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INSTITUTE OF MOLECULAR BIOPHYSICS, KASHA LABORATORY
AND DEPARTMENT OF CHEMISTRY & BIOCHEMISTRY

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Professor David Mobley
Department of Pharmaceutical Sciences
University of California, Irvine
Irvine, CA 92697

Dear David,

I am writing to give my enthusiastic support for your application to the NIH for funding of the SAMPL series of blind prediction challenges. I am currently a principal investigator at Florida State University working on development and application of advanced free energy calculation and sampling techniques for biomolecular simulaton studies among other topics. My group has participated twice (SAMPL3 and SAMPL4) in SAMPL challenges.

While I could write to express my enthusiasm for the SAMPL series of challenges and how I think it has helped and is helping the field, I understand that one of the criticisms of your previous proposal was that the proposed work relies on other researchers to come up with innovative new methods in response to these challenges. So, I wanted to share a brief explanation of how SAMPL has indeed driven progress in my group.

In the past years, my group has been actively developing a unique free energy sampling strategy, the orthogonal space sampling scheme. Due to its complexity and novelty, we have been using SAMPL host-guest challenges as our test grounds for the fact that SAMPL host-guest systems are relatively clean from the viewpoint of experimental condition and the measurements are reliable and accurate. In addition, a series of data provide us statistically meaningful assessment of our methods and implementations. To my group, who intends to develop generally powerful methods for the community, failure in SAMPL tests means much more than success; certainly success can provide further motivation and encourage. In SAMPL3, we obtained a set of host-guest binding predictions, which have one of the highest correlations with the target values, however very disappointing RMSDs. Through this test, we learned that our code had an issue of dealing with charged host systems due to the way that we treated PME in alchemical transformations. In SAMPL4, we planned to test a new high-order orthogonal space tempering implementation, which was preliminary with an approximate recursion design. In the SAMPL4 host-guest challenge, we obtained one of the best predictions in almost all the aspects. Though encouraging, we learned that our approximate recursion scheme definitely introduced some estimation error, correction of which should lead to much better predictions. Starting from the end of 2014, my group has been developing a mathematically rigorous recursion scheme, which was finalized very recently; this algorithm allows the high-order orthogonal space tempering to achieve accurate evaluation of free energy values.

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As shown above, SAMPL has been extremely helpful in method assessment and problem identification in my group, and I believe has had similar effects on many of the participating researchers and groups. If anything, one of the main limitations of SAMPL so far has been the uncertainty concerning its future. Because of the lack of funding of the initiative, it has to rely entirely on donated data, and it has always been uncertain if and when a new challenge will occur. Additionally, the lack of a clear roadmap has meant it is difficult to plan for participation in future challenges. This is certainly understandable for an initiative with no funding, but it also illustrates why funding is so vitally needed. I trust that having your proposal funded will allow you to remedy this.

Again I enthusiastically support your planned research directions. If funded, I believe the proposed SAMPL challenges will continue to benefit my research group and the modeling community more broadly, having increasing impact on the modeling community.

Wei Yang

Professor of Chemistry & Biochemistry
Associate Chair of Chemistry & Biochemistry