Open Force Field Virtual Meeting (May 4, 2020)

Discussion session 1

- D. Mobley gives an intro to discussion (slides)
- CB -- ForceBalance objective function vs comparison to QM geometries, potentially selecting for optimizing bonds vs relaxed geometry
- LPW -- the form of the objective function in FB is the same for all FF releases, and in it there is no evaluation of MM energies for QM geometries. This was discussed some months ago, and that's why the torsion profile has been introduced, which accounts for some of it. Evaluating QM and MM energies for the same geometry is the feature of FB, but it's not being used.
- JR -- Is there 1-4 weighting included, how was that handled?
- DM -- at this particular point, we are sticking with amber 1-4 scalings. However this is something that we can change in the FF file during fitting
- RW -- we looked a long time ago at doing it and create a parameter that is a function of scaling factor, we did it for lipids, but ended just with an additional parameter
- CarlosSimmerling (CSim) -- aren't these already variables, we already have vdw scaling implemented, but we haven't found great improvements as mentioned by the glycam folks
- JDC -- we have the ability to change scaling in the current SMIRNOFF implementation
- JamshedAnwar (JA) -- It would make perfect sense to use a different functional form for torsions that doesn't require 1-4 scaling
- David Case (DC) -- This goes to way back to Jorgensen, when you have a lot of repulsion in torsions, if you change vdw, you can compensate with torsions, you can't really do whatever you want there, you can't away with not doing anything
- CB -- scaling factor and torsional potential are strongly coupled, but you have to have some steric repulsion for 1-4, but using one scaling factor simplifies parameterization, as you can solve a lot of problems with this one parameter
- JA -- cosine series
- DM -- we might have to change how we handle non-polar interactions to account for that
- Carlos Simmerling -- you need a lot of terms in your cosine series
- BS -- Some FFs have separate scaling factor for LJ and coulomb.
- DC -- Amber also has a scaling factor by default
- Dave Cerutti (DCer) -- yes, its 1.2
- BS -- how energies between conformations are taken for MM and QM geometries? I just wanted to clarify the energy differences between minima on MM surface vs minima on QM surface. I wonder what those differences might do for kinetics? What to do with structures that don't correspond to minima on QM surface?
- DM -- we checked that we are in proximity of the related QM conformer

- LPW -- I think that classical potential energy is steeper, but I'm not entirely sure (80-90%)
- DM -- right now we wouldn't notice if we have some additional minima on our MM surface that are not present on the QM surface, we don't have any tests to check that
- JW -- energy ranking vs finding global minima -- it seems that FFs are good at one or the other, but rarely both
- CB -- I agree with BS that MM surface would be steeper than QM, do you have any implications how that might affect our FF performance?
- BS -- The asymmetry may indicate something about the underlying kinetics (change the barrier heights). It may be good to invoice saddle points in the training as well
- MKG -- Unlikely to just be kinetics. The physics in a binding site are somewhat particular and may defy our expectations
- CB -- We might have a lot of information already in our torsion scans to check out how are we doing on specific torsional conversions.
- DM -- We could have another spinoff project for using optimization trajectories, which represent non-minimum structures
- MKG -- If MM surface is more rugged, what about using softer and more realistic vdw potential? That could be another spinoff project. It could also have a big effect of 1-4.
- JDC -- It would be great to try different vdW forms, provided that they're supported by other engines
- DM -- we have some NIH funding for some longer term FF development and to explore some new directions, which we can use for this more speculative research
- KM -- You are looking at geometries in vacuo, are you planning to include some solvent effects there?
- DM -- Solvent effects aren't in that work. We're not sure how to deal with solvent-in-QM. We recognize that gas/vacuum phase QM isn't the best thing to train on, but there seems to be a general understanding that these ARE transferable.
- MKG -- 1-4 electrostatics play a role in torsions, so maybe solving that is something to think about it
- CB -- There seems to be a general understanding that, when there's a conjugated dipole in water, this will increase polarization.
- KM -- Can you analyze your dataset with respect to the molecules that are able to make intramolecular hbonds
- JW -- We generally exclude intermolecularly-hbonded molecules, since we know we'll model those energies poorly, and we don't want them distorting torsions
- DC -- D. Cerutti and I developed two sets of charges, one that resulted from the gas phase calculations, and the second that had solvent included. We then made the assumption that if you go to a solvent phase, all you do is change charges and you hope that this change maps all the difference between these phases. Maybe something like that could be used for small molecules, too.
- DM -- Gilson and schauperl did work motivated by this idea -- looking at a RESP2 model where charges are halfway between gas-phase and condensed-phase

- DC -- Difference between that and my idea is: When we fit torsion potentials or quantum results, we didn't use halfway in-between, use used gas-hase
- DM -- We would do that too. We don't want polarized charges when we're comparing to QM energetics in gas phase, since that will build in charge error
- Carlos -- You'd end up using other parameters to cancel out polarization
- PiV -- Idea in CHARMM is that everything is going to be in water anyway, so let's take water as a reference point.
- DM -- It may not be that we have one force field to rule them all for all applications, you might want to optimized to predict property X on this data, and then for property Y on another set
- PiV -- When I use some watery environments, I'd use CHARMM, but for polymers and some other cases, I'd use Compass -- FF for a specific application I know they were parameterized for
- CB -- I agree with David Case that, if we want to use gas-phase charges, then our QM charges should have some modeling for solvent added But if we want to do much more efficient vacuum calculations. We shouldn't mix gas phase fitting with ???
- DCer -- Carlos, you and Chuan had a solution to incorporate GB...
- Chuan Tian -- One problem with gas phase fitting is that, if you do gas phase calculation, you can get high accuracy. But if you do solution phase, you have to use the same method for solvent as solute, which will not be as accurate as gas-phase calc.
- CSim -- I don't think that our biggest error, I think we make bigger mistakes in other areas
- DM -- Considering where we are, do you see any dangers that we should/could avoid? What steps should we take to most rapidly improve accuracy with the least effort?
- JRW -- We will have a lot more compute power coming online shortly, so we can consider larger or more detailed QM.
- Julia Rice -- Re: What can we do short-term to improve accuracy -- I agree with Case, fit to quantum data in gas phase (?). Early, when FFs were being developed, that wasn't such a big deal, but now it's necessary.
- Michael shirts -- What do folks think about Case's idea -- two sets of charges -- One for torsions, another for gas phase?
- DM -- That's very much aligned with what Schauperl was doing
- Carlos S -- Case used explicit solvent model in quantum calcs.
- DC -- Carlos is correct, that's the choice we made, but I don't think that's the only choice to make -- maybe other models would be more water agnostic. The choice we made is not necessarily the best one for going forward.
- MKG -- Broader question is whether we should change how we do torsional fits to one where we use gas phase charges, but use solution phase charges in simulation. With Schauperl, we interpolated between gas and solution phase. For solution phase, we used implicit solvent model. Then we'd scale charges between gas and soln phase during fitting. Optimum scaling ended up being near 0.5.

- Julia Rice -- Polarizable continuum models in QM are not very reliable. We consider them to be approximate, and we usually rely on cancellation of errors to get accurate results. (No literature reference on this, unfortunately)
- MKG -- Do you have a paper that shows this?
- DC -- From my experience, Julia is correct that QM models don't polarize enough. My interpretation of why that is is that, in the early days of QC, the initial folks made the atomic radii too big. They're larger than GB of bonde radii. I think that may explain some of the accuracy issues, and I support Julia's point that a polarizable model necessarily provides accurate solvent effects.
- MKG -- Let me talk about what Schauperl did -- in some way, what he did protects us from that a little bit. If our aq charges are not as polarized as they should be, then the scaling would be shifted.
- DC -- I agree. I was thinking more about trying to do a torsional profile with QC results based on a polarizable continuum model. That would be more sensitive to models like that Julia was talking about. If there was a *systematic* lack of polarization, you could build that into an interpolation parameter.
- Chuan Tian -- I have a more general question -- if we are going to combine protein FF, like Amber, and a small molecule FF like Parsley, are we going to unify training of these FFs in the future?
- DM -- Yes. We're trying to lay the groundwork for that now by porting an AMBER protein FF into SMIRNOFF. We're also trying to upload/recreate QM training data in QCArchive.
- DCer -- The port is going well. Right now we're generating SMARTS for every atom. There are still some problems to solve, for example, gas phase vs solvent phase charges, etc. I'd use solvent density from iPolQ calculations. It would be good to use this data to identify parameters where MM and QM energies diverge heavily.
- JC -- To do this, we'd need cross-coupling terms like in class II force fields. Cross-coupling terms are very cheap to calculate. The limitation here is how many engines support such cross-coupling terms.
- CB -- Another interesting direction might be going in the bespoke direction-- how accurate parameters can be for a given molecule? We could test out how well the FF performs by creating a bespoke set of parameters for the chosen set of molecules.
- DC -- CHARMM community found out that adding 1-3 interactions (Urey-Bradley) forces to otherwise AMBER-like FFs went a long way toward getting coupling between bonds and angles. This is supported in AMBER, and probably other codes. Not clear if this is the best intermediate stage, but it IS available in many codes.
- DM -- That should be possible within our infrastructure
- MKG -- What do people think about using xtal structures for fitting?
- DM -- There's an open crystallographic database, and CSD offered to release some fraction of their data for us. But we haven't prioritized that yet, since we're not sure how to use that data in training.
- MS -- Other issues are that temperature can be weird, and that there are a lot of uncertainties. Our discussion about using them in fitting was to ensure that we just didn't screw them up.

- MKG -- Not clear how relevant the xtal structures are to our needs, since it's not a protein binding site.
- CB -- xtal is a weird phase, since it doesn't represent solution phase or bound state. Especially electrostatic/polarization situation will be very different from other situations that we're interested in.
- JDC -- It would probably take 1 person-year to work on this.
- CB -- I'd like to go back to Mobley's question on what could we do in short-term to improve accuracy. I watched Gilson's talk on the number of LJ parameters, and Lim's talk. The fastest way to improve accuracy is to figure out where we need to work on chemistry and identifying parameters that are too general and splitting them into more specific. Lowering the objective function could be achieved by splitting parameters when it's necessary.
    - Adding more diverse and challenging molecules to training seems to DEGRADE performance on more "normal" molecules, since the same parameter needs to cover more diverse chemistry. So we need to add new parameters, which we've done a few times. What do folks think?
- LPW -- After Parsley release, we spent a few weeks looking at whether we could make some easy parameter changes based on outliers. Hyesu would know more. I recall that, when we were looking at parameters to split, we raised new questions about which molecules to add to train and exercise the new parameters.
- Julia Rice -- Chaya's talk on fragmentation raised the idea that, when we do training, we need to extend the environment a bit more than we used to. So I'd think that we'd like to do more torsion drives to start capturing this.
- JDC -- We're working on adding more torsions all the time. W
- Julia Rice -- We the fragmentation idea, we say that the torsions are coupled. That kind of opens the can of worms.
- JDC -- We do have the capacity to do multidimensional torsion scans, but these are very expensive, as you know. We are also looking at different conformers and trying to get more information from energy gradients between them.
- Chaya Stern -- Doing a combinatorial exploration of fragments is a very good idea.
- CB -- Chaya is looking at immediate vicinity around an immediate functional form, whereas Jessica is forming clusters with a given chemical functionality. Jessica chooses a cluster member at random to get dataset diversity, but I wonder whether there's a lot of variation WITHIN the cluster.
    - One of the things that we might do is using Chaya's approach of evaluating if WBO of those bonds are within the cluster.
- DM -- Maybe WBO of key bonds should be part of fingerprinting/clustering.
- CB -- Once you have the cluster, maybe the cluster members should be interrogated further with WBO.
- Jamshed Anwar -- Regarding accuracy, do we know which terms are most critical. Like, which ones are most limiting? What if we add noise around 5% of the total value to each, and see how much the results of useful workflows change? This would help us identify the most "critical" parameters for downstream accuracy.

- JDC -- This is extremely difficult, as you can’t perturb a single parameter independently. There is a banana shaped manifold that needs to be explored if a single parameter is perturbed. It’s also difficult to identify which data or piece of information is the most useful in improving accuracy.
- DM -- I’d be interested to hear from industry folks -- Of cases where you’ve found problems where calculations are working badly, and you’ve been able to trace it back to the FF, what kinds of terms were the cause?
- CB -- When we are coming up with parmFrosst force field, getting the relative conformer energies and position of minima correct, as a function of torsional parameters.
- DM -- My guess is torsions, like Chris said, but also that it’s dependent on the target -- Like sometimes electrostatics may dominate, but other times torsions or LJ.
- Junmei Wang -- For protein-ligand, torsions probably aren’t that important, since binding pocket will constrain it. For example, docking doesn’t do a ton of work to model torsions.
- MS -- Torsions are not that important for binding, unless they are really important. In most cases, the torsions are probably fine, but I haven’t thought about it as much as other people. I think that charges probably have the largest effect.

Discussion Session 2

- KCJ -- I will present the roadmap’s current state; this lives on Confluence. This is a wishlist of things we would like to do; we hope to have people to do these things over time. Parsley 1.2.0 released May 2020. Sage released later this year (late 2020). The roadmap gives a table of studies we hope to do, with stated priority, expected effort, dependencies, time requirements, status, and who is working on it. For each study, we can see more details by viewing its dedicated page (Simon’s Binary Mixture Data Feasibility study is a good example).
- KCJ -- we have a similar roadmap for infrastructure. Many of the same fields, and priority for features determined based on your feedback.
- KCJ -- what is the most important thing for you? This helps us to prioritize our roadmap. We would like help determining the path we choose to take in getting to our stated destinations. We have recently had discussions about data sharing/hosting, but we are trying to work out best way to make our data available to other scientists. We’re interested in opinions and advice on this topic.
- DM -- all of the QM data is available on QCArchive; you will need to know what datasets were used, so things like getting a single tarball could probably be made easier if that’s desired.

- DM -- Specifically, what science should we devote more attention to? What are we doing well?
- Mark Mackey -- It's all looking very sensible. I have questions on longer term plans. Bleeding edge, people are looking at polarization, charge effects. At what point is OFF going to look at these things rather than working with existing functional forms?
- DM -- We want to get the infrastructure in place for this (like, polarization and off-site charges). Then we want to let the science progress, and see how the fitting performs in terms of accuracy on the same datasets against existing functional form.
- JC -- we would love to be able to ask questions about what new kinds of ff science is able to give improvements; to do that, we have to get ahead of anything people would like to explore. This lets us get these things into the infrastructure so people can start utilizing that. There is a lot of flexibility in the SMIRNOFF spec to use alternative functional forms with OpenMM (at least). Also exploring neural potentials for valence terms, which is more expensive than traditional forms, but cheaper than QM. So, there's a lot we can do, but we want your ideas on what *you* think is important.
- Katharina Meier -- KCJ asked whether we've done anything "well" -- I think you've done a good job over the last 1.5 years. Very happy to see automation of much of the infrastructure, and I believe that Parsley updates will come faster. Now we want to see more comparisons to more widely-used methods. I'm happy to see PL benchmarks. Would love to have more tools to do in-house parameterization and parameter quality checks.
- DM -- Josh is making good headway on that; Josh, do you have any timelines in mind for when people can test that?
- JH -- Not at the moment, maybe in the next month or two
- JW -- We realized in the process of doing it that it covers a lot of other needs. There is a huge quality problem of going from QM to MM space, which is not really easy. There are some things that are hard to perceive (protonation states and other geometry changes in QM geom. optimization). This is an infrastructure goldmine and it will enable a lot of cool science once it's done
- DM -- I had forgotten in my slides to give a 1.2 release ETA; expecting in about 2 weeks to have that out.
- KM -- Bayesian work will allow us to estimate error, which I'm excited to look into.
- Alberto Gobbi -- I'm very impressed, similar to KM. Interested to see more validation data. Regarding gas phase vs. solution phase -- There's no such thing as either of those. We only have explicit solvent, and less dense explicit solvent. What we want is something that will expose gas phase AND solution phase, and transitions in between. Seeing that continue is very exciting to me. It's possible that we want to focus on solution phase initially.
- JC -- key to that is to introduce some polarizability for consistency and accuracy. There is plan to put this into SMIRNOFF spec; doing this consistent experiment for whether polarizability delivers improved accuracy may help us determine if it's worth the computational hit.

- XL -- Agrees with Katharina, good job so far. The FEP quality is important for industry, it's the key so how far can we get with OpenFF. Torsions are also important. I'd also like to see how it compares to other force fields (and DFT?)
- JC -- On the free energy side, one issue is there is great demand to see increased accuracy, but the OpenFF effort is not the free energy effort. There is challenge in getting things into other tools that are not funded by this effort. There are efforts to seed open source efforts to improve the free energy calculation landscape, but we will need to work with package vendors to make progress.
- BS -- There's a lot of dependence on accurate experimental data. There's a lot of QM data around. Is there any attempt to gain access to more accurate exptl data?
- JC -- we've been working with NIST CRC? since the inception of this project; it's difficult to get existing data out of NIST, it's similarly difficult to get new data out of NIST. We are working with the *other* NIST to get density data. We have some in-house experimental capabilities to get binary and ternary densities, etc
- MS -- Right now we have an agreement with NIST, and they plan to release the ThermoML database, which will include their curated error estimates. This is being used for our LJ refits. Simon talked about this in his presentation. We're discovering that this lacks a lot of chemical coverage, since there aren't many incentives for investigators to do measurements of binary mixtures. We can't quite find things like heteroaromatic rings that we see in druglike molecules.
    - NIST Has curated what's out there in the literature, but there are many chemical gaps
    - Things with significant nitrogens or weird configurations won't be there.
- JC -- There is an opportunity here, NIST has been quite forthcoming with us about their error measurements, normally companies have to pay for a license to use that information.
    - They would be willing to make that open for the benefit of pharma; will likely cost some amount of dollars. There is potential, however, if there is considerable value.
- MS -- Timeline uncertain. Their effort is in curating datasets and estimating errors.
- MG -- I used to work there :). They really want to serve industry; if you John and Michael perceive that a letter or something could be helpful, then we can engage them. Will cost money because they have to support themselves.
- MS -- It is congressionally mandated to bring money in. They haven't worked with pharma that much, they collaborate more with bulk chemistry industry, oil industry, and similar
- MG - synthesising novel HG cyclodextrin derivatives, curating novels guest measurements (difficulty with solubility of guest). Want to try and design guests which will be most informative
    - Difficulties with COVID shutdowns.
- DK -- Good impressions for work done so far, it's important for us to find use cases where OpenFF does better than GAFF or another FF. Improving accuracy is a great way to move forward.

- MS - what would be needed in addition to DH work on P-L benchmarks. What beyond showing moderate improvements?
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- DK -- for me I don't think that would work in any case we are working with currently. We would like to know that for some key molecules this works well, so then we can expand usage to other projects.
- DM - David's FEP workflows are now available?
- DH - Yes my workflows are available; please reach out to me if you'd like any assistance getting set up.
- JC - Going to be systems where there is clear accuracy improvement (esp compared to currently available FFs).
    - Transformations very small, but even what we've done appears to be giving some improvement
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- JW -- I think people did a good job communicating to me that ways to run internal benchmark justify continued support; we put out parameter coverage after last meeting; did not indicated quality; does say, if you have a molecule set, would we be able to parameterize it; appear to get about 99% coverage. Were hoping to have conformer energetics with minimization. Will probably make this part of release with toolkit. In the future, will make available things being developed as part of bespoke workflow.
    - Global minimum energy conformer search
    - Other features allowing this kind of work
- DM - general comment - please let us know if there are specific things that would help make a case for extended funding.
- RW -- It would be good to see what would be the roadmap for Y3. It doesn't have to be long, but just to say -- this is what we've done, and we could do all this things with additional funding. If I can show savings because of this, that would make a great case, much better than just asking for additional money (for example, cutting Schrodinger license to cut in half)
- DM - what bar do we need to clear to show that you can cut Shrodinger license cost in half.
- CB - One of the things we've done with Parsley has been a consolidation of existing forcefield. Didn't try to change functional forms much. Sage will be first step forward incorporating WBOs, reparametrizing LJ. Given the timeline for Sage release, is that good timing for making the case for renewal for our partners?
- CB - Any justification has to be made on Parsley FF
- RW - Can also be made on projections. Can we trust you based on what you have achieved so far?
- MG - I would go back to questions about polarizability and off center charges. The extra computational cost is worth it, or is it worth it? Can start asking those questions.
- JC - Would estimates on how rapidly we think we can fulfil regions of your patent space be helpful?
    - We now have enough data that we can make reasonable projections on.

- RW -- The question is how much are we missing from coverage? Now the patentable space is 10^20 molecules. We could never store this information on disks. Is there any glaringly missing from datasets? Any structures missing that might cause problems?
- David Mobley - One of the things we're anecdotally seeing with 1.2 is tests with phosphates. When you have a protonated oxygen around a phosphorous the 1-4 electrostatics can mess with the geometry. Looks like we may have fixed accidentally.
- RW - that's been an issue since before the ark (?)
- DM - two things, small LJ radius on proton - can also correct possibly based on correcting angle parameters?
    - Latest refit may have fixed it.
    - My student found he can fix it by adjusting angles; migh have that covered in training set now.
    - Some of them have two protons(?)
- Hyesu - Looks like after including phosphate group in train the equilibrium angle increased a lot so suggestive it may be caused by angle parameter.
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- DC -- are you looking at tri and di phosphates instead of just monophosphates in this?
- Hyesu - I think we don't have triphosphate; with current preliminary ff we can see if we are better at reproducing; for now, don't have that in training set
- DM - We hadn't gone specifically to fix this issue - got fixed by the auto molecule selection methods, but if we try to fix specifically, can likely do even better.
- KCJ - We have to do a QM benchmarking study for charged molecules as well; on the agenda, but a step that's currently missing
- JC can sell Y3 as if you want tautomer and protonation states, need better charged QM benchmarking
- DM - find a good selection of charged molecules and determine if our FF is doing well for those
- KCJ - If anyone has advice on how to deal with charged species (pitfalls etc) - that would be useful to know about
- JR -- Yes, things to do with anions that we need to worry about. Datasets with diffuse functions because extra electron doesn't cling to the core of the mol. Cations, positively charged species generally less difficult. Even at DFT level need diffuse functions for anions. If not, can get complete garbage. Can suggest some particular basis sets depending on desired level of quality.
- CB - other thing I've found - working with charged small molecules - it increases conformational dependence on electrostatics. High throughput interaction of the monopole?
- JR -- Actually when Bill and I have looked at fitting electrostatic potentials, it's not a formal charge, it's distributed over whole molecule (or a portion of it). It's also true for polar molecules. In a charged species it doesn't just sit in one place as a +1
- AN - Echos a lot of the comments, made good progress on infrastructure, clearly demonstrated that the workflow is able to improve FF, think the promise of what's coming in SAGE exciting, excited to see what WBO brings and LJ params brings. Hopefully by

then can show clear improvements over other FFs. Also want to echo JW comments - wanting workflows for conformer generation, being able to model ligand confs and energies right important and very welcome.

- JC - are there other datasets that you typically compare to see ow well you're doing for conformer energetics; data we may not be including right now as part of our validation?
- AN - Not really. Tends to be a pretty bespoke process, running conf search, running QM, compare different methods on their ability to predict confs and energies.
- JC - So having a detailed way of browsing the deviations from QM may help determine if the ff was doing better.
- AN - Yes.
- AM - Would like to echo comments. Have reproduced similar FEP results to what JC showed. Will share which params is having trouble with w.r.t. FEP calculations.
- DM - you've been doing quite a bit of free energy calculations then?
- AM - Yes. Also working on structure based project. Compare with Schrodinger protocol and performing roughly the same.
- DM - if you run into issues with any that you want to compare with David Hahn, that would be worth connecting on.
- DH - that would be great to share experience.
- DK - Would be good to have follow up with DH.
- DM - Yeah no point in us all learning the same lessons independently of one another. Anybody I've missed?
- KCJ - coming closer to wrap-up discussion.
- DK - Can you remind me where you have the overview (what happens when)? November date?
- DM - don't know if we have firm timeline for things; Simon, did you have thoughts on LJ refits timeline?
- Couple of weeks to a month to conclude scientific study, this should also yield datasets we need for SAGE refits. Should see decent improvements on LJ refit.
- DM - When there's an unresolved scientific question, we have to spend time on it before we can determine firmer timelines for delivery of functionality (what features go where). Science must be mature enough to make it into infrastructure codebases.
- KCJ - will do our best to update the roadmap so we can project on timelines and priorities. This is why we adopted overarching goals / studies as can't accurately predict timelines and such.
- CB - I wonder if a key outcome of this discussion is where we need to be able to make good projections. Given the science we've worked out, such as MG's refits to different LJ choices, SB's choices of mixtures, etc., can come up with clear projections so that before November industry partners can set expectations on improvements in next year.
- DM - think we have enough where science is resolved / close to being and so we can provide information on this near term science and where to go after this.
- KCJ - definitely the plan, and we also realize we need milestones in addition to projections. Projections are doable, but rigid timelines are more challenging.

- JW - with that said - attended OE cup and heard trouble with dealing with uncertainty of when we will make FF releases. One thing starting to do is offer some projection on that front. Showing OFF FFs repo and the table of guestimates of when new FFs will be coming.
- DM - may be able to bump the Sage date earlier.
- YTZ - personally working fair bit with Jeff + Matt on designing system object, suppose we have some gradient w.r.t to system (applied) params, how to back-propogate into FF space.
    - Can be used downstream for fitting to other qm data, condensed phase properties, etc.
    - My personal mission for the next year or so to make it easier to reparameterize downstream.
    - Doing a lot of refits on our won right now to binding free energies. A bit wonky, non-direct. Using latest Parsley releases; can refit them without too much difficulty to binding free energies.
- DM - cool, thanks! As a reminder have talks up online, DC talk now online and he'll give shorter summary tomorrow morning. Tomorrow discussion will focus on some longer term aspects.
- KCJ - Nothing further to add.
- DM - really appreciate so many people taking time to join.
- KCJ - Thank you for bearing with us in this experimental meeting format.
- JC - thanks again for all of the valuable feedback - very important for the coming months ahead.