The classical picture

The classical approximation
The extensive computational demands of electronic structure calculations mean that their application to even modest-sized molecular systems is quite limited. Fortunately, to good approximation, we don’t need to solve the Schrödinger equation for many systems to accurately reproduce their properties.

Instead, we can use a classical description, which ignores the motions of the electrons and describes the time-evolution of the nuclear positions alone. A classical approach uses a force field or classical potential energy function that is an approximation to the quantum ground-state potential energy surface due to electronic structure and internuclear interactions, as a function of the positions of the nuclei.

Classical descriptions work very well under the following conditions:

- the Born-Oppenheimer approximation is valid
- the electronic structure is not of interest
- the temperature is modest (not too low)
- there is no bond breaking or forming
- electrons are highly localized (metals and pi-bonded systems are delocalized)

Basic features
In the classical approximation, we describe a system by the positions and momenta of all of the atomic nuclei:

\[ \mathbf{r}^N = (x_1, y_1, z_1, x_2, \ldots, y_N, z_N) \]
\[ \mathbf{p}^N = (p_{x,1}, p_{y,1}, p_{z,1}, p_{x,2}, \ldots, p_{y,N}, p_{z,N}) \]

Even though technically we deal with nuclei, we can think of the fundamental particle as an atom. Unlike quantum uncertainty, each atom has a definite position \( \mathbf{r} \) and momentum \( \mathbf{p} \).
Alternatively, we could consider the velocity $v$ instead of the momentum, since the two simply differ by a constant mass factor. We will actually use the momentum more often, since there are several reasons why it is a more natural in statistical mechanics.

A **microstate** is just one “configuration” of the system. In a classical system, one microstate is characterized by a list of the $3N$ positions $r^N$ and $3N$ momenta $p^N$, for a total of $6N$ pieces of information. For a microstate $m$ we might use the notation $(p^N_m, r^N_m)$ to indicate specific values of these variables.

For any microstate, we can calculate the total, potential, and kinetic energies. The potential energy function depends on the positions $U(r^N)$ and the kinetic energy function depends on the momenta $K(p^N)$. The **Hamiltonian** of a classical system is the function that gives the energy of a microstate:

$$H(p^N, r^N) = K(p^N) + U(r^N)$$

The kinetic energy term simply relates to the atomic momenta:

$$K(p^N) = \sum_i \frac{|p_i|^2}{2m_i}$$

Interactions between atoms are described by a potential energy function that depends on the positions but not the momenta of all of the atoms, $U(r_1, r_2, ...)$. Fundamentally, the potential energy function is an approximation to ground state energy that would be obtained by solving the electronic structure using Schrodinger’s equation.

The time evolution of the system is deterministic and described by Newton’s equations:

$$m_i \frac{d^2 r_i}{dt^2} = F_i \quad \text{for all atoms } i$$

Or alternatively,

$$\frac{dp_i}{dt} = - \frac{dU}{dr_i}(r_1, r_2, ...)$$

Here, the LHS gives the time rate of change of momentum of atom $i$ and the RHS gives the force on atom $i$ which, by definition, is the derivative of the potential energy function with respect to atom $i$’s position.

The total energy is constant during a system’s time evolution according to Newton’s laws. This is a statement of the conservation of energy. It is readily shown:
The atomic force field
The most important aspect of the classical description is the potential energy function $U(\mathbf{r}^N)$. This function takes in a set of positions of all of the atoms and returns an energy due to the interatomic interactions. This energy is an approximation to that which one would obtain by solving the Schrodinger equation for all of the electrons in the multi-atom system, for given fixed positions of the nuclei. The approximation comes from examining the various modes by which atoms can interact according to the Schrodinger equation, and patching simple, often first-order theoretical expressions for these together.

$U$ typically has two main components, energies due to intermolecular and intramolecular interactions. These arise as different interpretations of the solution of the Schrodinger equation for the electron clouds; it turns out that our notion of bonded interactions naturally manifest as solutions to the wavefunctions when atoms approach at close range.

Intramolecular interactions
Bond stretching

An accurate description of bond stretching that well-describes quantum-mechanical solutions is the empirical Morse potential:
where $d$ is the length of the bond, $a$ a constant, $d_0$ the equilibrium bond length, and $D_e$ the well depth minimum. However, this form is rarely used. It requires three parameters per bond and is somewhat expensive to compute in simulation due to the exponential term.

Since the energy scales of bond stretching are so high, bonds rarely deviate significantly from the equilibrium bond length. Thus we can use a second-order Taylor expansion around the energy minimum:

$$u(d) = a(d - d_0)^2$$

where $a$ is a different constant from above.

**Bond angle bending**

This accounts for deviations from the preferred hybridization geometry (e.g., sp3). Again a common form is a second-order Taylor expansion about the energy minimum:

$$u(\theta) = b(\theta - \theta_0)^2$$

where $\theta$ is the bond angle between three atoms and $b$ and $\theta_0$ are constants.

**Bond torsions**
These interactions occur among four atoms and account for energies of rotations along bonds. Unlike bonding and angle terms, these degrees of freedom are “soft” in that torsional energies are often not so high as to only allow small deviations from an equilibrium structure.

Generic torsional interactions can be approximated by a cosine expansion,

\[ u(\omega) = \sum_{n=0}^{N} c_n \cos(\omega)^n \]

where \( \omega \) is torsional angle, \( n \) is a summation index, \( c_n \) are summation coefficients, and \( N \) is the number of terms used in the summation expansion. In practice, an alternative but ultimately equivalent expression is often used:

\[ u(\omega) = \sum_{n=0}^{N} c_n [1 + \cos(n\omega - \gamma)] \]

where the \( c_n \) are different from above and the parameter \( \gamma \) is an additional parameter. This form has the advantage of converging faster for a given number of terms in the expansion.

**Intermolecular interactions**

The intermolecular interactions apply to any atoms that are not bonded, either within the same molecule or between two different molecules. These interactions are described using a pairwise decomposition of the energy.

Formally, we can decompose the potential energy function (the ground-state electronic structure energy surface) into interactions involving single atoms, pairs of atoms, triples of atoms, and so on and so forth:

\[
U(r^N) = \sum_{i=1}^{N} u_1(r_i) + \sum_{i=1}^{N} \sum_{j=i+1}^{N} u_2(r_i, r_j) + \sum_{i=1}^{N} \sum_{j=i+1}^{N} \sum_{k=j+1}^{N} u_3(r_i, r_j, r_k) + \cdots
\]

Typically, by symmetry, the two- and three-body terms do not depend on the absolute position of the molecules but on the relative positions:

\[
U(r^N) = \sum_{i=1}^{N} u_1(r_i) + \sum_{i=1}^{N} \sum_{j=i+1}^{N} u_2(r_{ij}) + \sum_{i=1}^{N} \sum_{j=i+1}^{N} \sum_{k=j+1}^{N} u_3(r_{ij}, r_{ik}, r_{jk}) + \cdots
\]

We see that multi-body effects are first included at the level of the pair potential. We would like to truncate this expansion beyond that point for the following reason: the two- and three-body interactions require a loop over atom pairs and triplets, respectively, and thus their
relative computational expense goes as $N^2$ and $N^3$. The cubic scaling would make our simulations prohibitive for modest system sizes.

By truncating the higher order interactions, we typically neglect important effects as these make nonnegligible contributions to the total energy. Instead, we build some of these effects back into the pair interactions. At this point, we have an effective pair potential rather than the one which would result from this systematic expansion:

$$U(r^N) \approx \sum_{i=1}^{N} u_i(r_i) + \sum_{i=1}^{N} \sum_{j=i+1}^{N} u_{\text{eff}}(r_{ij})$$

**Electrostatics**

In the classical approximation, atoms can have a net charge, which may be a partial or formal charge. Here, the charges are placed so as to reproduce the same electrostatic potential that would be given by the true electronic structure and electron density distribution.

Atoms with partial charges interact through Coulomb’s law,

$$u(r_{ij}) = \frac{q_i q_j}{4\pi \varepsilon_0 r_{ij}}$$

for the two atoms $i$ and $j$ separated by distance $r_{ij}$. The partial charges are given by $q_i$ and $q_j$, and $\varepsilon_0$ is the free space permittivity.

**van der Waals attractions**

Correlations between the instantaneous electron densities surrounding two atoms gives rise to an attractive energy. This is a general attractive force between all atoms, due to correlation between instantaneous dipoles between electron clouds, and can be derived from a model of interacting dipolar molecules (so called Drude molecules, Leach 4.10.1). Solving the Schrödinger equation shows that the attraction has this functional form:

$$u(r_{ij}) \propto r_{ij}^{-6}$$
where $r_{ij}$ is the distance between the two atoms. The constant depends on the kind of the two atoms (their elements and chemical environments). These forces are called **dispersion**, **van der Waals**, or **London forces**.

**Excluded volume repulsions**

When two atoms make close approach, they experience a steep increase in energy and a corresponding strong repulsion. This occurs because the electron clouds of the two atoms begin to overlap, and the Pauli principle forbids any two electrons from having the same quantum numbers. At moderate internuclear distances, this potential has the approximate form:

$$ u(r_{ij}) \propto \exp(-cr_{ij}) $$

where $c$ is a constant. However, this repulsion can often be successfully modeled by a simple power law that is much more efficient to compute than the exponential:

$$ u(r_{ij}) \propto r_{ij}^{-m} $$

where $m$ is greater than 6.

**Lennard-Jones interactions**

A common way to model both van der Waals and repulsive forces is to combine them into a single expression. Lennard-Jones proposed the following simple form for pairwise interactions of atoms:

$$ u(r_{ij}) = 4\epsilon \left[ \left( \frac{r_{ij}}{\sigma} \right)^{-12} - \left( \frac{r_{ij}}{\sigma} \right)^{-6} \right] $$

where $\epsilon$ and $\sigma$ are constants that depend on the particular types of atoms $i$ and $j$. The minimum in the potential occurs at:

$$ u(r_m = 2^{1/6}\sigma) = -\epsilon $$
The prefactor of 4 ensures that the minimum value of the potential is $-\varepsilon$.

Here, the attractive force enters with the $r_{ij}^{-6}$ term, while the repulsive energy is given by $r_{ij}^{-12}$. Why do we use the power of -12 for the repulsive part? It is mainly for convenience and simplicity, since it is just the square of the attractive term. It turns out that the properties of molecules aren’t so sensitive to the exact nature of the repulsive energy, so long as it is a steep function when atoms come close.

The LJ interaction can also be written in several equivalent forms using different parameter combinations:

$$u(r_{ij}) = \varepsilon \left[ \left( \frac{r_{ij}}{r_m} \right)^{-12} - 2 \left( \frac{r_{ij}}{r_m} \right)^{-6} \right] = A r_{ij}^{-12} - C r_{ij}^{-6}$$

with

$$A = 4 \varepsilon \sigma^{12} = \varepsilon r_m^{12}$$

$$C = 4 \varepsilon \sigma^6 = 2 \varepsilon r_m^6$$

**Buckingham interactions**

A sometimes-used alternative to the Lennard-Jones expression is the Buckingham potential:

$$u(r_{ij}) = \varepsilon \left[ \frac{6}{\alpha - 6} e^{-\alpha \left( \frac{r}{r_m} \right)} - \frac{\alpha}{\alpha - 6} \left( \frac{r}{r_m} \right)^{-6} \right]$$

This potential has three parameters: $\varepsilon, r_m, \alpha$. Like the Lennard-Jones potential, $\varepsilon$ and $r_m$ describe the energy well depth and distance. The parameter $\alpha$ controls the overall shape of the well (e.g., narrowness). This potential better-models the repulsive interaction at modest nuclear distances, but is often abandoned in favor of the LJ potential because it requires three (versus two) parameters and because the exponentiation is more computationally expensive.

**A minimal force field**

Putting all of these energy components together, we arrive at a classical picture of molecular systems described by a potential energy function with the following minimal form:

$$U(r_1, r_2, ...) = \sum_{\text{bonds } i} a_i (d_i - d_{i,0})^2 + \sum_{\text{angles } j} b_j (\theta_j - \theta_{j,0})^2$$
The potential energy is a function of all of the atomic positions \( \mathbf{r}^N \) because the bond distances \( d_i \), angles \( \theta_j \), torsions \( \omega_k \), and pairwise distances \( r_{ij} \) are functions of \( \mathbf{r}^N \). Of the four sums here, the most computationally expensive, by far, is that corresponding to the pairwise atomic sum, since its number of terms scales as \( N^2 \) rather than \( N \) as in the others.

**Force field parameterization and transferability**

The minimal force field above contains a large number of parameters:

\[
a_i, d_i, b_j, \theta_j, c_k, \gamma_k, q_i, \epsilon_{ij}, \sigma_{ij}
\]

Notice that there can be different sets of parameters for different types of bonds, angles, torsions, partial charges, and repulsive/dispersive interactions depending on the kinds of atoms involved and their chemical environment (i.e., an oxygen-bound carbon behaves differently than a nitrogen-bound one). This can result in a huge set of adjustable parameters that define a particular force field.

Values for force field parameters are typically taken from a combination of electronic structure calculations on small molecules and experimental data. The inclusion of experimental data tends to improve accuracy because it fits properties to “bulk” phases rather than the very small systems that ab initio methods can treat. As a result, these force fields are semi-empirical.

The minimal force field described above is typically fit in the following fashion:

1. Bond stretching and angle bending parameters are the easiest to fit because they are associated with “hard” or stiff degrees of freedom. These values can often be fitted to experimental vibrational spectra and structural data, sometimes in combination with electronic structure calculations on small molecular fragments.

2. The Lennard-Jones parameters can often be taken from van der Waals radii and energetics extracted from experimental crystal packing data and critical point data for small molecules. Iterative simulations of small molecule fragments are sometimes used to find the parameters that reproduce the correct bulk properties, such as phase envelopes or enthalpies of phase change.
3. Oftentimes, only the self-self interactions are determined for Lennard-Jones parameters, that is $\epsilon_{AA}$ and $\sigma_{AA}$ for the interaction between two atoms of the same type $A$. Then, approximate combining rules can be used to estimate the parameters between non-like atom types. The Lorentz-Berthelot rules are widely used:

$$\sigma_{AB} = \frac{1}{2} (\sigma_{AA} + \sigma_{BB})$$

$$\epsilon_{AB} = \sqrt{\epsilon_{AA}\epsilon_{BB}}$$

4. Partial charges are assigned on the basis of ab initio calculations of the electron density surrounding small molecular fragments. To perform such calculations, the nuclear conformation is often simultaneously optimized, and if a molecule has multiple relevant conformers (e.g., rotations around a torsional angle), a separate electron density must be computed for each. The continuous electron density can then be parsed into discrete atomic partial charges by a number of methods. The Restricted Electrostatic Potential Fit (RESP) algorithm does this in a manner so as to reproduce the electrostatic potential around the molecule.

5. Finally, torsional potentials are often used to adjust the energies of rotation around bonds to accommodate any remaining energies not already captured by van der Waals and partial charge interactions that are needed for agreement with electronic structure calculations. Some force fields have no torsional potentials at all, if van der Waals and electrostatic interactions sufficiently model the net energies of bond rotations.

One can imagine that there is a fair degree of flexibility in fitting the “soft” interactions: the van der Waals, partial charge electrostatics, and torsional interactions. These terms have significant overlap. One additional goal and constraint in fitting these parameters is transferability, that is, the ability to reuse the same sets of parameters for different molecules and systems.

Transferability is often informed by chemistry: there might be one set of parameters for SP2-hybridized carbons, one for SP3-hybridized, one for aromatic carbons, etc. Thus, force field developers often train the value of parameters to multiple molecules and systems at once, in order to find combinations that are the most widely transferable.

A number of community-developed force field efforts exist. Within each of these efforts, there are multiple versions of the force field, as they tend to be refined over time:

<table>
<thead>
<tr>
<th>force field</th>
<th>originated by (year)</th>
<th>used for / coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMBER</td>
<td>Kollman, UCSF (1994)</td>
<td>proteins, nucleic acids, carbohydrates</td>
</tr>
<tr>
<td>GROMOS</td>
<td>U. Groningen (1996)</td>
<td>proteins, nucleic acids, sugars, organics</td>
</tr>
</tbody>
</table>
The first three of these are perhaps the most widely used and developed, in part due to the widespread investigation of biomolecules using simulation. These three also refer to simulation packages that contain many popular algorithms for evaluating the properties of systems.

For water, there are many specialized force fields that can be used in combination with the above. The most used water models are the SPC/E model and the TIP4P models.

**Polarizable force fields**

The fixed-partial charge model described above isn’t able to account for induced polarization, that is, the rearrangement of a charge distribution in a molecule due to nearby interacting molecules. A number of methods have emerged for incorporating this effect into classical force fields. Two common approaches:

- fluctuating atomic partial charges
- induced dipoles on each atom

In each case, the partial charge or induced dipole on each atom must be solved iteratively *for each conformation of the molecule*. The iteration typically reaches a self-consistent state where the electric field due to the charges/dipoles is consistent with the induced response in the molecule.

Because of the need to iterate upon each step of a simulation, polarizable force fields are expensive to simulate and have not been widely used. However, with increased computing power and the recognition that polarizability can significantly improve the accuracy of a force field, these methods are beginning to be explored further.

**Special force fields**

A number of other classical force field forms have been developed to better capture specific behavior in atomic systems. These methods all aim to improve agreement with the true quantum-mechanical behavior and hence increase quantitative accuracy. Though we won’t discuss them here, we briefly mention some:

- hydrogen bonding potentials (highly directional interactions)
- water models
• systems involving metals and semiconductors (delocalized electrons, pi-bonding, and directional bonding interactions)

• ionic solids (coupling between polarizability and repulsions)

**Interactions with solid surfaces**

To reproduce the effects of a molecules interacting with solid surface or interface, one option can be to explicitly include several layers of surface atoms that have pairwise interactions with each other and with other molecules in the system. However, if the effects of the structure of the surface are not important or the subject of investigation, one can approximate these interactions without explicitly including surface atoms. This approach has the benefit of being far less computationally expensive since it replaces the interactions of a molecule with all of the atoms in a surface by a single interaction.

Consider an atom interacting with a surface built from many atoms. Assume the interaction between the atom and any surface atom is described by the Lennard-Jones potential. The total interaction of the atom with the surface is the sum of the interactions with all atoms out to infinity in the ±x, ±y, −z directions (assuming the surface is infinitely thick). We assume the atoms in the surface are uniformly distributed with number density \( \rho_S \). Therefore we can compute the total interaction as:

\[
u(z) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \int_{-\infty}^{-z} \rho_S dZ dxdy \times 4\epsilon \left[ \left( \frac{r}{\sigma} \right)^{-12} - \left( \frac{r}{\sigma} \right)^{-6} \right]
\]

\[
= \int_{0}^{2\pi} \int_{0}^{\infty} \int_{0}^{-z} \rho_S dZ Rd\theta \times 4\epsilon \left[ \left( \frac{r}{\sigma} \right)^{-12} - \left( \frac{r}{\sigma} \right)^{-6} \right]
\]
This 9-3 potential describes the interaction of a single atom with a virtual wall. This is a single-body term, not a pairwise or higher order interaction, and thus its computational expense scales as \( N \). Here, the \( z \) coordinate is given by the \( z \)-component of the atomic position of the atom, which corresponds to the wall being located at \( z = 0 \). If the wall is at some other location, say \( z_0 \), then the potential becomes

\[
u(z) = \frac{4\pi\varepsilon\rho_s\sigma^3}{3} \left[ \frac{1}{15} \left( \frac{z-z_0}{\sigma} \right)^{-9} - \frac{1}{2} \left( \frac{z-z_0}{\sigma} \right)^{-3} \right]
\]

Note that the potential involves the wall density. Typical crystalline close-packing densities can be used for this parameter, \( \rho_s\sigma_{\text{surface}}^3 = 0.74 \), where \( \sigma_{\text{surface}} \) gives the size of atoms in the surface and can be distinct from the atom-surface interaction parameter \( \sigma \).

**Implicit solvation**

In systems of solvated molecules, such as proteins or DNA, the requirement to have a very large number of solvent molecules can drastically increase the simulation expense (which goes as the number of atoms squared). When the details of the solvent are not of interest, it is possible to create a continuum approximation to it that correctly reproduces the thermodynamic properties of a system.

**Statistical-mechanical formulation**

Consider \( N \) solute atoms (perhaps part of a macromolecule) embedded in a solvent consisting of \( M \) solvent atoms. Assuming pairwise interactions, we can rigorously break the total potential energy into solute-solute (X-X), solute-solvent (X-S) and solvent-solvent (S-S) interactions:

\[
U(r_N^X, r_S^M) = U_{XX}(r_N^X) + U_{XS}(r_N^X, r_S^M) + U_{SS}(r_S^M)
\]

The total configurational part of the canonical partition function can be written as:

\[
Z = \int \int e^{-\beta U_{XX}(r_N^X)} e^{-\beta U_{XS}(r_N^X, r_S^M)} e^{-\beta U_{SS}(r_S^M)} dr_S^M dr_N^X
\]

This can be factored as:

\[
Z = \int \left[ \int e^{-\beta U_{XX}(r_N^X)} dr_N^X \right] \left[ \int e^{-\beta U_{XS}(r_N^X, r_S^M)} dr_S^M \right] dr_N^X
\]
Define

\[ F_S(r_X^N; \beta) = -k_B T \ln \int e^{-\beta U_{xs}(r_X^M) - \beta U_{ss}(r_S^M)} \, dr_S^M \]

This is the free energy of solvation for a particular solute conformation \( r_X^N \). Notice that this free energy depends on the temperature. We can now rigorously rewrite the total partition function as:

\[ Z = \int e^{-\beta U_{xx}(r_X^N) - \beta F_S(r_X^N; \beta)} \, dr_X^N \]

This becomes an integral over the solute conformations only. Thus, we can define an effective potential energy function for the system, in which we have averaged over the solvent degrees of freedom:

\[ U_{\text{eff}}(r^N) = U(r^N) + F_S(r^N; \beta) \]

Here, for simplicity we have removed the X subscript from the solute degrees of freedom. The challenge is to determine a good functional form for \( F_S(r^N; \beta) \). If we find an accurate one, by the derivation above, our potential will rigorously return the same thermodynamic properties as a fully atomic treatment of the solvent. Any kinetic properties associated with \( U_{\text{eff}} \), however, will be different since now we have averaged away any solvent degrees of freedom that would contribute to a viscosity.

**Simple approaches to continuum solvents**

The simplest approach is to assume the solvent is a continuous dielectric medium with a constant dielectric. In this case, all partial charges interacting in the solute will be reduced relative to the vacuum Coulomb case:

\[ u(r_{ij}) = \frac{1}{4\pi \varepsilon_0 \varepsilon} \frac{q_i q_j}{r_{ij}} \]

Here, \( \varepsilon \) is the dielectric constant for the medium of interest. For water, \( \varepsilon \approx 80 \). For vacuum, \( \varepsilon = 1 \).

A slightly better approximation that interpolates between a dielectric of \( \varepsilon = 1 \) at short distances and \( \varepsilon = \varepsilon_{\text{solvent}} \) at large distances is a distance-dependent dielectric:

\[ u(r_{ij}) = \frac{1}{4\pi \varepsilon_0 \varepsilon_{\text{eff}}(r_{ij})} \frac{q_i q_j}{r_{ij}} \]
\[ \varepsilon_{\text{eff}}(r) = \varepsilon_{\text{solvent}} - \frac{1}{2} \frac{\varepsilon_{\text{solvent}} - 1}{r^2 S^2 + 2 r S + 2} e^{-r S} \]

Here, \( S \) is a parameter, typically between 0.15 Å\(^{-1} \) and 0.3 Å\(^{-1} \).

Another approximate form suitable for use in dilute electrolyte solutions (systems with mobile charges) is the screened Coulomb potential:

\[ u(r_{ij}) = \frac{q_i q_j}{4 \pi \varepsilon \varepsilon_0 r_{ij}} e^{-\frac{r_{ij}}{\lambda_D}} \]

Here, \( \lambda_D \) is the Debye length, dependent on the salt concentration of the solution, and \( \varepsilon \) is the dielectric constant of the medium.

None of these methods, however, are particularly accurate at reproducing the net effect of the potential \( U_{\text{eff}} \) in the general case. What they neglect is the complex, multi-body rearrangement of the solvent in response to the solute. This effect is typically dominated by electrostatic interactions between the two.

**More accurate approaches**

A common approach to modeling \( F_S \) is to split it into several parts for which good analytical approximations can be made:

\[ F_S = F_{\text{elec}} + F_{\text{vdW}} + F_{\text{cav}} \]

This is an approximate separation into interactions between the solute and solvent involving: electrostatic, attractive van der Waals, and repulsive or cavity interactions. Typically the latter two can be successfully modeled for many macromolecules using a surface area approach:

\[ F_{\text{nonelec}}(r^N) = F_{\text{vdW}} + F_{\text{cav}} \approx \gamma A_{\text{SAS}}(r^N) \]

Here, \( \gamma \) is the surface tension of the molecular boundary with the solvent. It is typically treated as a universal constant, although some approaches choose a different surface tension value for each atom type at the boundary.

\( A_{\text{SAS}} \) is the solvent-accessible surface area. It is the area one would compute by tracing out the surface formed by rolling a solvent molecule over the solute(s). The surface area depends on the conformation of the solute(s) and there exist fast, approximate methods for computing it.

The electrostatic component is typically treated by considering the solvent to be a dielectric described by continuum electrostatics. The fundamental equation that must be solved for the solvent dielectric is the Poisson-Boltzmann equation:
\[ \nabla \cdot \varepsilon(\mathbf{r}) \nabla \phi(\mathbf{r}) - \kappa' \sinh[\phi(\mathbf{r})] = -4\pi \rho(\mathbf{r}) \]

Here, \( \varepsilon \) is the dielectric constant, which varies as a function of position in space. \( \phi \) is the electrostatic potential and also varies in space. \( \kappa' \) is a constant that depends on the ionic strength of the solution. \( \rho \) gives the charge density, which can be extracted from the atomic partial charges on the solute.

How does this equation work? In broad terms,

1. The dielectric \( \varepsilon(\mathbf{r}) \) is assumed to be equal to \( \varepsilon_{\text{solute}} \) everywhere inside the solute (often \( \varepsilon_{\text{solute}} = 1 \)) and equal to \( \varepsilon_{\text{solvent}} \) everywhere outside the solute (e.g., beyond the solvent accessible surface area). In practice, the transition is often made continuous over the solute boundary for numerical stability.

2. The charge density \( \rho(\mathbf{r}) \) is constructed from the atomic charges in the solute. In practice, these charges are often smeared over a grid in space.

3. One then solves for the electrostatic potential \( \phi(\mathbf{r}) \) everywhere in space by solving this nonlinear, second-order differential equation. This is the hard part.

4. With the solution for \( \phi(\mathbf{r}) \), one can compute the electrostatic component of the solvation free energy from a sum over partial charges in the solute:

\[ F_{\text{elec}} = \frac{1}{2} \sum_i q_i \phi(\mathbf{r}_i) \]

Solutions to the Poisson-Boltzmann approximation often give good estimates of the electrostatic component of the solvation free energy. The quality of these results relies on the extent to which the solvent behaves like an dielectric continuum. In cases where molecular granularity is important—for example, in which a single water molecule bridges an important interaction—this approach fails.

The Poisson-Boltzmann equation is fairly computationally demanding to solve. There are several approximate solutions that work well; however, a complete solution needs to be found every time the conformation of the solute changes.

Recently, there has been much interest in using fast, highly approximate solutions to the PB equation instead that don’t require solution of a differential equation. One that has gained much popularity in recent years is the so-called Generalized Born method. In this approach,

\[ F_{\text{elec}} \approx -\frac{1}{4\pi \varepsilon_0} \left( \frac{1}{\varepsilon_{\text{solute}}} - \frac{1}{\varepsilon_{\text{solvent}}} \right) \sum_{i=1}^{N} \sum_{j=i+1}^{N} \frac{q_i q_j}{\sqrt{r_{ij}^2 + a_i a_j e^{-r_{ij}^2/4a_i a_j}}} \]
Here, the summations proceed over all pairwise interactions of partial charges in the solute. This equation bears some resemblance to the Coulomb expression, most notably except for the square root term. The variables $a_i$ are called the Born radii of each atom in the solute. Generally speaking, they measure the radius from an atom to the solute-solvent boundary, and they must be computed as a function of solute conformation.

Generalized Born models are widely used in the simulation of large solvated biomolecules. While the computation of $F_{\text{elec}}$ is typically the most expensive calculation in the evaluation of the potential energy of these systems, the GB approach gives significant time savings relative to including large numbers of explicit water molecules.

Keep in mind that the PB and GB methods must be coupled with an approach to determine the nonelectrostatic component of the solvation free energy. The complete approaches we have discussed here are termed the Poisson-Boltzman Solvent Accessible Surface Area Method (PBSA):

$$U_{\text{eff}}(r^N) = U(r^N) + \gamma A_{\text{SAS}}(r^N) + F_{\text{elec, PB}}(r^N)$$

and the Generalized Born Solvent Accessible Surface Area Method (GBSA):

$$U_{\text{eff}}(r^N) = U(r^N) + \gamma A_{\text{SAS}}(r^N) + F_{\text{elec, GB}}(r^N)$$

In both cases, $U(r^N)$ simply corresponds to the kind of semi-empirical force field we described earlier for the interactions of atoms in the solute with each other.

**Simpler perspectives**

**Simplified and coarse-grained models**

Oftentimes, we are not interested in quantitative accuracy and do not need a highly detailed force field. We can examine a large range of behavior using very simplified models. This includes:

- scaling laws (e.g., dependence of properties on system size, chain length, molecular size or energy scales)
- microscopic mechanisms (e.g., of diffusion, binding, or conformational changes)
- relative magnitudes of different driving forces (e.g., electrostatic, dispersive, excluded volume/repulsive, hydrogen bonding, hydrophobic interactions)
• microscopic structure (e.g., conformational fluctuations, molecular packing, structure in bulk liquids, degree of geometric ordering)

• functional form of the dependence of these and other properties on state conditions (e.g., temperature, pressure, density, composition)

The simplified models themselves can be used to rationalize many universal behaviors in molecular systems. For example, simple bead-spring models are able to capture a huge array of polymer thermodynamics. Similarly, very simple Lennard-Jones type potentials can describe many features of critical phenomena for a wide range of single- and multi-component liquid-state systems.

There is an important philosophy here that goes well beyond practical simulation needs. To develop a basic \textit{physical} understanding of a particular system, we would like to identify a minimal model that best describes the basic qualitative features of its behavior.

In that respect, we ultimately want to pick the simplest model possible, use simulations to evaluate its behavior, and determine by comparison with experiment which properties are correctly reproduced and which are not. When then begin systematically building greater detail into the model, evaluating at each point which new properties improve agreement. By taking such a hierarchical approach, we can pinpoint exactly which aspects of the physics explain various features of a system's behavior, in terms of driving forces and interactions.

What are simple models? These are often called \textit{coarse-grained} or reduced models. They involve large \textit{pseudoatom} sites that are designed to represent combined groups of multiple atoms. For example, a bead-spring polymer model might involve one pseudoatom per monomer.

Basic considerations to make when constructing such models is to ask:

- What degrees of freedom need to be included? In other words, what is the basic chemical architecture of the molecules that drives the relevant physics? For example, is it desired to capture motions along a polymer backbone? If so, one needs several large pseudoatom sites along it. If the motions of side-chain groups hanging off of the backbone affect the physics, one will have to include pseudoatoms for those as well.

- What are the dominant length scales in the system? Excluded volume interactions will have to be modeled with repulsive terms in the pairwise energy functions for these.

- What are the dominant energy scales in the system? Will a Lennard-Jones functionality (repulsion + attraction) suffice to model these? Are other functionalities more appropriate? A hard-sphere term or a square-well model might also be appropriate here, alt-
hough discrete potentials can require special molecular dynamics methods if kinetics are to be investigated.

• How many different kinds of interaction potentials and pseudoatom types are needed? Ultimately, one wants to pick a minimal number of types that will allow an understanding of the basic physics.

**Dimensional analysis**

With highly simple models that involve only a very few length and energy scales, it is sometimes possible to perform simulations in reduced, dimensionless parameters. This approach is *not* recommended for simulations of detailed atomic-scale systems in which several energy functions are used and multiple scales/parameters are present.

Consider an atomic liquid modeled by the Lennard-Jones interaction. Such a model might represent argon or other noble gasses at a quantitative level, and many other molecular liquids at a qualitative level. Here, there are $N$ atomic molecules. The total potential energy is:

$$U(r^N) = \sum_{i<j} 4\epsilon \left[ \left( \frac{r_{ij}}{\sigma} \right)^{-12} - \left( \frac{r_{ij}}{\sigma} \right)^{-6} \right]$$

Imagine that we simulate this system in a cubic box of length $L$ (volume $V$) at a given temperature $T$. If we let the fundamental length unit in our system be $\sigma$ and the fundamental energy unit be $\epsilon$, we can rewrite the potential in dimensionless units as:

$$U^* (s^N) \equiv \frac{U}{\epsilon} = \sum_{i<j} 4\left[ s_{ij}^{-12} - s_{ij}^{-6} \right]$$

where $s^N$ now gives the dimensionless reduced positions:

$$s^N = \frac{r^N}{\sigma}$$

Notice that the reduced potential no longer contains the parameters $\epsilon$ and $\sigma$. This enables us to simulate a *generic* Lennard-Jones system in reduced parameter space. That is, we perform a simulation where our positions are the reduced $s^N$ and our energies are $U^*$.

We can define reduced simulation conditions. The reduced temperature:

$$T^* = \frac{k_BT}{\epsilon}$$
The reduced volume:

\[ V^* = \frac{V}{\sigma^3} \]

The reduced number density (number of molecules per volume, \(N/V\)):

\[ \rho^* = \rho \sigma^3 \]

The reduced pressure:

\[ p^* = p \frac{\sigma^3}{\epsilon} \]

To non-dimensionalize any quantities involving time, such as a diffusivity or viscosity, we need to incorporate the mass \(m\) of each of the particles. The reduced time is:

\[ t^* = t \frac{\epsilon}{m \sigma^2} \]

The reduced velocities and momenta are:

\[ p^* = p \sqrt{\frac{1}{m \epsilon}} \quad v^* = v \sqrt{\frac{m}{\epsilon}} \]

The reduced kinetic energy is:

\[ K^* = \frac{K}{\epsilon} = \frac{1}{2} \sum_i |p_i^*|^2 = \frac{1}{2} \sum_i |v_i^*|^2 \]

The reduced self-diffusivity is:

\[ D^* = D \frac{m}{\sqrt{\epsilon \sigma^2}} \]

The advantage of the dimensionless approach is the following. We can map out the entire behavior of this system in dimensionless state space (e.g., as a function of \(T^*\) and \(\rho^*\)) without specifying values of the parameters \(\epsilon\) and \(\sigma\). Our simulation results can then be scaled to specific values of \(\epsilon\) and \(\sigma\) for a particular system or set of systems using the relations above.
If our potential contained three parameters, we would have to evaluate our dimensionless system as a function of three different state conditions. Beyond three or four parameters, however, this approach grows unwieldy and is not particularly informative.

**Other example**

Generally, there are only three scales that can be chosen in the system: a length scale $\sigma_0$, an energy scale $\epsilon_0$, and a mass scale $m_0$. The mass scale does not affect any of the thermodynamic properties, but rather defines the time scale via the relation:

$$t_0 = \sqrt{\frac{m_0 \sigma_0^2}{\epsilon_0}}$$

Once the energy and length scales are chosen, there is a unique form of the dimensionless interaction potential.

It is important to choose scales that are representative of the length and energy scales that dominate the physics of interest in the system. Consider a system of particles that interacts through a screened Coulomb potential plus a soft-sphere repulsion:

$$u(r_{ij}) = \epsilon_{ss} \left( \frac{r_{ij}}{\sigma_{ss}} \right)^{-12} + \frac{1}{4\pi\epsilon_0 e} \frac{q_i q_j}{r_{ij}} e^{-\frac{r_{ij}}{\lambda_D}}$$

If the charges are specified in terms of the unit electron charge $e_0$, then this expression becomes

$$u(r_{ij}) = \epsilon_{ss} \left( \frac{r_{ij}}{\sigma_{ss}} \right)^{-12} + \frac{e_0^2}{4\pi\epsilon_0 e} \frac{q_i q_j}{r_{ij}} e^{-\frac{r_{ij}}{\lambda_D}}$$

To non-dimensionalize we first choose a length scale. There are two in this system, the soft-sphere diameter $\sigma_{ss}$ and the Debye length $\lambda_D$. The dimensionless density and volume fraction of our system is more naturally expressed in terms of the particle diameters, so we typically choose the particle size parameter as the length scale:

$$r_{ij}^* = \frac{r_{ij}}{\sigma_{ss}} \quad ; \quad V^* = \frac{V}{\sigma_{ss}^3}$$

The potential then becomes:

$$u(r_{ij}) = \epsilon_{ss} (r_{ij}^*)^{-12} + \frac{e_0^2}{4\pi\epsilon_0 e \sigma_{ss}} \frac{q_i q_j}{r_{ij}^*} e^{-r_{ij}^* (\sigma_{ss} / \lambda_D)}$$

We can now define two new parameters,
The latter is the Debye length expressed in units of particle diameter. Thus,

$$
e_{\text{Coul}} = \frac{e_0^2}{4\pi\varepsilon_0\varepsilon_{\text{SS}}}$$

$$\lambda_D^* = \frac{\lambda_D}{\sigma_{\text{SS}}}$$

Our second choice is the energy scale in the potential. We have two from which we can choose: $\varepsilon_{\text{SS}}$ and $\varepsilon_{\text{Coul}}$. Typically, we want to pick the one that will dominate the physical interactions of our system. Here, the soft-sphere term is relatively insensitive to $\varepsilon_{\text{SS}}$ because the exponent is so great. Consider the limit that the repulsive exponent becomes negative infinity; in this case, this term has the behavior:

$$\lim_{n \to \infty} \varepsilon_{\text{SS}}(r_{ij}^*)^{-n} = \begin{cases} \infty & r_{ij}^* < 1 \\ 0 & r_{ij}^* > 1 \end{cases}$$

In other words, we recover the hard-sphere interaction in this limit and $\varepsilon_{\text{SS}}$ becomes completely irrelevant to the system behavior.

As a result, we choose $\varepsilon_{\text{Coul}}$ as the energy scale in the system. This means that

$$u^*(r_{ij}) = \frac{\varepsilon_{\text{SS}}(r_{ij}^*)^{-12} + \varepsilon_{\text{Coul}} q_i q_j / r_{ij}^* e^{-r_{ij}^*/\lambda_D}}{\varepsilon_{\text{Coul}}}$$

We now have two dimensionless parameters that we can tune in our system in addition to the reduced temperature $T^*$ and density $\rho^*$:

$$\lambda_D^* ; \left(\frac{\varepsilon_{\text{SS}}}{\varepsilon_{\text{Coul}}}\right)$$

Since we might expect our system behavior to be relatively insensitive to $\varepsilon_{\text{SS}}$ for large negative values of the repulsive exponent, we might set
\[ \frac{\epsilon_{ss}}{\epsilon_{Coul}} \approx 1 \]

And a simpler potential would be

\[ u^*(r_{ij}^*) = (r_{ij}^*)^{-12} + \frac{q_i q_j}{r_{ij}^*} e^{-r_{ij}^*/\lambda_D^*} \]

Simulations in the canonical ensemble could now be performed for different values of \( T^*, \rho^*, \) and \( \lambda_D^* \) to map out the complete behavior of this simple system.