Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplemental material for "Extending scaled-interaction adaptive-partitioning QM/MM to covalently bonded systems"

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Abstract

This supplemental material contains a demonstration of the effect of scaling the strengths of interactions in a model system, the implementation details of the scaling of interactions in the density-functional tight-binding (DFTB) method, in the charge-optimized many-body (COMB) potential and in the CHARMM force field, the derivation of the z-vector method in the density-corrected pre-scaled algorithm, and the QM charges of n-butanol and n-butoxide anion.

1 The effect of scaling in a two-level model system

The QM calculation in the SISPA method is carried out with scaled interactions. I demonstrate with a simple model that the SISPA energy and forces change in a non-linear fashion with scaling factors, unlike in PAP and other AP-QM/MM methods with multiple QM calculations per time step.

Here I consider a model system of two identical atoms (A and B) with one basis function on each (ϕ_1 and ϕ_2) and ignore the MM potential. The distance between the atoms is R. The unscaled Hamiltonian and overlap matrices of the model system are

$$\mathrm{H} = \begin{pmatrix} \varepsilon & v \\ v & \varepsilon \end{pmatrix}, \tag{1}$$

and

$$\mathrm{S} = \begin{pmatrix} 1 & s \\ s & 1 \end{pmatrix}. \tag{2}$$

The corresponding orbitals and orbital energies are

$$\psi_\pm(\vec{r}) = \frac{1}{\sqrt{2}}\left(\phi_1(\vec{r}) \pm \phi_2(\vec{r})\right), \tag{3}$$

$$\varepsilon_\pm = \frac{\varepsilon \pm v}{1 \pm s}. \tag{4}$$

Assuming $\varepsilon_+ < \varepsilon_-$, the DFTB bond energy is

$$\begin{aligned} E_\mathrm{b} &= E - 2\varepsilon \\ &= 2\left\langle \psi_+ \right| \mathrm{H} \left| \psi_+ \right\rangle + E^\mathrm{rep} - 2\varepsilon \\ &= \frac{2(v - \varepsilon s)}{1+s} + E^\mathrm{rep}, \end{aligned} \tag{5}$$

where E^rep is the repulsive correction to the energy in DFTB.[1,2] The forces on atoms A and B are

$$\begin{aligned} \vec{F}_A &= -\frac{\partial E_b}{\partial R}\nabla_{\vec{R}_A} R, \\ \vec{F}_B &= -\frac{\partial E_b}{\partial R}\nabla_{\vec{R}_B} R. \end{aligned} \tag{6}$$

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Define $F = -\partial E_b/\partial R$, I have

$$F = -\frac{\partial E_\mathrm{b}}{\partial R} = -2\left(\frac{\partial v}{\partial R} - \frac{\varepsilon + v}{1+s}\frac{\partial s}{\partial R}\right) - \frac{\partial E^\mathrm{rep}}{\partial R}. \tag{7}$$

Choosing atom A as the center and atom B as a buffer atom, H and S becomes the following in SISPA:

$$\mathrm{H} = \begin{pmatrix} \varepsilon & \lambda v \\ \lambda v & \varepsilon \end{pmatrix}, \tag{8}$$

and

$$\mathrm{S} = \begin{pmatrix} 1 & \lambda s \\ \lambda s & 1 \end{pmatrix}, \tag{9}$$

where λ is the scaling factor of atom B. The SISPA bond energy and the magnitude of the forces of the model system are

$$E_\mathrm{b}^\mathrm{SISPA} = \frac{2\lambda(v - \varepsilon s)}{1 + \lambda s} + \lambda E^\mathrm{rep}, \tag{10}$$

$$F^\mathrm{SISPA} = -\frac{2\lambda}{1+\lambda s}\left(\frac{\partial v}{\partial R} - \frac{\varepsilon + \lambda v}{1+\lambda s}\frac{\partial s}{\partial R}\right) - \lambda\frac{\partial E^\mathrm{rep}}{\partial R} - \frac{\partial E_\mathrm{b}^\mathrm{SISPA}}{\partial \lambda}\frac{\partial \lambda}{\partial R}. \tag{11}$$

As a comparison, the bond energy and the magnitude of the forces with PAP are

$$E_\mathrm{b}^\mathrm{PAP} = \lambda E + (1-\lambda)\varepsilon_B - 2\varepsilon = \lambda\left(\frac{2v + \varepsilon(1-s)}{1+s}\right) - \varepsilon, \tag{12}$$

and

$$F^\mathrm{PAP} = -\frac{2\lambda}{1+s}\left(\frac{\partial v}{\partial R} - \frac{\varepsilon + v}{1+s}\frac{\partial s}{\partial R}\right) - \lambda\frac{\partial E^\mathrm{rep}}{\partial R} - \frac{\partial E_\mathrm{b}^\mathrm{PAP}}{\partial \lambda}\frac{\partial \lambda}{\partial R}. \tag{13}$$

Aside from the transition forces that are present in both SISPA and PAP, $E_\mathrm{b}^\mathrm{PAP}$ and F^PAP depend on λ linearly, while $E_\mathrm{b}^\mathrm{SISPA}$ and F^SISPA has a non-linear dependence on λ.

2 Scaling of interactions in the DFTB method

The DFTB method employs a valence-only atom-centered localized basis set. The Hamiltonian matrix elements are approximated by two-center integrals, which are further approximated by replacing the integrals with interpolations. SCC-DFTB[3] extends the original DFTB[1] by associating the atoms with self-consistent Mulliken-type partial charges.[4] This introduces long-range Coulomb interaction to the DFTB approximation, which greatly improved the accuracy and transferability of the method.

The unscaled QM potential energy of SCC-DFTB including the QM/MM coupling is

$$V^\mathrm{QM} = V_0^\mathrm{QM} + \frac{1}{2}\sum_{\alpha\beta}^{\mathrm{QM}} \sum_{\substack{l\in\alpha \\ l'\in\beta}} \gamma_{\alpha l \beta l'} \Delta q_{\alpha l} \Delta q_{\beta l'} + \sum_{\alpha}^{\mathrm{QM}} \sum_{A}^{\mathrm{MM}} \left(E_{\alpha A}^\mathrm{vdW} + \gamma_{\alpha A}^\mathrm{MM} q_A^\mathrm{MM} \sum_{l\in\alpha} \Delta q_{\alpha l} \right), \tag{14}$$

with V_0^QM being the QM potential energy of the original DFTB:

$$V_0^\mathrm{QM} = \sum_{i}^{\mathrm{occ}} n_i \varepsilon_i + \frac{1}{2}\sum_{\alpha\beta}^{\mathrm{QM}} (E_{\alpha\beta}^\mathrm{rep} + E_{\alpha\beta}^\mathrm{vdW}). \tag{15}$$

In Eqs. (14) and (15), n_i and ε_i respectively are the occupation number and orbital energy of orbital i, α, β denotes atoms, E^rep and E^vdW are the repulsive correction[1,5] and dispersion interaction energy[6,7] between two atoms, l, l' denotes the angular momentum quantum number ('shell'[8] in the following) of the basis functions associated with atom α and β, γ is the interaction parameter representing the Hartree and xc interactions between two shell-resolved QM partial charges,[3,9] γ^MM is the interaction parameter representing the Columbic interaction between a QM partial charge and an MM charge, and the shell-resolved Mulliken-type partial charge Δq is defined as

$$\Delta q_{\alpha\in\mathrm{QM},l} = q_{\alpha l} - q_{0,\alpha l}, \tag{16}$$

$$q_{\alpha\in\mathrm{QM},l} = \sum_{i}^{\mathrm{occ}} n_i \sum_{\mu\in\alpha,l} \sum_{\nu} c_{\mu i} c_{\nu i} S_{\mu\nu}, \tag{17}$$

where μ, ν label atom-centered basis functions, $c_{\mu i}$ is the expansion coefficient of the one-electron Kohn-Sham (KS) orbital ψ_i on basis ϕ_μ, so that

$$\psi_i(\vec{r}) = \sum_{\mu} c_{\mu p} \phi_\mu(\vec{r}). \tag{18}$$

I label occupied orbitals with i, j, virtual orbitals with a, b, and general orbitals with p, q. $q_{0,\alpha l}$ is $q_{\alpha l}$ evaluated on isolated atom α. The KS orbitals in terms of the c coefficients are obtained from the KS equation

$$\sum_{\nu} (H_{\mu\nu} - \varepsilon_p S_{\mu\nu}) c_{\nu p} = 0, \tag{19}$$

where $H_{\mu\nu}$ and $S_{\mu\nu} = <\mu|\nu>$ are respectively the Hamiltonian and overlap matrix elements, and ε_p is the orbital energy of orbital p. $H_{\mu\nu}$ of SCC-DFTB is defined by

$$\begin{aligned} H_{\mu\nu} =& H_{0,\mu\nu} + \frac{1}{2} S_{\mu\nu} \sum_{\beta}^{\mathrm{QM}} \sum_{l'\in\beta} \left(\gamma_{\substack{\alpha(\mu)l(\mu)\\ \beta l'}} + \gamma_{\substack{\alpha(\nu)l(\nu)\\ \beta l'}} \right) \Delta q_{\beta l'} \\ &+ \frac{1}{2} S_{\mu\nu} \sum_{A}^{\mathrm{MM}} \left(\gamma^{\mathrm{MM}}_{\alpha(\mu)A} + \gamma^{\mathrm{MM}}_{\alpha(\nu)A} \right) q_A^{\mathrm{MM}} \end{aligned} \tag{20}$$

where H_0 is the Hamiltonian of the original DFTB method

$$H_{0,\mu\nu} = \begin{cases} \varepsilon_\mu & \mu = \nu, \\ \left\langle \mu \left| \hat{T} + V_0^{\alpha(\mu)} + V_0^{\alpha(\nu)} \right| \nu \right\rangle & \alpha(\mu) \neq \alpha(\nu), \\ 0 & \text{otherwise}, \end{cases} \tag{21}$$

with $\alpha(\mu)$ denoting the atom on which the basis ϕ_μ is centered, $\hat{T}$ denoting the kinetic energy operator, and V_0^α being the KS potential of atom α corresponding to its spatially constrained density.

The scaling of SCC-DFTB is straightforward due to the pairwise form of the Hamiltonian. Applying SISPA scaling of Table I in the main text, the scaled SCC-DFTB Hamiltonian and overlap matrix elements become

$$\begin{aligned} H_{\mu\nu}^{\mathrm{SISPA}} =& H_{0,\mu\nu}^{\mathrm{SISPA}} \\ &+ \frac{1}{2} S_{\mu\nu}^{\mathrm{SISPA}} \sum_{\beta}^{\mathrm{QM}} \sum_{l'\in\beta} \left(\gamma^{\mathrm{SISPA}}_{\substack{\alpha(\mu)l(\mu)\\ \beta l'}} + \gamma^{\mathrm{SISPA}}_{\substack{\alpha(\nu)l(\nu)\\ \beta l'}} \right) \Delta q_{\beta l'}^{\mathrm{SISPA}} \\ &+ \frac{1}{2} S_{\mu\nu}^{\mathrm{SISPA}} \sum_{A}^{\mathrm{MM}} \left(\gamma^{\mathrm{MM,SISPA}}_{\alpha(\mu)A} + \gamma^{\mathrm{MM,SISPA}}_{\alpha(\nu)A} \right) q_A^{\mathrm{MM}}, \end{aligned} \tag{22}$$

where

$$H_{0,\mu\nu}^{\mathrm{SISPA}} = [\lambda_{\alpha(\mu)} \lambda_{\alpha(\nu)} (1 - \delta_{\alpha(\mu)\alpha(\nu)}) + \delta_{\alpha(\mu)\alpha(\nu)}] H_{0,\mu\nu}, \tag{23}$$

$$S_{\mu\nu}^{\mathrm{SISPA}} = [\lambda_{\alpha(\mu)} \lambda_{\alpha(\nu)} (1 - \delta_{\alpha(\mu)\alpha(\nu)}) + \delta_{\alpha(\mu)\alpha(\nu)}] S_{\mu\nu}, \tag{24}$$

$$\gamma^{\mathrm{SISPA}}_{\substack{\alpha\in\mathrm{QM},l\\ \beta\in\mathrm{QM},l'}} = [\lambda_\alpha \lambda_\beta (1 - \delta_{\alpha\beta}) + \delta_{\alpha\beta}] \gamma_{\substack{\alpha l\\ \beta l'}}, \tag{25}$$

$$\Delta q^{\mathrm{SISPA}}_{\alpha\in\mathrm{QM},l} = \sum_{i}^{\mathrm{occ}} n_i \sum_{\mu\in\alpha,l} \sum_{\nu} c^{\mathrm{SISPA}}_{\mu i} c^{\mathrm{SISPA}}_{\nu i} S^{\mathrm{SISPA}}_{\mu\nu} - q_{0,\alpha l}, \tag{26}$$

and

$$\gamma^{\mathrm{MM,SISPA}}_{\alpha\in\mathrm{QM},A\in\mathrm{MM}} = \lambda_\alpha (1 - \lambda_A)(1 - \delta_{\alpha A}) \gamma^{\mathrm{MM}}_{\alpha A}. \tag{27}$$

The SISPA QM potential energy is

$$\begin{aligned} V^{\mathrm{QM,SISPA}} =& \sum_{i}^{\mathrm{occ}} n_i \varepsilon_i^{\mathrm{SISPA}} + \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} (E^{\mathrm{rep,SISPA}}_{\alpha\beta} + E^{\mathrm{vdW,SISPA}}_{\alpha\beta}) \\ &+ \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} \sum_{\substack{l\in\alpha\\ l'\in\beta}} \gamma^{\mathrm{SISPA}}_{\substack{\alpha l\\ \beta l'}} \Delta q^{\mathrm{SISPA}}_{\alpha l} \Delta q^{\mathrm{SISPA}}_{\beta l'} \\ &+ \sum_{\alpha}^{\mathrm{QM}} \sum_{A}^{\mathrm{MM}} \left(E^{\mathrm{vdW,SISPA}}_{\alpha A} + \gamma^{\mathrm{MM,SISPA}}_{\alpha A} q_A^{\mathrm{MM}} \sum_{l\in\alpha} \Delta q^{\mathrm{SISPA}}_{\alpha l} \right), \end{aligned} \tag{28}$$

where

$$E^{\mathrm{rep,SISPA}}_{\alpha,\beta\in\mathrm{QM}} = [\lambda_\alpha \lambda_\beta (1 - \delta_{\alpha\beta}) + \delta_{\alpha\beta}] E^{\mathrm{rep}}_{\alpha\beta}, \tag{29}$$

$$E^{\mathrm{vdW,SISPA}}_{\alpha,\beta\in\mathrm{QM}} = [\lambda_\alpha \lambda_\beta (1 - \delta_{\alpha\beta}) + \delta_{\alpha\beta}] E^{\mathrm{vdW}}_{\alpha\beta}, \tag{30}$$

$$E^{\mathrm{vdW,SISPA}}_{\alpha\in\mathrm{QM},A\in\mathrm{MM}} = \lambda_\alpha (1 - \lambda_A)(1 - \delta_{\alpha A}) E^{\mathrm{vdW}}_{\alpha,A\in\mathrm{MM}}. \tag{31}$$

c^{SISPA} and $\varepsilon^{\mathrm{SISPA}}$ in Eqs. (26) and (28) are obtained by solving Eq. (19) with scaled Hamiltonian and overlap matrices.

3 The scaling of the COMB and CHARMM potentials

COMB is a pairwise MM potential with variable MM charges. The COMB potential energy is decomposed into the following terms:

$$V^{\mathrm{MM}} = \sum_{A}^{\mathrm{MM}} \left\{ E_A^{\mathrm{self}} + \frac{1}{2} \sum_{B \neq A}^{\mathrm{MM}} \left[E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}} + E_{AB}^{\mathrm{Repul}} + E_{AB}^{\mathrm{BO}} + \sum_{C \neq A,B}^{\mathrm{MM}} E_{ABC}^{\mathrm{ang}} \right] \right\} \quad (32)$$

where E^{self} is the self-energy, E^{vdW} is the dispersion energy, E^{Coul} is the Coulomb interaction energy, E^{Repul} is the repulsive energy, E^{BO} is the bond order interaction energy, and E^{ang} is the bond-bending interaction energy.

The scaled COMB potential energy in SISPA is

$$V^{\mathrm{MM,SISPA}} = \sum_{A}^{\mathrm{MM}} \left[(1-\lambda_A) E_A^{\mathrm{self}} + \frac{1}{2}(1-\lambda_A)(1-\lambda_B) \sum_{B \neq A}^{\mathrm{MM}} \left(E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}} + E_{AB}^{\mathrm{Repul}} + E_{AB}^{\mathrm{BO}} + \sum_{C \neq A,B}^{\mathrm{MM}} E_{ABC}^{\mathrm{ang}} \right) \right]. \quad (33)$$

The scaling COMB potential energy with the modified scaling is

$$V^{\mathrm{MM,sc}} = \sum_{A}^{\mathrm{MM}} \left[(1-\lambda_A) E_A^{\mathrm{self}} + \frac{1}{2}(1-\lambda_A)(1-\lambda_B) \sum_{B \neq A}^{\mathrm{MM}} \left(E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}} \right) + (1-\lambda_A\lambda_B) \sum_{B \neq A}^{\mathrm{MM}} \left(E_{AB}^{\mathrm{Repul}} + E_{AB}^{\mathrm{BO}} + \sum_{C \neq A,B}^{\mathrm{MM}} E_{ABC}^{\mathrm{ang}} \right) \right]. \quad (34)$$

The potential energy of the CHARMM force field can be written as

$$V^{\mathrm{MM}} = \sum_{(AB)}^{\mathrm{bonds}} E_{AB}^{\mathrm{BO}} + \sum_{(ABC)}^{\mathrm{angles}} \left(E_{AC}^{\mathrm{UB}} + E_{ABC}^{\mathrm{ang}} \right) + \sum_{(ABCD)} \mathrm{dihedrals} E_{ABCD}^{\mathrm{dihedral}} + \sum_{(ABCD)}^{\mathrm{impropers}} E_{ABCD}^{\mathrm{improper}} + \frac{1}{2} \sum_{A,B \neq A} \left(E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}} \right), \quad (35)$$

where E^{UB}, E^{ang}, E^{dihedral} and E^{improper} are the Urey-Bradley, angle, dihedral, improper dihedral potential energies. E^{BO}, E^{UB}, E^{ang}, E^{dihedral} and E^{improper} are non-zero only for pre-defined group of atoms. I use the following equation as the scaled CHARMM potential energy in SISPA:

$$\begin{aligned} V^{\mathrm{MM,SISPA}} &= \sum_{(AB)}^{\mathrm{bonds}} (1-\lambda_A)(1-\lambda_B) E_{AB}^{\mathrm{BO}} \\ &+ \sum_{(ABC)}^{\mathrm{angles}} \left[(1-\lambda_A)(1-\lambda_C) E_{AC}^{\mathrm{UB}} + (1-\lambda_A)(1-\lambda_B)(1-\lambda_C) E_{ABC}^{\mathrm{ang}} \right] \\ &+ \sum_{(ABCD)}^{\mathrm{dihedrals}} (1-\lambda_A)(1-\lambda_B)(1-\lambda_C)(1-\lambda_D) E_{ABCD}^{\mathrm{dihedral}} \\ &+ \sum_{(ABCD)}^{\mathrm{impropers}} (1-\lambda_A)(1-\lambda_B)(1-\lambda_C)(1-\lambda_D) E_{ABCD}^{\mathrm{improper}} \\ &+ \frac{1}{2} \sum_{A,B \neq A} (1-\lambda_A)(1-\lambda_B) \left(E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}} \right). \end{aligned} \quad (36)$$

The scaled CHARMM potential energy with the modified scaling is

$$V^{\mathrm{MM,SISPA}} = \sum_{(AB)}^{\mathrm{bonds}} (1-\lambda_A\lambda_B)E_{AB}^{\mathrm{BO}} + \sum_{(ABC)}^{\mathrm{angles}} \left[(1-\lambda_A\lambda_C)E_{AC}^{\mathrm{UB}} + (1-\lambda_A\lambda_B\lambda_C)E_{ABC}^{\mathrm{ang}}\right] + \sum_{(ABCD)}^{\mathrm{dihedrals}} (1-\lambda_A\lambda_B\lambda_C\lambda_D)E_{ABCD}^{\mathrm{dihedral}} + \sum_{(ABCD)}^{\mathrm{impropers}} (1-\lambda_A\lambda_B\lambda_C\lambda_D)E_{ABCD}^{\mathrm{improper}} + \frac{1}{2}\sum_{A,B\neq A} (1-\lambda_A)(1-\lambda_B)\left(E_{AB}^{\mathrm{vdW}} + E_{AB}^{\mathrm{Coul}}\right). \tag{37}$$

4 The z-vector method for the DCP algorithm

I use SCC-DFTB as the QM method in the following derivations. There is no difficulty in similar derivations using other QM methods. I use the superscript ‘pre’ and ‘sc’ to denote the pre-scaled and scaled quantities in DCP, respectively.

I follow the common practice of using the pre-scaled self-consistent KS orbitals as the new basis set.[10–13] The Hamiltonian in this representation can be partitioned into occupied-occupied, occupied-virtual, virtual-occupied, and virtual-virtual blocks. The basis transformations for orbitals and matrices are carried out by

$$\vec{u}_p^{\mathrm{pre}} = \left[\mathrm{C}^{(0)}\right]^{-1} \vec{c}_p^{\,\mathrm{pre}}, \tag{38}$$

and

$$\tilde{\mathrm{M}} = \left[\mathrm{C}^{(0)}\right]^{\mathrm{T}} \mathrm{M}\mathrm{C}^{(0)}, \tag{39}$$

where $\left(\vec{c}_p^{\,\mathrm{pre}}\right)_\mu = c_{\mu p}^{\mathrm{pre}}$ is the column vector of the coefficients in Eq. (18), $\mathrm{C}^{(0)}$ is the matrix formed by the $\vec{c}_p^{\,\mathrm{pre}}$ vectors, and the tilde in $\tilde{\mathrm{M}}$ signifies that the matrix is of the new basis set. With the new basis set, the Hamiltonian is a diagonal matrix of KS orbital energies, and the overlap matrix becomes identity.

The forces are obtained from the first order changes in the QM potential energy $V^{(1)}$ corresponding to perturbations in the the atomic positions. $V^{(1)}$ depends on the first order change in the KS orbitals $\mathrm{U}^{(1)}$, which is formed by the $\vec{u}_p^{\,\mathrm{pre},(1)}$ vectors. I only need the virtual-occupied block of $\mathrm{U}^{(1)}$ due to the following relations:[12]

$$u_{ij}^{\mathrm{pre}(1)} = -\frac{1}{2}\tilde{S}_{ij}^{\mathrm{pre}(1)}, \tag{40}$$

$$u_{ab}^{\mathrm{pre}(1)} = -\frac{1}{2}\tilde{S}_{ab}^{\mathrm{pre}(1)}, \tag{41}$$

$$u_{ia}^{\mathrm{pre}(1)} = -\tilde{S}_{ia}^{\mathrm{pre}(1)} - u_{ai}^{\mathrm{pre}(1)}. \tag{42}$$

To simplify the notations, I define the matrices $\mathrm{O}_{\alpha l}$, $\mathrm{M}_{\alpha l}^{\mathrm{pre}}$, $\mathrm{M}_{\alpha l}^{\mathrm{sc}}$, $\tilde{\mathrm{G}}'$, $\tilde{\mathrm{Q}}$, $\tilde{\mathrm{Q}}'$, $\tilde{\mathrm{R}}_{pq}^{\mathrm{pre}}$, $\tilde{\mathrm{R}}_{pq}^{\mathrm{sc}}$ as the following:

$$[\mathrm{O}_{\alpha l}]_{\mu\nu} = \begin{cases} S_{\mu\nu}^{\mathrm{pre}} & \mu \in \alpha, l, \\ 0 & \mu \notin \alpha, l, \end{cases} \tag{43}$$

$$\left[\mathrm{M}_{\beta l'}\right]_{\mu\nu}^{\mathrm{pre}} = \Big(\gamma^{\mathrm{pre}}_{\substack{\alpha(\mu)l(\mu)\\ \beta l'}} + \gamma^{\mathrm{pre}}_{\substack{\alpha(\nu)l(\nu)\\ \beta l'}}\Big)S_{\mu\nu}^{\mathrm{pre}}, \tag{44}$$

$$\left[\mathrm{M}_{\beta l'}\right]_{\mu\nu}^{\mathrm{sc}} = \Big(\gamma^{\mathrm{sc}}_{\substack{\alpha(\mu)l(\mu)\\ \beta l'}} + \gamma^{\mathrm{sc}}_{\substack{\alpha(\nu)l(\nu)\\ \beta l'}}\Big)S_{\mu\nu}^{\mathrm{sc}}, \tag{45}$$

$$\tilde{\mathrm{G}}' = \frac{1}{2}\sum_{\alpha}^{\mathrm{QM}}\sum_{l\in\alpha} \tilde{\mathrm{M}}_{\alpha l}^{\mathrm{sc}} \left(\frac{1}{2}q_{\alpha l}^{\mathrm{sc}} - q_{0,\alpha l}\right), \tag{46}$$

$$\tilde{\mathrm{Q}} = -\frac{1}{4}\sum_{ij}^{\mathrm{occ}} \tilde{S}_{ji}^{\mathrm{pre},(1)} \tilde{\mathrm{R}}_{(ji)} + \frac{1}{2}\sum_{\alpha}^{\mathrm{QM}}\sum_{l\in\alpha} \Big\{\tilde{\mathrm{M}}_{(\alpha l)}^{(1)} \Delta q_{\alpha l}^{\mathrm{pre}(0)} + \tilde{\mathrm{M}}_{(\alpha l)}^{(0)} \sum_{i}^{\mathrm{occ}} n_i \left[\vec{u}_i^{\,\mathrm{pre}(0)}\right]^{\mathrm{T}} \cdot \tilde{\mathrm{O}}_{(\alpha l)}^{(1)} \cdot \vec{u}_i^{\,\mathrm{pre}(0)}\Big\}, \tag{47}$$

$$\tilde{\mathrm{Q}}' = -\frac{1}{8}\sum_{ij}^{\mathrm{occ}} \tilde{S}_{ji}^{\mathrm{pre},(1)} \tilde{\mathrm{R}}_{(ji)} + \frac{1}{2}\sum_{\alpha}^{\mathrm{QM}}\sum_{l\in\alpha} \Big\{\tilde{\mathrm{M}}_{(\alpha l)}^{\mathrm{sc}(1)} \times \left(\frac{1}{2}q_{\alpha l}^{\mathrm{pre}(0)} - q_{0,\alpha l}\right) + \frac{1}{2}\tilde{\mathrm{M}}_{(\alpha l)}^{(0)} \sum_{i}^{\mathrm{occ}} n_i \times \left[\vec{u}_i^{\,\mathrm{pre}(0)}\right]^{\mathrm{T}} \cdot \tilde{\mathrm{O}}_{(\alpha l)}^{(1)} \cdot \vec{u}_i^{\,\mathrm{pre}(0)}\Big\}, \tag{48}$$

$$\tilde{\mathrm{R}}_{pq}^{\mathrm{pre}} = \sum_{\alpha}^{\mathrm{QM}}\sum_{l\in\alpha} \tilde{\mathrm{M}}_{\alpha l}^{\mathrm{pre}(0)} \left[\tilde{O}_{\alpha,ij}^{(0)} + \tilde{O}_{\alpha,ji}^{(0)}\right], \tag{49}$$

$$\tilde{\mathrm{R}}_{pq}^{\mathrm{sc}} = \sum_{\alpha}^{\mathrm{QM}}\sum_{l\in\alpha} \tilde{\mathrm{M}}_{\alpha l}^{\mathrm{sc}(0)} \left[\tilde{O}_{\alpha,ij}^{(0)} + \tilde{O}_{\alpha,ji}^{(0)}\right], \tag{50}$$

The DCP QM potential energy is

$$
\begin{aligned}
V^{\mathrm{QM,sc}} &= \sum_i^{\mathrm{occ}} n_i \left\langle \psi_i^{\mathrm{pre}} \right| \mathrm{H}^{\mathrm{sc}} \left| \psi_i^{\mathrm{pre}} \right\rangle \\
&+ \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} \sum_{\substack{l\in\alpha \\ l'\in\beta}} \gamma_{\alpha l \atop \beta l'}^{\mathrm{sc}} \Delta q_{\alpha l}^{\mathrm{pre}} \Delta q_{\beta l'}^{\mathrm{pre}} + \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} (E_{\alpha\beta}^{\mathrm{rep,sc}} + E_{\alpha\beta}^{\mathrm{vdW,sc}}) \\
&+ \sum_{\alpha}^{\mathrm{QM}} \sum_{A}^{\mathrm{MM}} (E_{\alpha A}^{\mathrm{vdW,sc}} + \gamma_{\alpha A}^{\mathrm{MM,sc}} q_A^{\mathrm{MM}} \sum_{l\in\alpha} \Delta q_{\alpha l}^{\mathrm{pre}}), \quad (51)
\end{aligned}
$$

The first order change in the QM potential energy can be derived from the perturbation theory:

$$
\begin{aligned}
V^{\mathrm{QM,sc(1)}} =& \mathscr{E}^{(1)} + \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} (E_{\alpha\beta}^{\mathrm{rep,sc(1)}} + E_{\alpha\beta}^{\mathrm{vdW,sc(1)}}) \\
&+ \sum_i^{\mathrm{occ}} \sum_a^{\mathrm{virt}} u_{ai}^{\mathrm{pre(1)}} \tilde{Y}_{ai},
\end{aligned}
\tag{52}
$$

where $\mathscr{E}^{(1)}$ is

$$
\begin{aligned}
\mathscr{E}^{(1)} =& \sum_i^{\mathrm{occ}} n_i \left[\vec{u}_i^{\mathrm{pre(0)}} \right]^{\mathrm{T}} \cdot \left(\tilde{\mathrm{H}}_0^{\mathrm{sc(1)}} + \tilde{\mathrm{Q}}' + \tilde{\mathrm{G}}^{\mathrm{MM,sc(1)}} \right) \\
& \cdot \vec{u}_i^{\mathrm{pre(0)}} - \frac{1}{2} \sum_{ij}^{\mathrm{occ}} n_i \tilde{S}_{ji}^{\mathrm{pre(1)}} \left(\tilde{H}_{0,ij}^{\mathrm{sc(0)}} + \tilde{H}_{0,ji}^{\mathrm{sc(0)}} + \tilde{G}_{ij}^{\prime(0)} + \tilde{G}_{ji}^{\prime(0)} \right) \\
&+ \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} \sum_{\substack{l\in\alpha \\ l'\in\beta}} \gamma_{\alpha l \atop \beta l'}^{\mathrm{sc(1)}} q_{0,\alpha l} q_{0,\beta l'} - \sum_{\alpha}^{\mathrm{QM}} \sum_{A}^{\mathrm{MM}} \gamma_{\alpha A}^{\mathrm{MM,sc(1)}} q_{0\alpha} q_A^{\mathrm{MM}},
\end{aligned}
\tag{53}
$$

and

$$
\begin{aligned}
\tilde{Y}_{ai} = n_i \Big\{ & \tilde{H}_{0,ia}^{\mathrm{sc(0)}} + \tilde{H}_{0,ai}^{\mathrm{sc(0)}} + \tilde{G}_{ia}^{\prime(0)} + \tilde{G}_{ai}^{\prime(0)} \\
&+ \tilde{G}_{ia}^{\mathrm{MM,sc(0)}} + \tilde{G}_{ai}^{\mathrm{MM,sc(0)}} + \frac{1}{4} \sum_j^{\mathrm{occ}} n_j \left[\vec{u}_j^{\mathrm{pre(0)}} \right]^{\mathrm{T}} \cdot \tilde{\mathrm{R}}_{(ai)}^{\mathrm{sc}} \cdot \vec{u}_j^{\mathrm{pre(0)}} \Big\}
\end{aligned}
\tag{54}
$$

with $\mathrm{G}^{\mathrm{MM,sc(1)}}$ being

$$
\mathrm{G}_{\mu\nu}^{\mathrm{MM,sc(1)}} = \frac{1}{2} S_{\mu\nu}^{\mathrm{pre}} \sum_A^{\mathrm{MM}} \left(\gamma_{\alpha(\mu)A}^{\mathrm{MM,sc}} + \gamma_{\alpha(\nu)A}^{\mathrm{MM,sc}} \right) q_A^{\mathrm{MM}}.
\tag{55}
$$

Eq. (52) does not explicitly write out the terms related to the transition forces. According to Eq. (52), the first order change in the energy depend on the first order change of the orbitals, which is determined by the coupled-perturbed equations[10]

$$
\sum_j^{\mathrm{occ}} \sum_b^{\mathrm{virt}} \tilde{\Gamma}_{(ai),(bj)} u_{bj}^{\mathrm{pre(1)}} = \tilde{B}_{ai}
\tag{56}
$$

where

$$
\tilde{\Gamma}_{(ai),(bj)} = \delta_{ij}\delta_{ab} \left(\varepsilon_i^{\mathrm{pre(0)}} - \varepsilon_a^{\mathrm{pre(0)}} \right) - \frac{1}{2} n_j \left[\tilde{R}_{bj} \right]_{ai}^{\mathrm{pre}},
\tag{57}
$$

and

$$
\tilde{B}_{ai} = \tilde{H}_{0,ai}^{\mathrm{pre(1)}} - \varepsilon_i^{\mathrm{pre(0)}} \tilde{S}_{ai}^{\mathrm{pre(1)}} + \tilde{Q}_{ai} + \tilde{G}_{ai}^{\mathrm{MM,pre(1)}}.
\tag{58}
$$

To get all the forces, it appears that one needs to solve Eq. (56) $3N_{\mathrm{at}}$ times, where N_{at} is the number of atoms. With the z-vector method, only one set of coupled-perturbed-like equations need to be solved. Treating $\tilde{\Gamma}$ as a super matrix and $\tilde{Y}$, $\tilde{B}$ and $u^{\mathrm{pre(1)}}$ as super vectors, Eq. (56) and (52) becomes

$$
\tilde{\Gamma} \cdot \vec{u}^{(1)} = \vec{\tilde{B}},
\tag{59}
$$

and

$$
\begin{aligned}
V^{\mathrm{QM,sc(1)}} =& \mathscr{E}^{(1)} + \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} (E_{\alpha\beta}^{\mathrm{rep,sc(1)}} + E_{\alpha\beta}^{\mathrm{vdW,sc(1)}}) \\
&+ \left[\vec{\tilde{Y}} \right]^{\mathrm{T}} \cdot \vec{u}^{(1)}.
\end{aligned}
\tag{60}
$$

Define the z-vector $\vec{\tilde{z}}$ by

$$
\left[\tilde{\Gamma} \right]^{\mathrm{T}} \cdot \vec{\tilde{z}} = \vec{\tilde{Y}},
\tag{61}
$$

Eq. (60) becomes

$$
\begin{aligned}
V^{\mathrm{QM,sc(1)}} =& \mathscr{E}^{(1)} + \frac{1}{2} \sum_{\alpha\beta}^{\mathrm{QM}} (E_{\alpha\beta}^{\mathrm{rep,sc(1)}} + E_{\alpha\beta}^{\mathrm{vdW,sc(1)}}) \\
&+ \left[\vec{\tilde{z}} \right]^{\mathrm{T}} \cdot \vec{\tilde{B}}.
\end{aligned}
\tag{62}
$$

Eq. (62) determines the DCP QM forces. Instead of solving for $\vec{u}^{(1)}$ for every atomic coordinate with Eq. (59), one solves for $\vec{\tilde{z}}$ once with Eq. (61). Since both $\tilde{\Gamma}$ and $\vec{\tilde{Y}}$ depend on zeroth order quantities only, $\vec{\tilde{z}}$ is invariant to the perturbation, and therefore Eq. (61) only need to be solved once instead of $3N_{\mathrm{at}}$ times as for Eq. (59).

The derivatives of the pre-scaling factors affect the force through the charge density and orbitals. The pre-scaling force can be obtained by calculating the derivative of the potential energy with respect to pre-scaling factors with the z-vector method as well.

I find that the DFTB method is not the optimal choice for DCP with the z-vector method, since the $\tilde{O}_{\alpha l}$ matrices cannot be obtained directly with quantities in the new basis set. They have to be calculated by explicit basis set transformation, which dominates the computational cost. These matrices are needed due to the Mulliken-charge approximation of DFTB. This problem does not exist in DFT, in which the z-vector method becomes highly effective.

5 QM charges of n-butanol and n-butoxide anion

Table 1 shows the QM charges of n-butanol and n-butoxide anion corresponding to the calculations in Sec. 3.4 of the main text. MM charges (standard values of the CHARMM force field) are also listed for comparison.

Table 1: QM charges of n-butanol and n-butoxide anion

			C_4H_9OH					
Method	O1	C1	C2	C3	H1	H3	H5	H10
MM	-0.65	0.05	-0.18	-0.18	0.09	0.09	0.09	0.42
QM	-0.49	0.16	-0.15	-0.09	0.01	0.07	0.05	0.31
mod-SISPA	-0.43	0.18	-0.27	N/A	0.01	0.08	N/A	0.32
mod-SISPA w/o trans. force	-0.45	0.18	-0.21	N/A	0.02	0.06	N/A	0.32
SISPA w/o trans. force	-0.46	0.19	-0.20	N/A	0.02	0.04	N/A	0.32
DCP	-0.48	0.14	-0.19	-0.10	0.03	0.10	0.01	0.32
DCP w/o trans. force	-0.49	0.18	-0.13	-0.10	0.02	0.08	0.00	0.32
			$C_4H_9O^-$					
MM	-0.92	-0.26	-0.18	-0.18	0.09	0.09	0.09	N/A
QM	-0.80	0.34	-0.26	-0.07	-0.13	0.03	0.03	N/A
mod-SISPA	-0.66	0.32	-0.52	N/A	-0.10	0.03	N/A	N/A
mod-SISPA w/o trans. force	-0.64	0.32	-0.39	N/A	-0.09	-0.05	N/A	N/A
SISPA w/o trans. force	-0.62	0.33	-0.45	N/A	-0.09	-0.04	N/A	N/A
DCP	-0.49	0.16	-0.18	-0.32	0.02	0.09	-0.19	N/A
DCP w/o trans. force	-0.55	0.23	0.00	-0.33	0.00	0.06	-0.24	N/A

References

(1) Porezag, D.; Frauenheim, T.; Köhler, T.; Seifert, G.; Kaschner, R. *Phys. Rev. B* **1995**, *51*, 12947.

(2) Refer to the supplemental material of this paper.

(3) Elstner, M.; Porezag, D.; Jungnickel, G.; Elsner, J.; Haugk, M.; Frauenheim, T.; Suhai, S.; Seifert, G. *Phys. Rev. B* **1998**, *58*, 7260.

(4) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(5) Levy, M.; Zahariev, F. *Phys. Rev. Lett.* **2014**, *113*, 113002.

(6) Rappé, A. K.; Casewit, C. J.; Colwell, K. S.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.

(7) Zhechkov, L.; Heine, T.; Patchkovskii, S.; Seifert, G.; Duarte, H. A. *J. Chem. Theory Comput.* **2005**, *1*, 841.

(8) Aradi, B.; Hourahine, B.; Frauenheim, T. *J. Phys. Chem. A* **2007**, *111*, 5678.

(9) Frauenheim, T.; Seifert, G.; Elstner, M.; Hajnal, Z.; Jungnickel, G.; Porezag, D.; Suhai, S.; Scholz, R. *Phys. Stat. Sol. (b)* **2000**, *217*, 41.

(10) Gerratt, J.; Mills, I. M. *J. Chem. Phys.* **1967**, *49*, 1719.

(11) Handy, N. C.; Schaefer, H. F., III *J. Chem. Phys.* **1984**, *81*, 5031.

(12) Neese, F.; Schwabe, T.; Grimme, S. *J. Chem. Phys.* **2007**, *126*, 124115.

(13) Pulay, P. *WIREs Comput. Mol. Sci.* **2013**, *4*, 169.