1. Recent MD and MM-GBSA calculations include:

SIRT3/Intermediate complex: constructed from SIRT3 from 4FVT, and Intermediate from 4BVG

SIRT3/Intermediate/NAM complex: constructed from 4FVT after converting carba-NAM/ac-ACS2 to Intermediate and NAM

SIRT3/Intermediate/NAM complex: constructed from 4FVT with binding loop replaced with those from 4BVG and converting carba-NAM/ac-ACS2 to Intermediate and NAM

Sir2TM/NAD+/Ac-p53 complex: constructed from 2H4F with an extra step of prime loop refinement of the binding loop

SIRT3/NAD+/ac-CS2/N-methyl-NAM complex: constructed from 4FVT with NAD+ in AB pose and N-methyl-NAM in C pocket.

The MM-PB(GB)SA results every 2ns from the MD trajectories are calculated and averaged values are also obtained. The results are combined with earlier MD studies with different settings are presented in MM-PBGBSA\_data\_summary\_v2.xlsx (available under Dropbox\PMC-AT PLIN)

It is hard to find a good MM-PB(GB)SA/pIC50 correlation as we have at most NAM, isoNAM, N-methyl-NAM binding results available, and averaged values do not have a good correlation. (Need further investigation of the setting of MD and MM-(PB)GBSA calculations.)

1. Correlations between MM-GBSA (Glide XP) scores from Schrodinger with pIC50

The best correlation is found when 4BVH is used as receptor (blue diamond below, 5 C pocket ligands included, including N-methyl-NAM, nicotinic acid 1-oxide, iso-NAM, nicotinic acid, pyridine 1-oxide).

Data points and other plotted are presented in file results\_12-26-2014.xlsx. (also available under Dropbox\PMC-AT PLIN)

The correlation calculations are not completed yet.

As of now, the long MD simulation following with MM-(PB)GBSA calculations approach is still need to tested and appropriate choices need to be made before producing any reliable results. The better option is to use appropriate receptor structures and relative simple docking/rescoring approach.