MULE Tutorial v0.2 beta

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Reference: Fu H., Chen H, Wang X, et al. Finding an Optimal Pathway on a Multidimensional Free-Energy Landscape. J. Chem. Inf. Model. 2020.

MUltidimensional Least Energy pathway (MULE) is an easy-to-use toolkit that can find optimal pathway connecting two points (states) on an energy surface. Compared with other codes, MULE has advantages of:

• Finding the true optimal pathway without approximation
• Dealing with periodic collective variables
• Handing energy surface of arbitrary dimensions
• Flexible restraints during exploration

Below, we will show how to find the least energy pathway characterizing the isomerization of alanine dipeptide on a 2D free-energy surface, while MULE can handle any dimensional energy surface in principle.

In folder `example1`, one can run

```
./mule.exe config
```

in powershell in Windows (or something similar in terminal in Linux and Mac OS). Then a `.traj` file describing the optimal pathway and a `.energy` file showing the corresponding energy change will be generated.

`config` is in classical `ini` format, below is the file corresponding the this example.

```
[mule]
directory       =   nanma_ref.pmf
initial         =    -156, 160
end             =      78, -58
pbc             =       1, 1
```

The first line is required in all the MULE configuration files and has no specific meaning. The second line shows the path of the energy surface file. If an NAMD `pmf` file is provided, no additional information about lowerboundary, upperboundary, etc. is needed. The third and forth lines are the coordinates of initial and end points, while the last line denotes whether the corresponding dimension is periodic or not. The result (pathway) is shown in Figure 1.

The pathway seems very interesting since both of the dimensions are periodic. Starting from (-156, 160), the system goes through the upperboundary of psi, reaching

(-156, -180). Then it moves to (-180, -46) and goes through the lowerboundary of phi, finally arriving at (78, -58).

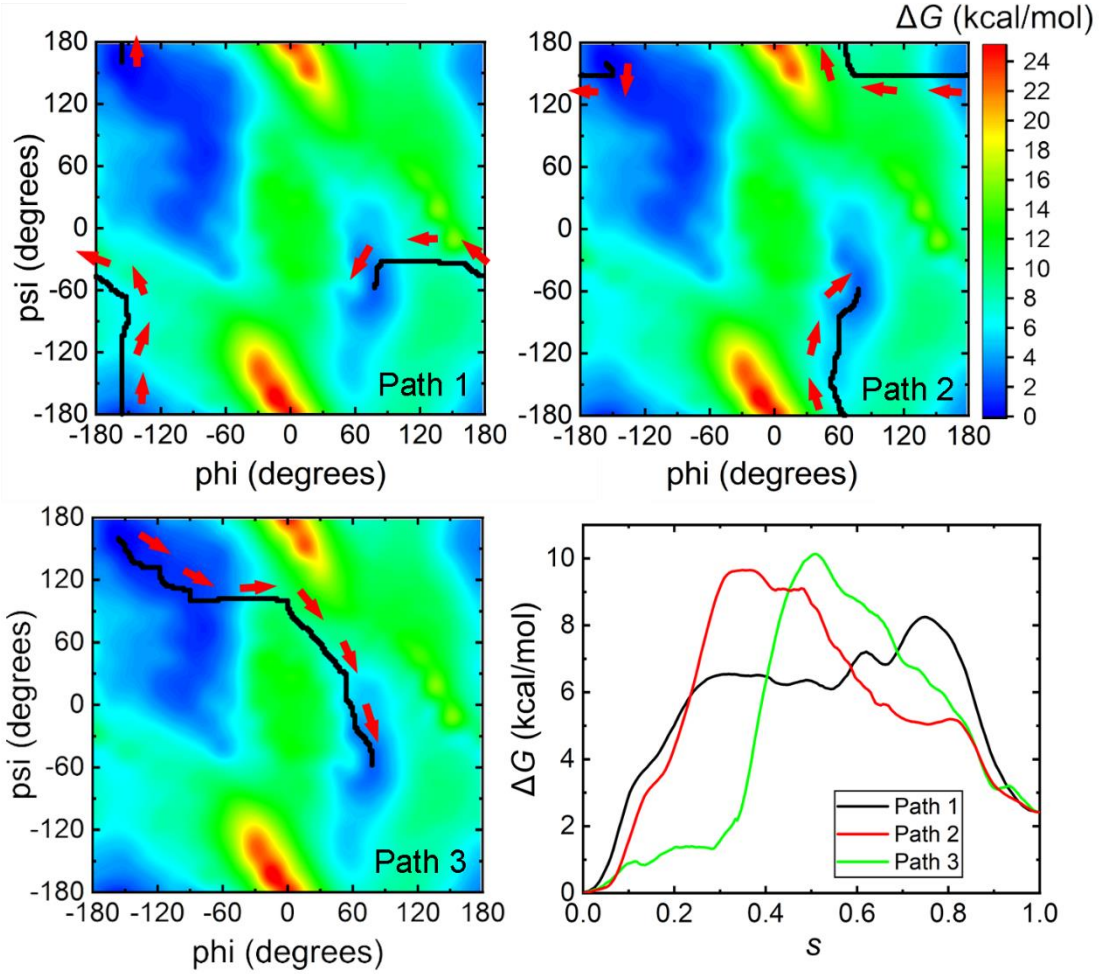

Figure 1. Three pathways characterizing the isomerization of alanine dipeptide.

Sometimes there are more than one equally likely pathways. or sometimes one may want to find the second optimal pathway. Anyway, one can achieve it by adding restraints using MULE. See `config` in folder `example2`.

```
[mule]
directory       =   nanma_ref.pmf
initial         =   -156, 160
end             =    78, -58
lowerboundary   =   -180, -180
upperboundary   =    178, 178
width           =     2, 2
pbc             =    1, 1
writeExploredPoints   =   1
target          =    136, -32, -0.1, -0.1
```

The first to the forth lines are the same as those in example1. In this case, a plain (dat format) `pmf` file is provided, making identifying lowerboundary, upperboundary

and width necessary. Option `writeExploredPoints` generate a `.explored` file, which records all the points explored during the pathway finding process. This option may be useful for advanced users in setting restraints. The last line defines a restraint,

$$E = -\frac{(\text{phi} - 136)}{\text{width}_{\text{phi}}} \times 0.1 - \frac{(\text{psi} + 32)}{\text{width}_{\text{psi}}} \times 0.1$$

which makes the algorithm tend to explore points away from (136, -32), that is, the transition state of the path 1. This restraint only affects the exploration and does not impact the true energy corresponding to the point (136, -32) in the result. It should be pointed out that a more complex restraint can be defined, for example,

```
target = 0, 100, 0.1, 0.1, 78, -58, 0.1, 0.1
```

defines a restraint

$$E = \frac{(\text{phi} - 0)}{\text{width}_{\text{phi}}} \times 0.1 + \frac{(\text{psi} - 100)}{\text{width}_{\text{psi}}} \times 0.1 + \frac{(\text{phi} - 78)}{\text{width}_{\text{phi}}} \times 0.1 + \frac{(\text{psi} + 58)}{\text{width}_{\text{psi}}} \times 0.1$$

After executing

```
./mule.exe config
```

One can identify the path 2 in Figure 1.

There is, obviously, a more intuitive pathway connecting (-156, 160) and (78, -58), one may want to find it out and compared it with the path 1 and 2. One can find it by `example3`.

```
[mule]
directory       =   nanma_ref.pmf
initial         =   -156, 160
end             =    78, -58
lowerboundary   =   -180, -180
upperboundary   =    178, 178
width           =     2, 2
pbc             =    1, 1
writeExploredPoints   =   1
target          =    0, 100, 0.1, 0.1
```

The config line defines a restraint,

$$E = \frac{(\text{phi} - 0)}{\text{width}_{\text{phi}}} \times 0.1 + \frac{(\text{psi} - 100)}{\text{width}_{\text{psi}}} \times 0.1$$

which makes the system tend to explore (0, 100).

After executing

```
./mule.exe config
```

one may get the intuitive pathway, namely the path 3 in Figure 1. One can then compare the free-energy barrier corresponding the three pathways by plotting the data

in `.energy` files.