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| **Date** | **Task** | **Remark** |
| July 1st | Setting up and calculating MM/GBSA scores from the **1ns** trajectory   1. Sirt3/INT/NAM - 4FVT rec/loop 2. Sirt3/INT/NAM - 4FVT recp/4BVG loop 3. Sirt3/2’-OAADPr- 4BVH rec/ loop 4. Sirt3/2’-OAADPr- 4BVH recp/3GLS loop 5. Sirt3/2’-OAADPr/Ac-cs2 deac-4FVT rec/loop 6. Sirt3/2’-OAADPr/ Ac-cs2 deac -4FVT rec/4BVG loop 7. 4FVT with NAD+/peptide (PLOS data) 8. **4FVT with NAD+/peptide loop from 4BVG** | **STATUS:**  **I was supposed to complete the system H today and send you the results. But I ran in to some issues while setting up MD (parametrizing NAD+)**  **, I will fix it later today or during the weekend.**  **NB: MM/GBSA and MM/PBSA scores for**  **systems A-G already updated on wiki** |
| July 1st | Extending the MD simulation for **systems**   1. **Sirt3/2’-OAADPr- 4BVH rec/ loop** 2. **Sirt3/2’-OAADPr- 4BVH recp/3GLS loop** 3. **4FVT with NAD+/peptide (Data available PLOS paper)** 4. **4FVT with NAD+/peptide loop from 4BVG** | This pair would be run in parallel  (~ 3days to complete)  System A and B will be schedule to run form tonight ( 11 ns simulation 1 ns already complete) |
| July 4th | Extending the MD simulation for system   1. 4FVT with NAD+/peptide loop from 4BVG   Calculating the MM/GBSA and MM/PBSA scores from the MD trajectory for  **Sirt3/2’-OAADPr- 4BVH rec/ loop**  **Sirt3/2’-OAADPr- 4BVH recp/3GLS loop** |  |
| July 5-7 th | Creating MD average of each structure.  Minimizing the MD averaged structure.  Using Prime MM/GBSA to calculate the energies  **(This is a time consuming task, please let me know if we should schedule it)**  **Total 12 calculations needs to be done**  **NB: Ping has taken only the average snapshot using the last 10 ps of the trajectory** | REASON: The average structure we get from MD will have improper geometries and bond length. They need to be further refined using minimization. Then we need to prepare the system for prime MMGBSA (each system 2-3 hrs) |
| July8th | Miscellaneous task items  3,8 and 10  Mostly methodology write-up work | Compute MM-PBSA and MM/GBSA binding energies from the 12ns MD trajectories  (It will be run in the background) |
| July 11-13th | Miscellaneous task items 1,2  (needs to write a Perl script) |  |
| July 14-15th | Miscellaneous task items  3,8 and 10  Mostly methodology write-up work |  |
| July 18-19th | Miscellaneous task items  4 -9 |  |
| July 20-21st | Work on side chain validation data  Presenting the data  Miscellaneous task 12 |  |

**The following are the tasks for the paper based on the priority and the time of availability of the data.**

1. Ligand interaction diagrams for Sirt3/INT/NAM complex (data available) the co-products from other systems (Sirt3/AADPr closed and open product complex data not available). Also Sirt3 ternary complex (Sirt3/NAD+/peptide with 4FVT and 4BVG loop). For the ternary complex open loop (4FVT) and closed loop (4BVG) MD averages, annotate the interatomic distances **between ribose C-N carbon and acetyl oxygen** ( distance plot). Does this for the ternary complex open loop MD average first since we already have the MD average for the full production simulation. Then report it for the 1 ns simulation MD averages for open and closed loops. Finally, report it for the closed loop MD average from that full production simulation.
2. Also consider showing a time series plot from t=0 (I believe that a continuous time series plot from t=0 to t= 12ns will require rerunning the trajectories from t= 0 to t=12 ns. We now have continuous data for t=2 to t=12 ns and for specified time intervals (2ns time window). In case if we decide to go by “successive times” as suggested in your earlier comment then we would end up with 6 plots for a single simulation ie, t=0-2, t=2-4, t=4-6 ….)
3. Creating probability density distribution plots based on the energies of each frame in the MD simulation. Plot needs to be created for a specified time interval (ie-2-ns window period). Perl script needs to be written to accomplish this task. Sirt3/INT/NAM complex data available. Sirt3/AADPr product and Sirt3/ternary complex data will be computed upon completion of the MD simulation. ( This script is generic so , I listed this task as 1 superseding task 2)
4. Starting structures for simulations (for SI)
5. Fig ------Simulated B factor values for Sirt3/2’-OAADPr product and ternary complex modeled based on open and closed loop conformation. Note Sirt3/INT/NAM Bfac data already completed.
6. Fig ------ Per-residue RMSD values for the cofactor binding loop region calculated with respect to MD averaged structure of Sirt3/2’-OAADPr complex based on open/closed loop conformation. Note Sirt3/INT/NAM rmsd plot already completed.
7. Revise the Table …..MM/GBSA and MM/PBSA conformational energies and binding affinity calculation based on the new simulation results (Sirt3/product closed/open loop) and sirt3/ternary open/closed loop complex. Also revise the earlier MM/GBSA and MM/PBSA table prepared for Sirt3/INT/NAM as suggested by Dr.Raj because NAM data shows insufficient sampling leading to convergence issue.
8. Time series plot of MM/GBSA and MM/PBSA energies for Sirt3/OAADPr and Sirt3/ternary complex closed/open closed/open loop conformation. Also revise the old plot (Sirt3/INT/NAM) with 2 or 3 traces as suggested by Dr.Raj (I guess we can show only 2 traces and not 3 traces).
9. Receptor with INT
10. Receptor with NAM
11. Complex energy ( conformational energy)
12. Identify B factors for any Sir2 simulations available from PL’s data if any to make the plot analogous to that for SIRT3.

(The following will be linked to the MD methodology section)

1. MD simulation method protocol and particular treatment of non-standard residues has to be written.
2. Method for Ligand/NAM placement needs to identified and written for the completeness of supplementary section.
3. Identifying all data on side chain validation carried out by Ping and present the data in a format so as to distinguish sampling/energy errors.
4. Incorporating the references for the computational section and a draft of the methodology has to be written (Will be adapted from the previous PLOS one paper).

**Miscellaneous task (less priority)**

1. Related structure alignment task: align the PLOS INT/NAM MD average with that from the latest INT/NAM simulation (closed loop), check RMSDs, including that of NAM, acetyl-Lys and rest of ADPR. Note energies cannot be compared since PLOS used 4BVG.
2. Make another version of each of these distribution figures wherein the x axis is RMSD with respect to starting structure. Annotate the location (RMSD) of the MD average structure in each case