SECTION OF INTEGRATIVE BIOLOGY

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Dear Editor,

Please find attached a new manuscript, entitled "Predicting virus-receptor mutant binding by molecular dynamics simulation," which we would like to submit for publication to JCTC. The paper addresses a topic that has many applications in biochemistry and molecular biology: how to measure the effect of mutations on a protein-protein interface. In our manuscript, we demonstrate that point mutations can generate large enough effects to produce statistically significant results within reasonable simulation time. Thus, with only minimal prior assumptions we can apply a first principles method to the problem of mutant evaluation. In addition, we also find that conclusions drawn from our data are reproducible and consistent with some comparable experimental data.

We apply a steered molecular dynamic (SMD) approach developed by Schulten et al. to pull apart the two proteins in a protein-protein interaction. While the method has been applied previously to calculate the absolute free energy of protein-protein binding, to our knowledge it has never been used in an attempt to parse small differences in a protein-protein interaction energy landscape. In addition, we find rather than the exhaustive sampling required for free energy calculations, using the maximum force or the area under the force versus distance curve we can distinguish point mutants in our system.

In summary, our manuscript (i) shows that SMD data can distinguish plausible reduced binding point mutants, (ii) offers computational evidence that one of two hydrogen bond networks in the protein-protein interaction is likely not critical for a high affinity interaction, and (iii) provides a first principles framework to investigate protein-protein interactions with no training data required. We expect that these results will be of interest and valuable to a theoretical chemistry and biochemistry audience, and therefore we believe that our manuscript is suitable for JCTC.

We are looking forward to your decision.

Sincerely Yours,

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