

COMMENTARY

Reply to Comment on “A Universal Approach to Solvation Modeling”

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CON SPECTUS

In a recent Account, we discussed a universal approach to solvation modeling. We included examples from various SM x models and compared the SM8 method with default versions of continuum solvation models implemented in widely available quantum chemistry programs. In that Account, the SM8 model was found to lead to “considerably smaller errors for aqueous and nonaqueous free energies of solvation for neutrals, cations, and anions, with particularly good performance for nonaqueous data.” Herein, we emphasize that alternative methods for electrostatic modeling can be employed instead of the electrostatics algorithm we employed in SM8: the key issue is not the electrostatics algorithm, but—as discussed in the Account—is rather the consistent treatment of electrostatic and nonelectrostatic contributions. We also discuss a number of other issues relevant to (i) understanding the solvent effect on the properties of molecules and chemical processes and (ii) evaluating solvation models based on a continuum representation of the solvent.

We recently summarized our work on quantum mechanical continuum universal solvation models.¹ The comparisons of methods in our Account stimulated our colleagues to provide further systematic tests of solvation methods.² Our Account is consistent with their main premise, namely, that equally good results could be obtained with alternative algorithms for treating the electrostatic part of the problem. Here we make this more clear and explain some underlying features of solvation modeling that can be useful in contrasting existing models and designing future ones.

Our definition of a universal solvation model is that it computes the free energy of solvation, ΔG_s , of a solute for essentially any solvent. We treat the solvent as a continuum with a bulk dielectric constant and an interfacial surface tension, where the interface is the solute–solvent boundary. In 1996, we reported our first universal solvation model and its results for the prediction of more than 2000 free energies of transfer for neutral and charged solutes from the gas phase into 90 different organic solvents³ and water.⁴ The contribution to ΔG_s of the non-bulk-electrostatic components is called G_{CDs} in the SM x models, and the component due to the bulk electrostatics, which is obtained by a self-consistent-reaction-field treatment, is called ΔG_{ENP} . Our Account discussed a series of closely related but successively improved solvation models called SM x , with $x = 1, 2, \dots, 8$.⁵ Our models allow the prediction of ΔG_s as needed to compute partition coefficients, reaction free

energies, and free energies of activation in liquid solution and also allow the calculation of liquid-phase solute charge densities and response properties.

In our Account,¹ among other discussion points, we compared SM8⁶ to four other models (PB, IEF-PCM, C-PCM, and a model called GCOSMO) in their default implementations in four popular software packages, two commercial (PB in *Jaguar* and IEF-PCM in *Gaussian03*) and two freely distributed (C-PCM in *GAMESS* and the one we called GCOSMO in *NWChem*). The Comment² raises two additional models for discussion, namely, the MST model (not currently in a distributed program) and the COSMO-RS model (in the commercial *COSMOtherm* package). We will also discuss here a seventh model, SMD⁷ (in the freely available *GESOL* add-on⁸ to the commercial *Gaussian03* package).

IEF-PCM

To compute ΔG_s , a model must address both bulk-electrostatic and non-bulk-electrostatic components.^{9–11} One of the models to which we compared in our Account is called IEF-PCM in *Gaussian03*. Confusion can arise because, depending on context, “IEF-PCM” has more than one meaning in the literature. “IEF-PCM” originally¹² referred to the formal integral-equation construction of the bulk electrostatic part of a polarized continuum model¹³ approach to solving the nonhomogeneous Poisson equation for a continuous solute charge distribution in

an arbitrary (but simply connected) solute cavity in a solvent. However, because the bulk electrostatic model has been implemented in the popular *Gaussian03* electronic structure program with a default set of cavity parameters and default non-bulk-electrostatic solvation terms, "IEF-PCM" is now widely used to imply this particular implementation. We will call this IEF-PCM-G03d, where G03d denotes *Gaussian03* default. IEF-PCM-G03d is presently defined for 25 solvents, which is not universal.

The non-bulk-electrostatic component of ΔG_S in IEF-PCM-G03d is a combination of dispersion–repulsion and cavitation terms that are estimated independently of the bulk electrostatics. The intrinsic arbitrariness in the bulk electrostatic term (which, unlike the full ΔG_S , is *not* a thermodynamic state variable) is discussed elsewhere;¹⁴ our main point here is not that the IEF-PCM electrostatics algorithm has "never been quantitatively parameterized for solvation free energies"² but rather, as stressed previously,^{1,9,14–16} that G_{CDS} compensates for the inescapable incompleteness of any bulk electrostatic model for ΔG_{ENP} , and it is very difficult to make the approach of mutually independent parameterization of ΔG_{ENP} and G_{CDS} succeed.

The Comment mentions that the default cavity definition (denoted UA0) in *Gaussian03* is not the best choice for quantitative calculations of ΔG_S ; we agree. We previously⁶ tested the UAHF parametrization scheme¹⁷ that is recommended for ΔG_S in the *Gaussian03* manual (the UAHF values of the atomic radii, which are the key parameters of the bulk electrostatic term, were developed¹⁷ to improve ΔG_S of neutral and ionic solutes in water and were judged to be satisfactory solely on the basis of calculated ΔG_S). Even though the UAHF radii depend on charge and type of functional group and are optimized to ΔG_S , the mean unsigned errors are reduced to only 1.18 kcal/mol for aqueous neutral solutes in aqueous solution, 3.94 kcal/mol for nonaqueous neutrals (in 17 supported nonaqueous solvents), and 8.15 kcal/mol for ions,⁶ as compared with 4.87, 5.99, and 9.73 for IEF-PCM-G03d (which has UA0 radii), and 0.55, 0.61, and 4.31 for SM8, which uses radii that are independent of charge and do not require functional group typing.

MST

The MST models¹⁸ use the IEF-PCM electrostatics algorithm. They model non-bulk-electrostatic terms in a fashion similar to the earlier SM1 model,¹⁹ namely, in terms of semiempirical atomic surface tensions, each multiplied by an atomic solvent-exposed surface area, A_m , for an atom m . The SMx and MST models assume a linear dependence of G_{CDS} on the A_m val-

ues because A_m provides a continuum measure of the number of solvent molecules in the first solvation shell of atom m , and most of the deviations of the full solvation free energy from a particular bulk-solvent electrostatics model may be attributed¹⁹ to first-solvation-shell effects like dispersion, hydrogen bonding, charge transfer, and a nonbulk local value of the effective dielectric constant. The MST tensions are *solvent-specific*; thus an MST model relies on a sufficient number of data being available in a given solvent to permit optimization of parameters for that solvent. Since statistically meaningful amounts of data are available for only a few solvents, MST models have been reported only for water,^{18,20–22} octanol,^{18,23} chloroform,^{18,24} and carbon tetrachloride.^{18,25} This is why the Comment² presents results only for these four solvents. Early versions of the SMx models, before the development of the universal approach, were also parametrized for some specific solvents, such as alkanes^{26,27} and chloroform.²⁸ One can obtain smaller errors in this fashion, but at the expense of losing universality.

The Comment points out that it is important to avoid overtraining a parameter set, and it notes that the MST mean signed error rises from 0.8 to 1.01 kcal/mol when they increase their original test set of 72 neutral solutes in water to a set of 127 such solutes. In an early stage of the development of the SMx models,²⁹ we developed a systematic method to assess whether a parametrization scheme was overtrained. In particular, we created four sets of data, each leaving out a different 25% of the total data originally used for training. We then separately parametrized our model using in turn each of these four smaller sets and predicted results not only for the reduced training sets but also for the 25% of the data that were not used in training. The average mean unsigned error over the entire database was only 1.47% higher than the error when the full set of data was used for training.²⁹ This shows that the procedures and databases we use do not involve overtraining.

We distinguish four types of continuum solvation models: (1) models that do not predict solute response to the reaction field of the solvent under consideration, (2) models that consider only electrostatics, (3) models in which non-bulk-electrostatic contributions to ΔG_S , for example, cavitation, dispersion, and repulsion, are estimated as fully independent quantities, and (4) models in which the non-bulk-electrostatic components of solvation are computed from atomic or group surface tensions that are developed to be consistent with an assumed form of polarized electrostatics. It was recently pointed out that most of the research effort spent in the development of IEF-PCM models has dealt with the calculation of the electrostatic

interaction;³⁰ in contrast, SMx development has also included consistency of the non-bulk-electrostatic terms with the bulk electrostatic ones.

Given that they use similar cavity-construction protocols, particularly for the most polar solvents, the electrostatics predicted by the IEF-PCM-G03d and MST models could be almost identical, but MST predicts more accurate values of ΔG_s . This is not because of the choice of radii or the inclusion of response considerations in one parametrization but not the other, but rather because MST models, like the SMx ones, are of type 4, whereas IEF-PCM-G03d is of type 3. Another indication that the solute radii are not the major source of the inaccuracy of the models to which we compared, at least for neutral solutes, is the success of the SM5.0 model^{31,32} for neutral solutes; SM5.0 does not include explicit electrostatics at all, which is equivalent to setting all solute radii equal to ∞ in the bulk-electrostatic step. However, while SM5.0 is useful for rapid screening of the solvation of neutral solutes, we agree that "the accurate prediction of solvation free energies is not the only requirement for a solvation method",² and in all of the SMx models except SM5.0 (and a closely related SM5.05), we have tried also to produce reasonable polarized solute wave functions and properties.^{6,21} For this reason, in developing SM8 we paid particular attention to ionic solvation free energies,^{33,34} which are especially sensitive to the partition into electrostatic and nonelectrostatic components.

C-PCM

The C-PCM model to which we compared is the default model in *GAMESS* and is a type-2 model. The C-PCM electrostatics algorithm is similar to that in IEF-PCM, but not the same. The C in C-PCM denotes "conductor-like" in reference to the procedure starting with screening in conductors, with the dielectric constant ϵ being infinite in a conductor. The algorithm (like the original COSMO algorithm discussed below) solves a scaled conductor boundary condition self-consistently. The scaling to a finite value of the dielectric constant is approximate, as discussed further below.

We tested the agreement of the C-PCM and IEF-PCM algorithms in *GAMESS*, comparing only electrostatics, for all data in our neutral testing set.⁷ For 482 neutral-solute data with $\epsilon \geq 32$, the mean unsigned deviation is 0.06 kcal/mol, but for 2150 neutral-solute data with $\epsilon < 32$, the mean unsigned deviation is 0.45 kcal/mol; a deviation of 0.45 kcal/mol is the same order of magnitude as the mean unsigned error compared with experiment for neutrals in SM8, so at the mean level of accuracy attainable with SMx solvation models, we

respectfully disagree that C-PCM is essentially identical to IEF-PCM, as stated² in the Comment.

GCOSMO

The "GCOSMO" model to which we compared is the default model in *NWChem*, and it is a type-2 model. The Comment states that it should not be called GCOSMO. To reduce confusion, it is useful to give a brief history of the abbreviation COSMO, which stands for CONductor-like Screening MODEL. The original COSMO model³⁵ started with a dielectric constant of ∞ in order to simplify the electrostatics algorithm; the scale factor that was then used to complete the calculation was $(\epsilon - 1)/(\epsilon + 1/2)$. Stefanovich and Truong³⁶ used a similar procedure but with the scale factor $(\epsilon - 1)/\epsilon$; they called this generalized COSMO, abbreviated GCOSMO. Both factors are allowed in *NWChem*, and we called the method GCOSMO because we used the default scaling factor, which is the one used in GCOSMO.³⁶ The difference in the two factors is small for large ϵ , but it can be appreciable for nonpolar solvents. For example, for *n*-hexane, which has $\epsilon = 1.8819$, the two factors are 0.37 and 0.47, with the second one being 27% larger. The possibility to use alternative scaling factors was already mentioned in the original COSMO paper,³⁵ and a better name for the default version of COSMO in the 2006 version of *NWChem* is COSMO-N06d, in analogy to the IEF-PCM-G03d notation introduced above.

COSMO-RS

COSMO-RS³⁷ is used in the Comment as a tool for predicting solvation free energies of neutral solutes (no ionic data were reported), but COSMO-RS is not a continuum solvation model in the usual sense of the term. The COSMO-RS protocol does begin with a quantal continuum calculation for a solute in a conductor-like solvent; however, the purpose of the calculation is solely to determine a screening charge distribution on the solute cavity surface (a so-called σ profile). Free energies of solvation are subsequently determined from a statistical mechanical procedure involving a match between solute σ profiles and corresponding σ profiles for solvents. COSMO-RS is a type-1 model (although the solute's response to a conductor-like medium is included in its σ profile). We are pleased to see the good results reported for neutrals with the COSMO-RS model, although full details of the parametrization unfortunately are unpublished, so it is difficult to evaluate them further.

Jaguar

The *Jaguar* model to which we compared is a type-4 model but had an antecedent type-3 model.³⁸ The evolution of the *Jaguar* model from type 3 to type 4 is instructive with respect to the importance of matching electrostatic and nonelectrostatic protocols. The Columbia group originally³⁸ employed a type-3 independent treatment of surface tensions and explicitly contrasted their approach to the SMx type-4 approach. They obtained a mean unsigned error of 0.6 kcal/mol for a test set of 29 aqueous solvation free energies but pointed out that tests for more complex molecules would be required for "ultimate evaluation of validity". In continuing work two years later,³⁹ they reported that extension of their model to more complex systems revealed "that there were serious deficiencies in the theory itself" and systematic errors for certain functional groups. They concluded that the errors in their approach were associated primarily with hydrogen bonding but also mentioned dispersion interactions and "differential organization of solvent structure" for different functional groups, in full agreement with the earlier SMx analysis of G_{CDS} . The Columbia group concluded that "prospects are good for continued development of a new generation of more accurate [continuum solvation] models [so long as they include] short-range corrections to dielectric continuum theory."

The *Jaguar* electrostatics are based on similar algorithms to those used in the MST and IEF-PCM models, and the *Jaguar* model can predict our full set of aqueous neutral absolute free energies of solvation with an error of only 0.86 kcal/mol (so we note that our Account *did* make reference to a non-SMx model with reasonably good performance). Thus, type-4 models (SMx, MST, and *Jaguar*) consistently provide much better accuracy than type-2 or type-3 models (of the type-4 models, only the SMx examples have been carried forward as *universal* solvation models with good accuracy for water, diverse organic solvents, and other complex media, which was the key issue that we emphasized in our Account). One reason that type-3 models face quantitative challenges is that energetically attractive dispersion and solvent-structure effects and positive cavitation and solvent-structure effects can both be quite large. While one cannot completely separate the components of non-bulk-electrostatic effects, various separations have been proposed; an example from one early such attempt²⁷ may be instructive: for fluorobenzene in *n*-hexadecane, the electrostatic contribution was estimated as -1 kcal/mol, the negative nonelectrostatic term (primarily dispersion) was estimated as -17 kcal/mol, and the positive nonelectrostatic contribution was estimated as $+14$ kcal/mol. Thus, small

percentage errors in either dispersion or cavitation individually can still be larger in magnitude than the net ΔG_{S} .

SMD

As we have stressed above, continuum solvation models can accurately predict free energies of solvation provided that one carefully matches the protocol and parameters for non-bulk-electrostatic effects to the specific model employed for bulk-electrostatic effects, as is the goal of type-4 models.^{1,9,14–16,19} The matching can be pushed to unphysical limits, as illustrated by the fact that a reasonably accurate model (the SM5.0 model discussed above) can be constructed even within the assumption that there is *zero* bulk electrostatic contribution to ΔG_{S} of a neutral solute.^{31,32} So, were a non-expert reader to infer from our original Account that the IEF-PCM algorithm for *electrostatics* was somehow flawed, as opposed to the IEF-PCM-G03d model for the computation of solvation free energies, that would certainly be unintended and unfortunate. Indeed, we had completed⁷ a new universal SMx model *based on IEF-PCM electrostatics* before receiving the Comment. The new model, called SMD, also works well with C-PCM electrostatics, and it exhibits an accuracy almost as good as our prior universal SMx models based on generalized Born electrostatics^{6,40–42} or COSMO electrostatics.⁴³

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Note Added after ASAP. This paper was posted to the web on February 17, 2009 with an error in the SMD section. The revised version was posted on February 25, 2009.

FOOTNOTES

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