

# Praktikum Physikalische Chemie

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## Molecular Dynamic Simulations

### Analysis

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## 1 Root-mean-square deviation (RMSD)

The root-mean-squared distance (RMSD) is a commonly used expression for the structural (dis)similarity between two or more conformations of a molecule. It is calculated by finding the difference between each observed ( $x_o$ ) and the predicted values ( $x_p$ ), squaring each difference, adding them up, and dividing them by the number of observed values or predicted values  $N$ :

$$RMSD(x, x_0) = \sqrt{\frac{1}{N} \sum_{i=1}^N (x_p - x_{0_i})^2} \quad (1)$$

In GROMOS the RMSD over a molecular trajectory is calculated with the package *rmsd*.

## 2 Conformational clustering

Clustering is the task of dividing the population or data points into a number of groups such that data points in the same groups are more similar to other data points in the same group than those in other groups. In simple words, the aim is to segregate groups with similar traits and assign them into clusters. In GROMOS the package cluster performs a conformational clustering based on a similarity matrix. Structures with RMSD values smaller than a user specified cutoff are considered to be structural neighbors. The structure with the highest number of neighbors is considered to be the central member of the cluster of similar structures forming a conformation. After removing all structures belonging to this first cluster, the procedure is repeated to find the second, third etc. most populated clusters.

## 3 Free Energy

The most straightforward way to determine the difference in free energy between two states of a system is simply to count the number of configurations in the corresponding states. For example, in the case of binding constants, this involves simply counting the number of bound configurations  $N_B$  and the number of unbound configurations  $N_A$  in an ensemble generated during a MD or MC simulation, with the difference in free energy being given by

$$\Delta F_{BA} = k_B T \ln\left(\frac{N_B}{N_A}\right) \quad (2)$$

This technique is only appropriate, when both bound and unbound configurations occur with sufficient frequency in the ensemble to obtain reliable statistics, i.e., when  $\Delta F_{BA}$  is small, and the barrier that determines the rate of binding and release is also small. Direct counting has the advantage that it does not depend on the definition of a reaction coordinate. It is particularly well-suited to situations in which the end states are

themselves ensembles of structures, such as in the study of peptide folding. By simply counting the proportion of configurations that satisfy a particular objective criterion such as the RMSD from a particular folded conformation, it is possible to make a direct comparison between the apparent stability of the peptide in a simulation and experimental data.[1]

## 4 Nuclear Overhauser Effect (NOE)

The Nuclear Overhauser Enhancement or Effect (NOE) is a relevant measure in liquid-state NMR for the characterization of the structure and dynamics of bio-macromolecules.[2] NOE is the cross-relaxation of spin polarization from one spin to another induced by dipole-dipole interaction.[2] Because its amplitude depends on the separation of the two spins, it can be used to measure the distance between them. [2]

The NOE distances are a very useful tool for comparison with MD simulations. NOEs are average distances whereas the simulations give you access to time resolution.

In GROMOS the package noe calculates and averages atom-atom restraint distances for specified NOE distances over a molecular trajectory. It will also calculate the deviations of these distances from the specified reference distance. These violations can be written to a time series file. The average violation is calculated as the sum of positive violations divided by the total number of NOE distances considered in the analysis.

## References

- [1] Wilfred F Van Gunsteren, Xavier Daura, and Alan E Mark. Computation of free energy. *Helv. Chim. Acta*, 85:3113–3129, 2002.
- [2] Vögeli Beat. *The Nuclear Overhauser Effect in NMR structure and dynamics analysis*. ETH, 2015.