Supporting Information

Heterogeneous Solvation in Distinctive Protein-Protein Interfaces Revealed by Molecular Dynamics Simulations

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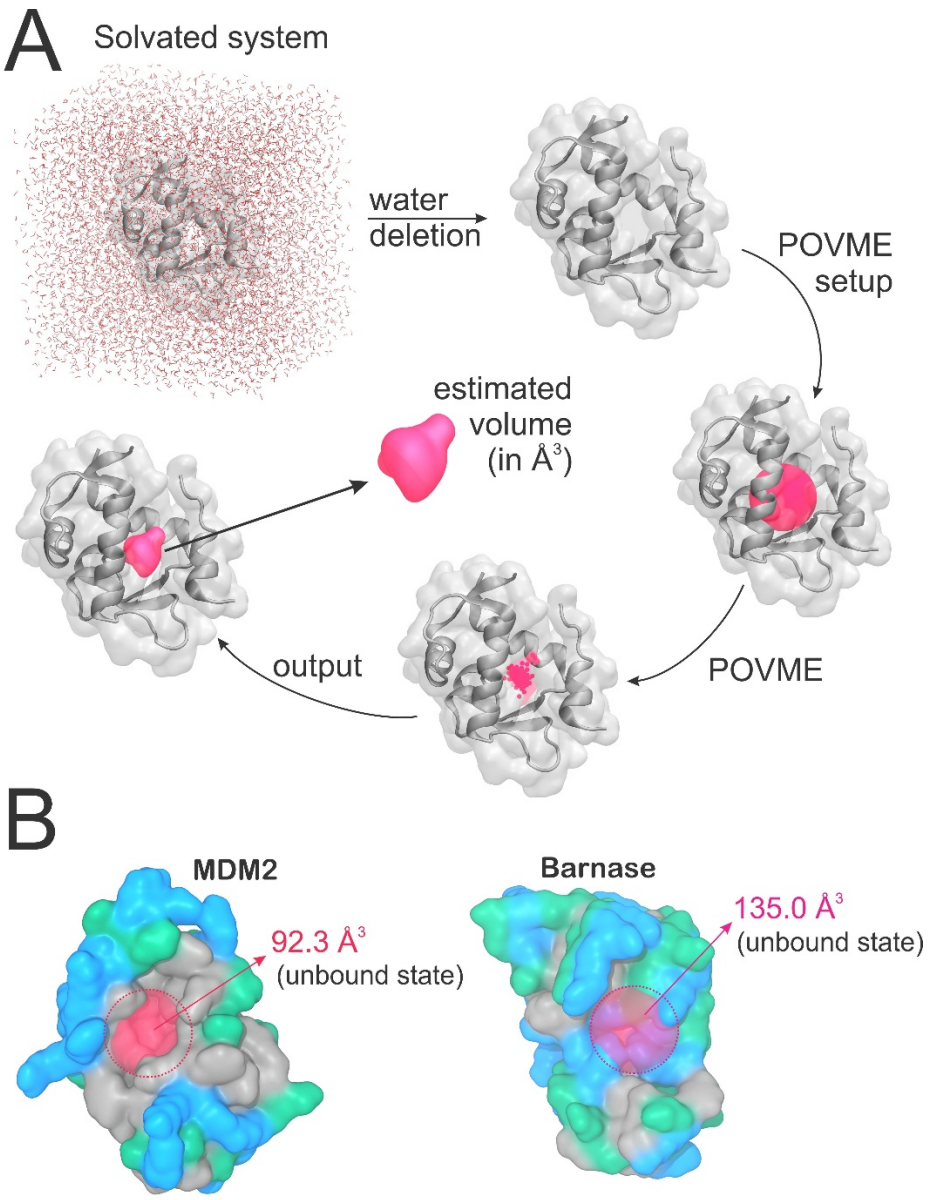

Figure S1. A) POVME-based approach to calculate the water-accessible volume in the binding region of a protein (in this example, MDM2). After water molecules were manually deleted, the binding region was defined as a sphere of radius = 6 Å (in magenta), centered at binding region of the receptor protein. POVME[Durrant *et al.* 2014] was then used to create a 1Å resolution grid within the selected region and to remove all grid points colliding with protein atoms. The resulting mesh of points provides an estimate of the water-accessible volume, in Å^3. This procedure was repeated for configurations with varying separation distances, *D*, because at close distances the binding partner can reduce the water-accessible volume of the binding region. B) Localization of the binding regions and corresponding water-accessible volumes in MDM2 and Barnase, in the unbound states (*D* = 15.2 Å). The water-accessible volumes for other separation distances, *D*, are reported in Table S1.

Table S1. Water-accessible volumes in the binding and interdomain regions, at different *D*.

Separation	Binding Regions (radius = 6 Å)		Interdomain Regions (radius = 18 Å)	
D / Å	Barnase	MDM2	Barnase	MDM2
1.9	31	5.0	5151	7455
3.8	75	42.6	5976	7601
5.7	123	81.0	6851	7999
7.6	125	87.6	7667	8467
9.5	126	88.0	8453	8892
11.4	128	88.8	9147	9224
13.3	133	90.5	9760	9434
15.2	135	92.3	10187	9588

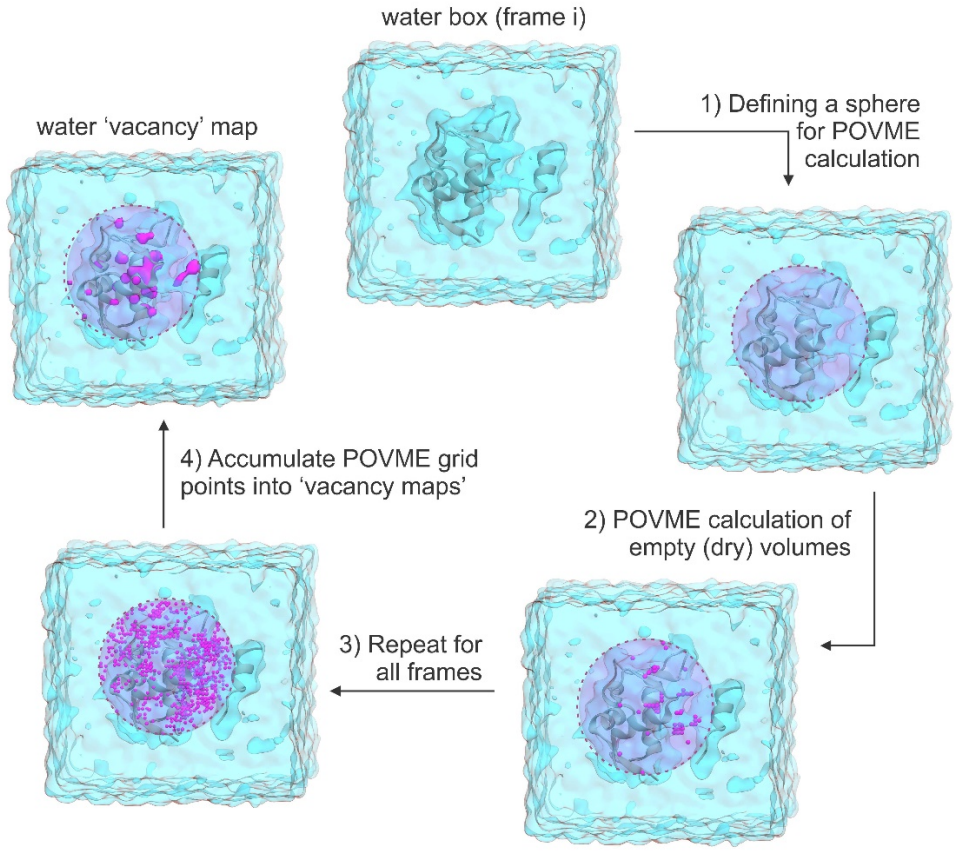

Figure S2. Scheme to calculate "dry volumes" and "water vacancy maps". Steps (1), (2), and (3) were performed with POVME,[1] and step (4) was performed with the VolMap plugin in VMD.[2]

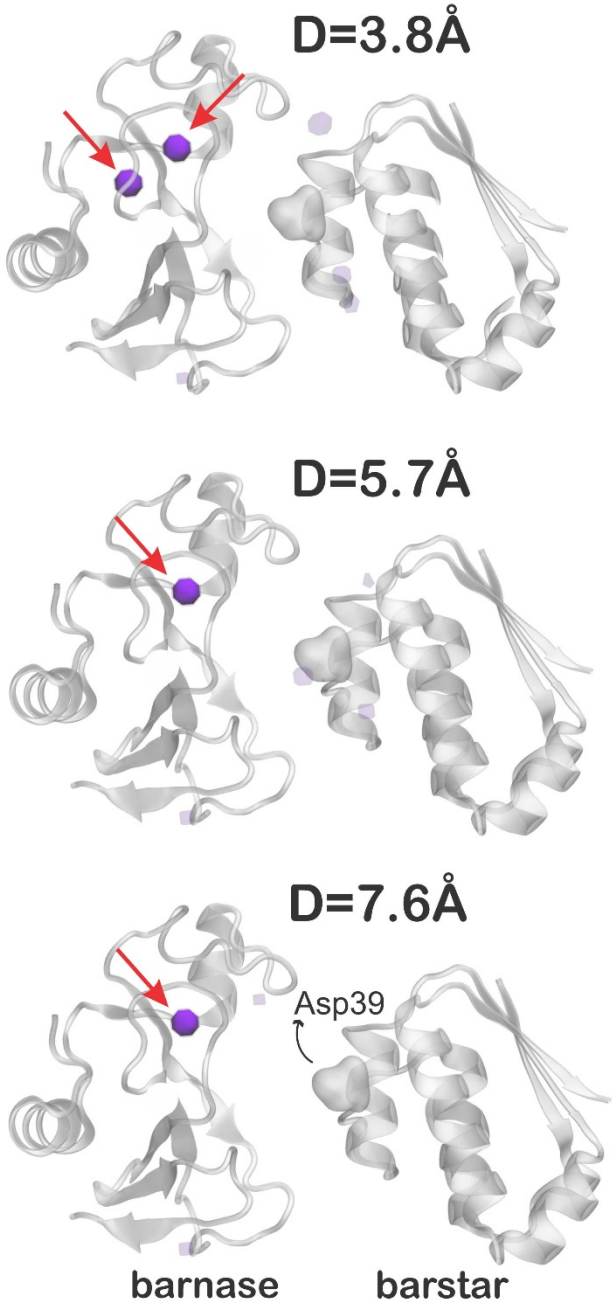

Figure S3. Water vacancy maps contoured at 0.25 (solid blobs) or 0.10 (transparent blobs), representing regions of the solvent that are frequently empty (i.e. *desolvated*) during the simulations of barnase and barstar, at separation distances of 3.8 to 7.6Å. These maps were calculated within a cutoff radius of 18Å from the center of barnase binding interface. Because of the strongly solvated character of this complex, the only consistent dewetting occurs within small internal pockets of barnase (red arrows).

REFERENCES

1. Durrant, J.D., Votapka, L., Sorensen, J., Amaro, R.E. (2014) POVME 2.0: an enhanced tool for determining pocket shape and volume characteristics. J. Chem. Theory Comput. 10, 5047-5056.
2. Humphrey, W., Dalke, A., Schulten, K. (1996) VMD – Visual Molecular Dynamics. J. Molec. Graphics, 14, 33-38.