Protein Conformational Changes and Low-Frequency Vibrational Modes: A Similarity Analysis

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Domenico Scaramozzino, Giuseppe Lacidogna, and Alberto Carpinteri

Abstract The study of protein vibration and dynamics is receiving increasing attention among researchers, both from a numerical and experimental perspective. By using terahertz spectroscopy techniques, it has been shown that conformational changes, crucial for protein biological function, are strictly related to low-frequency vibrational modes. These motions generally occur in the terahertz range (~0.1–2 THz) involving large portions of the protein. The present contribution aims at investigating the role of terahertz (expansion-contraction) vibrational modes to protein conformational change from a numerical viewpoint. Modal analysis is performed by using C_α-only coarse-grained mechanical models: the obtained mode shapes are compared, by means of three similarity indexes, to the displacement field of protein conformational change. In particular, lysine-arginine-ornithine (LAO) binding protein is selected as a case study.

Keywords Conformational change · THz vibrational modes · Modal analysis · Similarity indexes · LAO binding protein

Introduction

Every aspect of protein biological activity is ruled by conformational changes. These structural rearrangements of protein three-dimensional shape occur in ligand binding phenomena, signaling and transportation processes, protein-protein interactions, etc. For example, hemoglobin changes its shape when binding to oxygen molecules, switching from a deoxy- to an oxy-state. Molecular motors, such as kinesin and myosin, move on microtubules and actin filaments, respectively, because of large conformational changes in their motor heads caused by ATP hydrolysis. Vinculin-talin complex at focal adhesions is driven by conformational switches in vinculin that expose cryptic binding sites [1].

However, given the strict relationship between biological functionality and protein native shape, conformational changes should have their fundamental reasons in some intrinsic feature of protein structure. In particular, low-frequency vibrational modes are believed to represent the ideal candidates for governing such transitions [2]. These motions generally involve the whole protein structure, or large portions of it. Recently, some of the authors performed modal analysis on protein mechanical models, aimed at investigating the expansion-contraction motions, by using both all-atom [3, 4] and coarse-grained representation [5], and obtained that these mechanical vibrations occur in the terahertz range.

From an experimental viewpoint, low-frequency vibrations can be detected, among others, by Raman spectroscopy technique. Brown et al. [6] analyzed α-chymotrypsin samples and found that these vibrational motions involve the whole protein structure. More recently, some of the authors performed Raman measurements using ultra-low frequency (ULF) filters on lysozyme and Na^+/K^+-ATPase powder samples and found some strong peaks around 0.8 THz [3, 7]. Besides the detection of terahertz vibrations, spectroscopy techniques were also applied to investigate protein conformational changes [8]. For this purpose, THz-TDS (terahertz time-domain spectroscopy) turned out to be a promising tool in monitoring protein shape changes [9, 10].

From a numerical perspective, several researches correlated the slowest motions to protein conformational changes by means of normal mode calculations [11–13]. In this contribution, we present a similarity analysis between the displacement field of lysine-arginine-ornithine (LAO) binding protein conformational change and its terahertz (expansion-contraction) vibrational modes, evaluated by means of the coarse-grained mechanical model developed in [5]. The aim was to confirm that also expansion-contraction low-frequency vibrations strongly contribute to protein conformational change, as well as to investigate the involved frequency range.

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M. E. Grady (ed.), *Mechanics of Biological Systems and Materials & Micro-and Nanomechanics, Volume 4*,
Conference Proceedings of the Society for Experimental Mechanics Series, https://doi.org/10.1007/978-3-030-30013-5_2

Methodology

The analysis was conducted by means of three similarity indexes. The first one (*SI*) is defined by the following equation:

$$SI_i = \frac{| \boldsymbol{\delta_i}^T \boldsymbol{CC} |}{\sqrt{\boldsymbol{\delta_i}^T \boldsymbol{\delta_i}} \sqrt{\boldsymbol{CC}^T \boldsymbol{CC}}}, \tag{1}$$

where $\boldsymbol{\delta_i}$ and $\boldsymbol{CC}$ represent the ith vibrational mode and the conformational change displacement field, respectively. Both of them are *3N*-vectors, being *N* the number of protein residues, i.e., C_α atoms. The former was evaluated by means of modal analysis on protein coarse-grained model, as described in [5]; the latter was computed by vector difference of the two protein reference states, after they have been superimposed. In the remainder of the text, the two protein conformations will be referred to as "open state" and "closed state". By applying Eq. (1), one can evaluate a numerical estimate of the contribution of the ith mode to the conformational change. In particular, *SI* is equal to 1 if $\boldsymbol{\delta_i}$ is equal $\boldsymbol{CC}$, whereas it is equal to 0 if the vectors are orthogonal. Another coefficient was then introduced, i.e. the cumulative-squared similarity index (*CSSI*), defined by the following formula:

$$CSSI_i = \sum_{k=1}^{i} {SI_k}^2, \tag{2}$$

which aims at evaluating the contribution of the first *i* vibrational modes to the conformational change. Considering that the eigenmodes constitute a normal vector basis, by simple calculations, one obtains $CSSI_{3N} = 1$. Note that, if all the vibrational modes had the same contribution to the conformational change displacement field, i.e. $SI_i = SI_{const}$, one would obtain:

$$CSSI_{3N} = 1 = \sum_{k=1}^{3N} {SI_k}^2 = \sum_{k=1}^{3N} {SI_{const}}^2 \Rightarrow {SI_{const}}^2 = \frac{1}{3N}. \tag{3}$$

Therefore, a third similarity index can be defined, namely the normalized-squared similarity index (*NSSI*), which is defined as follows:

$$NSSI_i = \frac{{SI_i}^2}{{SI_{const}}^2}, \tag{4}$$

and provides a numerical estimate of the relative contribution of the ith vibrational mode to the conformational change, with respect to the case in which all the modes had the same involvement.

Results and Discussion

As a case study, lysine-arginine-ornithine (LAO) binding protein was selected, a 238-residues molecule. The reference open and closed states (Fig. 1) were taken from Protein Data Bank [14] (pdb codes: 2lao and 1lst, respectively).

After performing modal analysis on both coarse-grained structures, the similarity analysis was conducted for both the open-closed and closed-open transition (Figs. 2 and 3), and approximately the same results were obtained for both conformational changes. Coherently, it was found that the first six vibrational modes, which refer to rigid motions at zero-frequency, exhibit no contribution to the conformational change. The most involved expansion-contraction vibrational mode is the seventh one for both transitions, leading to $SI_7 = 0.41$ and $SI_7 = 0.46$, for the open-closed and closed-open change, respectively. The similarity index then decreases rapidly for higher mode numbers (Figs. 2a and 3a). As far as the cumulative index distribution is concerned, it can be noted that *CSSI* increases sharply for low mode numbers and then it advances more slightly (Figs. 2b and 3b). Finally, as can be seen from the normalized-squared similarity index distribution, very high values (up to 120–150) are found for the lowest modes, whereas it approaches to zero for higher mode numbers (Fig. 2c and 3c).

Although from a theoretical point of view, all vibrational modes are needed to define any displacement field, in this case, the first 100 ones (on a total of more than 700) are able to describe almost 90% of protein conformational change (Figs. 2b and 3b), thus confirming that also expansion-contraction low-frequency motions contribute more than high-frequency ones.

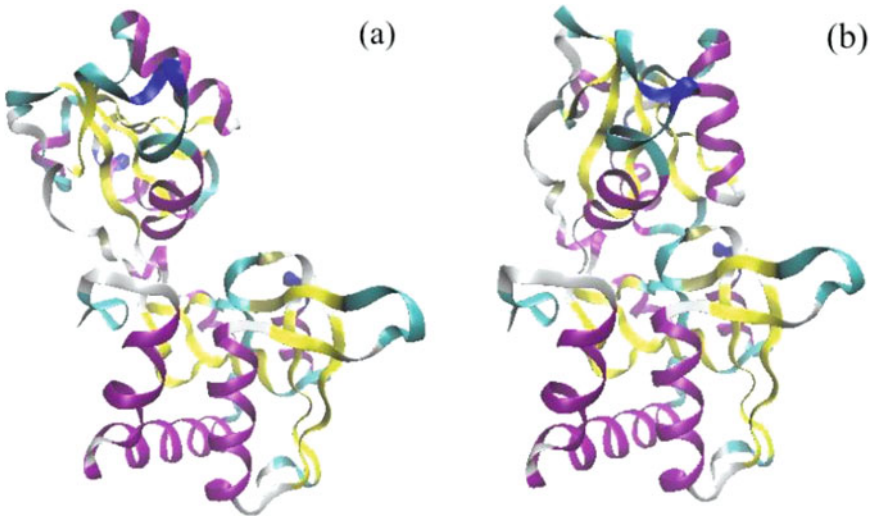

Fig. 1 LAO binding protein: (**a**) open state, (**b**) closed state. Figures obtained by VMD [15]

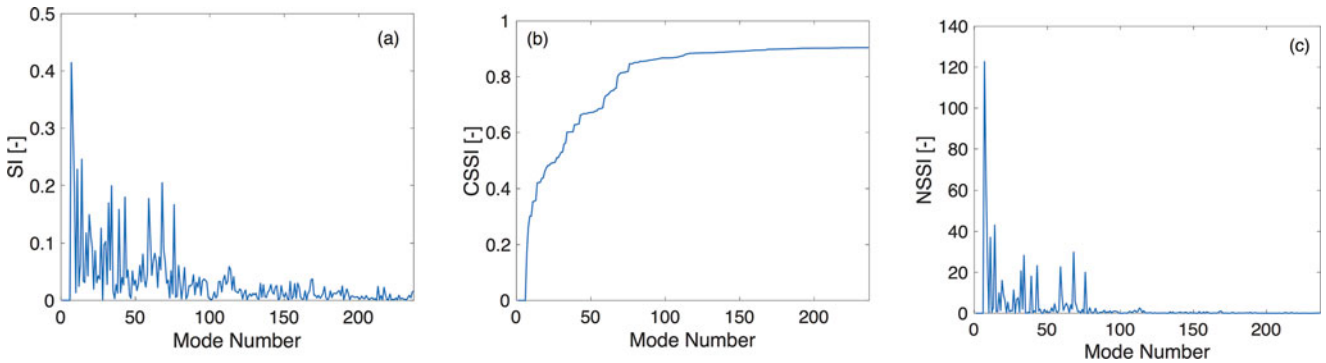

Fig. 2 Similarity indexes (open-closed conformational change): (**a**) *SI*, (**b**) *CSSI*, (**c**) *NSSI*

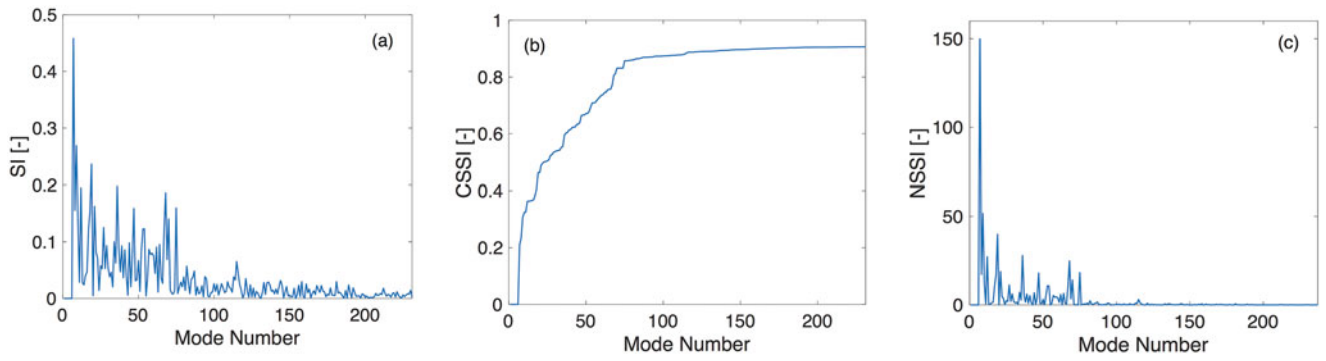

Fig. 3 Similarity indexes (closed-open conformational change): (**a**) *SI*, (**b**) *CSSI*, (**c**) *NSSI*

Finally, by associating each mode number to the corresponding frequency of vibration, one can observe that most of the conformational change occurs within the frequency range around and below 1 THz (~0.1–2 THz), which is the range in which *NSSI* shows very high values (Fig. 4).

It must be noted that the obtained similarity indexes are not so high, the maximum values being lower than 0.5. Besides the fact that only the expansion-contraction modes of the protein backbone are described here, other explanations could be provided for such results. First, modal analysis calculations deal with the evaluation of vibrations around the equilibrium position of the protein structure, i.e., under the assumption of small deformations and linear elasticity; however, the conformational transition may also imply large displacements which, in turn, can be associated with some (geometrical)

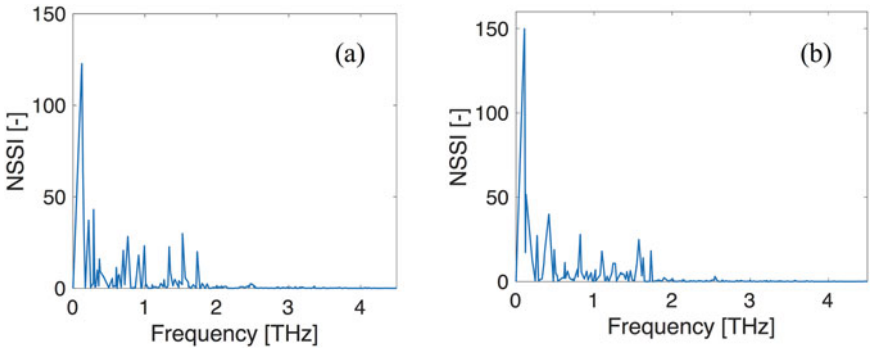

Fig. 4 *NSSI* vs vibrational frequencies: (**a**) open-closed, (**b**) closed-open conformational change

nonlinearities. Secondly, when evaluating the displacement field of the shape change as the vector difference between the two superimposed protein structures, one is implicitly assuming that it happens with a linear transition from the initial state to the final one; however, it is likely that the actual conformational change implies curve pathways as well.

Conclusions

In this contribution, we presented a similarity analysis between the displacement field of LAO binding protein conformational change and the expansion-contraction low-frequency (THz) vibrational modes, obtained via modal analysis by means of a simplified coarse-grained model. Numerical results confirmed that low-frequency motions are the most involved within the protein conformational change and, according to the developed mechanical model, it was found that the protein transition exhibits strong fingerprints within the frequency range between 0.1 and 2 THz. It is strongly believed by the authors that further experimental researches focusing on THz frequencies, for example by means of THz-TDS and low-frequency Raman spectroscopy, could provide interesting insights on the mechanisms underlying protein biological functionality.

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