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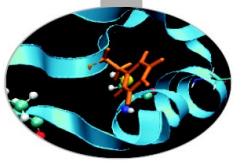
SuperComputing Applications and Innovation

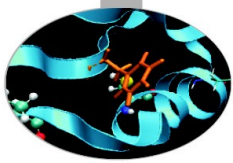


Analysis of MD trajectories (Essential Dynamics of Proteins)

A. Grottesi

PRACE CINECA

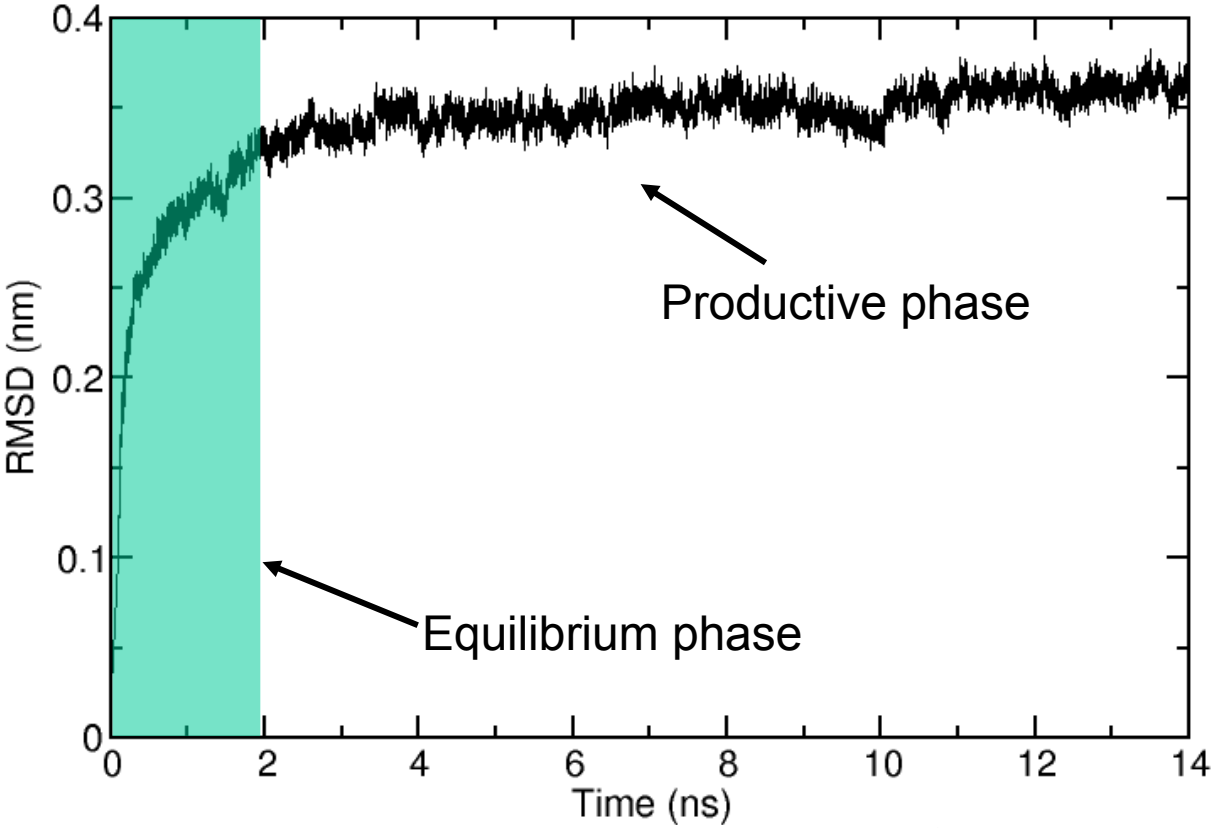
Did we reach equilibrium…?



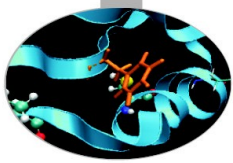
$$= \left[\frac{1}{M} \sum_{i=1}^{N} m_i \|\mathbf{r}_i(t_1) - \mathbf{r}_i(t_2)\|^2 \right]^{\frac{1}{2}}$$

Gromacs tool: g_rms

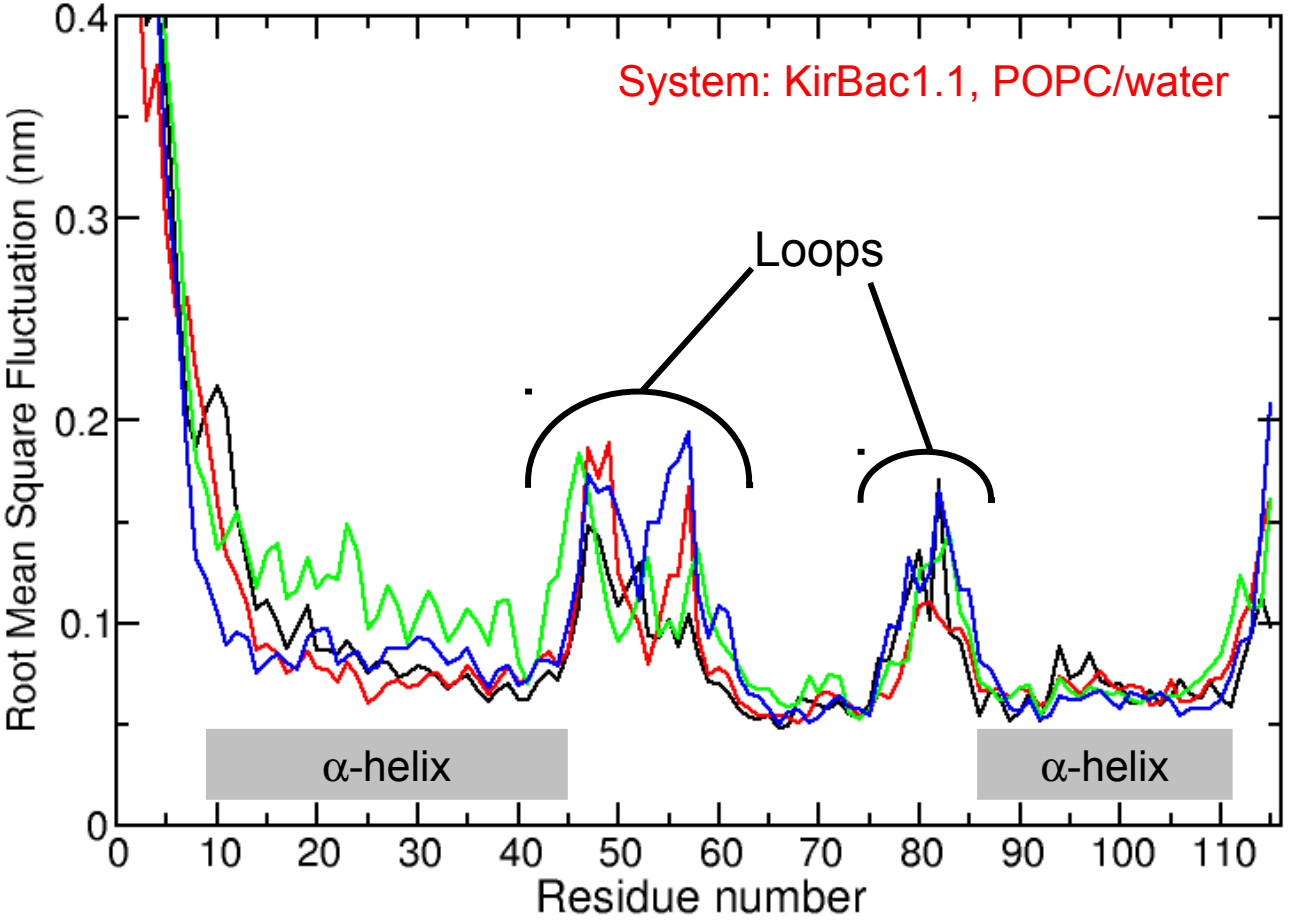
We need to make sure that all the chemical and physical properties of the system have reached an equilibrium, where their averages do not longer change as a function of time. A simple way to test this is by measuring the RMSD (root mean square deviation) of Cα carbon atoms position with respect to start.



Measuring chain flexibility

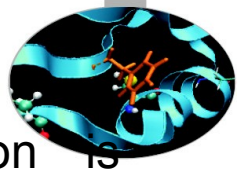


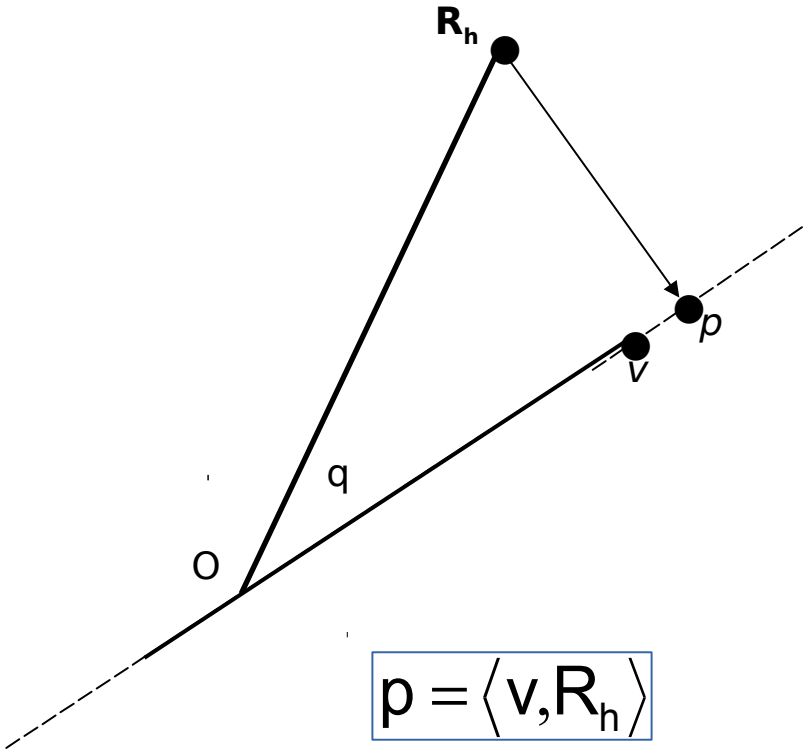
$$RMSF_i = \sqrt{\left\langle \left(r_i^{\min}(t) - \bar{r}_i \right)^2 \right\rangle}$$



RMSF is a simple tool to measure the rigidity of the polypeptide chain. It calculates the deviations of C-alpha atoms coordinates from their average position. The flexibility pattern reflects the location of secondary structure elements in the protein structure.

PCA: how it works





$$p = \langle v, R_h \rangle$$

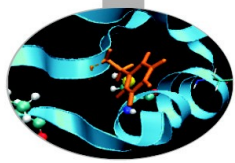
p is the projection of vector $\mathbf{R}_h$ onto unity vector **v** (dot product between **v** and $\mathbf{R}_h$)

Let's assume our simulation is defined by the vector Rn, that simply consists of the set of cartesian coordinates of Ca atoms at a given time step.

Question: what is the unity vector so that projection of $\mathbf{R}_h$ on vector **v** is the largest possible?

Answer: it is the vector **v**, so that the variance of the projected point p of Rn onto v is the largest possible

Eigenvalue equation



The average of projected points onto **v** is:

$$\mu(v) = \langle v, \bar{x} \rangle$$

$$Cv = \lambda v$$

Eigenvectors

Eigenvalues

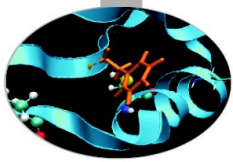
Variance of projected point onto **v** is:

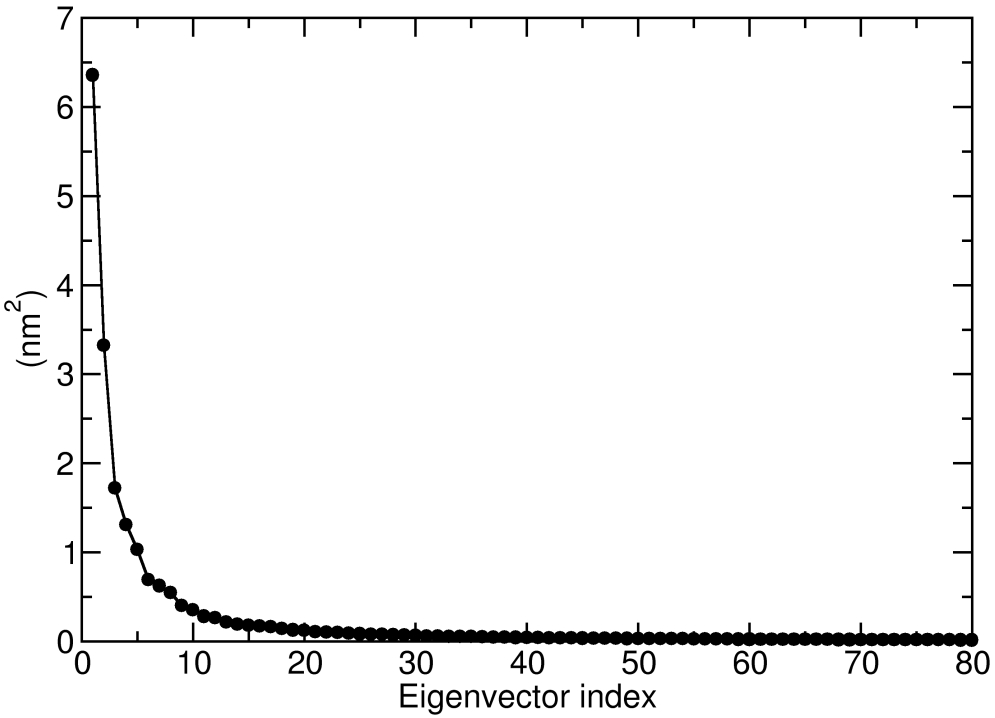
$$\sigma^2(v) = \langle Cv, v \rangle$$

Variance of projected points along vector ***v*** can be expressed in terms of dot product between ***v*** and ***Cv***.

Eigenvectors represents direction where the σ^2 returns its maximum value.
Moreover, it can be shown that σ^2 are numerically equivalent to calculated eigenvalues

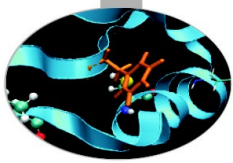
Essential Dynamics of Proteins

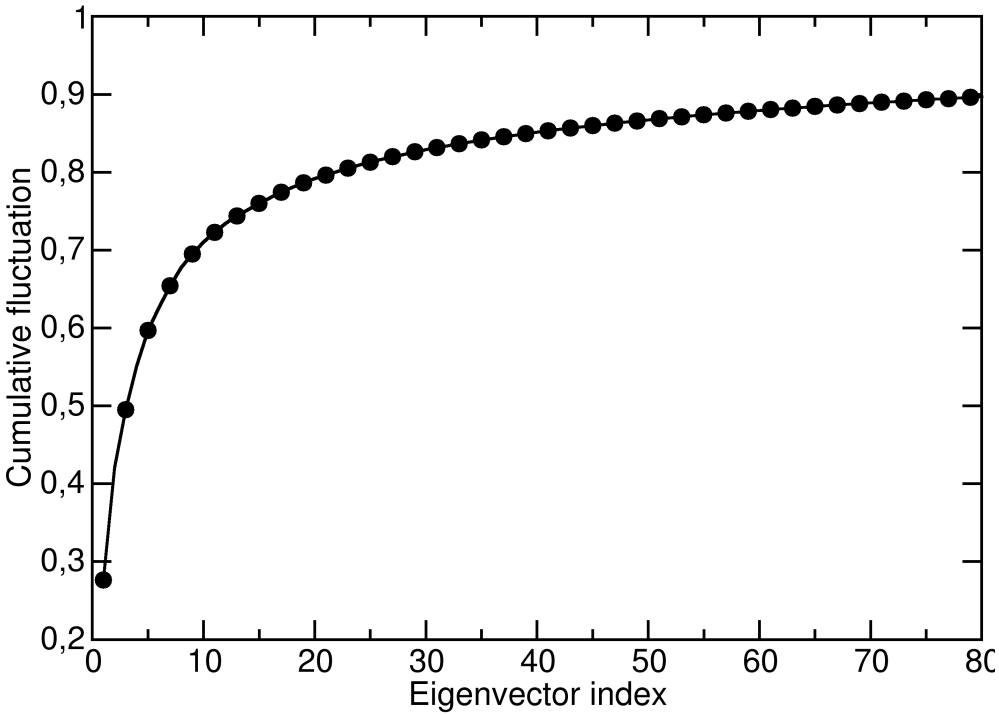




Eigenvalues are sorted in descending order: the first one corresponds to the maximum variance of the projected points. The corresponding eigenvectors are the best principal components of associated eigenvalues.

Essential Dynamics of Proteins

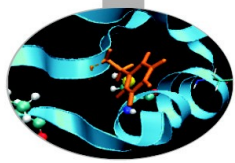




$$CF = \frac{\lambda_1 + \lambda_2 + \cdots + \lambda_n}{\sum_{i=1}^{N} \lambda_i}$$

The essential space, or subspace, of a biological protein is defined by the first 10 eigenvectors of the fluctuations covariance matrix. Indeed, it can be shown that about 70-75 % of all cumulative protein fluctuation is spanned by the first 10 principal components (eigenvectors)

Essential Dynamics: workflow in GROMACS



Least square fit of protein coordinates on respect to reference structure to remove roto-translation in the simulation box.

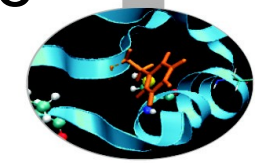
Calculate elements of the positional fluctuations covariance matrix of the Cα protein carbon atoms.

$$C_{ij} = \left\langle M_{ii}^{\frac{1}{2}}(x_i - \langle x_i \rangle) M_{jj}^{\frac{1}{2}}(x_j - \langle x_j \rangle) \right\rangle$$

Diagonalizzation of the covariance matrix and output of the corresponding eigenvectors and eigenvalues.

Sort eigenvector in descending eigenvalue index and determine principal componens

Essential Dynamics: general procedure



Essential Dynamics Analysis is based on the computation of the elements of positional fluctuations covariance matrix of protein Cα carbon atoms as follows:

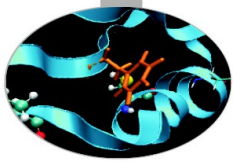
$$\Gamma_{ij} = \frac{1}{n}\sum_{h=1}^{n}\left(x_{hi} - \bar{x}_{\times i}\right)\times\left(x_{hj} - \bar{x}_{\times j}\right)$$

g_covar –f traj.xtc –s reference.gro –b start –e end –ascii

Output files:

Eigenvec.trr	→ eigenvector traj. file
Eigenval.xvg	→ eigenvalue set file
Covar.dat	→ covariance matrix in raw data format

Principal components analysis

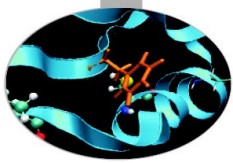


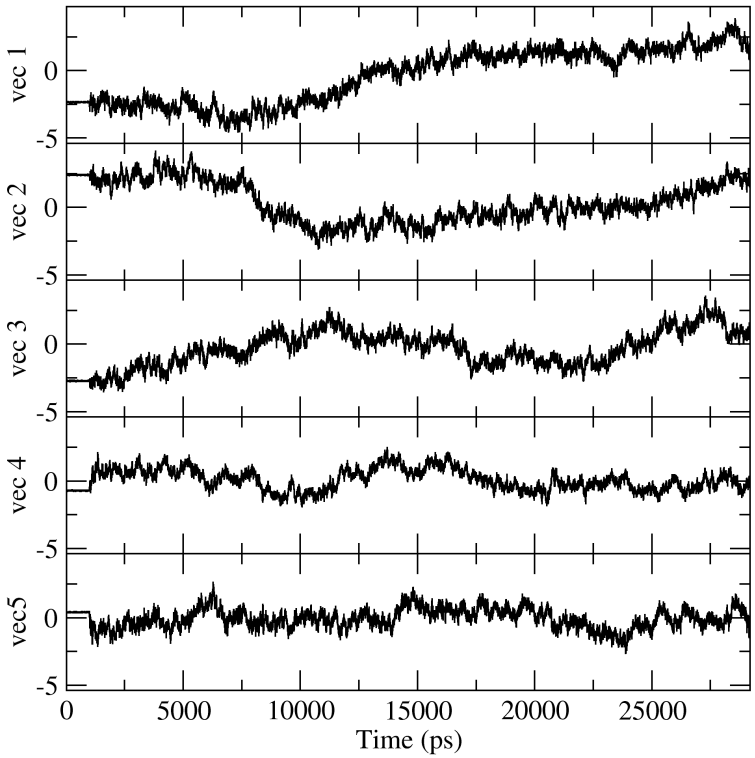
g_anaeig –f trajectory.xtc –v eigenvec.trr –eig eigenval.xvg
–s reference.gro –b *start* –e *end* -first *eig-first* -last *eig-last*

g_anaeig reads a set of eigenvectors and eigenvalues as input files and returns a set of output files that can be selected using appropriate flags:
Here are some examples:

-proj	to project an MD trajectory along a selected eigenvector
-rmsf	to calculate the RMSF along a selected eigenvector
-extr	to compute linear combinations of trajectory and selected eigenvectors
-filt	to filter trajectory along selected eigenvector

g_anaeig: output of flag –proj

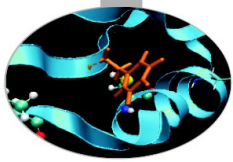


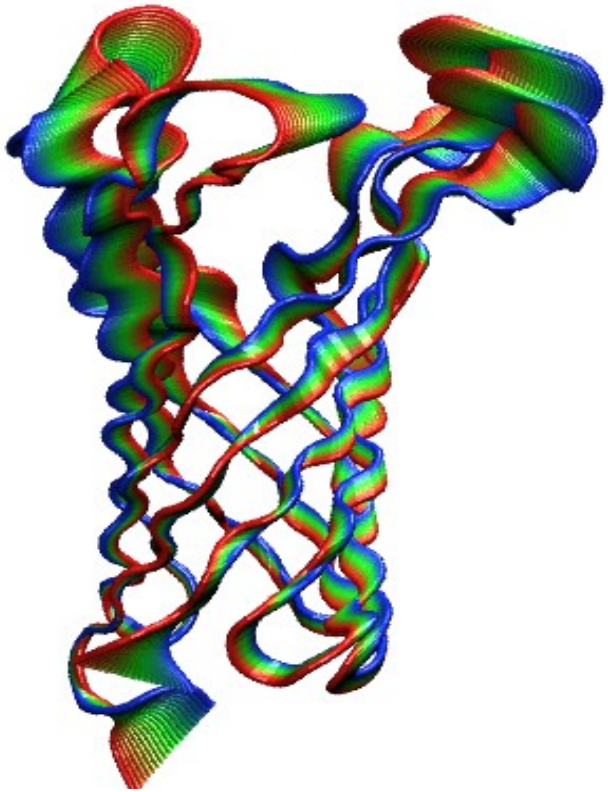


By default, 8 eigenvectors are considered for output using g_anaeig. This option can be set by using the flags `-first` and `-end`

g_anaeig -f trajectory.xtc -v eigenvec.trr -eig eigenval.xvg -s reference.gro
-proj proj.xvg -first 1 -last 5

g_anaeig: flag -extr

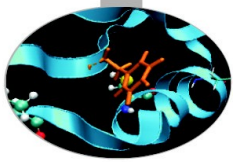


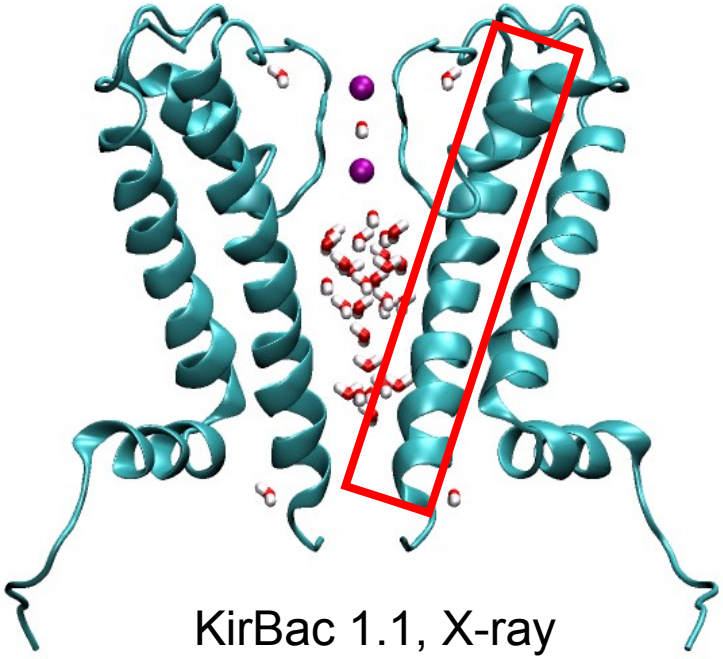


La dinamica essenziale ci aiuta a studiare i moti concertati tra gruppi di atomi all'interno di una struttura proteica. Nell'esempio si osserva un movimento concertato tra i loop extracellulari della porina OmpA lungo il primo autovettore.

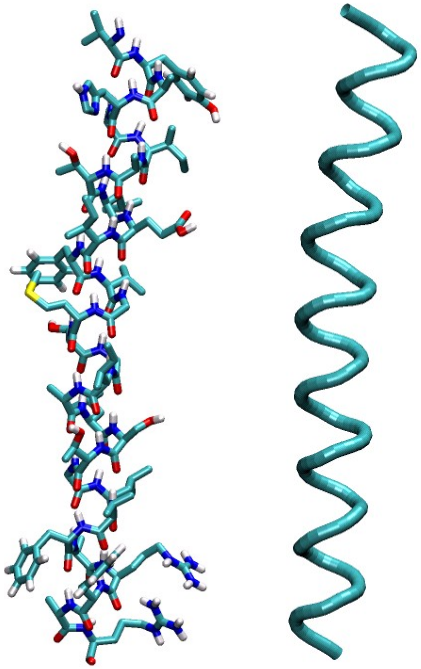
g_anaeig -f trajectory.xtc -v eigenvec.trr -eig eigenval.xvg -s reference.gro -extr extreme.pdb -first 1 -last 3 -nframes 50

g_anaeig: the flag –filt

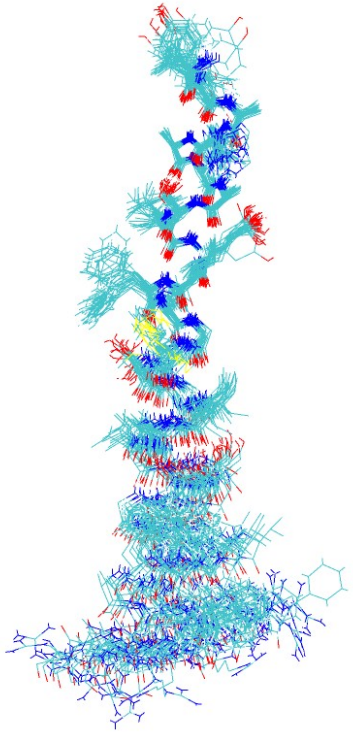




KirBac 1.1, X-ray

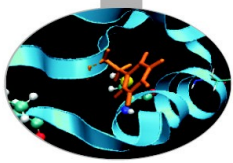


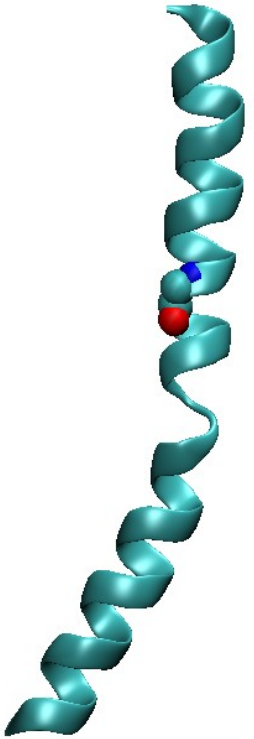
X-ray structure

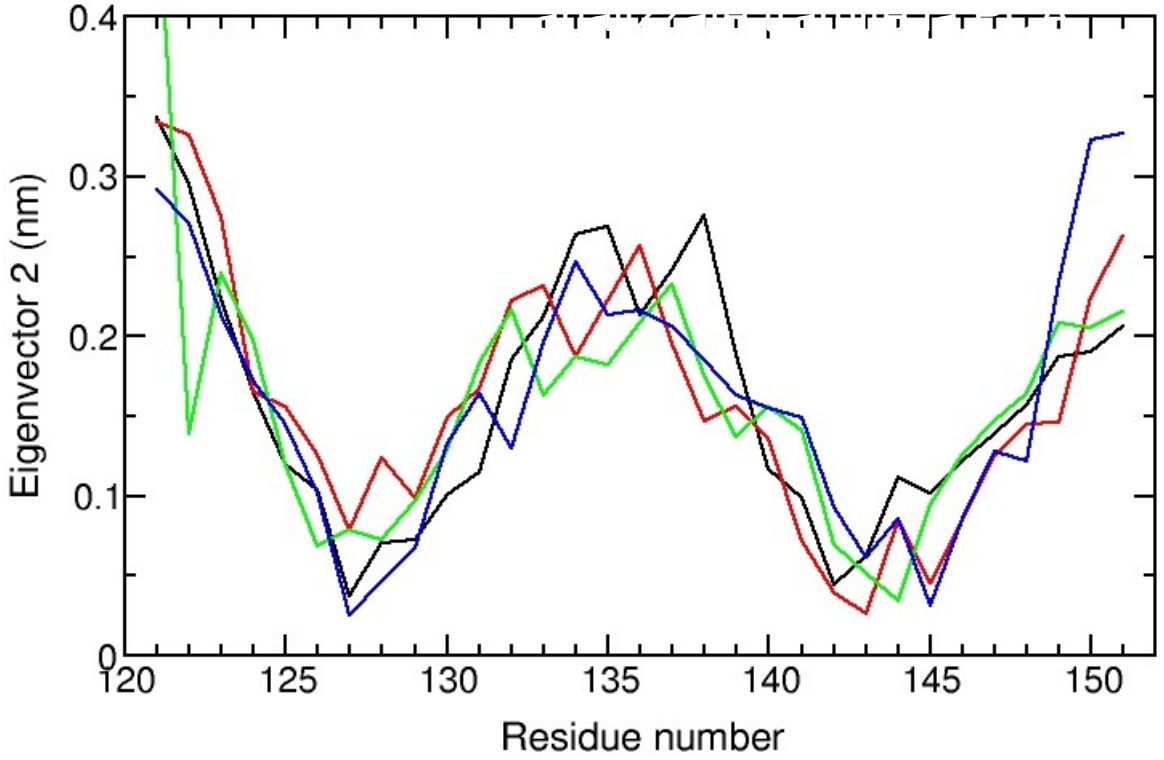


MD simulation

g_anaeig: the –rmsf flag

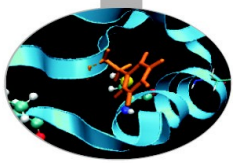


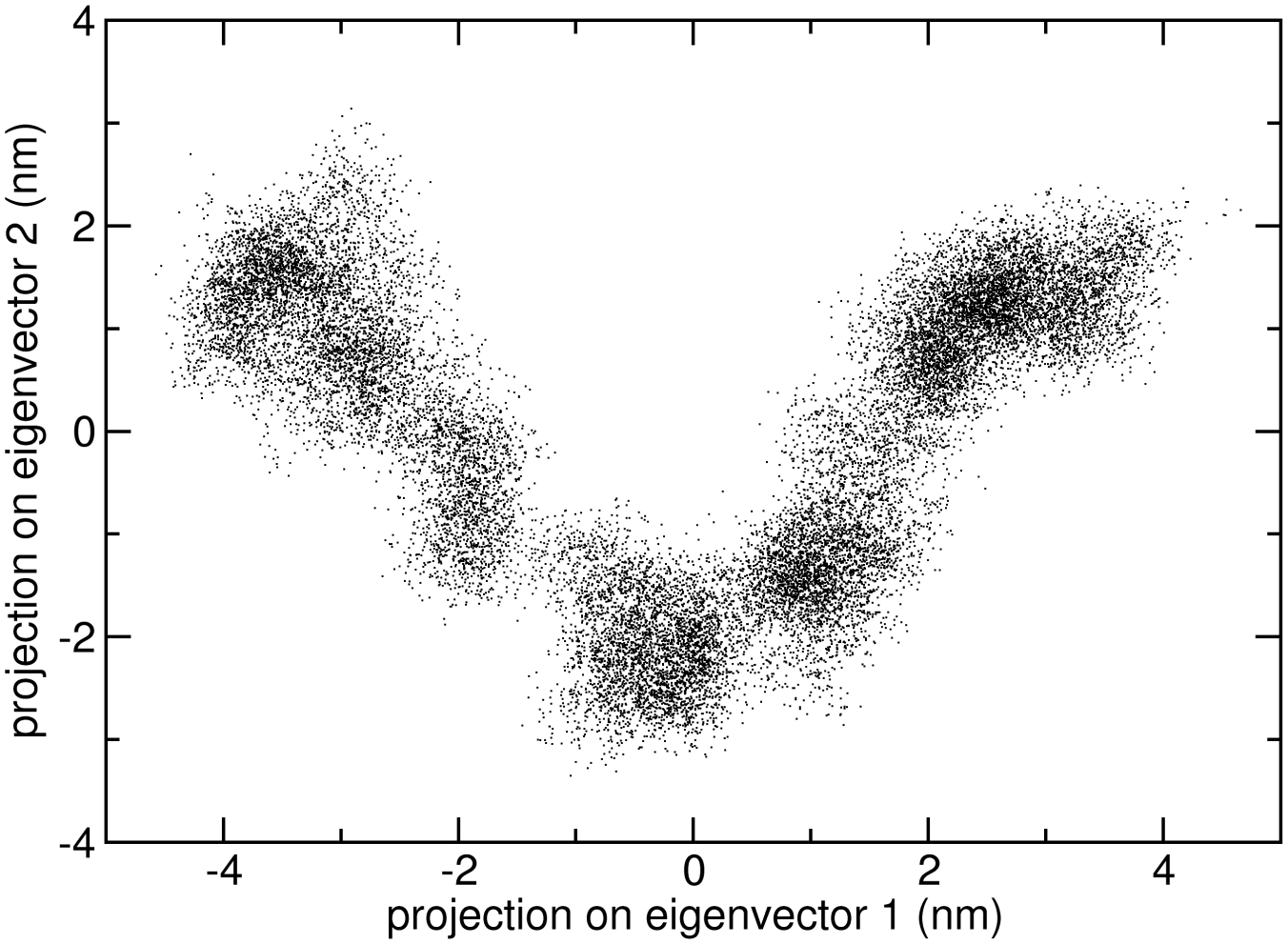




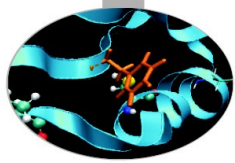
RMSF Analysis by means of principal components analysis. Fluctuations analysis by PCA on K channels simulations revealed that top flexibility on helix S6 is achieved at a conserved Gly-134 residue that is the most flexible in the polypeptide chain.

g_anaeig: the -2d or -3d flag





Essential Dynamics Tutorial: Principal Components Analysis of a small peptide



Input file on Eurora:

/gpfs/scratch/userinternal/agrottes/Corsi/Tutorial3/Essential-Dynamics

- cp -r <source_dir> ./
- cd Essential-Dynamics
- Run g_covar on file total19ns.xtc using start_prot.gro as reference
- Run g_anaeig with option -proj -extr -filt and -2d
- Get the first principal plane
- Run g_rms and g_rmsf