PROTEINS: Structure, Function, and Genetics 28:333–343 (1997)

Hydrophobic Patches on Protein Subunit Interfaces: Characteristics and Prediction

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ABSTRACT **Hydrophobic patches, defined as clusters of neighboring apolar atoms deemed accessible on a given protein surface, have been investigated on protein subunit interfaces. The data were taken from known tertiary structures of multimeric protein complexes. Amino acid composition and preference, patch size distribution, and patch contact complementarity across associating subunits were examined and compared with hydrophobic patches found on the solvent-accessible surface of the multimeric complexes. The largest or second largest patch on the accessible surface of the entire subunit was involved in multimeric interfaces in 90% of the cases. These results should prove useful for subunit design and engineering as well as for prediction of subunit interface regions. Proteins 28:333–343, 1997.** © 1997 Wiley-Liss, Inc.

Key words: protein structure; oligomeric structure; subunit interface; molecular recognition

INTRODUCTION

The biologically active form of many protein molecules is a complex of two or more polypeptide chains. The functions of such multimeric subunit associations include allosteric control mechanisms, signal transduction, binding of symmetrical substrates, interaction with active sites, and reduced diffusional mobility of the complex.

Molecular association involves loss of entropy for the monomers or subunits. In a dimeric complex, the negative entropy change arises from the loss of six motional degrees of freedom with additional losses in interface side-chain mobilities. Janin and coworkers[1] have estimated the entropic cost at 20–30 kcal/mol and have suggested that the burial, upon complexation, of exposed hydrophobic surface area (the hydrophobic effect) is the main driving force for oligomerization. The interface region of monomers has also been found to be more hydrophobic than their solvent-exposed surface, which supports this conclusion.[2] Principal studies of subunit association surfaces have included those of Argos,[2] Janin et al.,[1] Korn and Burnett,[3] and Jones and Thornton.[4]

We have recently described a method for detecting explicit, contiguous patches of hydrophobic surface and have applied it to a set of monomeric proteins. The protein's surface can be viewed as several clusters of neighboring carbon and sulfur atoms (hydrophobic surface) surrounded by polar or charged nitrogen and oxygen atoms (hydrophilic surface). The large hydrophobic patches are often connected by narrow hydrophobic "channels" resulting from the extended contiguity of touching apolar atoms. These channels can be eliminated to elicit the significant hydrophobic patches.[5] In the current investigation, we examine the hydrophobic patches found on the surface of subunit interfaces and address questions concerning the size and shape of the patches, their coincidence with the interface and contact with patches on the partner subunit, their amino acid compositional biases, and the prediction of their involvement in oligomeric association. This insight into the details of hydrophobic subunit interaction should prove valuable in protein engineering, design, and docking.

METHODS

A set of multimeric proteins was obtained from the Brookhaven protein tertiary structure data bank[6,7] by selecting entries, with the aid of the SRS information search system,[8,9] that contain more than one polypeptide chain, each longer than 50 residues, or display in the REMARK-section of the entry file words indicative of an oligomeric protein such as dimer, trimer, or tetramer. From this initial set, a subset containing the maximal number of protein chains with all pairwise sequence alignments of $<$45% in residue identity was constructed by the method of Heringa and coworkers.[10] For the latter set, we selected those structures where more than 1000 Å^2 of a surface is buried per chain upon complexation. This yielded 59 protein complexes of which 41 were dimeric, 2 trimeric, 13 tetrameric, 2 pentameric, and 1 hexameric, totaling 156 polypeptide chains. The PDB entry codes and chain identifiers (listed successively as single letters after the

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Received 11 June 1996; Accepted 27 February 1997

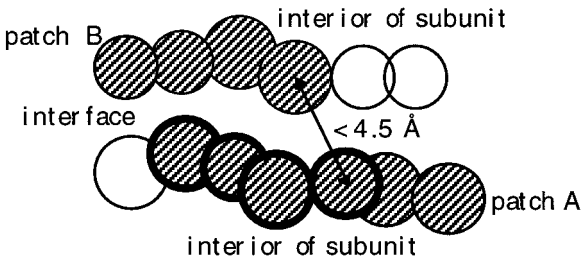

Fig. 1. The definition of patch overlap. Patches on two different subunit interfaces *A* and *B* are shown. Gray circles indicate hydrophobic atoms while white circles refer to hydrophilic atoms. Atoms of patch *A* with thick circumference indicate those that overlap with patch *B*. The sum of the full solvent accessibility of the latter atoms in the uncomplexed state is taken as the measure of the extent of overlap.

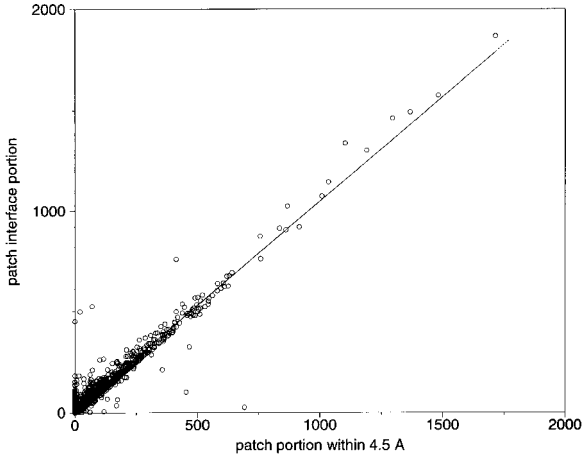

Fig. 2. A plot showing the actual loss of surface area upon subunit association versus the amount estimated on the basis of interatom contacts with distance criterion 4.5 Å. The linear regression line ($Y = 1.03 * X + 12.25$) has a correlation coefficient of 0.97 with the data.

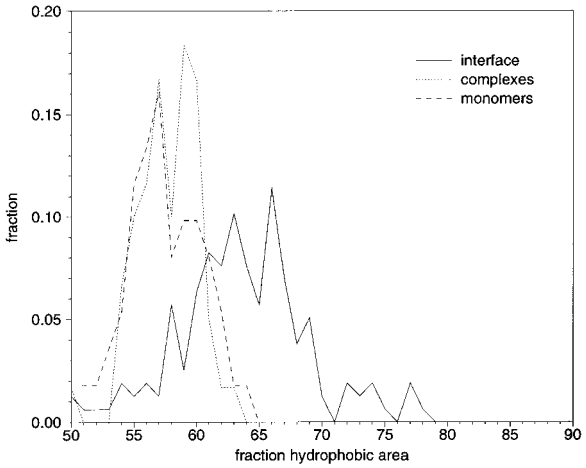

Fig. 3. A histogram of the percentage of solvent accessible surface that is hydrophobic. The solid line plot represents interface surface percentages, while the dotted and dashed lines apply to the hydrophobic fraction on the exterior surface of multimeric complexes studied here and to the monomeric proteins from our previous study.[5]

hyphen) of the proteins used in this work are as follows:

1ABR-AB, 1ALK-AB, 1AOR-AB, 1CAU-AB, 1CHM-AB, 1CMB-AB, 1EAP-AB, 1EBH-AB, 1FIA-AB, 1GER-AB, 1GLP-AB, 1GST-AB, 1HLD-AB, 1MRR-AB, 1NHK-LR, 1NSB-AB, 1POW-AB, 1PP2-LR, 1PVU-AB, 1PYD-AB, 1SES-AB, 1SRI-AB, 1TKB-AB, 1TPH-12, 1TPL-AB, 1VAA-AB, 2BBQ-AB, 2CST-AB, 2FB4-HL, 2FBJ-HL, 2NAD-AB, 2POL-AB, 2RSP-AB, 2SCP-AB, 2TMD-AB, 2UTG-AB, 3AAH-AC, 3SC2-AB, 4HVP-AB, 5RUB-AB, 8CAT-AB; 1BBP-ABCD, 1BOV-ABCDE, 1COM-ABC, 1CPC-ABKL, 1EPT-ABC, 1GD1-OPQR, 1HDC-ABCD, 1HJR-ABCD, 1HSA-ABDE, 1HUC-ABCD, 1NBA-ABCD, 1PYA-ABCDEF, 1RAI-ABCD, 1SAC-ABCDE, 2BBK-HLJM, 2HNT-LCEF, 2MTA-HLAC, 3PGA-1234.

The method used to delineate the hydrophobic patches has been previously described by us.[5] The solvent accessible surface of a folded polypeptide chain can be considered to consist of clusters of neighboring hydrophobic (carbon and sulfur) atoms surrounded by contiguous strings of hydrophilic (nitrogen and oxygen) atoms. However, it is very likely that the hydrophobic clusters will be connected by—sometimes narrow—"channels" consisting of strings of hydrophobic atoms. These channels can be closed through the expansion of the hydrophilic atoms (only if solvent-accessible) by a certain amount. With the remaining preliminary hydrophobic patches so identified, the expanded hydrophilic atoms are then reduced to their normal size and one layer of apolar atoms (if they were previously covered by the expansion) are added to each of the preliminary patches.

Subunit interface atoms were defined as those that displayed a difference in solvent accessibility between the fully complexed and monomeric states. In all cases, accessibility was determined by the numerical method of Eisenhaber and coworkers,[11] with reliance on a solvent probe radius of 1.4 Å. For complexes consisting of more than two chains, all pairwise interfaces involving one subunit were considered together; for example, in the trimer $\alpha\beta\gamma$, the α interface was the union of the $\alpha\beta$ and $\alpha\gamma$ interaction surfaces.

A hydrophobic patch was designated an interface patch if more than a certain fraction of it was buried upon subunit association. In our sample of 156 polypeptide chains from 59 multisubunit proteins, a total of 8252 patches were found, of which 2556 had some overlap with the interface, 1891 had more than 50% of their solvent accessible surface involved in the interface, 1447 more than 80% overlap, and 759

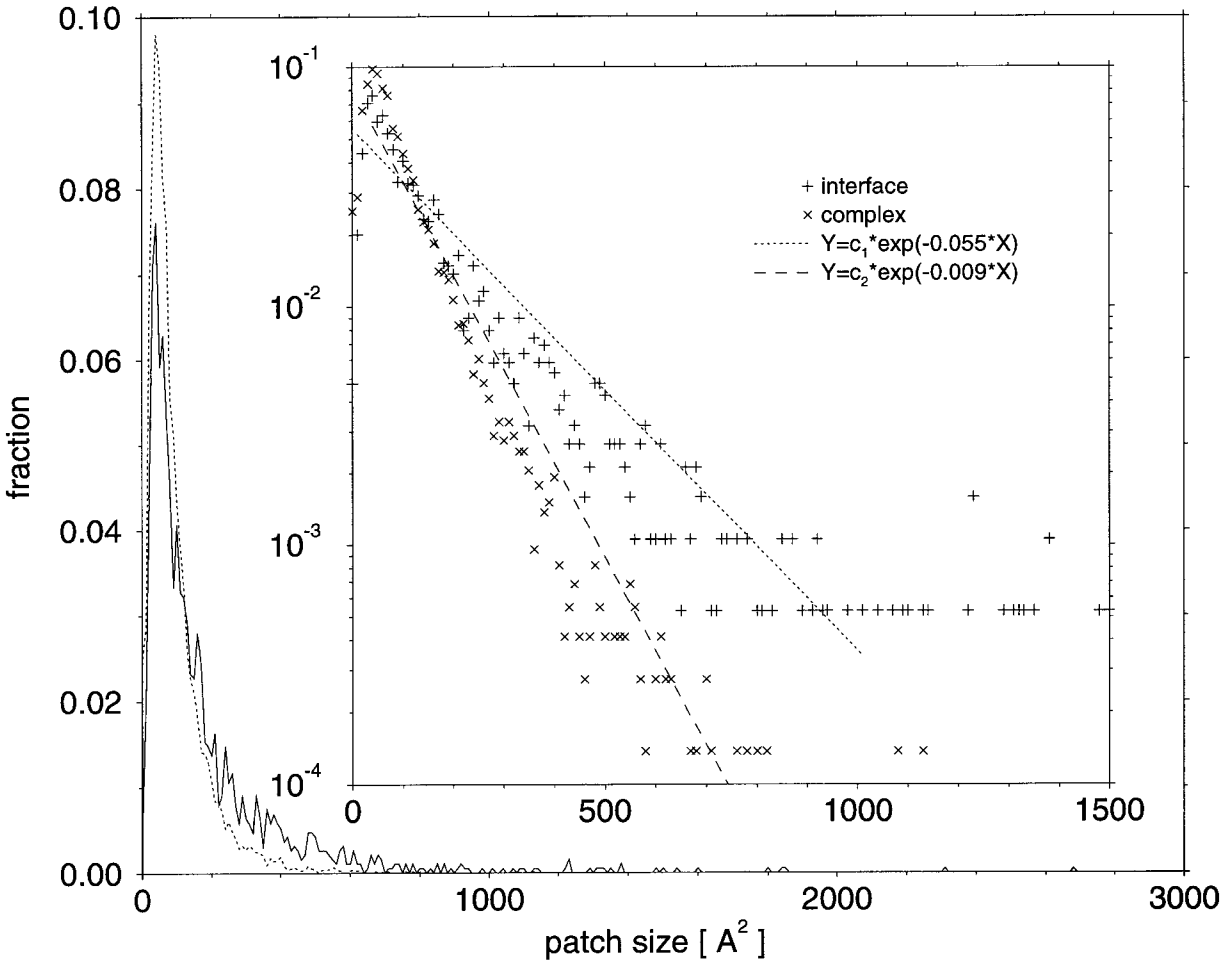

Fig. 4. The size distribution of hydrophobic patches with more than 50% of their individual accessible surface within the interface (solid line) and of hydrophobic patches on the exterior surface of multimeric protein complexes (dashed lines). The inset shows a logarithmic plot with regression lines given for both patch types (+ for interface and X for multimers). The correlation coefficient is 0.96 for the interface patches and 0.97 for patches on the exterior surface of complexes.

had a coincidence of more than 99%. In this work we defined an interface patch as one that has more than 50% of its area associated with subunit interface(s). When a different threshold is used, it will be stated explicitly.

To measure the overlap of interface patches from different subunits, we used the following criteria. For each atom of a patch A on one subunit, we consider it to display overlap with patch B on the other subunit if this atom is closer than 4.5 Å to any atom of patch B (Fig. 1). The contact distance 4.5 Å was employed as 4.0 Å represents about one carbon diameter with the extra 0.5 Å allowing for experimental error and hydrogen atoms. The sum of the (uncomplexed) atomic solvent-accessible surface areas of the atoms in patch A that, with the 4.5 Å criterion, are overlapped by atoms in patch B will be denoted overlap (A, B). Due to curvature effects, overlap (A, B) is generally not equal to overlap (B, A).

The sum of overlap (A, B_i) for patch A in overlap with several different patches B_i, divided by the entire area of patch A, is called the overlap factor $\Phi(A)$, that is,

$$\Phi(A) = \sum_i \frac{\text{overlap } (A, B_i)}{\text{area } (A)}$$

where $\Phi(A)$ is the fraction of a patch's area that overlaps with patches on the other subunit(s). Occasionally $\Phi(A)$ is larger than the area of patch A, as atoms of A can be counted doubly for different B_i. In this case the overlap factor was set to 1. Overall statistics were obtained by combining and averaging the results from overlap (A, B) and overlap (B, A).

Formally, the change in accessible surface on contact of every possible patch pair should be calculated; however, the computer calculations over all possible patch pairs and all interfaces were prohibitive, forcing the approximation through atom contacts and accessible surface summation. Since the actual area contributed by a patch to the interface

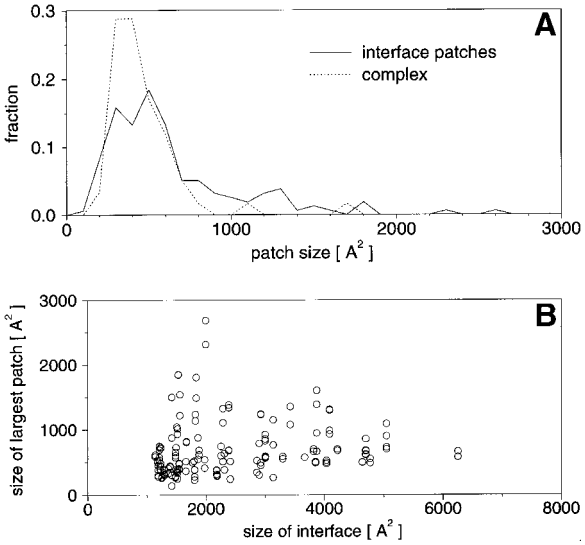

Fig. 5. **A:** The distribution of sizes of the largest hydrophobic interface patch in each subunit as well as for hydrophobic patches on the exterior surface of multimeric protein complexes. **B:** The size of the largest interface patch as a function of the size of the subunit interface. The latter is expressed as the total area loss upon subunit association per polypeptide chain.

had been determined through the monomeric/multimeric accessible surface calculations, the area of a given interface designated patch estimated by all contacting atoms from other subunit patches could be compared with the actual area. Figure 2 shows a plot of the two areas which display good correlation except for a few outliers.

In this work several distribution plots (histograms) are shown. In each case the vertical axis is labeled "fraction," while the horizontal axis is denoted by the name of a property examined over the protein monomers or multimeric complexes used in this work. The fraction label thus refers to the percentage (fraction) of all the proteins or patches studied that displayed particular values for a given structural characteristic labeled and plotted on the horizontal axis.

RESULTS AND DISCUSSION

Patch Size Distribution

Subunit interfaces are known to be more hydrophobic than the external protein surface.[2,3] This is confirmed in Figure 3, which shows histograms of the fraction of exposed (accessible) surface that is hydrophobic for several monomeric proteins (data from Ref. 12); for multimeric complexes used in this study; and for subunit interface surfaces. Regarding the fraction of the surface that is composed of hydrophobic atoms, the exterior surfaces of multisubunit complexes and monomeric proteins cannot be distinguished, while subunit interfaces show considerably elevated fractions. Monomeric and complex surfaces are all 50% to 65% hydrophobic, while interfaces mostly range between 58% and 70%.

The distribution of the sizes of hydrophobic patches is given in Figure 4 for interface and complex surfaces. Although the distributions generally appear similar, the plot for the exterior surface of complexes levels off sooner than that for interface patches, showing that the latter possess more large patches. This is expected, given the more hydrophobic subunit interfaces. Both distribution curves behave roughly exponentially, as demonstrated in the logarithmic plot of the inset of Figure 4. Regression lines fitted to the logarithm of the original distributions show good correlation. The fivefold difference in the factors of the fitted exponents confirm that there are more large hydrophobic patches on subunit interfaces.

Since there are more large patches on interfaces, it is possible that the largest patch in each interface is, on average, larger than the largest patch found on the exterior surface of the complex. This, however, is not the case, as shown in Figure 5a, which displays histograms of the size of the largest patches in each subunit or protein for interfaces and for complexes, respectively. Both histograms display similar peaks. There is also no relationship between the size of the interface and the size of the largest patch (Fig. 5b). This behavior resembles that found in monomeric proteins, where no correlation was found between the size of the protein and that of the largest patch.[12]

Number of Patches per Interface

In Figure 6 the number of hydrophobic patches per interface is shown according to various patch size thresholds. As expected, the average number of hydrophobic patches per interface decreases as the patch size considered increases. The number of patches larger than 100 Å^2 ranges between 2 and 14 for most interfaces, while, for patches larger than 300 Å^2, the most common number of patches per interface has reduced to just one. Patches larger than 600 Å^2 are found in only 40% of the interfaces.

Patch Overlap With Interface

Do the largest hydrophobic patches on subunit surfaces lie predominantly within the interface region, and do interface patches mostly coincide with the interface? These questions are addressed in Figure 7, which shows the distribution of overlap of patches with the interface, both for all patches and for the largest patch on the entire and isolated subunit surface of each chain considered. The large fraction of patches in the bin with 0–10% of their patch area overlapping the interface encompasses all the noninterface patches, many of which are

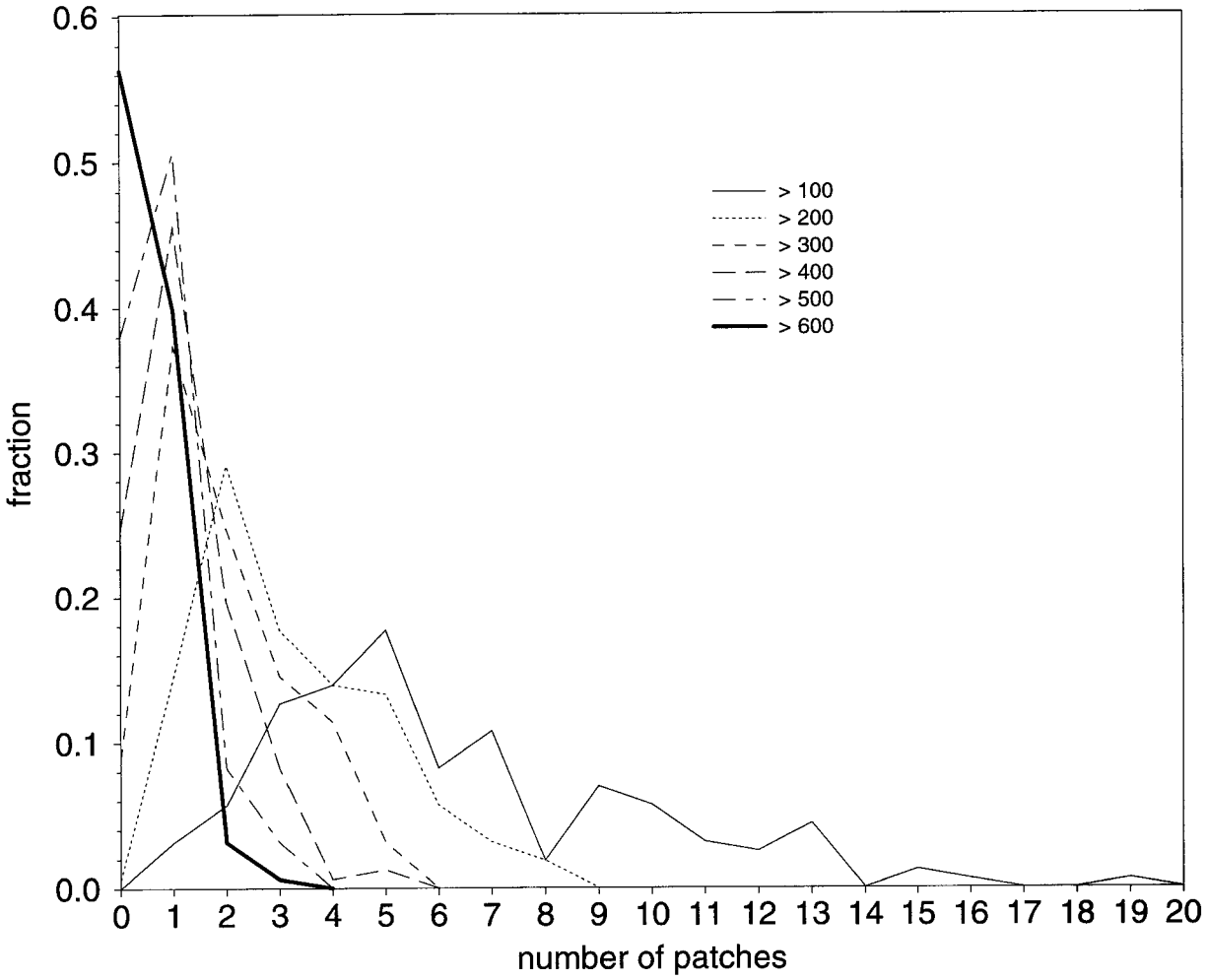

Fig. 6. A relative histogram of protein subunits having a certain number of hydrophobic interface patches as a function of the minimum size of the patches considered.

relatively small. The distribution peaks at the 90–100% bin, corresponding to nearly 40% of the proteins examined. Based on the current sample, this shows that if the largest patch has any overlap with the interface, it is most likely to have in fact an overlap of more than 90%. Also, the cumulative distribution shows that more than three-fourths of the largest patches on the entire subunit surface have an overlapping surface of more than 50% with the interface. Thus, for the largest patches, the transition from interface to exterior surface is rather abrupt, and this may well be an important factor in the process of recognition and complexation. Nonetheless, there is a reasonable fraction of largest patches not involved in the interface (16%), although they may have a functional role.[12]

Patch Rank and Occurrence in Interface

Large patches are frequently found in the interface, but is the largest patch of a subunit always involved in the interface? Figure 8 shows that this is the case for 75% of the multimers in our data set. From the cumulative histogram given in the inset, it can be seen that either the largest or the second largest hydrophobic patch of the entire subunit surfaces lies within the interface for 90% of the multimeric proteins examined. A patch is deemed to lie within an interface if more than 50% of its total surface is involved in subunit association. Young and coworkers[13] have noted a correlation between points of high hydrophobic potential and protein binding sites. Our finding should be very useful in the study of subunit-subunit docking, as it greatly limits the search space for recognition studies. Amino acid residues composing the largest patch are thus a likely target to alter oligomerization characteristics.

Patch Complementarity

When subunits associate, they mutually bury hydrophobic surface area. It should be useful to know

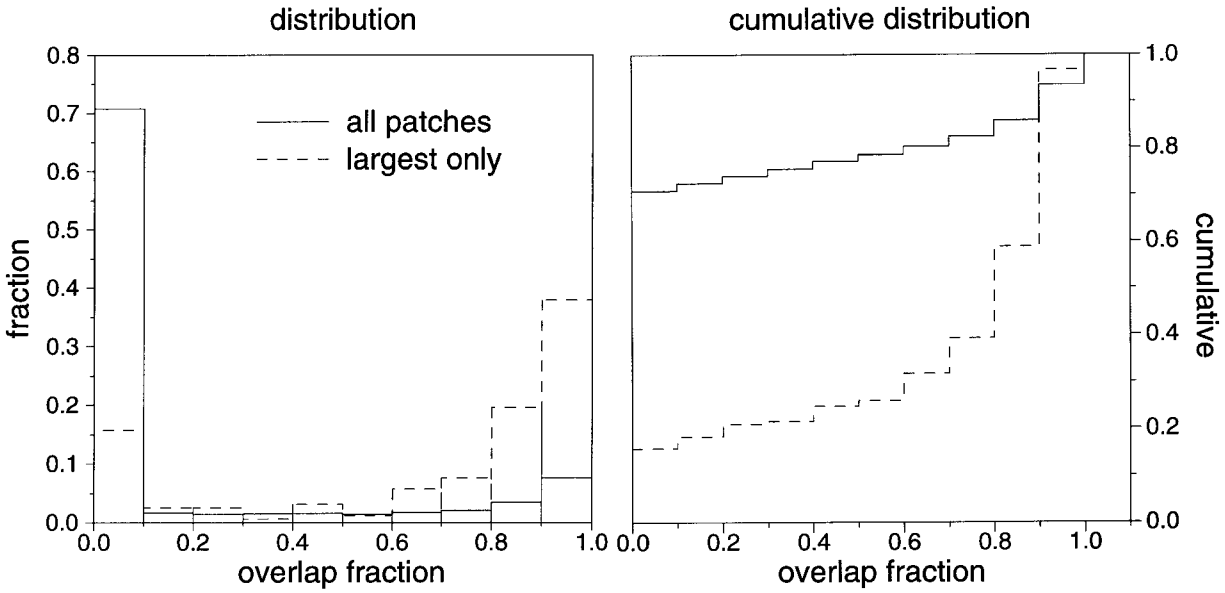

Fig. 7. The distribution of the overlap fraction of the total patch surface with the interface surface for all patches and for the largest patches only on the accessible surface of the associated subunits.

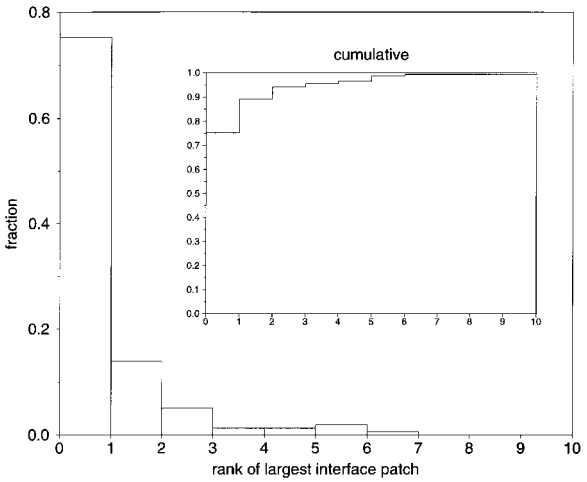

Fig. 8. The distribution of the rank number for the largest interface patch on each subunit. The cumulative distribution plot is also shown. The number taken for each subunit is the rank among all hydrophobic patches found on the entire subunit surface. The inset shows the cumulative distribution.

to what extent the larger hydrophobic patches on either subunit are brought into contact with each other upon association. Good "large patch complementarity" could be exploited in subunit–subunit docking studies. We have investigated patch complementarity using the measures described in the Methods section; for simplicity, only dimers were considered, since higher order multimers could well involve large patches being covered by those from several different subunits.

The distribution of the overlap factor $\Phi(A)$ (see the Methods section) is shown in Figure 9, which depicts the behavior of the overlap factor when selecting patches of various minimal sizes. For example, considering only patches 600 Å^2 or greater in surface area, over 60% of these A patches have only 0% to 10% of their total surface covered by the corresponding B patches of the same minimal size. The average fraction of all considered patches in Figure 9 are plotted according to the occurrence of their covering factor in the 10% ranges. For the largest patches (more than 600 Å^2 in area), only about 16% of them are covered to an extent of 60% or more of their surfaces by patches of similar size (see cumulative distribution, Fig. 9). When all patch sizes are used, the patch fraction is reasonably similar across the various overlap ranges as expected. As the minimum thresholds increase, the patch fraction without or with little contact increases. We therefore conclude that there is no significant preference for large patches on one subunit to meet and bury large patches on the other subunit.

Similar conclusions arise from a study of the number of patches that are in contact with those of any size on the other subunit. If the overlap $A(B)$ exceeded 25% of the (uncomplexed) accessible area of patch A, we counted it as a contact. The resulting distribution of the number of contacts per patch is shown in Figure 10. Most patches have just one contact; for patches larger than 400 Å^2, most do not have any overlap exceeding 25% of their area.

Shape of Patches

To assess the general form or shape of the hydrophobic interface patches, we fitted an ellipsoid to each patch by using the method of Taylor and

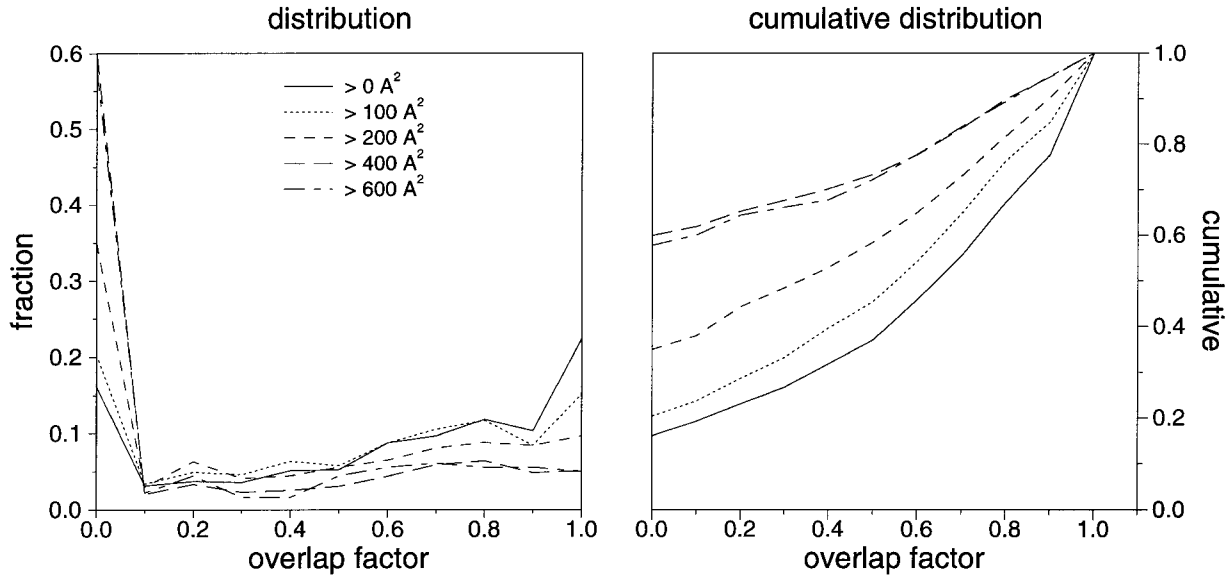

Fig. 9. Plot of the frequency versus the fraction of the interface patch surface on one subunit covered by interface patches on the other subunit, both patches being of an indicated minimum surface size. The cumulative distribution is also shown. The overlap fraction is plotted in ranges of 10%, such that, for example, at the overlap point 0.0 the fraction of cases is given for an overlap range 0 to <10%; at overlap fraction 0.1, the fraction of all cases is plotted for the 10 to <20%; and so forth to the last point plotted at 1.0 overlap fraction for 100% surface coverage.

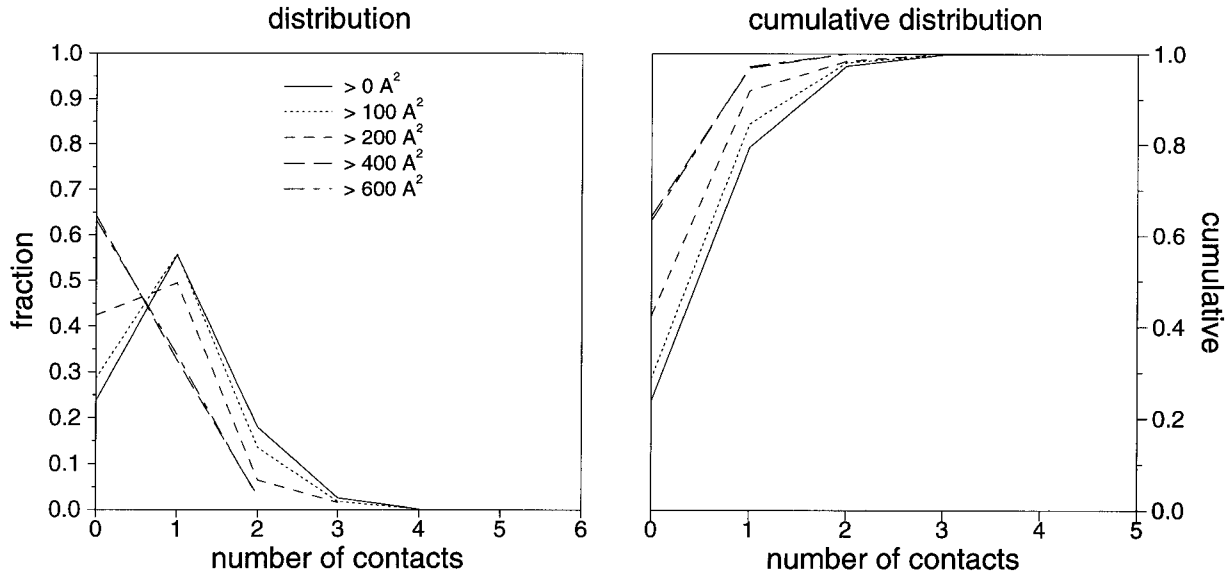

Fig. 10. The number of contacts across the interface for overlapping patches of varying sizes (see text for contact definition). The cumulative distribution is also given.

colleagues.[14] Their procedure yields the so-called equivalent ellipsoid, which follows the atom coordinate distribution more closely than does the inertial ellipsoid. The ellipsoidal axes so found were scaled by a common factor such that the centers of all the atoms that compose the patch were just contained in the ellipsoid. A scatter plot of the occurrence of the lengths of the two largest ellipsoid semiaxes is given in Figure 11. Most of the semiaxes have lengths below 15 Å, but some are much larger.

The ratio of the two largest semiaxes a and b quantifies the elongation of an ellipsoid; the inset of Figure 11 shows a histogram of the ratios. Close to 40% of the interface patches are roughly round in major cross section, having an a/b ratio of 1.5 or less; the rest can be described as elongated, with smaller

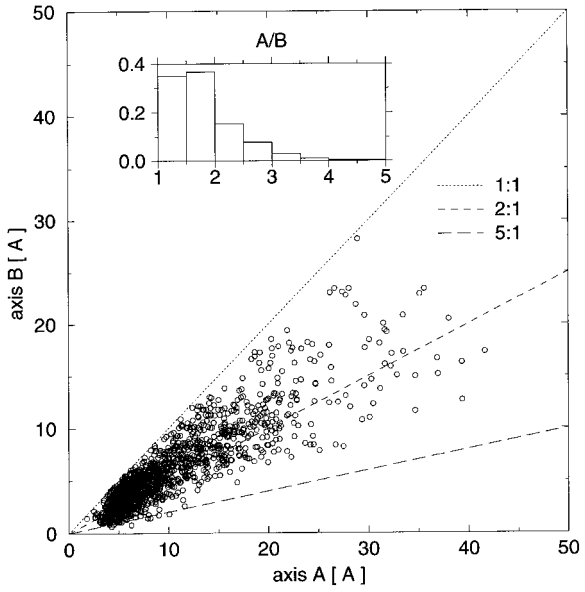

Fig. 11. A scatter plot of the occurrence of the two largest semiaxial lengths of equivalent ellipsoids fitted to the interface patches. The lines delineate the regions of the axial ratios noted in the plot. The inset shows the distribution of the ratios.

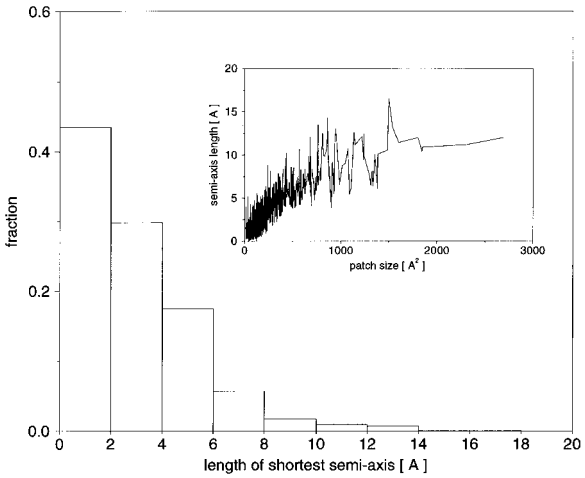

Fig. 12. Distribution of the lengths of the shortest semiaxis of the ellipsoids fitted to each interface patch as an indication of patch roughness. The inset shows this length as a function of the patch size.

occurrence as the patches become progressively more elongated.

The ellipsoids are generally oblique (disklike) as judged from their shortest semiaxis, *c*, substantially smaller than both *a* and *b* (Fig. 12). This is expected, given that they are fitted to a layer of solvent-accessible atoms. The length of semiaxis *c* provides a measure for patch "bumpiness." It is related to the root of the mean squared (RMS) distances of patch atom centers from the plane through the patch containing the *a* and *b* semiaxes. On average, the RMS distance is roughly 2.12 times the length of the semiaxis *c* for each patch. For large patches, the large-scale curvature of the protein will become noticeable in the measure for patch bumpiness. This effect can be seen in the inset to Figure 12, which shows a correlation of patch size with length of the shortest semiaxis. There are fewer occurrences of bumpy patches than of smooth ones as a result of the lower frequency of large patches. The results concerning patch form and bumpiness are indistinguishable from those found on monomeric protein surfaces (data not shown).

Composition

The amino acid composition of subunit interface patches was defined as the summed interface-accessible surface area of atoms of a given residue type contributing all patches of a certain size class divided by the total interface surface area of all patches in that size class. The results are shown in Figure 13. The largest contributors are the aliphatic and aromatic amino acids as well as proline. Leu, Ile, Phe, Val, and Pro occur progressively more often in larger patches, whereas the contributions of Trp and Tyr are roughly independent of the patch size. Ala and Met are intermediate contributors, the former as a consequence of its relative abundance, and the latter ensuing from its size and preference for interfaces.[2] The charged amino acids contribute to interface patches, but less so, and especially as the patch size grows. The Lys fraction is nonetheless considerable owing to the large apolar portion of its side chain.

There are some marked differences with the results found for monomeric protein surface patches (data not shown). The trends reflect the difference in composition between monomeric and interface surfaces. The contributions of Leu, Ile, Val, Phe, Tyr, and Met are higher in the interface patches than in the monomers with Lys, Asp, and Glu less common. The latter two show a more pronounced decrease with increasing patch size than in the monomeric case.

The differences between interface and exterior surface patches become clearer by taking the ratio of the surface composition for interfaces of a residue type to its composition on the exterior surface of protein multimeric complexes. If such propensity values are greater than or less than 1.0, the amino acid type is, respectively, preferred or avoided in the interface patches. The trends are shown in Figure 14. The aliphatic and particularly the aromatic amino acids are seen to prefer the interface patches, especially the larger patches. With the exception of Cys, the smaller polar residues do not display a strong preference for either environment. The charged residues, with the exception of Arg, show a definite dislike for interface patches, which is independent of their size. The preferences obtained here

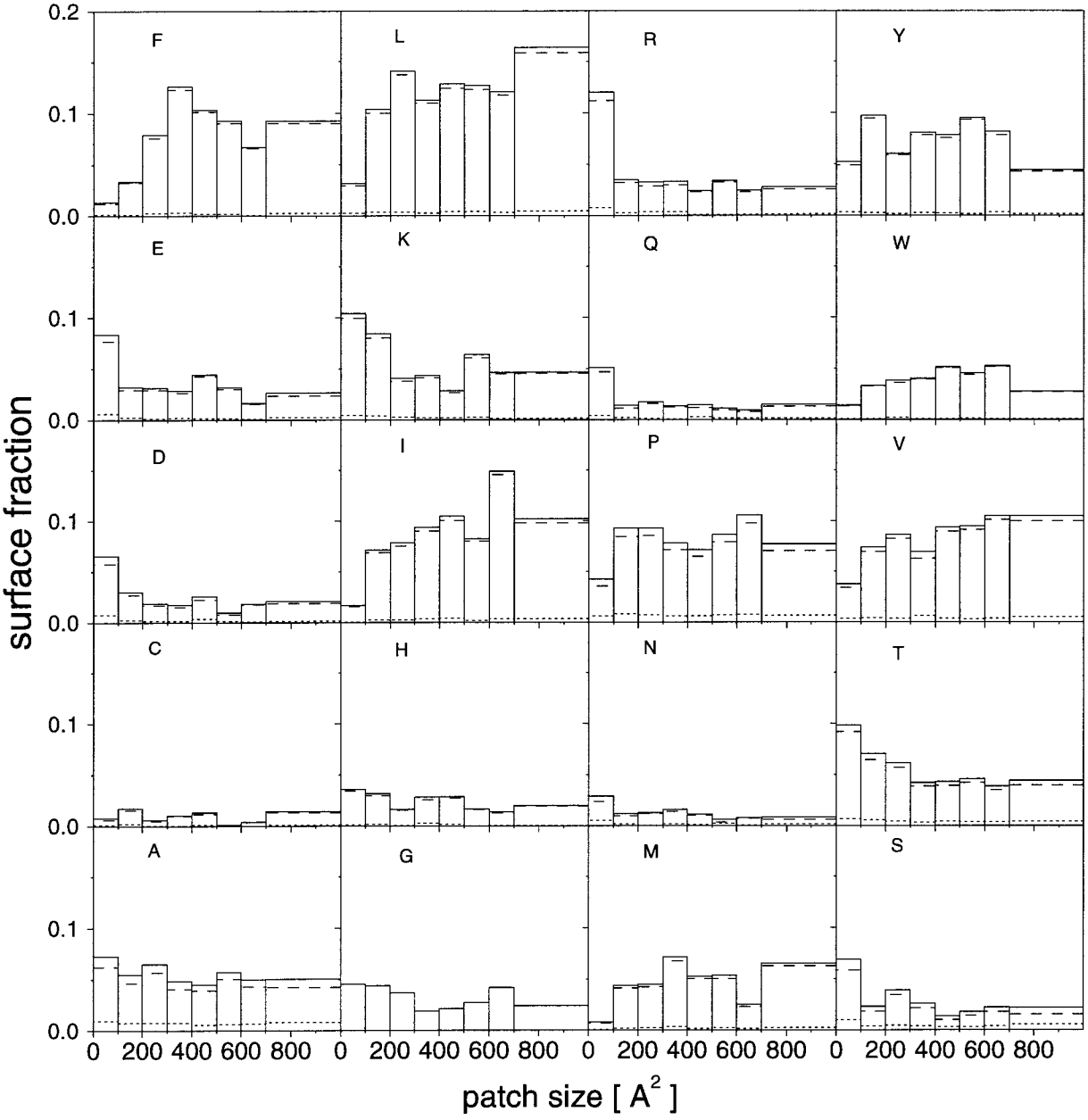

Fig. 13. The fractional surface contribution of amino acid types to interface hydrophobic patches according to their size. Values given are averages over the particular size range. All patches larger than 700 Å^2 were placed into the 700-and-greater bin. Solid lines indicate surface contributions from main- and side-chain atoms, while dotted and dashed lines show respective results for main chain only and side chain only atoms.

are in general agreement with those found for subunit interfaces by Argos.[2]

CONCLUSIONS

A survey of hydrophobic patches on the interfaces of protein subunits has shown many consistent characteristics. There are more large patches on interfaces than on protein exteriors. The distribution of the sizes of the largest patch in each subunit interface peaks at about 500 Å^2, albeit one patch displayed 2600 Å^2; and yet there is no correlation between the size of the largest patch and the size of the interface surface. The size distribution of the largest interface patch strongly resembles that for monomeric protein surfaces. If a hydrophobic patch displays any overlap with the interface, this overlap tends to be large, which could well be significant in the process of subunit association and recognition.

There is a very high coincidence between the largest patches on the exterior surface of a subunit

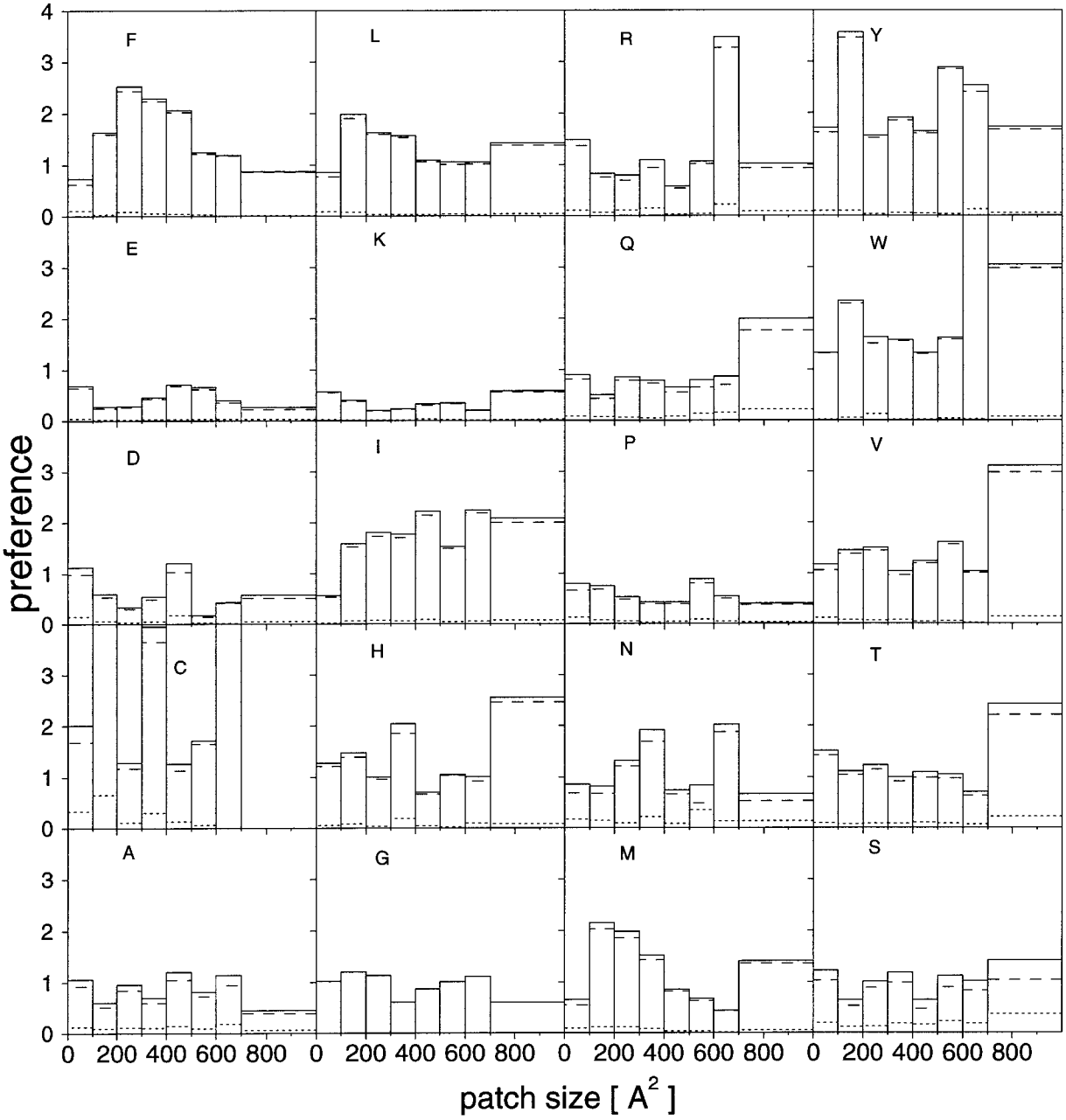

Fig. 14. The surface preference of amino acid types to be within interface patches relative to their contribution to exterior surface hydrophobic patches on the multimeric complexes. Values given are averages over the particular size range. All patches larger than 700 Å were placed into the 700-and-greater bin. Solid lines indicate preferences when considering surface contributions from main- and side-chain atoms, while dotted and dashed lines show respective results for contributions from main chain only and side chain only atoms.

and the interface: in 90% of the proteins in our sample, either the largest or the second largest constituted a significant portion of the interface. This should prove valuable in studies of protein–protein association. If the subunit association site of a polypeptide chain is not known, the largest or second largest patch is the most likely candidate. They are also the best mutagenesis targets if oligomerization potential is to be altered. Further, if the tertiary structure of a subunit is known, the two largest hydrophobic patches would greatly limit the search space for docking oligomers.

The complementarity of contacts of patches on different subunits was found to be low in the sense that large patches on one subunit do not often mostly cover large patches on the associating subunit. The

shielding of hydrophobic surface from water appears more important than contacts between similarly sized apolar surface patches. The relative contributions of amino acid types and their composition on patches of different sizes reflects their general composition on interfaces.

ACKNOWLEDGMENTS

The authors thank Jaap Heringa for helpful discussions and Nelly van der Jagt for invaluable assistance in the preparation of the manuscript.

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