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The Sensor Network in Molecular Structures of PrP(113-120) AGAAAAGA Amyloid Fibrils

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Abstract

The problem of locating sensors in telecommunication networks is a distance geometry problem (DGP). In such a case, the positions of some sensors are known (which are called anchors) and some of the distances between sensors (which can or cannot be anchors) are known. The DGP is to locate the positions of all the sensors. Molecular DGP (MDGP) looks sensors as atoms and their telecommunication network as a molecule for the determination of its three-dimensional (3D) structure. This Chapter defines some sensor networks for determining molecular structures of PrP(113-120) AGAAAAGA amyloid fibrils, which are unstable, noncrystalline, insoluble and hard to be determined in NMR or X-ray experimental laboratories. The amyloid fibril structure is the common structure associated with some 20 neurodegenerative amyloid diseases (including Parkinson's, Alzheimer's, Huntington's, and Prions'), and other diseases such as Type II diabetes, etc. The sensor networks established in this Chapter will benefit the study of 3D molecular structures of all these diseases and will be useful in the research areas such as structural materials, computer-aided or structure-based drug design, and the computational theory of molecular dynamics, and quantum mechanics/molecular mechanics.

Keywords: Sensor networks; Distance Geometry Problem (DGP); Molecular Distance Geometry Problem (MDGP); Amyloid fibril MDGP models; Neurodegenerative diseases

Introduction

Neurodegenerative diseases including Parkinson's, Alzheimer's, Huntington's, and Prions' are amyloid fibril diseases [1], where such as mad cow disease in cattle, scrapie in sheep and kuru and Creutzfeldt-Jakob disease (CJD) in humans are prion diseases. Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker (GSS) syndrome, Fatal familial insomnia (FFI) and Kuru are the main prion diseases affecting humans. The atomic structures of all these amyloid fibrils revealed steric zippers, with strong van der Waals (vdWs) interactions between β-sheets and hydrogen bonds (HBs) to maintain the β-strands [2]. As we all know, prion proteins have two regions: the N-terminal unstructured region and the C-terminal structured region. The prion AGAAAAGA palindrome hydrophobic region PrP^{C}(113-120) just falls within the N-terminal unstructured region PrP^{C}(1-123). According to Brown [3], AGAAAAGA is important for fibril formation and is an inhibitor of PrP^{Sc} neurotoxicity. However, to date the structural data on AGAAAAGA is very little, and traditional X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy experimental methods cannot be easily used to get the structural data of AGAAAAGA. Thus, the advanced computational methods introducing novel mathematical formulations and physical concepts into MDGPs of the molecular medicine field have some advantages under such a circumstance.

The atomic structures of all amyloid fibrils revealed steric zippers, with strong vdW interactions between β-sheets and HBs to maintain the β-strands [2]. The "amyloid fibril" problem can be looked as a MDGP [4], which arises in the interpretation of NMR (nuclear magnetic resonance) data and in the determination of protein structure [as an example to understand MDGP, the problem of locating sensors in telecommunication networks is a DGP. In such a case, the positions of some sensors are known (which are called anchors) and some of the distances between sensors (which can be anchors or not) are known: the DGP is to locate the positions of all the sensors. Here we look sensors as atoms and their telecommunication network as a molecule]. The three dimensional structure of a molecule with n atoms can be described by specifying the 3-Dimensional coordinate positions x_1, x_2, …, x_n in R^3 of all its atoms. Given bond lengths d_{ij} between a subset S of the atom pairs, the determination of the molecular structure is

$$\text{(P) to find } X_1, X_2, \ldots X_n \text{ subject to } \|X_i - X_j\| = d_{ij}, (i,j) \text{ in S,}$$

where $\|.\|$ denotes a norm in a real vector space and it is calculated as the Euclidean distance 2-norm in this article. (P) can be reformulated as a mathematical global optimization problem

$$\text{(GOP) } \min P(X) = \sum_{(i,j) \text{ in } S} w_{ij} \left(\|x_i - x_j\|^2 - d_{ij}^2 \right)^2$$

in the terms of finding the global minimum of the function P(X), where $w_{ij}, (i,j)$ in S are positive weights, $X = (x_1, x_2, \ldots, x_n)^T$ in R^{3n} [5] and usually S has many fewer than $n^2/2$ elements due to the error in the theoretical or experimental data [4,6]. There may even not exist any solution $X_1, X_2, \ldots X_n$ to satisfy the distance constraints in the orginal problem (P), for example when data for atoms *i, j, k* in S violate the triangle inequality; in this case, we may add a perturbation term $-\varepsilon^T X$ to $P(X)$:

$$(P\varepsilon) \quad \min P\varepsilon(X) = \sum_{(i,j) \text{ in } S} w_{ij} \left(\|x_i - x_j\|^2 - d_{ij}^2 \right)^2 - \varepsilon^T X,$$

where

In some cases, instead exact values d_{ij}, (i,j) in S can be found, we can only specify lower and upper bounds on the distances:

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$l_{ij} \le \|x_i - x_j\| \le u_{ij}, (i,j)$ in S; in such cases we may penalize all the unsatisfied constraints into the objective function of (Pε) by adding

$$\sum_{(i,j) \text{ in } S} \left(\max\{l^2_{ij} - \|x_i - x_j\|^2, 0\}\right)^2 + \left(\max\{\|x_i - x_j\|^2 - u^2_{ij}, 0\}\right)^2$$

into $P\varepsilon(X)$ [4,6], where we may let d_{ij} be the interatomic distance (less than 6 angstroms) for the pair in successive residues of a protein and set

$$l_{ij} = (1-0.05)d_{ij} \text{ and } u_{ij} = (1+0.05)d_{ij}$$

[4]. If we look at the prion AGAAAAGA molecular modeling problem as a MDGP with two anchors and two sensors, we can easily construct the prion AGAAAAGA amyloid fibril models. In fact we may let the coordinates of these two anchors being variable. But, these two anchors belong to one body of a chain of a molecule, and the two sensors belong to another body of another chain of the molecule. This is a simple two-body problem model of theoretical physics, i.e. Einstein's absolute relative theory. Hence, we may look the coordinates of two anchors being fixed.

This article will use do some homology modellings for the PrP^{Sc} unstructured region (113-120), AGAAAAGA. The atomic-resolution amyloid fibril structure of this peptide is a steric zipper, with strong vdW contacts and HBs to maintain the molecular structure. The minimization problem of vdW and HB contacts can be looked as a MDGP. In the section of Methods, we present the templates from the Protein Data Bank (http://www.rcsb.org, PDB), which will be used to construct the amyloid fibril models. How to build the models will also be presented in the Methods' section. Next, in the section of Results, we will show the optimized amyloid fibril models. At last, we give some comments in the section of Conclusions.

Methods

The constructions will be based on the most recently released experimental molecular structures in the PDB bank:

- 3NHC.pdb,
- 3MD4.pdb, 3MD5.pdb,
- 3NVE.pdb, 3NVF.pdb, 3NVG.pdb, 3NVH.pdb,

where

- 3NHC.pdb is a crystal structure of human prion segment (127-132) GYMLGS having Met at residue 129 [7]. This 6-residue segment of PrP centered on residue 129 is a "steric zipper", pairs of interacting β-sheets. This structure of the "homozygous steric zipper" reveals direct intermolecular interactions between Met in one sheet and the identical residue in the mating sheet. This structure, plus a structure-based model of the heterozygous Met steric zipper, suggests an explanation for the previously observed effects of this locus on prion disease susceptibility and progression;

- 3MD4.pdb and 3MD5.pdb are the crystal cross-beta spine structures of prion 127-132 peptides; and the following four X-ray crystal atomic structures of the same segment 137-143 from human, mouse, and hamster PrP, which is critical for forming amyloid and confers species specificity in PrP seeding experiments:

- 3NVE - MMHFGN segment 138-143 from Syrian Hamster prion [8];

- 3NVF - IIHFGS hexapeptide (residues 138-143) from human prion protein [8];

- 3NVG - MIHFGN hexapeptide (residues 137-142) from mouse prion protein [8];

- 3NVH - MIHFGND (residues 137-143) from mouse prion protein [8].

The models for prion 113-120 AGAAAAGA amyloid fibrils were built by the mutations in the use of SPDBV.4.01.PC (which make all the vdW contacts between the two β-sheets are very far), any Optimization Solver (which will remove the bad vdW/HB contacts) and Optimization program of Amber 11 (which furthermore refines the models and removes all the bad contacts and relax the models into a perfect way) [9]. The models after the mutations of SPDBV.4.01.PC are illuminated in the following Figure 1 (3NHC.pdb), Figure 2 (3MD4.pdb), Figure 3 (3MD5.pdb), Figure 4 (3NVE.pdb), Figure 5 (3NVF.pdb), Figure 6 (3NVG.pdb), and Figure 7 (3NVH.pdb), respectively.

The optimization problems (Pε) for each Figures are listed as follows. For Figure 1, fixing the coordinates of A.ALA3.CB and B.ALA4.CB (two anchors) ((6.014, 5.917, 0.065), (5.658, 1.630, -0.797)) and letting the coordinates of G.ALA4.CB and H.ALA3.CB (two sensors) be variables, there is a Pε-GOP:

$$\begin{aligned}(3\text{NHC}-\text{models})\min P\varepsilon(x_1,x_2) = 1/2\{&(x_{11}-6.014)^2+(x_{12}-5.917)^2+(x_{13}-0.065)^2-3.4^2\}^2\\ &+1/2\{(x_{21}-5.658)^2+(x_{22}-1.630)^2+(x_{23}+0.797)^2-3.4^2\}^2\\ (\text{MDGP1}) \qquad &-0.05x_{11}-0.05x_{12}-0.05x_{13}-0.05x_{21}-0.05x_{22}-0.05x_{23}\end{aligned}$$

For Figure 2, fixing the coordinate of B.ALA130.CB (the anchor) ((11.796, 7.063, 8.213)) and letting the coordinates of A.ALA130.CB (a sensor) or A.ALA132.CB (a sensor) be variables, we may get a simple MDGP with 3 variables:

$$\begin{aligned}(3\text{MD4}-\text{models})\min P\varepsilon(x_1) = 1/2\{&(x_{11}-11.796)^2+(x_{12}-7.063)^2+(x_{13}-8.213)^2-3.4^2\}^2\\ (\text{MDGP2}) \qquad &-0.05x_{11}-0.05x_{12}-0.05x_{13}\end{aligned}$$

For Figure 3, fixing the coordinates of B.ALA130.CB and B.ALA128.CB (two anchors) ((11.796, 7.063, 8.213), (5.849, 6.703, 6.531)) and letting the coordinates of A.ALA130.CB (a sensor) and A.ALA128.CB (another sensor) be variables, we may get a simple MDGP with 6 variables and its dual with 3 variable:

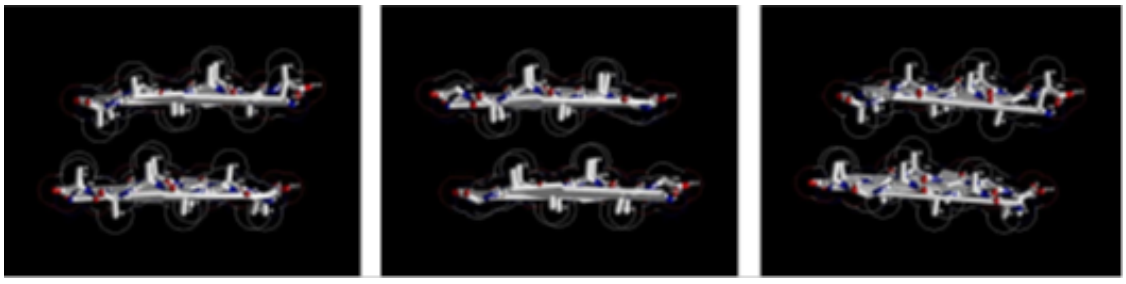

Figure 1: (3NHC-AGAAAA, GAAAAG, AAAAGA models 1~3).

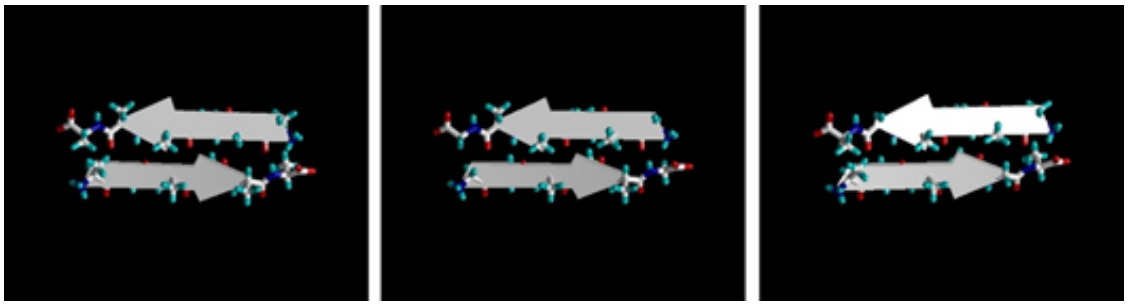

Figure 2: (3MD4-AGAAAA, GAAAAG, AAAAGA models 1~3).

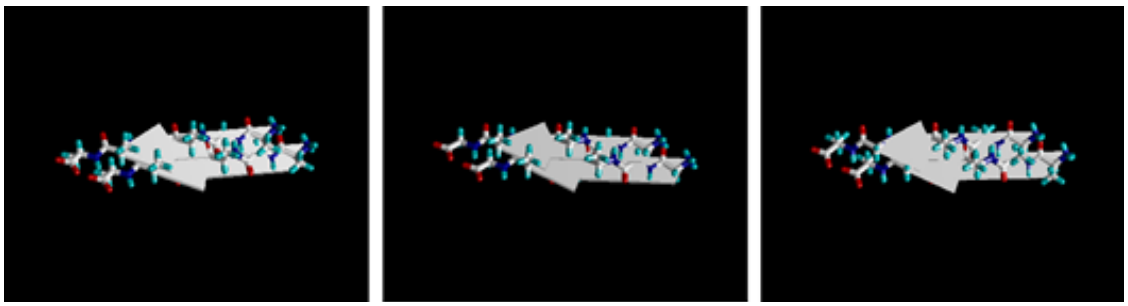

Figure 3: (3MD5-AGAAAA, GAAAAG, AAAAGA models 1~3).

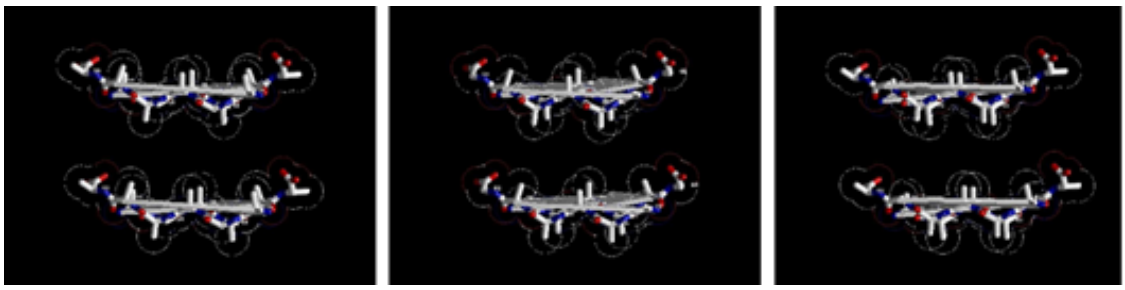

Figure 4: (3NVE-AGAAAA, GAAAAG, AAAAGA models 1~3).

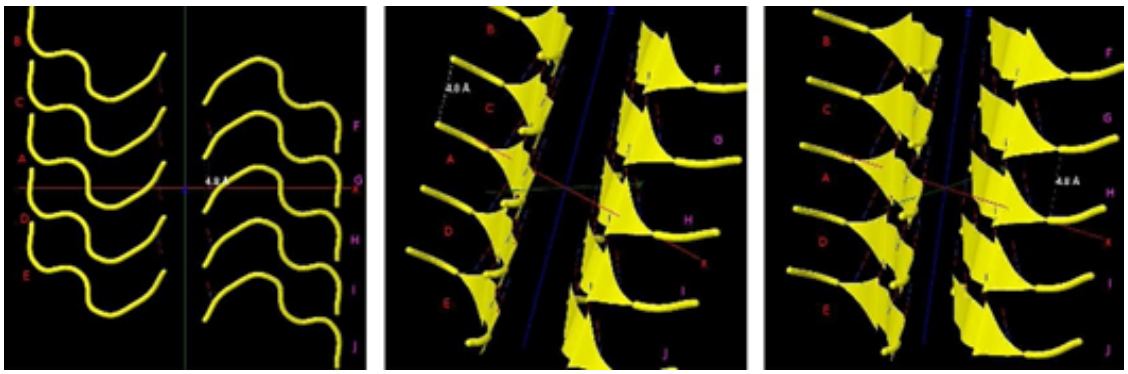

Figure 5: (3NVF-AGAAAA, GAAAAG, AAAAGA models 1~3).

$$(3\mathrm{MD5-models})\ \min P\varepsilon(x_1, x_2) = 1/2\left\{(x_{11} - 11.796)^2 + (x_{12} - 7.063)^2 + (x_{13} - 8.213)^2 - 3.4^2\right\}^2$$
$$+1/2\left\{(x_{11} - 5.849)^2 + (x_{12} - 6.703)^2 + (x_{13} - 6.531)^2 - 3.4^2\right\}^2$$
$$+1/2\left\{(x_{21} - 5.849)^2 + (x_{22} - 6.703)^2 + (x_{23} - 6.531)^2 - 3.4^2\right\}^2$$
$$(\mathrm{MDGP3}) \qquad -0.05x_{11} - 0.05x_{12} - 0.05x_{13} - 0.05x_{21} - 0.05x_{22} - 0.05x_{23}$$

For Figure 4, fixing the coordinates of A.ALA4.CB and B.ALA4.CB (two anchors) ((5.150, -1.295, 5.372), (-0.586, -0.444, 12.766)) for 3NVE-AGAAAAG model, fixing the coordinates of A.ALA4.CB, A.ALA2.CB (two anchors) ((5.150, -1.295, 5.372), (4.624, -0.327, 12.132)) for 3NVE-AGAAAAG, 3NVE-GAAAAGA models, letting the

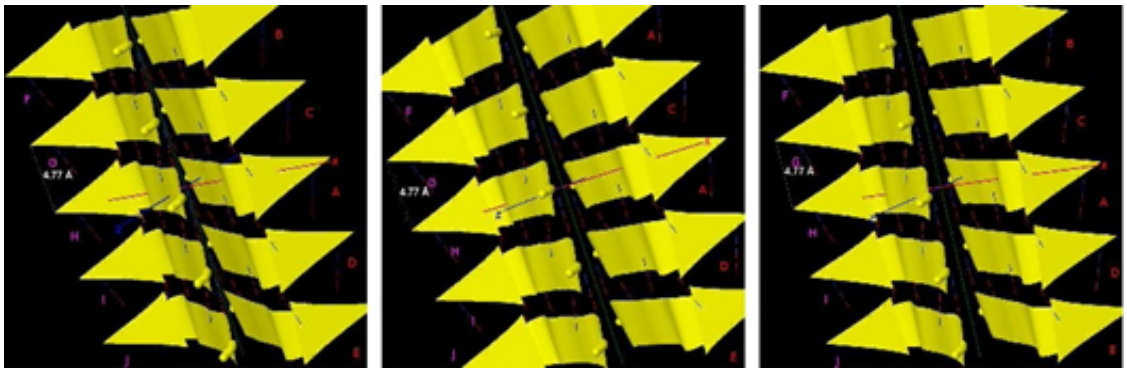

Figure 6: (3NVG-AGAAAA, GAAAAG, AAAAGA models 1~3).

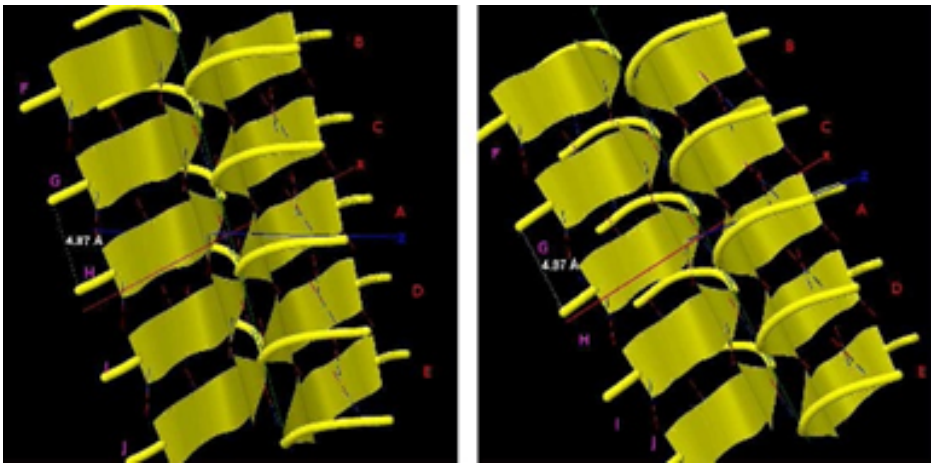

Figure 7: (3NVH-AGAAAAG, GAAAAGA models 1~2).

coordinates of G.ALA3.CB of 3NVE-models (one sensor) be variables, we may get a simple MDGP with 3 variables and its dual with 2 variables for 3nve-AGAAAAG model:

$$(3\text{NVE}-\text{model1})\min \mathrm{P}(x_1) = 1/2\left\{(x_{11}-5.150)^2+(x_{12}+1.295)^2+(x_{13}-5.372)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{11}+0.586)^2+(x_{12}+0.444)^2+(x_{13}-12.766)^2-3.4^2\right\}^2, \quad (\text{MDGP4})$$

And for 3NVE-GAAAAG, AAAAGA Models, similarly we may get a simple MDGP with 3 variables and its dual with 2 variables:

$$(3\text{NVE}-\text{models 2}\sim 3)\min \mathrm{P}\varepsilon(x_1) = 1/2\left\{(x_{11}-5.150)^2+(x_{12}+1.295)^2+(x_{13}-5.372)^2-3.4^2\right\}^2+1/2\{(x_{11}-4.624)^2$$
$$+1/2\left\{(x_{12}+0.327)^2+(x_{13}-12.132)^2-3.4^2\right\}^2$$
$$-(0.05x_{11}+0.05x_{12}+0.05x_{13}). \quad (\text{MDGP5})$$

For Figure 5, We know that for 3NVF-AGAAAA Model 1 at least the VDw interaction between A.GLY2.CA-H.GLY2.CA, A.ALA4.CB-H.GLY2.CA should be maintained, for 3NVF-GAAAAG Model 2 at least three vdW interactions between A.ALA4.CBH-ALA2.CB, A.ALA2.CB-H.ALA2.CB, A.ALA2.CB-H.ALA4.CB should be maintained, and for 3nvf-Model 3 at least three vdw interactions between A.ALA2.CB-H.ALA2.CB, A.ALA2.CB-H.ALA4.CB, A.ALA4.CB-H.ALA2.CB should be maintained. Fixing the coordinates of A.GLY2.CA and A.ALA4.CB (two anchors) ((-10.919, -3.862, -1.487), (6.357, 1.461, -1.905)) for 3NVF-AGAAAA Model 1, fixing the coordinates of A.ALA2.CB and A.ALA4.CB (two anchors) ((11.959, -2.844, -1.977), (6.357, 1.461, -1.905)) for 3NVF-GAAAAG, AAAAGA Models 2-3, letting the coordinates of H.GLY2.CA of 3NVF-AGAAAA Model 1 (two sensors) and the coordinates of H.ALA2.CB and H.ALA4.CB of 3NVF-GAAAAG, AAAAGA Models 2-3 (two sensors) be variables, we may get a simple MDGP with 3/6 variables and its dual with 2/3 variables for 3NVF-AGAAAA Model 1:

$$(3\text{NVF}-\text{model 1})\min \mathrm{P}\varepsilon(x_1) = 1/2\left\{(x_{11}+10.919)^2+(x_{12}+3.862)^2+(x_{13}+1.487)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{11}-6.357)^2+(x_{12}-1.461)^2+(x_{13}+1.905)^2-3.4^2\right\}^2$$
$$-(0.05x_{11}+0.05x_{12}+0.05x_{13}), \quad (\text{MDGP6})$$

For 3NVF-GAAAAG, AAAAGA Models 2-3, similarly we may get a simple MDGP with 6 variables and its dual with 3 variables:

$$(3\text{NVF}-\text{models 2}\sim 3)\min \mathrm{P}\varepsilon(x_1, x_2) = 1/2\left\{(x_{11}-11.959)^2+(x_{12}+2.844)^2+(x_{13}+1.977)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{21}-11.959)^2+(x_{22}+2.844)^2+(x_{23}+1.977)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{11}-6.357)^2+(x_{12}-1.461)^2+(x_{13}+1.905)^2-3.4^2\right\}^2$$
$$-(0.05x_{11}+0.05x_{12}+0.05x_{13}+0.05x_{21}+0.05x_{22}+0.05x_{23}). \quad (\text{MDGP7})$$

For Figure 6, We know that for 3NVG-AGAAAA Model 1 at least the three vdW interaction between A.GLY2.CA-H.GLY2.CA, A.GLY2.CA-H.ALA4.CB, A.ALA4.CB-H.GLY2.CA should be maintained, for 3NVG-GAAAAG Model 2 at least the three vdw interactions between A.ALA2.CB-H.ALA2.CB, A.ALA2.CB-H.ALA4.CB, A.ALA4.CB-H.ALA2.CB should be maintained, and for 3NVG-AAAAGA Model 3 at least the three vdw interactions between A.ALA2.CB-H.ALA2.CB, A.ALA2.CB-H.ALA4.CB, A.ALA4.CB-H.ALA2.CB should be maintained. Fixing the coordinates of A.GLY2.CA and A.ALA4.CB (two anchors) ((-11.159, -2.241, 4.126), (-5.865, -2.618, 8.696)) for 3NVG-AGAAAA Model 1, fixing the coordinates of A.ALA2.CB and A.ALA4.

CB (two anchors) ((-12.040, -2.675, 5.307), (-5.865, -2.618, 8.696)) for 3NVG-AGAAAA, GAAAAG Models 1-2, letting the coordinates of H.GLY2.CA and H.ALA4.CB of 3NVG-AGAAAA Model 1 (two sensors) and the coordinates of H.ALA2.CB and H.ALA4.CB of 3NVG-GAAAAG, AAAAGA Models 2-3 (two sensors) be variables, we may get a simple MDGP with 6 variables and its dual with 3 variables for 3NVG-AGAAAA Model 1:

$$(3\text{NVG}-\text{model 1})\ \min P\varepsilon(x_1, x_2) = 1/2\left\{(x_{11}+11.159)^2+(x_{12}+2.241)^2+(x_{13}-4.126)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{21}+11.159)^2+(x_{22}+2.241)^2+(x_{23}-4.126)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{11}+5.865)^2+(x_{12}+2.618)^2+(x_{13}-8.696)^2-3.4^2\right\}^2$$
$$(\text{MDGP8}) \qquad -(0.05x_{11}+0.05x_{12}+0.05x_{13}+0.05x_{21}+0.05x_{22}+0.05x_{23}),$$

For 3nvg-Models 2~3, similarly we may get a simple MDGP with 6 variables and its dual with 3 variables:

$$(3\text{NVG}-\text{models 2}\sim 3)\ \min P\varepsilon(x_1, x_2) = 1/2\left\{(x_{11}+12.040)^2+(x_{12}+2.675)^2+(x_{13}-5.307)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{21}+12.040)^2+(x_{22}+2.675)^2+(x_{23}-5.307)^2-3.4^2\right\}^2$$
$$+1/2\left\{(x_{11}+5.865)^2+(x_{12}+2.618)^2+(x_{13}-8.696)^2-3.4^2\right\}^2$$
$$(\text{MDGP9}) \qquad -(0.05x_{11}+0.05x_{12}+0.05x_{13}+0.05x_{21}+0.05x_{22}+0.05x_{23}).$$

For Figure 7, we may know that for 3NVH-AGAAAAG, GAAAAGA Models 1-2 at least one vdW interaction between A.ALA4.CB-H.ALA4.CB should be maintained. Fixing the coordinates of A.ALA4.CB (the anchor) ((1.731, -1.514, -7.980)) and letting the coordinate of H.ALA4.CB (one sensor) be variables, we may get a simple MDGP with 3 variables and its dual with 1 variable:

$$(3\text{NVH}-\text{models 1}\sim 2)\ \min P\varepsilon(x_1) = 1/2\left\{(x_{11}-1.731)^2+(x_{12}+1.514)^2+(x_{13}+7.980)^2-3.4^2\right\}^2$$
$$(\text{MDGP10}) \qquad -0.05x_{11}-0.05x_{12}-0.05x_{13}$$

Thus, we got the above ten MDGPs.

Results

Solving the ten MDGPs in the above section by any Optimization Solver (which will remove the bad vdW/HB contacts) [9-16] and then refining all the models by the Optimization program of Amber 11 [9,17]. At last we got the optimized prion 113-120 GAAAAGA amyloid fibril models, which are illuminated in Figures 8-14.

Conclusions

Sensor Network Problems (SNPs) can be looked as DGPs. MDGPs are SNPs, which look sensors as atoms and their telecommunication network as a molecule for the determination of its three-dimensional (3D) structure. Recently, the 2013 Workshop on Distance Geometry and Applications (2013DGA, http://dga2013.icomp.ufam.edu.br) united the DGPs and SNPs. Inspired by the reports of 2013DGA, this article

Figure 8: (Refined optimal 3NHC-AGAAAA, GAAAAG, AAAAGA models 1~3).

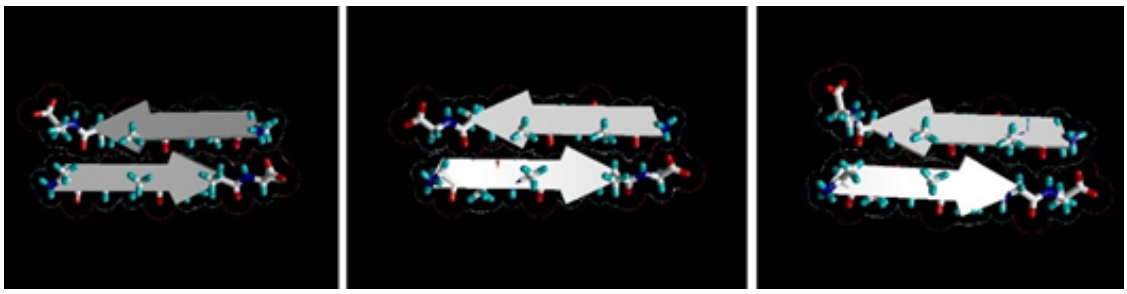

Figure 9: (Refined optimal 3MD4-AGAAAA, GAAAAG, AAAAGA models 1~3).

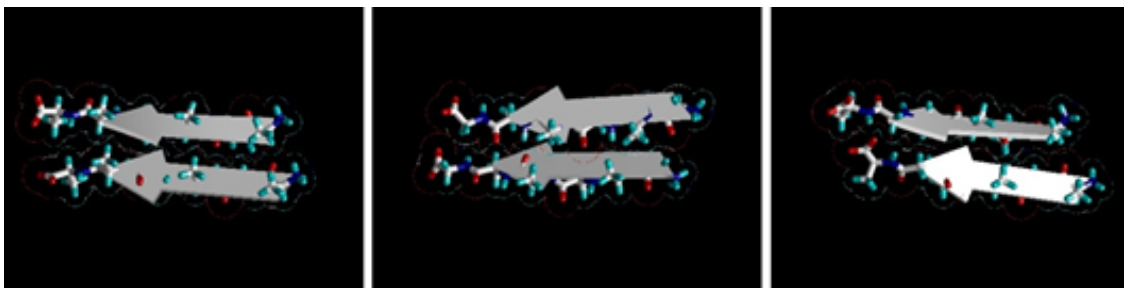

Figure 10: (Refined optimal 3MD5-AGAAAA, GAAAAG, AAAAGA models 1~3).

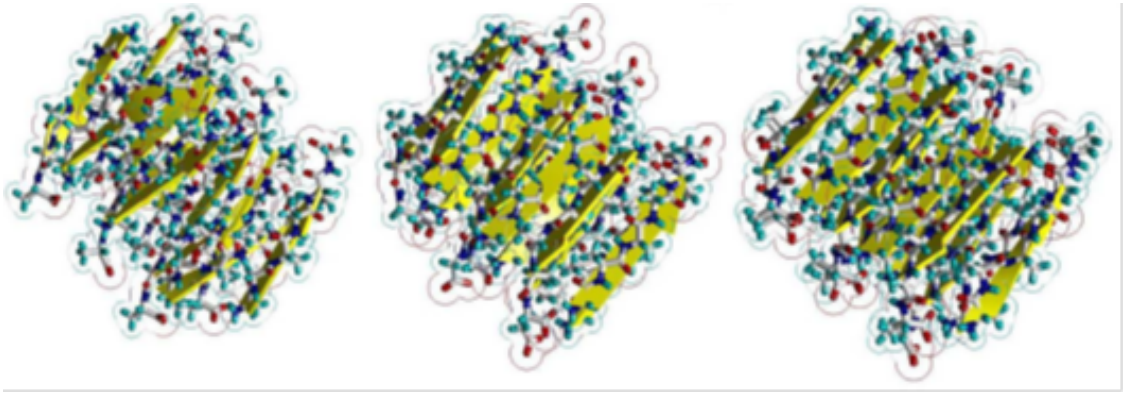

Figure 11: (Refined optimal 3NVE-AGAAAA, GAAAAG, AAAAGA models 1~3).

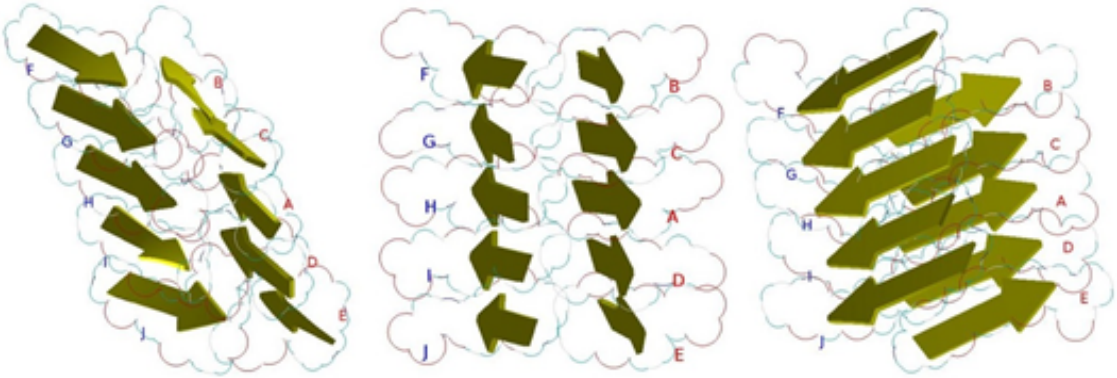

Figure 12: (Refined optimal 3NVF-AGAAAA, GAAAAG, AAAAGA models 1~3).

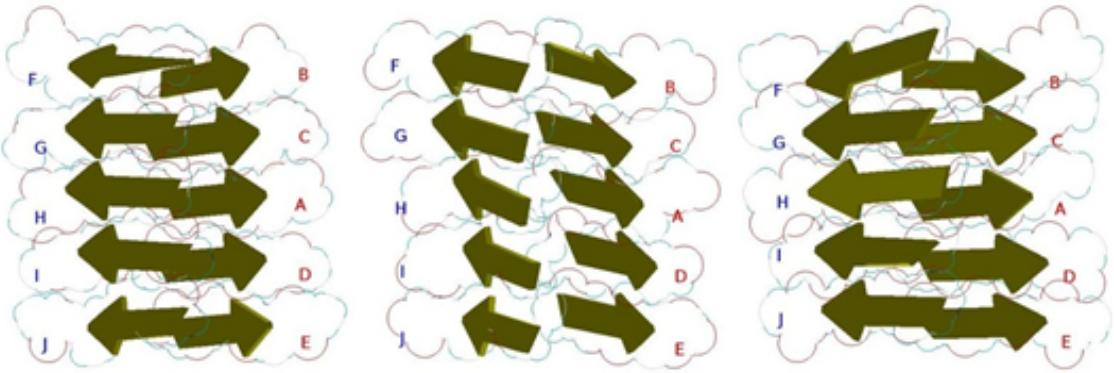

Figure 13: (Refined optimal 3NVG-AGAAAA, GAAAAG, AAAAGA models 1~3).

presented the amyloid fibril structures of all the neurodegenerative diseases as the SNPs, and then optimized and refined the models of prion 113-120 AGAAAAGA amyloid fibril models. These models can be acted as a reference for the laboratory researches on this region and helpful for the treatment of neurodegenerative prion diseases.

In conclusion, this paper presented molecular structure of amyloid fibril of all the neurodegenerative diseases as a Sensor Network Problem and further presented the solutions of its corresponding Distance Geometry Problem using optimization method. As the presented models to act as reference for future laboratory research, in the result section, the graphs presented not necessarily captured all the details of the optimized model result and is hard to use as reference directly without running the optimization again; thus we will deposit the optimized models as Support Materials into a standard online repository to share it (also be able to find from website https://sites.google.com/site/jiapuzhang/), so that the models would serve the reference purpose better.

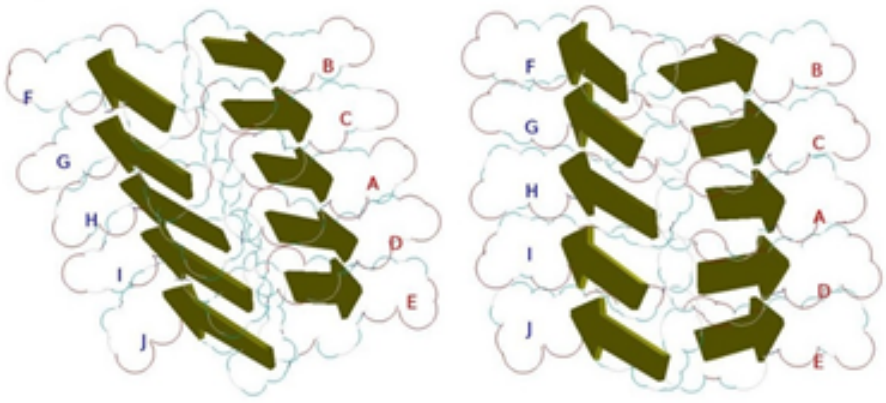

Figure 14: (Refined optimal 3NVH-AGAAAAG, GAAAAGA models 1~2).

Achnowledgements

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Support Materials

20 prion AGAAAGA amyloid fibril models (20 pdb files : optimized_models.zip)

3MD4_AAAAGA_model
3MD4_AGAAAA_model
3MD4_GAAAAG_model
3MD5_AAAAGA_model
3MD5_AGAAAA_model
3MD5_GAAAAG_model
3NHC_AAAAGA_model
3NHC_AGAAAA_model
3NHC_GAAAAG_model
3NVE_AAAAGA_model
3NVE_AGAAAA_model
3NVE_GAAAAG_model
3NVF_AAAAGA_model
3NVF_AGAAAA_model
3NVF_GAAAAG_model
3NVG_AAAAGA_model
3NVG_AGAAAA_model
3NVG_GAAAAG_model
3NVH_AGAAAAG_model
3NVH_GAAAAGA_model

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