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| **Date** | **Task** | **Remark** |
| July 7th  | **MD simulation on****4FVT with NAD+/peptide loop from 4BVG****STATUS:****Equilibration MD complete. Launched the 1ns MD simulation today morning.**MM/GBSA values for Equilibration data will be available by tomorrow **NB: Three MD jobs are running concurrently, I expect the 1ns MD to be complete by tomorrow evening. In fact pmcatgpu1 node is running to its maximum load. This causes the delay.**1. Extending the MD simulation (1 ns) for 4FVT with NAD+/peptide loop from 4BVG

 **(Done)** |   |
| July 7th (Afternoon)  | 1. Setting up the system for calculating MM/GBSA scores from the Equilibration data (4FVT with NAD+/peptide loop from 4BVG) – **NAD+ ligand** and **Ac-Pep** as **Ligand**
2. Calculate Prime MM/GBSA scores for 4FVT with NAD+/peptide loop from 4BVG using the last frame of the Equilibration run (**NAD+, and Ac-Pep as Ligand**)
3. Calculate the distance between ribose C-N carbon and acetyl oxygen (distance plot) for **4FVT with NAD+/peptide (**Ping old trajectory PLOS paper) **and 4FVT with NAD+/peptide with 4BVG loop** (Equilibration time data). This is a part of the Miscellaneous Task 1
 | **Background Jobs**  a) 4FVT with coproduct/peptide ( 11 ns simulation) b) 4FVT with 4BVG loop and coproduct/peptide (11 ns simulation)c) 4FVT with NAD+/peptide loop from 4BVG (1 ns simulation)d)MM/GBSA scoring for 4FVT with 4BVG loop and coproduct/peptide**( 2 jobs on cpus and 3 jobs on GPU)** |
| July 8 th  | 1. Extending the MD simulation (12 ns) for **4FVT with NAD+/Ac-peptide using loop from 4BVG**
2. Calculate the MM/GBSA scores from the **1ns run** (4FVT with NAD+/Ac-peptide loop from 4BVG) – **Ac-peptide as Ligand**
3. Calculate the MM/GBSA scores from the **1ns run** (4FVT with NAD+/Ac-peptide using loop from 4BVG) – **NAD+ as Ligand**
4. Calculate Prime MM/GBSA scores using the last frame of the 1ns run (4FVT with NAD+/peptide loop from 4BVG) **Ac-peptide ligand**
5. Calculate Prime MM/GBSA scores using the last frame of the 1ns run (4FVT with NAD+/peptide loop from 4BVG) **NAD+ ligand.**
 | **Background Jobs**  a) 4FVT with coproduct/peptide ( 11 ns simulation) b) 4FVT with 4BVG loop and coproduct/peptide (11 ns simulation) |
| July 9,10th **(Weekend)** **Background Job**4FVT with NAD+/Ac-peptide loop from 4BVG (12 ns MD simulation will be running on GPU | Prepare the setup for running Amber MM/GBSA calculations on 1. **4FVT/2-OAADPR/Deac-peptide using 2-OAADPR as ligand**

 ( 12 ns simulation)1. **4FVT/2-OAADPR/deac-peptide with**

 **4BVG loop using 2-OAADPR as ligand** (12 ns simulation) time interval of 1ns each ( 0-1, 1-2 , 2-3, 3-4 ... 11-12 ns) 12 jobsThe whole setup process should take me about 2 hrs. This will be done on Saturday to ensure that the data will be available by Monday and to save working days**.** | I expect that this run will take about 1 day to complete **(12\* 2 = 24** jobs will be running. We have 24 physical cpus on pmcatgpu1 and I will make sure that my shell script submits one job to each physical CPU)**NB: Similarly a second batch needs to be run using Deacetylated peptide as Ligand**  |
| July 11th  | 1. Calculate the distance between ribose C-N carbon and acetyl oxygen (distance plot) for **4FVT with NAD+/Ac-peptide with 4BVG loop using the 1ns data.** This is a part of the Miscellaneous Task 1
2. Send out a comparative distance plot Sirt3/ternary complex open vs closed for the 1 ns data
3. Prepare the setup for running Amber MM/GBSA calculations on **4FVT/NAD+/Ac-peptide using**

 **Ac-peptide as ligand**(12 ns simulation data)1. Prepare the setup for running Amber MM/GBSA calculations on

 **4FVT/ NAD+/Ac-peptide with**  **4BVG loop**  **using Ac-peptide as ligand** (12 ns simulation) Jobs A and B involves a time interval of 1ns each ( 0-1, 1-2 , 2-3, 3-4 ... 11-12 ns) 12 jobs  ( 12 \* 2 = **24 job**s) |  |
| July 12th  | 1. Interatomic distances between ribose C-N carbon and acetyl oxygen (distance plot) for the 12 ns ternary complex trajectory

**4FVT with NAD+/peptide (PLOS data)** and **4FVT with NAD+/peptide with loop replaced from 4BVG** (**12 ns simulation**) data will be send out ( part of miscellaneous task 11. Prepare the setup files for re-running Amber MM/GBSA calculations on 4FVT with NAD+/peptide loop using the old MD trajectory data (PLOS paper data)

 **Ac-peptide as Ligand ( 12 jobs)** **NAD+ as Ligand ( 12 jobs)**1. Rest of the time will be used for completing miscellaneous tasks 1-3
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| July 13-14 th  | Run Prime MM/GBSA calculations on the average snapshot of the last 10 ps of the 12 ns run for systems  1. 4FVT with co-product/peptide
2. 4FVT with co-product/peptide and 4BVG loop
3. 4FVT with NAD+/peptide loop from 4BVG
4. 4FVT with NAD+/peptide loop from 4BVG
 | **Please Advise**This involves a total of 8 calculations (treating co-factor and peptide as separate ligands) and I expect 2 -3 hrs for each calculation. Please let me know if this has to be listed in the schedule.These values are needed for the completeness of the xls sheet which we prepared (**We may save 2 days if we avoid this**)  |
| July 15th  | Update the xls sheet with all the scores for completeness 1. Equilibration data ( Prime /Amber MM/GBSA scores)
2. 1 ns Data (Prime /Amber MM/GBSA scores)
3. 12 ns Data (Prime /Amber MM/GBSA scores)

Update the excel sheet using all the MM/GBSA score Rest of the time will be used for performing Miscellaneous task items4 -9  |  |
| July 18-20th | Completion of pending task listed under miscellaneous items4 -9  |  |
| July 21-22nd  | Miscellaneous task items10-12  |  |
| July 22 and 25th | Work on side chain validation dataPresenting the dataMiscellaneous task 13 | NB: I anticipate that this task may take more time, as we need to locate all the raw data and then decide on how to present the data accordingly. We do have a crude documentation on this written by Ping. |
| July 26th | Reserve day to complete any pending items |  |

**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). **RC has added a new miscellaneous item under task 1 during previous revision:**

 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.

1. 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 ….)
2. 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)
3. Starting structures for simulations (for SI)
4. 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.
5. 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.
6. 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.
7. 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).
8. Receptor with INT
9. Receptor with NAM
10. Complex energy ( conformational energy)
11. 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. 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).
4. 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. ( **The format needs to be discussed with Dr.Raj**)

**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