Comparison between AMBER20 and OpenMM for ABFE calculations

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We present here a detailed comparison between the AMBER20 and OpenMM 7.7.0 simulation packages, using a series of ABFE calculations of the protein-ligand binding free energy from the 5uf0 crystal structure. This structure contains the second bromodomain of the BRD4 protein bound to the 2-methyl-5-(methylamino)-6-phenylpyridazin-3(2H)-one ligand. Two types of calculations for OpenMM were performed, as well as two types of calculations using AMBER20, which are explained below.

1. OpenMM calculations

In the case of OpenMM, the OpenMMTools 0.21.3 version was used for all free energy calculations. The total simulation time for a single calculation using OpenMM was 426 ns. The two calculation types here differ only in the expressions used for the torsional (or dihedral) restraints. The first expression we will call “periodic”, which uses the following restraining potential:

$$u_p = k_\phi[1+\cos(\phi-\phi_0-\pi)]$$

Here we consider the true minimum at φ_0 , which requires the π factor in the periodic expression above. The second expression we will call “harmonic”, which is the same used for all AMBER free energy calculations:

$$u_h = \frac{k_\phi}{2}(\phi-\phi_0)^2$$

It is easy to show that for small values of (φ-φ_0), for example when large spring constants are used, the two expressions approximate very well:

$$u_p = k_\phi[1+\cos(\phi-\phi_0-\pi)] = k_\phi[1-\cos(\phi-\phi_0)] \sim \frac{k_\phi}{2}(\phi-\phi_0)^2$$

Thus, we do not expect to see significant changes in the results using these two approaches for the torsional restraints.

The OpenMM calculations used 10 windows for the application/removal of restraints, and 23 windows for the decoupling/recoupling of the ligand in the binding site/bulk, which are listed below:

Restraint Lambdas: `[ 0.0000 0.0010 0.0024 0.0056 0.0133 0.0316 0.0750 0.1778 0.4217 1.0000 ]`

Decoupling lambdas: `[ 0.0001 0.02 0.04 0.06 0.08 0.10 0.15 0.20 0.25 0.30 0.40 0.50 0.60 0.70 0.75 0.80 0.85 0.90 0.92 0.94 0.96 0.98 0.9999 ]`

Each free energy component is identified by a letter, according to Table 1:

Table 1: Each free energy component, with its associated letter and the system in which the calculation is performed.

Description	Letter	System
Attachment of receptor conformational restraints	**a**	Complex
Attachment of ligand conformational restraints	**l**	Complex
Attachment of ligand TR restraints	**t**	Complex
Decoupling of ligand charge interactions (binding site)	**e**	Complex
Decoupling of ligand LJ interactions (binding site)	**v**	Complex
Decoupling of ligand charge interactions (bulk)	**f**	Ligand only
Decoupling of ligand LJ interactions (bulk)	**w**	Ligand only
Release of ligand TR restraints	**b**	Ligand only
Release of ligand conformational restraints	**c**	Ligand only
Release of receptor conformational restraints	**r**	Receptor only

Five replicas of each calculation type were performed, and the results are show in the Tables 2 and 3 below:

Table 2: Binding free energy results (in kcal/mol) using the OpenMM package with periodic torsional restraints. The two last columns show the average and the sigma value obtained from the five replicas, and the last row the total absolute binding free energy.

OpenMM with periodic torsional restraints							
Component	Replica					Average	σ
	1	2	3	4	5		
a	14.87	14.64	15.04	14.76	14.82	14.83	0.15
l	7.49	7.30	7.47	7.57	7.69	7.50	0.14
t	4.33	4.47	4.54	4.21	4.53	4.42	0.14
e	-9.02	-8.76	-8.81	-8.73	-8.82	-8.83	0.11
v	12.28	12.00	12.77	12.80	12.46	12.46	0.34
w	0.54	0.53	0.66	0.78	0.73	0.65	0.11
f	11.35	11.29	11.24	11.28	11.19	11.27	0.06
b	-11.69	-11.69	-11.69	-11.69	-11.69	-11.69	0.00
c	-7.77	-7.81	-7.75	-7.77	-7.81	-7.78	0.03
r	-15.31	-15.43	-14.94	-14.87	-14.91	-15.09	0.26
Total:	7.07	6.54	8.53	8.34	8.19	7.73	0.88

Table 3: Same as Table 2, but for the OpenMM package with harmonic torsional restraints.

OpenMM with harmonic torsional restraints							
Component	Replica					Average	σ
	1	2	3	4	5		
a	14.55	14.85	14.78	14.63	14.84	14.73	0.13
l	7.38	7.46	7.46	7.58	7.40	7.46	0.08
t	4.35	4.27	4.46	4.64	4.43	4.43	0.14
e	-9.00	-9.04	-8.73	-8.96	-8.82	-8.91	0.13
v	12.48	11.63	11.43	12.67	12.03	12.05	0.53
w	0.62	0.58	0.57	0.66	0.53	0.59	0.05
f	11.34	11.34	11.26	11.24	11.22	11.28	0.06
b	-11.69	-11.69	-11.69	-11.69	-11.69	-11.69	0.00
c	-7.86	-7.77	-7.86	-7.77	-7.70	-7.79	0.07
r	-15.02	-14.88	-15.20	-15.41	-15.00	-15.10	0.21
Total:	7.15	6.75	6.48	7.59	7.24	7.04	0.43

2. AMBER calculations

The two sets of calculations calculations using AMBER differ only in the decoupling components, using either MBAR or Thermodynamic Integration with Gaussian Quadrature (TI/GQ) to obtain the free energy difference between the coupled and decoupled states of the ligand. The AMBER calculations using TI/GQ took a total of 248.4 ns of simulations, and using MBAR a total of 427.6 ns.

For the restraint and the MBAR decoupling free energy calculations, the same lambda values were used as in the OpenMM case. For the decoupling calculations using TI/GQ, the following lambda values and Gaussian weights were used:

Decoupling lambdas: `[ 0.02544 0.12923 0.29707 0.5 0.70292 0.87076 0.97455 ]`

Associated Gaussian Weights: `[ 0.06474 0.13985 0.19091 0.20897 0.19091 0.13985 0.06474 ]`

The small number of lambdas significantly reduces the computational cost of the TI/GQ calculations when compared to MBAR.

Five calculation replicas for each decoupling protocol were performed, combined with five replicas of the restraint components, which were the same for both methods. The results are show in the Tables 4 and 5 below:

Table 4: Binding free energy results (in kcal/mol) using the AMBER20 package with MBAR for the decoupling windows. The two last columns show the average and the sigma value obtained from the five replicas, and the last row the total absolute binding free energy.

AMBER with MBAR decoupling (23 windows)							
Component	Replica					Average	σ
	1	2	3	4	5		
a	15.24	15.20	14.69	15.03	14.66	14.96	0.28
l	7.81	7.75	7.68	7.91	7.71	7.77	0.09
t	4.54	4.29	4.67	4.61	4.82	4.59	0.20
e	-8.61	-8.66	-8.64	-9.11	-8.90	-8.78	0.22
v	13.21	12.56	12.79	10.45	11.37	12.08	1.14
w	0.85	0.92	0.92	1.13	0.72	0.91	0.15
f	11.46	11.37	11.20	11.29	11.29	11.32	0.10
b	-11.69	-11.69	-11.69	-11.69	-11.69	-11.69	0.00
c	-8.60	-8.47	-8.44	-8.48	-8.23	-8.44	0.13
r	-15.97	-15.91	-15.88	-15.91	-16.30	-15.99	0.17
Total:	8.24	7.36	7.30	5.23	5.45	6.72	1.31

Table 5: Same as Table 4, but for the AMBER20 package with TI/GQ for the decoupling components. The restraint free energies are repeated from Table 4.

AMBER with TI/GQ decoupling (7 windows)							
Component	Replica					Average	σ
	1	2	3	4	5		
a	15.24	15.20	14.69	15.03	14.66	14.96	0.28
l	7.81	7.75	7.68	7.91	7.71	7.77	0.09
t	4.54	4.29	4.67	4.61	4.82	4.59	0.20
e	-8.04	-9.09	-8.38	-8.66	-8.43	-8.52	0.39
v	12.55	13.42	13.08	11.47	12.45	12.59	0.74
w	0.24	0.69	0.03	-0.28	0.80	0.30	0.45
f	11.14	11.53	11.17	11.34	11.27	11.29	0.16
b	-11.69	-11.69	-11.69	-11.69	-11.69	-11.69	0.00
c	-8.60	-8.47	-8.44	-8.48	-8.23	-8.44	0.13
r	-15.97	-15.91	-15.88	-15.91	-16.30	-15.99	0.17
Total:	7.22	7.72	6.93	5.34	7.06	6.85	0.90

3. Comparison between the two methods

Table 6 shows the comparison between the averages of the five replicas from each of the four methods, the two OpenMM and the two AMBER ones. There seems to be good consistency between the two torsional restraint approaches from OpenMM, as well as the two decoupling methods for AMBER. The calculated free energies from the two simulation programs also yield similar results, especially for the decoupling components **e**, **v**, **w** and **f**.

In the case of the restraints, there appears to be a consistent difference between OpenMM and AMBER, the latter producing larger absolute values for the restraint free energies when compared to the former. This difference partially cancels out when the free energies of attachment and release are combined, but not completely, since it is more pronounced in the release components. The reason for this difference could be the replica exchange procedure from OpenMM, which is not applied in the AMBER calculations, but there might be other causes.

Table 6: Comparison between the averages from all four calculation procedures, two for OpenMM and two for AMBER20.

Comparison of averages				
Component	Method			
	OpMM (periodic)	OpMM (harmonic)	AMBER (MBAR)	AMBER (TI/GQ)
a	14.83	14.73	14.96	14.96
l	7.50	7.46	7.77	7.77
t	4.42	4.43	4.59	4.59
e	-8.83	-8.91	-8.78	-8.52
v	12.46	12.05	12.08	12.59
w	0.65	0.59	0.91	0.30
f	11.27	11.28	11.32	11.29
b	-11.69	-11.69	-11.69	-11.69
c	-7.78	-7.79	-8.44	-8.44
r	-15.09	-15.10	-15.99	-15.99
Total:	7.73	7.04	6.72	6.85

4. Conclusion

The results demonstrate that there is good overall consistency between the free energy calculations performed using the two simulation packages tested here. Furthermore, the inclusion of the TI/GQ procedure in the OpenMM calculations could greatly reduce its computational cost, since the AMBER calculations show that it produces values consistent with the MBAR method. Even though a few adjustments could still be made, the OpenMM procedure is now properly validated and ready to be included in the BAT.py software.