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Department of Chemistry and Molecular Biology
Dr. Samuel Genheden

Re: testimonial on the SAMPL challenges

To Whom It May Concern

I am an early-career researcher that have participated in three SAMPL challenges (3–5) with basically three different research groups and with three different sets of methods.

When I participated in SAMPL3, I was a PhD student at the University of Lund and I assembled a research team consisting of myself, a new student in the lab and collaborators in Denmark and at AstraZeneca. The task was to assess the commonly used methods MM/PBSA and LIE on their ability to compute ligand-binding affinities. I had at that time been involved in extensive benchmarking of the methods and the SAMPL3 challenge gave us an opportunity to **finally test the methods in a prospective study.** To us, the results were clear: the methods were not particularly good; something we were expecting based on our benchmarking of published data. Thus, the SAMPL challenge allowed us to finally show that the MM/PBSA and LIE are inaccurate and imprecise methods. **The usage of these methods within the Lund research group has since then largely been discontinued**. The SAMPL3 challenge also introduced me and the Lund research group to guest–host systems, **leading to a broadening of our research program that has been very important** in our continued effort to develop novel methods based on a quantum mechanical (QM) approach.

At the time of the next challenge, SAMPL4, I was a postdoc fellowship at the University of Southampton. Within that group, we were using Monte Carlo-based (MC) techniques to compute solvation free energies, and therefore I saw the chance to, in a blind fashion, **compare MC with the more commonly used molecular dynamics-based (MD) methods**. The challenge also gave us the possibility to evaluate our recently developed QM-based correction. The SAMPL challenge showed us two things: i) that MC and MD did produce partially different results and ii) the expensive QM correction did not improve the results. This led us to pursuit several research projects that aimed at trying to pinpoint the source of the discrepancy between MC and MD. Thus, **SAMPL helped us highlight a potential problem with our methodology** that still today is poorly understood. Furthermore, the challenge led us to at least for the time being pause the development of expensive corrections,

Address: Dep. of Chemistry and Molecular Biology, University of Gothenburg, Box 462, 405 30 Gothenburg, Sweden | *Phone:* +46317863803 | *E-mail*: samuel.genheden@gu.se

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because we showed that it is very hard to improve the results of molecular mechanics (MM) predictions.

Finally, when SAMPL5 came around, I was back in Sweden, having taking up an independent research fellowship at the Gothenburg University. The challenge came very timely because I had recently developed an efficient method to compute partition coefficients based on a hybrid energy model (an all-atom/coarse-grained (AA/CG) model). SAMPL5 thus gave me an opportunity to **test the AA/CG method in a prospective study and to compare it blindly with the standard all-atom energy model.** I believe that the results were very encouraging because the simpler energy model performed equal to or better than the all-atom model. Therefore, **I have continued to develop the AA/CG model because of SAMPL**.

I strongly believe that community-wide and prospective challenges as SAMPL is an **essential instrument to gauge how well widely used method are at predicting important quantities** such as binding affinities, solvation free energies and partition coefficients. Me, personally, always look forward to future challenges and that so many groups are participating with a wide range of method is a testament that other researchers feel the same. Because I have moved between groups and applied different methods, I have so far not had the opportunity to systematically and continually work on the progress of a single method. This will change in the future, **and I intend if possible to participate with my AA/CG method in the planed challenges through 2022 and SAMPL10**. I firmly believe that my method will be better because of the efforts of the SAMPL organizers.

Kind regards,

Samuel Genheden

Address: Dep. of Chemistry and Molecular Biology, University of Gothenburg, Box 462, 405 30 Gothenburg, Sweden | *Phone:* +46317863803 | *E-mail*: samuel.genheden@gu.se