Symmetric Structures in the Universe of Protein Folds

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Insights in structural biology can be gained by analyzing protein architectures and characterizing their structural similarities. Current computational approaches enable a comparison of a variety of structural and physicochemical properties in protein space. Here we describe the automated detection of rotational symmetries within a representative set of nearly 10 000 nonhomologous protein structures. To find structural symmetries in proteins initially, equivalent pairs of secondary structure elements (SSE), i.e., α-helices and β-strands, are assigned. Thereby, we also allow SSE pairs to be assigned in reverse sequential order. The results highlight that the generation of symmetric, i.e., repetitive, protein structures is one of nature's major strategies to explore the universe of possible protein folds. This way structurally separated 'islands' of protein folds with a significant amount of symmetry were identified. The complete results of the present study are available at http://agknapp.chemie.fu-berlin.de/gplus, where symmetry analysis of new protein structures can also be performed.

INTRODUCTION

Analysis and detection of molecular similarity in proteins are essential to understand their function and evolution. In this context, intrinsic structural similarities, i.e., symmetries, can yield insights into the fold stability, folding process, and evolutionary history of proteins.

It has been shown in a previous work that protein structures often contain a certain degree of intrinsic rotational symmetry.[1] Additionally, the visual inspection of common structural motifs (superfolds) reveals that many of them are symmetric. Therefore, it was suggested that in early evolution proteins might have been assembled from multiple identical polypeptide chains. These assemblies were then replaced by single polypeptide chains encoding multiple repeats, which fold more reliably and efficiently.[2] A possible mechanistic explanation for the occurrence of symmetric protein structures is gene duplication, where the sequence might subsequently be altered by point mutations.[3]

A particular challenge in the detection of molecular symmetry is the definition of appropriate criteria. The correlation between intrinsic molecular symmetries and functional relationships on a nonredundant set of 967 protein structures was studied previously.[4] The structure alignment tool COSEC2[5] was employed to detect intrinsic symmetries. This tool compares the spatial arrangement of secondary structure elements (SSEs) of two protein structures by representing SSEs with 3D vectors. Based on their findings, the authors postulated that similar protein pairs belonging to different protein families often contain internal symmetries in their common folds. Furthermore, the foldability of symmetric proteins might be increased due to the availability of multiple folding pathways.[6]

In the past, structure alignment tools were applied to detect repetitive structural fragments in proteins by aligning the protein structure sequentially with itself, yielding a matrix of all against all residue pairs.[7,8] These matrices were analyzed by Fourier expansion to detect repetitive similarities. Although this strategy is often successful in detecting repetitive structural fragments, it can yield a substantial number of false positives, especially for protein structures which contain large inserts or a large number of α-helices. These protein structures possess a high symmetry score, but by visual inspection no structural symmetry could be detected. Consequently, the authors noted[7,8] that in about 30% of the 50 highest ranked proteins (from a total 1 530 nonredundant protein structures) the detected symmetry contained errors or was ambiguous.

For this work, we analyzed the intrinsic symmetry of protein structures in the ASTRAL40 database (SCOP version 1.73).[9] The set contains nearly 10 000 protein structures with a pairwise sequence identity of less than 40%. The evaluation was based on the quality of structure alignments generated by the nonsequential structure alignment tool GANGSTA+.[10,11] In contrast to the SSE-level representation used in COSEC2,[5] GANGSTA+ generates structure alignments on the residue level. Gapless residue sections are uniquely assigned in the same sequential order between a pair of protein structures, which results in higher accuracy. The symmetry analysis has also been performed considering the structural alignments with SSE pairs assigned in reverse sequential order. Examples of these SSE assignments in reverse sequential order can be found in our previous work.[10] In contrast to most previous approaches,[7,8] the strategy in the present study was to find maximally complete intrinsic symmetries of protein structures rather than finding a repetitive structural fragment of arbitrary size. Hence, the generated structure alignments were ranked by the fraction of symmetrically aligned residues (see Figure 1). To the best of our knowledge, only in the present study a search was performed for structural symmetry in proteins using nonsequential structure alignment on the residue level by assigning SSEs in the same and reverse

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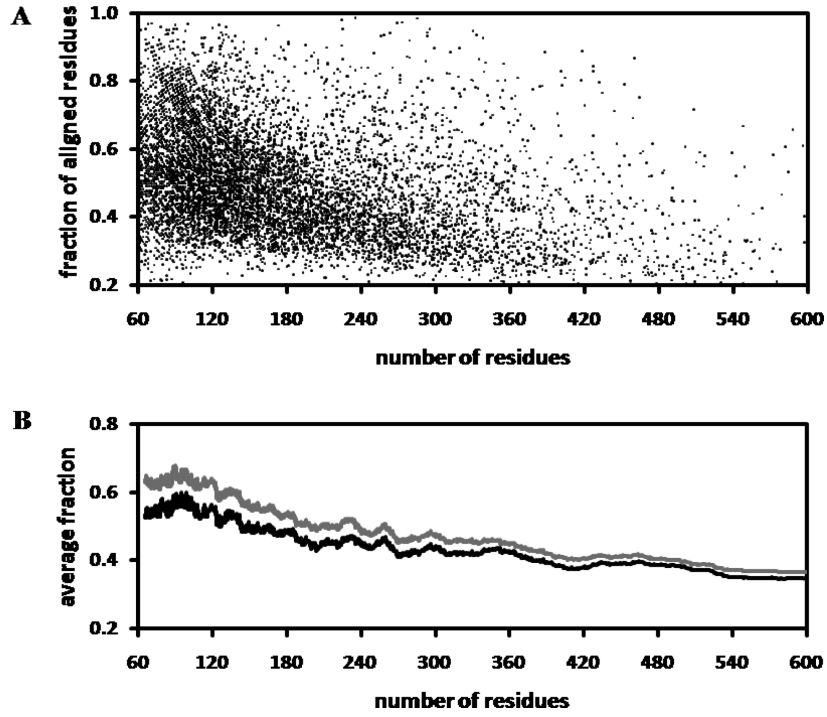

Figure 1. (A) Results of symmetry analysis with GANGSTA+ for the ASTRAL40 database (SCOP version 1.73) containing 8 738 protein structures, where each structure has been nonsequentially self-aligned with SSEs in the same sequential order. The fraction of aligned residues per protein structure is shown to correlate with the total number of residues. The root-mean-square deviation of each alignment is less than 4 Å. (B) Average fractions of self-aligned residues, considering nonsequential structure alignments with the SSEs, in same (black) and both sequential orders (gray).

sequential order. Additionally, the number of protein structures analyzed for intrinsic structural symmetry is the largest considered so far.

MATERIALS AND METHODS

To detect rotational symmetries of a protein structure, we generated nonsequential structure alignments of the protein with itself using GANGSTA+.[10] The algorithm of GANGSTA+ aligns protein structures hierarchically in three stages, starting with an alignment of SSE pairs, where only α-helices (including also three[10] helices) and β-strands were considered as SSEs. Since loops and coils connecting the SSEs were ignored, nonsequential structure alignment was facilitated. In the first stage, GANGSTA+ uses a combinatorial approach to explore similarities between two protein structures based on contact maps of the SSEs. In the second stage, GANGSTA+ performs preliminary alignments on the residue level for the highest ranked SSE assignments using rigid body energy minimization with attractive soft interactions between C_α atoms belonging to different proteins. Thus, the spatial distances of the assigned C_α atom pairs are minimized. In stage three, the preliminary structural overlay is used to assign the C_α atoms of both proteins to points on the same cubic grid. C_α atom pairs assigned to the same grid points are used for a more accurate and complete SSE assignment. Finally, the assignment on the residue level is repeated for residues belonging to loops and coils. The algorithm is also able to consider SSE alignments in reverse sequential order. A more detailed technical description of GANGSTA+ and its parameters is given in the supplement.[10]

To detect symmetries in protein structures, the alignment procedure of GANGSTA+ was alternated for the present study. In the first stage of SSE alignment, the trivial self-alignment assigning identical SSEs was ignored. On the residue level, false positives, e.g., identical self-alignments, were avoided by considering only self-aligned structure pairs whose root-mean-square deviation (RMSD) of equivalent C_α-atom pairs is larger than 10 Å. Pairwise structure alignments were restricted to RMSDs below 4 Å, considering only nonequivalent C_α-atom pairs. For the symmetry analysis, the parameters N_{max} and N_{map} (see supplement[10] for details) have been set to 5 000 and 1 000, respectively, to allow a wider search for structural similarities. Furthermore, the cut off parameters N_{Cheb} and N_{Euler} have been changed to 3 and 6 Å, respectively, to allow the detection of more complete residue assignments, which was, however, limited by a total C_α-atom RMSD of 4 Å.

As mentioned in the Introduction, the analysis was carried out on the nonredundant ASTRAL40 database (SCOP version 1.73), which contains 9 536 structures of protein domains possessing less than 40% sequence identity. From this set of protein domain structures, we considered only those possessing more than 60 residues and more than two SSEs. The latter was done to avoid protein structures containing mainly loop and coil sections, where the SSE assignments become ambiguous and rotational symmetries are likely rare. With these restrictions 8 738 protein domains remained. Since the threshold of 40% sequence identity might lead to structural redundancies within the ASTRAL40 database, we also considered the ASTRAL10 database (SCOP version 1.73) with less than 10% sequence identity, which contains 5 021 structures of protein domains with more than 60 residues and more than two SSEs. To study how the results are influenced by sequence redundancies, we also considered the ASTRAL70 database (SCOP version 1.73),

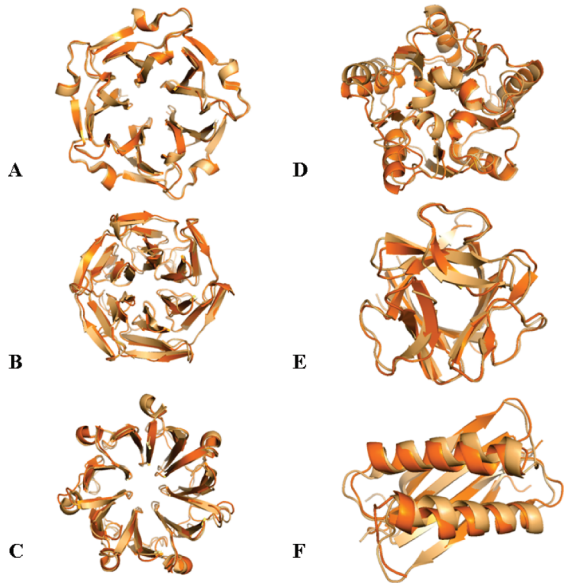

Figure 2. Examples of protein folds with rotational symmetry where more than 95% of all residues are aligned with SSEs in same sequential order: A) 1TL2,[13] B) 2FLU,[14] C) 1JTD,[15] D) 1G61,[16] E) 1DFC[17] and F) 1JX4.[18] The alignment results are illustrated in light and dark orange.

Table 1. Clusters Containing More than 10 Protein Folds Possessing Rotational Symmetry [Obtained from the ASTRAL40 database] with More Than 80% of All Residues Aligned with SSEs in the Same Sequential Order[a]

protein fold types of SCOP	symmetric proteins in cluster	
ferredoxin-like (Figure *3*B)	68	(37)
immunoglobulin-like β-sandwich	31	(13)
β-trefoil (Figure *2*E)	23	(11)
four helical up-and-down bundle	16	(12)
DNA clamp	14	(6)
seven bladed β-propeller (Figure *2*C)	13	(6)
TIM β/ α-barrel	12	(4)
γ-crystalline-like	10	(5)

[a] The corresponding cluster sizes in the ASTRAL10 database are shown in parentheses. The complete set of results is available at: http://agknapp.chemie.fu-berlin.de/gplus.

which contains 11 379 protein structures with more than two SSEs and more than 60 residues with less than 70% sequence identity.

RESULTS

Figure 1A characterizes the similarities found in the 8 738 protein structures of the ASTRAL40 database (SCOP version 1.73). The fraction of aligned residues in the protein structures, where rotational symmetry was found by aligning the SSEs in same sequential order, is correlated with the total number of residues for each protein. In 25 protein structures, the detected rotational symmetry involves more than 95% of all residues (see Figure 2). In 376 protein structures, symmetries were detected with more than 80% of all residues aligned with SSEs in same sequential order. Table 1 shows how these protein structures cluster according to the SCOP classification scheme.[9] The most frequently occurring protein fold with intrinsic 2-fold rotational symmetry is the ferredoxin-like fold. From the total number of 376 protein structures with rotational symmetry involving more than 80% of all residues, this fold appears in 68 symmetric protein

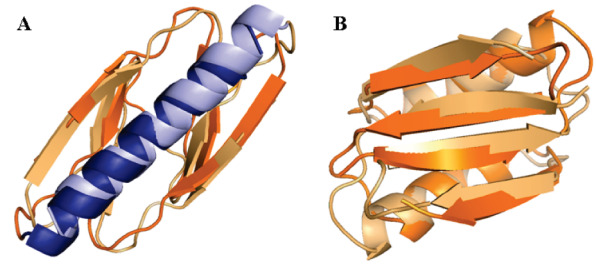

Figure 3. (A) Example of a protein fold with rotational symmetry with SSEs in both sequential orders where more than 98% of all residues are aligned at 2.44 Å RMSD: 1JJ2.[12] The sequentially aligned structural segments are illustrated in light and dark orange. The α-helix shown in light- and dark-blue, respectively, is aligned in reverse sequential order. (B) Symmetry analysis for the most frequently appearing protein fold, which is ferredoxin (1FE0[19]), found in 1 474 proteins of the ASTRAL40 database (SCOP version 1.73)[9] with GANGSTA+.[10] The symmetry is illustrated as structural superposition in light- and dark-orange, whereby 96% of all residues are aligned with SSEs in same sequential order at 3.93 Å RMSD.

structures. The ferredoxin-like fold is followed by the immunoglobulin-like β-sandwich and β-trefoil fold. The latter two are found in 31 and 23 symmetric protein structures of the ASTRAL40 database, respectively. The same analysis was carried out with the 5 021 protein structures of the ASTRAL10 database (SCOP version 1.73) with more than 60 residues and more than two SSEs. Here, 220 protein structures with rotational symmetries, involving more than 80% of all residues aligned with SSEs in the same sequential order, were identified (see Table 1 for a list of the most often occurring folds). Additionally, this procedure was repeated for each protein structure by allowing SSE alignments in same and reverse sequential order. Figure 1B illustrates the average quality of the resulting structure alignments with regard to rotational symmetries in the ASTRAL40 database, considering SSE assignments in same and both sequential orders. The variation of results with the difference in SSE alignment mode (strictly sequentially or in both sequential orders), is demonstrated with the example of the ribosomal protein L6 of archaeon *Haloarcula marismortui* (PDB: 1JJ2,[12] see Figure 3A). For this protein structure, the fraction of aligned residues increases from 71 to 98%, if SSE alignment in reverse sequential order is considered.

We also tried to align protein structures with their mirror counterparts to detect intrinsic mirror symmetries. Here, we obtained only 10 mirror symmetric protein structures with at least 60 residues and more than 80% of residues aligned. However, these protein structures also contained a rotational symmetry of higher quality with an even larger fraction of aligned residues. Note that structure alignments with the mirror image of a protein are impeded by α-helices, whose sense of rotation changes with the mirror image.

Next, an all-against-all database scan of ASTRAL40 was carried out to determine the most frequently appearing folds. The ASTRAL40 database (SCOP version 1.73) contains 8 738 protein structures with more than two SSEs and more than 60 residues. Each protein domain was ranked by the number of aligned protein structures that share at least 80% of its residues with an RMSD below 3 Å. The most frequently appearing fold with 2-fold rotational symmetry is the ferredoxin-like fold (1 474 structures in the ASTRAL40 database). The iron binding domain of ferredoxin (PDB:

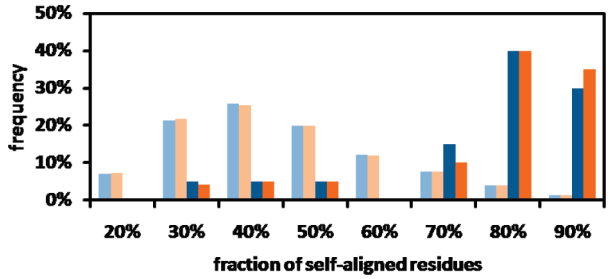

Figure 4. Distribution of symmetric protein structures found by self-alignment with the SSEs in same sequential order using GANGSTA+.[10] Symmetric proteins obtained from the ASTRAL40 database (SCOP version 1.73)[9] of 8 738 protein domains (with more than 60 residues and more than two SSEs) are displayed by light-orange bars. The light-blue bars show the distribution of symmetric proteins obtained from the ASTRAL10 database (SCOP version 1.73), containing 5 021 protein domains (with more than 60 residues and more than two SSEs). The compositions of the top 20 most frequent symmetric protein folds depend on the considered database of protein structures. The dark-blue and dark-orange bars show the distributions of these 20 most frequent symmetric protein folds derived from ASTRAL10 and ASTRAL40 databases (SCOP version 1.73), respectively.

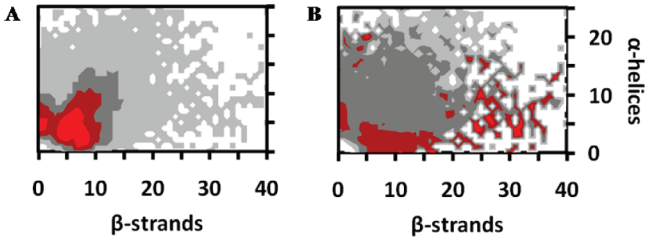

Figure 5. (A) Frequency of protein structures from the ASTRAL40 database as a function of SSE composition (number of α-helices and β-strands). SSE compositions detected in more than 80 protein structures are shown in light-red, 80 and 40 in dark-red, 40 and 20 in dark-gray and 20 and 1 in light-gray. (B) Average protein symmetry as a function of SSE composition. The average fraction of self-aligned residues of proteins from the ASTRAL40 database possessing intrinsic rotational symmetry is shown as a function of the SSE composition. SSE compositions with more than 80% of self-aligned residues on average are shown in light-red, 80 to 60% in dark-red, 60 to 40% in dark-gray and 40 to 20% in light-gray. The symmetry detection was performed with GANGSTA+, considering SSE alignments in same and reverse sequential order.

1FE0) involves six SSEs, two α-helices, and four β-strands, comprising of 66 residues. The structure alignment, which finds the 2-fold rotational symmetry, comprises all six SSEs and 96% of all residues at 3.93 Å RMSD with the SSEs aligned in same sequential order (see Figure 3B). Figure 4 illustrates the distribution of symmetric protein domains aligning the SSEs in same sequential order for all 8 738 protein domains from ASTRAL40 (SCOP version 1.73) and for the 20 most frequently appearing symmetric protein folds in ASTRAL40. Additionally, the corresponding distributions of symmetric protein domains, obtained by aligning the SSEs in same sequential order, are shown for the ASTRAL10 database (SCOP version 1.73).

Finally, we clustered all protein structures, depending on their SSE composition (number of α-helices and β-strands). Figure 5A depicts the number of protein structures in the ASTRAL40 database (SCOP version 1.73) for each SSE composition. The figure shows that most of the protein structures contain up to both 12 α-helices and 12 β-strands (5 990 out of 8 738). The remaining protein structures (2 748 out of 8 738) often have a very unique SSE composition, shared with only a few or no other protein structures. Figure 5B displays the average degree of intrinsic rotational symmetry detected in the set of proteins with the same SSE composition. Here, we considered SSE assignments in same and reverse sequential order in contrast to Figure 1A. The results show that a number of structurally separated and rarely populated SSE compositions contain protein structures with a high degree of intrinsic rotational symmetry. We define protein structures with these SSE compositions as 'islands of structural symmetry'. In particular, this can be observed for protein structures containing a large number of β-strands. On the other hand, large $\alpha\beta$-protein structures generally have a higher structural complexity, i.e., a lower degree of intrinsic rotational symmetry. The same procedure was repeated with ASTRAL10 and ASTRAL70 databases (SCOP version 1.73), considering SSE alignments in same and reverse sequential orders (see Supporting Information).

DISCUSSION

The analysis carried out in this work is a fully automated large-scale effort to detect structural symmetries of proteins in the ASTRAL40 database. We also performed an all-against-all protein structure alignment of the whole ASTRAL40 database and verified that frequently appearing protein folds often contain rotational symmetries (see Figure 4). About 4% of all protein domains in the ASTRAL40 database (SCOP version 1.73) contain rotational symmetries with more than 80% of all residues aligned with the SSEs in same sequential order and the RMSD below 4 Å. Considering protein symmetries where SSEs are allowed to be aligned in both sequential orders reveals additional symmetries with SSEs aligned in reverse sequential order as shown in Figure 3A.

The analysis of intrinsic mirror symmetries revealed that mirror symmetries are rare, which agrees with previous findings.[4] The 2-fold rotational symmetry of a protein structure can be generated by a single gene duplication event, but no simple genetic mechanism seems to be available to generate a mirror symmetric protein. Another reason for the rare detection of high-quality mirror symmetries of protein structures is the inverted sense of rotation of α-helices in the mirror images that reduces the alignment quality for mirror symmetries.

We clustered all protein structures depending on their SSE composition and determined the corresponding frequencies in the ASTRAL40 database (Figure 5A). We also determined the degree of intrinsic rotational symmetry of all proteins possessing structure symmetry as a function of the SSE composition, considering SSE alignments in same and reverse sequential order (Figure 5B). Combining the information from Figure 5A and B reveals that for specific SSE compositions only a small number of protein structures are available, which on average have a high degree of intrinsic rotational symmetry. These symmetric protein structures with specific SSE compositions are clearly separated from proteins with other SSE compositions found in the ASTRAL40 database (SCOP version 1.73). Thus, they appear as 'islands of structural symmetry' containing proteins that often possess a large fraction of β-strands (Figure 5B). These islands represent regimes in the high-dimensional universe of existing protein folds, which are not or only scarcely

surrounded by other protein structures with similar SSE compositions. The high degree of intrinsic rotational symmetry of protein structures in these islands suggests that during the course of evolution these islands were populated for instance by gene duplication processes, which can lead to protein structures with 2-fold rotational symmetry. Evidently, the surroundings of these islands were not populated by variation or increase of structural complexity most often due to point mutations or fusion operations.[2] One reason for the occurrence of these islands of symmetric proteins might be that other possible protein structures close to these islands are not needed, since the existing proteins in these islands are thermodynamically efficient and perform all necessary tasks. Alternatively, in these regimes of the protein universe, stable folds may only form if proteins possess high degrees of intrinsic rotational symmetry. For instance, folds with a high content of β-strands prefer to form barrels or trefoils to stabilize their structure. An increase in structural complexity may destroy this intrinsic symmetry. For large $\alpha\beta$-proteins with considerable complexity, the absence of symmetry in the structures can be observed (Figure 5B). Explaining the origins of such folds is not in the range of the present study, since it might require the understanding and the analysis of more complex evolutionary processes that serve to enlarge the universe of existing protein folds. In future studies, we will analyze the effect of additional genetic operations, such as circular permutations or fusion on a larger scale, which may allow further improvement in our understanding of the topology in the universe of possible versus existing protein folds.

CONCLUSION

The results of this study demonstrate on a large-scale that frequently appearing folds often contain rotational symmetries. Additionally, they highlight the fact that generating protein structures with intrinsic symmetries is one of nature's major strategies to explore the universe of possible protein folds. In this way, we could identify structurally separated sets of proteins ('islands of structural symmetry'), containing protein structures of significant symmetry content seemingly populated on purpose by nature's evolutionary processes. Interestingly, the structural complexity of these 'islands of structural symmetry' does not appear to be significantly altered or enlarged during evolution. From this we can conclude that the structural symmetry of proteins was conserved in the evolutionary processes with little or no successful exploration of the surrounding space of protein folds.

A more detailed description of the applied approach and a complete list of results are available at http://agknapp.chemie.fu-berlin.de/gplus.

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Supporting Information Available: Contains additional figures illustrating the frequency and average fraction of self-aligned residues of proteins possessing intrinsic rotational symmetry as a function of the SSE composition. The symmetry detection was performed with GANGSTA+ using the databases ASTRAL10, ASTRAL40, and ASTRAL70 (SCOP version 1.73).[9] SSE alignments were performed in same and reverse sequential orders. This material is available free of charge via the Internet at http://pubs.acs.org.

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