Results of the 2017 Roadmap survey of the Statistical Assessment of Modeling of Proteins and Ligands (SAMPL) challenge community

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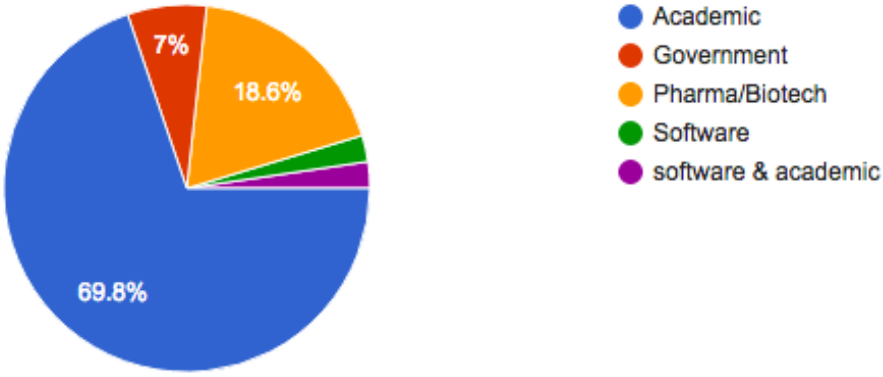
Abstract: The Statistical Assessment of Modeling of Proteins and Ligands (SAMPL) series of blind prediction challenges provide unbiased, prospective tests of computational methods, serving as a crowdsourcing mechanism to drive innovation. These challenges solicit submissions from the computational community to predict properties of interest, such as solvation, partition, or binding of drug-like molecules. These challenges provided substantial benefit to the community, and have led to roughly 100 publications, many of which are broadly cited (see attached bibliography). We are currently seeking **funding from the NIH** and surveyed the community concerning experiences with SAMPL and how our future plans for SAMPL can best align with the community's interests and needs. This document summarizes the results of this survey and describes our findings. On the whole, the community enthusiastically supports our plans for the future of SAMPL, and provided modest suggestions to further strengthen our plans. For up-to-date info please see the **SAMPL website**.

Survey methods and results

Here, we reproduce the results of the survey in full except for anonymizing respondents. Questions 1 and 2 dealt with identifying information (name and e-mail) and are thus bypassed here. There were 44 respondents, though not all respondents answered all questions. The survey was conducted via Google Forms from April 18 to June 19. The survey was advertised via Twitter and the Mobley Lab website, and e-mailed to to past participants.

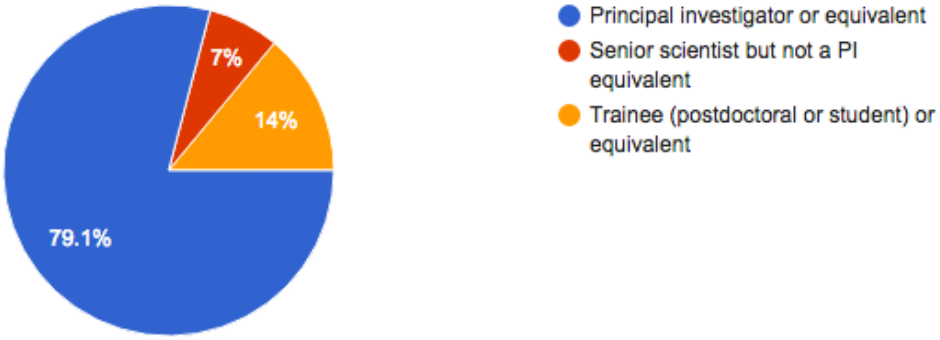
3. Affiliation

43 responses



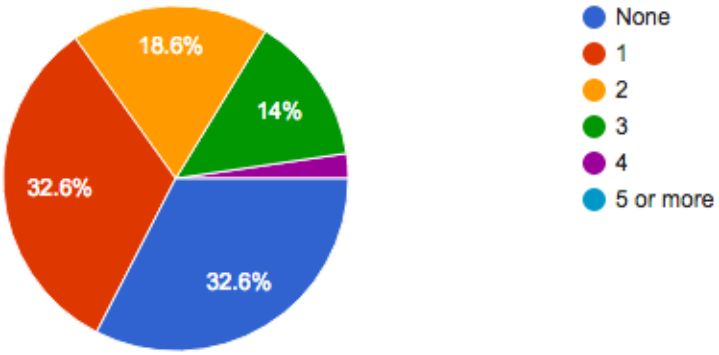
4. Career level

43 responses



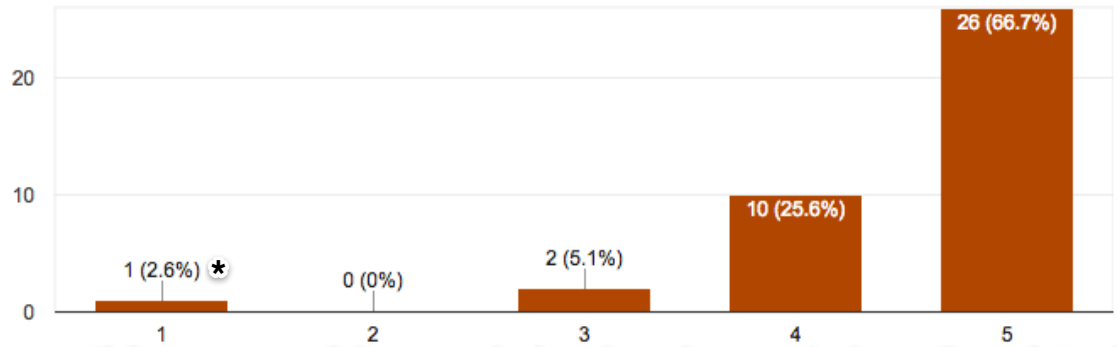
5. Number of SAMPL challenges you've participated in:

43 responses



6. Has your past experience with SAMPL been favorable (on a scale of 1-5 with 1 being unfavorable)?

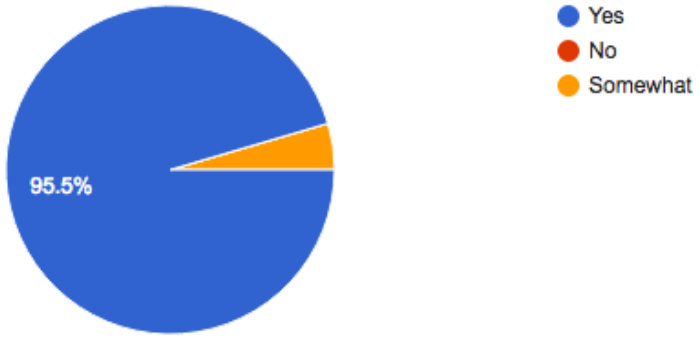
39 responses



*** - one participant reversed the numerical scale and gave a 1 when a 5 was intended**

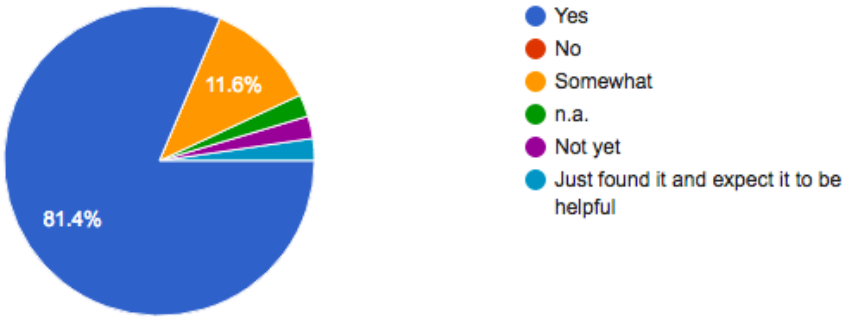
7. Do you see SAMPL as a valuable resource to the community?

44 responses



8. Has SAMPL been important in driving progress in the field or in your group?

43 responses



9. If you answered “yes” or “somewhat”, please explain how.

(Responses are grouped by category)

Comparing methods in order to learn or evaluate technology:

- Comparison of methodology that can be scrutinized is crucial to learning what works or does not.
- It facilitates the objective testing of different methods by providing test cases which each person can apply their own methods to. It lets one learn about other people's methods. It avoids the often laborious process of having to apply other people's methods oneself to compare them with one's own method. It provides a forum for the research community to come together and discuss methods and how to move the field forward.
- SAMPL is a very helpful way for us to quickly assess the state of the art in the field and what methods we should pursue in our company. It provides an honest assessment that cannot be altered based on knowing the answer. We have enhanced and accelerated our methods development work based on SAMPL results.
- SAMPL has been a great instrument to assess the methods we use, but I have not used them to refine or improve the methods, as I have changed methodology from challenge to challenge. But also on a larger scale it seems that SAMPL mainly has been used to assess methods (new or old) rather than to drive progress, at least for the "physical-properties"-challenges.
- Through the SAMPL series of blind test, we have gained a much better understanding on the strengths and weaknesses of binding free energy tools including DDM and BEDAM.
- It is very important to benchmark our work against other groups in a blind manner. It is also equally important to have test sets against which to test sets of varying complexity to test approaches. Finally the challenges allow members of the community of users to see and objectively judge progress as well as to understand when certain approaches do and do not work.
- We learned a bit on the extreme cases, and we were able to demonstrate the superior predictivity (and efficiency) of the COSMO-RS method.
- It has provided opportunity to thoroughly test and compare various methods, and also let us know about other people's problems and failures (and not only success stories). The "simple" nature of the systems used in SAMPL makes it possible to focus on specific aspects, which is not possible with other types of data.

Method validation, evaluation, standardization and pipelines:

- helps us standardize, validate and test robustness of all aspects of our pipeline for simulation of binding thermodynamics
- It provides a solid platform to assess various method components. Due to the unique nature of data "cleanness", it serves a complementary role to the D3R challenge.
- Because of the possibility to validate force field parameters
- Each SAMPL edition presents multiple challenges that are crucial to evaluate the performance of our docking software (i.e., pose prediction and scoring, binding energy prediction, etc..)
- We have made considerable use of SAMPL results to evaluate force fields for the Amber community. This includes comparisons of polarizable, ""advanced"" force fields and variants

of the general Amber force field. We also have used SAMPL to benchmark and test new implicit solvent models, especially those based on integral equation models like 3D-RISM.
- We have tried new methods and compared old methods
- New challenges are useful for testing new methods
- We were forced to sort out the pieces of research we had been doing in order to participate in the challenge and that was a good motivation.

The importance of prospective tests:
- Prediction challenges encourage a focus on method development and thinking about underlying physical and computational principles instead of reaching a specific accuracy goal – the temptation to tune the protocol to one specific outcome is removed. And the challenge aspect provides a big boost of motivation for students, postdocs and PIs alike.
- Best way to test a predictor method.
- As far as I know, as there are currently no other really blind challenges open to the community for the testing of protein-ligand free energy calculations, SAMPL is at the moment the best resource to allow an unbiased comparison of computational approaches as well as true prospective testing of the value of computational methods.
- It gives a critical test for assessing methods and performance of scientific ideas and developments. To perform well in a blind test is the ultimate challenge, and one that forces you to face concerns and issues that could have been glossed over in your previous efforts. If computational efforts for drug development and molecular design are ever going to elevate from a promising strategy to an essential tool for good, we will need such critical assessment to find the best path out of the woods.

Assessing the state-of-the-art:
- Helping us to understand the capabilities of our technologies.
- It allowed us to assess the quality of (truly prospective) predictions.
- We have seen limitations in the current paradigm and are trying to improve on it
- an unbiased assessment of the accuracy of our methods was unique and invaluable, helping us plan intelligently for the future research
- It has given us the ability to accurately measure the progress of the free energy methodologies developed within our group with respect to our competitors, in a clear and unambiguous way. It has also clearly shown us, and the rest of the field, how much further our methodology must come before it can be seen as a reliable compliment to experiment.
- Understanding of the limitations of computational approaches.

Driving innovation and discovery, including in force fields and methods:
- The SAMPL challenge raised awareness of possible sources of error (such as force field, parametrization) for calculating free energies and indicated venues for improvement. By drawing attention to the differences in force fields and the effect of the human factor in parametrization, it made evident the need for automating the process of preparing molecular systems and obtaining fast and reliable data. Addressing these issues will help advance the drug discovery field. For the SAMPL5 challenge, our group and our collaborators developed a new host-guest docking software, and focused on the effect of protonation states and of the ionic strength of the solution, all of which proved to be crucial in obtaining accurate results.
- As a part of work on the development of force field parameters and computational methods, we reply a lot on high-quality experimental data. The data obtained from SAMPL challenges have been a valuable source for our work.

- Collects disparate approaches to relevant problems resulting in cross pollination of ideas/ approaches to solve them
- Although I have not personally participated in the blind challenges themselves, I collaborate closely with several groups that have done so. And even non-blind, retrospective challenges, have had a big impact in methods and force field development in our community.
- SAMPL is one of very few sources that provide unbiased reference data for understanding the limits of our theories and to drive progress to overcome them, with considerable success. More details will be provided in the testimonial I am about to send.
- Participating in SAMPL has pushed us in new directions and caused us to rethink aspects of our methodologies. For example, SAMPL5 forced us to consider non-polar solvents and conformational sampling in implicit solvents, which were directions we were not thinking about.
- It has put some issues we knew were theoretically needed on the list of 'to do now'
- The methods and data generated by SAMPL and its participants have put the field of free energy simulations in very solid ground. We now have a flurry of methods coming, and a real platform to compare and contrast experiments and calculations.
- SAMPL has provided to us a solid platform to develop and test methodologies. It has also introduced to us chemical systems and applications that we would have not otherwise considered.
- This allowed us to develop new protocols and to improve existing ones, to identify existing problems with the force field and correct them, etc.

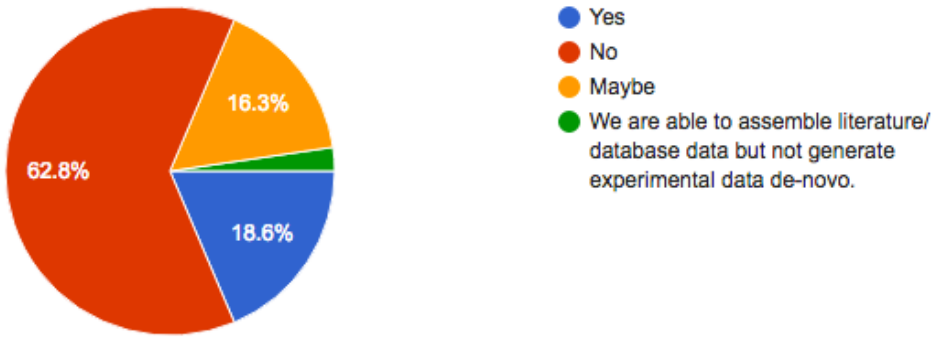
The value of the data sets themselves:
- Reference data set for force field developers
- Benchmarking data sets

Other, including publications:
- It has provided the data that fueled several papers.
- The time bound aspect of the competition keeps us on track. It is a wonderful process of evaluating your model and simulation techniques.

We then provided an executive summary (and a link to a full explanation of) our future SAMPL plans and asked questions about these future plans:

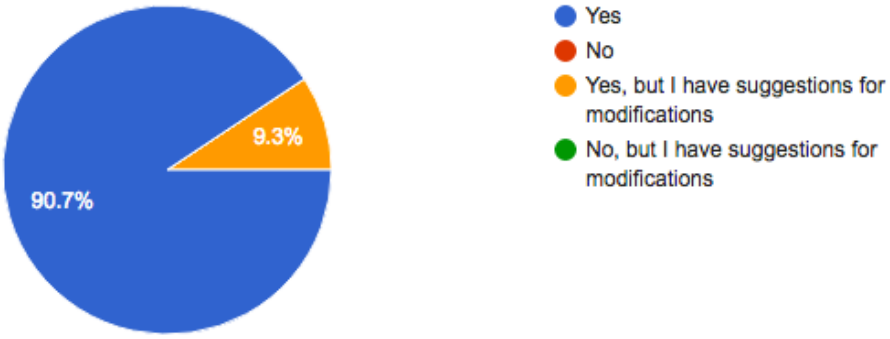
10. Are you able to generate adequate high quality data of your own to prospectively test your methods and advance physical modeling?

43 responses



11. Are you happy with the proposed future directions for SAMPL?

43 responses



12. What modifications would you suggest for our plans for SAMPL?

(Responses are grouped by category)

Adjustments to the size, variety, or scope of challenges:

- increase variety of systems included, esp. for host-guest modeling
- only thing I can think of is just more experimental values. for example in binding, would love to have multiple groups do the same experiments, as the I see some binding, with the same host-guest vary with variation up to 10 kcal/mol, making it super hard to make a model for it
- Personally, I would also like to have log D data in SAMPL7 (in addition to pKa). *[Ed. - This is already part of the plan but we have made it more clear in our proposal.]*

- My main concern is that the physical properties challenges require multiple, unrelated methods. This has been largely address in SAMPL6-8 with pKa calculations being separated out. However, for solubilities and membrane permeabilities in SAMPL9-10, I see many moving parts that need to come together to be successful. This will make it difficult to figure out where the weak points in the modeling are and will eliminate participants that don't have experience with a full toolset to complete such calculations. I hope that SAMPL9-10 can be broken into pieces the same way that SAMPL8 is.
- Especially in case of SAMPL4 and SAMPL5 molecules considered have ambiguous protonation states. It would be a great help if the protonation states are well defined experimentally. *[Ed. - These measurements are part of our plan.]*

SAMPL challenges on other types of data than proposed:
- methods to test conformational free energies
- I would not forget hydration tests as they're still difficult for the field. If partition coefficients are easier to get, then partition coefficients a good superset. I would try to add specific systems that probe sampling issues. Something where sampling deficiencies would give larger deviations than (ever-present) FF errors.

Follow-up experiments:
- Please make sure that experimental data, which are strongly questionable in the light of the simulation results (as the logD of adenosine in SAMPL5) can be remeasured afterward. It must be possible that simulation detects wrong exp. data, and this should not stay an unproven hypothesis for ever, but the measurements should be repeated and a final decision needs to be made, whether the initial measurement or the predictions are wrong.

More time for SAMPL challenges, less frequent challenges, or automated participation
- We have found that due to the limited resources, sometimes it is difficult to process all the molecules in the data set within the allowed time frame. So perhaps more time should be allowed for the challenge.
- Yearly competitions is somewhat too often if you use computational heavy methods (but of course you can skip some years).
- Increased use of 3rd party testing- i.e. by people other than ff developers- participation in SAMPL is extremely time consuming, especially if you are doing both development and testing

Post-challenge follow up, such as summaries for non-experts:
- Provide a 'basic' final evaluation and consensus that can be distributed to and understood by non-experts.
- At the end, provide a "lay person" summary so that novices, who may have access to software, can be instructed on where and how the software can be used. This would also be useful for editorial policies for relevant journals.

Positive comments on the plan:
- The outlined plan is great. I particularly welcome the efforts to obtain high-quality data on macromolecular systems.
- No modifications. I fully agree with the SAMPL proposal and I will be very happy to participate to future SAMPL challenges.
- In general, I like the push for increasing complexity or realism in the series for the SAMPL plans in the "Physical properties" category. You could actually consider partitioning beyond

Octanol, CHX, and water if you wanted to diversify. I do like the push to transferability of molecules between environments rather than coming up with a model that treats only a single environment well. The growth from partitioning to solubility to membrane permeability seems like a realistic growth in practical assessment. In the host-guest seems to have a similar growth curve, but it is less apparent (I'd need to read through the deep cavity sections more thoroughly, I suppose). In the protein-ligand cases don't appear to have a strong growth plan beyond "make new model mutants". It might help if you had a clearer set of targets for the community effort progression. At least, it might be more convincing.

- I am happy with the plans of SAMPL. I wish it all the best

Discussion of survey results

Participants overwhelmingly support the notion that SAMPL is valuable, drives progress, and they have had exclusively favorable* experiences with it. (* - One respondent accidentally used an inverted scale for Question 6 and gave a rating of 1 when he intended to give a value of 5).

Respondents were roughly 70% academic, with another 20% from pharma and industry, and 80% were from principal investigator (PI) or equivalent positions. Roughly a third had never participated in SAMPL, a third participated just once, and a third had participated two or more times. **97% of respondents see SAMPL as valuable to the community**, and 95% have had favorable experiences with it, with the remaining 5% in the “neutral” category. **Another 93% of respondents believe SAMPL has played an important role in driving progress.** And 78% of respondents have serious concerns about their ability to generate their own data to test their methods.

All respondents are happy with the proposed future directions for SAMPL, as previously submitted to the NIH — though some 9% had modest suggestions for modifications that are reproduced above; below, we explain how we are changing our plans to address these.

Participants highlighted a number of ways in which SAMPL has helped drive progress in the field. Some noted that, given the clean nature of the data, it is highly complimentary to the D3R effort, and provides an opportunity to test pipelines, validate and benchmark force fields, and do unbiased method comparison. A key theme was that SAMPL revealed how human error could introduce significant problems and highlighted the need for automation. Participants also highlighted how it allows methods to be compared head-to-head, revealing the state of the art, without a single researcher having to re-implement a variety of literature methods. One wrote, “**If computational efforts for drug development and molecular design are ever going to elevate from a promising strategy to an essential tool for good, we will need such critical assessment to find the best path out of the woods.**” Another noted how SAMPL has served a key role in putting the field of free energy simulations — currently undergoing a resurgence — on solid ground and leading to a flurry of new methods in the area.

Modifications to SAMPL plans based on community feedback

Some participants did have minor suggestions for adjustments of our planned directions. Some suggested allowing more time (which funding will allow us to do, since it will reduce our reliance on donated data and allow us to schedule data collection, challenges, etc.). Another

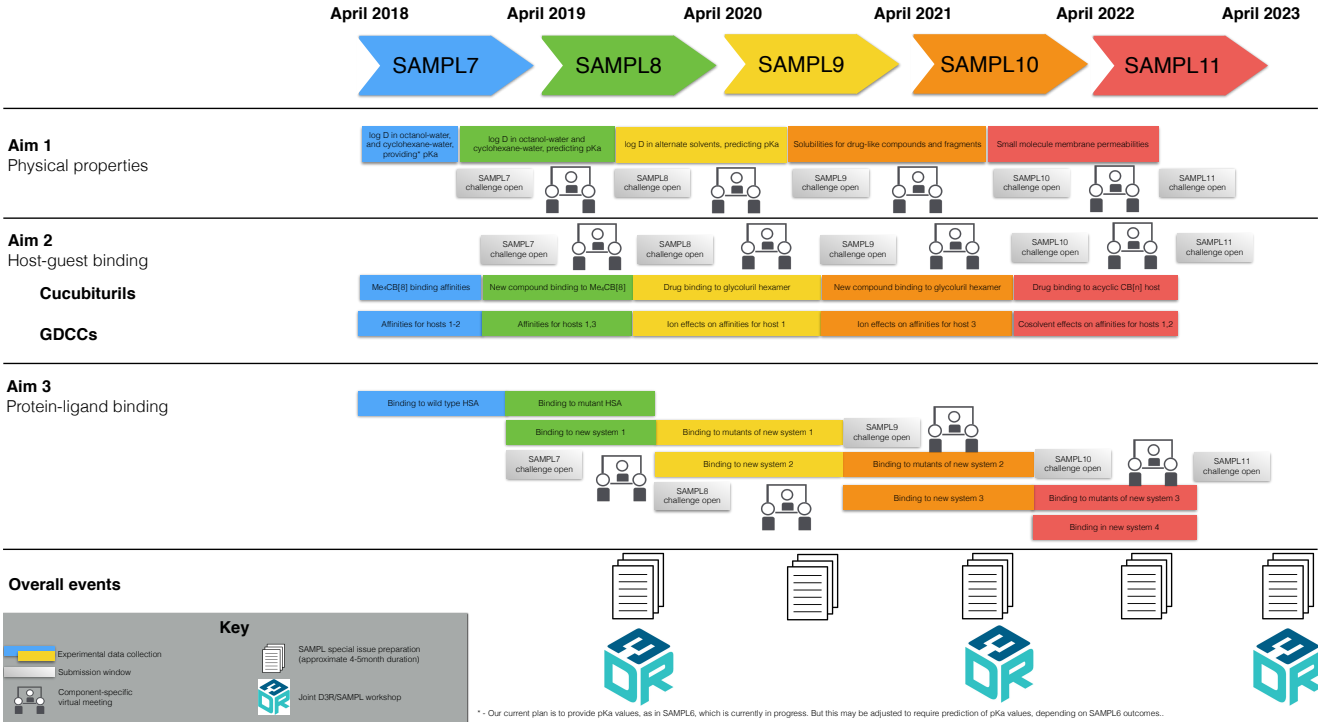
highlighted the need to be able to do follow-up experiments to re-check questionable experimental values, something which is already in our plans for SAMPL. Others highlighted the need for a summary of outcomes oriented towards a lay audience, which we now plan to do. And another suggested breaking SAMPL9-10 into component pieces as in SAMPL6-8; we agree that we want to maintain SAMPL's focus on learning by isolating specific points of failure, so we now discuss how we will isolate component pieces for these challenges as well.

Some feedback focused on other types of systems aside from those planned, such as including more varied host-guest systems (which we now plan to do), new hydration free energy data, and data on conformational free energies. Some of this requires new sources of data (for example, we have been unable to find someone with the capacity to measure hydration free energies on any reasonable scale), but we will be on the lookout for such sources of data, and we now discuss these aspects in our proposal.

Participants also were concerned about the investment of time that it requires to participate in SAMPL; we ultimately hope to shift to a model where participants submit a *method* rather than a set of predictions, and the method can automatically be run on cloud computing (such as AWS) to produce and submit predictions. We now discuss this, though it will likely take several years before we can roll this approach out on a large scale.

While we believed the community was enthusiastic about SAMPL, we were delighted that our respondents were so supportive and very much aligned with the directions we are proposing. We will certainly factor in their comments and suggestions as we plan the details of each subsequent challenge, and we hope that their responses help indicate how much the community needs SAMPL in order to drive progress.

SAMPL Graphical Roadmap



Full List of SAMPL References

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