Stiffness Matrix Calculations

Release

Mikulska-Ruminska, Karolina

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ONE

INTRODUCTION

This tutorial describes how to calculate the mechanical stiffness map for a given protein structure, using the coordinates in the native state as *input*. The map provides a measure of the effective resistance of all pairs of residues to increasing their inter-residue separation, in the context of the entire network.

This methodology can be successfully used for interpreting data from single molecule manipulation techniques results such as Single Molecule Force Spectroscopy (AFM) or optical tweezers. It may also be used for predicting the response to tension without performing expensive steered molecular dynamics simulations.

Theory and example of usage has been described in *[EB08]* and *[MRK17]*.

1.1 Required Programs

Besides **ProDy_**, the **Matplotlib_** library and **VMD_** program are required for some steps in this tutorial. **IPython_** is highly recommended for interactive usage.

1.2 Getting Started

To follow this tutorial, you will not need any additional files.

We recommend that you will follow this tutorial by typing commands in an IPython session, e.g.:

```
$ ipython
```

or with pylab environment:

```
$ ipython --pylab
```

First, we will make necessary imports from ProDy and Matplotlib packages.

```
In [1]: from prody import *

In [2]: from pylab import *

In [3]: ion()
```

We have included these imports in every part of the tutorial, so that code copied from the online pages is complete. You do not need to repeat imports in the same Python session.

1.3 How to Cite

If you benefited from Mechanical Stiffness Calculations in your research, please cite the following paper:

CHAPTER

TWO

MECHANICAL STIFFNESS CALCULATIONS

This example shows how to perform mechanical resistance calculation for GFP protein (**1gfl**) and visualize the results using **Matplotlib_** library and **VMD_** program.

An ANM instance that stores Hessian matrix and normal mode data describing the intrinsic dynamics of the protein structure will be used as an input (*model*) as well as cooridinates of protein structure (*coords*, *pdb*).

See *[EB08]* for more information about the theory of mechanical resistance calculations and more examples.

2.1 Parse structure

We start by importing everything from the ProDy package:

```
In [1]: from prody import *

In [2]: from pylab import *

In [3]: ion()    # turn interactive mode on
```

We start by parsing chain A of PDB structure **1gfl** together with the header, which will be used later for visualizing the secoundary structure.

```
In [4]: gfp, header = parsePDB('1gflA', header=True)

In [5]: gfp
Out[5]: <AtomGroup: 1gflA (1967 atoms)>
```

We want to use only Cα atoms for our calculations, so we select them into a new object *calphas*:

```
In [6]: calphas = gfp.ca

In [7]: calphas
Out[7]: <Selection: 'ca' from 1gflA (230 atoms)>
```

2.2 Build Hessian and calculate ANM modes

In the next step we instantiate an ANM instance:

```
In [8]: anm = ANM('GFP ANM analysis')
```

Then, build the Hessian matrix by passing selected atoms (230 Cα atoms) to ANM.buildHessian() method:

```
In [9]: anm.buildHessian(calphas, cutoff=13.0)
```

And calculate all anm modes as they will be needed for later:

```
In [10]: anm.calcModes(n_modes='all')
```

All modes are required to perform accurate mechanical stiffness calculations.

2.3 Stiffness Matrix Calculations

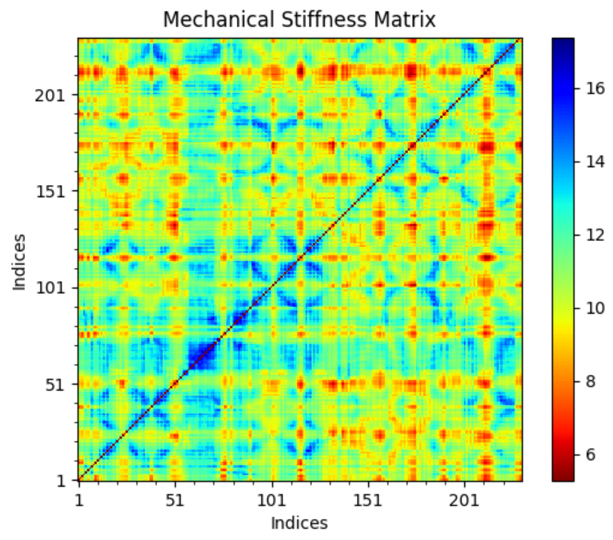
Mechanical stiffness calculations for the selected group of atoms can be performed using the `calcMechStiff()` function:

```
In [11]: stiffness = calcMechStiff(anm, calphas)

In [12]: stiffness
Out[12]:
array([[0.        , 8.54744466, 8.55133411, ..., 8.73270017, 8.36529536,
         7.42692504],
        [8.54744466, 0.        , 8.89990284, ..., 8.98097054, 8.61849698,
         7.77257692],
        [8.55133411, 8.89990284, 0.        , ..., 8.87863489, 8.55675667,
         7.84521673],
        ...,
        [8.73270017, 8.98097054, 8.87863489, ..., 0.        , 8.87731778,
         8.36590599],
        [8.36529536, 8.61849698, 8.55675667, ..., 8.87731778, 0.        ,
         9.52997339],
        [7.42692504, 7.77257692, 7.84521673, ..., 8.36590599, 9.52997339,
         0.        ]])
```

To show the stiffness matrix as an image map use the following function:

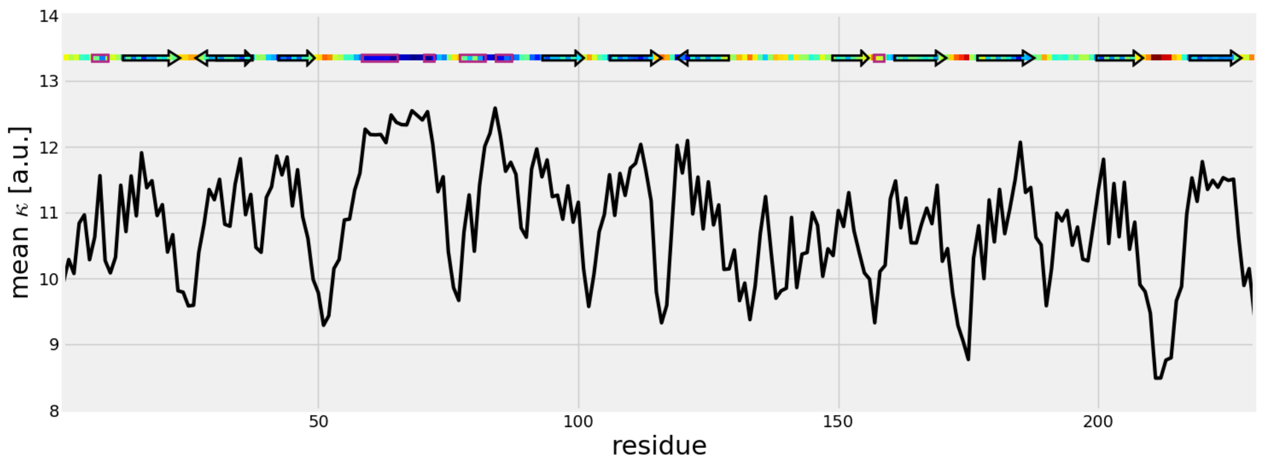
```
In [13]: show = showMechStiff(stiffness, calphas, cmap='jet_r')
```



Note that *'jet_r'* is the reverse of the jet colormap and is similar to the default coloring method of the **VMD_** program.

The mean values of the mechanical stiffness matrix for each residue can be calculated using the `showMeanMechStiff()` function where the secoundary structure of the protein is drawn using header information.

```
In [14]: show = showMeanMechStiff(stiffness, calphas, header, 'A', cmap='jet_r')
```



2.4 Mechanical Stiffness in VMD

We can generate tcl files for visualizing mechanical stiffness with **VMD_** using the `writeVMDstiffness()` function. Select one residue in *indices* (**[3]**) or series of residues (**[3, 7]** means from 3 aa to 7 aa inclusive) and a range of effective spring constant *k_range* (**[0, 7.5]**).

We provide *gfp* as well as *calphas* so **VMD_** has information about the complete protein structure, which it can use for graphical representations.

```
In [15]: writeVMDstiffness(stiffness, gfp, [3,7], [0,7.5], filename='1gfl_3-7aa')

In [16]: writeVMDstiffness(stiffness, gfp, [3], [0,7], filename='1gfl_3aa')
```

A TCL file will be saved automatically and can be used later in **VMD_** by running the following command line instruction. Results can be loaded automatically to **VMD_** by setting keyword `loadToVMD=True`.

:: vmd -e 1gfl_3aa.tcl

or typing the following in the **VMD_** *TKConsole* (*VMD Main*) for Linux, Windows and Mac users:

:: play 1gfl_3aa.tcl

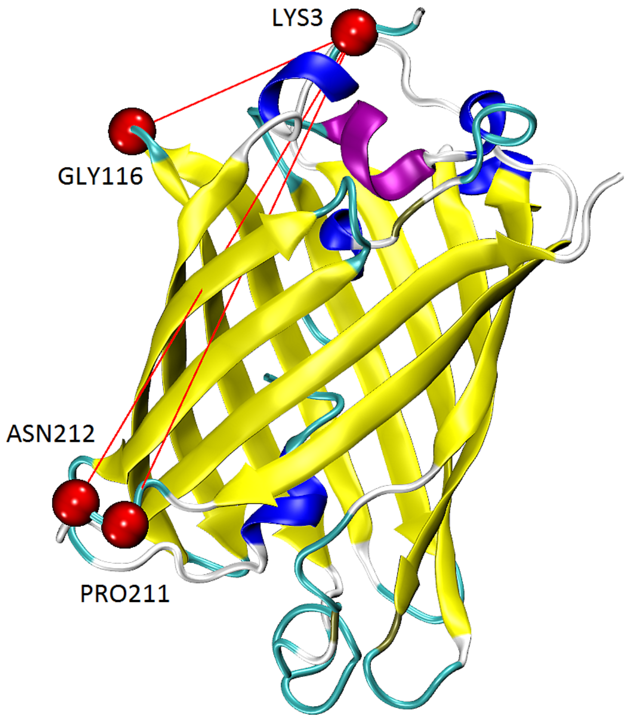
The tcl file contains a method for drawing lines between selected pairs of residues, which are highlighted as spheres. The color of the line can be modified by changing the `draw color red` line in the output file. Only colors from **VMD_** Coloring Method will work. Other changes can be done within **VMD_** in the *Graphical Representations* menu.

The figure shows GFP results from `writeVMDstiffness()` function opened in **VMD_**. Pairs of found residues LYS3-GLY116, LYS3-PRO211 and PRO211-ASN212 are shown as VDW spheres connected with red lines.

Additionally, `1gfl_3aa.txt` file is created. It contains a list of residue pairs with the value of effective spring constant (in a.u. because *kBT=1*) obtained from `calcMechStiff()`.

```
LYS3    GLY116   6.91650667766
LYS3    PRO211   6.85989128668
LYS3    ASN212   6.69507284967
...
```

The range of spring constant for *k_range* can be checked as follows:



```
In [17]: calcStiffnessRange(stiffness)
Out[17]: (5.271418245781293, 17.38490944653242)
```

See also `calcMechStiffStatistic()` and `calcStiffnessRangeSel()` functions for more detailed analysis of the stiffness matrix.

The results of the mean value of mechanical stiffness calculation can be seen in **VMD_** using:

```
In [18]: writeDeformProfile(stiffness, gfp, select='chain A and name CA', pdb_selstr='protein')
```

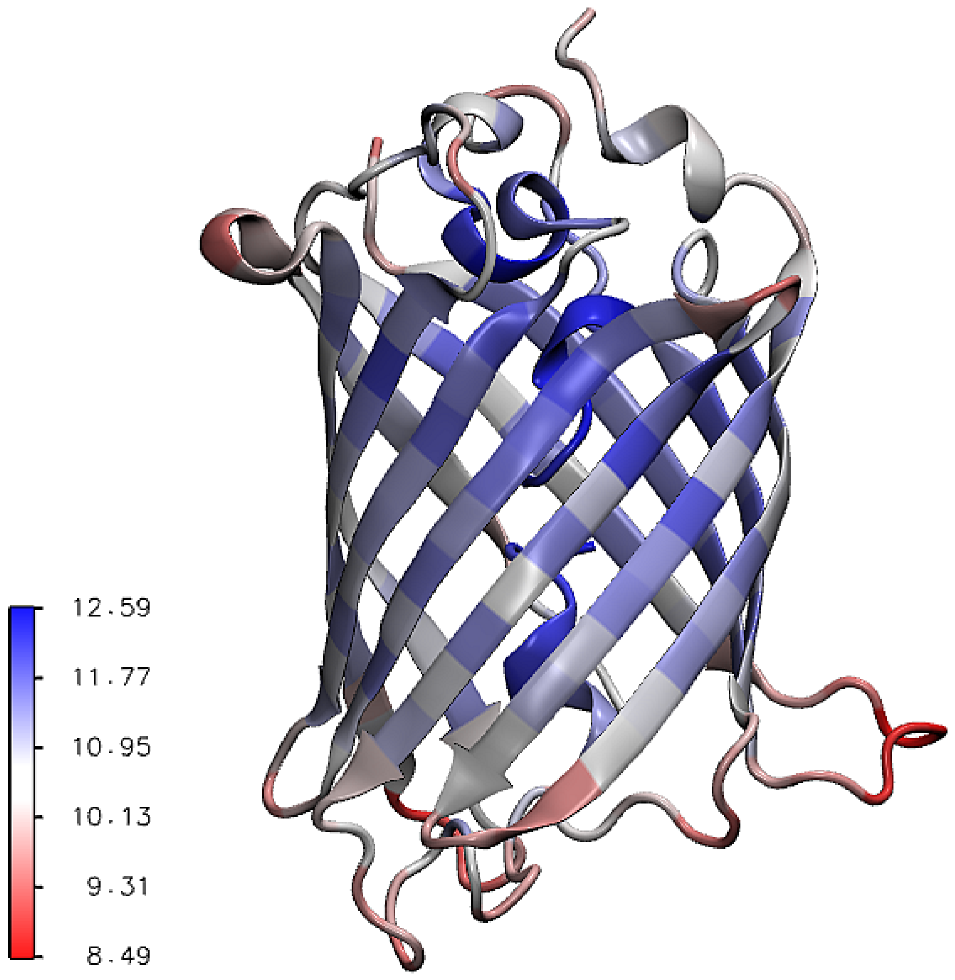
2.5 Calculate Distribution of Deformation

The distribution of the deformation in the distance contributed by each mode for a selected pair of residues has been described in *[EB08]*, see *Eq. (10)* and plots are shown on *Fig. (2)*.

These results can be plotted using `plotting.showPairDeformationDist()` or a list can be obtained using `analysis.calcPairDeformationDist()`.

```
In [19]: d0 = calcPairDeformationDist(anm, calphas, 3, 132)

In [20]: show = showPairDeformationDist(anm, calphas, 3, 132)
```


12.59
11.77
10.95
10.13
9.31
8.49

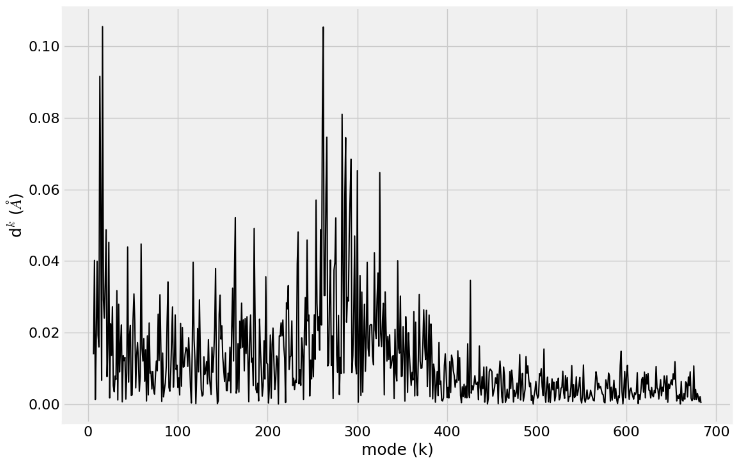


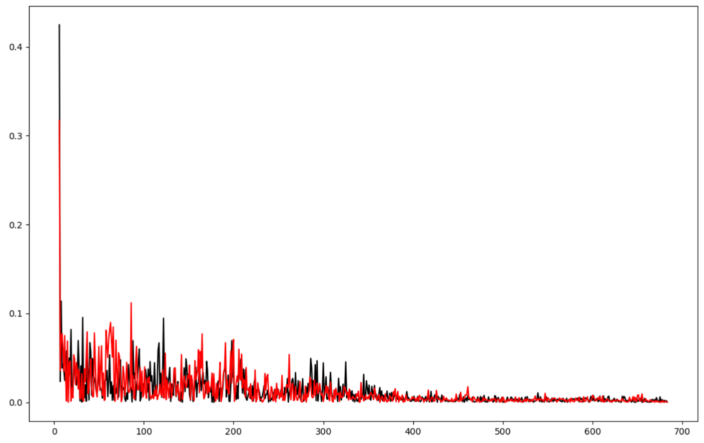
Figure shows the plotted distribution for deformations between 3-132 residue in each mode *k*.

To obtain results without saving any file type:

```
In [21]: d1 = calcPairDeformationDist(anm, calphas, 3, 212)

In [22]: d2 = calcPairDeformationDist(anm, calphas, 132, 212)

In [23]: plot(d1[0], d1[1], 'k-', d2[0], d2[1], 'r-')
Out[23]:
[<matplotlib.lines.Line2D at 0x7f42619f1d10>,
 <matplotlib.lines.Line2D at 0x7f42619f1dd0>]
```



Acknowledgments

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[1]http://www.nih.gov/

[EB08] Eyal E, Bahar I. Toward a Molecular Understanding of the Anisotropic Response of Proteins to External Forces: Insights from Elastic Network Models. *Biophys. J.* **2008** 94:3424-34355.

[MRK17] Mikulska-Ruminska K, Kulik A, Benadiba C, Bahar I, Dietler G, Nowak W. Nanomechanics of multidomain neuronal cell adhesion protein contactin revealed by single molecule AFM and SMD. *Sci. Rep.* **2017** 7:8852.