

# Quantum embedding electronic structure methods

## 1 | INTRODUCTION: QUANTUM EMBEDDING IN THE TIME OF PANDEMIC

This editorial serves as an introduction to a series of 10 papers collected under the special issue “Quantum Embedding Electronic Structure Methods.” The idea to assemble a special issue came during a symposium at the Spring 2019 meeting of the American Chemical Society where we (Adam and Michele) organized a Physical Chemistry symposium bearing the same name as the special issue. The symposium ran for the entire week and featured many flavors of embedding: from density embedding to embedding within lattice models, as well as continuum models and many-body expansions. While it may seem that these approaches are far removed from each other, the symposium highlighted common goals, such as the reduction of the computational effort through “divide-and-conquer” strategies, and stressed the importance of establishing a common language across all embedding methods.

It is clear that human interaction is key for scientific progress, and traveling to conferences is an important aspect of scientific research. Unfortunately, we write this introduction during a pandemic of historic proportions, when working on theoretical and computational chemistry may seem like an unacceptable luxury or an unjustified distraction. It is striking to remember how we interacted prior to the outbreak. Figure 1 provides a glimpse into the social nature of the symposium participants and the massive crowds at the conference.

The editorial is organized into three sections: *Origins*, where we briefly discuss the origins of embedding methods for newcomers to the field; *Present*, where we highlight some of the current efforts with an emphasis on the contributions submitted to this Special Issue of IJQC; and *Future*, where we enumerate a few of the open challenges in the field and speculate on some of its possible future directions.

## 2 | ORIGINS

Modern embedding methods can be broadly classified into three groups: density embedding, density-matrix and Green's function (GF) embedding, and classical (quantum mechanics / molecular mechanics (QM/MM) and continuum dielectrics) embedding. We briefly discuss the origins of these three approaches separately.

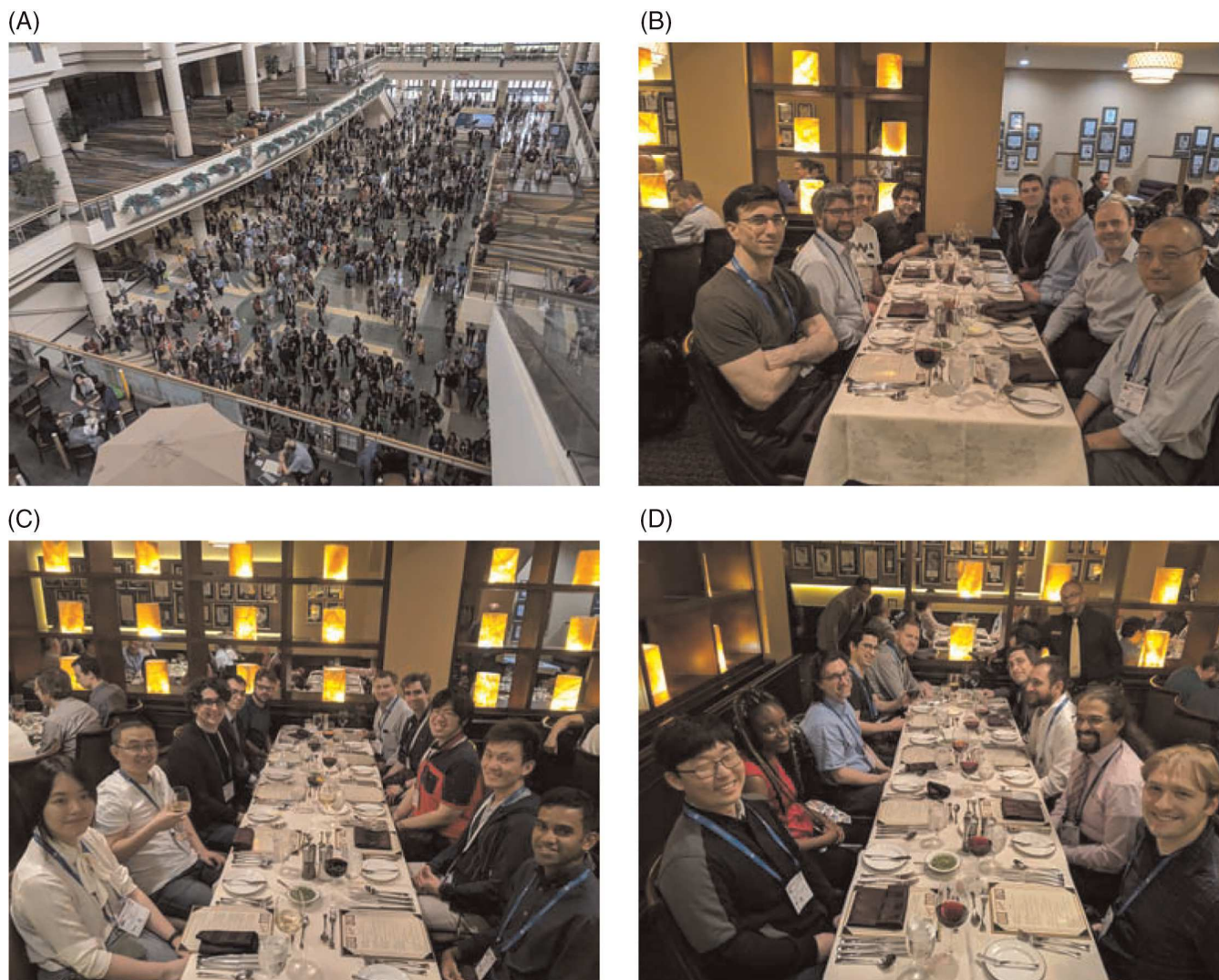
### 2.1 | Density embedding

The first density embedding calculations were performed by Gordon and Kim (GK),<sup>[1,2]</sup> who calculated the binding energy curves of rare-gas dimers based on the assumption that the electronic density of the molecules could be well approximated by the sum of their isolated-atom densities. Corrections to these were added to account for self-interaction errors,<sup>[3,4]</sup> as well as induction effects and dispersion forces.<sup>[5]</sup> All of these early calculations were non-self-consistent, but self-consistent versions of the GK model soon followed,<sup>[6]</sup> leading to the formulation of subsystem density functional theory (DFT)<sup>[7]</sup> and frozen-density embedding (FDE).<sup>[8]</sup>

In parallel to the development of other related methods,<sup>[9–14]</sup> an important advance was the ability to treat different fragments with different levels of theory, a strategy usually referred to as embedding-DFT.<sup>[15]</sup> The main equations to be solved in practice in most of these cases are the Kohn-Sham equations with constrained electron density (KSCED).<sup>[7,8,16]</sup> In the KSCED, the total electronic energy,  $E$ , is understood as a functional of the set of fragment densities  $\{n_\alpha(\mathbf{r})\}$ , which we denote with a bold  $\mathbf{n} \equiv \{n_\alpha(\mathbf{r})\}$ . In terms of KS quantities,  $E$  can be divided as:  $E[\mathbf{n}] = V_{\text{ext}}[\mathbf{n}] + E_{\text{H}}[\mathbf{n}] + E_{\text{XC}}[\mathbf{n}] + \sum_\alpha T_s[n_\alpha] + T_s^{\text{nad}}[\mathbf{n}]$ , where  $V_{\text{ext}}$  is the electron-nuclear energy;  $E_{\text{H}}$  is the Hartree energy;  $E_{\text{XC}}$  is the exchange-correlation energy; and  $T_s^{\text{nad}}[\mathbf{n}]$  is the *nonadditive*, noninteracting kinetic energy, defined simply as the difference  $T_s^{\text{nad}}[\mathbf{n}] = T_s[\mathbf{n}] - \sum_\alpha T_s[n_\alpha]$ . This rewriting of the total energy is still, in principle, exact as long as the fragment densities sum to the correct molecular density  $n(\mathbf{r})$ :

$$\sum_\alpha n_\alpha(\mathbf{r}) = n(\mathbf{r}) \quad (1)$$

In practical calculations,  $T_s^{\text{nad}}[\mathbf{n}]$  may be evaluated using approximate functionals, while fragment kinetic energies may be calculated using KS orbitals. The KSCED follows by requiring that  $E[\mathbf{n}]$  be minimized directly with regard to variations of the  $n_\alpha(\mathbf{r})$ . A different set of equations is



**FIGURE 1** Interactions during the Spring 2019 National ACS meeting in Orlando, FL, A, Crowds in search of a lunch spot. B, C, D, ACS-PHYS symposium “Quantum Embedding Electronic Structure Methods” banquet

obtained if one minimizes the sum of fragment energies,  $\sum_{\alpha} E[n_{\alpha}]$ , under the constraint of Equation (1), as is done in partition DFT,<sup>[17,18]</sup> with advantages and disadvantages discussed elsewhere.<sup>[19]</sup>

We refer the reader to the many important reviews on this subject.<sup>[19–25]</sup>

## 2.2 | Density-matrix and GF embedding

While we (the authors) are not experts on density matrix<sup>[26,27]</sup> (DM) and GF<sup>[28–30]</sup> embedding methods, we demonstrate here the main differences (goals, framework, etc.) with density-based embedding. Density embedding decouples the subsystems at the level of electron density. That is, Equation (1) is imposed. In DM and GF embedding, the decoupling of the subsystems takes place at the level of the wavefunction or GF. This requires defining at least a Fock space or a Hilbert space spanning the entire supersystem. The embedding then takes place within such a space, whereby a portion of the system (space) is treated at a higher level (typically a level that is exact in some limiting cases<sup>[29]</sup>). Strong correlations can be captured in small regions of space,<sup>[31]</sup> while mean-field methods can be used for the remainder of the system. This very idea applies well to bulk crystals containing transition metal elements<sup>[32]</sup> of, even more extremely, lanthanides and actinides.<sup>[33]</sup>

Similar embedding methods requiring the definition of a supersystem Hilbert space are those that reproduce KS-DFT while aiming to reduce the cost, for example, bootstrap embedding<sup>[34,35]</sup> and the projection-based embedding methods developed initially by the Piela group<sup>[36]</sup> and

more recently revived by the Chalasinaki group<sup>[37]</sup> in the context of symmetry adapted perturbation theory (SAPT) and by the groups of Hoffman,<sup>[38]</sup> Miller,<sup>[39–41]</sup> Carter,<sup>[42–44]</sup> and Neugebauer<sup>[45]</sup> in the context of DFT-in-DFT and wavefunction-in-DFT embedding. These hinge upon partitioning the orbital space into orthogonal subspaces, while embedded mean field methods employ multiple representations of the DM<sup>[46–48]</sup> to use smaller basis sets associated with cheaper local functionals for selected atoms.

### 2.3 | QM/MM and continuum dielectrics embedding

In parallel to the development of density and density-matrix embedding methods, significant advances have been made in QM/MM<sup>[49–51]</sup> and continuum embedding methods.<sup>[52–54]</sup> Continuum models are quite attractive because they are parametrized semiempirically and inherently include the effects of averaging over the solvent configurations. We note, however, that Wesolowski and coworkers have extended density embedding to treat configuration-averaged solvents.<sup>[55]</sup> Furthermore, continuum models have been extended to a number of interesting regimes, including the ones typical of electrochemical systems,<sup>[56]</sup> plasmonics,<sup>[57]</sup> and nonequilibrium systems,<sup>[58,59]</sup> and have even been exploited to cure some inconvenient effects of self-interaction in semilocal exchange-correlation energy density functionals.<sup>[60]</sup>

QM/MM has been at the forefront of chemical theory applied to biological systems, culminating with the 2013 Nobel prize to Karplus, Levitt and Warshel.<sup>[61]</sup> The main idea behind QM/MM is the possibility of finding an appropriate value of atom-centered charges such that the electrostatic potential in the region of a QM subsystem is well reproduced. Using that, the resulting embedding can be viewed as an electrostatic embedding. An often-stated justification for using QM environments rather than MM ones is the fact that the Coulomb potential singularity of MM charges can lead to a model's instability.<sup>[22]</sup>

In comparison to continuum models, QM/MM retains, in part, the atomistic nature of the environment. Particularly important are the extensions of QM/MM to explicitly treat polarization (electrostatic induction), which is critical in many biosystems.<sup>[51,62,63]</sup> Interesting combinations of QM/MM or density embedding and continuum models exist where the role of the continuum is to include polarizations from faraway environments.<sup>[64–66]</sup>

## 3 | PRESENT

*Density embedding:* Recent applications have included charge transfer reactions,<sup>[67]</sup> charge transfer excitation energies and diabatic couplings,<sup>[68]</sup> van der Waals interactions,<sup>[69]</sup> spectroscopy of complex systems and solvatochromatic shifts,<sup>[70–75]</sup> and many more.<sup>[21,76–78]</sup> Numerically accurate (although inadequate in practical calculations) methods can calculate  $\delta T_{\text{Snad}}/\delta n(r)$  for covalent bonds.<sup>[42,76]</sup> However, the performance of an approximate self-consistent subsystem DFT for potential energy curves is well understood, especially for weakly interacting systems.<sup>[79,80]</sup> To avoid relying on approximate expressions for  $T_s^{\text{nad}}[\mathbf{n}]$ , techniques have been developed to calculate *exact*  $T_s^{\text{nad}}[\mathbf{n}]$  via potential reconstruction.<sup>[81]</sup> These are ill-posed and can be numerically expensive, although recent advances have made density-to-potential inversions only slightly more computationally expensive than the direct solution of the KS equations.<sup>[82]</sup> Nevertheless, approximating the nonadditive kinetic energy functional for subsystem DFT,  $T_s^{\text{nad}}[\mathbf{n}]$ , remains a major challenge and pervades almost all applications of purely density-based embedding calculations.

*Approximating the nonadditive energy components:* Jiang et al.<sup>[83]</sup> derive two virial relations for fragments in molecules in the framework of partition DFT. These can be used to test approximations for  $T_s^{\text{nad}}[\mathbf{n}]$ . Huang<sup>[84]</sup> shows how the correlation energy from the random-phase approximation can be decomposed into two components, a long-wavelength and a short-wavelength component. The former is calculated using Huang's recent embedded-cluster density approximation,<sup>[85]</sup> where the molecular XC energy is approximated through a procedure that patches XC energy densities of user-defined clusters.

*Time-dependent extensions:* All density embedding methods are susceptible to time-dependent extensions.<sup>[86–89]</sup> Most applications are in the linear-response regime where excitation energies can be calculated. An important and difficult problem is determining how the coupling between fragments, or between a system and its surroundings, affects the excitation energies of isolated species. Scholz et al.<sup>[90]</sup> show how an earlier formulation of subsystem time-dependent density functional theory (TDDFT),<sup>[91]</sup> when made “exact” through projection-based techniques,<sup>[92,93]</sup> can be used to analyze the response of the environment on excitation energies. Systematic studies are also provided in Scholz et al.<sup>[90]</sup> to establish the effect of basis sets on excitation energies and, when projectors want to be avoided for the sake of efficiency, the effect of approximations for  $T_s^{\text{nad}}[\mathbf{n}]$ .

*Electron and nuclear dynamics with embedding:* Ab initio dynamics has been carried out with embedding methods both for the nuclei under the Born-Oppenheimer approximation<sup>[94–96]</sup> and for the electrons within the real-time time-dependent subsystem-DFT

formalism.<sup>[74,75,97]</sup> The electron dynamics has been particularly interesting because subsystem DFT allows us to dissect the dynamic interactions that take place between electrons of different subsystems. This opens the door to the computation of subsystem quantities (such as spectra and polarizabilities<sup>[70,98,99]</sup>) and how they are affected by the surrounding subsystems.<sup>[74,91]</sup> As shown by Umerbekova et al.,<sup>[100]</sup> this has repercussions with regard to the design of force fields when the polarizabilities are evaluated at an imaginary frequency, yielding the van der Waals  $C_6$  coefficients.<sup>[69,100,101]</sup> The contribution by Grimm et al.<sup>[102]</sup> shows that, within subsystem DFT, it is difficult to improve on the performance of the simple adiabatic local density approximation (ALDA) kernel for the nonadditive kinetic energy when considering its extensions to generalized gradient approximation (GGA) functionals. This is an important observation, especially because GGA kernels are substantially more complex and more computationally expensive than the ALDA kernel.

*Relativistic effects:* Relativistic effects on various electronic properties of complex systems can now be calculated accurately through advances on the two- and four-component relativistic formulations of KS-DFT in combination with embedding methods.<sup>[103]</sup> Halbert et al.<sup>[104]</sup> show how these new tools can be used to assess the importance of spin-orbit coupling and solvent effects for NMR shielding constants.

*DM and GF Embedding:* As mentioned in the previous section, projection-based density embedding<sup>[105]</sup> together with the recent embedded mean-field theory are useful embedding methods in the modern electronic structure toolbox. Recent improvements in both accuracy and efficiency suggest that further progress is forthcoming.<sup>[106]</sup> One of the most spectacular applications was the recent report of quantum dynamics of hydrogen atoms scattering from graphene, where the detailed mechanism could be established through a combination of imaging techniques and state-of-the-art embedding calculations.<sup>[48]</sup> Another important achievement has been the extension of projection-based embedding to treat periodic systems by the Goodpaster group.<sup>[106–108]</sup>

*Subsystems with fractional electron numbers:* Most embedding methods are designed to treat fragments with integer numbers of electrons. However, when considering a fragment in a molecule as an open system interacting with its environment, it is often convenient to treat that environment as a bath of electrons with which the fragment can exchange electrons and acquire, on average, a partial charge. This situation is especially relevant when describing intermolecular charge transfer.<sup>[109]</sup> Mosquera et al.<sup>[110]</sup> describe how their recent method that locally couples open subsystems<sup>[111]</sup> can naturally account for fractional electron numbers in the fragments. They also describe a related method for domain separation in DFT (DS-DFT) that can be used for many embedding applications, including wavefunction embedding.

In the wavefunction embedding world, it has been difficult to embed wavefunction in arbitrary environments because of the inability to properly account for the charge transfer between the wavefunction system and the surrounding, which leads to an unphysical scenario in which two subsystems “feel” a different chemical potential. Even though projection-based methods tackle part of the problem (only the mean field part of the charge transfer is included), a general theoretical framework had been missing. The  $N$ -centered ensemble-DFT for open systems of Senjean and Fromager<sup>[112]</sup> offers a promising route to address this problem. A crucial aspect of Senjean and Fromager<sup>[112]</sup> is the formulation of a quantum chemical framework based on ensemble density matrices that is capable of describing open systems through an explicit dependence of the relevant functionals on fractional electron numbers.

*Many-body expansions:* Many-body expansions (MBE; see Herbert<sup>[113]</sup> for a comprehensive review) offer an alternative approach to dividing and conquering the electronic structure and is of great current interest. MBE is based on an expansion equation that partitions the energy into terms involving interactions between growing number of fragments (ie, the bodies, labeled below by  $\alpha, \beta, \dots$ ). MBE takes the following form:

$$E = E_1 + \Delta E_2 + \Delta E_3 + \dots, \quad (2)$$

$$E_1 = \sum_{\alpha} E_{\alpha}, \quad (3)$$

$$\Delta E_2 = \sum_{\alpha < \beta} E_{\alpha\beta} - E_{\alpha} - E_{\beta}, \quad (4)$$

$$\Delta E_3 = \sum_{\alpha < \beta < \gamma} E_{\alpha\beta\gamma} - \Delta E_2 - E_1. \quad (5)$$

However, MBE is often combined with other embedding methods (such as ONIOM or QM/MM) to incorporate such terms in the energy as electrostatic induction and other many-body effects that would require going much beyond the low MBE orders.<sup>[114–117]</sup> In this context, the contribution by Schmitt-Monreal et al.<sup>[118]</sup> explores ways to combine subsystem DFT with MBE to improve convergence. Schmitt-Monreal and

Jacob<sup>[118]</sup> also explore ways to exploit a density-based MBE to achieve faster convergence. The crucial aspect is the flexibility provided by the underlying density embedding framework.

MBE is powerful because it can be optimized by exploiting the topology of the system. In this regard, bootstrap embedding<sup>[34]</sup> can exploit matching conditions for the density (or DM elements) of the “center” and the “edge” of fragments to, once again, improve convergence of the MBE. The contribution by Ricard et al.<sup>[119]</sup> exploits topology in a formal way, invoking graph theory within the embedding framework offered by ONIOM.<sup>[120]</sup>

## 4 | FUTURE

Clearly, challenges remain in each flavor of embedding. For subsystem DFT and partition-DFT, the nonadditive functionals and prescriptions for the partition potential are improving every year<sup>[80,121]</sup> but are not yet accurate enough to simultaneously embrace weak and strong inter-subsystem interactions. For DM and projection-based embedding, the biggest challenges are being addressed, such as tackling periodic systems and finding better ways to define the Hilbert space for projection in such a way that potential energy surfaces are smooth and that the computation is kept to a reasonably small overhead compared to the underlying KS-DFT solver.

A pressing question for the community is whether computational tools can assist in the development of either a vaccine or effective drugs to treat COVID-19 and related diseases. Unfortunately, we are still very far from being able to calculate the outcome of biochemical reactions with the staggering number of biological molecules that are involved in the metabolic pathways of different stages of a disease, but the quantum-embedding community has developed tools that can be used to simulate the behavior of systems as large as complete viruses.<sup>[122]</sup> Coupled to developments in machine-learning algorithms<sup>[123]</sup> and improved molecular dynamic simulations,<sup>[124]</sup> quantum-embedding methods will reach the ability to simulate realistic cell environments and provide invaluable quantitative information to assist in the design of new drugs.

Given that calculations are now possible on systems comprising hundreds of millions of atoms,<sup>[125]</sup> periodic systems,<sup>[126]</sup> and—very efficiently—in molecular codes,<sup>[127–129]</sup> we believe that quantum-embedding methods will reach the ability to simulate realistic cell environment conditions, as well as device-level length scales, and will thus play an increasingly useful role in biology and engineering.

The future will see a convergence of the various embedding methods into user-specific computational protocols. In this regard, the development of appropriate software is key to these efforts. New embedding-friendly software is being coded and is starting to surface,<sup>[129–131]</sup> giving a glimpse of some exciting news ahead. The future of quantum embedding is bright.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## REFERENCES

- [1] R. G. Gordon, Y. S. Kim, *J. Chem. Phys.* **1972**, *56*(6), 3122.
- [2] D. Ceperley, *Phys. Rev. B* **1978**, *18*, 3126.
- [3] A. Rae, *Chem. Phys. Lett.* **1973**, *18*(4), 574.
- [4] C. Wood, N. Pyper, *Mol. Phys.* **1981**, *43*(6), 1371.
- [5] R. A. Harris, *J. Chem. Phys.* **1984**, *81*(5), 2403.
- [6] G. Senatore, K. Subbaswamy, *Phys. Rev. B* **1986**, *34*(8), 5754.
- [7] P. Cortona, *Phys. Rev. B* **1991**, *44*(16), 8454.
- [8] T. A. Wesolowski, A. Warshel, *J. Phys. Chem.* **1993**, *97*(30), 8050.
- [9] L. Boyer, M. Mehl, *Ferroelectrics* **1993**, *150*(1), 13.
- [10] L. Boyer, H. Stokes, M. Mehl, *Ferroelectrics* **1997**, *194*(1), 173.
- [11] L. Boyer, H. Stokes, M. Mehl, *Phys. Rev. Lett.* **2000**, *84*(4), 709.
- [12] M. Mehl, H. Stokes, L. Boyer, *J. Phys. Chem. Solids* **1996**, *57*(10), 1405.
- [13] M. Ossowski, L. Boyer, M. Mehl, M. Pederson, *Phys. Rev. B* **2003**, *68*(24), 245107.
- [14] L. Boyer, H. Stokes, M. Ossowski, M. Mehl, *Phys. Rev. B* **2008**, *78*(4), 045121.
- [15] N. Govind, Y. A. Wang, A. J. R. da Silva, E. A. Carter, *Chem. Phys. Lett.* **1998**, *295*(1,Äi2), 129.
- [16] T. A. Wesolowski, J. Weber, *Chem. Phys. Lett.* **1996**, *248*(1), 71.
- [17] M. H. Cohen, A. Wasserman, *J. Phys. Chem. A* **2007**, *111*(11), 2229.
- [18] P. Elliott, K. Burke, M. H. Cohen, A. Wasserman, *Phys. Rev. A* **2010**, *82*(2), 024501.
- [19] J. Nafziger, A. Wasserman, *J. Phys. Chem. A* **2014**, *118*(36), 7623.
- [20] T. A. Wesolowski, One-Electron Equations for Embedded Electron Density: Challenge for Theory and Practical Payoffs in Multi-Level Modeling of Complex Polyatomic Systems. in *Computational Chemistry: Reviews of Current Trends*, Vol. 10 (Ed: J. Leszczynski), World Scientific, Singapore **2006**, p. 1.
- [21] C. R. Jacob, J. Neugebauer, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.* **2014**, *4*(4), 325.
- [22] T. A. Wesolowski, S. Shedge, X. Zhou, *Chem. Rev.* **2015**, *115*, 5891.
- [23] A. Krishnal, D. Sinha, A. Genova, M. Pavanello, *J. Phys.: Condens. Matter* **2015**, *27*(18), 183202.
- [24] P. Huang, E. A. Carter, *Annu. Rev. Phys. Chem.* **2008**, *59*(1), 261.
- [25] O. V. Gritsenko, On the Principal Difference Between the Exact and Approximate Frozen-Density Embedding Theory. in *Recent Advances in Orbital-Free Density Functional Theory* (Eds: T. A. Wesolowski, Y. A. Wang), World Scientific, Singapore **2013**, p. 355.
- [26] T. Zhu, Z. H. Cui, G. K. L. Chan, *J. Chem. Theory Comput.* **2019**, *16*(1), 141.
- [27] I. W. Bulik, W. Chen, G. E. Scuseria, *J. Chem. Phys.* **2014**, *141*(5), 054113.
- [28] T. Nguyen Lan, A. A. Kananenka, D. Zgid, *J. Chem. Theory Comput.* **2016**, *12*(10), 4856.
- [29] G. Kotliar, S. Y. Savrasov, K. Haule, V. S. Oudovenko, O. Parcollet, C. A. Marianetti, *Rev. Mod. Phys.* **2006**, *78*(3), 865.
- [30] N. Lin, C. A. Marianetti, A. J. Millis, D. R. Reichman, *Phys. Rev. Lett.* **2011**, *106*(9), 096402.
- [31] L. Lacombe, N. T. Maitra, *Phys. Rev. Lett.* **2020**, *124*(20), 206401.
- [32] J. Chen, A. J. Millis, C. A. Marianetti, *Phys. Rev. B* **2015**, *91*(24), 241111<sub>(R)</sub>.
- [33] I. Giannakis, J. Leshen, M. Kavai, S. Ran, C. J. Kang, S. R. Saha, Y. Zhao, Z. Xu, J. W. Lynn, L. Miao, L. A. Wray, G. Kotliar, N. P. Butch, P. Aynajian, *Sci. Adv.* **2019**, *5*(10), eaaw9061.
- [34] H. Z. Ye, N. D. Ricke, H. K. Tran, T. V. Voorhis, *J. Chem. Theory Comput.* **2019**, *15*(8), 4497.
- [35] H. Z. Ye, H. K. Tran, T. V. Voorhis, *J. Chem. Theory Comput.* **2020**, *16*(8), 5035.
- [36] M. Gutowski, L. Piela, *Mol. Phys.* **1988**, *64*(2), 337.
- [37] Ł. Rajchel, P. S. Żuchowski, M. M. Szczśniak, G. Chalasiński, *Phys. Rev. Lett.* **2010**, *104*(16), 163001.
- [38] P. K. Tamukong, Y. G. Khait, M. R. Hoffmann, *J. Phys. Chem. A* **2016**, *121*(1), 256.
- [39] J. D. Goodpaster, T. A. Barnes, F. R. Manby, T. F. Miller III., *J. Chem. Phys.* **2014**, *140*(18), 18A507.
- [40] T. A. Barnes, J. D. Goodpaster, F. R. Manby, I. I. I. T. F. Miller, *J. Chem. Phys.* **2013**, *139*(2), 024103.
- [41] J. D. Goodpaster, T. A. Barnes, F. R. Manby, T. F. Miller III., *J. Chem. Phys.* **2012**, *137*(22), 224113.
- [42] C. Huang, M. Pavone, E. A. Carter, *J. Chem. Phys.* **2011**, *134*(15), 154110.
- [43] C. Huang, E. A. Carter, *J. Chem. Phys.* **2011**, *135*(19), 194104.
- [44] X. Zhang, E. A. Carter, *J. Chem. Theory Comput.* **2018**, *15*(2), 949.
- [45] M. Bensberg, J. Neugebauer, *J. Chem. Theory Comput.* **2020**, *16*(6), 3607.
- [46] F. Ding, F. R. Manby, T. F. Miller, *J. Chem. Theory Comput.* **2017**, *13*(4), 1605.
- [47] M. Guidon, J. Hutter, J. VandeVondele, *J. Chem. Theory Comput.* **2010**, *6*(8), 2348.
- [48] M. Kammler, F. Ding, Y. Dorenkamp, F. R. Manby, H. Jiang, F. R. Manby, A. M. Wodtke, T. F. Miller, A. Kandratsenka, O. Bünermann, *Science* **2019**, *364*(6438), 379.
- [49] S. C. L. Kamerlin, M. Haranczyk, A. Warshel, *J. Phys. Chem. B* **2009**, *113*(5), 1253.
- [50] D. Loco, S. Jurinovich, L. Cupellini, M. F. S. J. Menger, B. Mennucci, *Photochem. Photobiol. Sci.* **2018**, *17*(5), 552.
- [51] C. Liu, J. P. Piquemal, P. Ren, *J. Chem. Theory Comput.* **2019**, *15*(7), 4122.
- [52] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*(8), 2999.
- [53] B. Mennucci, R. Cammi, *Continuum Solvation Models in Chemical Physics: From Theory to Applications*, John Wiley and Sons, West Sussex, England **2008**.

- [54] B. Mennucci, S. Caprasecca, C. A. Guido, Computational Studies of Environmental Effects and Their Interplay With Experiment. in *Advances in Physical Organic Chemistry*, Vol. 50, Elsevier, **2016**, p. 203.
- [55] A. Laktionov, E. Chemineau-Chalaye, T. A. Wesolowski, *Phys. Chem. Chem. Phys.* **2016**, 18(31), 21069.
- [56] M. Truscott, O. Andreussi, *J. Phys. Chem. B* **2019**, 123(16), 3513.
- [57] O. Andreussi, A. Biancardi, S. Corni, B. Mennucci, *Nano Lett.* **2013**, 13(9), 4475.
- [58] R. Cammi, B. Mennucci, *J. Chem. Phys.* **1999**, 110(20), 9877.
- [59] C. A. Guido, G. Scalmani, B. Mennucci, D. Jacquemin, *J. Chem. Phys.* **2017**, 146(20), 204106.
- [60] F. Nattino, C. Dupont, N. Marzari, O. Andreussi, *J. Chem. Theory Comput.* **2019**, 15(11), 6313.
- [61] M. Karplus, *Angew. Chem. Int. Ed.* **2014**, 53(38), 9992.
- [62] C. Curutchet, B. Mennucci, *Chem. Rev.* **2016**, 117(2), 294.
- [63] R. N. Tazhigulov, P. K. Gurunathan, Y. Kim, L. V. Slipchenko, K. B. Bravaya, *Phys. Chem. Chem. Phys.* **2019**, 21, 11642.
- [64] T. Vreven, B. Mennucci, C. O. da Silva, K. Morokuma, J. Tomasi, *J. Chem. Phys.* **2001**, 115(1), 62.
- [65] N. Schieschke, R. D. Remigio, L. Frediani, J. Heuser, S. Höfener, *J. Comput. Chem.* **2017**, 38(19), 1693.
- [66] A. Goez, J. A. Neugebauer, *J. Chem. Theory Comput.* **2015**, 11(11), 5277.
- [67] M. Pavanello, J. Neugebauer, *J. Chem. Phys.* **2011**, 135(23), 234103.
- [68] M. Pavanello, T. Van Voorhis, L. Visscher, J. Neugebauer, *J. Chem. Phys.* **2013**, 138(5), 054101.
- [69] R. Kevorkyants, H. Eshuis, M. Pavanello, *J. Chem. Phys.* **2014**, 141(4), 044127.
- [70] J. Neugebauer, *Phys. Rep.* **2010**, 489(1), 1.
- [71] J. Neugebauer, M. J. Louwerse, E. J. Baerends, T. A. Wesolowski, *J. Chem. Phys.* **2005**, 122(9), 094115.
- [72] X. Zhou, J. W. Kaminski, T. A. Wesolowski, *Phys. Chem. Chem. Phys.* **2011**, 13(22), 10565.
- [73] S. Höfener, A. S. P. Gomes, L. Visscher, *J. Chem. Phys.* **2013**, 139(10), 104106.
- [74] A. Umerbekova, S. F. Zhang, M. Pavanello, *Eur. Phys. J. B* **2018**, 91(10), 214.
- [75] S. K. P. A. Genova, M. Pavanello, *J. Phys. Chem. Lett.* **2017**, 8(20), 5077.
- [76] S. Fux, C. R. Jacob, J. Neugebauer, L. Visscher, M. Reiher, *J. Chem. Phys.* **2010**, 132(16), 164101.
- [77] A. S. P. Gomes, C. R. Jacob, *Ann. Rep. Sect. "C"(Phys. Chem.)* **2012**, 108, 222.
- [78] L. O. Jones, M. A. Mosquera, G. C. Schatz, M. A. Ratner, *J. Am. Chem. Soc.* **2020**, 142(7), 3281.
- [79] D. Schlüns, K. Klahr, C. Mück-Lichtenfeld, L. Visscher, J. Neugebauer, *Phys. Chem. Chem. Phys.* **2015**, 17(22), 14323.
- [80] W. Mi, M. Pavanello, *J. Phys. Chem. Lett.* **2019**, 11(1), 272.
- [81] D. Schnieders, J. Neugebauer, *J. Chem. Phys.* **2018**, 149(5), 054103.
- [82] D. S. Jensen, A. Wasserman, *Int. J. Quantum Chem.* **2018**, 118, e25425.
- [83] K. Jiang, M. A. Mosquera, Y. Quesis, A. Wasserman, *Int. J. Quantum Chem.* **2020**, 120, e26204.
- [84] C. Huang, *Int. J. Quantum Chem.* **2020**, 120, e26347.
- [85] C. Huang, *J. Chem. Theory Comput.* **2018**, 14(12), 6211.
- [86] M. E. Casida, T. A. Wesolowski, *Int. J. Quantum Chem.* **2004**, 96(6), 577.
- [87] M. Pavanello, *J. Chem. Phys.* **2013**, 138(20), 204118.
- [88] C. Huang, F. Libisch, Q. Peng, E. A. Carter, *J. Chem. Phys.* **2014**, 140(12), 124113.
- [89] M. A. Mosquera, D. Jensen, A. Wasserman, *Phys. Rev. Lett.* **2013**, 111(2), 023001.
- [90] L. Scholz, J. Tölle, J. Neugebauer, *Int. J. Quantum Chem.* **2020**, 120, e26213.
- [91] J. Neugebauer, *J. Chem. Phys.* **2007**, 126(13), 134116.
- [92] J. Tölle, M. Böckers, J. Neugebauer, *J. Chem. Phys.* **2019**, 150(18), 181101.
- [93] J. Tölle, M. Böckers, N. Niemyer, J. Neugebauer, *J. Chem. Phys.* **2019**, 151(17), 174109.
- [94] M. Iannuzzi, B. Kirchner, J. Hutter, *Chem. Phys. Lett.* **2006**, 421(1–3), 16.
- [95] A. Genova, D. Ceresoli, M. Pavanello, *J. Chem. Phys.* **2016**, 144(23), 234105.
- [96] W. Mi, P. Ramos, J. Maranhao, M. Pavanello, *J. Phys. Chem. Lett.* **2019**, 10(24), 7554.
- [97] A. Krishtal, D. Ceresoli, M. Pavanello, *J. Chem. Phys.* **2015**, 142(15), 154116.
- [98] S. Höfener, A. S. P. Gomes, L. Visscher, *J. Chem. Phys.* **2012**, 136(4), 044104.
- [99] C. Daday, C. König, O. Valsson, J. Neugebauer, C. Filippi, *J. Chem. Theory Comput.* **2013**, 9(5), 2355.
- [100] A. Umerbekova, M. Pavanello, *Int. J. Quantum Chem.* **2020**, 120, e26243.
- [101] D. Sinha, M. Pavanello, *J. Chem. Phys.* **2015**, 143, 084120.
- [102] S. A. Grimm, T. Q. Teodoro, L. Visscher, *Int. J. Quantum Chem.* **2020**, 120, e26111.
- [103] T. Saue, R. Bast, A. S. P. Gomes, H. J. A. Jensen, L. Visscher, I. A. Aucar, R. Di Remigio, K. G. Dyall, E. Eliav, E. Fasshauer, T. Fleig, L. Halbert, E. D. Hedegård, B. Helmich-Paris, M. Iliaš, C. R. Jacob, S. Knecht, J. K. Laerdahl, M. L. Vidal, M. K. Nayak, M. Olejniczak, J. M. H. Olsen, M. Pernpointner, B. Senjean, A. Shee, A. Sunaga, J. N. P. van Stralen, *J. Chem. Phys.* **2020**, 152(20), 204104.
- [104] L. Halbert, M. Olejniczak, V. Vallet, *Int. J. Quantum Chem.* **2020**, 120, e26207.
- [105] F. R. Manby, M. Stella, J. D. Goodpaster, T. F. Miller III., *J. Chem. Theory Comput.* **2012**, 8(8), 2564.
- [106] D. V. Chulhai, J. D. Goodpaster, *J. Chem. Theory Comput.* **2017**, 13(4), 1503.
- [107] D. V. Chulhai, J. D. Goodpaster, *J. Chem. Theory Comput.* **2018**, 14(4), 1928.
- [108] D. S. Graham, X. Wen, D. V. Chulhai, J. D. Goodpaster, *J. Chem. Theory Comput.* **2020**, 16(4), 2284.
- [109] A. Schulz, C. R. Jacob, *J. Chem. Phys.* **2019**, 151(13), 131103.
- [110] M. A. Mosquera, L. O. Jones, M. A. Ratner, G. C. Schatz, *Int. J. Quantum Chem.* **2020**, 120, e26184.
- [111] M. A. Mosquera, M. A. Ratner, G. C. Schatz, *J. Chem. Phys.* **2018**, 149(3), 034105.
- [112] B. Senjean, E. Fromager, *Int. J. Quantum Chem.* **2020**, 120, e26190.
- [113] J. M. Herbert, *J. Chem. Phys.* **2019**, 151(17), 170901.
- [114] K. Y. Liu, J. M. Herbert, *J. Chem. Phys.* **2017**, 147(16), 161729.
- [115] R. M. Richard, K. U. Lao, J. M. Herbert, *Acc. Chem. Res.* **2014**, 47(9), 2828.

- [116] P. J. Bygrave, N. L. Allan, F. R. Manby, *J. Chem. Phys.* **2012**, 137(16), 164102.
- [117] J. Hermann, R. A. DiStasio, A. Tkatchenko, *Chem. Rev.* **2017**, 117(6), 4714.
- [118] D. Schmitt-Monreal, C. R. Jacob, *Int. J. Quantum Chem.* **2020**, 120, e26228.
- [119] T. C. Ricard, A. Kumar, S. S. Iyengar, *Int J Quantum Chem.* **2020**;120, e26244.
- [120] L. W. Chung, W. M. C. Sameera, R. Ramozzi, A. J. Page, M. Hatanaka, G. P. Petrova, T. V. Harris, X. Li, Z. Ke, F. Liu, H.-B. Li, L. Ding, K. Morokuma, *Chem. Rev.* **2015**, 115(12), 5678.
- [121] K. Jiang, J. Nafziger, A. Wasserman, *J. Chem. Phys.* **2018**, 149(16), 164112.
- [122] S. Andermatt, J. Cha, F. Schiffmann, J. VandeVondele, *J. Chem. Theory Comput.* **2016**, 12(7), 3214.
- [123] G. Carleo, I. Cirac, K. Cranmer, L. Daudet, M. Schuld, N. Tishby, L. Vogt-Maranto, L. Zdeborov'a, *Rev. Mod. Phys.* **2019**, 91(4), 045002.
- [124] M. Karplus, J. A. McCammon, *Nat. Struct. Biol.* **2002**, 9(9), 646.
- [125] J. D. Durrant, S. E. Kochanek, L. Casalino, P. U. Jeong, A. C. Dommer, R. E. Amaro, *ACS Cent. Sci.* **2020**, 6(2), 189.
- [126] A. Genova, D. Ceresoli, A. Krishtal, O. Andreussi, R. A. DiStasio, M. Pavanello, *Int. J. Quantum Chem.* **2017**, 117, e25401.
- [127] C. R. Jacob, J. Neugebauer, L. Visscher, *J. Comput. Chem.* **2008**, 29, 1011.
- [128] J. P. Unsleber, T. Dresselhaus, K. Klahr, D. Schnieders, M. Bockers, D. Barton, J. Neugebauer, *J. Comput. Chem.* **2018**, 39(13), 788.
- [129] F. Manby, T. Miller, P. Bygrave, F. Ding, T. Dresselhaus, F. Batista-Romero, A. Buccheri, C. Bungey, S. Lee, R. Meli, K. Miyamoto, C. Steinmann, T. Tsuchiya, M. Welborn, T. Wiles, Z. Williams. entos: A Quantum Molecular Simulation Package, 2, [https://chemrxiv.org/articles/preprint/entos\\_A\\_Quantum\\_Molecular\\_Simulation\\_Package/7762646](https://chemrxiv.org/articles/preprint/entos_A_Quantum_Molecular_Simulation_Package/7762646); **2019**.
- [130] X. Shao, K. Jiang, W. Mi, A. Genova, M. Pavanello, *WIREs Comput. Mol. Sci.* **2020**.
- [131] D. G. A. Smith, L. A. Burns, D. A. Sirianni, D. R. Nascimento, A. Kumar, A. M. James, J. B. Schriber, T. Zhang, B. Zhang, A. S. Abbott, E. J. Berquist, M. H. Lechner, L. A. Cunha, A. G. Heide, J. M. Waldrop, T. Y. Takeshita, A. Alenaizan, D. Neuhauser, R. A. King, A. C. Simmonett, J. M. Turney, H. F. Schaefer, F. A. Evangelista, A. E. DePrince, T. D. Crawford, K. Patkowski, C. D. Sherrill, *J. Chem. Theory Comput.* **2018**, 14(7), 3504.