Medicinal chemistry
ISSN: 2161-0444

Zhang, Med chem (Los Angeles) 2016, 6:5
DOI: 10.4172/2161-0444.1000369

Research Article Open Access

Mathematical Formulas for Some Cross- B Structures of Human Aβ Protein

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Abstract

For amyloid fibril cross-β structures of Aβ human protein, we find theoretical calculations are agreeing with laboratory X-ray crystallography experiments. This mini article summarized mathematical formulas of amyloid fibril cross-β structures of segments of human Aβ protein. These formulas are accurate and correct some data in the Protein Data Bank (PDB). However, more mathematical formulas for core Chains AB (PDB IDs: 3OW9, 3PZZ, 2OKZ), or ABGH (PDB IDs: 3OVJ, 2Y3J, 2Y3K, 2Y3L) (or ABCD (PDB ID: 2ONA)) are still needed to present and optimize.

Keywords: Human Aβ protein; Cross-β structures; Theoretical calculations; Experimental laboratories; Mathematical formulas

Introduction

A general presentation of Alzheimer's disease, its increase in prevalence in modern post-industrial societies as the average life expectancy increases steadily and the burden it represents for healthcare systems worldwide, the progress achieved in recent decades in understanding the molecular pathology of the disease could be referred in the review articles [1,2], and the paradox that in spite of an abundant literature in this field including tens of thousands of published articles there is to date no single radical treatment effective in stopping progression of disease or reverting neuronal damage it produces. The disease results in form either overproduction of amyloid-β 42 in hereditary cases or an impeded clearance of this peptide in sporadic cases, mainly due to a less performant apolipoprotein E (ApoE4) isoform. Misfolding of amyloid-β 42 monomers in antiparallel β sheet (that can further oligomerize forming less selective transmembrane pores) leads to intracellular calcium inflow triggering excessive reactive oxygen species at mitochondrial level, activation of caspases, tau protein hyperphosphorylation and aggregation into neurofibrillary tangles with microtubule disorganization. Therefore understanding the mechanisms of amyloid-β 42 misfolding is of vital importance and this was the aim of the present study.

Materials and Methods

The material of this article is taken from the webpage of Ref. [3]. The software tools used to infer the coordinate transformation formulae and to compute the average free energy per residue in β-sheet conformation are JMol (www.jmol.org), VMD (www.ks.uiuc.edu/Research/vmd/). The procedures used to perform these computations and to derive the formulae are the observations of the PDB files of Ref. [3] and FORTRAN codes written by the author. The optimization or refinement of the formulas is obtained by the Amber package (ambermd.org).

Results

In Ref. [3], the author showed that theoretical calculation can predict the segments of PrP protein which can form amyloid fibrils after misfolding, leading thus to propagation of misfolded PrP proteins to adjacent normal PrP proteins, and ultimately to a number of vulnerable areas of the brain. Quite interestingly, such a mechanism ("misfolding / propagation" or "transconformation") appears to occur not only in Prion diseases, but also in other neurodegenerative diseases [3] (for example Alzheimer's disease discussed in the below). This brings a new link between structural biology and human disorders, and may be quite useful in translational medicine [3]. This paper will mathematically study the cross-β structures of human Aβ protein for Alzheimer's disease.

First, we give the sequence of Aβ protein (human):

```
1.......10........20........30........40.
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA    42 human
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In the use of the above sequence, we can predict the segments of Aβ protein which can form amyloid fibrils after misfolding (Figure 1). From Figure 1, we may see that the regions containing residues 15–23 and 29–42 have a strong propensity to form amyloid fibrils [4]. This observation agrees with the results of laboratory X-ray crystallography experiments [5,6]. For readers' conveniences to know thirteen Aβ amyloid fibril structures (Table 1), in the below we illuminate 13 colourful and beautiful pictures and give their accurate mathematical formulas to describe these structures.

In the below, to show the beautiful of symmetry of mathematics, we will always use the Pair of Sheets of the amyloid fibril structures.

2Y2A.pdb (Pair of Sheets)'s mathematical formulas are (Figure 2)

$$D=\begin{pmatrix}1&0&0\\0&-1&0\\0&0&-1\end{pmatrix}A-\begin{pmatrix}4.79\\5.925\\0\end{pmatrix},$$

$$G/J=A/D-\begin{pmatrix}0\\5.925\times 2\\0\end{pmatrix},$$

$$E(C)/K(I)=A/G+\begin{pmatrix}\pm 4.79\times 2\\0\\0\end{pmatrix},$$

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Received May 14, 2016; **Accepted** May 25, 2016; **Published** May 30, 2016

Citation: Zhang J (2016) Mathematical Formulas for Some Cross-B Structures of Human Aβ Protein. Med chem (Los Angeles) 6: 349-355. doi:10.4172/2161-0444.1000369

$$B/H = D/J + \begin{pmatrix} 4.79\times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$F/L = D/J + \begin{pmatrix} 4.79\times 2\times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$\begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 0 \\ 5.925 \\ 21.235 \end{pmatrix}.$$

$$\begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 0 \\ 5.925 \\ 21.235 \end{pmatrix}.$$

3OW9.pdb (Pair of Sheets)'s mathematical formulas are (Figure 3)

Aβ segment	PDB ID	Class of the cross-β
01 Aβ(16-21) KLVFFA (form 1) **02** (form 2) **03** (form 3) **04** (orange G)	2Y2A 3OW9 2Y29 3OVJ	Class 7 [6,7] Class 7 [6,7] Class 7 [6,7] Class 8 [8,7] ($P\ 2_1\ 2_1\ 2_1$)
05 Aβ(27-32) NKGAII (interface A) **06** (interface B)	3Q2X 3Q2X	Class 1 [6,7] Class 1 [6,7]
07 Aβ(29-34) GAIIGL	3PZZ	Class 6 [6,7]
08 Aβ(30-35) AIIGLM	2Y3J	Class 2 [6,7]
09 Aβ(35-40) MVGGVV (form 1) **10** (form 2)	2ONA 2OKZ	Class 8 [7] Class 8 [7]
11 Aβ(35-42) MVGGVVIA (form 1) **12** (form 2)	2Y3K 2Y3L	Class 2 [6,7] Class 7 [6,7]
13 Aβ(37-42) GGVVIA	2ONV	Class 4 [7]

Table 1: Some cross-β structures of human Aβ segments.

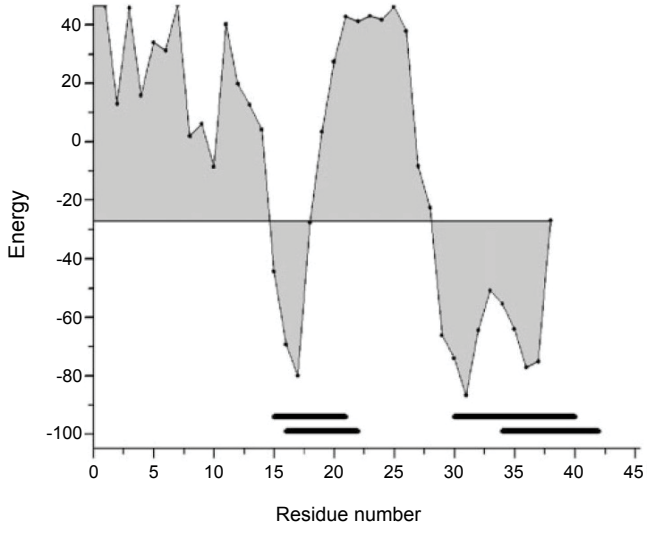

Figure 1: Fibril-forming prediction of Aβ(1–42). The boundary between the fibril-forming and non-forming sections was set at the energy threshold of -27 KCal/mol (where using the energy threshold –27 KCal/mol is corresponding to the maximum accuracy - the minimum P-value). The black horizontal bars indicate regions which have been found or suggested to form fibrils in experiments. The computations of total energy and its components for each structure generated in this study could be using a simple algorithm (e.g., NAMD Energy in VMD).

$$E(F)/C(D) = A(B) + \begin{pmatrix} 0 \\ \pm 9.561 \\ 0 \end{pmatrix},$$

$$G(H) = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A(B),$$

$$K(L)/I(J) = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A(B) + \begin{pmatrix} 0 \\ \pm 9.561 \\ 0 \end{pmatrix},$$

$$A(B) + \begin{pmatrix} 23.0265 \\ 9.561/2 \\ 0 \end{pmatrix},$$

$$\begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A(B) + \begin{pmatrix} 23.0265 \\ 9.561/2 \\ 0 \end{pmatrix}.$$

But the mathematical formula between Chains A and B should be found out.

2Y29.pdb (Pair of Sheets)'s mathematical formulas are (Figure 4)

$$D = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A - \begin{pmatrix} 4.795 \\ 6.035\times 3 \\ 0 \end{pmatrix},$$

$$G = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A - \begin{pmatrix} 4.795 \\ 6.035 \\ 0 \end{pmatrix},$$

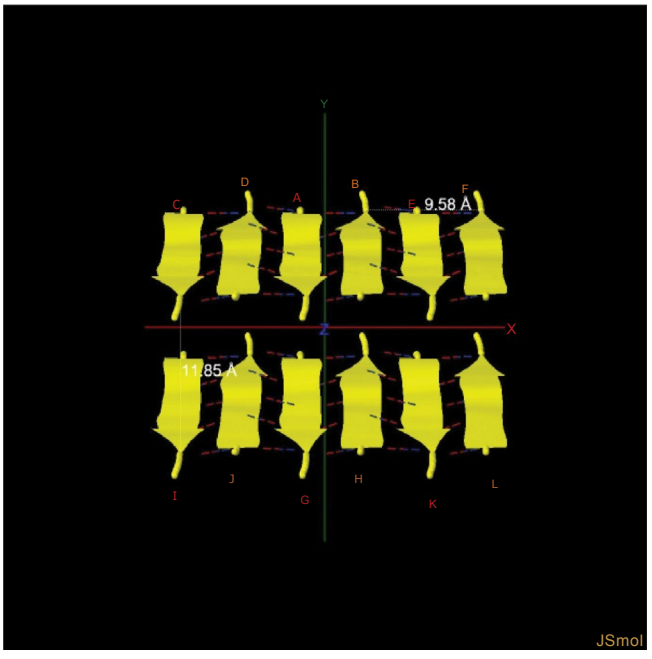

Figure 2: The Figure of 2Y2A.pdb (Pair of Sheets).

$$J = A + \begin{pmatrix} 0 \\ 6.035 \times 2 \\ 0 \end{pmatrix},$$

$$C(B)/E(F) = A/D + \begin{pmatrix} \pm 4.795 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$C(B)/E(F) = A/D + \begin{pmatrix} \pm 4.795 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$C(B)/E(F) = A/D + \begin{pmatrix} \pm 4.795 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$\begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 0 \\ 6.035 \\ 21.105 \end{pmatrix}.$$

3OVJ.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formulas to Chains A, B, G, H to get Chains C, D, I, J and Chains E, F, K, L: (Figure 5)

$$E(F)/C(D) = A/B + \begin{pmatrix} \pm 4.768 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$K(L)/I(J) = G/H + \begin{pmatrix} \pm 4.768 \times 2 \\ 0 \\ 0 \end{pmatrix}.$$

But the mathematical formulas among Chains A, B, G, H should be found out.

2Y2A.pdb – interface A – face-to-face (Pair of Sheets)'s mathematical formulas are (Figure 6)

$$F = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 12.747 \\ 2.419 \\ 23.903 \end{pmatrix},$$

$$B(D)/G(I) = A/F + \begin{pmatrix} 0 \\ \pm 2.419 \times 2 \\ 0 \end{pmatrix},$$

$$C(E)/H(J) = A/F + \begin{pmatrix} 0 \\ \pm 2.419 \times 4 \\ 0 \end{pmatrix}.$$

2Y2A.pdb – interface B – back-to-back (Pair of Sheets)'s mathematical formulas are (Figure 7)

$$F = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} -2.327 \\ 2.419 \\ 23.903 \end{pmatrix},$$

$$B(D)/G(I) = A/F + \begin{pmatrix} 0 \\ \pm 2.419 \times 2 \\ 0 \end{pmatrix},$$

$$C(E)/H(J) = A/F + \begin{pmatrix} 0 \\ \pm 2.419 \times 4 \\ 0 \end{pmatrix}.$$

3PZZ.pdb (Pair of Sheets)'s mathematical formulas are: applying the following to Chains A, B: (Figure 8)

$$G(H) = A(B) + \begin{pmatrix} -2.98449 \\ 11.38430 \\ 0 \end{pmatrix},$$

$$C(D)/E(F) = A(B) + \begin{pmatrix} \pm 4.735 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$I(J)/K(L) = G(H) + \begin{pmatrix} \pm 4.735 \times 2 \\ 0 \\ 0 \end{pmatrix}.$$

But the mathematical formula between Chain A and Chain B should be found out.

2Y3J.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formulas to Chains A, B, G, H to get Chains C, D, I, J and Chains E, F, K, L: (Figure 9)

$$E(F)/C(D) = A/B + \begin{pmatrix} \pm 4.78 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$K(L)/I(J) = G/H + \begin{pmatrix} \pm 4.78 \times 2 \\ 0 \\ 0 \end{pmatrix}$$

But the mathematical formulas among Chains A, B, G, H should be found out.

2ONA.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formulas to Chains A, B, C, D to get Chains I, J, K, L and Chains E, F, G, H: (Figure 10)

$$I(J/K/L) \ / \ E(F/G/H) = A(B/C/D) + \begin{pmatrix} \pm 4.8495 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$A + \begin{pmatrix} 0.51944 \\ 9.68508 \\ 0 \end{pmatrix}.$$

But the mathematical formulas among Chains A, B, C, D should be found out.

2OKZ.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formula to Chain A (Figure 11)

$$C = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} A + \begin{pmatrix} 4.788 \\ \end{pmatrix},$$

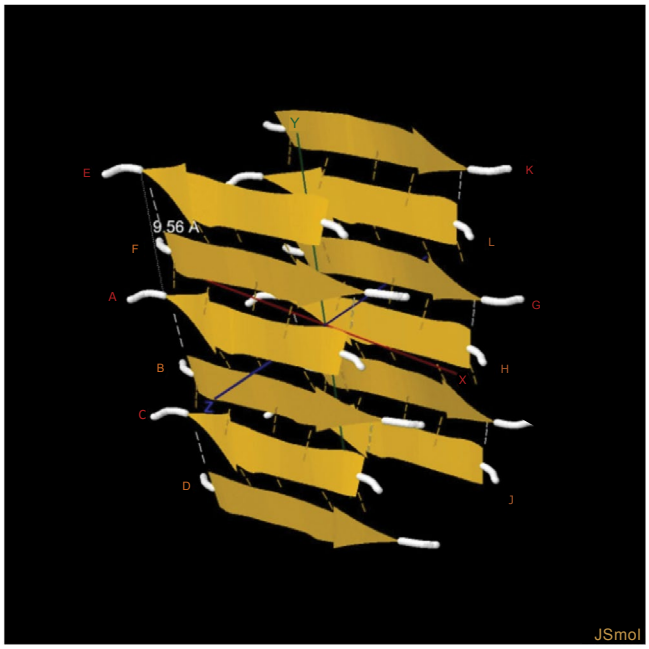

Figure 3: The Figure of 3OW9.pdb (Pair of Sheets).

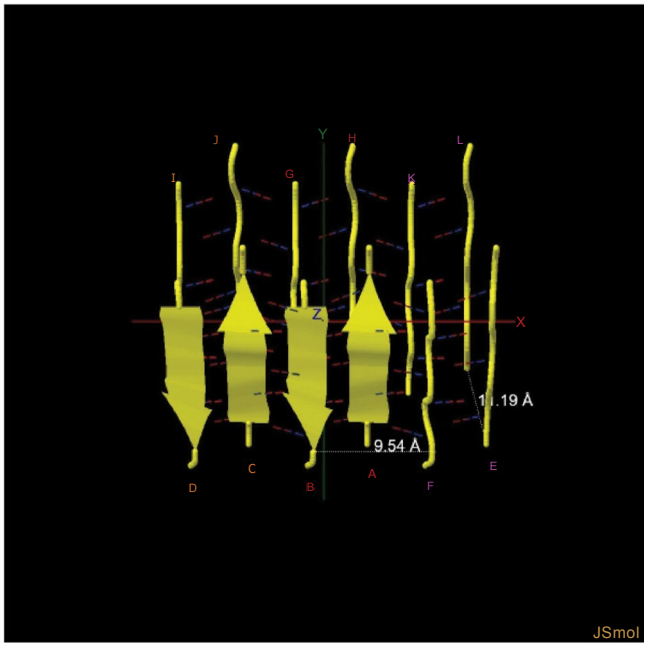

Figure 5: The Figure of 3OVJ.pdb (Pair of Sheets).

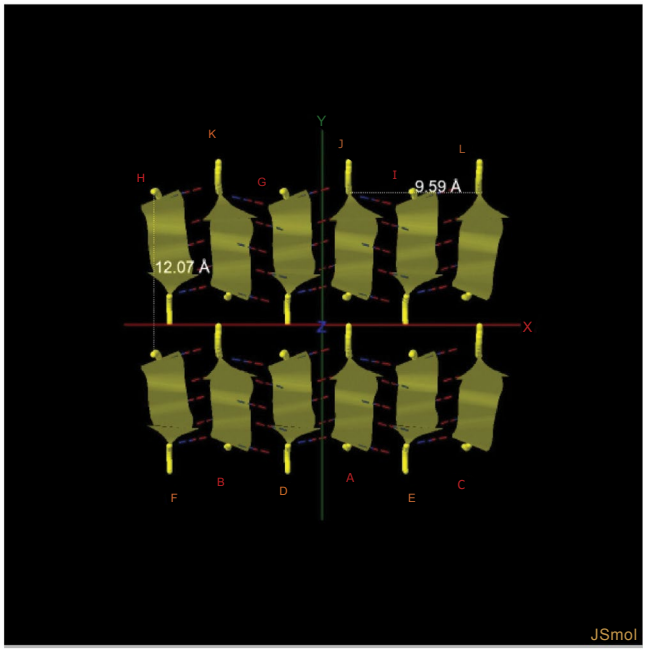

Figure 4: The Figure of 2Y29.pdb (Pair of Sheets).

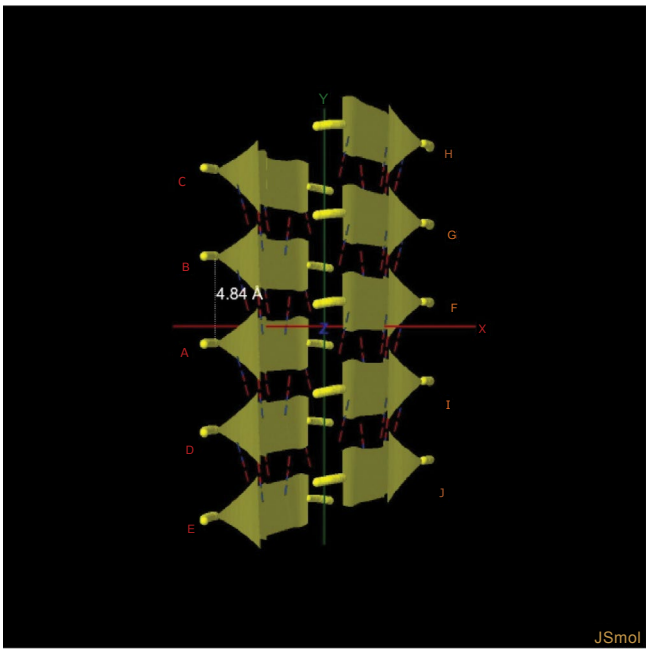

Figure 6: The Figure of 2Y2A.pdb – interface A – face-to-face (Pair of Sheets).

applying the following mathematical formulas to Chain B

$$D = \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} B + \begin{pmatrix} -2.85109 \\ -4.788 \\ 23.56012 \end{pmatrix},$$

and applying the following mathematical formulas to Chains A, B, C, D to get Chains I, J, K, L and Chains E, F, G, H:

$$E(F/G/H) \ / \ I(J/K/L) = A(B/C/D) + \begin{pmatrix} 0 \\ \pm 4.788 \times 2 \\ 0 \end{pmatrix}$$

But the mathematical formula between Chain A and Chain B should be found out.

2Y3K.pdb (Pair of Sheets)'s mathematical formulas are: applying

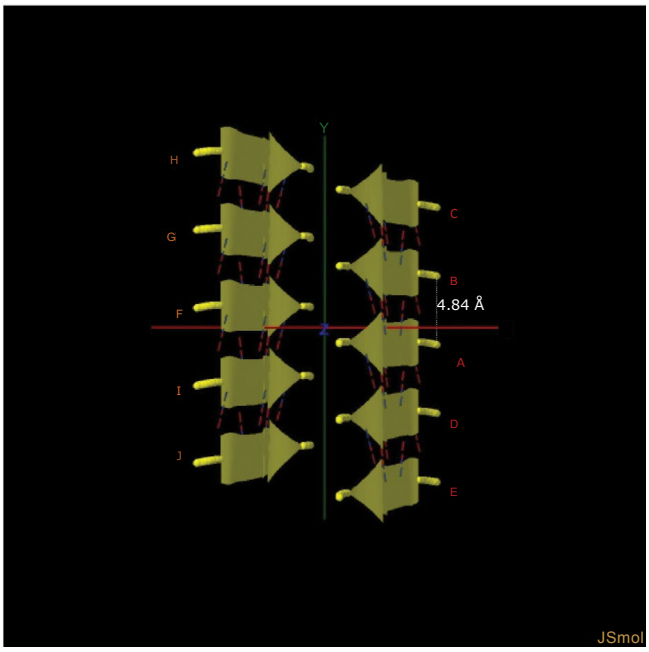

Figure 7: The Figure of 2Y2A.pdb – interface B – back-to-back (Pair of Sheets).

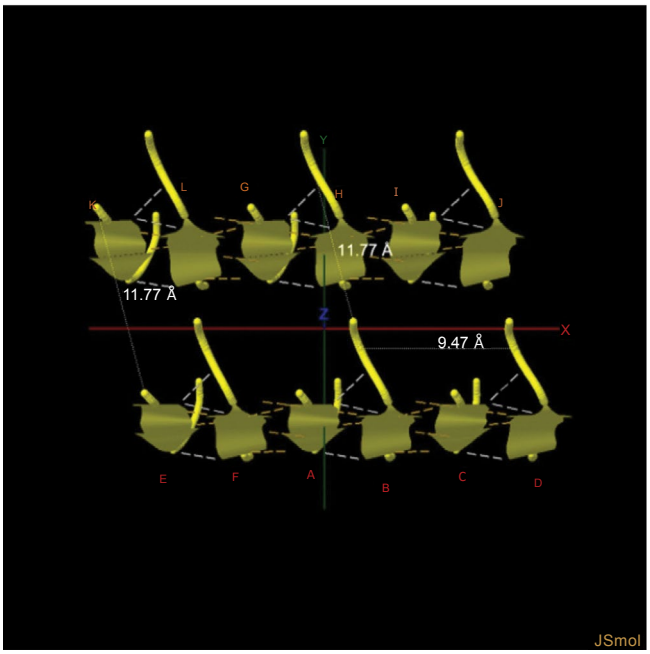

Figure 8: The Figure of 3PZZ.pdb (Pair of Sheets).

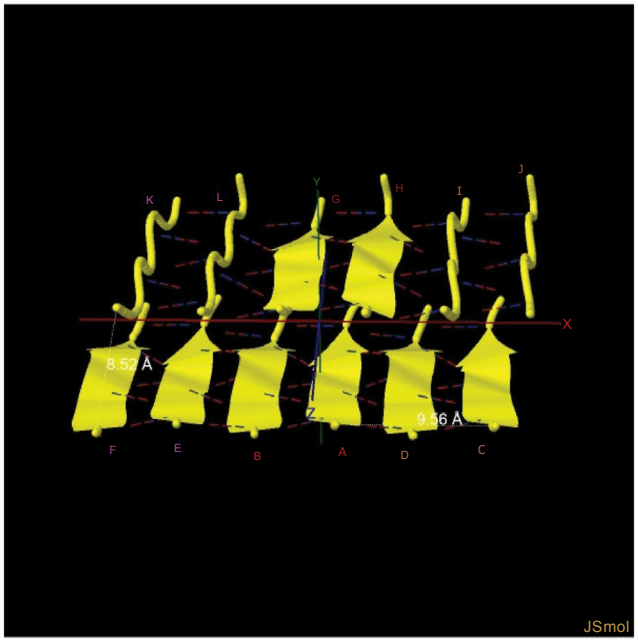

Figure 9: The Figure of 2Y3J.pdb (Pair of Sheets).

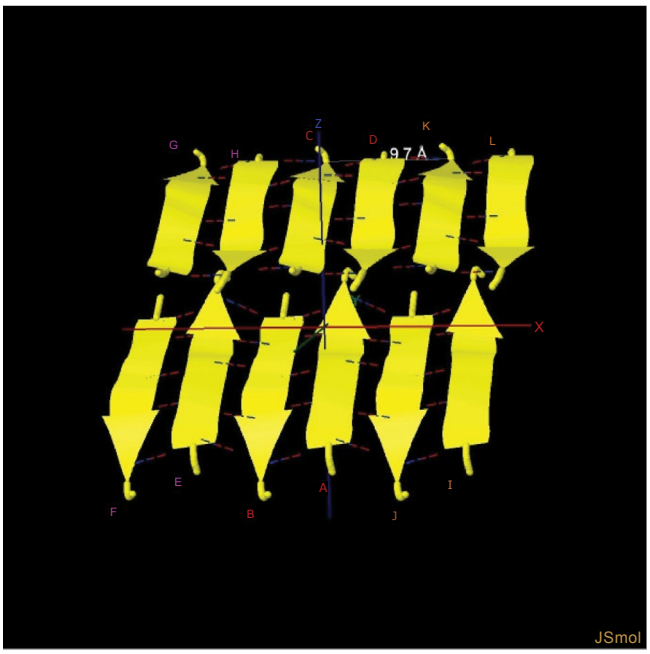

Figure 10: The Figure of 2ONA.pdb (Pair of Sheets).

the following mathematical formulas to Chains A, B, G, H to get Chains C, D, I, J and Chains E, F, K, L: (Figure 12)

$$C(D/I/J) \ / \ E(F/K/L) = A(B/G/H) + \begin{pmatrix} \pm 4.735 \times 2 \\ 0 \\ 0 \end{pmatrix}$$

But the mathematical formulas among Chains A, B, G, H should be found out.

2Y3L.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formulas to Chains A, B, G, H to get Chains C, D, I, J and Chains E, F, K, L: (Figure 13)

$$C(D/I/J) \ / \ E(F/K/L) = A(B/G/H) + \begin{pmatrix} \pm 4.735 \times 2 \\ 0 \\ 0 \end{pmatrix},$$

$$\begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 0 \\ 23.795 \\ 0 \end{pmatrix}.$$

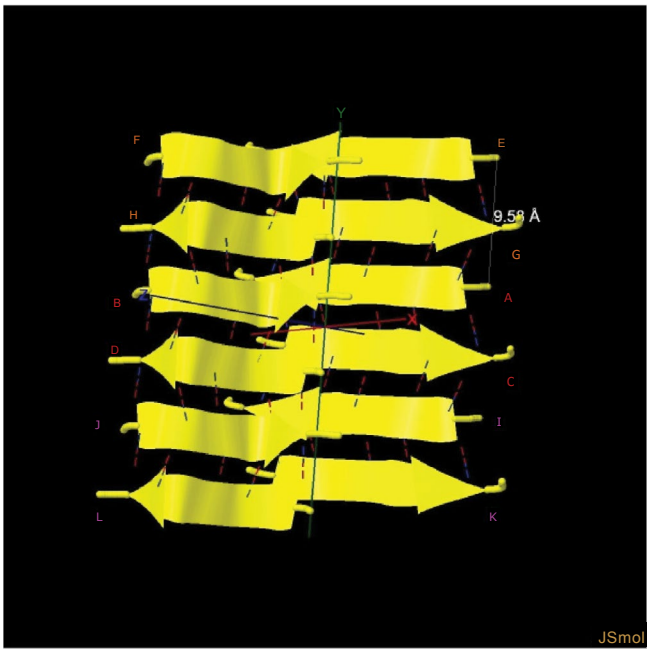

Figure 11: The Figure of 2OKZ.pdb (Pair of Sheets).

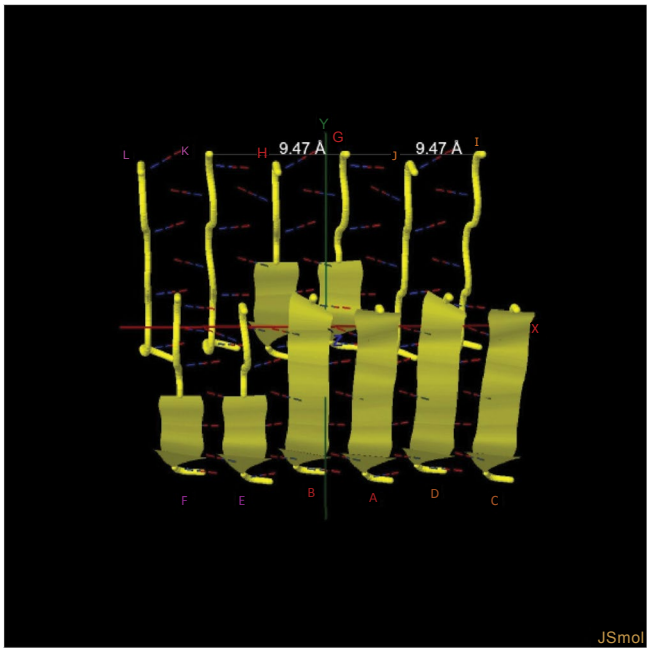

Figure 12: The Figure of 2Y3K.pdb (Pair of Sheets).

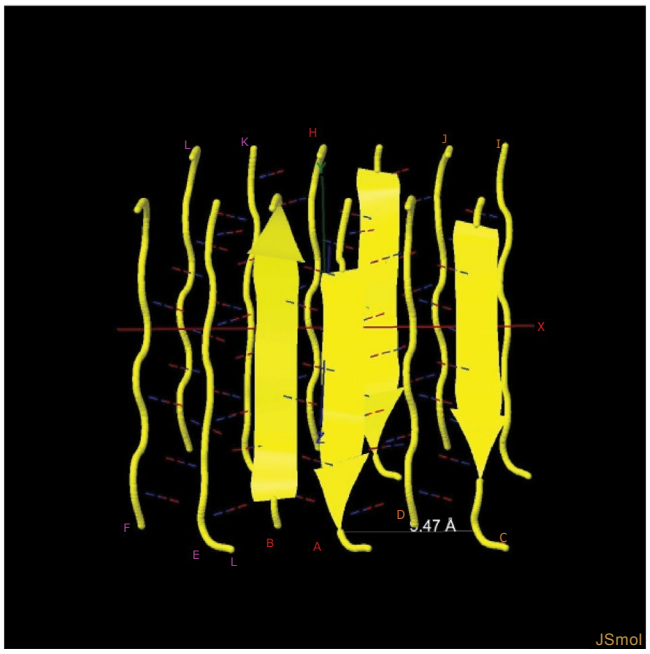

Figure 13: The Figure of 2Y3L.pdb (Pair of Sheets).

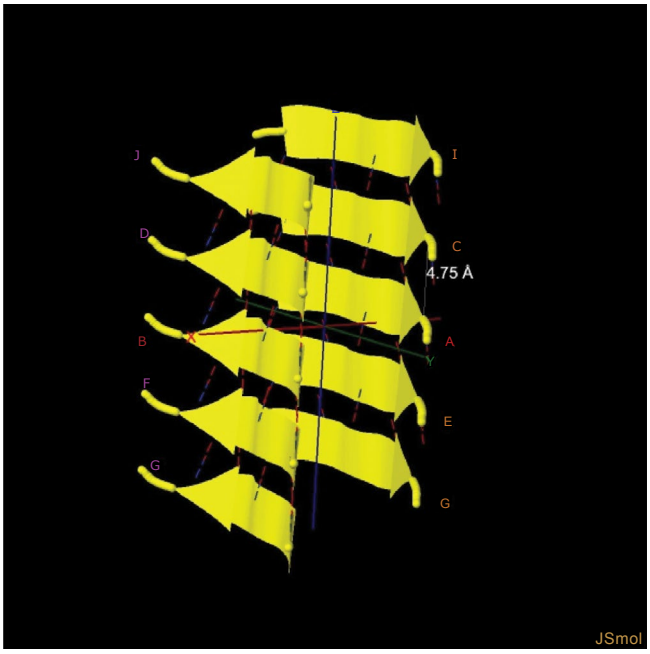

Figure 14: The Figure of 2ONV.pdb (Pair of Sheets).

But the mathematical formulas among Chains A, B, G, H should be found out.

2ONV.pdb (Pair of Sheets)'s mathematical formulas are: applying the following mathematical formulas to Chains A, B to get Chains CD, EF, IJ, GH: (Figure 14)

$$C/E(D/F) = A(B) + \begin{pmatrix} 0 \\ 0 \\ \pm 4.746 \end{pmatrix},$$

$$I/G(J/H) = A(B) + \begin{pmatrix} 0 \\ 0 \\ \pm 4.746 \times 2 \end{pmatrix},$$

and the mathematical formula between A, B Chains is:

$$B = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{pmatrix} A + \begin{pmatrix} 8.38 \\ 20.567 \\ 0 \end{pmatrix}.$$

Discussion

This paper has presented very useful information for the development of human Aβ protein for Alzheimer's disease (some recent works about the development of human Aβ protein structures and inhibitors are introduced, for example, in Ref. [7-14]).

The paper explores the symmetry properties of several structures representing crystallized short segments of amyloid-β 42 retrieved from the PDB repository, defining for each of them formulae including translation and rotation of atom coordinates such as to generate an entire array of regular secondary structure of paired β-sheets starting from seed segments of the polypeptide. This article is mathematically interesting. More mathematical formulas for the core Chains AB (PDB IDs: 3OW9, 3PZZ, 2OKZ), or ABGH (PDB IDs: 3OVJ, 2Y3J, 2Y3K, 2Y3L) (or ABCD (PDB ID: 2ONA)) are still needed to present [5,6,15,16] and optimize. The formulas in this paper are accurate, correcting the misprinting in PDB bank. The influence of these formulas on the whole structure human Aβ protein could be further discussed based on those data correction.

The basic contribution of this paper is to show 13 colourful and beautiful pictures (Figures 2-14) for Aβ (human) amyloid fibril structures and presents conveniences to readers for a quick reference Table (Table 1) and many accurate mathematical formulas.

Furthermore researches could be presenting some comments about the different structures included in this study and their relationship to the antiparallel β-sheet folding process of amyloid-β 42 monomers and subsequent propensity for oligomerization or fibrillation. We could indicate: whether the proposed structures may represent intermediate steps or local minima across the free energy landscape of β-amyloid folding; where would the folding process most likely start and how would it progress, which are the main energy barriers along the folding pathway; why amyloid-β 42 is so prone to form β-sheets and fibrils compared to amyloid-β 40, given it is only two residues longer at the C-terminal end; how does the β-sheet folding template propagate from one monomer to another; what is the relationship between X-ray crystallography-derived structures used in this study and NMR-derived structures of amyloid-β 42 in solution (e.g., 2BEG), and what is the likelihood that amyloid-β monomers/oligomers adopt these structures in realistic environments at physiological temperature; what is the propensity of these structures to form oligomeric transmembrane pores and thus be pathogenic in early stages of Alzheimer's disease (see, for example, Ref. [16]), etc.

Acknowledgments

This research was supported by a Victorian Life Sciences Computation Initiative (VLSCI) grant numbered FED0001 on its Peak Computing Facility at the University of Melbourne, an initiative of the Victorian Government (Australia). VLSCI's facilities and staff supports are gratefully acknowledged. Thanks also go to Landau M who let us know that the 3OVJ - steric zipper (perturbed by the small molecule orange G) belongs to Class 8. Last but not least, the author thanks the two anonymous referees for their numerous insightful comments, references offered, and furthermore research directions.

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