## 1. Purpose

The purpose of this document is to compare the one-dimensional Potential of Mean Force (PMF) results using various freely available techniques/tools. Two different datasets are used to compare the PMF results from different tools. The first input dataset is obtained from simulations of Dialanine, which is available from [5]. The second dataset is obtained from umbrella simulations of methane in water using Gromacs 5.1.4 [10].

**2. PMF tools**

There are several opensource tools available to compute the PMF for a given molecular system. The most widely used tools are the Weighted Histogram Analysis Method (WHAM) developed by Alan Grossfield [1] and g\_WHAM available in Gromacs [2]. Over the past years, several variants of WHAM have been developed. The list of the variants is not complete and only few are tested here. Bauer’s WHAM [5,6] is a fast implementation of WHAM written in Rust. It allows the calculation of multidimensional free energy profiles from umbrella sampling simulations. Shirui’s WHAM [7] is another implementation of WHAM in Python. JJgoings WHAM [8] is a binless WHAM implementation in Python. ATB Umbrella Integration [9] calculates the PMF using the technique based on Kaestner and Thiel (2005, J. Chem. Phys.) paper. Table 1. presents a brief overview of few PMF computing tools

Other techniques to compute the PMF are also developed. For example, UWHAM is the unbinned weighted histogram analysis method for multi-state free energy estimation and thermodynamic reweighting developed by researchers from Levy Group. The same group has also developed SWHAM, which solves UWHAM equations stochastically by using the protocols of Generalized-ensemble algorithms [3]. The code for UWHAM and SWAHM is available on Github [4]. These algorithms are not tested here due to lack of time.

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| --- | --- | --- | --- | --- |
| **Tool/Source** | **Test data availability**  **(Yes/No)** | **Ease of Use**  **Easy/Difficult** | **Tested on**  **(Win/Linux/Mac)** | **Algorithm** |
| WHAM [1] | No | Easy | Linux | Kumar et al., J. Comput. Chem.,16, 1995 |
| gmx WHAM [2] | No | Easy | Linux | Jochen et al., J. Chem. Theory Comp.,16, 2010 |
| Bauer’s WHAM [5,6] | Yes | Easy | Mac | Roux, B., CPC, 91(1), 275-282, 2005  Spoel, D. et al. JCTC, 6(12), 3713-3720,2010 |
| ATB-Umbrella Integration [9] | Yes | Easy | Linux/Mac | Kaestner and Thiel J. Chem. Phys., 2005 |
| Shirui’s Umbrella Integration [7] | No | Easy | Linux/Mac | Kaestner and Thiel J. Chem. Phys., 2005 |
| Jjoing’s WHAM [8] | No | Code is incompatible with the used input data. | Linux/Mac | No information |
| UWHAM/SWHAM [3,4] | Yes | ? | Not tested | Zhiqiang et al., *J. Chem. Phys.*, 136, 2012  Zhang et al., J. Phys. Chem. Lett., 6, 2015 |

**3. Results**

The PMF results are computed for two datasets using tools [1], [2], [5], [7], [8] and [9]. However, the results obtained from [7] are excluded as it is not close to any of the other results. The results for both the data sets are presented in Figure 1 a-b.

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| --- | --- |
| Chart, line chart  Description automatically generated  Figure 1a: PMF of Dialanine | Chart, line chart, histogram  Description automatically generated  Figure 1b: PMF of CH4 |

First dataset: The PMF plots from [1] and [5] agree well which is obvious as they both use the same algorithm. The results from [7] differ with [1] and [5] which could be either due to the binless WHAM (aka multistate Bennett acceptance ratio / MBAR) technique used in [7] or units which are not clearly described in [7]. The results from [8] could not be computed as the code needs modification to read the metadata format. The results from [2] and [9] don’t agree with PMF plots from [1], [5]. This may be a unit conversion problem which may need more careful inspection into the codes. Table 2 presents the units used in different tools.

Second dataset: The PMF results for CH4 in water all have a similar trend but with slight differences. The PMF of [2] and [9] are close enough compared to [1], [5].

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| --- | --- | --- | --- |
| **Tool** | **Distance/Angle** | **Force** | **Energy** |
| WHAM [1] | Angstrom  or  Degree | kcal/mol-A2  or  kcal/mol-deg2 | kcal |
| gmx WHAM [2] | Nanometer  or Degree  (pull-coord1-init) | kcal/mol-nm2  or kcal/mol-rad2  (pull-coord1-k) | kJ (default), but can be changed to kCal using -unit option |
| Bauer’s WHAM [5,6] | Not mentioned. May be same as Alan’s WHAM | Not mentioned. May be same as Alan’s WHAM | Not mentioned. May be same as Alan’s WHAM |
| ATB-Umbrella Integration [9] | Distance (A or nm) | kJ/mol distance^2 | kJ/mol |
| Shirui’s Umbrella Integration [7] | Not mentioned | Not mentioned | Not mentioned |
| Jjoing’s WHAM [8] | Not mentioned | Not mentioned | Not mentioned |
| UWHAM/SWHAM [3,4] | Not tested | Not tested | Not tested |

**4. References**

1. <http://membrane.urmc.rochester.edu/?page_id=126>
2. <https://manual.gromacs.org/documentation/2020/onlinehelp/gmx-wham.html>
3. <https://ronlevygroup.cst.temple.edu/software/UWHAM_and_SWHAM_webpage/index.html>
4. <https://github.com/pittbin/UWHAM-and-SWHAM>
5. <https://github.com/danijoo/WHAM>
6. [*https://doi.org/10.5281/zenodo.1488597*](https://doi.org/10.5281/zenodo.1488597)
7. <https://github.com/Shirui816/UmbrellaIntegrate.py>
8. <https://github.com/jjgoings/wham>
9. <https://github.com/ATB-UQ/umbrella_integration>
10. <https://lab.miletic.net/en/tutorials/gromacs/5-umbrella>

**5. Appendix**

The following scripts are used to produce the PMF results for the two datasets.

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| --- | --- |
| **Script** | **Purpose** |
| twoCol2GmxPDO.sh | Converts 1st dataset (two columns format) to Gromacs PDO data format |
| twoCol2ATB-UI.sh | Converts 1st dataset (two columns format) to ATB-UI data formats |
| Gmx2WHAMAndUI.sh | Converts 2nd dataset (gromacs format) to ALAN’s WHAM and ATB-UI data formats |
| generatePMF-1.sh | Generates the PMF results for the 1st dataset (CH4) |
| generatePMF-2.sh | Generates the PMF results for the 2nd dataset (Aline) |

NOTES:

* gmx WHAM [2] required converting the data to PDO format. A bash script (twoCol2GmxPDO.sh) is implemented to do the conversion.
* SHIRUI WHAM [7] only works from directory where the metadata is located.
* ATB Umbrella-Integration requires data conversion which is possible by adapting the example bash script provided along with the source code. The code runs with python 2.7 and requires little changes to work with higher versions.