11th World Congress on Computational Mechanics (WCCM XI)
5th European Conference on Computational Mechanics (ECCM V)
6th European Conference on Computational Fluid Dynamics (ECFD VI)
July 20 - 25, 2014, Barcelona, Spain

Development of Robust Elastic Network Model for Predicting the Experiment B-factor precisely

MIN HYEOK KIM[1] AND MOON KI KIM[1,2]

[1] SKKU Advanced Institute of Nanotechnology (SAINT) Sungkyunkwan University, 440-746, dmz2080@skku.edu, bioengineering.skku.ac.kr

[2] School of Mechanical Engineering Sungkyunkwan University, 440-746, mkkim@me.skku.ac.kr, bioengineering.skku.ac.kr

Key Words: *Elastic Network Model, B-factor, Protein dynamics, Low Frequency Mode.*

ABSTRACT

In order to describe the protein dynamics which are closely related to its biological functions, molecular dynamics (MD) and normal mode analysis (NMA) have been widely used. However, their all-atom based force fields cause significant computational burden resulting in a limitation of simulation scale in practice. Alternatively, coarse-grained elastic network model (CG-ENM) was introduced. In this model, a target system is modelled as a linear spring network among representative atoms, typically Cα in proteins. Even though CG-ENM efficiently predict the collective motions of proteins, its arbitrary assignment of spring constant and non-reflected symmetric constrains lead to inaccurate anisotropic temperature factors, yielding the low correlation between prediction and experiment B-factor of ~ 0.59 [1]. To improve the accuracy of B-factor prediction, we propose a new robust ENM which not only considers the experimental crystallization environment based on the space groups but use optimum spring constant by matching with the experimental B-factor. The optimal spring constant is determined by minimizing the root mean square deviation (RMSD) between experimental and predicted B-factors iteratively.

$$\gamma_{new} = 8\pi^2 k_B T \cdot trace[\sum_{k=7}^{3N} \lambda_k^{-1} u_k u_k^T] / \sum_{i=1}^{N} B_i \quad (1)$$

where k_B is Boltzmann constant, T is temperature, and B_i represent and experimental B-factor of i^{th} atoms. λ_k and u_k are the eigenvalue and eigenvector of the k^{th} mode obtained from following equation of motion in Eq.2. They can be interpreted as frequency and its corresponding mode shape, respectively.

$$M\ddot{\vec{\delta}} + K\vec{\delta} = 0 \quad (2)$$

Here M is global inertia matrix and K is the stiffness matrix both of which are formed by CG-ENM. For more details, a full mathematical derivation is available elsewhere [2].

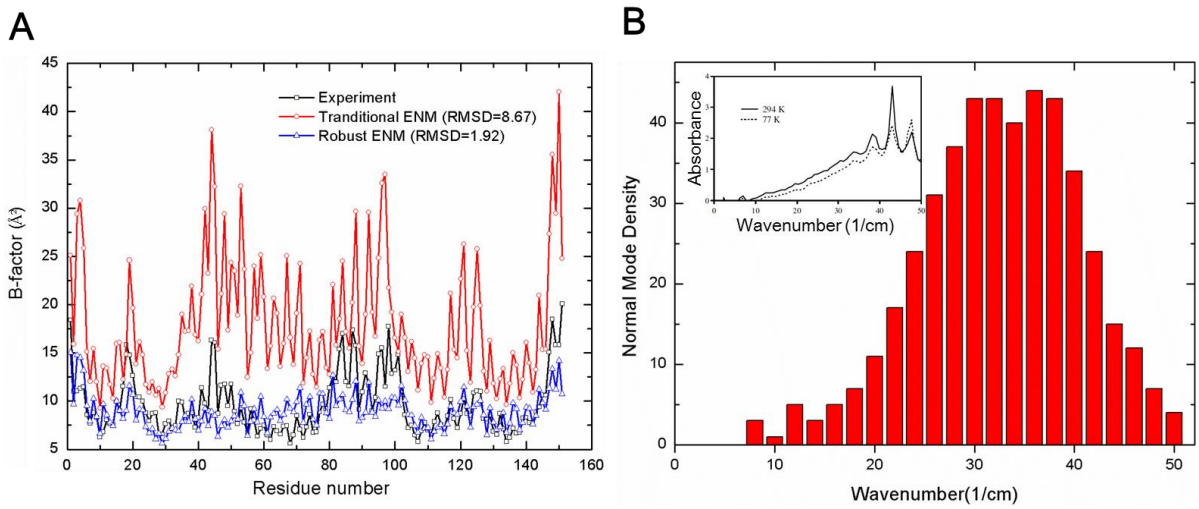

Figure 1. NMA results of horse heart myoglobin. A) Comparison of the experimental and calculated B-factors. The experimental B-factors are denoted by the black line, while the red and blue curves denote the calculated B-factors based on traditional ENM and robust ENM, respectively. B) Normal mode spectra have a range of 0 ~ 50 cm^{-1}. Inset: absorption spectra measurement by THz time domain spectroscopy [3].

Among more than 500 tested proteins, over the 90% structure results in the better accuracy of B-factor prediction based on proposed robust ENM having the optimum spring constant of $3\sim5\times10^4$ *dynes/cm* , regardless of space group and protein size. For further validation, additional protein such as horse heart oxy-myoglobin (PDB 1A6M) is arbitrary selected and its B-factor is predicted by the proposed method. RMSD value between experimental and predicted B-factor is dramatically reduced from 8.67 Å ² to 1.92 Å ² (Fig. 1A). Moreover, the predicted normal mode spectrum ranging from 0 ~ 50 cm^{-1} are very similar to those from THz time domain spectroscopy as shown Fig. 1B. In conclusion, the proposed robust ENM enable us to gain a much deeper insight into protein dynamic by providing a more precise model in consideration of its space group and optimal spring constant.

REFERENCES

[1] S. Kundu, J.S. Melton, D.C. Sorensen and G.N. Philips. Dynamics of proteins in crystals: comparison of experiment with simple models. *Biophys. J*, Vol. **83**, pp. 723–732, (2002).

[2] M. Kim, G. Chirikjian and R. Jernigan. Elastic Models of conformational transitions in macromolecules. *J. Mol. Graph. Model*, Vol. **21**, pp. 151-160, (2002).

[3] A. Markelz, S. Whitemire, J. Hillebrecht and R Birge, *Phys. Med. Biol*, Vol. **47**, pp. 3797-3805, (2002).