

I. MOLECULAR MECHANICS (MM): A CLASSICAL DESCRIPTION OF MOLECULES

A. The conceptual and chemical basis

Chemical bonding is a genuinely quantum effect, which cannot be understood on the grounds of classical physics. However, the solution of the Schrödinger equation is numerically very expensive, and only small molecules can be treated quantum mechanically (up to ≈ 100 atoms). To be able to treat larger molecules, it is necessary to find further approximations.

Two fundamental simplifications often made in quantum chemistry are the so called Born-Oppenheimer approximation (BOA) and the classical treatment of the nuclei. BOA requires the electron motion to be much faster than the motion of the nuclei (atoms), so that the electrons follow instantaneously the motion of the nuclei (being somehow ‘fixed’ to the nuclei).¹ The second approximation is the neglect of nuclear quantum effects, like tunneling effects (hydrogen) or zero-point vibrations.

With these simplifications, we have the picture of N electrons moving in the electrostatic potential of M nuclei. Then, we have to solve the Schrödinger equation for these N electrons, which can be a formidable task. Or, vice versa, we have the M nuclei ‘sitting’ within the ‘sea’ of N electrons! What is a chemical bond in such a case? What causes the attraction between two nuclei? In many cases, we do *not* have a large electron delocalization, thus there is nothing like a sea of electrons (which is the case in a metal). In organic molecules, we have two electrons in every bonding orbital, and that is how covalent bonding is explained. The main idea behind the empirical models of chemical bond is that the strength of, say, a C–H bond mediated through the bonding orbitals is similar in *all* C–H bonds. In other words, we have a localized/local phenomenon to deal with.

So, how can we model a covalent bond? Is it possible to use simple springs to approximate a bond? Consider the molecules H_2 , O_2 or N_2 : If we model the interaction between two atoms with a harmonic spring with the energy $E(x)$ given as a function of the interatomic

¹ This means, that the electrons never leave those orbitals that have been ‘assigned’ to them in the electronic ground state. But there are cases, when they ‘leave’ these ground state orbitals, e.g. in high energy collisions of nuclei. The electrons are excited then, a process not treated within the BO framework.

distance x

$$E(x) = \frac{1}{2}k(x - x_0)^2 \quad (\text{I.1})$$

then there are two parameters k and x_0 . The values of these parameters may be derived from spectroscopic measurements (bond length and vibrational frequency).²

In equilibrium, the force between the atoms

$$F(x) = -\frac{\partial E(x)}{\partial x} = k(x - x_0) \quad (\text{I.2})$$

vanishes for $x = x_0$, thus $x = x_0$ is the equilibrium geometry.

A diatomic molecule is a one-dimensional system, and thus it is equivalent to one particle with mass m connected to a spring with spring constant k .³ The force on the particle is due to Hooke's law proportional to $x - x_0$, and using Newton's second law, we have

$$F = ma = m\frac{d^2x}{dt^2} = -k(x - x_0) \quad (\text{I.3})$$

This ordinary differential equation has a solution

$$x(t) - x_0 = c_1 \cdot \sin \left[\sqrt{\frac{k}{m}} t \right] + c_2 \cdot \cos \left[\sqrt{\frac{k}{m}} t \right] \quad (\text{I.4})$$

The comparison with the known equation for harmonic motion

$$x(t) = c \cdot \sin(\omega t) \quad (\text{I.5})$$

provides the relation of the frequency with the force constant k and mass m :

$$\omega = \sqrt{\frac{k}{m}} \quad (\text{I.6})$$

From another point of view, we obtain k directly from the second derivative of the energy:

$$k = \frac{d^2 E(x)}{dx^2} \quad (\text{I.7})$$

This will hold in more complex molecules as well: the second derivatives of the energy with respect to the atomic coordinates determine the frequencies of (harmonic) motion of the atoms in a molecule.

² In addition, there is also the information about the heat of formation. However, a harmonic spring does not allow the bond to dissociate, therefore this information cannot be used until a "better" force field is used, like a Morse potential.

³ The strict derivation introduces the reduced mass of the system.

Therefore, we can parametrize a simple force field from experiment, once we know the equilibrium distances and the vibrational frequencies. Alternatively, we can obtain these values from quantum-chemical calculations.

Does this mean that we can take a protein molecule and put springs between all the atoms? If yes, does every bond need different values of k and x_0 , because every bond is in a different chemical environment? If this is the case, we would not obtain any benefit. The essence of empirical modeling of chemical bonding is that the number of necessary parameters is much smaller than the number of bonds. In other words, we will use several (not many) “types” of chemical bonds with assigned parameters to represent any bond in our molecules.

In the other extreme, can we assign (for instance) each C–H bond the same k and x_0 value? It is not quite simple, but let us see:

1. Spectroscopy

Molecules consist of units/groups that have similar properties in every molecule. For instance, every C–H has a length of $r = 1.06\text{--}1.11 \text{ \AA}$ and a vibrational frequency $\tilde{\nu} \approx 3100 \text{ cm}^{-1}$, whatever its environment in the molecule is.

2. Thermochemistry

Molecular enthalpies of formation are approximately additive, so that:



This illustrates that the C–H potential looks like the Morse potential for every C–H unit in any chemical environment. The depth of the minimum is adjusted to fit the enthalpies of formation.

3. The concept of atom type

These points indicate that bonds between atoms can be modeled by universal potentials, if one tries to identify *atom types* in similar chemical environments (groups):

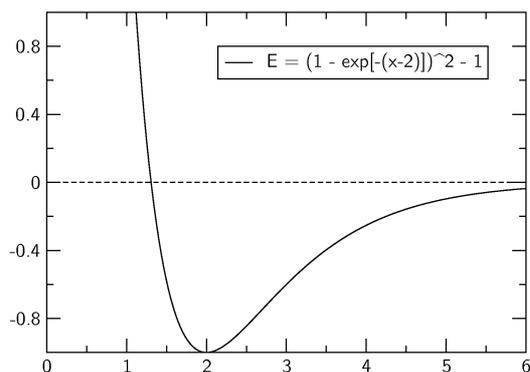


FIG. 1:

- Hybridization: clearly, an sp^3 carbon with four single bonds differs from an sp^2 carbon with a double bond or even an sp carbon with a triple bond. So, we need different potentials for the C–C, C=C and C \equiv C bonds. Also, there will be various different C atom types as well, like an aromatic carbon etc. Therefore, we introduce different carbons and determine the parameters (k, x_0) using some selected molecules which are typical for this chemical environment. For carbon, we use C_2H_6 , C_2H_4 , C_2H_2 and benzene to determine the parameters (k, x_0) for these four different carbons.
- A carbon atom bonded to an oxygen is electron deficient and this directly affects its bonding to other atoms. If we have a situation like in $O=CH-C\dots$, the C–C bond will be affected and it is thus desirable to introduce an additional C type – a carbonyl carbon, which uses different force constants for the adjacent C–C bond.

Biomolecular force fields typically use about 20 different C, 10 N and 5 O and H atom types.

4. Localization of the wavefunction

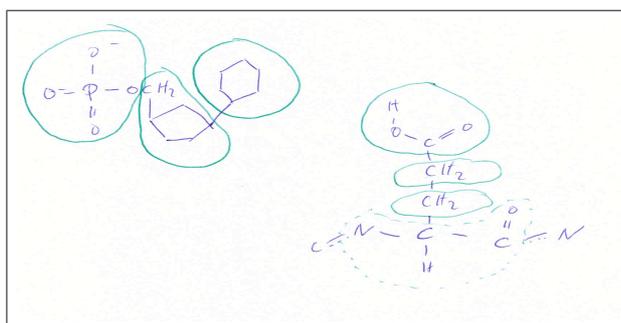
The quantum mechanical basis of these findings is that the electron wave function is localized. It can be localized in a bond, or localized on a fragment of a molecule. Such a fragments may constitute of functional groups or larger pieces like amino acids, DNA bases, sugars etc. The localization is crucial in at least two respects:

- Definition of the atom types: Electron delocalization can lead to different properties of the atomic fragments, like the different carbons in the carbonyl group, benzene etc.

- Electrostatic interactions. In the force fields, atomic charges are defined — i.e. every atom is assigned a point charge and interacts with other atoms according to Coulomb’s law

$$E_{\text{QQ}} \propto \frac{Q_1 Q_2}{R_{12}} \quad (\text{I.8})$$

These charges have to be estimated carefully, and it is very helpful to use the rule of *group neutrality*: Every functional group or molecular fragment has an integer charge.



5. Bonded and non-bonded interactions

Then, there are two distinct types of interactions between atoms in an extended molecule:

- interactions mediated by, and resulting directly from the presence of a covalent bond between the atoms. We usually put springs between the atoms and have to care about bond and dihedral angles. With this treatment, we describe all the quantum-mechanical phenomena like exchange and correlation using an effective potential between two atoms (like discussed above for a diatomic molecule).
- classical Coulomb interactions and van der Waals (vdW) forces between atoms, which are both long-range. For bonded atoms, these interactions are already effectively treated through the bonded parameters. These interactions are thus excluded between atoms which are neighbors (up to the fourth neighbor).⁴

⁴ Usually, the non-bonded interaction between an atom and its third neighbor, so called 1–4 interaction, is taken into account but scaled down by a multiplicative (“fudge”) factor.

B. Determination of the non-bonding parameters: Coulomb and vdW forces

The Coulomb interaction consists of three contributions: the nucleus–nucleus repulsion

$$\frac{1}{2} \sum_{ij} \frac{Z_i \cdot Z_j}{R_{ij}} \quad (\text{I.9})$$

the nucleus–electron attraction,

$$-\sum_i \int \frac{Z_i \cdot \rho(r)}{|R_i - r|} dr \rightarrow -\sum_{ij} \frac{Z_i \cdot Q_j}{R_{ij}} \quad (\text{I.10})$$

(the electron charge density $\rho(r) \rightarrow \sum_j Q_j$ is approximated by the sum of atomic point charges Q_j),

and the classical (Hartree) electron–electron interaction term is approximated as interaction of point charges sitting on the atoms

$$\frac{1}{2} \iint \frac{\rho(r) \cdot \rho(r')}{|r - r'|} \rightarrow \frac{1}{2} \sum_{ij} \frac{Q_i \cdot Q_j}{R_{ij}} \quad (\text{I.11})$$

If we define an *effective atomic net charge* as $q_i = -Q_i + Z_i$, we can write the total Coulomb energy as:

$$E_{QQ} = \frac{1}{2} \sum_{ij} \frac{q_i \cdot q_j}{R_{ij}} \quad (\text{I.12})$$

Thus, we have to determine the effective atomic charge for every atom type (or atom).⁵ This may be conveniently done by performing quantum-chemical calculations. Making use of the localization of the wave function, we can calculate the typical molecular fragments and try to determine the charges from there. These fragments are individual amino acid residues for proteins and the bases (e.g. uracil in Fig. 2), sugars and phosphates for DNA. In the uracil example, we can see that there are three different hydrogen atom types, one nitrogen, one oxygen and two carbons. However, there are two issues associated with this procedure:

First, atomic charges are difficult to define at all; there are several schemes to calculate them and it might be difficult to judge which is the best. Nowadays, Mulliken charges are no longer used because their drawbacks have become evident. A popular strategy is to use the

⁵ The term “atom type” is used with respect to bonded and vdW interaction. Usually, the atomic charges must be determined for more specifically defined atoms.

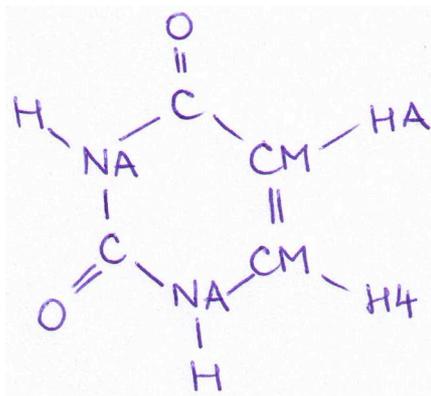


FIG. 2:

so-called *potential-derived charges*. Here, one calculates the *electrostatic potential* (ESP) of the molecule at its surface (see Fig. 3) and then fits the atomic charges in order to reproduce ESP for a set of points one the surface. The fitting constitutes in minimizing the error R :

$$R = \sum_i (\phi_i - \phi_i^0)^2 \quad (\text{I.13})$$

with ϕ_i being ESP induced by the system of point charges at the reference point i and ϕ_i^0 being the ESP obtained previously in the quantum-chemical calculation.

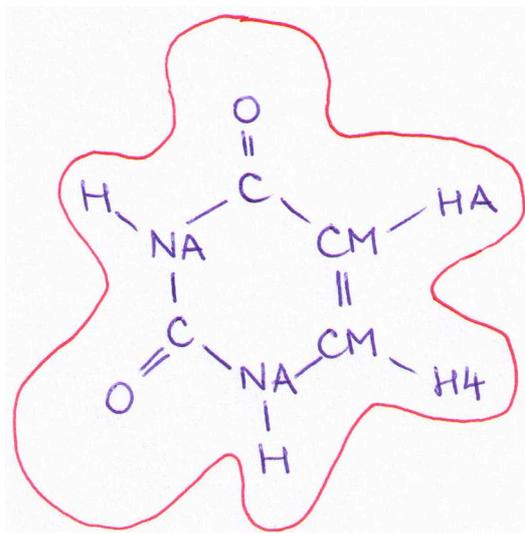


FIG. 3:

Second, charges are calculated in the gas phase (i.e. for an isolated molecule), while the electrostatic situation in an aqueous solution is different — molecules are more polar. As an example, the water molecule has a dipole of about 1.8 D in the gas phase, while it is about

2.4 D in solution. To account for that, charges may be taken to be larger than the gas phase values. A widely used strategy has been to use a small basis sets in the QM calculations, as it is known that such calculations overestimate molecular dipole moments.

These force fields use static atomic charges and, therefore, neglect the effects of polarization and charge transfer between the atoms. Presently, *polarizable force fields* are becoming more and more popular. Here, *atomic polarizability* α_i is assigned to every atom i . In a linear response approach, an external electric field induces a dipole at the atom:

$$\vec{\mu}_i = \overleftrightarrow{\alpha}_i \cdot \vec{E} \quad (\text{I.14})$$

Of course, the external electric field is generated by all other atoms present in the system. This phenomenon will be discussed later on.

A further important non-bonded contribution is the repulsion driven by Pauli exclusion principle. In contrast to the classical Coulomb interaction, it is of a purely quantum-mechanical origin. Two electrons with same spin try to avoid a large spatial overlap. A typical example is the interaction of two neutral, closed-shell systems like two He atoms.⁶ If the electron densities of both He atoms start to overlap as in Fig. 4, the Pauli repulsion sets in. This interaction is an *exchange effect* and decays exponentially with the spatial overlap. Despite its pure quantum-mechanical character, we can model this effect conveniently by an exponential term

$$E_{\text{ex}} \propto \exp[-a \cdot R_{ij}] \quad (\text{I.15})$$

As we will see later, the the exponential decay is not a computationally efficient model, and most empirical force fields use a R^{-12} decay.

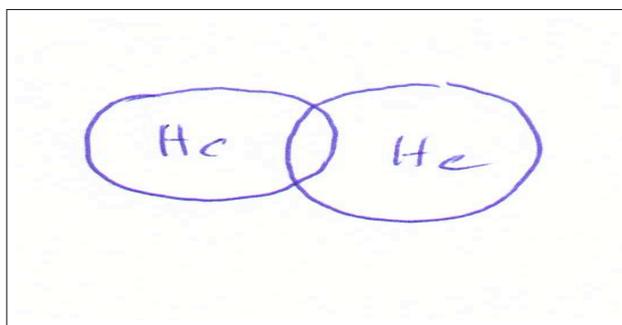


FIG. 4:

⁶ ...being the crudest approximation of two benzene molecules :-)

The Pauli repulsion relates to the motion of electrons with the same spin, on short intermolecular distances. In addition, we also have a correlation of electrons irrespective of their spin, which remains even on longer distances. Two electrons repel each other due to the Coulomb interaction, trying to move apart from each other as far as possible. Consider now two atomic fragments with no overlap as in Fig. 5. Due to the zero-point energy, no quantum particle is ever at rest. If an electron in the neutral fragment A fluctuates in such a way, that it creates a dipole in A, then this dipole will induce a dipole in the opposite direction in the fragment B. Thus, the fluctuations of dipoles will be correlated due to the Coulomb interaction. This correlated fluctuation of dipoles in the two fragments leads to an

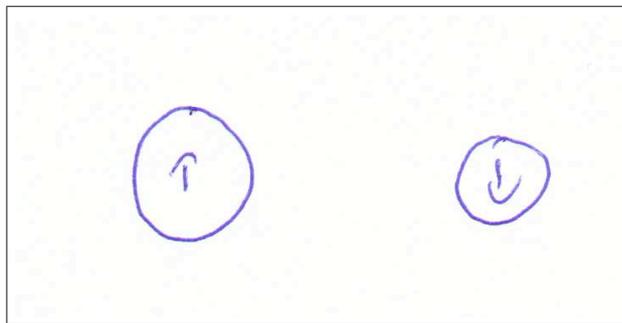


FIG. 5:

effective attractive interaction of the fragments, because of the opposite orientation of the interacting dipoles.⁷

A simple model in Fig. 6 describes this qualitatively. Two systems of one negative and one positive charge each are connected with a spring at a distance r . The negative and positive charge in every pair can be separated by z_1 and z_2 , if some force acts on them. The complex system has a force constant k and (reduced) mass m with $\omega = \sqrt{k/m}$. The separation of charges in small systems brings on dipole moments of $\mu_1 = z_1q$ and $\mu_2 = z_2q$. The Schrödinger equation for one oscillator

$$-\frac{\hbar^2}{2m} \frac{\partial^2 \psi}{\partial z_1^2} + \frac{1}{2} k z_1^2 \psi = E \psi \quad (\text{I.16})$$

has a set of solutions given by

$$E = \left(\nu + \frac{1}{2} \right) \cdot \hbar \omega \quad (\text{I.17})$$

⁷ This effect is not described at the Hartree–Fock level of quantum mechanics, and is also missing in density-functional theory. MP2 or CI would cover it.

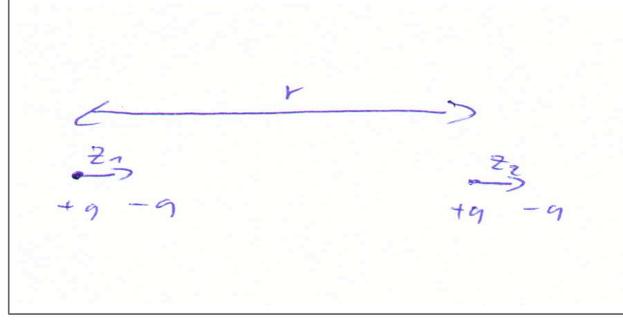


FIG. 6:

Now, let us couple the oscillators due to the dipole-dipole interaction:

$$V(r) = -\frac{2\mu_1\mu_2}{4\pi\epsilon_0 r^3} \quad (\text{I.18})$$

If we insert this interaction potential into the Schrödinger equation, we find

$$E(r) = -\frac{q^4\hbar\omega}{2(4\pi\epsilon_0)^2 K^2 r^6} \quad (\text{I.19})$$

Now, the force on a point charge q in an electric field of intensity E is

$$F = qE \quad (\text{I.20})$$

i.e. this force leads to a displacement z , $F = kz$:

$$qE = kz \quad (\text{I.21})$$

Therefore, the induced dipole moment of such an oscillator in the electric field (E) is

$$\mu_{ind} = qz = q^2 E/k \quad (\text{I.22})$$

At the same time, we have

$$\mu_{ind} = \alpha E \quad (\text{I.23})$$

Therefore

$$\alpha = q^2/k \quad (\text{I.24})$$

and we can write Eq. I.19 as

$$E(r) = -\frac{\alpha^2\hbar\omega}{2(4\pi\epsilon_0)^2 k^2 r^6} \quad (\text{I.25})$$

This is the well-known expression for the dispersive interaction, which is attractive with a R^{-6} dependence and dependent on the polarizabilities of the interaction partners.

The most common function which combines the Pauli repulsion and the dispersive interaction is the Lennard-Jones 12-6 potential

$$V(r) = 4\epsilon \left(\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right) \quad (\text{I.26})$$

which is shown in Fig. 7. The minimum lies at $r_m = 2^{1/6}\sigma$ and the well depth is $-\epsilon$, and σ and ϵ are treated as empirical parameters. The slight issues with the exp-6 potential

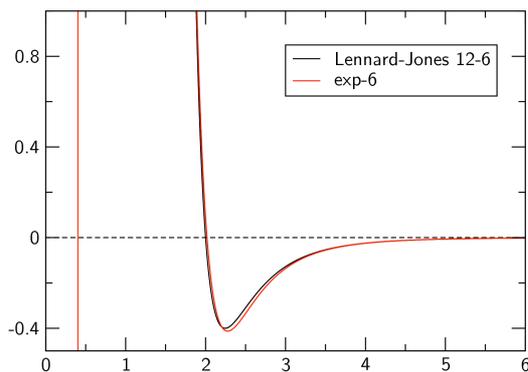


FIG. 7: The Lennard-Jones potential with $\epsilon = 0.4$ and $\sigma = 2$, and a similar exp-6 potential.

are shown in Fig. 7 as well. It might be difficult to find appropriate parameters, which would render the vdW minimum correctly, and the function becomes negative for small r . However, the main reason for the exp-6 potential not to be used (except if vitally needed)⁸ is that it is much more computationally intensive to evaluate the exponential function than R^{-6} .

To find the vdW parameters for heteronuclear interactions, several “mixing rules” have been proposed, the simplest being:

$$\begin{aligned} \sigma_{AB} &= \frac{\sigma_{AA} + \sigma_{BB}}{2} \\ \epsilon_{AB} &= \sqrt{\epsilon_{AA} \cdot \epsilon_{BB}} \end{aligned} \quad (\text{I.27})$$

To find a good set of non-bonded parameters is a challenging task, and force fields are constantly being improved, meaning that new sets of parameters are proposed. A crucial

⁸ which may be the case in the studies of phase transitions like freezing

test and calibration of a force field is the density and the heat of vaporisation of organic liquids, since these properties depend critically on the magnitude of non-bonded parameters — the charges and vdW parameters.

C. Hydrogen Bonding

Early force fields contained special potentials to describe hydrogen bonding. Hydrogen bond is the attractive interaction between a hydrogen atom and an electronegative atom like oxygen or nitrogen. The hydrogen must be covalently bonded to another electronegative atom, so that this covalent bond is polarized and the hydrogen bears a partial positive charge. A typical example is the hydrogen bond between two water molecules in Fig. 8 left. Typical binding energies are around 20 kJ/mol but may reach higher values if the binding partners are strongly polarized or even charged, or if there are several hydrogen bonds between them, like in the GC base pair in DNA, see Fig. 8 right.

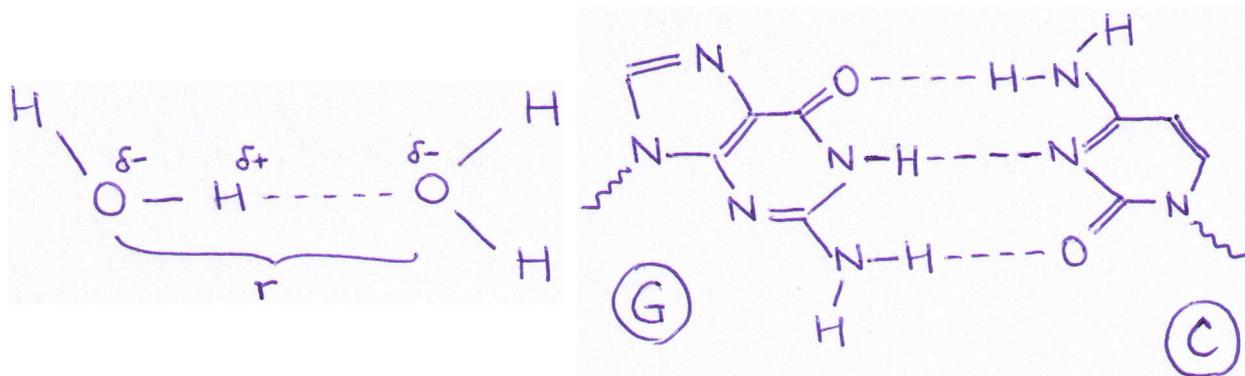


FIG. 8: Water dimer (left) and the guanine:cytosine nucleobase pair (right).

Clearly, Coulomb interaction is the dominant contribution to the hydrogen bond, but vdW interaction can become important also, especially in weakly bound systems. It has been shown that they become crucial especially to describe the angular dependence of the interaction energy in complexes like $\text{H}_2\text{CO} \dots \text{H}_2\text{O}$ and similar.

Thus, force fields have everything in place to describe these phenomena (Coulomb and vdW terms), and most modern force fields do not require a special treatment for this bonding type. However, a third contribution, the *charge transfer* (Fig. 9), is not captured by force fields at all. It may be included in the other terms in an effective way.

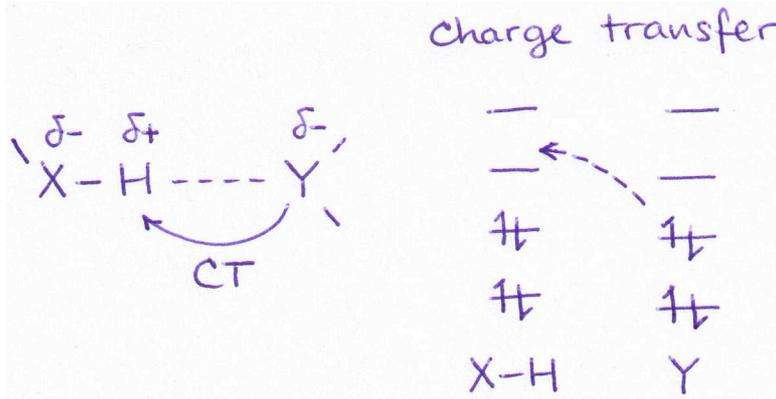


FIG. 9: Charge transfer between the charge donor (Y) and acceptor(X-H).

D. Determination of the bonded parameters: harmonic springs

1. Bonds

A bond dissociation curve typically looks like that in Fig. 1, and is well reproduced by the Morse potential with the functional form

$$E(r) = D (1 - \exp[-\alpha(r - r_0)])^2 \quad (\text{I.28})$$

In principle, the Morse potential allows for a quite good representation of the potential, in a broad range of distances. However, it is computationally quite inefficient, because of the presence of the exponential, and the Morse potential is rarely used in molecular mechanics studies.

A way to approximate virtually any function is to apply the Taylor expansion

$$E(r) = E(r_0) + \frac{dE}{dr}(r_0) \cdot (r - r_0) + \frac{1}{2} \frac{d^2E}{dr^2}(r_0) \cdot (r - r_0)^2 + \dots \quad (\text{I.29})$$

Most force fields use a harmonic approximation, i.e. the Taylor expansion cut after the second-order term. $E(r_0)$ is a constant which we set to zero, and the first derivative $\frac{dE}{dr}(r_0)$ vanishes if the function has a minimum in r_0 . Therefore, with the definition of the force constant k we have, in the second order:

$$E(r) = \frac{1}{2}k(r - r_0)^2 \quad (\text{I.30})$$

We can immediately see in Fig. 10 that the approximation of the true potential with a quadratic function is quite crude and holds only in a quite narrow interval of distances

around the minimum. Importantly, the vibrations of covalent bonds exhibit quite a small magnitude (of several tenths of ångström) and so we actually never need to describe the potential beyond this narrow interval.⁹ The application of harmonic approximation is then justified. To parametrize such a force field, we need two parameters per bond: the force constant k and the equilibrium distance r_0 .

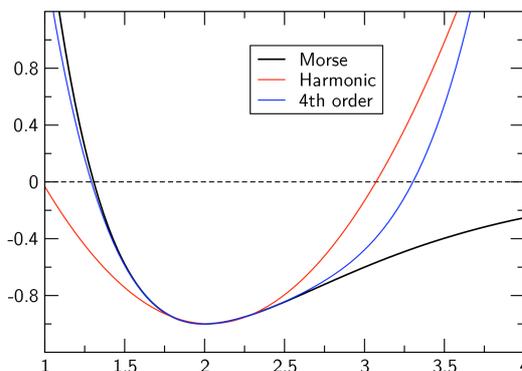


FIG. 10: Comparison of the harmonic and quartic functions with the Morse potential

To be able to compute accurate vibration frequencies, terms up to fourth order can be important to describe the curvature of the potential energy dependence; Fig. 10 compares the Morse potential with the harmonic and fourth-order functions. Also, the quartic function approximates the Morse potential a wider interval of distances.

2. Angles

As for the bonds, we apply a harmonic approximation for the angle deformation and get the potential

$$E_{\text{bend}}(\vartheta) = \frac{1}{2}k_{\vartheta}(\vartheta - \vartheta_0)^2 \quad (\text{I.31})$$

Again, we can obtain the parameters from experiment. For instance, let us consider a



⁹ of course, if we do not aim at studying chemical reactions, i.e. having covalent bonds created or broken

water molecule, which has an equilibrium bond angle of $\vartheta_0 = 104^\circ$ and a bending vibration frequency of about 1700 cm^{-1} .

3. Dihedrals

Dihedral angles describe the rotation around covalent bonds. Four atoms are needed to define this angle (ω):

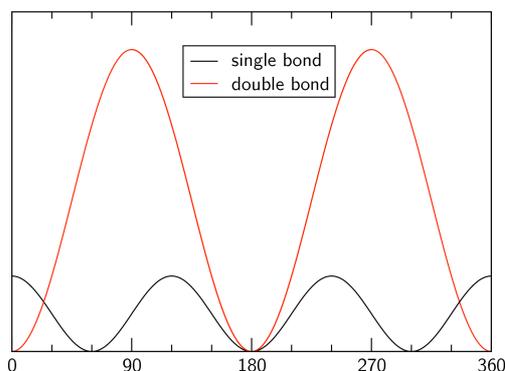


Clearly, the dependence of potential energy on the dihedral angle will be described with a periodic function, and a usual way to express this is a sum of several cosine functions:

$$E(\omega) = \sum_{n=1,2,3,4,6} V_n \cos [n \cdot \omega - \gamma_n] \quad (\text{I.32})$$

with V_n being the height of the torsional barrier, n giving the periodicity ($n = 1$: 360° , $n = 2$: 180° , $n = 3$: 120°) and phase offsets γ_n .

Now, consider the C–C single and the C=C double bonds as examples. The single bond has a periodicity of 120° , i.e. we have three minima for one full rotation of 360° , and the potential energy is described as



$$E_{C-C}(\omega) = V \cdot \cos 3\omega \quad (\text{I.33})$$

The C=C double bond has a 180° -periodicity and thus only two minima for the full rotation. The energy is given by

$$E_{\text{C=C}}(\omega) = V \cdot \cos [2\omega - 90^\circ] \quad (\text{I.34})$$

E. The complete equation

Adding up all contributions, the total energy of a typical biomolecular force field reads

$$\begin{aligned} E(R^N) = & \frac{1}{2} \sum_i k_i (r_i - r_i^0)^2 + \frac{1}{2} \sum_j k_j^\vartheta (\vartheta_j - \vartheta_j^0)^2 + \frac{1}{2} \sum_n V_n \cdot \cos [n\omega - \gamma_n] \\ & + \sum_i^N \sum_{j=i+1}^N \left\{ 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) + \frac{1}{4\pi\varepsilon_0} \frac{q_i q_j}{r_{ij}} \right\} \end{aligned} \quad (\text{I.35})$$

F. Exercises

1. Show for the Lennard-Jones potential (Eq. I.26) that the minimum is at $r_m = 2^{1/6}\sigma$ and the well depth is $-\varepsilon$.
2. Calculate the first and second derivative of the general force field (Eq. I.35). Only the terms dependent on r_i and r_{ij} are required.