Generalization of the Elastic Network model for the study of large conformational changes in proteins

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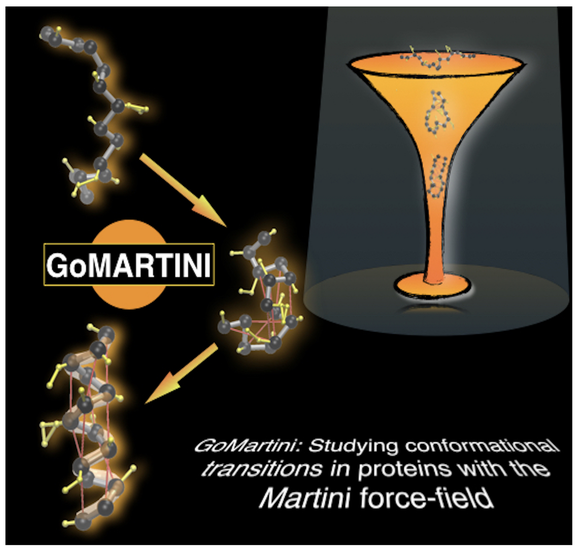
Abstract

The Elastic Network (EN) is a prime model that describes the long-time dynamics of biomolecules. However, the use of harmonic potentials renders this model insufficient for studying large conformational changes (e.g. stretching of proteins, folding and thermal unfolding). Here, we extend the capabilities of the EN model by using:

- A harmonic approximation described by Lennard–Jones (LJ) interactions for far contacts and Go-like contacts for native ones.
- We derive the energy scale separation between backbone and (non) native contacts.

Introduction

One of the most useful coarse grained (CG) force fields for proteins (Monticelli et al..[1]) is often simulated in combination with an elastic network (EN) model (the Elnedyn model [2]) which maintains the overall structure (e.g. secondary structure). However, the use of the EN model restricts the use of the MARTINI force field for the study of large conformational changes (e.g. folding). Our model the GoMARTINI [3] removes this limitation. Here, we investigate its implication and generalization for the EN model.



In particular, the EN is based on a single-parameter harmonic potential between residues that are represented by the C_α atoms. In this model, the harmonic interaction is included when the VdW radii of two residues overlap. This interaction aims to mimic the electrostatic and van der Waals interactions. The covalent bonds along the backbone of C_α are also describe by the same potential (Fig. 1).

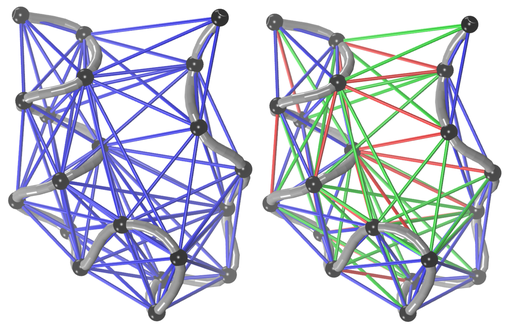


Figure 1: Left panel shows the EN model for a protein (PDB id: 1L2Y), the "unbreakable" harmonic EN contacts are shown in blue color. Right panel shows the Generalized EN model. Additional color lines are used to describe native and non-native contacts.

Generalized Elastic Network (GEN) model

The EN model define harmonic potentials by the form $V_{\rm harm} = C(r - r_0)^2$, where r_0 is the distance between C_α atoms in the native structure of the protein and C a constant indicating its strength. The energy scale associated to the EN model is given by $\epsilon_{\rm EN} = CR_c^2$.
In our model (GEN) we replace the EN bonds by a Go-like description as follows:

$$U_{\rm LJ}(r) = 4\epsilon_{\rm ij}\left[\left(\frac{\sigma_{\rm ij}}{r}\right)^{12} - \left(\frac{\sigma_{\rm ij}}{r}\right)^{6}\right], \qquad (1)$$

where r is the distance between any pair of i and j C_α atoms in the system. The relation between the effective harmonic term and the strength of the LJ potential described by the formula: $\epsilon_{ij} = \epsilon_{\rm harm}$, where $\epsilon_{\rm harm}$ is simply $\epsilon_{\rm harm} = C\sigma_{\rm ij}^2 36^{-1}(2^{-2/3})$ and $\sigma_{\rm ij} = 2^{-1/6} r_0$.

SIMULATION RESULTS

- We benchmark the GEN model with EN model by computing the Normal Modes in protein (Fig. 2).
- In simulation GEN model allows study of conformational changes (see stretching results in Fig. 3).

Important Result

We enable the use of the EN model for the description of large conformational changes in proteins while it retains its analytical capabilities such as the determination of the normal modes.

Result 1: Validation with EN model

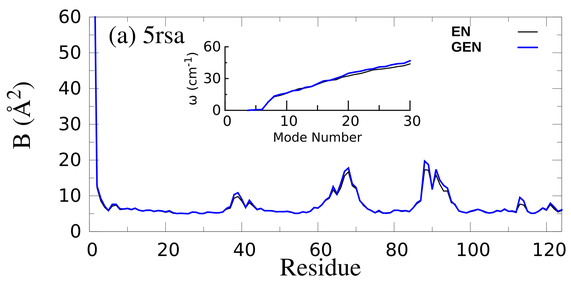


Figure 2: The B-factors for the lowest 30 modes for protein with PDF file 5rsa. Inset shows frequency ω^{-1}.

Result 2: Unfolding via stretching

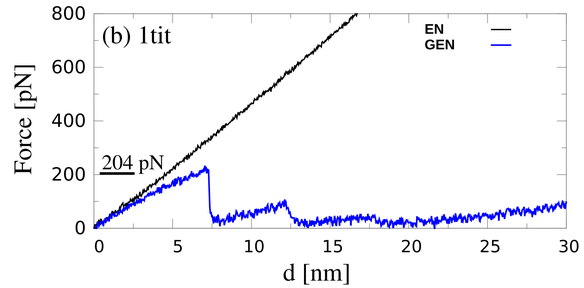


Figure 3: Force vs. displacement for I27 domain of titin. Experimental $F_{\rm max} = 204 \pm 30$ pN [4] is indicated by horizontal line.

Conclusion

- We show that the GEN model maintains a close match with the EN, while it reproduces the $F_{\rm max}$ in AFM-pulling experiments.
- And its foundation is based on the EN model with no assumption about the backbone connectivity and the only requirement is the energy scale separation ($\epsilon_{\rm EN} > \epsilon_{\rm cm} > \epsilon_{\rm harm}$) between contacts.

References

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Acknowledgments

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Futher Information

- Please visit: GoMARTINI and GOEN codes tutorials at: website: htttp://info.ifpan.edu.pl/~panos/panos/GoMartini.html

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