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14. ABSTRACT Our ARO-supported work includes key contributions to the development of rigorous quantum embedding methods for the calculation of ground- and excited-state potential energy surfaces. Quantum embedding has long been recognized as a promising strategy for vastly reducing the cost of rigorous electronic structure theory calculations. However, prior to our work in this area, density functional and wavefunction embedding approaches were only applicable to weakly interacting systems, a severe constraint that excluded essentially all condensed-phase and reactive chemical applications. By developing both inversion-based and projection-based strategies to enable					
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Report Title

Final Report: Exactly embedded density functional theory: A new paradigm for the first-principles modeling of reactions in complex systems

ABSTRACT

Our ARO-supported work includes key contributions to the development of rigorous quantum embedding methods for the calculation of ground- and excited-state potential energy surfaces. Quantum embedding has long been recognized as a promising strategy for vastly reducing the cost of rigorous electronic structure theory calculations. However, prior to our work in this area, density functional and wavefunction embedding approaches were only applicable to weakly interacting systems, a severe constraint that excluded essentially all condensed-phase and reactive chemical applications. By developing both inversion-based and projection-based strategies to enable accurate embedding in the context of strongly interacting (i.e., covalently or hydrogen-bonded) systems, we have expanded the applicability of quantum embedding methodologies, an area of intense interest. In addition to developing new algorithms and software, we have demonstrated that our approach enables simulation of large systems with sub-linear scaling of the required computational time; and we have further demonstrated that it dramatically reduces the cost of accurately describing transition-metal complexes and large molecules and clusters. This work opens new doors for the accurate description of decomposition, catalytic, and electronically non-adiabatic processes in complex systems. This research meets the aims of the Army Research Office by significantly advancing the scope and accuracy of first-principles molecular simulations in complex, reactive systems.

Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

<u>Received</u>	<u>Paper</u>
09/03/2012	1.00 Jason D. Goodpaster, Nandini Ananth, Frederick R. Manby, Thomas F. Miller. Exact nonadditive kinetic potentials for embedded density functional theory, <i>The Journal of Chemical Physics</i> , (08 2010): 84103. doi: 10.1063/1.3474575
09/03/2012	4.00 Frederick R. Manby, Martina Stella, Jason D. Goodpaster, Thomas F. Miller. A Simple, Exact Density-Functional-Theory Embedding Scheme, <i>Journal of Chemical Theory and Computation</i> , (07 2012): 2564. doi: 10.1021/ct300544e
09/03/2012	3.00 Jason D. Goodpaster, Taylor A. Barnes, Thomas F. Miller. Embedded density functional theory for covalently bonded and strongly interacting subsystems, <i>The Journal of Chemical Physics</i> , (03 2011): 164108. doi: 10.1063/1.3582913
09/03/2012	2.00 Thomas F. Miller, Nandini Ananth. Exact quantum statistics for electronically nonadiabatic systems using continuous path variables, <i>The Journal of Chemical Physics</i> , (12 2010): 234103. doi: 10.1063/1.3511700
10/01/2013	8.00 Jason D. Goodpaster, Frederick R. Manby, Thomas F. Miller, Taylor A. Barnes. Accurate basis set truncation for wavefunction embedding, <i>The Journal of Chemical Physics</i> , (07 2013): 24103. doi: 10.1063/1.4811112
10/01/2013	9.00 Jason D. Goodpaster, Taylor A. Barnes, Frederick R. Manby, Thomas F. Miller. Density functional theory embedding for correlated wavefunctions: Improved methods for open-shell systems and transition metal complexes, <i>The Journal of Chemical Physics</i> , (12 2012): 224113. doi: 10.1063/1.4770226
10/01/2013	7.00 Scott Habershon, David E. Manolopoulos, Thomas E. Markland, Thomas F. Miller. Ring-Polymer Molecular Dynamics: Quantum Effects in Chemical Dynamics from Classical Trajectories in an Extended Phase Space, <i>Annual Review of Physical Chemistry</i> , (04 2013): 387. doi: 10.1146/annurev-physchem-040412-110122
10/12/2014	10.00 Taylor A. Barnes, Frederick R. Manby, Jason D. Goodpaster, Thomas F. Miller. Accurate and systematically improvable density functional theory embedding for correlated wavefunctions, <i>The Journal of Chemical Physics</i> , (05 2014): 18507. doi: 10.1063/1.4864040
TOTAL:	8

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

<u>Received</u>	<u>Paper</u>
09/03/2012 6.00	Scott Habershon, David Manolopoulos, Thomas Markland, Thomas Miller. Ring polymer molecular dynamics: Quantum effects in chemical dynamics from classical trajectories in an extended phase space, Annual Review of Physical Chemistry, (05 2013): 0. doi:
TOTAL:	1

Number of Papers published in non peer-reviewed journals:

(c) Presentations

1. Dreyfus Foundation Teacher-Scholar Symposium. New York, NY. 24 October 2014.
2. Conference in Honor of David Chandler's 70th Birthday. MIT, Boston, MA. 18 October 2014.
3. Biophysics Colloquium. Brandeis University, Boston, MA. 16 October 2014.
4. Chemistry Departmental Seminar. Purdue University, Indianapolis, IN. 15 October 2014.
5. Chemistry Departmental Seminar. Duke University, Durham, NC. 25 September 2014.
6. Chemistry Departmental Seminar. University of North Carolina, Chapel Hill, NC. 24 September 2014.
7. 2014 Caltech-Tsinghua Workshop on Frontiers in Science and Technology, Caltech. 13-15 September 2014.
8. Workshop on Current Topics in Theoretical Chemistry. Nha Trang, Vietnam. 25-29 August 2014.
9. 248th ACS National Meeting & Exposition, PHYS Symposium on Modeling and simulations of electrochemical interfaces and materials for energy storage. San Francisco, CA. 10-14 August 2014.
10. 248th ACS National Meeting & Exposition, PHYS Symposium on Quantum Chemical Calculation of Molecular Properties: A Tribute to Professor Nicholas C. Handy Symposium. San Francisco, CA. 10-14 August 2014.
11. Gordon Research Conference on Electron Donor-Acceptor Interactions. Newport, RI. 3-8 August 2014.
12. American Conference on Theoretical Chemistry. Telluride Science Research Center, Telluride, CO. 21-24 July 2014.
13. Large-scale DFT Technical Interchange. Army Research Laboratory, Aberdeen, MD. 15-16 July 2014.
14. 26th Canadian Symposium on Theoretical and Computational Chemistry. Sir George Williams Campus, Concordia University Montreal, Quebec, Canada. 6-11 July 2014.
15. Workshop on Condensed Phase Dynamics. Telluride Science Research Center, Telluride, CO. 23-28 June 2014.
16. AFOSR Molecular Dynamics and Theoretical Chemistry Program Review Arlington, VA. 19-21 May 2014.
17. American Physical Society March Meeting, Functional Dynamics of Proteins from Physics to Biology. Denver, CO. 3-7 March 2014.
18. Theo Murphy International Meeting on Frontiers of Computer Simulation in Chemistry and Materials Science in honor of Paul Madden. Buckinghamshire, UK. 6-7 February 2014.
19. Chemistry Departmental Seminar. Harvey Mudd College, Claremont, CA. 29 October 2013.
20. Meeting on Molecular Simulation. Mexico City, Mexico. 11-13 December 2013.
21. Chemical Physics Colloquium. Weizmann Institute of Science, Rehovot, Israel. 2 December 2013.
22. CECAMWorkshop on Quantum Dynamics in Molecular and Nano-Materials: Mechanisms and Functionality. Tel Aviv, Isreal. 28 November - 1 December 2013.
23. Physics Departmental Seminar, Soft Matter and Biophysics Series. Georgia Tech, Atlanta, GA. 8 October 2013.
24. Chemistry Departmental Seminar. Columbia University, New York, NY. 3 October 2013.
25. 246th ACS National Meeting & Exposition, PHYS Symposium on Quantum Mechanics in Many Dimensions: New Challenges and Solutions for Chemical Theory. Indianapolis, IN. 8-13 September 2013.
26. Transatlantic Frontiers of Chemistry (TFOC) Meeting. Kloster Seon, Germany, August 8-11, 2013.
27. Symposium on Fundamentals in Chemistry and Applications in honor of the 90th birthday of Prof. Rudy Marcus. Nanyang Technological University, Singapore. 22-24 July 2013.
28. Workshop on Quantum effects in condensed-phase systems. Telluride Science Research Center, Telluride, CO. 8-12 July 2013.
29. Battery Research Group Seminar. Jet Propulsion Laboratory (JPL), Pasadena, CA. 24 June 2013.
30. CECAMWorkshop on Quantum Dynamics with (Non)Classical Trajectories. Lausanne, Switzerland. 17-20 June 2013.
31. Symposium on Quantum Matter. University of Pittsburgh, Pittsburgh, PA. 18-19 April 2013. (Keynote Speaker)
32. EMBO Conference on From structure to function of translocation machines. Dubrovnik, Croatia. 13-17 April 2013.
33. Physical Chemistry Seminar. Massachusetts Institute of Technology, Cambridge, MA. 2 April 2013.
34. Physical Chemistry Seminar. Princeton University, Princeton, NJ. 22 March 2013.
35. Workshop on Membrane Biophysics. Telluride Science Research Center, Telluride, CO. 4-8 March 2013.

36. Chemistry Departmental Seminar. Tufts University, Medford, MA. 12 February 2013.
37. Chemistry and Chemical Engineering Divisional Seminar. California Institute of Technology, Pasadena, CA. 5 February 2013.
38. Physical Chemistry Seminar. University of California, Riverside, CA. 28 January 2013.
39. Physical Chemistry Seminar. University of California, San Diego, CA. 22 January 2013.
40. Physical Chemistry Seminar. Università della Svizzera Italiana, Lugano, Switzerland. 14 January 2013.
41. 16th Workshop on Computational Physics and Materials Science: Total Energy and Force Methods. Trieste, Italy. 10-12 January 2013.
42. AFOSR/AFRL Chemical Synthesis Review. Pasadena, CA. 3-4 December, 2012.
43. Physical Chemistry Seminar. University of California, Berkeley, CA. 27 November 2012.
44. Physical Chemistry Seminar. Karlsruhe Institute of Technology, Karlsruhe, Germany. 9 November 2012.
45. Competence Center for Computational Chemistry (C4) Seminar. ETH, Zurich, Switzerland. 8 November 2012.
46. Physical Chemistry Seminar. EPFL, Lausanne, Switzerland. 6 November 2012.
47. Physical Chemistry Seminar. University of California, Los Angeles, CA. 15 October 2012.
48. Department of Chemistry Seminar. Wake Forest University, Winston-Salem, NC. 26 September 2012.
49. 244th ACS National Meeting & Exposition, PHYS Symposium on electron and energy transfer phenomena. Philadelphia, PA. 19-23 August 2012.
50. Gordon Research Conference on Computational Chemistry. Mount Snow, VT. 22-27 July 2012.
51. Workshop on Condensed Phase Dynamics. Telluride Science Research Center, Telluride, CO. 25-29 June 2012.
52. Low-scaling and Unconventional Electronic Structure Techniques (LUEST) Conference. Telluride Science Research Center, Telluride, CO. 18-22 June 2012.
53. CECAM Workshop on Path Integral Molecular Dynamics. Toulouse, France. 4-8 June 2012.
54. Quantum Effects in Biological Systems 2012. Berkeley, CA. 4-6 June 2012.
55. Physical Chemistry Seminar. University of California, Irvine, CA. 8 May 2012.
56. Physical Chemistry Seminar. Princeton University, Princeton, NJ. 24 April 2012.
57. 243rd ACS National Meeting & Exposition, Nonadiabatic Dynamics: Surface Hopping and Beyond PHYS Symposium in honor of John Tully. San Diego, CA. 25-29 March 2012.
58. 243rd ACS National Meeting & Exposition, Applications of Computational Methods to Environmentally Sustainable Solutions. San Diego, CA. 25-29 March 2012.
59. American Physical Society March Meeting, Density Functional Theory for Chemical Physics. Boston, MA. 27 February - 2 March 2012.
60. 52nd Sanibel Symposium. St. Simons Island, GA. 19-24 February 2012.
61. Berkeley Mini Stat Mech Meeting. University of California, Berkeley, CA. 13-15 January 2012.
62. Physical Chemistry Seminar. University of California, Santa Barbara, CA. 28 November 2011.
63. Keynote Address, Caltech Alumni Association Dinner in Boston. Harvard Faculty Club, Cambridge, MA. 9 November 2011.
64. Symposium on Collective Variables in Molecular Simulations. University of Nottingham, Nottingham, UK. 4-6 November 2011.
65. Biochemistry Departmental Seminar. Texas A&M University, College Station, TX. 27 October 2011.
66. Physical Chemistry Seminar. Texas A&M University, College Station, TX. 26 October 2011.
67. Horizons in Chemistry Freshman Seminar. Texas A&M University, College Station, TX. 26 October 2011.
68. 242nd ACS National Meeting & Exposition, Excited State Dynamics Symposium PHYS Symposium. Denver, CA. 28 August - 1 September 2011.
69. 242nd ACS National Meeting & Exposition, Computational Chemistry of Batteries COMP Symposium. Denver, CA. 28 August - 1 September 2011.
70. Workshop on New Frontiers in Electron Correlation. Telluride Science Research Center, Telluride, CO. 25-28 July 2011.
71. Physical Chemistry Special Seminar. University of Oxford, Oxford, UK. 16 June 2011.
72. Materials Research Seminar. United States Army Research Laboratory, Adelphi, MD. 1 June 2011.
73. Biology Faculty Seminar. California Institute of Technology, Pasadena, CA. 20 May 2011.
74. 219th Electrochemical Society Meeting; Microstructure, Mechanisms, and Modeling of Battery Materials Symposium. Montreal, Quebec, Canada. 1-6 May 2011.
75. 241st ACS National Meeting & Exposition, Membrane protein structure and function PHYS session. Anaheim, CA. 27-31 March 2011.
76. Young Faculty Speaker, Physical Chemistry Student Lecture Series (PCSLs). The Ohio State

University, Columbus, OH. 7 March 2011.

77. China Lake Distinguished Speakers Colloquium Series. Naval Air Weapons Station, China Lake, CA. 11 February 2011.

78. Biophysics Seminar. University of Basel, Basel, Switzerland. 3 January 2011.

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received

Paper

09/03/2012 5.00 Jason Goodpaster, Taylor Barnes, Nandini Ananth, Thomas Miller. EXACTLY EMBEDDED DENSITY FUNCTIONAL THEORY METHODS FOR THE FIRST-PRINCIPLES MODELING OF REACTIONS IN COMPLEX SYSTEMS, Proceedings of the 27th Army Science Conference. 29-NOV-10, . . . ,

TOTAL: 1

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received

Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received

Paper

TOTAL:

Number of Manuscripts:

Books

Received Book

TOTAL:

Received Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Camille Dreyfus Teacher-Scholar Award (2013)
Associated Students of Caltech (ASCIT) Teaching Award (2012)
National Science Foundation CAREER Award (2011)
American Chemical Society Hewlett-Packard Outstanding Junior Faculty Award (2011)
China Lake Distinguished Speaker, Naval Air Weapons Station, China Lake, CA (2011)
Alfred P. Sloan Research Fellowship (2010)
Editor's Choice Selection from the Journal of Chemical Physics (2010)

Graduate Students

<u>NAME</u>	<u>PERCENT SUPPORTED</u>	Discipline
Jason Goodpaster	0.75	
FTE Equivalent:	0.75	
Total Number:	1	

Names of Post Doctorates

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
Pengfei Frank Huo	0.34
Jakub Kaminski	0.58
FTE Equivalent:	0.92
Total Number:	2

Names of Faculty Supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>	National Academy Member
Thomas Miller	0.02	
FTE Equivalent:	0.02	
Total Number:	1	

Names of Under Graduate students supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:..... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):..... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:..... 0.00

Names of Personnel receiving masters degrees

<u>NAME</u>
Total Number:

Names of personnel receiving PHDs

<u>NAME</u>	
Jason Goodpaster	
Total Number:	1

Names of other research staff

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

See Attachment

Technology Transfer

We have already completed the development of a user-friendly implementation of the new projection-based approach to DFT-in-DFT and WFT-in-DFT embedding in the Molpro quantum chemistry package, which is available to users in over 500 institutions. We recognize that WFT-in-DFT embedding will have application domains that relate to all aspects of simulation and modeling of complex chemical systems, and we anticipate that a sizable user community will benefit from our methodological and software developments. This work provides new tools for the accurate description of catalytic and electronically non-adiabatic processes in complex systems, and it opens the door for widespread adoption of rigorous quantum embedding approaches in computational chemistry.

Indeed, our recent WFT-in-DFT implementation in the Molpro program has been shared with and is currently being tested and utilized by a range of theoretical chemistry groups, including those of:

- Prof. Donald Truhlar (U. Minnesota)
- Prof. Qiang Cui (U. Wisconsin)
- Prof. Berend Smit (UC Berkeley)
- Prof. Andres Kohn (U. Stuttgart)
- Prof. Daniel Lambrecht (U. Pittsburgh)
- Prof. John Keith (U. Pittsburgh)
- Prof. Jeremy Harvey (U. Bristol)
- Dr. Betsy Rice (ARO)
- Prof. Fred Manby (U. Bristol) and Kaito Miyamoto (U. Bristol / Toyota Co.)

Award Number: W911NF1110256

Principal Investigator (PI): Thomas F. Miller III
Institution: California Institute of Technology

Title of Research: Exactly embedded density functional theory:
A new paradigm for the first-principles
modeling of reactions in complex systems

OVERVIEW

Research from the past funding period has focused on the development of ab initio electronic structure to enable the simulation of reaction dynamics in general, condensed-phase systems. The embedded density functional theory (e-DFT) method has been combined with recent theoretical advances, including an exact treatment of the non-additive kinetic energy and a molecular embedding strategy that achieves sub-linear scaling on large-scale parallel computers. The primary objectives of the proposed research are (i) to fully benchmark and refine the new e-DFT approach and (ii) to demonstrate that it provides systematically improvable accuracy for large molecules and condensed-phase systems. Accomplishment of these research objectives meets the aims of the Army Research Office by significantly advancing the scope and accuracy of first-principles molecular simulations in complex, reactive systems.

In recent years, a central achievement of my research program has been to develop simulation methods that reveal, with new depth, the mechanistic details of quantum mechanical processes that are central to chemical reactions. The nature of this achievement is three-fold: firstly, we have worked from the foundation of rigorous quantum statistical mechanics and semiclassical dynamics to develop path-integral methods that significantly expand the scope and reliability of condensed-phase quantum dynamics simulations [1–9]. Secondly, we have overcome fundamental limitations in quantum embedding theories to dramatically improve the description of molecular interactions in systems with subtle electronic properties [10–17]. And finally, we have established a leadership role in the application of such methods to the elucidation of genuinely complex systems, including enzyme reactions and inorganic electron-transfer and proton-coupled electron transfer processes.

With ARO support in the last funding period, the Miller group has made key contributions to rigorous multi-level partitioning methodologies for the calculation of potential energy surface calculations. Multi-level partitioning, or quantum embedding, has long been recognized as a promising strategy for vastly reducing the cost of rigorous electronic structure theory calculations [18–29]. However, prior to our work in this area, accurate density functional and wavefunction embedding approaches were limited to weakly interacting systems, a severe constraint that excluded essentially all condensed-phase and reactive chemical applications. By developing both inversion-based [10–12] and projection-based [13–17] strategies to enable accurate embedding in the context of strongly interacting (i.e., covalently or hydrogen-bonded) systems, we have expanded the applicability of quantum embedding methodologies (Fig. 1A), an area of intense interest. In addition to developing new algorithms and software, we have demonstrated that our approach enables simulation of large systems with sub-linear scaling of the required computational time (Fig. 1C); and we have further demonstrated that it dramatically reduces the cost of accurately describing transition-metal complexes [12, 17] (Fig. 1B) and large molecules, clusters, and liquids [11, 13–16]. This

work opens new doors for the accurate description of decomposition, catalytic, and electronically non-adiabatic processes in complex systems.

Publications from our previous period of ARO funding include:

1. Goodpaster JD, Barnes TA, Ananth N, and Miller TF. Exactly embedded density functional theory methods for the first-principles modeling of reactions in complex systems. Proceedings of the 27th Army Science Conference (2010).
2. Ananth N and Miller TF. Exact quantum statistics for electronically nonadiabatic systems using continuous path variables. *J. Chem. Phys.*, 133 (2010) 234103.
3. Goodpaster JD, Barnes TA, and Miller TF. Embedded density functional theory for covalently bonded and strongly interacting subsystems. *J. Chem. Phys.*, 134 (2011) 164108.
4. Manby FR, Stella M, Goodpaster JD, Miller TF. 'A simple, exact density-functional-theory embedding scheme.' *J. Chem. Theory Comput.*, 8 (2012) 2564.
5. Goodpaster JD, Barnes TA, Manby FR, Miller TF. 'Density functional theory embedding for correlated wavefunctions: Improved methods for open-shell systems and transition metal complexes.' *J. Chem. Phys.*, 137 (2012) 224113.
6. Habershon S, Manolopoulos DE, Markland TE, and Miller TF. 'Ring-Polymer Molecular Dynamics: Quantum effects in chemical dynamics from classical trajectories in an extended phase space.' *Annu. Rev. Phys. Chem.*, 64 (2013) 387.
7. Barnes TA, Goodpaster JD, Manby FR, and Miller TF. 'Accurate basis-set truncation for wavefunction embedding.' *J. Chem. Phys.*, 139 (2013) 024103.
8. Goodpaster JD, Barnes TA, Manby FR, Miller TF. 'Accurate and systematically improvable density functional theory embedding for correlated wavefunctions.' *J. Chem. Phys.*, *J. Chem. Phys.*, 140 (2014) 18A507.
9. Barnes TA, Kaminski J, Borodin O, Miller TF. 'Oxidation potential of ethylene carbonate and dimethyl carbonate calculated using projection-based embedding,' in prep.
10. P. Huo, J. D. Goodpaster, T. F. Miller, III, 'Reaction pathways in cobalt-based hydrogen reduction catalysts,' in prep.

Expanded Discussion: Embedding methods to bridge lengthscales in electronic structure.

The use of computational modeling to investigate complex chemical systems faces extraordinary challenges from the perspective of electronic structure theory. Target applications combine large system sizes with subtle interactions, and in many cases, multiple dynamical timescales and electronically nonadiabatic effects. The development of new methods to perform reliable, on-the-fly electronic structure calculations at a computational cost that makes feasible the simulation of chemical reactions in large systems remains a central theoretical challenge.

At its heart, the electronic structure problem requires a compromise between accuracy and feasibility that is dictated by system size. Kohn-Sham density functional theory (KS-DFT) – the workhorse method for condensed-phase systems [32, 33] – is well known to have fundamental deficiencies associated with currently available exchange-correlation (XC) functionals [34, 35]; these deficiencies include both self-interaction errors and failure to describe systems exhibiting significant static correlation. Resulting artifacts include incorrect spin-state predictions for transition metal complexes, charge-transfer errors, and underestimation of hydrogen-transfer barriers [36–38]. Wavefunction theories, such as CCSD(T) and CASPT2, address these problems but are too costly to use for most applications in large systems.

Methods that exploit the intrinsic locality of molecular interactions show significant promise in making tractable the electronic structure calculation of large-scale systems. In particular, embedded density functional theory (e-DFT) offers a formally exact approach to electronic structure calculations in which complex condensed-phase chemical problems are decomposed into the self-consistent solution of individual smaller subsystems [39–46]. The objectives of the e-DFT approach are thus similar to those of more approximate partitioning and fragmentation schemes [47–52], including the QM/MM and ONIOM methods, but e-DFT avoids the uncontrolled approximations (such as link atoms) and errors associated with subsystem interfaces that fundamentally limit these other widely used methods.

However, in practice, previous e-DFT studies have employed substantial approximations in the description of subsystem interactions [42, 53, 54]. The subsystem embedding potentials that emerge in the e-DFT framework include non-additive kinetic potential (NAKP) terms that enforce Pauli exclusion among the electrons of the various subsystems. Without knowledge of the exact functional for the non-interacting kinetic energy, previous e-DFT studies have employed approximate NAKP treatments that break down in cases for which the subsystem densities significantly overlap (which include hydrogen-bonded or covalently bonded subsystems). Prior to our work in this area, e-DFT studies were thus limited to weakly interacting subsystems, a severe constraint that excluded essentially all condensed-phase and reactive chemical applications.

To overcome this constraint, my group has focused on the development of numerically exact methods for obtaining subsystem embedding potentials in e-DFT. We have made key contributions that include (i) the development of optimized-effective-potential-based (OEP-based) methods for the exact evaluation of NAKP contributions to the embedding potential, (ii) the combination of exact embedding potentials with correlated wavefunction theory (WFT) methods to enable seamless WFT-in-DFT embedding for general systems, (iii) the development of a simple, robust method to perform numerically exact e-DFT calculations without any need for OEP operations. By enabling accurate quantum embedding in the context of strongly interacting (i.e., covalently or hydrogen-bonded) systems, we have expanded the applicability of quantum embedding methodologies. In addition to developing key algorithms and software, we have demonstrated that the e-DFT approach enables simulation of large systems with sub-linear scaling of the required computational time; and we have further demonstrated that it dramatically reduces the cost of accurately describing transition-metal complexes [12, 17], large molecules and clusters [14, 15], and liquid mixtures

that include lithium-ion battery electrolytes [16]. This work provides new tools for the accurate description of catalytic and electronically non-adiabatic processes in complex systems, and it opens the door for widespread adoption of rigorous quantum embedding approaches in computational chemistry.

The remainder of this section describes key aspects of our work in this area. In this developing field, my research group has In particular, we have contributed to the development and application of OEP-based methods for the scalable and accurate treatment of complex systems [10–12]. Moreover, we have recently introduced a new method for the exact treatment of the e-DFT embedding potential that completely mitigates any need for OEP calculations (see Section 2.b) [13]; this approach, which has become one of the most heavily downloaded articles from the *Journal of Chemical Theory and Computation (JCTC)* for years 2012, 2013, and 2014, provides the needed simplicity and robustness to enable broad utilization by the computational chemistry user community in the near term.

2.a. OEP-based methods for exact embedding.

In our initial contributions to the methodology of e-DFT, we developed accurate and scalable OEP-based treatments for the NAKP in e-DFT. In particular, we introduced a numerically exact protocol for computing the NAKP contributions to the subsystem embedding potentials; we demonstrated the effectiveness of this protocol for systems with both weakly and strongly overlapping subsystem densities [10, 11]; we combined the exact embedding potentials with WFT methods to enable seamless WFT-in-DFT embedding [12]; and we demonstrated the advantageous parallel scaling of the e-DFT approach [11].

2.a.1. DFT-in-DFT embedding: Our original e-DFT protocol [10] utilizes OEP techniques, such as those of Zhao, Morrison, and Parr [58] or Wu and Yang [59], which involve a search for the local potential that yields one-electron orbitals that both reproduce a target electronic density and minimize the orbital-dependent total energy functional. During each iterative update of the subsystem densities and embedding potentials, the OEP calculation is combined with an orbital-dependent expression for the NAKP, and at self-consistency, the iterative procedure yields a total electronic density and a total energy that are identical to those obtained from a KD-DFT calculation performed over the full system. Because the e-DFT calculation yields the same results as the full KS-DFT calculation (for a given orbital basis set and approximate XC functional), no new errors are introduced through the embedded subsystem description; it is in this sense that we achieve a numerically exact DFT-in-DFT embedding protocol.

Fig. 1A provides a demonstration of our general e-DFT implementation in the Molpro quantum chemistry package. The figure illustrates the well-known breakdown of approximate treatments of the NAKP for applications involving strongly overlapping subsystem densities. It further shows that our exact treatment of the NAKP overcomes this large error, yielding the first numerical demonstration of DFT-in-DFT embedding for chemical bond-breaking with chemical accuracy [11]. In addition to the $\text{Li}^+\text{-Be}$ curve shown in the figure, dissociation curves for the $\text{CH}_3\text{-CF}_3$ molecule, transition-metal complexes, and hydrogen-bonded water clusters have been reported [11, 12], demonstrating in all cases that the exact e-DFT protocol preserves excellent agreement with reference KS-DFT calculations, whereas approximate treatments of the NAKP lead to qualitative failures in the calculated energies and equilibrium structures. Further examples have been reported in which the subsystem densities correspond to valence and core electronic shells in atomic systems [10], again illustrating the expected breakdown due to standard NAKP approximations, with errors of 30-80% in the calculated ionization energies; by contrast, the exact protocol is found to be accurate and stable.

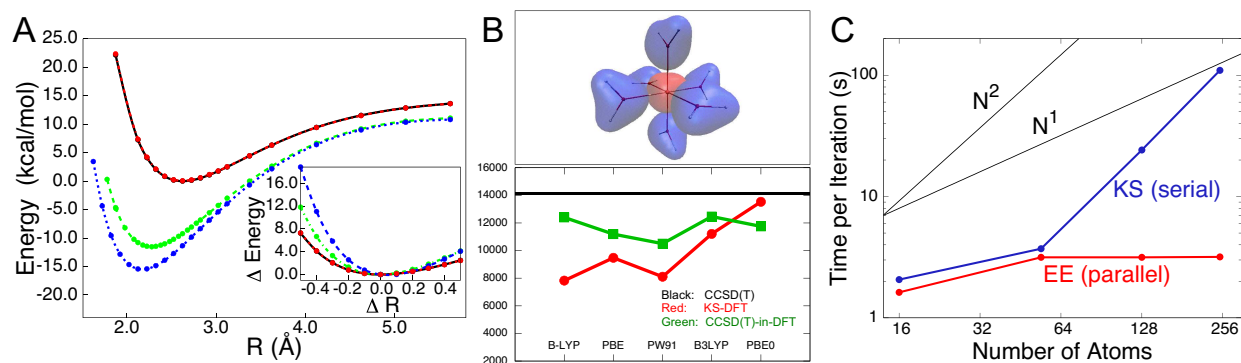


FIG. 1: (A) The Li⁺-Be potential energy curve for heterolytic bond cleavage, obtained using our exact OEP-based description for DFT embedding (red) and using approximate (Thomas-Fermi, LC94) descriptions for the embedding potential (blue, green). Results from the reference Kohn-Sham DFT method are also included (black) and are graphically indistinguishable from our e-DFT results. We have demonstrated similar successes for water cluster dissociation, C-C bond cleavage, and transition metal complexes [11]. The inset presents the potential energy curves, shifted vertically and horizontally to align the minimum. (B) WFT-in-DFT embedding results for the [Fe(H₂O)₆]²⁺ cation [12]. Above, the density partitioning is illustrated, for which only the density associated with the transition metal atom (red) is treated at the CCSD(T) level while the density for the surrounding waters (blue) is treated at the DFT level. Below, the low-spin/high-spin energy splitting of the complex (in cm⁻¹) is calculated using standard KS-DFT with various XC functionals (red) and with CCSD(T)-in-DFT embedding with only the transition metal atom treated at the CCSD(T) level (green). The quantum embedding treatment provides results that are far less sensitive to the choice of approximate DFT XC functional and that are generally improved in comparison to the reference CCSD(T) calculation for the full system (black). (C) Wall-clock timings for lattices of hydrogen molecules, ranging in size from 16 to 250 atoms. The black lines indicate ideal quadratic and linear scaling; the blue curve shows the serial implementation of Kohn-Sham DFT in Molpro; the red curve shows the timings for DFT embedding, using a number of processors equal to the number of molecules in the system [11].

2.a.2. WFT-in-DFT embedding: Fig. 1B illustrates the most important practical feature of the e-DFT approach [12]: It provides a versatile, yet rigorous, framework to describe different regions of the system at different levels of electronic structure theory [42–44, 57, 60–65]. In this example calculation for the low-spin/high-spin splitting energy of the hexaaquairon(II) cation, a subsystem comprised of the Fe atom is treated at the CCSD(T) level of theory, whereas another subsystem comprised of the water ligands is treated using KS-DFT; the e-DFT framework simply is used to determine the external potential that is created for each subsystem by the other. Since the CCSD(T) level of theory is applied only to a single atom, the computational cost for the WFT-in-DFT embedding calculation is reduced by a factor of 50 relative to a CCSD(T) calculation over the full system.

The calculations in Fig. 1B were made possible by new techniques that improve the accuracy and stability of WFT-in-DFT embedding calculations [12]. In particular, we derived spin-dependent embedding potentials in both restricted and unrestricted orbital formulations and provided the first implementation of WFT-in-DFT embedding for open-shell systems, and we developed an orbital-occupation-freezing technique to improve the convergence of the OEP operations. The top panel in Fig. 1B illustrates the density partitioning among the two subsystems. Below, the low-spin/high-spin energy splitting of the complex (in cm⁻¹) is calculated using standard KS-DFT with various XC functionals (red) and with CCSD(T)-in-DFT embedding with only the transition metal atom treated at the CCSD(T) level (green). The quantum embedding treatment provides

results that are far less sensitive to the choice of approximate DFT XC functional and that are generally improved in comparison to the reference CCSD(T) calculation for the full system (black). Additional studies of the dissociation curve for the ethylene-propylene dimer [12] reveals that WFT-in-DFT embedding reproduces full CCSD(T) energies to within 0.1 kcal/mol at all distances, thus mitigating errors in the dispersion interactions due to conventional XC functionals while simultaneously avoiding errors due to subsystem partitioning across covalent bonds [12].

These calculations illustrate that WFT-in-DFT embedding, when employed in combination with exact methods for treating the NAKP contributions to the embedding potential, offers significant opportunities for the multi-level (or multi-physics) description of complex systems. WFT-in-DFT embedding achieves the objectives of the QM/MM and ONIOM schemes for interfacing different levels of electronic structure theory; however, in comparison to these widely used methods, WFT-in-DFT embedding exhibits clear advantages that include (i) a more rigorous and systematically improvable approach to multi-level electronic structure calculations and (ii) a more computationally efficient multi-level description, since the rigorous description of the subsystem interfaces allows much smaller WFT subsystems to be employed.

2.a.3. Parallelizability and scaling. Another important feature of the e-DFT approach is that it leads to highly parallel electronic structure methods [11, 54]. For our Molpro implementation of the exact e-DFT protocol, Fig. 1C demonstrates that ideal, constant scaling of the wall-clock computation time with increasing system size can be achieved [11]. Intrinsic linear-scaling complexity arises from the loose coupling among the individual subsystem calculations, and additional parallelization is achieved by treating each subsystem on a different distributed-memory computer processor. The accuracy of the calculated energies and electronic densities do not degrade with increasing system size.

2.b. A simple, exact e-DFT method that avoids OEP calculations.

Earlier this year, we made a significant breakthrough in the efficiency and robustness of e-DFT calculations [13]. An exact scheme was developed that correctly accounts for NAKP contributions via a projection technique, while completely avoiding any numerically demanding OEP calculations. This work introduces three simple innovations: (i) We replaced the iterated DFT-in-DFT with a single conventional KS calculation. (ii) We completely avoided the issue of the NAKP through the use of a level-shifting projection operator to keep the orbitals of one subsystem orthogonal to those of another (Fig. 2). And, (iii) we developed a simple but effective perturbation theory to eliminate practically all dependence on the level-shift parameter.

Numerical tests of the new e-DFT method for a range of molecular systems, including those with conjugated and multiply-bonded subsystems, were shown to consistently yield DFT-in-DFT embedding with errors below 10^{-6} kcal/mol; these results mark a dramatic improvement over the system-dependent 0.1 – 1 kcal/mol errors that can be expected using existing OEP-based approaches. Additionally, we demonstrated that the method allows for accurate and robust WFT-in-DFT embedding calculations and embedded many-body expansions [13]. Moreover, in extremely encouraging preliminary results that we have obtained for (CAS-PT2)-in-DFT embedding for cobalt-based hydrogen reduction catalysts [17], the embedding calculations recover the full accuracy of the full CAS-PT2 method for proton-transfer barriers and driving forces while reducing the cost of the full calculation by over a factor of 700.

The new projection-based embedding approach only relies on existing, stable, well-developed software technologies [13]. It requires nothing more than a KS code, an orbital localization scheme, some elementary matrix operations in the atomic orbital basis, and any wave function method that can accept an arbitrary core Hamiltonian. Since these ingredients are available in

practically all molecular electronic structure codes, we anticipate no barriers to widespread adoption of the approach.

We have already completed the development of a user-friendly implementation of the new projection-based approach to DFT-in-DFT and WFT-in-DFT embedding in the Molpro quantum chemistry package, which is available to users in over 500 institutions. We recognize that WFT-in-DFT embedding will have application domains that relate to all aspects of simulation and modeling of complex chemical systems, and we anticipate that a sizable user community will benefit from our methodological and software developments. This work provides new tools for the accurate description of catalytic and electronically non-adiabatic processes in complex systems, and it opens the door for widespread adoption of rigorous quantum embedding approaches in computational chemistry.

Indeed, our recent WFT-in-DFT implementation in the Molpro program has been shared with and is currently being tested and utilized by a range of theoretical chemistry groups, including those of:

- Prof. Donald Truhlar (U. Minnesota)
- Prof. Qiang Cui (U. Wisconsin)
- Prof. Berend Smit (UC Berkeley)
- Prof. Andres Köhn (U. Stuttgart)
- Prof. Daniel Lambrecht (U. Pittsburgh)
- Prof. John Keith (U. Pittsburgh)
- Prof. Jeremy Harvey (U. Bristol)
- Dr. Betsy Rice (ARO)
- Prof. Fred Manby (U. Bristol) and Kaito Miyamoto (U. Bristol / Toyota Co.)

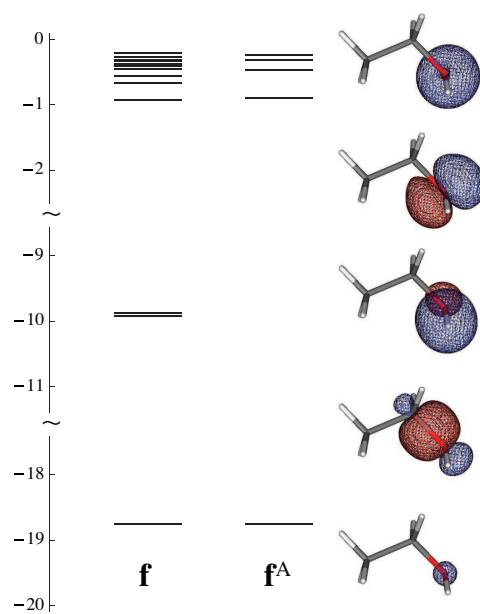


FIG. 2: Demonstration of the projection technique that is employed in the new exact embedding scheme, using the example of embedding the 10 electrons of the -OH moiety of ethanol in the environment produced by the ethyl subsystem. Following projection, the subsystem orbitals are explicitly orthogonalized, thus eliminating non-additive kinetic energy contributions [12].

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