Mean curvature as a major determinant of β-sheet propensity

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ABSTRACT

Motivation: Despite the importance of β-sheets as building blocks in proteins and also toxic elements in the pathological disorders, ranging from Alzheimer’s disease to mad cow disease, the principles underlying their stability are not well understood. Non-random β-sheet propensities of amino acids have been revealed both by their distinct statistical preferences within known protein structures and by the relative thermodynamic scales through the experimental host-guest systems. However, recent fitting analysis has proved that a native β-sheet conforms to a minimal surface with zero mean curvature, like the physical model of soap films.

Results: We here suggest that the stability of a residue in the all β-sheet proteins can be measured with its mean curvature parameter, using discrete differential geometry. The sharply decreasing mean curvature with increasing number of β-strands identifies a significant cooperative effect whereby the interstrand interaction increases in strength with the number of β-strands. Furthermore, strong correlations of mean curvatures with previous β-sheet propensities of amino acids show that their intrinsic differences in adopting the ideal β-sheet structure are affected by the water-accessible area of side-chains, and result in the distinct statistical and thermodynamic β-sheet propensities. Therefore, we conclude that mean curvature should be considered as the significant stability index of a β-sheet structure.

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1 INTRODUCTION

Most proteins are composed predominantly of α-helices and β-strands, with a core region formed by close packing of these secondary structural elements. α-helices are quasi-one-dimensional structures by local-range interactions, and have a more rigid arrangement in native proteins (Yang and Honig, 1995a; Emberly et al., 2003). But extended β-strands are slowly organized into complex hydrogen-bonded assemblies, β-sheets, by long-range and inter-chain interactions (Chothia, 1973; Yang and Honig, 1999b; Emberly et al., 2004). Unlike the classical flat model proposed by Pauling and Corey (Pauling and Corey, 1951), all observed β-sheets in proteins are twisted to some extent in the right-handed direction and have an intrinsic flexibility with the significant variation of their coiling (Chothia, 1973; Ho and Curmi, 2002; Salemme, 1981; Salemme and Weatherford, 1981a, b; Emberly et al., 2004).

In the approach to predict the unknown conformation of a polypeptide chain from its known amino acid sequence (folding problem), the first step is to predict secondary structural elements from its sequence and the second step is the three-dimensional arrangement of its secondary elements. The second step is more difficult than the first one, and is still far from being solved. So it is of main interest in the folding problem to characterize the dominant energetic factors and their complex counterbalance in the process of assembling the secondary elements to the native conformation. In this paper, we focus on the second step and, in particular, the geometrical arrangement of several β-strands gathered in one β-sheet.

The stereochemistry of the polypeptide chain in a β-sheet naturally defines three principal, approximately orthogonal directions: the C-direction (backbone direction), the H-direction (hydrogen bonding direction) perpendicular to the C-direction on the surface of the sheet and the S-direction (side chain direction) roughly normal to the surface (Pauling and Corey, 1951; Novotny et al., 1984). It is generally known that backbone conformations are determined in the response to non-covalent interactions of the side chains (Chou et al., 1982; Chou and Scheraga, 1982). Statistical surveys of proteins with known structures reveal a non-random distribution in the occurring frequency of each amino acid in β-sheets (Chou and Fasman, 1973). The relative β-sheet forming propensities of amino acids are experimentally measured by the host-guest system in the two individual polypeptides: zinc-finger peptide (labeled ZincF, Kim and Berg, 1993) and immunoglobin-binding domain B1 from protein G (labeled GB1, Minor and Kim, 1994a; Smith et al., 1994). It follows that the amino acids have their own definite conformational preferences to cause the different β-sheet forming propensities.

A number of theoretical studies have investigated the geometries of β-sheets to suggest the principal energetic factors in the stability of the β-strand arrangement. Early, Salemme proposed that the isotropically stressed configuration model, in which the intrastrand tendency of the individual chains to twist or coil is in equilibrium with the tendency of the interstrand hydrogen-bonding to resist twisting of the sheet as a whole (Salemme, 1981). Experiments on small designed proteins suggest that the formation of β-sheets is aided by a cooperative effect making the strength of the interaction between the polypeptide strands increasing with the
number of strands (Kortemme et al., 1998). The ab initio density function theory shows that the cooperative effect is related to a coupling between interstrand bonding and intrastrand elastic properties (Rossmeisl et al., 2004). Recent work (Koh and Kim, 2005) has presented the argument that β-sheet structures are the result of the tendency to minimize surface areas, based on the catenoid-fitting data of 1729 native β-sheets with <10 strands. The extremely small fitting errors (0.90 ± 0.55Å) have supported the minimal surface model for an ideal β-sheet (Koh and Kim, 2005).

From the results, we propose that the β-sheet surface structure is mainly determined by the ideal conformation (minimal surface) of β-strand backbones, and the side chains make only small perturbations on the minimal surface delineated by the backbones. By all accounts, it could be ascertained that the tendency of β-sheets to minimize surface areas is one of the principal energetic factors to stabilize the β-sheets, and also amino acids with a suitable backbone conformation to the minimal surface (that is the smaller mean curvature, Do Carmo, 1976; Nitsche, 1989) can have high propensity to form a native β-sheet.

2 METHODS

Knowledge of the curvature of surfaces is important in a number of applications such as flow simulations, computer graphics and animations, and pattern matching. It is of particular importance in applications dealing with evolving surface geometry. Such applications usually do not have smooth analytical forms for the surfaces forming the model geometry. Instead, they have to deal with discrete data consisting of points on the surface connected to form an unstructured mesh (Garimella and Swartz, 2003). This environment is similar to those of applications in β-sheet structure. Extended β-strands, one of the two most common types of polypeptide chain conformation, are assembled into the quasi-two-dimensional β-sheet structure. To characterize the physical principles of protein folding in β-sheets, the shape of these surface structures have to be analyzed. But the information in the observed protein structure is expressed with discrete data consisting of atoms coordinates, especially in the main chain of the polypeptide chain. This condition with no smooth data induces us to apply the commonly used, discrete mean curvature estimation to the folding problem in all β-sheet protein classes.

2.1 Mean curvature estimation for β-sheet surfaces

In a recent work (Koh and Kim, 2005), it is shown that all connected β-sheets with <10 strands are well approximated with the minimal surface like Figure 1 and that the region with high mean curvature (>0.10) contains β-edges do not form hydrogen bonded β-bridges. As previously noted, the results suggest that the interior residue in β-sheets has the propensity to conform the ideal β-sheet, that is, minimal surface with vanishing mean curvature. Thus, the stability of each residue could be measured by the mean curvature value at its point in the β-sheet region. In this section, we introduce the algorithm to directly calculate the mean curvature at the observed β-sheet residues in the Protein Data Bank (PDB).

Consider the discrete information in the real β-sheet structure.

- Let S be the connected β-sheet with m strands, β₁...βₘ.
- Let βᵢ be the β-strand with the nᵢ residues, Cᵢ(1)...Cᵢ(nᵢ).

Except the two end residues of each β-strand [Cᵢ(1) and Cᵢ(nᵢ), i = 1...m] and the β-edge residues having only one hydrogen-bonded β-bridge (for example, the residues in β₁ and βₐ), all residues [Cᵢ(j) in Fig. 2(a)] in the β-sheet have eight neighboring residues, consisting of the two intrastrand adjacent residues [Cᵢ(j−1) and Cᵢ(j+1)] and six interstrand adjacent residues [Cᵢ−₁(k−1), Cᵢ−₁(k), Cᵢ−₁(k+1), Cᵢ₊₁(k−1), Cᵢ₊₁(k) and Cᵢ₊₁(k+1)]. Figure 2(a) represents the eight neighboring residues of the center residue Cᵢ(j), in the case of the antiparallel β-sheet.

To estimate the mean curvature H at the residue Cᵢ(j) on the β-sheet surface, we introduce a mean curvature estimation method using spatial averaging of triangulation data with discrete differential geometry concepts. Given a patch of triangles surrounding point x as shown in Figure 3, the estimates for the mean curvature H at x, given by Meyer et al. (Meyer et al., 2002):

\[
2HH = \frac{1}{2A} \sum_i \left( \cot a_i + \cot b_i \right) (x - x_i),
\]

where

- \(x_1, \ldots, x_n\) are the vertices adjacent to \(x\),
- \(a_i\) and \(b_i\) are the angles opposite edge \(xx_i\), in the two incident triangles,
- \(\hat{n}\) is the normal vector at \(x\) defined by Equation (1),
- and \(A\) is some area around \(x\).

Meyer et al. show that the error in the curvature computation is minimized when \(A\) is chosen to be the Voronoi area, defined in each triangle by the point \(x\), the midpoints of the triangle edges and the circumcenter of the triangle, summed over all the triangles (Meyer et al., 2002). The Voronoi area suggested by the authors (gray region in Fig. 3) is given by:

\[
A_{\text{Voronoi}} = \frac{1}{8} \sum_i \left( \cot a_i + \cot b_i \right) \|x - x_i\|^2
\]

In the case of obtuse triangles (where the circumcenter is outside the triangle), they suggest that \(A_{\text{Voronoi}}\) could be replaced with a modified area, using the midpoint of the edge opposite to the obtuse angle instead of the circumcenter. Their method could be applied to the discrete geometric structure of β-sheets. The mean curvature \(H\) at the residue \(Cᵢ(j)\) in Figure 2(b) could be approximated by the following equation:

\[
H = T_k = \frac{1}{4A_{n_i}} \sum_j (\cot a_j + \cot b_j)(C - C_j)
\]
Mean curvature determines the $\beta$-sheet propensity

Fig. 2. Adjacent residues in a $\beta$-sheet. (a) Part diagram of an antiparallel $\beta$-sheet to represent a $\beta$-center residue [$C_i(j)$], which has eight adjacent residues: two intrastrand residues [$C_i(j-1)$ and $C_i(j+1)$] and six interstrand residues [$C_{i-1}(k-1)$, $C_{i-1}(k)$, $C_{i+1}(k-1)$, $C_{i+1}(k+1)$, $C_{i+1}(k')$ and $C_{i+1}(k'+1)$]. (b) Triangulation to measure the mean curvature at the $\beta$-center residue of the quasi-two-dimensional $\beta$-sheet surface. Thick lines represent $\beta$-strands and dashed lines the hydrogen-bonded $\beta$-bridges between the $\beta$-strands. And $a_i$ and $b_i$ are the angles opposite edge $CC_i$. See Section 2.1.

Fig. 3. A vertex $x$ and the related variables for this local configuration, where $a_i$ and $b_i$ are the angles of opposite edge $x_i$. Gray colored 1-ring neighborhood of vertex $x$ indicates the subarea for using the method of Meyer et al. (Meyer et al., 2002)

\[ A_o = \frac{\text{Area}(CC_iC_j) + \sum_{i=1}^{7} \text{Area}(CC_iC_{i+1})}{4} \tag{4} \]

and $\text{Area}(CC_iC_j)$ is the area of triangle $CC_iC_j$. Here note that their triangles in the observed $\beta$-sheets are mostly obtuse triangles near the right triangles, and the previous modified area in Meyer et al. could be obtained by $A_o$.

2.2 Structural data collection from all $\beta$-protein class

Our purpose is to extract the geometric value (mean curvature) from actual $\beta$-sheet protein structures, and to examine the propensity of the $\beta$-sheet residue to minimize the mean curvature value. To achieve this, coordinates of the three-dimensional structures of the different $\beta$-sheets are taken from the Protein Data Bank (PDB). To reduce the repetition of the mean curvature value by reason of the sequence similarity, we referred to the non-redundant domains in the all $\beta$-protein class of Structural Classification of Proteins database (SCOP, Murzin et al., 1995) 1.63 version with <40% sequence identity. And all connected $\beta$-sheets are collected from the protein domains in all $\beta$-protein classes.

Since the undulation of the C$\alpha$ positions in each strand makes it difficult to obtain the optimal mean curvature value from the $\beta$-sheet surface structure, we used the center of mass of each peptide bond as a reference point, instead of the C$\alpha$ coordinates. So, domains with only C$\alpha$ coordinates deposited in the PDB were excluded from this analysis. Dictionary of Protein Secondary Structure (DSSP, Kabsch and Sander, 1983) files were also modified to have the center of mass of peptide bonding as a reference point of each residue. For the all $\beta$-sheet protein domains thus selected, an in-house program (BetaMC, Koh&Kim) was used to map the $\beta$-sheet in these structures onto a plane. The program used the previously modified DSSP files as input and initially considered only those ‘E’ segments that form intrastrand $\beta$-ladders as $\beta$-strands. Residues engaging in a single $\beta$-bridge (marked ‘B’ in DSSP files) with an edge strand in the main $\beta$-sheet were ignored. Since the tertiary context affects $\beta$-sheet formation (Minor and Kim, 1994b), we consider only residues in central strands, bordered on both sides by other $\beta$-strands (namely central residues), excluding those in edge strands. And to quantify the intrinsic backbone conformation of amino acids without the effect of the strand directions, residues in only antiparallel sheets are chosen, though mean curvatures of a parallel sheet are mostly smaller than those of an antiparallel sheet. From the 1857 connected $\beta$-sheets, we choose the residue points satisfying the following conditions:

- Not an end residue of each $\beta$-strand [$C_i(1)$ and $C_{i+1}(n_i)$ in Section 2.1].
- Not $\beta$-edge residues, having only one hydrogen-bonded $\beta$-bridge (for example, all residues in the edge strands, $\beta_1$ and $\beta_6$ in Section 2.1).
- Having exactly two intrastrand adjacent residues and six antiparallel interstrand adjacent residues as its neighboring residues. (See Section 2.1).

Throughout this paper, we denote the residue points satisfying the previous conditions as the $\beta$-center residues. In Figure 2(a), $C_i(j)$ is an example of a $\beta$-center residue in an antiparallel $\beta$-sheet.

3 RESULTS
3.1 Distribution of mean curvature at the $\beta$-center residues

From the 1857 connected $\beta$-sheets in the all $\beta$-protein class (40% SCOP version 1.63), 7988 residues were chosen as the $\beta$-center residues having eight neighboring residues like $C_i(j)$ in Figure 2(a). For each $\beta$-center residue, the mean curvature is estimated by Equation (3). The distribution of mean curvature is represented in Figure 4. Their almost vanishing mean curvature values prove that the polypeptide chain of the $\beta$-sheet has the tendency to conform the zero-mean curvature surface, i.e. minimal surface.
3.2 More β-strands in a β-sheet, less mean curvature and more stable conformation

To identify the cooperative effect in the β-sheet formation (Rossmeisl et al., 2004), the mean curvature \( H \) at all 7988 central residues are measured by Equation (2) and are averaged for each sheet. The strong correlation \( R = 0.74 \) in Fig. 5) in the distribution of the mean curvature versus the number of β-strands in each sheet, indicates that the mean curvature value is significantly decreasing as the number of strands in each sheet is increasing, and proves the cooperative effect making the strength of the interaction between the polypeptide strands increases with the number of strands in a β-sheet (Kortemme et al., 1998). The significantly small mean curvature value, particularly in larger sheets with >20 β-strands, is also notable in Figure 5.

3.3 Mean curvature as a major determinant of the β-sheet propensities of amino acids

And to investigate the origin of the distinct β-sheet propensities of amino acids, we divided all 7988 β-center residues into 19 amino acid classes, excluding those not occurring proline in the central residues and cysteine in a disulfide bond. Table 1 represents the average mean curvature value for each amino acid class, as well as the previously known propensity parameters and the occurring frequencies in the 7988 β-center residues. Amino acids with the three highest occurring frequencies are valine, leucine and isoleucine, which were known to have the three largest hydropathy scales (Kyte and Doolittle, 1982).

In the classified amino-acid groups excluding cysteine in the disulfide bridge and those not occurring proline in the central residues, the curved extent of backbone shape in each amino acid is determined by averaging mean curvature values. And the distinct mean curvature values verify that amino acids are different in the intrinsic backbone conformations to adapt the ideal sheet surface having zero mean curvature, i.e. minimal surface.

The relative mean curvatures, listed in Table 1, are strongly correlated \( R = 0.75 \) excluding Asn in Fig. 6d) with the non-polar water-accessible surface area in its side chain, namely accessible area (Livingstone, 1991). It proves that the larger accessible area in the side chain enables the amino acid to take the smaller mean curvature in the backbone surface, and to constitute the minimal surface easily.

And it could be also suggested that when the twenty natural amino acids are substituted into a central residue by site-directed

\[ R = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}} \]

where \( x \) is the mean curvature value, \( y \) is the occurring frequency, \( \bar{x} \) and \( \bar{y} \) are the average mean curvature value and occurring frequency, respectively.

### Table 1. Comparison of β-sheet propensity parameters with mean curvature values for amino acids

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>No.</th>
<th>MC</th>
<th>Kim</th>
<th>Minor1</th>
<th>Minor2</th>
<th>Acc.Area</th>
<th>( P_{\text{interstrand}} )</th>
<th>( P_b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (Phe)</td>
<td>567</td>
<td>0.0522</td>
<td>-0.55</td>
<td>-0.86</td>
<td>-1.08</td>
<td>168.4</td>
<td>1.73</td>
<td>1.38</td>
</tr>
<tr>
<td>W (Trp)</td>
<td>180</td>
<td>0.0525</td>
<td>-0.48</td>
<td>-0.54</td>
<td>-1.04</td>
<td>177.2</td>
<td>1.49</td>
<td>1.37</td>
</tr>
<tr>
<td>Y (Tyr)</td>
<td>460</td>
<td>0.0535</td>
<td>-0.50</td>
<td>-0.02</td>
<td>-0.37</td>
<td>137.4</td>
<td>1.53</td>
<td>1.47</td>
</tr>
<tr>
<td>M (Met)</td>
<td>186</td>
<td>0.0542</td>
<td>-0.46</td>
<td>-0.72</td>
<td>-0.90</td>
<td>125.0</td>
<td>1.08</td>
<td>1.05</td>
</tr>
<tr>
<td>N (Asn)</td>
<td>171</td>
<td>0.0543</td>
<td>-0.38</td>
<td>-0.08</td>
<td>-0.52</td>
<td>41.9</td>
<td>0.46</td>
<td>0.89</td>
</tr>
<tr>
<td>V (Val)</td>
<td>1200</td>
<td>0.0559</td>
<td>-0.56</td>
<td>-1.00</td>
<td>-1.25</td>
<td>154.0</td>
<td>1.87</td>
<td>1.60</td>
</tr>
<tr>
<td>T (Thr)</td>
<td>523</td>
<td>0.0559</td>
<td>-0.48</td>
<td>-1.10</td>
<td>-1.36</td>
<td>88.7</td>
<td>1.07</td>
<td>1.19</td>
</tr>
<tr>
<td>L (Leu)</td>
<td>975</td>
<td>0.0568</td>
<td>-0.48</td>
<td>-0.51</td>
<td>-0.45</td>
<td>156.0</td>
<td>1.47</td>
<td>1.30</td>
</tr>
<tr>
<td>A (Ala)</td>
<td>487</td>
<td>0.0569</td>
<td>-0.35</td>
<td>0</td>
<td>0</td>
<td>80.4</td>
<td>0.71</td>
<td>0.83</td>
</tr>
<tr>
<td>H (His)</td>
<td>170</td>
<td>0.0569</td>
<td>-0.46</td>
<td>-0.96</td>
<td>-1.63</td>
<td>99.1</td>
<td>0.93</td>
<td>0.87</td>
</tr>
<tr>
<td>C (Cys)</td>
<td>104</td>
<td>0.0570</td>
<td>-0.47</td>
<td>-0.52</td>
<td>-0.78</td>
<td>47.4</td>
<td>1.22</td>
<td>1.19</td>
</tr>
<tr>
<td>E (Glu)</td>
<td>327</td>
<td>0.0572</td>
<td>-0.41</td>
<td>-0.01</td>
<td>-0.23</td>
<td>57.0</td>
<td>0.66</td>
<td>0.57</td>
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<tr>
<td>S (Ser)</td>
<td>433</td>
<td>0.0577</td>
<td>-0.39</td>
<td>-0.70</td>
<td>-0.87</td>
<td>57.4</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>K (Lys)</td>
<td>323</td>
<td>0.0578</td>
<td>-0.41</td>
<td>-0.45</td>
<td>-0.10</td>
<td>109.3</td>
<td>0.65</td>
<td>0.74</td>
</tr>
<tr>
<td>Q (Gln)</td>
<td>225</td>
<td>0.0597</td>
<td>-0.40</td>
<td>-0.23</td>
<td>-0.38</td>
<td>47.3</td>
<td>0.78</td>
<td>1.10</td>
</tr>
<tr>
<td>R (Arg)</td>
<td>377</td>
<td>0.0618</td>
<td>-0.44</td>
<td>-0.44</td>
<td>-0.35</td>
<td>84.5</td>
<td>1.03</td>
<td>0.94</td>
</tr>
<tr>
<td>D (Asp)</td>
<td>175</td>
<td>0.0623</td>
<td>-0.41</td>
<td>0.94</td>
<td>0.85</td>
<td>48.9</td>
<td>0.36</td>
<td>0.54</td>
</tr>
<tr>
<td>G (Gly)</td>
<td>292</td>
<td>0.0649</td>
<td>0</td>
<td>1.20</td>
<td>1.21</td>
<td>45.9</td>
<td>0.45</td>
<td>0.75</td>
</tr>
<tr>
<td>Correlation coefficients for all 19 amino acids (excluding no occurring P)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td>1</td>
<td>0.70</td>
<td>0.67</td>
<td>0.72</td>
<td>0.64</td>
<td>0.58</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>( P_{\text{interstrand}} )</td>
<td>0.58</td>
<td>0.67</td>
<td>0.63</td>
<td>0.58</td>
<td>0.78</td>
<td>1</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>( P_b )</td>
<td>0.56</td>
<td>0.56</td>
<td>0.54</td>
<td>0.52</td>
<td>0.70</td>
<td>0.91</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

1Occurring frequency of each amino acid among 7988 β-central residues in antiparallel β-sheets.
2Average mean curvature value in 19 amino acid types, except no occurring Proline.
3The β-sheet propensity scales (kcal/mol) from ZinF (Kim and Berg, 1993) and GB1 (Minor and Kim, 1994a;1994b; Koehl, and Levitt, 1999).
4Water-accessible non-polar surface areas \( (A^2) \) of the side chains in the fully extended β-form of Gly-X-Gly, by using the Richmond algorithm (Richmond 1984) and van der Waals radii of Richards (Richards, 1977).
5Residue abundances in antiparallel β-sheets calculated by dividing the antiparallel occurring frequency (%) by the global frequency of each amino acid (Wouters and Curmi, 1995).
6Chou-Fasman statistical β-sheet propensity parameter for amino acids (Chou and Fasman 1973).
7Cysteine forming the disulfide bonding are excluded.
mutagenesis, an amino acid with a larger mean curvature is more thermally unstable than one with a smaller mean curvature. To test this, we examined the relation between their distinct mean curvature values and free energies thermally measured in both ZincF and GB1 by the host-guest system, in which the stability of each amino acid, substituted for a guest residue in the solvent-exposed surface having zero mean curvature, is the minimal surface delineated by a smooth surface having zero mean curvature and the high mean curvature (>0.110) region in the smooth surface delineated by a β-sandwich is exactly the separated region without β-hydrogen bonding between adjacent β-strands, whereas the interior region connected by the β-hydrogen bonding between adjacent β-strands has small mean curvature (<0.018) (Koh and Kim, 2005). From statistical distribution and experimental studies (Chou and Fasman, 1973; Minor and Kim, 1994a; Smith et al., 1994), it is known that there are intrinsic differences in β-sheet propensities of amino acids. Our discrete geometrical analyses for whole domain sets in all β-protein class repeatedly confirm the minimal surface model of the ideal β-sheet, and reveal that the structural basis for these β-sheet propensities is in how readily each amino acid can adopt the ideal β-sheet structure, which is the minimal surface delineated by β-strand backbones. Furthermore, the sharply decreasing mean curvatures with increasing number of β-strands certified the cooperative effect, by which the strength of the intrastrand interactions are increasing with the number of strands (Kortemme et al., 1998) and is related to an equilibrium between intrastrand bonding and intrastrand elastic properties (Rossmeis et al., 2004). Consequently, the intrinsic mean curvature value of each amino acid in the β-sheet surface mainly determines the β-sheet propensities (Fig. 7). This coherent principle of β-sheet stability should facilitate our understanding of protein structure and protein design.

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4 DISCUSSIONS
Taken together, the least-square fitting method suggests that each connected β-sheet backbone conforms to the minimal surface with
and Engineering Foundation through the Protein Network Research Center.

Conflict of Interest: none declared.

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