Molecular Biology at the Quantum Level: Can Modern Density Functional Theory Forge the Path?

Brian Kolb and T. Thonhauser
Department of Physics, Wake Forest University, 1834 Wake Forest Road, Winston-Salem, NC 27109, USA
kolbba5@wfu.edu, thonhauser@wfu.edu

Recent years have seen vast improvements in the ability of rigorous quantum-mechanical methods to treat systems of interest to molecular biology. In this review article, we survey common computational methods used to study such large, weakly bound systems, starting from classical simulations and reaching to quantum chemistry and density functional theory. We sketch their underlying frameworks and investigate their strengths and weaknesses when applied to potentially large biomolecules. In particular, density functional theory—a framework that can treat thousands of atoms on firm theoretical ground—can now accurately describe systems dominated by weak van der Waals interactions. This newfound ability has rekindled interest in using this tried-and-true approach to investigate biological systems of real importance. In this review, we focus on some new methods within density functional theory that allow for accurate inclusion of the weak interactions that dominate binding in biological macromolecules. Recent work utilizing these methods to study biologically-relevant systems will be highlighted, and a vision for the future of density functional theory within molecular biology will be discussed.

Keywords: Molecular biology, van der Waals interactions, quantum chemistry, density functional theory

1. Introduction

The scientific disciplines (e.g. biology, chemistry, physics) once stood well separated from each other, with practitioners from each approaching different questions in different ways. These divisions are beginning to blur, however, as answers to questions from one field increasingly require techniques and knowledge built up in another. There is evidence of this effect in the increasing need for interdisciplinary collaborations to solve problems arising in distinct fields. A particularly poignant example of this blurring of lines is the field of molecular biology, where researchers try to build an understanding of biological systems starting at the molecular level. Concepts from chemistry and physics arise naturally in such endeavors and this has bred a symbiotic relationship between biologists, chemists, and physicists, who now seek to answer similar questions.

Some of the most important questions arising in this arena relate to the structure and function of biological macromolecules. For example, for rational drug design to be viable, a detailed knowledge of the interactions between a target protein and a potential drug molecule is necessary to understand whether the drug will bind to the protein at the right location and in the right way. From there, an atomic-level understanding of the protein itself is necessary to understand how allosteric effects turn a drug binding event into a change in the behavior of the protein. These details cannot come...
from a top down investigation of the molecules, nor can they come from simply observing the changing behavior as a function of drug binding. Part of the physics lies in the statistical mechanics of protein conformations, and part resides in the communication networks within the protein, the elucidation of which hinges on the detailed physics of the binding event and the transmission of information from the binding site to a possibly distant effector site.

The same can be said of the “holy grail” of molecular biology—understanding protein folding and how the structure of a protein relates to its function. Coarse-grained models provide some insight into the process of protein folding but a true understanding of the process and the ability to reliably predict how a protein will fold requires an atomic-level understanding of the interactions within a particular protein. There are many other examples of the need for atomistic detail in molecular biology. Ultimately, all properties of biological macromolecules—such as DNA, RNA, proteins—are governed by minute details involving the atomic and electronic structure of their constituent parts as well as the interactions between neighboring pieces of the molecule. Even dynamic conformational changes that may be essential to a particular process are ultimately governed by these interactions and similar interactions with the surrounding environment.

Developing an atomic-level understanding of large molecular systems is not an easy task and, until recently, the application of accurate quantum mechanical methods to such systems was infeasible. This review highlights recent advances made in the fields of computational physics and physical chemistry that can aid in building such an understanding. After discussing classical simulations and common quantum-chemistry approaches, we focus specifically on advances within density functional theory (DFT)—a framework used successfully for decades in the field of condensed matter physics—which affords unprecedented accuracy and utility in treating large, weakly bound molecular systems. These new methods will be discussed and paired with a survey of their use on biologically-relevant molecular systems. Possible future applications of these methods will also be addressed.

2. Survey of Common Computational Methods

2.1. Classical simulations

For many purposes, the best present-day methods to study biologically-relevant systems are classical force field models. Such methods allow one to study the large-scale dynamics of systems with perhaps millions of atoms over biologically-relevant timescales. This is by far the most common computational method of study for macromolecules, and has provided indispensable insight into numerous biological systems.

The main goal of a force field is simple: to represent the energy and forces of a collection of atoms using a physically-motivated, yet relatively straight-forward, algebraic expression. This simplicity is what allows the simulation of large systems over significant timescales. Generally, the physical motivation for terms in the energy Hamiltonian come from macroscopic physics. For example, many force fields treat bond stretches and angle flexes as classical harmonic oscillators obeying Hooke’s law. This is, in fact, what is meant by the phrase classical force field.

In its most basic form, a typical force field can be written as a sum of separate contributions to the total energy i.e.

$$E_{\text{ff}} = E_{\text{bonds}} + E_{\text{angles}} + E_{\text{dihedrals}} + E_{\text{non-bonded}}$$

$$= \sum_b \frac{1}{2} k_b (d_b - d_0)^2 + \sum_a \frac{1}{2} k_a (\theta_a - \theta_0)^2 + \sum_d \frac{1}{2} k_d [1 + \cos(n\phi - \delta)] + \sum_{nb} \left[ \frac{q_i q_j}{r_{ij}} + \left( \frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6} \right) \right]. \quad (1)$$

The first term on the right hand side of Eq. (1) represents an harmonic oscillator (with spring constant $k_b$) in bond length between each pair of covalently-bonded atoms within the system. The second does the same for the three-atom angle term. Dihedral angles are treated with a fairly shallow periodic potential, represented by the third term. The last line of Eq. (1) represents non-bonded interactions and includes a coulomb term for charge-charge interactions and a Lennard-Jones (6–12) potential to account for van der Waals type interactions.
Some force fields add additional terms for out-of-plane motions (improper dihedrals) or higher-order terms. Variations on the functional form are also sometimes applied. For example, a Morse potential can be used in place of the harmonic bond term to allow for bond breaking during a simulation.\(^\text{[9,11]}\)

For all their usefulness, so-called “Class I” force field approaches suffer from some drawbacks. First, treating microscopic phenomena using macroscopic theory is, in essence, a mean-field approach. The quantum-mechanical interactions between electron clouds are averaged over. This, along with the assumed form for all physical interactions, does not allow new physics to be uncovered. The only physics present in the simulation is what was explicitly included, meaning one cannot gain any true atomic-level insight into the underpinnings of interesting phenomena. Second, the simplicity of the mean-field approach used in force field simulations means that they are generally incapable of transferably achieving chemical accuracy.\(^\text{[14]}\) While bulk motions and general trends can often be gleaned from such simulations, the precise movements and behavior of atoms are probably not accurate. This poses a significant problem for applications such as drug design, where one seeks to find a small molecule (an enzyme inhibitor perhaps) that binds with a certain affinity to a site in the protein.

Biophysicists and biochemists have already made substantial headway against this problem.\(^\text{[14]}\) Originally, force fields included the partial charge on an atom as a fitting parameter. The charge was assumed fixed during the simulation so effects of polarization could not be treated. The next generation of force fields incorporates the ability of charge to rearrange during a simulation. Such polarizable force fields incorporate some of the quantum effects necessary to accurately model molecular systems. One example of this new type of force field is the AMOeba force field, which includes both static and dynamic polarizabilities and represents a significant step towards accurate energetics from a force field.\(^\text{[16]}\) In addition, newer force fields often include cross-terms that account for how changes in one internal coordinate affect other energy terms. These help improve accuracy and transferability but cannot correct for the lack of an explicit quantum mechanical treatment.

2.2. Incorporating quantum mechanics

The obvious solution to the shortcomings of the classical force field methods is to directly include quantum mechanics in calculations. Therefore, the solution to the problem is straight-forward; one simply has to solve the time-independent Schrödinger equation

\[
\hat{H} |\Psi\rangle = \varepsilon |\Psi\rangle ,
\]

where the Hamiltonian \(\hat{H}\) in atomic units is given by

\[
\hat{H} = -\frac{1}{2} \sum_i^n \nabla_i^2 - \sum_{i,J} \frac{Z_J}{|\vec{r}_i - \vec{R}_J|} + \frac{1}{2} \sum_{i \neq j} \frac{1}{|\vec{r}_i - \vec{r}_j|} + \frac{1}{2} \sum_{I \neq J} \frac{Z_I Z_J}{|\vec{R}_I - \vec{R}_J|} .
\]

Here, lower-case letters represent electronic degrees-of-freedom, upper-case letters represent nuclear degrees-of-freedom (including charge \(Z\)), \(\varepsilon\) is the energy of the system, and the explicit representation of the Hamiltonian \(\hat{H}\) follows from specialization to an isolated system of atoms under the Born-Oppenheimer approximation.

The unknown function \(|\Psi\rangle\) is the wave function for the electrons and from it (along with knowledge of the nuclear positions \(\{\vec{R}_I\}\)) one can calculate all accessible properties of the system. Unfortunately, \(|\Psi\rangle\) depends on the coordinates of all electrons within the system and, as a result, direct solution of Eq. (3) for the full many-body wave function is difficult or impossible for all but the most trivial systems. For example, a single neutral water molecule has 10 electrons, so its wave function is a function of 30 variables (i.e. 10 electron positions in three dimensions). While an analytical solution in this simple case is already not possible, it is conceivable that the Schrödinger equation could be solved numerically. However, to store the wave function on a numerical grid consisting of 10 points in each dimension (a laughably coarse grid) using single precision numerics would take \(4 \times 10^{30}\) bytes (approximately \(10^{18}\) TB) of storage. This is “the curse of dimensionality” on a grand scale and renders full solution of the Schrödinger equation for most systems utterly intractable.

Surmounting this fundamental problem in a physical way is not easy and has consumed the efforts of chemists and physicists alike for decades. From those efforts, however, have sprung a number
of useful approaches. These can be split into two categories, wave function theories and density functional theory, both of which we will discuss in detail below.

All the methods described in what follows have exhibited great success in describing various quantum-mechanical properties of molecules and materials in general. However, when dealing with biologically-relevant systems two special considerations arise: (i) such systems are typically quite large and (ii) their structure and binding is often dominated by weak van der Waals interactions. Since this review is focused on biological applications of quantum-mechanical methods, special attention will be paid to the ability of each method to scale well with system size and to adequately describe van der Waals interactions. As such, the ability of a method to treat large systems involving van der Waals interactions will determine its applicability to the biologically-relevant systems considered here.

2.3. Wave function approaches

A simple solution to the dimensionality problem introduced by Eq. (3) is to seek solutions of the form

$$\Psi(\{\vec{r}_i\}) = \phi_1(\vec{r}_1) \phi_2(\vec{r}_2) \cdots \phi_n(\vec{r}_n),$$  (4)

that is, to assume that the total electron wave function can be separated and written as a product of single-electron states (orbitals) $\phi_i$. The Pauli-exclusion principle and the anti-symmetry of the wave function can be enforced by forming a Slater determinant of the single-particle solutions. Since the Fock operator used to find the orbitals depends explicitly on those orbitals, the resulting equations are generally solved self-consistently. This approach is a form of mean-field theory where each electron responds to the average field created by all other electrons residing in their single-particle orbitals. The advantage of this approach is that each orbital is now a function of the three spatial coordinates, making numerical calculations computationally feasible. Wave function methods are described in detail in Ref. 16.

The Hartree-Fock (HF) method, which takes this approach, is relatively fast and based on sound quantum mechanics, but the approximations invoked by its use miss some crucial physics. In particular, electrons are dynamic entities. The total energy of the system can be lowered if, averaged over some degree-of-freedom, the electrons correlate their behavior. Correlation is (almost) completely missed in the Hartree-Fock method, which explicitly assumes single-particle states—the static correlation due to the Pauli exclusion principle is fully accounted for. Nevertheless, HF theory is a good first-order starting point for corrections that incorporate electron correlation into the total wave function and its associated energy. Such methods are termed post-HF methods, since they use the results of a HF calculation as a starting point to incorporate electron correlation explicitly.

There are many post-HF methods that exhibit various accuracies coming at related computational costs. One of the best features of the wave function methods is their segregation into a hierarchy of so-called "levels of theory". Thus, one knows in some sense, to what degree a result can be trusted, depending on the precise method used. If better results are desired, one merely has to progress to a higher level of theory. Basis sets (the set of functions used to expand the wave functions) are also of critical importance. They too, however, exhibit a hierarchy of complexity and applicability. Figure 1 gives a cartoon depiction of how one can approach the numerically exact solution $|\Psi\rangle$ by combining a large basis set with a high level of theory.

Fig. 1. Map of the route from classical physics to quantum physics via quantum chemistry. Basis sets are represented on the horizontal axis and increase in size as more functions are added. The level of theory is indicated on the vertical axis. There is a concomitant increase in computational complexity as one moves along the path from classical physics to quantum physics. A plot of this nature is often called a Pople diagram.
The most rigorous method to include electron correlation is full configuration interaction (CI). In the CI method, one starts as usual with the orbitals found by a Hartree-Fock calculation. Instead of using a single Slater determinant of these functions, however, a linear combination of Slater determinants is formed, each one corresponding to one possible ordering of electrons in the orbitals. In other words, all possible combinations of electron excitations are given a Slater determinant, and the optimized linear combination of these yields the numerically exact wave function. This renders Full CI a combinatorial problem—taking a given number of electrons and producing all possible excitations to a given set of orbitals. Thus, full CI scales factorially with the number of basis functions used and therefore is not practical in all but the smallest of systems.

Perhaps the next best thing to a full CI calculation is to use coupled cluster theory. The coupled cluster approach mimics CI but using only small numbers of electron excitations, usually considering only excitations of one to three electrons. The most common variant of coupled-cluster theory is notated CCSD(T), which includes single and double excitations iteratively, and triple excitations perturbatively. This has proven incredibly reliable and represents the "gold standard" for accurate quantum-chemistry calculations. Although it has polynomial (rather than factorial) scaling in the number of basis functions used, the asymptotic scaling of $O(N^7)$ for the generally used form renders this approach mainly useful on relatively small systems of perhaps 30–50 atoms.

Among the most used post-HF methods is Møller-Plesset perturbation theory at second order (MP2) or higher order (MP3, MP4, ...). In perturbation theory, one seeks to find the solution of

$$\hat{H} |\psi\rangle = \left[ \hat{H}_0 + \lambda \hat{H}' \right] |\psi\rangle = E |\psi\rangle ,$$

where the perturbation strength factor $\lambda$ is assumed small, and the solution to the unperturbed problem ($\lambda = 0$) is already known. In this case, $\hat{H}$ is the non-interacting Hartree-Fock Hamiltonian and $\hat{H}'$, which is assumed to be small in effect relative to $\hat{H}_0$, is the Hamiltonian for inclusion of electron correlation. MP2 expands this expression in terms of powers of $\lambda$ up to second order. This can be used to correct both energies and wave functions.

MP2 has shown great success, but it is not perfect. Comparison with coupled cluster and full CI methods have shown that MP2 often significantly overestimates the correlation, especially in delocalized $\pi$ systems. Usage of the higher-order expansions (e.g. MP4) may yield increased accuracy, but the results are not as straightforward as one might hope, as convergence of the Møller-Plesset series has been shown to be unreliable. In many cases, estimates of correlation may get worse with increasing order; sometimes oscillating or even diverging in the worst cases. Convergence depends on both the system under study and the basis set being employed, with poor results often accompanying use of the diffuse functions required to correctly model dispersion interactions. Nevertheless, MP methods are highly prized in quantum-chemistry wave function calculations because they contain a good balance of accuracy and computational efficiency. The asymptotic scaling of MP2 (as $O(N^5)$) makes it substantially cheaper than high-level coupled cluster methods. MP2 can be used on systems of respectable size. A system with a hundred atoms or more is not out of the reach of an MP2 calculation on a high-end computer.

Fig. 2. Maximal system size (measured by number of atoms) that various quantum mechanical methods can treat, as a function of time. “Exact treatment” refers to an exact solution to the Schrödinger equation and QMC stands for Quantum Monte Carlo (not discussed here). All other methods are discussed throughout the text. (Reprinted with permission from Ref. [21]; © 2008 American Physical Society).
2.4. Density functional theory

Wave Function theories have a number of nice properties, but they scale poorly with systems size. A completely different approach, density functional theory (DFT), scales as $\mathcal{O}(N^3)$, and is therefore much more amenable to calculation of large systems. Calculations can be performed on systems consisting of perhaps several thousand atoms, making it applicable to biochemical systems.

In 1964 Hohenberg and Kohn\cite{hohenberg1964} published a seminal paper showing that the quantum-mechanical energy of a set of atoms can be written uniquely as a functional of the electron charge density (within the Born-Oppenheimer approximation). Furthermore, the charge density $n_0(\vec{r})$ that minimizes this functional is the ground-state charge density for the system, and all measurable properties of the system can be written in terms of this optimal charge density. This avoids the dimensionality problem of Eq. \eqref{eq:energy} by shifting the quantity of interest to the charge density in real space, a function of only three variables regardless of the number of electrons.

Density functional theory as a modern approach was initiated when Kohn and Sham\cite{kohn1965} wrote the energy as a density functional of the form
\begin{equation}
E_{\text{DFT}}[n(\vec{r})] = E_k[n(\vec{r})] + E_{\text{N-e}}[n(\vec{r})] + E_{\text{ec}}[n(\vec{r})] + E_{\text{xc}}[n(\vec{r})] + E_{\text{N-N}} , \tag{6}
\end{equation}
where $E_k$ is the total kinetic energy of the system, in principle written as a density functional, but in practice written as a functional of the Kohn-Sham orbitals. An analytical density functional for $E_k$ is not known, but approximations to it lead to so called orbital-free methods. The final term in Eq. \eqref{eq:energy} is the nucleus-nucleus repulsion term, which can be treated as a simple additive constant since it is uniquely determined by the positions of the nuclei and these are decoupled from the quantum-mechanical problem by use of the Born-Oppenheimer approximation. Analytical expressions are known for both $E_{\text{N-e}}$ (the nucleus-electron, effective 1-body term) and $E_{\text{ec}}$ (the Hartree term giving the average electron-electron interaction), leaving the exchange-correlation functional $E_{\text{xc}}[n(\vec{r})]$ as the sole unknown object in Eq. \eqref{eq:energy}.

If the exchange-correlation functional and its functional derivative with respect to the density were known, they could be used to optimize the total energy functional ($E_{\text{DFT}}[n(\vec{r})]$) with respect to the density, thereby finding the ground-state density. Since, $E_{\text{xc}}$ is not known however, it must be approximated in some way. This is the main approximation in DFT and determines the method’s applicability to a particular system. Not surprisingly then, much effort is put into improving the approximations made in generating $E_{\text{xc}}[n(\vec{r})]$.

One approach is to assume that the exchange-correlation energy is a local functional of the density—one that depends on $n(\vec{r})$ in a point-wise fashion.\cite{kohn1965,becke1988} This local density approximation (LDA) is good when the density is slowly varying, becoming exact in the limit of a uniform electron density.

Despite its simplicity, the LDA is amazingly good in many systems, especially in those with relatively concentrated charge density such as crystalline environments where metallic or covalent bonding dominates. For molecules, where directional covalent bonds are the primary interaction, it tends to perform less adequately. One can imagine the LDA as the zeroth-order term in the Taylor expansion of the density about each point, and envision adding additional, derivative-dependent terms. A functional depending on the density and its gradient (first derivative) in a point-wise fashion is called a semi-local functional, and the approximation of the true energy functional in this way is called the generalized gradient approximation (GGA).\cite{pauling1990,becke1988} This approximation is a substantial improvement over LDA in many systems, particularly molecules.

The $E_{\text{xc}}$ term in Eq. \eqref{eq:energy} must approximate the effects of both exchange, which removes the unphysical electron self interaction while enforcing the Pauli exclusion principle, and correlation, which roughly speaking, accounts for the fact that each electron experiences a highly dynamic environment rather than a mean field of the other electrons. In Hartree-Fock theory, the form of the exchange operator is known, so exchange could be treated exactly and combined with an approximate correlation functional. Unfortunately, most functionals exhibit serendipitous error cancellations between their exchange and correlation pieces, making just using the correlation contribution prone to large errors. In 1993 Becke proposed using a 50%-50% mix of exact exchange and LDA,\cite{becke1988} eventually leading to the 3-parameter B3LYP functional\cite{becke1993,becke1993b} and similar hybrid functionals, which are among the most accurate functionals for covalently-bound molecules. Early successes of hybrid functionals led some to
erroneously believe that they could describe weak van der Waals interactions. Unfortunately, hybrid functionals, being a linear combination of exact exchange and (semi)-local exchange-correlation approximations, cannot account for van der Waals interactions. This is because van der Waals interactions are a non-local correlation effect, and any functional that is local or semi-local in correlation is—by construction—not able to reliably describe them. There is ample discussion in the literature of the poor performance of standard hybrid functionals in weakly bound complexes.

2.5. van der Waals interactions in DFT

As evident from the discussion in Section 2.4 and Fig. 2, DFT is capable of treating large systems of perhaps thousands of atoms, which is one of the requirements if it is to be applicable to systems of interest in molecular biology. However, at the same time, it also has to be able to accurately describe weak van der Waals interactions, which play an important role in biomolecules. Historically, DFT has not performed well when applied to systems with van der Waals interactions—this is probably the single most important problem that has prevented DFT from gaining a strong foothold in molecular biology. Below we discuss the shortcomings of standard DFT and several recent developments that overcome this barrier, leading to a full applicability of DFT to large biomolecules.

In standard DFT, the exchange-correlation functional is often assumed to be local, i.e. a single spacial integral of the exchange-correlation energy density, which depends explicitly on the charge-density. This approach leads to the so called local density approximation (LDA). Adding a dependence on the gradient of the charge density results in the generalized gradient approximation (GGA), while inclusion of higher-order derivative terms yield meta-GGA functionals. However, this approach fails to correctly account for van der Waals (vdW) interactions, which are non-local correlation effects; they occur between physically separated regions of charge, generally with little overlap of their density functions. Capturing these effects correctly requires a functional that expresses the exchange-correlation energy as (at minimum) a double spacial integral. van der Waals interactions, ubiquitous in polyatomic systems, occur when electron motions in one atom (or within one molecule) correlate with electron motions in a nearby atom (or molecule) setting up transient but interacting multipoles within each. Correlation between electrons lowers their energy relative to uncorrelated electrons, so the van der Waals force is always attractive. In some systems, crystalline NaCl for example, the contribution of these interactions to the overall binding are negligible. In other systems these interactions can be an appreciable part of the overall interaction. Nobel gas dimers such as Ar and Kr are held together entirely by van der Waals interactions. Large diffuse molecular systems (prime examples being biological macromolecules) rely quite heavily on van der Waals interactions for their stability, so such interactions play an integral role in their behavior.

With this in mind, numerous attempts were made to include the ability to capture van der Waals interactions within conventional DFT. A thorough account of all these efforts is beyond the scope of the present review, but several promising approaches will be discussed.

2.6. DFT-D

As stated earlier, van der Waals interactions arise when electronic motions within separated atoms correlate, setting up transient multipole moments within the individual atoms. One can expand the dispersion energy of two arbitrary, polarizable charge densities in terms of the interactions of induced multipoles. If a point of interest is located at a distance $r$ that is large compared to some characteristic length scale of the charge distribution, the pairwise dispersion energy can be expanded in powers of $1/r$ as

$$E_{\text{disp}} = -\frac{C_6}{r^6} - \frac{C_8}{r^8} - \frac{C_{10}}{r^{10}} - \cdots ,$$

where the constants $C_i$ correspond to a particular system and determine the relative strengths of the various terms.

For sufficiently large distances $r$, the dipole-dipole term dominates and dispersion interactions go as $1/r^6$. This observation is the basis of the density functional theory with added dispersion (DFT-D) method. Typically, this method works by adding to the total energy a pairwise atomic correction of the form

$$E_{\text{vdW}} = -\frac{1}{2} \sum_{l \neq J} f_{\text{damp}}(R_{i,j}) \frac{C_{ij}}{R_{i,j}} ,$$
where $E_{\text{vdW}}$ is the dispersion energy, $C_{IJ}$ is an empirically-derived coefficient that is atom-pair-dependent, $f_{\text{damp}}(R_{IJ})$ is a damping function, and the sum runs over all pairs of atoms. The damping function ranges from 0 at small $R_{IJ}$ to 1 for larger separations, and is required because the asymptotic $1/R^6$ form becomes unphysical as distances become small. The specific form of the damping function plays a role in the accuracy of the technique.\textsuperscript{29,30} Too weak a damping with decreasing distance results in over-counting of the interaction energy. Too strong a damping will weaken the vdW interactions at relevant ranges. The most critical aspect of the damping function is how it behaves at intermediate distances near the bonding length of a vdW bond. Much attention has been paid to the form of the damping function, and opinions differ on its optimal form. Commonly, the damping function is given the form\textsuperscript{29,30}

$$f_{\text{damp}} = \frac{1}{1 + e^{-\alpha (R_{IJ} - R_0)}} ,$$

where $\alpha$ is a chosen constant and $R_0$ sets the relevant distance scale for the interaction of atoms $I$ and $J$ and is generally chosen to be the sum of their van der Waals radii. This was the form chosen by Grimme in 2004\textsuperscript{13} when he published a set of $C_6$ coefficients based on a database of dipole oscillator strength distributions, for a number of important atoms and demonstrated the method’s effectiveness on a large set of molecular systems. The values of the $C_6$ coefficients (and corresponding vdW-radii) depend somewhat on the choice of exchange-correlation functional, so Grimme added an empirical parameter he called $s_0$ that scales the interaction, adjusting its strength to the functional being used. Approaches like the DFT-D method are not new, dating back at least as far as London himself\textsuperscript{13} but they have proved extremely useful at many levels of atomic theory, and continue to be so within DFT.

### 2.7. DFT+vdW

The pairwise dispersion correction given by Eq. (8) is not a density-functional, but instead relies on fitting to a chosen set of external data. The data used in the fit and the interaction between the dispersion correction and the functional coupled with it both affect the results obtained. Such a fitting procedure can limit transferability between systems. The original DFT-D approach of Grimme has been re-parameterized many times both for improved accuracy and for application to other systems.\textsuperscript{13,39,40}

To improve on the transferability and overall accuracy of DFT-D, Tkatchenko and Scheffler proposed an alteration, which uses a relative $C_6$ coefficient calculated on-the-fly from the charge density.\textsuperscript{44} In this approach (hereafter referred to as DFT+vdW) they define the effective volume for an atom $A$ within a system, relative to the free-atom volume as:

$$\frac{V^\text{eff}_A}{V^\text{free}_A} = \left( \frac{V_A^\text{eff}}{V_A^\text{free}} \right)^2 C_6^\text{free} ,$$

with the hetero-nuclear combination rule for atoms $A$ and $B$ defined as:

$$C_6^{AB} = \frac{2C_6^{AA}C_6^{BB}}{\alpha_A C_6^{AA} + \alpha_B C_6^{BB}} ,$$

where $\alpha_i$ is the static polarizability of atom $i$. Thus, in the DFT+vdW approach one may write

$$E_{\text{vdW}}[n(\vec{r})] = -\frac{1}{2} \sum_{I \neq J} C_6^{IJ}[n(\vec{r})] \frac{1}{R_{IJ}^6} ,$$

with $I$ and $J$ ranging over all atoms. That is, the dispersion energy can be written as a functional (albeit a non-universal one that depends on the arrangement of nuclei) of the charge density. Writing the $C_6$ coefficients as density functionals allows for the polarizability of atoms to be a dynamic, environment-dependent quantity. If it could be calculated, the functional derivative of this expression with respect to the charge density would yield the Kohn-Sham potential for the dispersion energy, allowing the latter to be calculated self-consistently. It is not clear at present whether this would significantly affect the interaction energies of vdW compounds when using the DFT+vdW method. Tkatchenko and Scheffler do note, however, that the use of Eq. (11) largely cancels the charge density differences arising from the use of different functionals,
making their method less sensitive to the particular exchange-correlation functional used compared with static $C_6/r^6$ approaches.\footnote{44}

In 2008, Tkatchenko and von Lilienfeld noted that many body effects can play a significant role in the energetics of vdW-rich systems.\footnote{45} This is especially true in bulk, where close-packed atoms can be geometrically arranged in many complex ways. In particular, three-body, triple-dipole interactions can contribute substantially to binding energies, typically raising them relative to pure pairwise interactions. Given the recent surge of inquiry into metal organic frameworks and other molecular crystals,\footnote{46} the ability to account for this fact may become of increasing interest. In 2010, an expanded formulation of this expression into a density functional then follows in a fashion similar to that of Eq. (15) with respect to the charge density $\rho$.

$$E^{non-local}_{\text{xc}}$$ is a non-local piece, which is evaluated by considering all pairwise points in the charge density. The kernel function $\phi$ describes how charge densities at $\vec{r}_i$ and $\vec{r}_j$ correlate.

A meaningful form for $\phi$ was described by Dion et al. in 2004, leading to the van der Waals density functional (vdW-DF).\footnote{47} This functional evolved from a less general one restricted to planar geometries.\footnote{48} The analytical form of $\phi$ and its numerical computation are onerous, but since $\phi$ itself does not depend on the density, it can be calculated and tabulated once-and-for-all. The functional derivative of Eq. (15) with respect to the charge density was given in 2007,\footnote{49} allowing for completely self-consistent calculation of energies and forces using this method.

The functional as originally proposed required the evaluation of a double integral over three-dimensional space, as one might expect from a non-local functional. This made the use of the functional costly relative to other local or semi-local options. However, in 2009 Román-Pérez and Soler effected a great simplification, by transforming the double integral into a single integral over Fourier transforms using the convolution theorem.\footnote{50} Since Fourier transforms are efficiently obtained and/or readily available in plane-wave DFT codes, this dropped dramatically the time required to evaluate the vdW-DF functional and made the cost of its use on par with that of a similar GGA calculation.

It was quickly noted that, when used on vdW-rich systems, the functional produced binding distances that were slightly larger compared with experiment or high-level calculations.\footnote{51} This led to the assertion that the revised Perdew-Burke-Ernzerhoff exchange functional\footnote{52} originally chosen to accompany the vdW-DF because it exhibited minimal spurious binding of its own, was too repulsive.\footnote{53} Lee et al. revised the approach in 2010, recommending the use of a less repulsive revised version of the Perdew-Wang\footnote{54}\footnote{55} exchange functional and changing the value of a gradient coefficient.\footnote{56} These small changes improved the method’s accuracy for both energy and geometry in many systems. For an in-depth review of this approach see Ref. \cite{57}.

### 2.8. vdW-DF

An alternative approach to the addition of pairwise atomic dispersion terms is to express the total energy of a system directly as a non-local functional of the density. That is, to write the exchange-correlation functional in such a way that it depends simultaneously on the charge density at multiple points. In principle, this is the optimal approach because the true exchange-correlation functional is fundamentally a non-local functional. Treating it on such a footing allows for its integration into DFT in a seamless and self-consistent manner.

In the van der Waals density functional (vdW-DF) approach, the exchange-correlation functional $E_{\text{xc}}$ takes the form

$$E_{\text{xc}} = E_{\text{xc}}^{\text{local}} + E_{\text{xc}}^{\text{non-local}}$$

where $E_{\text{xc}}^{\text{local}}$ is a local-like piece of the functional that is assumed to be well modeled by standard functionals and $E_{\text{xc}}^{\text{non-local}}$ is a non-local piece, which is evaluated by considering all pairwise points in the charge density. The kernel function $\phi$ describes how charge densities at $\vec{r}_i$ and $\vec{r}_j$ correlate.

The three-body term was given in 2007,\footnote{58} allowing for completely self-consistent calculation of energies and forces using this method.

The functional as originally proposed required the evaluation of a double integral over three-dimensional space, as one might expect from a non-local functional. This made the use of the functional costly relative to other local or semi-local options. However, in 2009 Román-Pérez and Soler effected a great simplification, by transforming the double integral into a single integral over Fourier transforms using the convolution theorem.\footnote{59} Since Fourier transforms are efficiently obtained and/or readily available in plane-wave DFT codes, this dropped dramatically the time required to evaluate the vdW-DF functional and made the cost of its use on par with that of a similar GGA calculation.

It was quickly noted that, when used on vdW-rich systems, the functional produced binding distances that were slightly larger compared with experiment or high-level calculations.\footnote{60} This led to the assertion that the revised Perdew-Burke-Ernzerhoff exchange functional\footnote{61} originally chosen to accompany the vdW-DF because it exhibited minimal spurious binding of its own, was too repulsive.\footnote{62} Lee et al. revised the approach in 2010, recommending the use of a less repulsive revised version of the Perdew-Wang exchange functional and changing the value of a gradient coefficient.\footnote{63} These small changes improved the method’s accuracy for both energy and geometry in many systems. For an in-depth review of this approach see Ref. \cite{64}.

### 2.9. Other methods

There are a number of other approaches that are capable of describing van der Waals interactions within a DFT framework. A full listing is beyond the scope of this review, but several of the more...
common approaches are briefly discussed here.

In symmetry adapted perturbation theory (SAPT), the interaction energy of a system is written as a perturbative expansion in terms of physically-meaningful interactions. The Hamiltonian for a superposition of non-interacting monomers is taken as \( \hat{H}_0 \), with the interaction between monomers forming the perturbing potential. Terms in the perturbation generally include electrostatic, exchange, induction, and dispersion interactions. The principle advantage of this approach is that the relative contributions from different physical interactions can be determined explicitly. This leads to an intuitive interpretation of the interaction energy. The downside to the approach is its computational cost since the method scales as \( O(N^6) \) (when taken to second order) with increasing system size. It is therefore limited to relatively small systems. See Ref. 60 for an excellent overview of SAPT and its applications.

Zhao and Truhlar have developed a series of functionals designed to obtain accurate energies for weakly-bound systems. These functionals have been shown to work well for the \( \pi \)-stacking and hydrogen bonding interactions that are omnipresent in biological macromolecules. The advantage of these functionals is their efficiency, being essentially the same computational cost as a typical DFT calculation. There are several families of these functionals, designed and parameterized to apply to different chemical situations. The functionals are known to poorly describe dispersion interactions in the asymptotic limit, where they decay exponentially rather than as \( 1/r^6 \). Nevertheless, they have seen heavy use recently for their ability to accurately and efficiently capture the short-ranged contributions to dispersion interactions.

In the dispersion-corrected atom-centered potential (DCACP) approach of von Lilienfeld et al., van der Waals interactions are handled by means of an effective electron-core interaction. Typical plane-wave density functional theory approaches utilize pseudopotentials, which treat nuclei and core electrons together as an effective, angular momentum-dependent potential. The potential is designed such that the all-electron wave-function is reproduced faithfully. In the DCACP approach, the non-local piece of this effective core potential is optimized to reproduce high-level calculations of molecular properties, specifically, the dispersion energies and forces within molecules. Since the DCACP method uses the same type of effective core potential that is traditionally used in plane-wave calculations, its use does not impose additional computational complexity. The effective potential is designed as a van der Waals correction to standard gradient-corrected exchange-correlation functionals, so potentials must be optimized for each type of atom and for every exchange-correlation functional that the method is to be paired with. Optimized effective potentials have been generated for all the standard biological atoms (carbon, nitrogen, oxygen, hydrogen, sulfur, and phosphorus), each with several gradient-corrected functionals. The method shows good transferability and has been used in molecules as well as solid-state applications.

Although van der Waals interactions are generally thought of as a correlation effect, the approach of Becke and Johnson takes a wholly different viewpoint, treating them instead as arising from interactions between an electron-exchange hole pair in one system and an induced dipole in another. This viewpoint is motivated by the fact that the exchange hole is, in general, not spherically symmetric, so the electron-exchange hole system has a non-zero dipole moment. This dipole moment does not affect the energy of the system containing the electron-exchange hole pair since only the spherical average of the exchange hole enters the energy expression for a system. This electron-hole dipole can correlate with a separate system, however, yielding a dispersion-like interaction. When averaged over the entirety of a system, the approach yields molecular \( C_6 \) coefficients in good agreement with those from high-level methods. These can be decomposed into atomic \( C_6 \) coefficients and used in a scheme similar to that in the DFT-D approach. A required component of the approach is the dipole moment of the exchange hole, which Becke and Johnson conveniently cast as a meta-GGA functional by utilizing the approximate Becke-Roussel form for the exchange hole. Further development led to the ability to calculate \( C_8 \) and \( C_{10} \) coefficients. This approach is simple, elegant, and performs well over a variety of systems.

3. Applications to Biochemistry and Molecular Biology

As can be seen from Fig. 2 of all the quantum mechanical methods discussed above, only DFT is currently capable of treating systems consisting of several hundred to several thousand atoms—i.e.
the lower end of the range of biologically relevant molecules. As such, in this application section we will almost exclusively focus on studies that have used DFT to investigate such systems.

The methods outlined above represent current state-of-the-art DFT as it applies to vdW-rich systems. In what follows, these methods’ ability to do useful biochemistry will be highlighted through a brief survey of recent studies conducted both to test them and to learn from them. This survey is intended to act as a showcase of the capabilities of modern DFT, rather than a comparison of particular methods of its implementation.

3.1. Small molecules

Small molecules make a natural proving ground for new methods in DFT because calculations can be compared with quantum chemistry methods. There exists an extensive body of work, much of it carried out by Šponer and Hobza\textsuperscript{75,77} and, independently, by Stefan Grimme\textsuperscript{78} benchmarking the DFT methods discussed above against accurate wave function approaches with special focus being placed on biologically-relevant molecular systems. This work has yielded encouraging results and forms the foundation upon which studies of the physics in these systems rests. But studying small molecules is useful in its own right, since these play a pivotal role in biochemistry. Most notable among the biologically-relevant small molecules are water and the building blocks of macromolecules themselves, namely, DNA bases and amino acids.

3.2. Water

Water has received special attention in the literature, both because of its great importance to (bio)chemistry and because an accurate first-principles understanding of it has proven surprisingly elusive. Most molecular interactions within living systems occur in an aqueous environment, so an understanding of water is a necessary precursor to developing an understanding of in vivo biochemistry.

These days, the bulk behavior of water (e.g. phase diagram, radial distribution functions) is well modeled by parameterized force fields.\textsuperscript{79–81} Although these force fields get many of the properties of water correct compared with experiment, the fact that they were parameterized to do just that limits their usefulness as a tool for understanding the atomistic interactions in water. At the fundamental level there are quantum effects, most notably the quantum-mechanical nature of the hydrogen nuclei\textsuperscript{82,83} that cannot be easily reproduced with classical models. This clouds the connection between microscopic effects and bulk behavior. A full understanding of the behavior of water can only come from a quantum mechanical description that applies at the microscopic level, but can be extended up to the macroscopic limit.

The behavior of small water clusters (H\textsubscript{2}O\textsubscript{n})\textsuperscript{n} with \textit{n} less than about 6 has been extensively studied at the quantum level and is largely understood\textsuperscript{84–90} Minimum energy geometries can be calculated with high level wave function methods and these have been compared with various DFT treatments. At this level, standard DFT does a reasonable job at describing the geometric and energetic properties of water, but some improvement can be made by including dispersion interactions.\textsuperscript{91–93} Although the hydrogen bonds that govern water’s structure are not typically thought of as a van der Waals effect, recent studies have shown that geometries, energies, dipole moments, and vibrational frequencies of small water clusters are all improved by inclusion of van der Waals interactions,\textsuperscript{94–96} as can be seen in Figs. 3 and 4.

![Fig. 3. Systematic improvement in the description of water properties with the inclusion of van der Waals interactions. Calculations on small water clusters including van der Waals interactions (vdW-DF) compared with standard local (LDA) and gradient-corrected (PBE) functionals. Shown are the binding energies, equilibrium geometries, and dipole moments for each cluster. (Reprinted with permission from](image-url)
The improved description of water when van der Waals effects are included is not limited to small water clusters, but continues into the bulk. Through a series of \textit{ab initio} molecular dynamics simulations Lin et al.\cite{92} showed that the radial distribution functions produced by standard gradient-corrected functionals tend to produce water that is over-structured compared with experiment. This was also evident in the average number of hydrogen bonds and the self-diffusion coefficient, both of which show an over-structuring of the water molecules. These results mirror obtained by numerous other groups working with a variety of different codes, exchange-correlation functionals, and basis sets\cite{95,102} This over-structuring is mitigated to a large degree by a proper treatment of van der Waals interactions. The self diffusion coefficient increases three-fold and the over-structuring evident in the radial distribution functions softens when van der Waals interactions are included. This is also true for bulk ice in its standard hexagonal form (I\textsubscript{h}) where inclusion of van der Waals interactions again improves the description of structural and electronic properties.

It is worth pointing out that the results of DFT calculations can vary quite widely depending on the choice of basis set and exchange-correlation functional used, and great care must be taken with their selection. For example, when coupled to the non-local piece of the vdW-DF, the overly repulsive revised PBE exchange functional actually produces water that is under-structured compared with experiment, in contrast to most other exchange functionals. This is related to the aforementioned tendency of the original vdW-DF to predict intermolecular interaction distances that are large compared with experiment and high-level wave-function methods. Additionally, it has been pointed out that the properties of liquid water calculated within DFT can depend quite strongly on the choice of basis set.\cite{102}

Calculations similar to those shown in Fig. 4 were carried out by Zhang et al. and showed considerably less improvement in the oxygen-oxygen radial distribution function compared to experiment.\cite{103} The basis sets used in the two sets of calculations were fundamentally different, making a direct comparison of their appropriateness difficult. Despite these issues, it is generally agreed that, when properly chosen basis sets and exchange-correlation functionals are used, the inclusion of van der Waals interactions fundamentally improves the DFT description of water, both at the microscopic level and in bulk.

It is interesting to note that, although inclusion of van der Waals interactions greatly improves the description of water, this alone does not complete the picture of important effects within water. The standard Born-Oppenheimer approximation used in quantum-mechanical studies treats all nuclei as classical point particles. Recent work by a number of groups, however, has shown that nuclear quantum effects may play a significant role in determining the properties of water.\cite{83,104,105,106} In fact, it has been shown that such nuclear quantum effects may be more far-reaching, playing a substantial role in hydrogen bonds in general, not just between water molecules.\cite{83} This would, of course, have enormous consequences for a proper description of interactions within biological molecules such as proteins and DNA, where hydrogen bonds often dominate the binding. For example, it has been proposed\cite{107} that the keto form of DNA nucleobases (the standard form required for Watson-Crick hydrogen bonding) can spontaneously tautomerize via hydrogen tunneling to the enol form, a process

![Fig. 4. Decomposition of the oxygen-oxygen radial distribution function as calculated by a standard gradient-corrected functional (PBE) and vdW-DF (here called DRSLL-PBE). The interactions are broken into (from top to bottom) first coordination shell hydrogen bonds, second coordination shell hydrogen bonds, and higher-order interactions. (Reprinted with permission from Ref. \cite{106}. © 2011 American Institute of Physics).](image)
which could be responsible for some types of DNA damage. A recent study by Pérez et al. found that, although such tunneling does occur, the metastable enol form has a lifetime too short to play a significant role in DNA mismatch damage. In fact, the effects of quantum nuclei appear to dynamically stabilize the keto form. For a recent review of these considerations see Ref. 109.

3.3. DNA nucleobases

The four nucleobases, arranged in different sequences along strands of a sugar-phosphate polymer, have enabled the information of life to be stored and propagated since life began. Each of these relatively simple molecules contains an aromatic ring capable of engaging in multiple hydrogen bonds. When these bases come together in a Watson-Crick, edge-on manner, they can form hydrogen bonds strong enough to hold two DNA strands together. When brought together in a parallel face-on fashion, they form π–π stacking interactions strong enough to give it an average persistence length of roughly 50 nm with some sequences having even larger persistence lengths."}

Cooper, Thonhauser, and Langreth calculated the base interaction energy as a function of distance for a Watson-Crick, edge-on approach of two base pairs (see Fig. 5). This was done for the A:T, A:U, and G:C combinations. The G:C base pair exhibits a maximum interaction energy of about twice that of the other pairs, not surprising since it has an extra hydrogen bond, and all three show similar equilibrium binding distances.

The base stacking energy as a function of geometry has been studied by several groups. The binding energies as a function of twist angle for all possible stacked base pairs are shown in Fig. 6. It is noted that the methyl substitution that differentiates thymine from uracil stabilizes the systems with respect to twist.

In 2006, Jurecka et al. published a set of accurate, quantum-chemical binding energies of 22 molecular dimers, selected for the importance of van der Waals interactions within them. The set (dubbed the S22 dataset) was broken into three distinct groups: (i) dimers for which hydrogen bonding is the key component of binding, (ii) dimers for which pure dispersion is the key component of binding, and (iii) dimers which exhibit a mixture of both of these effects. Comparison with this dataset became the de facto metric for assessing the ability of fledgling methods within DFT to correctly account for van der Waals interactions. Within this set (which was later revised, expanded, and placed in a convenient online database) were a homodimer of uracil and an A:T heterodimer.

In 2010, a landmark paper by von Lilienfeld and Tkatchenko showed that the uracil-uracil U:U and adenine-thymine A:T stacked bases exhibit large 3-body dispersion terms. Going a step further, the authors addressed the magnitude of two and three-body dispersion interactions across the entire S22 dataset. Some of their results are shown in Fig. 7. Using the DFT+vdW approach enhanced with the triple-dipole term (as discussed in Section 2), they found that the three distinct groups of the S22 set show markedly different dependencies on three-body dispersion interactions. The systems showing large 3-body dispersion terms (which include the stacked U:U and A:T dimers) were the systems deemed dispersion-dominant and those with essentially no 3-body dispersion interactions were systems dominated by hydrogen bonding. The authors argue that 3-body effects may be more important than previously thought. Interestingly, for stacked nucleobases the 3-body dispersion term seems to be relatively constant, especially compared with the pairwise dispersion term. Figure 8 shows the 2 and 3 body dispersion terms calculated by von Lilienfeld and Tkatchenko for 42 stacked nucleobases and...
base pairs. The 3-body contribution to the energy is relatively constant across the entire dataset while the 2-body term varies considerably, especially for the weaker-binding systems.
3.4. DNA intercalation

The $\pi-\pi$ stacking interactions of DNA bases discussed in the previous section are important for another reason. Many cancer-causing agents act by intercalating between base pairs within a strand of DNA, preventing it from carrying out its normal functions. Ironically, some anti-cancer drugs can also act in this way. In the latter case the DNA is intentionally disturbed either to prevent its replication or to trigger cell death.

One well known intercalating anticancer drug is the poly-aromatic ellipticine molecule. This molecule can intercalate between base pairs of DNA where it is believed to interfere with the process of replication, effectively killing the cell. Li et al. calculated the binding energy between the neutral ellipticine molecule and a single C:G base pair to be $-18.4$ kcal/mol. Not surprisingly, the strength of the binding was shown to have a substantial dependence on the relative angle between the ellipticine and DNA bases, showing a relatively strong (several kcal/mol) preference for near parallel and anti-parallel conformations. Chun Lin et al. investigated the intercalation of ellipticine between a cytosine-guanine base step (i.e. a pair of C:G base pairs). As shown in Fig. 9, they found that ellipticine is significantly attracted to the DNA complex even when it is several angstroms away and ultimately intercalates with a binding energy of about 37 kcal/mol, in perfect accord with the earlier results found by Li et al. Further, they found that the interaction was repulsive when van der Waals interactions were excluded from the calculations. von Lilienfeld and Tkatchenko found that the pairwise dispersion energy for this system to be a substantial $-57$ kcal/mol and the 3-body correction term was 8.9 kcal/mol. This is certainly a significant binding event and shows the strength with which aromatic molecules can interact with the loose $\pi$ electrons within DNA. Such interactions are common for $\pi$-stacked molecules such as benzene and the large number of relatively close neighbors within the $\pi$-conjugated DNA bases is believed to be responsible for the large interaction energy.

The intercalation of both positively charged and neutral proflavine has also been studied. Neutral proflavine was found to bind to a C:G base pair with an energy of about $-20.3$ kcal/mol and charged proflavine with an energy near 12.1 kcal/mol. The difference between the charged and uncharged binding was attributed to electrostatic effects rather than those of correlation. This conclusion was reached largely because the results of standard PBE calculations, although they get the interaction energy of each system wrong, exhibit a similar difference between the two binding energies. It is interesting to note that the binding energy is larger for the positively charged proflavine even though the negatively charged backbone was omitted from these calculations. Again, a substantial preference for near parallel and anti-parallel relative angles was found.

The energetics of the interaction between proflavine and a T:A base pair was also studied,
with results qualitatively similar to those of the proflavine–C:G system. Proflavine was found to bind to T:A with a binding energy of ~18 kcal/mol, again showing preference for near parallel and anti-parallel configurations. Steric clashes with the methyl group on the thymine base produced some interesting features in the rotation curve but did not change the overall preferred structures.

Perhaps the most interesting finding of Li et al. was that both intercalators studied were found to have stronger interactions with a C:G base pair than a C:G base pair has with another C:G base pair, and that the angular dependence of these interactions qualitatively differ. A C:G base pair dimer has a double-well minimum centered around 0°, with the minimum-energy configurations at a twist of about 35° and −35°. The intercalators, by contrast, exhibit only one of these minima. This may partially explain the disruption of secondary structure observed upon intercalation of these molecules, which may play an important role in their anti-cancer function.

3.5. Proteins

Owing to their large size and complexity, simulation of proteins often proves to be a formidable challenge even for simple parameterized models. The application of quantum mechanics to a full protein is, unfortunately, still beyond the reach of modern DFT. Recently, however, significant steps toward a quantum understanding of proteins have been made.

Helical chains of alanine molecules are often studied because they are relatively simple yet they exhibit the canonical helix structure present in so many proteins. In addition, when capped with a charged species they can be formed experimentally so computed properties may be compared with experiment. In one study, Tkatchenko et al. looked at three helical forms (α, π, and 310) of polyalanine chains. By comparing with PBE, a standard gradient-corrected functional, they found significant van der Waals stabilization of all three helix types relative to the fully extended structure. In fact, PBE predicts nearly equal stabilization energies for all three whereas the van der Waals calculations showed a splitting of about 2 kcal/mol between the α-helix and 310 structures. The authors note that the van der Waals effects are of much shorter range than the standard hydrogen bond stabilizations in the helical forms, since the helices are long-ranged structures exhibiting periodic hydrogen bonds. Despite this, the study found that van der Waals interactions were critical to explain the observed stability of poly-alanine helices up to about 700 K. Through ab initio molecular dynamics calculations Tkatchenko et al. found that, when van der Waals effects were excluded, the helical structure gave way to the fully extended form at a temperature well below that observed experimentally, even though hydrogen bonds were still correctly accounted for. Agreement with experiment was recovered when van der Waals interactions were included in the calculations, which showed a breaking up of the helical structure between 700 and 800 K.

Drug discovery is a multi-billion dollar business and much effort is being put into so called rational drug design where potential drug molecules are scored based on their predicted binding affinity to a particular protein target. This transfers the trial-and-error phase away from the lab, where experiments to test drug binding affinities can be relatively expensive and time-consuming, to the computer, where thousands of potential drugs can be tested for binding at relatively low cost.

Working toward this end, Antony et al. studied the interactions of a number of protein active sites with their respective biological ligands. They found that exclusion of van der Waals interactions can substantially change the ordering of ligand binding affinities. Further, they found that neglect of these interactions can actually lead to the computed binding energies for a ligand with its target receptor being of the wrong sign.

Another study, carried out by Rutledge and Wetmore focused on ligands that interact with their host protein via π–π stacking interactions and T-shaped π interactions. As before, they found that inclusion of van der Waals effects is imperative to obtain accurate energetics in such systems.

4. Future Directions

With the utility of these methods established, attention can be turned toward the future and what can be accomplished with them. Computation of a full macromolecule in atomistic detail is still beyond the reach of DFT, even for the most advanced computers, but the method can still be used as a tool to aid in our understanding of such systems.

One useful approach that has been adopted by some groups is to use DFT to parameterize new force fields. Typically, these are parameterized either to reproduce experimental results or the re-
sults of high-level quantum chemistry calculations. As discussed in Section 2, quantum chemistry methods are limited to fairly small systems. Parameterizing force fields using the much larger systems that DFT is capable of simulating might help average out size effects and better represent the environment that exists within macromolecules. Additionally, solid-state parameter sets could be developed to deal with molecular crystals.

Another useful application of DFT is in the refinement of experimental structures. Typical x-ray and NMR techniques provide data that is consistent with more than one structure. Also problematic is the placement of the x-ray invisible hydrogen atoms. Given this, experimentalists often use semi-empirical calculations to refine the observed structure. Use of high-level DFT calculations including van der Waals interactions could yield a better result, since large systems can be calculated very accurately.

Drug discovery is another area where useful progress is being made by incorporating DFT calculations and it is expected that DFT will play an important role in this area soon. Although an entire protein may not be able to be treated quantum mechanically, hybrid methods that apply varying levels of theory to regions within a protein are being used with much success. One can treat the drug molecule and its binding site with full quantum-mechanical rigor while treating distant regions using well-tested classical or semi-empirical approaches. This allows the most important physics to be treated accurately and coupled to a sufficient treatment of the less important parts of the problem. This is not only a useful approach for drug design but also applies to understanding the normal operation of ligand-binding proteins. Such methods are general referred to as QM/MM, i.e. quantum mechanics/molecular mechanics.

Finally, although the applicability of DFT to calculations on full macromolecules is currently limited, linear scaling DFT methods are becoming popular and provide a tantalizing way forward. These approaches, which make use of special algorithms and highly-localized basis functions, can easily treat thousands of atoms—see Fig. 2. Such capabilities make computation of full macromolecular systems feasible. For example, the fledgling linear-scaling code ONETEP has been used to calculate properties of a 20 base-pair strand of DNA containing almost 1300 atoms. If augmented with the ability to adequately treat dispersion interactions, such linear scaling DFT approaches may provide a practical means to apply full quantum mechanics to biological problems of real interest in the near future.

References
1. A. A. Deniz, S. Mukhopadhyay and E. A. Lemke, J. R. Soc. Interface 5, 15 (2008).
2. E. F. Keller, J. Hist. Bio. 23, 389 (1990).
3. H. V. Westerhoff and B. O. Palsson, Nature Biotechnology 22, 1249 (2004).
4. P. E. Wright and H. J. Dyson, J. Mol. Biol. 293, 321 (1999).
5. D. J. Müller, H. Janovjak, T. Lehto, L. Kuerschner and K. Anderson, Prog. Biophys. & Mol. Bio. 79, 1 (2002).
6. C. L. Verlinde and W. G. Hol, Structure 2, 577 (1994).
7. Q. Cui and M. Karplus, Pro. Sci. 17, 1295 (2008).
8. C. Clementi, Curr. Opinion Struct. Bio. 18, 10 (2008).
9. A. D. MacKerell Jr., J. Comp. Chem. 25, 1584 (2004).
10. C. Oostenbrink, A. Villa, A. E. Mark and W. F. Van Gunsteren, J. Comp. Chem. 25, 1656 (2004).
11. A. K. Rappé, C. J. Casewit, K. S. Colwell, W. A. Goddard III and W. M. Skiff, J. Am. Chem. Soc. 114, 10024 (1992).
12. T. A. Halgren, J. Comp. Chem. 17, 520 (1996).
13. A. D. MacKerell, Jr. and N. Foloppe, Biopolymers 56, 257 (2000).
14. A. T. Hagler and C. S. Ewig, Comp. Phys. Comm. 84, 131 (1994).
15. J. W. Ponder, C. Wu, P. Ren, V. S. Pande, J. D. Chodera, M. J. Schnieders, I. Haque, D. L. Mobley, D. S. Lambrecht, R. A. DiStasio Jr., M. Head-Gordon, G. N. I. Clark, M. E. Johnson and T. Head-Gordon, J. Phys. Chem. B 114, 2549 (2010).
16. A. Szabo and N. S. Ostlund, Modern Quantum Chemistry: Introduction to Advanced Electronic Structure Theory (Dover, New York, 1996).
17. T. Schwabe and S. Grimme, J. Phys. Chem. A. 113, 3005 (2009).
18. S. Grimme, J. Comput. Chem. 25, 1463 (2004).
19. Y. He and D. Cremer, Mol. Phys. 98, 1415 (2000).
20. M. L. Leininger, W. D. Allen, H. F. Schaefer III and C. D. Sherrill, J. Chem. Phys. 112, 9213 (2000).
21. M. Head-Gordon and E. Artacho, Phys. Today 61, 58 (2008).
22. P. Hohenberg and W. Kohn, Phys. Rev. 136, B864 (1964).
23. W. Kohn and L. J. Sham, Phys. Rev. 140, A1133 (1965).
24. J. P. Perdew and A. Zunger, Phys. Rev. B 23, 5048 (1981).
25. D. M. Ceperley and B. J. Alder, Phys. Rev. Lett. 45, 566 (1980).
26. J. P. Perdew, K. Burke and M. Ernzerhof, Phys. Rev. Lett. 77, 3865 (1996).
27. A. D. Becke, J. Chem. Phys. 98, 1372 (1993).
28. P. Stephens, F. J. Devlin, C. F. Chabalowski and M. J. Frisch, J. Phys. Chem. 98, 11623 (1994).
29. R. H. French, V. A. Parsegian, R. Podgornik, R. F. Rajter, A. Jagota, J. Luo, D. Asthagiri, M. K. Chaudhury, Y.-M. Chiang, S. Granick, S. Kalinin, M. Kardar, R. Kjellander, D. C. Langreth, J. Lewis, S. Lustig, D. Wesolowski, J. S. Wettlaufer, W.-Y. Ching, M. Finnis, F. Houlihan, O. A. Von Lilienfeld, C. J. Van Oss and T. Zemb, Rev. Mod. Phys. 82, 1887 (2010).
30. Y. Zhao and D. G. Truhlar, Phys. Chem. Chem. Phys. 7, 2701 (2005).
31. F. Ortmann, K. Hannewald and F. Bechstedt, J. Phys. Chem. B 112, 1540 (2008).
32. L. R. Rutledge and S. D. Wetmore, Can. J. Chem. 88, 815 (2010).
33. R. Huenerbein, B. Schirmer, J. Moellmann and S. Grimme, Phys. Chem. Chem. Phys. 12, 6940 (2010).
34. K. S. Thanthiriwatte, E. G. Hohenstein, L. A. Burns and C. D. Sherrill, J. Chem. Theory Comput. 7, 88 (2011).
35. S. Grimme, R. Huenerbein and S. Ehrlich, Chem. Phys. Chem. 12, 1258 (2011).
36. O. A. Von Lilienfeld and A. Tkatchenko, J. Chem. Phys. 132, 234109 (2010).
37. S. Grimme, J. Comput. Chem. 27, 1787 (2006).
38. S. Grimme, J. Antony, T. Schwabe and C. Mück-Lichtenfeld, Org. Biomol. Chem. 5, 741 (2007).
39. T. A. Halgren, J. Am. Chem. Soc. 114, 7827 (1992).
40. Y. Liu and W. A. Goddard, III, Mat. Trans. 50, 1664 (2009).
41. Q. Wu and W. Yang, J. Chem. Phys. 116, 515 (2002).
42. U. Zimmerli, M. Parrinello and P. Koumoutsakos, J. Chem. Phys. 120, 2693 (2004).
43. S. Grimme, Comp. Mol. Sci. 1, 211 (2011).
44. A. Tkatchenko and M. Scheffler, Phys. Rev. Lett. 102, 073005 (2009).
45. F. London, Zeitschrift für Physik 63, 245 (1930).
46. S. Grimme, J. Antony, S. Ehrlich and H. Krieg, J. Chem. Phys. 132, 154104 (2010).
47. O. A. Tkatchenko, von Lilienfeld, Phys. Rev. B 78, 045116 (2008).
48. Y. Yao, N. Nijem, J. Li, Y. J. Chabal, D. C. Langreth and T. Thonhauser, Phys. Rev. B 85, 064302 (2012).
49. M. Dion, H. Rydberg, E. Schröder, D. C. Langreth and B. I. Lundqvist, Phys. Rev. Lett. 92, 246401 (2004).
50. H. Rydberg, M. Dion, N. Jacobson, E. Schröder, P. Hyldgaard, S. Simak, D. C. Langreth and B. Lundqvist, Phys. Rev. Lett. 91, 126402 (2003).
51. T. Thonhauser, V. R. Cooper, S. Li, A. Puzder, P. Hyldgaard and D. C. Langreth, Phys. Rev. B 76, 125112 (2007).
52. G. Román-Pérez and J. M. Soler, Phys. Rev. Lett. 103, 096102 (2009).
53. T. Thonhauser, A. Puzder and D. Langreth, J. Chem. Phys. 124, 164106 (2006).
54. Y. Zhang and W. Yang, Phys. Rev. Lett. 80, 890 (1998).
55. V. R. Cooper, Phys. Rev. B 81, 161104(R) (2010).
56. J. P. Perdew and W. Yue, Phys. Rev. B 33, 8800 (1986).
57. E. D. Murray, K. Lee and D. C. Langreth, J. Chem. Theory Comput. 5, 2754 (2009).
58. K. Lee, E. D. Murray, L. Kong, B. I. Lundqvist and D. C. Langreth, Phys. Rev. B 82, 081101(R) (2010).
59. D. C. Langreth, B. I. Lundqvist, S. D. Chakarova-Käck, V. R. Cooper, M. Dion, P. Hyldgaard, A. Kelkkanen, J. Kleis, L. Kong, S. Li, P. G. Moses, E. Murray, A. Puzder, H. Rydberg, E. Schröder and T. Thonhauser, J. Phys.: Condens. Matter 21, 084203 (2009).
60. B. Jeziorski, R. Moszyński and K. Szalewicz, Chem. Rev. 94, 1887 (1994).
61. A. J. Misquitta, R. Podeszwa, B. Jeziorski and K. Szalewicz, J. Chem. Phys. 123, 214103 (2005).
62. K. Patkowski, K. Szalewicz and B. Jeziorski, J. Chem. Phys. 125, 154107 (2006).
63. Y. Zhao and D. G. Truhlar, J. Phys. Chem. A 108, 6908 (2004).
64. Y. Zhao, N. E. Schultz and D. G. Truhlar, J. Chem. Theory Comput. 2, 364 (2006).
65. Y. Zhao and D. G. Truhlar, J. Chem. Theory Comput. 3, 289 (2007).
66. O. A. von Lilienfeld, I. Tavernelli, U. Rothlisberger and D. Sebastiani, Phys. Rev. Lett. 93, 153004 (2004).
67. L-C. Lin, M. D. Coutinho-Neto, C. Felsenheimer, O. A. von Lilienfeld, I. Tavernelli and U. Rothlisberger Phys. Rev. B 75, 205131 (2007).
68. P. C. Aeberhard, J. S. Arey, I.-C. Lin and U. Rothlisberger J. Chem. Theory Comput. 5, 23 (2009).
69. M. Casella, I.-C. Lin, I. Tavernelli and U. Rothlisberger J. Chem. Theory Comput. 5, 2930 (2009).
70. L-C. Lin, O. A. V. Lilienfeld, M. D. Coutinho-Neto, I. Tavernelli and U. Rothlisberger, J. Phys. Chem. B 111, 14346 (2007).
71. A. D. Becke and E. R. Johnson, J. Chem. Phys. 122, 154104 (2005).
72. E. R. Johnson and A. D. Becke, J. Chem. Phys.
124. M. A. Patel, E. Deretey and I. G. Csizmadia, *J. Mol. Struct.: Theocem* 492, 1 (1999).