Molecule-specific Uncertainty
Quantification in Quantum Chemical
Studies

Markus Reiher*

ETH Zürich, Laboratorium für Physikalische Chemie,
Vladimir-Prelog-Weg 2, 8093 Zürich, Switzerland

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Abstract
Solving the electronic Schrödinger equation for changing nuclear coordinates provides access to the Born-Oppenheimer potential energy surface. This surface is the key starting point for almost all theoretical studies of chemical processes in electronic ground and excited states (including molecular structure prediction, reaction mechanism elucidation, molecular property calculations, quantum and molecular dynamics). Electronic structure models aim at a sufficiently accurate approximation of this surface. They have therefore become a cornerstone of theoretical and computational chemistry, molecular physics, and materials science. In this work, we elaborate on general features of approximate electronic structure models such as accuracy, efficiency, and general applicability in order to arrive at a perspective for future developments, of which a vanguard has already arrived. Our quintessential proposition is that meaningful quantum mechanical predictions for chemical phenomena require system-specific uncertainty information for each and every electronic structure calculation, if objective conclusions shall be drawn with confidence.

*contact: markus.reiher@phys.chem.ethz.ch; ORCID: 0000-0002-9508-1565
1 Introduction

Electronic structure theory is at the core of many theoretical and computational approaches in the molecular sciences as well as in condensed matter and solid state physics. The Born-Oppenheimer approximation introduces the electronic Schrödinger equation that treats all electrons of an atomistic system as dynamical entities moving in the field of a fixed nuclear scaffold. The success of computational molecular and materials science is rooted in this framework, and naturally, an ever growing number of electronic structure models has been devised in the past decades that aim at improving on existing approximations in terms of general applicability, increased accuracy, and optimized efficiency with respect to computational time. The rate of introduction, adoption, and use of capital-letter acronyms that denote the various models and approximations may serve as a good measure of these efforts. In this work, we assume a bird’s eye view on the current status of developments in an attempt to assess and determine feasible options for future models. Before we provide our perspective on these developments, we first dwell on the theoretical foundations of electronic structure models.

2 Theoretical Foundations

The explicit decoupling of nuclear and electronic degrees of freedom through the Born-Oppenheimer approximation is, in many cases, an efficient and reliable approximation, but most importantly, it can be systematically improved to include nonadiabatic and rovibronic couplings.

The Born-Oppenheimer approximation introduces the concept of molecular structure as a spatial arrangement of nuclear positions, making a local minimum structure the representative of a stable compound. The emergence of (classical) molecular structure can be studied within a full quantum framework (see Refs. 4–7 and references therein), but the application of such a general pre-Born-Oppenheimer approach for calculations on large systems is unfeasible in practice. The reason for this is not only the prohibitive computational cost of a truly accurate all-particle quantum calculation, but also the lack of understanding when the concept ‘potential energy surface’, i.e., the change of the electronic energy with nuclear coordinates, is simply not available. Instead, in pre-Born-Oppenheimer quantum theory, we obtain only a spectrum of (molecular) energy eigenvalues for the total system of electrons and nuclei without any direct relation to molecular structure. For this reason, electronic structure theory in the Born-Oppenheimer approximation has become the prevailing theoretical approach because it allows us to think in
terms of classical molecular structure and to improve on this approximation a posteriori in an efficient manner.

From the perspective of practical considerations and numerical calculations, the Born-Oppenheimer approximation has therefore become the key entry point for actual calculations of molecules. Its most decisive consequence is the assignment of an energy, the electronic energy, to a given molecular structure – which may be an equilibrium structure of a chemical compound or an arbitrarily distorted nuclear scaffold – by virtue of the emerging electronic Schrödinger equation (contributions of the nuclear degrees of freedom can be included subsequently).

The decisive difference of quantum chemical models compared to other types of atomistic modeling approaches – such as force fields that govern the interactions of atoms (as new emergent entities, rather than electrons and nuclei) – is that the interaction of their dynamical objects, i.e., the electrons and nuclei, is well known and determined by the laws of quantum electrodynamics. If the speed of light is taken to be infinite, then the interaction law will be known exactly and simply be given by the electrostatic Coulomb interaction of two point charges promoted to an operator, whereas magnetic interactions and retardation effects vanish in this limit. This advantage together with the fact that any atomistic system is built of electrons and atomic nuclei makes quantum chemical models universally applicable. Hence, these models that rest on the first principles of quantum mechanics enjoy a special status in theoretical chemistry and molecular physics.

It is often taken for granted that successful electronic structure models can be applied to arbitrarily sized molecules (of course, up to a point where the size of the molecule will be in conflict with computational feasibility). In other words, if the size of a molecule under study changes (e.g., by a substitution of a residue, for which benzene and toluene may be taken as an example), then we will still expect our computational models to work if we start the computer program that calculates an approximation to the electronic energy. Hence, an implicit requirement for the development of general approaches designed to solve the electronic Schrödinger equation has been that they can be applied efficiently for a fixed but otherwise variable number of electrons; only the scaling behavior of an approximation with system size will put some upper limit on this generality depending on the actual computer hardware available.

Irrespective of available hardware, very accurate electronic structure methods scale unfavorably with system size and therefore require a significant computational effort. As a consequence, they can only be applied to far smaller systems than those accessible to more approximate approaches, which trade accuracy for applicability. Although system size is a moving target in view of
continuously evolving algorithmic improvements and hardware capabilities, the situation does not change in principle: very large systems are approached with rather approximate methods, whereas very accurate methods remain to be bound to very small molecules.

It is mostly for historical reasons that all electronic structure models have been first devised for the (‘non-relativistic’) Schrödinger equation rather than for many-electron Hamiltonians based on Dirac’s theory of the electron, which delivers an equation of motion that is Lorentz covariant for a single electron in a classical electromagnetic field. Considering the fact that observables such as energies are the prime target quantity of computations, the fundamental Einsteinean framework of special relativity requiring Lorentz invariance of all fundamental physical equations has been reduced to its numerical effect on observables obtained by relativistic quantum chemical methods. For example, Taylor series expansions in powers of the inverse speed of light have been considered early on and introduced new concepts such as spin-orbit, spin-spin, spin-other-orbit interactions, and kinematic relativistic effects. Although there exist convergence issues with this type of Taylor series expansions, they deliver well-defined analytical expressions for operators that can be used in perturbation theory to correct the electronic energy for such effects. Naturally, efficient variational relativistic procedures have also been devised.

Important for the assessment of errors of approximate relativistic energy operator expressions is that the dependence of relativistic approximations on nuclear charge, electron kinematics, and spin appears to be such that no appreciable error accumulation or growing uncertainties are found in relative quantities such as reaction energies. This is due to the fact that relativistic effects are often atomically conserved (e.g., during reaction) and therefore remain largely unchanged in chemical transformations. This is also the reason why surrogate potentials that model relativistic atomic cores (e.g., effective core potentials and pseudo potentials) are reliable in capturing relativistic effects (and even reduce the computational effort through elimination of core electrons and alleviate the discretization error of a finite basis set through elimination of the nodal structure of the wave function in the core region).

For what follows below, the most important consequence is that no (approximate) relativistic method will introduce an error in the electronic energy that will be difficult to control when the underlying nuclear scaffold changes (e.g., during chemical reaction). In other words, the change of electronic energy due to the principles of Einstein’s theory of special relativity and quantum electrodynamics is very well understood, up to the point where it has become possible to calculate the binding energy of molecular hydrogen to an absolutely remarkable precision, in excellent agreement with high-4
precision spectroscopic measurements.\textsuperscript{14,15} Effects that transgress the realm of quantum electrodynamics (such as electroweak effects\textsuperscript{16}) are known to be orders of magnitude smaller.

**Statement 1:** *The theoretical foundations of electronic structure theory are very well established and understood.*

Various well-defined relativistic generalizations of the standard non-relativistic electronic Schrödinger equation have been developed, which connect the quantum theory for atomistic systems to the fundamental theory of quantum electrodynamics.\textsuperscript{8} Since these relativistic variants do not pose any unsurmountable hurdle to approximations designed for the efficient solution of the non-relativistic electronic Schrödinger equation, electronic structure methods developed in the non-relativistic regime apply equally well in the relativistic domain. By contrast, electronic structure theory has been plagued by the peculiarities of many-electron systems in general, which are first and foremost the Coulomb interactions of the (point) particles featuring a singularity where the particle coordinates coalesce.

**Statement 2:** *The quantum mechanical Coulomb interaction of two electrons is the crucial challenge for accurate approximations.*

### 3 Electronic Structure Models

Two main classes of approximations have emerged in electronic structure theory: wave-function-based theories\textsuperscript{1} and density functional theory (DFT)\textsuperscript{2}, with variants that bridge both classes. In actual calculations, DFT is often applied as a parametrized model because of approximations in the exchange-correlation energy functional that require parameters, in most cases determined for some reference data. Despite the universal nature of these parameters, which are taken to be valid for any sort of atomistic system, and despite the first-principles nature of DFT per se, actual applications are sometimes classified as 'semi-empirical' referring to the parameter dependence on the reference (training) data and to the, to a certain degree arbitrary, assumptions on the analytical form of a functional. Proposals to improve on this situation have been numerous, but the general dilemma of electronic structure theory, i.e., the ineluctability to compromise accuracy for computational efficiency, also hampers these attempts. This is already seen in the standard approximations of DFT, which Perdew ranked as a Jacob’s ladder\textsuperscript{17} (a hierarchical ranking that has been confirmed in rigorous and extensive numerical
studies\textsuperscript{18–20}), for which improved accuracy comes at significantly increased computational cost.

Although the existence of the exact exchange-correlation energy functional has been proven\textsuperscript{21,22} its exact analytical form is and most likely will remain unknown. In view of the increasing complexity of advanced density functionals\textsuperscript{23} one is struck by the impression that the exact exchange-correlation functional (or a very accurate approximation to it) will be as hard to evaluate as a wave-function model of the same accuracy.

By contrast, wave function theories often allow for systematic improvement owing to a systematic and well-controllable construction of the electronic wave function through basis-set expansion techniques – at least in principle, but not to an arbitrary degree in practice. In a mathematically stringent way, the electronic wave function can be expanded in terms of a complete many-electron basis set. The many-electron basis functions can be systematically built (usually as determinants) from products of one-electron functions (e.g., Hartree-Fock orbitals or some general type of energy-optimizing orbitals), which themselves can be generated as a linear combination of pre-defined and therefore known one-electron basis functions (representing the well-known linear combination of atomic orbitals).

All standard models – such as configuration interaction, coupled cluster (CC), complete active space self-consistent field, or Møller-Plesset perturbation theory – approximate the electronic wave function by a superposition of these many-electron basis functions, of which an ordered set is generated and classified according to orbital substitutions compared to a (dominant) reference determinant (so-called ’excitations’). Although this choice of singles (S), doubles (D), triples (T), ... excitations for the definition of classes of many-electron basis functions produces a well-defined approximation hierarchy, it does, a priori, not guarantee optimum convergence as it is not clear which ’excitations’ will be decisive for the model to achieve a given accuracy. However, as long as changes in molecular structure are local (as is the breaking of a chemical bond in a chemical reaction), very high excitations may be avoided. A vast body of numerical results has therefore led to the wide acceptance of the CCSD(T) coupled cluster model\textsuperscript{24} as a ’gold standard’ for quantum chemical calculations. It is, however, important to emphasize that, although this approach can deliver results of chemical accuracy of about 1 kcal/mol in benchmark calculations, the precise accuracy of the approach for some given case is, in general, not known. Instead, one resorts to ensure some general constraints on the electronic structure of a molecule under investigation that must be fulfilled in order to achieve a high accuracy with the CCSD(T) model. These constraints require a (close to) equilibrium molecular structure, a closed-shell electronic structure, absence
of multi-reference effects that are typical for open shells and so forth.

Unfortunately, no such model of similar reliability, but universal applicability could be established for the general multi-configurational case. Although many open-shell and bond-breaking situations may be well captured by ground-state coupled cluster theory with a not too high degree of excitations in the electronic wave function, it is troublesome that the most general case has escaped attempts to produce an equally accurate and broadly applicable electronic structure model. Surely, modern complete-active-space approaches such as the density matrix renormalization group (DMRG) or full configuration interaction quantum Monte Carlo (FCIQMC) have pushed the limits to a degree where any (for reaction chemistry) relevant active orbital space can be treated (i.e., of up to one hundred active spatial orbitals). However, the neglected dynamic correlation from the huge number of weakly correlated orbitals, which are outside the active space, escapes a treatment on the same level of accuracy; typically only multi-reference perturbation theory to second order represents the highest level of accuracy achievable. Continuous efforts have tried to improve on this situation; examples are tailored coupled cluster, combinations with short-range DFT or transcorrelation to treat the electron-electron cusp due to the singularity of the Coulomb interaction, to mention only a few. Already the amount of suggestions for accurate multi-configurational methods (not reflected in the list of references of this work and beyond its scope) may be taken as an indication that no universally satisfactory and generally accepted best solution has been found so far. At the same time, multi-reference coupled cluster theory has suffered from formal difficulties by which each of the various ansätze is plagued to a different degree. It is therefore no surprise that other advanced configuration interaction (CI) methods have been developed in recent years as a potential way to approach full configuration interaction (FCI) results.

Hence, one may doubt whether this situation can in principle be improved on, and a quantum leap to solve these principal problems, that will also need to stand scrutiny in terms of computational feasibility, appears not very likely on traditional computers. Naturally, many have wondered whether there are other, better suited approaches that await discovery or just need to flourish. Hence, alternative approaches have been sought for, but all developments rely on more or less the same principles and technologies and still wait for an eventual breakthrough. Even if this happens in the future, history teaches us to expect that there will always be strings attached that will eventually restrict the range of applicability and the achievable accuracy. And therefore, the basic train of thought of this work will persist.

The most dramatic improvement may come from hardware development
in the future, of which the most prominent example is the hope to solve
electronic structure problems with quantum hardware to be developed,\textsuperscript{58–62}
which may deliver FCI-quality results up to a pre-defined accuracy by quan-
tum phase estimation (QPE). Although current implementations rely mostly
on the variational quantum eigensolver,\textsuperscript{63} QPE can be shown to be feasible
on moderately sized future quantum computers for actual chemical (rather
than toy) problems.\textsuperscript{64,65} In this context, it is important to understand that
a typical electronic structure problem represented in an orbital basis of, say,
1000 one-electron basis functions, will require 2000 logical qubits to repre-
sent the state (which, in turn, will require orders of magnitude more physical
qubits for error correction purposes), let alone the problems of initial state
preparation and loading the Hamiltonian parametrization in second quan-
tized form into the machine (consider, in particular, the two-electron inte-
grals for an active space of 1000 orbitals). However, if such large universal
digital quantum computers become available in the future and if they are
widely accessible, then they can produce results of FCI quality for molecular
sizes that can accurately describe any (usually local) chemical reaction
event, which will render very many traditional electronic structure models
superfluous (for instance, the separation into static and dynamic correlation
may become unnecessary).

As a side remark, the ongoing efforts in establishing a universal quantum
computer show that one must be willing to cool down a quantum computer
to very low temperature. However, such a strategy will also be beneficial for
traditional approaches directed towards cryogenic computing.

For the reasoning in this paper, we adopt the point of view that we
will have to cope with the situation as it presents itself to us today in the
near and maybe also in the distant future. Namely, that we will accomplish
incremental improvements in all directions, but that no generalist approach
of arbitrary accuracy for some system under study is likely to emerge.

\textbf{Hypothesis:} The current situation of electronic-structure models might
represent the end point of our efforts to devise universally applicable,
accurate, and feasible electronic structure models. In view of the tricks and
techniques used in all developments, it appears to be unlikely that
paradigm-shifting new ideas will emerge in the (near) future in view of the
fact that all viable approaches eventually rely on some version of the
configuration interaction expansion.

Even if this hypothesis will be falsified in the future, it is the best start-
ing point for a discussion on how to deal best with our current arsenal of
electronic-structure methods for solving pressing chemical problems.
4 The Role of One-Electron Basis Sets

It is hard to obtain accurate quantities for many-electron problems. Already the choice of a typical one-electron basis set usually affects the total electronic energy significantly, because basis sets are designed for specific purposes and compromise on others for the sake of computational feasibility. For instance, to allow for sufficiently accurate results of relative electronic energies for chemical reactions, ‘atomic orbital’ basis sets attempt to represent the valence-shell region well by suitable polarization and diffuse functions. The core shells, i.e., those molecular orbitals that appear like atomic 1s-type orbitals, are not very well represented, which affects their orbital energy. If one expresses the total electronic energy as a function of orbital energies (e.g., as the sum of all canonical orbital energies plus the one-electron integrals in Hartree-Fock theory divided by two) then it is obvious that the large core-shell orbital energies affected by a large error propagate this error to the total electronic energy. However, for relative electronic energies of processes where atomically conserved features of the electronic structure are unimportant, these errors will drop out as they are conserved in reactants and products.

Very many numerical studies have been conducted to demonstrate the role of the various ingredients (including quasi-relativistic Hamiltonians) of which we may refer to three studies presented in Refs. 66–68. Apart from the electronic energy, also calculations of its derivatives – which define molecular properties through response theory and can be taken as ‘relative quantities’ by definition (as is particularly obvious in the finite-field approach) – usually factor in error compensation, but may require special functions to represent a property well. For instance, polarizabilities naturally require one to allow for polarization effects, and hence, polarization functions will be very important. Taking further derivatives, e.g., for the calculation of Raman and Raman Optical Activity spectra has led to the proposal of tiny skeleton basis sets with polarization functions to reduce the computational effort, which turn out to be quite accurate for these ‘relative’ quantities.

The singularity at the coalescence of the electron-electron Coulomb interaction will demand extended one-electron basis sets, especially for correlated electronic structure methods. To achieve chemical accuracy with decent triple-zeta basis sets requires the introduction of explicitly correlated functions, as elaborated into the now established F12 ansatz or a modification of the Hamiltonian as in the transcorrelation approach or through range separation by short-range DFT.

In general, even large orbital basis sets therefore suffer from errors that are well above 1 milliHartree, an accuracy that nevertheless may be approached
for relative quantities due to the fortunate error compensation of atomically conserved parts of electronic structures. While this observation has been central to the application of electronic structure models in computational quantum chemistry, rigorous mathematical results on the discretization error introduced by finite basis sets are still needed (see Ref. [74]).

Large standard valence-optimized one-electron basis sets will not allow one to reach a high accuracy in the total electronic energy of, say, 1 nanoHartree, for which one is advised to switch to explicitly correlated basis functions such as geminals.\textsuperscript{75,76} Depending on the target problem, such an accuracy might be needed. While kinetic details of a reaction will require one to know the relative electronic energy to an accuracy better than 1 kJ/mol, which is somewhere inbetween milliHartree and microHartree accuracy, nanoHartree accuracy may become important for high-resolution spectroscopy, of which the measurement of the H\textsubscript{2} binding energy is a prime example.\textsuperscript{12–15} It is therefore obvious that the required target accuracy needs to be factored into the effort one spends on solving the electronic structure problem.

\textbf{Statement 3:} While the discretization error introduced by orbital and geminal basis sets – as well as any other error that results from the technical implementation of solution procedures – may be systematically reduced, its value in an actual calculation is usually not precisely known.

5 Can We Know the Error by Which a Specific Quantum Chemical Result is Affected?

The Ritz variational principle provides us with a means to judge the reliability of total electronic energies obtained with approximate (variational) electronic structure models by assuring that they are upper bounds to the ground-state energy eigenvalue of the electronic Hamiltonian. As a consequence, we know that the lowest approximate energy represents the lowest upper bound and, hence, the best approximation to the exact total electronic energy. To assess the remaining error requires, however, a lower bound that can be efficiently computed. Despite continuous development devoted to establishing such rigorous lower bounds for Hermitian operators (see Refs. \textsuperscript{77–79} and references therein), this ansatz remains underexplored. Moreover, even if such a lower bound can be efficiently computed, this does not imply that the uncertainty obtained as the difference between both bounds will be sufficiently small to allow for a tight bracketing of the error so that it is eventually useful.
Analytical error assignment based on the structure of the underlying differential equations (i.e., the electronic Schrödinger equation or its descendants, the self-consistent field equations) is very hard as well. The external potential created by the nuclear scaffold presents a complicated variety as a coefficient function in the partial differential equations. At the level of total electronic states, compared to some reference molecular structure, slightly shifted nuclear positions create a shifted energy eigenvalue spectrum. This can then represent a very different electron correlation pattern and may even give rise to emerging avoided crossings or conical intersections. At the orbital level, the fact that construction of the electron-electron interaction requires knowledge of the orbitals themselves – which is dealt with in the self-consistent field procedure – makes the corresponding one-electron partial differential equations hard to analyze.

A change in the external potential (e.g., as it occurs along a reaction coordinate) is continuous and typically changes the error of an electronic structure model in a smooth and continuous, non-abrupt fashion (even if this error may, in some cases, successively become very large as, for instance, in coupled cluster calculations of at most doubles excitations in double-bond breaking processes). As such, the error is systematic and, obviously, it does not depend on any sort of noise (as long as the computer hardware is reliable, which cannot be strictly guaranteed). However, this usually does not allow one to explicitly know the error in a specific quantum chemical calculation without carrying out an improved calculation. Unfortunately, the latter is, for various reasons, typically unfeasible (otherwise one would have chosen the more accurate (and, hence, more expensive) calculation from the start).

Statement 4: The individual absolute error of a specific quantum chemical result is usually very hard, if not impossible, to assess accurately.

6 Systematic Improvability

For the purpose of this work, it is instructive to now look at electronic structure methods from the point of view of how errors introduced by various approximations are actually assessed in routine calculations.

It is the specific nature of first-principles methods to be well-defined in terms of the fundamental interactions requiring hardly any model assumptions on the interaction operators – other than those that emerge from quantum electrodynamics. This formally convenient and intellectually appealing situation has given rise to the romantic belief that a general electronic structure model – applicable to any atomistic system with sufficient accuracy (say,
with chemical accuracy of at least 1 kcal/mol) and feasible – can actually be devised if we only search for it with sufficient devotion and dedication. Because of this attitude that we may be able to approximate the exact solution of the electronic Schrödinger equation with sufficient accuracy, the modeling of electronic structure has hardly been scrutinized by rigorous uncertainty quantification procedures applied routinely to specific atomistic systems under investigation.

It is natural for many-particle basis-set expansion approaches such as configuration interaction and coupled cluster theories that one can approximate the exact solution of the electronic Schrödinger equation to arbitrarily high accuracy under the provision (i) that one ignores the exponentially scaling wall created by the exploding number of many-electron basis functions with system size (even when acknowledging that there may be a lot of deadwood in many-electron Hilbert space that might be avoided by smart procedures, such as DMRG and FCIQMC mentioned above) and (ii) that one has chosen some suitable finite one-electron (orbital) basis set in which an accurate solution can be obtained. Following the excitation hierarchy in these schemes allows one to systematically approach a 'complete' (finite) many-particle basis set and, hence, the full configuration interaction energy in this basis.

Interestingly, this idea of systematical improvability is hardly pushed to the limit in practical calculations, where one prefers to pick just one well-established generalist model (such as CCSD(T)) to have only one calculation to rely on. Only then, one does not drown in numerical data, can focus on the scientific question to be answered, and does not spend additional computational time on it. However, in such cases it is not at all clear how reliable the calculated data are for answering a chemical question (regarding, for instance, the elucidation of mechanistic pathways). While the prevailing assumption is that CCSD(T) combined with a suitable one-particle basis set will be sufficiently accurate, this situation actually points toward the need for system-specific error assignment with little additional computational effort.

Pople and co-workers arranged wave-function-theory models according to their expected accuracy, in order to establish extrapolation schemes that allow one to exploit orbital bases of different size to make the high-excitation-degree wave functions accessible, leading to combination theories such as G2\22{\textsuperscript{82,83}} and G3\22{\textsuperscript{85,86}}. Such composite models have been further developed by other groups (see, for instance, Refs.\22{88,89} to mention only a few). At the same time, the result of such approaches is still affected by an error, even if it may be significantly reduced, which is not known precisely for a specific system under study (despite recent efforts to equip composite protocols with uncertainties for specific quantities and pre-defined classes of molecules\22{96,97}).

In DFT, the situation is more cumbersome because of the more or less
empirical introduction of parameters and analytical functional forms that
define the approximate exchange-correlation energy functionals. They do
not allow for a systematic improvement as one has no idea about what to
change in order to arrive at a more accurate answer. In other words, having
obtained a DFT result with some density functional, by and large, presents
us with the problem that it is not clear how to improve on it or even how
to scrutinize it. Surely, climbing up the notorious Jacob’s ladder\textsuperscript{17} could be
one option, but this concept is more heuristic than rigorous at its core. In
particular, improved results can only be expected in an average manner,\textsuperscript{19}
whereas a specific result for a specific system may not improve even if one
takes the next rung of the ladder.

**Observation:** Electronic structure models are affected by some error that
is usually not assessed in a specific application. Instead one often relies on
experience and intuition gained with some approach. Most approximations
relies on error compensation that leads to more reliable results for relative
quantities, but their precise accuracy for a specific case under study is
typically not known either.

Whereas one may quote very many examples for this observation, which
would be far beyond the scope and purpose of this work, we may instead
take it as a stepping stone in our gedanken experiment that weighs in on
the future of electronic structure methods. We may therefore continue our
discussion from this conclusion:

**Conclusion 1:** While we have a very good understanding of what
approximations in electronic structure theory are feasible and efficient, they
are, in all cases, affected by an error that will be unknown for a specific
molecular structure under consideration, even if this error is expected to be
small for certain approaches.

7 Traditional Error Assessment Strategies

Rigorous error estimation approaches based on reference results are not with-
out difficulties. The generalist approach of electronic structure has relied on
representative benchmarking, where reference or training data have been se-
lected based on chemical intuition or simply based on availability. As a result,
transferability – usually implicitly assumed if mean absolute deviations are
found to be sufficiently small for training or test data sets – may not come
without accepting the fact that one may encounter large unexpected errors.

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Large absolute deviations obtained for reference data might differ significantly from the mean absolute deviation, which may be taken as a first hint of compromised transferability. However, these standard measures can only provide indications about errors to be expected for test data if the reference data can be shown to be related in some way to the test data. The latter condition is not trivial to demonstrate and certainly not a question of experience or chemical intuition. Moreover, only few more sophisticated ways have been proposed to improve on the stochastic insight gained for benchmarking against a specific test data set.

A major problem has been that, historically, reference data sets have not been rigorously developed based on stringent stochastic criteria, but often emerged as being determined by availability of reliable data rather than by demand of specific data. The general situation improved in the new millennium, but accurate reference data is still lacking for challenging problems such as transition metal complexes or (very) large molecules. Despite meritorious efforts to enlarge these reference sets (see, for example, Refs. 19,104–107) in order to cover typical chemical phenomena with data points that appear to be reasonable.

While the focus here is mostly on the primary quantity obtained in an electronic structure calculation, i.e., the electronic energy, we emphasize that other molecular properties and atomistic decompositions thereof have also been the subject of detailed benchmarking studies (for two examples see Refs. 108,109).

A main problem which remains is that parametrized models are usually not scrutinized by expansive statistical means. Surely, the adoption of a parametrized model introduces an error that cannot be overcome within this model, but fixing the model parameters at some reference data may be affected by biases that have gone unnoticed. It is for this reason that we have advocated basic standard tools such as bootstrapping and jackknifing for the elucidation of confidence intervals and the assessment of the importance of individual data points, respectively, in quantum chemical calculations.

With bootstrapping and jackknifing, we were able to demonstrate, for instance, that the error development of an increasing number of pairwise semiclassical dispersion corrections may not necessarily lead to error compensation, but instead to error accumulation. While this is true for the absolute value of the total dispersion energy, also relative dispersion energies can be affected by error accumulation and blindly trusting in error compensation in comparisons may be too risky. These findings may cast some doubt on the general transferability of such corrections to large molecular systems, whose size transgresses that of those molecules for which the corrections were
parametrized.

More importantly, results obtained for benchmark sets suffer from the fact that one does not know to what degree they are transferable to an actual case at hand. Surely, how severe this transferability issue is will also depend on the required target accuracy in such a way that a tolerable low accuracy may alleviate transferability concerns. Still, one will require some objective measure by which the actual accuracy can be assessed or, at least, estimated.

Transferability of a given electronic structure model to a specific new atomistic problem is not guaranteed, and unexpectedly large errors can be encountered, often without warning (for examples see Refs. [113][118]). These encounters of unexpected outliers may be taken as an indication that reference data are likely to be incomplete if chemical accuracy shall be reached for arbitrary systems and point to the need of continuous benchmarking monitored by an uncertainty quantification protocol. It is even questionable whether we will ever have enough benchmark data at our disposal that allow us to show that transferability to unseen molecular systems is guaranteed in a way that a certain small error margin is not exceeded, ignoring the fact that this would also require one to define a reliable measure of transferability.

**Corollary:** *Transferability of benchmark results to a specific case under investigation cannot be guaranteed in a rigorous manner.*

### 8 Bayesian Uncertainty Quantification

A crucial conclusion for and from numerical studies with various electronic structure models is that the exact error of a given model for a specific molecule is not known. For instance, if the largest absolute deviation obtained for a model on some benchmark data turns out to be much larger than what would be tolerable for drawing sufficiently reliable conclusions from the calculated data, no guarantee can be given that calculated results will be sufficiently reliable for the specific problem. For most electronic structure models, this actually implies that system-specific uncertainty quantification will be imperative, if predictive (de novo) work shall be accomplished – even if chemical accuracy, which does not pose a very tight constraint compared to spectroscopic accuracy, tolerates certain errors. If one follows this line of thought, the next question is how uncertainty quantification can be conducted in a way that is reliable and does not come with a computationally prohibitive overhead.

In a theory proposed by Sethna and co-workers\textsuperscript{119} for DFT calculations, the sampling error of a class of functionals is mapped onto the real error
at a benchmark data set in such a way that one can exploit the sampling of calculated results for error estimates for systems unrelated to the benchmark set. Unfortunately, the mapping affects only the linear parameters in a functional. Nevertheless, this Bayesian approach that transfers knowledge obtained for benchmark data to unseen molecular structures led to the development of Bayesian error estimation functionals. Unfortunately, it turns out that mean and largest absolute deviations remain comparatively large for this class of functionals. Concerns have been raised that the parametric uncertainty does not necessarily have the same functional shape as the model error’s amplitude in general.

In principle, a system-focused approach that re-adjusts the non-linear parameters to system-specific benchmark data achieves a significantly increased accuracy. Still, even for such a system-specific optimization of a state-of-the-art density functional, the error estimation turns out to be not flawless on the training data, i.e., it does not reproduce the known error bars in all cases. Hence, even a system-specific approach suffers from the fact that the analytical form of the density functional is not flexible enough. Another issue with this methodology is that it requires extensive DFT recalculations when benchmark data is extended for a given functional.

Acclaimed machine learning models may step in and provide an alternative approach with various benefits. For one, they can provide a glue between data of different origin. Hence, they can connect data obtained with a fast-but-inaccurate model to those of an accurate, but computationally more expensive model. In this way, they even access the model-inherent error of a parametrized model (such as DFT or semiempirical methods) compared to an accurate model with less parameters or assumptions (such as explicitly correlated coupled cluster theory). Moreover, specific machine learning models such as Gaussian process regression (GPR) come with built-in uncertainty quantification that allow one to rate the results obtained. However, any machine learning model may be straightforwardly equipped with suitable statistical measures such as standard deviations and confidence intervals, even neural networks.

Since machine learning approaches are data driven, they rely on reference data and provisions must be taken for their production (see below). As such, they are Bayesian in their very nature, and therefore, these protocols are not easy to accept from a puristic first-principles point of view, in which one attempts to approach the exact solution to a problem – at least in principle.

For example, we have demonstrated how to exploit machine learning to improve on semiclassical dispersion corrections (in this case by GPR) and on a classical force field. In these cases, the existing model remains intact and the machine learning approach corrects for deficiencies in this fixed
model. The idea behind this procedure is that the physical model may capture much of the physics of the problem, leaving only deficiencies for the machine learning model to learn and correct so that, ideally, less reference data will be required in such a ∆-machine learning type of approach.

Machine learning models are data driven, but agnostic with respect to the type of data. As an example, we note that GPR has been successfully applied to exploit system-specific information on confidence intervals for the optimization of molecular structures.

We also exploited machine learning (again GPR) to assess the accuracy of approximate electronic structure models deployed in the elucidation of large amounts of related molecular structures (e.g., encountered in reaction-network and chemical-space exploration or first-principles molecular dynamics) by comparing to more accurate reference data. Here, the key advantage of GPR is to determine for which structure a reference calculation is required. This is encoded in a measure of molecular similarity, for which many inputs are available such as the Coulomb matrix and the smooth overlap of atomic positions. However, more work on such measures will be required as they also need to be faithful for relating very similar molecular structures such as an educt and product connected by a transition state structure. Here, the former two may be affected by similar errors in the approximate method while the error can be larger for the transition state structure, although it is more similar to educt and also to product than educt and product to one another.

Our approach has two key advantages: It is computationally cheap to backtrack new benchmark data which were determined by the machine learning model, and it is reference-data-economic as such data are only demanded where needed in a rigorous, objective fashion whose accuracy only depends on the choice of the molecular-similarity measure. At first sight, this seems to come with the disadvantage that reference data must be provided on demand. However, coupled cluster calculations can be easily launched for single-reference cases, and even multi-configurational calculations can be launched in a fully automated fashion. To obtain accurate electronic structures and energies for molecules of increasing size, one may resort to embedding approaches (see Refs. and references therein) so that the quantum region which must be accurately described remains to be of constant size.

It is important to appreciate that machine learning approaches can also take into account the residual error in the reference data (see, e.g., Ref. for an application). Clearly, this only shifts the whole error-assessment problem to the model of higher accuracy: it will require system-specific error estimation for the accurate reference, which will become increasingly diffi-
cult for large molecules and therefore some sort of error archigenesis will be inevitable. As long as a rigorous error cannot be calculated based on the structure of the underlying partial differential equations, highly accurate calculations on small systems need to be carried out and assumptions on the residual error must be made. Then, such an axiomatic error may be scaled up to the actual molecular size in an incremental scheme in which long-range correlations are sampled.

Here, it is implicitly assumed that the more reliable the error assessment is, the more demanding it will become in terms of computational effort. It is for this reason that a hierarchical deployment of electronic structure models of different degree of reliability is a reasonable way to proceed in expansive computational campaigns in order to accomplish reliable error estimation in a systematic hierarchical manner. At the level of error archigenesis, the sampling of long-range correlations is likely to be time consuming which will restrict the number of such calculations to be feasible in practice. Hence, a comparatively small number of highly accurate reference results must be well chosen to connect to a vast number of results obtained with an approximate model in order to assess its error for the individual molecules under consideration.

**Conclusion 2:** Bayesian uncertainty quantification is a way out of the error-assessment problem, but requires continuous benchmarking – ideally with error assignment for the reference data themselves. This benchmarking needs to be adjusted to the specific systems under study. Reference data point calculations must be selected on the basis of confidence intervals taken, for instance, from an underlying machine learning model. Its accuracy will depend on the measure with which one strides across the parameter space (e.g., the space of all molecular structures defined by nuclear scaffolds that parametrize a Born-Oppenheimer surface).

### 9 The Fate of Electronic Structure Models

The historical development of electronic structure models has delivered many different classes of approximations with different advantages and, hence, different areas of applications where they can blossom. Among these classes, variations appear to be numerous and are typically characterized by capital-letter acronyms. Whereas only some of them are designed to clearly replace older versions, most acronyms never die and are likely to survive in the future. The fact that very many physical effects need to be approximated to eventually allow for a direct comparison with experiment (such as increasing
molecular sizes and complex environments (solvents, surfaces, enzymes, zeolites, metal organic frameworks, ...) together with the desire to propose new, potentially more successful methods has led to an ever increasing number of acronyms. Already now, there are so many of them that it is difficult even for experts to keep track, and one wonders where this will lead to in a few decades because we may get lost in a plethora of acronyms for variations of methods that may eventually choke scientific progress.

By contrast, the discussion in the last section points to the possibility to stay with a sufficiently reliable approximation of a generalist electronic structure model and to improve on it by selective and directed refinement through system-specific benchmarking. Such a Bayesian approach supplements any approximate model with uncertainty quantification for cases where no reference data is available and may even produce a system-focused variant of increased accuracy. The system-specific uncertainty quantification alleviates the problem of questionable or unknown transferability of traditional benchmark sets and eventually allows us to make better founded predictions on chemical processes.

This is clearly a compelling path forward, but it might render many models superfluous. For instance, if electronic energies and molecular structures can be predicted with uncertainties assigned, only one rather than one hundred variations of some type of approximation will be sufficient (such as one density functional at a given rung of Jacob's ladder or even one for the whole ladder, for which a computationally efficient one can be chosen). This consequence is in accord with the conclusions drawn from the massive search for functionals by Mardirossian and Head-Gordon who showed that not a single unique functional would emerge, but very many functionals that differ only slightly in terms of accuracy measured at a large reference data set. A slight change of this reference data set would then favor a different functional out of the pool of well-performing ones.

**Conclusion 3:** One needs to know how accurate a computed result will be for a specific application and Bayesian error estimation can be the key to provide this information, also weeding models of similar type and accuracy, hence reducing the number of models that will be required.

## 10 System-Focused First-Principles Models

Consider the idea that benchmark sets will, in general, never be large enough for transferable parametrizations that are reliable (even if a parametrized first-principles model features a high degree of flexibility). Hence, reliable
uncertainty quantification for a specific new molecular structure will uncover features that are not well represented in the already existing benchmark data – based on a suitable measure for molecular and electronic similarity that is key for the transferability assessment of already existing data. Then, continuous benchmarking (i.e., benchmarking upon request) will be the only way out if results shall be supplemented by reliable Bayesian error estimates. However, this comes with the benefit that one may re-adjust model parameters for a specific molecular system to increase the accuracy of the approximate model in the local region of chemical space assigned by the similarity measure. Surely, one is advised to restrict such a reparametrization to values in the vicinity of the literature values, provided that they define a suitable generalist model, in order to avoid a skew model that might not even be transferable within a set of very similar molecular structures.

Hence, such a system-focused re-parametrization can increase the accuracy of an approximate electronic structure model in such a way that a subsequent $\Delta$-machine learning is likely to require less reference data because it may be anticipated that it will be easier to learn differential rather than absolute effects, if the physical model is suitable and flexible and if reference data are limited.

A system-focused model may be developed in the neighborhood of a well-established one. Whether or not such a procedure is worthwhile will depend on the type of application. If only few calculations are to be carried out, one is advised to choose a model that may be considered to have generally small errors (such as a coupled cluster model). If, however, a massive computational campaign (as in reaction network explorations, first-principles molecular dynamics studies, or high-throughput quantum chemical screening calculations) is part of solving a scientific problem, then a delicate balance of fast methods equipped with uncertainty quantification through automated benchmarking upon request will be required. In order to limit the number of computationally expensive calculations needed for the continuous production of reference data, one may exploit existing data of such a campaign to refine the fast, but inaccurate model in a system-focused manner, as shown in Refs. 125,139.

If system-focused reparametrizations are carried out in the neighborhood of existing electronic structure models, more accurate ab initio reference data can be used for this purpose so that the procedure does not introduce additional empiricism, but may result in a potential loss of generality of the parent model. However, this is made up for by the simultaneous assignment of uncertainty, for instance, through a machine learning model such as GPR or a neural network representation that mediates between the fast-approximate results and the fewer accurate-but-expensive reference points.

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Naturally, it will be beneficial to collect expensive reference data of known accuracy in globally accessible data bases for permanent re-use.

Requirements for a successful system-specific readjustment of parameters to decrease uncertainties are: (1) reparametrization must be fast (i.e., no computational bottleneck must be created), (2) autonomy of the reparametrization must be established (i.e., no or hardly any human interference or input in order to be practical), and as a consequence, (3) full automation of all calculation steps must be guaranteed (especially for the automated launch of reference calculations, which may require multi-configurational approaches).

**Conclusion 4:** Generalist electronic structure models cannot be accurate and fast at the same time (for large molecules or molecular aggregates). A significant gain in computational efficiency requires approximations that compromise transferability and accuracy. System-focused models can be made fast and accurate, but their transferability, i.e., their accuracy for related structures, must be monitored because they have not been tested on some arbitrary reference data. However, such reference data will be incomplete anyways if scrutinized with a suitable measure of molecular and electronic similarity. Having system-focused models requires autonomy regarding parametrization and uncertainty quantification, and therefore, efficient automated procedures are needed in order to be practical.

**11 Outlook**

To know the systematic error – within a well-defined confidence interval – of a numerical result obtained from an approximate electronic structure model is key for assessing the reliability and usefulness of a computational prediction in (bio)chemistry, molecular physics, and materials science. It is risky, if not unacceptable, to rely on standard statistical measures such as the mean absolute deviation obtained for some reference data whose relation to the case under study is not clear in a quantitative sense. In this work, possible options to deal with this problem have been discussed. What has been elaborated here for electronic-structure methods also extends to other branches of theoretical chemistry and to natural sciences in general (consider, for instance, vibrational structure problems with a Taylor series representation of the electronic energy or strong-correlation methods in physics).

Rigorous Bayesian uncertainty quantification measures have been developed, but having error estimation in place comes with an additional computational burden. Apart from the uncertainty quantification procedure itself, a significant portion of the extra effort is due to the necessity of (continuous)
benchmarking on demand. Still, this should be embraced given that running reference calculations continuously is a way to produce system-specific error estimates in a well-defined objective manner and a way to get rid of numerous variations of computational results for the same quantity owing to the ever increasing number of electronic structure models. It is critical for the reference data generated that also the uncertainty of the reference data is assessed and fed into the overall error estimation process. Eventually, such a nesting procedure of methods ranging from fast but rather inaccurate to accurate but computationally expensive approaches with decreasing uncertainty in the calculated result obtained for a specific molecular system will require some sort of error archigenesis that estimates the error still immanent in the most accurate approach available.

It is obvious that the accuracy of a calculated electronic structure result will not be sufficient for comparison with experiment. Additional effects need to be taken into account, most importantly those of molecular structure. In other words, nuclear motion and nuclear coordinates will affect the result that is eventually to be compared with an experimentally measured quantity. Clearly, any additional computational modeling step will then also require rigorous uncertainty quantification. As an example, we refer to the role of nuclear coordinates in spectroscopy that introduces uncertainties in the spectra discussed in Refs. 148,149. A key challenge, that is likely to remain to a certain degree at the discretion of the person conducting a computational study – especially for large, nano-scale, composite atomistic systems – is the choice of the atomistic configuration as a whole. If a selected atomistic structure does not represent the problem well, no reliable uncertainty quantification will be able to detect this, and the calculated results, even when equipped with rigorous error estimates, will not at all relate to the experimental situation (the assignment of protonation sites in a protein is only one example that highlights the problem of choosing the proper molecular structure for a large system).

The ubiquitous availability of computing resources will make high-throughput calculations more and more routine. In such cases, very many calculations on rather similar molecular structures are to be performed. Examples are again first-principles molecular dynamics simulations,135 high-throughput virtual property screenings,133,134 and exploration of complex reaction networks128,132. For these applications, it is clearly advantageous to employ a fast approximate method (possibly refined in a system-focused manner) as often as possible and to restrict resource-intensive benchmark calculations to a minimum.

Having system-specific benchmark data available comes with the advantage that a system-focused model development becomes easily possible
through reparametrization of the fast model in the vicinity of the existing parameters of its generalist version. This bears the option to improve on the accuracy of the fast model for further calculations and to save on additional expensive reference calculations. The connection between results obtained from the many fast and few accurate calculations can be made by data driven approaches. Obviously, to be feasible and routinely applicable, system-focused reparametrizations must be autonomous, which requires fully automated procedures.

Although computational resources are ubiquitous these days, the environmental footprint of quantum chemical calculations must be reduced. It is for this reason that also reference data supplemented with quality labels derived from uncertainty quantification should be stored in a globally accessible data base rather than being re-calculated locally. Moreover, having nested computations of controlled accuracy covering a range from fast to expensive models that is controlled by uncertainty quantification is a way to reduce the overall amount of atomistic simulations required. Of course, this demands that uncertainty measures are of high reliability so that sufficiently accurate predictions are obtained and clear-cut conclusions can be drawn. Such uncertainty-measure equipped results can also provide a trustful basis for qualitative analysis, reasoning, and understanding in terms of chemical concepts.

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