1. Controlled Annealed Importance Sampling

We'd like to see how, for a fixed computational budget (i.e. the number of MD steps we are allowed to take), how the error in the free energy changes as the number of lambda windows changes with the number of MD steps in every propagation step.

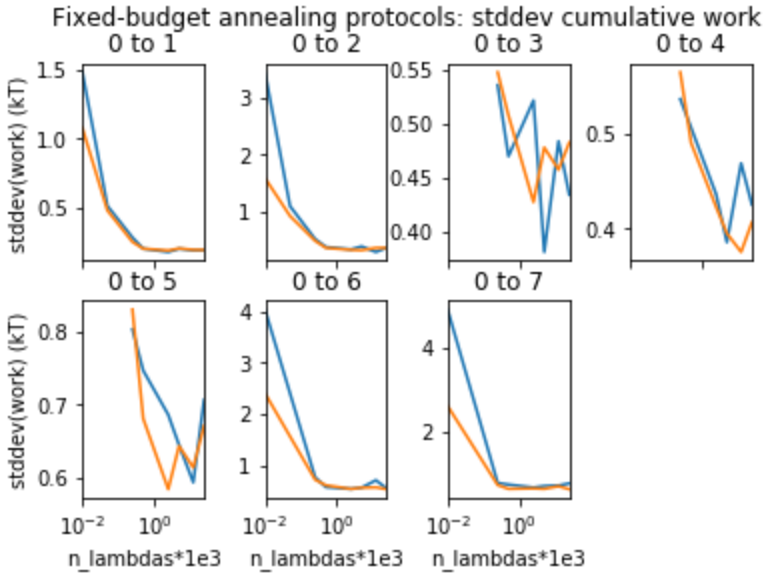
a. Linear Protocol, Fixed-Budget AIS

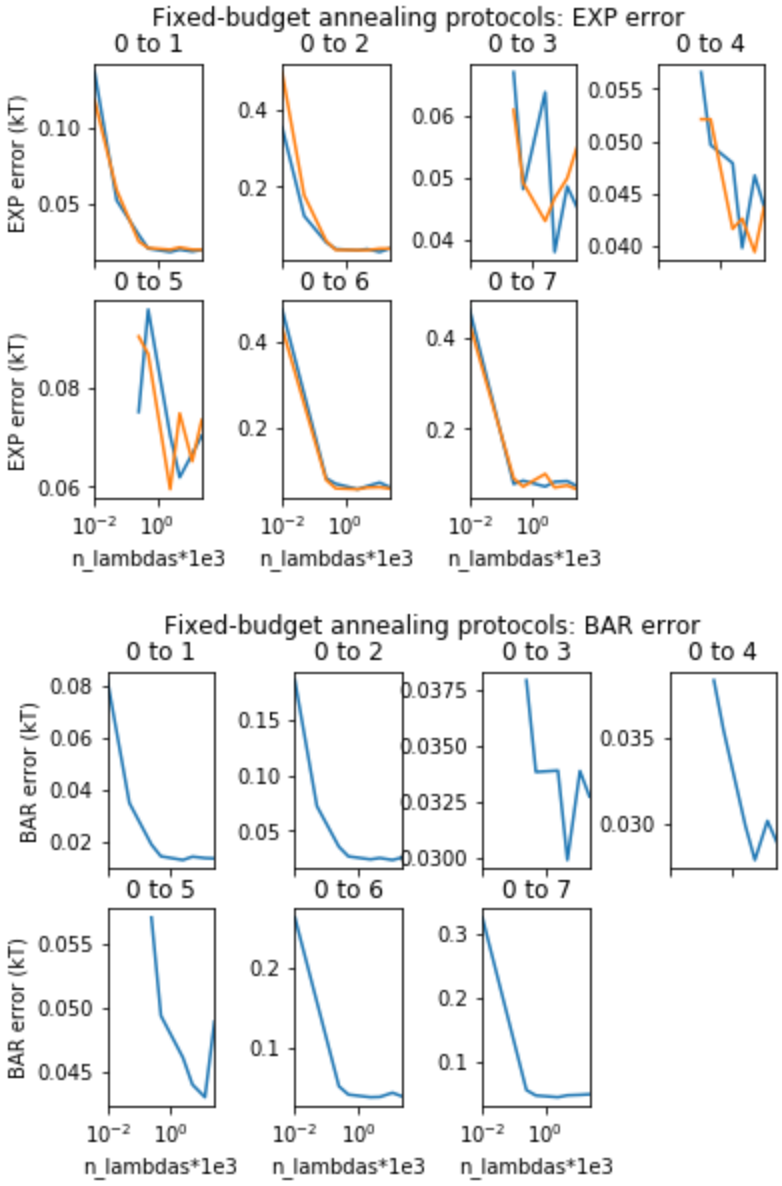
In the following experiment, we fix the total computational budget at 25e3 MD steps and change the number of lambdas on a dense, linear grid over a protocol. The constraint is explicit as follows: lambda_windows * MD_steps_per_window = 25e3. We report on the standard deviation of the forward and reverse work distributions, the error in the forward and reverse EXP error, as well as the BAR error estimator for a set of seven (7) benzene derivative relative alchemical transformations (from benzene) in TIP3p water with a collision rate of 1/ps at 300K. Specifically, the indices of the species are as follows:

index	Name of compound
1	fluorobenzene
2	methylbenzene
3	phenol
4	aniline
5	ethylbenzene
6	anisole
7	1-methylaniline

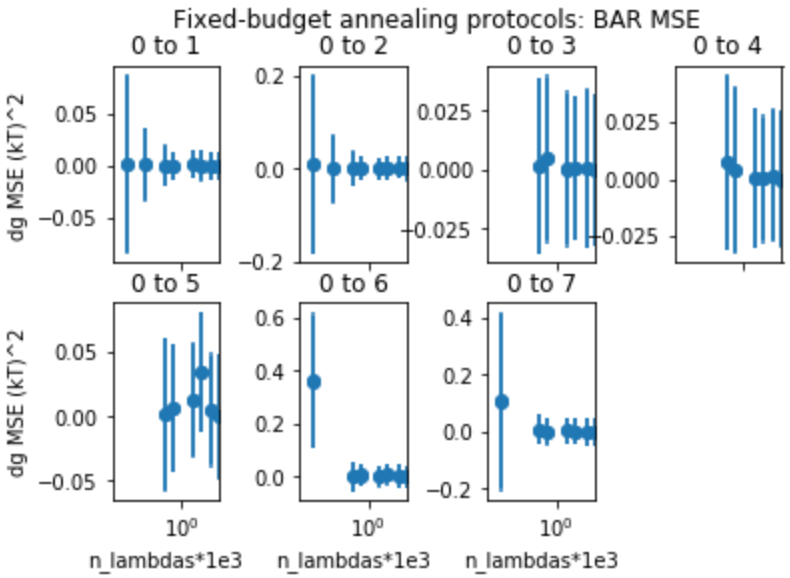
Table 1. Benzene derivatives for solvent leg of free energy calculation from benzene.

Below, we illustrate the deviations in the cumulative work distributions for each of the relative calculations. In the `stddev cumulative work` and `EXP error`, orange and blue represent forward and reverse protocols, respectively.

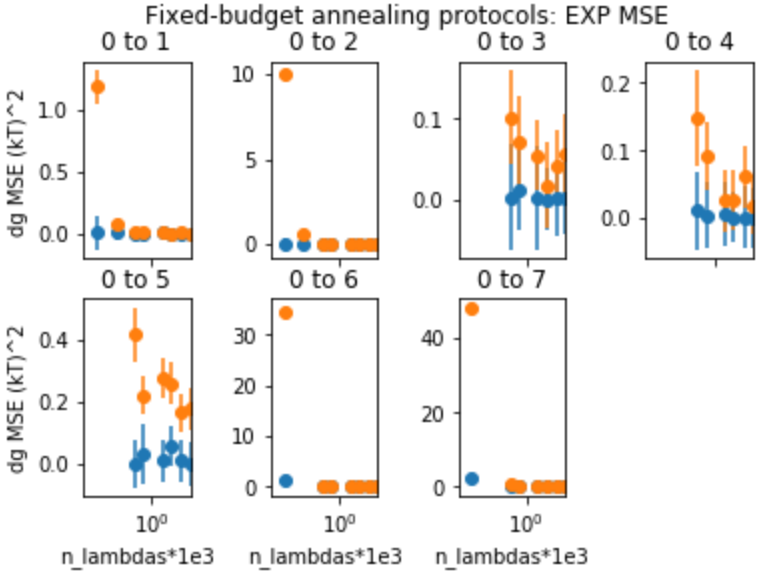




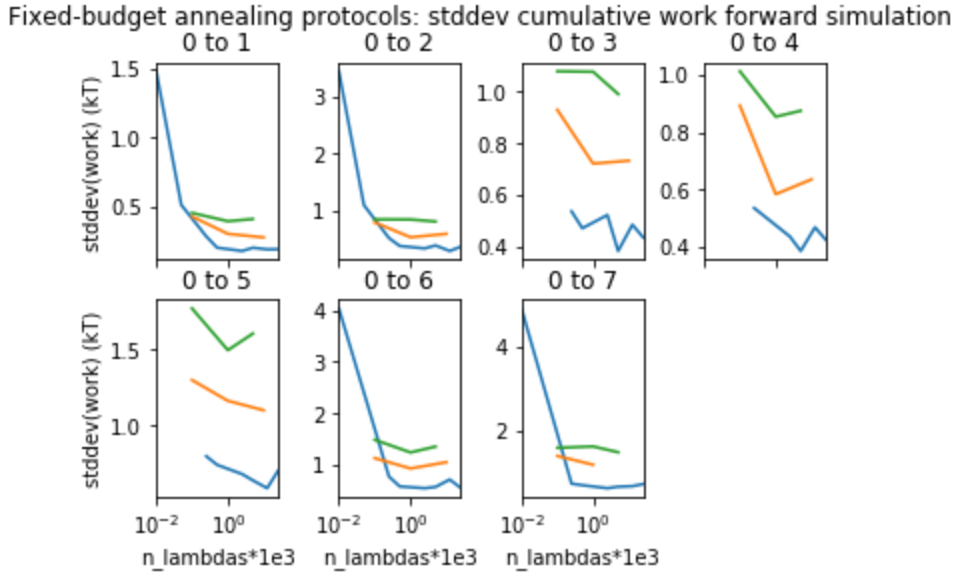
Below depicts the bootstrapped MSE free energies of the BAR estimator for various annealing protocols at fixed computational budget (see above). The error bars denote the standard deviations of the free energy after one thousand bootstrap recalculations of the BAR estimate. BAR estimation seems robust up to ~500 linearly spaced lambda windows (i.e. 500 MD steps with each proposal step).

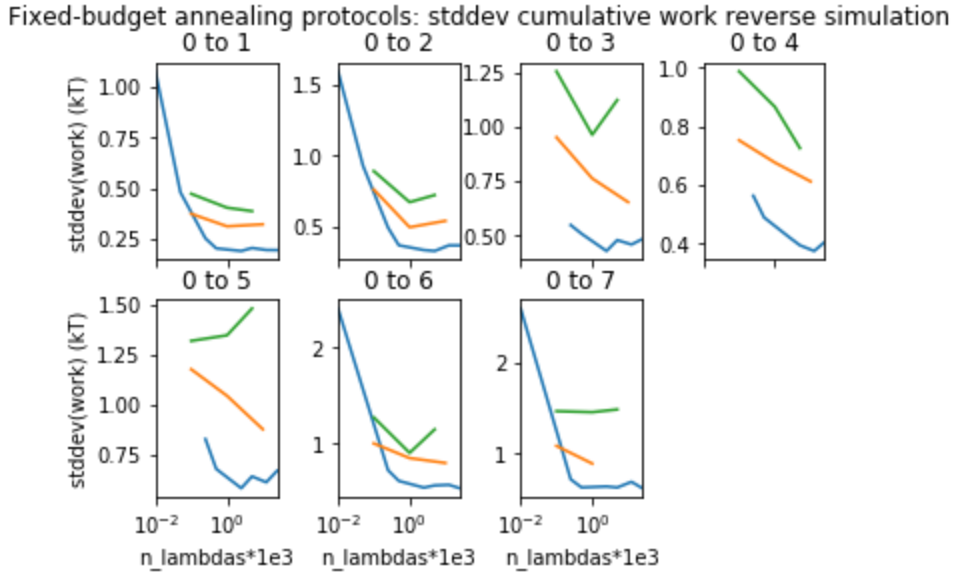


Below depicts the bootstrapped MSE free energies of the EXP estimator for various annealing protocols at fixed computational budget in both the forward and reverse directions. The error bars denote the standard deviations of the free energy after one thousand bootstrap recalculations of the EXP estimate.

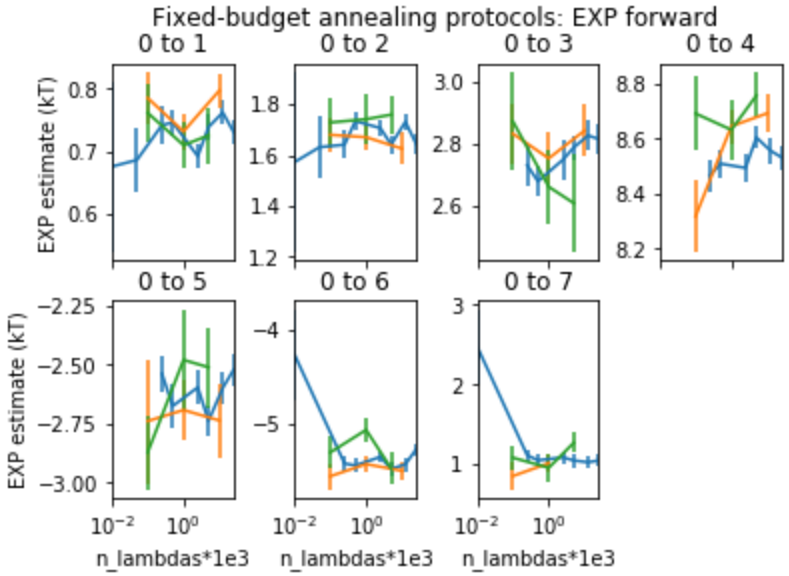


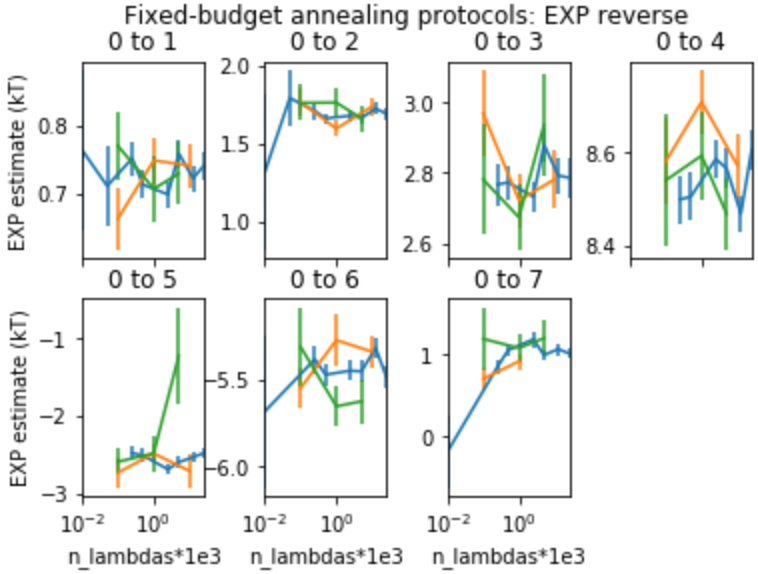
What happens if we look at the forward and reverse work standard deviations for several iso-cost curves?

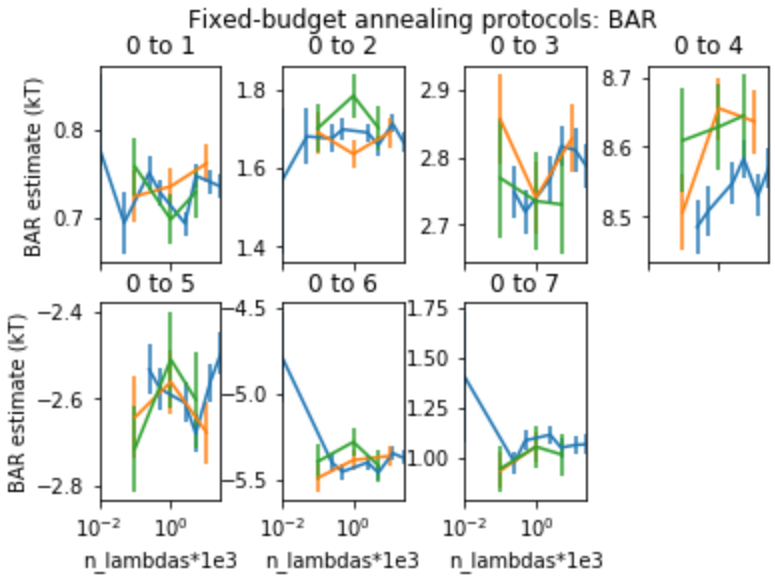




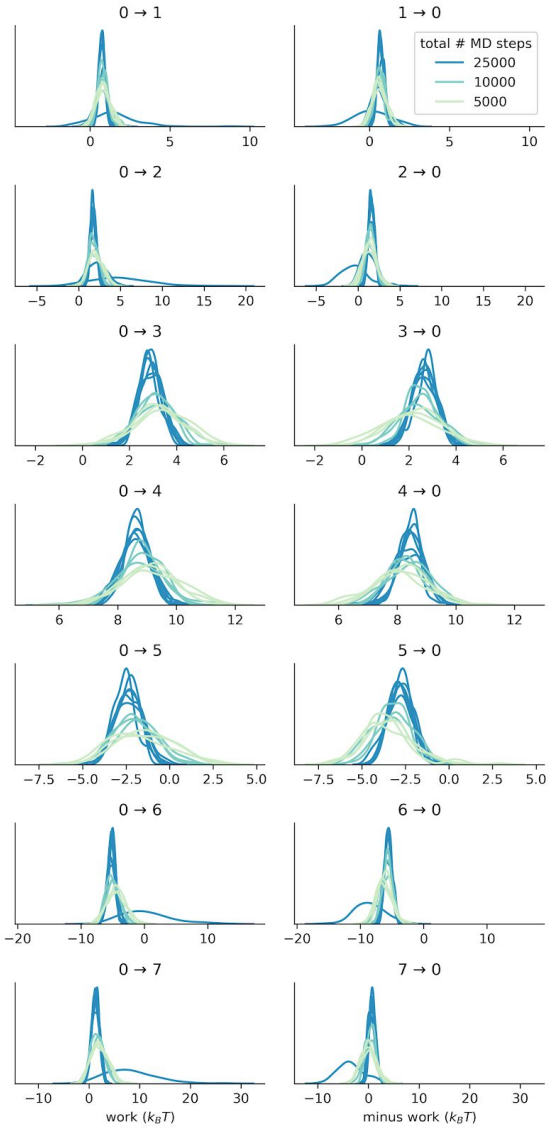
Green, orange, and blue represent iso-cost curves for 5e3, 10e3, and 2.5e4 MD propagation steps.


Fixed-budget annealing protocols: EXP forward
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
EXP estimate (kT)
n_lambdas*1e3

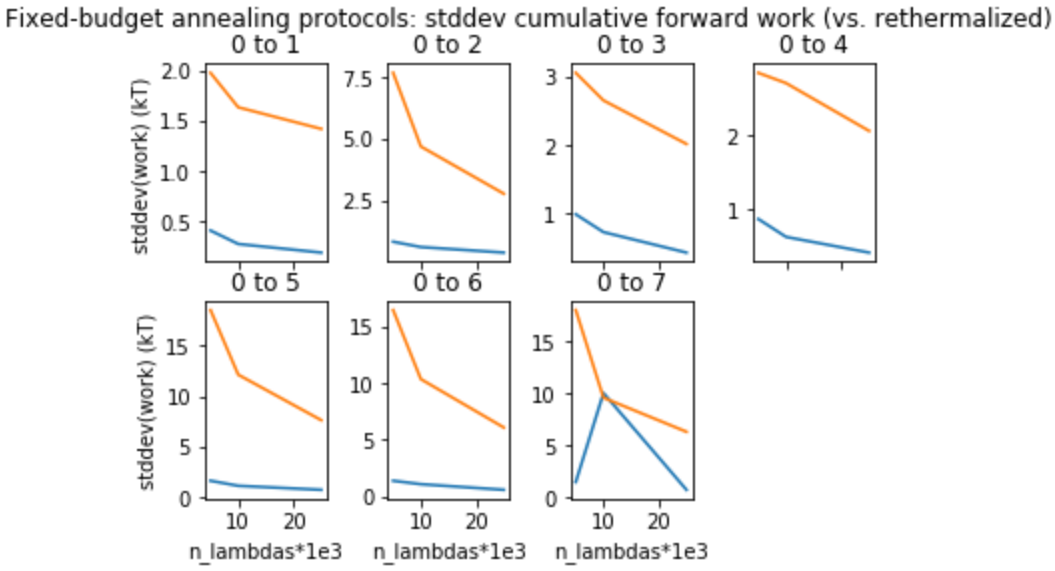

Fixed-budget annealing protocols: EXP reverse
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
EXP estimate (kT)
n_lambdas*1e3

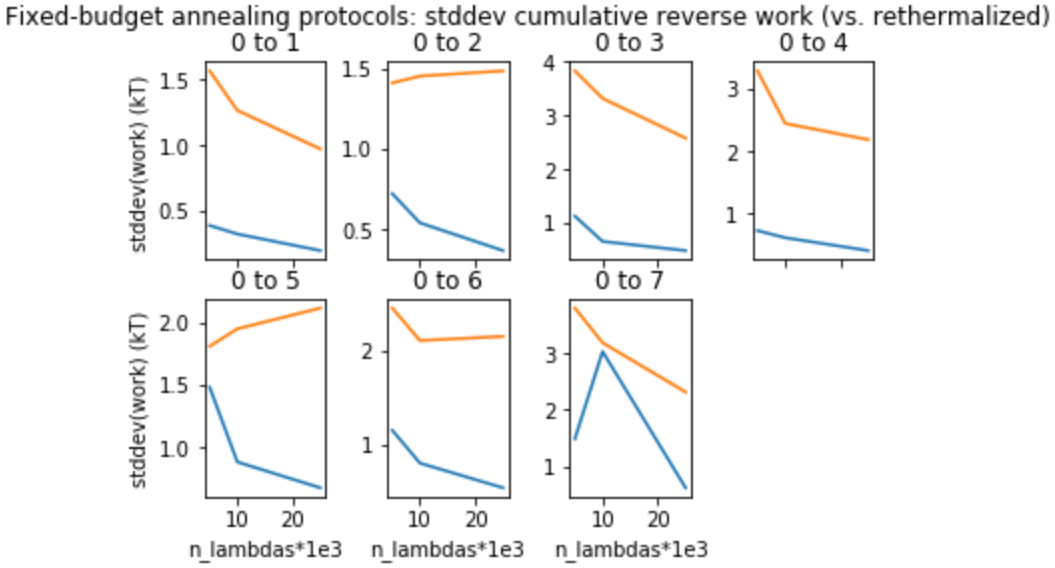


And below, we have the forward and reverse distributions of the isocost curves, courtesy of josh fass.

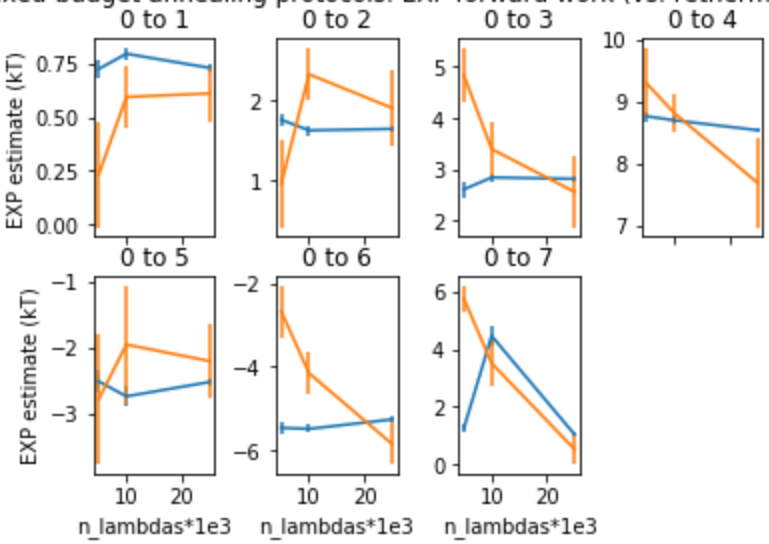

0 → 1
1 → 0
total # MD steps
25000
10000
5000
0 → 2
2 → 0
0 → 3
3 → 0
0 → 4
4 → 0
0 → 5
5 → 0
0 → 6
6 → 0
0 → 7
7 → 0
work (k_BT)
minus work (k_BT)

Below, we look at the work distributions and free energy estimates for the 25k, 10k, and 5k lambda intervals (all with 1MD step proposals) when we do not (blue) and do resample velocities at every step (orange)

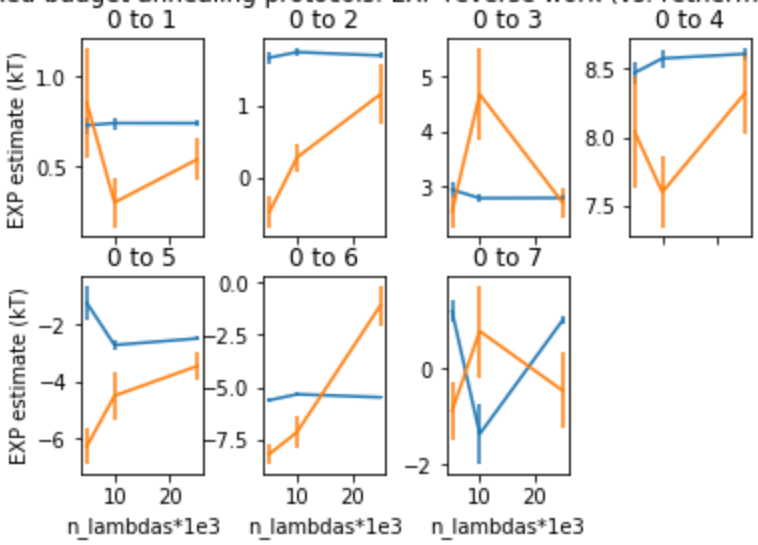


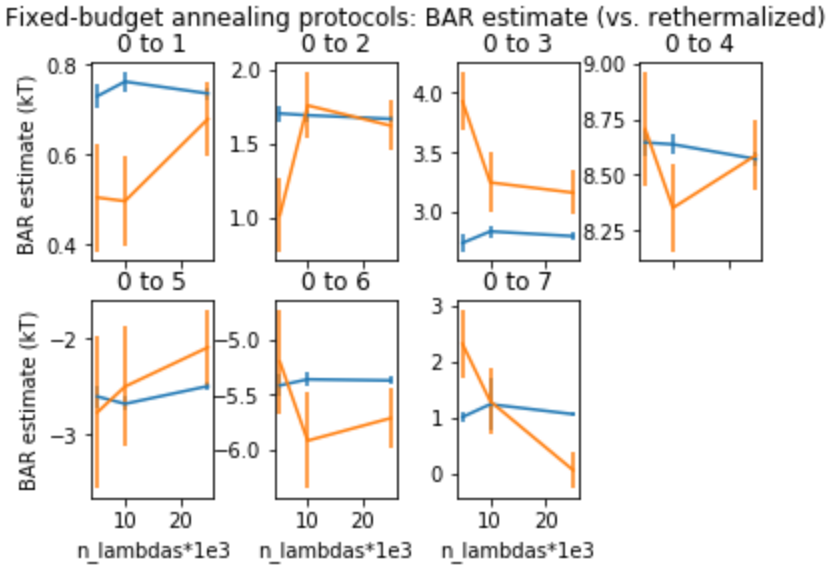


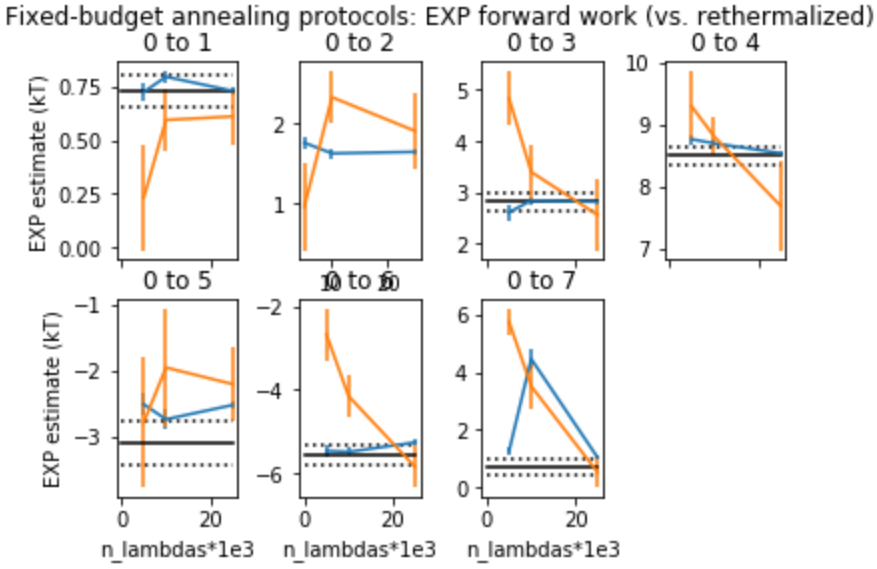
Fixed-budget annealing protocols: EXP forward work (vs. rethermalized)

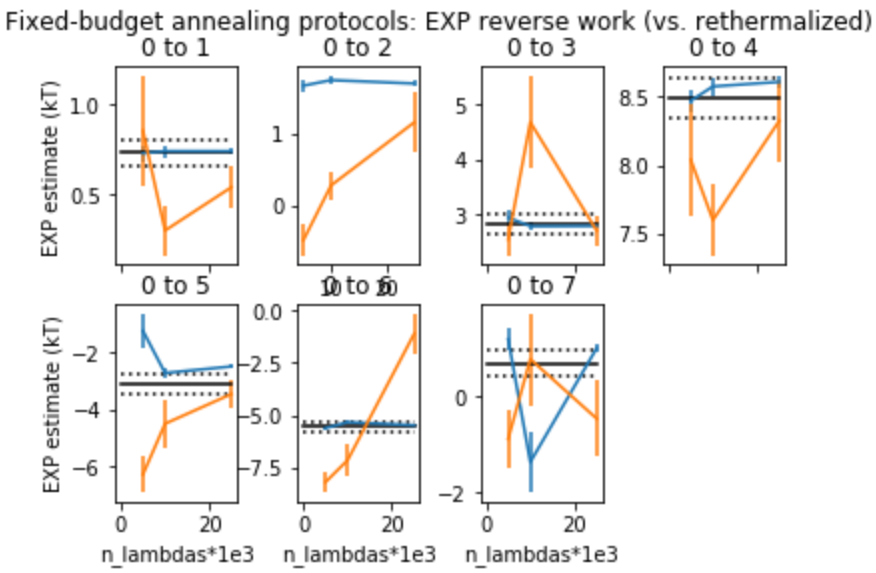


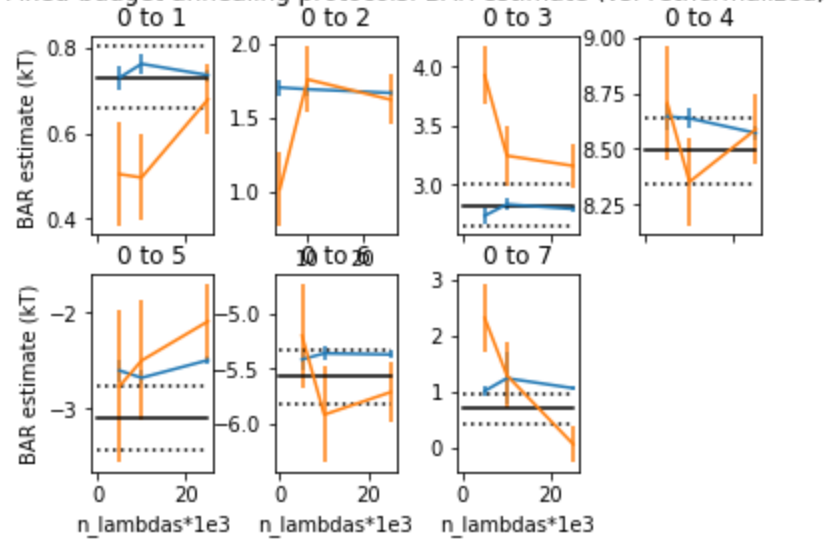
Fixed-budget annealing protocols: EXP reverse work (vs. rethermalized)




Fixed-budget annealing protocols: BAR estimate (vs. rethermalized)
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
BAR estimate (kT)
n_lambdas*1e3


Fixed-budget annealing protocols: EXP forward work (vs. rethermalized)
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
EXP estimate (kT)
n_lambdas*1e3


Fixed-budget annealing protocols: EXP reverse work (vs. rethermalized)
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
EXP estimate (kT)
n_lambdas*1e3


Fixed-budget annealing protocols: BAR estimate (vs. rethermalized)
0 to 1
0 to 2
0 to 3
0 to 4
0 to 5
0 to 6
0 to 7
BAR estimate (kT)
n_lambdas*1e3