2\text{X}$.

	RHF	QCP1	QCP4	Link atom	Pseudobond	Present
Errors of the relative energies with respect to ethane ($\times 10^{-3}$ a.u.)						
C_3H_8	-117.6128	4.03	3.21	2.89	-7.22	0.33
$\text{C}_2\text{H}_5\text{NH}_2$	-133.5008	5.71	2.45	6.06	-11.25	1.94
$\text{C}_2\text{H}_5\text{OH}$	-153.2203	6.69	0.46	9.66	-17.24	-0.83
$\text{C}_2\text{H}_5\text{F}$	-177.1073	4.68	-2.88	11.64	-16.81	-0.03
$\text{C}_2\text{H}_5\text{COOH}$	-265.3545	1.09	2.11	6.93	-5.71	0.20
$\text{C}_2\text{H}_5\text{NH}_3^+$	-133.8845	-9.66	-6.90	11.09	-14.58	-2.10
$\text{C}_2\text{H}_5\text{OH}_2^+$	-153.5487	-11.19	-10.07	15.60	-17.57	-0.64
$\text{C}_2\text{H}_5\text{COO}^-$	-264.7568	17.14	15.07	9.95	0.92	7.20
Errors of the Mulliken populations on C_2						
C_3H_8	6.44	0.12	-0.23	0.09	-0.18	-0.30
$\text{C}_2\text{H}_5\text{NH}_2$	6.22	0.13	-0.20	0.09	-0.15	-0.26
$\text{C}_2\text{H}_5\text{OH}$	6.07	0.13	-0.18	0.10	-0.10	-0.24
$\text{C}_2\text{H}_5\text{F}$	5.97	0.13	-0.16	0.10	-0.07	-0.22
$\text{C}_2\text{H}_5\text{COOH}$	6.56	0.10	-0.26	0.04	-0.22	-0.31
$\text{C}_2\text{H}_5\text{OH}_2^+$	6.18	0.12	-0.16	0.03	-0.10	-0.21
$\text{C}_2\text{H}_5\text{NH}_3^+$	6.29	0.12	-0.19	0.04	-0.14	-0.24
$\text{C}_2\text{H}_5\text{COO}^-$	6.55	0.12	-0.25	0.10	-0.20	-0.32

reproduced. Our effective Hamiltonian also reproduced these quantities rather well, because it was determined to reproduce the energy and the wave function, not some selected properties. Another interesting property is the rotational barrier around the C–C bond. Our effective Hamiltonian also reproduced this dihedral angle dependence within the error of 0.18 kcal/mol. Other QM/MM potentials alone are of course difficult to reproduce this barrier because they are spherically symmetric. In fact they sometimes stabilized cis isomer slightly because of the subtle structure difference. Thus other methods need some calibrated MM energy.

Table II also compares the Mulliken populations. C_1 , $C_2(s)$, and $C_2(p)$ in this table indicate the negative of the net charges on the terminal methyl group, and s and p AO populations on carbon 2, respectively. As shown in this table, QCP1, link atom, and our methods show larger deviations of the Mulliken charges than the QCP4 and the pseudobond methods. Pseudocarbon (C_1) has extra 0.16 electrons and C_2 atom seems to be less electronegative in our effective Hamiltonian. The best Mulliken populations were obtained by the pseudobond method. The errors of the populations on other atoms were smaller and all the methods reproduced them accurately. It is interesting to examine the Mulliken populations on C_1 in detail. Since the sp^3 hybrid orbitals form C–C σ -bond, an electron would occupy $C_1(s)$ and $C_1(p_z)$ 1/4 and 3/4 in average, respectively. The calculated results indicate that the valence electron mainly occupies $C_1(s)$ orbital in QCPs while it occupies $C_1(p_z)$ orbital in our effective Hamiltonian; the nature of the chemical bond is somewhat different.

In order to investigate the transferability of this effective Hamiltonian we substituted one terminal methyl group of $\text{CH}_3\text{CH}_2\text{X}$ molecules ($\text{X}=\text{CH}_3$, NH_2 , OH , F , COOH , NH_3^+ , OH_2^+ , and COO^-) with it and the Hartree–Fock results were compared with other methods. STO3G basis set²³ was used for the interface carbon atom and 3-21G basis set²³ for other atoms. The 3-21G basis set was used for the pseudobond calculation. For simplicity we assumed the same

local structure of C_2H_5 in $\text{CH}_3\text{CH}_2\text{X}$ molecules. The C–X bond lengths were rescaled by the factors determined from the experimental C–X and C–H bond lengths to give the corresponding C–H bond lengths in Eq. (23).

Table III compares the errors of the relative energies with respect to ethane. Our effective Hamiltonian reproduced the relative energies very accurately except for $\text{C}_2\text{H}_5\text{COO}^-$. Other methods showed larger energy deviations. Some energy errors of the link atom and the pseudobond methods are predictable; their errors tend to cancel for the small structural changes like $\text{OH}\rightarrow\text{OH}_2^+$ or $\text{NH}_2\rightarrow\text{NH}_3^+$. However larger structural changes introduce rather unpredictable errors. This table also compares the Mulliken populations on carbon 2. In this case the present effective Hamiltonian gave the worst populations; it always underestimated the number of electrons on C_2 by the amount of 1/4, as in ethane. Such constant deviations can be observed in other methods. The best populations were obtained by the link atom method.

V. CONCLUSIONS

QM/MM methods have a long-standing problem for the consistent treatment of the interface between the quantum and the classical subsystems, for example the double-counting of the energy. This is due to the empiricism of the previous QM/MM and the lack of theory that establishes the transparent connection with the *ab initio* method. In this paper we proposed a minimum principle and demonstrated how one can derive a QM/MM method from this principle.

In this approach we search for the structure-dependent effective Hamiltonian that approximates the *ab initio* Hamiltonian in a least-squares sense. By using the normal-ordered products we determined the structure-dependent energy that corresponds to the classical MM energy and the extra one-electron potential that takes account of the interface effects. This minimum principle reproduced some of the previous QM/MM methods, like the local SCF,⁶ pseudobond,¹² quantum capping potential,¹³ and the effective group potential.¹⁴

As a numerical example we determined the one-electron effective Hamiltonian for the methyl group. This effective Hamiltonian was applied to the ethane and $\text{CH}_3\text{CH}_2\text{X}$ molecules ($\text{X}=\text{CH}_3, \text{NH}_2, \text{OH}, \text{F}, \text{COOH}, \text{NH}_3^+, \text{OH}_2^+, \text{and COO}^-$). It reproduced the relative energies, potential energy curves, and the Mulliken populations fairly well.

This minimum principle established the transparent connection between the *ab initio* and the QM/MM Hamiltonians and enabled us to derive a QM/MM without the double-counting issue and the artificial truncation of the localized MOs. In addition it directs us to the following extensions. The interface for the semiempirical (SE) method can be derived similarly, because the major difference between the *ab initio* and the SE Hamiltonians is the specific form of the one- and two-electron integrals. We can also derive a more elaborate model in which the extra one-electron potential for the interface depends on the structure explicitly. The electron correlation effects of the interface can be considered by the perturbation theory, because the correlation effects on RDMs are well understood.^{22,24} It also provides the basis to go beyond the separable ansatz. Extension to the density functional theory²⁵ is almost trivial, because the Kohn-Sham Hamiltonian is just a one-electron operator.

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APPENDIX: PROOF OF THEOREM 2

Define two sets of creation and annihilation operators and vacuum states, $\{a_{i\sigma}^\dagger, a_{j\sigma}, |0\rangle\}$, $\{b_{i\sigma}^\dagger, b_{j\sigma}, |O\rangle\}$. It is clear that if $|\Phi\rangle = \prod_{k=1}^N \prod_{\sigma} a_{k\sigma}^\dagger |0\rangle$ is the Hartree-Fock solution of the Hamiltonian $H(a_{i\sigma}^\dagger, a_{j\sigma})$ where

$$H(a_{i\sigma}^\dagger, a_{j\sigma}) = \sum_{ij\sigma} v_{ij} a_{i\sigma}^\dagger a_{j\sigma} + \frac{1}{2} \sum_{ijkl\sigma\tau} w_{ijkl} a_{i\sigma}^\dagger a_{j\tau}^\dagger a_{l\tau} a_{k\sigma},$$

then $|\Phi'\rangle = \prod_{k=1}^N \prod_{\sigma} b_{k\sigma}^\dagger |O\rangle$ is the Hartree-Fock solution of the Hamiltonian $H(b_{i\sigma}^\dagger, b_{j\sigma})$ with the same energy. Now define $b_{j\sigma}$ as the following particle-hole transform of $a_{j\sigma}$:

$$\begin{aligned} b_{j\sigma} &= a_{j\sigma} \quad (1 \leq j \leq M) \\ &= a_{j\sigma}^\dagger \quad (M < j \leq N). \end{aligned}$$

The vacuum state and the Hartree-Fock solution then become

$$\begin{aligned} |O\rangle &= \prod_{k=M+1}^N \prod_{\sigma} a_{k\sigma}^\dagger |0\rangle, \\ |\Phi'\rangle &= \pm \prod_{k=1}^M \prod_{\sigma} a_{k\sigma}^\dagger |0\rangle. \end{aligned}$$

$|\Phi'\rangle$ is the eigenfunction of the number operator, $N_{\sigma} = \sum_k a_{k\sigma}^\dagger a_{k\sigma}$, while $H(b_{i\sigma}^\dagger, b_{j\sigma})$ does not commute with N_{σ} . Define another two-body Hamiltonian H' as the number conserving part of $H(b_{i\sigma}^\dagger, b_{j\sigma})$. Both Hamiltonians give the

same expectation values for any eigenfunctions of N_{σ} . In particular the expectation values with respect to $|\Phi'\rangle$ are the same: $\langle \Phi' | H(b_{i\sigma}^\dagger, b_{j\sigma}) - H' | \Phi' \rangle = 0$. This indicates that $|\Phi'\rangle$ is the Hartree-Fock solution of H' with the same energy. We can obtain the one- and the two-electron integrals by expressing the $b_{i\sigma}^\dagger$ and $b_{j\sigma}$ in H' with $a_{i\sigma}^\dagger$ and $a_{j\sigma}$.

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