

# Computational biophysics

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# Chapter 1

## Introduction and proteins

### 1.1 Introduction

Biomolecular modelling has seen a recent increase in its use in the recent years, with a field still destined to expand. Most of this models take a top-down approach, starting from the macroscopic rather than to build simulation from the fundamental and quantistic concepts. Examples of systems studied through biomolecular modelling are:

- Channels.
- Photosynthetic systems.
- Viruses.
- DNA/RNA interactions.
- Inorganic systems.

Through biomolecular modelling it is possible to obtain:

- Molecular rationale for biological processes like proteins' function or its misfolding.
- A quantitative evaluation of molecular driving forces.
- A prediction of properties of macromolecular structures and architectures.
- A comparative assessment of molecular affinities through the binding free energy.

### 1.2 Proteins

Proteins have different functions within a cell:

- Give structure.
- Provide exchange of materials.
- Code for messages.
- Transport ions.
- Catalytic.
- Movement.
- Storage.
- Act as toxins.

Proteins are a polymer of amino-acids and occupy a space-scale of  $10\text{nm}$ . The amino-acids are in the range of  $1\text{nm}$ . They are built through a polymerization reaction as chain of amino-acids coded through a degenerate code of RNA nucleotides. Three bases of RNA code for an amino-acid.

## 1.2. PROTEINS

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### 1.2.1 Amino-acids

Amino-acids are the monomers of a protein. They have a general structure with an amino and a carboxyl terminal group for all of them. They are distinguished by a residue on the  $\alpha$ -carbon which gives them different chemical and physical properties.

### 1.2.2 Structure

There are four level of a protein structure.

- Primary structure: the amino-acid sequence.
- Secondary structure: here  $\alpha$ -helices and  $\beta$ -sheet can be distinguished.
- Tertiary structure: the spatial, 3D dynamic configuration of a protein which arise during protein folding.
- Quaternary structure: the interaction of multiple correctly-folded proteins.

# Chapter 2

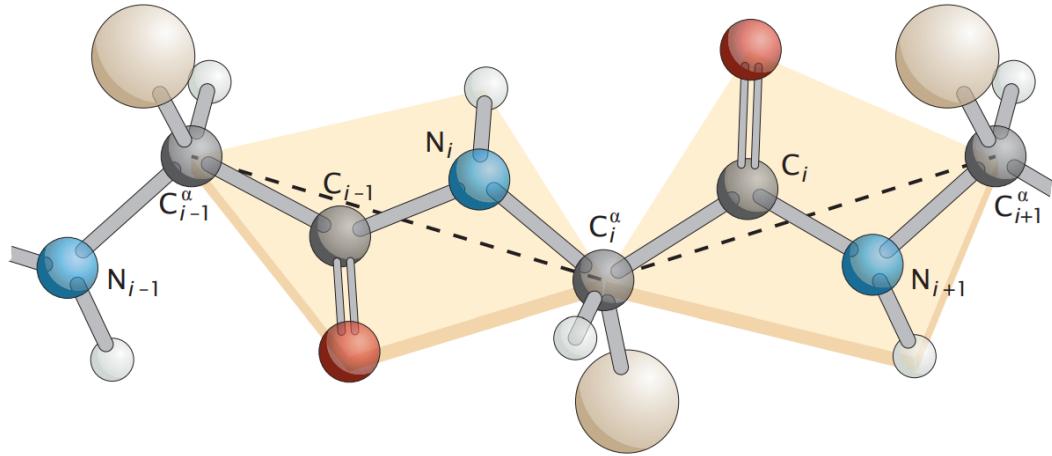
## Proteins' geometry

### 2.1 Introduction

The study of the geometry of proteins involve what can be learned from protein's coordinates.

### 2.2 The peptide bond

A protein is a collection of amino acids linked together by a peptide bond. A carboxylic end and an amino end of two amino acid react together losing a water molecule and forming a peptide bond. Beside the  $\alpha$ -carbon there is another one bonded to the oxygen in the carboxylic group and a nitrogen bond in the amino group. The  $\alpha$  carbon is linked to the nitrogen in the amino group of another amino acid. The carbon and nitrogen display  $sp^2$  hybridization, the central atom and the 3 that form a bond with it form a plane, so the peptide bond is planar. A plane of the peptide bond is formed and rotation of the plane is allowed only around one axis.



**Figure 2.1:** sp<sub>2</sub> hybridization of backbone C and N (not  $C^\alpha$ ). This is an experimental finding which needs to be incorporated into the system: in this way (and by taking into consideration all the knowledge on proteins), the degree of freedom of the system can be reduced.

### 2.2.1 Trans and cis

Looking at the peptide bond the carbon atom of the carboxylic group  $C'$  and the nitrogen  $N$  are each bonded to a different  $\alpha$ -C and a trans or cis conformation can happen. Trying to visualize the atoms that belong to the molecules these repel through the Van der Waals interactions, that can be computed through the Lennard-Jones potential (represented in figure 2.2):

$$U_{LJ}(r) = E_0 \left[ \left( \frac{r_0}{r} \right)^{12} - 2 \left( \frac{r_0}{r} \right)^6 \right]$$

Where:

- $r_0$  is the distance where the energy is minimum.
- $r_{min}$  is the distance at which the energy becomes high.
- $r$  is the distance between two atoms.

### 2.3. THE RAMACHANDRAN ANGLES

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**Figure 2.2:** Graphical representation of the energy plotted along the distance between atoms.  $r_0$  is the equilibrium distance and it explains the reason why the trans configuration is preferred over the cis configuration

With atoms most of the time the distance between them will be close to  $r_0$ . When decreasing the distance a lot of energy is needed and strain is introduced in the molecule. Plotting the values for the energy,  $r_0$  and  $r_{min}$  the expected distance for each couple of atoms can be seen. Focusing on the C-C interaction:

- $r_0 = 3.4\text{\AA}.$

- $r_{min} = 3.0\text{\AA}.$

When two carbons atoms are below the minimum value the conformation is strained. Looking back at the conformation of the peptide bond it can be seen that the cis conformation creates a distance of  $2.8\text{\AA}$  between the two  $\alpha$ -C, so it is not favourable. So the trans conformation is the least energy-hungry and the most present.

Note that the Lennard-Jones potential is not the only one possible. Although it is preferred in most scenarios, other types of potential (e.g., buckingham potential or LJ with different powers) there exist.

## 2.3 The Ramachandran angles

The planes formed by the peptide bonds can rotate with respect to each other. So the Ramachandran angles  $\phi$  and  $\psi$  can be defined between these planes. For each  $\alpha$ -C:

- $\phi$  describes the rotation around its bond with the nitrogen.
- $\psi$  describes the rotation around its bond with the carboxylic group.

These are the angles between the subsequent planes. Some of the angles will require more energy.

## 2.3. THE RAMACHANDRAN ANGLES

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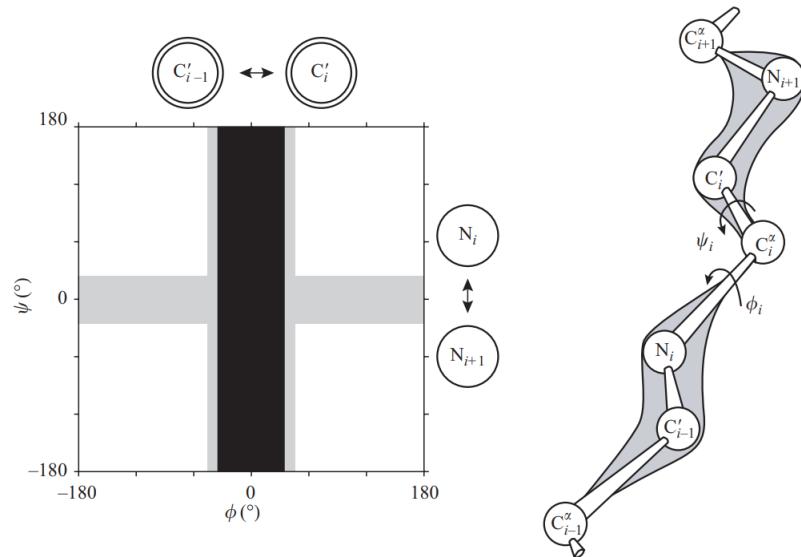
### 2.3.1 Difficulty of rotation

It can be seen how a rotation of the  $\phi$  angle could cause the two  $C'$  to come at a distance of 2.9Å (where  $r_{min} = 3.0\text{\AA}$ ). On the other hand a rotation of the  $\psi$  angle could cause the two  $N$  to come at the same distance, but in this case  $r_{min}(N - N) = 2.7\text{\AA}$ . In the case of carbon atoms the distance is less than the minimum distance, while in the case of nitrogen it is greater than the minimum allowed value. Looking at this it can be seen how the  $\psi$  rotation is easier.

### 2.3.2 Ramachandran plot

A Ramachandran plot is a map with the  $\phi$  angle on the  $x$  axis and the  $\psi$  angle on the  $y$  axis. Because a rotation along the  $\phi$  angle is highly disfavoured the angle 0 is strongly disfavoured and is represented like a black stripe (disallowed region). If the amino acids where composed only by carbon and nitrogen atom the Ramachandran map would be the one represented in figure 2.3, where it can be found:

- A forbidden region in the middle.
- Some strained region like for  $\psi = 0$ .

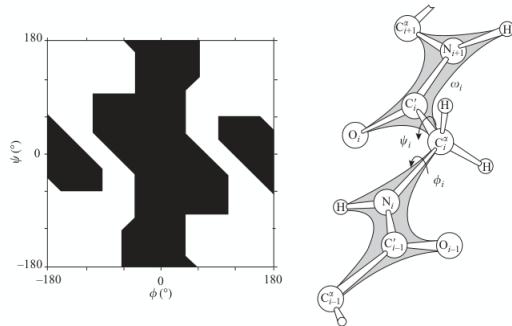


**Figure 2.3:** This is how Ramachandran plots of the disallowed (black stripe), strained (grey stripe), and fully allowed (white regions) ( $\phi$ ,  $\psi$ ) conformations of the fragment  $C^\alpha C' N - C^\alpha - C' N - C^\alpha$  would look, provided all these atoms had no other atoms attached (right) and atoms of residues  $i - 1$  and  $i + 1$  had no interactions.

Looking at a real protein the complexity is increased and the other oxygen and nitrogen atoms are included 2.4 and other regions become disallowed due to steady clashes. It can be seen how the regions are quite complex.

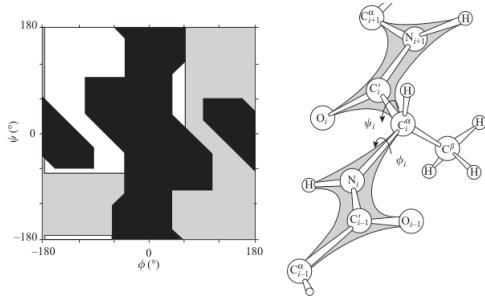
### 2.3. THE RAMACHANDRAN ANGLES

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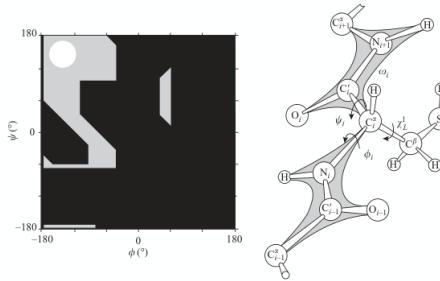
**Figure 2.4:** Ramachandran plot of a peptide bond with other atoms.

Looking at a glycine and alanine complex it can be seen in 2.5 the space becomes even more complex.



**Figure 2.5:** Theoretical representation of a Ramachandran plot of a glycine-alanine complex.

In this case the white regions is very small and a strained region can be seen and the black one. Including other residues the allowed region reduces 2.6. This is due to the presence of larger residues.



**Figure 2.6:** Ramachandran plot of a larger residue.

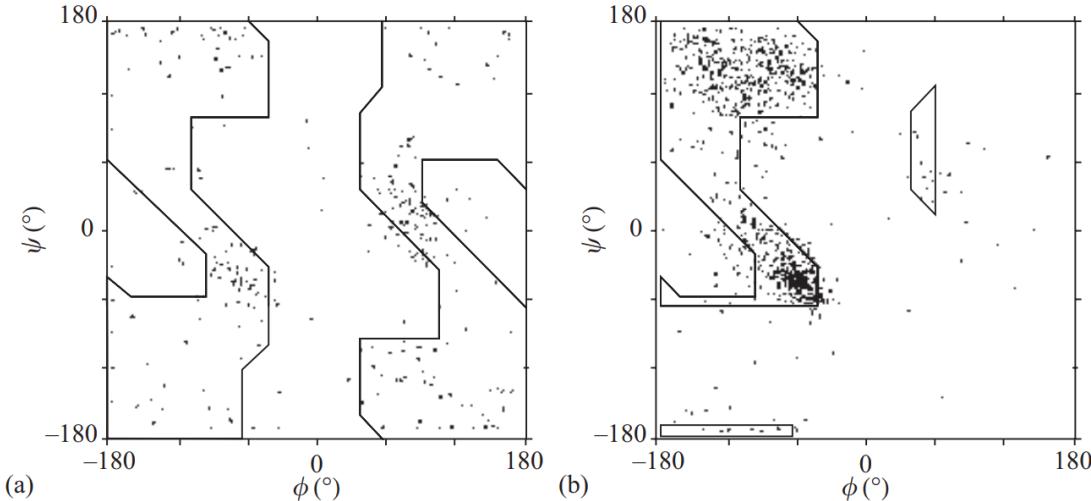
#### 2.3.2.1 Observed Ramachandran plot

Trying to plot for each amino acid its angles an amino acid is represented as a dot. Most of the points fall inside of the allowed regions but there are some outliers. In some conformation the protein

## 2.4. CONTACT MAP OF PROTEINS

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forces the amino acid to assume strange conformations. This is done to check if the structure places the amino acids in a proper way. A typical observed Ramachandran plot looks like the one in 2.7.



**Figure 2.7:** Observed conformations (dots) of glycine (a) and of other amino acid residues (b) in proteins. The sterically allowed regions are contoured.

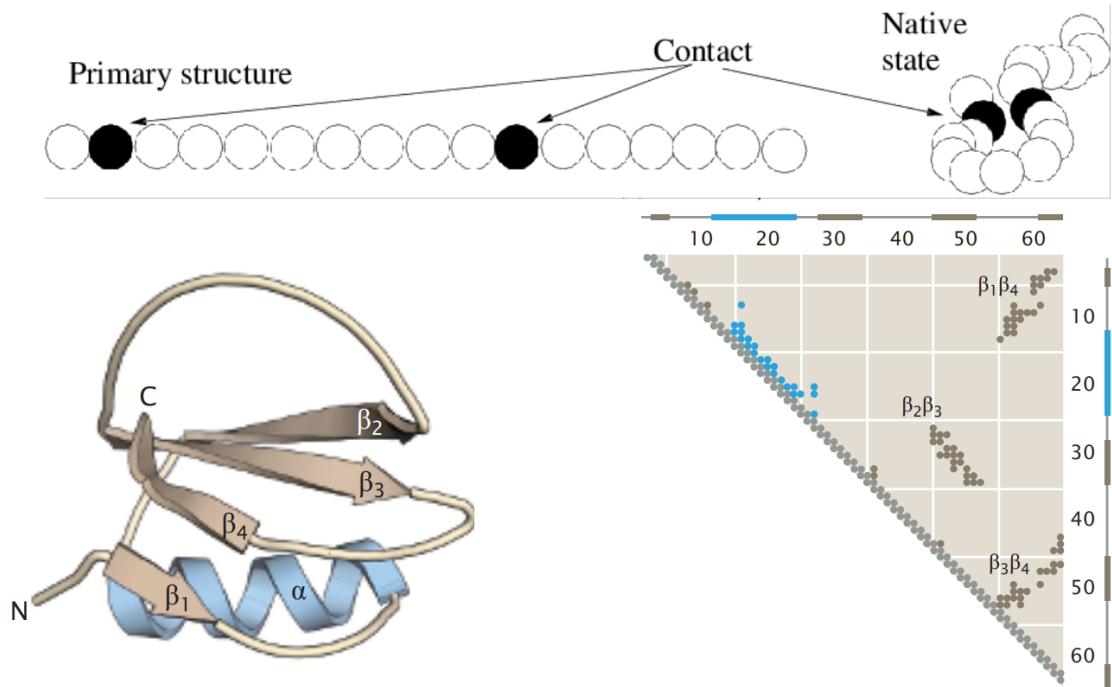
## 2.4 Contact map of proteins

Starting from the coordinates a contact map can be built. It is a matrix that map all the contact between the amino acids. A primary structure can be represented as a collection of beads which will be in contact in the 3D structure. A square matrix can be built such that each entry in the matrix will determine whether there is a contact or not. This matrix will be symmetric with diagonal elements with value 1 and two parallel diagonals for the neighbouring amino acids (figure 2.8). Secondary structures will have specific signatures:

- $\alpha$ -helices: is usually represented by a line parallel to the diagonal. This is because the amino acids  $i$  is interacting with  $i + 4$ .
- $\beta$ -strands: the situation is complicated. For parallel  $\beta$  sheets can be parallel to the diagonal. For anti-parallel it can be anti-parallel to the diagonal.

## 2.5. TOPOLOGY DIAGRAM

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**Figure 2.8:** Example of a contact map for a protein.

### 2.4.1 Defining a contact

The contact between two amino acids needs to be defined. To do so the distance between  $\alpha$ -C or the distance between the tail of the residue and an  $\alpha$ -C. There is also the need to make a trade-off between computational speed and cost. Also the dimension of the protein need to be considered when choosing the distance.

## 2.5 Topology diagram

Having found the secondary structures with a contact map a topology diagram help to understand how those interact with each other (figure 2.9). In a topology diagram the start is the *N* terminus and the end the *C* terminus.  $\beta$ -strands are represented as arrows. If the strands always change direction they will form an anti-parallel  $\beta$ -sheet.  $\alpha$ -helices are represented as small cylinder. Usually color codes represent the nature of the structure. This helps with numbering of the secondary structures.

## 2.6. COORDINATES

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**Figure 2.9:** The topology of a protein structure is a highly simplified description of its fold including only the sequence of secondary structure elements, and their relative spatial positions and approximate orientations. This information can be embodied in a two-dimensional diagram of protein topology, called a TOPS cartoon. (from pubmed)

## 2.6 Coordinates

The coordinates of all atoms in a protein are described in a PDB file. This is a tabulated file containing different columns:

- Atom record: ATOM.
- Atom number: a unique identifier for the atom.
- Atom identifier: an identifier for the type of atom.
- Amino type: the amino acid from which the atom is from.
- Chain identifier: identifier for the chain.
- Residue sequence number: the number of the residue in the chain.
- $x, y, z$ : the coordinates in angstrom.
- Occupancy: the probability of an atom to be in that space (confidence space).
- B-factor: how mobile that atom is in the crystal, it represent the noise in the x-ray diffraction map (it represents the fluctuations for the coordinate of the atoms. For example, loops in trans-membrane proteins are very mobile and a high B-factor is to be expected).
- Element symbol: the symbol of the element of the atom.

Once the coordinates of a protein is obtained, some geometrical properties can be directly computed.

### 2.6.1 Protein centre of mass

The protein centre of mass is the average position for the protein centre. It is an average weighted by the mass of the atom.

$$\vec{R}_{cm} = \frac{\sum_{i=1}^N m_i \vec{r}_i}{\sum_{i=1}^N m_i}$$

### 2.6.2 Radius of gyration

Once the centre of mass is known the radius of gyration can be computed. This measures the size of the protein as if it was a sphere. It is a good indication of the globular size of a protein. It also indicates an elongating/shrinking behaviour, and useful to check whether a protein is going toward equilibrium in the simulation. The distance of each atom and the centre of mass is computed and the square is taken, weighted with the mass of the atom.

$$R_g = \sqrt{\frac{\sum_{i=1}^N m_i (\vec{r}_i - \vec{R}_{cm})^2}{\sum_{i=1}^N m_i}}$$

### 2.6.3 Comparing protein structures

Proteins have structures that loop in a similar way, with similar regions within each other. To quantify the similarity between the protein structure a procedure needs to be followed:

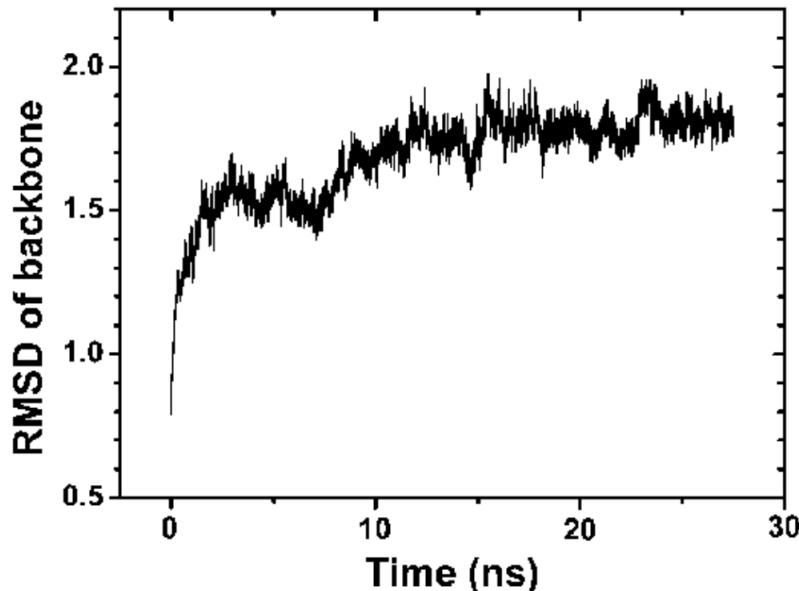
- Select common regions: a 1-1 correspondence between amino acid need to be found: the parts present only in one protein are not considered. A correspondence is built between the common regions on the single amino-acids. These can be different, usually the coordinates are confronted between the  $\alpha$ -C atom and the residue is not considered. One of the things that can be done is to look at the secondary structures and add loops only when they look similar.
- Align the two structures: compute the centre of mass of the two proteins and translate the proteins so the centre of masses coincide.
- Finding the optimal rotation: the principal axes are computed and the proteins are rotated so that they superimpose. Once the optimal rotation is obtained the difference can be quantified.
- Compute RMSD (root mean square deviation): take the coordinates of the amino-acid  $i$  in protein  $A$  and  $B$ , their squared difference is computed and an average over all amino acid is computed and squared:

$$RMSD = \sqrt{\frac{1}{N} \sum_{i=1}^N (\vec{r}_{Ai} - \vec{r}_{Bi})^2}$$

the RMSD is a length, usually in angstrom scale. This can be done for two proteins or for the protein taken at two different time step in a molecular dynamics simulation:

$$RMSD(t) = \sqrt{\frac{1}{N} \sum_{i=1}^N (\vec{r}_i(t) - \vec{r}_i(0))^2}$$

Now the  $RMSD$  can be plotted with respect to time. It can be seen how at  $t = 0$   $RMSD = 0$  and after the value will increase. When the number reaches a plateau the protein should be in equilibrium. The plateau can jump to another value, meaning that the state is a meta-stable state of the protein, or the protein has more stable states or a loop is making something. This value is assigned to very complicated structures and different structures can have the same  $RMSD$ . Clearly, a reference structure needs to be picked. In MD of a protein evolving in time, the reference structure is the initial configuration of the protein. One can also decide to focus on a specific region. The  $RMSD$  is an indicator of equilibrium: it is a necessary but not sufficient condition.



**Figure 2.10:** RMSD of the backbone ( $C^\alpha$ ,  $N$ , ...). We can see the typical steep jump a fluctuations towards the end of the plot. However, this is not enough to state that the protein reached equilibrium.

#### 2.6.4 Native state

The native state is the functional state of a protein. It is not the state found for a crystallized protein, but only closely related to it, it is rather an ensemble in space and time of structures. This is due to proximity effect and the fact that the protein is not a static system. Proteins are extremely flexible and are moving a lot because the temperature corresponds to a constant movement of water molecule around causes movement in the protein. The native state is an ensemble of closely related states, all compatible with the conditions of the situation studied. Proteins need to be studied in

## 2.6. COORDINATES

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the isothermal-isobaric ensemble. All the calculation need to be done at constant temperature and pressure. The native state is so a collection of functional state.

In the case of the unfolded state the possibilities are too many to sample all of them.

### 2.6.5 RMSF

The flexibility of each amino acid can be computed. With flexibility is intended the movement of amino acid with respect to one another. In the  $\alpha$ -helix, for example, less fluctuation is expected, while in loops more fluctuation is expected. This quantity is computed in the root mean squared fluctuation, which will be computed for each amino acid in the protein. With  $f$  referring to the frame, let:

- $\langle \vec{r}_i \rangle = \frac{1}{M} \sum_{f=1}^M \vec{r}_{i,f}$ , the average position of atom  $i$ .
- $\Delta \vec{r}_{i,f} = \vec{r}_{i,f} - \langle \vec{r}_i \rangle$ , the displacement of each atom in each frame with respect to its average.
- $\langle \Delta \vec{r}_o^w \rangle = \frac{1}{M} \sum_{f=1}^M (\vec{r}_{i,f} - \langle \vec{r}_i \rangle)^2$ , the average squared distance over the frames.

So, the root mean squared fluctuation is:

$$RMSF_i = \sqrt{\langle \Delta \vec{r}_i^2 \rangle}$$

Plotting the  $RMSF$  with respect to residue number and the more mobile residue can be identified. This can be mapped onto the sequence so loops, helices and strands can be recognized. Usually the fluctuating part correspond to loops. The terminus have the highest  $RMSF$ .

#### 2.6.5.1 B-factors

$RMSF$  can be translated into B-factors. They are the Debye-Waller factors and are a scaled version of the  $RMSF$  squared. So the result of a simulation can be compared with the B-factor and a strong correspondence can be seen. The differences are due to the fact that the crystal is a different environment with respect to the normal one and packing effect can happen (some regions of the protein can interact with the image of the protein in the crystal).

$$B_i = \frac{8\pi^2}{3} \langle \Delta \vec{r}_i^2 \rangle = \frac{8\pi^2}{3} RMSF_i^2$$

# Chapter 3

## Semi-empirical force fields

### 3.1 Introduction

A protein system can be modelled using a force field. Whenever a simulation is started the interactions between atoms need to be determined. To do so a topology file is built. This file will contain the connecting information. This is important because the kind of force field is specified here. Semi-empirical force field will be used because a very complicated process is modelled using formula that can be easily computed. These formulae are not rigorous and what it is done is to compare the result of the simulation with an experiment. Because of these the used force fields will be called semi-empirical.

### 3.2 Potential energy surface

Any system will correspond to a given potential energy surface. There are states which correspond to minima of this energy where the system will spend most of its time. In the global minimum the system is expected to be in equilibrium. There are also local minima where the system can spend some time and the system will go from the global to some other local minima and the time spent there depends on how deep that minimum is. There will be transitions from one minimum to another exploring the potential energy surface passing through a set of points. In principle the potential energy surface is known because it is assumed that there is a potential energy for all the interaction that there are in the system. This is not that simple because of temperature: at 0 temperature the potential energy surface will tell everything: the system goes through the global minimum and stay there. At finite and high temperatures the system will jump with a certain frequency, which depends on temperature, from one state to another. In this case statistical mechanics is necessary to compute the potential energy and the free energy surface and the entropy. The entropy part is the most difficult. In order to compute entropy the conformational space need to be explored: so the compatible conformation in certain condition need to be found. The phase space, the possibilities of a molecule need to be explored. These are so many in the case of a protein that estimating entropy will be the more costly process. In order to estimate entropy long simulation are needed as the conformational space will be explored as much as possible. In this chapter entropy will not be considered.

The potential energy surface or PES is the landscape of what values the potential energy of an atom can assume. Different points can be recognized like:

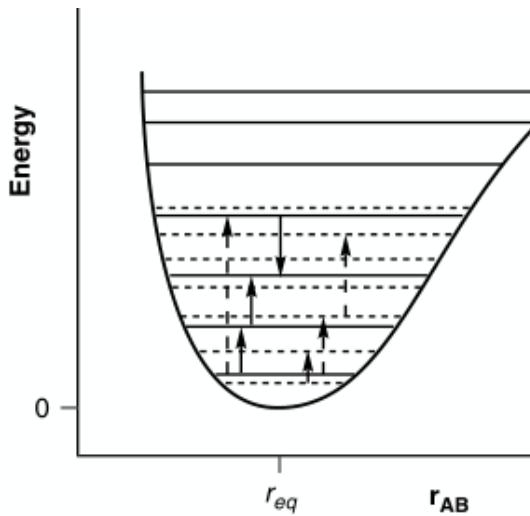
## 3.2. POTENTIAL ENERGY SURFACE

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- Saddle point.
- Local minimum.
- Local maximums.

### 3.2.1 Bond stretching

In figure 3.1 the typical potential energy for a chemical bond can be seen. Let  $r_{eq}$  the distance for which the energy is minimal, where the equilibrium is. Moving from it the energy increases. There are transitions between different states and in that case quantum physics should be used.



**Figure 3.1:** Typical potential energy of a chemical bond

Everything will be assumed to be described using classical mechanics. This is valid when dealing with conformational transitions. So all variables are continuous. Using this assumption light absorption and a chemical reactions cannot be described. The potential energy surface used to describe an unbreakable bond can be seen in figure 3.1. When close to the minimum the well can be assumed symmetric, but with some asymmetry later: the left part is steeper. An approximation for these potential energy is built into the force field. The potential energy surface can be reconstructed using vibrational spectroscopy and then it is reconstructed using a mathematical model. Using a Taylor expansion the potential energy is approximated at point  $r$  by taking the value at the equilibrium and then constructing all the corrections. The first one is the first derivative at the value at equilibrium multiplied by the distance. Then for the second correction the second derivative and so on. If the potential is symmetric the first derivative is 0, as it happens near the equilibrium. So the first correction can be neglected. Also the third order term is either 0 because the third derivative is 0 if the minimum is really shallow. This term is really small if  $r$  is really close to the equilibrium so it can be neglected.

$$U(r) = U(r_{eq}) + \frac{dU}{dr}|_{r=r_{eq}}(r - r_{eq}) + \frac{1}{2!} \frac{d^2U}{dr^2}|_{r=r_{eq}}(r - r_{eq}^2) + \frac{1}{3!} \frac{d^3U}{dr^3}|_{r=r_{eq}}(r - r_{eq}^3) + \dots$$

$$U(r) = U(r_{eq}) + \cancel{\frac{dU}{dr}|_{r=r_{eq}}(r - r_{eq})} + \frac{1}{2!} \frac{d^2U}{dr^2}|_{r=r_{eq}}(r - r_{eq}^2) + \cancel{\frac{1}{3!} \frac{d^3U}{dr^3}|_{r=r_{eq}}(r - r_{eq}^3)} + \dots$$

So that in the end the typical harmonic potential is obtained.

$$U(r_{AB}) = \frac{1}{2} k_{AB} (r_{AB} - r_{AB,eq})^2$$

The constant  $k$  is related to the second derivative with respect to the distance. The distances and the  $k$  constants are labelled with  $A$  and  $B$ , which stand for the fact that this interaction has to be described for each couple of atom. Transferability of these parameter is an issue: using a particular force field then the parameters cannot be used for another. So each force field will come with its own set of parameters.

### 3.2.1.1 Anharmonic force constant

Considering that the shape is not completely symmetric the third order term can be inserted because it can be important. This introduces an asymmetry in the system: an anharmonic force constant.

$$U(r_{AB}) = \frac{1}{2} [k_{AB} + k_{AB}^{(3)}(r_{AB} - r_{AB,eq})] (r_{AB} - r_{AB,eq})^2$$

### 3.2.1.2 Quartic correction

Also the fourth order term can be inserted.

$$U(r_{AB}) = \frac{1}{2} [k_{AB} + k_{AB}^{(3)}(r_{AB} - r_{AB,eq}) + k_{AB}^{(4)}(r_{AB} - r_{AB,eq})^2] (r_{AB} - r_{AB,eq})^2$$

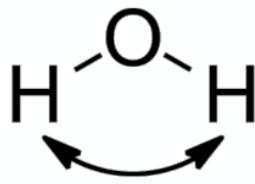
### 3.2.1.3 Morse potential

The Morse potential is used in implicit solvent simulation and uses the exponential because it can describe screen interaction that happens with implicit solvent. The exponential is quite expensive for a computer to compute. It is useful also for soft-systems or coarse grained systems.

$$U(r_{AB}) = D_{AB} [1 - e^{-\alpha_{AB}(r_{AB} - r_{AB,eq})^2}]$$

## 3.3 Valence angle bending

Chemical bonds are not described only by strings and beads but also bending of the bonds can happen. These are valence angle bending, like the one in figure 3.2.



**104.5°**

**Figure 3.2:** A valence angle

These bonds cannot be broken during a classical molecular dynamic simulation. In order to describe them a Taylor expansion introducing an equilibrium angle is built. The first order term is not considered as it will be equal to 0. Then the second introduces the harmonic and the third for the anharmonic one, in principle also the quartic correction could be added. This formula is similar to the previous one but all the constant have to be described between each triplet of atoms.

$$U(\theta_{ABC}) = \frac{1}{2} [k_{ABC} + k_{ABC}^{(3)}(\theta_{ABC} - \theta_{ABC,eq}) + k_{ABC}^{(4)}(\theta_{ABC} - \theta_{ABC,eq})^2 + \dots] (\theta_{ABC} - \theta_{ABC,eq})^2$$

### 3.3.1 Multiple minima

There is another problem with valence angle bending: angles are not varying continuously: the Taylor expansion is good if the angles are not varying too much. If the angles invert the Taylor expansion cannot take track of it. In order to take this into account the potential energy is built using a Fourier expansion. A Fourier expansion introduces a periodic function like  $\cos$  that contains oscillations in a period, allowing to model any possible periodic potential. Since the angles are being considered the potential is periodic. So in the parametrization of the angle bending interaction the Fourier term is introduced, labelling terms with the value  $j$ . So the amplitude, the value that multiplies each Fourier component is decreasing with  $j$  and a cut-off of the given value of  $j$  is given. In this case only low-frequency components are considered.

$$U(\theta_{ABC}) = \sum_{\{j\}_{ABC}} k_{j,ABC}^{fourier} [1 + \cos(j\theta_{ABC} + \psi_j)]$$

Where the amplitude:

$$k_{j,ABC}^{fourier} = \frac{2k_{ABC}^{harmonic}}{j^2}$$

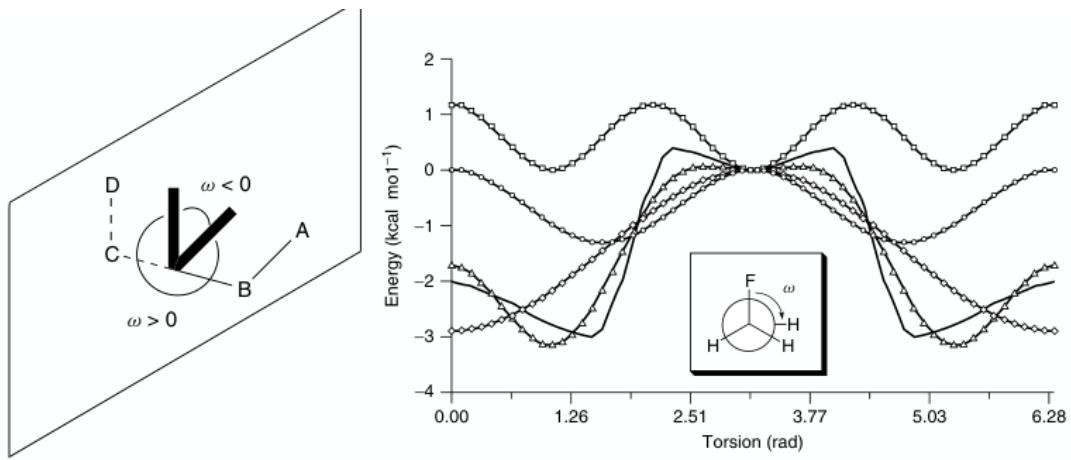
Dividing by  $j^2$  makes the contribution smaller for higher  $j$ .

## 3.4 Torsions

In order to describe torsion 4 atoms bonded by subsequent bonds are considered  $A - > B - > C - > D$ , like in figure 3.3.

### 3.4. TORSIONS

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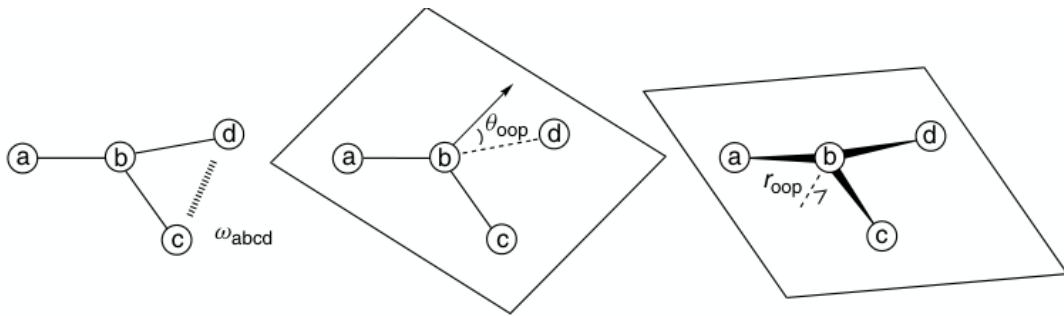
**Figure 3.3:** An example of torsion

In this case two planes  $ABC$  and  $BCD$  are built and the angle  $\omega$  between two plane is built. If they are on the same plane the angle is 0. So an angle  $\omega$  is computed to describe the torsion that is around the bond  $B \rightarrow C$ . In order to compute the angle the perpendicular vectors between the planes is computed and the angle between these two vector is  $\omega$ . In this case the harmonic oscillation and the Taylor expansion are not used but the Fourier expansion and the periodic potential is used. This is because the value of the energy will be the same after a rotation. In principle torsions will be explored during a simulation. All the possible groups with permutations and repetitions of 4 atoms need to be considered to parametrize torsions.

$$U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD} [1 + (-1)^{j+1} \cos(j\omega_{ABCD} + \psi_{j,ABCD})]$$

#### 3.4.1 Improper torsions

Improper torsions happen when the bonds are  $A \rightarrow B \rightarrow C$  and  $B \rightarrow D$  like in figure 3.4.



**Figure 3.4:** An example of improper torsion

$B$  can be in the same plane of  $A, C, D$  or it can pop out. In this case two planes are built, usually  $ABC$  and  $BCD$  and the angle between them will be built. The potential will describe the energy

### 3.5. VAN DER WAALS INTERACTIONS

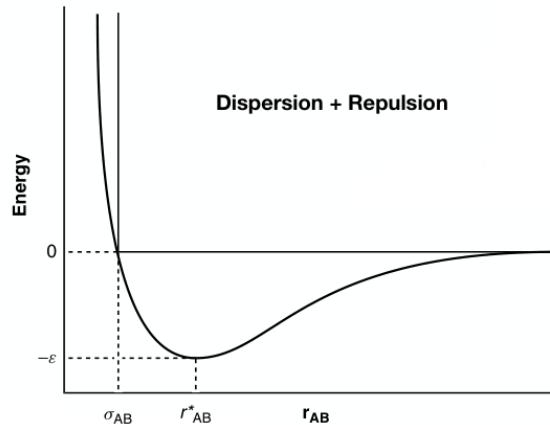
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of the angle. The angle can be described as the out of plane angle  $OOP$ , obtaining the equation for the plane  $ACD$  and how much  $B$  is out of that plane. Here all possibilities of an atoms connected with other 3 atoms need to be considered. In the case of  $sp^2$  the four atoms need to be in a plane.

$$U(\omega_{ABCD}) = \frac{1}{2} \sum_{\{j\}_{ABCD}} V_{j,ABCD} [1 + (-1)^{j+1} \cos(j\omega_{ABCD} + \psi_{j,ABCD})]$$

## 3.5 Van der Waals interactions

Van der Waals interactions happen whenever two atoms come close to one another without any chemical bond connecting them. This interaction is called dispersion interaction and depends on the interaction between the electron clouds that become correlated. Even if electrons are not shared the fluctuation of the electron clouds of an atom will interact with the one of an atom close to it. Looking at the interaction energy in figure 3.5. This can be computed and described by an attraction that goes with the 6th power of the distance. This interaction is the Van der Waals interaction. This attraction is an attractive force and will decrease with the 6th power of the distance. Also a repulsion happen. The repulsion is due to the occupancy of the possible orbitals. The problem is then Pauli's exclusion principle: whenever two atoms come close the energy level becomes occupied and the atoms cannot come to close to one another. This is difficult to compute but it can be modelled assuming that is a repulsion with an hard limit. The energy becomes very high when the distance becomes less than the equilibrium. If the attraction is modelled with the 6th power this interaction can be modelled by the 12th power. In this case if the distance is too small the energy becomes very high.



**Figure 3.5:** Energy of a Van der Waals interaction

### 3.5.1 Lennard-Jones potential

The discussion done above lead to the introduction of the Lennard-Jones potential. This models Van der Waals interaction using the 6th power for the dispersion and the repulsion due to Pauli's exclusion principle is modelled by the 12th power. This power is used to make the computation cheap and has no physical basis. In this way this formula is obtained:

$$\begin{aligned} U(r_{AB}) &= \frac{a_{AB}}{r_{AB}^{12}} - \frac{b_{AB}}{r_{AB}^6} = \\ &= 4\epsilon_{AB} \left[ \left( \frac{\sigma_{AB}}{r_{AB}} \right)^{12} - \left( \frac{\sigma_{AB}}{r_{AB}} \right)^6 \right] \end{aligned}$$

And the distance with minimum energy or equilibrium.

$$r_{AB}^* = 2^{\frac{1}{6}} \sigma_{AB}$$

And it can be seen how it is a multiple of  $\sigma_{AB}$  or the Van der Waals radius, the distance where the value of the energy is exactly equal to 0.  $-\epsilon$  is the minimum value of the energy (equilibrium). In this way dispersion and repulsion of any couple of atoms can be described. A value of  $\sigma_{AB}$  have to be introduced for any couple of atom type.

### 3.5.2 Morse potential

The Morse potential and the Hill potential can be used with coarse grained system. Dealing only with all-atom simulation these will be rarely used. Working in soft-matter simulation these could be used. These have the same features of the Lennard-Jones potential.

$$U(r_{AB}) = D_{AB} [1 - e^{-a_{AB}(r_{AB} - r_{AB,eq})^2}]$$

### 3.5.3 Hill potential

$$U(r_{AB}) = \epsilon_{AB} \left[ \frac{6}{\beta_{AB} - 6} e^{\beta_{AB} \frac{1-r_{AB}}{r_{AB}^*}} - \frac{\beta_{AB}}{\beta_{AB} - 6} \left( \frac{r_{AB}^*}{r_{AB}} \right)^6 \right]$$

In some force fields 1-4 interactions (successive bonds atoms can be numbered) are reduced by a scaled factor. Atom 1 and 4 are close to each other in a proper torsion but attraction and repulsion has been already described by the torsion, so in some force fields, the torsions takes into account the proximity of those atoms. So the Van der Waals interactions are excluded for 1-4 atoms as they are already been described by the torsion interaction.

## 3.6 Electrostatic interactions

Electrostatic interactions, together with Van der Waals one are two kind of non-bonded interactions. Moreover interactions between molecules that might be charged or that can be polar. The distribution of charges need to be described. In principle a multiple expansion should be performed: the cloud of positive and negative charges should be described by using given shapes of the clouds. And each molecule should be described and all the molecules should be described by these multiple expansion and they should be multiplied as matrix.

$$U_{AB} = \vec{M}^{(A)} \vec{V}^{(B)}$$

Now, summing over all molecules:

$$U_{AB} = \sum_A \sum_{B>A} \vec{M}^{(A)} \vec{V}^{(B)}$$

This is a very costly procedure but accurate.

## 3.6. ELECTROSTATIC INTERACTIONS

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### 3.6.1 Point like charges

To make the computation easier molecules are represented as point-like partial charges. In a chemical molecule partial charges can be assumed that are point-like and are located on the atom. The electron cloud is displaced toward the negative cloud and away from the positive one. In this way the distribution of charges can be represented by number placed on each atom. Once this is done an electric charge is associated with each bead and the Coulomb interaction is used:

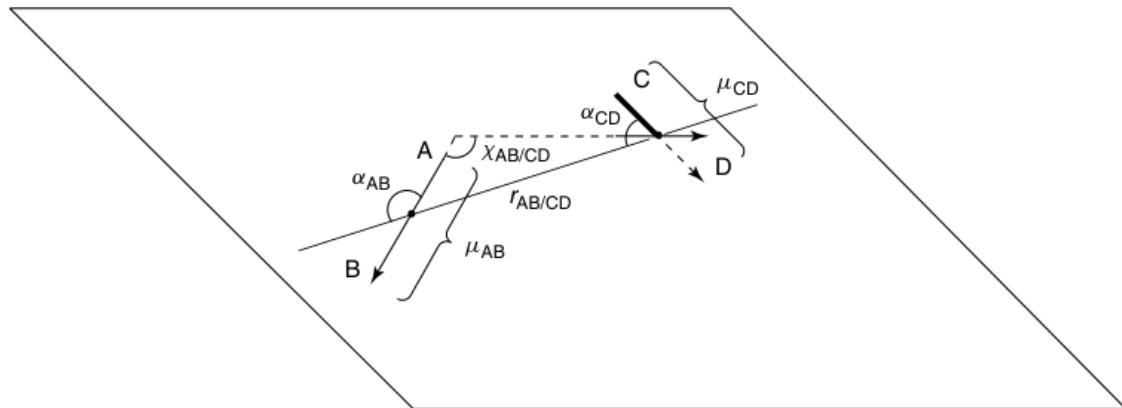
$$U_{AB} = \frac{q_A q_B}{\epsilon_{AB} r_{AB}}$$

The dielectric constant is 1 in the case of explicit solvent, but in the case of the implicit one it will be the one of the solvent.

### 3.6.2 Dipolar interactions

Dipolar interaction can be included when considering electrostatic forces. These formulae are mostly used in coarse grained models. Because in that case the approximation of single charges on a bead cannot be made and dipoles are considered. In this case a functional form and the parameters need to be included.  $\mu$  is the dipole of two molecules. Then there is the dielectric constant, the cube of the distance and the cosine term represent the orientation of the two dipoles.

$$U_{AB/CD} = \frac{\mu_{AB}\mu_{CD}}{\epsilon_{AB/CD} r_{AB/CD}^3} (\cos \chi_{AB/CD} - 3 \cos \alpha_{AB} \cos \alpha_{CD})$$



**Figure 3.6:** An example of a dipolar interaction

### 3.6.3 Dielectric constants

$$U_{AB} = \frac{q_A q_B}{\epsilon_{AB} r_{AB}}$$

The dielectric constant can assume different values. If they are connected by a chemical bond or if there is a valence angle between the atoms the dielectric constant is  $\infty$  and the interaction is not

### 3.7. CROSS TERMS

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computed as it is already taken into account by other terms. In several force field a factor of 2 is added for 1-4 interaction. In the last case the value depend on the force field.

$$\epsilon_{AB} = \begin{cases} \infty & \text{if } A \wedge \text{Bare 1,2- or 1,3-related} \\ 3.0 & \text{if } A \wedge \text{Bare 1,4-related} \\ 1.5 & \text{otherwise} \end{cases}$$

## 3.7 Cross terms

There are also cross terms: angle bending and bond stretching and other movement are not independent: all the possible degrees of freedom should be considered together. This is done only by some force fields.

$$\begin{aligned} U(\vec{q}) = & U(\vec{q}_{eq}) + \sum_{i=1}^{3N-6} (q_i - q_{i,eq}) \frac{\partial U}{\partial q_i} |_{\vec{q}=\vec{q}_{eq}} + \\ & + \frac{1}{2!} \sum_{i=1}^{3N-6} \sum_{j=1}^{3N-6} (q_i - q_{i,eq})(q_j - q_{j,eq}) \frac{\partial^2 U}{\partial q_i \partial q_j} |_{\vec{q}=\vec{q}_{eq}} + \\ & = \frac{1}{3!} \sum_{i=1}^{3N-6} \sum_{j=1}^{3N-6} \sum_{k=1}^{3N-6} (q_i - q_{i,eq})(q_j - q_{j,eq})(q_k - q_{k,eq}) \frac{\partial^3 U}{\partial q_i \partial q_j \partial q_k} |_{\vec{q}=\vec{q}_{eq}} + \dots \end{aligned}$$

This is done by starting from a Lagrangian describing all the interaction and compute all the terms. In practice everything is done without considering them.

$$U(r_{AB}, \theta_{ABC}) = \frac{1}{2} k_{AB,ACB} (r_{AB} - r_{AB,eq}) (\theta_{ABC} - \theta_{ABC,eq})$$

## 3.8 Parametrization

All the interactions need a large set of parameters. The number of parameters increases with the number of atoms  $N$ :

$$p = N + (N - 1) + (N - 2) + \dots = N \frac{N + 1}{2}$$

In order to obtain these parameters data from experiments are used. This is the reason why the force-field are semi-empirical. To do so the results of the experiments are compared from the results of simulations. Then the penalty function:

$$Z = \left[ \sum_i^{\text{observables}} \sum_j^{\text{occurrences}} \frac{(calc_{i,j} - expt_{i,j})^2}{w_i^2} \right]^{\frac{1}{2}}$$

Sums over all the data from all the observables and all possibilities. Then all the observable are measured and are compared with the simulation result. Then the square is taken to not compensate the error and it is divided by a weight. This penalty function is minimized changing the parameters until some reasonable compromise is obtained. The more experimental data is obtained the more accurate the description. This is the reason for the constant update of the force fields. A way

### 3.9. FORCE FIELD ENERGIES

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to reduce the number of parameters is to employ a strategy so that a parameter to each atom is computed and then it is computed the interaction between two atoms:

$$\begin{aligned}\sigma_{AB} &= \sigma_A + \sigma_B \\ \epsilon_{AB} &= (\epsilon_A \epsilon_B)^{\frac{1}{2}}\end{aligned}$$

## 3.9 Force field energies

In molecules the ground state of one molecule is different from the ground state of another. Molecules can have different states and when they come in contact the ground state have to be taken into account. So parametrizing the force field is very complicated.

### 3.9.1 Geometry optimization

Once the force fields are obtained some atoms can be missing from the model and have to be included by hand. Sometimes it may happen that two atoms are too close to each other and by using the potential energy it can be high leading to high forces, causing the atom that experience them to be kicked out. So the simulation will explode. In order to avoid this a geometry optimization is done to obtain the parameters or to minimize so to avoid high forces values at the start of a simulation. When starting a simulation the system will be at an energy value which be greater than the equilibrium. The gradient of the energy is computed and the system is moved toward the minimum energy. The derivative need to be computed of  $U$  with respect to each component in the system.

$$\vec{g}(\vec{q}) = \begin{bmatrix} \frac{\partial U}{\partial q_1} \\ \frac{\partial U}{\partial q_2} \\ \vdots \\ \frac{\partial U}{\partial q_n} \end{bmatrix}$$

Such that the cost reaches a global minimum  $J_{min}(\vec{w})$ .

### 3.9.2 Derivative of the potential function

First the derivatives need to be computed. All the potentials are given in term of the mutual distance of two atoms. So, considering  $x$  the coordinates of a point:

$$\frac{\partial U}{\partial x_A} = \sum_{i \in A} \frac{\partial U}{\partial r_{Ai}} \frac{\partial r_{Ai}}{\partial x_A}$$

Taking the derivative of this:

$$U(r_{AB}) = \frac{1}{2} [k_{AB} + k_{AB}^{(3)}(r_{AB} - r_{AB,eq}) + k_{AB}^{(4)}(r_{AB} - r_{AB,eq})^2](r_{AB} - r_{AB,eq})^2$$

With the respect on the distance:

$$\frac{\partial U}{\partial r_{Ai}} = \frac{1}{2} [2k_{Ai} + 3k_{Ai}^{(3)}r_{Ai} - r_{Ai,eq} + 4k_{Ai}^{(4)}(r_{Ai} - r_{Ai,eq})^2](r_{Ai} - r_{Ai,eq})$$

In order to take the derivative with respect to  $r$  with respect to  $x$  need to be known:

$$\frac{\partial r_{Ai}}{\partial x_A} = \frac{x_A - x_i}{\sqrt{(x_A - x_i)^2 + (y_A - y_i)^2 + (z_A - z_i)^2}}$$

Then this formula can be plugged in according to the chain rule.

### 3.9.2.1 Newton-Raphson

To perform the minimization as an iterative procedure, the Newton-Raphson method is employed. Here  $(n)$  refers to the iteration. This allows to obtain iteration  $k+1$  starting from iteration  $k$  and is a Taylor expansion of coordinates at iteration  $k$ :

$$U(\vec{q}^{(k+1)}) = U(\vec{q}^{(k)}) + (\vec{q}^{(k+1)} - \vec{q}^{(k)})\vec{g}^{(k)} + \frac{1}{2}(\vec{q}^{(k+1)} - \vec{q}^{(k)})H^{(k)}(\vec{q}^{(k+1)} - \vec{q}^{(k)})$$

This is done to find eventually the coordinates at iteration  $k+1$  which are unknown. Where  $H$  is the Hessian matrix built:

$$H_{ij}^{(k)} = \frac{\partial^2 U}{\partial q_i \partial q_j} \Big|_{\vec{q}=\vec{q}^{(k)}}$$

Everything is computed from a Taylor expansion from coordinates at iteration  $k$ . And:

$$\frac{\partial U(\vec{q}^{(k+1)})}{\partial q_i^{(k+1)}} = \frac{\partial \vec{q}^{(k+1)}}{\partial q_i^{(k+1)}} \vec{g}^{(k)} + \frac{1}{2} \frac{\partial \vec{q}^{(k+1)}}{\partial q_i^{(k+1)}} H^{(k)}(\vec{q}^{(k+1)} - \vec{q}^{(k)}) + \frac{1}{2}(\vec{q}^{(k+1)} - \vec{q}^{(k)})H^{(k)} \frac{\partial \vec{q}^{(k+1)}}{\partial q_i^{(k+1)}}$$

This formula tells that:

$$\vec{g}_i^{(k+1)} = \vec{g}_i^{(k)} + [H^{(k)}(\vec{q}^{(k+1)} - \vec{q}^{(k)})]_i$$

Where at the end it should be obtained a stationary condition, where the system does not change after an iteration:

$$\vec{0} = \vec{g}^{(k)} + H^{(k)}(\vec{q}^{(k+1)} - \vec{q}^{(k)}) \Rightarrow \vec{q}^{(k+1)} = \vec{q}^{(k)} - [H^{(k)}]^{-1}\vec{g}^{(k)}$$

Because the starting point was a Taylor expansion the new coordinates will not be exact, and so other iterations will be needed. This process is repeated until convergence is reached, choosing a given tolerance on  $\vec{0}$ .

### 3.9.3 Types of force fields

Force fields can be categorized as:

- All atoms: one atom corresponds to one bead.
- Coarse grained: groups of atoms correspond to one bead.
- More atoms: more atoms correspond to one bead.
- Polarizable force fields: point charges are variables.

As a golden rule parameters from different force fields should never be mixed.

# Chapter 4

## Classical mechanics

### 4.1 Newton's laws

So the mass times the acceleration is equal to the force. A dot on top of a vector is a derivative with respect to the time.

$$m_i \frac{d^2 \vec{r}_i}{dt^2} = m_i \ddot{\vec{r}}_i = \vec{F}_i$$

The index  $i$  in a simulation represent a particle, usually atoms.

#### 4.1.1 Forces

In all the force fields the forces come always from pairs of atoms: all the forces depend on the distance between atom. This is not true for angles and torsions, but they can be re-conducted to forces that involve two atoms, respecting Newton's third law. The forces acting on each particle depend on the coordinates of all the atoms and they might depend on the velocity of atom  $i$ . Sometimes some frictional forces depend on the velocity. All the forces can be represented as forces between pairs of atom that depend on their mutual distance, in particular  $\vec{f}_{ij} = -\vec{f}_{ji}$ . All the external forces like friction or some fields depend on the position of atom  $i$  and its velocity. In the case of biological system viscosity and temperature are the major external forces.

$$\vec{F}_i(\vec{r}_1, \dots, \vec{r}_N, \dot{\vec{r}}_i) = \sum_{j \neq i} \vec{f}_{ij}(\vec{r}_i - \vec{r}_j) + \vec{f}^{(ext)}(\vec{r}_i, \dot{\vec{r}}_i)$$

The forces are computed starting from the interactions:

- Bond stretching:  $U = \frac{k_l}{2}(l - l^0)^2$ .
- Bond bending:  $U = \frac{k_\theta}{2}(\theta - \theta^0)^2$ .
- Bond torsion:  $U = k_\phi[1 + \cos(n\phi - \phi^0)]$ .
- Van der Waals interactions:  $U = \left[ \frac{a_{ij}}{r_{ij}^{12}} - \frac{b_{ij}}{r_{ij}^6} \right]$ .
- Electrostatic interactions:  $U = \frac{332q_i q_j}{\epsilon r_{ij}}$ . Where factor 332 is necessary to compute in in  $\frac{kcal}{mol}$ .

### 4.1.2 Phase space

When dealing with a system with  $N$  atoms, each with 3 dimensions their position and momenta need to be considered:

$$\vec{p}_i = m_i \vec{v}_i = m_i \dot{\vec{r}}_i$$

Newton's law can be re-written in term of particle momenta.

$$\vec{F}_i = m_i \ddot{\vec{r}}_i = \dot{\vec{p}}_i$$

Then the full dynamics of a system in 3 dimension is specified by  $6N$  functions, where  $N$  is the numbers of the body in the system:

$$\{\vec{r}_1(t), \dots, \vec{r}_N(t), \vec{p}_1(t), \dots, \vec{p}_N(t)\}$$

In this way at each instant of time each position and momenta of each particle is specified. Each microscopic state at time  $t$  is completely specified by  $6N$  numbers, as each position and momenta need to be described. This creates the phase space vector which is  $6N$  dimensional:

$$\vec{x} + \{\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N\}$$

A state of a system is a point in this  $6N$  dimensional space. The trajectory represent a curve in the space:

$$\vec{x}_t = \{\vec{r}_1(t), \dots, \vec{r}_N(t), \vec{p}_1(t), \dots, \vec{p}_N(t)\}$$

### 4.1.3 One particle in one dimension

Considering one particle in one dimension the phase space is 2 dimensional. On the  $x$  axis there are the coordinates and on the  $y$  axis the momentum. In the case of motion at constant velocity the trajectory will be an horizontal line. This is the case of a free particle.

#### 4.1.3.1 Harmonic oscillator

In the case of an harmonic oscillator, it will be described by equation:

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

Where the acceleration is equal to minus the elastic force. And:

$$\omega = \sqrt{\frac{k}{m}}$$

Then the solution for the trajectory:

$$x(t) = x(0) \cos \omega t + \frac{p(0)}{m\omega} \sin \omega t$$

That depends on the initial velocity and initial position. The momentum as a function of time and the coordinate verify the equation:

$$\frac{p^2(t)}{2m} + \frac{1}{2}m\omega^2 x^2(t) = C$$

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This equation represent an ellipse and is the conservation of energy. The constant  $C$  will have an effect on the length of the two axes on the ellipse, which will be:  $(2mC)^{\frac{1}{2}}$  and  $(2\frac{C}{m}\omega^2)^{\frac{1}{2}}$ .

### 4.1.3.2 Hill potential

The Hill potential is important in chemistry. A bead may approach the hill of potential from the left with positive momentum or from the right with negative momentum. If it is slow the kinetic energy will be not sufficient to overcome the hill, so the particle will stop and go back. For a particle coming from the right the momentum is negative and if it is slow it will not overcome the hill and go back. If the velocity is enough to reach the top of the hill the particle will stay forever on top of it. If the velocity is more than that the bead will traverse the hill and fall on the other side. A trajectory in the phase space can be different with the one considering just the position.

## 4.2 Lagrangian formulation

Classical mechanics can be formulated using the Lagrangian formalism. In order to have the Lagrangian formulation only conservative forces are considered, from which potential forces are obtained:

$$\vec{F}_i(\vec{r}_1, \dots, \vec{r}_N) = -\nabla_i U(\vec{r}_1, \dots, r_N)$$

Where  $\nabla_i$  is the gradient of the potential and is the force. For conservative forces the work done is computed as the difference of the potential energy and the path can be excluded:

$$W_{AB} = \int_A^B \vec{F}_i d\vec{l} = U_A - U_B = -\Delta U_{AB}$$

And on closed pathways, according to the previous formula:

$$\oint \vec{F}_i d\vec{l} = 0$$

To define the Lagrangian, one term is the kinetic energy, which in the case for  $N$  particles, the total kinetic energy of the system is:

$$K(\dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) = \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i^2$$

Which depends on the mass and their velocity. And the Lagrangian is defined as the difference of the potential and kinetic energy:

$$\mathcal{L}(\vec{r}_1, \dots, \vec{r}_N, \dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) = K(\dot{\vec{r}}_1, \dots, \dot{\vec{r}}_N) - U(\vec{r}_1, \dots, \vec{r}_N)$$

It can be seen how the Lagrangian depends on all the coordinates and all the velocities. Here momenta is not included, but only velocity and position. It can be seen how the kinetic energy depends only on the velocity and the potential one only from the position.

### 4.2.1 Euler-Lagrange equations

Once the Lagrangian is obtained the Euler-Lagrange equation can be computed. Where the difference of the derivative with respect to time of the derivative of the Lagrangian with respect to the velocity and the derivative of the Lagrangian with respect to the position is equal to 0:

$$\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{r}_i} \right) - \frac{\partial \mathcal{L}}{\partial r_i} = 0$$

Now, as an example consider:

$$\mathcal{L} = \underbrace{\frac{1}{2} \sum_i m_i \dot{r}_i^2}_{\text{Kinetic energy}} - U(\vec{r}_1, \dots, \vec{r}_N)$$

And computing the equation of the Euler-Lagrange equation:

$$\begin{aligned} \frac{\partial \mathcal{L}}{\partial \dot{r}_i} &= m_i \dot{r}_i \\ \frac{\partial \mathcal{L}}{\partial r_i} &= -\frac{\partial U}{\partial \vec{r}_i} \end{aligned}$$

So that, putting everything together:

$$m_i \ddot{r}_i + \underbrace{\frac{\partial U}{\partial \vec{r}_i}}_{= \vec{F}_i} = 0 \Rightarrow \underbrace{m_i \ddot{r}_i}_{\text{Newton's equation}} = \vec{F}_i$$

#### 4.2.1.1 Harmonic oscillator

Considering for example the harmonic oscillator the Lagrangian will be:

$$\mathcal{L}(x, \dot{x}) = \underbrace{\frac{1}{2} m \dot{x}^2}_K - \underbrace{\frac{1}{2} k x^2}_U$$

And, taking all the derivatives:

$$\frac{d}{dt} (m \dot{x}) + kx = 0 \Rightarrow m \ddot{x} - kx = 0$$

The equation for the harmonic oscillator is obtained.

### 4.2.2 Conservation of energy

The Lagrangian equation can be applied even to very complex systems. Another issue involves the energy. Let the equation of the energy be:

$$E = \underbrace{\frac{1}{2} \sum_i m_i \dot{r}_i^2}_K + U(\vec{r}_1, \dots, \vec{r}_N)$$

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The sum of the potential and kinetic energy.

Then, taking the derivative of energy with respect to time:

$$\begin{aligned}\frac{dE}{dt} &= \sum_i m_i \dot{\vec{r}}_i \ddot{\vec{r}}_i + \sum_i \frac{\partial U}{\partial \vec{r}_i} \dot{\vec{r}}_i = \\ &= \sum_i \dot{\vec{r}}_i \left[ m_i \ddot{\vec{r}}_i + \frac{\partial U}{\partial \vec{r}_i} \right] = \\ &= \sum_i \dot{\vec{r}}_i [m_i \ddot{\vec{r}}_i - \vec{F}_i] = 0\end{aligned}$$

So that the energy is conserved in time. Following Lagrangian mechanics then the energy will be conserved. If energy is not conserved serious mistake are done in a molecular simulation.

### 4.2.3 Generalized coordinates

Introducing generalized coordinates, for example when studying small molecules in chemistry:

$$q_\alpha = f_\alpha(\vec{r}_1, \dots, \vec{r}_N) \quad \alpha = 1, \dots, 3N$$

These are functions of the coordinates and are  $3N$  generalized coordinates that take the place of the Cartesian coordinates. To go back from generalized to Cartesian coordinates:

$$\vec{r}_i = \vec{g}_i(q_1, d \dots, q_{3N}) \quad i = 1, \dots, N$$

Trying to write the Lagrangian in generalized coordinates the kinetic part has to be recomputed. The velocity of particle  $i$  with respect to the new generalized coordinates. So the derivative of  $\vec{r}_i$  with respect to  $q_\alpha$  multiplied by the derivative in time of  $q_\alpha$ . This is summed over all the generalized coordinates.

$$\dot{\vec{r}}_i = \sum_{\alpha=1}^{3N} \frac{\partial \vec{r}_i}{\partial q_\alpha} \dot{q}_\alpha$$

Writing the kinetic energy as a function of the generalized coordinates the velocity has to be included twice.

$$\tilde{K}(q, \dot{q}) = \frac{1}{2} \sum_{\alpha=1}^{3N} \sum_{\beta=1}^{3N} \left[ \sum_{i=1}^N m_i \frac{\partial \vec{r}_i}{\partial q_\alpha} \frac{\partial \vec{r}_i}{\partial q_\beta} \right] \dot{q}_\alpha \dot{q}_\beta$$

And introducing the metric mass tensor  $G_{\alpha\beta} = \left[ \sum_{i=1}^N m_i \frac{\partial \vec{r}_i}{\partial q_\alpha} \frac{\partial \vec{r}_i}{\partial q_\beta} \right]$ :

$$\tilde{K}(q, \dot{q}) = \frac{1}{2} \sum_{\alpha=1}^{3N} \sum_{\beta=1}^{3N} G_{\alpha\beta} \dot{q}_\alpha \dot{q}_\beta$$

Then the Lagrangian in generalized coordinates becomes:

$$\mathcal{L}(q, \dot{q}) = \frac{1}{2} \sum_{\alpha=1}^{3N} \sum_{\beta=1}^{3N} G_{\alpha\beta} \dot{q}_\alpha \dot{q}_\beta - U(q_1, \dots, q_{3N})$$

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And the Euler-Lagrange equations:

$$\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) - \frac{\partial \mathcal{L}}{\partial q_\alpha} = 0$$

In a molecular simulations the objective is to solve the Lagrangian's equation in the Hamiltonian form.

### 4.2.4 Legendre transforms

Legendre transforms will be used to go from a Lagrangian to an Hamiltonian description and are also useful in thermodynamics. Thermodynamics potentials are all Legendre transforms of one another. To go from one ensemble to another a Legendre transform is used. The aim of a Legendre transform is to express the function  $f(x)$  in terms of its first derivative  $s$ :

$$s = f'(x) \equiv g(x)$$

The derivative of a function is the slope of the function in each point. In principle from the slope the function at each point it is not possible to reconstruct the original function. The reason for that is that translation information is lost when taking the derivative. To be able to perform this operation the intersection of the tangent at each point with the  $x$  axis in the curve the full function can be reconstructed. So at each point the slope and where the tangent intersect the  $x$  axis is needed to reconstruct the original function:

$$f(x_0) = f'(x_0)x_o + b(x_0)$$

Where  $b(x_0)$  is the intersection of the tangent with the  $x$  axis. Considering the general form:

$$f(x) = f'(x)x + b(x)$$

$b$  represent the functions in term of  $s$ . There is a need to isolate the  $b$  contribution and then write everything in term of  $s$ . So there is a need to invert  $g$  to obtain  $x$  as a function of  $s$ .

$$f'(x) = g(x) = s \Rightarrow x = g^{-1}(s)$$

Hence  $b(x)$  contains the same information as  $f(x)$ :

$$b(g^{-1}(s)) = f(g^{-1}(s)) - sg^{-1}(s) \equiv \tilde{f}(s)$$

The Legendre transom is then:

$$\tilde{f}(s) = f(x(s)) - sx(s)$$

#### 4.2.4.1 Legendre transform for multiple variables

Considering  $n$  variables:

$$s_1 = \frac{\partial f}{\partial x_1} = g_1(x_1, \dots, x_n), \dots, s_n = \frac{\partial f}{\partial x_n} = g_1(x_1, \dots, x_n)$$

So the Legendre transform:

$$\tilde{f}(s_1, \dots, s_n) = f(x_1(s_1, \dots, s_n), \dots, x_n(s_1, \dots, s_n)) - \sum_i s_i x_i(s_1, \dots, s_n)$$

This holds for a subset of variables. This is important as most of the thermodynamics quantities can be expressed as derivatives of some other quantity, so everything is expressed in term of another variable.

### 4.3 Hamiltonian formulation

In the Hamiltonian formulation the conjugate momentum is obtained from the Lagrangian: the derivative of the Lagrangian with respect to velocity is the momentum.

$$\vec{p}_i \equiv \frac{\partial \mathcal{L}}{\partial \dot{\vec{r}}_i} = \frac{\partial}{\partial \dot{\vec{r}}_i} \left[ \frac{1}{2} \sum_{j=1}^N m_j \dot{\vec{r}}_j^2 - U(\vec{r}_1, \dots, \vec{r}_N) \right] = m_i \dot{\vec{r}}_i$$

To express everything as a function of coordinate and momenta a Legendre transform of the Lagrangian needs to be performed, observing that the momentum is the derivative of the Lagrangian with respect to velocity.

$$\begin{aligned} \tilde{\mathcal{L}}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) &= \mathcal{L}(\vec{r}_1, \dots, \vec{r}_N, \dot{\vec{r}}_1(\vec{p}_1), \dots, \dot{\vec{r}}_N(\vec{p}_N)) - \sum_i \vec{p}_i \dot{\vec{r}}_i(\vec{p}_i) = \\ &= \underbrace{\frac{1}{2} \sum_{i=1}^N m_i \left( \frac{\vec{p}_i}{m_i} \right)^2}_{\text{Lagrangian}} - U(\vec{r}_1, \dots, \vec{r}_N) - \sum_{i=1}^N \vec{p}_i \frac{\vec{p}_i}{m_i} = \\ &= - \underbrace{\sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i}}_{\text{Kinetic energy}} - U(\vec{r}_1, \dots, \vec{r}_N) \end{aligned}$$

It can be seen how the Legendre transform of the Lagrangian is the opposite of the total energy of the system. The Hamiltonian is then defined as the opposite of the Legendre transform of the Lagrangian:

$$\mathcal{H}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) = -\tilde{\mathcal{L}}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N)$$

So that it is the sum of the kinetic and potential energy:

$$\mathcal{H}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) = \sum_i \vec{p}_i \dot{\vec{r}}_i(\vec{p}_i) - \mathcal{L}(\vec{r}_1, \dots, \vec{r}_N, \dot{\vec{r}}_1(\vec{p}_1), \dots, \dot{\vec{r}}_N(\vec{p}_N))$$

Or the total energy of the system:

$$\mathcal{H}(\vec{r}_1, \dots, \vec{r}_N, \vec{p}_1, \dots, \vec{p}_N) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N)$$

The Hamiltonian is related to the Legendre transform of the Lagrangian. Using the Hamiltonian description, it is expected that the Hamiltonian formulation has the same results from the Lagrangian formulation. Another equation needs to be added.

### 4.3.1 Generalized coordinates

The same thing can be done to generalized coordinates:

$$p_\alpha = \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} = \sum_\beta G_{\alpha\beta} \dot{q}_\beta \Rightarrow \dot{q}_\alpha = \sum_\beta G_{\alpha\beta}^{-1} p_\beta$$

So that the Hamiltonian becomes:

$$\begin{aligned} \mathcal{H}(q_1, \dots, q_{3N}, p_1, \dots, p_{3N}) &= \sum_\alpha p_\alpha \dot{q}_\alpha - \mathcal{L}(q_1, \dots, q_{3N}, \dot{q}_1, \dots, \dot{q}_{3N}) = \\ &= \frac{1}{2} \sum_\alpha \sum_\beta p_\alpha G_{\alpha\beta}^{-1} p_\beta + U(q_1, \dots, q_{3N}) \end{aligned}$$

### 4.3.2 Hamilton's equations

Now two sets of equations are obtained, but both are first order derivative in time, so that they are easier to solve both analytically and numerically with respect to the Euler-Lagrangian equation. Because of this the simulations will use Hamilton's equation.

$$\dot{q}_\alpha = \frac{\partial \mathcal{H}}{\partial p_\alpha} \quad \dot{p}_\alpha = -\frac{\partial \mathcal{H}}{\partial q_\alpha}$$

Taking the derivative of the Hamiltonian with respect to time:

$$\begin{aligned} \frac{d\mathcal{H}}{dt} &= \sum_\alpha \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \dot{q}_\alpha + \frac{\partial \mathcal{H}}{\partial p_\alpha} \dot{p}_\alpha \right] = \\ &= \sum_\alpha \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} - \frac{\partial \mathcal{H}}{\partial p_\alpha} \frac{\partial \mathcal{H}}{\partial q_\alpha} \right] = \\ &= \sum_\alpha \left[ \cancel{\frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha}} - \cancel{\frac{\partial \mathcal{H}}{\partial p_\alpha} \frac{\partial \mathcal{H}}{\partial q_\alpha}} \right] = 0 \end{aligned}$$

Because the Hamiltonian is the total energy of the system it should be conserved as it describes the same system as the Lagrangian. In conclusion Hamiltonian mechanics keeps energy constant:

$$\mathcal{H}(q_1, \dots, q_{3N}, p_1, \dots, p_{3N}) = \text{const}$$

So energy conservation should hold for any simulation written for Hamiltonian mechanics.

### 4.3.3 Conservation laws

This process can be generalized for any conserved quantity. Let  $a(x_t)$  a property that depends on the trajectory of the system. In order to check if the property is conserved or not the derivative with respect to time have to be taken:

$$\frac{da}{dt} = \frac{\partial a}{\partial x_t} \dot{x}_t = \sum_\alpha \left[ \frac{\partial a}{\partial q_\alpha} \dot{q}_\alpha + \frac{\partial a}{\partial p_\alpha} \dot{p}_\alpha \right] = \sum_\alpha \left[ \frac{\partial a}{\partial q_\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} - \frac{\partial a}{\partial p_\alpha} \frac{\partial \mathcal{H}}{\partial q_\alpha} \right] = \{a, \mathcal{H}\}$$

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Where the Poisson brackets of two quantities depending on  $q$  and  $p$ :

$$\{a, b\} = \sum_{\alpha} \left[ \frac{\partial a}{\partial q_{\alpha}} \frac{\partial b}{\partial p_{\alpha}} - \frac{\partial a}{\partial p_{\alpha}} \frac{\partial b}{\partial q_{\alpha}} \right]$$

To check if a quantity is conserved its Poisson bracket with the Hamiltonian need to be considered. If it is 0, then the quantity is conserved:

$$\{a, \mathcal{H}\} = 0 \Rightarrow \frac{da}{dt} = 0$$

So conservation laws are directly translated into this property of the Poisson brackets.

#### 4.3.4 Compressibility

Compressibility of an equation is the divergence of the velocities. Define:

$$\dot{x} = \eta(x) = (\dot{q}_1, \dots, \dot{q}_{3N}, \dot{p}_1, \dots, \dot{p}_{3N})$$

The time derivative of all points in the phase space. This vector  $\eta$  because of Hamilton equation will be equal to:

$$\eta(x) = \left( \frac{\partial \mathcal{H}}{\partial p_1}, \dots, \frac{\partial \mathcal{H}}{\partial p_{3N}}, -\frac{\partial \mathcal{H}}{\partial q_1}, \dots, -\frac{\partial \mathcal{H}}{\partial q_{3N}} \right)$$

The divergence of this quantity is computed, taking the derivative of each component with respect to the coordinate itself.

$$\begin{aligned} \nabla_x \dot{x} &= \sum_{\alpha} \left[ \frac{\partial \dot{p}_{\alpha}}{\partial p_{\alpha}} + \frac{\partial \dot{q}_{\alpha}}{\partial q_{\alpha}} \right] = \\ &= \sum_{\alpha} \left[ -\frac{\partial}{\partial p_{\alpha}} \frac{\partial \mathcal{H}}{\partial q_{\alpha}} + \frac{\partial}{\partial q_{\alpha}} \frac{\partial \mathcal{H}}{\partial p_{\alpha}} \right] = \\ &= \sum_{\alpha} \left[ -\frac{\partial^2 \mathcal{H}}{\partial p_{\alpha} \partial q_{\alpha}} + \frac{\partial^2 \mathcal{H}}{\partial q_{\alpha} \partial p_{\alpha}} \right] = \\ &= \sum_{\alpha} \left[ \cancel{-\frac{\partial^2 \mathcal{H}}{\partial p_{\alpha} \partial q_{\alpha}}} + \cancel{\frac{\partial^2 \mathcal{H}}{\partial q_{\alpha} \partial p_{\alpha}}} \right] = 0 \end{aligned}$$

So, in conclusion  $\nabla_x \dot{x} = 0$  and the divergence of the velocity is 0, then Hamilton's equations are incompressible: they lead to an incompressible flow of points in phase-space. This is a way to check whether a system is Hamiltonian.

#### 4.3.5 Symplectic structure

Hamilton's equations have a symplectic structure and can be written as:

$$\dot{x} = M \frac{\partial \mathcal{H}}{\partial x} \quad M = \begin{pmatrix} 0 & I \\ -I & 0 \end{pmatrix}$$

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A trajectory in phase space  $x_t = x_t(x_0)$  is a function of the initial positions and momenta or velocity. However it can be viewed also as a transformation of variables. This is done through the Jacobian:

$$J_{kl} = \frac{\partial x_t^k}{\partial x_o^l}$$

Applying the Jacobian transformation to the symplectic matrix  $M$  the original matrix is obtained:  $M = J^T M J$ . This is called the symplectic property and Hamilton's equations satisfy it.

# Chapter 5

## Theoretical foundations of statistical mechanics

### 5.1 Introduction

#### 5.1.1 Loschmidt's paradox

When studying Newton's equation in any formulation, inverting the arrow of time, it is always possible to trace back any trajectory and to obtain the solutions. This is intrinsic in the Newton's equations. In reality this is not the case: some of the processes cannot be traced back and are irreversible. This is Loschmidt's paradox: the problem is that macroscopic systems are composed of a too large number of particles. And although in principle, the trajectory of each of them can be known, in the macroscopic process things are not obvious and a reasoning in term of probability have to be done. This is the objective of statistical mechanics: try to describe system with a very large number of degrees of freedom.

### 5.2 Thermodynamics

#### 5.2.1 Thermodynamic system

A thermodynamic system is any macroscopic system. In general a macroscopic system has a number of particles similar to the Avogadro number. This is not the case for molecular simulations, but the system is close to the thermodynamic limits but it is not a macroscopic system. The system is not really a thermodynamic system.

##### 5.2.1.1 Isolated systems

A system is defined as isolated whenever no energy or mass transfer can be seen across its boundary. Considering the system's boundaries in molecular simulations periodic boundaries conditions are used and the reason that they are used is because boundaries effects have to be avoided. The boundaries will be more important the smaller the system is.

### 5.2.2 Thermodynamic equilibrium

A thermodynamic system is in thermodynamic equilibrium if its thermodynamic state does not change in time. When dealing with biological system the equilibrium is never reached, but only stationary or steady-states. This means that the system is in a local equilibrium and will remain there most of the time.

### 5.2.3 Thermodynamic state

A thermodynamic state is specified in terms of macroscopic parameters that are measurable quantities like:

- Pressure  $P$ .
- Volume  $V$ .
- Temperature  $T$ .
- Total mass  $M$ .
- Number of particles  $N$ .

This is important because some procedures are needed to measure starting from the coordinates and the velocity of the system these quantities in a simulation. These are the parameters that are compared with the experimental results.

### 5.2.4 Equation of state

Whenever a thermodynamic system is being described an equation can be written and that equations establishes a relations between the measurables:

$$g(N, P, V, T) = 0$$

As an example the equation of state for the ideal gas is:

$$PV - nRT = 0$$

The equation of state deals with thermodynamics state, which are assumed to be at equilibrium. So the equation of state describes only equilibrium states.

### 5.2.5 Thermodynamic transformations

A thermodynamic transformation is a change of thermodynamic state. At equilibrium the only way to change it is to change the external conditions, like changing pressure. These transformations can be:

- Reversible: following equilibrium states and it is always possible to have the reverse transformation.
- Irreversible: non-equilibrium states are reached and when going back a different path is created. It is possible to reverse the process but the transformation is different from the forward one.

### 5.2.6 State function

A state function is defined as:

$$f(n, P, V, T)$$

It does not depend on the pathway of a transformation. And its change depends only on the initial and final states. There are many state functions like entropy or total energy. They are important because they can describe the effect of a transformation without knowing the nature of the transformation. The state functions itself depend on some parameters, which are the thermodynamics variables, which are not independent to each other.

### 5.2.7 Work

A reversible work performed on a system is defined as:

$$dW_{rev} = -PdV + \mu dN$$

So an infinitesimal amount of work come from a pressure contribution and the other is the contribution coming from the change of particles in the system. In this case the work is positive when the volume is decreasing, adding particles there is work performed on a system.  $\mu$  is the chemical potential.

### 5.2.8 Heat

The heat added to the system is:

$$dQ_{rev} = CdT$$

Heat is assumed to be positive when it is added to the system and that it is added in a reversible manner. A change in heat correspond to a change in temperature if there is not a phase transition. During a phase transition the temperature remains fixed but heat is still added.  $C$  is the specific heat.

### 5.2.9 First law of thermodynamics

In any thermodynamic transformation if a system absorbs an amount of heat  $\Delta Q$  and has an amount of work  $\Delta W$  performed on it, its internal energy will change by an amount  $\Delta E$  given by:

$$\Delta E = \Delta Q + \Delta W$$

This law is the conservation of energy: adding heat or performing work on the system energy is being provided. Where  $E$  is a state function, although  $Q$  and  $W$  are not:

$$\Delta E = \Delta Q_{rev} + \Delta W_{rev} = \Delta Q_{irrev} + \Delta W_{irrev}$$

So the change in energy depend only on the initial and final state: it is always possible to compute the difference in energy for every transformation knowing only the initial and final state.

### 5.2.10 Second law of thermodynamics

There are two statements for the second law of thermodynamics which are completely equivalent.

### 5.3. THE ENSEMBLE

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#### 5.2.10.1 Kelvin's formulation

There exists no thermodynamic transformation whose sole effect is to extract a quantity of heat from a high-temperature source and convert it entirely into work.

#### 5.2.10.2 Clausius' formulation

There exists no thermodynamic transformation whose sole effect is to extract a quantity of heat from a cold source and deliver it to a hot source.

#### 5.2.11 Entropy

The second law allow to define entropy. Entropy is a state function defined as:

$$\Delta S = S_2 - S_1 = \int_1^2 \frac{dQ_{rev}}{T}$$

The change in entropy depends only on the initial and the final state. It is a direct measure of the disorder of the system. There is no tool that can measure directly entropy.

#### 5.2.12 Third law of thermodynamics

The third law of thermodynamics allow to find a reference state which can help to compute the absolute value of entropy. The reference state is the one at  $0K$ . The entropy of a system at the absolute zero of temperature is a universal constant, which can be taken to be zero. Finding a reversible transformation from  $0K$  to any state an absolute value for any state and system can be found.

### 5.3 The ensemble

Defining thermodynamics from a macroscopic perspective the central concept is the ensemble. A collection of systems described by the same set of microscopic interactions and sharing a common set of macroscopic properties is said to be an ensemble. Only equilibrium ensembles will be considered. In equilibrium ensembles the systems in them evolve in time, but average quantities remain the same. So all particles move in time, but the average quantities of the macroscopic measurables remain the same. Now considering a macroscopic observable  $A$ :

$$A = \frac{1}{Z} \sum_{\lambda=1}^N \underbrace{a(x_\lambda)}_{\text{Phase space microscopic function}} \quad \equiv \quad \overbrace{\langle a \rangle}^{\text{Ensemble average}}$$

So any macroscopic observable is an average of the ensemble. So during a simulation there are several copies of a system, then a simulation of each copy must be taken and the average will be the result.

#### 5.3.1 Phase space volume

Let a microstate of a system is a point in the phase space:

$$x_0 = (q_1(0), \dots, q_{3N}(0), p_1(0), \dots, p_{3N}(0))$$

### 5.3. THE ENSEMBLE

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Assuming that this is the initial state of the system and its evolution according to Hamilton's equation will be observed. The phase space volume element  $dx_0$  contains a collection of microstates surrounding  $x_0$ . Thinking in term of ensemble the difference in macroscopic quantities will be small and will contain a number of microstate that can or not be part of the ensemble. This volume element evolves according to Hamilton's equation into  $dx_t$ , another volume element:

$$dx_t = J(x_t; x_0) dx_0$$

Where:

- $J(x_t; x_0) = \det J$ .
- $J_{kl} = \frac{\partial x_t^k}{\partial x_0^l}$  is the Jacobian.

The time evolution of the phase space volume requires knowledge of the time evolution of the Jacobian.

#### 5.3.1.1 Time evolution of the Jacobian

Consider the determinant of the Jacobian:

$$\det J = e^{Tr(\ln J)}$$

This is the exponential of the trace of the logarithm of  $J$  and this allow to take easier derivatives. The trace operator is the some of the diagonal element of the matrix and it has the property to be always the same of a matrix: it is an invariant. In the case of the Jacobian:

$$Tr J = \sum_k J_{kk} = \sum_k \lambda_k$$

Where  $\lambda_k$  are the eigenvalues. Then:

$$e^{Tr(\ln J)} = e^{\sum_k \ln \lambda_k} = \prod_k \lambda_k$$

Now the time evolution of the Jacobian:

$$\begin{aligned} \frac{d}{dt} J(x_t; x_0) &= \frac{d}{dt} \det J = \frac{d}{dt} e^{Tr(\ln J)} = e^{Tr(\ln J)} Tr\left(\frac{dJ}{dt} J^{-1}\right) = \\ &= J(x_t; x_0) \sum_{k,l} \left( \frac{dJ_{kl}}{dt} J_{lk}^{-1} \right) = J(x_t; x_0) \sum_{k,l} \left( \frac{\partial \dot{x}_t^k}{\partial x_0^l} \frac{\partial x_0^l}{\partial x_t^k} \right) = \\ &= j(x_t; x_0) \sum_k \frac{\partial \dot{x}_t^k}{\partial x_t^k} = 0 \end{aligned}$$

It is equal to zero because it is the compressibility of the system. So the time derivative of the quantity is equal to zero, so it means that the quantity itself is constant, so that the quantity, the determinant is equal to zero.

### 5.3. THE ENSEMBLE

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#### 5.3.2 Liouville's theorem

In particular:

$$\frac{dJ(x_t; x_0)}{dt} = 0 \Rightarrow J(x_t; x_0) = \text{const}$$

However:

$$J(x_0; x_0) = 1 \Rightarrow J(x_t; x_0) = 1$$

This is because a transformation into itself is an identity matrix, so it is always equal to 1, so the determinant of the Jacobian is always equal to 1. The phase space element  $dx_0$  does not change in time and  $dx_t = dx_0$ .

#### 5.3.3 Ensemble distribution function

Focussing on a point  $x$  in phase space and on a small volume around it. The ensemble distribution function  $f(x, t)dx$  is the fraction of the total ensemble members contained in the phase space volume element  $dx$  at time  $t$ .  $f(x, t)$  verifies the typical properties of a probability density:

$$f(x, t) \geq 0$$

And integrating over the entirety of the phase space:

$$\int f(x, t)dx = 1$$

So there is a relation between the probability density and the ensemble distribution function. The objective of statistical mechanics is to find the shape of this function  $f$ .

#### 5.3.4 Outward flux

Now the focus is how the ensemble distribution function evolves in time. The rate of decrease of ensemble members in a given volume  $\Omega$  is:

$$-\frac{d}{dt} \int_{\Omega} f(x_t, t)dx_t = - \int_{\Omega} dx_t \frac{\partial f(x, t)}{\partial t}$$

So the integral over a volume element  $\Omega$ , counting the fraction of ensemble members in the volume, minus the time derivative of that is the rate of decrease. Assuming that  $\Omega$  is not changing in time,  $dx_t$  does not change because of Liouville's theorem. The only thing that might change is the ensemble distribution function, and it changes only if the ensemble distribution function has an explicit time dependence. The only way to change the number of the ensemble member is only if the ensemble distribution function has an explicit time dependence. There are no sink or sources of ensemble member and they change only if ensemble members pass through the surface  $S$  of the volume  $\Omega$ . The outward flux of ensemble members leaving  $\Omega$  is then

$$\int_S \dot{x}_t \cdot \hat{n} f(x_t, t)$$

Where  $\dot{x}_t$  is the velocity in phase space with a dot product with a vector  $\hat{n}$ , a unit vector normal to the surface times the ensemble distribution function. With this quantity the divergence theorem can be applied:

$$\int_S \dot{x}_t \cdot \hat{n} f(x_t, t) = \int_{\Omega} \nabla_{x_t} \cdot [\dot{x}_t f(x_t, t)] dx_t$$

So the surface integral is translated in a volume integral taking the divergence of vector  $\dot{x}_t f(x_t, t)$ .

### 5.3.5 Liouville's equation

Writing down together the previous two results, the volume integral, the rate of decrease of ensemble element is equal to the flux:

$$\int_{\Omega} \nabla_{x_t} \cdot [\dot{x}_t f(x_t, t)] dx_t = - \int_{\Omega} \frac{\partial f(x_t, t)}{\partial t} dx_t$$

So the number inside the integral have to coincide:

$$\int_{\Omega} \left\{ \frac{\partial f(x_t, t)}{\partial t} + \nabla_{x_t} \cdot [\dot{x}_t f(x_t, t)] \right\} dx_t = 0 \Rightarrow \frac{\partial f(x_t, t)}{\partial t} + \nabla_{x_t} \cdot [\dot{x}_t f(x_t, t)] = 0$$

This implies that the argument of the integral has to be equal to 0 because it is valid for any value of  $\Omega$ , obtaining a differential equation that will be satisfied for the ensemble distribution function. Writing down the equation more explicitly on the divergence:

$$\frac{\partial f(x_t, t)}{\partial t} + (\nabla_{x_t} \cdot \dot{x}_t) f(x_t, t) + \dot{x} \cdot \nabla_{x_t} f(x_t, t) = 0$$

Note that the divergence of the velocity is the compressibility, so that it is equal to zero, cancelling out the second element:

$$\frac{\partial f(x_t, t)}{\partial t} + \dot{x}_t \cdot \nabla_{x_t} f(x_t, t) = 0 \Rightarrow \frac{df(x_t, t)}{dt} = 0$$

So that the total derivative of  $f$  is equal to zero. This means that the ensemble distribution function, won't change in time.

#### 5.3.5.1 Consequence on averages

Considering the previous result:

$$\frac{df(x_t, t)}{dt} = 0 \Rightarrow f(x_t, t) = f(x_0, 0)$$

And putting together Liouville's theorem and equation:

$$f(x_t, t) dx_t = f(x_0, 0) dx_0$$

So that there is a conserved fraction of ensemble members and averages can be performed at any time. So the result on averages is always the same because the ensemble members will be conserved during the trajectory.

### 5.3. THE ENSEMBLE

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#### 5.3.5.2 A more elegant form

In a more elegant formalism the same formula can be written introducing  $\eta$  the velocity, written down in term of the Hamiltonian

$$\frac{\partial f(x, t)}{\partial t} + \dot{x} \cdot \nabla_x f(x, t) = \frac{\partial f(x, t)}{\partial f} + \eta(x, t) \cdot \nabla_x f(x, t) = 0$$

So that the function corresponds to the Poisson's brackets:

$$\frac{\partial f(x, t)}{\partial t} + \{f(x, t), \mathcal{H}(x, t)\} = 0$$

#### 5.3.6 Equilibrium solutions

For a macroscopic observable  $A$ :

$$A = \langle a(x) \rangle = \int a(x) f(x, t) dx$$

This is an average over an ensemble of a microscopic coordinate. This can be written as the integral using the ensemble distribution function and that is the ensemble average. So to have  $A$  constant in time  $f$  cannot depend on time. An explicit time dependence of  $t$  implies an explicit time dependence of  $A$  hence at equilibrium it is required that:

$$\frac{\partial f(x, t)}{\partial t} = 0 \Rightarrow \{f(x, t), \mathcal{H}(x, t)\} = 0$$

So ensemble distribution functions must satisfy this equation. So there is a general solution:

$$f(x) \propto \mathcal{F}(\mathcal{H}(x))$$

Where the ensemble distribution function, a probability density must be proportional to some function of the Hamiltonian. So that the solution can be written exactly:

$$Z = \int dx \mathcal{F}(\mathcal{H}(x)) \Rightarrow f(x) = \frac{1}{Z} \mathcal{F}(\mathcal{H}(x))$$

So that the number  $Z$  a function of the thermodynamics parameters is a partition function and  $f$  can be written exactly. The integral is on the entire phase space. Most of statistical mechanics involves on computing the partition function, allowing to find the ensemble distribution function to find all the macroscopic observables allowing to compare with experimental results.

# Chapter 6

## Microcanonical ensemble

### 6.1 Introduction

All the other algorithm used in molecular simulation are evolutions of the microcanonical ensemble. The microcanonical ensemble is a collection of systems which share the same macroscopic parameters and corresponds to different microstates. When comparing with an experimental observable the average of these quantities has to be taken. The microcanonical is the starting point of statistical mechanics. The number of particles, the total volume and the energy are kept fixed. This has some resemblance on Hamiltonian ensemble and so the microcanonical ensemble will be the natural ensemble for Hamiltonian mechanics.

### 6.2 State function depending on number of particle, volume and energy

Since volume, number of energy and number of particles are fixed a state function has to be defined. Starting from the first law of thermodynamics:

$$dE = dQ_{rev} + dW_{rev}$$

From the definition of entropy an infinitesimal variation of entropy will be:

$$dS = \frac{dQ_{rev}}{T} \Rightarrow dQ_{rev} = TdS$$

Looking now at  $dW$ :

$$dW_{rev} = -PdV + \mu dN$$

Where  $\mu$  is the chemical potential. Putting everything together with the energy:

$$dE = TdS - PdV + \mu dN$$

So that the state function of  $N$ ,  $V$  and  $E$  is entropy:

$$dS = \frac{1}{T}dE + \frac{P}{T}dV - \frac{\mu}{T}dN$$

## 6.2. STATE FUNCTION DEPENDING ON NUMBER OF PARTICLE, VOLUME AND ENERGY

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### 6.2.1 Thermodynamic derivatives

Now, starting from the state function, the infinitesimal variation of  $S$  with respect to the variables can be written as:

$$\begin{aligned} dS &= \frac{1}{T}dE + \frac{P}{T}dV - \frac{\mu}{T}dN = \\ &= \left(\frac{\partial S}{\partial E}\right)_{V,N} dE + \left(\frac{\partial S}{\partial V}\right)_{N,E} dV + \left(\frac{\partial S}{\partial N}\right)_{V,E} dN \end{aligned}$$

Now a formula for the three elements of the state function can be found:

$$\bullet \left(\frac{\partial S}{\partial E}\right)_{V,N} = \frac{1}{T}. \quad \bullet \left(\frac{\partial S}{\partial V}\right)_{N,E} = \frac{P}{T}. \quad \bullet \left(\frac{\partial S}{\partial N}\right)_{V,E} = \frac{\mu}{T}.$$

If entropy is known as a function of energy, volume and number of molecule, temperature, pressure and the chemical potential all the thermodynamics can be reconstructed.

### 6.2.2 Dirac's delta function

Dirac's delta function is a function in the form:

$$\delta(x) = \begin{cases} +\infty & x = 0 \\ 0 & \text{otherwise} \end{cases}$$

This function has some interesting properties:

$$\begin{aligned} \bullet \delta(x) &= \delta(-x). & \bullet \int_{-\infty}^{+\infty} dx \delta(x) &= 1. \\ \bullet \delta(x) &= \frac{d\theta(x)}{dx}, \text{ where: } \theta(x) = \begin{cases} 1 & x \geq 0 \\ 0 & x < 0 \end{cases}. & \bullet \int_{-\infty}^{+\infty} dx \delta(x) f(x) &= f(0). \end{aligned}$$

### 6.2.3 Computing entropy

The problem in the microcanonical ensemble is to find  $S$ . Considering Boltzmann's relation  $S(N, V, E) = k \ln \Omega(N, V, E)$ , where  $\Omega(N, V, E)$  is the number of microscopic states of the system. The number of microscopic states of the system compatible with the condition of the system given by the values of  $N$ ,  $V$  and  $E$ . To compute  $\Omega$  the distribution function in the case of the microcanonical function:  $f(x) = \mathcal{F}(\mathcal{H}(x)) = M \Delta(\mathcal{H}(x) - E)$ . So that the energy is equal to the Hamiltonian. The constant  $M$  is a normalization constant to make  $f$  a distribution function. Now to count the number of the microscopic state all the microstate compatible with a given condition need to be summed over:

$$\Omega(N, V, E) = M_N \int d\vec{p}_1 \cdots \int d\vec{p}_N \int_{D(V)} d\vec{r}_1 \cdots \int_{D(V)} d\vec{r}_N \delta(\mathcal{H}(\vec{r}, \vec{p}) - E)$$

So integrating over all the momenta and all the coordinates in the domain of  $V$   $D(V)$ , so the coordinates vary in the coordinate of  $V$  which is fixed. Or, for simplicity the function can be written as:

$$\Omega(N, V, E) = M_N \int d\vec{p} \int_{D(V)} d\vec{r} \delta(\mathcal{H}(\vec{r}, \vec{p}) - E) = M \int dx \delta(\mathcal{H}(x) - E)$$

Where  $x$  is a point in phase space and  $M_N$  is:

$$M_N = \frac{E_0}{N! h^{3N}}$$

Where  $h$  is Planck's constant and  $N!$  is added in order to solve Gibbs paradox and is correct Boltzmann counting.

### 6.3 Average quantities

An average quantity can be obtained through:

$$A = \langle a \rangle = \frac{M_N}{\Omega(N, V, E)} \int dx a(x) \delta(\mathcal{H}(x) - E) = \frac{\int dx a(x) \delta(\mathcal{H}(x) - E)}{\int dx \delta(\mathcal{H} - E)}$$

There is no time dependence so equilibrium is assumed. The last term is a typical formula, with at the numerator an integral over the average of the microscopic property and at the denominator an integral of a partition function. Considering a given variable  $x_i$ , an object in phase space times the derivative on the Hamiltonian over another object in phase space.  $x_i$  and  $x_j$  are two distinct objects. To do so:

$$\begin{aligned} \left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle &= \frac{M_N}{\Omega(N, V, E)} \int dx x_i \frac{\partial \mathcal{H}}{\partial x_j} \delta(E - \mathcal{H}(x)) = \\ &= \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int dx x_i \frac{\partial \mathcal{H}}{\partial x_j} \theta(E - \mathcal{H}(x)) = \\ &= \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int_{\mathcal{H}(x) < E} dx x_i \frac{\partial \mathcal{H}}{\partial x_j} = \\ &= \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int_{\mathcal{H}(x) < E} dx x_i \frac{\partial(\mathcal{H} - E)}{\partial x_j} \end{aligned}$$

#### 6.3.1 Virial theorem

The Virial theorem allows to find the ensemble average of that quantity:

### 6.3. AVERAGE QUANTITIES

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$$\begin{aligned}
\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle &= \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int_{\mathcal{H}(x) < E} dx x_i \frac{\partial(\mathcal{H} - E)}{\partial x_j} = \\
&= \underbrace{\frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int_{\mathcal{H} < E} dx \delta_{ij} (E - \mathcal{H})}_{\text{Integrating by part}} = \\
&= \frac{M_N}{\Omega(N, V, E)} \frac{\partial}{\partial E} \int dx \delta_{ij} (E - \mathcal{H}) \theta(E - \mathcal{H}) = \\
&= \frac{E_0}{N! h^{3N} \Omega(N, V, E)} \delta_{ij} \int dx \theta(E - \mathcal{H}) = \\
&= \delta_{ij} \frac{\Sigma(E)}{\frac{\partial \Sigma(E)}{\partial E}}
\end{aligned}$$

Where:

- $\Sigma(N, V, E) = \frac{1}{N! h^{3N}} \int dx \theta(E - \mathcal{H})$ , the uniform ensemble and is all the points where the Hamiltonian is less than the energy.
- $\Omega(N, V, E) = E_0 \frac{\partial \Sigma(N, V, E)}{\partial E}$ .

So:

$$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = \delta_{ij} \frac{\Sigma(E)}{\frac{\partial \Sigma(E)}{\partial E}} = \delta_{ij} \left( \frac{\partial \ln \Sigma(E)}{\partial E} \right)^{-1}$$

Considering Boltzmann's relation:

$$S(N, V, E) = k \ln \Omega(N, V, E) \simeq k \ln \Sigma(N, V, E) = \tilde{S}(N, V, E)$$

The difference between  $S$  and  $\tilde{S}$  is close to the logarithm of  $N$ . If  $N$  is very big the difference is not very significative.

Then:

$$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = k \delta_{ij} \left( \frac{\partial \tilde{S}(E)}{\partial E} \right)^{-1} \simeq k \delta_{ij} \left( \frac{\partial S(E)}{\partial E} \right)^{-1} = kT \delta_{ij}$$

So that  $\ln \Sigma(E)$  can be substituted with  $k \tilde{S}(E)$

$$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = kT \delta_{ij}$$

So that the ensemble average of a quantity made in that way its average is  $kT \delta_{ij}$ .

#### 6.3.2 Application of Virial theorem

This is useful because it allows to construct microscopic phase space functions whose ensemble averages yield macroscopic thermodynamics observables.

$$\left\langle x_i \frac{\partial \mathcal{H}}{\partial x_j} \right\rangle = kT \delta_{ij}$$

## 6.4. THERMAL CONTACT

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In this way calculation can be not performed and a direct exact result starting from macroscopic phase-space variables and compute ensemble averages exactly. This theorem need to be respected in simulations.

### 6.3.2.1 An example

Consider an Hamiltonian like the following and take the ensemble average of  $\left\langle p_i \frac{\partial \mathcal{H}}{\partial p_i} \right\rangle$ .

$$\mathcal{H} = \sum_i \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N) \Rightarrow \left\langle p_i \frac{\partial \mathcal{H}}{\partial p_i} \right\rangle = kT$$

So that:

$$\left\langle p_i \frac{\partial \mathcal{H}}{\partial p_i} \right\rangle = \left\langle \frac{p_i^2}{m_i} \right\rangle = kT$$

So that the kinetic energy of a single particle in three dimensions:

$$\left\langle \frac{p_i^2}{2m_i} \right\rangle = \frac{3}{2}kT$$

And the total kinetic energy:

$$\sum_{i=1}^N \left\langle \frac{p_i^2}{2m_i} \right\rangle = \frac{3}{2}NkT$$

The temperature of the simulation can be computed starting from the kinetic energy of the particles, so that an instantaneous temperature of the system can be computed. In the microcanonical ensemble the energy is fixed, but the temperature is not.

## 6.4 Thermal contact

Consider an isolated system composed by two systems 1 and 2 be divided by a heat conducting divider: volumes are fixed and molecules do not travel across it, only heat. Considering them together:

$$N = N_1 + N_2 \quad \wedge \quad V = V_1 + V_2 \quad \wedge \quad \mathcal{H}(x) = \mathcal{H}_1(x_1) + \mathcal{H}_2(x_2)$$

And the state equations:

$$S_1(N_1, V_1, E_1) = k \ln \Omega_1(N_1, V_1, E_1) \quad \wedge \quad S_2(N_2, V_2, E_2) = k \ln \Omega_2(N_2, V_2, E_2)$$

Now considering the two  $\omega$  functions:

$$\omega_1(N_1, V_1, E_1) = M_{N_1} \int dx_1 \delta(\mathcal{H}_1 - E_1) \quad \wedge \quad \omega_2(N_2, V_2, E_2) = M_{N_2} \int dx_2 \delta(\mathcal{H}_2 - E_2)$$

To compute the entropy of the total system  $\Omega$  of the entire system needs to be computed:

$$\Omega(N, V, E) = M_N \int dx \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E) \neq \Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E_2)$$

## 6.5. SOME EXAMPLES

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So  $\Omega$  is not the product of the two  $\Omega_1$  and  $\Omega_2$ . In particular, fixing the value of energy of system 1 in  $E_1$  and doing so the energy for the second system is fixed as  $E - E_1$ . For each microstate in system 1 there are  $\Omega_2$  microstates for system 2. So the product of the combination for each single value of  $E_1$  has to be taken into account for the total  $\Omega$ :

$$\Omega(N, V, E) = C \int_0^E dE_1 \Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E - E_1)$$

This integration should be solved exactly, however, assuming that  $\bar{E}_1$  is the value that maximises the product  $\Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E - E_1)$ . Now the sum will be greater than the maximum but it will be less than the maximum times the number of elements. In the case where the number of trial is great this difference becomes negligible:

$$S(N, V, E) = k \ln \Omega(N, V, E) \simeq k \ln [\Omega_1(N_1, V_1, \bar{E}_1) \Omega_2(N_2, V_2, E - \bar{E}_1)] + o(\ln N)$$

So, in the thermodynamics limit:

$$S(N, V, E) = k \ln \Omega_1(N_1, V_1, \bar{E}_1) + k \ln \Omega_2(N_2, V_2, E - \bar{E}_1) = S_1(N_1, V_1, \bar{E}_1) + S_2(N_2, V_2, E - \bar{E}_1)$$

So in the thermodynamic limit entropy is additive.

### 6.4.1 Temperature

Another consequence of the previous result is that considering the last equation  $\bar{E}_1$  is the value of  $E_1$  that maximizes the quantity:

$$k \ln \Omega_1(N_1, V_1, E_1) \Omega_2(N_2, V_2, E - E_1)$$

Since  $\bar{E}_1 + \bar{E}_2 = E$  and  $E$  is fixed,  $d\bar{E}_1 + d\bar{E}_2 = 0 \Rightarrow d\bar{E}_1 = -d\bar{E}_2$ . Considering the formula:

$$S(N, V, E) = S_1(N_1, V_1, \bar{E}_1) + S_2(N_2, V_2, \bar{E}_2)$$

Taking the derivative with respect to  $\bar{E}_1$  and  $\bar{E}_2$ :

$$0 = \frac{\partial S_1(N_1, V_1, \bar{E}_1)}{\partial \bar{E}_1} + \frac{\partial S_2(N_2, V_2, \bar{E}_2)}{\partial \bar{E}_1} = \frac{\partial S_1(N_1, V_1, \bar{E}_1)}{\partial \bar{E}_1} - \frac{\partial S_2(N_2, V_2, \bar{E}_2)}{\partial \bar{E}_2}$$

And so, remembering the derivative of the entropy with respect to energy:

$$\frac{1}{T_1} - \frac{1}{T_2} = 0 \Rightarrow T_1 = T_2$$

Obtaining that two system in thermal contact have the same temperature at equilibrium.

## 6.5 Some examples

### 6.5.1 Free particle in one dimension

In order to study the ideal gas the free particle in 1D have to be solved. This particle has Hamiltonian:

## 6.5. SOME EXAMPLES

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$$\mathcal{H} = \frac{p^2}{2m}$$

Considering a particle confined in a length  $L$ :

$$\Omega(1, L, E) = \frac{E_0}{h} \int_0^L dx \int_{-\infty}^{+\infty} dp \delta\left(\frac{p^2}{2m} - E\right) = \frac{E_0 L}{h} \int_{-\infty}^{+\infty} dp \delta\left(\frac{p^2}{2m} - E\right)$$

Considering  $y^2 = \frac{p^2}{2m}$ :

$$\int_{-\infty}^{+\infty} dp \delta\left(\frac{p^2}{2m} - E\right) = \sqrt{2m} \int_{-\infty}^{+\infty} dy \delta(y^2 - E)$$

And remembering another property of the  $\delta$  function:

$$\delta(f(x)) = \sum_{i \in \text{zeros of } f(x)} \frac{1}{|f'(x_i)|} \delta(x - x_i) \Rightarrow \delta(y^2 - E) = \frac{1}{2\sqrt{E}} [\delta(y - \sqrt{E}) + \delta(y + \sqrt{E})]$$

Computing the integral:

$$\sqrt{2m} \int_{-\infty}^{+\infty} dy \delta(y^2 - E) = \sqrt{2m} E \Rightarrow \Omega(1, V, E) = \frac{E_0 L}{h} \sqrt{\frac{2m}{E}}$$

### 6.5.2 Classical ideal gas

Considering  $N$  free particles in  $3D$ , or the classical ideal gas, which it will be close to one particle in  $1D$ :

$$\Omega(N, V, E) = \frac{E_0}{N! h^{3N}} \int d^N \vec{p} \int_{D(V)} d^N \vec{r} \delta\left(\sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} - E\right) = \frac{E_0 V^N}{N! h^{3N}} \int d^N \vec{p} \left(\sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} - E\right)$$

Where  $N!$  is correct Boltzmann counting and  $h$  is Plank's constant, the sum of all kinetic energy is because they are all free particles. Computing the integral and using Boltzmann relation the entropy can be computed:

$$\Omega(N, V, E) = \frac{1}{N!} \left[ \frac{V}{h^3} \left( \frac{4\pi m E}{3N} \right)^{\frac{3}{2}} \right]^N e^{\frac{3N}{2}} \Rightarrow S(N, V, E) = Nk \ln \left[ \frac{V}{h^3} \left( \frac{4\pi m E}{3N} \right)^{\frac{3}{2}} \right] + \frac{3Nk}{2} - k \ln N!$$

So the entropy for the ideal gas can be obtained starting from the Hamiltonian. Now the thermodynamics derivatives can be used to obtain all thermodynamic properties:

$$\frac{1}{T} = \left( \frac{\partial S}{\partial E} \right)_{N,V} = \frac{3Nk}{2E} \Rightarrow E = \frac{3}{2} NkT$$

$$\frac{p}{T} = \left( \frac{\partial S}{\partial V} \right)_{N,E} = \frac{Nk}{V} \Rightarrow pV = NkT$$

$$\frac{\mu}{T} = - \left( \frac{\partial S}{\partial N} \right)_{V,E} = k \ln N - k \ln \left[ \frac{V}{h^3} \left( \frac{4\pi m E}{3N} \right)^{\frac{3}{2}} \right] \Rightarrow \mu = -kT \ln \left[ \frac{V}{Nh^3} \left( \frac{4\pi m E}{3N} \right)^{\frac{3}{2}} \right]$$

## 6.6 Gibbs paradox

Considering Boltzmann equation the factorial factor is due to the fact that particles are undistinguishable.

$$S(N, V, E) = Nk \ln \left[ \frac{V}{h^3} \left( \frac{4\pi mE}{3N} \right)^{\frac{3}{2}} \right] + \frac{3Nk}{2} - \cancel{k \ln N!}$$

If the factorial is not added Gibbs paradox comes into play, obtaining the formula for classical entropy.

$$S^{(cl)}(N, V, T) = Nk \ln \left[ \frac{V}{h^3} (2\pi mkT)^{\frac{3}{2}} \right] + \frac{3Nk}{2}$$

Assume that there are  $N_1$  particles in one box and  $N_2$  particles in another box. Now, computing the entropy of the total system and of the mixed system:

$$\begin{aligned} S_1^{(cl)}(N_1, V_1, T) &= N_1 k \ln \left[ \frac{V_1}{h^3} (2\pi mkT)^{\frac{3}{2}} \right] + \frac{3N_1 k}{2} & S_2^{(cl)}(N_2, V_2, T) &= N_2 k \ln \left[ \frac{V_2}{h^3} (2\pi mkT)^{\frac{3}{2}} \right] + \frac{3N_2 k}{2} \\ S^{(cl)}(N_1 + N_2, V_1 + V_2, T) &= (N_1 + N_2) k \ln \left[ \frac{V_1 + V_2}{h^3} (2\pi mkT)^{\frac{3}{2}} \right] + \frac{3(N_1 + N_2) k}{2} \end{aligned}$$

Now the entropy of the mixed system:

$$\begin{aligned} \Delta S_{mix}^{(cl)} &= S^{(cl)}(N_1 + N_2) - S_1^{(cl)}(N_1) - S_2^{(cl)}(N_2) = \\ &= (N_1 + N_2) k \ln(V_1 + V_2) - N_1 k \ln V_1 - N_2 k \ln V_2 = \\ &= N_1 k \ln \frac{V}{V_1} + N_2 k \ln \frac{V}{V_2} > 0 \end{aligned}$$

This result is greater than 0, so mixing the two gases entropy will increase.

- $\Delta S_{mix}^{(cl)} > 0$ : this results makes sense if the two gases are different.
- $\Delta S_{mix}^{(cl)} \neq 0$ : if the same gas is present in the two boxes it should be equal to 0, but the

formula predicts that the entropy increases. This is because when inserting back the wall the same situation at the start should be obtained and this is not possible because entropy is a state function.

### 6.6.1 Correct Boltzmann counting

To solve the paradox correct Boltzmann counting is introduced, the  $N!$  factor. In fact inserting it the correct formula becomes:

$$S^{(ST)}(N, V, T) = Nk \ln \left[ \frac{V}{Nh^3} (2\pi mkT)^{\frac{3}{2}} \right] + \frac{3Nk}{2}$$

Or the Sackur-Tetrode formula. Using Stirling's approximation for the factorial. Using this formula in the following cases:

## 6.6. GIBBS PARADOX

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- $\Delta S_{mix} = N_1 k \ln \frac{V}{V_1} + N_2 k \ln \frac{V}{V_2} > 0$ : for two different gases.
- $\Delta S_{mix} = N_1 k \ln \frac{V}{N} \frac{N_1}{V_1} + N_2 k \ln \frac{V}{N} \frac{N_2}{V_2} = 0$ : for the same gas.

# Chapter 7

## Introduction to molecular dynamics

### 7.1 Introduction

#### 7.1.1 Hamilton's equations

The starting point to a Molecular dynamics simulation is Hamilton's equation. Hamilton's equation will yield Newton's equation at the end, allowing to study the system as first order differential equations.

$$\dot{q}_\alpha = \frac{\partial \mathcal{H}}{\partial p_\alpha} \quad \dot{p}_\alpha = -\frac{\partial \mathcal{H}}{\partial q_\alpha}$$

The objective is to obtain a numerical result from these equation. Remembering that solving Hamilton's equation means integrating them keeping the energy constant.

$$\frac{d\mathcal{H}}{dt} = \sum_\alpha \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \dot{q}_\alpha + \frac{\partial \mathcal{H}}{\partial p_\alpha} \dot{p}_\alpha \right] = \sum_\alpha \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} - \frac{\partial \mathcal{H}}{\partial p_\alpha} \frac{\partial \mathcal{H}}{\partial q_\alpha} \right] = 0$$

All the work is done in the microcanonical ensemble.

$$\mathcal{H}(q_1, \dots, q_{3N}, p_1, \dots, p_{3N}) = const$$

The quantities obtained through Hamilton's equations are representative of the microcanonical ensemble. The time-dependent solutions will be rigorous, conformations or state that are separated by an energy barrier, local minima cannot be escaped.

#### 7.1.2 Ergodicity

When a property has to be measured in an ensemble, what is measured is the average over an ensemble:

$$A = \langle a \rangle = \frac{\int dx a(x) \delta(\mathcal{H}(x) - E)}{\int dx \delta(\mathcal{H}(x) - E)} = \lim_{\tau \rightarrow \infty} \frac{1}{\tau} \int_0^\tau dt a(x_t) \equiv \bar{a}$$

Assuming that the system will visit during in dynamics all the possible state of its ensemble the average over the ensemble can be substituted over an average over time. Usually the time average

is indicated by a bar:  $\bar{a}$ . The numerical integrator will give the value of  $a(x_t)$  at different time steps and from that a discretized time average will be obtained:

$$A = \langle a \rangle = \frac{1}{M} \sum_{n=1}^M a(\bar{x}_{n\Delta t})$$

This discretized time average for sure is not the ensemble average. In order for this to be true the system has to have the property of ergodicity. Ergodicity means that in a simulation, while exploring different state and point in time, all possible states compatible with a macrostate are being explored. So all the state belonging to the ensemble are being explored in the phase-space. This is not easy to assume for complex states and depends on the energy profile of the system.

### 7.1.3 Basic components of a molecular dynamics simulation

The basic components of a MD simulation are:

- The model: the chosen force field, the model used to represent chemical bonds and reality.
- Calculation of energies and forces: accurate and efficient. So how to compute the energies and forces, numerical steps in the model characterized by some error.
- The algorithm: used to integrate the equations of motion.

## 7.2 Verlet algorithm

An algorithm used to integrate the equations of motion is the Verlet algorithm. Starting from the Taylor expansion of the coordinates at time  $t + \Delta t$  and then they can be written using Newton's law.

$$\vec{r}_i(t + \Delta t) \approx \vec{r}_i(t) + \Delta t \dot{\vec{r}}_i(t) + \frac{1}{2} \Delta t^2 \ddot{\vec{r}}_i(t) \quad \approx \vec{r}_i(t + \Delta t) + \Delta t \vec{v}_i(t) + \frac{\Delta t^2}{2m_i} \vec{F}_i(t)$$

Similarly, integrating backward in time:

$$\vec{r}_i(t - \Delta t) \approx \vec{r}_i(t) - \Delta t \vec{v}_i(t) + \frac{\Delta t^2}{2m_i} \vec{F}_i(t)$$

Summing up the two equations the first order terms will cancel:

$$\vec{r}_i(t + \Delta t) + \vec{r}_i(t - \Delta t) = 2\vec{r}_i(t) + \frac{\Delta t^2}{m_i} \vec{f}_i(t)$$

In these equations the third order terms will also cancel, so that this sum is correct until the forth order term. So this equation is correct up to the forth order term. So the coordinates at time  $t + \Delta t$  are:

$$\vec{r}_i(t + \Delta t) = 2\vec{r}_i(t) - \vec{r}_i(t - \Delta t) + \frac{\Delta t^2}{m_i} \vec{F}_i(t)$$

## 7.2. VERLET ALGORITHM

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In order to get the coordinates at the previous instant in time have to be stored. The velocity can be computed using velocity's definition:

$$\vec{v}_i(t) = \frac{\vec{r}_i(t + \Delta t) - \vec{r}_i(t - \Delta t)}{2\Delta t}$$

The best thing to do is to compute the average velocity over 2 time step as to have a numerically more stable solution. This algorithm is time-reversible and will keep energy constant. Some problem about it is that the velocity are the kinetic energy and is related to the temperature of the system.

### 7.2.1 Velocity Verlet

A variation over Verlet providing the same trajectory, but computing velocities and coordinates at the same time. Again the starting point is the Taylor expansion:

$$\vec{r}_i(t + \Delta t) = \vec{r}_i(t) + \Delta t \vec{v}_i(t) + \frac{\Delta t^2}{2m_i} \vec{F}_i(t)$$

Now integrating backward in time considering the velocities:

$$\vec{r}_i(t) = \vec{r}_i(t + \Delta t) - \Delta t \vec{v}_i(t + \Delta t) + \frac{\Delta t^2}{2m_i} \vec{F}_i(t + \Delta t)$$

By substituting  $\vec{r}_i(t + \Delta t)$  with the first equation:

$$\vec{v}_i(t + \Delta t) = \vec{v}_i(t) + \frac{\Delta t}{2m_i} [\vec{F}_i(t) + \vec{F}_i(t + \Delta t)]$$

With the average of the forces at the two time steps. The velocities and the coordinates are updated at the same time. Time reversibility is necessary because Hamilton's equations are being solved. Moreover these algorithms have a symplectic structure, a property related with their numerical stability: this means that the trajectories that are obtained using this algorithms although it is not exactly the same, the errors will not diverge from the classical trajectory.

### 7.2.2 Initial condition

When starting a simulation initial coordinates have to be provided. This can be done by taking data from experimental data or guessed. Also the initial velocities are needed for the Verlet algorithm. The best thing to guess the velocities are to take them randomly from a Maxwell-Boltzmann distribution:

$$f(v) = \left( \frac{m}{2\pi kT} \right)^{\frac{1}{2}} e^{-\frac{mv^2}{2kT}}$$

This is a Gaussian distribution whose variance depends on the temperature:

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{x^2}{2\sigma^2}}$$

The wider the spread the higher the temperature. So in a simulation an initial temperature is given and then the velocities are extracted from the Maxwell-Boltzmann distribution. In the microcanonical simulation the energy is fixed but the temperature is not, so most of the time the temperature will not be kept fixed and after some time it will reach a constant value, depending on the initial conditions.

### 7.2.3 Action integral

Because the molecules present bonds these will oscillate, but the characteristic time for their oscillation will be smaller of the  $\Delta t$  of the time step of the algorithm. If the oscillation needs to be represented the time step should be smaller than their oscillation, so smaller than a femtosecond. This time step should be larger so, the bonds can be treated as rigid bonds. Constraints will be posed on the chemical bonds so that their length will be kept fixed. This constraints allow to use a time step in the order of femtoseconds. In order to implement a constraint in the Verlet algorithm the Lagrangian formalism should be obtained from an action integral. Consider the coordinates such that  $Q$  is the coordinates and  $\dot{Q}$  is the velocities, both generalized.

$$Q \equiv \{q_1, \dots, q_{3N}\} \quad \dot{Q} \equiv \{\dot{q}_1, \dots, \dot{q}_{3N}\}$$

Now the action integral is:

$$A[Q] = \int_{t_1}^{t_2} \mathcal{L}(Q(t), \dot{Q}(t)) dt$$

This is a number that integrates a path from  $(Q(t_1), \dot{Q}(t_1))$  and  $(Q(t_2), \dot{Q}(t_2))$  and summing over all the trajectory. The value of the action depends on the path taken when changing position in the phase-space. Each path will be characterized a different value of the action integral. So  $A$  is a function of a function, the path. The path  $Q$  that renders the action stationary is:

$$\bullet Q(t_1) = Q_1. \quad \bullet Q(t_2) = Q_2. \quad \bullet \dot{Q}(t_1) = \dot{Q}_1. \quad \bullet \dot{Q}(t_2) = \dot{Q}_2.$$

Stationary means that making a small variation to the path the corresponding variation of the action is zero in the first order. So the starting and ending coordinates will be exactly the same for all the paths. So that the variation at time  $t_1$  and at time  $t_2$  will be equal to zero:

$$\bullet \delta Q(t_1) = \delta Q(t_2) = 0. \quad \bullet \delta \dot{Q}(t_1) = \delta \dot{Q}(t_2) = 0.$$

So at the boundaries the variation will be equal to zero. Now computing the variation on the action when changing the path. Since the variation is small a Taylor expansion can be performed on the integral, considering all the partial derivatives, making the derivative equal to zero:

$$\begin{aligned} \delta A &= \int_{t_1}^{t_2} \mathcal{L}(Q(t) + \delta Q(t), \dot{Q}(t) + \delta \dot{Q}(t)) dt - \int_{t_1}^{t_2} \mathcal{L}(Q(t), \dot{Q}(t)) dt = \\ &= \int_{t_1}^{t_2} \sum_{\alpha=1}^{3N} \left[ \frac{\partial \mathcal{L}}{\partial q_\alpha} \delta q_\alpha(t) + \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \delta \dot{q}_\alpha(t) \right] dt = \\ &= \sum_{\alpha=1}^{3N} \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \delta q_\alpha(t) \Big|_{t_1}^{t_2} + \int_{t_1}^{t_2} \sum_{\alpha=1}^{3N} \left[ \frac{\partial \mathcal{L}}{\partial q_\alpha} \delta q_\alpha(t) - \frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) \delta q_\alpha(t) \right] dt = 0 \end{aligned}$$

Thus, remembering the boundaries conditions and since the formula will be valid for any  $\alpha$ , so the integral itself will be equal to zero, because all the  $\delta q_\alpha$  are independent from each other if there are no constraints:

$$\frac{\partial \mathcal{L}}{\partial q_\alpha} - \frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) = 0 \Rightarrow \frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) - \frac{\partial \mathcal{L}}{\partial q_\alpha} = 0$$

### 7.3. CONSTRAINTS

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Obtaining the Euler-Lagrangian equations from a variational principles. The Euler-Lagrangian equations correspond to the path that will render the action integral stationary. So the two formulation are completely equivalent to each other.

## 7.3 Constraints

Constraints refer to chemical bond that are kept fixed during the simulation time. Defining constraints:

- Holonomic constraints:  $\sigma_k(q_1, \dots, q_{3N}, t) = 0 \quad k = 1, \dots, N_C$ . This means that the equation corresponding to the constraint can be written as above. There will be one equation for each constraint in the system, so that the constraint is an equation that depends on all coordinates and time. So fixing a bond is a holonomic constraints.
- Nonholonomic constraints: there is also a relation on the velocities  $\zeta(q_1, \dots, q_{3N}, \dot{q}_1, \dots, \dot{q}_{3N}) = 0$ . Coordinates and velocities are not independent.

Each constraint adds an equation to the system, reducing the degrees of freedom, from  $3N$  to  $3N - N_C$  because the coordinates will depend on each other. This means that the number of generalized coordinates will be  $3N - N_C$ . A particular condition from non-holonomic constraint is an example:

$$\frac{1}{2} \sum_i m_i \dot{r}_i^2 - C = 0$$

Constraining the total kinetic energy to be constant. This is a nonholonomic constraint.

### 7.3.1 Differential forms

These constraints can be written in a differential form, defined as:

$$\sum_{\alpha=1}^{3N} a_{k\alpha} dq_\alpha + a_{kt} dt = 0 \quad k = 1, \dots, N_C$$

Depending on the variation of coordinates and time.  $\alpha$  refers to the coordinates ant  $k$  to the constraints.

#### 7.3.1.1 Holonomic constraints

Going from their equation to their differential form, taking the derivative of the holonomic constraint equation:

$$\sum_{\alpha=1}^{3N} \frac{\partial \sigma_k}{\partial q_\alpha} dq_\alpha + \frac{\partial \sigma_k}{\partial t} dt = 0 \quad k = 1, \dots, N_N \quad a_{k\alpha} = \frac{\partial \sigma_k}{\partial q_\alpha} \quad a_{kt} = \frac{\partial \sigma_k}{\partial t}$$

### 7.3. CONSTRAINTS

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#### 7.3.1.2 Nonholonomic constraints

For nonholonomic constraints is easy for some exception, for example on the one on kinetic energy:

$$\frac{1}{2} \sum_i m_i \dot{\vec{r}}_i^2 - C = 0 \Rightarrow \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i \frac{d\vec{r}_i}{dt} - C = 0 \Rightarrow \frac{1}{2} \sum_i m_i \dot{\vec{r}}_i d\vec{r}_i - C dt = 0$$

So that:

$$a_{1i} = \frac{1}{2} m_i \dot{\vec{r}}_i \quad a_{1t} = -C$$

In general only constraint that can be written as:

$$\sum_{\alpha=1}^{3N} a_{k\alpha} dq_\alpha = 0$$

Will be considered, in particular holonomic constraints without an explicit time dependence.

#### 7.3.2 Lagrange multipliers

If the constraints can be written in an integrable form then the Euler-Lagrange equations can be written directly following a variational principle. This can be done writing Lagrange multipliers. The problem is that the derivation of the Euler-Lagrange equation was based on the fact that the coordinates were independent from each other. Dealing with constraints this cannot be done: there are  $3N - N_C$  independent coordinates and the  $\delta q_\alpha$ . To make them independent other variables need to be introduced: the Lagrange multipliers, so that the sum will be equal to zero because of the integrable form. Now looking inside the square brackets a sum introduced that is equal to zero.  $N_C$  unknowns ( $\lambda_k$ ) are introduced so that there are  $3N - N_C + N_C = 3N$  independent coordinates. The last thing to do so is to obtain the values for  $\lambda_k$  which will have specific values.

$$\int_{t_1}^{t_2} \sum_{\alpha=1}^{3N} \left[ \frac{\partial \mathcal{L}}{\partial q_\alpha} - \frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) + \sum_{k=1}^{N_C} \lambda_k a_{k\alpha} \right] \delta q_\alpha(t) dt = 0$$

A modified version of the Euler-Lagrange equation is obtained.

$$\frac{d}{dt} \left( \frac{\partial \mathcal{L}}{\partial \dot{q}_\alpha} \right) - \frac{\partial \mathcal{L}}{\partial q_\alpha} = \sum_{k=1}^{N_C} \lambda_k a_{k\alpha}$$

To obtain all the  $\lambda_k$   $N_C$  additional equations are needed. These are the equations of the constraints:

$$\sum_{\alpha=1}^{3N} a_{k\alpha} \dot{q}_\alpha + a_{kt} = 0 \quad k = 1, \dots, N_C$$

So that all the velocities, coordinates and  $\lambda_k$  can be computed.

So there are  $3N + N_C$  equations for  $3N + N_C$  unknowns.

### 7.3. CONSTRAINTS

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#### 7.3.3 Hamiltonian formulation

The Hamiltonian formulation can be obtained for these constraints. For time-independent holonomic constraints:

$$\begin{cases} \dot{q}_\alpha = \frac{\partial \mathcal{H}}{\partial p_\alpha} \\ \dot{q}_\alpha = -\frac{\partial \mathcal{H}}{\partial q_\alpha} - \sum_{k=1}^{N_C} \lambda_k a_{k\alpha} \\ \sum_{\alpha=1}^{3N} a_{k\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} = 0 \end{cases}$$

The constraints equations appear in the same place of the forces: whenever constraints are introduced in the system constraints forces are added to the system. So that integrating the system of equation, its derivative with respect to time should be equal to 0:

$$\begin{aligned} \frac{d\mathcal{H}}{dt} &= \sum_{\alpha} \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \dot{q}_\alpha + \frac{\partial \mathcal{H}}{\partial p_\alpha} \right] = \\ &= \sum_{\alpha} \left[ \frac{\partial \mathcal{H}}{\partial q_\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} + \frac{\partial \mathcal{H}}{\partial p_\alpha} \left( \frac{\partial \mathcal{H}}{\partial q_\alpha} + \sum_k \lambda_k a_{k\alpha} \right) \right] = \\ &= \sum_k \lambda_k \sum_{\alpha} \frac{\partial \mathcal{H}}{\partial p_\alpha} a_{k\alpha} = 0 \end{aligned}$$

So no work is done on a system by the imposition of holonomic constraints.

#### 7.3.4 Constraints in a simulation

To implement the constraints in a simulation, forces coming from the constraints are called the constraints forces, so the forces are:

$$m_i \ddot{r}_i = \vec{F}_i + \underbrace{\sum_{k=1}^{N_C} \lambda_k \nabla_i \sigma_k}_{\text{Constraint forces}}$$

So these equations need to keep the constraints, adding a condition on the gradient of  $\sigma_k$ :

$$\frac{d}{dt} \sigma_k(\vec{r}_1, \dots, \vec{r}_N) = 0 \Rightarrow \dot{\sigma}_k = \sum_{i=1}^N \nabla_i \sigma_k \cdot \vec{r}_i = 0$$

Now a condition on the velocities is added: they need to be perpendicular to the gradient of the constraint equation. To compute  $\lambda_k$  while the simulation is running the constraints are implemented directly in the algorithm. Considering the velocity Verlet:

$$\vec{r}_i(\Delta t) = \vec{r}_i(0) + \Delta t \vec{v}_i(0) + \frac{\Delta t^2}{2m_i} \vec{F}_i(0) + \frac{\Delta t^2}{2m_i} \sum_k \lambda_k \nabla_i \sigma_k(0)$$

To obtain  $\lambda_k$ :

$$\vec{r}'_i = \vec{r}_i(0) + \Delta t \vec{v}_i(0) + \frac{\Delta t^2}{2m_i} \vec{F}_i(0)$$

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$$\vec{r}_i(\Delta t) = \vec{r}'_i + \frac{1}{m_i} \sum_k \tilde{\lambda}_k \nabla_i \sigma_k(0)$$

Considering the notation:

$$\tilde{\lambda}_k = \frac{\Delta t^2}{2} \lambda_k$$

#### 7.3.4.1 Constraint condition

Considering that the new coordinates need to satisfy the constraints equations. This is where the constraint equations come into place:

$$\sigma_l(\vec{r}_1(\Delta t), \dots, \vec{r}_N(\Delta t)) = 0 \quad l = 1, \dots, N_C$$

Now there are  $N_C$  equations for the new coordinates, with  $N_C$  unknowns. These equations will allow to compute the  $\lambda_k$  and to solve the constraint equations:

$$\sigma_l \left( \vec{r}'_1 + \frac{1}{m_1} \sum_k \tilde{\lambda}_k \nabla_1 \sigma_k(0), \dots, \vec{r}'_N + \frac{1}{m_N} \sum_k \tilde{\lambda}_k \nabla_N \sigma_k(0) \right) = 0 \quad l = 1, \dots, N_C$$

There are different strategies to solve this system. The first thing to do is to assume that all the sum of the sum over the  $\lambda_k$  are slight corrections to the new coordinates. The new values of the coordinates are those obtained without constraints with a slight modification given by the constraints. Because of this a Taylor expansion can be done and considering the method SHAKE, an iterative solution is given from an initial guess  $\tilde{\lambda}_k^{(1)}$ :

$$\vec{r}_i^{(1)} = \vec{r}'_i + \frac{1}{m_i} \sum_k \tilde{\lambda}_k^{(1)} \nabla_1 \sigma_k(0)$$

In SHAKE an initial guess on  $\tilde{\lambda}_k^{(1)}$  is done and then a Taylor expansion is done. The exact solution:  $\tilde{\lambda}_k = \tilde{\lambda}_k^{(1)} + \delta \tilde{\lambda}_k^{(1)}$ , so related with the initial guess with an assumed small variation, then the coordinates at  $\delta t$  will be:

$$\vec{r}_i(\Delta t) = \vec{r}_i^{(1)} + \frac{1}{m_i} \sum_k \delta \tilde{\lambda}_k^{(1)} \nabla_1 \sigma_k(0)$$

Now adding the guess to the initial formula:

$$\sigma_l \left( \vec{r}_1^{(1)} = \frac{1}{m_1} \sum_k \delta \tilde{\lambda}_k \nabla_1 \sigma_k(0), \dots, \vec{r}_N^{(1)} + \frac{1}{m_N} \sum_k \delta \tilde{\lambda}_k \nabla_N \sigma_k(0) \right) = 0$$

And the Taylor expansion is performed assuming a small  $\delta \tilde{\lambda}$  to be small and stopping at the first term (linearising the equation):

$$\sigma_l(\vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)}) + \sum_{i=1}^N \sum_{k=1}^{N_C} \frac{1}{m_i} \nabla_i \sigma_l(\vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)}) \nabla_i \sigma_k(\vec{r}_1(0), \dots, \vec{r}_N(0)) \delta \tilde{\lambda}_k \approx 0$$

Now assuming that to be 0 the  $\delta \tilde{\lambda}_k$  can be obtained inverting the resulting matrix. This will be a linear system that can be solved efficiently. So the matrix can be inverted or it can be simplified. This

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guess is done iteratively to continuously obtain corrections on the guesses, making the constraints equations to become more and more accurate. The process will stop when the equation will be less than an arbitrary tolerance. This is important because if it is too strict this will require a lot of iterations, making the simulation too slow. If the tolerance is too high the constraints will not be satisfied any more and systems will explode, making the particles far apart, because the forces will be too high.

#### 7.3.4.2 Possible algorithms

$$\sigma_l(\vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)}) + \sum_{i=1}^N \sum_{k=1}^{N_C} \frac{1}{m_i} \nabla_i \sigma_l(\vec{r}_1^{(1)}, \dots, \vec{r}_N^{(1)}) \nabla_i \sigma_k(\vec{r}_1(0), \dots, \vec{r}_N(0)) \delta \tilde{\lambda}_k \approx 0$$

There are different techniques to solve this matrix.

**7.3.4.2.1 Direct inversion** In direct inversion method like Matrix-shake or M-SHAKE the matrix is inverted and the  $\tilde{\lambda}$  are computed and this procedure must be repeated because the equation above is a linear approximation.

**7.3.4.2.2 Quick trick** In Quick trick only diagonal elements are considered without any matrix inversion.

**7.3.4.2.3 RATTLE** The same procedure can be employed for velocities like in RATTLE. The algorithm is the same thing as in Shake and the same thing is done for velocities, where the Lagrange multipliers for the velocities will be called  $\tilde{\mu}$ .

**7.3.4.2.4 LINCS** LINCS or linear constraint solver is based on the same principle and it is implemented in GROMACS. It is a slight variation on the Matrix-Shake.

# Chapter 8

## Direct translation

### 8.1 Introduction

The direct translation method is a formal representation of the Verlet and the Velocity Verlet algorithms. It has direct effect on those.

### 8.2 Liouville operator

The Liouville operator can be computed for any quantity  $a$  that depends on the coordinates in phase space. And its derivative is:

$$\frac{da}{dt} = \frac{\partial a}{\partial x_t} \dot{x}_t = \sum_a \left[ \frac{\partial a}{\partial q_a} \dot{q}_a + \frac{\partial a}{\partial p_a} \dot{p}_a \right] = \sum_a \left[ \frac{\partial a}{\partial q_a} \frac{\partial \mathcal{H}}{\partial p_a} - \frac{\partial a}{\partial p_a} \frac{\partial \mathcal{H}}{\partial q_a} \right] = \{a, \mathcal{H}\}$$

The Liouville operator is defined as:

$$iL_a = \{a, \mathcal{H}\} \Rightarrow \frac{da}{dt} = iL_a$$

The operation of the Liouville operator is to compute the Poisson brackets of  $a$  with  $\mathcal{H}$ . So that the dependence on time of  $a$  can be written. In abstract terms the operator acts on something and computes the Poisson brackets with the Hamiltonian:  $iL \cdots = \{\cdots, \mathcal{H}\}$ . It can also be written as:

$$iL = \sum_a \left[ \frac{\partial \mathcal{H}}{\partial q_a} \frac{\partial}{\partial q_a} - \frac{\partial \mathcal{H}}{\partial p_a} \frac{\partial}{\partial p_a} \right]$$

A formal solution to the equation can be written:

$$\frac{da}{dt} = iL_a \Rightarrow a(x_t) = e^{\overbrace{iL t}^{\text{Classical propagator}}} a(x_0)$$

Obtaining the value of  $a(x_t)$ . It is called a classical propagator because it propagates  $a$  from time 0 to  $t$ .

### 8.2.1 Liouville operator split

This classical propagator is difficult to solve analytically so it needs to be approximated. The Liouville operator can be split in two operators:

$$iL = \sum_a \left[ \frac{\partial \mathcal{H}}{\partial p_a} \frac{\partial}{\partial q_a} - \frac{\partial \mathcal{H}}{\partial q_a} \frac{\partial}{\partial p_a} \right] = iL_1 + iL_2$$

$$iL_1 = \sum_a \frac{\partial \mathcal{H}}{\partial p_a} \frac{\partial}{\partial q_a} \quad iL_2 = - \sum_a \frac{\partial \mathcal{H}}{\partial q_a} \frac{\partial}{\partial p_a}$$

These two operators are non-commuting:

$$iL_1 iL_2 \phi(x) \neq iL_2 iL_1 \phi(x)$$

Formally, the commutator:

$$iL_1 iL_2 - iL_2 iL_1 \equiv [iL_1, iL_2]$$

If it is equal to zero the operators are commuting. In the case for the Liouville's operator split they are not commuting.

### 8.2.2 One dimensional example

To demonstrate that the two Liouville's operator are not commuting consider the Hamiltonian:

$$\mathcal{H} = \frac{p^2}{2m} + U(x)$$

So that the two operators are:

$$iL_1 = \frac{\partial \mathcal{H}}{\partial p} \frac{\partial}{\partial x} = \frac{p}{m} \frac{\partial}{\partial x} \quad iL_2 = - \frac{\partial \mathcal{H}}{\partial x} \frac{\partial}{\partial p} = - \frac{\partial U}{\partial x} \frac{\partial}{\partial p} = F(x) \frac{\partial}{\partial p}$$

Applying the two operators in sequence to a function  $\phi(x, p)$ . Here the operator  $iL_2$  is applied first:

$$iL_1 iL_2 \phi(x, p) = \frac{p}{m} \frac{\partial}{\partial x} \left[ F(x) \frac{\partial}{\partial p} \right] \phi(x, p) = \frac{p}{m} F(x) \frac{\partial^2 \phi}{\partial x \partial p} + \frac{p}{m} F'(x) \frac{\partial \phi}{\partial p}$$

Here the operator  $iL_1$  is applied first:

$$iL_2 iL_1 \phi(x, p) = F(x) \frac{\partial}{\partial p} \left[ \frac{p}{m} \frac{\partial}{\partial x} \right] \phi(x, p) = \frac{p}{m} F(x) \frac{\partial^2 \phi}{\partial x \partial p} + \frac{F(x)}{m} \frac{\partial \phi}{\partial x}$$

Computing the commutator:

$$[iL_1, iL_2] \phi(x, p) = \frac{p}{m} F'(x) \frac{\partial \phi}{\partial p} - \frac{F(x)}{m} \frac{\partial \phi}{\partial x} \neq 0$$

### 8.3 Trotter theorem

Since the two operators do not commute this equality is false:

$$iL_1 iL_2 \phi(x) \neq iL_2 iL_1 \phi(x) \Rightarrow e^{iL_1 t} \neq e^{iL_1 t} e^{iL_2 t}$$

This is important because although the classical propagator cannot be written, in many situation the propagator corresponding to  $iL_1$  and  $iL_2$  can be derived, so that the classical propagator could be obtained. However, according to the Trotter theorem:

$$e^{A+B} = \lim_{P \rightarrow \infty} [e^{\frac{B}{2P}} e^{\frac{A}{P}} e^{\frac{B}{2P}}]^P$$

Therefore, considering the Liouville's split:

$$e^{iL_1 t} = e^{iL_1 t + iL_2 t} = \lim_{P \rightarrow \infty} [e^{\frac{iL_2 t}{2P}} e^{\frac{iL_1 t}{P}} e^{\frac{iL_2 t}{2P}}]^P$$

#### 8.3.1 $\Delta t = \frac{t}{P}$

$$e^{iL_1 t} = e^{iL_1 t + iL_2 t} = \lim_{P \rightarrow \infty} [e^{\frac{iL_2 t}{2P}} e^{\frac{iL_1 t}{P}} e^{\frac{iL_2 t}{2P}}]^P$$

This formula can be written as:

$$e^{iL_1 t} = e^{iL_1 t + iL_2 t} = \lim_{P \rightarrow \infty, \Delta t \rightarrow 0} [e^{\frac{iL_2 \Delta t}{2}} e^{iL_1 \Delta t} e^{\frac{iL_2 \Delta t}{2}}]^P$$

Assuming that  $\Delta t = \frac{t}{P}$ . When a simulation there will be a finite value of  $P$ , which will be a natural value:

$$e^{iL_1 t} \approx [e^{\frac{iL_2 \Delta t}{2}} e^{iL_1 \Delta t} e^{\frac{iL_2 \Delta t}{2}}]^P + \underbrace{o(P \Delta t^3)}_{\text{Global error}}$$

So that the classical propagator is equal to the term in the limit with an error due to the truncation to a finite value of  $P$ . Taking the  $\frac{1}{P}$  power:

$$e^{iL_1 t} \approx e^{\frac{iL_2 \Delta t}{2}} e^{iL_1 \Delta t} e^{\frac{iL_2 \Delta t}{2}} + \underbrace{o(\Delta t^3)}_{\text{Local error}}$$

For a small time step  $\Delta t$ . So following a trajectory for a huge number of step the error is  $o(\Delta t^2)$ . In this way an algorithm that comes from Trotter factorization can be built. This algorithm will have a limited global error of the order of  $o(\Delta t^2)$ , so it will have a strong numerical stability.

#### 8.3.2 One-dimensional example

In one-dimensional example everything can be written as:

$$iL_1 = \frac{\partial \mathcal{H}}{\partial p} \frac{\partial}{\partial x} = \frac{p}{m} \frac{\partial}{\partial x} \quad iL_2 = F(X) \frac{\partial}{\partial p}$$

So the Trotter algorithm can be written as:

$$e^{iL_1 t} \approx e^{\frac{iL_2 \Delta t}{2}} e^{iL_1 \Delta t} e^{\frac{iL_2 \Delta t}{2}} + o(\Delta t^3)$$

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And making everything explicit:

$$e^{iL\Delta t} \approx e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} e^{\Delta t \frac{p}{m} \frac{\partial}{\partial x}} e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} + o(\Delta t^3)$$

Applying the operator to the coordinates in phase space:

$$\begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} = e^{iL\Delta t} \begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} \approx e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} e^{\Delta t \frac{p}{m} \frac{\partial}{\partial x}} e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} \begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix}$$

### 8.3.3 Exponential operators

An exponential operator can be computed as:

$$e^{c \frac{\partial}{\partial x}} g(x) = \sum_{k=0}^{\infty} \frac{1}{k!} \left( c \frac{\partial}{\partial x} \right)^k g(x) = \sum_{k=0}^{\infty} \frac{1}{k!} c^k \frac{d^k g(x)}{dx^k} = g(x + c)$$

This is another way to compute the Taylor expansion of  $g$  in  $x + c$ . So the operator translates the argument of  $g$  by a quantity  $c$ . Now applying the exponential operators to the points:

$$\begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} = e^{\frac{\Delta t}{2} F(x(0)) \frac{\partial}{\partial p(0)}} e^{\Delta t \frac{p(0)}{m} \frac{\partial}{\partial x(0)}} e^{\frac{\Delta t}{2} F(x(0)) \frac{\partial}{\partial p(0)}} \begin{pmatrix} x(0) \\ p(0) \end{pmatrix}$$

Computing the first exponential operator:

$$e^{\frac{\Delta t}{2} F(x(0)) \frac{\partial}{\partial p(0)}} \begin{pmatrix} x(0) \\ p(0) \end{pmatrix} = \begin{pmatrix} x(0) \\ p(0) + \frac{\Delta t}{2} F(x(0)) \end{pmatrix}$$

Now doing the same for all the other operators:

$$\begin{aligned} \begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} &= e^{\frac{\Delta t}{2} F(x(0)) \frac{\partial}{\partial p(0)}} e^{\Delta t \frac{p(0)}{m} \frac{\partial}{\partial x(0)}} \begin{pmatrix} x(0) \\ p(0) + \frac{\Delta t}{2} F(x(0)) \end{pmatrix} = \\ &= e^{\frac{\Delta t}{2} F(x(0)) \frac{\partial}{\partial p(0)}} \begin{pmatrix} x(0) + \Delta t \frac{p(0)}{m} \\ p(0) + \frac{\Delta t}{2} F(x(0)) + \Delta t \frac{p(0)}{m} \end{pmatrix} = \\ &= \begin{pmatrix} x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \\ p(0) + \frac{\Delta t}{2} F(x(0)) + \frac{\Delta t}{m} \left( x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \right) \end{pmatrix} \end{aligned}$$

## 8.4 Trotter algorithm

This is the result of Trotter algorithm:

$$\begin{pmatrix} x(\Delta t) \\ p(\Delta t) \end{pmatrix} = \begin{pmatrix} x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \\ p(0) + \frac{\Delta t}{2} F(x(0)) + \frac{\Delta t}{m} \left( x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \right) \end{pmatrix}$$

Looking at the first line:

$$x(\Delta t) = x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right) \Rightarrow x(\Delta t) = x(0) + v(0)\Delta t + \frac{\Delta t^2}{2m} F(0)$$

And considering the second line:

$$p(\Delta t) = p(0) + \frac{\Delta t}{2} F(x(0)) + \frac{\Delta t}{2} F\left(x(0) + \frac{\Delta t}{m} \left( p(0) + \frac{\Delta t}{2} F(x(0)) \right)\right)$$

So that:

$$p(\Delta t) = p(0) + \frac{\Delta t}{2} [F(x(0)) + F(x(\Delta t))] \Rightarrow v(\Delta t) = v(0) + \frac{\Delta t}{2m} [F(0) + F(\Delta t)]$$

So that inside the square brackets it is an average of the forces at time 0 and at time  $\Delta t$ . The two final formulae are the one needed to update the positions and velocities of the system. These two formulas are the Velocity Verlet algorithm. This is an important result telling that the Velocity Verlet is the best algorithm for molecular dynamics.

### 8.4.1 Direct translation

There is a quick way to compute the results of the Trotter algorithm, which leads to direct translation. What there is to do is to work in a sloppy matter on the operators. In this way the formulae can be written directly into lines of code.

#### 8.4.1.1 Momentum translation

Considering the first operator, it is translating the momentum by the quantity  $\frac{\Delta t}{2} F(x)$ . So this will translate  $p$  from time zero to time  $\frac{\Delta t}{2}$ . So when applying this operator  $p$  will change and  $x$  will remain the same.

$$e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} \begin{pmatrix} x(0) \\ p(0) \end{pmatrix} = \begin{pmatrix} x(0) \\ p\left(\frac{\Delta t}{2}\right) = p(0) + \frac{\Delta t}{2} F(x(0)) \end{pmatrix}$$

Corresponding code:

---

```
p = p + 0.5 * Δt * F
```

---

#### 8.4.1.2 Position translation

Applying the second operator only  $x$  will be translated:

$$e^{\frac{\Delta}{m} p \left( \frac{\Delta t}{2} \right) \frac{\partial}{\partial x}} \begin{pmatrix} x(0) \\ p\left(\frac{\Delta t}{2}\right) = p(0) + \frac{\Delta t}{2} F(x(0)) \end{pmatrix}$$

Corresponding code:

---

```
x = x + Δt * F * p/m
```

---

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### 8.4.1.3 Momentum translation with updated forces

Now applying the third operator  $p$  will be translated by another  $\frac{\Delta t}{2}$ . Looking at this formula the same result of the Trotter theorem is obtained. In this third step also the forces are updated.

Corresponding code:

$$e^{\frac{\Delta t}{2} F(x) \frac{\partial}{\partial p}} \left( x(\Delta t) \left( \frac{\Delta t}{2} \right) \right) = \left( p(\Delta t) = p \left( \frac{\Delta t}{2} \right) + \frac{\Delta t}{2} F(x(\Delta t)) \right)$$


---

$$p = p + 0.5 * \Delta t * F$$


---

## 8.4.2 Multiple time step integration

The problem when studying a force field, there are several term that correspond to the bonded interactions and the non-bonded interactions:

$$\begin{aligned} U(\vec{r}_1, \dots, \vec{r}_N) = & \frac{1}{2} \sum_{bonds} K_{bond}(r - r_0)^2 + \frac{1}{2} \sum_{bends} K_{bend}(\theta - \theta_0)^2 + \sum_{torsions} \sum_{n=0}^6 A_n [1 + \cos(C_n \phi + \delta_n)] + \\ & + \sum_{i,j \in nb} \left\{ \left[ 4\epsilon_{ij} \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \right\} \end{aligned}$$

It can be assumed that the atoms will be subject to forces with different time scales: the bonded interactions will change more rapidly than the non-bonded interactions. This is because the positions on the atoms do not change so much. It can be seen how the non-bonded interaction, which are the slow forces are very expensive to compute. So there is no reason to recompute the non-bonded interactions every time the fast forces are changing. So the Hamiltonian can be split into a reference Hamiltonian corresponding to the fast forces and another corresponding to the slow ones:

$$\mathcal{H}_{ref} = \frac{p^2}{2m} + U_{fast}(x) \quad \dot{x} = \frac{p}{m} \quad \dot{p} = F_{fast}(x) + F_{slow}(x)$$

In this case the Liouville's operator will be:

$$iL = \frac{p}{m} \frac{\partial}{\partial x} + [F_{fast}(x) + F_{slow}(x)] \frac{\partial}{\partial p}$$

So that there will be a fast Liouville's operator and a slow one.

### 8.4.3 Reference system propagator

The reference system propagator is referred to the reference Hamiltonian. Considering:

$$iL = \frac{p}{m} \frac{\partial}{\partial x} + [F_{fast}(x) + F_{slow}(x)] \frac{\partial}{\partial p} = iL_{fast} + iL_{slow}$$

And:

$$\mathcal{H}_{ref} = \frac{p^2}{2m} + U_{fast}(x)$$

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The reference system propagation for the fast forces and the slow part of the slow propagator:

$$iL_{fast} = \frac{p}{m} \frac{\partial}{\partial x} + F_{fast}(x) \frac{\partial}{\partial p} \quad iL_{slow} = F_{slow}(x) \frac{\partial}{\partial p}$$

Applying Trotter factorisation:

$$e^{iL\Delta t} = e^{iL_{slow} \frac{\Delta t}{2}} e^{iL_{fast} \Delta t} e^{iL_{slow} \frac{\Delta t}{2}}$$

### 8.4.4 RESPA

RESPA is the reference system propagator algorithm, where  $\Delta t$  is chosen according to the time scale of the slow forces, allowing to use a much bigger  $\Delta t$  with respect to the one considering all the forces together. It comes from the split of the Hamiltonian into a slow and fast part. It allows to compute the electrostatic and Van der Waals forces less times than the calculation of the bonded interactions, saving a lot of computational power. Focussing on the fast part of the RESPA algorithm:

$$e^{iL_{fast} \Delta t} = \left[ e^{\frac{\delta t}{2} F_{fast} \frac{\partial}{\partial p}} e^{\delta t \frac{p}{m} \frac{\partial}{\partial x}} e^{\frac{\delta t}{2} F_{fast} \frac{\partial}{\partial p}} \right]^n \quad \delta t = \frac{\Delta t}{n}$$

This part can be factorized again using the fact that  $\Delta t$  is sub-divided in  $n$  intervals, where  $\delta t$  is the time-step where the fast forces will act. This will be applied  $n$  times so it corresponds to one time step. Writing down the entire classical propagator the fast operator is in-between the slow one.

$$e^{iL\Delta t} = e^{\frac{\Delta t}{2} F_{slow} \frac{\partial}{\partial p}} \left[ e^{\frac{\delta t}{2} F_{fast} \frac{\partial}{\partial p}} e^{\delta t \frac{p}{m} \frac{\partial}{\partial x}} e^{\frac{\delta t}{2} F_{fast} \frac{\partial}{\partial p}} \right]^n e^{\frac{\Delta t}{2} F_{slow} \frac{\partial}{\partial p}}$$

And for a direct translation in pseudocode:

---

```

p = p + 0.5 * Δt * Fslow
for i = 1 to n
    p = p + 0.5 * *(\$\\delta t\$*) * Ffast
    x = x + δt * p/m
    Recompute only fast forces
    p = p + 0.5 * δt * Ffast
endfor
Recompute slow forces
p = p + 0.5 * δt * Fslow

```

---

## 8.5 Symplectic solver

By demonstrating the applicability of the Trotter algorithm, the symplectic property of the Verlet algorithm has been demonstrated. The Hamiltonian is not strictly conserved, however it conserves a shadow Hamiltonian  $\tilde{\mathcal{H}}(x, \Delta t)$  that is close to the true Hamiltonian  $\mathcal{H}(x)$  such that:

$$\lim_{\Delta t \rightarrow 0} \tilde{\mathcal{H}}(x, \Delta t) = \mathcal{H}(x)$$

This property guarantees that this algorithm is numerically stable for any amount of time.

# Chapter 9

## Evaluation of energies and forces

### 9.1 Introduction

During a simulation some parameters deal with how energies and forces are computed. This determine the accuracy of the simulation, especially for electrostatic interactions.

### 9.2 Periodic boundary conditions

The first thing to deal with are periodic boundary conditions. These are implemented because the number of particles that can be simulated is limited. Since the system is small many particles are at the boundary. Boundary effects matter for small systems. In a system of one hundred thousand particles, at least 40% of the particle deal with the boundary. To deal with this effect an infinite number of cells are considered such that when a particle cross a boundary it enters the system in the other direction. The system should be at the centre of the cell and its distance with the boundaries should be high to avoid interaction between the system of interest and any periodic image. In the case of electrostatic interaction besides the cutoff the system will interact with its periodic image, but if there is enough space that interaction can be neglected. For example it can be screened by counter ions above the bi-length distance. This length can be much more, so it is always good to give a certain distance between the system and the boundary. Using periodic boundary conditions do not complicate the computations and can be exploited to compute long range forces using Fourier transforms, using beside the space the reciprocal space. The reciprocal space has the property that anything that is long range in the normal space is short range in the reciprocal one. The typical non-bonded interaction in a simulation looks like:

$$U_{nb}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{i>j \in nb} \left\{ 4e_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{r_{ij}} \right\}$$

Wan der Waals can be regarded as short range, while electrostatic interactions are long range. Periodic boundary conditions allow to obtain a Fourier representation of the system. This is useful because interaction that is long ranged in space will be short ranged in the reciprocal or Fourier space. The strategy is to divide en impera the long and short ranged contributions: the system is divided into small systems and the problem will be divided into two problems, one dealing with short range and one with long range contribution.

### 9.2.1 The error function

An error function is defined such that:

$$\text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_0^x dt e^{-t^2}$$

This is the integral of a Gaussian and it has some properties:

- $\lim_{x \rightarrow \infty} \text{erf}(x) = 1.$
- $\text{erf}(0) = 0$

The complement error function is one minus the error function:

$$\text{erfc}(x) = 1 - \text{erf}(x) = \frac{2}{\sqrt{\pi}} \int_x^\infty dt e^{-t^2}$$

Such that:

- $\lim_{x \rightarrow \infty} \text{erfc}(x) = 0.$
- $\text{erf}(x) + \text{erfc}(x) = 1.$

So the error function starts from 0 and goes to 1 and the complement goes from 1 to 0. Looking at the error function it is a representation of a long range function, while the complement is a short range function. An interaction that goes with the reciprocal of the distance can be represented as the sum of the complementary and normal error function, respectively for long and short range contribution.

$$\frac{1}{r} = \underbrace{\frac{\text{erfc}(\alpha r)}{r}}_{\text{short-ranged}} + \underbrace{\frac{\text{erf}(\alpha r)}{r}}_{\text{long-ranged}}$$

So the complement take care of the short range contribution of the electrostatic interaction and the normal of the long range part.

### 9.2.2 Divide et impera

The non-bonded interaction is divided into a short and long range contribution.

$$U_{nb}(\vec{r}_1, \dots, \vec{r}_N) = U_{short}(\vec{r}_1, \dots, \vec{r}_N) + U_{long}(\vec{r}_1, \dots, \vec{r}_n)$$

Looking at the short range contribution:

$$U_{short}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{\vec{S}} \sum_{i>j \in nb} \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij,\vec{S}}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij,\vec{S}}} \right)^6 \right] + \frac{q_i q_j \text{erfc}(\alpha r_{ij,\vec{S}})}{r_{ij,\vec{S}}} \right\}$$

Looking at the long term contribution:

$$U_{long}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{\vec{S}} \sum_{i>j \in nb} \frac{q_i q_j \text{erf}(\alpha r_{ij,\vec{S}})}{r_{ij,\vec{S}}}$$

In this formulae interactions for all particles are counted only once. The vector  $\vec{S}$  represent the periodic images of the cells:

$$r_{ij,\vec{S}} = |\vec{r}_i - \vec{r}_j + \vec{S}| \quad \vec{S} = \vec{m}L$$

In case of a cubic box  $\vec{S}$  is a vector where each component is an integer number of the side of the box, so  $\vec{m}$  is always composed of integer numbers. The distances have to be computed for all periodic representations. The sum over  $\vec{S}$  is the sum over an infinite number of term. Two methods can be used to compute the short contribution and another for the long range ones. The factor  $\alpha$  has as dimension the reciprocal of length and has to be found during the simulation. In this representation charges are point-like. To each point charge a Gaussian distribution of charges of opposite sign is summed up. Then the same distribution is summed with the same sign, so to not change anything, but from the point of view of electrostatic then in this case a distribution of charges is obtained. From Gauss' theorem the electric field will be equal to zero, so after a given distance there is no more electric charge. So the point-charge is screened with the cloud and then the opposite cloud is used to compute the long-range contribution. This allow to separate the long and short contributions. So the original distribution of charges is equal to the sum in direct space of the screened electrostatic interactions and the sum in reciprocal space of the Gaussian clouds of charges.

### 9.3 Short range forces

The short range forces are due to the Wan der Waals interaction described with the Lennard-Jones potential and the short range part of the electrostatic potential, which corresponds to a point charge with a Gaussian cloud with opposite charges.

$$U_{short}(\vec{r}_1, \dots, \vec{r}_N) = \sum_{\vec{S}} \sum_{i>j \in nb} \left\{ 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r_{ij,\vec{S}}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij,\vec{S}}} \right)^6 \right] + \frac{q_i q_j erfc(\alpha r_{ij,\vec{S}})}{r} \right\}$$

$\alpha$  will affect the spread of the Gaussian distribution and is chosen by a cutoff radius. Considering a cutoff, the distance over which the short term part is computed,  $r_C \approx 10\text{-}12\text{\AA}$ , then  $\alpha = \frac{3.5}{r_C}$ . Now the problem is that the cutoff is used to assume that beyond a given distance the short-range interactions are negligible and can be assumed equal to 0:

$$\tilde{U}_{short}(r_{ij}) = \begin{cases} U_{short}(r_{ij}) - U_{short}(r_C) & r < r_C \\ 0 & r > r_C \end{cases}$$

The short contribution are shifted by  $r_C$  so that when the distance is the cutoff radius the potential is assumed exactly equal to zero, eliminating the problem of the Lennard-Jones potential. Doing something like this, the derivative of the potential is not continuous, so the force is discontinuous, which means that when travelling across the cutoff the force goes abruptly from 0 to a high amount, generating problems, allowing to violates the third law of thermodynamics, and the new force will affect the constraint equations, making satisfying them impossible and making the simulation stop.

#### 9.3.1 Switching function

To avoid this discontinuity switching functions are applied so that they will provide a continuous potential and derivative:

$$\tilde{U}_{short}(r_{ij}) = U_{short}(r_{ij})S(r_{ij}) \quad S(r) = \begin{cases} 1 & r < r_C - \lambda \\ 1 + \left(\frac{r-r_C+\lambda}{\lambda}\right)^2 \left(2\frac{r-r_C+\lambda}{\lambda} - 3\right) & r_C - \lambda < r \leq r_C \\ 0 & r > r_C \end{cases}$$

Where:

- $S$  is the switching function.
- $\lambda$  is the switching distance.

So there are many interactions for which after a given distance is equal to zero. So the interactions can be computed only with a list of neighbours, reducing the amount of calculations. Applying the switching function modifies the short range interaction and this modification could change the dynamics of the system, but it will affect the total energy and the pressure, so they must be corrected. These corrections will add up, but this can be computed and has to be taken into account when comparing them with experimental data.

### 9.3.2 Minimum image convention

Particle  $i$  interacts with the periodic image of particle  $j$  to which it is closest. Given a short range interactions, for each particle  $i$  only the interactions with other particles and the periodic images of the one with the shortest distance. This is enough because the cutoff radius is much less than half of the cell. So for each couple of interactions the minimum distance between the particle and its periodic image is enough. Reducing the computational cost to only one periodic image for each particle.

### 9.3.3 Verlet Neighbour list

Another trick to compute short functions quicker is to compute the Verlet Neighbour list. For each particle a list of close particles is built, so particles that are beyond a cutoff and a small distance or skin depth  $\delta$  and the interactions only in the list are computed.

1. A list of neighbours for all particles is given.
2. At each time step  $k\Delta t$  the displacements for each particle is:  $\Delta_i = |\vec{r}_i(k\Delta t) - \vec{r}_i(0)|$ , which is computed.
3. Now the maximum displacement at each time step is computed:  $\Delta_{max} = \max \Delta_i$ .
4. If  $\Delta_{max} > \frac{\delta}{2}$  the lists are updated because the displacement has moved a particle away from the crown or inside the cutoff range.

In this way the computation scales with  $n \log n$ . In a more efficient alternative like the linked list algorithm the system is divided into cells of size equal or slightly larger than  $r_C$ , separating the simulation box in small cells and doing it for small cells.

## 9.4 Long range forces

The problem in the long range part is reduced to a system with Gaussian clouds of charges, allowing to perform exact computations. In order to compute them the Fourier transformations have to be

## 9.4. LONG RANGE FORCES

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employed. Assume a cubic cell of volume  $V = L^3$  the reciprocal space vectors are  $\vec{g} = \frac{2\pi}{L}\vec{n}$ , where  $\vec{n}$  is a vector of all the possible combination of integers. Considering the Poisson summation rule:

$$\sum_{\vec{S}} \frac{\operatorname{erf}(\alpha|\vec{r} + \vec{S}|)}{|\vec{r} + \vec{S}|} = \frac{1}{V} \sum_{\vec{g}} C_{\vec{g}} e^{i\vec{g} \cdot \vec{r}}$$

Where  $\vec{S}$  are the vectors that corresponds to the distance between the cells. This grants a perfect representation of the system. Now  $C_{\vec{g}}$  is computed as:

$$C_{\vec{g}} = \sum_{\vec{S}} \int_{D(V)} d\vec{r} \frac{\operatorname{erf}(\alpha|\vec{r} + \vec{S}|)}{|\vec{r} + \vec{S}|} e^{-i\vec{g} \cdot \vec{r}} = \int_{\text{all space}} d\vec{r} \frac{\operatorname{erf}(\alpha r)}{r} e^{i\vec{g} \cdot \vec{r}} = \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}$$

So  $C_{\vec{g}}$  is the integral over all the space in each coordinates, where  $r$  is the distance and the final formula is valid for each vector  $\vec{g}$  except for  $\vec{n} = (0 \ 0 \ 0)$ , and that case has to be treated separately. The problem has been transformed into something that is known and  $C_{\vec{g}}$  is a contribution that decrease with  $\vec{g}$ , so for large values of  $\vec{g}$  the contribution is negligible so the sum can be computed up to a maximum value of  $\vec{g}$ . So the sum is truncated with  $|\vec{g}| < g_{max}$ .

### 9.4.1 Summing up

Performing the sum of the previous formula. Considering the property that  $C_{\vec{g}} = C_{-\vec{g}}$  and  $\mathcal{S}$  the positive hemisphere, the contribution of positive and negative  $\vec{g}$  is exactly the same.

$$\begin{aligned} \frac{1}{V} \sum_{\vec{g}} C_{\vec{g}} e^{i\vec{g} \cdot \vec{r}} &= \frac{2}{V} \sum_{i>j} q_i q_j \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{2\alpha^2}} e^{i\vec{g} \cdot (\vec{r}_i - \vec{r}_j)} \\ &= \frac{1}{V} \sum_{i \neq j} q_i q_j \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{2\alpha^2}} e^{i\vec{g} \cdot (\vec{r}_i - \vec{r}_j)} \end{aligned}$$

This is the computation of the Poisson summation rule for the long range contribution of the electrostatic interactions. Adding and subtracting the term with  $i = j$ :

$$U_{long} = \frac{1}{V} \sum_{i,j} q_i q_j \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} e^{i\vec{g} \cdot (\vec{r}_i - \vec{r}_j)} - \underbrace{\frac{1}{V} \sum_i q_i^2 \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}}_{\text{Self interaction term}}$$

Looking at this formula it can be seen how the two sums are independent and the sum over  $q_i^2 e^{i\vec{g} \cdot \vec{r}_i}$  is the structure factor and doing the same with  $j$  is the complex conjugate of the structure factor, a measurable of the system, indicated as the modulus squared:

$$U_{long} = \frac{1}{V} \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} \underbrace{|\sum_i q_i e^{i\vec{g} \cdot \vec{r}_i}|^2}_{\text{Structure factor}} - \frac{1}{V} \sum_i q_i^2 \sum_{\vec{g} \in \mathcal{S}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}$$

### 9.4.2 Ewald sum

The Ewald sums allow to speed up computations:

$$\begin{aligned}
 U_{long} &= \frac{1}{V} \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} \left| \sum_i q_i e^{\vec{g} \cdot \vec{r}_i} \right|^2 - \frac{1}{V} \sum_i q_i^2 \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} = \\
 &= \frac{1}{V} \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} |S(\vec{g})|^2 - \frac{1}{2V} \underbrace{\sum_i q_i^2}_{\text{do not change during the simulation}} \sum_{\substack{g \neq (0 \ 0 \ 0) \\ g \neq (0 \ 0 \ 0)}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}}
 \end{aligned}$$

However:

$$\frac{1}{V} \sum_{\substack{g \neq (0 \ 0 \ 0) \\ g \neq (0 \ 0 \ 0)}} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} = \lim_{r \rightarrow 0} \frac{\operatorname{erf}(\alpha r)}{r} = \lim_{r \rightarrow 0} \frac{2}{r\sqrt{\pi}} \int_0^{\alpha r} e^{-t^2} dt = \lim_{r \rightarrow 0} \frac{2\alpha e^{-\alpha^2 r^2}}{\sqrt{\pi}} = \frac{2\alpha}{\sqrt{\pi}}$$

Considering the self-interaction correction:

$$U_{long} = \frac{1}{V} \sum_{\vec{g} \in S} \frac{4\pi}{|\vec{g}|^2} e^{-\frac{|\vec{g}|^2}{4\alpha^2}} |S(\vec{g})|^2 - \frac{\alpha}{\sqrt{\pi}} \sum_i q_i^2$$

This is the potential energy for the long range interactions.

## 9.5 Alternatives

The alternatives to Ewald sum consider some properties of the system. The structure factor  $S(\vec{g})$  leads to an interaction between all charged particles, because they are already counted in the bonded interactions, so unwanted interactions need to be subtracted.

### 9.5.1 Smooth particle mesh Ewald

The smooth particle mesh Ewald SPME method uses splines to interpolate charge distributions on a grid. Major algorithms use variations of the Ewald sum, representing the continuous functions on a grid. A grid is placed on the simulation box and many functions can be regarded as continuous and can be represented as smooth function instead of point like functions, then splines are interpolated between the grid. So only the charge density is kept track of for each point on the grid and the splines are used to interpolate with any other point in the system. The representation of a charge grid is more accurate if the dimension of the grid is the dimension of the atom. Using too many grid point makes the mesh too crowded.

### 9.5.2 Particle-particle particle-mesh Ewald

The particle-particle particle mesh Ewald or PPPM or P3M uses the density function to compute the structure factor. This is an hybrid system where the charges are represented as a charge density and to compute the structure factor, the Fourier transform of the charge density can be used.

$$\begin{aligned}
 \rho(\vec{r}) &= \sum_i q_i \delta(\vec{r} - \vec{r}_i) \\
 \rho(\vec{g}) &= \int d\vec{r} \rho(\vec{r}) e^{i\vec{g} \cdot \vec{r}} = \sum_i q_i e^{i\vec{g} \cdot \vec{r}_i}
 \end{aligned}$$

## 9.5. ALTERNATIVES

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Considering Poisson equation:

$$\nabla^2 \phi(\vec{r}) = -\nabla \cdot \vec{E} = -4\pi\rho(\vec{r})$$

The potential can be found, which is related to the structure factor:

$$g^2 \phi(\vec{g}) = 4\pi\rho(\vec{g}) = 4\pi S(\vec{G})$$

The Fourier transform has to be computed through special packages like *FFT* or *FFTW*. This is the one used in a lot of software.

### 9.5.3 Other less computationally intensive options

Other cheap options include:

- Spherical truncation.
- Reaction field on a molecule.
- Fast multiple methods FMM.
- Multilevel summation method MSM,
- Maxwell equation molecular dynamics MEMD.

# Chapter 10

## Canonical ensemble

### 10.1 Introduction

In the canonical ensemble energy can fluctuate and is not conserved, temperature is conserved. The system is put into contact with an heat reservoir, which it will exchange energy with the system maintaining constant the temperature.

### 10.2 Thermodynamics derivatives

In the canonical ensemble the thermodynamics parameters that are fixed are the number of particles, the volume and temperature. Everything will be expressed in term of these parameters. Entropy, the state function for the microcanonical ensemble, will not be useful, because it do not depend on the fixed variables. From the microcanonical ensemble and thermodynamics:

$$\frac{1}{T} = \left( \frac{\partial S}{\partial E} \right)_{N,V} \quad \frac{P}{T} = \left( \frac{\partial S}{\partial V} \right)_{N,E} \quad -\frac{\mu}{T} = \left( \frac{\partial S}{\partial N} \right)_{V,E}$$

These thermodynamics derivatives can always be re conducted to the first law of thermodynamics, which in differential form is:

$$dE = TdS - PdV + \mu dN$$

Expressing  $S$  as a differential form the three previous derivatives are found. The temperature will be the derivative of the energy with respect to entropy:

$$T = \left( \frac{\partial E}{\partial S} \right)_{N,V} \quad -P = \left( \frac{\partial E}{\partial V} \right)_{N,S} \quad \mu = \left( \frac{\partial E}{\partial N} \right)_{V,S}$$

Pressure can be obtained as the derivative of the energy with respect to the volume, this works keeping fixed the number of particles and entropy. Keeping entropy fixed is complex on the experimental side. The chemical potential is the derivative of the energy with respect to the number of particles keeping fixed entropy and volume. The objective is to express everything in terms of number of particles, volume and temperature. Because temperature is the derivative of the energy with the respect of entropy, the energy should be expressed as a function of its derivative with respect to entropy.

### 10.2.1 Legendre transform of E

To do so energy is Legendre transformed. Recalling the formula for a Legendre transform:

$$\tilde{f}(s) = f(x(s)) - sx(s) \quad s = f'(x)$$

Applying this to energy:

$$\tilde{E}\left(N, V, \frac{\partial E}{\partial S}\right) = E\left(N, V, S\left(N, V, \frac{\partial E}{\partial S}\right)\right) - \left(\frac{\partial E}{\partial S}\right)_{N,V} S\left(N, V, \frac{\partial E}{\partial S}\right)$$

The Legendre transformed is called  $A$ , which will have the form:

$$A(N, V, T) = E(N, V, T) - TS(N, V, T)$$

### 10.2.2 The Helmholtz free energy

The function  $A$  is the Helmholtz free energy, the Legendre transform of Energy when it is expressed as a function of number of particles, volume and temperature. This is the state function of the canonical ensemble:

$$A(N, V, T) = E(N, V, T) - TS(N, V, T)$$

Computing the differential of  $A$ , its infinitesimal variation:

$$dA = dE - TdS - SdT = \underbrace{TdS - PdV + \mu dN - TdS - SdT}_{\text{first law of thermodynamics}}$$

So that:

$$dA = -SdT - PdV + \mu dN$$

Writing the thermodynamics derivatives with respect to this formula:

$$S = -\left(\frac{\partial A}{\partial T}\right)_{N,V} \quad P = -\left(\frac{\partial A}{\partial V}\right)_{N,T} \quad \mu = \left(\frac{\partial A}{\partial N}\right)_{V,T}$$

So now the thermodynamics of the systems can be computed.

### 10.2.3 Thermal contact

To link the macroscopic quantities to the microscopic ones the distribution function has to be found. Looking at the canonical ensemble there is a thermal reservoir that surrounding the system, so much that the energy will remain constant. It can be assumed that the energy of system one is so small that  $E_2$  is much more than  $E_1$ . Assume that the system is in the microcanonical ensemble and that the two system exchange energies. The universe can be described with the microcanonical ensemble.

$$E = E_1 + E_2 \quad E_2 \gg E_1$$

$$N = N_1 + N_2 \quad N_2 \gg N_1$$

$$E = E_1 + E_2 \quad E_2 \gg E_1$$

$$\mathcal{H}(c) = \mathcal{H}(x_1) + \mathcal{H}(x_2)$$

The microcanonical partition function of the universe is:

$$\Omega(N, V, E) = M_N \int dx \delta(\mathcal{H}(x) - E) = M_N \int dx_1 dx_2 (\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)$$

The objective is to compute the distribution function for system 1. The energy can assume all values between 0 and total energy  $E$ , all with some probability. The objective is to find the function that represent the probability of system 1 to have energy  $E$ . To do that the distribution function of the system (the Dirac delta function) is used and all variables corresponding to system 2 needs to be integrated out.

#### 10.2.3.1 Phase space distribution

Doing this the phase space distribution for system 1 is obtained, so the objective. So assume phase space distribution function  $f$  of the microcanonical ensemble, so the distribution function of the universe is considered and all the terms corresponding to system 2 are integrated out. It is better to consider the logarithm of  $f$ :

$$f(x_1) = \int dx_2 \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E) \quad \ln f(x_1) = \ln \int dx_2 \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)$$

Considering that  $E_1$  is very small when compared to  $E_2$ , so  $\mathcal{H}_1 \ll \mathcal{H}_2$ , so a Taylor expansion from  $\mathcal{H}_1(x_1) = 0$  can be performed, approximating the logarithm to the first order:

$$\ln f(x_1) \approx \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) + \frac{\partial}{\partial \mathcal{H}_1(x_1)} \ln \int dx_2 \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)|_{\mathcal{H}_1(x_1)=0} \mathcal{H}_1(x_1)$$

Considering the fact that the sum of the two Hamiltonian is equal to the energy the dependence of the delta function is linear with respect to the Hamiltonian and the Energy.

$$\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E = 0 \Rightarrow \frac{\partial}{\partial \mathcal{H}_1(x_1)} \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E) = -\frac{\partial}{\partial E} \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)$$

So the derivative with respect to  $\mathcal{H}$  can be substituted with  $-$  the derivative with respect to  $E$ :

$$\ln f(x_1) \approx \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) - \frac{\partial}{\partial E} \ln \int dx_2 \delta(\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2) - E)|_{\mathcal{H}_1(x_1)=0} \mathcal{H}_1(x_1)$$

Considering  $\mathcal{H}_1(x_1) = 0$ :

$$\ln f(x_1) \approx \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) - \frac{\partial}{\partial E} \ln \int dx_2 \delta(\mathcal{H}_2(x_2) - E) \mathcal{H}_1(x_1)$$

The first integral is  $\Omega$  depending on  $N_2$ ,  $V_2$  and  $E$ , so the formula for the microcanonical ensemble:

$$\int dx_2 \delta(\mathcal{H}_2(x_2) - E) \propto \Omega_2(N_2, V_2, E)$$

Or the number of micro states corresponding to those state variables not considering a normalization constant. Remembering that  $\Omega_2$  is related to the entropy and remembering that  $k$  is the Boltzmann constant:

$$\begin{aligned} \ln f(x_1) &\approx \ln \Omega_2(N_2, V_2, E) - \mathcal{H}_1(x_1) \frac{\partial}{\partial E} \ln \Omega_2(N_2, V_2, E) \\ &\approx \frac{S_2(N_2, V_2, E)}{k} - \frac{\mathcal{H}_1(x_1)}{k} \frac{\partial S_2(N_2, V_2, E)}{\partial E} \end{aligned}$$

Considering that the derivative of entropy with respect to energy is  $\frac{1}{T}$  and taking the exponential:

$$\ln f(x_1) \approx \frac{S_2(N_2, V_2, E)}{k} - \frac{\mathcal{H}_1(x_1)}{kT} \Rightarrow f(x_1) \propto e^{-\frac{\mathcal{H}_1(x_1)}{kT}}$$

So there is a given probability at which system 1 will assume a value  $\mathcal{H}_1(x_1)$ . Omitting subscript 1:

$$f(x) \propto e^{-\beta \mathcal{H}(x)} \quad \beta = \frac{1}{kT}$$

This is the probability distribution function for the canonical ensemble, where  $\beta$  is the Boltzmann factor. Normalizing the probability distribution:

$$\int dx f(x) = 1 \Rightarrow f(x) = \frac{e^{-\beta \mathcal{H}(x)}}{N! h^{3N} Q(N, V, T)}$$

Where  $Q$  is the partition function:

$$Q(N, V, T) = \frac{1}{N! h^{3N}} \int dx e^{-\beta \mathcal{H}(x)}$$

### 10.3 From micro to macro

Notice that:

$$A = E - TS = E + T \left( \frac{\partial A}{\partial T} \right)_{N,V} = E - \beta \left( \frac{\partial A}{\partial \beta} \right)_{N,V}$$

However, energy varies in the canonical ensemble and the Hamiltonian assume values from the Boltzmann distribution, so to find a measurable value of the energy an average over the ensemble has to be found, so energy is the average value of the Hamiltonian over the canonical ensemble:

$$E = \langle \mathcal{H} \rangle = \frac{1}{N! h^{3N}} \frac{\int dx \mathcal{H}(x) e^{-\beta \mathcal{H}(x)}}{\int dx e^{-\beta \mathcal{H}(x)}} = -\frac{1}{Q(N, V, \beta)} \frac{\partial Q(N, V, \beta)}{\partial \beta} = -\frac{\partial \ln Q(N, V, \beta)}{\partial \beta}$$

Hence the function of  $A$  and its solution are:

$$A + \frac{\partial \ln Q}{\partial \beta} + \beta \frac{\partial A}{\partial \beta} = 0 \Rightarrow \ln Q(N, V, \beta) = -\beta A(N, V, \beta)$$

So the relationship between the Helmholtz free energy and the partition function is:

$$A(N, V, T) = -kT \ln Q(N, V, T)$$

Now when dealing with the canonical ensemble the partition function has to be found and once that is computed the Helmholtz free energy can be computed.

### 10.3.1 Energy and temperature

The energy can be obtained by performing an average in the canonical ensemble:

$$E = \langle \mathcal{H}(x) \rangle = \frac{C_N \int dx \mathcal{H}(x) e^{-\beta \mathcal{H}(x)}}{C_N \int dx e^{-\beta \mathcal{H}(x)}} = \frac{1}{Q} \frac{\partial Q}{\partial \beta} \quad C_N = \frac{1}{N! h^{3N}}$$

Where  $\mathcal{H}(x)$  is the energy estimator. Taking the average of the Hamiltonian the energy is obtained. Also an estimator of temperature can be obtained, and this will be related to the kinetic energy by applying the equipartition theorem:

$$\left\langle \sum_i \frac{\vec{p}_i^2}{2m_i} \right\rangle = \frac{3}{2} N k T \Rightarrow T = \frac{2}{3Nk} \left\langle \sum_i \frac{\vec{p}_i^2}{2m_i} \right\rangle = \frac{1}{3Nk} \left\langle \sum_i \frac{\vec{p}_i^2}{m_i} \right\rangle = \langle \mathcal{T}(x) \rangle$$

So  $\mathcal{T}(x)$  is the temperature estimator, so that temperature is the average of the estimator:

$$\mathcal{T}(x) = \frac{1}{3Nk} \sum_i \frac{\vec{p}_i^2}{m_i} \quad T = \langle \mathcal{T}(x) \rangle = \frac{C_N \int dx \mathcal{T}(x) e^{-\beta \mathcal{H}(x)}}{C_N \int dx e^{-\beta \mathcal{H}(x)}}$$

#### 10.3.1.1 Energy fluctuations

Energy will be fluctuating, so computing the energy fluctuations, which are defined as:

$$\Delta E = \sqrt{\langle (\mathcal{H}(x) - \langle \mathcal{H}(x) \rangle)^2 \rangle} \quad \langle (\mathcal{H}(x) - \langle \mathcal{H}(x) \rangle)^2 \rangle = \langle \mathcal{H}^2(x) \rangle - \langle \mathcal{H}(x) \rangle^2$$

Now, computing:

$$\langle \mathcal{H}^2(x) \rangle = \frac{C_N \int dx \mathcal{H}^2(x) e^{-\beta \mathcal{H}(x)}}{C_N \int dx e^{-\beta \mathcal{H}(x)}} = \frac{1}{Q} \frac{\partial^2 Q}{\partial \beta^2} \quad \langle \mathcal{H}(x) \rangle^2 = \left[ \frac{C_N \int dx \mathcal{H}(x) e^{-\beta \mathcal{H}(x)}}{C_N \int dx e^{-\beta \mathcal{H}(x)}} \right]^2 = \left[ \frac{1}{Q} \frac{\partial Q}{\partial \beta} \right]^2$$

Computing the second derivative of the logarithm of  $Q$  with respect to  $\beta$ :

$$\frac{\partial^2 \ln Q}{\partial \beta^2} = \frac{\partial}{\partial \beta} \left[ \frac{1}{Q} \frac{\partial Q}{\partial \beta} \right] = -\frac{1}{Q^2} \left[ \frac{\partial Q}{\partial \beta} \right]^2 + \frac{1}{Q} \frac{\partial^2 Q}{\partial \beta^2} = \langle \mathcal{H}^2(x) \rangle - \langle \mathcal{H}(x) \rangle^2 = \Delta E^2$$

So the fluctuation squared and considering that  $\frac{\partial \ln Q}{\partial \beta} = -E$ :

$$\Delta E^2 = \frac{\partial^2 \ln Q}{\partial \beta^2} = -\frac{\partial E}{\partial \beta} = -\left( \frac{\partial E}{\partial T} \right) \frac{\partial T}{\partial \beta} = kT^2 \frac{\partial E}{\partial T} = kT^2 C_V$$

Where  $C_V$  is the specific heat of the system. Comparing the fluctuation of the energy with the energy to see if they are negligible or big. Considering that  $C_V$  and  $E$  increase linearly with the number of particles:

$$\frac{\Delta E}{E} = \frac{\sqrt{kT^2 C_V}}{E} \sim \frac{\sqrt{N}}{N} \sim \frac{1}{\sqrt{N}}$$

So if  $N$  is small the factor is not negligible, and becomes more negligible as it increases. So when working with a thermodynamics system the fluctuation with respect to energy are negligible. So in the thermodynamics limit the energy fluctuations in the canonical ensemble are negligible. The difference between the microcanonical and canonical ensemble is that the energy is fixed only in the first, but in the second the fluctuation of the energy is negligible, so that from a practical point of view all the results from the two ensembles are equivalent.

### 10.3.2 Pressure estimator

Considering pressure:

$$P = -\left(\frac{\partial A}{\partial V}\right)_{N,T} = kT\left(\frac{\partial \ln Q}{\partial V}\right)_{N,T} = \frac{kT}{Q}\left(\frac{\partial Q}{\partial V}\right)_{N,T}$$

The objective is to look on the dependence of the partition function on volume and not considering normalization constant:

$$\frac{1}{Q}\left(\frac{\partial Q}{\partial V}\right)_{N,T} = \frac{1}{\int d\vec{p}_1 \cdots d\vec{p}_N d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta\mathcal{H}(\vec{r}, \vec{p})}} \frac{\partial}{\partial V} \int d\vec{p}_1 \cdots d\vec{p}_N d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta\mathcal{H}(\vec{r}, \vec{p})}$$

Considering the Hamiltonian it will have the kinetic and potential energy part. The kinetic part will always be the same and do not depend on the volume and it will be integrated out, this is called configuration partition function, so the integral can be written only over the coordinates and only the potential energy.

$$\frac{1}{Q}\left(\frac{\partial Q}{\partial V}\right)_{N,T} = \frac{1}{\int d\vec{p}_1 \cdots d\vec{p}_N d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})}} \frac{\partial}{\partial V} \int d\vec{p}_1 \cdots d\vec{p}_N d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})} = \frac{1}{Z} \frac{\partial Z}{\partial V}$$

Where  $Z$  is the configuration partition function:

$$P = \frac{kT}{Z} \frac{\partial Z}{\partial V} \quad Z(N, V, T) = \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})}$$

Now considering  $Z$  it is an integral over all the coordinates and  $U$  is the force fields. The problem is that the integral depends on volume through its limits, in order to do that all the possible dependencies on the integral on the volume. The best thing to do is to consider dimensionless coordinates. Changing coordinates and considering a cubic box, the coordinates are scaled into  $\vec{s}_i$ , where  $L$  is the side of the cube and considering there are  $3N$  coordinates:

$$\vec{s}_i = \frac{1}{L} \vec{r}_i = V^{-\frac{1}{3}} \vec{r}_i \Rightarrow d\vec{r}_1 = V^{\frac{1}{3}} d\vec{s}_1 \quad Z(N, V, T) = \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})} = V^N \int d\vec{s}_1 \cdots d\vec{s}_N e^{-\beta U(V^{\frac{1}{3}} \vec{s})}$$

In this way the dependence on volume has been highlighted and the derivative of  $Z$  with respect to volume can be taken:

$$\begin{aligned}
 \frac{\partial Z(N, V, T)}{\partial V} &= \frac{N}{V} V^N \int d\vec{s}_1 \cdots d\vec{s}_N e^{-\beta U(V^{\frac{1}{3}} \vec{s})} + V^N \int d\vec{s}_1 \cdots d\vec{s}_N e^{-\beta U(V^{\frac{1}{3}} \vec{s})} \sum_{i=1}^N \left( -\beta \frac{\partial U}{\partial V^{\frac{1}{3}} \vec{s}_i} \right) \left( \frac{1}{3} V^{-\frac{2}{3}} \vec{s}_i \right) = \\
 &= \frac{N}{V} Z - \frac{\beta}{3V} \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})} \sum_{i=1}^N \frac{\partial U}{\partial \vec{r}_i} = \\
 &= \frac{N}{V} Z + \frac{\beta}{3V} \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})} \sum_{i=1}^N \vec{F}_i \cdot \vec{r}_i
 \end{aligned}$$

Reconsidering now the formula for pressure and considering  $kT\beta = 1$ :

$$P = \frac{kT}{Z} \frac{\partial Z}{\partial V} = \frac{NkT}{V} + \frac{1}{3VZ} \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r})} \sum_{i=1}^N \vec{F}_i \cdot \vec{r}_i = \frac{NkT}{V} + \frac{1}{3V} \left\langle \sum_{i=1}^N \vec{F}_i \cdot \vec{r}_i \right\rangle$$

This formula makes sense as when considering ideal gas there are no internal forces, so they are all equal to 0, obtaining the ideal gas law. So the second part contains the correction that considers these internal forces. Considering that temperature can be expressed as an average:

$$T = \frac{1}{3Nk} \left\langle \sum_i \frac{\vec{p}_i^2}{m_i} \right\rangle \Rightarrow P = \frac{1}{3V} \left\langle \sum_i \frac{\vec{p}_i^2}{m_i} \right\rangle + \frac{1}{3V} \left\langle \sum_{i=1}^N \vec{F}_i \cdot \vec{r}_i \right\rangle$$

Now, recollecting everything into one single formula:

$$P = \frac{1}{3V} \left\langle \sum_i \left[ \frac{\vec{p}_i^2}{m_i} + \vec{F}_i \cdot \vec{r}_i \right] \right\rangle = \langle \mathcal{P}(\vec{r}, \vec{p}) \rangle$$

So the pressure estimator is:

$$\mathcal{P}(\vec{r}, \vec{p}) = \frac{1}{3V} \sum_i \left[ \frac{\vec{p}_i^2}{m_i} + \vec{F}_i \cdot \vec{r}_i \right]$$

# Chapter 11

## Thermostats

### 11.1 Introduction

When dealing with computer simulation of a biomolecule temperature has to be constant, so the effect of a thermostat has to be included. So the particles will interact with the particles in the thermal bath. The idea is to check whether the kinetic energy is what is expected for the particular temperature and take action when that is not the case.

#### 11.1.1 Velocity rescaling

The velocity rescaling technique involve having a target kinetic energy compatible with the temperature. Considering  $N_f$  the number of degrees of freedom.

$$\bar{K} = \frac{N_f}{2\beta}$$

This is what is expected from the equipartition theorem. When running a simulation, the actual kinetic energy is:

$$K = \frac{1}{2} \sum_i m_i \vec{v}_i^2$$

The objective is to have  $K = \bar{K}$ , so the velocities are rescaled by a rescaling factor  $\alpha = \sqrt{\frac{\bar{K}}{K}}$  where  $\vec{v}_i \rightarrow \frac{\vec{v}_i}{\alpha}$ . This allows to obtain the rescaled kinetic energy:

$$\frac{1}{2} \sum_i m_i \frac{\vec{v}_i^2}{\alpha^2} = \frac{\bar{K}}{2K} \sum_i m_i \vec{v}_i^2 = \bar{K}$$

So that the target kinetic energy is obtained in the simulation. Velocities are rescaled at a predetermined frequency or using a threshold value on the actual kinetic energy to allow for its fluctuations. This algorithm either provide more velocities to particles or it slows them down. In the first case there will be problems in satisfying all the constraints. This kind of thermostat is rigorously correct only in the thermodynamics limit:  $N \rightarrow \infty$ . It is not recommended for a small number of particles.

## 11.2 Type of thermostats

### 11.2.1 Andersen's thermostat

Consider a collision frequency  $\nu$ , then  $\nu\Delta t$  is the probability of a collision in  $\Delta t$ . In particular every  $\frac{1}{\nu}$  there will be a collision. To implement the changes in kinetic energy considering the probability  $\nu\Delta t$ , a random number  $\rho$  from a uniform probability distribution in  $[0, 1]$ , if  $\rho < \nu\Delta t$  the velocity is reassigned to the particle, extracting it from the Maxwell-Boltzmann distribution:

$$P(p) = \left( \frac{\beta}{2\pi m} \right)^{\frac{3}{2}} e^{-\beta \frac{p^2}{2m}}$$

So this distribution samples the canonical ensemble. This is done for all the particles. This causes abrupt discontinuity in the velocities, making it difficult to satisfy the constraints.

### 11.2.2 Andersen revisited - Heyes

A modification on Andersen thermostat has been done by Heyes. There is a mixture between the velocity algorithm and Andersen's thermostat. The target kinetic every  $K_t$  is selected from a distribution:

$$P(K_t)dK_t \propto K_t^{\frac{N_f}{2}-1} e^{-\beta K_t} dK_t$$

This is what would be obtained from the Maxwell-Boltzmann distribution, corrected by the number of degrees of freedom. The target kinetic energy is not fixed, but it will vary and then the velocities are re-scaled. It is more gentle than the Andersen's thermostat and it is more rigorous than the velocities rescaling because the target kinetic energy can vary according to the distribution. Once the actual kinetic energy is obtained:

$$K = \frac{1}{2} \sum_i m_i \vec{v}_i^2$$

A scaling factor is computed  $\alpha = \sqrt{\frac{K_t}{K}}$  and the velocities are updated:  $\vec{v}_i \rightarrow \frac{\vec{v}_i}{\alpha}$  at a predetermined frequency or considering some threshold. The rescaled kinetic energy will then be:

$$\frac{1}{2} \sum_i m_i \frac{\vec{v}_i^2}{\alpha^2} = \frac{K_t}{2K} \sum_i m_i \vec{v}_i^2 = K_t$$

This is rigorously correct in the thermodynamics limit:  $N \rightarrow \infty$ . The thermodynamics limit will be reached sooner than the velocity rescaling algorithm.

### 11.2.3 Langevin thermostat

The Langevin thermostat is based on Langevin equation. Friction with a friction coefficient  $\gamma$  is introduced, dissipating some of the energy and also some random velocities  $\eta_i$  are introduced to keep the temperature and the kinetic energy fixed. The random velocities model the collisions between system and thermal bath particles. The Langevin equations will be used for both the solute and solvent particles. Using Langevin's thermostat the canonical solution is sampled. The properties of the random velocities are:

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1. Collisions between solute and solvent and thermal bath particles are many and independent. Components of the random velocities are sampled from a Gaussian distribution.
2. On average there is no net momentum exchange between the thermal bath and the solute particles:  $\langle \eta_i(t) \rangle = 0$ .
3. Frequent and instantaneous collisions. To have instantaneous collisions the auto correlation function of the velocities decays fast:  $\langle \eta_i(t)\eta_j(t) \rangle = 6D\delta_{ij}\delta(t-t')$  where  $D = \frac{kT}{m\gamma}$  is the diffusion coefficient.

Now everything is implemented considering the equation of motions. The equations of motion are coupled overdamped Langevin equations. There is no acceleration because in the overdamped limit the mass term is negligible and the change in velocities is:

$$\dot{\vec{r}}_i(t) = \beta D \vec{F}_i(\vec{r}_1(t), \dots, \vec{r}_N(t)) + \eta_i(t)$$

This is used for computing the velocities in the Verlet algorithm. Writing this down the configuration obtained will sample the Fokker-Planck equation:

$$\frac{\partial}{\partial t} P(\vec{x}, t) = D \sum_{i=1}^N \nabla_i \cdot [\nabla_i + \beta \nabla \mathcal{H}(\vec{x})]$$

The Boltzmann distribution  $P(\vec{x}) = Ce^{-\beta \mathcal{H}(\vec{x})}$  is the stationary solution of the Fokker-Planck equation. Guaranteeing that in the long time limit the solution the velocities will be sampled from the Boltzmann distribution. This implies that simulations have to be long and the effect of the random velocities has to be considered. To integrate the Langevin equation:

$$\dot{\vec{r}}_i(t) = \beta D \vec{F}_i(\vec{r}_1(t), \dots, \vec{r}_N(t)) + \eta_i(t)$$

$$\langle \eta_i(t)\eta_j(t) \rangle = 6D\delta_{ij}\frac{\delta_{kl}}{\Delta t}$$

The random velocity is sampled from a Gaussian distribution with a non-unitary variance:

$$\sigma^2 = \langle \eta_i(0)\eta_i(0) \rangle = \frac{6D}{\Delta t}$$

Where 6 is 2 times the number of dimensions. Now a random force  $\xi_i(t_k)$  satisfying the unitary variance condition:

$$\xi_i(t_k) = \sqrt{\frac{\Delta t}{6D}} \eta_i(t_k) \quad \langle \xi_i(t_k) \rangle = 0 \quad \langle \xi_i(t_k)\xi_l(t_l) \rangle = \delta_{ij}\delta_{kl}$$

Random velocities are rescaled to obtain a variance equal to 1. Considering a discretized Langevin equation:

$$\frac{\vec{r}_i(t + \Delta t) - \vec{r}_i(t)}{\Delta t} = \beta D \vec{F}_i(\vec{r}_1(t), \dots, \vec{r}_N(t)) + \sqrt{\frac{6D}{\Delta t}} \xi_i(t)$$

Thus:

$$\vec{r}_i(t + \Delta t) = \vec{r}_i(t) + \Delta t \frac{\vec{F}_i(\vec{r}_1(t), \dots, \vec{r}_N(t))}{m_i \gamma} + \sqrt{\frac{6kT\Delta t}{m_i \gamma}} \xi_i(t)$$

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$\xi_i$  are random numbers with average 0 and variance 1, allowing to obtain the coordinate at time  $t + \Delta t$ , getting a stationary solution in the long term of the Fokker-Planck equation, which is the Boltzmann distribution.

## 11.3 Bussi velocity Verlet

The Bussi velocity Verlet is a generalized version of the velocities rescaling based on velocity rescale with the following algorithm:

- Evolve the system for a single time step with Hamilton's equations, using a time-reversible area-preserving integration scheme like the velocity Verlet or any integration scheme for the microcanonical ensemble.
- Compute the kinetic energy, which becomes a variables with its own dynamics.
- Evolve the kinetic energy for a time corresponding to a single time step using an auxiliary continuous stochastic dynamics equations.
- Rescale the velocities so as to enforce this new value of the kinetic energy.

The equations that represent the auxiliary dynamics on kinetic energy:

$$dK = \left( D(K) \frac{\partial \log P(K)}{\partial K} + \frac{\partial D(K)}{\partial K} \right) dt + \sqrt{2D(K)} dW$$

Where  $dW$  is a stochastic variation and the first part is completely deterministic. The probability distribution for the kinetic energy is taken from Heyes' algorithm:  $P(K_t) dK_t \propto K_t^{\frac{N_f}{2}-1} e^{\beta K_t} dK_t$ :

$$dK = \left( \frac{N_f D(K)}{2K\bar{K}} (K - \bar{K}) - \frac{D(K)}{K} + \frac{\partial D(K)}{\partial K} \right) dt + \sqrt{2D(K)} dW$$

A possible choice for  $D(K)$  is:

$$D(K) = \frac{2K\bar{K}}{N_f \tau}$$

So that:

$$dK = (K - \bar{K}) \frac{dt}{\tau} + \sqrt{\frac{2K\bar{K}}{N_f} \frac{dW}{\sqrt{\tau}}}$$

This is the auxiliary variable stochastic dynamics equation for the kinetic energy. Neglecting the stochastic term Berendsen's thermostat is obtained:

$$dK = (K - \bar{K}) \frac{dt}{\tau}$$

Here the kinetic energy changes only when it is different from  $\bar{K}$ . This is not sampling the canonical distribution. So there is no known ensemble that can be simulated. This is useful for simulating at a given temperature and to perform an equilibration step. Once equilibrium is obtained a proper thermostat is used. Reconsidering the stochastic part there are two important limits:

$$\tau \rightarrow 0 \Rightarrow \tau dK = (K - \bar{K})dt + \sqrt{\frac{2K\bar{K}\tau}{N_f}}dW \Rightarrow (K - \bar{K})dt = 0 \text{ (Heyes)}$$

Sampling the kinetic energy from the Heyes distribution. The other limit is when:

$$\tau \rightarrow \infty \Rightarrow dK = (K - \bar{K})\frac{dt}{\tau} + \sqrt{\frac{2K\bar{K}}{N_f}}\frac{dW}{\sqrt{\tau}} \Rightarrow dK = 0 \text{ (Hamiltonian dynamics)}$$

In this way Hamiltonian dynamics are obtained: the kinetic energy will be treated as any other observable and has no dynamics. If  $\tau$  is in between the two values a family of algorithms with all possible  $\tau$  are obtained. The solution to the differential equation leads to a scaling factor ( $R_i$  independent Gaussian random numbers):

$$\alpha^2 = e^{-\frac{\Delta t}{\tau}} + \frac{\bar{K}}{N_f K}(1 - e^{-\frac{\Delta t}{\tau}}) \sum_{i=1}^{N_f} R_i^2 + 2e^{-\frac{\Delta t}{2\tau}} \sqrt{\frac{\bar{K}}{N_f K}(1 - e^{-\frac{\Delta t}{\tau}})R_1}$$

The scaling factor on the velocities depends on a sequence of random numbers, one for each degree of freedom. This has the same computational cost as the velocity rescaling algorithm with two advantages:

- The canonical distribution is obtained.
- The velocities remain continuous and there are no problem with the constraints.

## 11.4 Nosè Hamiltonian

Nosè Hamiltonian or the extended phase space involves to introducing an extra variable introducing a Maxwell daemon and when it sees that the particles have a higher velocity than expected it will assign a new velocity according to the Maxwell distribution keeping the temperature constant. Doing so an extra variable in the Hamiltonian  $s$  is obtained, for which its conjugated momentum  $p_s$  is obtained.

$$\mathcal{H}_N = \sum_i \frac{\vec{p}_i^2}{2m_i s^2} + U(\vec{r}_1, \dots, \vec{r}_n)_{\frac{p_s^2}{2Q}} + gkT \log s$$

Where  $g$  is a parameter. For the conjugate momentum there is an extra term and  $Q$  works like mass and is an inertial term for  $p_s$ , the bigger  $Q$  the smaller the variation in kinetic variation. In total there are  $6N+2$  variables in the system. Assuming that this is the Hamiltonian, following Hamilton's equation the microcanonical ensemble is being simulated. Considering the microcanonical partition function for Nosè Hamiltonian:

$$\Omega = \int d^N \vec{r} d^N \vec{p} ds dp_s \delta \left( \sum_i \frac{\vec{p}_i^2}{2m_i s^2} + U(\vec{r}_1, \dots, \vec{r}_N) + \frac{p_s^2}{2Q} + gkT \log s - E \right)$$

Where  $\Omega$  is the total number of configuration. The integration is over all the coordinates and the momenta and also on the extra coordinate and its conjugate momentum that depends on Maxwell's daemon. The delta function is the function of the Nosè Hamiltonian minus the energy. Scaling the momentum  $\frac{\vec{p}}{s} \rightarrow \vec{p}$ :

$$\Omega = \int d^N \vec{r} d^N \vec{p} ds dp_s s^{dN} \delta \left( \mathcal{H} + \frac{p_s^2}{2Q} + gkT \log s - E \right)$$

Where  $N$  is the dimensionality of the system. This can be solved using the property of the  $\delta$  function, allowing to integrate over the two new variables:

$$\delta(f(s)) = \frac{\delta(s - s_0)}{|f'(s_0)|} \quad f(s) = \mathcal{H} + \frac{p_s^2}{2Q} + gkT \log s - E \quad f'(s) = \frac{gkT}{s}$$

Computing the zero of  $f(s)$ :

$$s_0 = e^{\frac{1}{gkT} (E - \mathcal{H} - \frac{p_s^2}{2Q})} \Rightarrow f'(s_0) = gkT e^{-\frac{1}{gkT} (E - \mathcal{H} - \frac{p_s^2}{2Q})}$$

Substituting  $\delta(f(s))$  with  $\frac{\delta(s - s_0)}{|f'(s_0)|}$ :

$$\delta(f(s)) = \frac{1}{gkT} e^{\frac{1}{gkT} (E - \mathcal{H} - \frac{p_s^2}{2Q})} \delta \left( s - e^{\frac{1}{gkT} (E - \mathcal{H} - \frac{p_s^2}{2Q})} \right)$$

Plugging it in the microcanonical partition function:

$$\Omega = \int d^N \vec{r} d^N \vec{p} ds dp_s s^{dN} \delta \left( \mathcal{H} + \frac{p_s^2}{2Q} + gkT \log s - E \right)$$

Computing the integral in  $s$  the net result is substituting  $s$  with the value of  $s_0$ :

$$\Omega = \frac{1}{dkT} \int d^N \vec{r} d^N \vec{p} dp_s e^{\frac{dN+1}{gkT} (E - \mathcal{H} - \frac{p_s^2}{2Q})}$$

Determining the value of the parameter  $g$  and considering the integral in  $p_s$  this is a Gaussian integral:

$$g = dN + 1 \Rightarrow \Omega = \frac{e^{\frac{E}{kT}} \sqrt{2\pi Q kT}}{(dN + 1) kT} \int d^N \vec{r} d^N \vec{p} e^{-\frac{\mathcal{H}}{kT}}$$

So that in the integral is remaining the partition function of the canonical ensemble. Using the Nosè Hamiltonian the canonical ensemble in the original Hamiltonian is sampled. The microcanonical partition function for the extended Nosè Hamiltonian corresponds to the canonical partition function for the original Hamiltonian non considering multiplicative factors.

### 11.4.1 Nosè equations

Considering the original Nosè Hamiltonian

$$\mathcal{H}_N = \sum_i \frac{\vec{p}_i^2}{2m_i s^2} + U(\vec{r}_1, \dots, \vec{r}_N) + \frac{p_s^2}{2Q} + gkT \log s$$

Applying Hamilton's equation to the coordinates and the momenta:

$$\dot{\vec{r}}_i = \frac{\partial \mathcal{H}_N}{\partial \vec{p}_i} = \frac{\vec{p}_i}{m_i} s^2 \quad \dot{\vec{p}}_i = -\frac{\partial \mathcal{H}_N}{\partial \vec{r}_i} = -\frac{\partial U}{\partial \vec{r}_i} = \vec{F}_i$$

There are two extra equations that corresponds to the time evolution of the extra coordinates and of its conjugate momentum:

$$\dot{s} = \frac{\partial \mathcal{H}_N}{\partial p_s} = \frac{p_s}{Q} \quad \dot{p}_s = -\frac{\partial \mathcal{H}_N}{\partial S} = \sum_i \frac{\vec{p}_i^2}{m_i s^3} - \frac{gkT}{s} = \frac{1}{s} \left[ \sum_i \frac{\vec{p}_i^2}{m_i s^2} - gkT \right]$$

### 11.4.2 Nosè-Hoover equations

Performing a noncanonical change of variables, so that there is no way that the new equations can be obtained starting from the Hamiltonian.

$$\vec{p}'_i = \frac{\vec{p}_i}{s} \quad p'_s = \frac{p_s}{s} \quad dt' = \frac{dt}{s}$$

Changing the derivative of position with the new time and momentum:

$$\frac{d\vec{r}_i}{dt} = \frac{\vec{p}_i}{m_i s^2} \Rightarrow \frac{d\vec{r}'_i}{dt'} = \frac{\vec{p}'_i}{m_i} \quad \frac{d\vec{p}'_i}{dt'} = \vec{F}_i - \frac{sp'_s}{Q} \vec{p}'_i$$

The derivative of positions become the one in the original Hamiltonian. The derivative of momenta has the original force and a correction on it, extra forces proportional to the velocities and that look like friction terms, but it is not guaranteed to be a negative contribution. This can allow the temperature to be constant.

$$\begin{aligned} \frac{ds}{dt'} &= \frac{s^2 p'_s}{Q} \\ \frac{dp'_s}{dt'} &= \frac{1}{s} \left[ \sum_i \frac{(\vec{p}'_i)^2}{m_i} - gkT \right] - \frac{s(p'_s)^2}{Q} \end{aligned}$$

These are Nosè equations and are computed applying Hamilton's equation to it. Now in this new form the look similar to Hamilton's equation to the original Hamiltonian. Performing another change of variables:

$$\frac{1}{s} \frac{ds}{dt'} = \frac{d\eta}{dt'} \quad p_s = p_\eta = sp'_s$$

And starting from the equations a new set is obtained:

- $\dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i}$ .
- $\dot{\vec{p}}_i = \vec{F}_i - \frac{p_\eta}{Q} \vec{p}_i$ .
- $\dot{\eta} = \frac{p_\eta}{Q}$ .
- $\dot{p}_\eta = \sum_i \frac{\vec{p}_i^2}{m_i} - dNkT$ . This is exactly twice the kinetic energy and the difference between this term and the double of the kinetic energy. Whenever the kinetic energy differs from the expected then the momentum  $\dot{p}_\eta$  and that will act as a friction term.

These are the dynamics of the thermostat.

## 11.5 Non Hamiltonian statistical mechanics

The Nosè-Hoover cannot be derived from an Hamiltonian. The equations were obtained from a non-canonical transformation of variables. There is a need to define what happens in non-Hamiltonian systems. Liouville's equations can be extended to non-Hamiltonian systems. When describing the system and its surroundings the universe can be thought as an isolated system, which can be described through Hamiltonian dynamics: the energy is fixed. When describe the system without the surrounding all the variables of the second have to be integrated out so they do not appear in the results. This operation lead to obtain non-Hamiltonian dynamics. The non-Hamiltonian equations of motion are:

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

This is the velocity in phase space. Considering phase space compressibility for non-Hamiltonian dynamics:

$$\nabla \cdot \dot{x} = \nabla \cdot \xi(x, t) = \kappa(x, t) \neq 0$$

Where  $\kappa$  is the compressibility, which is 0 for Hamiltonian systems. For a non-Hamiltonian system the compressibility might be different from 0.

### 11.5.1 Phase space metric

To study non-Hamiltonian systems the phase-space metric has to be investigated:

$$\frac{d}{dt} J(x_t; x_0) = J(x_t; x_0) \nabla \cdot \dot{x}_t \Rightarrow \frac{d}{dt} J(x_t; x_0) = J(x_t; x_0) \kappa(x_t, t)$$

Where  $J$  is the Jacobian of the transformation from the coordinates at time 0 to the ones at time  $t$ . Because of the dependence on compressibility  $J$  can be variable. Because of this the Liouville theorem  $dx_t = dx_0$  no longer holds, but the solution of the derivative above is:

$$J(x_t; x_0) = e^{\int_0^t ds \kappa(x_s, s)}$$

This is the multiplicative factor that has to be added to the Liouville theorem to obtain the system evolution. Considering that there exists a function  $w(x_t, t)$  whose derivative is  $\kappa(x_t, t)$ , so that the integral can be re-written:

$$\kappa(x_t, t) = \frac{dw(x_t, t)}{dt} \quad J(x_t; x_0) = e^{w(x_t, t) - w(x_0, 0)}$$

Applying it to the infinitesimal volume element:

$$dx_t = J(x_t; x_0) dx_0 \Rightarrow dx_t = e^{w(x_t, t) - w(x_0, 0)} dx_0$$

Multiplying for  $e^{-w}$ :

$$e^{-w(x_t, t)} dx_t = e^{-w(x_0, 0)} dx_0$$

Obtaining a generalization of Liouville's theorem. In this case it is not the volume that is conserved, but it is the weighted phase space volume is conserved, where the factor is  $e^{-w(x_t, t)}$ . This metric allow to define the volume element in space and the phase space is a non Euclidean space or

Reimannian manifold, which is locally curved. The Jacobian is the ratio of the metric determinant factors:

$$J(x; y) = \frac{\sqrt{g(y)}}{\sqrt{g(x)}} \Rightarrow J(x_t; x_0) = \frac{\sqrt{g(x_0, 0)}}{\sqrt{g(x_t, t)}} \quad \sqrt{g(x_t, t)} = e^{-w(x_t, t)}$$

Any phase space integral or ensemble average should be performed using  $\sqrt{g(x)}dx$  as a volume element without time dependence. This is because the infinitesimal volume element is always multiplied by the metric factor. Because equilibrium solutions are searched there will be no explicit time dependence.

### 11.5.2 Liouville equation

When applying the previous result to Liouville's equation. The equation for the time evolution of the probability distribution function should be generalized:

$$\frac{\partial}{\partial t}(f(x, t)\sqrt{g(x, t)}) + \nabla \cdot (\dot{x}\sqrt{g(x, t)}f(x, t)) = 0$$

Considering the derivative of  $J$ :

$$\frac{d}{dt}J(x_t; x_0) = J(x_t; x_0)\kappa(x_t, t) \Rightarrow \frac{d}{dt}\frac{\sqrt{g(x_0, 0)}}{\sqrt{g(x_t, t)}} = \frac{\sqrt{g(x_0, 0)}}{\sqrt{g(x_t, t)}}\kappa(x_t, t)$$

From this equation:

$$\frac{d}{dt}\sqrt{g(x_t, t)} = -\kappa(x_t, t)\sqrt{g(x_t, t)}$$

Substituting into the generalized Liouville equation:

$$\frac{\partial}{\partial t}f(x, t) + \dot{x} \cdot \nabla f(x, t) = 0 \Rightarrow \frac{d}{dt}f(x, t) = 0$$

Noticing that partial and total derivatives are different. This is the same result of Hamiltonian systems. The ensemble distribution function is conserved in a space with a non-trivial metric:

$$f(x_t, t)\sqrt{g(x_t, t)}dx_t = f(x_0, 0)\sqrt{g(x_0, 0)}dx_0$$

From this the total number of conformation can be computed using the microcanonical ensemble.

### 11.5.3 Equilibrium solutions

Considering Liouville's result:

$$f(x_t, t)\sqrt{g(x_t, t)}dx_t = f(x_0, 0)\sqrt{g(x_0, 0)}dx_0$$

Trying to find an equilibrium solution, this should not present an explicit time dependence:

$$f(x_t)\sqrt{g(x_t)}dx_t = f(x_0)\sqrt{g(x_0)}dx_0$$

Averages can be performed at any instant of time with the correct metric factor. The same expression as in the equilibrium Liouville equation:

$$\xi(x) \cdot \nabla f(x) = 0$$

Since there is no Hamiltonian there are no Poissons brackets. However since  $\frac{df}{dt} = 0$  a general equilibrium solution can be built inserting all the conservation laws satisfied by the equation of motion. Consider  $N_C$  conservation laws:  $\Lambda_k(x_t) - C_k = 0$ ,  $\frac{d\Lambda_k(x_t)}{dt} = 0$ ,  $k = 1, \dots, N_C$ :

$$f(x) = \prod_{k=1}^{N_C} \delta(\Lambda_k(x_t) - C_k)$$

The number of microstates available to the systems is determined by  $f(x)$  when it is integrated with respect to the conserved volume element  $\sqrt{g(x)}dx$ . Considering the microcanonical partition function:

$$\mathcal{E} = \int dx \sqrt{g(x)} f(x) = \int dx \sqrt{g(x)} \prod_{k=1}^{N_C} \delta(\Lambda_k(x_t) - C_k)$$

#### 11.5.4 Analysis of non Hamiltonian equations

Performing an analysis of the Nosè-Hoover equations:

$$\dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i} \quad \dot{\vec{p}}_i = \vec{F}_i - \frac{p_\eta}{Q} \vec{p}_i \quad \dot{\eta} = \frac{p_\eta}{Q} \quad \dot{p}_\eta = \sum_i \frac{\vec{p}_i^2}{m_i} - dNkT$$

Given the equations of a non-Hamiltonian system, the kind of simulated ensemble has to be found. Using this equations the conserved quantity is:

$$\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) = \mathcal{H}(\vec{r}, \vec{p}) + \frac{p_\eta^2}{2Q} + dNkT\eta \quad \frac{d\mathcal{H}'}{dt} = 0$$

$\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta)$  is not an Hamiltonian, but a conserved quantity: there is no way to obtain the Nosè-Hoover equations applying Hamiltons equations to  $\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta)$ . Computing the compressibility of this equation:

$$\kappa = \sum_{i=1}^N [\nabla_{\vec{p}_i} \cdot \dot{\vec{p}}_i + \nabla_{\vec{r}_i} \cdot \dot{\vec{r}}_i] + \frac{\partial \dot{\eta}}{\partial \eta} + \frac{\partial \dot{p}_\eta}{\partial p_\eta} = -Nd\frac{p_\eta}{Q} = -Nd\dot{\eta}$$

Where  $d$  is the number of dimensions. However, writing the compressibility as a time derivative:

$$\kappa = \frac{dw}{dt} \Rightarrow w = -dN\eta \Rightarrow \sqrt{g} = e^{-w} = e^{dN\eta}$$

Which is the metric factor, which has to be applied to any integral performed on space.

#### 11.5.5 Partition function

Considering the conserved quantity and the metric factor:

$$\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) = \mathcal{H}(\vec{r}, \vec{p}) + \frac{p_\eta^2}{2Q} + dNkT\eta \quad \sqrt{g} = e^{dN\eta}$$

The partition function can be written starting from:

$$\mathcal{E} = \int dx \sqrt{g(x)} \prod_{k=1}^{N_C} \delta(\Lambda_k(x_t) - C_k)$$

Which translate into:

$$\mathcal{E}_T(N, V, C_1) = \int d^N \vec{p} \int_{\mathcal{D}(V)} d^n \vec{r} \int dp_\eta d\eta e^{dN\eta} \delta \left( \mathcal{H}(\vec{r}, \vec{p}) + \frac{p_\eta^2}{2Q} + dNkT\eta - C_1 \right)$$

This function depends on the number of particles, volume and the constant  $C_1$ . And where  $\Lambda_k = \mathcal{H}'$  and so temperature is a parameter,  $\mathcal{D}(V)$  is the volume of the system. Now, considering the  $\delta$  function to find a value  $\eta_0$  to exploit the property of the  $\delta$  function:

$$\delta \left( \mathcal{H}(\vec{r}, \vec{p}) + \frac{p_\eta^2}{2Q} + dNkT\eta - C_1 \right) = \frac{1}{dNkT} \delta(\eta - \eta_0) \quad \eta_0 = \frac{1}{dNkT} \left( C_1 - \mathcal{H}(\vec{r}, \vec{p}) - \frac{p_\eta^2}{2Q} \right)$$

So the  $\delta$  function can be re-written:

$$\mathcal{E}_T(N, V, C_1) = \frac{e^{\beta C_1}}{dNkT} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^n \vec{r} \int dp_\eta e^{-\frac{\beta p_\eta^2}{2Q}} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})}$$

Now integrating over  $p_\eta$  because it is a Gaussian integral:

$$\mathcal{E}_T(N, V, C_1) = \frac{e^{\beta C_1} \sqrt{2\pi Q k T}}{dNkT} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^n \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})}$$

Finding a pre-factor depending on temperature, but the microcanonical partition function is the canonical partition function, non considering a multiplicative factor. Time is rescaled so it is no longer correct and has to be corrected when performing dynamics where time is explicitly stated. In the absence of external forces  $\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta)$  is not the only conserved quantity. There are three conservation laws, because the momentum is conserved in each direction:

$$\vec{P} = \sum_{i=1}^N \vec{p}_i \quad \vec{K} = \vec{P} e^\eta \Rightarrow \frac{d\vec{K}}{dt} = 0$$

The extra factor  $e^\eta$  and so  $\vec{K}$  is conserved. And these should be included as  $\delta$  factors.

### 11.5.5.1 Harmonic oscillator

Performing a simulation of the harmonic oscillator in one dimension then, applying the Nosè-Hoover equations a strange result is obtained. This is completely wrong because where there is a maximum there is 0. The reason for this is the fact that  $\mathcal{H}'$  is not the only conserved quantity.

### 11.5.6 Nosè-Hoover chains

The trick to solve the problem a huge number of  $\eta$  variables all the possible conservation laws should be included. This creates Nosè-Hoover chains: extra variables that are thremostatting each extra-variable, so  $\eta$  become  $\eta_1$  and  $\eta_2$  takes care of  $\eta_1$  and so on up to  $M$ .

- $\dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i}$ .
- $\dot{\vec{p}}_i = \vec{F}_i - \frac{p_{\eta_1}}{Q_1} \vec{p}_i$ .
- $\dot{\eta}_j = \frac{p_{\eta_j}}{Q_j} \quad j = 1, \dots, M.$
- $\dot{p}_{\eta_1} = \left[ \sum_i \frac{\vec{p}_i^2}{m_i} - dNkT \right] - \frac{p_{\eta_2}}{Q_2} p_{\eta_1}$ .
- $\dot{p}_{\eta_j} = \left[ \sum_i \frac{\vec{p}_i^2}{m_i} - dNkT \right] - \frac{p_{\eta_{j+1}}}{Q_{j+1}} p_{\eta_j} \quad j = 2, \dots, M-1.$
- $\dot{p}_{\eta_M} = \frac{p_{\eta_{M-1}}^2}{Q_{M-1}} - kT.$

This is done so each extra variable is exactly weighted with the kinetic energy, all the parameters  $Q_i$  has to be found. The optimal choice for the  $Q$ s:  $Q_1 = dNkT\tau^2$  and  $Q_j = kT\tau^2$ , with  $\tau$  the characteristic time. With this plausible equations the partition function can be re-written. Now from the compressibility of these equation the kind of ensemble can be found. The conserved quantity becomes:

$$\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) = \mathcal{H}(\vec{r}, \vec{p}) + \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} + dNkT\eta_1 + kT \sum_{j=2}^M \eta_j$$

Computing the compressibility:

$$\kappa = -dN \frac{P_{\eta_1}}{Q_1} - \sum_{j=2}^M \frac{p_{\eta_j}}{Q_j} = -dN\dot{\eta}_1 - \dot{\eta}_c \quad \eta_c = \sum_{j=2}^M \eta_j$$

Then, to obtain the metric factor:

$$\kappa = \frac{dw}{dt} \Rightarrow w = -dN\eta_1 - \eta_c \Rightarrow \sqrt{g} = e^{-w} = e^{dN\eta_1 + \eta_c}$$

#### 11.5.6.1 Partition function

Now the partition function can be computed. Considering the conserved quantity:

$$\mathcal{H}'(\vec{r}, \eta, \vec{p}, p_\eta) = \mathcal{H}(\vec{r}, \vec{p}) + \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} + dNkT\eta_1 + kT \sum_{j=2}^M \eta_j$$

And the metric factor:

$$\sqrt{g} = e^{dN\eta_1 + \eta_c}$$

$$\begin{aligned} \mathcal{E}_T(N, V, C_1) &= \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} \int d^M p_\eta d^M \eta e^{dN\eta_1 + \eta_c} \delta \left( \mathcal{H}(\vec{r}, \vec{p}) + \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} + dNkT\eta_1 + kT\eta_c - C_1 \right) \\ \delta \left( \mathcal{H}(\vec{r}, \vec{p}) + \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} + dNkT\eta_1 + kT\eta_c - C_1 \right) &= \frac{1}{dNkT} \delta(\eta_1 - \eta_0) \quad \eta_0 = \frac{1}{dNkT} \left( C_1 - \mathcal{H}(\vec{r}, \vec{p}) - \sum_{j=1}^M \frac{p_{\eta_j}^2}{2Q_j} - kT\eta_c \right) \\ \mathcal{E}_T(N, V, C_1) &= \frac{e^{\beta C_1}}{dNkT} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} \prod_{j=1}^M \left( \int dp_\eta e^{-\beta \frac{p_{\eta_j}^2}{2Q_j}} \right) \prod_{j=2}^M \left( \int d\eta_j \right) e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \end{aligned}$$

Assuming that all the  $\eta_j$  are limited:

$$\mathcal{E}_T(N, V, C_1) = \mathcal{M} \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})}$$

In this way the canonical distribution is obtained. Using the Hoover-Chains simulate exactly the canonical ensemble.

#### 11.5.6.2 Harmonic oscillator

It can be seen now how the Nosè-Hoover chains allow to simulate the harmonic oscillator exactly. Going on on the Nosè-Hoover chains points in the canonical ensemble is being simulated, but not in the exact sequence of time. This doesn't allow to compute dynamic properties of the system.

# Chapter 12

## The isobaric ensembles

### 12.1 Introduction

The isobaric ensemble is useful in molecular dynamics as the subject of investigation are biological systems, therefore all simulation should run at constant temperature and pressure.

#### 12.1.1 Legendre transform of E

In order to get to constant temperature and pressure the first step is to perform a Legendre transform of the energy, obtaining in this way the isobaric-isoenthalpic ensemble. The same reasoning was made when the canonical ensemble was introduced from microcanonical one.

$$\tilde{f}(s) = f(x(s)) - sx(s) \quad s = f'(x)$$

The Legendre transform will be taken of the energy, with respect to its derivative with respect to its entropy.

$$\tilde{E}(N, \frac{\partial E}{\partial V}, S) = E(N, V(P), S) - \left( \frac{\partial E}{\partial V} \right)_{N,S} V(N, \frac{\partial E}{\partial V}, S)$$

So the Legendre transform should be expressed in term of the temperature: the derivative of the function with respect to its entropy. Pressure is being introduced as the derivative of the energy with respect to the volume. This function would contain the number of molecules and volume will be expressed in term of the pressure. Moreover defining the enthalpy as:

$$H(N, P, S) = E(N, P, S) + PV(N, P, S)$$

As it is usually done for thermodynamic potentials, its differential form is equal to:

$$dH = dE + PdV + VdP = TdS - PdV + \mu dN + PdV + VdP$$

From the first principle of thermodynamics:

$$dE = TdS - PdV + \mu dN$$

Where  $\mu$  is the chemical potential. Then:

$$dH = TdS + \mu dN + VdP$$

From this the following derivatives can be obtained:

$$T = \left( \frac{\partial H}{\partial S} \right)_{N,P} \quad \langle V \rangle = \left( \frac{\partial H}{\partial P} \right)_{N,S} \quad \mu = \left( \frac{\partial H}{\partial N} \right)_{P,S}$$

The volume is averaged because in this ensemble it is not fixed, but will vary.

### 12.1.2 Legendre transform of A

In the exact same way the Legendre transform can be applied to the Helmholtz free energy, with the formulas being very similar to before:

$$\tilde{f}(s) = f(x(s)) - sx(s) \quad s = f'(x)$$

Again it is a Legendre transform with respect to its derivative with respect to volume, so the derivative of  $A$  with respect to volume. This derivative is related to the pressure, so the Legendre transform will be equal to the Helmholtz itself, minus the derivative of  $A$  with respect to volume times volume, which will be expressed in terms of the derivative of  $A$  with respect to volume:

$$\tilde{A}(N, \frac{\partial A}{\partial V}, T) = A(N, V(P), T) - \left( \frac{\partial A}{\partial V} \right)_{N,T} V(N, \frac{\partial A}{\partial V}, T)$$

A thermodynamic potential is derived, that is called Gibbs free energy:

$$G(N, P, T) = A(N, P, T) + PV(N, P, T)$$

The Gibbs free energy is the Legendre transform of the  $A$ , like the enthalpy is the Legendre transform of the energy. Considering now the infinitesimal variation of  $G$ :

$$dG = dA + PdV + VdP = -PdV + \mu dN - SdT + PdV + VdP$$

Like before, the  $PdV$  cancel out:

$$dG = \mu dN + VdP - SdT$$

Considering now the thermodynamics derivatives:

$$S = - \left( \frac{\partial G}{\partial T} \right)_{N,P} \quad \langle V \rangle = \left( \frac{\partial G}{\partial P} \right)_{N,T} \quad \mu = \left( \frac{\partial G}{\partial N} \right)_{P,T}$$

Obtaining as a result:

- The isobaric-isoenthalpic ensemble as a Legendre transform of the microcanonical ensemble;
- The isobaric-isothermal ensemble as the Legendre transform of the canonical ensemble.

This is the same process to follow when changing simulation: it has to be noted that molecular simulations are carried in the NPT ensemble.

### 12.1.3 Phase space distribution of the isoenthalpic-isobaric ensemble

Pressure and enthalpy are kept fixed as the energy and the volume where in the microcanonical ensemble. The conserved quantity is therefore  $H$ , the enthalpy:

$$H = \mathcal{H}(v) + PV$$

The phase-space distribution must be the solution for the Liouville equation. This is some function of the Hamiltonian. Because  $H$  will be kept fixed and it is itself a function of the Hamiltonian, the solution will be:

$$f(x) = F(\mathcal{H}(x)) = \mathcal{M}\delta(\mathcal{H}(x) + PV - H)$$

Now considering a function analogous to the configuration of the microcanonical ensemble, similar to the  $\Omega$ . The pressure varies from 0 to  $\infty$ , so there is a need to integrate the constant enthalpy hypersurface over the volume:

$$\Gamma(N, P, H) = \mathcal{M} \int_0^\infty dV \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} \delta(\mathcal{H}(\vec{r}, \vec{p}) + PV - H)$$

The integral  $\int_0^\infty dV$  is on the left side of the equation because the molecules (coordinates) are integrated over the volume, depending on it. This is very similar to the microcanonical ensemble, when the function  $\Omega$  was correlated to the entropy. This process can be repeated obtaining the Boltzmann relation. The entropy as a function of the number of particles, the pressure and the enthalpy are:

$$S(N, P, H) = k \ln \Gamma(N, P, H)$$

$$dH = TdS + \mu dN + VdP$$

All the thermodynamics derivatives can be derived and the system described:

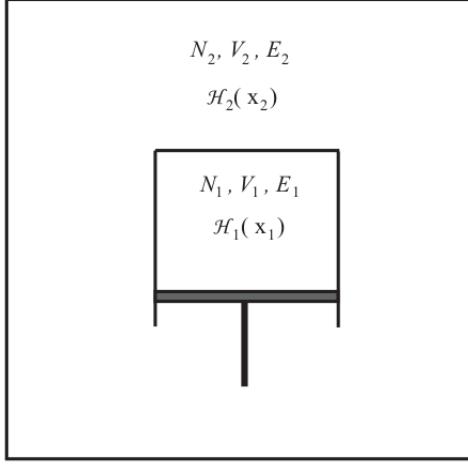
$$\frac{1}{T} = \left( \frac{\partial S}{\partial H} \right)_{N,P} \quad \frac{\langle V \rangle}{T} = - \left( \frac{\partial S}{\partial P} \right)_{N,H} \quad \frac{\mu}{T} = - \left( \frac{\partial S}{\partial N} \right)_{P,H}$$

## 12.2 Isothermal-isobaric ensemble

Considering now the isothermal-isobaric ensemble the thermodynamics variables have to be written down. The reasoning behind this derivations is the same of the canonical and microcanonical ensemble. Now the objective is to go from the analogous microcanonical (isobaric-isoenthalpic) to the analogous canonical (isothermal-isobaric). Figure ?? proves the similarity between the system, with the only difference being the piston at the bottom, since the pressure is not constant in both compartment.

- $E = E_1 + E_2 \quad E_2 \gg E_1.$
- $V = V_1 + V_2 \quad V_2 \gg V_1$
- $N = N_1 + N_2 \quad N_2 \gg N_1.$
- $\mathcal{H}(x) = \mathcal{H}_1(x_1) + \mathcal{H}_2(x_2).$

At fixed volumes  $V_1$  and  $V_2$ :



**Figure 12.1:** Two systems in contact with a common thermal reservoir at temperature T. System 1 has  $N_1$  particles in a volume  $V_1$ ; system 2 has  $N_2$  particles in a volume  $V_2$ . Both  $V_1$  and  $V_2$  can vary.

$$Q(N, V, T) = C_N \int dx_1 dx_2 e^{-\beta[\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2)]} = g(N, N_1, N_2) C_{N_1} \int dx_1 e^{-\beta\mathcal{H}_1(x_1)} C_{N_2} \int dx_2 e^{-\beta\mathcal{H}_2(x_2)}$$

Which is the same expression for the microcanonical ensemble.  $C_{N_1}$  and  $C_{N_2}$  are the two constants that are needed to separate the system in two canonical ensemble with the same temperature  $\beta$ . The partition function for the system is:

$$Q(N, V, T) \propto Q(N_1, V_1, T) Q(N_2, V_2, T)$$

### 12.2.1 Phase space distribution

Now allowing the volume to change and considering the combined system:

$$f(x) = \frac{C_N e^{-\beta\mathcal{H}(x)}}{Q(N, V, T)} = \frac{g(N, N_1, N_2)}{Q(N, V, T)} C_{N_1} e^{-\beta\mathcal{H}_1(x_1)} C_{N_2} e^{-\beta\mathcal{H}_2(x_2)}$$

To simplify the variables that describe the system 2 there is a need to integrate over the  $x_2$  variables.

$$f(x_1) = \frac{g(N, N_1, N_2)}{Q(N, V, T)} C_{N_1} e^{-\beta\mathcal{H}_1(x_1)} C_{N_2} \int dx_2 e^{-\beta\mathcal{H}_2(x_2)} = \frac{Q_2(N_2, V - V_1, T)}{Q(N, V, T)} g(N, N_1, N_2) C_{N_1} e^{-\beta\mathcal{H}_1(x_1)}$$

The quantity  $C_{N_2} \int dx_2 e^{-\beta\mathcal{H}_2(x_2)}$  is exactly the partition function for the system 2, considered as a canonical ensemble, with a fixed number of particles and a given volume and temperature. Thus being equal to  $Q_2$ : considering now this quantity. First, the normalization is correct:  $\int dV_1 \int dx_1 f(x_1, V_1) = 1$ . Generally the partition function ( $Q_2$  in this case) is equal to  $e^{\beta[A]}$ . Writing this equation with the correct argument for the Helmholtz free energy.

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$$\frac{Q_2(N_2, V - V_1, T)}{Q(N, V, T)} = e^{-\beta[A(N - N_1, V - V_1, T) - A(N, V, T)]}$$

Through a Taylor expansion:

$$A(N - N_1, V - V_1, T) = A(N, V, T) - N_1 \frac{\partial A}{\partial N} |_{N_1=0, V_1=0} = A(N, V, T) - \mu N_1 + PV_1$$

The phase-space distribution for variable  $x_1$  is:

$$f(x_1) = g(N, N_1, N - N_1) e^{\beta \mu N_1} e^{-\beta PV_1} C_{N_1} e^{-\beta \mathcal{H}_1(x_1)} \quad I_{N_1} = \frac{1}{V_0 N_1! h^{3N_1}}$$

A quantity  $\Delta(N, P, T)$  is defined to be the integral of the entire phase-space, including the volume, of the constant  $I_N$ . The phase-space distribution is  $e^{-\beta(\mathcal{H}(x)+PV)}$ : the analogous distribution function of the canonical ensemble, but instead of having the energy in the Boltzmann factor there is the enthalpy:

$$\Delta(N, P, T) = I_N \int_0^\infty dV \int dx e^{-\beta(\mathcal{H}(x)+PV)} \Rightarrow e^{\beta \mu N} \Delta(N, P, T) = 1$$

Because of Euler, the quantity  $\mu N$  is exactly  $G$ :

$$\Delta(N, P, T) = e^{-\beta \mu N} = e^{-\beta G(N, P, T)}$$

Now an analogous relation has been obtained:  $e^{\beta A} \rightarrow e^{\beta G}$ . And:

$$\Delta(N, P, T) = \frac{1}{V_0 N! h^{3N}} \int_0^\infty dV e^{-\beta PV} \int dx e^{-\beta \mathcal{H}(x)} = \frac{1}{V_0} \int_0^\infty dV e^{-\beta PV} Q(N, V, T)$$

### 12.2.1.1 Further proof

A further proof that this is indeed a "good" system is provided, starting this time from the Gibbs free energy:

$$G = A + P\langle V \rangle = \langle E + PV \rangle - TS = \langle \mathcal{H}(x) + PV \rangle + T \frac{\partial G}{\partial T}$$

The average  $\langle E + PV \rangle$  can be obtained by performing the average over the phase-space distribution just introduced. There is a need to integrate over the volume and all the coordinates. The quantity  $(\mathcal{H}(x) + PV)$  (remember that  $V$  now is a constant) must be weighted by the corresponding Boltzmann factor, which includes not only the Hamiltonian but also  $PV$ .

$$\begin{aligned} \langle E + PV \rangle &= \frac{I_N \int_0^\infty dV \int dx (\mathcal{H}(x) + PV) e^{-\beta(\mathcal{H}(x)+PV)}}{I_N \int_0^\infty dV \int dx e^{-\beta(\mathcal{H}(x)+PV)}} = -\frac{1}{\Delta(N, P, T)} \frac{\partial \Delta(N, P, T)}{\partial \beta} = -\frac{\partial \ln \Delta(N, P, T)}{\partial \beta} \\ G(N, P, \beta) &= -\frac{\partial \ln \Delta(N, P, \beta)}{\partial \beta} - \beta \frac{\partial G}{\partial \beta} \end{aligned}$$

Plugging in the following solution:  $G(N, P, \beta) = -\frac{1}{\beta} \ln \Delta(N, P, \beta)$  in the previous differential equation we get 0. Now the system can be described:

$$\langle V \rangle = \left( \frac{\partial G}{\partial P} \right)_{N, T} \quad S = - \left( \frac{\partial G}{\partial T} \right)_{N, P}$$

### 12.2.2 Maxwell's square

Putting everything into perspective: in the NPT ensemble the average volume can be obtained as the derivative with respect to pressure of the Gibbs free energy and entropy can be taken as the derivative with respect to temperature keeping fixed  $N$  and  $T$ : Let's put everything into perspective.

$$\bullet \langle V \rangle = \left( \frac{\partial G}{\partial P} \right)_{N,T} . \quad \bullet S = - \left( \frac{\partial G}{\partial T} \right)_{N,P} .$$

Moreover the following equations from the isobaric-isoenthalpic ensemble were found:

$$\bullet T = \left( \frac{\partial H}{\partial S} \right)_{N,P} . \quad \bullet \langle V \rangle = \left( \frac{\partial H}{\partial P} \right)_{N,S} .$$

While the following are coming from the microcanonical ensemble:

$$\bullet T = \left( \frac{\partial U}{\partial S} \right)_{N,V} . \quad \bullet P = - \left( \frac{\partial U}{\partial V} \right)_{N,S} .$$

And the canonical ensemble:

$$\bullet P = - \left( \frac{\partial A}{\partial V} \right)_{N,T} . \quad \bullet S = - \left( \frac{\partial A}{\partial T} \right)_{N,V} .$$



**Figure 12.2:** Maxwell's square

### 12.2.3 Pressure viral theorem

The internal pressure that was calculated by the estimator was a function of all the coordinates and all the momenta. The internal pressure  $P^{int}$  would be the average of this estimator. This quantity should be equal to the external pressure for the equations to be valid:

$$P^{(int)} = \langle \mathcal{P}(\vec{r}, \vec{p}) \rangle = \left\langle \frac{1}{3V} \sum_i \left[ \frac{\vec{p}_i^2}{m_i} + \vec{F}_i \cdot \vec{r}_i \right] \right\rangle = kT \frac{\partial \ln Q}{\partial V}$$

To take average of this quantity for our new ensemble (NPT) the partition function should be put at the denominator and then there should be an integration over the volume.

$$\begin{aligned} \langle P^{(int)} \rangle &= \frac{1}{\Delta(N, P, T)} \int_0^\infty dV e^{-\beta PV} Q(N, V, T) \frac{kT}{Q} \frac{\partial Q}{\partial V} = \frac{kT}{\Delta(N, P, T)} \int_0^\infty dV e^{-\beta PV} \frac{\partial Q}{\partial V} = \\ &= \frac{kT}{\Delta(N, P, T)} e^{-\beta PV} Q(N, V, T)|_0^\infty - \frac{kT}{\Delta(N, P, T)} \int_0^\infty dV \left( -\frac{P}{kT} \right) e^{-\beta PV} Q(N, V, T) = \\ &= \frac{P}{\Delta(N, P, T)} \int_0^\infty dV e^{-\beta PV} Q(N, V, T) = P \end{aligned}$$

### 12.3. ANDERSEN'S HAMILTONIAN

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Consider the integration by parts of the quantity  $\frac{kT}{\Delta(N,P,T)} e^{-\beta PV} Q(N, V, T)|_0^\infty$ : when the volume tends to  $\infty$  the exponential goes to zero; when instead the volume is zero the partition function is zero, because there are no states where  $V = 0$ . Now only the second term is there and its integral is exactly  $\Delta$ . Again, the quantity  $dV e^{-\beta PV} Q(N, V, T)$  is equal to  $\Delta$ , obtaining the external pressure  $P$ . Considering that taking the average of the internal pressure over the NPT ensemble exactly the external pressure  $P$  is obtained, this is the expected result. This also means that when comparing the result of the simulation with the external pressure that is being fixed, the internal pressure should be computed and then its average over many simulations. So, in conclusion, the volume-average internal pressure is equal to the external one.

#### 12.2.4 Work Virial theorem

Multiplying the internal pressure for the changing volume:

$$P^{(int)}V = kTV \frac{\partial \ln Q}{\partial V}$$

The same equation as before are obtained, but with the inclusion of  $V$ :

$$\begin{aligned} \langle P^{(int)}V \rangle &= \frac{1}{\Delta(N,P,T)} \int_0^\infty dV e^{-\beta PV} Q(N, V, T) \frac{kTV}{Q} \frac{\partial Q}{\partial V} = \frac{kT}{\Delta(N,P,T)} \int_0^\infty dV e^{-\beta PV} V \frac{\partial Q}{\partial V} = \\ &= \frac{kT}{\Delta(N,P,T)} e^{-\beta PV} V Q(N, V, T)|_0^\infty - \frac{kT}{\Delta(N,P,T)} \int_0^\infty dV \frac{\partial}{\partial V} (V e^{-\beta PV}) Q(N, V, T) = \\ &= \frac{1}{\Delta(N,P,T)} \left[ -kT \int_0^\infty dV e^{-\beta PV} Q(N, V, T) + P \int_0^\infty dV V e^{-\beta PV} Q(N, V, T) \right] = \\ &= -kT + P\langle V \rangle \Rightarrow \langle P^{(int)}V \rangle + kT = P\langle V \rangle \end{aligned}$$

The term  $\int_0^\infty dV V e^{-\beta PV} Q(N, V, T)$  is the average of the volume: the volume is multiplied by a weighting factor and divided by the partition function in the NPT ensemble. The work is equal to the average quantity  $\langle P^{(int)}V \rangle$ , plus  $kT$ . Now,  $kT$  indicates that this equation is the analogous of the equipartition theorem, but there's an extra degree of freedom, the varying volume. This is the reason why an additional  $kT$  is present. To be fair,  $kT$  is very small and it does not change much the final equation. In conclusion it can be seen how there is an extra degree of freedom, the volume. These theorems are particularly important, since the algorithms described later are all written for the isobaric-isoenthalpic ensemble, but are easily obtained adding a thermostat.

### 12.3 Andersen's Hamiltonian

The best way to deal with the volume as an extra degree of freedom is to add it to the Hamiltonian as an extra variable, obviously with its own momentum. This is the case of the Andersen's Hamiltonian, defined as:

$$\mathcal{H}_A = \sum_{i=1}^N \frac{V^{-\frac{2}{3}} \pi_i^2}{2m_i} + U(V^{\frac{1}{3}} \vec{s}_1, \dots, V^{\frac{1}{3}} \vec{s}_N) + \frac{p_V^2}{2W} + PV \quad W = (3N+1)kT\tau_b^2$$

Hamilton's equation has to be written down to obtain the time evolution for each of these coordinates:

### 12.3. ANDERSEN'S HAMILTONIAN

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- $\dot{\vec{s}}_i = \frac{\partial \mathcal{H}_A}{\partial \pi_i} = \frac{V^{-\frac{2}{3}} \pi_i}{m_i}$ .
- $\dot{\pi}_i = -\frac{\partial \mathcal{H}_A}{\partial \vec{s}_i} = -\frac{\partial U}{\partial (V^{\frac{1}{3}} \vec{s}_i)} V^{\frac{1}{3}}$ .
- $\dot{V} = \frac{\partial \mathcal{H}_A}{\partial p_V} - \frac{p_V}{W}$ .
- $\dot{p}_V = -\frac{\partial \mathcal{H}_A}{\partial V} = \frac{1}{3} V^{-\frac{5}{3}} \sum_{i=1}^N \frac{\pi_i^2}{m_i} - \frac{1}{3} V^{-\frac{2}{3}} \sum_{i=1}^N \frac{\partial U}{\partial (V^{\frac{1}{3}} \vec{s}_i)} \cdot \vec{s}_i - P$ .

The derivative of  $\dot{p}_V$  is slightly more complicated, since the dependence on  $p$  is present on three terms. Inverting the transformation (the same inversion we performed to go from original coordinates to the scaled coordinates):

$$s_i = V^{-\frac{1}{3}} \vec{r}_i \Rightarrow \dot{s}_i = V^{-\frac{1}{3}} \dot{\vec{r}}_i - \frac{1}{3} V^{-\frac{4}{3}} \dot{V} \vec{r}_i$$

$$\pi_i = V^{\frac{1}{3}} \vec{p}_i \Rightarrow \dot{\pi}_i = V^{\frac{1}{3}} \dot{\vec{p}}_i + \frac{1}{3} V^{-\frac{2}{3}} \dot{V} \vec{p}_i$$

Now these equations need to be substituted to the ones that were previously derived:

- $\dot{\vec{s}}_i = \frac{\partial \mathcal{H}_A}{\partial \pi_i} = \frac{V^{-\frac{2}{3}} \pi_i}{m_i} \rightarrow \dot{r}_i = \frac{p_i}{m_i} + \frac{\dot{V}}{3V} r_i$
- $\dot{\pi}_i = -\frac{\partial \mathcal{H}_A}{\partial \vec{s}_i} = -\frac{\partial U}{\partial (V^{\frac{1}{3}} \vec{s}_i)} V^{\frac{1}{3}} \rightarrow \dot{p}_i = -\frac{\partial U}{\partial r_i} - \frac{\dot{V}}{3V} p_i$ .
- $\dot{V} = \frac{\partial \mathcal{H}_A}{\partial p_V} - \frac{p_V}{W} \rightarrow \dot{V} = \frac{p_V}{W}$ .
- $\dot{p}_V = -\frac{\partial \mathcal{H}_A}{\partial V} = \frac{1}{3} V^{-\frac{5}{3}} \sum_{i=1}^N \frac{\pi_i^2}{m_i} - \frac{1}{3} V^{-\frac{2}{3}} \sum_{i=1}^N \frac{\partial U}{\partial (V^{\frac{1}{3}} \vec{s}_i)} \cdot \vec{s}_i - P \rightarrow \dot{p}_V = \frac{1}{3V} \sum_{i=1}^N \left[ \frac{p_i^2}{m_i} - \frac{\partial U}{\partial r_i} r_i \right] - P$ .

Notice how the new term  $\frac{\dot{V}}{3V}$  accounts for the compressibility of the variable, letting it inflate and deflate. Notice that the last quantity is exactly the internal pressure estimator. Now a variation in the momentum is present, that is conjugate to the volume, whenever the internal pressure differs from the external one ( $\dot{p}! = 0$ ). The compressibility is equal to 0 so the system is incompressible. To calculate the compressibility the derivative of  $\dot{r}$  with respect to  $r_i$  has to be computed. This yields the factor  $\frac{\dot{V}}{3V}$  for each particle and every degree of freedom, which are three for each particle.

#### 12.3.1 Andersen's equations

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• <math>\dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i} + \frac{\dot{V}}{3V} \vec{r}_i \Rightarrow \dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i} + \frac{\dot{V}}{3V} \vec{r}_i</math></li> <li>• <math>\dot{\vec{p}}_i = -\frac{\partial U}{\partial \vec{r}_i} - \frac{\dot{V}}{3V} \vec{p}_i \Rightarrow \dot{\vec{p}}_i = -\frac{\partial U}{\partial \vec{r}_i} - \frac{\dot{V}}{3V} \vec{p}_i</math>.</li> <li>• <math>\dot{V} = \frac{p_V}{W} \Rightarrow \dot{V} = \frac{p_V}{W}</math>.</li> </ul> | <ul style="list-style-type: none"> <li>• <math>\dot{p}_V = \frac{1}{3V} \sum_{i=1}^N \left[ \frac{\vec{p}_i^2}{m_i} - \frac{\partial U}{\partial \vec{r}_i} \cdot \vec{r}_i \right] - P \Rightarrow \dot{p}_V = \frac{1}{3V} \sum_{i=1}^N \left[ \frac{\vec{p}_i^2}{m_i} - \frac{\partial U}{\partial \vec{r}_i} \cdot \vec{r}_i \right] - P</math>.</li> </ul> |
|--|---|

The conserved quantity:

$$\mathcal{H}' = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N) + \frac{p_V^2}{2W} + PV$$

## 12.4. MTK ALGORITHM (NPT)

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Notice how  $\mathcal{H}'$  looks very similar to the enthalpy, aside from the kinetic energy part. As usual, when working in a system that is not Hamiltonian, since if it was obtained from a different Hamiltonian,  $\mathcal{H}'$  does not give back Anderson's equations, the partition function has to be derived:

$$\Omega_P = \int dp_V \int_0^\infty \int d^N \vec{p} \int_{\mathcal{D}(V)} d^N \vec{r} \delta \left( \mathcal{H}(\vec{r}, \vec{p}) + \frac{p_V^2}{2W} + PV - H \right)$$

According to the Virial theorem:

$$\left\langle \frac{p_V^2}{2W} \right\rangle = k \frac{T}{2} \Rightarrow \mathcal{H}(\vec{r}, \vec{p}) + PV \text{ is conserved}$$

The average of the pressure will be kept constant, as for the enthalpy.

## 12.4 MTK algorithm (NPT)

One of the best choices for thermostating the system is the MTK algorithm, developed by Martyna-Tobias-Klein in 1994. This algorithm introduces a new variable  $\epsilon$ :

$$\begin{aligned} \epsilon &= \frac{1}{3} \ln \frac{V}{V_0} \Rightarrow \dot{\epsilon} = \frac{\dot{V}}{3V} = \frac{p_\epsilon}{W} \\ \bullet \quad \dot{\vec{r}}_i &= \frac{\vec{p}_i}{m_i} + \frac{p_\epsilon}{W} \vec{r}_i. & \bullet \quad \dot{V} &= \frac{dV p_\epsilon}{W}. \\ \bullet \quad \dot{\vec{p}}_i &= -\frac{\partial U}{\partial \vec{r}_i} - \frac{p_\epsilon}{W} \vec{p}_i. & \bullet \quad \dot{p}_\epsilon &= dV (\mathcal{P}^{(int)} - P). \end{aligned}$$

Considering compressibility:

$$\begin{aligned} \kappa &= \sum_{i=1}^N \left[ \frac{\partial}{\partial \vec{r}_i} \cdot \dot{\vec{r}}_i + \frac{\partial}{\partial \vec{p}_i} \cdot \dot{\vec{p}}_i \right] + \frac{\partial \dot{V}}{\partial V} + \frac{\partial \dot{p}_V}{\partial p_V} = \\ &= dN \frac{p_\epsilon}{W} - dN \frac{p_\epsilon}{W} = d \frac{p_\epsilon}{E} = \frac{\dot{V}}{V} \end{aligned}$$

To obtain the incompressible equations that conserve  $\mathcal{H}(\vec{r}, \vec{p}) + PV + \frac{p_V^2}{2W}$  some modifications have to be applied:

$$\dot{\vec{p}}_i = -\frac{\partial U}{\partial \vec{r}_i} - \left( 1 + \frac{d}{N_f} \right) \frac{p_\epsilon}{W} \vec{p}_i \quad \dot{p}_\epsilon = dV (\mathcal{P}^{(int)} - P) + \frac{d}{N_f} \sum_{i=1}^N \frac{\vec{p}_i^2}{m_i}$$

With  $F$  being the number of degrees of freedom of the system.

### 12.4.1 Langevin piston

In many programs and applications the Langevin thermostat will be used. The only equation different from Andersen's ones is the last, with a friction acting on the volume and a last term representing a random force or "kick".

$$\bullet \quad \dot{\vec{r}}_i = \frac{\vec{p}_i}{m_i} + \frac{\dot{V}}{3V} \vec{r}_i.$$

## 12.5. SUMMARY

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- $\dot{\vec{p}_i} = -\frac{\partial U}{\partial \vec{r}_i} - \frac{\dot{V}}{3V}\vec{p}_i.$
- $\dot{V} = \frac{p_V}{W}.$
- $\dot{p}_V = \frac{1}{3V} \sum_{i=1}^N \left[ \frac{\vec{p}_i^2}{m_i} - \frac{\partial U}{\partial \vec{r}_i} \cdot \vec{r}_i \right] - P - \gamma \dot{V} + R(t).$

$$\langle R(0)R(t) \rangle = \frac{2\gamma kT}{W} \delta(t)$$

The Langevin piston is mostly preferred as a barostat.

## 12.5 Summary

- The formalism of the isobaric ensembles has been constructed, starting by performing the Legendre transform of the microcanonical ensemble to obtain the isobaric-isoenthalpic ensemble; then the same reasoning was applied to the canonical ensemble to obtain the isobaric-isothermal (NPT) ensemble.
- It was demonstrated that the steps and the reasoning to modify the equations of the microcanonical ensemble to go to the canonical ensemble, apply in the same way also for the isobaric-isoenthalpic in the NPT.
- In the NPT ensemble everything can be computed like a canonical ensemble, however the volume is now a variable.
- The pressure Virial theorem, important for molecular simulations, and work Virial theorem, useful for the derivation of Andersen's Hamiltonian, were introduced.

# Chapter 13

## The grand canonical ensemble

### 13.1 Introduction

The Gran Canonical (GC) ensemble comes in handy when the number of molecules cannot be kept fixed during the simulation. This is one of the main differences between MD and MC approaches: it is not possible to perform MD simulations with varying number of molecules.

#### 13.1.1 Euler's theorem

Homogeneous function  $f(x_1, \dots, x_N)$  of degree  $n$  in  $x_1, \dots, x_k$ :

$$f(\lambda x_1, \dots, \lambda x_k, x_{k+1}, \dots, x_N) = \lambda^n f(x_1, \dots, x_k, \dots, x_N)$$

This property states that if each variable  $(x_1, \dots, x_k)$  is increased by a certain value  $\lambda$ , then the net result is that the value of the function is increased by a factor  $\lambda^n$ . An example of this property can be showed by the homogeneous function  $f(x) = x^2$ ,  $f(x, y, z) = xy^2 + z^3$ . The degree is 3 and each variable  $(x, y, z)$  is increased by a factor  $\lambda$ . Taking the derivative:

$$\frac{d}{d\lambda} f(\lambda x_1, \dots, \lambda x_k, \dots, x_N) = n\lambda^{n-1} f(x_1, \dots, x_k, \dots, x_N)$$

If the partial derivative is calculated with respect to each variable and then the derivative of the variable itself with respect to  $\lambda$  is obtained:

$$\frac{d}{d\lambda} f(\lambda x_1, \dots, \lambda x_k, \dots, x_N) = \sum_{i=1}^k \frac{\partial f(x_1, \dots, x_k, \dots, x_N)}{\partial x_i} x_i$$

Meaning that the two quantities are equal and the following property (for an homogeneous function) can be obtained:

$$\lambda = 1 \Rightarrow \sum_{i=1}^k \frac{\partial f}{\partial x_i} x_i = n f(x_1, \dots, x_N)$$

### 13.1.2 Applications

Euler's theorem has important consequences in thermodynamics, as it means that all of the thermodynamics function can be expressed in terms of other parameters, and it is valid for every substance. Applying Euler's theorem to the internal energy  $U$ :

$$U(\lambda N, \lambda V, \lambda S) = \lambda U(N, V, S) \Rightarrow U(N, V, S) = \frac{\partial U}{\partial N} N + \frac{\partial U}{\partial V} V_{\frac{\partial U}{\partial S}} S = \mu N - PV + TS$$

Each of the above partial derivatives are easily calculated through Maxwell square. Applying the theorem to Helmholtz free energy:

$$A(\lambda N, \lambda V, T) = \lambda A(N, V, T) \Rightarrow A(N, V, T) = \frac{\partial A}{\partial N} N + \frac{\partial A}{\partial V} V = \mu N - PV$$

The difference here is that the extensive quantities are  $N$  and  $V$ , while  $T$  is an intensive quantity. The function is not homogeneous in  $T$ , e.g. if  $T$  is increased by a factor  $\lambda$  the whole function is not increased. Applying it now to the enthalpy:

$$H(\lambda N, \lambda S, P) = \lambda H(N, S, P) \Rightarrow H(N, S, P) = \frac{\partial H}{\partial N} N + \frac{\partial H}{\partial S} S = \mu N + TS$$

Like for  $A$ , the enthalpy is a homogeneous function for two of its variables, but not for  $P$ . Finally, considering Gibbs free energy:

$$G(\lambda N, P, T) = \lambda G(N, P, T) \Rightarrow G(N, P, T) = \frac{\partial G}{\partial N} N = \mu N$$

It has only one dependency on an extensive quantity: the number of particles. The fact that the chemical potential  $\mu$  is exactly  $G$  divided by  $N$ , as demonstrated in the previous chapter can be obtained.

### 13.1.3 Legendre transform of A

Applying the same reasoning that was applied to the isobaric ensembles:

$$\tilde{f}(s) = f(x(s)) - sx(s) \quad s = f'(x)$$

The Legendre transform will not be applied in terms of volume, but instead in terms of its derivative with respect to the number of molecules:

$$\begin{aligned} \tilde{A}\left(\frac{\partial A}{\partial N}, V, T\right) &= A(N(\mu), V, T) - \left(\frac{\partial A}{\partial N}\right)_{N,V} N\left(\frac{\partial A}{\partial N}, V, T\right) = \\ &= A(N(\mu), V, T) - \mu N = \mu N - PV - \mu N = -PV \end{aligned}$$

From the results obtained before, the result of the Legendre transform is simply  $-PV$ . Now the infinitesimal variation of the transformed  $A$  has to be computed:

$$d\tilde{A} = dA - Nd\mu - \mu dN = -PdV - SdT + \mu dN - Nd\mu - \mu dN$$

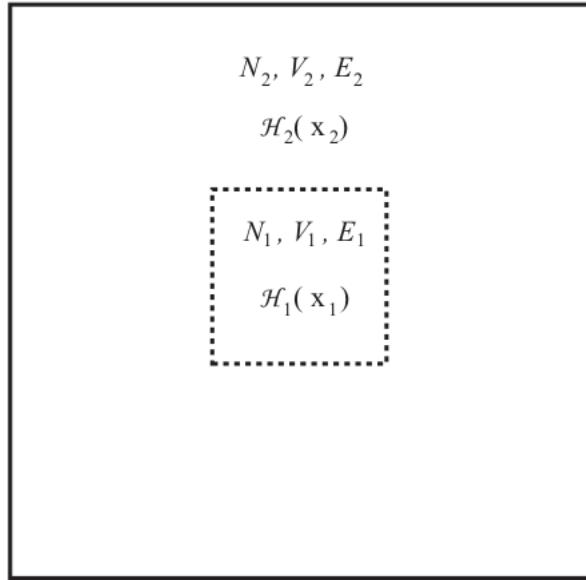
$$d\tilde{A} = -PdV - SdT - N d\mu$$

$$\tilde{A}(\mu, \lambda V, T) = \lambda \tilde{A}(\mu, V, T) \Rightarrow \tilde{A}(\mu, V, T) = \frac{\partial \tilde{A}}{\partial V} V = -PV$$

Notice that  $\tilde{A}$  depends on only one extensive variable ( $V$ ), so Euler's theorem can be applied again.

## 13.2 Grand canonical ensemble

As for the previous ensembles, the analysis starts from the definition of the main variables of the equations and in figure 13.1 the two systems are depicted.



**Figure 13.1:** Two systems in contact with a common thermal reservoir at temperature  $T$ . System 1 has  $N_1$  particles in a volume  $V_1$ ; system 2 has  $N_2$  particles in a volume  $V_2$ . The dashed lines indicate that systems 1 and 2 can exchange particles.

- $E = E_1 + E_2 \quad E_2 \gg E_1.$
- $N = N_1 + N_2 \quad N_2 \gg N_1.$
- $V = V_1 + V_2 \quad V_2 \gg V_1.$
- $\mathcal{H}(x, N) = \mathcal{H}_1(x_1, N_1) + \mathcal{H}_2(x_2, N_2).$

The partition function is the same as a canonical ensemble when the exchange of molecules between the two systems is stopped:

$$Q(N, V, T) = \frac{1}{N! h^{3N}} \int dx_1 \int dx_2 e^{-\beta[\mathcal{H}_1(x_1) + \mathcal{H}_2(x_2)]}$$

At fixed  $N_1$  and  $N_2$ , not allowing any other exchange of particles, then the partition function is:

### 13.2. GRAND CANONICAL ENSEMBLE

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$$Q(N, V, T) = \frac{N_1! N_2!}{N!} \frac{1}{N_1! h^{3N_1}} \int dx_1 e^{-\beta \mathcal{H}_1(x_1)} \frac{1}{N_2! h^{3N_2}} \int dx_2 e^{-\beta \mathcal{H}_2(x_2)} = \frac{N_1! N_2!}{N!} Q_1(N_1, V_1, T) Q_2(N_2, V_2, T)$$

With a varying particle numbers:

$$Q(N, V, T) = \sum_{N_1=0}^N g(N_1, N - N_1) \frac{N_1!(N - N_1)!}{N!} Q_1(N_1, V_1, T) Q_2(N - N_1, V - V_1, T)$$

The factor  $g$  is a combinatorial (or degeneracy) factor, and indicates in how many ways the particles can be divided in one box and the other, or in how many ways there are  $N_1$  particles in system 1 and  $N_2$  particles in system 2. It is defined as:

$$g(N_1, N - N_1) = \frac{N!}{N_1!(N - N_1)!}$$

- $N_1 = 0 \Rightarrow g(0, N) = 1.$
- $N_1 = 1 \Rightarrow g(1, N - 1) = \frac{N!}{N!}.$
- $N_1 = 2 \Rightarrow g(2, N - 2) = \frac{N(N-1)!}{2!}.$

So the total partition function is defined as:

$$Q(N, V, T) = \sum_{N_1=0}^N Q_1(N_1, V_1, T) Q_2(N - N_1, V - V_1, T)$$

However for the full system, considered as a canonical ensemble, the partition function is known:

$$f(x, N) = \frac{e^{-\beta \mathcal{H}(x, N)}}{N! h^{3N} Q(N, V, T)} \Rightarrow dx f(x, N) = 1$$

And the phase space distribution of system 1:  $\sum_{N_1=0}^N \int dx_1 f(x_1, N_1) = 1.$

$$\begin{aligned} f(x_1, N_1) &= \left( \frac{e^{-\beta \mathcal{H}_1(x_1, N_1)}}{Q(N, V, T) N_1! h^{3N_1}} \right) \frac{1}{(N - N_1)! h^{3(N - N_1)}} \int dx_2 e^{-\beta \mathcal{H}_2(x_2, N - N_1)} = \\ &= \frac{Q_2(N - N_1, V - V_1, T)}{Q(N, V, T)} \frac{1}{N_1! h^{3N_1}} e^{-\beta \mathcal{H}_1(x_1, N_1)} \end{aligned}$$

$$\frac{Q_2(N - N_1, V - V_1, T)}{Q(N, V, T)} = e^{-\beta[A(N - N_1, V - V_1, T) - A(N, V, T)]}$$

$$A(N - N_1, V - V_1, T) \approx A(N, V, T) - \frac{\partial A}{\partial N} N_1 - \frac{\partial A}{\partial V} V_1 = A(N, V, T) - \mu N_1 + PV_1$$

### 13.2.1 Grand partition function

The phase-space distribution is:

$$f(x_1, N_1) = \frac{1}{N_1! h^{3N_1}} e^{\beta \mu N_1} e^{-\beta PV_1} e^{\beta \mathcal{H}_1(x_1, N_1)}$$

In the equation there's no dependence on  $N_2$  and the subscript 1 can be dropped :

$$f(x, N) = \frac{1}{N! h^{3N}} e^{\beta \mu N} e^{-\beta PV} e^{\beta \mathcal{H}(x, N)}$$

Taking exactly the normalization condition:

$$\sum_{N=0}^{\infty} \int dx f(x, N) = \sum_{N=0}^{\infty} e^{-\beta PV} \frac{1}{N! h^{3N}} e^{\beta \mu N} \int dx e^{-\beta \mathcal{H}(x, N)} = 1$$

The same function as in the canonical ensemble is obtained, and the partition function of the grand-canonical ensemble is  $e^{\beta PV}$ , as supposed by Euler's theorem.

$$\sum_{N=0}^{\infty} \frac{1}{N! h^{eN}} e^{\beta \mu N} \int dx e^{-\beta \mathcal{H}(x, N)} = e^{\beta PV}$$

Now the equation of state of the system can be written:

$$\begin{aligned} \mathcal{E}(\mu, V, T) &= \sum_{N=0}^{\infty} e^{\beta \mu N} \frac{1}{N! h^{3N}} \int dx e^{-\beta \mathcal{H}(x, N)} = \sum_{N=0}^{\infty} e^{\beta \mu N} Q(N, V, T) = e^{\beta PV} \\ &\quad \frac{PV}{kT} = \ln \mathcal{E}(\mu, V, T) \end{aligned}$$

Moreover the average of the particles can be computed:

$$\langle N \rangle = \frac{1}{\mathcal{E}(\mu, V, T)} \sum_{N=0}^{\infty} N e^{\beta \mu N} Q(N, V, T) = kT \left( \frac{\partial}{\partial \mu} \ln \mathcal{E}(\mu, V, T) \right)_{V, T}$$

Including the fugacity:

$$z = e^{\beta \mu}$$

The grand canonical partition function can be written down in an easier way to remember:

$$\mathcal{E}(z, V, T) = \sum_{N=0}^{\infty} z^N Q(N, V, T)$$

This time it is not even necessary to write down the derivatives, as the equation of state simply derives from its definition. However, the above equation is not very easy to deal with, as it is a function of the chemical potential of the fugacity, the volume and the temperature, and it is not the usual way in which the equation of state is written. The derivative of  $z$  with respect to  $\mu$  returns the average number of molecules.

$$\frac{\partial}{\partial \mu} = \frac{\partial z}{\partial \mu} \frac{\partial}{\partial z} = \beta z \frac{\partial}{\partial z} \Rightarrow \langle N \rangle = z \frac{\partial}{\partial z} \ln \mathcal{E}(z, V, T)$$

The quantity  $\langle N \rangle$  is the relation between the chemical potential (or grand-canonical partition function) and the number of molecules.

### 13.2.2 Ideal gas

Applying the grand canonical equation to an ideal gas, the canonical partition function will be:

$$Q(N, V, T) = \frac{1}{N! h^{3N}} V^N \left[ \int dp e^{-\beta \frac{p^2}{2m}} \right]^{3N} = \frac{1}{N!} \left[ V \left( \frac{2\pi m}{\beta h^2} \right)^{\frac{3}{2}} \right]^N = \frac{1}{N!} \left( \frac{V}{\lambda^3} \right)^N$$

The term  $\left( \frac{2\pi m}{\beta h^2} \right)^{\frac{3}{2}}$  has the dimension of a length to the power of  $-3$ , and it is called the **thermal wave length**, and is indicated with  $\lambda$ .

Performing the sum of the series to obtain the grand canonical partition function:

$$\mathcal{E}(z, V, T) = \sum_{N=0}^{\infty} z^N \frac{1}{N!} \left( \frac{V}{\lambda^3} \right)^N = \sum_{N=0}^{\infty} \frac{1}{N!} \left( \frac{zV}{\lambda^3} \right)^N = e^{\frac{zV}{\lambda^3}}$$

Notice that also this time it is written in terms of the fugacity. Again, this form of the equation is hard to work with, so the average of the number of particles can be computed by taking the logarithm of the partition function and multiplying it for the derivative of the fugacity:

$$\langle N \rangle = z \frac{\partial}{\partial z} \ln \mathcal{E}(z, V, T) = V \frac{z}{\lambda^3} \Rightarrow z = \frac{\langle N \rangle \lambda^3}{V}$$

Meaning that the equation of state can be written as:

$$\frac{PV}{kT} = \ln \mathcal{E}(z, V, T) = \frac{V_z}{\lambda^3} = \langle N \rangle$$

It is easy to recognize the usual equation of state for an ideal gas, proving that this procedure works, as it yields the exact result for the ideal gas.

## 13.3 Particle number fluctuations

The grand canonical ensembles are extremely important in statistical mechanics, as they allow for easier calculations with respect to the canonical or microcanonical ensembles. The fact that the GC ensemble provides for a sum over a series makes the calculations easier, specifically in quantum statistical mechanics. However, when in the GC ensemble, the net thermodynamics should not change. In other words, the GC ensemble should be completely equivalent to the canonical one, in the sense that the thermodynamics results obtained must be the same. The difference between the two is the number of particles. The fluctuations in the particle number has to be quantified: if they're too big, we could run into problems. The particle number fluctuations are defined as:

$$\Delta N = \sqrt{\langle N^2 \rangle - \langle N \rangle^2}$$

Defining them in terms of thermodynamics derivatives:

$$\begin{aligned} z \frac{\partial}{\partial z} z \frac{\partial}{\partial z} \ln \mathcal{E}(z, V, T) &= z \frac{\partial}{\partial z} \frac{1}{\mathcal{E}} z \frac{\partial}{\partial z} \sum_{N=0}^{\infty} z^N Q(N, V, T) = z \frac{\partial}{\partial z} \frac{1}{\mathcal{E}} \sum_{N=0}^{\infty} Nz^N Q(N, V, T) = \\ &= \frac{1}{\mathcal{E}} \sum_{N=0}^{\infty} N^2 z^N Q(N, V, T) - \frac{1}{\mathcal{E}^2} \left[ \sum_{N=0}^{\infty} Nz^N Q(N, V, T) \right]^2 = \langle N^2 \rangle - \langle N \rangle^2 \end{aligned}$$

### 13.3. PARTICLE NUMBER FLUCTUATIONS

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The double derivative  $z \frac{\partial}{\partial z} z \frac{\partial}{\partial z}$  is exactly equal to the average number of particles. By the definition of fugacity:

$$kT \frac{\partial}{\partial \mu} = z \frac{\partial}{\partial z} \Rightarrow \Delta N^2 = (kT)^2 \frac{\partial^2}{\partial \mu^2} \ln \mathcal{E}(\mu, V, T) = (kT)^2 \frac{\partial^2}{\partial \mu^2} \frac{PV}{kT} = kTV \frac{\partial^2 P}{\partial \mu^2}$$

The result obtained is:

$$\Delta N^2 = kTV \frac{\partial^2 P}{\partial \mu^2}$$

But in order to get to something measurable other calculations have to be performed. First of all, considering an "intensive Helmholtz free energy", this can be computed by dividing from the extensive Helmholtz free energy the number of particles and expressing it with intensive quantities:

$$a(v, T) = \frac{1}{N} A\left(N, \frac{V}{N}, T\right) \Rightarrow \mu = \frac{\partial A}{\partial N} = a(v, T) + N \frac{\partial a}{\partial v} \partial v \partial N = a(v, T) - V \frac{\partial a}{\partial v}$$

Where  $v$  is the specific volume. The pressure can be expressed in terms of the intensive Helmholtz:

$$P = -\left(\frac{\partial A}{\partial V}\right)_{N,T} = -N \frac{\partial a}{\partial v} \frac{\partial v}{\partial V} = -\frac{\partial a}{\partial v} \quad \frac{\partial P}{\partial \mu} = \frac{\partial P}{\partial v} \partial v \partial \mu = -\frac{\partial^2 a}{\partial v^2} \frac{\partial v}{\partial \mu}$$

Taking the derivative of the chemical potential with respect to the specific volume:

$$\frac{\partial \mu}{\partial v} = \frac{\partial a}{\partial v} - \frac{\partial a}{\partial v} - v \frac{\partial^2 a}{\partial v^2} \Rightarrow \frac{\partial P}{\partial \mu} = \frac{1}{v}$$

Moreover, considering the second derivative:

$$\begin{aligned} \frac{\partial^2 P}{\partial \mu^2} &= -\frac{1}{v^2} \frac{\partial v}{\partial \mu} = \frac{1}{v^2} \left( v \frac{\partial^2 a}{\partial v^2} \right)^{-1} = -\frac{1}{v^3} \frac{\partial P}{\partial v} \\ \Delta N^2 &= kTV \frac{\partial^2 P}{\partial \mu^2} \quad \frac{\partial^2 P}{\partial \mu^2} = -\frac{1}{v^3} \frac{\partial P}{\partial v} \end{aligned}$$

Solving all the terms the thermal compressibility  $\kappa_T$  is obtained, a measurable quantity:

$$\kappa_T = -\frac{1}{V} \frac{\partial V}{\partial P} = -\frac{1}{v} \frac{\partial v}{\partial P} = -\frac{1}{v} \frac{\partial P}{\partial v} \Rightarrow \Delta N^2 = \frac{kTV}{v^2} \kappa_T = \frac{\langle N \rangle kT}{v} \kappa_T$$

The term  $-\frac{1}{V}$  is added because when pressure is applied, the volume is expected to decrease. This thermal compressibility determines how much the system is compressible with respect to pressure. The fluctuation needs to be compared to the quantity of interest, obtaining the relative fluctuation:

$$\frac{\Delta N}{\langle N \rangle} = \sqrt{\frac{kT}{v \langle N \rangle}} \kappa_T \sim \frac{1}{\sqrt{\langle N \rangle}}$$

If the average number of particles is "high", which it usually is, being in the thermodynamic limit, then the fluctuation is negligible. Meaning that every calculation performed in the GC ensemble is equal to the canonical one. However,  $k_T$  is not always a finite number, in particular during a phase transition, in which the thermal compressibility can be quite high. In such a case, since the particles are moving from one phase to another, the only usable ensemble is one that takes into account the fact that the number of particles is not constant: the grand canonical ensemble.

# Chapter 14

## Quantifying uncertainties and sampling quality

### 14.1 Introduction

Dealing with huge systems and huge amounts of data is not sufficient to interpret the biological relevance of a molecular definition. There is a need to perform thoughtful analysis on the obtained data. Data interpretation is a fundamental step to asses the validity of a simulation. The methods presented in this chapter will be useful also when dealing with Monte Carlo simulations, although the simulation is more difficult to interpret as time becomes moves.

#### 14.1.1 Key definitions

##### 14.1.1.1 Expectation value

The Expectation value is defined as:

$$\langle x \rangle = \int x P(x) dx = \sum_j x_j P(x_j)$$

In the case of molecular dynamics simulations time will be discretized, so the probability distribution will be discretized.

##### 14.1.1.2 Estimate of expectation value

The estimate of the expectation value, or arithmetic mean is computed as:

$$\bar{x} = \frac{1}{n} \sum_{j=1}^n x_j$$

##### 14.1.1.3 Variance

The variance is computed as:

$$\sigma_x^2 = \int dx P(x)(x - \langle x \rangle)^2 = \sum_j P(x_j) (x_j - \langle x \rangle)^2$$

#### 14.1.1.4 Standard deviation

The standard deviation is  $\sigma_x$  and its estimate is the experimental standard deviation:

$$s(x) = \sqrt{\frac{\sum_{j=1}^n (x_j - \bar{x})^2}{n-1}}$$

The estimates are necessary in molecular dynamics as the probability distribution is not known.

#### 14.1.1.5 Linear correlation

Two variables are defined as linearly uncorrelated observables:

$$\langle (x - \langle x \rangle)(y - \langle y \rangle) \rangle = 0$$

Linear uncorrelation does not imply independent variables.

#### 14.1.1.6 Experimental standard deviation

The experimental standard deviation of the mean is computed as:

$$s(\bar{x}) = \frac{s(x)}{\sqrt{n}}$$

If all the  $x_j$  are assumed to be linearly uncorrelated, this is used to estimate error in computer simulations.

#### 14.1.1.7 Correlation time

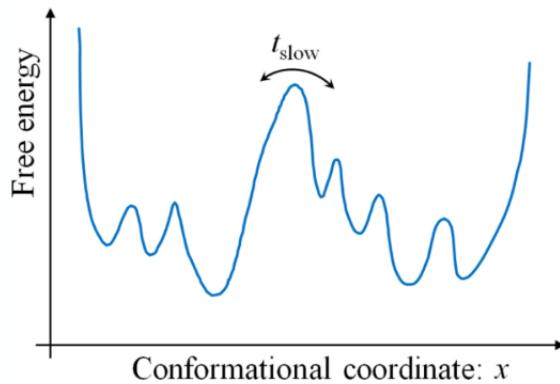
The correlation time  $\tau$  is the longest separation time  $\Delta t$  over which  $x(t)$  and  $x(t + \Delta t)$  remain linearly correlated. This is important as only data that are separated more than the correlation time are linearly uncorrelated and can be used when computing the standard deviation of mean. If they would be included the standard deviation would be underestimated.

#### 14.1.1.8 Two sided confidence interval

Once the standard deviation is computed the two-sided confidence interval can be obtained:  $\langle x \rangle = \bar{x} \pm U$  with  $U = ks(\bar{x})$  and  $k$  the coverage factor for a given level of confidence  $p$  expressed in percentage. Usually  $k = 2$  to obtain a level of confidence about 95%, so that the expectation value is expected with 95% probability to lie in the interval. This is the ideal situation, but there is no certainty that the molecular simulation will explore the entirety of the phase-space compatible with the macroscopic conditions.

### 14.1.2 Time scales

Before starting a simulation the time scale of the process of interest has to be estimated. For instance, looking at protein folding, obtained through experimental measure, the time scale could change from microseconds to minutes depending on the dimension of the protein. The latter case cannot be explored with a standard molecular simulation, so a coarse-grained model or other methods should be used to accelerate the dynamics (using approximations out of control, biasing the dynamics).



**Figure 14.1:** Time scales

Figure 14.1 depicts a free energy profile. Usually when starting a simulation the starting point is a minimum. Sampling the simulation for a long time a transition to other minima could be observed, but these processes that happen to processes that happen on a faster time-scale with respect to processes that need to surpass a higher energy barrier. The time-scale of the transition depends exponentially on the height of the transition, so the higher the barrier the longer the time to observe the transition. Whenever a simulation is started an estimate of the slowest time scale involved in the process need to be understood.

## 14.2 Equilibration

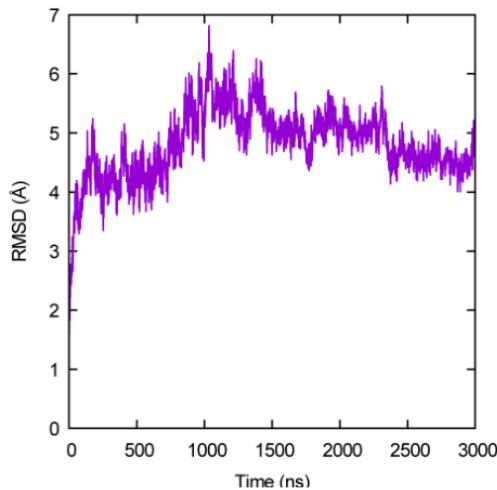
When performing a simulation it is fundamental to consider if the simulation is equilibrated enough, so if the system has equilibrated after the simulation. This is very difficult to understand, but it is easy to tell if a system is non-equilibrated. Some of the variables that can be checked to see for non-equilibration are scalar values:

- System size which depends on the ensemble: in the case of NPT it is important. If it is equilibrated the volume would fluctuate around an average.
- Membrane area for membrane proteins: when simulating a protein at the beginning the membrane adapt to the protein and after a while equilibration is reached and area per lipid does not change and so does total membrane area.
- Potential energy or total energy, this is expected to fluctuate around an average value. At the beginning it varies due to temperature or initial configuration before reaching an average, so it is equilibrated in a local minimum of an average.

## 14.2. EQUILIBRATION

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- Temperature in the NVE ensemble, so temperature will be constant when the system is at equilibrium.
- Density of simulated molecules in the NPT ensemble.
- Pressure, not recommended because in pressure there are huge variation because it depends on the Virial, so the average value will be  $1\text{ atm}$ , but the fluctuation will be huge.
- Radius of gyration is an overall information on the protein structure. There is the possibility to reach the same value in different conformation, a problem that applies to other overall distance measures. Even if there are conformation with the same value of gyration they could be different. If the



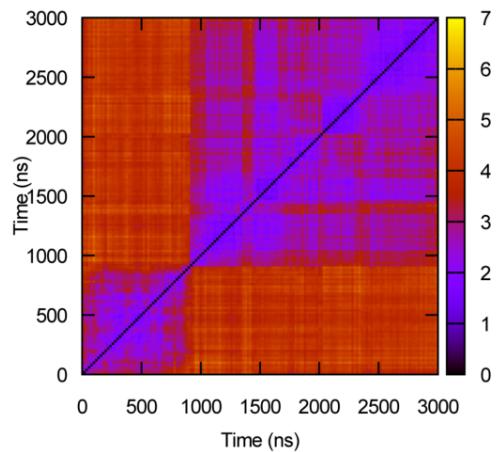
**Figure 14.2:** RMSD

radius of gyration is constantly increasing or decreasing the simulation has not equilibrated yet.

- Configurational distance measures like RMSD, all-to-all RMSD map. The discussion for radius of gyration holds for this measures. Considering RMSD:

$$RMSD(\vec{r}, \vec{s}) = \sqrt{\frac{1}{N} \sum_{i=1}^N |\vec{r}_i - \vec{s}_i|^2}$$

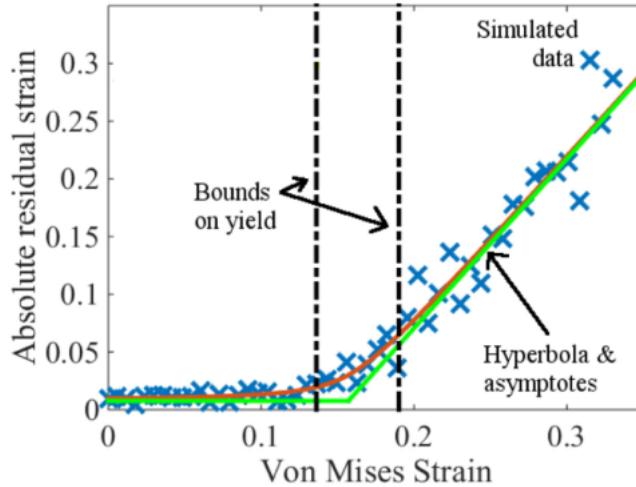
This will reach a constant value with some fluctuation. The all-to-all RMSD map checks the RMSD for all the conformation present in the molecular dynamics simulation, obtaining a matrix of distances that can be plotted as in 14.3.



**Figure 14.3:** All-to-all RMSD map, in blue low values and in red high value

It is very difficult to interpret data from 14.2, but it is easier in 14.3. Looking at the latter two conformations can be seen, where there are the basins. It can be seen how once the protein exits from the lower basin it does not come back and goes into the other. Moreover in the bigger basis different conformation can be seen that are easily traversed. This two basin are expected with starting with crystal's coordinate the first is the local basin corresponding to the crystal structure, which can be biased.

### 14.2.1 Qualitative behaviour



**Figure 14.4:** Qualitative behaviour

Knowing some qualitative features of the simulation can allow for a more constructive analysis of the data. Looking at 14.4 a simulation of a material is considered. In this case an expected behaviour is seen and then the simulated data is fitted into a known function, so in this case the expected behaviour is being reproduced, meaning that the simulation has provided good results.

### 14.2.2 Independent simulations

In principle a set of independent simulations should be run. Most of the time running independent simulation is not a good choice in the case of protein. This is because all the independent simulation are independent only in the velocities: the coordinates are the same not considering the solvent. This is very computational expensive, so a more efficient way would be to run long simulation starting from equilibrating structure and randomizing the velocities.

#### 14.2.2.1 Autocorrelation analysis

Another method is to start from a single simulation and perform an autocorrelation analysis, to asses whether two snapshots of the simulation are independent. To do so the autocorrelation of two quantities like RMSD is computed:

$$C(x_k, x_{k+j}) \equiv \frac{(x_k - \bar{x})(\bar{x}_{k+j} - \bar{x})}{s^2(x)} \Rightarrow C_j$$

Where:

- $x_c$  is data point at time  $c$ .
- $\bar{x}$  is the arithmetic mean.

This would be done for all the  $k$  values and if it does not depend by  $k$  but only on  $j$  the property has been equilibrated. If the function depends on  $k$  the simulation has equilibrated.

### 14.2.2.2 Combined clustering

Combined clustering as in 14.5. In combined clustering a measure of the distance of the conformation is obtained. Then using one clustering algorithm the conformations will be clustered. There will be a number of cluster. Assume doing so for two independent simulations, or for two part of a long simulation, called in 14.5 1 and 2. Then for each of this two simulation the time the simulation spent in one cluster is computed for each cluster. This is plotted in the data. If the point are off-diagonal the trajectories are not the same so the system has not equilibrated.

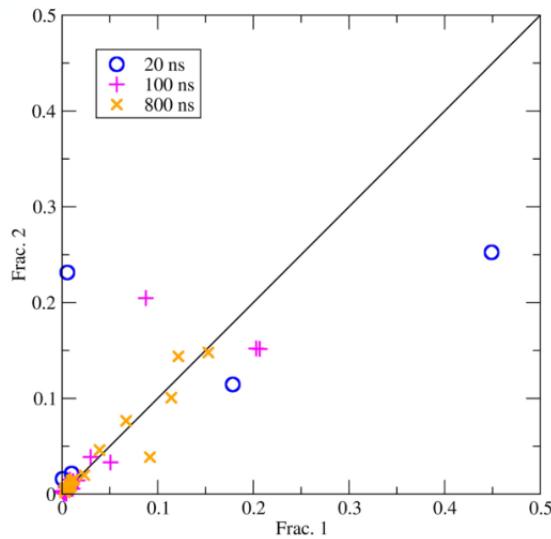
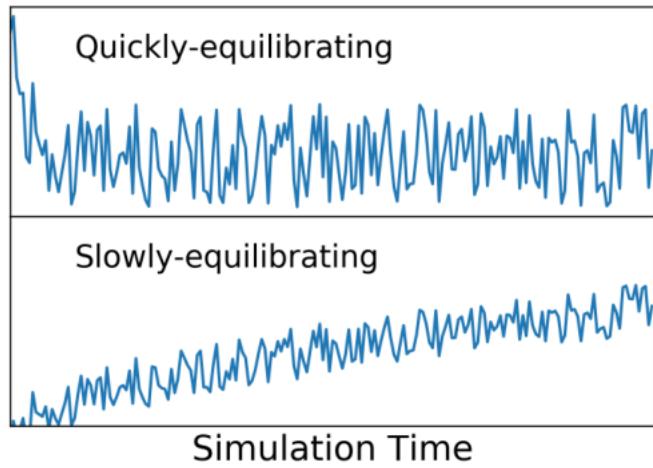


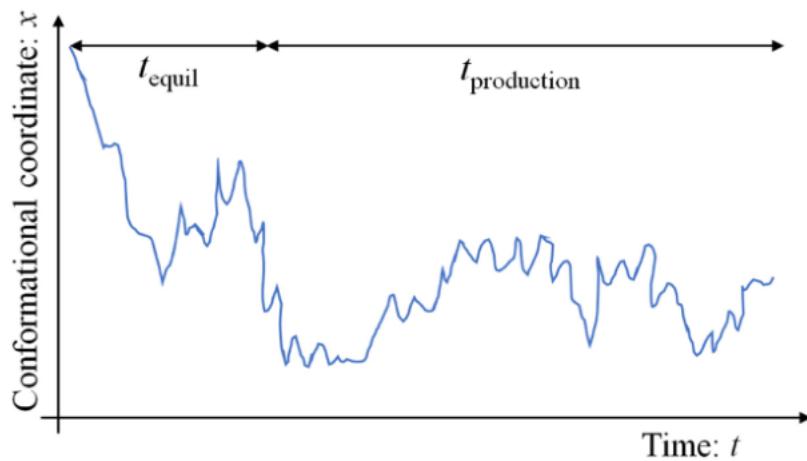
Figure 14.5: Combined clustering

### 14.2.3 Equilibration and production

It can be seen in the case of slowly-equilibrating of figure 14.6 a drift can be observed so there is no certainty of equilibration.

**Figure 14.6:** Behaviour during equilibration

Once we are confident that equilibration has been reached the trajectory has to be separated into the equilibration and production part. This can be seen in 14.7. Now equilibration is discarded and no longer considered in the analysis. In the analysis just the production will be considered.

**Figure 14.7:** Comparison of equilibration and production

#### 14.2.4 Equilibration workflows

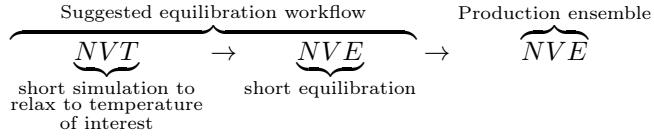
For the equilibration there are different type of workflow and the choice depends on the system in use.

## 14.3. AUTOCORRELATION

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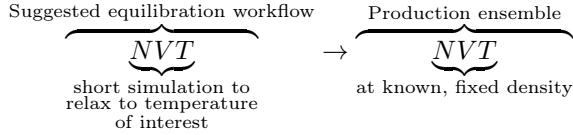
### 14.2.4.1 First workflow

In this first workflow the simulated times are the physical time as in the NVE ensemble the Hamiltonian dynamics are considered because there is no thermostat. So this is a good workflow for observing dynamical properties.



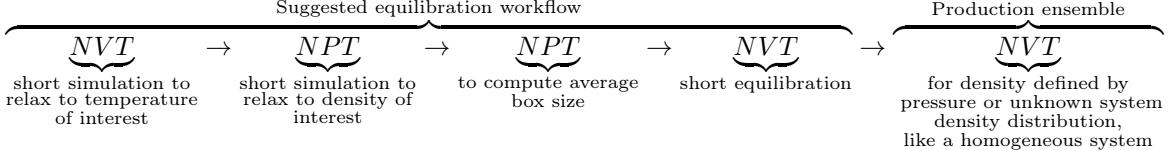
### 14.2.4.2 Second workflow

In this second workflow the volume is kept fixed, the first simulation is used to adapted to the temperature and then the simulation is run. In this case the simulation is run at fixed density. This would be used for a liquid material.



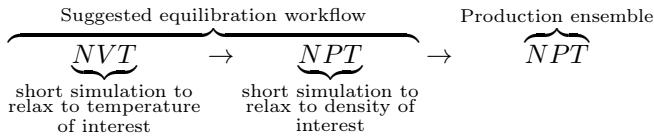
### 14.2.4.3 Third workflow

This third workflow is typical for proteins. So a combination of NPT and NVT to converge the volume and then the system is simulated without a barostat.



### 14.2.4.4 Forth workflow

This is a typical simulation for a membrane protein.



## 14.3 Autocorrelation

### 14.3.1 Autocorrelation function

The autocorrelation function is useful to understand whether a system is equilibrated enough and how many independent conformations there are in the analysis. This is possible only when the correlation time is computed for an observable. So there is an autocorrelation function and time for

### 14.3. AUTOCORRELATION

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each observable. Let  $f(x)$  an observable, a function of the coordinates or the momenta. Then the autocorrelation function:

$$C_f(t') = \frac{\langle (f(x) - \langle f \rangle)(f(t + t') - \langle f \rangle) \rangle}{\sigma_f^2}$$

When  $t' = 0$   $C_f(t') = 1$ . This function will decrease with  $t'$ . Using both the equilibration and production part of the simulation  $C_f(t')$  will also depend on time  $t$ . Using only the production run the dependence of  $t$  is lost and the autocorrelation function can be computed. The function will go to 0 with an exponential behaviour and fluctuate around that value. Performing this on a discretized time and the time ordered sequence of values  $f_j = f(t = j\Delta t)$ :

$$C_f(t') = \frac{1}{\sigma_f^2} \frac{1}{N} \sum_{j=1}^{N-\frac{t'}{\Delta t}} (f(j\Delta t) - \langle f \rangle)(f(j\Delta t + t') - \langle f \rangle)$$

Computing the autocorrelation function starting after an increasing time if the system has equilibrated within the first time chosen the curves superimpose in the first part.

#### 14.3.2 Autocorrelation time

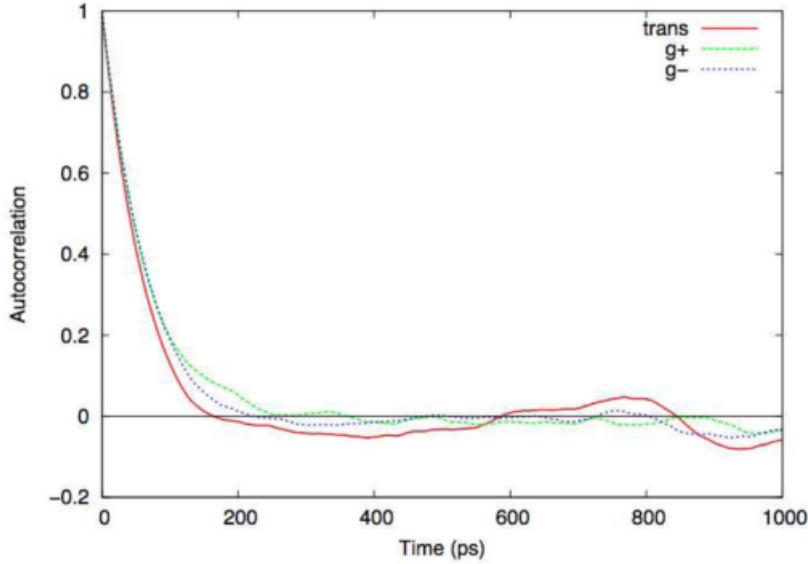
The autocorrelation time is defined as:

$$\tau_f = \int_0^{+\infty} dt' C_f(t')$$

If the autocorrelation function is an exponential this is a good way to estimate the autocorrelation time. Looking at figure 14.8, although it seems that after 200ps the autocorrelation time is reached in this way the number of independent conformation is obtained. It could be that this number is not sufficient to sample the system properly. In that case the system is spending too much time in one conformation and not according to the Boltzmann distribution. The autocorrelation time will provide an idea on how many independent conformation there are in the system.

#### 14.4. BLOCK AVERAGING ANALYSIS

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**Figure 14.8:** Autocorrelation time

The autocorrelation time  $\tau_f$  is specific for each observable  $f$  and allows to obtain the number of independent values of  $f$  in the simulation:

$$N_f^{ind} \simeq \frac{t_{sim}}{\tau_f}$$

Where  $t_{sim}$  is the total simulation time. Once the number of independent value is estimated the standard deviation of the mean can be computed using this number:

$$SE(f) = \frac{\sigma_f}{\sqrt{N_f^{ind}}} \sim \sigma_f \sqrt{\frac{\tau_f}{t_{sim}}}$$

A confidence interval at 95% implies:  $\pm 2SE(f)$ .

## 14.4 Block averaging analysis

The block averaging analysis is another way to compute the autocorrelation time. In this method a trajectory with  $N = M \cdot n$  snapshots is divided into  $M$  segments of length  $n$  with  $n = 1, 2, \dots$ . Compute  $M$  averages, one in each block:

$$\langle f \rangle_i, \quad i = 1, \dots, M$$

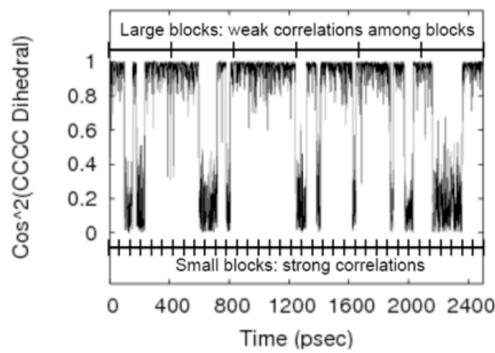
Compute the standard deviation  $\sigma_n$  for each value of  $n$ . Running estimate of the overall standard error:

$$BSE(f, n) = \frac{\sigma_n}{\sqrt{M}}$$

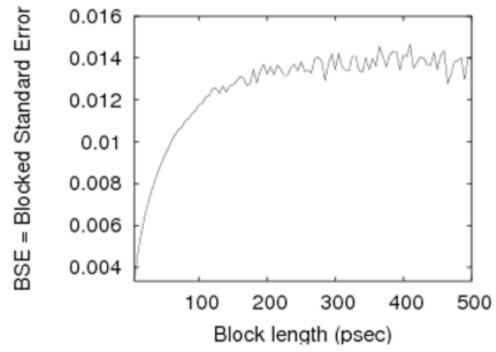
#### 14.4. BLOCK AVERAGING ANALYSIS

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For small values of  $n$  and high values of  $M$ , the *BSE* under-estimates the statistical error. The *BSE* is constant once the blocks are essentially independent of one another, or when the block length is substantially greater than the correlation time.



**Figure 14.9:** Varying block length



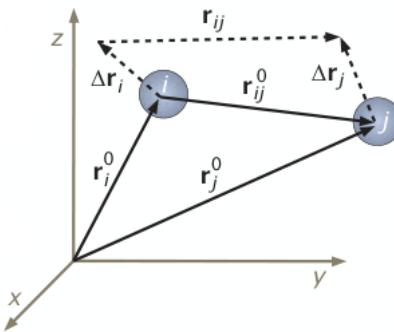
**Figure 14.10:** BSE at varying block length

# Chapter 15

## Protein motions

### 15.1 Elastic network models (ENM)

In elastic network models ENM the structure of the protein is considered, with no attention to the kind of interactions. The focus is on the topology: the protein is seen as a network of springs that connect beads.



**Figure 15.1:** Elastic network models

Now considering the Gaussian network model, a kind of elastic network model. Let  $i$  and  $j$  be two amino-acids as seen in 15.1. Usually the analysis is limited to centroids of residues: its  $\alpha$ -carbon atom. A protein is represented by a configuration vector with the position of all its  $\alpha$ -carbon atoms:  $\vec{r} = [\vec{r}_1, \vec{r}_2, \dots, \vec{r}_N]$ . It can be assumed that the structure obtained from the protein data bank is equilibrated. Now computing the deviation of each  $\alpha$ -carbon atom from the equilibrium position (PDB structure):

$$\Delta\vec{r}_i = \vec{r}_i - \vec{r}_i^0$$

Instantaneous changes in the positions of all residues can be recorded in a vector with  $3N$  components:

$$\Delta\vec{r} = [\Delta\vec{r}_1, \Delta\vec{r}_2, \dots, \Delta\vec{r}_N]$$

## 15.1. ELASTIC NETWORK MODELS (ENM)

The equilibrium separation between two beads  $i$  and  $j$ :  $\vec{r}_{ij}^0 = \vec{r}_j^0 - \vec{r}_i^0$ . The instantaneous separation between two beads  $i$  and  $j$ :  $\vec{r}_{ij} = \vec{r}_j^0 + \Delta\vec{r}_{ij}$ ,  $\Delta\vec{r}_{ij} = \Delta\vec{r}_j - \Delta\vec{r}_i$ .

### 15.1.1 Gaussian network model (GNM)

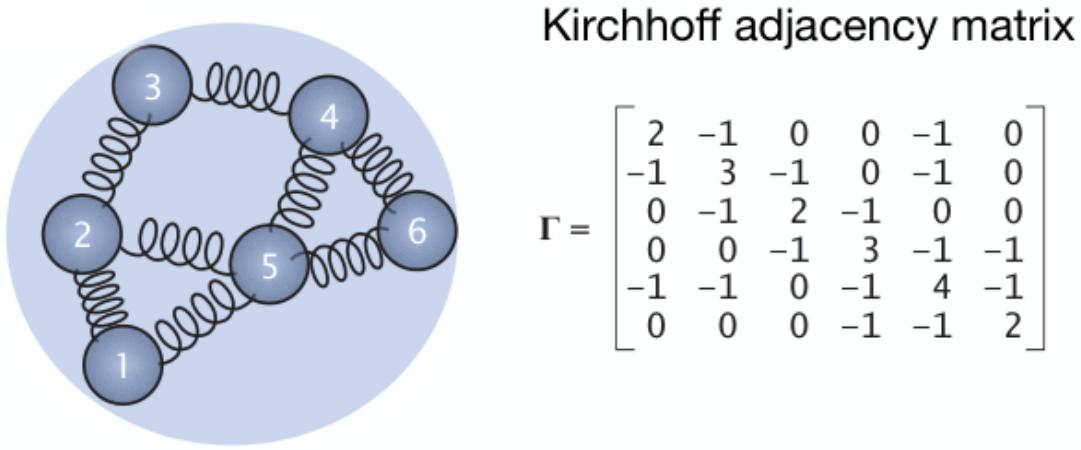
In Gaussian network model a potential energy is built up and it is assumed that each couple interact through an harmonic potential. So the potential energy for each couple:

$$U_{ij} = \gamma_{ij}(\Delta\vec{r}_j - \Delta\vec{r}_i) \cdot (\Delta\vec{r}_j - \Delta\vec{r}_i) = \gamma_{ij}\Delta\vec{r}_{ij}^2$$

Where the constant  $\gamma$  depends on the couple of amino acid that are interacting. Now total elastic energy can be written as:

$$U_{GNM} = \frac{1}{2} \sum_i \sum_j \gamma_{ij}\Delta\vec{r}_{ij}^2 = \frac{\gamma}{2} \sum_i \sum_j \Delta\vec{r}_{ij}^2$$

Another assumption, which is less problematic than the first one, does not affect the result. This assumption states that all amino acids that are interacting they interacting with the same constant  $\gamma$  for all the couples there are. All the spring between the beads are the same. An interaction between two  $\alpha$ -carbon happens when they are closer than a cut-off radius usually set at  $r_c = \text{\AA}$ . Now Kirchhoff adjacency matrix  $\Gamma$  is built, such that there is a 1 (the sign is a convention) whenever there is an interaction or 0 otherwise. This matrix will be symmetrical and the negative of the sum of rows or column and will be put on the diagonal. So in the diagonal there is the number of neighbours for each bead.



**Figure 15.2:** Kirchhoff adjacency matrix

So the total elastic energy:

$$U_{GNM} = \frac{\gamma}{2}\Delta\vec{r}(t)^T \Gamma \Delta\vec{r}(t)$$

## 15.1. ELASTIC NETWORK MODELS (ENM)

---

### 15.1.1.1 Correlated motions

The average of displacement for each amino-acid and the correlated motion, so whether the displacement of an amino-acids correlates with the movement of another. To do so:

$$\langle \Delta\vec{r}_i \cdot \Delta\vec{r}_j \rangle = \frac{1}{Q} \int \Delta\vec{r}_i \cdot \Delta\vec{r}_j e^{-\frac{U}{kT}} d^N \Delta\vec{r}$$

Since  $U$  can be written as a matrix product the integral is a generalized Gaussian integral:

$$\langle \Delta\vec{r}_i \cdot \Delta\vec{r}_j \rangle = \frac{3kT}{\gamma} [\Gamma^{-1}]_{ij}$$

So that it can be exactly computed. Where  $\Gamma^{-1}$  is a pseudoinverse matrix as the Kirchhoff matrix has zero determinant and cannot be inverted. To build the pseudoinverse matrix consider the eigenvalue decomposition:  $\Gamma = U\Lambda U^T$ :

$$U = [\vec{u}_1, \dots, \vec{u}_{N_1}] = \begin{bmatrix} u_{1,1} & \cdots & u_{N-1,1} \\ \vdots & \ddots & \vdots \\ u_{1,N} & \cdots & u_{N-1,N} \end{bmatrix} \quad \Lambda = \begin{bmatrix} \lambda_1 & 0 & 0 & \cdots & 0 \\ 0 & \lambda_2 & 0 & \cdots & 0 \\ 0 & 0 & \lambda_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \lambda_{N-1} \end{bmatrix}$$

Where  $U$  is the matrix of eigenvectors and  $\lambda_0$  is discarded. The pseudoinverse matrix is obtained by this matrix multiplication discarding  $\lambda_0$  in  $\Lambda$ .

### 15.1.1.2 Gaussian network model and B-factors

Considering the average fluctuation and the correlation of amino-acids, if  $i = j$  is the average fluctuation for each fluctuation, which can be obtained from the diagonal elements of the pseudoinverse matrix is:

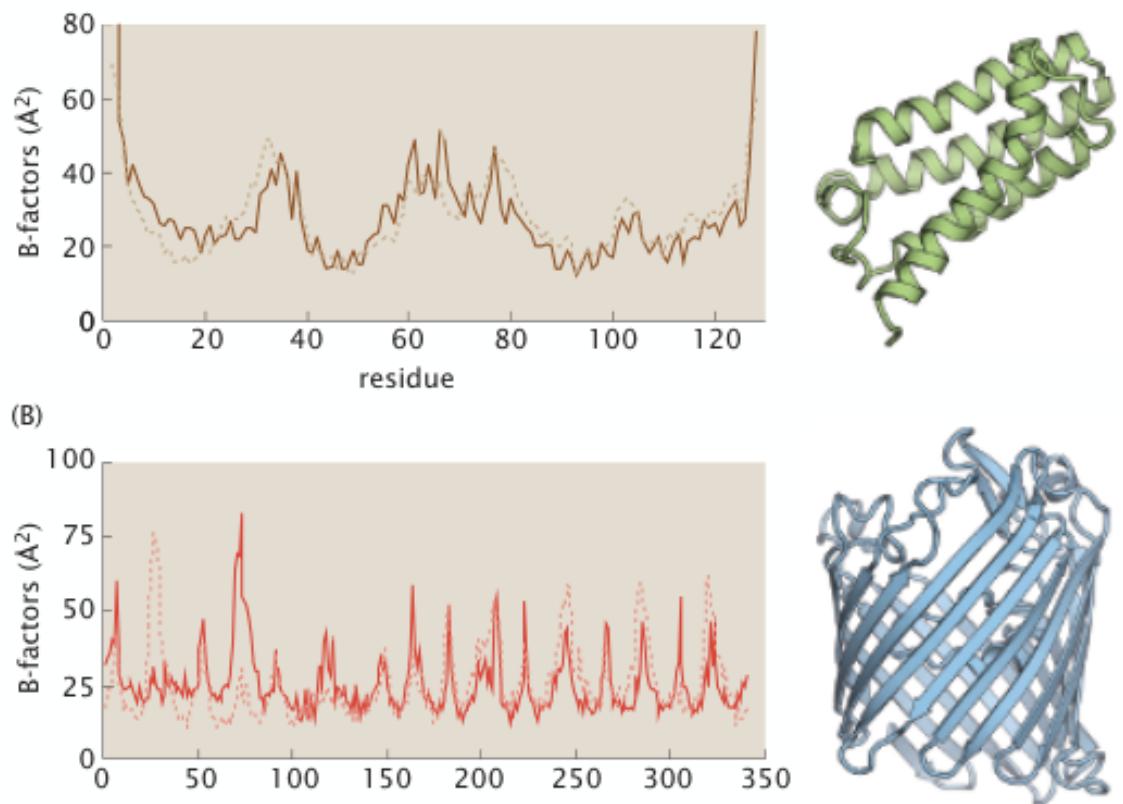
$$\langle \Delta\vec{r}_i \cdot \Delta\vec{r}_i \rangle = \frac{3kT}{\gamma} [U\Lambda^{-1}U^T]_{ii} = \frac{3kT}{\gamma} \sum_k [\lambda_k^{-1} \vec{u}_k \vec{u}_k^T]_{ii} = \sum_k [\Delta r_i^2]_k$$

The root-mean squared deviation can be represented as a sum of fluctuation for each of the modes or eigenvectors. Considering the Debye-Waller factors:

$$B_i = \frac{8\pi^2}{3} \langle \Delta r_i^2 \rangle$$

Which are found in the PDB file and the factor  $\gamma$  can be obtained by comparison of a result of the Gaussian network model so that the data look similar to the Debye-Waller factors. In figure 15.3 the Debye-Waller are the continuous line while the dotted line is the average fluctuation computed from the Gaussian network model. Pay attention to proximity effects that arise from the crystal structure.

## 15.1. ELASTIC NETWORK MODELS (ENM)

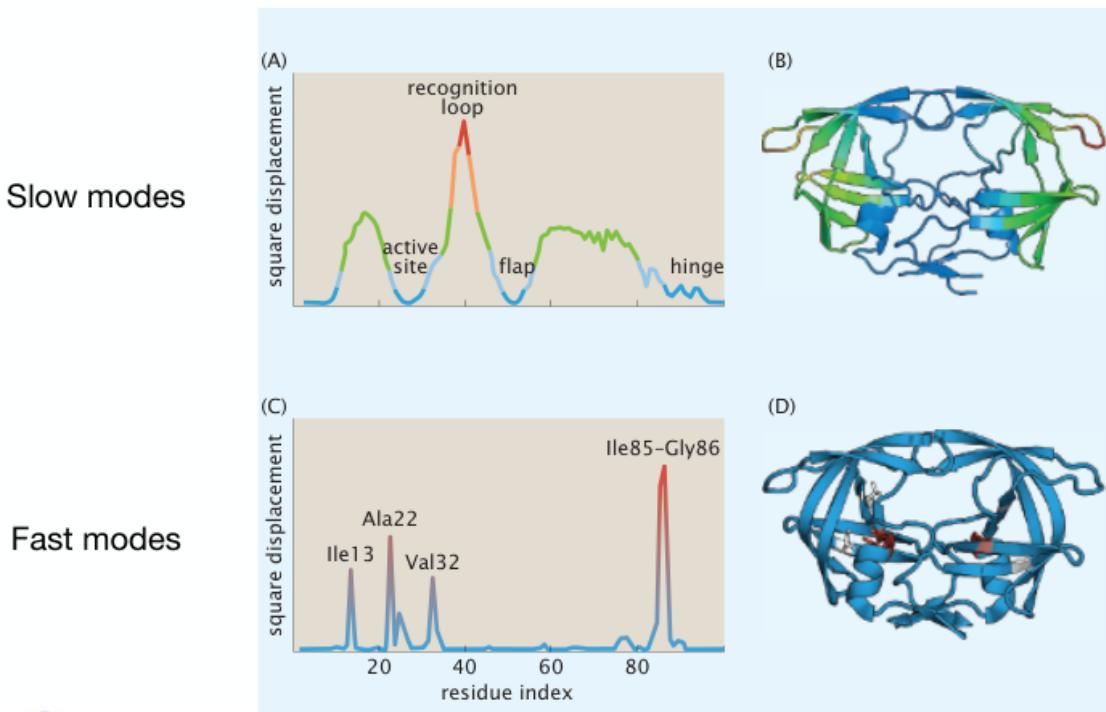


**Figure 15.3:** GNM and B-factors

### 15.1.1.3 Biological relevance

Focussing on the slow of figure 15.4 the contribution of each mode to the root mean squared deviation scales with the  $-1$  power with respect to the eigenvalues: the smaller eigenvalue contribute more to the fluctuation and are the one more spread over the region of the protein. Looking at the fast mode with high eigenvalue are usually concentrated and characterized with spikes and are localized on amino-acids that corresponds to hydrophobic pocket of the protein and are fundamental for their structure. Inserting a mutation on one of the amino-acids could make the structure unstable.

## 15.1. ELASTIC NETWORK MODELS (ENM)



**Figure 15.4:** Biological relevance

### 15.1.1.4 Normal mode analysis

Assuming that the approximation of the GNM is too crude and considering the fact that there are  $3N - 6$  degree of freedom. To be more rigorous the atomistic force field should be used and the potential function should be expanded through a Taylor expansion around an equilibrium position:

$$U = U_0 + \sum_i \frac{\partial U}{\partial q_i} \Big|_{q^0} (q_i - q_i^0) + \frac{1}{2} \sum_i \sum_j \frac{\partial^2 U}{\partial q_i \partial q_j} \Big|_{q^0} (q_i - q_i^0)(q_j - q_j^0) + \dots$$

If  $q^0$  represent the equilibrium the sum of the forces and in turn the first order term will be equal to 0, so at equilibrium:

$$U = \frac{1}{2} \Delta \vec{q}^T H \Delta \vec{q} = \frac{1}{2} \sum_i \sum_j H_{ij} (q_i - q_i^0)(q_j - q_j^0)$$

Where  $H$  is the Hessian matrix:

$$H_{ij} = \frac{\partial^2 U}{\partial q_i \partial q_j} \Big|_{q^0}$$

A matrix that can be computed analytically or numerically. This process is expensive because numerical derivatives have to be taken, but it is cheaper with respect to a molecular dynamics simulation. Now a covariance matrix can be computed:

$$C = \langle \Delta\vec{q}\Delta\vec{q}^T \rangle = \frac{1}{Q} \int \Delta\vec{q}\Delta\vec{q}^T e^{-\frac{\Delta\vec{q}^T H \Delta\vec{q}}{2kT}} d^N \Delta\vec{q} = kTH^{-1}$$

Where  $H^{-1}$  is a pseudoinvers as the Hessian matrix will have 6 0-eigenvalues because the degrees of freedom are  $3N - 6$  because overall translations and rotations are excluded.

### 15.1.2 Anisotropic network model (ANM)

In the anisotropic network model a normal mode analysis is performed, while assuming that each pair of interacting amino-acids have the same constant  $\gamma$  and there is an harmonic potential between them:

$$U_{ANM} = \frac{1}{2} \sum_{ij} \gamma(r_{ij} - r_{ij}^0)^2 \Rightarrow \frac{\partial^2 U}{\partial x_i \partial y_j i} = -\gamma \frac{(x_i - x_j)(y_i - y_j)}{t_{ij}^2}$$

So now the Hessian matrix can be computed easily:

$$H_{ij} = \frac{\gamma}{r_{ij}^2} \begin{bmatrix} x_{ij}^2 & x_{ij}y_{ij} & x_{ij}z_{ij} \\ x_{ij}y_{ij} & y_{ij}^2 & y_{ij}z_{ij} \\ x_{ij}z_{ij} & y_{ij}z_{ij} & z_{ij}^2 \end{bmatrix}$$

This matrix will be a  $N \times N$  matrix with each amino acid and all the elements are  $3 \times 3$  matrices. Now the eigenvalue decomposition  $H = U\Lambda U^T$  can be performed and the 0-eigenvalue will be discarded.

$$\Lambda = \begin{bmatrix} \lambda_1 & 0 & 0 & \cdots & 0 \\ 0 & \lambda_2 & 0 & \cdots & 0 \\ 0 & 0 & \lambda_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \lambda_{3N-6} \end{bmatrix}$$

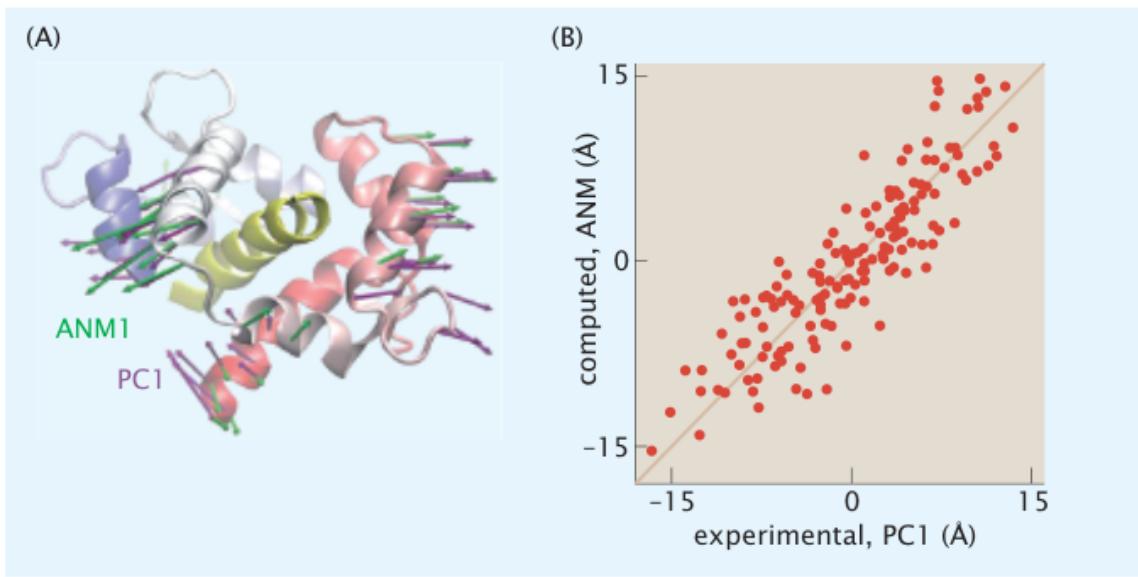
#### 15.1.2.1 Correlated motions

Computing now the correlation between amino-acids and focussing on the specific motion of each mode represented by an eigenvector.

$$\langle \Delta\vec{r}_i \cdot \Delta\vec{r}_j \rangle = \frac{3kT}{\gamma} [U\Lambda^{-1}U^T]_{ij} = \frac{3kT}{\gamma} \sum_k \lambda_k^{-1} [\vec{u}_k \vec{u}_k^T]_{ij}$$

The displacement of a protein can be computed from the modes. The direction of each mode is considered. This model does not treat all direction as the same.

### 15.1. ELASTIC NETWORK MODELS (ENM)



**Figure 15.5:** Correlated motions

There are other instructive quantities that tells something more on the motion of the protein. For example the correlation cosine: projecting an eigenvector to the displacement between state  $A$  and  $B$  of the protein. The objective is to determine whether the transition was determined by the mode in consideration. The correlation cosine is computed as:

$$I_k = \frac{\Delta \vec{q}_{AB} \cdot \vec{u}_k}{|\Delta \vec{q}_{AB}|} \quad \Delta \vec{q}_{AB} = \vec{q}^B - \vec{q}^A$$

The cumulative overlap is the number of mode that contribute to a motion:

$$C_0 = \sqrt{\sum_k I_k^2}$$

Another quantity is the degree of collectivity, which will also be used in PCA. It is a factor that looks like a Shannon-entropy and it is defined as:

$$\kappa_k = N^{-1} e^{-\sum_{i=1}^N \alpha(\Delta r_i)^2 |_k \log(\alpha \Delta r_i)^2 |_k}$$

Where  $\alpha$  is normalized.

$$\sum_{i=1}^N \alpha(\Delta r_i)^2 |_k = 1$$

When the degree of collectivity is close to 1 there is a collective mode, so a mode that involves a large number of residues, while when it is close to 0 the motion is localized on some portion of the protein.

## 15.2 Essential dynamics

Essential dynamics is based on principal component analysis: once a trajectory is obtained from a molecular dynamics simulation, the objective is to reduce the number of degrees of freedom to just those that are relevant to describe the motion of the system. Not all of the degrees of freedom and a proper transformation of variable can be found so that the relevant of degrees of freedom are found. They can be computed starting from the result of a molecular dynamics simulation.

1. Obtain trajectories from molecular dynamics simulations, better if equilibrated. Equilibration is not mandatory as the new set of coordinates can be not equilibrated. There might be more than one trajectory that can be compared.
2. Remove overall translations and rotations by aligning each frame to a reference structure. The reference frame can be the starting frame.
3. Choose the set of atoms for the analysis like  $\alpha$ -carbons. In principle this analysis can be performed on all the atoms, but this is pointless. It is better to select on a subset of atoms, focussing on  $\alpha$ -carbons or on one sub-region of the protein.
4. Obtain the covariance matrix:

$$C_{ij} = \overline{(x_i(t) - \bar{x}_i(t))(x_j(t) - \bar{x}_j(t))}$$

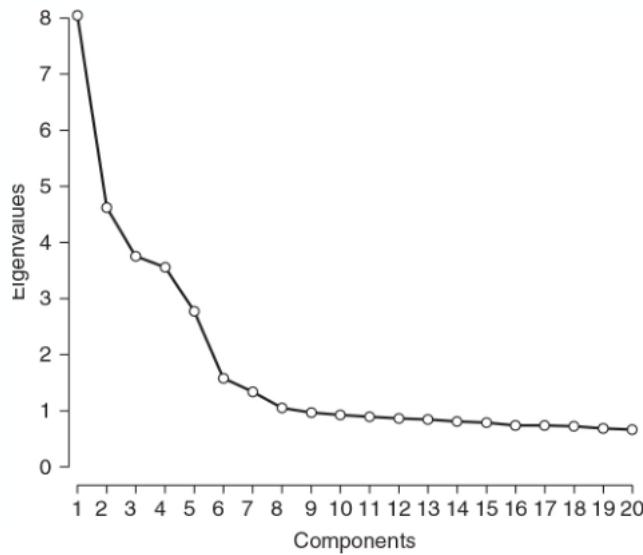
The covariance matrix is an average in time.

5. If the fluctuations display some non-homogeneous behaviour, for example when there are loops that fluctuates a lot, it is better to employ the correlation matrix:

$$R_{ij} = \frac{\overline{(x_i(t) - \bar{x}_i(t))(x_j(t) - \bar{x}_j(t))}}{\sigma_{x_i}\sigma_{x_j}}$$

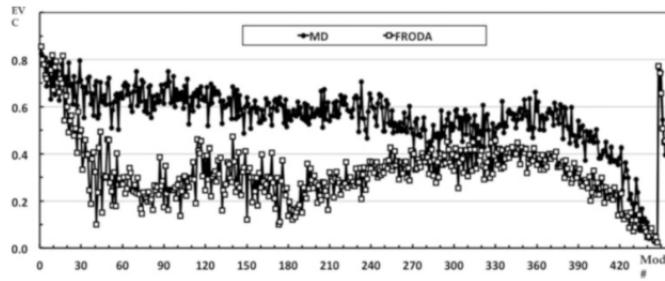
Which is the covariance matrix normalized by the standard deviation.

6. Diagonalize  $C$  or  $R$  employing eigenvalue decomposition EVD as in elastic network models.
7. Examine the eigenvalue scree plot to determine the number of eigenvectors to include in the reduced vector space that describes the most relevant features. An example can be seen in figure 15.6. It can be seen how after a number of eigenvalues the other components have small eigenvalues. This behaviour is typical for a protein simulation, if the interaction describe a network.



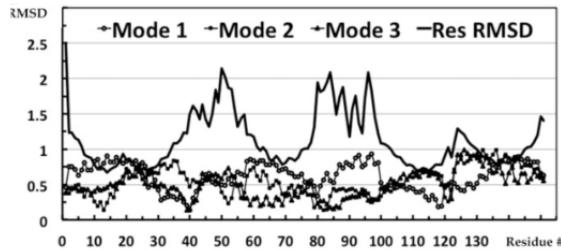
**Figure 15.6:** Eigenvalue scree plot

8. Select the top set of eigenvectors to form the principal components (PCs) (usually between 2 and 20).
9. Examine the eigenvector collectivity for each mode defined as in the ANM: top modes tend to be more collective than lower modes, indicating that many residues are participating in collective motions.



**Figure 15.7:** Eigenvalue collectivity

10. Construct the weighted RMSD modes  $\langle \Delta \vec{r}_i^2 \rangle_k = \lambda_k [\vec{u}_k \vec{u}_k^T]_{ij}$ . Visualize which residues contribute most to the fluctuation of each PCA mode. Comparing against the overall RMSD and looking where the most important contribution on the movement as in 15.8

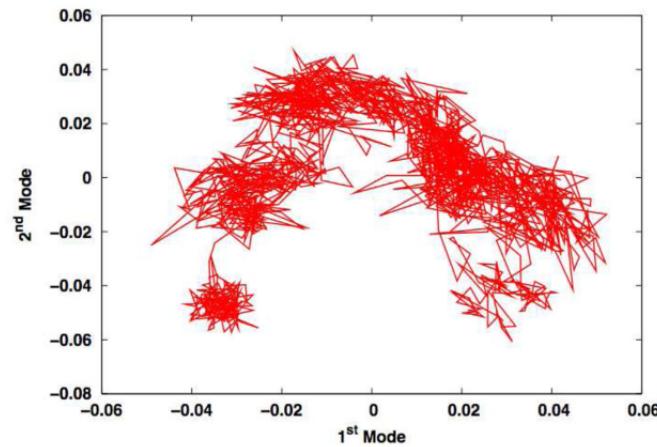


**Figure 15.8:** Weighted RMSD modes

11. Construct the displacement vectors  $\vec{d}_i(t) = \vec{r}_i(t) - \bar{\vec{r}}_i$  for each snapshot and construct the PCs projecting the displacement vectors onto the eigenvectors obtained:

$$PC_k(t) = \sum_{i=1}^N \vec{d}_i(t) \cdot \vec{u}_i^k \quad \text{with } k = 1, \dots, 3N - 6$$

Each snapshot now is described by a single point with  $3N - 6$  numbers. Looking at these point in the multi-dimensional space and plotting them onto the first two principal component as in figure 15.9.

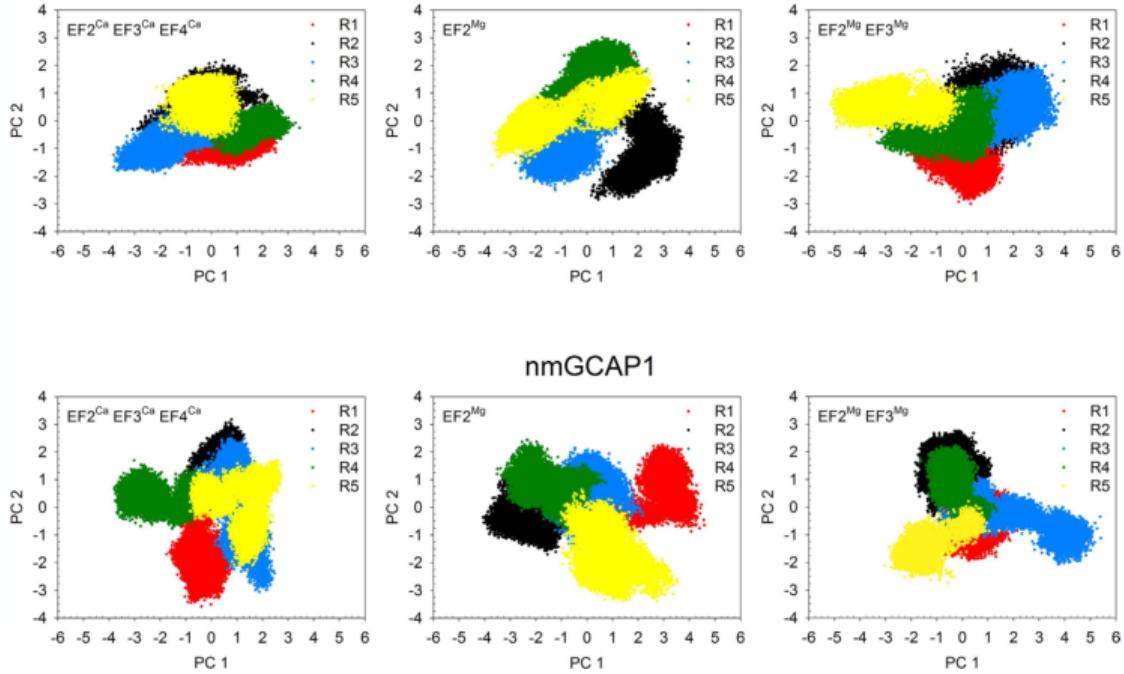


**Figure 15.9:** Scatter plot of first and second mode for PCs

The snapshots can be coloured according to time so to see the movement in the space as in figure 15.10

## 15.2. ESSENTIAL DYNAMICS

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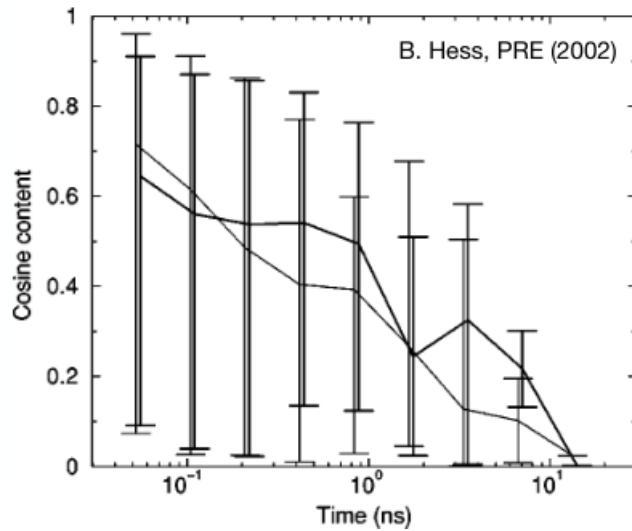


**Figure 15.10:** Scatter plot of PCs, different replicas, the color indicates time of simulation.

12. Examine the cosine content for each mode  $k$ , defined as the superposition with the cosine obtained from a simple diffusion in a high dimensional harmonic potential:

$$c_k = \frac{2}{T_{sim}} \left( \int_0^{T_{sim}} \cos\left(\pi \frac{k_B T}{\lambda_k} t\right) PC_k(t) dt \right)^2 \left( \int_0^{T_{sim}} PC_k^2(t) dt \right)^{-1}$$

The cosine content compares the principal component, which are a function of time, representing a time-series to the trajectory with the cosine that represents the diffusion of the system in a high-dimensional harmonic potential. If it is equal to 1 one single basin is being explored, so the smaller the better, so that the system explores more basins and has equilibrated. An example can be seen in 15.11. It can be seen how the cosine content decrees along the time of the simulation. The error bars can be obtained performing several simulation or dividing a simulation into pieces. This is another way to measure whether the system has equilibrated or not.



**Figure 15.11:** Cosine content for the modes

13. Examine the similarity between trajectories or between portions of the same trajectory by examining the Covariance overlap:

$$\Omega_{A,B} = 1 - \left[ \frac{\sum_{k=1}^{3N-6} (\lambda_k^A + \lambda_k^B) - 2 \sum_{k=1}^{3N-6} \sum_{j=1}^{3N-6} \sqrt{\lambda_k^A \lambda_j^B} (\vec{u}_k^A \cdot \vec{u}_j^B)^2}{\sum_{k=1}^{3N-6} (\lambda_k^A + \lambda_k^B)} \right]^{\frac{1}{2}}$$

$\Omega_{A,B} = 1$  if and only if the two covariance matrices are identical, while it is zero when the sampled subspaces are completely orthogonal.

# Chapter 16

## Clustering and protein structure networks

### 16.1 Introduction

The aim of clustering is to find a way to group a set of data into clusters of similar properties. This is done because:

- Labelling is expensive.
- To gain insight into the structure of data.
- Find prototypes in the data.

In molecular simulations data usually refers to protein, DNA or RNA conformations. So, given a set of data points, each described by a set of attributes, the clusters have to be found such that:

- Intra-cluster similarity is maximized: all the points in a cluster are as much similar as possible.
- Inter-cluster similarity is minimized: all the points between clusters are as much dissimilar between each other.

#### 16.1.1 Distance measures

To define similarity let  $O_1$  and  $O_2$  be two objects from the universe of possible objects. The distance or dissimilarity between  $O_1$  and  $O_2$  is a real number  $D(O_1, O_2)$ . A distance measure should have the following properties:

- Symmetry:  $D(A, B) = D(B, A)$ .
- Constancy of self-similarity:  $D(A, A) = 0$ .
- Positivity (separation):  $(A, B) = 0 \Leftrightarrow A = B$ .
- Triangular inequality:  $D(A, B) \leq D(A, C) + D(B, C)$ .

An example of this for molecular dynamics and two protein conformation is the root mean squared deviation, computing the all-to-all RMSD matrix.

#### 16.1.2 Types of clustering

## 16.2. HIERARCHICAL CLUSTERING

- Hierarchical algorithms: create a hierarchical decomposition of the set of objects using some criterion.
- Partitional algorithms: construct various partitions and then evaluate them by some criterion,

### 16.1.3 Distance measures

The distance between objects in a cluster or clusters can be computed in several ways:

- Single linkage or nearest neighbour: the distance between two clusters is determined by the distance of the two closest objects (nearest neighbours) in the different clusters.
- Complete linkage or furthest neighbour: the distance between two clusters is the greatest distance between two objects in the different clusters.
- Group average linkage: the distance between two clusters is computed as the average distance between all pairs of objects in the two different clusters.

## 16.2 Hierarchical clustering

### 16.2.1 Dendograms

In a dendrogram (16.3) the similarity between two objects is represented as the height of the lowest internal node they share. Each object is represented as a leaf. Dendograms give a direct visual representation of the groups of data.

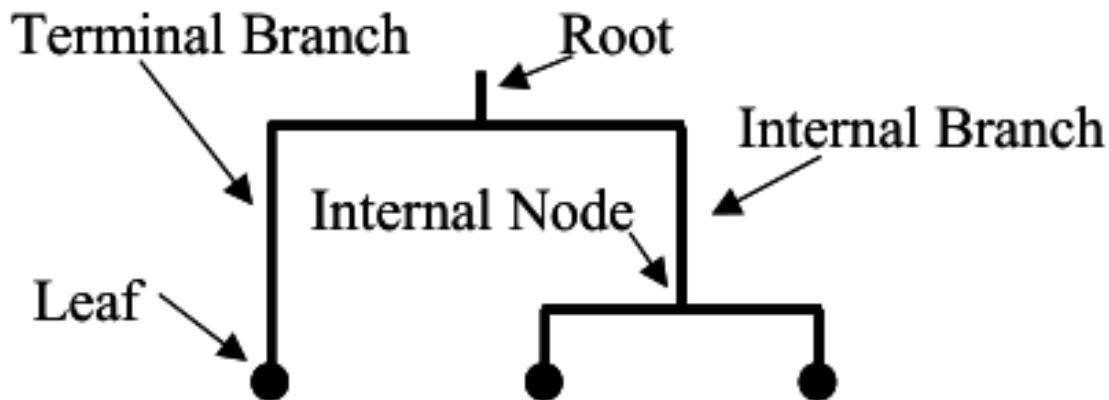


Figure 16.1: Dendrogram structure

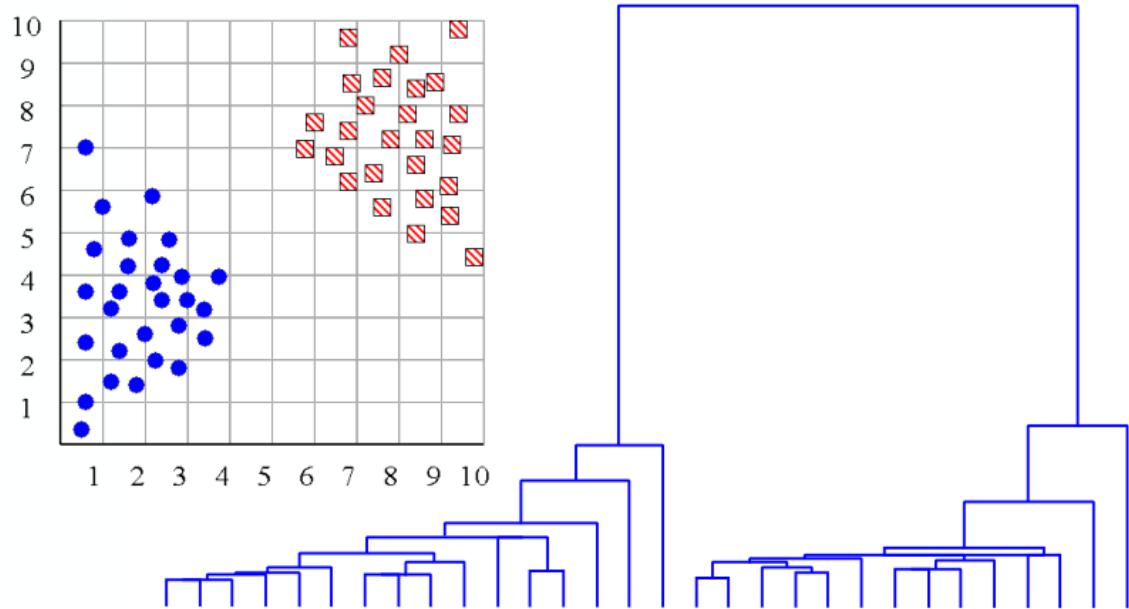
### 16.2.2 Interpretation

Hierarchical clustering sometimes show pattern that are meaningless or spurious. So the interpretation of the algorithm has to be performed.

### 16.2.3 Advantages of hierarchical clustering

#### 16.2.3.1 Correct number of clusters

One advantage of hierarchical clustering is that the correct number of cluster is obtained looking at the dendrogram.



**Figure 16.2:** Correct number of clusters

#### 16.2.3.2 Outliers

Moreover when using hierarchical clustering the outliers are easily identified.

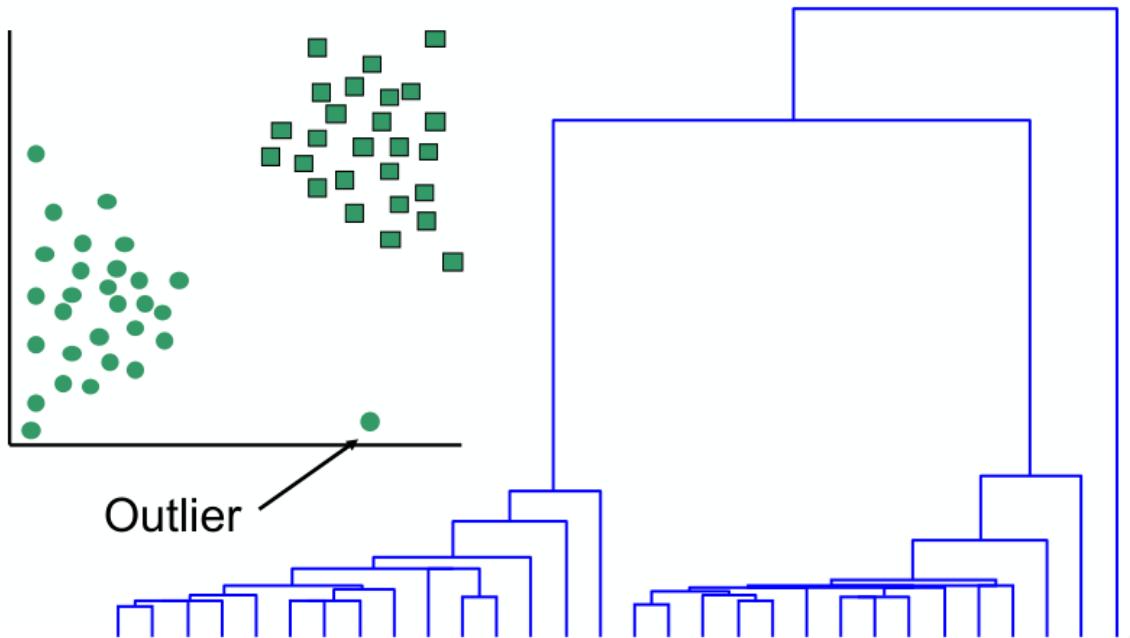


Figure 16.3: Outliers

#### 16.2.4 Hierarchical clustering approach

The number of dendograms  $D$  with  $n$  leafs are:

$$D = \frac{(2n - 3)!}{2^{n-2}(n - 2)!}$$

They can be built with two approaches:

- Bottom-up or agglomerative approach: each item is grouped alone into its own cluster and then the best pair to merge into a new cluster is found. This is repeated until all clusters are fused together.
- Top-down or divisive approach: all the data is grouped into a single cluster, then the best division into two cluster is chosen and this is repeated recursively on both sides.

#### 16.2.5 Summary of hierarchical methods

- No need to specify the number of clusters in advance.
- The hierarchical nature maps nicely onto human intuition for some domains.
- They do not scale well:  $O(n^2)$ .
- The interpretation of the results is very subjective.

## 16.3 Partitional clustering

In partitional clustering each item is placed in exactly one of  $K$  non-overlapping clusters. The number of cluster is provided as input.

### 16.3.1 K-means

1. Choose the value  $k$ .
2. Initialize the  $k$  cluster centres randomly.
3. Decide the class memberships of the  $N$  objects by assigning them to the nearest cluster centre.
4. Re-estimate the  $k$ -cluster centres by assuming the memberships found are correct.
5. If none of the  $N$  objects changed memberships in the last iteration exit, otherwise go back to step 3.

#### 16.3.1.1 Conclusion

- Relatively efficient:  $O(tkn)$  where  $n$  is the number of objects,  $k$  is the number of clusters and  $t$  the number of iterations.
- It often terminates at a local optimum.
- It is applicable only when a mean can be defined.
- The number of cluster has to be specified in advance.
- It is unable to handle noisy data or outliers.
- It is not suitable to discover clusters with non-convex shapes.

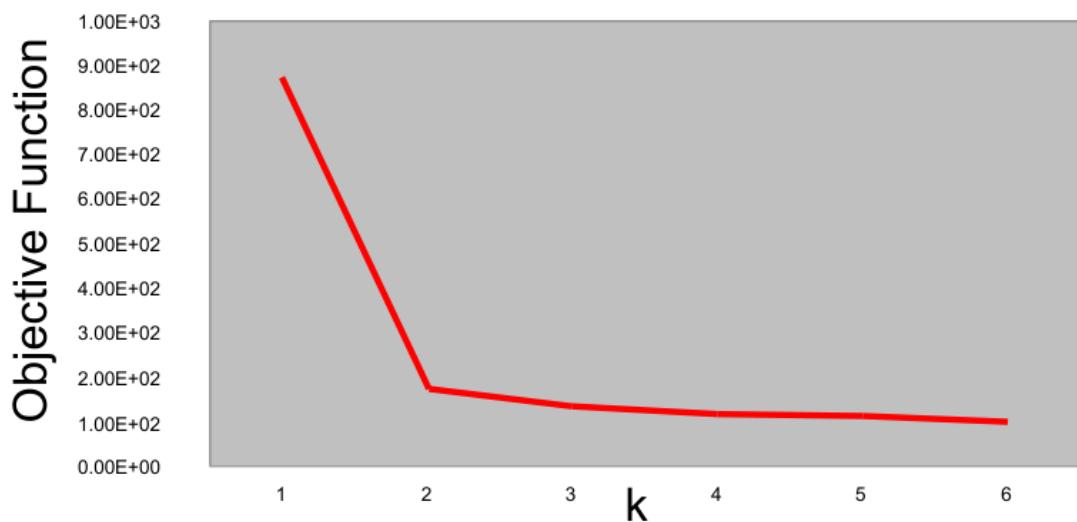
### 16.3.2 Sum of squared errors

The sum of squared error will be the objective function that determines how well the data is divided into clusters.

$$SE_{K_i} = \sum_{j=1}^m [D(C_{ij}, C_{K_i})]^2$$
$$SE_K = \sum_{i=1}^j SE_{K_i}$$

### 16.3.3 Choosing K

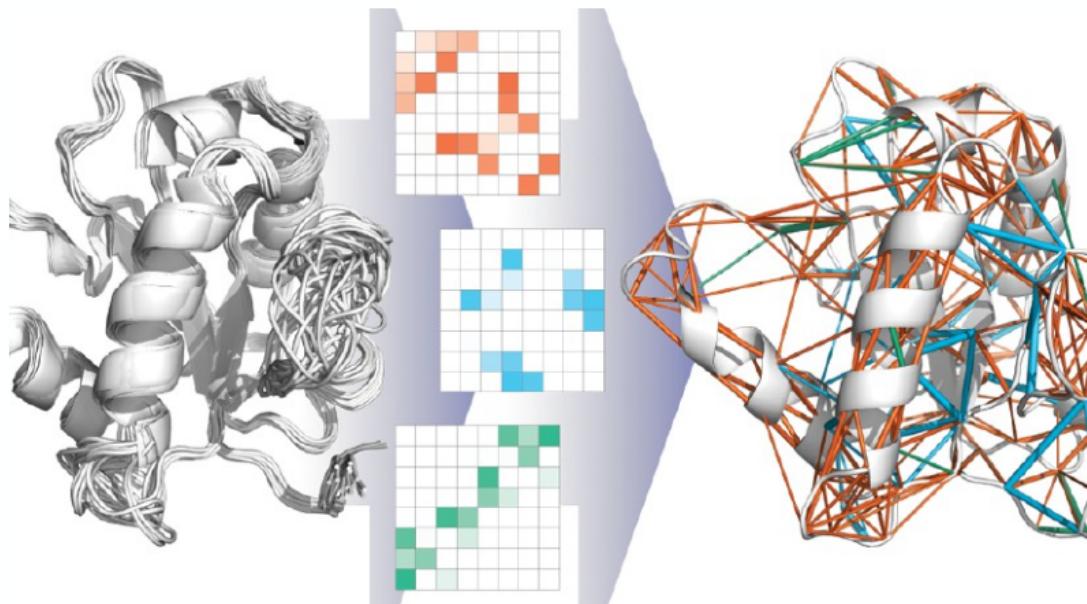
The optimal  $k$  is the one such that the  $\min SE$  is found. It can be chosen running the algorithm with iteratively increasing value of  $k$  and looking at the knee or elbow plot of  $k$  in relation with  $SE$  as in 16.4.



**Figure 16.4:** Knee or elbow plot

## 16.4 Protein structure networks

Protein structure networks represent proteins as networks built after the molecular dynamics simulation is performed.



**Figure 16.5:** Protein structure network

### 16.4.1 PyInteraph

PyInteraph is an algorithm to analyse the trajectories. The protein is represented as a graph where the nodes are the side chains of protein residues and the edges can be defined in term of:

- Distance.
- Atomic contacts.
- Van der Waals interactions.
- Interaction energy.

Then a graph analysis approach to the intramolecular interaction network IIN is performed.

### 16.4.2 Classes of interactions

This interactions are non-bonded interactions that are not present in the force-field.

#### 16.4.2.1 Hydrophobic contacts

In the hydrophobic contacts the centre of mass of the two side chains are distant less than 5Å. The centres of mass is specified by the force field for different masses, so they will be force-field specific. It has default residues, the typically hydrophobic residues that are checked by pyInteraph.

- Ala.
- Val.
- Met.
- Pro.
- Ile.
- Phe.
- Trp.

#### 16.4.2.2 Salt bridges

Salt bridges corresponds to the interaction of groups with opposite charge. They are formed between atom pairs belonging to two charged groups of two different residues with distance less than 4.5Å.

#### 16.4.2.3 Hydrogen bonds

Hydrogen bond happen when the distance between the acceptor and the hydrogen atom is less than 3.5Å and the donor-hydrogen-acceptor angle is greater than 120°.

### 16.4.3 Persistence

Persitence is the fraction of the number of structures in the ensemble in which the interaction was observed: the interactions are computed for each frame. For hydrogen-bond one or more interactions may exist between two residues. PyInteraph will generate interaction matrix for each type of interaction. Then for each interaction the edge weight is given, corresponding to the persistence value. Then these three interaction network are filtered according to a measure providing a persistence threshold. When the value of the persistence is higher than the threshold a contact is assumed true. After that the macro-intramolecular-interaction network that collects informations about all the different of interactions is built.

#### 16.4.4 Persistence threshold

To choose the persistence threshold the connected components of the protein structure network have to be found. A connected component is a subgraph in which a path exists between any two vertices, but no path exist to any other vertices of the main graph: there are no edges connecting two connected components. After having obtained them for each value of the persistence, so that a connection is defined whenever the persistence is higher than the value. It can be seen how decreasing the threshold the size of the connected components increase. In a typical graph of persistence over component size a kink can be found and that will be the persistence threshold.

#### 16.4.5 Graph analysis

Some analysis provided by pyInteraph are:

- Computing the highly connected residues or hubs: residues with with more than 3 or 4 edges. A list of hubs and their respective connectivity degree (how many residue are connected to them) is computed. Hubs indicates that their residues will play a key role in the structure or function of the protein.
- Connected components. The groups and part of the protein are connected and can be assumed to behave as rigid object in the protein. These can find domains that behave mechanical in the same way in the protein.
- Shortest path between two specified residues. This is useful because many proteins have allosteric communication pathways and they could be explored by this analysis, finding the amino acids that transport the mechanical signal from one side of the protein to another.

#### 16.4.6 Examples

##### 16.4.6.1 p53 DNA binding domain

Hydrophobic interactions play a crucial role in the stabilization of the protein core and in the maintenance of the 3D structure and stability. In general hydrophobic interaction play a crucial role in the folding, structure and function of the protein.

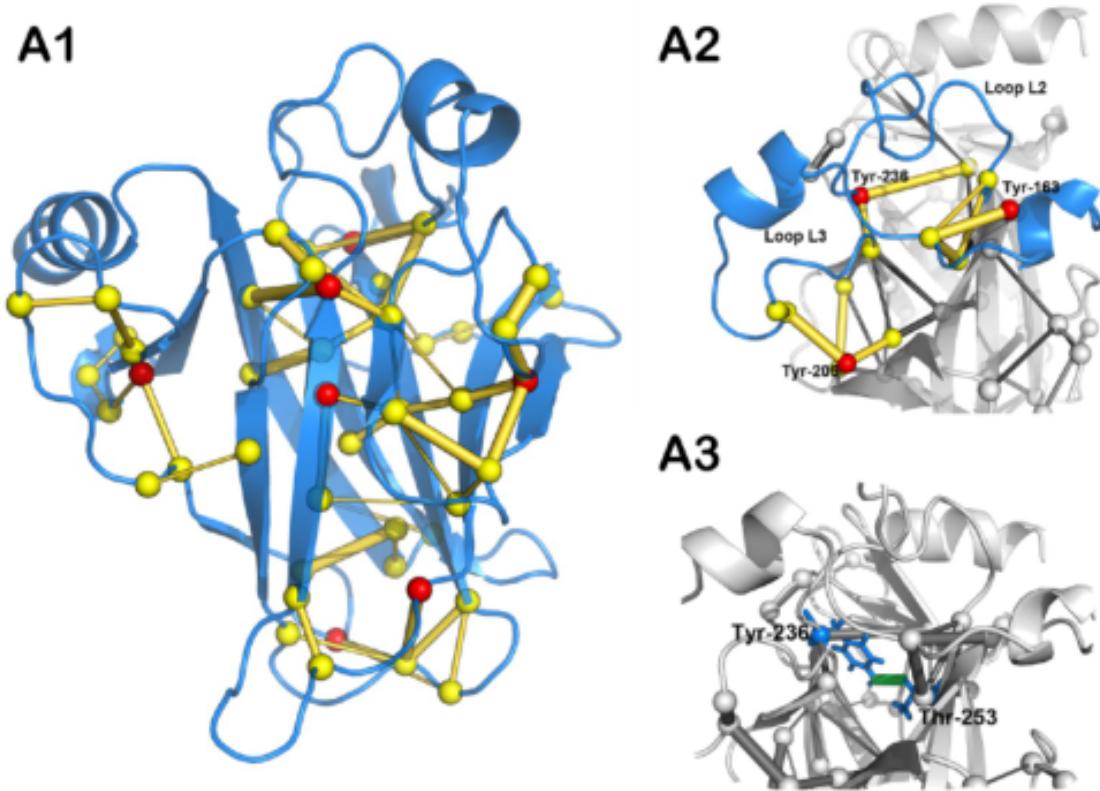


Figure 16.6: p53

#### 16.4.6.2 Vibrio proteinase (VAP)

Salt bridges or hydrogen bonds are highly flexible and cooperatively organized in networks across the protein structure or for temperature adapted organisms.

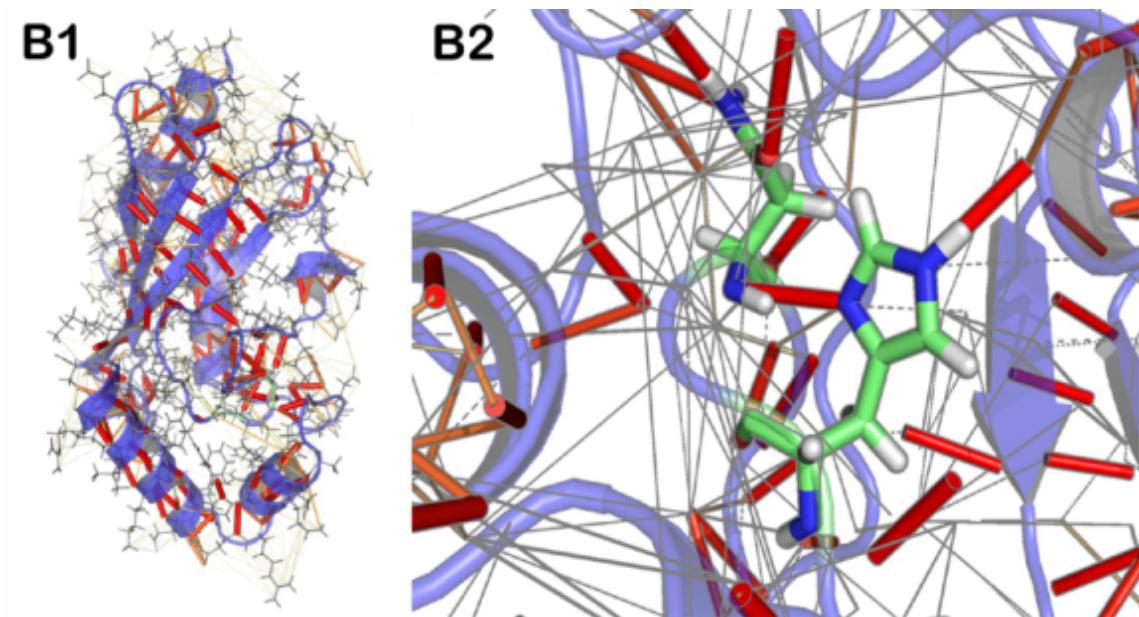


Figure 16.7: VAP

# Chapter 17

## Monte Carlo methods

### 17.1 Introduction

Monte Carlo methods are based on games of chance. The basic idea is to evaluate the value of integrals, for example:

$$I = \int_0^1 dx \int_0^{\sqrt{1-x^2}} dy = \frac{\pi}{4}$$

This is done when analytical methods cannot be applied.

#### 17.1.1 Central limit theorem

This method is important in statistical mechanics as the aim is to evaluate integrals that define the average value of a quantity. Let  $f$  be a distribution function such that:

$$f(x) \geq 0 \quad \int f(x)dx = 1$$

And  $\phi$  an arbitrary function. The integral that has to be evaluated to obtain the average value:

$$I = \int dx \phi(x) f(x) \equiv \langle \phi \rangle_f$$

Let  $x_1, \dots, x_M$  n-dimensional vectors sampled from  $f(x)$ . Then by the central limit theorem:

$$\tilde{I}_M = \frac{1}{M} \sum_{i=1}^M \phi(x_i) \quad \lim_{M \rightarrow \infty} \tilde{I}_M = I$$

Now the average is a good estimator for the integral with some error considering the fluctuation of the function  $\phi$  sampled by  $f$ :

$$\int dx \phi(x) f(x) = \frac{1}{M} \sum_{i=1}^M \phi(x_i) \pm \frac{1}{\sqrt{M}} [\langle \phi^2 \rangle_f - \langle \phi \rangle_f^2]^{\frac{1}{2}}$$

In this way beside a good estimate of the integral also the error can be evaluated. So increasing the number of points decreases the error.

### 17.1.2 Sampling distributions

Random number generators are fundamental during Monte Carlo simulations. Consider a one dimensional distribution function:

$$\int_a^b f(x)dx = 1 \quad f(x) \geq 0$$

The cumulative probability is defined as:

$$P(X) = \int_a^X f(x)dx \quad X \in [a, b]$$

$P(X)$  is the probability that any chosen  $x$  from the distribution  $f(x)$  lies in  $[a, X]$ .  $P(X)$  is a monotonically increasing function of  $X$ , moreover:

$$f(X) = \frac{dP}{dX}$$

Performing a variable transformation  $x \rightarrow y$  with  $y = g(x)$  a non decreasing function of  $x$ :

$$X \geq x \Rightarrow g(X) \geq g(x)$$

Defining  $\tilde{P}(Y = g(X))$  as the probability that  $g(X) = Y \geq y \geq g(x)$  is the probability that  $X \geq x$ , then:

$$\tilde{P}(Y) = P(X)$$

This allows to obtain random number distributed according to any distribution starting from any other. As an example:

$$w(r) = \begin{cases} 1 & 0 \leq r \leq 1 \\ 0 & \text{otherwise} \end{cases} \quad W(\xi) = \int_0^\xi w(r)ds = \begin{cases} 0 & \xi < 0 \\ \xi & 0 \leq \xi \leq 1 \\ 1 & \text{otherwise} \end{cases}$$

$W(\xi) = \xi$  is the probability that a value of  $r$  that has been chosen randomly lies in  $[0, \xi]$ . Now the function  $g$  has to be found such that  $r = g(x)$  with  $g(x)$  a non decreasing function: solve  $P(X) = \xi$ .

#### 17.1.2.1 An example

Assume that random number has to be obtained using the function:

$$f(x) = ce^{-cx} \quad x \in [0, +\infty[$$

Now computing the cumulative distribution function that corresponds to that distribution function and then assuming that  $P(X) = \tilde{P}(Y)$ , the cumulative distribution function for the uniform random number that was equal to  $\xi$ . In this way the relation between  $X$  and  $\xi$  is found.

$$P(X) = \int_0^X ce^{-cx}dx = 1 - e^{-cX} = \xi \Rightarrow X = -\frac{1}{C} \ln(1 - \xi)$$

Now any number obtained from the uniform distribution function is the value of  $\xi$ , which if it is plugged into the previous equation the number distributed according to the desired distribution is obtained. The same procedure can be generalized to more than one random variable easily when

$f(x)$  is separable into a product of  $n$  single-variable distributions. This is the procedure that most of the integrator employs to generate velocities and initial conditions to the momenta.

### 17.1.3 Importance sampling

Going back to the problem of the integral. Let  $I$  be the integral of an observable  $\phi$ .

$$I = \int dx \phi(x) f(x) = \int dx \left[ \frac{\phi(x) f(x)}{h(x)} \right] h(x) = \int dx \psi(x) h(x)$$

Let  $h$  be another distribution function defining  $\psi(x) = \frac{\phi(x)}{h(x)}$ . Applying the central limit theorem:

$$I = \int dx \psi(x) h(x) = \frac{1}{M} \sum_{i=1}^M \psi(x_i) \pm \frac{1}{\sqrt{M}} [\langle \psi^2 \rangle_h - \langle \psi \rangle_h^2]^{\frac{1}{2}}$$

This is done because  $h(x)$  might be easier to sample or it might behave better than  $f(x)$ . In the canonical ensemble for example it is better to compute first the Boltzmann-Weight of the conformation before sampling the conformation from the distribution function. Another distribution function is used instead of the original, so the optimal choice for this probability distribution function  $h(x)$ :

$$\sigma^2[h] = \int dx \psi^2(x) h(x) - \left[ \int dx \psi(x) h(x) \right]^2 = \int dx \frac{\phi^2(x) f^2(x)}{h(x)} - \left[ \int dx \phi(x) f(x) \right]^2$$

Minimize the functional  $\sigma^2[h]$  with the constraint  $\int dx h(x) = 1$  driven by the normalization of  $h(x)$ . To do so the methods of Lagrange multiplier is used introducing an extra variable  $\lambda$  and introducing the functional:  $F[h] = \sigma^2[h] - \lambda \int dx h(x)$ . Taking the functional derivative:  $\frac{\delta F[h]}{\delta h(x)} = 0$  with  $\delta F[h] = F[h + \delta h] - F[h]$  will allow to find an equation for  $\lambda$  that will be made explicit using the normalization condition. The equality equal to 0 to minimize  $\sigma^2[h]$ . Now using the Taylor expansion of the first factor on  $\delta h$ :

$$\begin{aligned} \delta F[h] &= \int dx \left[ \frac{\phi^2(x) f^2(x)}{h(x) + \delta h(x)} - \frac{\phi^2(x) f^2(x)}{h(x)} \right] - \lambda \delta h(x) = \\ &= -\frac{\phi^2(x) f^2(x)}{h^2(x)} \delta h(x) - \lambda \delta h(x) \end{aligned}$$

Now taking the derivative equal to 0 an equation to obtain  $h$  is found:

$$\frac{\delta F[h]}{\delta h(x)} = 0 \Rightarrow \frac{\phi^2(x) f^2(x)}{h^2(x)} + \lambda = 0 \Rightarrow h(x) = \frac{1}{\sqrt{-\lambda}} \phi(x) f(x)$$

Looking at the normalization condition:

$$\int dx h(x) = 1 \Rightarrow \sqrt{-\lambda} = \int dx \phi(x) f(x) = I$$

So the optimal choice is  $h(x) = \frac{\phi(x) f(x)}{I} \Rightarrow \sigma^2[h] = 0$ . Where  $h$  is the function used in importance sampling.  $I$  is needed, but it is the objective of this computation. This means that the true function  $h$  cannot be obtained, but there are some tricks to generate a number of points distributed to the function  $h$ . This is called importance sampling and to sample the phase space according to

## 17.1. INTRODUCTION

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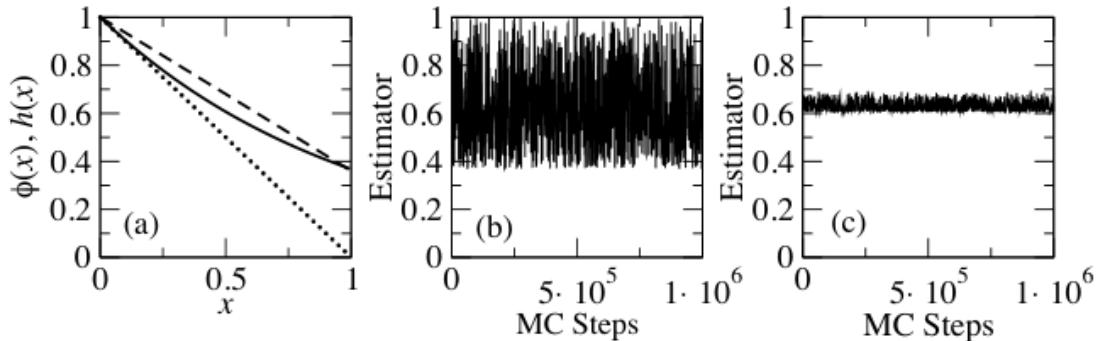
the optimal choice of the distribution function the Metropolis algorithms will be used. In this way sampling is efficient and the estimate is a good one. A system will be simulated and points distributed according to  $h$  will be extracted.

### 17.1.3.1 An example

Computing the integral:

$$\int_0^1 dx e^{-x}$$

It can be seen how the function to be integrate is the solid line ( $\phi(x)$ ) in the left panel of figure 17.1. Two importance functions can be found:  $1 - x$  for the dotted line and  $1 - 0.64x$  for the dashed one. Looking at the two functions using importance sampling convergence will be faster. Looking at the middle panel the result of sampling from 0 and 1 uniformly looking at the estimator of the integral. There are huge fluctuation. Using instead one of the two functions the convergence will be improved as in the right panel the fluctuation are much smaller.



**Figure 17.1:** The integrand and two possible importance functions

### 17.1.4 Molecular dynamics and Monte Carlo methods

In molecular dynamics:

- All particles move at once, but the  $\Delta t$  is usually quite small.
- Information on dynamics are available.
- Parallel architectures: molecular dynamics is more parallelizable and it is naturally implemented on parallel computers.

In Monte Carlo:

- There is no limit on the range of moves: the only limit is the Boltzmann weights, but also unphysical moves can be considered. The dynamics of the movement is not important.
- Natural thermostats and barostats: they are easily implemented in a Monte Carlo simulation.

- Flexibility: it can be applied to any possible system, playing with the moves makes it extremely flexible.
- Ergodicity can be achieved thinking about a strange move that moves in the phase space.

## 17.2 Markov chains

A Markov chain is a rule to obtain the point at the next iteration starting from a point. The state of the system depends only on the previous instant of time. The vectors  $x_1, x_2, \dots, x_M$  can be generated sequentially in a Markov chain: a rule to generate  $x_{i+1}$  given  $x_i$  is given. This points will be sampled according to the same distribution from which we want to sample:

$$\tilde{I}_M = \frac{1}{M} \sum_{i=1}^M \phi(x_i)$$

This rule is defined as  $R(x|y)$ , the probability to obtain  $x$  given  $y$ . If there are two micro states it is the probability to move to a microstate  $x$  from a microstate  $y$ .

### 17.2.1 Detailed balance condition

To define a rule a detailed balance condition is imposed

$$R(x|y)f(y) = R(y|x)f(x)$$

This means that the probability to go from  $y$  to  $x$  times the probability of being in  $y$  is equal to the inverse movement. Some features of the detailed balance condition are:

- It represents microscopic reversibility.
- It is an unbiased sampling of phase space.
- It is sufficient but not strictly necessary condition to ensure proper sampling of phase space. Unbiased sampling can be obtained without the detailed balance condition.

### 17.2.2 Rejection methods

Using the detailed balance condition a rejection method is built. Let  $T(x|y)$  a rule to generate a trial move or proposed move from  $y$  to  $x$ . This is the probability to go from  $y$  to  $x$  by the way the proposed move are constructed. This quantity is normalized:

$$\int dx T(x|y) = 1$$

So the probability to go from state  $y$  to anywhere is 1. Let  $A(x|y)$  be the probability to accept the move from  $y$  to  $x$ . Now the probability to go from  $y$  to  $x$  is the product of the probability of generating the move and the probability of accepting that move:

$$R(x|y) = A(x|y)T(x|y)$$

By applying the detailed balance condition:

$$A(x|y)T(x|y)f(y) = A(y|x)T(y|x)f(x)$$

By looking at this equation it can be seen how the acceptance probabilities are related. In this way the integral is cancelled because it is at the denominator for  $f$ . If the algorithm is symmetrical the probability of the inverses moves is equal. The acceptance probability are related to each other and are not independent. Writing down this relation:

$$A(x|y) = \frac{T(y|x)f(x)}{T(x|y)f(y)} A(y|x) = r(x|y) A(y|x)$$

Where  $\frac{T(y|x)f(x)}{T(x|y)f(y)} = r(x|y)$ . If  $A(x|y) = 1$  the move  $y \rightarrow x$  is favoured  $\Rightarrow A(y|x) < 1 \Rightarrow r(x|y) > 1$ . If  $A(x|y) < 1$ ,  $y \rightarrow x$  is not entirely favoured  $\Rightarrow A(y|x) = 1 \Rightarrow r(x|y) < 1$ . Writing down this  $A$  can be defined as:

$$A(x|y) = \min[1, r(x|y)]$$

So the acceptance probability of the move from  $y$  to  $x$  is the minimum between 1 and  $r(x|y)$ .

### 17.2.3 Metropolis algorithm

In order to build the acceptance rate the trial distribution  $T(x_{k+1}|x_k)$  has to be written to be able to propose a move  $x_k \rightarrow x_{k+1}$  and there is a need to be able to compute:

$$r(x_{k+1}|x_k) = \frac{T(x_k|x_{k+1})f(x_{k+1})}{T(x_{k+1}|x_k)f(x_k)}$$

If  $r(x_{k+1}|x_k) > 1$  accept the move, otherwise accept the move with probability given by  $r(x_{k+1}|x_k)$ : extract a random number  $\xi \in [0, 1]$ . If  $\xi < r(x_{k+1}|x_k)$  accept the move. Rejections do count: when a move is rejected that particular conformation will be counted twice because the importance sampling samples the system with a distribution function that is required by it, which means that points that are more representative for the representation functions will be explored more: if a move is rejected that point counts more in the average.

#### 17.2.3.1 Proof

Let the associated probability for each point  $x_1, \dots, x_n$ :  $\pi_1(x), \dots, \pi_n(x)$ . With a huge number of moves the probability is equal to the desired distribution.

$$\lim_{n \rightarrow \infty} \pi_n(x) = f(x)$$

Proof by recursive relation:  $\pi_{n+1}(x)$  receives contributions from accepted moves starting at  $y$  and ending in  $x$  and from attempted moves to  $y$  that are rejected:

$$\pi_{n+1}(x) = \int A(x|y)T(x|y)\pi_n(y)dy + \pi_n(x) \int [1 - A(y|x)]T(y|x)dy$$

If  $\pi_n(x) = f(x)$ :

$$\pi_{n+1} = \int A(x|y)T(x|y)f(y)dy + f(x) \int [1 - A(y|x)]T(y|x)dy$$

Considering the detailed balance condition:  $A(x|y)T(x|y)f(y) = A(y|x)T(y|x)f(x)$  two terms cancel each other out:

$$\pi_{n+1}(x) = f(x) \int T(y|x) dy = f(x)$$

So if the system arrives at the distribution function  $f$  it will stay there.

### 17.2.3.2 Summary

Everything sums up to evaluate the ratio of the final over probabilities of generating the moves to the initial and final states.

$$r(x|y) = \frac{T(y|x)f(x)}{T(x|y)f(y)}$$

The acceptance probability is computed according to:

$$A(x|y) = \min[1, r(x|y)]$$

For a uniform choice of  $T(x|y)$ , so the same probability from  $x$  to  $y$  and from  $y$  to  $x$ :

$$r(x|y) = \frac{f(x)}{f(y)} \Rightarrow A(x|y) = \min\left[1, \frac{f(x)}{f(y)}\right]$$

Considering the Boltzmann distribution in this ratio the partition function would be cancelled.

### 17.2.4 Canonical distribution

In the canonical distribution the partition function, where the integrand is the Boltzmann weight:

$$Q(N, V, T) = \frac{1}{N! \lambda^{3N}} \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N)}$$

So the acceptance probability for a move from  $r$  to  $r'$  will be:

$$A(r'|r) = \min[1, e^{-\beta(U(r') - U(r))}]$$

$\Delta U < 0$  accept the move, so when decreasing the energy the move is accepted.  $\Delta U > 0$  accept the move with probability  $e^{-\beta \Delta U}$  if the energy has increased. In this way points that are distributed according to Boltzmann distribution can be simulated. Considering the acceptance, the Monte Carlo method will be efficient for an acceptance rate neither too high (not exploring enough) nor to low (never moving). The acceptance probability depends on the energy difference. Changing the coordinates of all the particles randomly it is highly probable to generate a huge energy difference (energy is an extensive quantity), causing the acceptance rate to be small. Because of this it is better to move the particles one by one. The particle to be updated should be chosen randomly because, when doing it sequentially the reverse move has not the same probability so the probability will not be symmetrical. A Monte Carlo pass is equivalent to  $N$  trial moves: particles must be chosen randomly. On average each particle has seen at least one attempt to be moved. Considering a possible trial move:

$$\begin{cases} x'_i = x_i + \frac{1}{\sqrt{3}}(\xi_x - 0.5)\Delta \\ y'_i = y_i + \frac{1}{\sqrt{3}}(\xi_y - 0.5)\Delta \\ z'_i = z_i + \frac{1}{\sqrt{3}}(\xi_z - 0.5)\Delta \end{cases}$$

Where  $\xi$  is the random number, and the 0.5 is needed to generate forward and backward moves, centring it around zero so to have the same probability to generate the backward move (when it is less than 0). In one Monte Carlo pass each particle on average has seen one attempt. It is not necessary to recompute all the energy  $U(r')$  in full at each move, because changing only the coordinates of one particle and taking its list of neighbours, the energy for that particle and list of neighbours are updated.  $\Delta$  is the magnitude of the movement. If it is too big the probability to accept the move will be small. If it is too small the phase space is not being explored too well. As a rule of thumb after trying of simulation and keeping track of the acceptance rate, a good value should have an acceptance rate between 30 and 50%.

## 17.3 Simulating ensembles

### 17.3.1 Isothermal-isobaric ensemble

Considering the partition function for the ensemble:

$$\Delta(N, P, T) = \frac{1}{V_0} \int dV e^{-\beta PV} Q(N, V, T) = \frac{1}{V_0} \frac{1}{N! \lambda^{3N}} \int_0^\infty dV e^{-\beta PV} \int_V d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N)}$$

The scheme is the same as in the canonical ensemble with another trial move on the volume volume:  $V' = V + (\xi_V - 0.5)\delta$ . The percentage of volume moves has to be chosen. Volume changes imply scaling of particle coordinates:  $r'_i = \left(\frac{V'}{V}\right)^{\frac{1}{3}} r_i$ . Making the dependance on volume explicit:

$$\Delta(N, P, T) = \frac{1}{V_0} \frac{1}{N! \lambda^{3N}} \int_0^\infty dV V^N e^{-\beta PV} \int_V d\vec{s}_1 \cdots d\vec{s}_N e^{-\beta U(V^{\frac{1}{3}} s_1, \dots, V^{\frac{1}{3}} s_N)}$$

Now the distribution function is obtained and the acceptance probability will be:

$$A(V'|V) = \min\left[1, e^{-\beta P(V' - V)} e^{N \ln \frac{V'}{V}} e^{-\beta(U(r') - U(r))}\right]$$

$\delta$ , the variation on the volume, should be small to accept the move because if inflating the system too much the difference in energy would be huge. This is computational demanding because the coordinates of all the particles are being changed so the force has to be recomputed for all of them, so it is less frequent with higher acceptance.

### 17.3.2 Gran canonical ensemble

In Monte Carlo simulations in the grand canonical ensemble can be performed. Considering the partition function:

$$\mathcal{E}(\mu, V, T) = \sum_{N=0}^{\infty} e^{\beta \mu N} Q(N, V, T) = \sum_{N=0}^{\infty} e^{\beta \mu N} \frac{1}{N! \lambda^{3N}} \int d\vec{r}_1 \cdots d\vec{r}_N e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N)}$$

So a move of the coordinates is the previous scheme with trial moves with particle insertion and particle deletion. Considering particle insertion:

$$A(N+1|N) = \min\left[1, \frac{V}{\lambda^3(N+1)} e^{\beta \mu} e^{-\beta(U(r') - U(r))}\right]$$

Considering particle deletion:

$$A(N-1|N) = \min\left[1, \frac{\lambda^3 V}{V} e^{-\beta\mu} e^{-\beta(U(r') - U(r))}\right]$$

Now it can be simulated at constant chemical potential. This is not so expensive:  $U(r')$  requires only the change in energy due to one particle.

## 17.4 Hybrid Monte Carlo

Hybrid Monte Carlo is a technique in which both Monte Carlo and molecular dynamics are used. Molecular dynamics is used as an engine to generate Monte Carlo moves: This is useful so that it can be tried to use a very big  $\Delta t$  in molecular dynamics, generating new coordinates and momenta and using the metropolis criterion the moves will be accepted or not. In this way the correctness of the move is determined by the acceptance probability.

$$A(r', p' | r, p) = \min\{1, e^{-\beta[\mathcal{H}(r', p') - \mathcal{H}(r, p)]}\} = \min\{1, e^{-\beta\Delta\mathcal{H}}\}$$

If the algorithm in molecular dynamics is symplectic and time-reversible algorithm:

$$T(r', p' | r, p) = T(r, -p | r', -p')$$

One move is quite expensive, so it is better to have a higher acceptance rate between 40 and 70%. In the case of a rejected move  $p$  is re-sampled to obtain a new move as Molecular Dynamics is deterministic. If the integrator is time-reversible the detailed balance holds.

### 17.4.1 Detailed balance

The detailed balance condition or the result is:

$$\int d^N p d^N p' T(r', p' | r, p) A(r', p' | r, p) f(r, p) = \int d^N p d^N p' T(r, p | r', p') A(r, p | r', p') f(r', p')$$

Considering the acceptance rate and the distribution:

$$A(r', p' | r, p) f(r, p) = \frac{1}{Q_N(V, T)} \min\left[1, e^{-\beta(\mathcal{H}(r', p') - \mathcal{H}(r, p))}\right] e^{-\beta\mathcal{H}(r, p)}$$

Multiplying inside the Boltzmann weight:

$$A(r', p' | r, p) f(r, p) = \frac{1}{Q_N(V, T)} \min\left[e^{-\beta\mathcal{H}(r, p)}, e^{-\beta\mathcal{H}(r', p')}\right]$$

Similarly:

$$A(r, p | r', p') f(r', p') = \frac{1}{Q_N(V, T)} \min\left[e^{-\beta\mathcal{H}(r', p')}, e^{-\beta\mathcal{H}(r, p)}\right]$$

Therefore:

$$A(r', p' | r, p) f(r, p) = A(r, p | r', p') f(r', p')$$

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So that:

$$A(r', p' | r, p) f(r, p) = \frac{1}{Q_N(V, T)} \min[1, e^{-\beta(\mathcal{H}(r', p') - \mathcal{H}(r, p))}] e^{-\beta \mathcal{H}(r, p)}$$

Using the property of the symplectic time-reversible algorithm, inverting the velocities the movement is reversed.

$$T(r', p' | r, p) = T(r, -p | r', -p')$$

Substituting this into the second integral:

$$\int d^N p d^N p' T(r', p' | r, p) A(r', p' | r, p) f(r, p) = \int d^N p d^N p' T(r, -p | r', -p') A(r, p | r', p') f(r', p')$$

Performing a change of variables:  $p, p' \rightarrow -p, -p'$ :

$$\int d^N p d^N p' T(r', p' | r, p) A(r', p' | r, p) f(r, p) = \int d^N p d^N p' T(r, p | r', p') A(r, p | r', p') f(r', p')$$

In this way the detailed balance condition is satisfied.

# Chapter 18

## Free energy calculations

### 18.1 Free energy perturbation theory

The need for Free Energy Calculations arises from the fact that most of the time there is a need to compare the results with affinities, or binding energies, which are related to free energy. It's only thanks to free energy differences that some insight on the system can be defined. For example, calculating the binding process of the inhibitor of an enzyme, represented in figure 18.1.



**Figure 18.1:** Binding of an enzyme

Assuming that there are two states  $A$  and  $B$  and let the potential  $U_A$  the interaction-free potential and the potential  $U_B$  the interactions between the enzyme and the inhibitor:

$$U_A(\vec{r}_1, \dots, \vec{r}_n) \wedge U_B(\vec{r}_1, \dots, \vec{r}_N)$$

The potential  $U_B$  would be the one used in the simulations, while in potential  $U_A$  the only way in which the enzyme and the inhibitor could meet is through entropy, so allowing the water molecules to explore all of the configurations. The free energy difference for state  $A$  and state  $B$  is:

$$\Delta A_{AB} = -kT \ln Q_B + kT \ln Q_A = -kT \ln \frac{Z_B}{Z_A}$$

Which can be written through the configurational partition function, the partition function with the integration over the momenta already taken.

The two quantities:

$$Z_A = \int d^N \vec{r} e^{-\beta U_A(\vec{r}_1, \dots, \vec{r}_N)} \quad Z_B = \int d^N \vec{r} e^{-\beta U_B(\vec{r}_1, \dots, \vec{r}_N)}$$

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Are extremely difficult to compute because the sum over all the possible states would have to be computed to get all of the contributions. However, there are a few tricks that can be used. Writing the partition function for state  $B$ :

$$Z_B = \int d^N \vec{r} e^{-\beta U_B(\vec{r}_1, \dots, \vec{r}_N)} = \int d^N \vec{r} e^{-\beta [U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} e^{-\beta U_A(\vec{r}_1, \dots, \vec{r}_N)}$$

In the second equality the Boltzmann factor for state  $A$  is multiplied, so that the following equality can be written:

$$\frac{Z_B}{Z_A} = \frac{1}{Z_A} \int d^N \vec{r} e^{-\beta [U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} e^{-\beta U_A(\vec{r}_1, \dots, \vec{r}_N)}$$

The difference in energy between the states is then:

$$\Delta A_{AB} = -kT \ln \frac{Z_B}{Z_A} \quad \frac{Z_B}{Z_A} = \left\langle e^{-\beta [U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} \right\rangle_A$$

So that the free energy perturbation formula (Zwanzig, 1954) is:

$$\Delta A_{AB} = -kT \ln \left\langle e^{-\beta [U_B(\vec{r}_1, \dots, \vec{r}_N) - U_A(\vec{r}_1, \dots, \vec{r}_N)]} \right\rangle_A$$

Where the exponent is an energy difference, taken from the same force field, by switching off and on the interactions between the two objects of interest defined by the potentials. The difficulty in using this equilibrium is that while sampling the canonical distribution for state  $A$ , there's very little probability of finding an overlap between the two states. In case of poor overlap the same formula as before is used, but applied to each step in this calculation:

$$\Delta A_{AB} = 0kT \sum_{\alpha=1}^{M-1} \ln \left\langle e^{-\beta \Delta U_{\alpha, \alpha+1}(\vec{r}_1, \dots, \vec{r})^N} \right\rangle_\alpha$$

The average has to be calculated for every state  $\alpha$ . This also means that each simulation is independent from each other and they can be run in parallel.

### 18.1.1 Adiabatic switching

Instead of using a discretized version of the free energy perturbation, a switching function to the two potentials can be applied. The resulting potential is a combination of the potential describing state  $A$  and the one describing state  $B$ :

$$U(\vec{r}_1, \dots, \vec{r}_N, \lambda) \equiv f(\lambda)U_A(\vec{r}_1, \dots, \vec{r}_N) + g(\lambda)U_B(\vec{r}_1, \dots, \vec{r}_N)$$

The function  $\lambda$  is defined as:

$$f(0) = 1, \quad f(1) = 0, \quad g(0) = 0, \quad g(1) = 1$$

The partition function from the canonical ensemble now will depend on  $\lambda$ :

$$Q(N, V, T, \lambda) = C_N \int d^N \vec{p} d^N \vec{r} e^{-\beta \left[ \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N, \lambda) \right]}$$

Also the Helmholtz free energy will depend on  $\lambda$ :

$$A(N, V, T, \lambda) = -kT \ln Q(N, V, T, \lambda)$$

Taking the derivative of the Helmholtz free energy with respect to  $\lambda$ :

$$\frac{\partial A}{\partial \lambda} = -\frac{kT}{Q} \frac{\partial Q}{\partial \lambda} = -\frac{kT}{Z} \frac{\partial Z}{\partial \lambda}$$

Since  $\lambda$  only appears in the potential and not on the kinetic energy, the derivative can be written as  $-\frac{kT}{Z} \frac{\partial Z}{\partial \lambda}$ . The derivative can be written in a better way:

$$\frac{kT}{Z} \frac{\partial Z}{\partial \lambda} = \frac{kT}{Z} \frac{\partial}{\partial \lambda} \int d^N \vec{r} e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N, \lambda)} = \frac{kT}{Z} \int d^N \vec{r} \left( -\beta \frac{\partial U}{\partial \lambda} \right) e^{-\beta U(\vec{r}_1, \dots, \vec{r}_N)} = -\left\langle \frac{\partial U}{\partial \lambda} \right\rangle$$

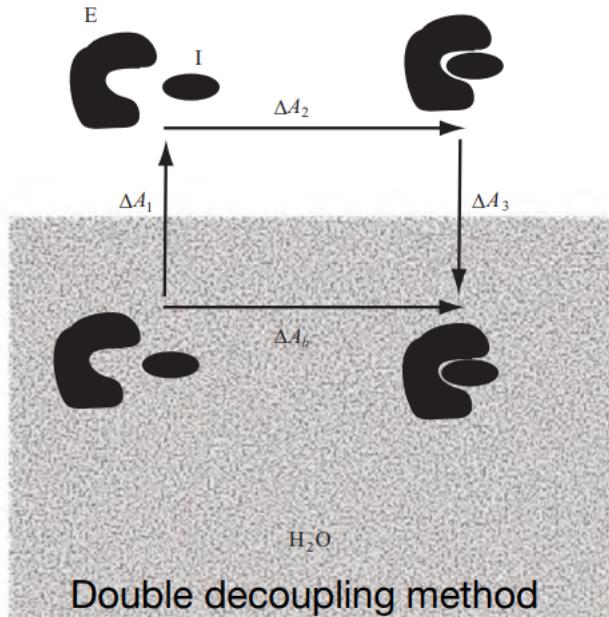
At the end the derivative of  $U$  with respect to  $\lambda$  is obtained. One trivial function that satisfies the first relation would be  $f = 1 - \lambda$  and  $g = \lambda$ . For such a function, the adiabatic switching looks like the Zwanzig's procedure, but this allows to use any function for  $\lambda$ .

### 18.1.2 Thermodynamics integration

The free energy difference between  $A$  and  $B$  can be defined as the formula below, using the result from the adiabatic switching:

$$\Delta A_{AB} = \int_0^1 \left( \frac{\partial A}{\partial \lambda} \right) d\lambda = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda$$

There are many ways in which integrals can be computed, like for example Gaussian Quadrature, which gives the best approximation for a small number of points. In this case, every value of  $\lambda$  would be an independent run of a simulation, so many simulations can be run at the same time and the found points used to compute the integral. There's however another method: thermodynamic integration. The aim of the method is to make the region between  $\lambda = 0$  and  $\lambda = 1$  energetically unfavourable. Indeed, the difference between the energy of the states only depends on the initial and final state and does not depend on the route the system takes to make such a transition.



**Figure 18.2:** Representation of two thermodynamic pathways for the calculation of the binding free energy of an enzyme  $E$  and inhibitor  $I$ . According to the figure  $\Delta A_b = \Delta A_1 + \Delta A_2 + \Delta A_3$

In the real case, some water molecules may affect the dynamics of the system and we cannot arbitrarily remove all the molecules of the solvent.

### 18.1.3 Adiabatic Free Energy Dynamics

There are several other methods to calculate the free energy difference. For the methods seen before, the difference between all of the states in the middle of the two states of interest have to be calculated. However the focus should be on the states  $A$  and  $B$ . In Adiabatic Free Energy Dynamics,  $\lambda$  becomes a variable in the Hamiltonian with associated momenta:

$$\mathcal{H}_\lambda(\vec{r}, \lambda, \vec{p}, p_\lambda) = \frac{p_\lambda^2}{2m_\lambda} + \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N, \lambda)$$

In the partition function, the integration happens also over the values of  $\lambda$ :

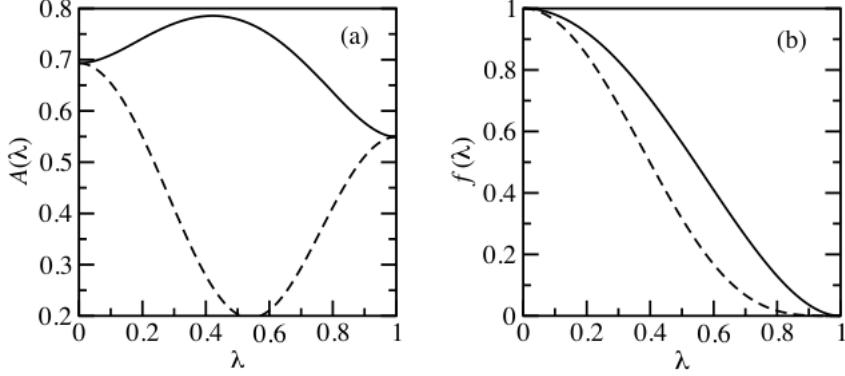
$$Q(N, V, T) = \int d\vec{p}_\lambda \int d^N \vec{p} \int_0^1 d\lambda \int d^N \vec{r} e^{-\beta \mathcal{H}_\lambda(\vec{r}, \lambda, \vec{p}, p_\lambda)}$$

The probability distribution is  $P(\lambda') = \langle \delta(\lambda - \lambda') \rangle$ . Once the probability distribution is obtained the free energy profile can be defined:

$$A(\lambda') = -kT \ln P(\lambda')$$

This free energy profile would be negative only with very high value of  $P(\lambda')$ , like in a deep well in the potential.  $P(1)$  would be the partition function for state  $B$ , and  $P(0)$  would be the partition function for state  $A$ :

$$A(1) = A(0) = -kT \ln \frac{P(1)}{P(0)} = -kT \ln \frac{Q_B}{Q_A} = \Delta A_{AB}$$



**Figure 18.3:** (a) Free energy profiles. The solid line indicates switches  $f(\lambda) = (\lambda^2 - 1)^2$  and  $g(\lambda) = ((\lambda - 1)^2 - 1)^2$ , and the dashed line indicates  $f(\lambda) = (\lambda^2 - 1)^4$  and  $g(\lambda) = ((\lambda - 1)^2 - 1)^4$ . (b) Corresponding switch  $f(\lambda)$ .

In figure 18.3(a) we can see the energy profiles for different functions. The free energy difference is the same for the two methods, but the profile is very different. In the profile that displays a minimum, it is expected to be spending more time away from the configurations of interest, in regions which are not physical. In the second case, which shows a maximum point, the configurations in which more time is spent are the ones closer to  $\lambda = 0$  and  $\lambda = 1$ . If the system has a barrier  $U^\ddagger$ , the probability to cross a barrier  $U^\ddagger$  is proportional to  $e^{-\frac{U^\ddagger}{kT}}$ . In Adiabatic free energy dynamics the idea is to raise the temperature of the  $\lambda$  degree of freedom:

$$\left\langle \frac{p_\lambda^2}{2m_\lambda} \right\rangle = kT_\lambda$$

The term  $\lambda$  is now very hot, more than the actual temperature at which the system has to be simulated. However, this makes  $\lambda$  fluctuate a lot, which is not desirable, so the mass is increased. This is called adiabatic decoupling: it increases  $m_\lambda$  until the  $\lambda$  degree of freedom is decoupled from all other degrees of freedom. Now  $\lambda$  is almost fixed:

$$Z(\lambda, \beta) = \int d^N \vec{r} e^{-\beta U(\vec{r}, \lambda)} \quad \text{Correct if } \lambda \text{ is fixed}$$

The temperature  $\beta$  is the objective temperature at which the system will be simulated. Because of decoupling, it is assumed that in the simulation there's enough time for the system to equilibrate and to explore all its possible conformations in a particular value of  $\lambda$ . Now define the potential of mean force can be defined in  $\lambda : -\frac{1}{\beta} \ln Z(\lambda, \beta)$ . Because of adiabatic decoupling,  $\lambda$  moves quasi-independently from the physical degrees of freedom in the potential of mean force, subject to an effective Hamiltonian:

$$\mathcal{H}_{eff}(\lambda, p_\lambda) = \frac{p_\lambda^2}{2m_\lambda} - \frac{1}{\beta} \ln Z(\lambda, \beta)$$

In this Hamiltonian, the kinetic energy is thermostatted by  $\lambda$  and the potential of mean force acts as a potential. Notice that in this Hamiltonian the potential depends on the temperature, which is usually not the case this is the reason why it is an "effective" Hamiltonian.  $\lambda$  is thermostatted at a temperature  $T_\lambda > T$ , hence the obtained canonical distribution  $adb$  because it is obtained through decoupling)is:

$$P_{adb}(\lambda, p_\lambda, \beta, \beta_\lambda) \propto e^{-\beta_\lambda \mathcal{H}_{eff}(\lambda, p_\lambda)}$$

To obtain the probability distribution for  $\lambda$  there is a need to integrate over  $p_{lambda}$ :

$$\tilde{P}_{adb}(\lambda, \beta, \beta_\lambda) = \int dp_\lambda P_{adb}(\lambda, p_\lambda, \beta, \beta_\lambda) \propto e^{\beta_\lambda \ln \frac{Z(\lambda, \beta)}{\beta}} = [Z(\lambda, \beta)]^{\frac{\beta_\lambda}{\beta}}$$

Taking the free energy profile for the probability distribution  $[Z(\lambda, \beta)]^{\frac{\beta_\lambda}{\beta}}$ :

$$A(\lambda) = -kT_\lambda \ln \tilde{P}_{adb}(\lambda, \beta, \beta_\lambda) = -kT \ln Z(\lambda, \beta) + const$$

Obtaining the free energy profile for the temperature at which the free energy difference has to be computed, and not for the temperature used for the  $\lambda$  degree of freedom.

## 18.2 Jarzynski's equality

The free energy difference is called in this way because there exists the work-free energy inequality:  $W_{AB} \geq \Delta A_{AB}$ . In every thermodynamic transformation, the work is equal to  $\Delta A_{AB}$  only if the transformation is fully reversible. To calculate the work, an estimator for it has to be defined. The objective is to obtain a quantity that is equal to the free energy difference, no matter which transformation is happening.  $W_{AB}$  is a thermodynamic quantity and can be expressed as a thermodynamic average:

$$W_{AB} = \langle \mathcal{W}_{AB}(x) \rangle$$

Considering an initial distribution of microstates  $x_0 \in A$ . They can be all the microstates compatible with the conditions that define state  $A$ , for example state  $A$  has its own temperature, so the microstates will be weighted by the Boltzmann factor (Canonical distribution). The work  $\mathcal{W}_{AB}(x_0)$  is a functional of the path  $\mathcal{W}_{AB}[x_t] = \mathcal{W}_{AB}[x_t(x_0)] = \mathcal{W}_{AB}(x_0)$ . For each microstate, the system will evolve in a different path. The thermodynamic value for the work is then:

$$W_{AB} = \langle \mathcal{W}_{AB}(x_0) \rangle_A = \frac{C_N}{Q_A(N, V, T)} \int dx_0 e^{-\beta \mathcal{H}_A(x_0)} \mathcal{W}_{AB}(x_0) \geq \Delta A_{AB}$$

Jarzynski's theorem states that if instead of calculating the average over all initial conditions  $\langle \mathcal{W}_{AB}(x_0) \rangle_A$  it is computed

$$\langle e^{-\beta \mathcal{W}_{AB}(x_0)} \rangle_A$$

Which looks like a Boltzmann weight for the work estimator, then it is obtained exactly  $e^{-\beta \Delta A_{AB}}$ , whatever the transformation is:

$$\langle e^{-\beta \mathcal{W}_{AB}(x_0)} \rangle_A = \frac{C_N}{Q_A(N, V, T)} \int dx_0 e^{-\beta \mathcal{H}_A(x_0)} e^{-\beta \mathcal{W}_{AB}(x_0)} = e^{-\beta \Delta A_{AB}}$$

This equality also hold for irreversible transformations, that can be used to obtain quantities that describe states at equilibrium. This has huge implication in computational and experimental physics: in practice it is more difficult to design an experiment with a reversible transformation, rather than one with an irreversible one.

### 18.2.1 Jarzynski's equality Proof

There are several proofs for Jarzynski's equality theorem. Considering one define:

$$\Delta A_{AB} = -kT \ln \langle e^{-\beta W_{AB}(x_0)} \rangle_A$$

And the time dependent Hamiltonian:

$$\mathcal{H}(\vec{r}, \vec{p}, t) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}, t)$$

Then:

$$\frac{d\mathcal{H}}{dt} = \nabla_{x_t} \mathcal{H} \cdot \dot{x}_t + \frac{\partial \mathcal{H}}{\partial t}$$

So that:

$$\int_0^\tau \frac{d\mathcal{H}}{dt} dt = \underbrace{\int_0^\tau \nabla_{x_t} \mathcal{H} \cdot \dot{x}_t dt}_{\text{Heat}} + \underbrace{\int_0^\tau \frac{\partial \mathcal{H}}{\partial t} dt}_{\text{Work}}$$

Using Hamiltonian dynamics without dissipative forces, the heat factor is equal to zero. The formula above also represents the first law of thermodynamics. The estimator for the work is  $\mathcal{W}_{t'}(x_0)$ :

$$\mathcal{W}_{t'}(x_0) = \int_0^{t'} \frac{\partial \mathcal{H}(x_t(x_0), t)}{\partial t} dt \quad \mathcal{W}_{AB}(x_0) = \mathcal{W}_\tau(x_0)$$

Notice that if the Hamiltonian is not explicitly time-dependent this would be null because no work is done in the system. If Hamilton's equations are used:

$$\nabla_{x_t} \mathcal{H} \cdot \dot{x}_t = 0 \Rightarrow \frac{\partial \mathcal{H}}{\partial t} = \frac{d\mathcal{H}}{dt}$$

Meaning that the partial time derivative can be substituted with the total time derivative and the integral can be calculated quite easily:

$$W_{t'}(x_0) = \int_0^{t'} \frac{\partial \mathcal{H}(x_t(x_0), t)}{\partial t} dt = \int_0^{t'} \frac{d\mathcal{H}(x_t(x_0), t)}{dt} dt = \mathcal{H}(x_{t'}(x_0), t') - \mathcal{H}(x_0, 0)$$

Then the estimator is:

$$\mathcal{W}_{AB}(x_0) = \mathcal{W}_\tau(x_0) = \mathcal{H}(x_\tau(x_0), \tau) - \mathcal{H}(x_0, 0) \quad \mathcal{H}(x_0, 0) = \mathcal{H}_A(x_0)$$

Hence, taking the average of the quantity  $e^{-\beta \mathcal{W}_{AB}}$  by using the canonical ensemble for state A, then this is equal to the usual normalization constant divided by the partition function for state A, and the integral for all possible initial values for the compatible microstates:

$$\langle e^{-\beta \mathcal{W}_{AB}} \rangle_A = \frac{C_N}{Q_A(N, V, T)} \int dx_0 e^{-\beta \mathcal{H}_A(x_0)} e^{-\beta [\mathcal{H}(x_\tau(x_0), \tau) - \mathcal{H}_A(x_0)]} = \frac{C_N}{Q_A(N, V, T)} \int dx_0 e^{-\beta \mathcal{H}(x_\tau(x_0), \tau)}$$

The coordinates can be changed from  $x_0$  to  $x_\tau(x_0)$ . Then, according to Liouville's theorem  $dx_\tau = dx_0$ :

$$\langle e^{-\beta \mathcal{W}_{AB}} \rangle_A = \frac{C_N}{Q_A(N, V, T)} \int dx_\tau e^{-\beta \mathcal{H}_B(x_\tau)} = \frac{Q_B(N, V, T)}{Q_A(N, V, T)} = e^{-\beta \Delta A_{AB}}$$

$\mathcal{H}$  at time  $\tau$  is exactly the Hamiltonian that described the system when the transformation is completed, so the Hamiltonian that describes the system in state  $B$ . So  $\int dx_\tau e^{-\beta \mathcal{H}_B(x_\tau)}$ , multiplied by the normalization constant, is exactly the partition function for state  $B$ .

### 18.2.2 Application of Jarzynski's Equation

Other versions of this proof are available, with thermostats for instance. There are several applications like pulling experiments, mainly performed on small peptides.



**Figure 18.4:** Pulling experiment on a small peptide (Tuckerman, pg 328)

The idea is to fix an end of the peptide and pull the other end, for example with optical tweezers in an experimental setting (shown in picture 18.4). Computationally, a time-dependent potential

## 18.2. JARZYNSKI'S EQUALITY

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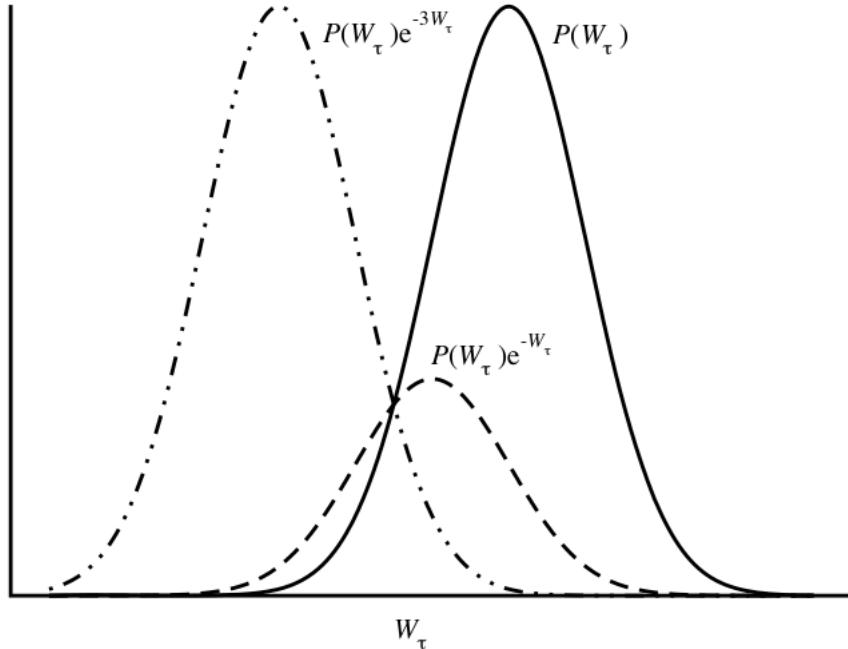
drives the end-to-end distance  $|\vec{r}_1 - \vec{r}_N|$  of a peptide away from its equilibrium value in the folded state:

$$U(\vec{r}_1, \dots, \vec{r}_N, t) = U_o(\vec{r}_1, \dots, \vec{r}_N) + \frac{1}{2}k(|\vec{r}_1 - \vec{r}_N| - r_{eq} - vt)^2$$

There is a potential to describe the system and a harmonic term. The pulling is performed at speed  $v$ . The ensemble of initial conditions with different pulling rates is:

$$\langle e^{-\beta W_{AB}} \rangle_A = e^{-\beta \Delta A_{AB}}$$

The estimate gets better with the number of simulations performed. There are several problems, for example work values have a distribution  $P(W_\tau)$ , as shown in figure 18.5.



**Figure 18.5:** Shift in a Gaussian work distribution as a result of the multiplication by  $\exp(-\beta W_\tau)$  for various values of  $\tau$ .

There is a to be very careful with defining the quantity:

$$\langle e^{-\beta W_\tau} \rangle = \int W_\tau P(W_\tau) e^{-\beta W_\tau}$$

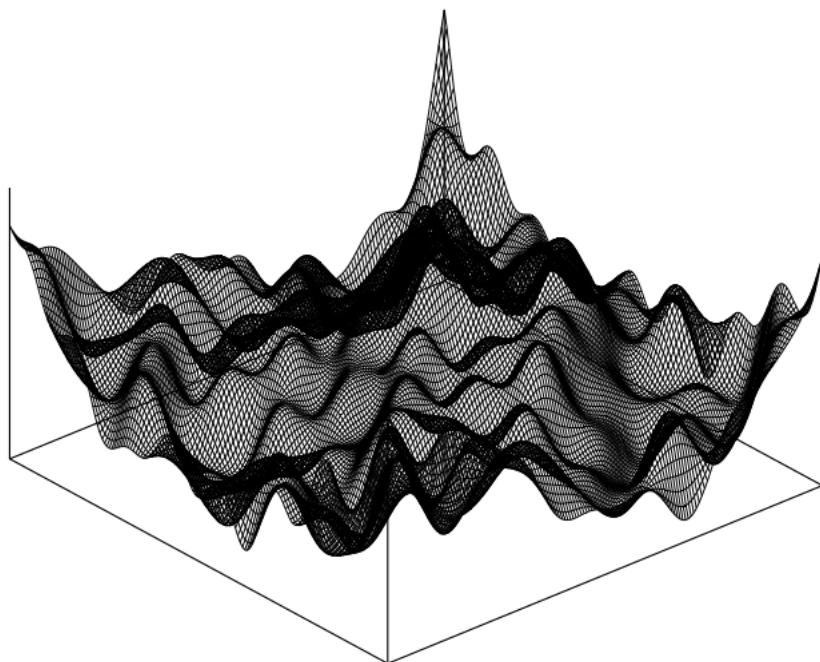
There are however some tricks that can be performed. For example if, and only if,  $P(W_\tau)$  is known to be Gaussian:

$$\ln \langle e^{-\beta W_\tau} \rangle \simeq -\beta \langle W_\tau \rangle + \frac{\beta^2}{2} (\langle W_\tau^2 \rangle - \langle W_\tau \rangle^2)$$

There is no assurance that in the end of the simulation the system reaches equilibrium. Moreover if the force is too strong the system will be forced out of the equilibrium and convergence will never be reached.

### 18.3 Replica exchange Monte Carlo

Replica exchange Monte Carlo is not a free energy calculation method. However, in the case of proteins, the free energy profile is complicated, with a lot of free energy minima and maxima: they have a rough free energy profile, like the one in figure 18.6.

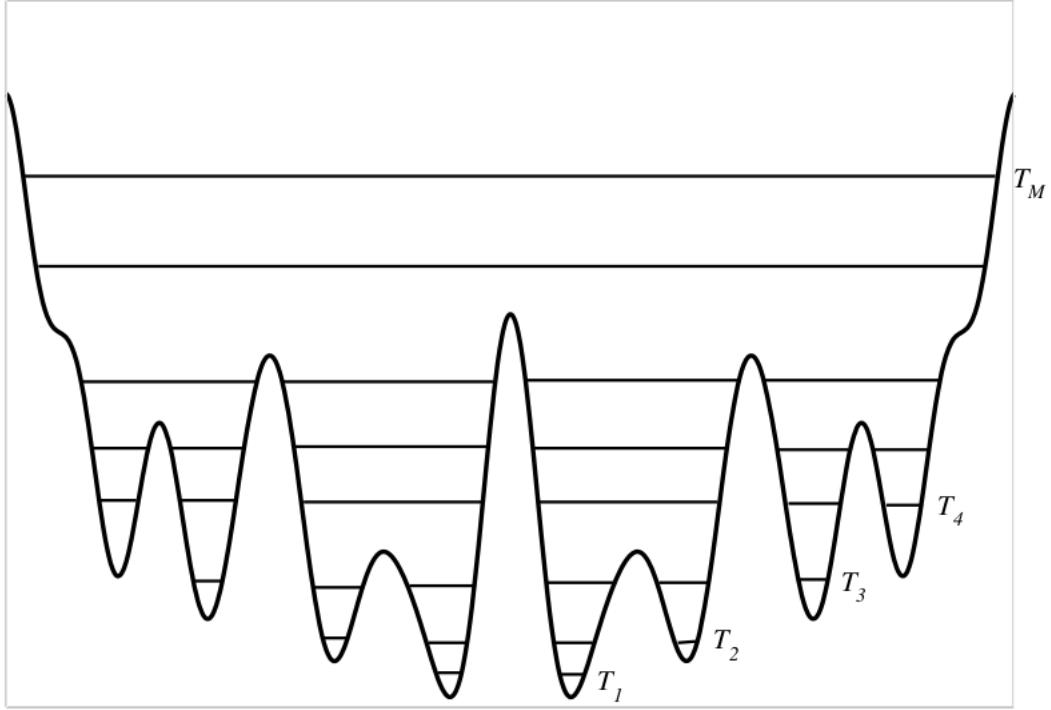


**Figure 18.6:** A two-dimensional rough potential energy surface.

The problem with exploring such complicated potentials is the high probability of getting stuck in a minimum. The way out of this is to build  $M$  independent copies of a system: each replica is assigned a different value of some physical control variable or parameter. The simulations are performed independently from each other, but at a certain time a transition from one replica to another is tried. There are several methods to perform these “jumps”.

#### 18.3.1 Parallel tempering

Consider  $M$  independent copies of a system:  $T_M > T_{M-1} > T_{M-2} > \dots > T_1$ , where  $T_1$  is the temperature of the canonical distribution to be sampled.



**Figure 18.7:** Schematic of the parallel-tempering replica exchange Monte Carlo.

At temperature  $T_M$  everywhere can be sampled, but every now and then there is a need to try to switch coordinates. Considering the configuration of independent replicas  $\vec{r}^{(1)}, \dots, \vec{r}^{(M)}$ , so that the total probability distribution is:

$$F(\vec{r}^{(1)}, \dots, \vec{r}^{(M)}) = \prod_{K=1}^M f_K(\vec{r}^{(K)}) \quad f_K(\vec{r}^{(K)}) = \frac{e^{-\beta_K U(\vec{r}^{(K)})}}{Q(N, V, T_K)}$$

Selecting randomly two neighbouring replicas and attempting replica exchange:

$$(\vec{r}^{(K)}, \vec{r}^{(K+1)}) \rightarrow (\tilde{\vec{r}}^{(K)}, \tilde{\vec{r}}^{(K+1)}) \quad \text{with} \quad \tilde{\vec{r}}^{(K+1)} = \vec{r}^{(K)} \wedge \tilde{\vec{r}}^{(K+1)} = \vec{r}^{(K)}$$

The coordinates are merely exchanged:

$$T(\tilde{\vec{r}}^{(K)}, \tilde{\vec{r}}^{(K+1)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) = T(\vec{r}^{(K)}, \vec{r}^{(K+1)} | \tilde{\vec{r}}^{(K)}, \tilde{\vec{r}}^{(K+1)})$$

The  $T$  is the trial probability for a move that takes the system from coordinates  $\text{vec}r^{(K)}, \vec{r}^{(K+1)}$  to the coordinates  $\tilde{\vec{r}}^{(K)}, \tilde{\vec{r}}^{(K+1)}$ . The acceptance probability is given by the metropolis rule:

$$A(\tilde{\vec{r}}^{(K)}, \tilde{\vec{r}}^{(K+1)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) = A(\vec{r}^{(K+1)}, \vec{r}^{(K)} | \vec{r}^{(K)}, \vec{r}^{(K+1)})$$

The probability for a new state is given by  $f_K(\vec{r}^{(K+1)})f_{K+1} * \vec{r}^{(K)}$ .

$$A(\vec{r}^{(K+1)}, \vec{r}^{(K)} | \vec{r}^{(K)}, \vec{r}^{(K+1)}) = \min \left[ 1, \frac{f_K(\vec{r}^{(K+1)}) f_{K+1} * \vec{r}^{(K)}}{f_K(\vec{r}^{(K)}) f_{K+1}(\vec{r}^{(K+1)})} \right] = \min[1, e^{-\Delta_{K,K+1}}]$$

$$\Delta_{K,K+1} = (\beta_k - \beta_{K+1})[U(\vec{r}^{(K+1)}) - U(\vec{r}^{(K)})]$$

<sup>1</sup>

Some switches of replicas can be done up high, meaning the system will percolate, that will therefore go through barriers in this way.

### 18.3.2 Wang-Landau sampling

The Wang-Landau sampling is a clever way to build the partition function at any possible temperature by simply running a simulation. It is an iterative method. The partition function can be derived by using Boltzmann weights and the densities of states, the number of states at energy  $E$ :

$$Q(N, V, T) = \frac{1}{E_0} \int_0^\infty dE e^{-\beta E} \Omega(N, V, E) \Rightarrow Q(\beta) = \int_0^\infty dE e^{-\beta E} \Omega(E)$$

The partition function becomes an integral over all values of energy of the function given by the Boltzmann factor and the density. The idea is to obtain directly  $\Omega(E)$ , the inverse of the probability of state  $E$ . Assign  $\Omega(E) = 1 \forall E$  (discretized), meaning all energy values are equally probable (which is not really the case). Then a trial move is performed:  $E_1 \rightarrow E_2$  and it is accepted by the metropolis rule:

$$A(E_2 | E_1) = \min \left[ 1, \frac{\Omega(E_1)}{\Omega(E_2)} \right]$$

After each move:  $\Omega(E) \rightarrow \Omega(E)f$   $f > 1$ . Visiting one particular value of the energy, the density of states for that value will increase. Thus meaning that the probability of visiting again that state will decrease. The histogram  $h(E)$  of visited states can be built, considering that it will become always more flat with time. Once  $h(E)$  is flat enough a new value  $f_{new} = \sqrt{f_{old}}$  is switched and the algorithms continue until convergence. There is no detailed balance due to  $f$ .

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<sup>1</sup>In the Tuckerman these two terms have opposite sign.

# Chapter 19

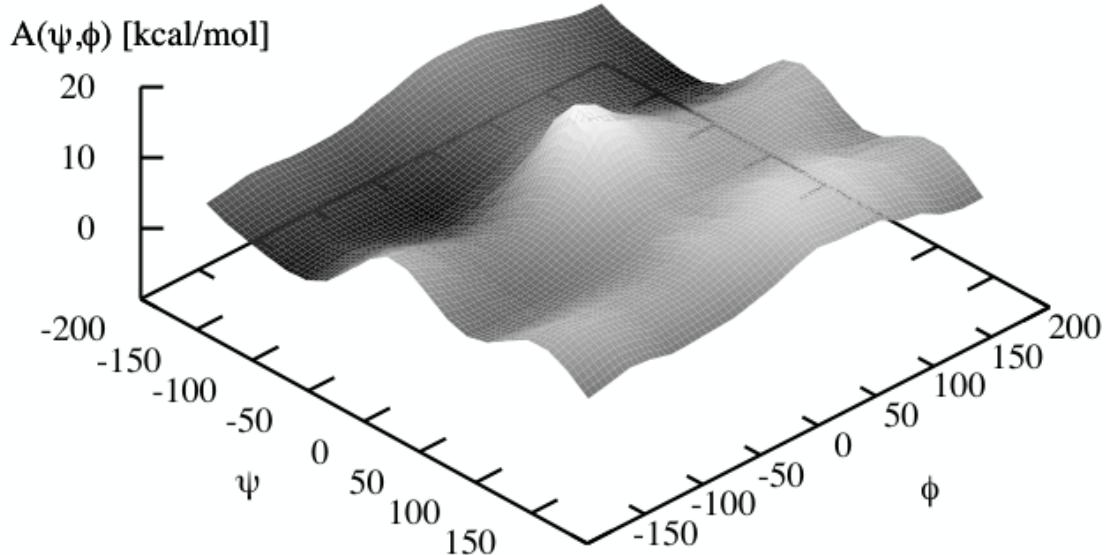
## Rare events

### 19.1 Introduction

Many observed transitions observed in biology could be considered rare events in the time scales of all atoms simulations. This is because many processes require time-scales of seconds.

#### 19.1.1 Rough free energy surfaces

The problem is that we have to deal with rough free energy surface with lots of local minima. Even in the case of 19.1 there are 4 local minima. Moreover the number of local minima which is exponential for proteins with respect to their size.



**Figure 19.1:** Rough free energy surfaces

Because of this the problem of studying this transition is difficult.

### 19.1.2 Variables in rare events

Describing the free-energy surface is difficult because the energies surfaces is complex. The variables necessary to study these events can be called:

- Reaction coordinates: how to describe a transition between states.
- Order parameters: they describe the transition between one energy minimum from another.
- COLVARs: collective variables.

## 19.2 Reaction coordinates

There might be several reaction coordinates and the first problem is how to choose them. This is system dependent. For example considering dissociation reactions  $AB \rightarrow A + B$  a good reaction coordinate could be the distance between the centre of mass of the atoms  $r = |\vec{r}_B - \vec{r}_A|$ . Considering a protein, describing the transition from folded to unfolded one global measure is the radius of gyration:

$$R_G = \sqrt{\frac{1}{N_b} \sum_{i=1}^{N_b} \left( \vec{r}_i - \frac{1}{N_b} \sum_{j=1}^{N_b} \vec{r}_j \right)^2}$$

This gives a measure of how compact a protein is. This is a good measure of foldedness in case of globular proteins, but this is not true for all proteins. Another example is considering the number of hydrogen bonds between two elements of length  $d_0$  between  $n_O$  oxygens and  $n_H$  hydrogens a good measure is:

$$N_H = \sum_{i=1}^{n_O} \sum_{j=1}^{n_H} \frac{1 - \left[ \frac{\vec{r}_i - \vec{r}_j}{d_0} \right]^6}{1 - \left[ \frac{\vec{r}_i - \vec{r}_j}{d_0} \right]^{12}}$$

The objective is to obtain a single coordinate from the Cartesian coordinates as to understand the process that is happening. After having obtained the reaction coordinates the aim is to obtain the probability distribution function of a subset of  $n$  reaction coordinates of interest  $q_\alpha = f_\alpha(\vec{r}_1, \dots, \vec{r}_N)$  with  $\alpha = 1, \dots, n$  which will not be in general factorized and can be written as:

$$P(s_1, \dots, s_n) = \frac{C_N}{Q(N, V, T)} \int d^N \vec{p} d^B \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \prod_{\alpha=1}^n \delta(f_\alpha(\vec{r}_1, \dots, \vec{r}_N) - s_\alpha)$$

For the canonical ensemble. Once the probability is obtained the free energy hypersurface can be obtained directly:

$$A(s_1, \dots, s_n) = -fT \ln P(s_1, \dots, s_n)$$

If the right reaction coordinates are not chosen then free energy profiles might not be describing the system correctly. To judge the quality of the chosen reaction coordinates is the committor distribution, an extremely expensive process but that can be worthwhile.

**19.2.1 Blue moon ensemble**

One method to obtain rare events is the blue moon ensemble. When choosing a reaction coordinate the objective is to force a transition between states. The idea behind the blue moon ensemble is that considering for semplicity a single reaction coordinate  $q_1 = f_1(\vec{r}_1, \dots, \vec{r}_N)$ , its probability distribution is:

$$P(s) = \frac{C_N}{Q(N, V, T)} \int d^N \vec{p} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \delta(f_1(\vec{r}_1, \dots, \vec{r}_N) - s)$$

And the free energy profile:

$$A(s) = -kT \ln P(s)$$

A holonomic constraint is introduced  $\sigma(\vec{r}_1, \dots, \vec{r}_N) = f_1(\vec{r}_1, \dots, \vec{r}_N) - s$ . Then the sampling happens at that given value. So that the reaction coordinates assume a given set of values. Use this constraint to drive the reaction coordinate from an initial value  $s^{(i)}$  to a final value  $s^{(f)}$ . The blue moon ensemble yields  $\frac{dA}{ds} = -\frac{kT}{P(s)} \frac{dP}{ds}$ . From this quantity then the free energy at any value of reaction coordinate  $q$  can be reconstructed knowing the initial value. The free energy difference can be also computed:

$$A(q) = A(s^{(i)}) + \int_{s^{(i)}}^q \frac{dA}{ds} ds \quad \Delta A = \int_{s^{(i)}}^{s^{(f)}} \frac{dA}{ds} ds$$

The probability distribution for the reaction coordinate  $s$  is given by:

$$P(s) = \frac{C_N}{Q(N, V, T)} \int d^N \vec{p} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \delta(f_1(\vec{r}_1, \dots, \vec{r}_N) - s) = \langle \delta(f_1(\vec{r}_1, \dots, \vec{r}_N) - s) \rangle$$

The quantity obtained from the simulation:

$$\frac{1}{P(s)} \frac{dP}{ds} = \frac{C_N}{Q(N, V, T)} \frac{\int d^N \vec{p} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \frac{\partial \delta(f_1(\vec{r}) - s)}{\partial s}}{\langle \delta(f_1(\vec{r}) - s) \rangle}$$

Introduce  $3N$  generalized coordinates  $q_\alpha = f_\alpha(\vec{r}_1, \dots, \vec{r}_N)$  so that  $q_1$  is the reaction coordinate of interest and their conjugate momenta  $p_\alpha$ , The transformation is canonical, hence the Jacobian is one:  $d^N \vec{p} d^N \vec{r} = d^{3N} p d^{3N} q$ , so the quantity is:

$$\frac{1}{P(s)} \frac{dP}{ds} = \frac{C_N}{Q(N, V, T)} \frac{\int d^{3N} p d^{3N} q e^{-\beta \tilde{\mathcal{H}}(q, p)} \frac{\partial \delta(q_1 - s)}{\partial s}}{\langle \delta(q - s) \rangle}$$

However  $\frac{\partial}{\partial s} \delta(q_1 - s) = -\frac{\partial}{\partial q_1} \delta(q_1 - s)$  substituting in the integral and integrating by parts:

$$\begin{aligned} \frac{1}{P(s)} \frac{dP}{ds} &= -\frac{\beta C_N}{Q(N, V, T)} \frac{\int d^{3N} p d^{3N} q \frac{\partial \tilde{\mathcal{H}}(q, p)}{\partial q_1} e^{-\beta \tilde{\mathcal{H}}(q, p)} \delta(q_1 - s)}{\langle \delta(q_1 - s) \rangle} = \\ &= -\frac{\beta}{\langle \delta(q_1 - s) \rangle} \left\langle \frac{\partial \tilde{\mathcal{H}}}{\partial q_1} \delta(q_1 - s) \right\rangle \stackrel{\text{cond}}{=} -\beta \left\langle \frac{\partial \tilde{\mathcal{H}}}{\partial q_1} \right\rangle \end{aligned}$$

In this way everything can be expressed in term of the conditional average subject to the condition that  $q_1 = s$ . The simulation is run and the average value of the quantity is taken thanks to the

holonomic constraint. This is measured with different initial values so that in the end the free energy as a function of the reaction coordinate:

$$A(q) = A(s^{(i)}) + \int_{s^{(i)}}^q \left\langle \frac{\partial \tilde{\mathcal{H}}}{\partial q_1} \right\rangle_s^{cond} ds$$

### 19.2.2 Umbrella sampling

Umbrella sampling substitutes the rigid holonomic constraints of blue moon sampling with a more flexible harmonic restraint. An extra potential or bias potential is introduced such that the reaction coordinates are constraint to be close to the value  $s_k$ :

$$W_k(f_1(\vec{r}_1, \dots, \vec{r}_N), s_k) = \frac{1}{k}[f_1(\vec{r}_1, \dots, \vec{r}_N) - s_k]^2$$

The probability distribution for  $s$  is biased to be close to  $s_k$ . The biased probability distributions obtained will be:

$$P(s, s^{(k)}), k = 1, \dots, n, \quad s^{(1)} = s^{(i)}, s^{(n)} = s^{(f)}$$

From this a collection of biased probability distribution, one for each value of  $k$  is obtained. This probability distribution should be used to reconstruct the real one. To do so the weighted histogram analysis method is used.

### 19.2.3 WHAM

The weighted histogram analysis method is used to obtain from the collection of biased probability distribution obtained from umbrella sampling the real one. For each of the  $k$  biased probability distributions generated by umbrella sampling:

$$\tilde{P}(q, s^{(k)}) = e^{\beta A_k} \int d^N \vec{r} e^{-\beta U(\vec{r})} e^{-\beta W_k(f_1(\vec{r}), s^{(k)})} \delta(f_1(\vec{r}) - q)$$

Where  $e^{\beta A_k}$  is the normalization factor and  $A_k$  is the free energy associated with the biasing potential apart from constants so that:

$$e^{-\beta A_k} = \int d^N \vec{r} e^{-\beta U(\vec{r})} e^{-\beta W_k(f_1(\vec{r}), s^{(k)})} = e^{-\beta A_0} \left\langle e^{-\beta W_k(f_1(\vec{r}), s^{(k)})} \right\rangle$$

The average is taken with respect to the unbiased potential:

$$e^{-\beta A_0} = \int d^N \vec{r} e^{-\beta U(\vec{r})}$$

To unbiase the probability distributions the Boltzmann factor is introduced:

$$P_k(q) = e^{-\beta(A_k - A_0)\beta W_k(q, s^{(k)})} \tilde{P}(q, s^{(k)})$$

A collection of  $n$  unbiased probability distribution is obtained that describe a single region of the possible values of the reaction coordinates. To reconstruct the full probability distribution the objective is to combine them into a single one. To do that these distribution are combined with weights  $C_k$  such that  $\sum_{k=1}^n C_k = 1$ , so the total probability distribution is:

$$P(q) = \sum_{k=1}^n C_k(q) P_k(q) = \sum_{k=1}^n C_k(q) e^{-\beta(A_k - A_0)} e^{\beta W_k(q, s^{(k)})} \tilde{P}(q, s^{(k)})$$

The values of  $C_k$  have to be obtained using a criterion, so the statistical error in the distribution generated by the WHAM procedure is minimized. To obtain the biased probability distribution let  $\tilde{H}_k(q)$  be the biased histogram obtained from each molecular dynamics or Monte Carlo simulation. The system will be in that position from a given number of frame. The estimate for the biased distributions is:

$$\tilde{P}(q, s^{(k)}) \approx \frac{1}{n_k \Delta q} \tilde{H}_k(q)$$

Where:

- $n_k$  is the number of frames in an umbrella window.
- $\Delta q$  takes into account that the possible value of the reaction coordinate are in bins.

The statistical error for the umbrella window is

$$\tilde{\sigma}_k^2 = \frac{\epsilon_k(q) \tilde{H}_k(q)}{n_k \Delta q}$$

Where  $\epsilon_k$  is a given factor. This is because since there are a number of occurrences of these stochastic process the number of occurrences is a Poisson process. The error in  $P_k(q)$  (the unbiased probability distribution) is given by applying the square of the unbiasing factor:

$$\sigma_k^2 = e^{-2\beta(A_k - A_0)} e^{2\beta W_k(q, s^{(k)})} \tilde{\sigma}_k^2$$

The total error will be:

$$\sigma^2 = \sum_{k=1}^n C_k^2(q) \sigma_k^2$$

To minimize the total statistical error considering the condition that the sum over the  $C_k$  is equal to 1. To do so Lagrange multipliers are used. Then the function to minimize is:

$$\Sigma^2 = \sum_{k=1}^n C_k^2(q) e^{-2\beta(A_k - A_0)} e^{w\beta W_k(q, s^{(k)})} \frac{\epsilon_k(q) \tilde{H}_k(q)}{n_k \Delta q} - \lambda \left( \sum_{k=1}^n C_k(q) - 1 \right)$$

The unknowns are  $C_k$  and  $\lambda$ , so now to minimize:

$$\frac{\partial \Sigma^2}{\partial C_k(q)} = 0 \Rightarrow C_k(q) = \frac{\lambda n_k \Delta q}{2\epsilon_k(q) \tilde{H}_k(q) e^{-2\beta(A_k - A_0)} e^{2\beta W_k(q, s^{(k)})}}$$

All the  $C_k$  depends on  $\lambda$ .  $\lambda$  is unknown and to determine it the normalization condition is used:

$$\lambda = \frac{1}{\sum_{k=1}^n \frac{n_k \Delta q}{2\epsilon_k(q) \tilde{H}_k(q) e^{-2\beta(A_k - A_0)} e^{2\beta W_k(q, s^{(k)})}}}$$

The solution for  $C_k$  is obtained:

$$C_k(q) = \frac{n_k l [\epsilon_k(q) \tilde{H}_k(q) e^{-2\beta(A_k - A_0)} e^{2\beta W_k(q, s^{(k)})}]}{\sum_{j=1}^n n_j l [\epsilon_j(q) \tilde{H}_j(q) e^{-2\beta(A_j - A_0)} e^{2\beta W_k(q, s^{(j)})}]}$$

Considering the following simplifying assumption that they need to be checked in the system:

- $\epsilon_k(q)$  is the same for all umbrella windows.  
This does not imply that all the umbrella windows are of the same size, but that the quality of sampling is the same for all of them.
- $\tilde{H}_k(q) \propto e^{\beta(A_k - A_0)} e^{-\beta W_k(q, s^{(k)})} P(q)$ . The histogram of the probability distribution is proportional to the real distribution biased by the two factors.

Assuming these  $C_k$  can be simplified into:

$$C_k(q) = \frac{n_k e^{\beta A_k} e^{-\beta W_k(q, s^{(k)})}}{\sum_{j=1}^n n_j e^{\beta A_j} e^{-\beta W_j(q, s^{(j)})}}$$

Using this formula the full probability distribution will be:

$$P(q) = \sum_{k=1}^n C_k(q) P_k(q) = \frac{\sum_{k=1}^n n_k \tilde{P}(q, s^{(k)})}{\sum_{k=1}^n n_k e^{\beta(A_k - A_0)} e^{-\beta W_k(q, s^{(k)})}}$$

However:

$$e^{\beta(A_k - A_0)} = \int dq P(q) e^{-\beta W_k(q, s^{(k)})}$$

These two equations are self consistent because one depends on the other, so the algorithm starts with a guess for  $A_k$  and iterates until convergence.

#### 19.2.4 Wang-Landau sampling

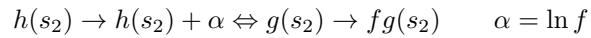
In the Wang-Landau approach the density of states were the objective with a Monte Carlo simulation. After devising some moves they where accepted with probability:

$$A(\vec{r}_2 | \vec{r}_1) = \min \left[ 1, \frac{\Omega(E_1)}{\Omega(E_2)} \right]$$

With scaling factor  $f$  to scale the density of state each time one state was visited. The same can be extended to reaction coordinates: generate a function  $g(s)$  that approaches the probability distribution  $P(s)$ . Start  $g(s) = 1$  and  $h(s) = \ln g(s) = 0$  everywhere, then the same procedure is performed: a move is generated and accepted with:

$$A(\vec{r}_2 | \vec{r}_1) = \min \left[ 1, \frac{e^{-\beta U(\vec{r}_2)}}{e^{-\beta U(\vec{r}_1)}} \frac{g(s_1)}{g(s_2)} \right] = \min \left[ 1, \frac{e^{-\beta U(\vec{r}_2)}}{e^{-\beta U(\vec{r}_1)}} \frac{e^{-h(s_1)}}{e^{-h(s_2)}} \right]$$

Every time a new value of  $s$  is visited  $h$  is updated by adding a factor  $\alpha$ :



Iterate until the histogram  $H(s)$  becomes flat, then reduce  $f$  and repeat until convergence. When convergence is reached  $P$  is obtained. Its efficiency and accuracy depends on the choice of reaction coordinates.

# Chapter 20

## Advanced methods

### 20.1 Adiabatic dynamics

In the free energy adiabatic dynamics the idea is to obtain the free energy hypersurface as a function of some reaction coordinates. Let's assume the reaction coordinates  $n < 3N$  reaction coordinates with generalized coordinates  $q_\alpha$ : the interest is in the free energy hypersurface  $A(q_1, \dots, q_n)$ . The partition function is defined, in the case of the canonical ensemble, as:

$$Q(N, V, T) = C_N \int d^N \vec{p} d^N \vec{r} e^{-\beta \left[ \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + U(\vec{r}_1, \dots, \vec{r}_N) \right]}$$

Transformation to generalized coordinates  $q_\alpha = f_\alpha(\vec{r}_1, \dots, \vec{r}_n)$  only for the configurational part, leaving momenta unchanged:

$$Q(N, V, T) = C_n \int d^N \vec{p} d^{3N} q e^{-\beta \left[ \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + \tilde{V}(q_1, \dots, q_{3N}, \beta) \right]}$$

Where, considering the Jacobian of the transformation:

$$\tilde{V}(q_1, \dots, q_{3N}, \beta) = \tilde{U}(q_1, \dots, q_{3N}) - kT \ln J(q_1, \dots, q_{3N})$$

This is a function of all of the  $3N$  coordinates. This term looks like a potential in term with the generalized coordinates and the Jacobian. In this term the potential is temperature dependent. This is because  $\tilde{V}$  has  $\beta$  as a temperature parameter. Using the Hamiltonian in the transformation during the simulation the canonical distribution is being sampled. So consider the temperature dependent potential included into this fake Hamiltonian:

$$\tilde{\mathcal{H}}(q, \vec{p}, \beta) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + \tilde{V}(q_1, \dots, q_{3N}, \beta) = \sum_{i=1}^N \frac{\vec{p}_i^2}{2m_i} + \tilde{U}(q_1, \dots, q_{3N}) - kT \ln J(q_1, \dots, q_{3N})$$

To conjugate the momenta to the velocities they need to be renamed. This is not the original Hamiltonian but can be used as a Hamiltonian. Renaming the momenta:

$$\tilde{H}(q, p, \beta) = \sum_{\alpha=1}^{3N} \frac{p_{\alpha}^2}{2m'_{\alpha}} + \tilde{V}(q_1, \dots, q_{3N}, \beta)$$

Where  $m'_{\alpha}$  is a fictitious mass defined during the simulation. As in adiabatic free energy dynamics the first  $n$  variables are thermostatted as a temperature  $T_q \gg T$  with their masses increased so to adiabatically decouple them from the others. So the system should have enough time to equilibrate for each variable.

### 20.1.1 TAMD

The previous idea can be implemented as TAMD (temperature accelerated molecular dynamics). Using the Hamiltonian with the renamed momenta:

$$\tilde{H}(q, p, \beta) = \sum_{\alpha=1}^{3N} \frac{p_{\alpha}^2}{2m'_{\alpha}} + \tilde{V}(q_1, \dots, q_{3N}, \beta)$$

So that the differential equation to update positions:

$$\dot{q}_{\alpha} = \frac{p_{\alpha}}{m'_{\alpha}}$$

And momenta, where they are coupled with the thermostat variables needed to couple them to the Nosè-Hoover chain:

$$\dot{p}_{\alpha} = -\frac{\partial \tilde{V}}{\partial q_{\alpha}} - \frac{p_{\eta_1}}{Q_1} p_{\alpha} \quad \alpha = 1, \dots, n \quad \dot{p}_{\alpha} = -\frac{\partial \tilde{V}}{\partial q_{\alpha}} - \frac{p_{\eta_e}}{Q_2} p_{\alpha} \quad \alpha = n_1, \dots, 3N$$

Then the variable for the thermostats:

$$\dot{\eta}_j = \frac{p_{\eta_j}}{Q_j}$$

Then the thermostat variable for the first  $n$  generalized coordinates with  $T_q$  higher than  $T$ , while the others are coupled for the temperature  $T$ .

$$\dot{p}_{\eta_1} = \sum_{\alpha=1}^n \frac{p_{\alpha}^2}{2m'_{\alpha}} - nkT_q \quad \dot{p}_{\epsilon_2} = \sum_{\alpha=n+1}^{3N} \frac{p_{\alpha}^2}{2m'_{\alpha}} - (3N-n)kT$$

It is possible to show that  $A(q_1, \dots, q_n) = -kT_q \ln P_{adb}(q_1, \dots, q_n) + const.$  So the free energy profile obtained by reconstructing the probability distribution for these  $n$  generalized coordinate is equal to the one obtained for the energy profile at temperature  $T$  in which the interest is in. An example can be seen in 20.1, where it can be seen how the free energy profile using the bare potential is difficult to reconstruct the true analytical free energy. The others refers to TAMD and it can be seen how the mass associated to the reaction coordinate is much more the free energy profile is reconstructed well. This is because only in this case the system has enough time to explore the space at that value.

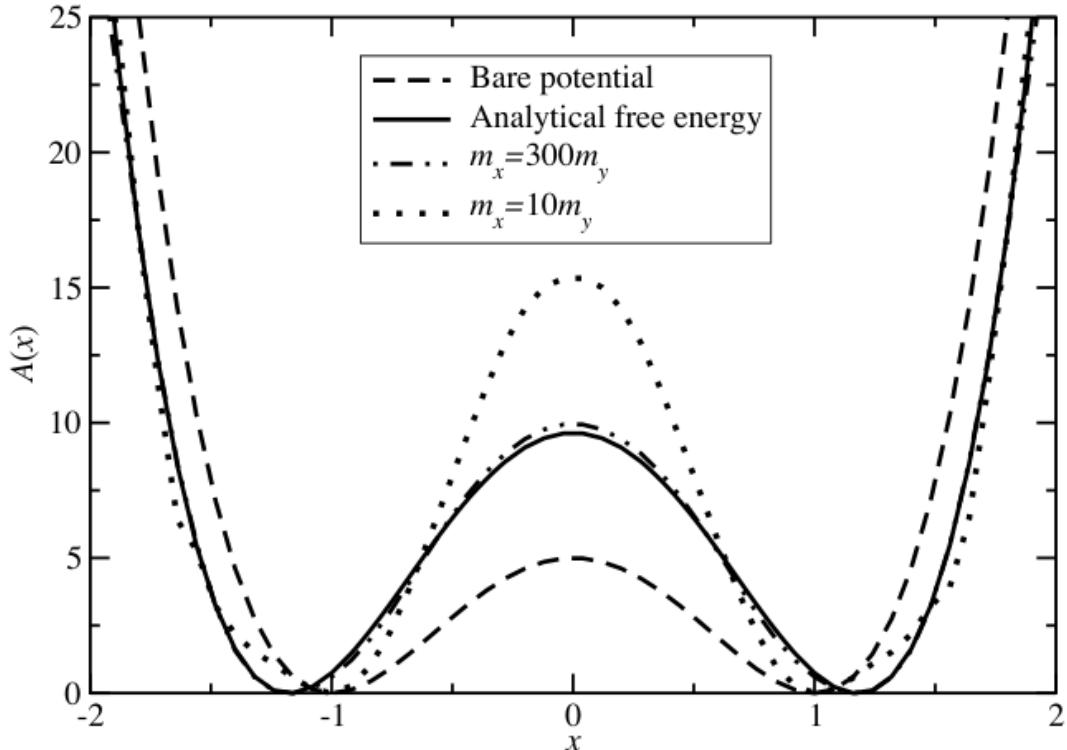


Figure 20.1: TAMD

## 20.2 Metadynamics

The objective is to reconstruct a probability for a set of reaction coordinates  $s_1, \dots, s_n$  and the objective is to obtain the ensemble average for a function of reaction coordinates:

$$P(s_1, \dots, s_n) = \left\langle \prod_{\alpha=1}^n \delta(f_\alpha(\vec{r}_1, \dots, \vec{r}_N) - s_\alpha) \right\rangle$$

Replacing phase space average with a time average over a trajectory. This can be done only if the trajectory is ergodic:

$$P(s_1, \dots, s_n) = \lim_{T \rightarrow \infty} \frac{1}{T} \int_0^T dt \prod_{\alpha=1}^n \delta(f_\alpha(\vec{r}_1, \dots, \vec{r}_N) - s_\alpha)$$

Where  $T$  is time. However considering the following property of the delta function:

$$\delta(x - \alpha) = \lim_{\sigma \rightarrow 0} \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\alpha)^2}{2\sigma^2}}$$

So adding this property to the probability distribution:

$$P(s_1, \dots, s_n) = \lim_{\tau \rightarrow \infty} \lim_{\Delta s \rightarrow 0} \frac{1}{\tau} \frac{1}{\sqrt{2\pi\Delta s^2}} \int_0^\tau dt \prod_{\alpha=1}^n e^{-\frac{(s_\alpha - f_\alpha(\vec{r}_1(t), \dots, \vec{r}_N(t)))^2}{2\Delta s^2}}$$

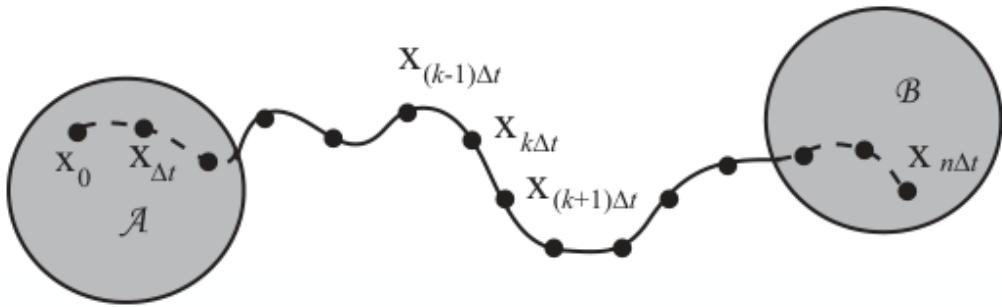
This looks like adding to the probability a factor similar to the Boltzmann factor and related to it because it looks like a Gaussian. It looks like a Gaussian is added every time a value for a reaction coordinate  $\alpha$  is visited so that the system will be forced to go somewhere else. Building up these Gaussian potential they can be used as a bias potential:

$$U_G(\vec{r}_1, \dots, \vec{r}_N, t) = W \sum_{t-\tau_G, 2\tau_G, \dots} e^{-\sum_{\alpha=1}^n \frac{(f_\alpha(\vec{r}) - f_\alpha(\vec{r}_G(t)))^2}{2\Delta s^2}}$$

This Gaussian potential is added at every  $\tau_G$ , the conformation already visited will be less favoured and the system will go somewhere else. Taking all the Gaussian added this amount to summing over all the Gaussian it is the negative of the free-energy profile, so keeping track of the added Gaussians, their sum is minus the free energy profile. This is done only when the free diffusion of the system is observed, meaning that the algorithm has reached convergence. Judging convergence is not easy for metadynamics. In principle it is continued until free diffusion is observed for a number of times. Another issue is that every time energy is being added to the system, which might cause problem. For example in a membrane it would cause membrane disruption.

## 20.3 Transition path ensemble

In many situations the interest is in reconstructing a path for a transition going from state  $A$  to state  $B$ . Assume that by some method a pathway to go from state  $A$  to state  $B$  is obtained.



**Figure 20.2:** Transition path ensemble

To obtain the most probable path the transition path ensemble has to be introduced. In order to reconstruct one point of the pathway in molecular dynamics Trotter factorization is applied:

$$x_{(k+1)\Delta t} = e^{iL_2 \frac{\Delta t}{2}} e^{iL_1 \Delta t} e^{iL_2 \frac{\Delta t}{2}} x_{k\Delta t} \equiv \phi_{\Delta t}(x_{k\Delta t})$$

Considering in term of Monte Carlo moves instead:

$$T(x_{(k+1)\Delta t} | x_{k\Delta t}) = \delta(x_{(k+1)\Delta t} - \phi_{\Delta t}(x_{k\Delta t}))$$

### 20.3. TRANSITION PATH ENSEMBLE

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Assigning a weight to a single trajectory:

$$\mathcal{P}[X(\mathcal{T})] = f(x_0) \prod_{k=0}^{n-1} T(x_{(k+1)\Delta t} | x_{k\Delta t}) \quad f(x_0) = \frac{e^{-\beta \mathcal{H}(x_0)}}{Q(N, V, T)}$$

This probability is given by starting from starting in  $x_0$ , which depends on the canonical distribution. So  $\mathcal{P}$  is the probability associated with a single trajectory.

$$\mathcal{P}[X(\mathcal{T})] = f(x_0) \prod_{k=0}^{n-1} T(x_{(k+1)\Delta t} | x_{k\Delta t})$$

Defining the probability of a path  $X$  going from  $A$  to  $B$  multiplies the probability associated for the path  $X$  multiplied by  $h_A$  and  $h_B$ , meaning that the starting point should be in the basin of state  $A$  and the final point in the basin of state  $B$ , they are either 0 or 1.

$$\mathcal{P}_{AB}[X(\mathcal{T})] = \frac{1}{\mathcal{F}_{AB}(\mathcal{T})} h_A(x_0) \mathcal{P}[X(\mathcal{T})] h_B(x_{n\Delta t})$$

And  $\mathcal{F}_{AB}$  is a normalization constant.

$$\mathcal{F}_{AB}(\mathcal{T}) = \int dx_0 \cdots dx_{n\Delta t} h_A(x_0) \mathcal{P}[X(\mathcal{T})] h_B(x_{n\Delta t})$$

For deterministic molecular dynamics trajectories:

$$\begin{aligned} \mathcal{F}_{AB}(\mathcal{T}) &= \int dx_0 \cdots dx_{n\Delta t} h_A(x_0) f(x_0) \prod_{k=1}^{n-1} \delta(x_{(k+1)\Delta t} - \phi_{\Delta t}(x_{k\Delta t})) h_B(x_{n\Delta t}) = \\ &= \int dx_0 h_A(x_0) f(x_0) h_B(x_{n\Delta t}(x_0)) \end{aligned}$$

#### 20.3.1 Transition path sampling

Following the same method in Monte Carlo methods and Metropolis algorithm, introduce  $\mathcal{R}_{AB}[X(\mathcal{T})|Y(\mathcal{T})]$ , the conditional probability to generate a trajectory  $X(\mathcal{T})$  starting from  $Y(\mathcal{T})$ . Considering the detailed balance condition:

$$\mathcal{R}_{AB}[X(\mathcal{T})|Y(\mathcal{T})] \mathcal{P}_{AB}[Y(\mathcal{T})] = \mathcal{R}_{AB}[Y(\mathcal{T})|X(\mathcal{T})] \mathcal{P}_{AB}[X(\mathcal{T})]$$

Splitting the conditional probabilities in two: one of generating the move and the other the probability to accept the move.

$$\mathcal{R}_{AB}[X(\mathcal{T})|Y(\mathcal{T})] = \Lambda_{AB}[X(\mathcal{T})|Y(\mathcal{T})] \mathcal{T}_{AB}[X(\mathcal{T})|Y(\mathcal{T})]$$

So now the acceptance probability can be written as:

$$\Lambda_{AB}[X(\mathcal{T})|Y(\mathcal{T})] = \min \left[ 1, \frac{\mathcal{T}_{AB}[Y(\mathcal{T})|X(\mathcal{T})] \mathcal{P}_{AB}[X(\mathcal{T})]}{\mathcal{T}_{AB}[X(\mathcal{T})|Y(\mathcal{T})] \mathcal{P}_{AB}[Y(\mathcal{T})]} \right]$$

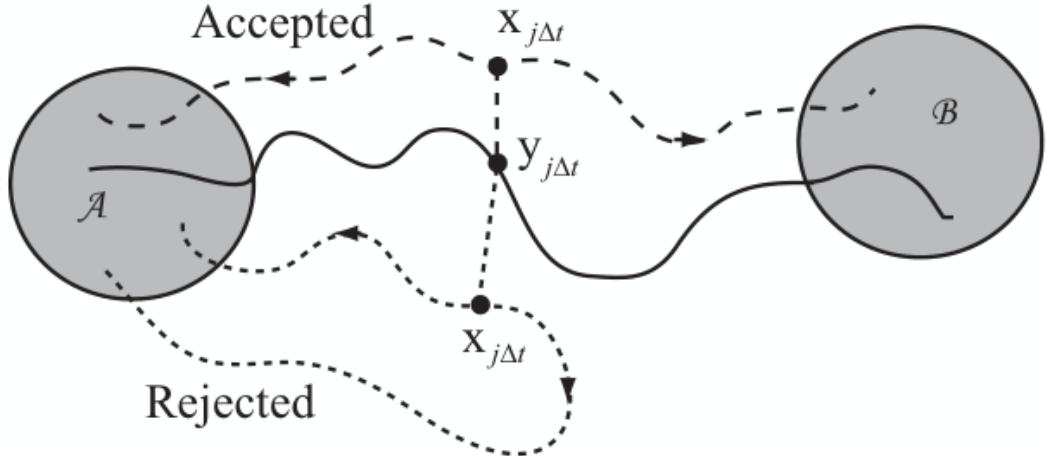
In order to generate a move from  $Y$  to  $X$ , it is assumed that  $Y[\mathcal{T}]$  is a proper trajectory from  $A$  to  $B$ , hence  $h_A(y_0) = 1$  and  $h_B(y_{n\Delta t}) = 1$ . This means that the trajectory starts at  $A$  and ends at  $B$ . Now a shooting move is performed: assuming that all the trajectories  $Y$  start from state  $A$  and

### 20.3. TRANSITION PATH ENSEMBLE

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end up in state  $B$ , then the only thing to check is the fact that the new trajectory starts at state  $A$  and ends in state  $B$ :

$$\Lambda_{AB}[X(\mathcal{T})|Y(\mathcal{T})] = h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{\mathcal{T}_{AB}[Y(\mathcal{T})|X(\mathcal{T})]\mathcal{P}_{AB}[X(\mathcal{T})]}{\mathcal{T}_{AB}[X(\mathcal{T})|Y(\mathcal{T})]\mathcal{P}_{AB}[Y(\mathcal{T})]} \right]$$



**Figure 20.3:** Shooting move

Assuming that  $Y$  is a given trajectory and starting from a random point  $y_{i\Delta t}$  in  $Y$ , starting from the point the momenta are regenerated so there is a new position in the system  $x_{j\Delta t}$ . With this coordinate and momenta it is integrated forward and backward in time. Now if integrating backward it is ended in  $A$  and forward in  $B$ . If integrating forward going back to state  $A$ , this move has to be rejected because this new path does not start from state  $A$  and ends up in state  $B$ . In the first case the move is accepted. In this way new pathways starting from a reasonable one can be generated, exploring the ensemble associated to the transition paths.  $\tau(x_{j\Delta t}|y_{j\Delta t})$  is the rule to generate the shooting point. So a randomly chosen  $y$  point in time, so the coordinates are not changed but the momenta are generated from a Boltzmann distribution. Then the probability to generate path  $X$  to path  $Y$  it the product of the probability of generate the point, the probability to shoot forward in time and the probability to shoot backward in time:

$$\mathcal{T}_{AB}[X(\mathcal{T})|Y(\mathcal{T})] = \tau(x_{j\Delta t}|y_{j\Delta t}) \left[ \prod_{k=j}^{n-1} T(x_{(k+1)\Delta t}|x_{k\Delta t}) \right] \left[ \prod_{k=1}^j T(x_{(k-1)\Delta t}|x_{k\Delta t}) \right]$$

Using a deterministic rule the  $T$  becomes delta functions. Looking at the acceptance probability, making explicit the  $\mathcal{T}$ s it can be seen how the forward part can be simplified and assuming that  $T$  is symmetric another simplification can be made.

$$\begin{aligned}
 \Lambda_{AB}[X(\mathcal{T})|Y(\mathcal{T})] &= h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{\mathcal{T}_{AB}[Y(\mathcal{T})|X(\mathcal{T})]\mathcal{P}_{AB}[X(\mathcal{T})]}{\mathcal{T}_{AB}[X(\mathcal{T})|Y(\mathcal{T})]\mathcal{P}_{AB}[Y(\mathcal{T})]} \right] = \\
 &= h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{f(x_0)}{f(y_0)} \left( \prod_{k=0}^{n-1} \frac{T(x_{(k+1)\Delta t}|x_{k\Delta t})}{T(y_{(k+1)\Delta t}|y_{k\Delta t})} \right) \left( \frac{\tau(y_{i\Delta t}|x_{j\Delta t})}{\tau(x_{j\Delta t}|y_{j\Delta t})} \cdot \prod_{k=j}^{n-1} \frac{T(y_{(k+1)\Delta t}|y_{k\Delta t})}{T(x_{(k+1)\Delta t}|x_{k\Delta t})} \prod_{k=0}^{j-1} \frac{T(y_{k\Delta t}|y_{(k+1)\Delta t})}{T(x_{k\Delta t}|x_{(k+1)\Delta t})} \right) \right] = \\
 &= h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{f(x_0)}{f(y_0)} \frac{\tau(y_{j\Delta t}|x_{j\Delta t})}{\tau(x_{j\Delta t}|y_{j\Delta t})} \prod_{k=0}^{j-1} \frac{T(x_{(k+1)\Delta t}|x_{k\Delta t})}{T(y_{(k+1)\Delta t}|y_{k\Delta t})} \frac{T(y_{k\Delta t}|y_{(k+1)\Delta t})}{T(x_{k\Delta t}|x_{(k+1)\Delta t})} \right] = \\
 &= h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{f(x_0)}{f(y_0)} \frac{\tau(y_{j\Delta t}|x_{j\Delta t})}{\tau(x_{j\Delta t}|y_{j\Delta t})} \right]
 \end{aligned}$$

For a symmetric move  $\tau(y_{j\Delta t}|x_{j\Delta t}) = \tau(x_{j\Delta t}|y_{j\Delta t})$ :

$$\Lambda_{AB}[X(\mathcal{T})|T(\mathcal{T})] = h_A(x_0)h_B(x_{n\Delta t}) \min \left[ 1, \frac{f(x_0)}{f(y_0)} \right]$$

So now the probability of the acceptance is the rate of the Boltzmann factors. So now an algorithm is obtained so that the phase space displacement  $\Delta = (0, \delta p)$  and the algorithm can be built up:

1. Choose an index  $j$  randomly on the old trajectory  $Y(\mathcal{T})$ .
2. Generate a random phase space displacement  $\Delta$  in order to generate the new shooting point  $x_{j\Delta t}$  from the old point  $y_{j\Delta t}$ .
3. Integrate the equations of motion backwards in time from the shooting point to the initial condition  $x_0$ .
4. If the initial condition  $x_0$  is not in the phase space region  $A$ , reject the trial move.
5. If  $x_0 \in A$  accept the move with probability  $\min \left[ 1, \frac{f(x_0)}{f(y_0)} \right]$ .
6. Integrate the equations of motion forward in time to generate the final point  $x_{n\Delta t}$ .
7. If  $x_{n\Delta t} \in B$ , accept the trial move, and reject it otherwise.
8. If the path is rejected at steps 4, 5 or 7, then the old trajectory  $Y(\mathcal{T})$  is counted again in the calculation of averages over the transition path ensemble Otherwise invert the momenta along the backward part of the path to yield a forward moving transition path  $X(\mathcal{T})$  and replace the old trajectory  $Y(\mathcal{T})$  by the new one  $X(\mathcal{T})$

## 20.4 The committor distribution

The real with reaction coordinates is to find good reaction coordinates. One way to check whether the reaction coordinate is a good one is the committor distribution. The committor is the probability

$p_B(\vec{r})$  that a trajectory initiated from a configuration  $\vec{r}$  with velocities sampled from a Maxwell-Boltzmann distribution will arrive in state  $B$  before state  $A$ . By definition the committor distribution is 0 in state  $A$  and 1 in state  $B$ . Moreover isocommittor surfaces at different probabilities: all point in that surface will end up in state  $B$  with the probability that defines it. In the transition state the isocommittor surface is  $p_B = \frac{1}{2}$ .

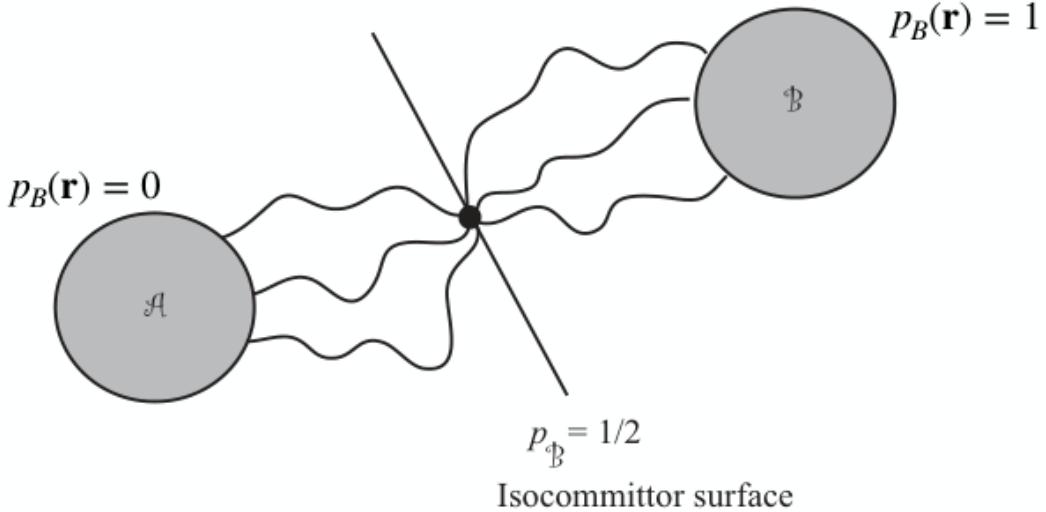


Figure 20.4: The committor

#### 20.4.1 Histogram test

The committor  $p_B(\vec{r})$  is an exact reaction coordinate for any system, but there is no analytic expression for it and obtaining it numerically is intractable. The reaction coordinate  $q(\vec{r})$  is good when the isosurfaces  $q(\vec{r}) = \text{const}$  approximates the isosurfaces  $p_B(\vec{r}) = \text{const}$  of the committor. The committor distribution is the probability that  $p_B(\vec{r}) = p$  when  $q(\vec{r}) = q^\ddagger$ , the value of  $q(\vec{r})$  at a presumptive transition state. Focussing on the transition state, the probability of the committor is:

$$P(p) = \frac{C_N}{Q(N, V, T)} \int d^N \vec{p} \int_{q(\vec{r})=q^\ddagger} d^N \vec{r} e^{-\beta \mathcal{H}(\vec{r}, \vec{p})} \delta(p_B(\vec{r}_1, \dots, \vec{r}_N) - p)$$

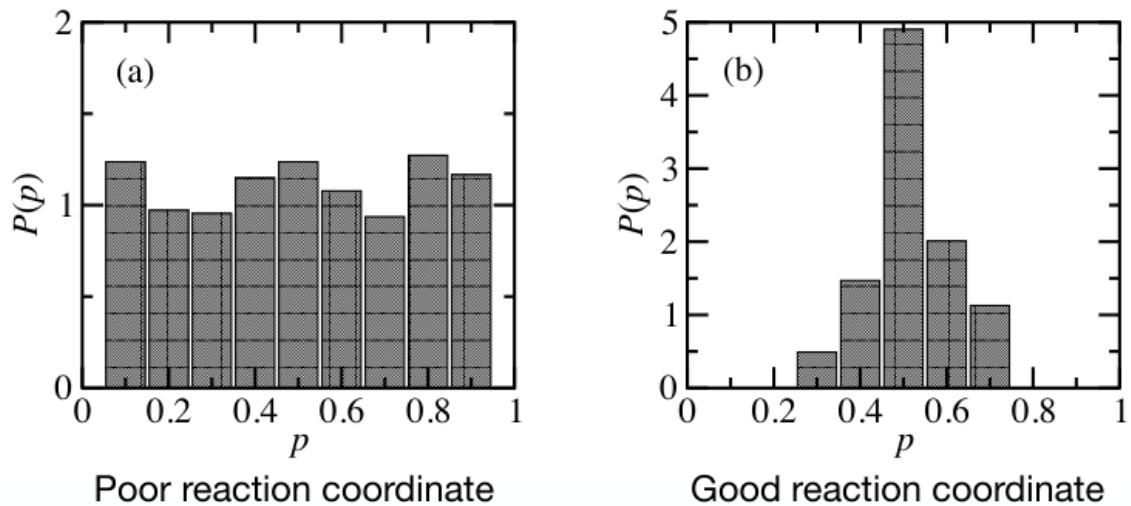
#### 20.4.2 Histogram test on $q_1(\vec{r}) = q^\ddagger$

To build up the histogram of the probabilities:

1. Fix the value  $q_1(\vec{r}) = q^\ddagger$  at the transition state.
2. Generate  $M$  configurations for the other variables  $q_2^{(k)}(\vec{r}), \dots, q_{3N}^{(k)}(\vec{r})$ . Generate  $M$  replicas for the system for which the reaction coordinate is fixed and the others are generated randomly.
3. For each value of  $k$ , sample a set of initial velocities from a Maxwell-Boltzmann distribution.

4. For each configuration  $q^\ddagger, q_2^{(k)}(\vec{r}), \dots, q_{3N}^{(k)}(\vec{r})$ , use each set of sampled velocities to initiate a trajectory and run it until the system ends up in A or B. Assign the trajectory the value 1 if it ends up in state  $B$  and 0 if it ends up in state  $A$ . Take the average for this value of  $k$  and store it as  $p^{(k)}$ .
5. Repeat for all of the configurations sampled in step 2 to generate  $p^{(1)}, \dots, p^{(M)}$ .
6. Plot a histogram for  $p^{(1)}, \dots, p^{(M)}$ .

If the histogram peaks at 0.5 then the reaction coordinate was a good one.



**Figure 20.5:** Histogram test example