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Numerical Evaluation of Protein Global Vibrations at Terahertz Frequencies by means of Elastic Lattice Models

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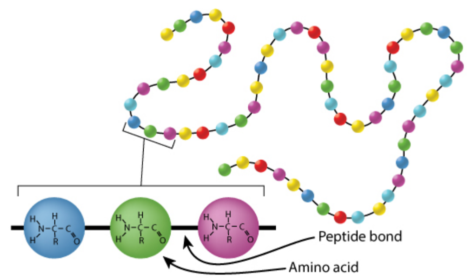
Outline of the Work

1. Introduction
2. Elastic Lattice Models (ELMs) for Protein Vibrations
3. Validation of the Numerical Models: B-factors
4. Protein Normal Modes and Biological Mechanism
5. Conclusions and Future Developments

Protein: Sequence of several different amino acids, with a complex three-dimensional shape and function

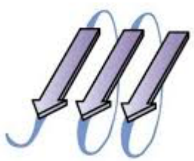
Three structural levels

Primary structure



Secondary structures

α helix

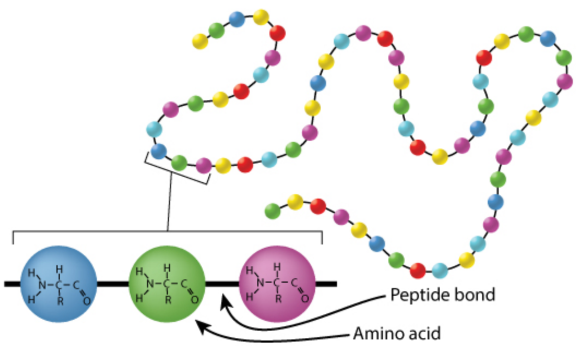


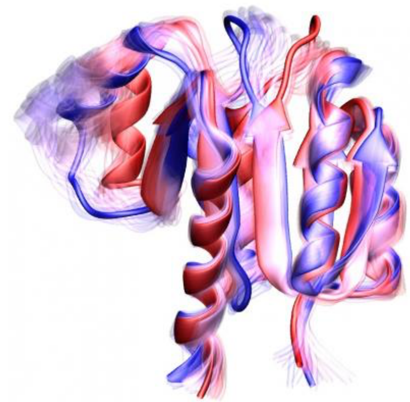
β sheet

Tertiary structure

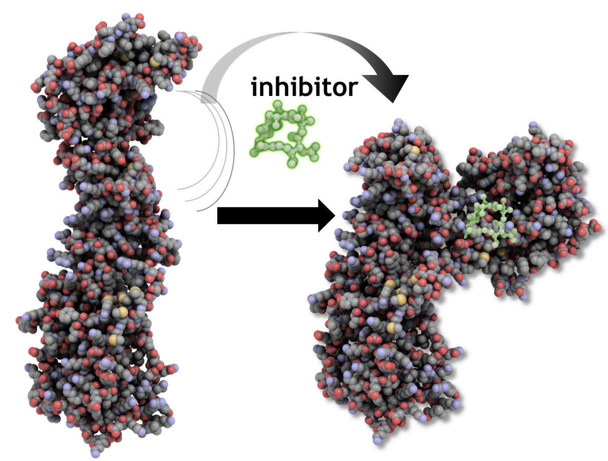
Protein folding

The fundamental paradigm of protein action





Sequence → Structure → Dynamics → Function



How to study the Structure – Dynamics relationship?

Increasing model complexity

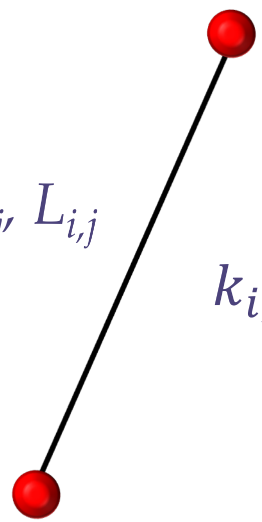
Type of analysis	Protein representation	Form of potentials	Type of output
Molecular Dynamics (MD)	All atoms	Complex semi-empirical	Trajectories
Normal mode analysis (NMA)	All atoms	Multi-parameter harmonic	Normal modes
All-atom Elastic Lattice Model (aaELM)	All atoms	Single-parameter harmonic	Normal modes
Coarse-grained Elastic Lattice Model (cgELM)	Only one node per amino acid	Single-parameter harmonic	Normal modes

Increasing computational efficiency

Elastic Lattice Model (ELM)

From the single bar element…

$i\ (x_i, y_i, z_i)$

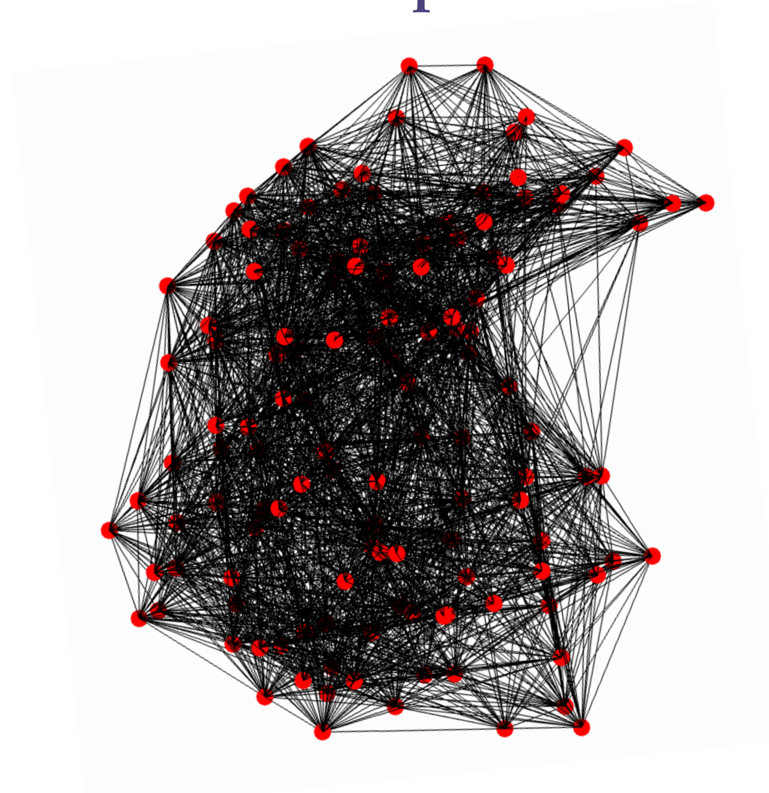


$E_{i,j}, A_{i,j}, L_{i,j}$

$$k_{i,j} = \frac{E_{i,j} A_{i,j}}{L_{i,j}}$$

$j\ (x_j, y_j, z_j)$

… to the spatial ELM



Elastic Lattice Model (ELM) – Finite Element (FE) approach

$$\mathbf{k_{i,j}}^* = \frac{E_{i,j}A_{i,j}}{L_{i,j}}\begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix}$$

2x2 stiffness matrix of the elastic bar in the local system

$$\mathbf{N_{i,j}} = \begin{bmatrix} \frac{x_j - x_i}{L_{i,j}} & \frac{y_j - y_i}{L_{i,j}} & \frac{z_j - z_i}{L_{i,j}} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{x_j - x_i}{L_{i,j}} & \frac{y_j - y_i}{L_{i,j}} & \frac{z_j - z_i}{L_{i,j}} \end{bmatrix}$$

2x6 rotation matrix of the elastic bar, between the local and global systems

$$\mathbf{k_{i,j}} = \mathbf{N_{i,j}}^T \mathbf{k_{i,j}}^* \mathbf{N_{i,j}}$$

6x6 stiffness matrix of the elastic bar in the global system

Elastic Lattice Model (ELM) – Finite Element (FE) approach

$$\mathbf{k_{i,j}} = \mathbf{N_{i,j}}^T \mathbf{k_{i,j}}^* \mathbf{N_{i,j}} = \begin{bmatrix} \boldsymbol{\alpha}_{\mathbf{i,j}} & -\boldsymbol{\alpha}_{\mathbf{i,j}} \\ -\boldsymbol{\alpha}_{\mathbf{i,j}} & \boldsymbol{\alpha}_{\mathbf{i,j}} \end{bmatrix}$$

$$\boldsymbol{\alpha}_{\mathbf{i,j}} = \frac{E_{i,j}A_{i,j}}{L_{i,j}} \begin{bmatrix} \frac{(x_j - x_i)^2}{L_{i,j}^{\,2}} & \frac{(x_j - x_i)(y_j - y_i)}{L_{i,j}^{\,2}} & \frac{(x_j - x_i)(z_j - z_i)}{L_{i,j}^{\,2}} \\ \frac{(x_j - x_i)(y_j - y_i)}{L_{i,j}^{\,2}} & \frac{(y_j - y_i)^2}{L_{i,j}^{\,2}} & \frac{(y_j - y_i)(z_j - z_i)}{L_{i,j}^{\,2}} \\ \frac{(x_j - x_i)(z_j - z_i)}{L_{i,j}^{\,2}} & \frac{(y_j - y_i)(z_j - z_i)}{L_{i,j}^{\,2}} & \frac{(z_j - z_i)^2}{L_{i,j}^{\,2}} \end{bmatrix}$$

6x6 stiffness matrix of the elastic bar in the global system

Elastic Lattice Model (ELM) – Finite Element (FE) approach

$$\mathbf{K} = \sum_{i,j|L_{i,j}<r_c} \mathbf{C_{i,j}}^T \mathbf{N_{i,j}}^T \mathbf{k_{i,j}}^* \mathbf{N_{i,j}} \mathbf{C_{i,j}} \longrightarrow \mathbf{C_{i,j}}$$

3Nx3N stiffness matrix of the ELM

6x3N expansion matrix of the elastic bar to reach the dimension of the structural problem

$$\mathbf{M} = \begin{bmatrix} \mathbf{M_1} & \mathbf{0} & \dots & \mathbf{0} \\ \mathbf{0} & \mathbf{M_2} & \dots & \mathbf{0} \\ \dots & \dots & \dots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \mathbf{M_N} \end{bmatrix}$$

3Nx3N mass matrix of the ELM

$$\mathbf{M_i} = \begin{bmatrix} m_i & 0 & 0 \\ 0 & m_i & 0 \\ 0 & 0 & m_i \end{bmatrix}$$

3x3 mass matrix of the i^{th} node

Elastic Lattice Model (ELM) – Anisotropic Network Model (ANM)

$$\mathbf{H} = \begin{bmatrix} \mathbf{H_{1,1}} & \mathbf{H_{1,2}} & \dots & \mathbf{H_{1,N}} \\ \mathbf{H_{2,1}} & \mathbf{H_{2,2}} & \dots & \mathbf{H_{2,N}} \\ \dots & \dots & \dots & \dots \\ \mathbf{H_{N,1}} & \mathbf{H_{N,2}} & \dots & \mathbf{H_{N,N}} \end{bmatrix}$$

3Nx3N Hessian matrix of the ANM

$$\mathbf{H_{i,j}} = \begin{bmatrix} \frac{\partial^2 V_{i,j}}{\partial x_i \partial x_j} & \frac{\partial^2 V_{i,j}}{\partial x_i \partial y_j} & \frac{\partial^2 V_{i,j}}{\partial x_i \partial z_j} \\ \frac{\partial^2 V_{i,j}}{\partial y_i \partial x_j} & \frac{\partial^2 V_{i,j}}{\partial y_i \partial y_j} & \frac{\partial^2 V_{i,j}}{\partial y_i \partial z_j} \\ \frac{\partial^2 V_{i,j}}{\partial z_i \partial x_j} & \frac{\partial^2 V_{i,j}}{\partial z_i \partial y_j} & \frac{\partial^2 V_{i,j}}{\partial z_i \partial z_j} \end{bmatrix}$$

$$\mathbf{H_{i,i}} = -\sum_{j=1, j \neq i}^{N} \mathbf{H_{i,j}}$$

$$V_{i,j} = \frac{\gamma}{2}\left(r_{i,j} - r_{i,j}{}^{0}\right)^2$$

$$\gamma \propto \frac{1}{r_{i,j}{}^{p}}$$

It can be easily demonstrated that there exists complete consistency between the FE-based ELM stiffness matrix *K* and the ANM Hessian matrix *H*

Elastic Lattice Model (ELM) – Modal Analysis

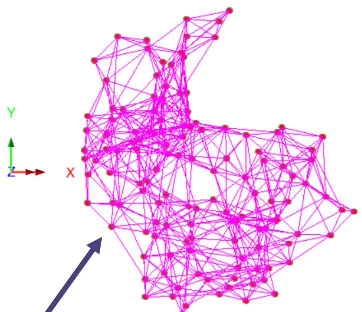
$$\mathbf{Ku} + \mathbf{M\ddot{u}} = \mathbf{0} \xrightarrow{\mathbf{u} = \boldsymbol{\delta}\sin\omega t} (\mathbf{K} - \omega^2\mathbf{M})\boldsymbol{\delta} = \mathbf{0} \xrightarrow{\text{Non-trivial solution}} |\mathbf{K} - \omega^2\mathbf{M}| = \mathbf{0}$$

Set of 3N-6 non-zero eigenvalues $\omega_n = 2\pi f_n$

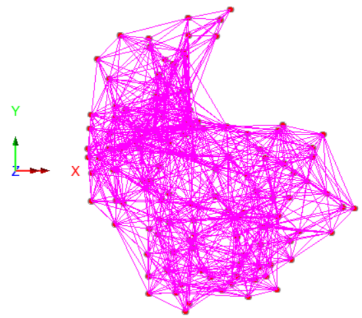
⟵

Set of 3N-6 non-rigid eigenvectors (mode shapes) $\boldsymbol{\delta}_\mathbf{n}$

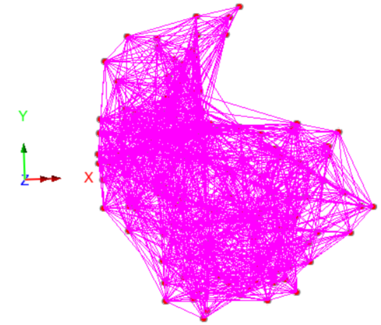
Effect of the selected cutoff value on the generated ELM



r_c = 8Å

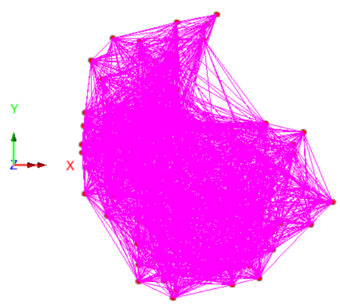


r_c = 10Å

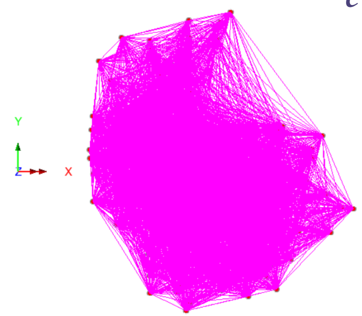


r_c = 12Å

*The C^{α} atoms of the protein are the representative points for each amino acid!



r_c = 15Å

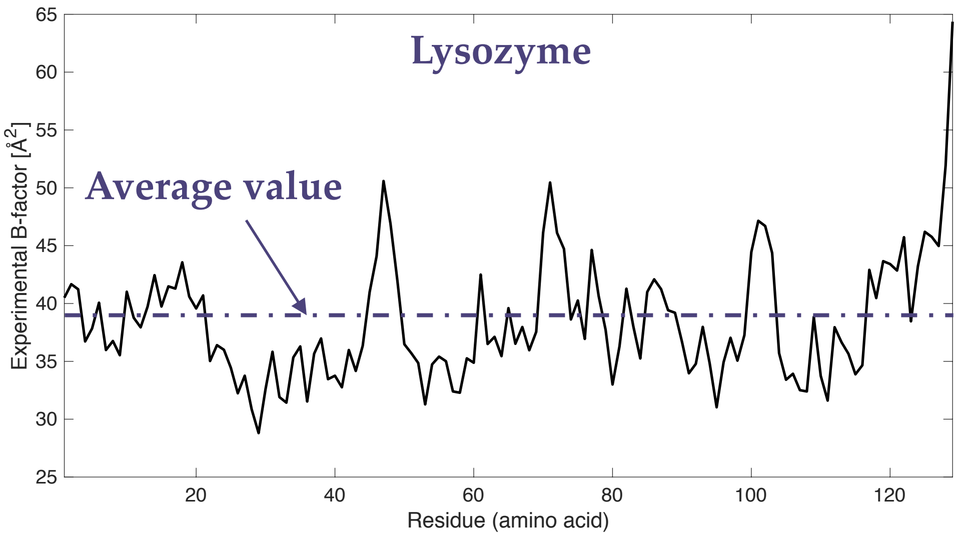


r_c = 20Å

Lysozyme (PDB: 4YM8) – LUSAS FE software used for the construction of the model

How to set up the values of the axial rigidity *EA*? With the B-factors!

B-factors are a measure of the protein flexibility and can be found in the PDB file, as obtained from the X-ray crystallographic experiment



B-factors can also be associated to the normal modes

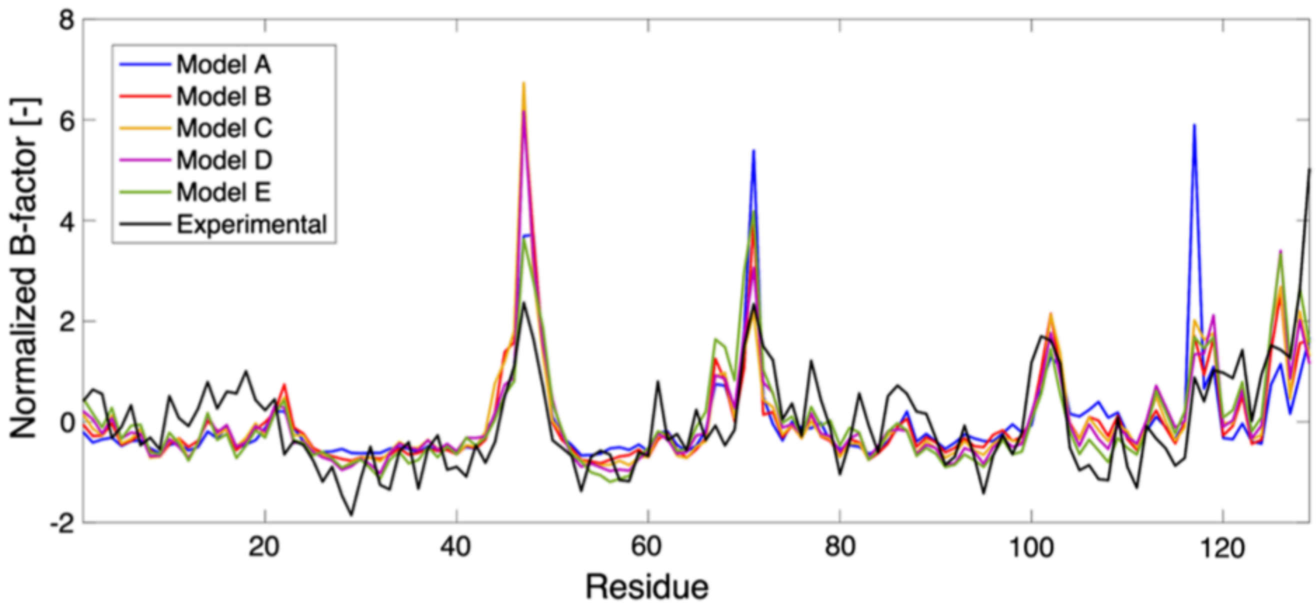
$$B_i = \frac{8}{3}\pi^2 k_B T \sum_{n=7}^{3N} \frac{{\delta_{i,n}}^2}{{\omega_n}^2}$$

How to set up the values of the axial rigidity *EA*? With the B-factors!

Imposing that the average value of the computed B-factors matches the average value of the experimental ones allows to define the rigidity of the ELM elastic bars

Model	Cutoff (Å)	Mean length of the elastic bar (Å)	*EA* (pN)	Stiffness of the mean connection (N/m)
A	8	5.71	831	1.455
B	10	7.21	235	0.326
C	12	8.61	124	0.144
D	15	10.59	71	0.067
E	20	13.46	45	0.033

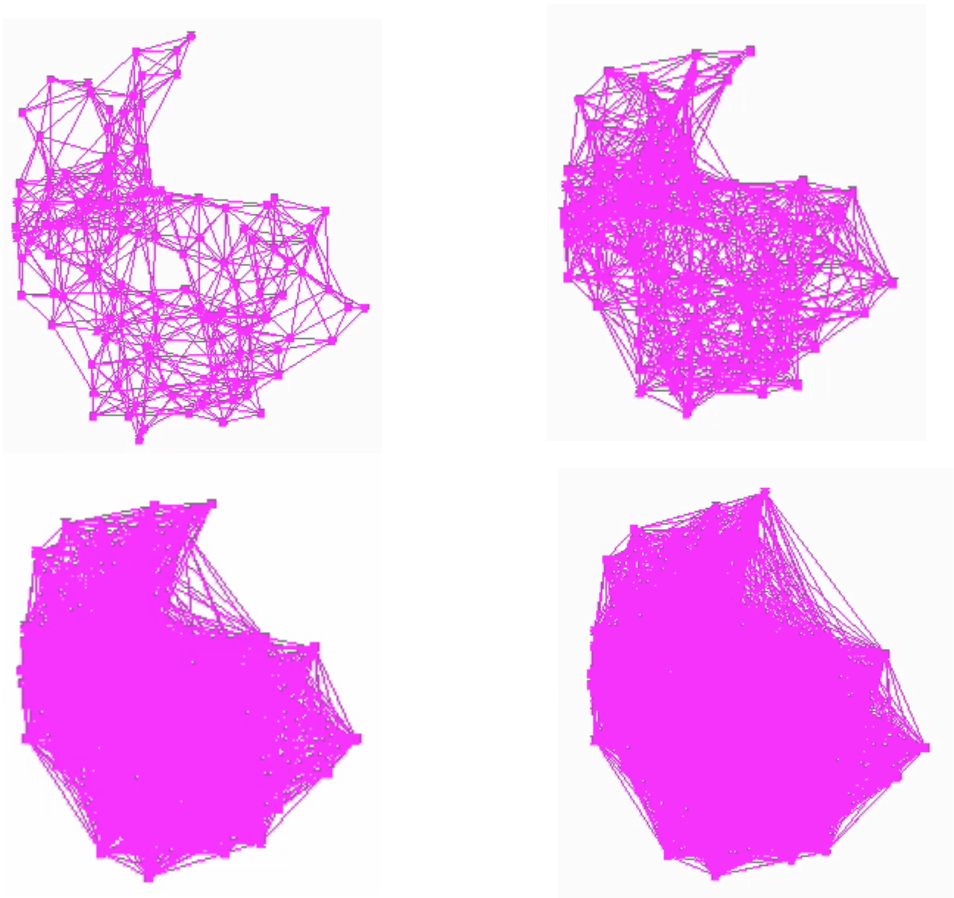
How to validate the models? With the B-factors!



Model	Correlation
A	0.57
B	0.67
C	0.66
D	0.69
E	0.72

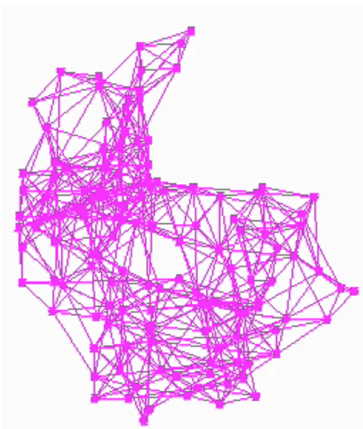
Correlation coefficients from 57% to 72%! These are very high values if you think how much the model is simplified and how much the physics of the problem is complex!

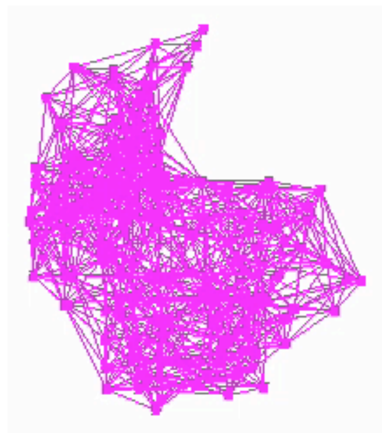
Looking at the 1st vibration modes…

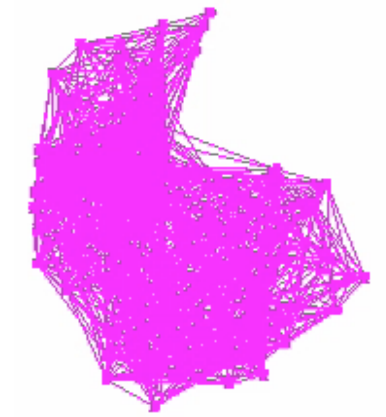


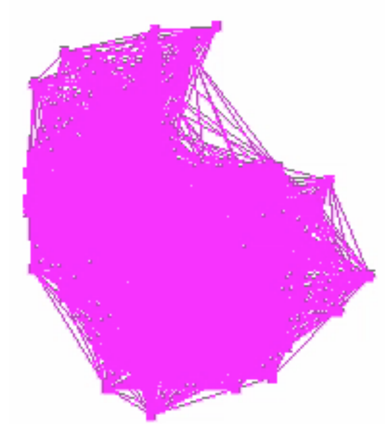
… we find a clear representation of the cleft opening-closing motion, which is known to be the actual biological mechanism of the lysozyme

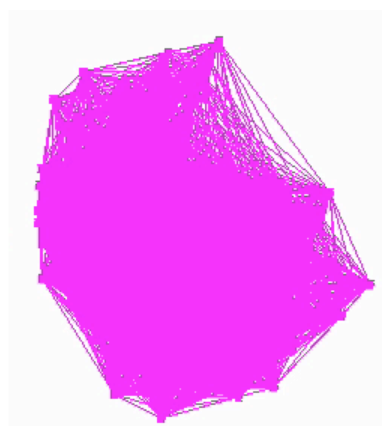
Looking at the 2nd vibration modes…







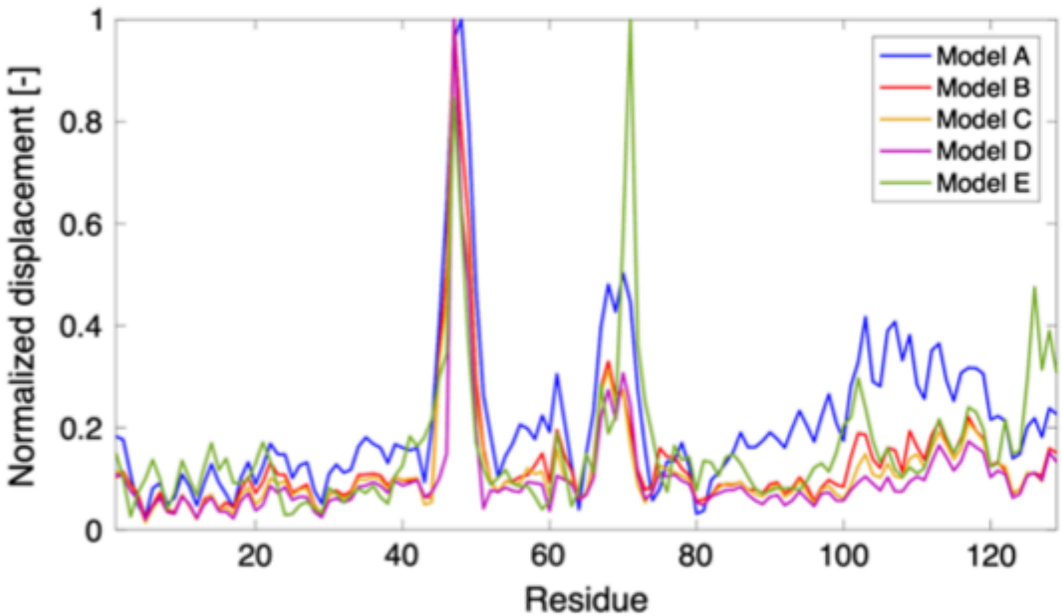




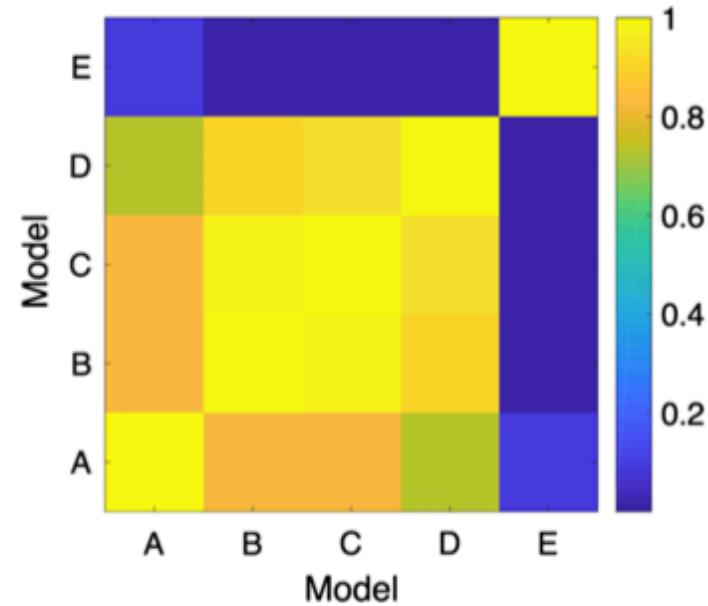
… we find an overall torsional twisting of the lysozyme, still with a significant flexibility in the cleft region

Does the cutoff parameter affect the mode shapes?

1st vibration mode



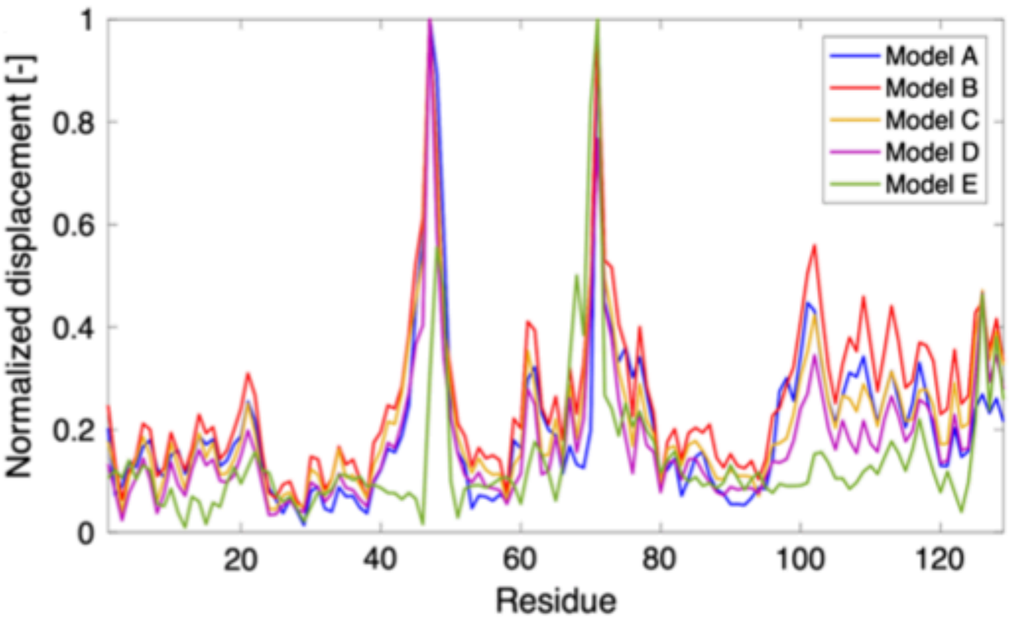
Absolute displacements



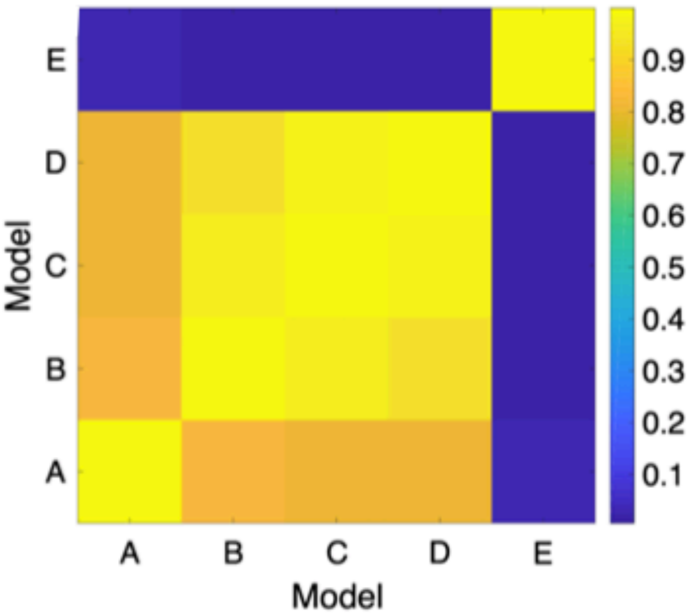
MAC matrix

Does the cutoff parameter affect the mode shapes?

2nd vibration mode

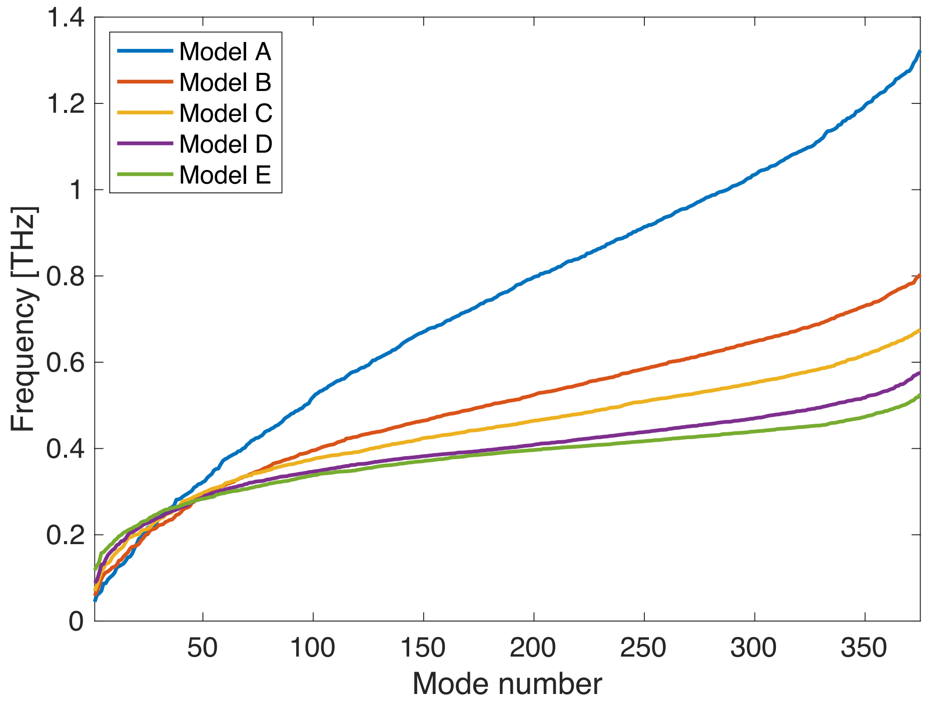


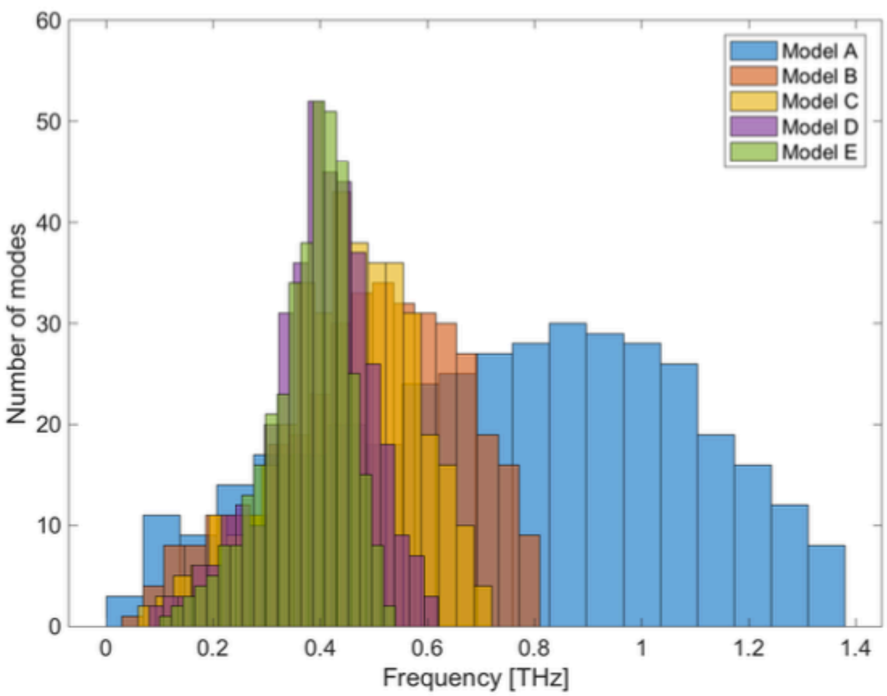
Absolute displacements



MAC matrix

What about the vibrational frequencies?





… we are in the (sub-)THz frequency range!

Conclusions

- We have shown that simplified mechanical models, such as ELMs, can be efficiently used to extract the vibrational states of proteins;
- The computed B-factors from the normal modes have a good correlation with the experimental values, although the cutoff parameter has a certain influence;
- The resulting mode shapes are well correlated with the biological mechanism of the protein;
- The corresponding vibrational frequencies lie in the (sub-)THz frequency range;
- Might resonances at these frequencies play a role in the conformational changes and biological processes?

Future Developments

What happens if we also apply (dynamic) forces to the protein ELM?

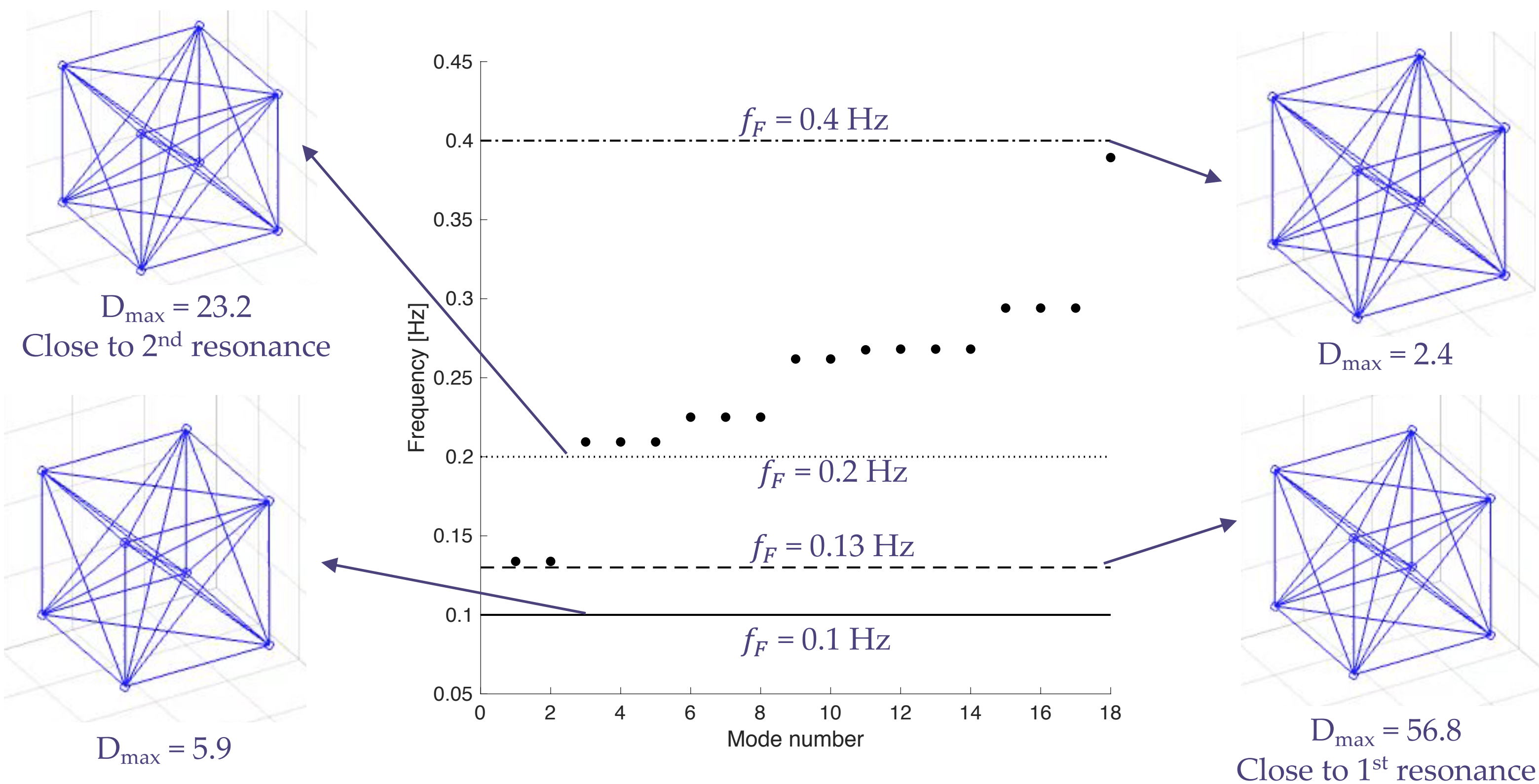
MDOF forced modal analysis ⟶ $\mathbf{Ku} + \mathbf{M\ddot{u}} = \mathbf{F}\, sin(\omega_F t)$

$$\mathbf{u}(t) = \sum_{n=7}^{3N} \boldsymbol{\delta}_\mathbf{n} p_n(t) \longrightarrow p_n(t) = \frac{{\boldsymbol{\delta}_\mathbf{n}}^T \mathbf{F}}{{\omega_n}^2 - {\omega_F}^2}\left[\sin(\omega_F t) - \frac{\omega_F}{\omega_n}\sin(\omega_n t)\right]$$

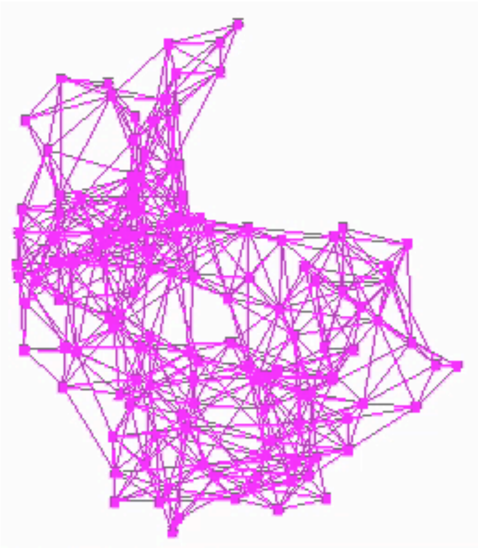
${\omega_F}^2 \rightarrow {\omega_n}^2$ ⟶ **Resonance according to the nth mode**

Future Developments

Toy model with random force field applied at various frequencies



Thank you for your attention!



D. Scaramozzino, G. Lacidogna, G. Piana, A. Carpinteri (2019) A finite-element-based coarse-grained model for global protein vibration. *Meccanica*. 54, 1927-1940.