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

A. The conceptual and chemical basis

Chemical bonding is a genuine quantum effect and can not 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 (≈ 100). 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 (BO) approximation and the classical treatment of the nuclei. The BO approximation requires, that the electron motion is much faster than the motion of the nuclei (atoms), so that the electrons follow instantaneously the motion of the nuclei (they are somehow 'fixed' to the nuclei [1]. The second approximation is the neglect of nuclear quantum effects, e.g. tunneling effects (hydrogen) or zero point vibrational energies.

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' in the 'sea' of N electrons! What is a bond then? What causes the attraction between two nuclei? In many cases, we do *not* have a large electron delocalization, i.e. there is not a sea of electrons (like in a metal). We have two electrons in bonding orbitals, thats what how we explain covalent bonding. The main idea behind empirical models of the chemical bond is that the strength of e.g. the C-H bond mediated through the two bonding orbitals is similar in all C-H bonds, i.e. we have a localized/local phenomenon.

So, how can we model a covalent bond? Is it possible, to use simple springs to approximate a bond? Consider the H_2 , O_2 or N_2 Molecules: If we model the diatomic interaction with a spring, i.e. write the energy E(x) of the dimer as a function of the distance x with:

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

then we have two parameters k and x_0 . From Spectroscopy we have the information about bond length and vibrational frequency [2].

In equilibrium, the force between the atoms is zero, i.e.

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

which is zero for $x = x_0$, i.e. $x = x_0$ is the equilibrium geometry.

The system of the dimer has one coordinate, i.e. it looks like a simple particle with mass m connected to a spring [3]. The force on the particle is due to Hooks law proportional to $(x - x_0)$, i.e. using Newtons law, we have:

$$F = ma = m\ddot{x} = -k(x - x_0) \tag{I.3}$$

We know the solution of this ordinary differential equation:

$$x(t) \sim \sin(\sqrt{\frac{k}{m}}t), \qquad x(t) \sim \cos(\sqrt{\frac{k}{m}}t).$$
 (I.4)

I.e. since ω is the frequency of the harmonic motion $sin(\omega t)$, we find that the frequency is directly related to the **force constant** k and mass m.

On the other hand we get k directly from the second derivative of the energy:

$$k = \frac{\partial^2 E(x)}{\partial x^2} \tag{I.5}$$

This will hold also for more complex molecules, the second derivatives of the energy with respect to the atomic coordinates determine the frequencies of the (harmonic) motion of the atoms in a molecule. Therefore, we can parametrize a simple force field from experiment if we know equilibrium distances and vibrational frequencies. Alternatively, we can get these values also from quantum chemical calculations.

Does this mean, that we can take a protein and put springs between all the atoms? If yes, does every bond need a different k and x_0 value, since every bond is in a different chemical environment? If this would be the case, we would gain nothing. The whole story about empirical modeling of chemical bonds is, that the number of different parameters is much smaller than the number of bonds. In the other extreme, can we assign e.g. each C-H bond the same k and x_0 value? Its not that simple, but lets see:

1. Spectroscopy

Molecules consist of units, where similar groups have similar properties, e.g.: C-H:

r=1.06-1.11 Å and $\nu \approx 3100 \ cm^{-1}$,

the CH unit has similar properties in different environments.

2. Thermochemistry

Molecular enthalpies are (approximately) additive, i.e.:

 $\label{eq:charge} \begin{array}{l} {\rm CH}_4 \cong 4 \ {\rm C-H} \\ \\ {\rm C}_2 {\rm H}_6 \cong 6 \ {\rm C-H} + {\rm C-C} \end{array}$



Here, we have the picture that the C-H potential looks like this Morse potential for every C-H unit in whatever chemical environment.

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):

- Hybridization: clearly, sp3 Carbon in single bonds is different with respect to sp2 Carbon in double or sp Carbon triple bonds. Therefore, we need different potentials for the C-C, C=C and C≡C bonds. There will be a couple of other C atom types as well, as e.g. in benzene etc. Therefore, we introduce different Carbons and determine the parameters (k, x₀) using molecules typical for this chemical environment, i.e. we use C₂H₆, C₂H₄, C₂H₂ and benzene to determine the parameters (k, x₀) for these four different Carbons (and there are more!).
- A Carbon atom bonded to an Oxygen is electron deficient and this directly affects also its bonding to other partners. If we have a situation like in O=CH-C..., the C-C bond will be affected and it is therefore wise, to introduce an additional C type, the Carbonyl oxygen which uses a different force constants for the C-C bond.

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

3. Localization of the wavefunction

The quantum mechanical basis of these findings is, that the electron wavefunction is localized. It can be localized in a bond, or localized on a fragment of a molecule. These fragments can be 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 for the different Carbons in the carbonyl group, benzene etc.
- Electrostatic interactions. In force fields, atomic charges are defined, i.e. every atom contains a charge and interacts via Coulombs law

with other atoms. These charges have to be determined and it is very helpful to use the rule of group neutrality, i.e. every functional group has a non-fractional charge.



4. Bonding and non-bonding interactions

We therefore have two types of interactions in an extended molecule:

- interactions resulting directly from the covalent bond. We put springs between the atoms and have to care about bond and dihedral angles. Here we describe all the quantum mechanical phenomena like Exchange and Correlation by an effective potential between two atoms (like the diatomics discussed above).
- On the other hand, we have classical Coulomb interactions between the atoms and VdW forces, which are long range. For bonded atoms, these interactions are already effectively treated through the bonded parameters, therefore, usually, these interactions are excluded between atoms which are neighbors (up to forth neighbor).

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

The Coulomb interaction consists of three contributions, the core core repulsion,

$$\frac{1}{2}\sum_{ij}\frac{Z_iZ_j}{R_{ij}}$$

the core-electron interaction,

$$-\sum_{i} \int \frac{Z_{i}\rho(r)}{|R_{i}-r|} dr \to -\sum_{ij} \frac{Z_{i}Q_{j}}{R_{ij}}$$

where we approximate the electron charge density $\rho(r) \to \sum_j Q_j$ by the sum of atomic point charges Q_j and the classical (Hartree) electron-electron interaction term is approximated as an interaction of charges sitting on atoms

$$\frac{1}{2} \int \int \frac{\rho(r)\rho(r')}{|r-r'|} \rightarrow \frac{1}{2} \sum_{ij} \frac{Q_i Q_j}{R_{ij}}$$

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

$$\frac{1}{2}\sum_{ij}\frac{q_iq_j}{R_{ij}}$$

Therefore, we have to determine effective atomic charges for every atomype. This is conveniently done by performing quantum chemical calculations. Making use of the localization of the wavefunction, we can calculate typical molecular fragments and try to determine the charges from there. These are individual amino acids for proteins and the bases, e.g. uracil in Fig. 1, sugars and phosphates for DNA. In the uracil example we can see, that there are two different H atomypes, 1 N and O, and two or three Carbons. However, there are



FIG. 1:

two difficulties associated with this procedure: First, atomic charges are difficult to define and there are several schemes to calculate them. Nowadays, Mulliken charges are no more used since people became aware of their drawbacks. A popular strategy is to use so called potential derived charges. Here, one calculates the electrostatic potential of the molecule at the VdW surface (see Fig. 2), and then fits atomic charges in order to reproduce this potential for a set of points at the surface, i.e. minimizes R:

$$R = \sum_{i} (\phi_i - \phi_i^0)$$



FIG. 2:

with ϕ_i being the potential from the point charges at the reference point i and ϕ_i^0 being the QM potential.

Second, charges are calculated in gas phase, while the electrostatic situation in solution is different, molecules are more polar. As an example, the water molecule has a dipole of about 1.8 D in gas phase, while it is about 2.4 D in solution. To account for that, charges were taken to be larger than the gas phase values. One strategy was, to use small basis sets in the QM calculations, since it is known that these calculations overestimate molecular dipole moments.

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

$$\overrightarrow{\mu_i} = \alpha_i \, \overline{E}$$

This external electric field is of course generated by the other atoms in the system. We will come back to this later on.

A further contribution important for the nonbonding interactions is the Pauli Repulsion. In contrast to the classical Coulomb interaction, this is a purely quantum mechanical effect. Two electrons with same spin try to avoid a large spacial overlap. The typical example is the interaction of two neutral, closed shell systems like two He atoms (or benzene molecules). If the electron densities of the He atoms start to overlap as in Fig. 3, the Pauli repulsion sets in. This interaction is an exchange effect and decays exponentially with the spacial overlap. Although it is purely quantum mechanical, we can model this effect by an exponential repulsion

$$\sim exp(-aR)$$

As we will see later, the the exponential decay is not a convenient model, therefore most empirical force fields use a R^{-9} or R^{-12} decay.





The Pauli Repulsion is a result of the correlated motion of electrons with same spin. In addition, we also have a correlation of electrons with opposite spin. Two electrons repel each other due to the Coulomb interaction, i.e. they try to move apart from each other as far as possible. Consider now two atomic fragments without overlap as in Fig. 4. Due to the zero point energy, no quantum particle is ever at rest. If an electron in the neutral fragment A fluctuates in a way, that it creates a dipole in A, this dipole will induce a dipole in opposite direction in fragment B, the fluctuations of the dipoles will be correlated due to the Coulomb interaction. This correlated dipole fluctuation in the two fragments leads to



FIG. 4:

an effective interaction of the fragments, since the instantaneous dipole in A leads to an induced dipole of opposite direction in B and vice versa. This effect is not included at the Hartree Fock level, and is also missing in a Density Functional (DFT) description. MP2 or

CI would cover it.

A simple model Fig. 5 describes this qualitatively. Two systems of one negative and one positive charge connected with a spring in the distance r from each other. The negative and positive charge can be separated by z_1 and z_2 , if a force acts on them. The individual systems have a force constant k and (reduced) mass m with

$$\omega = \sqrt{k/m}.$$

The separation leads to dipole moments of



FIG. 5:

$$\mu_1 = z_1 q, \qquad \mu_2 = z_2 q$$

If we solve the Schrödinger equation for one oszillator,

$$-\frac{\hbar^2}{2m}\frac{\partial^2\psi}{\partial z_1^2} + \frac{1}{2}kz_1^2\psi = E\psi,$$

we get:

$$E = (\nu + 0.5)\hbar\omega.$$

Now we couple them due to the dipole-dipole interaction:

$$V(r) = -\frac{2\mu_1\mu_2}{4\pi\epsilon_0 r^3}$$

and if we insert this interaction potential in the Schrödinger equation, we find:

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

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

$$F = qE$$
,

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

$$qE = kz$$

Therefore, the induced dipolemoment of such and oszillator in an electric field E is:

$$\mu_{ind} = qz = q^2 E/k$$

and we have on the other side:

$$\mu_{ind} = \alpha E$$

Therefore

$$\alpha = q^2/k$$

and we can write eq. I.7:

$$E(r) = -\frac{\alpha^2 \hbar \omega}{2(4\pi\epsilon_0)^2 k^2 r^6} \tag{I.7}$$

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

The most common function, which combines the Pauli repulsion and the dispersion interaction is the Lennard-Jones Potential:

$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right]$$
(I.8)

which is shown in Fig. 6. The Minimum is at $r_m = 2^{1/6}\sigma$ and the well depth is $-\epsilon$. σ and $-\epsilon$ are treated as empirical parameters. The problem with the exp-6 potential is shown in Fig. 7. It is difficult to find parameters which result in a VdW Minimum and the function becomes negative for small r.

To find the VdW parameters for heteronuclear interactions, several 'mixing rules' have been proposed, the simplest being:

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



FIG. 6: The 12-6 Potential with $\epsilon = 0.4$ and $\sigma = 2$



FIG. 7: The exp-6 Potential

and

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

To find a good set of parameters is a difficult task, and force fields are constantly improved, i.e. new sets of parameters are proposed. A crucial test and calibration is the density and the heat of vaporisation of organic liquids, since these properites depend critically on the the charges and VdW parameters.

C. Hydrogen Bonding

Early force fields contained special potentials to describe hydrogen bonding. Weak hydrogen bonds are mostly formed between neutral partners, like in the water dimer Fig. 8 and typical binding energies are around 5 kcal/mole.



FIG. 8: Water Dimer

In strong hydrogen bonds where the binding energy is typically more than 20 kcal/mole, one or both molecules are charged like in Fig. 9. Clearly, Coulomb interaction is the dominant contribution to the hydrogen bond, but also VdW interaction can become important, especially in weakly bound systems. It has been shown, that they become crucial especially to describe the angular dependence of the interaction energy in systems like $H_2CO \dots H_2O$ and similar molecules. Therefore, force fields have everything in place to describe these



FIG. 9:

phenomena, Coulomb and VdW terms, and most modern force fields therefore do not have a special treatment for this bonding type. A third contribution, the charge transfer (Fig. 10), however, is not captured by force fields. It may be included in the other terms in an effective way.



FIG. 10: Charge transfer between donor and acceptor

D. Determination of the bonding parameters: Springs between atoms

1. Bonds

A bond dissociation curve typically looks like that in Fig. 11, which is the graph of the Morse potential with the functional form:

$$E(r) = D \left[1 - exp[-\alpha(r - r_0)] \right]^2$$
(I.9)

In principle, the Morse potential allows for a quite good representation of the potential, it is usually accurate up to $r - r_0 \leq 0.8$. However, it is not so efficient for MD simulations, especially for geometry optimization.



FIG. 11: The Morse Potential

A steeper potential for large r would lead to a faster convergence, i.e. the minimum would be reached with less computing time. Therefore, most force fields use a harmonic approximation:

$$E(r) = E(r_0) + \frac{dE}{dr}(r - r_0) + \frac{1}{2}\frac{d^2E}{dr^2}(r - r_0)^2 + \dots$$
(I.10)

 $E(r_0)$ is a constant which we set to zero and $\frac{dE}{dr} = 0$. Therefore, with the definition of the force constant k we have in second order:

$$E(r) = \frac{1}{2}k(r - r_0)^2$$
(I.11)

To compute accurate frequencies, terms up to forth order can be important due to the anharmonicity of the potential, Fig. 12 compares the Morse with the harmonic and forth order potential. Of course, the potential is accurate only for small deviations from the equilibrium, as a rule of thumb for kinetic energies of up to 10 kcal/mole. This seems to be good enough, since at 300K every atom has about 1 kcal/mole kinetic energy, i.e., at the relevant temperatures the harmonic and Morse potential are identical. To parametrize the force field, we need two parameters per bond, the force constant k and the equilibrium distance r_0 .



FIG. 12: Comparison of the Morse potential with x^2 and x^4

2. Angles

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

$$E_{bend}(\theta) = k_{\theta}(\theta - \theta_0)^2 \tag{I.12}$$

 $P_{\theta} = C_{\theta}$

Again, we can get the parameters from experiment, think e.g. of the water molecule, which



has an equilibrium bond angle of $\theta_0 = 104^0$ and a bend frequency of about 1700 cm⁻¹.

3. Dihedrals

Dihedral angles describe the rotation around a bond, four atoms are needed to define this angle, as can be seen in Fig. 14. Clearly the rotation around a bond is periodic, i.e. we can



FIG. 14:

describe it by a cosine function:

$$E(\omega) = \sum_{n} V_n \cos(n\omega) \tag{I.13}$$

with V_n being the height of the torsional barrier and n giving the periodicity: n=1: 360° n=2: 180° n=3: 120° Now consider the C-C single and double bonds as examples:

The C-C single bond has 120° periodicity, i.e. we have 3 Minima for the rotation of 360° , which is described by:

$$\frac{1}{2}\left[1-\cos(3\omega)\right]$$



FIG. 15: Potential to describe the rotation around a single bond

The C=C double bond has 180° periodicity, i.e. we have 3 Minima for the rotation of 360° , which is described by:

$$\frac{1}{2}\left[1-\cos(2\omega)\right]$$



FIG. 16: Potential to describe the rotation around a double bond

Adding all contributions, the total energy of typical biomolecular force fields can be written as:

$$E(\vec{r}) = \frac{1}{2} \sum_{i} k_{i} (\vec{r}_{i} - \vec{r}_{i}^{0})^{2} + \frac{1}{2} \sum_{j} k_{j}^{\theta} (\theta_{j} - \theta_{j}^{0})^{2} + \frac{1}{2} \sum_{n} V_{n} [1 - \cos(n\omega)]$$

+
$$\sum_{i}^{N} \sum_{j=i+1}^{N} \left[4\epsilon_{ij} \left[(\frac{\sigma_{ij}}{r_{ij}})^{12} - (\frac{\sigma_{ij}}{r_{ij}})^{6} \right] + \frac{q_{i}q_{j}}{4\pi\epsilon_{0}r_{ij}} \right]$$
(I.14)

E. Exercizes

1. Show for the Lennard Jones Potential eq. I.8, that the Minimum is at $r_m = 2^{1/6}\sigma$ and the well depth is $-\epsilon$.

2. Calculate the first and second derivative of the general force field eq. I.14 (only r-dependent terms).

II. GEOMETRY OPTIMIZATION

Consider again the H_2 molecule. The total energy of the force field is

$$E(x) = \frac{1}{2}k(x - x_0)^2,$$
(II.1)

i.e. the energy is positive, when the distance between the atoms x is not equal the (equilibrium) bond length x_0 .

Consider the case, that we get a geometry of the dimer with bond distance $x_1 \neq x_0$. How can we determine the equilibrium distance in that case? We calculate the force F on the two atoms, which is the negative of the gradient g of the energy:

$$F(x) = -g = -\frac{\partial E(x)}{\partial x} = -k(x - x_0)$$
(II.2)

To find the minimum, we calculate the force at the distance x_1 ,

$$F(x_1) = -k(x_1 - x_0)$$

If we now move the atoms in direction of the force until the force is zero, we will move towards the minimum. Now we have to check, that its a minimum and not a saddle point. We can do this by calculating the second derivative.

$$k = \frac{\partial^2 E(x)}{\partial x^2} \tag{II.3}$$

If this is positive (positive frequency), we have a stable minimum, if negative, we would have a saddle point (which is not possible for the harmonic potential). k is the curvature of the potential and is directly related the vibrational frequency. This procedure is what we call geometry minimization.

Generally, our energy function depends on 3N atomic coordinates (x,y,z for N atoms). It is convenient to write all the atom positions in one vector

$$\overrightarrow{x} = (\overrightarrow{x_1}, \dots \overrightarrow{x_N})$$

In three dimensions (1 atom), the gradient is:

$$\overrightarrow{g} = \overrightarrow{\nabla} E(\overrightarrow{x}) = (\frac{\partial E}{\partial x}, \frac{\partial E}{\partial y}, \frac{\partial E}{\partial z})$$

For N atoms, \overrightarrow{g} and \overrightarrow{F} are 3N dimensional vectors. The unit vector along the gradient is given by:

$$\overrightarrow{e} = \frac{\overrightarrow{g}}{|\overrightarrow{g}|}$$

A. Steepest descent minimization (SD)

The steepest descent method moves along the direction of the force,

$$\overrightarrow{h} = \alpha \overrightarrow{e}.$$

The critical point is the choice of the step size α . If it is too large, we follow the gradient down the potential but may miss the minimum along the gradient and go up the valley at the opposite side. If it is too small, we need too many steps and too many energy evaluations.

One way to overcome this problem, is to perform a line search along the search direction



FIG. 17: Steepest descent minimization

 \overrightarrow{h} to find the minimum. I.e., we choose a value of α_k that \mathbf{x}_{k+1} is the minimum along the search direction \mathbf{h}_k ,

$$\overrightarrow{x}_{k+1} = \overrightarrow{x}_k + \alpha_k \overrightarrow{h}_k.$$

The interesting point is, that two successive search directions are orthogonal to each other, i.e.

$$\overrightarrow{h_{k-1}}\overrightarrow{h_k} = 0,$$

but in a narrow valley, the second next search direction can be similar. An efficient strategy



FIG. 18: Steepest descent and line search



FIG. 19: Line search

therefore tries to avoid this double work and find search directions, which are orthogonal to all the past ones.



FIG. 20: Problem of SD in a narrow valley

B. Conjugate gradient minimization

Consider a Taylor series expansion of the 3N dimensional function

$$E(\overrightarrow{x}) = E(\overrightarrow{0}) + \sum_{i} \frac{\partial E}{\partial x_{i}} x_{i} + \frac{1}{2} \sum_{ij} \frac{\partial^{2} E}{\partial x_{i} \partial x_{j}} x_{i} x_{j}$$
(II.4)

$$=\overrightarrow{c}-\overrightarrow{b}\overrightarrow{x}+\frac{1}{2}\overrightarrow{x}\overrightarrow{A}\overrightarrow{x}$$
(II.5)

with

$$\overrightarrow{c} = E(0), \qquad \overrightarrow{b} = -\overrightarrow{\nabla}E, \qquad [\mathbf{A}]_{ij} = \frac{\partial^2 E}{\partial x_i \partial x_j}$$

If we take the derivative of E, we find (since $\overrightarrow{c}, -\overrightarrow{b}$ and A are constant):

$$\overrightarrow{\nabla} E(\overrightarrow{x}) = \mathbf{A}\overrightarrow{x} - \overrightarrow{b}$$

To minimize E means, to find the point $\overrightarrow{\nabla} E(\overrightarrow{x}) = 0$, i.e. to solve the linear equation:

$$\mathbf{A}\overrightarrow{x} = \overrightarrow{b} \tag{II.6}$$

To do this, we could calculate the first (\overrightarrow{b}) and second (A) energy derivative and solve the linear equation. With that, we directly get the minimum \overrightarrow{x} , however:

- To calculate the second derivative is computationally very expensive, if possible, we try to avoid this step whenever we can (to calculate the gradient, we need 3N derivatives, while for the Hessian we need (3N)²).
- Usually, the potentials of interest are not simple harmonic potentials, i.e. we only make a local harmonic approximation. This means, the x we get by solving the linear equation is not the minimum we are looking for, but only a step further to the minimum. Therefore, practically we would have to iterate this process, which would become very time-consuming.

Therefore, we look for methods which use the information from gradients only. As we have seen in the SD method, successive gradients can have directions, which lead to a lot of double work. The conjugate gradient method constructs successive search directions, which are conjugate to each other.

Practically, at the starting point we move along the gradient \overrightarrow{g} with:

$$\overrightarrow{h}_1 = -\overrightarrow{g}_1$$

The second step should be 'conjugate' to the first step, i.e. it should not go in the same direction.

Now, how does the gradient of E change if we move along a certain direction $\overrightarrow{h_k}$? Consider two successive steps k and k+1. We have:

$$\overrightarrow{g}_k = (\overrightarrow{\mathbf{A} x}_k - \overrightarrow{b}),$$

$$\overrightarrow{g}_{k+1} = (\overrightarrow{\mathbf{A}}_{k+1} - \overrightarrow{b})$$

and

$$\overrightarrow{g}_{k+1} - \overrightarrow{g}_k = \mathbf{A}(\overrightarrow{x}_{k+1} - \overrightarrow{x}_k)$$

This means, going along the search direction $\overrightarrow{h}_k = -\overrightarrow{g}_k$, we get the change of the gradient $\Delta_k \overrightarrow{g} = \overrightarrow{g}_{k+1} - \overrightarrow{g}_k$. This is the effect of the search direction $-\overrightarrow{g}_k$. Now, when we move along the next search direction \overrightarrow{h}_{k+1} , we do not want to spoil the work done so far, i.e. we want to keep the change of gradient $\Delta_k \overrightarrow{g}$ already achieved, i.e. the gradient shall remain perpendicular to \overrightarrow{h}_k . Otherwise, e.g. we could introduce a gradient change in the next step, which This can be achieved, if the change in gradient along \overrightarrow{h}_{k+1} is perpendicular to \overrightarrow{h}_k , i.e.:

$$\overrightarrow{h}_{k}\Delta_{k+1}\overrightarrow{g} = 0 = \overrightarrow{h}_{k}(\overrightarrow{g}_{k+2} - \overrightarrow{g}_{k+1}) = \overrightarrow{h}_{k}\mathbf{A}(\overrightarrow{x}_{k+2} - \overrightarrow{x}_{k+1}) = \overrightarrow{h}_{k}\mathbf{A}\overrightarrow{h}_{k+1}$$

The last condition is a generalization of the concept of orthonormality, the two vectors \vec{h}_{k+1} and \vec{h}_k are called 'conjugate'. They are orthonormal if the matrix **A** is the unity matrix.

Now, we want to make steps as with the line search algorithm,

Α

$$\overrightarrow{x}_{k+1} = \overrightarrow{x}_k - \alpha_k \overrightarrow{g}_k, \qquad (\text{II.7})$$
$$(\overrightarrow{x}_{k+1} - \overrightarrow{x}_k) = -\alpha_k \mathbf{A} \overrightarrow{g}_k = \overrightarrow{g}_{k+1} - \overrightarrow{g}_k.$$

If we choose α_k such, that \overrightarrow{x}_{k+1} is the minimum along the search direction \overrightarrow{g}_k , we know that the two successive gradients are orthogonal. We can multiply the last equation with \overrightarrow{g}_k to get:

$$\alpha_k = \frac{\overrightarrow{g}_k \overrightarrow{g}_k}{\overrightarrow{g}_k \mathbf{A} \overrightarrow{g}_k} \tag{II.8}$$

This equation assures the orthogonality of g_k and g_{k+1} , i.e. the next search direction is orthogonal to the previous one and determines the step size. For that, we need the gradient and the Hessian. However, often the calculation of the Hessian is too costly, and the stepsize is determined by line search.

Eq. II.8 determines the stepsize along the search direction and the new search direction at x_{k+1} is calculated via (without proof):

$$h_{k+1} = -g_{k+1} + \gamma_k h_k \tag{II.9}$$

with



FIG. 21: Conjugate gradients

$$\gamma_k = \frac{\overrightarrow{g}_{k+1} \overrightarrow{g}_{k+1}}{\overrightarrow{g}_k \overrightarrow{g}_k},$$

assuring:

$$\overrightarrow{g}_{k}\overrightarrow{g}_{l}=0,\qquad \overrightarrow{g}_{k}\overrightarrow{h}_{l}=0,\qquad \overrightarrow{h}_{k}\mathbf{A}\overrightarrow{h}_{l}=0$$

- This has to be compared with the steepest descent method. In steepest descent, the search directions $-\overrightarrow{g}_{k+1}$ and $-\overrightarrow{g}_k$ are orthogonal to each other, which can lead to the case, that successive steps spoil the efforts of each other. The h_k are not orthogonal to each other, they are by purpose constructed NOT to be orthogonal, but due to the property $\overrightarrow{h}_k \mathbf{A} \overrightarrow{h}_l = 0$ they are called to 'conjugate' to each other.
- In principle, CG determines the minimum in a N-dimensional quadratic potential in N steps. Every vector in N dimensions can be constructed from N basis vectors. In many cases, these are choosen to be orthogonal. It can be shown, that the \overrightarrow{h}_k form a linearly independent set of vectors, i.e. they form an optimal set of search directions to

$$\overrightarrow{x}^* - \overrightarrow{x}_1 = \sum_k \alpha_k \overrightarrow{h}_k$$

C. Hessian update based methods: Newton Raphson and Quasi Newton Raphson

Now consider the vector

$$\overrightarrow{x} = \overrightarrow{x}^* - \overrightarrow{x}_1$$

where \vec{x}^* is the global minimum and \vec{x}_1 an arbitrary starting point. Since the gradient is zero at the Minimum, we find from

$$\mathbf{A}\overrightarrow{x} = \overrightarrow{b}$$
$$\overrightarrow{x} = \mathbf{A}^{-1}\overrightarrow{b}$$

or

$$\overrightarrow{x}^* = \overrightarrow{x}_1 + \mathbf{A}^{-1} \overrightarrow{b} \tag{II.10}$$

i.e. we find the minimum of a quadratic potential in one step by inverting the Hessian. This is a very nice property, since in CG we need around N steps (N: dimension. The Hessian contains the information about the curvature of the function, large curvature gives large eigenvalues. Therefore, the inverse of the Hessian leads to large steps for low curvature and small steps for large curvature. This speeds up the convergence for shallow potentials, where gradient following would be very slow.

The trivial example is the parabola $f(x) = x^2$. For this function, the so called Newton-Raphson (NR) method as expressed in eq. II.10 gives:

$$0 = x_1 - 0.5 * 2 * x_1$$

(with f''(x) = 2 and f'(x) = 2x).

Compare this now with a flat potential like $f(x) = 0.1x^2$. The inverse of the second derivative f''(x)=0.2 is $[f''(x)]^{-1}=5$, i.e. the step-size becomes very large. However, practically

- the determination of the Hessian and its inversion (N³ step) can be very costly, that a CG method becomes computationally cheaper, in particular when
- the potential is not harmonic. Then, NR even can fail (converge to saddle point, wrong direction etc.) and it may not be a good method.

Therefore, usually one starts (when forces are big) an optimization with SD and CG and then later on NR is invoked (close to the minimum, where the harmonic approximation starts to work).

Very efficient are so called Hessian update methods, where the Hessian is not calculated, but updated during the optimization.

$$x_{k+1} = x_k - \mathbf{A}_k^{-1} g_k.$$

Here, one starts with $\mathbf{A}_1^{-1} = \mathbf{I}$ and the matrix is 'updated' that for large k it is identical to the inverse Hessian. This means, in the beginning one follows the gradient and the information about the curvature is collected along the way.

All techniques need some criterion to stop optimization, a common procedure is to stop when the gradient and the energy between two steps become small.

D. Harmonic approximation to vibrational frequencies: normal modes

The displacement from equilibrium of the harmonic oszillator x(t) is given by the solution of the ordinary differential equation:

$$m\ddot{x} = -kx$$

with k being the second derivative of the potential with respect to the displacement x. If we insert $x(t) = Asin(\omega t)$, we immeadely get:

$$-m\omega = -k,$$

therefore we obtain the vibrational frequency $\omega = k/m$.

If we think of large molecules like proteins with N atoms, the problem becomes quite complicated. Every atom interacts with each other, we have N² interactions, which are usually not harmonic (coupling of several atoms, Coulomb and VdW interactions, although the bonding terms are harmonic!). In the *harmonic* approximation, we again take the force field energy I.14 and apply a Taylor series approximation around the equilibrium positions of the atoms, the x_j being the deviations from the equilibrium (the first derivative vanishes at equilibrium):

$$E(\overrightarrow{x}) = E(\overrightarrow{x_0}) + \frac{1}{2} \sum_{i,j}^{N} \frac{\partial^2 E}{\partial x_i \partial x_j} x_i x_j$$

With

$$k_{ij} = \frac{\partial^2 E}{\partial x_i \partial x_j}$$

and setting $E(\vec{x_0}) = 0$ we have:

$$E(\overrightarrow{x}) = \frac{1}{2} \sum_{i,j}^{N} k_{ij} x_i x_j.$$

Caution: the k_{ij} introduced here are different form the force constants in the force field energy E!

The force on atom i is now the (negative) derivative of the energy with respect to the atomic coordinate x_i , i.e.

$$F_i = -\frac{\partial E}{\partial x_i} = -\sum_j^N k_{ij} x_j$$

Looking at atom i, we have:

$$m_i \ddot{x}_i = F_i = -\sum_j^N k_{ij} x_j.$$

Since we have E, we know how to calculate the second derivatives, once we have located the minimum. The movement of atom i is now coupled to all other atoms, the equations we have to solve become quite complicated. In case of a diagonal matrix $k_{ij} = k_{ii}\delta_{ij}$, we would have;

$$m_i \ddot{x}_i = k_{ii} x_i,$$

for which we know the solution:

$$x_i(t) = a_i exp(-i\omega t),$$

where we have a system of uncoupled oscillators. We can use this as an Ansatz for our coupled system, to get:

$$m_i \omega^2 a_i = -\sum_j^N k_{ij} a_j.$$

The $\overrightarrow{a} = (a_1...a_{3N})$ are vectors, which give the amplitude of the motion, i.e. determine how much an atom is involved in the motion and we define $\lambda = \omega^2$ and the (diagonal) mass-matrix $[\mathbf{M}]_{ii} = m_i$. With that, we can write:

$$\lambda \mathbf{M} \overrightarrow{a} = \mathbf{k} \overrightarrow{a} \tag{II.11}$$

Multiplying from left with \mathbf{M}^{-1} , we get:

$$\lambda \overrightarrow{a} = \mathbf{M}^{-1} \mathbf{k} \overrightarrow{a} \tag{II.12}$$

This is an eigenvalue problem for the Matrix $\mathbf{M}^{-1}\mathbf{k}$, which we know how to solve. The only problem is, that this matrix is not symmetric, which makes the numerical solution more difficult. Therefore, we look how we get an eigenvalue-problem for a symmetric matrix.

This can be done if we define

$$\overrightarrow{b} = \mathbf{M}^{1/2} \overrightarrow{a}$$

and get instead of :

$$\lambda \mathbf{M}^{1/2} \overrightarrow{b} = \mathbf{k} \mathbf{M}^{-1/2} \overrightarrow{b}$$

Now we multiply from left with $\mathbf{M}^{-1/2}$ and have:

$$\lambda \overrightarrow{b} = \mathbf{M}^{-1/2} \mathbf{k} \mathbf{M}^{-1/2} \overrightarrow{b} = \widetilde{\mathbf{k}} \overrightarrow{b}$$
(II.13)

with the symmetric matrix $\widetilde{\mathbf{k}}$

$$[\widetilde{\mathbf{k}}]_{ij} = \frac{k_{ij}}{\sqrt{m_i}\sqrt{m_j}}$$

We now can solve the well known eigenvalue problem:

$$\left[\widetilde{\mathbf{k}} - \lambda \mathbf{I}\right]\overrightarrow{b} = 0$$

to get the eigenvalues λ_{ν} and eigenvectors \overrightarrow{b}_{ν} . The NxN matrix $\widetilde{\mathbf{k}}$ has N eigenvalues λ_{ν} and eigenvectors \overrightarrow{b}_{ν} , which correspond to the *normal modes* of the system. These represent independent modes of motion of the molecule. Every eigenvector \overrightarrow{b}_{ν} contains the amplitudes of every atom in the system, contributing the particular normal mode ν ,

$$\overrightarrow{b}_{\nu} = (b_1^{\nu}, b_2^{\nu}, \dots b_N^{\nu}).$$

Think of e.g. the three modes of vibration of the water molecule.

Example:

Consider a fictitious, linear three-atomic molecule, with two equal bond lengths and force constants, masses m_1 , m_2 and $m_3=m_1$ and springs only between atom 1 and 2 and atom 2 and 3. The potential energy E is then

$$E = \frac{1}{2}k(x_1 - x_2)^2 + \frac{1}{2}k(x_2 - x_3)^2,$$

the x_i being the displacements from the equilibrium positions. We have the Hessian:

$$\mathbf{k} = \begin{pmatrix} k & -k & 0 \\ -k & 2k & -k \\ 0 & -k & k \end{pmatrix},$$
$$\mathbf{M} = \begin{pmatrix} m_1 & 0 & 0 \\ 0 & m_2 & 0 \\ 0 & 0 & m_1 \end{pmatrix}$$

and the mass weighted Hessian

the mass matrix

$$\mathbf{k} = \begin{pmatrix} \frac{k}{m_1} & -\frac{k}{\sqrt{m_1m_2}} & 0\\ -\frac{k}{\sqrt{m_1m_2}} & 2\frac{k}{m_2} & -\frac{k}{\sqrt{m_1m_2}}\\ 0 & -\frac{k}{\sqrt{m_1m_2}} & \frac{k}{m_1} \end{pmatrix}.$$

Solution of the eigenvalue leads to the three eigenmodes:

$$\lambda = \frac{k}{\sqrt{m_1}}, \qquad b_1 = -b_3, \qquad b_2 = 0$$

 $\lambda = 0, \qquad b_1 = b_3, \qquad b_2 = \sqrt{m_2/m_1}b_1$

$$\lambda = k(m_2 + 2m_1)/m_1m_2, \qquad b_1 = b_3, \qquad b_2 = -2\sqrt{m_1/m_2}b_1$$

The first mode describes a motion, where the middle atom is at rest, and m_1 and m_2 vibrate with opposite eigenvectors (symmetric stretch). The second motion is the pure translation of the whole system. Since $a_1 = a_3 = \frac{b_1}{\sqrt{m_1}}$, we find that $a_2 = a_1$. In the last mode, the middle atom moves in opposite direction to the outer atoms (asymmetric stretch).

E. Exercises

1. Consider the function

$$f(x,y) = x^2 + 2y^2.$$

Calculate the gradient at the point (2,2) and the Hessian in the origin. Would you hit the minimum when moving along that gradient? What are the Eigenvalues of the Hessian at (0,0)? Start at the point (0,1) and move along the gradient with stepsize 1. Where do you arrive?

2. When starting at point (9,9), a line search in the first step finds the point (4,-1). Show, that at this point the new search direction constructed with CG directly hits the origin.

3. Show, that you arrive at the minimum in one step, when you use the Newton Raphson method.

4. Consider

$$f(x,y) = x^4 + 4x^2y^2 - 2x^2 + 2y^2.$$

Plot this function and determine the eigenvalues at the minimum (1,0) and the saddle point (0,0). What are the eigenvectors?

5. Proof the Hessian of the artificial linear three-atomic system.

III. TECHNIQUES TO LOCATE A TRANSITION STATE

In addition to the location of minima, the calculation of transition states and reaction pathways is an interesting task for Quantum Chemistry (QC). The calculation of these properties can be an important complement to experimental data, since information about the transition state geometry, reaction pathways, and activation energies is often difficult to obtain. When interested in isomerization reactions and structural transitions, MM methods can be applied. When studying chemical reactions where bond breaking is involved, QM methods are required most times.

But there should be one warning from the beginning: the QC calculation of reaction rates from transition state theory is difficult, since due to the exponential factor a chemical accuracy ≤ 1 kcal/mole is necessary to get meaningful rates. This requires high level calculations, which are often computationally too expensive, SE, HF or DFT methods are mostly not accurate enough. However, information about mechanisms and relative rates is much more easy to obtain.

Methods for locating transition states can be divided into so called local and global optimization methods. Local methods use local information only, i.e. the gradient at one point of the energy hypersurface. If we specify a point 'sufficiently' close to the transition state (TS), the Hessian will have one negative eigenvalue (see Chap.2, exercise 4.). We can the use the NR method to follow this eigenvalue until the TS is reached.

The negative eigenvalue exists only in a neighborhood of the TS. Consider as an example the function

$$f(x) = x^4 - x^2$$

as shown in Fig. 22. The second derivative is

$$f''(x) = 12x^2 - 2x^2 - 2x^2$$

That means, the second derivative is negative for $|x| \leq \sqrt{1/6}$.

Global optimization methods start from the knowledge of the product and reactant



structures and calculate the whole pathway connecting them, of course including the transition state. Pathways of interest are so called minimum energy pathways, as shown in Fig. 23. In simple cases, they can be obtained by steepest descent optimization starting at the (first order) saddlepoint (TS), moving in both directions indicated by the negative eigenvalue. In more difficult cases, methods like CPR or NEB are used.



FIG. 23: The minimum energy path

A. Conjugate Peak Refinement: CPR

The CPR method developed by Fischer and Karplus in the early 90s (Chem. Phys. Lett. 194 (1992) 252) is not described in mathematical detail, but its principle is illustrated in



Fig. 24. The starting point of the method are the structures of product (P) and reactant

FIG. 24: Scheme of the CPR method from: http://spider.iwr.uniheidelberg.de/fischer/research/cpr.html

(R) , which have to be well optimized using techniques described above. From these points, CPR works by performing these steps:

- Interpolate the geometries of P and R along the connecting line.
- Find the point with maximum (MAX) energy along this line.
- Optimize the geometry starting from MAX **conjugate** to the direction \overrightarrow{EP} to find the point E_1 .
- Now interpolate between R and S_1 and S_1 and P and repeat the procedure.

A path of minimal energy (MEP: minimum energy path) will result from this procedure. Methods like CPR (NEB) are computionally very costly, i.e. several 1000 to 10000 energy and gradient evaluations are necessary, therefore, it can be applied only for fast QM methods.

B. Nudged Elastic Band: NEB

The NEB method starts like CPR from the optimized R and P structures and interpolates between them by constructing N copies (images), Fig. 25. The interpolation is illustrated for a simple proton transfer reaction in 26. The $\vec{x_i}$ denote the coordinates of all atoms in



FIG. 25: Interpolation between R and P



FIG. 26: R, TS and P images for a simple proton transfer reaction.

copy i, i=1,...N. We have the potential energy of the i-th system, $V(\vec{x_i})$. The basic idea is to optimize the energy of all N systems simultaneously, but to keep the N-2 non-minimum structures along the path, we put springs between them, i.e. we optimize the energy:

$$E = \sum_{i=1}^{N} V(\overrightarrow{x_i}) + \sum_{i=1}^{N-1} 0.5k(\overrightarrow{x_{i+1}} - \overrightarrow{x_i})^2,$$

a cartoon of the situation is given in Figs. 27 and 28. We can easily imagine, that the



FIG. 27: Springs between the copies.

FIG. 28: NEB-springs between the R, TS and P images, where only the central H+ moves. The three images connected by the springs are different only in the H position.

springs with force constants k 'hold' the images even in regions with large forces, depending on the spring constant. Now, two problems arise:

- If the spring constants are too small, the images at steep potentials will slide down the potential energy hill, generated by $\sum_{i} V(\vec{x_i})$, and all images will be in the valley, none be at or close to the transition state.
- If the spring constants are too large, the images will move away from the MEP, the corners will be cut.

To get this clearer, lets consider the forces parallel and perpendicular to the NEB path as given by the sequence of images i=1,...N (Fig. 29). We can calculate the tangent vector on the path:

 $\overrightarrow{\tau_i}$

The forces, which make the images slide down the hill are the contributions of $V(\vec{x_i})$ parallel to the NEB path:

$$\nabla V(\overrightarrow{x_i}) * \overrightarrow{\tau_i}.$$

Therefore, we project those out to get the contributions of the potential perpendicular to the NEB path:

$$[F_i^s]_{\perp} = [\nabla V(\overrightarrow{x_i})]_{\perp} = \nabla V(\overrightarrow{x_i}) - \nabla V(\overrightarrow{x_i}) * \overrightarrow{\tau_i}.$$
 (III.1)

The forces leading to the corner cutting come from the contributions of the springs perpen-



FIG. 29: Forces parallel and perpendicular to the NEB path.

dicular to the NEB path $[F_i^s]_{\perp}$, therefore, we consider only those parallel to the path:

$$[F_i^s]_{\parallel} = [\nabla V(\overrightarrow{x_i})]_{\parallel} = [k(\overrightarrow{x_{i+1}} - \overrightarrow{x_i}) - k(\overrightarrow{x_i} - \overrightarrow{x_{i-1}})] \overrightarrow{\tau_i}$$
(III.2)

If we now optimize the whole system only using the forces from the equations III.1 and III.2, we will find images evenly spaced along the NEB path, perfectly following the MEP. Practically, we construct all the images, calculate the tangents τ_i and remove the forces of the MM force field which are parallel to the tangents. Then we add the forces due to the springs, again projected. We will move the atoms then due to the resultant forces.

We can use a SD optimizer then, CG and NR do not work due to the following reason: When deriving the CG and NR methods, we always made use of the fact, that the forces (gradients) are the gradients of the energy function, since we used the Hessian of the energy. In NEB, this is no longer the case, therefore we can not use these optimizers and have to stick to the very inefficient SD method.

CPR and NEB are powerful tools, when the reaction considered is dominated by the
potential energy, protein dynamics and entropy do not play a significant role. If the protein fluctuates a lot, the reaction can be different for different protein conformations. An example is shown in Fig. 30, where the barrier and reaction energy varies over several kcal/mole. Clearly, the protein undergoes important structural fluctuations during its



FIG. 30: Energy profiles (acylation reaction) for various protein conformations: from Zhang et al. JPCB 107 (2003) 4459.

dynamics, meeting various local minima. For many proteins, the notion of a single global minimum does not make sense any more. To describe a reaction, we have to average over all the reaction energies for the various minima. Doing this, we leave the potential energy surface and consider the free energy surface. For that, we have to describe the molecular dynamics of the protein.

IV. MOLECULAR DYNAMICS SIMULATIONS

Consider a chemical reaction in solution: The solvent molecules are surrounded by many water molecules, which fluctuate and thereby have different hydrogen bonding interactions with the solute, have through different orientations different dipole moments acting on the molecule. As a result

- the energy of the systems will fluctuate a lot.
- Since there will be a multitude of local minima close in energy, the search for a global minimum will not be meaningful and practically this will be impossible.
- Even if we would find a global minimum, the reactant state of the reaction may have a very different global minimum than the product state with respect to the conformation of the water molecules. In this case, we do not know how to compare the energies at all!

The (micro) state of a system is completely determined, if we know the positions \vec{x}_i and the momenta \vec{p}_i of all the particles. We call the 6-dimensional space spanned by the coordinates and the momenta the **phase space**, $\{\vec{r}_i, \vec{p}_i\}$.

A **trajectory** in phase space is the set of points $\{\overrightarrow{r}_i(t), \overrightarrow{p}_i(t)\}$ passed by during the dynamics of the system.

Example:

Consider the simple harmonic oscillator. We can plot the time dependence of the coordinates

$$x(t) = a\cos(\omega t)$$

or even the time-dependence of the velocities

$$v(t) = -a\omega sin(\omega t)$$

but we also can plot the velocities versus the coordinates in the 2-dimensional phase space, and we see easily, that the motion in phase space is elliptic:

$$\left(\frac{x(t)}{a}\right)^2 + \left(\frac{v(t)}{a\omega}\right)^2 = 1$$

The total energy of the harmonic oscillator is $E = T + V = 0.5m\omega^2 a^2$. Therefore, different energies mean different values of a and ω . The trajectories in phase space never cross for so called **conservative systems**. If we have friction (non-conservative), the harmonic oscillator looses energy and the motion will look like spirals ending in the origin of the coordinate system. Here, different trajectories can cross.

Now, coming back to our molecule in solution. To look at a single structure does not make any sense, but we could have the idea to take the average over all structures. For example, we follow the trajectory in phase space for some time, calculate the energy for many **snapshots** $\{\vec{r}_i(t_k), \vec{p}_i(t_k)\}$ along the trajectory, i.e. calculate for the times t_k (k=1,...M) the energies E_k and average:

$$\langle E \rangle = \frac{1}{M} \sum_{k=1}^{M} E_M.$$
 (IV.1)

We do this for the product and for the reactant, get average energies for the product and the reactant, and by this an energy difference. In principle, this is a very good idea, but there are a few questions:

- How can we be sure, that we have enough points to be representative for all relevant conformations occurring during the dynamics?
- How do we get the trajectory? \rightarrow perform MD! But how to incorporate temperature?
- Suppose we know the structure of the reactant, how do we get the structure of the product and how the whole reaction path? This is a difficult problem and we will have to spent some time on that!
- What about entropy? Is an average of the energy enough? Yes, a difficult problem as well, so we will have to look deeper into Thermodynamics and Statistics. And now we are at the core of bio-molecular simulations: It is easy to understand the total energy of the force field, and how geometry optimization works. The main issue is to make proper use of the energy function to get the thermodynamic properties right. Bio-molecular simulations are all about Thermodynamics, in contrast to Quantum

Chemistry, where people look at small molecules with more simple structures and with a focus on total energies.

We will leave the last two points to the next chapters and focus for the moment on the first two.

If we have trajectories, we can calculate so called **time averages** as done for the energy. For any property A(t), we are interested in, e.g. x(t), v(t), E(t) etc. A generalization of eq. IV.1 is:

$$\langle A(t) \rangle_t = \frac{1}{t_1 - t_0} \int_{t_0}^{t_1} A(t) dt$$
 (IV.2)

On the other hand, any experimental sample usually contains a large number of molecules. This number is so large, that we can assume all relevant conformations of molecule and solvent to be present. Think of a large number of harmonic oscillators, then there will be for every point in phase space \overrightarrow{r}_i , \overrightarrow{p}_i (i.e. every point on the ellipse) one system, which is at that point. Such collection of systems we call an **ensemble**.

Now we count how many molecules (oscillators) in the ensemble are at phase space point $\overrightarrow{r}_i, \overrightarrow{p}_i$, how many at all the other points. Doing this, we get the so called **phase space density**, i.e. the number of molecules at each point in the phase space (per volume unit),

 $\rho(\overrightarrow{r},\overrightarrow{p}).$

If we integrate ρ over the whole (phase-) space, we get the total number of systems,

$$Z = \int \rho(\overrightarrow{r}, \overrightarrow{p}) d\overrightarrow{r} d\overrightarrow{p}$$
(IV.3)

We can use this phase space density to calculate the **ensemble average**:

$$\langle A \rangle_e = \frac{1}{Z} \int A\rho(\overrightarrow{r}, \overrightarrow{p}) d\overrightarrow{r} d\overrightarrow{p}$$
 (IV.4)

Experimentally, we always measure **ensemble averages**, but in simulation, we always have one system, for which we calculate time-averages. To be able to compare both, we always assume that the systems we study are **ergodic**, i.e. that during the MD the system passes all points in phase space, which constitute the real ensemble.

$$\langle A \rangle_e = \langle A \rangle_t \tag{IV.5}$$

We leave the statistics for a moment and have a look, how we can get the trajectories in computer simulations.

A. Integration of the equations of motion

The total energy E=T+V is often also called Hamilton-function, in Quantum Mechanics it is the Hamilton operator. The Hamilton formalism is very practical, since it allows to generate equations of motion, if we know the total energy:

$$\dot{x}_i = \frac{\partial H}{\partial p_i} \qquad \dot{p}_i = -\frac{\partial H}{\partial x_i}$$
 (IV.6)

We can not prove these equations here, but give an example (p = mv):

$$H = \frac{1}{2}mv^{2} + \frac{1}{2}kx^{2} = \frac{p^{2}}{2m} + \frac{1}{2}kx^{2}$$
$$\dot{x} = \frac{\partial H}{\partial p} = p/m = v$$
$$\dot{p} = m\ddot{x} = -\frac{\partial H}{\partial x} = -kx$$

which are the known equations of motion of the harmonic oscillator. These are ordinary differential equations (ODE) of 1st and 2nd order.

A 1st order differential equation is e.g.:

$$\dot{x} = kx,$$

which has the solution: x(t) = exp(kt). Examples in nature following these kind of exponential laws are radioactive decay or the dynamics of populations.

More general, we can write these ODEs as:

$$\dot{x} = f(x, t)$$

A 2nd order ODE is then:

$$\ddot{x} = f(x, \dot{x}, t)$$

An example is $\ddot{x} = -\frac{k}{m}x$, or, when we introduce friction:

$$\ddot{x} = -r\dot{x} - \frac{k}{m}x$$

Friction is assumed to be proportional to velocity, which is very often the case. We can reduce the 2nd order ODE to two first order ODEs by introducing v:

$$\dot{x} = v$$
$$\dot{v} = -rv - \frac{k}{m}x$$

Now we have to solve these ODEs numerically. There are several methods available, which are briefly discussed.

B. The Euler method

To solve

$$\dot{x} = f(x, t)$$

we proceed by a Taylor series expansion $(\Delta t = t - t_0)$:

$$x(t) = x(t_0) + \dot{x}(t_0)\Delta t + \frac{1}{2}\ddot{x}(t_0)\Delta t^2 + \dots$$

The **Euler approximation** is a first order approximation, i.e. we neglect second and higher orders

$$x(t) \approx x(t_0) + \dot{x}(t_0)\Delta t$$

For numerical integration we start at time t_0 , take a timestep Δt and get the value of x and v at the time $t = t_0 + \Delta t$.

For our MD simulation, we have:

$$x(t_0 + \Delta t) = x(t_0) + v(t_0)\Delta t$$
$$v(t_0 + \Delta t) = v(t_0) + a(t_0)\Delta t$$

$$a(t_0) = -\frac{1}{m} \frac{\partial H}{\partial x}$$

H is the Hamilton function, we also can use the potential V only, and the derivative of V is the force at the atom.

To start the MD, we have to give the initial conditions x_0 and v_0 and calculate the force at the position x_0 to get a_0 . Then, we can use the Euler equations to get the positions and velocities at the time $t_0 + \Delta t$. That means, to get the trajectory over a time of T, we have to calculate the forces on the atoms $M=T/\Delta t$ times, i.e. make M steps. The computational cost of the force calculation therefore determines, how many steps we can make. The step-size is crucial. There is one numerical and one physical constraint on the stepsize:

- Numerical: Since we neglect contributions in Δt² and higher orders we make an error in the order of Δt². One possibility is, to make the step-size very small, then the error is small. But then we need many steps to simulate a certain time T. If we make the step-size too large, we introduce an error in the integration. We see this error in the total energy: E=T+V should be constant, and if we monitor the total energy during the MD we can see, how good our integration is.
- The fastest motions in biological systems are the movements of the hydrogens. Therefore, our step-size has to be much smaller than the time for one vibration of an hydrogen. Practically, this leads to step sizes around 1 fs.

The step-size of 1 fs is the fundamental time unit in MD. That means, we need 1 Million force calculations to get 1 ns MD. For large systems, ns simulations can be done, for smaller ones even the microsecond regime is reached.

C. The Verlet method

The error of the Euler Method is too large, to allow for time-steps of 1 fs. Therefore, methods with errors in Δt^3 are necessary. One of them is the so called Verlet method. Here, we make a step in positive time and 'negative' time and expand up to second order:

$$x(t_0 + \Delta t) = x_0 + \dot{x}(t_0)\Delta t + \frac{1}{2}\ddot{x}(t_0)\Delta t^2$$

$$x(t_0 - \Delta t) = x_0 - \dot{x}(t_0)\Delta t + \frac{1}{2}\ddot{x}(t_0)\Delta t^2$$

Then, we add both equations to get:

$$x(t_0 + \Delta t) = 2 * x_0 - x(t_0 - \Delta t) + \ddot{x}(t_0)\Delta t^2$$
$$a(t_0) = \ddot{x}(t_0) = -\frac{1}{m}\frac{\partial V}{\partial x}$$

This equation is strange, it needs the positions x_0 and the acceleration $a(t_0)$, but in addition also the positions $x(t_0 - \Delta t)$! This is a problem, since when we start a MD we know only $x(t_0)$, $v(t_0)$ and $a(t_0)$ but never $x(t_0 - \Delta t)$. That means, Verlet can not be started. We have to use the Euler Method for the first step, to start Verlet. Then, we also can calculate velocities with:

$$\dot{x}(t_0) = v(t_0) = \frac{x(t_0 + \Delta t) - x(t_0 - \Delta t)}{2 * \Delta t}$$

This is the so called Verlet normal form.

An algorithm, which is equivalent to the Verlet is the so called **velocity Verlet** algorithm:

$$x(t_0 + \Delta t) = x_0 - v(t_0)\Delta t + \frac{1}{2}a(t_0)\Delta t^2$$
$$a(t_0) = -\frac{1}{m}\frac{\partial V}{\partial x} = \frac{F}{m}$$

where we calculate the velocities as:

$$v(t_0 + \Delta t) = v_0 + \frac{1}{2} (a(t_0) + a(t_0 + \Delta t)) \Delta t$$

Here, we can start the MD with knowledge of x_0 and v_0 , but in the next step, to know $v(t_0 + \Delta t)$ we first have to calculate the positions to get the forces at $x(t_0 + \Delta t)$. It can be shown, that the two forms of Verlet algorithms are equivalent.

D. Exercises

1. Derive the equations of motion for the linear three atomic system

$$H = \frac{1}{2} \sum_{i=1}^{3} m_i v_i^2 + \frac{1}{2} k(x_1 - x_2)^2 + \frac{1}{2} k(x_2 - x_3)^2$$

2. Derive the equations of motion for the particle i, x_i and p_i using the Hamilton formalism for:

$$H = \frac{1}{2} \sum_{i} m_i v_i^2 + \frac{1}{2} \sum_{ij} V_{ij}.$$

 V_{ij} is given by the Lennard-Jones Potential discussed above. These are the equations we have to solve when doing MD

V. THERMODYNAMIC ENSEMBLES

A system of classical particles interacting with a potential V is a **deterministic system**. Knowing the **initial conditions**, i.e. the positions and velocities of all particles at a certain time, we can calculate the **trajectory** of the system, i.e. the positions x(t) and velocities v(t) at all times t. We can have **analytic** solutions, as e.g. in the case of the harmonic oscillator, where we have the trajectories in a closed form:

$$x(t) = x_0 cos(\omega t)$$
 $v(t) = v_0 cos(\omega t)$

or, when the system becomes too complicated, we have to compute the trajectories **numerically** using e.g. the Verlet method.

Note, that so called **chaotic** systems are also strictly deterministic. For exactly specified initial conditions the system is perfectly predictable. The point here is, that two trajectories which are initially close in phase space depart exponentially from each other, while in non-chaotic systems they stay close (e.g. harmonic oscillator). This can already happen for very simple systems like the double pendulum!



FIG. 31: For a 'chaotic' system, two initially close trajectories depart exponentially. Therefore, small differences in the initial conditions can lead to very different behavior of the system, although being completely deterministic!

A motion becomes **stochastic**, if we do not have the information about all degrees of freedom, e.g. like for a dust particle moving in an erratic fashion. If we could keep track about all movements of the air molecules, the particle motion would be completely deterministic for us. Therefore, we have to describe systems using **Statistical Mechanics**, when we can not keep track with all degrees of freedom.

We are now interested to find simulation techniques, where we can control the temperature. The temperature is crucial, since this determines which parts of phase space we reach during the MD. The phase space sampled at high temperatures will be different from those sampled at low temperatures. In particular, we have to find a way to model the system, that we simulate the right phase space density.



FIG. 32: A high energy E=T+V allows to sample different parts of the phase space. The difference E-V is the kinetic energy.

A. The microcanonical ensemble: closed systems

A system is called closed, when it does not exchange heat, work or particles with the environment. In this case, the total energy of the system is simply given by the kinetic energy T and potential energy V

$$E = T + V$$

Like for the harmonic oscillator, kinetic and potential energy are transformed into each other all the time keeping the total energy constant, i.e. the kinetic energy fluctuates. This is what we describe when using the plain Verlet method for a large molecule after specifying initial conditions. Looking into different regions of the molecule, the kinetic energy can be very different locally.

From kinetic gas-theory we know, that the kinetic energy can be related to temperature by:

$$\langle E_{kin} \rangle = \frac{3}{2}NkT$$

with $\langle E_{kin} \rangle = \frac{1}{2} \sum_{i} m_{i} \langle v_{i}^{2} \rangle$. So, if we would stick a thermometer into different regions (with N particles), we would measure different temperatures, fluctuating in time. This is not the situation we normally have, our systems are in **equilibrium**



FIG. 33: Closed systems

with the environment, i.e. they have the same temperature (or pressure) as the environment.

The canonical ensembles allows for the exchange of heat, work and particles (grandcanonical). If we keep the volume, temperature and particle number constant, we call the system a **NVT ensemble**. If we keep pressure, particle number and temperature constant, thereby allowing volume to change, it is call **NPT ensemble**.

B. The canonical NVT ensemble: open systems for heat exchange



FIG. 34: Exchange of heat in the canonical ensemble

In the **canonical ensemble** the **equilibration** with the environment leads to an exchange

of heat (work, particles) until the same temperature T as in the environment is reached. Temperature is strictly only defined through this equilibration process, and therefore not applicable to the closed systems as discussed above.

For a classical system in thermal equilibrium we know, that the velocity distribution is described by the **Maxwell distribution**(which we will derive later on):

$$p(v_{xj}) = \frac{m}{2\pi kT} exp\left(\frac{-mv_{xj}^2}{kT}\right) \tag{V.1}$$

With this we can derive the **equi-partition theorem** (Gleichverteilungssatz):

$$kT = m < v_{xj}^2 > \tag{V.2}$$

Since every atom j has three degrees of freedom (xj,yj,zj), we find

$$\frac{1}{2}\sum_{j}m < v_{xj}^2 > = < E_{kin} > = \frac{3}{2}NkT \tag{V.3}$$

The point is, that this special velocity distribution is a property of systems in contact with a heat reservoir, which is not the case for the micro-canonical ensemble.

We can use this formular to control temperature in our system in a very simple way. Algorithms, which allow to control temperature during the MD are called **thermostats**.

1. Scaling of velocities

We start the simulation using e.g. the Verlet algorithm, specifying some initial positions and velocities. Usually, we have initial position from the structure (PDB) and velocities can be **initializes** randomly (random number generator).

In the next step, we can calculate the temperature at time t using:

$$T(t) = \frac{2}{3} \frac{E_{kin}}{Nk}$$



FIG. 35: The Maxwell distribution (from PC1 script by KH Gericke)

This temperature will be different than the target temperature (of the heat bath) T_{target} , i.e. we have a difference between the desired and actual temperature in our system:

$$\Delta T = T_{target} - T = \tag{V.4}$$

$$\frac{1}{3}\sum \frac{m_i(\lambda v_i)^2}{Nk} - \frac{1}{3}\sum \frac{m_i v_i^2}{Nk}$$
(V.5)

Now, we have done two strange things: first, the kinetic energy is defined by the averages

$$\frac{1}{2}m < v^2 > = \frac{3}{2}kT,$$

which we simply dropped.

Second, we have the idea that we can introduce a simple scaling parameter λ , by which we increase or reduce the velocities v_i to get the target temperature.

Doing this, we find:

$$\Delta T = T_{target} - T = (\lambda^2 - 1)T,$$

therefore, we have to scale the velocities every step by:

$$\lambda = \sqrt{\frac{T_{target}}{T}} \tag{V.6}$$

This is a very crude way of controlling the temperature. From time to time, we knock the system by rescaling the velocities, we do not let the system evolve. This is quite drastic and can lead to artifacts. More importantly, the system does not represent a canonical ensemble, i.e. its **phase space density** ρ is not that of a canonical ensemble. For the velocity part, we make never sure that the velocity distribution follows the Maxwell distribution. And this is important, since we calculate all properties of interest as averages $(d\Gamma = drdp)$:

$$\langle A \rangle = \frac{1}{Z} \int \rho A d\Gamma.$$

Using the velocity scaling method, it could be that our system **samples** other parts of the phase space, thereby leading to wrong averages. The

2. Berendsen thermostat

does not yield a canonical distribution either, but avoids the severe cuts in the dynamics, by more smoothly adjusting the temperature and do not introduce such a temperature jump as by simple scaling.

We ask the temperature to change between two time steps $\delta t = t_{i+1} - t_i$ according to:

$$\frac{dT}{dt} = \frac{1}{\tau} (T_{target} - T),$$

i.e., we get:

$$\Delta T = \frac{\delta t}{\tau} (T_{target} - T).$$

We still scale the velocities as above,

$$\Delta T = T_{target} - T = (\lambda^2 - 1)T,$$

but get:

$$\lambda^2 = 1 + \frac{\delta t}{\tau} \left(\frac{T_{target}}{T} - 1 \right) \tag{V.7}$$

For $\delta t = \tau$ we get the simple velocity scaling, for larger values (≈ 0.4 ps) the system temperature fluctuates around the reference temperature.

$$\sigma_T = \langle T^2 \rangle - \langle T \rangle^2$$

and get for the relative variance:

$$\frac{\sigma_T}{< T >^2} = \frac{2}{3N} \tag{V.8}$$

For large N, the fluctuation vanishes but for finite systems, it fluctuates. So, if we keep the kinetic energy constant as with the rigorous velocity scaling, we would not have the fluctuations and would not sample the phase space of the canonical ensemble.

3. Andersen thermostat

The Andersen thermostat has a different working principle. From time to time, some particles are selected to undergo a 'collision' with a heat bath in a stochastic manner.

- Start the MD with the normal Verlet.
- Select randomly atoms, which shall undergo a collision.
- For these particles, new velocities are assigned according to the Maxwell distribution. All other particles are unaffected.

4. Nose thermostat

The Nose thermostat rigorously represent a canonical ensemble, therefore it is preferable to use. However, it is conceptionally and mathematically difficult to understand, however, here are the basic ideas.

The heat reservoir is treated as a part of the system and it is assigned one degree of freedom s. With this degree of freedom (coordinate) associated is a mass Q.

The kinetic energy is:

$$E_{kin}^r = \frac{1}{2}Q\ddot{s}$$

and the potential energy:

$$E_{pot}^r = (f+1)kTln(s)$$

f is the number of degrees of freedom in the system. Now, we add these two energy contributions to the Hamiltonian:

$$H = \frac{1}{2} \sum_{i} m_i v_i^2 + V + E_{kin}^r + E_{pot}^r, \qquad (V.9)$$

i.e. the Hamilton function now depends on the new variables also:

$$H = H(\overrightarrow{r}, \overrightarrow{p}, s, p_s) \tag{V.10}$$

Using the Hamilton formalism, we can derive equations of motion:

$$\dot{r_i} = v_i \tag{V.11}$$

$$\dot{p_i} = -\frac{\partial V}{\partial r_i} - \chi p_i \tag{V.12}$$

$$\dot{\chi} = \frac{1}{Q} \left(\frac{1}{2} \sum_{i} m_i v_2^2 - (f+1)kT \right)$$
(V.13)

We see, that there are extra forces χp_i , which are responsible for the equilibration. The term is proportional to the velocity, i.e. can be interpreted as a friction term. This term is calculated by solving the last equation for χ . The last term contains something like the difference of actual and desired temperature, coupled by Q. Q determines, how much the system interacts with the bath.

The Nose thermostat is used frequently and it can be shown, that the ensemble average taken with the Nose ensemble is identical to that of the canonical ensemble.

5. NPT ensembles

Similar to temperature, we can calculate the pressure from the trajectories. Then, there are equivalents of the Berendsen or Nose thermostat to maintain constant pressure. This means, the Volume is not constant but can expand or contract.

C. Exercises

1. Proof the equi-partition theorem eq. V.2 using the Maxwell distribution eq. V.1 as the phase-space density to calculate the ensemble average $\langle v_{xj}^2 \rangle_{ens}$ eq. IV.4. To do this, you have to solve the integrals

$$\int_0^\infty x^2 exp(-a^2x^2) dx$$

and

$$\int_0^\infty exp(-a^2x^2)dx,$$

which you find in the book of Bronstein.

VI. SOME BASICS OF STATISTICAL MECHANICS

In the last chapter, we have often used the notion, that a particular ensemble does not represent the canonical one. It means, that the phase space sampled by this ensemble is different from that of the canonical. But how does the **canonical probability distribu-tion function** look like? Lets first have a look into the micro-canonical ensemble.

Interestingly, Statistics is simpler for Quantum Mechanics (QM) than for Classical Mechanics (CM). The reason is, that in QM we can talk about discrete states, while in CM everything is continuous. In CM, we would have to select small volumes of phase space and calculate a density in this volume. In QM, we can use e.g. the discrete energy states of molecules or quantum oscillators as simple examples, as we will do in the following:

A. Micro states for a fixed energy

Consider a system of three particles having three energy quanta. These three energy quanta can be distributed as shown in figure 36. We find 10 **microstates** and three classes of systems, which we call configurations A, B and C:

Now we want to count, in how many ways we can distribute the energy quanta ϵ , i.e. how many micro states we have. In principle, we do it in the following way: One particle gets n quanta, then next m quanta, and the last l quanta of energy, where n+m+l=3.

- We start to pick a first particle and give it some energy. We have 3 choices, which one to choose.
- Having fixed the first particle, we have 2 choices which to pick next.
- Having fixed the second particle, we have 1 choice which to pick next.
- This makes $3^{*}2^{*}1=3!$ choices in total

Now, we can distribute the energy in (n,l,m) like: (3,0,0): configuration A



FIG. 36: Possible micro states, when three energy quanta are in the system.

(2,1,0): configuration B

(1,1,1): configuration C

But there are some degeneracies, e.g. for A we do not find 6 different microstates!

• Configuration B: We give particle 1 2 quanta, then particle 2 1 quantum. This is different from giving particle 1 2 quanta and particle 3 1 quantum, as can be seen in fig. 36.

Going on, we have $3^*2^*1 = 3!$ possibilities to distribute the quanta, i.e. we have 6 microstates.

• Configuration A: We give particle 1 3 quanta, then particle 2 0 quantum. This is the same as giving particle 1 3 quanta and particle 3 0 quantum, as can be seen in fig. 36.

We have 2 particles, which get the same energy quanta, i.e. 2 assignements are not distinguishable, lead to the same result. If we count both ways, we overestimate the number of microstates, i.e. we have to divide by 2*1 (2 times 1 assignement). Therefore we have:

$$\frac{3!}{2!} = 3$$

microstates.

• Configuration C: Again, we have three possibilities to start, but then, we three times 2^*1 equal states, i.e. we have $3^*2^*1 = 3!$ degenerate states, which makes:

$$\frac{3!}{3!} = 1.$$

Generally, if we have N particles, we have N ways to pick the first, (N-1) to pick the second, i.e. we have N! ways to build up the system. But then, we have n_a particles with the same energy quanta, i.e. we have to divide N! by n_a !. Generally, we find the number of microstates W for one conformation in a system with N particles:

$$W = \frac{N!}{(n_a!)(n_b!)....}$$
 (VI.1)

 n_a , n_b are the number of particles with the same energy quanta (or generally, with other properties!), which we also can call occupation numbers of the energy levels.

W is a large number, in these cases it is practical to take the logarithm.

$$lnW = ln\left(\frac{N!}{(n_a!)(n_b!)...}\right) = ln(N!) - ln(n_a!) - ln(n_b!)... = ln(N!) - \sum_i ln(n_i!)$$

using Stirlings approximation

$$ln(N!) = NlnN - N$$

we find:

$$lnW = Nln(N) - \sum_{i} n_{i}ln(n_{i})$$
(VI.2)

$$p_i = \frac{n_i}{N}$$

is the fraction of particles in state i, i.e. p_i is the probability, to find a particle in state i. We can also write:

$$lnW = \sum_{i} n_i ln(N) - \sum_{i} n_i ln(n_i) = -\sum_{i} n_i ln(\frac{n_i}{N}) = -N \sum_{i} p_i lnp_i$$
(VI.3)

Method of Lagrange multipliers:

We have the following problem:

We want to find the maximum of a function f(x) under the condition that certain constraints $y_k(x) = 0$ are applied. Then, we can search for the maximum by taking these constraints into account in the following way:

$$\frac{\partial}{\partial x} \left[f(x) - \sum_{k} \lambda_k y_k(x) \right] = 0$$

i.e., we set the derivative to zero after including the constraints.

No we want to apply this to the micro-canonical ensemble: Lets find the minimum of (we leave out the constant factor N in lnW!)

$$-\sum_i p_i ln p_i$$

under the normalization condition

$$\sum_{i} p_i = 1,$$

which we can formulate as:

$$\left(\sum_{i} p_i - 1\right) = 0$$

This is the constraint we have to include in the Lagrange method:

$$\frac{\partial}{\partial p_i} \left[-\sum_i p_i ln p_i - \lambda (\sum_i p_i - 1) \right] = 0, \qquad (\text{VI.4})$$

which leads to:

$$-ln(p_i) - 1 - \lambda = 0$$

This means, all p_i are equal, and to determine them we insert:

$$p_i = exp(-\lambda - 1).$$

into the constraint condition

$$\sum_{i} p_i = Nexp(-\lambda - 1) = 1,$$

which gives:

$$p_i = \frac{1}{N}$$

Therefore, in the micro-canonical ensemble all states have equal population, i.e. equal probability p_i !

Consider again the harmonic oscillator: having N copies of the system, we will find any position x with the same probability. A similar example is a particle in a box. We will find any position of this particle with the same probability. The energy constraint in the micro-canonical ensemble defines the accessible phase space. Within this phase space, every point has equal probability.

The distributions $p_i = \frac{1}{N}$ and 1,0,00 are the extreme cases. In the first case, lnW is the maximum

$$lnW = NlnN$$

and in the second case a minimum:

$$lnW = Nln1 = 0$$

We define the microscopic Entropy as:

$$S = -k_B \sum_{i} p_i ln p_i \tag{VI.5}$$

This property tells us something about the distribution in phase space. If it is small, only few states are occupied, if its large, all states are occupied.

Entropy can be related to the order in the system. If it is small, only a small part in phase space is accessible, and we consider the system to be ordered, while when it is large, the whole accessible phase space is covered. Think of the books on in your room. When they are all stapled on your desk, you consider this state as ordered, while when they are freely distributed over the whole room, you consider this disordered.

There is a second route to Entropy, via the so called Information Entropy. If entropy is minimal, we have perfect knowledge about a system, it is in state i since $p_i = 1$. When entropy has its maximum, we have no information at all, every possibility is equally probable. Think again about the books in your room: if S = 0, $p_1 = 1$ and you know, the particular book is on your desk. When $S = k \ln N$, you know the book is at one of the N possible places in your room! In this case, you have no idea where to look first!

The second law of Thermodynamics claims, that entropy increases in every irreversible process, i.e.

$$\frac{\partial}{\partial t}S \ge 0.$$

For a closed system, the microscopic entropy does not have this property. This can be most easily seen in a quantum mechanical example:

Consider particles in a box with a wavefunction Ψ , for which we solve the Schrödinger equation,

$$-i\hbar\dot{\Psi} = \hat{H}\Psi.$$

We can expand this in a set of eigenfunctions of the box, ϕ_i ,

$$\Psi = \sum_{i} c_i \phi_i,$$

to get:

$$-i\hbar\dot{\Psi} = \hat{H}\Psi = \sum_{i} c_{i}\hat{H}\phi_{i} = -i\hbar\sum_{i} c_{i}\dot{\phi}_{i}$$

We see the following:

$$p_i = |c_i|^2$$

is the probability, to find a particle in state ϕ_i , and this does not change during the dynamics, i.e.

$$\dot{p}_i = 0.$$

However, this leads to the entropy change of:

$$\frac{\partial}{\partial t}S = \dot{S} = k\frac{\partial}{\partial t}\left(-k_B\sum_i p_i lnp_i\right) = 0$$

Therefore, the microscopic equations do not lead to any change in entropy, which is in contradiction to the second law of Thermodynamics. And we can understand, that this has to be like that. Consider, we know the initial conditions of a system, i.e. we know the p_i . Then, since our equations of motion are perfectly deterministic, we know how every trajectory evolves, i.e. we know the p_i at every time! That means, the change in information entropy is zero!

In the example of your books on the desk. Initially, they are all on the desk. Since you know all the equations of motion of every book, you know exactly where every book is at any later time T. So, you have perfect knowledge of your system and the entropy change is zero!

B. Systems in equilibrium: The canonical distribution

For the micro-canonical ensemble, we optimized lnW, i.e. looked for the distribution of probabilities p_i , which give the largest number of states, which maximizes the entropy. In our example, W is the number of microstates for a certain distribution of particles over the energy states ϵ_i in the system (ϵ_1, ϵ_2 ... the energy states). We saw, that for the occupation numbers (2,1,0) in conformation B we got the largest number of states. This is the dominating distribution in that sense, that most of the micro states belong to it. Therefore, if we pick a micro state, it is most probable, that we pick a state belonging to the dominant distribution.

Therefore, if we want to know the distribution of p_i with the largest number of micro-states, we have to vary the n_i in order to maximize lnW. And this is the most probable distribution.

Now, we consider the system to be in contact with the environment. In addition to the normalization condition of the micro canonical ensemble, the average of the energy is to be kept fixed, i.e., we have to find the maximum of lnW with respect to the following conditions:

$$\sum_{i} p_i \epsilon_i = E, \qquad \sum_{i} p_i = 1.$$

Using the Lagrange Formalism, we get

$$\frac{\partial}{\partial p_i} \left[-\sum_i p_i ln p_i - \sigma(\sum_i p_i - 1) - \beta(\sum_i p_i \epsilon_i - E) \right] = 0, \qquad (\text{VI.6})$$

which leads to:

$$-ln(p_i) - 1 - \sigma - \beta \epsilon_i = 0$$

or,

$$p_i = exp(-1 - \sigma)exp(-\beta\epsilon_i).$$

Now, we use the constraint to determine the parameters:

$$1 = \sum_{i} p_{i} = \sum_{i} exp(-1 - \sigma)exp(-\beta\epsilon_{i})$$

leads to:

$$exp(-1 - \sigma) = \frac{1}{\sum_{i} exp(-\beta \epsilon_i)}$$

i.e.,

$$Z = exp(-1 - \sigma)$$

is a normalization factor.

Therefore, we find the famous **Boltzmann distribution** of p_i :

$$p_i = \frac{exp(-\beta\epsilon_i)}{\sum_i exp(-\beta\epsilon_i)}$$
(VI.7)

To derive what β means, we have to remember some basic Thermodynamics:

The Energy as a basic thermodynamic potential is dependent on the extensive variables Entropy, Volume and particle number, i.e.

$$E = E(S, V, N) = TS - pV - \mu N$$

Therefore,

$$\frac{\partial E}{\partial S} = T,$$

or, inverting this equation, we have

$$\frac{\partial S}{\partial E} = \frac{1}{T}.$$

Now, we can use the microscopic definition of S to calculate:

$$\frac{1}{T} = \frac{\partial S}{\partial E} = \frac{\partial S}{\partial \beta} \frac{\partial \beta}{\partial E} =$$
(VI.8)

$$\left(-k\sum_{i}\frac{\partial p_{i}}{\partial\beta}\left[-\beta\epsilon_{i}-lnZ+1\right]\right)\left(\sum_{i}\frac{\partial p_{i}}{\partial\beta}\epsilon_{i}\right)^{-1}=k\beta$$
(VI.9)

when using

$$\sum_{i} \frac{\partial p_i}{\partial \beta} = \frac{\partial}{\partial \beta} \sum_{i} p_i = \frac{\partial}{\partial \beta} 1 = 0$$

Therefore, we have:

$$\beta = \frac{1}{kT}$$

For continuous systems, the spacing between the energy levels becomes infinitesimally small and we can write

$$\rho(r,p) = \frac{1}{Z} exp(-E(r,p)/kT)$$
(VI.10)

with the partition function (Zustandsumme)

$$Z = \int exp(-E/kT)d\Gamma$$

C. Exercises

1. You have 20 (identical) cookies and 6 boxes (for your 6 friends, i.e. the boxes are different properties). How many possibilities to you have to distribute them as follows: $\{1,0,3,5,10,1\}$ (this is the distribution of cookies in the 6 boxes). Use equation VI.1.

2. Proof eq.VI.9.

3. Calculate the average energy of the classical harmonic oscillator using the Boltzmann distribution.

VII. SOME BASICS OF THERMODYNAMICS

A. Internal Energy U

In Thermodynamics, the total energy E of our system (as described by an empirical force field) is called internal energy U. U is a state function, which means, that the energy of a system depends only on the values of its parameters, e.g. T and V, and not on the path in the parameters space, which led to the actual state.

This is important in order to establish a relation to the **microscopic energy E** as given by the force field. Here, E is completely determined by the actual coordinates and velocities, which define the microscopic state $\{r_i, p_i\}$.

The first law of Thermodynamics states the conservation of energy,

$$U = const$$
 (VII.1)

and we have used this in the microcanonical ensemble, where the total energy is fixed.

In open systems, heat (Q) can be exchanged with the environment, and this situation is modeled in the canonical ensemble.

$$\Delta U = Q,$$

if the Volume V is constant. If the Volume is not fixed, work (W) can be exchanged with the environment,

$$dW = -Fdz = -pdV \tag{VII.2}$$

The first law therefore reads:

$$dU = dQ + dW = dQ - pdV$$
(VII.3)



FIG. 37: Exchange of heat and work with the environment

B. Entropy and Temperature

In Newtonian Mechanics, all processes are perfectly reversible, i.e. they can happen in forward and backward direction. An example is a stone falling down to earth. It could also go up, when someone has thrown it. This means, we can look at the 'movie' of this process and it would look right also when we would view it backwards in time.

However, in Thermodynamics there are many processes which would not 'look right' when being reversed although they obey the 1st law, two common examples can be found in Fig. 38.



FIG. 38: Irreversible processes: the reverse direction would NOT violate the 1st law!

This means, the first law is not enough to characterize thermodynamics processes, the second law is crucial:

$$\Delta S \ge 0$$

Microscopically, the second law results from the fact, that the most probable distribution dominates, i.e., the energy will be distributed over the possible states (in the example in the last chapter) in order to maximize the number of micro-states.

The entropy of a system depends therefore on the energy E and other parameters x_{α} , like Volume, particle number etc.,

$$S = S(E, V, \ldots) = k ln W(E, V, \ldots).$$

For a given system, the driving force therefore is not energy minimization (as in geometry optimization), since the energy is constant due to the first law, but the maximization of the entropy!

To introduce Temperature in the framework of Statistical Mechanics, two ways can be usually found:

The first way is to use the knowledge from Thermodynamics. From there, we know that

$$\frac{\partial S}{\partial E} = \frac{1}{T}.$$

This would motivate us, to define a microscopic quantity:

$$\beta = \frac{\partial lnW}{\partial E}$$

Since S=klnW, we see immediately, that $\beta^{-1} = kT$. Note, that in this way Thermodynamics is used to define quantities of Statistical Mechanics!

A different route is to examine the equilibration process. Consider systems A and A' in thermal contact as in Fig. 39. The equilibration will be driven by the maximization of entropy,

$$S = S_1 + S_2 = max.$$

Therefore, in equilibrium, the entropy change will be zero, i.e.

$$dS = dS_1 + dS_2 = 0$$

which is:

$$\frac{\partial S_1}{\partial U_1} dU_1 + \frac{\partial S_2}{\partial U_2} dU_2 = 0$$

which leads to $(dU_1 = -dU_2)$:

$$\frac{\partial S_1}{\partial U_1} = \frac{\partial S_2}{\partial U_2}$$

or:

 $\beta_1 = \beta_2.$

Therefore, equilibrium forces the equality for the β -parameters (and other properties not discussed here) leads to the identification of β with the Temperature T.



FIG. 39: Two systems A and A' exchanging a small amount of heat dQ

Consider our system A in contact with a heat bath A', exchanging an infinitesimal amount of heat dQ. The number of states in A' therefore changes by:

$$dlnW(E') = lnW(E' + dQ) - lnW(E') \approx \frac{\partial lnW}{\partial E} dQ = \beta dQ.$$
(VII.4)

Abbreviating:

$$\frac{\partial lnW}{\partial E} = \beta = \frac{1}{k} \frac{\partial S}{\partial E}$$

leads to the well know expression for the **reversible** entropy change:

$$dS = kdlnW(E) = \frac{\partial S}{\partial E}dQ = \frac{dQ}{T}$$
(VII.5)

- We can understand this formular microscopically e.g. for our example in the last chapter: by heating, we e.g. introduce one more energy quantum into the system, now having four energy quanta. It is obvious, that the number of possible microstates increases, i.e. the entropy increases. And it increases, depending on how much energy (Temperature) is already in the system. So, the increase will be smaller when going from 1000 to 1001 energy quanta than going from 3 to 4!
- Using the first law, we can rewrite the internal energy as:

$$dU = dQ = TdS$$

Therefore, we changed the dependence of the internal energy from U(T) to U(S).

Including volume change, we can write:

$$dQ = TdS = dU - dW \tag{VII.6}$$

C. Reversible and irreversible processes

Consider two examples as shown in Fig. 40. Heating a system by keeping the volume constant changes the distribution, i.e. the entropy is changed:

$$dU = dQ = TdS$$

or

$$dS = \frac{dQ}{T}.$$

When moving the piston infinitesimally slow, the distribution function will remain the same and only the spacing between the states will change, therefore, no heat will be transferred and dS=0.



FIG. 40: Heating a system changes the distribution, thereby changing entropy. Reversible work only changes the states, not the occupation.

Both **reversible** processes are infinitesimally slow. If we move the piston very fast, we will get changes of the occupation and thereby a **non-reversible** entropy change. This entropy change can not be reversed, without changing the environment in a way, that the total entropy is increased.

Therefore, we have the reversible entropy change of $dS_{rev} = \frac{dQ}{T}$ and an irreversible part. The second law states, that the entropy production is positive, i.e. we can write:

$$dS - \frac{dQ}{T} \ge 0.$$

dS is the total entropy-change and dQ/T is the reversible part. If we have dV=0, we can write:

$$TdS - dU \ge 0.$$

This is the condition, that a process happens spontaneously. I.e., processes will happen in a way, that the property TS-U becomes a maximum, or, vice versa,

$$U - TS = min.$$

I.e., nature minimizes the value of U-TS in its processes.

We could interpret this as follows:

Nature allows processes, which minimize the internal energy U of a system and its entropy S simultaneously. However, this is not completely right!

We always have to consider the system and its environment. If U of the system changes, energy is transferred to the environment, according to the first law the total energy is unchanged! Therefore, minimization of the system energy U is **no driving force** in nature. Energy minimization has NO meaning!

Since the total energy is conserved, the only driving force is the second law, the entropy will be maximized.

$$dS = dS_1 + dS_2 \ge 0$$

(1 is the system, 2 the environment) The entropy change of the environment, dS_2 is given by the heat exchanged,

$$dS_2 = \frac{dQ}{T} = -\frac{dU_1}{T}$$

 $(U_1 \text{ is the change of internal energy of the system})$. Therefore,

$$-\frac{dU_1}{T} + dS_1 \ge 0$$

combines the 1st and 2nd law to derive the driving force for the system 1 (remember, that we have V=const. in the whole discussion!).

The driving force for complex processes is the maximization of the entropy of the total system. Since we can not handle the whole universe in all our calculations, we found a way to concentrate on our subsystem by looking at U-TS. This is called the Helmholz free energy:

$$F = U - TS \tag{VII.7}$$

This is the fundamental property we are intersted in, because:

- F=F(T,V): F depends on the variables T and V, which are experimentally controllable, while U=U(S,V) depends on S and V. We do not know, how to control entropy in experiments. In particular, F is the energetic property which is measured when T and V are constant, a situation we often model in our simulations.
- $\Delta F = F_f F_i = W_{max}$ is the maximum amount of work a system can release between an initial (i) and final (f) state. In the first law dU = dQ + dW, we can substitute dQ

by TdS, since the latter is always large due to second law $TdS \geq dQ$ to get:

$$dU \le TdS + dW,$$

or:

$$dW \ge dU - TdS = dF$$

Therefore, the maximal work is always greater or equal the free energy. In other words, a certain amount of internal energy dU can **never** be converted completely into work, a part is always lost due to entropy production.

• If the system is in contact to environment, there is no more a minimum (internal) energy principle available. In principle, energy minimization as we have discussed before, does not make any sense, neither for the subsystem, not for the whole. Energy is simply conserved and we have a micro-canonical ensemble, however, including the whole universe. The free energy however, restores a minimization procedure again: Systems will evolve in order to minimize the free energy. This, however, is nothing else than entropy maximization of the whole system.

The latter point is in particular important if we want to study chemical reactions and energy profiles along reaction coordinates. We are used to look to minima of total (internal) energies, as e.g. drawn in Fig. 43. The minima of the total/internal energy, however, may have no more meaning, while the minima of the free energy have!

Question: why do we still use energy minimized structures in many cases? (Exercises!)


FIG. 41: Minima and transition states along a reaction coordinate for the free energy F and the internal energy U

D. State functions and relation of Statistical Mechanics to Thermodynamics

Complete differential

Consider an infinitesimal change of a function F(x,y),

$$dF = F(x + dx, y + dy) = \frac{\partial F}{\partial x}dx + \frac{\partial F}{\partial y}dy = Adx + Bdy$$

Integrating F between two points

$$\Delta F = F_f - F_i = \int_i^f dF = \int_i^f (Adx + Bdy)$$

leads to a value ΔF , which is not dependent on the integration pathway. In this case, we call F (in Thermodynamics) a state function. F is also called an complete differential (vollständiges Differential). A function F is a state function, when it is a complete differential, which mathematically means

$$\frac{\partial^2 F}{\partial x \partial y} = \frac{\partial^2 F}{\partial y \partial x} \to \frac{\partial B}{\partial x} = \frac{\partial A}{\partial y}$$

U(S,V) is a state function, it depends only on the values of the parameters, not on the path the state has been reached. Microscopically, U depends on the set of coordinates and velocities, which also only depend on the actual state and not on history.

 $S(E,V) = k \ln W(E,V)$ also is a state function, while the work and heat exchanged along a certain path are not.

Internal energy U

Using the expression for the reversible entropy, we can rewrite the internal energy:

$$dQ = TdS = dU + pdV,$$

or:

$$dU = TdS - pdV.$$

Now, U depends on the variables S and V,

$$U = U(S, V)$$

First derivatives:

$$dU = \frac{\partial U}{\partial S} dS + \frac{\partial U}{\partial V} dV,$$
$$T = \frac{\partial U}{\partial S} \qquad p = -\frac{\partial U}{\partial V}$$

Second derivatives (Maxwell relations):

$$\frac{\partial p}{\partial S} = \frac{\partial T}{\partial V}$$

Enthalpy H

Consider a function H = U + pV, using d(pV) = pdV + Vdp:

$$d(U+pV) = dU + pdV + Vdp = TdS + Vdp$$

This means, H depends on the variables p and S. First derivatives:

$$dH = \frac{\partial H}{\partial S} dS + \frac{\partial H}{\partial p} dp,$$
$$T = \frac{\partial H}{\partial S} \qquad V = \frac{\partial H}{\partial p}$$

Second derivatives (Maxwell relations):

$$\frac{\partial V}{\partial S} = \frac{\partial T}{\partial p}$$

The variables of the Thermodynamic Potentials connect to the experimental conditions. Since it is experimentally difficult to control the entropy, while it is easy to control temperature, volume or pressure, it is convenient to introduce further potentials.

Free energy F

$$F = U - TS, d(TS) = TdS + SdT,$$

 $dF = d(U - TS) = dU - TdS - SdT = TdS - pdV - TdS - SdT = -pdV - SdT$
 $F = F(V,T),$ first derivatives:

$$dF = \frac{\partial F}{\partial T}dT + \frac{\partial F}{\partial V}dV,$$
$$-S = \frac{\partial F}{\partial T} \qquad -p = \frac{\partial F}{\partial V}$$

Second derivatives (Maxwell relations):

$$\frac{\partial S}{\partial V} = \frac{\partial p}{\partial T}$$

This is the property we simulate in a canonical ensemble, keeping temperature and V constant.

E. Equilibrium

We are interested in the equilibrium of a system, i.e. the state the system approaches after some time (equilibration). Lets look into the change of the thermodynamic potentials U, H and F:

$$dU = dQ - pdV$$
$$dH = dQ + VdP$$
$$dF = dQ - TdS - SdT - pdV$$

Using

$$dS \ge \frac{dQ}{T}$$

we find:

$$dU \le TdS - pdV$$
$$dH \le TdS + VdP$$
$$dF \le -SdT - pdV$$

The change of the potential in a process is always smaller than the right hand side. In particuar, if we fix parameters in an experimental situation, the change is always smaller than zero, and the energy runs into a minimum, which is defined by thermal equilibrium.

$$dU \le 0$$
, for $S = const, V = const$

Therefore, we could search for the Minimum of the internal energy, if we would keep the entropy and Volume constant. But how to do that?

$$dH \le 0$$
, for $S = const, p = const$
 $dF \le 0$, for $T = const, V = const$

As discussed above, this is easy to realize, therefore, we look for the minima of the free energy.

F. Relation to the partition function

Consider the canonical distribution $(\beta^{-1} = kT)$:

$$p_i = \frac{1}{Z} exp(-\beta E_i)$$

The expectation value of the energy is:

$$\langle E \rangle = \frac{1}{Z} \sum_{i} E_i exp(-\beta E_i)$$

A nice mathematical trick is:

$$-\frac{\partial}{\partial\beta}Z = -\sum_{i}\frac{\partial}{\partial\beta}exp(-\beta E_{i}) = \sum_{i}E_{i}exp(-\beta E_{i}).$$

Therefore,

$$\langle E \rangle = -\frac{1}{Z} \frac{\partial}{\partial \beta} Z = -\frac{\partial lnZ}{\partial \beta}$$
 (VII.8)

To relate the free energy to Z, the easiest way is to use the thermodynamic relation:

$$F = U - TS.$$

Multiplying with β ,

$$\beta F = \beta U - S/k$$

Taking the derivative

$$\frac{\partial(\beta F)}{\partial\beta} = U = \langle E \rangle$$

and comparing with eq. VII.8 gives the expression for the free energy:

$$F = -kT lnZ \tag{VII.9}$$

and for the entropy S = -F/T - U/T:

$$S = k l n Z + k \beta < E > \tag{VII.10}$$

This is a remarkable result, since the only thing we have to do in our simulations it to get the partition function Z, i.e. we have to get the phase space distribution ρ , i.e. the density of points in phase space from the simulation and then integrate it over phase space to get Z. Everything follows from there.

G. Exercises

1. Consider the Thermodynamic Potential G(p, V). Derive it using a coordinate transformation and write down the corresponding Maxwell relations.

2. Why do we still use energy minimized structures in many cases?

3. Calculate the energy of a **quantum** harmonic oscillator at temperature T using eq. VII.8,

 $E_n = (n + 0.5)\hbar\omega$. Determine Z first by using the formula for the geometrical series.

VIII. THERMODYNAMIC PROPERTIES OF MOLECULES

Now, we want to apply the formalism to calculate enthalpies and free energies of molecules. The main trick we learned is, that we only have to calculate the partition function Z, since from there we get all thermodynamic potentials:

$$\begin{split} U = < E > = -\frac{\partial lnZ}{\partial\beta} \\ H = U + pV \\ S = klnZ + k\beta U \\ F = -kTlnZ \\ G = F + pV \end{split}$$
 Therefore, the computational problem is to determine Z.

Discrete Systems

In the Chapter about Statistical Physics, we have considered a **discrete** system, i.e. a quantum mechanical system with discrete energy levels. For that, we found:

$$Z = \sum_{i} exp(-\beta E_i)$$

and the (discrete) distribution function

$$p_i = \frac{1}{Z} exp(-\beta E_i)$$

which is the probability, to find the system in state i with energy E_i . One prominent example is the harmonic oscillator with energy states:

$$E_i = (i + \frac{1}{2})\hbar\omega$$

Continuous Systems

On the other hand, we disussed the dynamics of molecules, where temperature allows to sample a certain part of the protein conformations. That means, that at a certain temperature only certain values of the coordinates (x_i) and, due to the Maxwell distribution,



FIG. 42: States of the quantum harmonic oscillator. The thermal distribution of the energy over the vibrational states leads to the number of micro states and a value for the entropy/free energy. $exp(-\beta E_i)/Z$ is the propability, to find the oscillator in state i with energy E_i



FIG. 43: Complex energy landscape E(x,p). Note, that the p-axis is not shown. For p=0, the system is on the potential energy surface (black line), for $p \neq 0$, different trajectories (phase space volumes) are accessible indicated by the blue and red curves.

also only certain values of the impulses (p_i) are reached, i.e. only a **part of phase space** is sampled. The phase space density $\rho(\vec{x}, \vec{p})$ gives the probability to find a system at positions \vec{x} and impulses \vec{p} . Now, since we force the dynamics to obey the canonical distribution, we know the following:

- Due to the force field we use, every point in phase space has an energy depending on the coordinate x, V(x), coming from the force field and a kinetic energy related to p. Therefore, every point (x,p) in phase space has a certain energy.
- From the canonical distribution we know, that the probability to find the system in a

state with the energy E is:

$$p(x,p) = \rho(x,p) = \frac{1}{Z} exp[-E(x,p)/kT]$$

• To get the partition function Z, we no have to substitute the summation in the discrete case by the integral

$$Z = \int exp[-E(x,p)/kT] dxdp$$

over the whole phase space.

The canonical distribution function gives the probability to find a system at phase space point (x,p). Therefore, typically the system will be only sampling part of the phase space, as schematically shown in Fig. 44. When we start a MD, we only know the form of the



FIG. 44: Part of the phase space, sampled during the dynamics: Example of classical harmonic oscillator.

potential (Force Field) and kinetic energy. The central aim of the MD is therefore, to determine the phase space density! From this, we get via integration the partition function and from that the thermodynamic potentials U,F etc. However, from Z we only get the thermodynamic potentials, if the phase space density is equal to the canonical ensemble, otherwise, all derivations in the last chapter would not be valid! Therefore, we have the following agenda:

• Perform a MD to get a trajectory in phase space. The conditions have to be in that way, that we simulate the canonical ensemble, i.e. we have to choose the right thermostat! Only then, the distribution in phase space would be the same as that given by the canonical ensemble.

• Now we can use the 'Ergodentheorem: The time series we get can be used as the distribution of systems to calculate ensemble averages.

In Quantum chemistry, we commonly use both, the discrete and continuous situation, to compute thermal corrections to the total energy E in order to get U, H, S or F. Here we consider the two situations as follows:

- If we have simple molecules, like e.g. benzene, which has only one local minimum, we can use the harmonic oscillator approximation. The energy is given by the ground state energy of the molecule plus the translation, rotational and vibrational contributions to the energy. From the vibrational Hamiltonian we compute the Boltzmann distribution, from that the partition function and from that the thermodynamic potentials.
- For molecules where at T ≥ 0 a multitude of local minima can be reached, the single minimum does not make sense any more. Here, we perform MD simulations to get the phase space density, from that the partition function and from that the thermodynamic potentials.

A. Vibrational contribution to the free energy

Consider a simple molecule with one or only a small number of well characterizable minima. For one of the minima, we can calculate the electronic energy (here: the force field energy), the translational, rotational and vibrational energy, i.e. we have:

$$E = E_{el} + E_{trans} + E_{rot} + E_{vib}$$

The partition function:

$$Z = exp \left[-\beta (E_{el} + E_{trans} + E_{rot} + E_{vib}) \right] =$$
$$exp \left[-\beta E_{el} \right] exp \left[-\beta E_{trans} \right] exp \left[-\beta E_{rot} \right] exp \left[-\beta E_{vib} \right] = Z_{el} Z_{trans} Z_{rot} Z_{vib}$$

Since we often need lnZ, we have:

$$lnZ = lnZ_{el} + lnZ_{trans} + lnZ_{rot} + lnZ_{vit}$$

1. Electronic Energy

For example, the contribution of E_{el} to the internal energy is:

$$U_{el} = -\frac{\partial ln Z_{el}}{\partial \beta} = -\frac{\partial (-\beta E_{el})}{\partial \beta} = E_{el}$$

2. Translational and rotational contribution

These contributions will not discussed in detail: They are calculated from the quantum mechanical particle in a box and from the quantum mechanical rotator. For one mole of particles, one gets:

$$U_{trans} = \frac{3}{2}RT$$

and

$$U_{rot} = \frac{3}{2}RT$$

For both motions, also entropic contributions can be calculated. With those, we can estimate free energies.

3. Vibrational contribution

To get this contribution, we have to optimize the geometry of a molecule and calculate its vibrational frequencies ω_k . Each normal mode represents one vibrating mode, i.e. one harmonic oscillator k (e.g. water has three modes, k=1..3). Every harmonic oscillator has the energies:

$$E_k^m = (m + 0.5)\hbar\omega_k$$

 $E_k^0 = 0.5\hbar\omega_k$ is called the zero point vibrational energy. Lets calculate the partition function of one harmonic oscillator:

$$Z_k = exp\left(\sum_{m=0}^{\infty} -\beta(m+0.5)\hbar\omega_k\right) = e^{-0.5\beta\hbar\omega_k}\sum_{m=0}^{\infty} e^{-\beta m\hbar\omega_k} = \frac{e^{-0.5\beta\hbar\omega_k}}{1-e^{-\beta\hbar\omega_k}}.$$

In the last step, we used the formula form the geometric series $\left(\sum_{k=0}^{\infty} x^k = \frac{1}{1-x}\right)$.

$$lnZ_k = -0.5\beta\hbar\omega_k - ln(1 - e^{-\beta\hbar\omega_k})$$
$$U_k = -\frac{\partial lnZ_k}{\partial\beta} = 0.5\hbar\omega_k - \left(\frac{\hbar\omega_k e^{-\beta\hbar\omega_k}}{1 - e^{-\beta\hbar\omega_k}}\right) = \hbar\omega_k \left(\frac{1}{2} + \frac{1}{e^{\beta\hbar\omega_k} - 1}\right)$$

Now, we have to do this for the N-6 degrees of freedom of the molecule, i.e. each molecule consists of N-6 harmonic oscillators. We then get for the internal energy

$$U = \sum_{k=1}^{N-6} U_k = \sum_{k=1}^{N-6} \hbar \omega_k \left(\frac{1}{2} + \frac{1}{e^{\beta \hbar \omega_k} - 1} \right)$$

The zero point vibrational energy contributions are not temperature dependent, and they are usually added to the electronic part of the energy (see above), that the vibrational part of the internal energy is defined as:

$$U_{vib} = \sum_{k=1}^{N-6} \left(\frac{\hbar \omega_k}{e^{\beta \hbar \omega_k} - 1} \right)$$

and for the corresponding entropy contribution we find:

$$S_{vib} = k ln Z_k + k\beta U_{vib} = \sum_{k=1}^{N-6} \left[\frac{\hbar\omega_k}{e^{\beta\hbar\omega_k} - 1} - ln(1 - e^{-\beta\hbar\omega_k}) \right]$$

Free energy (also excluding zero point energies):

$$F = -kTlnZ = \sum_{k=1}^{N-6} kTln(1 - e^{-\beta\hbar\omega_k})$$
4. pV-Term

To get the enthalpy, we have to add the pV term to the internal energy. This term would be difficult to estimate, however, we can get it via the ideal gas:

$$pV = nRT.$$

Therefore, the enthalpy is:

$$H = U + pV = U + nRT.$$

Similarly, when considering the free energy, we get:

$$G = F + nRT.$$

Many quantum chemistry (e.g. Gaussian) and force field (Charmm) programs calculate the thermal contributions by default, when a vibrational analysis is requested, since to get the vibrational energies is the main work to do so.

B. Free energy simulations

For a molecule with many conformations, we have to get the phase space density with MD simulations $(\overrightarrow{x} = (x_1...x_{3N}), \overrightarrow{x} = (p_1...p_{3N}))$:

$$\rho(\overrightarrow{x}, \overrightarrow{p}) = \frac{e^{-\beta E(\overrightarrow{x}, \overrightarrow{p})}}{Z}$$

which is the (canonical) probability to find the system at the point $(\overrightarrow{x}, \overrightarrow{p})$.

The central point now is, how long we can perform a MD simulation. If we perform 1 pico-second, we will have 1 thousand points in the trajectory, if we perform a nano-second, we have a million points etc., where a nano second is close to the limit what we can do!

Imagine we simulate for one ps: Then, we will barely have points (\vec{x}, \vec{p}) sampled, for which

$$\rho(\overrightarrow{x}, \overrightarrow{p}) \le \frac{1}{1000}$$

i.e. all points with high energy will not be reached, while the low energy region is sampled very well! We get the problem, when we calculate the averages:





$$U = < E > = \sum_{i=1}^{M} E(\overrightarrow{x}, \overrightarrow{p}) \rho(\overrightarrow{x}, \overrightarrow{p})$$

 $\rho(\vec{x}, \vec{p})$ tells us the relative frequency of point (\vec{x}, \vec{p}) , i.e., how often this point has been reached during the MD. Now, if we sample not long enough, ρ will be zero for large energies

 $E(\vec{x}, \vec{p})$, i.e., we will miss these large energies in the average; one could think, that since we miss large values, the average will be systematically wrong. However, for the internal energy this is not a very serious problem, since for large energies we have for the canonical ensemble:

$$\rho(\overrightarrow{x}, \overrightarrow{p}) = \frac{e^{-\beta E(\overrightarrow{x}, \overrightarrow{p})}}{Z}$$

i.e., for large energies the phase space density is small, so that we have to some degree an error compensation.

For the free energy, however, the situation is much worse, since we can write $(d\Gamma = d\vec{x} d\vec{p}, E = E(\vec{x}, \vec{p}))$:

$$F = -kT lnZ = kT ln \frac{1}{Z} = kT ln \left[\frac{\int \int e^{\beta E} e^{-\beta E} d\mathbf{\Gamma}}{\int \int e^{-\beta E} d\mathbf{\Gamma}} \right] =$$
(VIII.1)

$$kTln\left[\int\int e^{\beta E}\rho(\overrightarrow{x},\overrightarrow{p})d\mathbf{\Gamma}\right]$$
(VIII.2)

Now, we have a real problem, since the large values of the energy enter exponentially in the calculation of the free energy, i.e. large energies contribute significantly: So, if we have too few points at high energy points, we will find large errors in the calculated averages. Therefore, we really need a good idea.

IX. FREE ENERGY METHODS

There are several computational tricks in order to overcome the problems discussed so far, which we will discuss briefly. These are thermodynamic perturbation theory, thermodynamic integration and umbrella sampling.

A. Thermodynamic perturbation theory (TPT)

Lets consider any reaction or conformational transition between two states A and B (two conformers, reactant and product etc.), which have energies E_A and E_B , and partition functions Z_A and Z_B . We want to calculate the free energy change ΔF between these states as:

$$\Delta F = F_B - F_A = -kT ln \frac{Z_B}{Z_A}$$
(IX.1)
$$= -kT ln \left(\frac{\int \int e^{-\beta E_B} d\Gamma}{\int \int e^{-\beta E_A} d\Gamma} \right)$$
$$= -kT ln \left(\frac{\int \int e^{-\beta E_B} e^{\beta E_A} e^{-\beta E_A} d\Gamma}{\int \int e^{-\beta E_B} e^{\beta E_A} \rho_A(\overrightarrow{x}, \overrightarrow{p}) d\Gamma} \right)$$
$$= -kT ln \left(\int \int e^{-\beta (E_B - E_A)} \rho_A(\overrightarrow{x}, \overrightarrow{p}) d\Gamma \right)$$

The integral has the form of an average of a property S taken with the phase space density of state A,

$$\langle S \rangle_A := \int \int S \rho_A(\overrightarrow{x}, \overrightarrow{p}) d\Gamma,$$

we therefore can write:

$$\Delta F = -kT \ln \langle e^{-\beta(E_B - E_A)} \rangle_A . \tag{IX.2}$$

In the same way, we can write:

$$\Delta F = -kT \ln \langle e^{-\beta(E_A - E_B)} \rangle_B . \tag{IX.3}$$

Therefore, we can in principle run the dynamics in the state A and calculate the average of the exponential of the difference of energies of state B and A (or vice versa). Practically, we start a MD in state A to get the phase space density ρ_A , and then calculate the difference between the energies of states A and B for the relevant points in phase space.

- You want to get the free energy of protonation of an amino acid side chain in a protein. Then, run the dynamics for the un-protonated species to get ρ, and then calculate the energy difference between protonated and un-protonated species in order to get the average of the exponential. Practically, e.g. you run 1ns MD, take out 10.000 points along this MD and do the energy computation. Clearly, the advantage is that you only have to run one MD instead of two (for A and B). However, this will only work if the conformations of the protein sampled along the MD are very similar for protonated and unprotonated form.
- You can do something similar if you want to study the ionization of a molecule. Again, important is that the conformations sampled are similar.
- Same story for a chemical reaction.
- Consider the case, you want to study a conformational transition, e.g. between the C_5 and C_7 conformer of alanine. You would run a MD for the C_5 conformation. But to get the energy of the C_7 along the C_5 trajectory, it is not clear how to do that. You would somehow have to change the conformation for every point, but again, this is not easy to do.

For the last case, one could think of running two MDs for the two conformers, calculating the free energies of both states individually and then taking the difference.

$$\Delta F = -kT \ln \langle e^{-\beta E_B} \rangle_B + kT \ln \langle e^{-\beta E_A} \rangle_A$$

But remember, that the energy difference is very small, a few kcal/mole but the total energies are very large, sometimes hundreds or thousands of kcal/mole (if we include all the surrounding water). This means, we have to subtract two large numbers in order to get a small one. However, a small error in a large number is still large. So, we have to get these large numbers very accurate, which means again, we have to do very long MD simulations, which we often can not afford! That is why we try to avoid two individual MDs for the two end states and have to try do it in one MD. Then, we have the same **sampling error** in the calculation of both averages, which tend to cancel!

For the following, the concept of overlap in phase space or overlap of the phase space densities is important. This means, the conformations sampled in the MD have to be very similar, i.e. the phase space densities have an overlap, as schematically shown in Fig. 46. Mathematically this means, that the phase space density of state A does not lead to a



FIG. 46: Overlap of phase space densities.

good average of the energy of state B, and vice versa. As a rule of thumb, this is the case if:

$$|E_B - E_A| \ge kT$$

If we insert an intermediate state called 1 which 'overlaps with A and B', we can try to





FIG. 47: Intermediate state overlapping with state A and B

$$\Delta F = F_B - F_1 + F_1 - F_A = -kT ln \left(\frac{Z_B}{Z_1} \frac{Z_1}{Z_A}\right)$$

$$= -kT ln < e^{-\beta(E_B - E_1)} >_1 - kT ln < e^{-\beta(E_1 - E_A)} >_A$$
(IX.4)

Now, we have to perform two MD simulations for the states 1 and A and calculate the averages. If the difference of A and B is 'large' we can insert N intermediates,

$$\Delta F = -kT ln \left(\frac{Z_B}{Z_1} \frac{Z_1}{Z_2} \dots \frac{Z_N}{Z_A} \right)$$

and then we have to perform N+1 MD simulations.

This sounds complicated, but it is implemented in standard force field programs in a convenient way. Practically, there are several ways to perform this, typically one introduces a parameter λ which 'converts' the force field total energy from state A to B:

$$E_{\lambda} = (1 - \lambda)E_B + \lambda E_A$$

Since we can change the chemistry in this way, this procedure is often called **computa-tional alchemy**.

Examples:

• Calculate the relative free energy of Ar vs. Xe in water solution. The two atoms differ only in the VdW parameters. The VdW parameters are the well depth ϵ and VdW radius σ . If we want to 'convert' the energy function from one species to another, we can do that in this way:

$$\epsilon_{\lambda} = (1 - \lambda)\epsilon_B + \lambda\epsilon_A$$

and

$$\sigma_{\lambda} = (1 - \lambda)\sigma_B + \lambda\sigma_A.$$

In the simulation, we start from $\lambda = 0$ and change it in small steps from 0 to 1. For each step, we make a MD with the actual values of the VdW parameters and calculate the relative free energies:

$$\Delta F(\lambda_i \to \lambda_{i+1}) = -kT \ln \langle e^{-\beta(E_i - E_{i+1})} \rangle_{i+1}$$

• If we want to interchange e.g HCN in CNH, the situation is a little more complicated, since the two molecules have a different **topology**, i.e. we need different topology files! To overcome this, we make so called **dual topology** simulations: we have both molecules simultaneously in the simulation. But the two molecules do not interact with each other and during the simulation we slowly switch off the interaction of one species with the solvent, while in the same time we switch on the other.

B. Thermodynamic integration (TI)

In the last chapter, we have written the energy E as a function of the parameter λ . This means, that the free energy also becomes dependent on λ :

$$F = F(\lambda)$$

with $F(0) = F_A$ and $F(1) = F_B$. We therefore can write:

$$\Delta F = F_B - F_A = \int_0^1 \frac{\partial F(\lambda)}{\partial \lambda} d\lambda$$

with

$$F(\lambda) = -kT ln Z(\lambda).$$

This leads to:

$$\Delta F = -kT \int_0^1 \frac{\partial \ln Z(\lambda)}{\partial \lambda} d\lambda = -\int_0^1 \frac{kT}{Z_\lambda} \frac{\partial Z_\lambda}{\partial \lambda} d\lambda$$

Since

$$\frac{\partial Z_{\lambda}}{\partial \lambda} = -\int \int \beta \frac{\partial E_{\lambda}}{\partial \lambda} e^{-\beta E_{\lambda}} d\mathbf{\Gamma}$$

we get:

$$\frac{\partial F}{\partial \lambda} = \int \int \frac{\partial E_{\lambda}}{\partial \lambda} \rho_{\lambda}(\overrightarrow{x}, \overrightarrow{p}) d\mathbf{\Gamma} = <\frac{\partial E_{\lambda}}{\partial \lambda} >_{\lambda}$$

The free energy difference is:

$$\Delta F = \int_0^1 < \frac{\partial E_\lambda}{\partial \lambda} >_\lambda d\lambda$$

Since we usually take discrete values of λ , λ_i , the integral becomes a sum:

$$\Delta F = \sum_{i} < \frac{\partial E_{\lambda}}{\partial \lambda} >_{\lambda_{i}} \Delta \lambda_{i}.$$

In the thermodynamic integration method, we therefore have to take the derivative of the energy with respect to the parameter λ and have to run MD for every value of λ_i , in order to average the energy derivative.

C. Thermodynamic cycles

Consider as an example the binding of a ligand molecule A to a protein B as shown in Fig. 48. Usually, we are interested in differences of binding free energies (enthalpies) of two



FIG. 48: Binding of a ligand at a receptor site

molecules A and A':

$$A + B \leftrightarrows AB \qquad \Delta G_1$$

$$A' + B \leftrightarrows A'B \qquad \Delta G_2$$

The binding of the molecule can induce large structural changes in the protein, which are very difficult to sample efficiently. This means, we may have large errors. Therefore, if we perform two individual calculations for A and A', we subtract to large numbers with significant error, which may lead to errors larger than the effective binding energy. Therefore, we try to calculate the energy difference in a way, that we get error compensation: Consider the thermodynamic cycle as shown in fig. 49. At the end of the day, we want a difference

$$\begin{array}{cccc}
 & A6_{n} \\
 & H+B \stackrel{>}{\Rightarrow} & HB \\
 & A6_{3} & 11 \\
 & H'+B \stackrel{>}{\Rightarrow} & H'B \\
 & A6_{2} \\
 \end{array}$$

FIG. 49: Binding of a ligand at a receptor site

in binding, i.e. a

$$\Delta \Delta G = \Delta G_1 - \Delta G_2 = \Delta G_4 - \Delta G_3.$$

Now, the ΔG_4 and ΔG_3 are much more easy to calculate, e.g. using TPT or TI.

Another typical example would be the difference in solvation energy of two different molecules.

D. Potential of mean force (PMF): Umbrella sampling

Umbrella sampling is the method of choice, if we want to have the change of free energy along a certain reaction coordinate q for the transition between state A and B. The reaction coordinate can be the distance between to atoms, the position of a proton when moving between donor and acceptor or something more complicated.

Now, we make a coordinate transformation from $\overrightarrow{x} = (x_1...x_{3N})$ to a set $(u_1...u_{3N-1}, q)$: q

is the degree of freedom represented by the reaction coordinate, and \overrightarrow{u} the remainder, that we can write:

$$d\overrightarrow{x} = d\overrightarrow{u}dq$$

When we look for the free energy for a certain value of q, we average over all remaining degrees of freedom, i.e. we perform and MD and sample all degrees of freedom except for q. An example would be the free energy for the formation of an ion pair in solution, as shown in Fig. 50. For every value of q, a MD is performed to calculate the free energy for that value of the reaction coordinate.



FIG. 50: Na^+ and Cl^- in water solution: the distance between the ions is the reaction coordinate q, all other degrees of freedom (water), which are represented by u, are allowed to vary.

The free energy is given by:

$$F = -kT ln \int \int e^{-\beta E(\overrightarrow{x}, \overrightarrow{p})} d\mathbf{\Gamma}.$$

If we want to have one coordinate fixed at a certain value, e.g. q_0 , it is convenient to use the delta function:

$$\delta(q-q_0).$$

With that, we can write the free energy for the fixed reaction coordinate:

$$F(q_0) = -kTln \int \int \delta(q - q_0) e^{-\beta E(\overrightarrow{x}, \overrightarrow{p})} d\overrightarrow{p} d\overrightarrow{u} dq \qquad (IX.5)$$

$$= -kTln \left(Z \int \int \delta(q - q_0) \frac{e^{-\beta E(\overrightarrow{x}, \overrightarrow{p})}}{Z} d\overrightarrow{p} d\overrightarrow{u} dq \right)$$

$$= -kTln \left(Z \int \int \delta(q - q_0) \rho(\overrightarrow{x}, \overrightarrow{p}) d\overrightarrow{p} d\overrightarrow{u} dq \right)$$

$$= -kTln \left(Z < \delta(q - q_0) > \right)$$

$$= -kTlnZ - kTln < \delta(q - q_0) >$$

How can we interpret this? $\rho(\vec{x}, \vec{p})$ is the probability, that the system is at the point (\vec{x}, \vec{p}) . Then,

$$P(q_0) = \int \int \delta(q - q_0) \rho(\overrightarrow{x}, \overrightarrow{p}) d\Gamma = <\delta(q - q_0) >$$

is the probability $P(q_0)$, that the system is at the value of the reaction coordinate q_0 , since the integral 'sums' over the whole phase space and the delta function 'cancels out' all points, where the reaction coordinate is NOT at q_0 ! I.e., the integration collects all points in phase space, where the reaction coordinate has this specific value!

In the example of the ion pair: we perform an MD for the system, and then only count, how often the reaction coordinate is found at a specific value, i.e. calculate the probability $P(q_0)$ to find the system at q_0 .

Therefore, the difference of free energy for two states A and B is:

$$F_B - F_A = -kT ln Z - kT ln < \delta(q - q_B) > +kT ln Z + kT ln < \delta(q - q_A)) >$$
(IX.6)
$$= -kT ln \frac{<\delta(q - q_B) >}{<\delta(q - q_A) >}$$

$$= -kT ln \frac{P(q_B)}{P(q_A)}$$

So, the task is clear: perform a MD, specify a coordinate, and then just count, how often the system is at special values of the reaction coordinate: the difference of these numbers gives the free energy difference!



FIG. 51: Schematic energy profile along a reaction coordinate and the probability distribution. The barrier region is sampled poorly.

This is nice, but we also know the problem: If we have to cross a high barrier along the reaction coordinate to come from A to B, a pure MD will never do it. Therefore, we have to **drive** the system 'somehow': This can be done, by applying an additional potential V!

Lets try something:

$$\begin{split} F(q_0) &= -kTln\left(\frac{\int \int \delta(q-q_0)e^{-\beta E}d\Gamma}{\int \int e^{-\beta E}d\Gamma}\right) \\ &= -kTln\left(\frac{\int \int \delta(q-q_0)e^{\beta V}e^{-\beta(E+V)}d\Gamma}{\int \int e^{-\beta(E+V)}d\Gamma}\frac{\int \int e^{-\beta(E+V)}d\Gamma}{\int \int e^{-\beta(E+V)}d\Gamma}\right) \\ &= -kTln\left(<\delta(q-q_0)e^{\beta V}>_{E+V}\frac{\int \int e^{-\beta(E+V)}d\Gamma}{\int \int e^{\beta(V)}e^{-\beta(E+V)}d\Gamma}\right) \\ &= -kTln\left(<\delta(q-q_0)e^{\beta V}>_{E+V}\frac{1}{< e^{\beta V}>_{E+V}}\right) \\ &= -kTln\left(e^{\beta V(q_0)} < \delta(q-q_0)>_{E+V}\frac{1}{< e^{\beta V}>_{E+V}}\right) \\ &= -kTln < \delta(q-q_0)>_{E+V} - V(q_0) + kTln < e^{\beta V}>_{E+V} \\ &= -kTlnP^*(q_0) - V(q_0) + kTln < e^{\beta V}>_{E+V} \end{split}$$

The last equation has the form:

$$F(q) = -kTlnP^*(q) - V(q) + K$$
(IX.7)

This result is very interesting: we have added an arbitrary potential V to our system: Now we have to calculate the averages using the ensembles with the energy E+V, that is indicated by $\langle \rangle_{E+V}$. Now, we get the probability $P^*(\vec{q}_0)$ to find the system at the value of the reaction coordinate for the ensemble E+V, which can be very different from that of the ensemble E, $P(\vec{q}_0)$!

But we still get the right free energy $F(\vec{q_0})$, if we use the probability $P^*(\vec{q_0})$ and subtract the potential $V(\vec{q_0})$ at the value of the reaction coordinate and the red term K.

We can use this scheme efficiently, when we move harmonic potentials along the reaction coordinate as shown in Fig. 52. In this case, we perform k simulations with the potentials



FIG. 52: Additional harmonic potentials to keep the system in the region of the desired value of the reaction coordinate

 V_k and get:

$$F(q) = -kTlnP^*(q) - V^k(q) + K_k$$

For each of these k simulations, we extract the probability $P^*(q)$ for every value of q and can calculate the term $V^k(q)$. The curves of $-kTlnP^*(q) - V^k(q)$ for of simulation k and (k+1) differ by a constant shift, which is given by the difference of the K values, as shown in Fig. 54. The main task is, therefore, to find a good way to match the pieces together. One way is to fit the K_k in order to get a smooth total F(q) curve. This is possible, if the pieces k and (k+1) have sufficient 'overlap'. Another, quite involved method is the weighted



FIG. 53: Offset in free energy between two simulations k and (k+1). The offset is given by K_k - K_{k+1}

histogram method (WHAM), which will not be discussed further. The main point is, to join the histogram from several simulations in a way, which minimizes the error.



FIG. 54: Matching of histograms from different simulations

X. ELECTROSTATIC INTERACTIONS

There are several reasons, to take care in particular for the electrostatic interactions:

- the electrostatic interactions are a key to understand the structure, function and in particular the efficiency of many proteins. It is the electrostatic interaction of the protein with the ligand molecules, which is responsible for the efficiency of the reaction, color of the chromophore etc. The solvent surrounding is responsible for the particular structure of polypeptides and proteins (hydrophobic-hydrophilic residues) etc.
- The electrostatic interaction is treated in MM by two-body potentials: therefore, the computational effort is N² and becomes the dominant effort for large systems. Therefore, to make MM more efficient, the electrostatic interactions is the place to look at.
- Solvation is crucial to understand structure and function of bio-molecules. However, the amount of water is often extremely large an easily can become the main cost. Therefore, there is a need to include the effects of water solvation, which is a dominant electrostatic (due to the large dipole of the water molecules), in more efficient ways.

A. Basics

The electrostatic interaction energy of two point charges q and Q with distance r is given by coulombs law:

$$E^{el} = \frac{1}{4\pi\epsilon_0} \frac{qQ}{r}.$$

The concept of the electrostatic potential, resulting from the charge Q located at $\vec{x_1}$ at the point \vec{x} is a key concept,

$$\phi(\overrightarrow{x}) = \frac{1}{4\pi\epsilon_0} \frac{Q}{|\overrightarrow{x} - \overrightarrow{x_1}|}.$$

The main point is, if we know the electrostatic potential at a point in space, we know the total energy of a charge q at that point:

$$E^{el}(\overrightarrow{x}) = \phi(\overrightarrow{x})q$$

In this way, we can have an 'electrostatic potential energy surface' in analogy to mechanics. E.g. if we know the topography of the Alps, we know the potential energy of a person with e.g. 70 kg at every point. In a similar way, if we know the electrostatic potential resulting from a protein, we know e.g. the (binding) energy of a point charge (e.g. ion) at every place. The electrostatic potential resulting from many charges can be written as:

$$\phi(\overrightarrow{x}) = \frac{1}{4\pi\epsilon_0} \sum_i \frac{Q_i}{|\overrightarrow{x} - \overrightarrow{x_i}|}$$

with the energy of a point charge q at \overrightarrow{x} :

$$E^{el}(\overrightarrow{x}) = \phi(\overrightarrow{x})q.$$

In case of a continuous charge distributions, we have to consider the charge density $\rho = Q/V$, $\rho(\vec{x})$ is the charge density at \vec{x} .

 $Q_i = \rho(x_i)V_i = \rho(x_i)dV$ is the charge in the i-th volume element V_i . Summing over all elements

$$\phi(\overrightarrow{x}) = \frac{1}{4\pi\epsilon_0} \sum_{i} \frac{\rho(x_i)dV}{|\overrightarrow{x} - \overrightarrow{x_i}|}$$

If we make the volume elements infinitesimally small, we get $(d^3 \overrightarrow{x} = dV)$:

$$\phi(\overrightarrow{x}) = \frac{1}{4\pi\epsilon_0} \int \frac{\rho(\overrightarrow{x}')}{|\overrightarrow{x} - \overrightarrow{x}'|} d^3 \overrightarrow{x}'$$

The electrostatic energy of a charge distribution $\rho(\vec{x})$ is:

$$E = \frac{1}{2} \int \phi(\overrightarrow{x}) \rho(\overrightarrow{x}) dV = \frac{1}{8\pi\epsilon_0} \int \int \frac{\rho(\overrightarrow{x}')\rho(\overrightarrow{x})}{|\overrightarrow{x} - \overrightarrow{x}'|} d^3 \overrightarrow{x} d^3 \overrightarrow{x}'$$

The main task is, to get the electrostatic potential from a charge distribution. For that, one has to solve the so called Poisson equation:

$$\nabla^2 \phi(\overrightarrow{x}) = -\frac{4\pi\rho(\overrightarrow{x})}{\epsilon} \tag{X.1}$$

If ϵ is not a constant, we have:

$$\nabla \epsilon \nabla \phi(\vec{x}) = -4\pi \rho(\vec{x}) \tag{X.2}$$

B. Accelerating the summation of the non-bonded interactions: Cutoffs

As mentioned above, the summation of the non-bonded terms becomes a bottleneck for large systems, since the 1/r term is very long-ranged, which implies that one has to sum over many atoms, although the contributions for large r become small and one could think of neglecting them. One could simply stop the summation, if two atoms are large apart than a certain radius r_c . This, however, would lead to a jump in the potential, which would be a disaster for the forces, which would become infinite at that point.

The first idea would be to shift the whole potential with $V(r_c)$. We would have:

$$V_s(r) = V(r) - V(r_c), \quad for \quad r \le r_c; \quad 0 \quad otherwise$$

However, at r_c the first derivatives (forces) are still not continuous! To eliminate this force jump, one can use the so called 'shift-force' potential:

$$V_s(r) = V(r) - V(r_c) - \frac{dV}{dr}(r - r_c), \quad for \quad r \le r_c; \quad 0 \quad otherwise.$$

The drawback of this method is, that the coulomb energy is changed!



FIG. 55: Shift force and switch 'cutoff' for the non-bonded interactions

An alternative is the switch-potential. Here, at a certain distance r_1 an additional potential is applied, which brings the coulomb interaction to zero, as shown in Fig. 55. The drawback of this method is, that the forces are altered in the cutoff region.

Both methods can be applied to either the energy or the forces: when applied to the energy, forces follow through differentiation, when applied to forces, energy through integration. Cutoff can be based only on atomic distances, or based on groups. Usually the latter is employed, to assure charge conservation in the Coulomb interaction. Both methods allow to treat a smaller part of the system, e.g. a protein and in a spherical water bubble. It is important to assure the proper conditions on the boundary, i.e. to have the right pressure, keep the temperature etc. In many cases, however, it turned out that these methods are not sufficient, therefore, more accurate methods have been applied.



FIG. 56: System in a water bubble

C. Accelerating the summation of the non-bonded interactions: Periodic boundary conditions

The most accurate treatment is to apply periodic boundary conditions (PBC): it is not enough e.g. to put the protein in a (quadratic) box filled with water and with the appropriate size, to have the right density (and pressure). If we would only have a box with protein and water in vacuum, the water molecules at the boundary would have no electrostatic interactions with neighbors beyond the boundary, which would introduce errors in the calculation. Therefore, in the method of periodic boundary conditions one replicates the system in all directions, as shown in Fig 57. This method is of course not perfect, now, we have an **artificial periodicity** which may cause artifacts, however, this treatment is much better than using a too small system with artificial vacuum at the boundary. Practically, the implementation has the following features (Minimum image convention):

- Only the coordinates of the unit cell are recorded.
- If one particle leaves the box, another particle enters the box from the other side.



FIG. 57: Replication of the system using periodic boundary conditions

• The atom interacts only with the N-1 particles with closest periodic image. This is to avoid that a particle interacts twice with another atom, or even with itself. If the system is in cubic box with boxsize L, then each atom can interact only with all atoms closer than L/2. I.e. peridic boundary conditions have to be combined with cutoffs.

D. Accelerating the summation of the non-bonded interactions: Ewald summation

In many cases, e.g. for the simulation of DNA, the use of cutoffs is a bad approximation. E.g., due to the artificial forces when using a switch function, ions can accumulate at the cutoff distance (around DNA). Therefore, it is desirable to sum up all the Coulomb interactions:

Lets introduce a vector \vec{n} , which runs over all neighboring cells, i.e. it denotes the images of the unit cell.

- For $|\vec{n}| = 0$ we have $\vec{n} = (0, 0, 0)$, i.e. it denotes the central unit cell.
- For $|\vec{n}| = 1$ we have $\vec{n} = (0, 0, \pm L), \vec{n} = (0, \pm L, 0), \vec{n} = (\pm L, 0, 0)$, i.e. the vector points to six neighboring unit cells.
- ...

With this vector, we write the sum over all Coulomb interactions as:

$$E_{coulom} = \frac{1}{2} \sum_{i,j} \sum_{images|\vec{n}|} \frac{q_i q_j}{|\vec{r_{ij}} + \vec{n}|}$$
(X.3)

This is an infinite sum which has special convergence problems. This sum decays like $1/\vec{n}$ and is a **conditionally convergent** series. A series is called conditionally convergent, when $\sum_{i=1}^{\infty} a_i$ is convergent, but $\sum_{i=1}^{\infty} |a_i|$ not. The problem is, that the convergence is slow and depends on the order of summation, as shown by an example in the box.

$$ln2 = \sum_{n=1}^{\infty} \frac{(-1)^{n-1}}{n} = 1 - \frac{1}{2} + \frac{1}{3} - \frac{1}{4} + \frac{1}{5} - \frac{1}{6} + \frac{1}{7} - \frac{1}{8} \dots$$
$$\frac{1}{2}ln2 = \frac{1}{2} - \frac{1}{4} + \frac{1}{6} - \frac{1}{8} \dots$$
$$\frac{3}{2}ln2 = 1 + \frac{1}{3} - \frac{1}{2} + \frac{1}{5} + \frac{1}{7} - \frac{1}{4} \dots$$
$$= 1 - \frac{1}{2} + \frac{1}{3} - \frac{1}{4} + \frac{1}{5} - \frac{1}{6} \dots = ln2!!!$$

Therefore, we need a clever way to calculate the potential, resulting from all the charges in all unit cells

$$\phi(\vec{r_i}) = \sum_j \sum_{images|\vec{n}|} \frac{q_j}{|\vec{r_{ij}} + \vec{n}|}$$
(X.4)

in order to evaluate the Coulomb energy of the charges \mathbf{q}_i from the unit cell.

$$E_{coulom} = \frac{1}{2} \sum_{i,j} q_i \phi(\vec{r_i}) \tag{X.5}$$

Since the sum over the point charges leads to the convergence problems with the conditionally convergent sums, the idea is to use charges smeared out by gaussian distributions:

$$q_j \to q_j \left(\frac{\alpha}{\pi}\right)^{3/2} exp(-\alpha |\vec{r_j}|^2)$$

To get the potential from this smeared charge distribution, we have to solve the Poisson equation:

$$\nabla^2 \phi(r) = -4\pi \rho(r)$$

Since

$$\nabla^2 = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right),$$

we have to integrate the Gaussian twice. This leads us to the so called error function:

$$erf(r) = \frac{2}{\sqrt{\pi}} \int_0^r e^{-t^2} dt$$

And we get for the potential of the gaussian distribution:

$$\phi(\vec{r}) = \frac{q_j}{r} erf(\sqrt{\alpha}r) \tag{X.6}$$

Especially for r=0, we have:

$$\phi(\vec{0}) = q_j \frac{2\alpha}{\sqrt{\pi}} \tag{X.7}$$

If we sum up all charges for the potential with X.6, we get:

$$\phi(\vec{r_i}) = \sum_j \sum_{images|\vec{n}|} \frac{q_j erf\left(\sqrt{\alpha}|\vec{r_{ij}} + \vec{n}|\right)}{|\vec{r_{ij}} + \vec{n}|} \tag{X.8}$$

This has to be compared with the potential for the point charges eq. X.4. The difference between X.4 and X.8 is given by the complementary error function,

$$erfc(r) = 1 - erf(r) \tag{X.9}$$

Therefore, we can describe the real potential of the point charges by:

$$\phi(\vec{r_i}) = \sum_{j} \sum_{images|\vec{n}|} \frac{q_j erf(\sqrt{\alpha}|\vec{r_{ij}} + \vec{n}|)}{|\vec{r_{ij}} + \vec{n}|}$$
(X.10)

+
$$\sum_{j} \sum_{images|\vec{n}|} \frac{q_j erfc(\sqrt{\alpha}|\vec{r_{ij}} + \vec{n}|)}{|\vec{r_{ij}} + \vec{n}|}$$
 (X.11)

The second term X.11 is graphically shown in Fig. 58. The point charges are canceled after some distance by the gaussian charge distribution, which have opposite sign. The range depends on the gaussian width α . Therefore, a small width would lead to a rapid convergence.



FIG. 58: Point charges (lines) and gaussian charge distributions, which cancel each other rapidly.

However, the first term X.10 is calculated by using Fourier transform techniques. This needs a large gaussian width for fast convergence. Therefore, the chosen values of α are usually a compromise.

After calculating these two terms (Fig. 59), a third one has to be taken into account. Since



FIG. 59: Real space and reciprocal space contributions to the Ewald sum

we have a broadened charge distribution, it interacts with itself, as shown in Fig. 60. The potential of the broadened gaussian is given by eq. X.7, which leads to the energy:

$$E_{self} = \sum_{j} q_j \phi(\vec{0}) = \sum_{j} q_j q_j \frac{2\alpha}{\sqrt{\pi}}$$
(X.12)

At the end, we have the three energy contributions, from the 'real space' evaluation of $\phi_r eal$ in eq. X.11, which gives:



FIG. 60: Interaction of the charge with the gaussian distribution

$$E_{real} = \frac{1}{2} \sum_{j} q_j \phi_{real}(\vec{r_j}) \tag{X.13}$$

from the 'reciproal space' evaluation of ϕ_{rec} in eq. X.10, which gives:

$$E_{rec} = \frac{1}{2} \sum_{j} q_j \phi_{rec}(\vec{r_j}) \tag{X.14}$$

and E_{self} ,

$$E_{Ewald} = E_{real} + E_{rec} - E_{self} \tag{X.15}$$

E. Continuum electrostatic methods: Free energy of solvation

Up to now, we either treated molecules in gas phase or with explicit solvation, i.e. we treated the surrounding water molecules within the MM framework. Then, we can calculate the difference in the solvation energy e.g. by thermodynamic perturbation theory or umbrella sampling.

Consider again the example of polyalanine α helix and β sheet. The energy difference of the two structures is given by:

• the difference of the total energies of the optimized structures.

- the entropic contributions to the free energy (vibrational or conformational).
- the solvation contribution to the free energy.

The α helix has a much larger dipole moment than and β sheet structure (due to the same direction of all the HNCO groups in the helix), therefore, it is better solvated in a polar medium. To finally decide, which is the most stable structure we also have to include the solvation free energy. Here, we discuss how to do this using an implicit treatment. Since the number of water molecules is very large, it would often take too long simulation times, in order to sample the phase space for the water.

When solving a molecule, we have to consider three energy contributions:

- A cavity (Fig. 61) in the solvent against the outside pressure has to be formed, which also includes rearrangement of the solvent molecules at the surface, which includes entropic cost and loss of solvent-solvent interactions, ΔG_{cav} .
- The VdW interactions of the solute molecule with the solvent: ΔG_{VdW} (Fig. 62).
- The electrostatic interactions of the solute with the solvent: ΔG_{ele} (Fig. 62).



FIG. 61: Formation of the cavity

The total solvation energy is then:

$$\Delta G_{solv} = \Delta G_{cav} + \Delta G_{VdW} + \Delta G_{ele} \tag{X.16}$$

The terms ΔG_{cav} and ΔG_{VdW} are proportional to the surface area S. Since arbitrary surfaces are difficult to determine, it is convenient to try to get the total surface of the molecule from



FIG. 62: Electrostatic and VdW interactions when filling the cavity with the molecule

the (e.g. VdW) surfaces of the individual atoms S_i of the molecule. A practical approach is to write:

$$\Delta G_{cav} + \Delta G_{VdW} = \sum_{i} c_i S_i.$$

Since this term does not contain electrostatic contributions, it a appropriate to parametrize it with respect to solvation energies of hydrocarbons.

The electrostatic term is discussed in more detail below.

When does it work?

- works probably, when only the electrostatic effect of the surrounding solvent is dominant, e.g. to shield solvent exposed charges or free energy of solvation.
- not successful, when direct hydrogen bonding interactions with the solvent are important, e.g. to stabilize the structure. This is the case, e.g. when studying the dynamics of small amino acids in water, where the amino acids can form either intramolecular Hbonds (C7 structure) or with the solvent. This balance is hard to represent only via general electrostatic interactions.

In the following, we will discuss several models to calculate the term ΔG_{ele} . As discussed above, the electrostatic energy of a point charge located at \vec{r} is:

$$E_{ele} = q\phi(\vec{r})$$

where $\phi(\vec{r})$ is the electrostatic potential from a charge distribution (from e.g. the atoms of the protein). To get the solvation energy, we have to calculate the electrostatic potential of
the protein in vacuo, $\phi_{vac}(\vec{r})$, and in solution, $\phi_{solv}(\vec{r})$. The solvation energy is then:

$$\Delta E_{ele} = q\phi_{solv}(\vec{r}) - q\phi_{vac}(\vec{r})$$

With the definition of the reaction field

$$\phi_{rf}(\vec{r}) = \phi_{solv}(\vec{r}) - \phi_{vac}(\vec{r}),$$

the solvation energy is:

$$\Delta E_{ele} = q\phi_{rf}(\vec{r}).$$

Now, as we learned up to now, the energy E as potential energy is related to one point on the potential energy surface. When moving to the free energy, we average over all solvent conformations to include entropy contributions, and the enthalpy includes in addition the pV term (pV=nRT; ideal gas). Therefore, we can try to determine the reaction field in a way, that it includes these contribution, so that we effectively get a free enthalpy:

$$\Delta G_{ele} = q\phi_{rf}(\vec{r}).$$

1. Continuum electrostatic methods: Born and Onsager models

Born (1920) determinded **analytically** the work, to bring a charge q with radius a from vacuo into a solvent with dielectric constant ϵ (Fig. 63):

$$\Delta G_{ele} = -\frac{q^2}{2a} \left(1 - \frac{1}{\epsilon} \right) \tag{X.17}$$

(ϵ : water=80, protein=2-20, vacuo=1). In this model, the cavity is spherical.

Onsager and Kirkwood (1930) developed a model for a dipole in a cavity (Fig. 64). The dipole moment of the molecule μ induces charges at the surface, i.e. the solvent as a reaction to the molecule produces an electric potential, the so called reaction field (which is, as defined above, the difference of the vacuo and solvent electrostatic potentials :

$$\phi_{rf} = \frac{2\epsilon - 1}{(2\epsilon - 1)a^3}\mu \tag{X.18}$$

and the solvation free enthalpy is:



FIG. 63: Solvation of a charge



FIG. 64: Solvation of a dipole

$$\Delta G_{ele} = -\frac{1}{2}\phi_{rf}\mu \tag{X.19}$$

These models are implemented in many standard quantum chemistry packages, to calculate solvation energies. Of course, even for small molecules the point charge or dipole approximation in combination with a spherical or elliptic surface is not very realistic. The polarizable continumm method (PCM) therefore extends these schemes to arbitrary surfaces calculated from teh VdW radii of the atoms. Alternative approaches are the COSMO models, which start by approximating the environment as a conductor. For large molecules, other approximations developed starting from the PBE.

2. Continuum electrostatic methods: Poisson Boltzmann equations (PBE)

The poisson equation

$$\nabla \epsilon \nabla \phi = -4\pi\rho \tag{X.20}$$

is as partial differential equation. Here, ρ is given as the charge distribution and we want to solve the equation for ϕ . One way to solve it is to discretize the problem (like for the MD) and solve the problem on a 3d grid. Here, we have a charge distribution and the ϵ , which as 2-20 inside the protein and 80 (water) outside, distributed on a grid, and the ϕ is calculated on every gridpoint iteratively (Fig. 65) using finite differences for the second derivative.



FIG. 65: Representation of ϕ , ρ and ϵ on a grid.

Very often, we want to include ions in the calculation. If we do direct MD, we get the ion distribution from the simulation, but how can we get it for a continuum representation. Definitely, ions are very important, e.g. for DNA simulations, here counterions are necessary to compensate for the charges on the phosphate groups. But, if we know the electrostatic potential in the system, the energy of an ion is

$$E_i(r) = q_i \phi(r)$$

and with the Boltzmann distribution, the density at that point is:

$$n_i(r) = n_i^0 e^{-q_i \phi(r)/kT}.$$

 n_i^0 being the number density in bulk solution (concentration). Therefore, anions concentrate at regions with positive ϕ and cations in regions with negative ϕ . Multiplying with the ionic charges, we get the charge distribution of the ions:

$$\rho_{ions} = \sum_{i} q_{i} n_{i}^{0} e^{-q_{i}\phi(r)/kT}$$

Now, if we have e.g. Na⁺ and Cl⁻ with $q = \pm 1$ in solution, we will have terms like:

$$1 * e^{-1 * \phi(r)/kT} - 1 * e^{1 * \phi(r)/kT},$$

and we can combine the two terms using:

$$e^x - e^{-x} = 2sinh(x).$$

Therefore, when we add the charge distribution from the ions to the Poisson equation, we get:

$$\nabla \epsilon \nabla \phi = -4\pi \rho + \sum_{i} q_{i} n_{i}^{0} sinh[q_{i} \phi(r)/kT], \qquad (X.21)$$

which is the so called Poisson Boltzmann equation. Often, this equation is transformed into the following one:

$$\nabla \epsilon \nabla \phi = -4\pi \rho + k' sinh[\phi(r)] \tag{X.22}$$

with

$$k^2 = \frac{k^{\prime 2}}{\epsilon} = \frac{8\pi N_A e^2 I}{1000\epsilon kT},$$

with N_A being the Avogadro constant and the ionic strength $I = 0.5 \sum_{i} c_i z_i^2$ (c_i : concentration, z_i charge of the ion). Often, the linearized version is solved, which comes from a Taylor expansion of sinh:

$$\nabla \epsilon \nabla \phi - k' \phi(r) = -4\pi\rho \tag{X.23}$$

The PBE describes two effects of solvation: First, the charge distribution of the protein polarizes the (high: $\epsilon = 80$) dielectric outside the molecule. This leads to a screening of the effect of the solvent exposed charges. The solvent molecules will arrange around a charge and dipoles will be build up, so that the charge will be canceled. Effectively, charges pointing into the solvent will be nearly zeroed out. The second effect is, that ions will accumulate also in way, that net charges are diminished. E.g., if a negative charge points into the solvent, positive ions will accumulate around it, thus effectively reducing it influence on the protein electrostatic field. These two points can become important, when describing (photo-) chemical reactions in proteins. The solvent around a protein should always be taken into account.

$$\phi_{rf} = \phi_{\epsilon=80} - \phi_{\epsilon=1}$$

The solvation free energy is then:

$$G_{elec} = \frac{1}{2} \sum_{i} q_i \phi_{rf} \tag{X.24}$$

The solution of the PBE is too costly in order to do it several Million of times during a MD (for every MD step!). Therefore approximations have been developed.

F. The Generalized Born (GB) model

A simple idea, is to use the born equation X.17 for the atomic charges of the biomolecule to calculate the solvation energy of the charges:

$$\Delta G_{ele}^1 = -\left(1 - \frac{1}{\epsilon}\right) \sum_i \frac{q_i^2}{2a_i} \tag{X.25}$$

Now, lets have a look at the interaction of the charges in a medium with dielectric constant $\epsilon \neq 1$:

$$E_{elec} = \frac{1}{2} \sum_{i \neq j} \frac{q_i q_j}{\epsilon r_{ij}} =$$

$$= \frac{1}{2} \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} - \frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} \qquad (X.26)$$

The red terms are the usual Coulomb terms, and the blue terms are the reaction field contributions, which add the contributions due to solvations,

$$\Delta G_{ele}^2 = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} \tag{X.27}$$

Therefore, the solvation contribution is given by the terms $\Delta G_{ele}^1 + \Delta G_{ele}^2$,

$$\Delta G_{ele} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \left[\sum_{i} \frac{q_i^2}{a_i} + \sum_{i \neq j} \frac{q_i q_j}{r_{ij}} \right]$$
(X.28)

This formula describes the interaction of charges, which have the spherical extension a_i . Therefore, the derivation is only valid, when $r_{ij} \gg a_i + a_j$, i.e. this is an assumption underlying this formular.

Eq. X.28 can be viewed as a formular for the interaction of the charges q_i and q_j , where we have the two limiting cases:

- when i=j, the energy is q_i^2/a_i .
- when $i \neq j$ and $r_{ij} \rightarrow \infty$, the energy is: $q_i q_j / r_{ij}$

Therefore, the interaction of two charges with finite radii becomes the interaction of point charges, when the distance is large: but what is the energy for intermediate distances from $1\mathring{A}$ to 10 \mathring{A} ? We somehow need a formula, which interpolates between the two cases.

$$f(r_{ij}) = \sqrt{r_{ij}^2 + a_i a_j exp(-r_{ij}^2/4a_i a_j)}$$

has a functional form, which exactly does that! For large r, the exponent approaches zero, and for small r it approaches 1! With this function, we can write:

$$\Delta G_{ele} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) \left[\sum_{i,j} \frac{q_i q_j}{f(r_{ij})} \right]$$
(X.29)

This is now the free enthalpy of solvation for charges based on the Born approximation: it includes

- (a) the solvation energy of every charge due to the Born formular and
- (b) the change of the Coulomb-interaction of the charges with themselves due to solvation!

The equation, however, has a basic problem: the Born equation was derived for a charge with radius a, directly solvated! But many charges will be deeply buried inside the protein! They will not 'feel' much of the solvent, and therefore, using the same a for all charges, their solvation energy will be grossly overestimated!

But we can make an empirical model out of it: The solvation energy of charge q_i

$$\Delta G_{ele-i}^1 = -\frac{1}{2} \left(1 - \frac{1}{\epsilon} \right) q_i^2 / a_i$$

depends on a_i . Therefore, if we want to use that formula for all charges, then a charge inside the protein will have a larger value a_i than the same charge sitting at the surface. Now we only have to determine a_i for every charge:

We could do that by performing PBE calculations for every charge, calculating ΔG^{1}_{ele-1} , getting the a_i from that for the used in GB. However, thats too costly, doing the PBE is exactly what we wanted to avoid. We need an approximation to calculate the a_i .

1. A simple approximation to the Generalized Born (GB) model

The work, to bring of a charge distribution into a polarizable medium is:

$$\Delta G = \frac{1}{2} \int \rho \phi dV.$$

Now, consider a charge q_i inside a protein surrounded by water (ϵ_W) . It can be shown, that the energy of this charge can be written as:

$$\Delta G^i_{ele} = -\frac{1}{8\pi} (1 - \frac{1}{\epsilon_W}) \int_{ext} \frac{q_i^2}{r^4} dV$$

where the integration is over the 'exterior' of the protein, i.e. over the whole space outside the protein. Comparing with the Born formula, we find:



FIG. 66: Integration over 'int' or 'ext'

$$\frac{1}{a_i} = \frac{1}{4\pi} \int_{ext} \frac{1}{r^4} dV \tag{X.30}$$

r is the distance from the charge to the 'space outside the protein', over which is integrated. By this, the a_i will be different when located at the protein surface or inside protein, i.e. it will be larger inside! The integral over the outside of the protein can be transformed into an integral over the 'interior' of the protein using the vdW radius R_{vdW}^i of the atom i:



FIG. 67: The simple GB model

$$\frac{1}{a_i} = \frac{1}{R_{vdW}^i} - \frac{1}{4\pi} \int_{r > \alpha_i, int} \frac{1}{r^4} dV$$
(X.31)

One approximation of this is to fill the space inside with spheres and approximate thereby the volume by the volume of the individual spheres:

$$\frac{1}{a_i} = \frac{1}{\alpha_i} - \sum_{j \neq i} \frac{1}{4\pi} \int_{sphere_j} \frac{1}{r^4} dV,$$

however, it turns out that this approximation is not accurate enough. Therefore, one can try to model the space to be integrated over by an formula with parameters to be fitted empirically:

the model has to represent the space 'int' in eq. X.31, over which we have to integrate. Every atom has a volume V_j , and since $\Delta G_i a_i^{-1}$, the volumes of the other atoms reduces the solvation energy of atom i, i.e. it increases a_i in the following way:

$$\frac{1}{a_i} = \frac{1}{R_{vdW}^i} - \frac{V_j}{r_{ij}^4}$$

 r_{ij} is the distance between the charge i and the atom j, which reduces its solvation energy. The model has the following terms:



FIG. 68: The empirical GB model: blue are the binding neighbors, black the angle an green the nonbond 'atoms'

$$a_i^{-1} = \frac{1}{\lambda * R_{vdW,i}} - P_1 \frac{1}{R_{vdW,i}^2} - \sum_j^{bond} \frac{P_2 V_j}{r_{ij}^4} - \sum_j^{angle} \frac{P_3 V_j}{r_{ij}^4} - \sum_j^{nonbond} \frac{P_4 V_j}{r_{ij}^4} * CCF(P_5, r_{ij}) (X.32)$$

The Born radius of atom i in solution is $\lambda * R_{vdW,i}$, and then reduced due to a quadratic term, the sum over the bonded, neighbors (bonded, angles) and the all non-bonded interactions. For the latter, the function CCF is 1.0 when the atoms do not have overlap, but reduced when they overlap. The parameters λ , $P_1...P_5$ are fitted to reproduce the PBE results for the solvation energies of atoms in peptides and proteins. This model works (in contrast to the simple analytical one discussed above Fig. 67) due to the empirical fitting of the parameters.

- 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
- [2] In addition there is also the information about the heat of formation. However, a spring does not allow to dissociate, therefore we do not need this information, except for reactive force fields like Morse potentials
- [3] The strict derivation introduces the reduced mass of the system.