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Editorial: Quantum Mechanical/Molecular Mechanical Approaches for the Investigation of Chemical Systems – Recent Developments and Advanced Applications

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Editorial on the Research Topic

Quantum Mechanical/Molecular Mechanical Approaches for the Investigation of Chemical Systems – Recent Developments and Advanced Applications

With the advent of microprocessor technology in the late 1960s (Moore, 1965; Whitworth, 1979; Brinkman et al., 1997) the foundation to a novel interdisciplinary field of research known today as scientific computing was laid. Located at an intersection between mathematics and computational sciences on the one hand and scientific disciplines such as physics and chemistry on the other, computational methods assumed a dominant role in modern science and engineering, enabling investigations of a broad variety of phenomena in effectively every sub-discipline of these vast fields of research.

One of the main challenges for the successful application of computational models to study chemical systems rests with the accurate description of the interaction between atoms and molecules, the two main approaches being quantum mechanics (QM) (Parr and Yang, 1994; Szabo and Ostlund, 1996; Helgaker et al., 2000; Koch and Holthausen, 2002; Cook, 2005; Sholl and Steckel, 2009) and molecular mechanics (MM) (Leach, 2001; Jensen, 2006; Ramachandran et al., 2008) methods. The latter employs empirical (*i.e.,* parametrised), classical representations of the interactions, based on comparably simple potential formulations such as harmonic springs to describe bonds and valence angles as well as Coulomb and Lennard-Jones interactions to account for charge-charge and non-bonded contributions, respectively. These approaches, often referred to as molecular force fields (FFs) provide a versatile and efficient description of chemical systems, provided that the large number of involved parameters are perfectly adjusted and balanced among each other. Typical applications for FF-based studies are located in the realm of biomolecular simulations such as proteins and nucleic acids. Nevertheless, some systems relevant for material sciences can be treated equally well with these approaches and particularly polymer chemistry studies (comprised of the same elements with similar functional groups as found for instance in peptides and proteins) often include FF-based methods.

MM models have also been extended to include more complex phenomena such as polarization (Yu and van Gunsteren, 2005; Baker, 2015; Lemkul et al., 2016) and many-body contributions (Stone, 1995), extending their applicability to areas in which simplistic force field approaches are unreliable, such as studies of solid-state interfaces and semi-conducting systems as well as metals and alloys. However, a key shortcoming inherent to the majority of FF approaches is the inability to describe the formation and cleavage of covalent chemical bonds. While so-called reactive force fields (van Duin et al., 2001; Mahadevan and Garofalini, 2007; Hartke and Grimme, 2010; Liang et al., 2013) have been developed to make such processes accessible in the regime of molecular mechanics, a quantum description of the system is often the natural choice.

QM-based descriptions of chemical systems (Parr and Yang, 1994; Szabo and Ostlund, 1996; Helgaker et al., 2000; Koch and Holthausen, 2002; Cook, 2005; Sholl and Steckel, 2009) partition the atoms into the nuclei and the surrounding electrons, inherently taking all shifts in the electron density resulting from polarization, many-body contributions and even charge-transfer into account. Although a key challenge of QM methods is the accurate description of the correlated motion of electrons (Raghavachari and Anderson, 2010; Popelier, 2011; McDonagh et al., 2017), the hierarchy of quantum chemical approaches established over the last decades (Szabo and Ostlund, 1996; Helgaker et al., 2000; Cook, 2005) provides a versatile framework for the study of challenging chemical phenomena. Since no empirical parameters are required in a QM-based description, quantum chemical methods are not restricted to a particular class of molecules and, thus, generally applicable to achieve first principle descriptions of chemical systems. Unfortunately, these benefits come with a cost, which in this case is a substantially increased computational effort over MM-based approaches and thereby, dramatically limiting their treatable system size.

In order to combine the advantages of MM and QM methods, hybrid QM/MM approaches (Gao, 1993; Bakowies and Thiel, 1996; Lin and Truhlar, 2007; Senn and Thiel, 2007, 2009; Metz et al., 2014; Pezeshki and Lin, 2015; Zheng and Waller, 2016) have been devised: In this framework the most relevant part of the chemical system is treated on the basis of a suitable quantum chemical method, while classical MM potentials are considered sufficiently accurate to model the remaining part of the system. This innovative idea was pioneered by Martin Karplus, Michael Levitt and Arieh Warshel (Warshel and Levitt, 1976; Field et al., 1990; Lyne et al., 1990; Aaqvist and Warshel, 1993; Warshel, 2002) in the 1970s, who were awarded the Nobel prize in chemistry *for the development of multiscale models for complex chemical systems* in 2013. Today, four decades after these influential developments, QM/MM methods are regarded as one of the most influential approaches for the description of challenging chemical phenomena. Initially conceived in the framework of biomolecular simulations (Friesner and Guallar, 2005; Hu and Yang, 2009; van der Kamp and Mulholland, 2013; de Visser et al., 2014; Cui, 2016; Lu et al., 2016; Quesne et al., 2016), the range of QM/MM methods has been substantially extended to include other areas accessing *inter alia*

solid-state chemistry and material science (Gonis and Garland, 1977; Krüger and Rösch, 1994; Stefanovich and Truong, 1996; Jacob et al., 2001; Herschend et al., 2004; Keal et al., 2011; Bjornsson and Bühl, 2012; Golze et al., 2013, 2015; Hofer and Tirler, 2015) and solution chemistry (Staib and Borgis, 1995; Tuñón et al., 1995, 1996; Gao, 1996; Hofer et al., 2010, 2011, 2012; Weiss and Hofer, 2012; Hofer, 2014) as well. These QM/MM studies have given insight into how Nature works, and, for instance, explain regio- and stereochemical selectivities during substrate activation (Faponle et al., 2016, 2017; Timmins et al., 2017). Furthermore, using computational modeling, predictions can be made to engineer proteins and enzyme and in a recent example the computationally proposed change led to a full enantioselectivity reversal (Pratter et al., 2013a,b).

Despite their success and widespread recognition, the development of advanced QM/MM methodologies is still an active field of research, aiming to push the accuracy and applicability of this versatile approach even further. This article collection aims to present an overview of present research activities focused on the development and application of modern QM/MM formulations, demonstrating the versatile capabilities of this celebrated methodology.

A total of 12 exciting contributions by 48 authors from 12 different countries in four continents have been included in this article collection that contains ten original research contributions and two review articles.

Scherlis and his team compiled a review article that covers recent applications of their graphical-processor accelerated LIO code for density functional theory calculations (Marcolongo et al.). The presented examples include the decomposition of nitroxyl in aqueous solution, a comparison of the reactivity of thiols against peroxides in aqueous solution and the active site of a peroxiredoxin enzyme. The latter studies are linked to molecular spectroscopy such as the vibrational spectrum of aqueous peroxynitrite anion and $LiAlH_4$ and AlH_4^-. Furthermore, using their novel code they predict the UV/Vis spectra of $(HO)NS_2$ and the so-called NO/H_2S "cross-talk" system.

The second review article by Marazzi et al. presents a comprehensive overview of recent research activities in studying electronic spectroscopy via QM/MM approaches. A broad variety of examples in the fields of linear absorption, non-linear optical properties and circular dichroism applied to organic molecules, proteins and nucleic acid systems is presented.

Prejanò et al. compared the application of a QM cluster model to the decarboxylation of 5-carboxyvanillate by LigW with results obtained from a more elaborate QM/MM setup. Their study indicates that the reaction is mainly influenced by the constituents of the active side and the cluster model already delivers a reliable description for the presented system.

The article of Esccorcia and Stein explored the influence of a conserved arginine residue of the *E. coli* Hyd-1 [NiFe]-Hydrogenase on the H_2 oxidation reaction via DFT-based QM/MM calculations. This study highlights the key influence of this Arg-residue in promoting both the access of molecular

hydrogen to the catalytically active Ni-atom as well as the associated proton transfer to nearby terminal cysteine residues.

Xu et al. present a novel force balanced simulation approach, separating a protein system into hydrogen-bonded fragments that are computed quantum-mechanically, while the AMOEBA force field is employed to describe long-range non-bonded interactions. To conserve the total energy of the system, a force balancing of the hydrogen link-atoms is carried out. The applicability of this approach is demonstrated for linear ACE-(ALA)$_9$-NME as well as the 56 residue GB3 peptides.

The contribution of Sahoo and Nair presents a combination of polarizable Drude oscillators with the well-established Car-Parrinello Molecular Dynamics framework via an extended Lagrangian QM/p-MM method. The approach is demonstrated for a H$_2$O(QM)+4H$_2$O(p-MM) test system and applied to study an O-vacancy in α-cristobalite, the hydrogenation of ethene via Y-Zeolite-supported Rh-Clustes and the H$^+$-exchange between methane and a H-ZSM-5 zeolite.

The difference between additive and subtractive QM/MM protocols has been highlighted in the contribution by Cao and Ryde, focusing inter alia on the different correction schemes to account for errors introduced by the application of link–atoms. Three different systems of increasing complexity have been studied, namely an isolated ethanol molecule, sulfite oxidase and the conversion of oxophlorin to verdohaem by haem oxygenase.

Berraud-Pache et al. studied the keto-enol tautomerisation reaction of oxyluciferin representing the emissive species in the bioluminescent system of fireflies. By combing classical molecular dynamics studies of the active species in a polarisable continuum and explicit QM/MM calculations, the keto-OxyLH$^-$ species was identified as the most likely candidate to act as emitter in bioluminescence.

He and colleagues applied an automated fragmentation QM/MM protocol to study ^{1}H chemical shifts of the apo- and holo-neocarzinostatin-chromophore binding complex (Jin et al.). The calculated NMR data obtained by the fragmented QM/MM approach proved to be in good agreement with results of large-scale calculations as well as experimental data.

The research team of Lin studied the migration of Cl$^-$ through the transmembrane domain of a prototypical *E. coli* chloride-channel (Wang et al.), thereby including the entire pore section into the quantum–mechanically treated zone. The obtained results demonstrate that the influence of electron delocalization, inherently taken into account at the QM level of theory, appear to be more critical than previously considered.

Timmins and De Visser investigated the impact of different mutations in prolyl-4-hydroxylase via a combined QM/MM and MD study. Based on the results of this extensive study two mutants with the potential of displaying notably changes in the regio- and stereoselectivity could be identified.

Hitzenberger et al. provided a contribution combining docking and pharmacophore modeling with QM-based molecular dynamics simulations to investigate the binding of the only known inhibitor robotnikinin to the Zn-site of the extracellular signaling protein Sonic Hedgehog. Comparison to a purely classical molecular dynamics highlights the substantially improved description of the binding observed in the QM/MM MD simulation.

In the contribution of Frau and Glossman-Mitnik the influence of different range-separated hybrid DFT methods in the prediction of chemical reactivity descriptors was evaluated.

Finally, Li and coworkers investigated the interaction mechanism between cyclopeptide DC3 and an androgen receptor via free energy calculations and extensive molecular dynamics simulations Zhang et al..

Clearly, the scope of topics covered by the contributions in this article collection demonstrates the widespread capabilities of the QM/MM technique as a general and versatile approach to address a broad spectrum of research questions. Moreover, the research field is as active as ever and moving into many different research directions. In conjunction with the formulation of advanced theoretical approaches, efficient simulation programs and the development of improved computational infrastructure, QM/MM methods proved to be an indispensable tool in modern chemical research, providing a highly successful alternative route for the study of complex chemical phenomena, which can be expected to play an even more dominant role in the coming years.

AUTHOR CONTRIBUTIONS

REFERENCES

Aaqvist, J., and Warshel, A. (1993). Simulation of enzyme reactions using valence bond force fields and other hybrid quantum/classical approaches. *Chem. Rev.* 93:2523. doi: 10.1021/cr00023a010

Baker, C. M. (2015). Polarizable force fields for molecular dynamics simulations of biomolecules. *WIREs Comp. Mol. Sci.* 5, 241–254. doi: 10.1002/wcms.1215

Bakowies, D., and Thiel, W. (1996). Hybrid models for combined quantum mechanical and molecular mechanical approaches. *J. Phys. Chem.* 100:10580. doi: 10.1021/jp9536514

Bjornsson, R., and Bühl, M. (2012). Modeling molecular crystals by QM/MM: self-consistent electrostatic embedding for geometry optimizations and molecular property calculations in the solid. *J. Chem. Theory Comput.* 8, 498–508. doi: 10.1021/ct200824r

Brinkman, W. F., Haggan, D. E., and Troutman, W. W. (1997). A history of the invention of the transistor and where it will lead us. *IEEE J. Solid St Circ.* 32, 1858–1865. doi: 10.1109/4.643644

Cook, D. B. (2005). *Handbook of Computational Chemistry*. New York, NY: Dover Publications.

Cui, Q. (2016). Perspective: Quantum mechanical methods in biochemistry and biophysics. *J. Chem. Phys.* 145, 140901/1–14090/12. doi: 10.1063/1.4964410

de Visser, S. P., Quesne, M. G., Martin, B., Comba, P., and Ryde, U. (2014). Computational modelling of oxygenation processes in enzymes and biomimetic model complexes. *Chem. Commun.* 50, 262–282. doi: 10.1039/C3CC47148A

Faponle, A. S., Quesne, M. G., and de Visser, S. P. (2016). Origin of the regioselective fatty acid hydroxylation versus decarboxylation by a cytochrome

P450 peroxygenase: what drives the reaction to biofuel production? *Chem. Eur. J.* 22, 5478–5483. doi: 10.1002/chem.201600739

Faponle, A. S., Seebeck, F. P., and de Visser, S. P. (2017). Sulfoxide synthase versus cysteine dioxygenase reactivity in a nonheme iron enzyme. *J. Am. Chem. Soc.* 139, 9259–9270. doi: 10.1021/jacs.7b04251

Field, M. J., Bash, P. A., and Karplus, M. (1990). A combined quantum mechanical and molecular mechanical potential for molecular dynamics simulations. *J. Comput. Chem.* 11:700. doi: 10.1002/jcc.540110605

Friesner, R. A., and Guallar, V. (2005). Ab initio quantum chemical and mixed quantum mechanics/molecular mechanics (QM/MM) methods for studying enzymatic catalysis. *Ann. Rev. Phys. Chem.* 56, 389–427. doi: 10.1146/annurev.physchem.55.091602.094410

Gao, J. (1993). Potential of mean force for the isomerization of DMF in aqueous solution: a monte carlo QM/MM simulation study. *J. Am. Chem. Soc.* 115:2930. doi: 10.1021/ja00060a047

Gao, J. (1996). Hybrid quantum and molecular mechanical simulations An alternative avenue to solvent effects in organic chemistry. *Acc. Chem. Res.* 29, 298. doi: 10.1021/ar950140r

Golze, D., Hutter, J., and Iannuzzi, M. (2015). Wetting of water on hexagonal boron nitride@Rh(111): a QM/MM model based on atomic charges derived for nano-structured substrates. *Phys. Chem. Chem. Phys.* 17:14307. doi: 10.1039/C4CP04638B

Golze, D., Iannuzzi, M., Nguyen, M., Passerone, D., and Hutter, J. (2013). Simulation of adsorption processes at metallic interfaces: An image charge-augmented QM/MM approach. *J. Chem. Theory Comput.* 9:5086. doi: 10.1021/ct400698y

Gonis, A., and Garland, J. W. (1977). Multishell method: exact treatment of a cluster in an effective medium. *Phys. Rev. B* 16:2424. doi: 10.1103/PhysRevB.16.2424

Hartke, B. and Grimme, S. (2010). Reactive force fields made simple. *Phys. Chem. Chem. Phys.* 17, 16715–16718. doi: 10.1039/C5CP02580J

Helgaker, T., Jørgensen, P., and Olsen, J. (2000). *Molecular Electronic Structure Theory*. Chichester: Wiley

Herschend, B., Baudin, M., and Hermansson, K. (2004). A combined molecular dynamics+quantum mechanics method for investigation of dynamic effects on local surface structures. *J. Chem. Phys.* 120:4939. doi: 10.1063/1.1635802

Hofer, T. S. (2014). Perspectives for hybrid ab initio/molecular mechanical simulations of solutions: from complex chemistry to proton-transfer reactions and interfaces. *Pure Appl. Chem.* 86:105. doi: 10.1515/pac-2014-5019

Hofer, T. S., Hitzenberger, M., and Randolf, B. R. (2012). Combining a Dissociative Water Model with a Hybrid QM/MM Approach - A Simulation Strategy for the Study of Proton Transfer Reactions in Solutions. *J. Chem. Theory Comput.* 8:3586. doi: 10.1021/ct300062k

Hofer, T. S., Rode, B. M., Pribil, A. B., and Randolf, B. R. (2010). Simulations of Liquids and Solutions Based On Quantum Mechanical Forces. *Adv. Inorg. Chem.* 62:143. doi: 10.1016/S0898-8838(10)62004-1

Hofer, T. S. and Tirler, A. O. (2015). Combining 2d-periodic quantum chemistry with molecular force fields: a novel QM/MM procedure for the treatment of solid-state surfaces and interfaces. *J. Chem. Comput. Theory* 11, 5873–5887. doi: 10.1021/acs.jctc.5b00548

Hofer, T. S., Weiss, A. K. H., Randolf, B. R., and Rode, B. M. (2011). Hydration of highly charged ions. *Chem. Phys. Lett.* 512:139. doi: 10.1016/j.cplett.2011.05.060

Hu, H. and Yang, W. (2009). Development and application of ab initio QM/MM methods for mechanistic simulation of reactions in solution and in enzymes. *J. Mol. Struct. Theochem* 898, 17–30. doi: 10.1016/j.theochem.2008.12.025

Jacob, T., Fricke, B., Anton, J., Varga, S., Bastug, T., Fritzsche, S., et al. (2001). Cluster-embedding method to simulate large cluster and surface problems. *Eur. Phys. J. D* 16, 257–260. doi: 10.1007/s100530170105

Jensen, F. (2006). *Introduction to Computational Chemistry, 2nd Edition*. Chichester: John Wiley & Sons Ltd.

Keal, T. W., Sherwood, P., Dutta, G., Sokol, A. A., and Catlow, C. R. A. (2011). Characterization of hydrogen dissociation over aluminium-doped zinc oxide using an efficient massively parallel framework for QM/MM calculations. *Proc. R. Soc. A* 467:1900. doi: 10.1098/rspa.2010.0613

Koch, W. and Holthausen, M. C. (2002). *A Chemist's Guide to Density Functional Theory, 2nd Edition*. Weinheim: Wiley–VCH.

Krüger, S., and Rösch, N. (1994). The moderately-large-embedded-cluster method for metal surfaces; a density-functional study of atomic adsorption. *J. Phys.Condens. Matter* 6:8149. doi: 10.1088/0953-8984/6/40/007

Leach, A. R. (2001). *Molecular Modelling, 2nd Edn.* Harlow: Prentice-Hall.

Lemkul, J. A., Huang, J., Roux, B., and MacKerell, A. D. Jr. (2016). An empirical polarizable force field based on the classical drude oscillator model: development history and recent applications. *Chem. Rev.* 116, 4983–5013. doi: 10.1021/acs.chemrev.5b00505

Liang, T., Shin, Y. K., Cheng, Y., Yilmaz, D. E., Vishnu, K. G., Verners, O., et al. (2013). Reactive potentials for advanced atomistic simulations. *Ann. Rev. Mater. Res.* 43:109. doi: 10.1146/annurev-matsci-071312-121610

Lin, H. and Truhlar, D. G. (2007). Qm/mm: what have we learned, where are we, and where do we go from here? *Theor. Chim. Acta* 117:185. doi: 10.1007/s00214-006-0143-z

Lu, X., Fang, D., Ito, S., Okamoto, Y., Ovchinnikov, V., and Cui, Q. (2016). QM/MM free energy simulations: recent progress and challenges. *Mol. Sim.* 42, 1056–1078. doi: 10.1080/08927022.2015.1132317

Lyne, P. D., Hodoscek, M., and Karplus, M. (1990). A hybrid QM-MM potential employing Hartree-Fock or density functional methods in the quantum region. *J. Phys. Chem. A* 103:3462. doi: 10.1021/jp982115j

Mahadevan, T. S. and Garofalini, S. H. (2007). Dissociative Water Potential for Molecular Dynamics Simulations. *J. Phys. Chem. B* 111:8919. doi: 10.1021/jp072530o

McDonagh, J. L., Silva, A. F., Vincent, M. A., Popelier, P., and Paul, L. A. (2017). Quantifying Electron Correlation of the Chemical Bond. *J. Phys. Chem. Lett.* 8, 1937–1942. doi: 10.1021/acs.jpclett.7b00535

Metz, S., Kästner, J., Sokol, A. A., Keal, T. W., and Sherwood, P. (2014). ChemShell-a modular software package for QM/MM simulations. *WIREs Comput. Mol. Sci.* 4:101. doi: 10.1002/wcms.1163

Moore, G. (1965). Cramming more components onto integrated circuits. *Electronics* 38, 114–117.

Parr, R. G. and Yang, W. (1994). *Density-Functional Theory of Atoms and Molecules*. Oxford: Oxford University Press.

Pezeshki, S., and Lin, H. (2015). "Recent progress in adaptive-partitioning QM/MM methods for Born-Oppenheimer molecular dynamics," in *Quantum Modeling of Complex Molecular Systems, Challenges and Sdvances in Computational Chemistry and Physics,* Vol. 21, eds J-L. Rivail, M. Ruiz-Lopez, and X. Assfeld (Cham: Springer International Publishing), 93–113.

Popelier, P. (ed.) (2011). *Solving the Schrodinger Equation: Has Everything Been Tried?* Singapore: World Scientific.

Pratter, S. M., Konstantinovics, C., DiGiuro, C. L. M., Leitner, E., Kumar, D., de Visser, S. P., et al. (2013a). Inversion of enantio-selectivity of a mononuclear non-heme iron(II)-dependent hydroxylase by tuning the interplay of metal-center geometry and protein structure. *Angew. Chem. Int. Ed.* 52, 9677–9681. doi: 10.1002/anie.201304633

Pratter, S. M., Konstantinovics, C., DiGiuro, C. L. M., Leitner, E., Kumar, D., de Visser, S. P., et al. (2013b). Inversion of enantio-selectivity of a mononuclear non-heme iron(II)-dependent hydroxylase by tuning the interplay of metal-center geometry and protein structure. *Angew. Chem.* 125, 9859–9863. doi: 10.1002/ange.201304633

Quesne, M. G., Borowski, T., and de Visser, S. P. (2016). Quantum Mechanics/Molecular Mechanics Modelling of Enzymatic Processes: Caveats and Breakthroughs. *Chem. Eur. J.* 22, 2562–2581. doi: 10.1002/chem.201503802

Raghavachari, K. and Anderson, J. B. (2010). Electron Correlation Effects in Molecules. *J. Phys. Chem.* 100, 12960–12973. doi: 10.1021/jp953749i

Ramachandran, K. I., Deepa, G., and Namboori, K. (2008). *Computational Chemistry and Molecular Modeling: Principles and Applications* (Berlin: Springer.)

Senn, H. M., and Thiel, W. (2007). QM/MM studies of enzymes. *Current Opinion in Chemical Biology* 11:182. doi: 10.1016/j.cbpa.2007.01.684

Senn, H. M. and Thiel, W. (2009). QM/MM Methods for Biomolecular Systems. *Angew. Chem. Int. Ed.* 48, 1198–1229. doi: 10.1002/anie.200802019

Sholl, D. S. and Steckel, J. A. (2009). *Density Functional Theory-A Practical Introduction*. Hoboken, NY: Wiley.

Staib, A., and Borgis, D. (1995). Molecular dynamics simulation of an excess charge in water using mobile Gaussian orbitals. *J. Chem. Phys* 103:2642. doi: 10.1063/1.470524

Stefanovich, E. V., and Truong, T. N. (1996). Embedded density functional approach for calculations of adsorption on ionic crystals. *J. Chem. Phys.* 104, 2946–2955. doi: 10.1063/1.471115

Stone, A. J. (1995). *The Theory of Intermolecular Forces*. Oxford, UK: Oxford University Press.

Szabo, A., and Ostlund, N. S. (1996). *Modern Quantum Chemistry*. New York, NY: Dover Publications.

Timmins, A., Saint-André, M., and de Visser, S. P. (2017). Understanding how prolyl-4-hydroxylase structure steers a ferryl oxidant toward scission of a strong C-H bond. *J. Am. Chem. Soc.* 139, 9855–9866. doi: 10.1021/jacs.7b02839

Tuñón, I., Martins-Costa, M. T. C., Millot, C., and Ruiz-López, M. F. (1995). Coupled density functional/molecular mechanics Monte Carlo simulations of ions in water. The bromide ion. *Chem. Phys. Lett.* 241:450. doi: 10.1016/0009-2614(95)00615-B

Tuñón, I., Martins-Costa, M. T. C., Millot, C., Ruiz-López, M. F., and Rivail, J. L. (1996). A coupled density functional-molecular mechanics Monte Carlo simulation method: the water molecule in liquid water. *J. Comput. Chem.* 17:19. doi: 10.1002/(SICI)1096-987X(19960115)17:1<19::AID-JCC2>3.0.CO;2-3

van der Kamp, M. W. and Mulholland, A. J. (2013). Combined quantum mechanics/molecular mechanics (QM/MM) methods in computational enzymology. *Biochemistry* 52, 2708–2728. doi: 10.1021/bi400215w

van Duin, A. C. T., Dasgupta, S., Lorant, F., and Goddard, W. A. (2001). ReaxFF A reactive force field for hydrocarbons. *J. Phys. Chem. A* 105, 9396. doi: 10.1021/jp004368u

Warshel, A. (2002). Molecular dynamics simulations of biological reactions. *Acc. Chem. Res.* 35:385. doi: 10.1021/ar010033z

Warshel, A., and Levitt, M. (1976). Theoretical studies of enzymic reactions: dielectric, electrostatic and steric stabilization of the carbenium Ion in the reaction of lysozyme. *J. Mol. Biol.* 103:227. doi: 10.1016/0022-2836(76)90311-9

Weiss, A. K., and Hofer, T. S. (2012). Exploiting the capabilities of quantum chemical simulations to characterise the hydration of molecular compounds. *RSC Adv.* 3:1606. doi: 10.1039/C2RA21873A

Whitworth, I. (1979). Review of microprocessor architecture. *Microprocess Microsy.* 3, 21–28. doi: 10.1016/0141-9331(79)90088-7

Yu, H. and van Gunsteren, W. F. (2005). Accounting for polarization in molecular simulation.. *Comp. Phys. Commun.* 172, 69–85. doi: 10.1016/j.cpc.2005.01.022

Zheng, M., and Waller, M. P. (2016). Adaptive quantum mechanics/molecular mechanics methods. *WIREs Comput. Mol. Sci.* 6, 369–385. doi: 10.1002/wcms.1255