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August 19, 2017

Dr. Brian Matthews
Editor, Protein Science
proteinscience@proteinsociety.org

Dear Dr. Matthews:

Thank you for your consideration of our manuscript PRO-17-0207. We have revised the manuscript based on the reviewers' comments (changes marked in red) and have summarized our changes in this letter. We have also added an author (David Gohara) who was mistakenly left off the first draft of the paper.

Our responses to the reviewer comments are provided below:

> *This is a reasonable paper to (re)acquaint readers with the APBS suite. It does a reasonable job of providing a description of this program. However, the paper could do a better job of telling an eager novice why they want to use this program. If (as suggested in Fig 1) it would be to assign titration states then some more information about this should be provided. Gain the use of the other (APBS only) electrostatic properties should be described briefly. The paper does not describe and specific results so the reviewing questions are not always applicable.*

We appreciate the feedback and have added sentences to emphasize the features of APBS. However, we were reluctant to have the paper sound too much like "marketing" and avoided introducing too much additional text encouraging users to try APBS over other Poisson-Boltzmann software.

> *The first draft of this paper did not include the figures. I rooted around and found the version with figures in the SI section of the Journal review site. Then this version retains notes between the authors.*

I apologize for our error and the need for the reviewer to find other versions of the manuscript. This revised version should be complete.

> *Generally, when an innovation is introduce that should speed up solution of the problem (eg TABI-PB vs PB or Graph theory vs MC) it would be useful to know how much faster it is. Or to know that the innovation is faster under a certain set of conditions. The authors should also ensure that the references give the necessary comparison of accuracy between older and newer techniques.*

The text has been revised to emphasize the difference between new and existing methods.

> *page 1. Put in a reference for use of explicit electrostatic models.*

This has been added to the introduction (Ren, 2012).

Unclear if the Course-graining in paragraph 1 is the continuum solvent. If so then add a reference and describe the properties that will be effected by this choice.

This has been clarified by revised "coarse-graining" to "continuum".

page 4: its useful to know the PQR files simply replaces standard columns to the right of a pdb file with charge and radius, but I'm not sure we need to know this started as a SED script.

While we are sad about the loss of the old-school SED "shout-out", we have deleted this sentence from the manuscript.

Page 5: A reference should be given for the debump algorithm.

This reference (Dolinsky, 2004) has been added to the description of the de-bump algorithm.

The Monte Carlo methods for finding protonation states as a f(pH) generally converge readily despite the formal problem being O(2N). While N may be large for the whole protein is is modest at any given pH and MC works well. However, having different methods to arrive at a goal is an advantage.

The discussion about the relative merits between stochastic and deterministic methods is best left to another manuscript. However, a statement about this has been added to the paper.

Page 6. It should be noted that these force fields are primarily for amino acids. What is done for other ligands found in the structure?

A statement to this effect has been added to the manuscript.

Page 7. 3.1 What is the length scales for which each method should be used?

All of the methods are appropriate for the length scales at which continuum methods can be used. A detailed discussion of the limitations of continuum methods is beyond the scope of this paper.

3.2 What terms are contained in the nonpolar component? Does this include the implicit van der Waals and the cavity formation terms (which are not so easily separable)? What value is used (kcal/Å2)?

Text has been added to the manuscript to provide citations for these nonpolar solvation terms.

Fig 3 should give a standard PB potential surface to compare with the PB-AM model. It would be useful to note when the spherical cow is fine and when it is not. Perhaps combine fig 2, 3 and 4 for one or 2 proteins using the different methods Fig 6 should provide a scale in Å for the proteins. I don't understand what red and blue mean in this figure. If it is electrostatic potential give the scale and the net charge of each protein.

The manuscript has been revised to provide such a comparison by consolidating figures.

What program is used to make this display (as APBS uses others for the visual interface).

This information has been emphasized in the manuscript to explain the methods that have been used for graphics in the paper (VMD) as well as other methods that can be used for biomolecular visualization.

> *Fig 5 and 6. I'm not sure what these figures are trying to show. These are not produced by APBS. In what way does the graphical program use APBS input and not its own surface algorithms.*

The manuscript has been revised to clarify surface coloring and graphical representations.

> *The manuscript describes current status of the popular software APBS and associated resources. The manuscript is clearly written and easy to follow. I have only two minor points:*
>
> *1) Please, correct DelPhi reference to https://www.ncbi.nlm.nih.gov/pubmed/22583952*

This has been done.

> *2) There are some leftovers from the editing as for example "**Dave: please make sure this is true! ⋆⋆". The manuscript should be proofread.*

We apologize for the error; this has been fixed.

Thank you again for your consideration of this manuscript.

Sincerely,

Nathan Baker
Director
Advanced Computing, Mathematics, and Data Division