

2012 AASRI Conference on Computational Intelligence and Bioinformatics

## Prion Protein Motion Modes Analysis with Gaussian Network Model

Li-sheng Qi <sup>a\*</sup>

<sup>a</sup> Key Lab of Biophysics in Universities of Shandong

<sup>a</sup> Department of Physics, Dezhou University, Dezhou 253023, Shandong, China

---

### Abstract

Prion diseases are fatal neurodegenerative disorders caused by an aberrant accumulation of the misfolded cellular prion protein (PrP<sup>C</sup>) conformer, denoted as infectious scrapie isoform (PrP<sup>Sc</sup>). The slow and fast motion models of huPrP and huPrP (E200K) structures were analyzed with the GNM in this paper. It can be seen that the largest fluctuation values corresponding to the helix 1. Residue 147 and residue 150 play an important role in the stability of the helix 1. The major consequence of the E200K substitution appears to be the redistribution of surface charges, resulting in an altered electrostatic potential in the mutant protein. This change is likely to affect the stability of the helix 1. Thus, their behavior might reflect that of wild-type PrP or that of mutants associated with transmissible forms of the disease.

2012 Published by Elsevier B.V. Selection and/or peer review under responsibility of American Applied Science Research Institute Open access under [CC BY-NC-ND license](https://creativecommons.org/licenses/by-nc-nd/4.0/).

**Keywords:** Prion Protein; Mutant; GNM; Motion mode

---

### 1. Introduction

Prion proteins (PrP) are associated with the transmissible spongiform encephalopathies (TSE) in a variety of mammals, including bovine spongiform encephalopathy (BSE) in cattle and Creutzfeldt-Jakob disease (CJD) in humans. According to the “protein only” hypothesis, the key event in the pathogenesis of prion

---

\*E-mail address: [qlsheng@126.com](mailto:qlsheng@126.com).

disorders is the conversion of a normal prion protein, PrP<sup>C</sup>, into a pathogenic (scrapie) form, PrP<sup>Sc</sup> [1, 2]. The transition between PrP<sup>C</sup> and PrP<sup>Sc</sup> occurs without any detectable covalent modifications to the protein molecule [3]. PrP<sup>C</sup> is a soluble protein with a high content of  $\alpha$ -helices, whereas PrP<sup>Sc</sup> is characterized by a high  $\beta$ -sheet content [4]. Considering that the “protein-only” hypothesis suggests a change of protein conformation as a possible cause of the onset of TSEs, the three-dimensional PrP structures have attracted keen interest. So far, NMR solution studies have been described for monomeric, cellular forms of PrP [5, 6]. Although some studies provide valuable insights into the PrP, the mechanism of conformational transitions of the PrP<sup>C</sup>-PrP<sup>Sc</sup> is not fully clear [7, 8].

In this work, we used a simple model called the Gaussian Network Model (GNM) to study the dynamic properties of PrP. It is a coarse-grained model which is topology-based and independent of sequence specificity [9]. This model can provide the dynamic properties of proteins near an equilibrium state (usually native state). In this model, each residue is represented by its C-alpha atom, and the detailed interactions between residues to be in contact in the native state are replaced with springs. Some studies have indicated that such a simple treatment of the interactions in the native protein is sufficient to account for many experimental facts [10,11].

## 2. Materials and methods

### 2.1. Materials

The NMR structures of huPrP include a globular domain and an N-terminal flexibly disordered “tail”. The globular domain contains of three  $\alpha$ -helices that encompass residues 144–154 (helix 1), 173–194 (helix 2), and 200–228 (helix 3) and a short anti-parallel  $\beta$ -sheet comprising the residues 129–131 and 161–163 (PDB: 1QM2) [5]. The structure of the E200K variant of huPrP was characterized by NMR spectroscopy (PDB: 1FKC), which is similar to the wild-type huPrP [6].

### 2.2. Gaussian Network Model (GNM)

The GNM describes a three-dimensional protein structure as an elastic network of C-alpha atoms connected by harmonic springs within a certain cutoff distance. For all springs, the force constant is taken as identical. The dynamics of the structure in the GNM is fully defined by the topology of contacts described by the Kirchhoff matrix  $\Gamma$ . For a network of  $N$  interacting sites, the elements of  $\Gamma$  are defined as [9]

$$\Gamma_{ij} = \begin{cases} -1 & \text{if } i \neq j \text{ and } R_{ij} \leq r_c \\ 0 & \text{if } i \neq j \text{ and } R_{ij} > r_c \\ -\sum_{i,i \neq j} \Gamma_{ij} & \text{if } i = j \end{cases} \quad (1)$$

where  $R_{ij}$  represents the distance between the  $i$ th and  $j$ th nodes and  $r_c$  for the cutoff distance. The mean-square fluctuations of each node and the cross-correlation fluctuations between different nodes are in proportion to the diagonal and off-diagonal elements of the pseudo inverse of the Kirchhoff matrix. The inverse matrix of the Kirchhoff matrix can be decomposed as

$$\Gamma^{-1} = U\Lambda^{-1}U^T \quad (2)$$

where  $U$  is an orthogonal matrix with eigenvectors of  $\Gamma$  as its columns vectors  $u_k (1 \leq k \leq N)$ .  $\Lambda$  is a diagonal matrix with the eigenvalues of Kirchhoff matrix. The cross-correlation fluctuations between the  $i$ th and  $j$ th residues can be calculated by

$$\langle \Delta R_i \cdot \Delta R_j \rangle = 3k_B T [\Gamma^{-1}]_{ij} / \gamma \quad (3)$$

where  $k_B$  is Boltzmann constant,  $T$  is absolute temperature. When  $i=j$ , the mean-square fluctuations of the  $i$ th residue can be obtained. The mean-square fluctuation of the  $i$ th residue associating with the  $k$ th mode is given by

$$\langle \Delta R_i \cdot \Delta R_i \rangle_k = 3k_B T \lambda_k^{-1} [u_k]_i [u_k]_i / \gamma \quad (4)$$

### 3. Results and discussion

#### 3.1. The slow and fast motion modes of the huPrP

The slow modes represent functionally relevant motions of protein. The fast modes correspond to geometric irregularity in the local structure and the fluctuations associated with fast modes are accompanied by a decrease in entropy larger than that for slow modes. Therefore, residues acting in the fast modes are thought to be kinetically hot residues and they are critically important for the stability of the tertiary fold [9].

The slow and fast motions of huPrP structure were calculated by the GNM, as shown in Fig. 1. The ordinates in Fig. 1(a) show the normalized distribution of squared fluctuations driven by the first slowest modes. From the figure, the domain (residues 140-160) exhibit large fluctuation values. The structure has the common hinge axes located around 131 and 160, among which Beta1 and Beta2, with the fluctuation values approximate to zero. It is also seen in Fig. 1(a), there is a local minimum (residue 147) in the region of large fluctuation. The ordinates in Fig. 1(b) show the normalized distribution of squared fluctuations driven by the fastest six modes of huPrP. From the figure, it is found that residue 147 and 150 exhibit a local maximum fluctuation value. Helix 1 is formed in the early protein folding process. These results show that the helix 1 may play an important role in the stability of the protein.

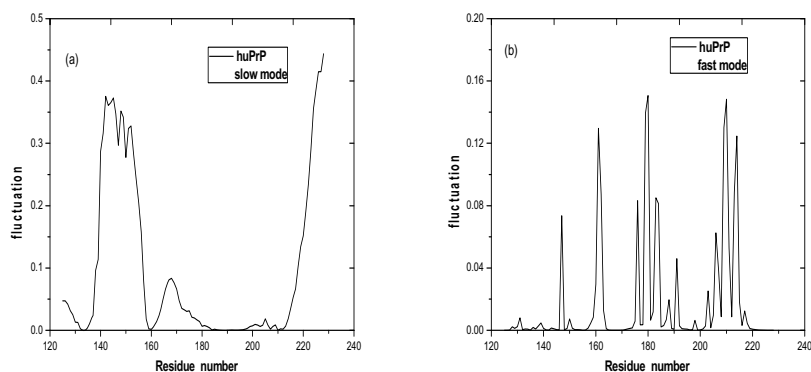


Fig. 1 Slow (a) and fast (b) motion modes of huPrP

#### 3.2. The slow and fast motion modes of the huPrP (E200K)

Although Glu<sup>200</sup>→Lys substitution has very little effect on the thermodynamic stability of PrP, numerous observations argue for a causative role of this mutation in CJD [7]. The structure of the E200K variant of huPrP was characterized by NMR [6]. Residue 200 is located at the beginning of helix 3 and is fully

accessible to the solvent. The substitution has a major effect on the distribution of charges on the protein surface. The slow and fast motions of huPrP (E200K) structure were calculated by the GNM, as shown in Fig. 2. It is seen in Fig. 2(a) that the slow motions of mutant is similar to the wild-type PrP. The flexibility of helix 1 in the mutant is higher than that of the wild-type PrP. This indicates that the helix 1 can show more large movement and this may be result in the conformational transitions of protein. But the fluctuation of residue 147 in the mutant PrP decreased remarkably, and the residue 150 with the fluctuation values approximate to zero in the fast motion mode, as shown in Fig. 2(b). The peaks of the fast modes correspond to residues that were thought, in the GNM, to be important for the stability of the protein. The fluctuation decrease of two residues implies that the PrP became more unstable in the mutant structure than in the wild-type structure.

Helix 1 mainly contains some charge and hydrophilic residues. So the ability of hydrophobic interactions is poor. The stability and conformational transitions of helix 1 are mainly affected by the electrostatic interactions. The Glu<sup>200</sup>—Lys replacement has an effect on the distribution of charges on the protein surface, thus the change affects the stability of helix 1. The presence of additional positively charged patches in the E200K variant could further promote these interactions, placing the protein in an environment that is especially conducive to the transition into the pathogenic PrP<sup>Sc</sup> conformation.

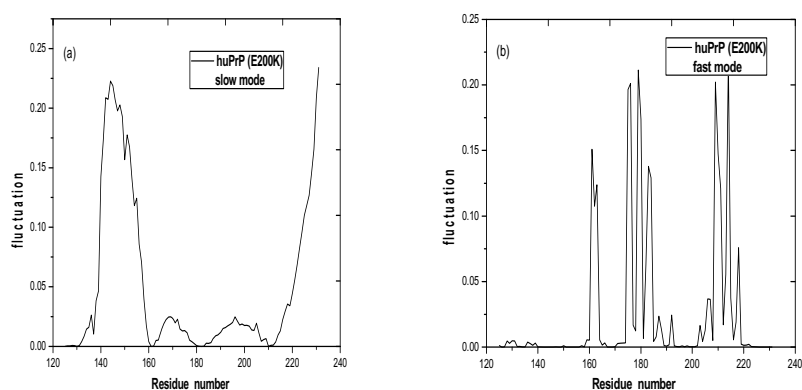


Fig. 2 Slow (a) and fast (b) motion modes of huPrP (E200K)

#### 4. Conclusions

The PrP<sup>C</sup> to PrP<sup>Sc</sup> transformation involves a conversion from a soluble and predominantly  $\alpha$ -helical protein to an aggregated form, which is substantially enriched in  $\beta$ -sheet. The slow and fast motion models of huPrP and huPrP (E200K) structures were calculated by the GNM in this paper. It can be seen that the largest fluctuation values corresponding to the helix 1. Residue 147 and residue 150 play an important role in the stability of the helix 1. The major consequence of the E200K substitution appears to be the redistribution of surface charges, resulting in an altered electrostatic potential in the mutant protein. The above change is likely to affect the stability of the helix 1. Thus, their behavior might reflect that of wild-type PrP or that of mutants associated with transmissible forms of the disease.

#### Acknowledgements

This work was supported by a grant from Shandong Natural Science Foundation (Grant No. ZR2010CQ033).

## References

- [1] Kuwata K, Li H, Yamada H. Locally disordered conformer of the hamster prion protein: a crucial intermediate to PrPSc?. *Biochemistry*, 2002; 41:1277–83.
- [2] Aguzzi A, Sigurdson C, Heikenwaelder M. Molecular mechanisms of prion pathogenesis. *Annu Rev Pathol*, 2008; 3:11–40.
- [3] Hornemann S, Schroetter C, Damberger F. Prion protein-detergent micelle interactions studied by NMR in solution. *J Biol Chem*, 2009; 284:22713–721.
- [4] Collinge J. Prion diseases of humans and animals: Their causes and molecular basis. *Annu Rev Neurosci*, 2001; 24:519–550.
- [5] Zahn R, Liu A. NMR solution structure of the human prion protein. *PNAS*, 2000; 97:145-150.
- [6] Zhang YB, Swietnicki W, Zagorski MG. Solution structure of the E200K variant of human prion protein. *J Biol Chem*, 2000; 275: 33650-654.
- [7] Mancuso M, Siciliano G. Creutzfeldt–Jakob disease with E200K PRNP mutation: a case report and revision of the literature. *Neurol Sci*, 2009; 30: 417-420.
- [8] Lee S, Antony L, Hartmann R. Conformational diversity in prion protein variants influences intermolecular beta-sheet formation. *Embo J*, 2010; 29: 251-262.
- [9] Haliloglu T, Bahar I. Gaussian dynamics of folded proteins. *Phys Rev Lett*, 1997; 79: 3090–93.
- [10] Kilho E and Sungso N. Coarse-grained elastic models of protein structures for understanding their mechanics and dynamics. *PNAS*, 2010; 7: 1-17.
- [11] Rader AJ, Karimi HA. iGNM: a database of protein functional motions based on Gaussian network model. *Bioinformatics*, 2005; 21: 2978–87.