Vijayan,

While waiting for the latest data updates requested, I'm providing some very brief initial comments from analysis based on the consolidated xls alone. I did not look at the side chain prediction data yet (I know this will have more information regarding energy errors).

--As you know, several of the complex energies are not entirely consistent with experimental data. Although we have made some changes to the ligands compared to the xtal structures, these still appear to be significant differences. What I mean is that prime and amber do not appear to be able to properly rank order the open and closed loops hence pointing to some energy errors -- let alone accurately predict the loop conformations including sampling. This is interesting given the reported capability of prime to not only score but accurately predict long loop conformations.

--In order to explore this point further, I started to estimate by hand some of the receptor energies (without either ligand, i.e., apoenzyme), by either taking one of the "receptor" energies

you reported (including one ligand) and then subtracting the energies of the other ligand and its binding energy. I did this so we could rapidly cross-compare the corresponding receptors, which should be identical in composition and similar in backbone conformation. I did this quickly and by hand but here are the results I got for your info:

-ternary open

prime: -11130

amber 2-12 ns: -6978

-ternary closed

prime: -11745

amber 2-12 ns: -7360

-INT/NAM open

prime: -11890

amber 2-12 ns: -6757

-INT/NAM closed

prime: -11794

amber 2-12 ns: -6787

Relevant comparisons are ternary vs INT/NAM open and ternary vs INT/NAM closed. All these are receptor only -- ligands only refer to the structures from which receptor energies were derived.

Note the significant differences in energy (even for single point, with no MD) for the prime scores

for open loop receptor conformation, with INT/NAM giving a much lower energy. Recall in this regard that prime

scores the open loop complex much lower in energy than the closed loop complex for INT/NAM, despite the fact that the xtal structure

(without NAM) shows the closed loop is favored.

In all but one case the results were almost identical irrespective of the method of calculation; the only exception was INT/NAM closed loop with prime, where I found a discrepancy that is consistent with

the complex energies for the two ligands for some reason being reported as different in that case.

--On the other hand the binding energies are generally consistent with experiments/expectation.

This is understandable.

--I think you should review the side chain prediction results in this context.

Note that it does not appear that side chain prediction is solely responsible.

Whereas we do find that both energy functions predict that the ternary closed loop complex (to which side chain prediction was applied)

has much lower energy than open loop complex (to which side chain prediction was not applied),

we do not see this effect in the case of INT/NAM, where prime predicts that the open loop complex (to which side chain prediction was not applied)

has much lower energy.

We will need to decide whether to focus on binding energy comparisons, or whether further analysis of energy errors will be warranted.

The MM component-wise energies from your script will be helpful in this regard.

Other options are under consideration and can be discussed.

I know you are out of town 2 days this week so I want to settle the plan soon.

Raj