Charge Question Discussions:

1. The current perception of modeling in the biomedical and clinical research community, what needs to change to encourage more acceptance?

This is a key area for all of our work. To improve perception and reduce doubt in experimentalists, one needs to show that computation can be quantitative and of value. One concern is that models have too many parameters so it is hard to get a handle on these. One can make numerous models that fit data, and can look for the most probable models , but we are often lacking enough data to completely specify a model. Thus, we need more experimental data to help further nail down model details (this could take the form of experimental tests of models or experimental determination of parameters to go into models).

One key is to show the predictive ability of these models, as opposed to their ability to match the data with which they were constructed. Also, we expect that certain “Killer Apps” will be helpful to drive acceptance. These applications would be classic applications which share challenges with a broad range of other applications and also have a wealth of experimental data in order to test and validate the computation. Moreover, this would ideally take the form of some success story in which modeling combined with experiment clearly leads to something greater than experiment alone.

In addition, we feel that there is a strong need for interdisciplinary education, both in terms of students (eg at the undergraduate and graduate level) as well as the possibilities for education of our peers and colleagues, for example through pedagogical reviews and workshops.

2. Future biomedical and clinical applications for models, based on current success stories, things that couldn't be solved without models, time to cure – e.g comparative effectiveness research

There are numerous appealing success stories already to draw from, including:

- A spectacular example of drugs made famous through molecular modeling successes are inhibitors of the two viral enzymes HIV protease and reverse transcriptase (RT) Protease inhibitors and RT inhibitors are now regular components in HIV drug cocktail therapies.
- The SARS virus inhibitor was identified by computer-aided molecular design three years after the global effort coordinated by WHO mapped the SARS genome.
- Potent thrombin inhibitors for blood clotting diseases were also based on molecular modeling by Merck scientists.

- Other drugs developed in large part by computational techniques include the glaucoma treatment Dorzolamide, the migraine medication Zolmitriatan, and the well known Viagra (initially developed for hypertension and then angina).
- Notable herbicides and fungicides were also developed by QSAR techniques.

Also, it is important for us to learn from failures, both to see how can we push in certain areas for improvement as well as to educate more broadly the limitations of a given model. Finally, there are cultural barriers and traditional training in many fields is not completely amendable to computational fields.

3. Future directions for model development – e.g. explicit models for predictions versus implicit or embedded models in technology, enabling technologies and infrastructures for modeling

One key area for modeling infrastructure is the ability to share models. There are well known for sharing experimental structural data, eg the Protein Data Base (PDB), but nothing for model sharing. We are really missing this even for atomic scale models of structures, which are usually depreciated in the PDB (i.e. not easily accessible or searchable).

We need a model sharing resource to share many aspects, including structural data, force fields, and metadata. This also leads to a data provenance issue as well as highlighting the need to have a formal way to facilitate collaboration. There are existing tools for sharing code and perhaps that could be used as a model. The PDB works because the community knows that is where all structures go, as driven by journals. One solution would be for journals to encourage some sort of data or code sharing plan, such as the initiative suggested by *PLoS Comp. Bio*.

4. Model validation and the availability of appropriate data

The most important aspect of validation is whether a model has predictive value. Clearly, no model is perfect, but the only question is whether it is predictive and under what regime. Moreover, this means that model invalidation is important, since all models have assumptions and regimes of applicability and one needs to know in which regime you can trust a given model.

5. Uncertainty quantification and predictability of outcomes

At the atomic scale, calculating the uncertainty of a given model is hard to do quantitatively, so it is often neglected. This suggests the natural question of how can one give an implied uncertainty (eg general sense of what is the level of

statistical uncertainty), at the very least. Unlike experimental work, our community does not have this level of standard and this is an important area for moving forward. There are examples of uncertainty calculations, especially in methods driven by Statistical Mechanics, such as Monte Carlo or Molecular Dynamics calculations, where one can perform error estimates.

This suggests that an important goal would be to raise the bar in this area, especially in order to facilitate acceptance by the medical community. As a community or from the point of view of a journal, we may not want to set 'rules' maybe just recommendations. Finally, we have been discussing statistical uncertainties above, but each type of model also has systematic errors, which are important to consider as well.

6. The current state of model development – e.g. community-developed versus custom-made models

At the molecular scale, there is a stronger culture towards community developed codes than community developed models, in part since models generally come from detailed experiments, such as X-ray crystallography. However, there are exceptions, such as models of the nuclear pore complex, which required a community to build, due to the challenges involved. This suggests that higher order scales would need community development, but not the single-protein scale.

To be clear, in the discussion above, the "model" is defined as the atomic coordinates of a structural model of a given protein or protein complex; we stress that the other components of a model, such as force fields have a strong history of community development at the atomic scale.

7. The current state of peer review for modeling research – e.g. changes that need to occur in the community

Peer review for modeling research is a major challenge for the acceptance of modeling in general. There is a catch-22 that modeling will not be accepted without high profile successes, yet many results will not be published in high profile places without broader acceptance of modeling in general. For example, many biology and chemistry journals return without review modeling manuscripts that do not include experimental validation.

This is a cultural difference from, for example, the physics community, in which theoretical prediction has a long and grand history. Indeed, the best way to make "true predictions" (and not predictions perceived as "postdictions") is to publish the results prior to experimental validation, but this is currently not

supported by many journals. Finally, high profile predictions could encourage experimentalists to test predictions, which would either gain acceptance of these models (if the prediction is successful) or improve those models (if the prediction is not successful). However, such an approach does come with a significant potential pitfall, as a controversial failure of a model could itself be a disaster in terms of gaining acceptance of modeling in the experimental community.