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David Mobley
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Dear David,

I am writing to strongly support your application to the NIH for funding of the SAMPL series of blind prediction challenges. I am currently the Team Leader of Molecular Modeling at the Human Health Therapeutics Portfolio of the National Research Council Canada. Our major focus is on protein design with a particular interest in antibody modeling. As part of this research, we have over the years developed and applied computational tools for solvation free energies, docking and binding affinity prediction, among other things. I have participated in 4 SAMPL challenges.

I understand that one of the criticisms your previous proposal received was that the impact of the proposed work depends on innovations by other researchers in response to these challenges. I personally see that not as a flaw but as having a multiplier effect spurring innovation at multiple sites. Let me share how my lab has benefitted from SAMPL.

Our participation in various SAMPL challenges over the years has influenced the development of some of the computational tools used in my laboratory. SAMPL-1 motivated us to explore and test the inclusion of a continuum van der Waals term in our solvation model. The lessons learned in SAMPL-1 guided us in producing our next generation solvation model, FiSH (First Shell Hydration model), which included a more sophisticated continuum van der Waals term and an environment-dependent Born radius for continuum electrostatics. SAMPL-2 provided a blind test to validate our FisH solvation model and allowed us to fine tune our parametrization. SAMPL-3 revealed a weakness in the nonpolar terms of FiSH model with respect to polychlorinated aromatics. In particular, there was an imbalance between the cavity term and the continuum van der Waals term for chlorine atoms. This deficiency probably arose from the underparametrization of the continuum van der Waals term for aromatic chlorines due to a dearth chlorinated aromatics in our original parametrization set. SAMPL-3 provided a valuable data set for calibrating or solvation model for this important class of compounds.

The SAMPL challenges 1 to 4 have also influenced the development of our SIE (Solvated Interaction Energy) scoring function for binding affinity prediction. Through various iterations of SAMPL we were able to test the use of various solvation models as part of the SIE scoring function. Similarly, our participation in docking challenges has shown us that our relatively simple scoring functions for docking coupled with very thorough sampling methods can be quite successful, informing us that the major effort we have placed and continue to place on developing and refining exhaustive sampling methods is a good investment of resources.

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I believe that SAMPL has benefitted not just my lab but other groups as well and has helped guide the direction of their research. I have no doubt that SAMPL has spurred innovation in multiple labs. Having your proposal funded will allow SAMPL to continue in its valuable role.

Regards,

Enrico O. Purisima
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