Reply to 'Comment on "The hydrophobic effect"' by G. Graziano, *Phys. Chem. Chem. Phys.*, 2004, 6, DOI: 10.1039/b405824k

B. Widom, P. Bhimalapuram† and K. Koga‡

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York, 14853, USA

To put the matter briefly, the author of the Comment criticizes the model we analyze in Section IV of our paper because the "solvent" in our model does not look like water. That is true, but wholly misses the point of the model. To ensure that the readers of our paper were informed of the literature in which realistic water models were treated we included an extensive list of references to such papers, many of which, we said, were sophisticated studies, and two of which were by the author of the present Comment.

We wrote that our model incorporated the basic mechanism of hydrophobicity, which the Comment's author took to mean *detailed microscopic* mechanism, which of course the model cannot do and was never intended to do. We made it abundantly clear that what we meant by the "mechanism" was only having the property that the unfavorable free energy of accommodation of a solute molecule arose from an unfavorable entropy change that overweighed a favorable energy change. We may quote here from our Summary the whole of the sentence from which the Comment quotes only the last few words: "The model was designed to make the accommodation of a solute in the solvent energetically favorable but entropically unfavorable, and *thus* [present emphasis added] to incorporate the basic mechanism of hydrophobicity as revealed by the thermodynamics."

The model, as is true of any model, is an abstraction and an analogy. It incorporates the aspects of hydrophobicity referred to above in a way that is *analogous* to, but not literally the same as, the way real water does. The Comment contains a fair and useful summary of one's present understanding of water and of the importance of the cavities in water as the seat of the unfavorable entropy of accommodation of the solute. In our model that idea is abstracted: a solute molecule can be accommodated only when the neighboring solvent molecules are in a special configuration. It is clear from the context that the passage "accommodation of a solute..." quoted from our paper in the Comment describes the construction of the *model*. That is how the model imitates the "cavities" in more realistic pictures of water. Going at least as far back as the pioneering work of Pratt and Chandler[1] it was clear that the major contributor to the effective attraction between a pair of hydrophobic solute molecules is the cavity–cavity correlation function in the pure solvent, and that appears with great clarity in our stripped-down model: the potential-distribution theorem applied to the model immediately gives the solvent-mediated part of the potential of mean force between the hydrophobic pair to be determined by the "cavity–cavity" (if we may now be allowed to use that expression) distribution function in the pure solvent.

To be sure, the model in question, like any model, has some artificialities (including, in the present case, the sign of the parameter *v*, which the Comment's author remarks on, as we ourselves did with emphasis, in another of the passages in our paper quoted in the Comment). The art is to know, or guess, which properties of the model are artifacts and which are model-independent universals.

The main purpose of the model in question was to relate quantitatively the strength of the hydrophobic attraction to the magnitude of the free energy of hydration. The idea was to fit the model's parameters to known values of the latter and then to calculate or predict the former. By removing the necessarily distracting clutter of detail from the more realistic pictures (however interesting and important that detail assuredly is for other purposes), the model illuminates and exposes the quantitative origins of that connection. It finds the strength of the attraction at 300 K to be hardly greater than the thermal energy kT, which, for the reasons explained in the paper, is a most important fact. It is in the range of values found by experiment for the interaction of the non-polar amino-acid side chains of proteins.[2] It is less by a factor of 3 or more than the single-molecule hydration free energy. The actual value found from the model, $1.2kT$, may be compared with the values calculated[3] from the results of Smith and Haymet[4] and Garde *et al.*,[5] *viz.*, $0.8kT$ and $1.4kT$, respectively, with what were intended to be realistic pictures of the solvent structure. To test further the universality of the result, *i.e.*, its near independence of the model's details, we may note from Fig. 8 of our paper that when the coordination number, which is one of the model's parameters, varies from 2 (the linear chain) to infinity, so over an infinite range, the calculated strength of the hydrophobic attraction varies only by about a factor of 2.

The same figure makes the prediction that over the temperature range from 273 to 333 K the strength of the attraction, expressed as a multiple of kT, should increase nearly linearly with the hydration free energy expressed in the same units, and that the slope of the corresponding plot should be around 0.7, again nearly independently of the assumed coordination number. Such a relation would hardly have been discerned or sought had it not first been suggested by an abstract model stripped of much extraneous detail. Now the predicted near linearity of the connection between the strength of the hydrophobic attraction and the magnitude of the hydration free energy has been found in the simulations by Paschek,[6] for the temperature range 275 to 325 K, with the corresponding slopes 0.8 for TIP5P water and roughly 0.4 for SPCE water. It remains as a challenge to experiment to determine, for real solutes in real water, the connection between these two different measures of hydrophobicity and to test the model predictions.

---

† Present address: SSCU, Indian Institute of Science, Sir C. V. Raman Avenue, Bangalore 560 012, India.
‡ Present address: Department of Chemistry, Faculty of Science, Okayama University, Okayama 700-8530, Japan.

That the model, although its "solvent" does not look like real water, is nevertheless illuminating and useful, and its predictions realistic, we believe to have been demonstrated.

References

1   L. R. Pratt and D. Chandler, *J. Chem. Phys.*, 1977, **67**, 3683.

2   H. A. Scheraga, *J. Biomol. Struct. Dynam.*, 1998, **16**, 447.
3   K. Koga, P. Bhimalapuram and B. Widom, *Mol. Phys.*, 2002, **100**, 3795.
4   D. E. Smith and A. D. J. Haymet, *J. Chem. Phys.*, 1993, **98**, 6445.
5   S. Garde, G. Hummer and M. E. Paulaitis, *Faraday Discuss.*, 1996, **103**, 125.
6   D. Paschek, *J. Chem. Phys.*, 2004, **120**, 6674.