CHAPTER 6.C

Ligand binding cavity encoded as a local hydrophobicity deficiency

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The above diagram illustrates the specific deviation from the theoretical distribution of hydrophobicity which is associated with the presence of a ligand binding cavity.

An example of strong affinity of a polypeptide chain for a specific "alien" (non-protein) molecule is provided by erythrocruorin (PDB ID: 1ECD) [1]. We note the characteristic presence of a strongly hydrophobic ligand — heme,

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located centrally in a β-barrel structure (CATH code 1.10.490.10 — mainly alpha orthogonal bundle).

Erythrocruorin (1ECD) is a large oxygen-carrying protein. PDB lists its monomeric structure in complex with heme. Its FOD status is presented in Table 6.C.1. As shown, the protein as a whole does not conform to the theoretical distribution of hydrophobicity. Eliminating residues which participate in ligand binding lowers the overall value of RD; however, the value remains greater than 0.5.

Ligand binding residues are characterized by particularly high values of RD, indicating strong deviation from the monocentric Gaussian distribution. Further analysis of theoretical and observed profiles reveals other discordant residues, which do not participate in protein-ligand interactions. Eliminating such residues from calculations produces an RD value lower than 0.5 for the remainder of the chain. This enables us to identify fragments which adopt a micellar conformation and stabilize the protein.

Table 6.C.1 Fuzzy oil drop parameters for 1ECD. The status is presented for the entire chain, for ligand-binding residues (Lig), for parts of the chain following elimination of ligand-binding residues (No Lig) and for the remainder of the chain following elimination of other discordant fragments (i.e. for fragments which ensure structural stabilization).

		RD		Correlation coefficient		
Erythrocruorin (1ECD)	**Fragment**	**T-O-R**	**T-O-H**	**HvT**	**TvO**	**HvO**
		0.560	0.377	0.509	0.520	0.760
Lig		**0.629**	0.391	0.653	0.205	0.656
No Lig		**0.522**	0.350	0.459	0.569	0.676
Residues eliminated	51—54 114—117	0.468	0.298	0.491	0.642	0.803

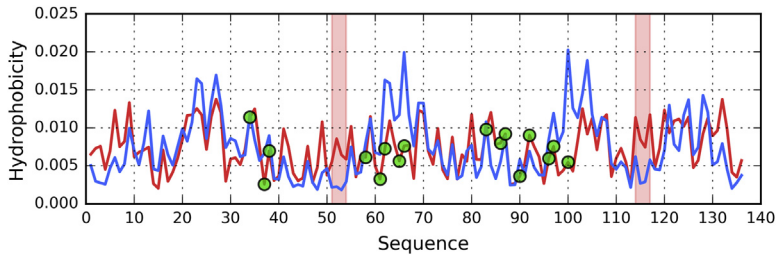

Fig. 6.C.1 Theoretical (T, blue) and observed (O, red) hydrophobicity distribution profiles for 1ECD. Green circles mark residues involved in P-P interaction. Red background indicates a discordant fragment (51—54, 114—117).

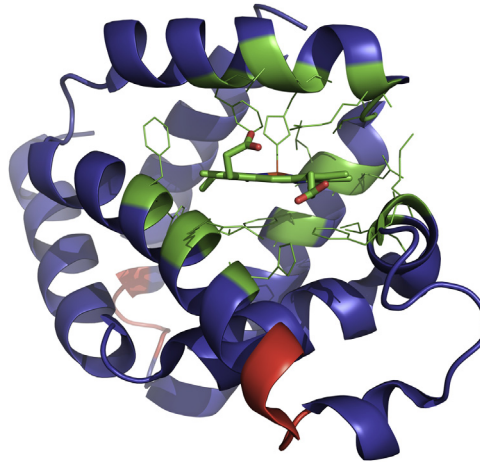

Fig. 6.C.2 3D presentation of 1ECD. Residues engaged in interactions between protein and heme are highlighted in green and have side chains displayed. Fragments of exposed hydrophobicity (51–54, 114–117) are shown in red.

It should be noted that there is a notable exposure of hydrophobicity at positions 51–54, possibly indicating a complexation interface. The biologically active form of erythrocruorin, identified *in vivo*, is a complex consisting of multiple chains.

Correlation coefficients appear balanced, suggesting that intrinsic hydrophobicity is not a dominant factor, and that the molecule generally adopts a micellar form (Figs. 6.C.1 and 6.C.2).

Further information concerning the structure of ligand-binding cavities can be found in Refs. [2–4].

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