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ABSTRACT

Nuclear quantum effects play crucial roles in determining the structure, dynamics, and reactivity of hydrogen-containing systems. Incorporating these effects into routine quantum chemistry calculations and molecular simulations remains challenging, in part because widely available treatments that combine accuracy, efficiency, and straightforward workflows are still limited. The constrained nuclear-electronic orbital (CNEO) framework addresses this challenge by treating some or all nuclei quantum mechanically while preserving the conventional molecular-structure picture through constraints on nuclear position expectation values. This formulation leads to the CNEO effective potential energy surface, which directly includes zero-point energy, nuclear quantum delocalization, and shallow tunneling effects. Molecular dynamics (MD) on this surface, termed CNEO-MD, has demonstrated systematic improvements in predicted vibrational frequencies for hydrogen-involving motions, including both terminal hydrogen vibrations and hydrogen-bonded vibrations. Applications to reaction kinetics reveal substantial rate enhancements arising from shallow tunneling, and CNEO transition state theory provides accurate predictions without empirical scaling factors or separate tunneling corrections. Recent extensions to excited-state calculations and nonadiabatic dynamics enable studies of photochemical processes in which nuclear quantum effects influence both energetics and dynamics, while integration with solvation models, QM/MM schemes, and periodic boundary conditions extends the capability of the CNEO framework to complex environments. The computational costs of these approaches are comparable with those of conventional electronic-structure methods or *ab initio* MD. Overall, the CNEO framework provides an efficient route for the quantum-mechanical treatment of nuclei that is suitable for broad use in quantum chemistry calculations and molecular simulations.

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I. INTRODUCTION

Nuclear quantum effects represent one of the most fundamental challenges in quantum chemistry calculations and molecular simulations.^{1–6} The quantum-mechanical nature of nuclei, particularly light nuclei such as hydrogen, manifests through zero-point motion and quantum tunneling. It can strongly influence spectroscopy, chemical reactivity, and biological function. In spectroscopy, nuclear quantum effects influence vibrational frequencies and intensities, and in hydrogen-bonded environments, they

control characteristic peak shifts and line broadening.^{7–9} In chemical reactivity, zero-point energy and tunneling modify effective free-energy barriers and can reshape reaction pathways along hydrogen-transfer coordinates, leading to substantial changes in reaction rates and kinetic isotope effects.^{10–12} In biological settings, where proton motion is central to hydrogen-bond networks and acid-base chemistry, nuclear quantum effects tune structure and dynamics and can modulate the efficiency and selectivity of proton, hydrogen-atom, and hydride-transfer steps in enzymes and bioenergetic processes.^{13–16}

Several computational approaches provide powerful routes for incorporating nuclear quantum effects and each method occupies a distinct accuracy–cost regime. Wave-packet dynamics methods, such as the multiconfigurational time-dependent Hartree (MCTDH) approach,¹⁷ can achieve very high accuracy for small systems, although the computational cost grows rapidly with the number of degrees of freedom. Multilayer variants¹⁸ extend the feasible system size, but applications to systems beyond a few tens of degrees of freedom remain challenging.^{19–22}

Path-integral-based methods are currently the most widely used framework for capturing nuclear quantum effects.²³ They map a quantum system onto an ensemble of classical replicas connected by harmonic springs and yield a ring-polymer representation that enables rigorous equilibrium sampling^{24,25} and approximate real-time nuclear dynamics.^{26–32} In many applications, convergence near room temperature is obtained on the order of 16–32 replicas, while lower temperatures often require more replicas, which increases the cost, especially when coupled with *ab initio* potential energy surfaces.^{33–35}

Vibrational perturbation theory (VPT2)^{36–39} remains a practical and widely used approach for anharmonic corrections, although strongly anharmonic systems, such as shared-proton complexes and hydrogen-bond networks, with strong intermode coupling effects can challenge its reliability.

Beyond the adiabatic picture, nonadiabatic dynamics approaches, such as Ehrenfest dynamics⁴⁰ and surface hopping,^{40,41} are valuable for photochemical processes and electron-transfer reactions, but they typically treat nuclei classically. Methods that combine nonadiabatic dynamics with quantum nuclei, including nonadiabatic ring-polymer molecular dynamics,^{42–44} are also available and they provide an important route forward at the cost of additional methodological complexity.

Over the past few years, our group has developed the constrained nuclear–electronic orbital (CNEO) framework to incorporate nuclear quantum effects in quantum chemistry calculations and molecular simulations.^{45–47} The central idea is to treat some or all nuclei quantum mechanically while preserving a clear molecular structure picture by constraining nuclear position expectation values. This construction yields an effective potential energy surface expressed in terms of these expectation-value coordinates, which allows many standard electronic-structure and molecular-simulation workflows to be applied while incorporating important nuclear quantum effects.

This Perspective traces the evolution of the CNEO framework from its theoretical formulation to practical tools and applications. Section II introduces the methodological foundations and key working equations. Subsequent sections summarize representative applications in vibrational spectroscopy and reaction kinetics and then describe recent extensions to excited-state properties, nonadiabatic dynamics, complex environments (including solution, QM/MM, and periodic systems), and quantum computation. We then discuss integration of CNEO with existing quantum chemistry and molecular simulation packages. Section IX provides concluding remarks and highlights future directions that may further broaden the scope and impact of the CNEO approach.

II. CHALLENGES OF CONVENTIONAL MULTICOMPONENT QUANTUM CHEMISTRY AND EMERGENCE OF CNEO THEORY

A. Conventional multicomponent quantum chemistry methods

The CNEO theory originates from multicomponent quantum chemistry,^{5,6,48–51} in which more than one type of particle, most often electrons and nuclei, receives an explicit quantum-mechanical treatment. This strategy departs fundamentally from the Born–Oppenheimer approximation (Fig. 1). Under the Born–Oppenheimer approximation, nuclear and electronic degrees of freedom are separated and the electronic problem is solved first with nuclei represented as fixed point charges. Subsequent treatments of nuclear motion, either quantum mechanical or classical, take place on the resulting electronic potential energy surface. In contrast, in multicomponent frameworks, electrons and some or all nuclei receive a joint quantum description, which provides a direct route to coupled electron–nuclear phenomena that become especially important for light nuclei.

The conceptual foundations of multicomponent quantum chemistry trace back to early work by Thomas beginning in 1969,^{48,52} who investigated coupled electronic and nuclear structure in small molecules, starting with ammonia. These pioneering studies established the central idea that an explicit quantum treatment of nuclei, together with electrons, can provide fundamental new

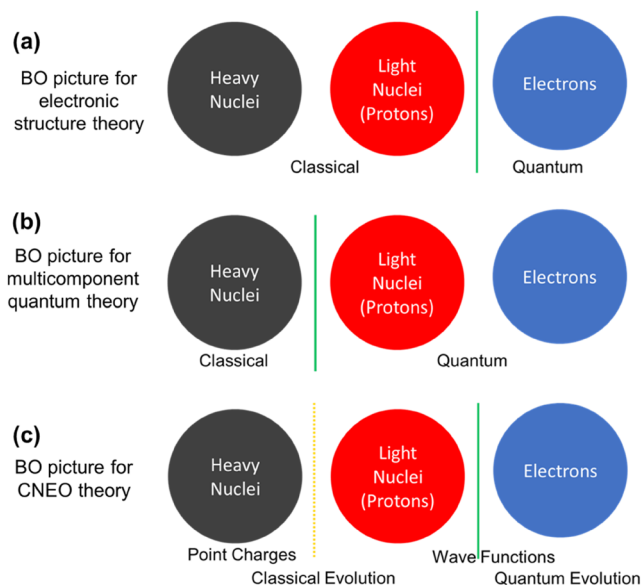


FIG. 1. Schematic comparison of the Born–Oppenheimer picture in (a) electronic structure theory, (b) conventional multicomponent quantum theory without constraints, and (c) the CNEO framework. The CNEO picture more closely resembles conventional electronic structure theory, but it treats some or all nuclei quantum mechanically. The quantum nuclear position expectation values still evolve classically according to Newton’s equation.

insights into molecular structure and chemical bonding. Later, Parr *et al.*,⁴⁹ Gidopoulos,⁵³ and Kreibich and Gross⁵⁰ established and further developed multicomponent density functional theory for combined electron–nuclear systems, which provided a formal theoretical foundation for quantum chemistry calculations beyond the Born–Oppenheimer separation. When the theory adopts a molecular-orbital description for both electrons and quantum nuclei, the approach often carries the name nuclear–electronic orbital (NEO) theory,⁵ a term introduced by Hammes-Schiffer. In typical NEO implementations, at least two nuclei remain classical to define the molecular frame,⁵ while the electrons and the remaining nuclei receive a quantum treatment within a molecular-orbital picture. Within this framework, a range of methods has been developed, including NEO Hartree–Fock,⁵⁴ multireference approaches,⁵⁴ explicitly correlated methods,⁵⁵ coupled-cluster theory,⁵⁶ and density functional methods.⁵⁷ These methods have been applied to hydrogen-involving systems to quantify how nuclear delocalization and zero-point energy affect optimized structures, proton affinities, vibrational spectra, isotope effects, and reaction dynamics in both gas-phase and condensed-phase environments.⁵ In particular, multicomponent density functional theory enables practical and often quantitative predictions of proton-sensitive observables, such as proton affinities and vibrational frequencies;^{58–67} correlated and multireference multicomponent wave function methods provide benchmark-quality ground-state properties for small to moderate systems;^{56,68–72} and recent interface with implicit and explicit solvents and real-time formulations extend these capabilities to solution, enzymatic environments, and excited-state proton-transfer dynamics.^{73–80}

B. Challenges with conventional multicomponent methods

The conceptual elegance of treating electrons and nuclei on an equal quantum-mechanical footing comes with practical and interpretive challenges, which have limited the broad adoption of conventional multicomponent methods.

In a fully quantum multicomponent description, no set of classical nuclear coordinates exists. As a result, the familiar molecular structure picture is lost with the total electron–nuclear Hamiltonian and eigenstates invariant to overall translation and rotation. Structural information can only be extracted through reduced density matrices rather than through a single set of geometric parameters.^{81,82} In this setting, the conventional potential energy surface concept vanishes and loses its central role.⁸³

A common practical alternative uses a subset of classical nuclei to define a molecular frame, as in conventional NEO theory, which removes complications associated with overall translation and rotation.^{5,54} This compromise, however, introduces a Born–Oppenheimer-like separation between classical and quantum nuclei [Fig. 1(b)], and the resulting potential energy surface depends only on the coordinates of the classical nuclei. In this sense, the surface has a lower dimension than the conventional potential energy surface.⁶⁶ Dynamics on such a surface essentially assumes an adiabatic response of the quantum nuclei to the motion of the classical nuclei. Because the mass ratio between heavy and light nuclei is modest and far smaller than the nucleus–electron mass ratio that underlies the conventional Born–Oppenheimer approximation, this

separation is physically questionable. As a result, a single adiabatic surface generally cannot support reliable nuclear dynamics and non-adiabatic effects between the classical and quantum nuclear motions are highly important. These considerations necessitate more expensive treatments, such as Ehrenfest dynamics or surface-hopping approaches.^{74,75,84,85}

C. Expectation-value constraints and return of molecular geometry with full-dimensional PES

CNEO addresses these fundamental limitations through a conceptual innovation that retains quantum nuclei within a multicomponent framework while restoring molecular geometry as an explicit set of coordinates. The key insight is that quantum nuclei, although delocalized, remain sufficiently localized in most chemical environments of interest. Therefore, a classical geometric description remains meaningful. This localization arises from the large nuclear masses, which confine nuclear delocalization to length scales much smaller than typical molecular dimensions.

This localization also enables a second simplification. In chemically relevant systems, quantum nuclei typically occupy well-separated regions of space, and overlap between identical nuclei remains small and nuclear exchange effects become negligible. The validity of this point has also been numerically confirmed in prior multicomponent calculations.⁸⁶ The CNEO framework, therefore, adopts a distinguishable-particle approximation for the quantum nuclei. This choice avoids explicit treatment of nuclear permutation symmetry and nuclear statistics, which simplifies the formulation while preserving high accuracy for the target class of chemical problems.

On the basis of these physical considerations, CNEO imposes a position-expectation constraint for each quantum nucleus I ,⁴⁵

$$\langle \hat{\mathbf{R}}_I \rangle = \mathbf{R}_I^{\text{geo}}, \quad (1)$$

where $\hat{\mathbf{R}}_I$ denotes the position operator of quantum nucleus I and $\mathbf{R}_I^{\text{geo}}$ denotes the associated geometric coordinate. This constraint introduces a quantum–classical duality. In particular, the set $\{\mathbf{R}_I^{\text{geo}}\}$ defines a classical geometry in the usual chemical sense, while the multicomponent wave function yields quantum nuclear densities around these centers and captures delocalization, zero-point motion, and shallow tunneling. As a result, $\{\mathbf{R}_I^{\text{geo}}\}$ plays the same geometric role as classical nuclear coordinates

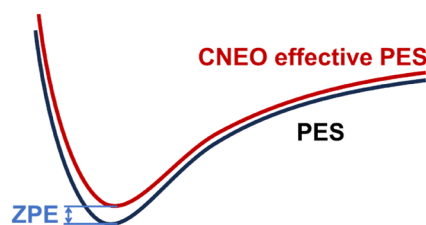


FIG. 2. Schematic comparison of conventional potential energy surface (black) and CNEO effective potential energy surface (red). In CNEO, zero-point energy (ZPE) is incorporated into the effective surface and effectively becomes a coordinate-dependent contribution that varies across geometries due to differences in nuclear quantum delocalization.

in Born–Oppenheimer theory, but the quantum nature of the constrained nuclei remains explicit.

With this treatment, the CNEO potential energy surface (Fig. 2) depends on both the classical nuclear coordinates and the constrained expectation-value coordinates of the quantum nuclei. This surface is full-dimensional and does not invoke the adiabatic, instantaneous-response assumption between classical and quantum nuclei.

III. THEORETICAL FORMULATION OF THE CNEO FRAMEWORK AND PRACTICAL IMPLEMENTATION

A. CNEO density functional theory and Kohn–Sham formalism

With the distinguishable-particle approximation and the position-expectation constraints, many multicomponent quantum chemistry methods can be modified to incorporate the constraint within the CNEO framework. Among them, multicomponent Kohn–Sham density functional theory offers an especially favorable balance of efficiency and accuracy for routine applications. In CNEO-DFT, the electronic and nuclear Kohn–Sham equations form a coupled set,⁴⁵

$$\left(-\frac{1}{2}\nabla^2 + V^e[\rho^e, \{\rho^n\}]\right)\phi^e = \varepsilon^e \phi^e,$$

$$\left(-\frac{1}{2M^n}\nabla^2 + V^n[\rho^e, \{\rho^n\}] + \mathbf{f} \cdot (\mathbf{R} - \mathbf{R}^{\text{geo}})\right)\phi^n = \varepsilon^n \phi^n. \quad (2)$$

Here, M^n is the mass of nuclei. $V^e[\rho^e, \{\rho^n\}]$ and $V^n[\rho^e, \{\rho^n\}]$ are effective Kohn–Sham potentials for electrons and nuclei, respectively, which typically include external potential, Hartree potential, electronic exchange–correlation potential, and electron–nuclear correlation potential. ρ^e and $\{\rho^n\}$ denote the electronic density and the set of nuclear densities, respectively, and ϕ^e and ϕ^n are the corresponding Kohn–Sham orbitals with orbital energies ε^e and ε^n , respectively. The term that enforces the constraint appears in the nuclear equation through the constraint potential $\mathbf{f} \cdot (\mathbf{R} - \mathbf{R}^{\text{geo}})$, with $\mathbf{f}$ being the Lagrange multiplier associated with the constraint. The coupled Kohn–Sham equations require a self-consistent field (SCF) solution because the effective potentials depend on both electronic and nuclear densities and the expectation-value constraints must hold at convergence.

B. CNEO SCF procedure

For conventional single-component Kohn–Sham DFT, the direct inversion in the iterative subspace (DIIS) technique^{87,88} is often used to accelerate convergence. For multicomponent Kohn–Sham systems, a simultaneous DIIS convergence strategy has been developed.⁸⁹ This strategy combines SCF residuals from all components into a single composite residual and applies the DIIS extrapolation uniformly across components. With the position constraints, this approach can be modified to provide an efficient solver for CNEO-DFT under the distinguishable-particle approximation.

Because the DIIS-based solver for CNEO has not been reported before, this section provides a detailed description of such a robust implementation (Fig. 3). This implementation separates the inexpensive update of the constraint Lagrange multipliers from the more expensive reconstruction of Kohn–Sham matrix elements.

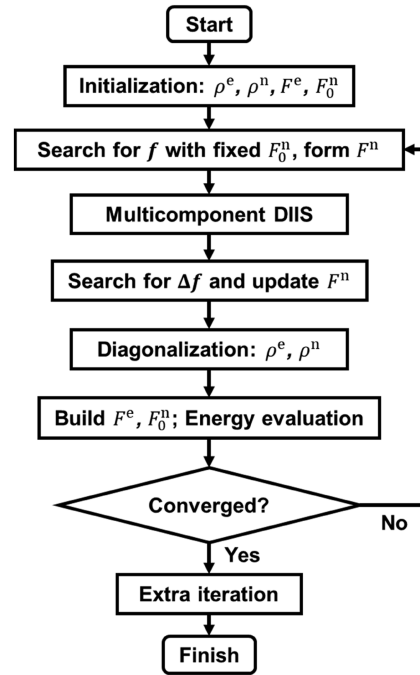


FIG. 3. Flow chart of the multicomponent simultaneous DIIS procedure along with the efficient position-constraint solver used in CNEO-DFT calculations.

- Electronic initial guess.** An initial electronic density matrix is constructed with standard initialization methods. During this step, all quantum nuclei are represented as point charges to define the external potential for the electronic subsystem.
- Nuclear initial guess.** An initial density matrix is constructed for each quantum nucleus. The initial nuclear potential uses the electronic density from step 1, with all other quantum nuclei represented as point charges.
- Initial Kohn–Sham matrix construction.** Electronic and nuclear Kohn–Sham (Fock) matrices are built from the initial density matrices. The initial total energy is also evaluated.
- Quantum nuclear position constraint enforcement.** For each quantum nucleus I , Lagrange multiplier $\mathbf{f}_I$ is updated while the unconstrained part of the nuclear Kohn–Sham matrix $\mathbf{F}_0^{n,I}$ is held fixed. Diagonalization of $\mathbf{F}^{n,I} = \mathbf{F}_0^{n,I} + \mathbf{f}_I \cdot (\mathbf{R}_I - \mathbf{R}_I^{\text{geo}})$ yields the lowest energy nuclear orbital, after which the constraint condition $\langle \widehat{\mathbf{R}}_I \rangle = \mathbf{R}_I^{\text{geo}}$ is evaluated and the error is used to guide updates of $\mathbf{f}_I$ until the error falls below a chosen threshold. This design avoids repeated construction of Kohn–Sham matrix elements during the $\mathbf{f}_I$ update.
- Simultaneous DIIS extrapolation.** A DIIS extrapolation accelerates convergence of the coupled electronic and nuclear SCF procedure.⁸⁹ At iteration k , an SCF residual vector $\mathbf{e}_k^\alpha$ is constructed for each component in an orthonormal representation,

$$\mathbf{e}_k^\alpha = \text{vec}\left(\mathbf{C}_{\text{orth},\alpha}^T (\mathbf{F}^\alpha \mathbf{D}^\alpha \mathbf{S}^\alpha - \mathbf{S}^\alpha \mathbf{D}^\alpha \mathbf{F}^\alpha) \mathbf{C}_{\text{orth},\alpha}\right), \alpha \in \{e, (n, 1), (n, 2), \dots\}. \quad (3)$$

Here, $\mathbf{S}^\alpha$, $\mathbf{D}^\alpha$, and $\mathbf{F}^\alpha$ denote the overlap, density, and Kohn–Sham matrices for component α , $\mathbf{C}_{\text{orth},\alpha}$ denotes the predefined orthonormal orbital coefficients, and $\text{vec}(\cdot)$ denotes vectorization of a matrix. Note that for each quantum nucleus I , the nuclear matrix $\mathbf{F}^{n,I}$ includes the constraint term that uses $\mathbf{f}_I$. The multicomponent DIIS residual vector is then formed by stacking residual vectors from all components,

$$\mathbf{e}_k = \begin{pmatrix} \mathbf{e}_k^e \\ \mathbf{e}_k^{n,1} \\ \mathbf{e}_k^{n,2} \\ \vdots \end{pmatrix}. \quad (4)$$

Residuals from the most recent m iterations are used to construct the DIIS error-overlap matrix,

$$B_{ij} = \mathbf{e}_i^T \mathbf{e}_j, \quad i, j = 1, \dots, m. \quad (5)$$

Then, the DIIS coefficients, $\mathbf{c} = (c_1, \dots, c_m)^T$, which satisfy $\sum_{i=1}^m c_i = 1$, are obtained by solving

$$\begin{pmatrix} \mathbf{B} & \mathbf{1} \\ \mathbf{1}^T & 0 \end{pmatrix} \begin{pmatrix} \mathbf{c} \\ \eta \end{pmatrix} = \begin{pmatrix} \mathbf{0} \\ 1 \end{pmatrix}, \quad (6)$$

where $\mathbf{1}$ denotes an m -dimensional vector of ones and η denotes a Lagrange multiplier associated with the requirement $\sum_{i=1}^m c_i = 1$. The extrapolated Kohn–Sham matrices are then constructed as

$$\tilde{\mathbf{F}}_k^e = \sum_{i=1}^m c_i \mathbf{F}_i^e, \quad \tilde{\mathbf{F}}_k^{n,I} = \sum_{i=1}^m c_i \mathbf{F}_i^{n,I}, \quad (7)$$

with

$$\mathbf{F}_i^{n,I} = \mathbf{F}_{0,i}^{n,I} + \mathbf{f}_{I,i} \cdot (\mathbf{R}_I - \mathbf{R}_I^{\text{geo}}). \quad (8)$$

- Post-extrapolation constraint enforcement.** After DIIS extrapolation, the lowest energy nuclear orbital from $\tilde{\mathbf{F}}_k^{n,I}$ may not satisfy $\langle \tilde{\mathbf{R}}_I \rangle = \mathbf{R}_I^{\text{geo}}$. The constraint is, therefore, enforced again through an additional multiplier $\Delta \mathbf{f}_{I,k}$, with the extrapolated part held fixed, until the constraint violation meets the chosen threshold. The final constrained nuclear matrix is

$$\tilde{\mathbf{F}}_k^{n,I} = \tilde{\mathbf{F}}_k^{n,I} + \Delta \mathbf{f}_{I,k} \cdot (\mathbf{R}_I - \mathbf{R}_I^{\text{geo}}). \quad (9)$$

- Diagonalization of DIIS Fock and new Fock construction.** The electronic matrix $\tilde{\mathbf{F}}_k^e$ and the constrained nuclear matrices $\tilde{\mathbf{F}}_k^{n,I}$ are diagonalized to obtain updated orbitals. Updated electronic and nuclear density matrices are then constructed and used to build the next-iteration Kohn–Sham matrices. The total energy is also evaluated according to the updated density matrices. Convergence is checked through energy and density matrix differences against last iteration. If convergence is not achieved, go back to step 4.
- Post-convergence iteration.** After SCF convergence is achieved using the DIIS algorithm, an extra SCF iteration is

performed without incurring DIIS (diagonalization of latest Fock with quantum nuclear position constraints in the same way as step 4, density update, and finally, energy evaluation). The purpose is to remove possible DIIS artifacts that can enter molecular orbital energies (such as level shift for the electronic subsystem).

CNEO-DFT retains the formal scaling of conventional density functional theory. In practice, with the same computational resource, the wall time typically increases by only 10%–20% relative to conventional DFT, even when all hydrogen atoms receive a quantum-mechanical treatment. Therefore, applications to moderately large molecular systems remain practical.

C. Analytic gradient and Hessian

CNEO-DFT provides analytic gradients⁴⁶ with respect to both classical nuclear coordinates and quantum-nuclear position expectation values, which enables standard geometry optimizations, transition-state searches, and reaction-path calculations on CNEO energy surfaces. In the complete-basis-set limit, the derivative of the CNEO-DFT energy with respect to a quantum-nuclear expectation coordinate has a particularly simple form: the gradient equals the negative of the corresponding constraint multiplier $\mathbf{f}_I$.⁴⁶ This relation gives the Lagrange multiplier $\mathbf{f}_I$ a direct interpretation as the classical force associated with quantum nucleus I . In practical calculations with finite basis sets, because the electronic and nuclear basis functions depend on the expectation-value coordinates, additional Pulay-type terms contribute in addition to the constraint term. It is worth noting that when a single set of Gaussian basis functions centered at $\mathbf{R}_I^{\text{geo}}$ is used for the corresponding quantum nucleus, which is the most common setup for CNEO-DFT calculations, the contribution of $\mathbf{f}_I$ to the gradient disappears because of an exact cancellation from Pulay-type terms, and the same cancellation also holds for the CNEO–Ehrenfest dynamics to be discussed later.⁹⁰

Analytic second derivatives require a solution of CNEO coupled-perturbed Kohn–Sham (CNEO-CPKS) equations⁴⁷ that account for the response of electronic orbitals, nuclear orbitals, and the constraint multipliers to infinitesimal displacements of both classical nuclear coordinates and quantum-nuclear expectation coordinates. This response formalism enables evaluation of an analytic CNEO Hessian suitable for stationary-point characterization and harmonic vibrational analysis on the CNEO energy surface.⁴⁷ It is also noteworthy that, as in the gradient case, when Gaussian basis functions are strictly centered at $\mathbf{R}^{\text{geo}}$ for the associated quantum nucleus, the explicit second-derivative terms involving $\mathbf{f}$ vanish. Nevertheless, derivatives of $\mathbf{f}$ still enter the CNEO-CPKS equations to enforce the nuclear position constraint under a perturbed molecular geometry.

D. CNEO molecular dynamics and constrained minimized energy surface formalism

The CNEO potential energy surface is a full-dimensional energy surface that supports classical molecular dynamics, which defines CNEO molecular dynamics (CNEO-MD).⁹¹ A theoretical justification follows from the constrained minimized energy surface molecular dynamics (CMES-MD) formalism.⁹² In the CMES formalism, a quantum state is associated with a point in a classical phase

space specified by the expectation values of position and momentum ($\mathbf{X}, \mathbf{P}$). Under an adiabatic approximation, the state at a given phase-space point is defined as the minimum-energy wave function that satisfies these position and momentum expectation value constraints. The momentum constraint leads to a uniform momentum field $\mathbf{P}$, while the effective potential V_{CMES} only depends on $\mathbf{X}$. In the effective potential $V_{\text{CMES}}(\mathbf{X})$, there are contributions from both the underlying potential energy and the quantum nuclear delocalization (zero-point) energy of the constrained wave packet.

Employing the energy conservation principle and the adiabatic approximation, the dynamics of the expectation variables follows classical equations of motion with the Newtonian form⁹²

$$\dot{\mathbf{X}} = M^{-1}\mathbf{P}, \quad \dot{\mathbf{P}} = -\nabla_{\mathbf{X}} V_{\text{CMES}}(\mathbf{X}), \quad (10)$$

where M denotes the mass of the nuclei. We note that this formulation rests on the adiabatic approximation rather than on direct propagation of the time-dependent Schrödinger equation. The approximation assumes full relaxation of the wave function to the constrained minimum at each $(\mathbf{X}, \mathbf{P})$. Therefore, $V_{\text{CMES}}(\mathbf{X})$ corresponds to a zero-temperature-limit effective potential within this construction.

For practical molecular systems, CMES quantities can be evaluated on the fly through multicomponent electronic structure theory. CNEO-DFT minimizes the total multicomponent energy under position-expectation constraints and, therefore, provides direct access to the CMES energy and its forces. Within this viewpoint, CNEO-MD corresponds to a CMES-MD realization that includes the electronic degrees of freedom explicitly in the constrained energy minimization.⁹²

This viewpoint also clarifies the connection to path-integral-based methods. Because $V_{\text{CMES}}(\mathbf{X})$ coincides with the centroid molecular dynamics (CMD) centroid potential in the zero-temperature limit,^{93,94} CNEO-MD can be viewed as an efficient, CMD-like dynamics on an *ab initio* potential energy surface, in which the effect of quantum nuclear delocalization is incorporated through the constrained minimized wave function rather than through a ring-polymer representation. As a result, CNEO-MD avoids bead discretization and the short time steps that are often required for CMD simulations.

A key limitation is the temperature dependence of the CNEO effective potential. In principle, the centroid potential is temperature-dependent, and CMD captures this dependence through the underlying path-integral ensemble. In the current CNEO formulation, however, the effective potential is obtained from a particular constrained state within the CMES construction and is temperature-independent. Incorporating an explicit temperature dependence of the effective surface is an important direction for future development.

The CMES concept also extends beyond the lowest-energy constrained state.⁹⁵ Higher-order CMES surfaces can be defined through constrained minimization within a specified quantum-nuclear state manifold, which yields effective surfaces associated with vibrational excitation and can account for hot-band contributions.⁹⁵ Dynamics on these higher-order surfaces offers a possible route for connecting CNEO-based dynamics to vibrationally excited behavior within a consistent CMES framework.

IV. APPLICATIONS OF CNEO

A. Vibrational spectroscopy

Vibrational spectroscopy has been one of the central successes of the CNEO framework because many long-standing challenges in computed spectra originate from the quantum nature of hydrogen motion. Two complementary routes have been developed within CNEO. The first route uses the mass-weighted CNEO-DFT Hessian, built with respect to the expectation-value coordinates of quantum nuclei and the classical coordinates of the remaining nuclei, to yield normal modes and frequencies in a CNEO harmonic analysis.^{47,96} This approach remains harmonic in form, but it often goes beyond conventional harmonic DFT in practice because quantum nuclear delocalization is already present in the underlying constrained wave function. As a result, substantial improvements are obtained for modes dominated by hydrogen motion, while this route retains the interpretability and low cost of Hessian-based analysis.⁴⁷

However, the limitations of this static route become apparent in hydrogen-bonded systems.^{97–100} In these systems, key spectral signatures depend not only on local anharmonicity but also on intermode coupling effects across the hydrogen-bond network. CNEO harmonic analysis does not capture such coupling effects in general, thus peak positions, intensities, and line shapes can remain inaccurate even when nuclear quantum delocalization has been incorporated. This motivates the second route, CNEO-MD, which propagates classical dynamics on the CNEO effective potential energy surface and activates intermode coupling effects through finite-temperature time evolution.⁹¹ In the time-correlation-function formulation, power, IR, and Raman spectra are obtained from Fourier transforms of velocity, dipole, and polarizability autocorrelation functions,^{91,101} respectively, computed from CNEO-MD trajectories. This route generally provides more accurate peak shifts, line shapes, and broadening.^{91,97} It can also produce nonfundamental contributions in some favorable cases, although a systematic description of overtones and combination bands remains challenging for classical-dynamics-based approaches.⁹⁷

Water clusters and protonated water clusters that are highly anharmonic highlight the relative performances between these two routes.^{97–99} In H_7O_3^+ , CNEO harmonic analysis still overestimates the dominant bound O–H stretch feature, whereas CNEO-MD shifts the main peak toward the experimental band and reproduces the characteristic progression that reflects strong coupling between bound stretches and low-frequency network modes.⁹⁷ For H_9O_4^+ , CNEO harmonic analysis already provides a reasonable baseline and CNEO-MD yields a smaller refinement, which indicates weaker coupling corrections in the dominant spectral region for that cluster.⁹⁷ Notably, these cases, with water dimer as an example (Fig. 4), also help explain why conventional DFT-based AIMD does not reliably improve upon DFT harmonic analysis. Although anharmonic intermode coupling effects are present in conventional AIMD, nuclear quantum delocalization is absent. As a result, error cancellation can sometimes favor the purely harmonic treatment and DFT harmonic analysis may outperform conventional AIMD in some cases.⁹⁷

Shared-proton complexes pose an even stricter test because the relevant proton-transfer modes are strongly anharmonic and conventional perturbative treatments can fail qualitatively. In representative systems (H_5O_2^+ , H_3O_2^- , and a proton-bound formate dimer), CNEO predicts equal proton sharing, whereas conventional

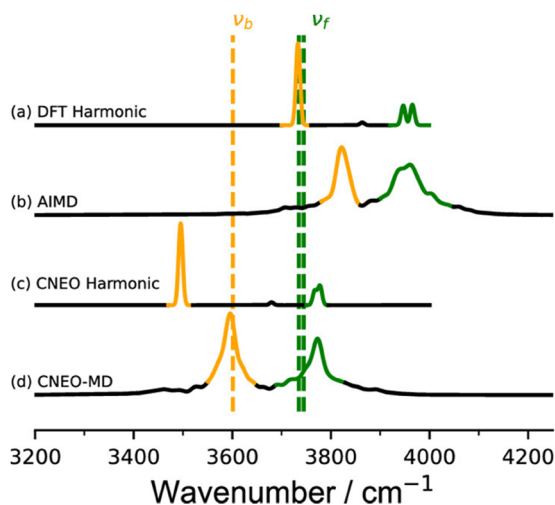


FIG. 4. Calculated IR spectra of H_4O_2 by (a) DFT harmonic analysis, (b) AIMD, (c) CNEO harmonic analysis, and (d) CNEO-MD. Experimental reference positions are indicated by the dashed lines. The improved agreement of CNEO-MD reflects the combined incorporation of nuclear quantum effects through the CNEO framework and intermode coupling effects through molecular dynamics. Adapted with permission from Zhang *et al.*, *J. Chem. Theory Comput.* **19**, 9358–9368 (2023). Copyright 2023 American Chemical Society.

electronic DFT with classical nuclei can, in some cases, favor asymmetric localization.⁹⁸ For these systems, both CNEO harmonic analysis and CNEO-MD capture the key proton-transfer fundamental modes and outperform DFT harmonic analysis, DFT-VPT2, and conventional AIMD. The failure of AIMD is especially evident in H_3O_2^- , where an asymmetric proton placement from DFT eliminates the experimental proton-transfer feature near 700 cm^{-1} , while CNEO-MD recovers the proton-transfer mode in the correct frequency range.⁹⁸

Recent work on $\text{OH}^-(\text{H}_2\text{O})_n$ ($n = 2$ and 3) clusters illustrates how these capabilities translate into practical spectral assignments.⁹⁹ The CNEO Hessian route provides a baseline for mode characterization and approximate peak placement, while a series of temperature-dependent CNEO-MD simulations reveals coupling-induced peak shifts, spectral broadening, and intensity redistribution that are essential for interpreting experimental spectra and for assignments involving mode mixing and intensity borrowing.⁹⁹

Raman spectroscopy provides an additional, stringent benchmark because it probes both vibrational frequencies and the polarizability response.¹⁰¹ In the mixed water dimer/trimer jet spectrum, CNEO-MD provides the most accurate overall description of both free and hydrogen-bonded O–H stretching features by capturing nuclear quantum delocalization together with intermode coupling effects that shape the hydrogen-bonded peaks and their intensity distributions.¹⁰¹

Finally, a practical aspect of CNEO-MD recurs across these systems. Since nuclear zero-point effects enter the CNEO effective potential energy surface directly, the primary role of molecular dynamics is not to introduce zero-point energy in a quasi-classical manner. Instead, it is mainly used to activate anharmonic intermode coupling effects by sampling regions away from the minimum.

Temperature, therefore, acts as an empirical control parameter for coupling strength, and it was found that values near 300 K often produced spectra with good agreement for hydrogen-bonded systems and protonated water clusters.^{97–99}

B. Reaction kinetics

Reaction kinetics has been another major success of the CNEO framework because nuclear quantum effects often control reaction barriers and rate constants for hydrogen-transfer processes. Coordinate-dependent zero-point energy and proton delocalization can reshape the effective free-energy landscape, shift the dynamical bottleneck, introduce Arrhenius curvature, and strongly influence kinetic isotope effects.^{102,103} The CNEO framework incorporates these effects directly within the underlying electronic-structure calculation and yields the CNEO effective potential energy surface that can be used for free-energy barrier and rate calculations. On this basis, CNEO transition state theory (CNEO-TST) was developed for computing rate constants on CNEO effective surfaces.¹⁰⁴

In CNEO-TST, the transition structure is located on the CNEO effective surface and used as the dividing surface for rate calculations. Because the CNEO surface includes coordinate-dependent zero-point energy, the resulting transition structure often lies close to the vibrationally adiabatic bottleneck that variational transition state theory (VTST)^{12,105} seeks by maximizing the generalized free energy along the minimum-energy path. This feature allows CNEO-TST to better approximate the dynamical bottleneck without an explicit VTST optimization.¹⁰⁴ In addition, shallow tunneling is captured implicitly through proton delocalization on the CNEO surface.¹⁰⁴

These features also lead to practical advantages in cost and complexity. The current standard for accurate quantum rate calculations, canonical variational transition state theory with small-curvature tunneling (CVT/SCT),¹⁰⁶ typically requires construction of an extended reaction path, extensive normal-mode analyses along the path,^{107,108} and evaluation of tunneling transmission coefficients. CVT/SCT also often relies on specific reaction parameter¹⁰⁹ (SRP) scaling to compensate for limitations of harmonic zero-point energies with standard scale factors. In contrast, CNEO-TST performs a conventional transition-state theory calculation directly on the CNEO surface, with nuclear quantum effects incorporated automatically through the underlying CNEO electronic-structure calculation.¹⁰⁴ Relative zero-point energies between reactants and transition states are obtained from the multicomponent framework rather than from harmonic approximations, which no longer rely on empirical anharmonicity scaling factors. The improved CNEO harmonic vibrational frequencies also yield more reliable vibrational free-energy contributions without empirical scaling. Finally, because proton delocalization lowers the effective barrier on the CNEO surface, which corresponds to shallow tunneling effects, CNEO-TST can often provide reasonable kinetics at moderately low temperatures without explicitly invoking tunneling correction models.^{104,110}

A few prototypical hydrogen-atom-transfer reactions illustrate that CNEO-TST can reproduce experimental rate constants with reasonable accuracy. For the $\text{D} + \text{H}_2 \rightarrow \text{DH} + \text{H}$ reaction, CNEO-TST achieves results comparable with CVT/SCT through much simpler calculations, with the effective barrier height lying

substantially below conventional CVT barriers due to nuclear delocalization effects.¹⁰⁴ More complex polyatomic reactions, such as $\text{CH}_4 + \text{OH} \rightarrow \text{CH}_3 + \text{H}_2\text{O}$ (Fig. 5), further highlight the practical advantages, where CNEO-TST predictions achieve reasonable agreement with experimental rate constants, particularly near room temperature.¹⁰⁴ Kinetic isotope effects provide additional validation, with CNEO-TST producing reasonable isotope ratios for $\text{CH}_4/\text{CD}_4 + \text{OH}$ reactions, although with slight underestimation compared to experimental values.¹⁰⁴

The integration of CNEO methods with enhanced-sampling techniques enables nuclear-quantum-effect inclusive free-energy and rate calculations for complex systems.¹¹⁰ Within the CNEO framework, nuclear quantum effects enter directly through the CNEO effective potential and then free-energy profiles can be computed on that surface using standard enhanced-sampling workflows, such as umbrella sampling^{111,112} and metadynamics.¹¹³ This capability also integrates naturally with modern machine-learning acceleration.¹¹⁴ A practical strategy is to generate configurations spanning the relevant reaction-coordinate region using inexpensive sampling and enhanced-sampling protocols, evaluate CNEO energies and forces for those configurations, and then train a machine-learning force field that reproduces the CNEO surface.^{99,110} Simulations with the resulting model can deliver NQE-inclusive free-energy profiles at a cost comparable with conventional machine-learning force field simulations trained on DFT data, while retaining the underlying nuclear quantum effects.

The finite-temperature double proton transfer in the formic acid dimer provides a clear demonstration.¹¹⁰ In that study, a machine-learning force field trained on CNEO energies and forces yields substantially lower free-energy barriers than the corresponding DFT surface. This reduction is consistent with the physical

picture that coordinate-dependent zero-point energies and proton delocalization on the CNEO effective surface reshape the free-energy landscape. Rate calculations based on these profiles show a large (10^3 – 10^5) kinetic acceleration on the CNEO surface relative to DFT.¹¹⁰ Transmission coefficients obtained from flux-side correlation functions are smaller for CNEO at the same temperature, which is consistent with increased recrossing on the lower-barrier surface.¹¹⁰ Overall, this example illustrates that CNEO-based surfaces can support both free-energy barrier estimation and dynamical corrections within a standard correlation-function framework.

More broadly, these kinetic and dynamical results demonstrate the promise of using CNEO effective potential energy surfaces to support both equilibrium and dynamical predictions. In this picture, improved relative zero-point energies refine free-energy differences and barrier heights, while classical dynamics on the CNEO surface provides a practical route to studying real-time dynamical processes.

Finally, the regime of deep tunneling still requires explicit attention. CNEO-TST includes shallow tunneling in the sense that proton delocalization across an effective barrier is already contained in the CNEO potential; therefore, no separate tunneling transmission coefficient is introduced. However, at sufficiently low temperatures where deep tunneling dominates, underestimation can occur,¹⁰⁴ and addressing this limitation will be an important target for future development.

V. CNEO EXCITED-STATE CALCULATIONS AND NONADIABATIC DYNAMICS

To incorporate nuclear quantum effects into photochemistry, the CNEO framework has been extended to electronic excited states.¹¹⁵ These developments provide NQE-inclusive excited-state potential energy surfaces and analytic derivatives, which enable excited-state structure characterization, vibrational analysis, and molecular dynamics in regimes where proton delocalization and zero-point motion affect both energetics and spectroscopy. In addition, CNEO-based nonadiabatic dynamics have been developed to provide access to electronically nonadiabatic processes in which nuclear quantum effects influence both barrier shapes and transition dynamics.⁹⁰ Together, these developments make it feasible to investigate excited-state proton and hydrogen transfer, photoacid and photobase behavior, and related photochemical reactivity in hydrogen-containing systems with an explicit and computationally efficient treatment of quantum nuclei.

A. CNEO time-dependent density functional theory

To obtain NQE-inclusive potential energy surfaces for electronic excited states, CNEO time-dependent density functional theory (CNEO-TDDFT) has been developed.¹¹⁵ It assumes that nuclear densities remain unchanged during vertical electronic excitation, which essentially corresponds to the Franck–Condon approximation. The electronic response is then described within standard linear-response theory. The excited-state energy at a given geometry can, therefore, be expressed as the CNEO-DFT ground-state energy plus the electronic excitation energy computed on the CNEO reference. Nuclear quantum effects enter the excited-state surface through (i) nuclear zero-point kinetic energy and delocalization already present in the CNEO-DFT reference, (ii) electron–nucleus interactions evaluated with delocalized quantum nuclear densities,

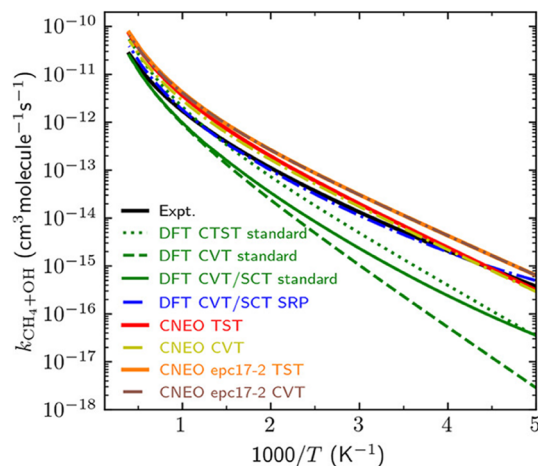


FIG. 5. Hydrogen atom transfer reaction rate constants for the $\text{CH}_4 + \text{OH} \rightarrow \text{CH}_3 + \text{H}_2\text{O}$ reaction. Without empirical scaling, CNEO with a simple transition-state-theory treatment provides an accurate description of the rate constants by directly incorporating nuclear quantum delocalization effects. In contrast, conventional DFT requires canonical variational TST (CVT), small-curvature tunneling (SCT) corrections, and specific reaction parameter (SRP) scale factors to achieve comparable accuracy. Adapted with permission from Chen *et al.*, J. Chem. Theory Comput. **21**, 590–604 (2025). Copyright 2025 American Chemical Society.

and (iii) changes in the excitation energy that arise from those delocalized nuclei.

The distinction from conventional TDDFT originates from the underlying ground-state calculation. Conventional TDDFT constructs excitation energies from Kohn–Sham orbitals obtained with nuclei represented as classical point charges. In CNEO-TDDFT, the reference orbitals and orbital energies are obtained from CNEO-DFT; thus, the electronic degrees of freedom see quantum nuclear densities rather than point charges, while the linear-response formalism for the excitation energy remains unchanged.

Analytic gradients of the CNEO-TDDFT excited-state surface require a multicomponent response treatment that accounts for the electronic response, the coupled quantum-nuclear degrees of freedom in the reference, and the position-expectation constraints.¹¹⁵ This treatment can be formulated through modified Z-vector equations¹¹⁶ that incorporate the multicomponent orbital structure and the constraint Lagrange multipliers. With this formulation, excited-state gradients can be evaluated with a computational cost comparable with conventional TDDFT gradients. As a result, excited-state geometry optimizations, harmonic vibrational analysis on NQE-inclusive excited-state surfaces, and direct excited-state dynamics on top of these surfaces become practical within the same CNEO workflow.

Benchmark tests on excited-state vibrational frequency calculations for a series of small molecules demonstrate substantial improvements over conventional TDDFT. For high-frequency stretching modes above 2800 cm^{-1} that involve hydrogen motion, conventional TDDFT systematically overestimates frequencies by more than 100 cm^{-1} , whereas CNEO-TDDFT reduces these errors to $10\text{--}20\text{ cm}^{-1}$.¹¹⁵ The improvements are less pronounced for mid-range and low-frequency modes dominated by heavy-atom motion, as expected when nuclear quantum effects are small for the unquantized nuclei in the chosen CNEO treatment.¹¹⁵ These results support the use of CNEO-TDDFT as an accurate approach to excited-state vibrational spectroscopy for hydrogen-containing systems, while maintaining computational efficiency comparable with conventional TDDFT.

B. CNEO nonadiabatic dynamics

Nonadiabatic dynamics has been formulated within the CNEO framework by combining CNEO effective electronic surfaces with

standard mixed quantum–classical algorithms.⁹⁰ In this way, nuclear quantum delocalization enters through ZPE-corrected PES, while nuclear motion and nonadiabatic transition remain in a conventional mixed quantum–classical form. Two complementary variants have been developed: CNEO-Ehrenfest dynamics and CNEO fewest-switches surface hopping (FSSH).⁹⁰

In CNEO-Ehrenfest dynamics, a mean-field electron–nuclear coupling picture is assumed, as in conventional Ehrenfest dynamics. The electronic wave function, ϕ_e , evolves according to a time-dependent Schrödinger-type equation with an effective Hamiltonian that depends on the instantaneous nuclear density. The quantum nuclear position expectation values $\langle R_t \rangle$, together with their associated velocities, evolve under Newton-like equations of motion on an effective potential defined by the instantaneous electronic state, while the quantum-nuclear amplitude A is determined at each time step via a constrained minimization.⁹⁰ The classical nuclei are propagated simultaneously using classical equations of motion. Overall, this workflow closely parallels conventional Ehrenfest dynamics, but it employs a quantum-nuclear description and requires determination of A through the constrained minimization. It thus differs fundamentally from NEO-Ehrenfest dynamics, in which both the electrons and the quantum nuclei are propagated in real time by time-dependent Schrödinger-type equations, whereas only the classical nuclei follow classical equations of motion. The relationships and differences among these three Ehrenfest dynamics schemes are summarized schematically in Fig. 6. Similar to the adiabatic CMES evolution picture, a direct connection between the force and the constraint multiplier can be established in the analytic or complete-basis limits, with additional Pulay-type contributions when the finite basis set follows the expectation coordinates.⁹⁰

CNEO fewest-switches surface hopping employs a different strategy. Electronic state populations undergo stochastic transitions according to conventional hopping algorithms,⁴¹ but the underlying adiabatic energy surfaces are constructed using ground-state nuclear densities from CNEO calculations rather than classical nuclear point charges.⁹⁰ This frozen nuclear density approach for surface construction adopts a Franck–Condon picture for electronic transitions, which is also consistent with the CNEO-DFT/TDDFT combination used for obtaining CNEO effective potential energy surfaces.¹¹⁵

Model tests on the Shin–Metiu system¹¹⁷ for one-dimensional proton-coupled electron transfer show the intended effects of these

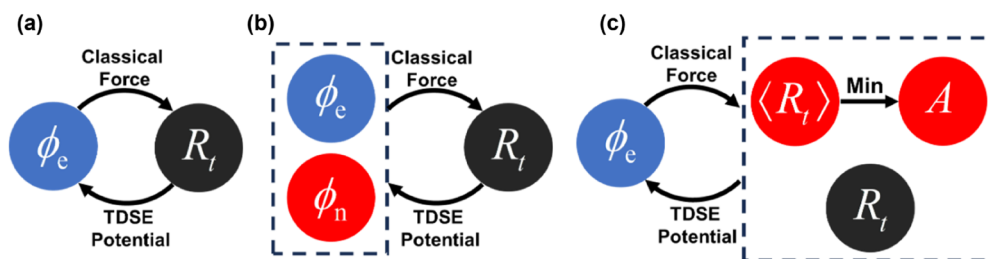


FIG. 6. Schematic illustrations of (a) conventional Ehrenfest dynamics, (b) NEO-Ehrenfest dynamics, and (c) CNEO-Ehrenfest dynamics. In all cases, the electronic wave function evolves according to a time-dependent Schrödinger-type equation (TDSE) and provides forces that drive the classical dynamics of the classical nuclei, which in turn provide the potential experienced by the electrons. In NEO-Ehrenfest dynamics, the quantum nuclei are also propagated fully quantum mechanically, whereas in CNEO-Ehrenfest dynamics, the quantum-nuclear expectation values are propagated with classical equations of motion and the nuclear wave function amplitude is obtained at each time step via a constrained minimization.

constructions. In the low-momentum regime, conventional Ehrenfest dynamics and conventional FSSH slightly underestimate transmission, whereas CNEO-Ehrenfest and CNEO-FSSH reduce the deviation.⁹⁰ The improvement is mainly attributed to a reduced effective barrier on the CNEO ground-state surface. CNEO-FSSH consistently shows the best overall agreement with exact quantum reference calculations across all tested model parameter sets. In the high-momentum regime, the CNEO-based and conventional methods converge to the same behavior, which indicates that the CNEO correction improves the quantum regime without degrading the classical regime.⁹⁰

Practical tests on realistic molecular systems for CNEO-Ehrenfest dynamics and CNEO-FSSH remain to be performed, although the implementations are straightforward. For CNEO-FSSH, the computational scaling resembles that of conventional *ab initio* FSSH since both require on-the-fly electronic structure calculations, with the primary difference being the use of CNEO-DFT/TDDFT rather than conventional DFT/TDDFT for surface construction. For CNEO-Ehrenfest dynamics, the computational requirements will differ because it requires solving the nuclear wave functions under the CMES approximation.

VI. CNEO FOR COMPLEX ENVIRONMENTS

Extending NQE treatments to realistic environments is essential for practical applications because most chemically and biologically relevant processes occur in solution, heterogeneous media, or condensed phases where the environment can reshape both electronic structure and nuclear quantum effects. Recent developments have, therefore, focused on interfacing CNEO with standard environment models, with the goal of retaining efficiency and familiar workflows of conventional electronic-structure and dynamics calculations.

A. Solvation model integration for solution

CNEO-DFT has been interfaced with widely used implicit solvation models, including the domain-decomposed conductor-like screening model (ddCOSMO)^{118–122} and the polarizable continuum model (PCM).^{123,124} These integrations also provide analytic gradients, which enable geometry optimizations and CNEO molecular dynamics in solutions. For CNEO-PCM, analytic second derivatives have also been derived and implemented, which makes harmonic normal-mode analysis available on solvated CNEO potential energy surfaces.

A representative illustration by Xu is the vibrational spectroscopy of the formate ion in solution, where the C–H stretch exhibits an unusual solvatochromic shift that is difficult to reproduce when nuclear quantum effects are neglected.¹²¹ For the isolated formate ion, conventional DFT shows the familiar systematic bias in hydrogen-involving modes, whereas CNEO-DFT brings the absolute frequencies much closer to the experiment.¹²¹ In solution, the frequency shift adds an additional sensitivity to the solvent electrostatic environment. Implicit solvation captures part of this effect, but explicit solvent molecules are required to recover the full experimental shift. When CNEO is combined with implicit solvation and explicit solvent coordination, both the absolute vibrational frequencies and the solvatochromic shift are reproduced more consistently,

which highlights that quantum nuclear delocalization responds strongly to the local electrostatic field generated by the surrounding solvent.¹²¹

B. CNEO QM/MM for biological systems

Biological environments contain complex hydrogen-bond networks and frequent proton-transfer motifs for which nuclear quantum effects can be decisive. To make such effects accessible in realistic biomolecular settings, CNEO-DFT has been integrated with QM/MM under an electrostatic-embedding scheme.¹²⁵ Because some nuclei in the QM region are treated quantum mechanically, additional QM–MM interaction terms arise from interactions between quantum nuclear densities and the MM environment. Both electrostatic and van der Waals contributions are added as explicit quantum-nuclei–MM (q-MM) terms, and the MM external potential enters the electronic and nuclear CNEO Kohn–Sham equations on the same footing as the usual external potentials.¹²⁵ Analytic gradients can be formulated with respect to classical QM nuclei, quantum-nuclear expectation-value coordinates, and MM atom positions, which enable CNEO-QM/MM geometry optimization and molecular dynamics at modest overhead relative to conventional DFT-QM/MM.¹²⁵

The glutamic acid–glutamate complex provides a representative biological test case because it features a short, strong, low-barrier hydrogen bond with a shared proton, and both structure and dynamics depend sensitively on proton delocalization.^{126–129} In this system, CNEO-QM/MM yields a more central shared-proton distribution and shorter, more compact hydrogen-bond metrics than conventional DFT-QM/MM, consistent with experimental indications of pronounced proton sharing.¹²⁵ In dynamics, substantially more frequent proton-transfer events are obtained with CNEO-QM/MM than with DFT-QM/MM, in both gas-phase and aqueous environments, because quantum delocalization leads to more overlapped O–H and O···H bond length distributions that support transfer.¹²⁵

C. CNEO with periodic boundary conditions for extended systems

Efficient incorporation of nuclear quantum effects into surfaces, interfaces, and crystalline materials remains essential for predictive modeling of heterogeneous catalysis and condensed-phase hydrogen chemistry. To this end, CNEO-DFT has been extended to periodic boundary conditions within the Gaussian and augmented plane wave (GAPW)^{130,131} framework in CP2K,¹³² which enables quantum-mechanical treatment of nuclei in extended systems while retaining the standard periodic electronic-structure workflow. In this periodic formulation,¹³³ quantum nuclei are treated within the distinguishable-particle approximation, which avoids nuclear Bloch states and is physically justified by the strong spatial localization and minimal overlap of nuclear wave functions in typical chemical environments. Periodicity is preserved through the collective nuclear distribution, and position constraints enforce the nuclear expectation positions that define geometry within the unit cell. Analytic gradients with respect to both classical nuclear coordinates and quantum-nuclear expectation positions have also been implemented, which supports geometry optimization and

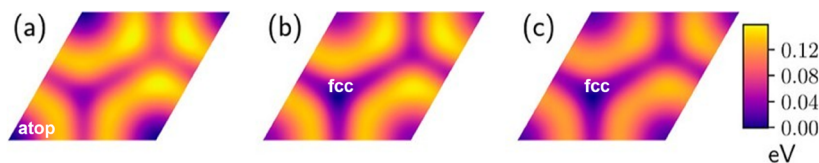


FIG. 7. Comparison of hydrogen adsorption on Pt(111) from different computational approaches. (a) Conventional DFT potential energy surface showing the atop site as the most stable configuration. (b) ZPE-corrected DFT potential energy surface revealing the fcc hollow site as the most stable configuration. (c) CNEO-DFT potential energy surface also preferring the fcc hollow site. The energy surfaces span one unit cell of the Pt(111) surface and energies are given relative to the respective global minimum. Reproduced with permission from Chen and Yang, *J. Chem. Theory Comput.* **21**, 7865–7877 (2025). Copyright 2025 Authors, licensed under a Creative Commons Attribution 4.0 License.

molecular dynamics on the NQE-inclusive periodic energy surface with minimal additional cost beyond conventional periodic DFT.¹³³

Hydrogen adsorption on Pt(111) provides a clear demonstration that NQEs can qualitatively alter predictions of surface structure and thermodynamics.^{134,135} Conventional DFT favors the atop site, whereas both ZPE-corrected DFT and CNEO-DFT favor the fcc hollow site (Fig. 7), consistent with a quantum reference description.^{133,134} Within CNEO-DFT, this site preference emerges directly from the underlying multicomponent treatment, which captures the key zero-point contribution without requiring additional harmonic analysis.

Beyond site preferences, periodic CNEO-DFT provides improved thermodynamic descriptions of hydrogen mobility on surfaces. The in-plane differential entropy for hydrogen motion on Pt(111), computed from classical integrations over effective energy surfaces,¹³⁴ shows that CNEO-DFT matches the quantum reference most closely across the full temperature range studied, with particularly strong performance in the catalytically relevant regime of 500–800 K.¹³³ This accuracy arises from two connected effects: correct stabilization of the fcc hollow site and a systematically reduced diffusion barrier between neighboring sites on the CNEO-DFT surface relative to ZPE-corrected DFT.

Collectively, these results illustrate how periodic CNEO-DFT can provide NQE-sensitive structural and thermodynamic quantities for extended systems within a practical computational framework.

The successful integration of CNEO with solvation models, QM/MM schemes, and periodic boundary conditions demonstrates the method's capacity to address nuclear quantum effects across diverse chemical environments. These developments enable systematic investigation of how nuclear quantum effects influence molecular behavior in the complex environments where hydrogen-related chemistry occurs, from biological systems to heterogeneous catalysis. They also provide a foundation for more accurate and broadly applicable computational predictions.

VII. CNEO ON QUANTUM COMPUTERS

The combination of nuclear quantum effects and quantum computing offers a natural route toward multicomponent treatments that remain challenging on classical hardware.^{136–140} Classical implementations of methods that incorporate nuclear quantum effects can face exponential scaling, whereas quantum computing approaches may offer a potential advantage.^{141–143} In

the CNEO setting, a practical hybrid workflow can be defined: a quantum computer is used to solve the correlated multicomponent electronic-structure problem under the CNEO position-expectation constraints and to provide NQE-inclusive energies and forces on the CNEO potential energy surface, while a classical computer propagates nuclear dynamics on that surface.

A proof-of-principle realization has been performed using CNEO full configuration interaction (CNEO-FCI) and CNEO unitary coupled cluster with singles and doubles (CNEO-UCCSD) within a variational quantum eigensolver framework.^{144–147} The electronic and nuclear creation and annihilation operators are mapped to qubits via the Jordan–Wigner transformation,¹⁴⁸ and the expectation-value constraints are enforced through a penalty term in the energy functional that restrains each quantum-nuclear expectation position to a target value using a second-quantized position-operator representation.¹⁴⁴

For H₂, HD, and D₂, CNEO-UCCSD yields energies, equilibrium expectation geometries, and harmonic vibrational frequencies in excellent agreement with CNEO-FCI.¹⁴⁴ In these systems, more than 99% of the correlation energy is recovered over most bond distances, geometries match to the reported digits, and harmonic frequencies differ by only 2–4 cm^{−1}. Beyond energies and structures, it is also possible to perform an explicit quantum-information analysis of electron–nuclear correlations within the CNEO framework. Here, von Neumann entropies and mutual information were evaluated along bond dissociation of H₂, HD, and D₂. In the dissociation limit, the mutual information between the two quantum nuclei approaches zero, alongside a nontrivial approach to equality in the strong-subadditivity relation among the electronic and nuclear subsystems.¹⁴⁴

The successful demonstration of quantum algorithms establishes a proof of principle for quantum computing approaches to nuclear quantum effects within the CNEO framework and highlights the natural synergy between multicomponent quantum chemistry and quantum information science.

VIII. INTEGRATION WITH QUANTUM CHEMISTRY INFRASTRUCTURE

A key practical strength of the CNEO framework is that it fits naturally within existing quantum chemistry workflows. Because CNEO retains an explicit geometry through nuclear expectation-value coordinates and produces a well-defined potential energy surface, standard capabilities, such as SCF iterations, analytic

gradients and Hessians, geometry optimization, transition-state searches, vibrational analysis, and molecular dynamics, can be enabled with targeted modifications rather than wholesale redesign of electronic-structure infrastructure. This compatibility has facilitated implementations of CNEO methods by our group in several widely used packages, including PySCF,^{149,150} CP2K,¹³² and NWChem,¹⁵¹ as well as by the Hammes-Schiffer and Kanai groups in QChem¹⁵² and FHI-aims.¹⁵³ The availability of a Python interface within GROMACS¹⁵⁴ further enables QM/MM simulations in which CNEO calculations from PySCF provide energies as well as forces for both the QM and MM parts. Collectively, these developments lower the barrier to adoption and make NQE-inclusive calculations accessible to non-specialists.

More broadly, this software integration illustrates how CNEO addresses a longstanding practical bottleneck for multicomponent approaches. Conventional multicomponent methods often sacrifice the familiar molecular-structure and potential-energy-surface picture, which complicates the use of standard computational chemistry tools. CNEO restores this picture so that nuclear quantum effects can be incorporated while retaining established workflows. This combination of conceptual continuity and computational efficiency positions CNEO as a practical route for routine inclusion of nuclear quantum effects in problems involving light nuclei.

IX. CONCLUDING REMARKS

In this Perspective, we presented the CNEO framework as a practical and interpretable route for incorporating NQEs into electronic-structure calculations and molecular simulations, while preserving the familiar language of molecular geometry and potential energy surfaces. The central idea is that position-expectation constraints restore molecular geometry as a set of coordinates with some or all nuclei treated quantum mechanically. As a direct consequence, CNEO yields a well-defined, full-dimensional, Born–Oppenheimer-like potential energy surface in terms of classical nuclear coordinates and constrained quantum-nuclear expectation coordinates. Zero-point energy, nuclear delocalization, and shallow tunneling emerge naturally from the multicomponent quantum-chemistry formalism. This potential-energy-surface picture is the key reason that CNEO integrates naturally with established infrastructure, including analytic gradients and Hessians, geometry optimization, transition-state searches, harmonic analysis, and molecular dynamics.

To date, the most visible successes of CNEO have been in vibrational spectroscopy and in hydrogen-related reaction kinetics and dynamics, where nuclear quantum effects are often decisive. In vibrational spectroscopy, CNEO harmonic analysis improves the description of hydrogen-dominated vibrational modes by accounting for quantum delocalization, and CNEO-MD captures intermode coupling effects that influence line shapes and peak positions in strongly anharmonic hydrogen-bonded systems. In reaction kinetics, CNEO-based free-energy and rate calculations demonstrate how coordinate-dependent zero-point contributions reshape effective barriers and influence rate estimates, while standard dynamical corrections can still be applied on top of the CNEO effective surface.

The same philosophy extends beyond the ground state. CNEO excited-state theory provides NQE-inclusive excited-state surfaces and analytic derivatives, and CNEO-based nonadiabatic dynamics

enables photochemical modeling in regimes where quantum nuclei influence both excited-state energetics and transition dynamics. Together, these excited-state extensions open a path toward photochemical applications where quantum nuclei can influence both adiabatic excited-state landscapes and nonadiabatic transition dynamics.

In complex environments, interfaces with implicit solvation models, QM/MM embedding, and periodic boundary conditions further demonstrate that CNEO can treat nuclear quantum effects in realistic settings, ranging from solution-phase chemistry and biological systems to extended periodic materials.

Finally, the formulation of correlated CNEO solvers for quantum computing points to a longer-term route for multicomponent correlation treatments that are difficult to scale on classical hardware, while retaining the structure-based CNEO workflow.

At the same time, several limitations and opportunities define important directions for continued development. First, the deep-tunneling regime, where quantum effects dominate nuclear motion, poses fundamental challenges for mean-field treatments and current electron–proton correlation functionals, although such extreme behavior is relatively uncommon in typical molecular systems. Second, the temperature dependence of the effective CNEO potential remains an important topic, particularly for reaction kinetics that can depend sensitively on effective barrier heights and sampling. Third, more systematic assessment across broader chemical spaces will be valuable for identifying where CNEO provides the largest and most robust gains and where further improvements in electron–nuclear correlation functional design are needed. Fourth, from a practical standpoint, continued progress on software availability, automated workflows, and machine-learning acceleration will further lower the barrier for routine use in large-scale calculations.

Overall, CNEO occupies a distinct and useful position among multicomponent quantum methods. It preserves the conceptual clarity of molecular geometry and potential energy surfaces, maintains computational efficiency comparable with conventional electronic-structure workflows, and incorporates key nuclear quantum effects directly in the underlying energy evaluation. As the methodology continues to expand in scope, CNEO offers a promising route toward making quantum nuclei a routine component of quantum chemistry calculations and molecular simulations and toward advancing our understanding of chemical processes where the quantum nature of nuclei determines molecular behavior.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Zehua Chen: Conceptualization (equal); Writing – original draft (lead); Writing – review & editing (supporting). **Yang Yang:** Conceptualization (equal); Writing – original draft (supporting); Writing – review & editing (lead).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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