Supporting Information

for

Simulating Protein Mediated Hydrolysis of ATP and Other Nucleoside Triphosphates by Combining QM/MM Molecular Dynamics with Advances in Metadynamics

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An input example (only metadynamics part) for MBMetaD simulations with PLUMED. The additionally required parameters for MBMetaD are denoted in blue with a brief explanation in red. A detailed user manual is available upon request at gavoth@uchicago.edu. The other parameters are required by a regular MetaD simulation (i.e. WTMetaD), and the most recent user manual of PLUMED can be found at https://plumed.github.io/doc-v2.3/user-doc/html/index.html.

```
n: METAD ...
   ARG=CV
   SIGMA=0.050
   HEIGHT=1.0
   PACE=40
   BIASFACTOR=5
   STORE_GRIDS
   TEMP=310
   GRID_NOSPLINE
   GRID_WSTRIDE=80
   GRID_WFILE=3cv-1.dat
   GRID_MIN=0.5
   GRID_MAX=2.5
   GRID_BIN=200
   FILE=HILLS
   BIASFACTOR=6.0
   # Calling MBMetaD functional
   USE_DOMAINS
   # The range that MBMetaD fills is updated along the simulation
   USE_ADAPTIVE_DOMAINS
   # The region is checked for a new definition every finite number of steps (i.e. 40)
   ADAPTIVE_DOMAINS_STRIDE=40
   # The maximum bias energy is referred to the minimum/transition state in CV space
   ADAPTIVE_DOMAINS_REFERENCE=minimum
   # The maximum bias energy value (i.e. 6 kcal/mol)
   ADAPTIVE_DOMAINS_ENERGY_OFFSET=6
   # The region is redefined if the energy at the boundary has changed by (i.e. 0.154 kcal/mol)
   ADAPTIVE_DOMAINS_ENERGY_INCREMENT=0.154
   # The numerical integrals will add hills once every finite number of points (i.e. 3.5) rather than
every single point.
   ADAPTIVE_DOMAINS_DOWNSAMPLING=3.5
   # The histogram of the CV values in MBMetaD simulation
   ADAPTIVE_DOMAINS_HISTOGRAM_WFILE=3cv_histo-1
... n:
```

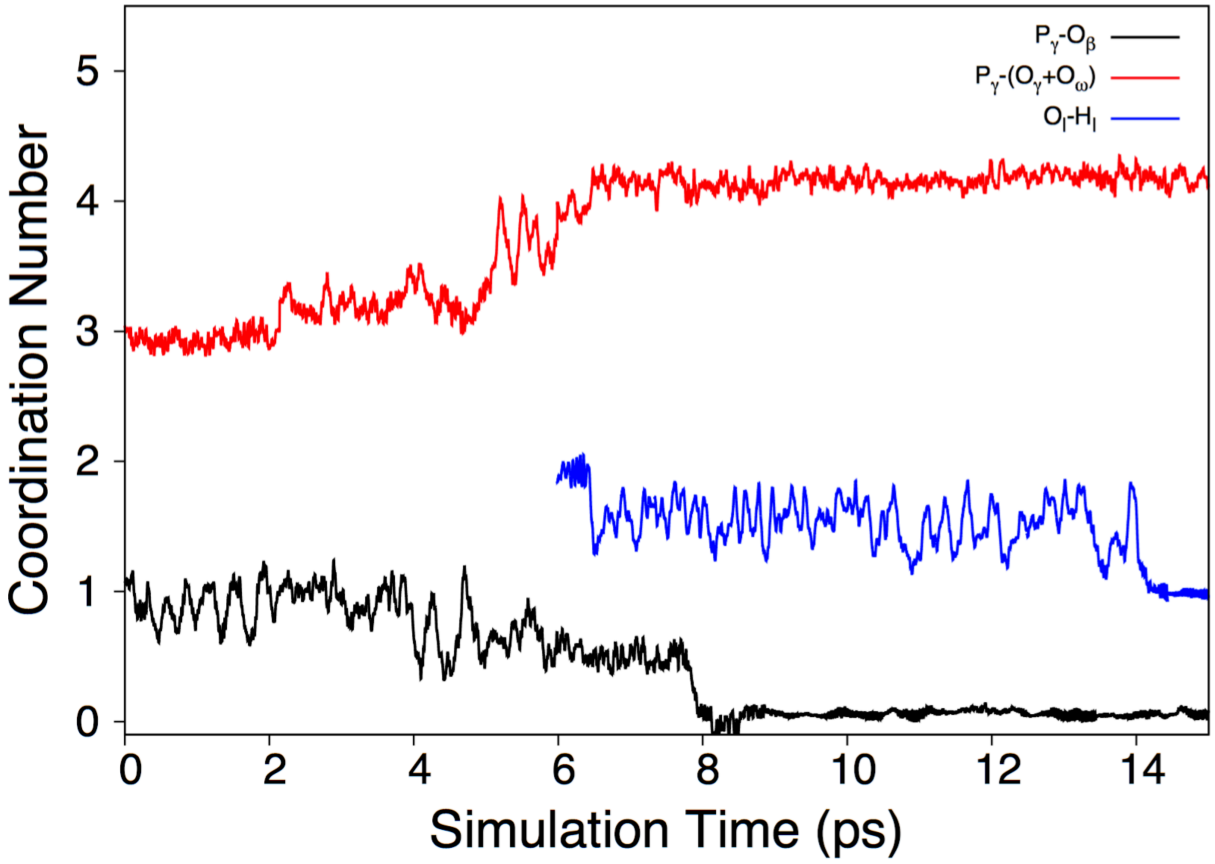

Figure S1. The evolution of the CVs for the testing trajectory of hydrolysis in F-Actin. The MBMetaD biasing CV (blue) is applied after the formation of $[H_2O\text{--}PO_3]^-$ intermediate.

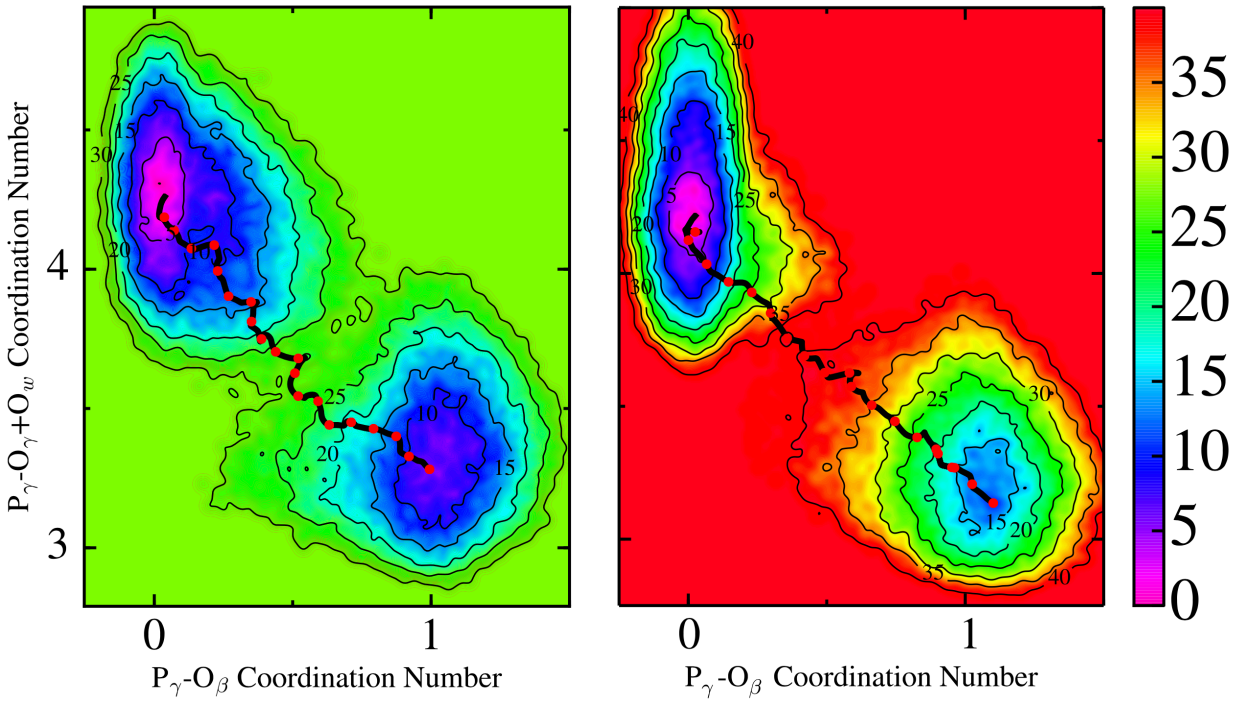

Figure S2. The ATP hydrolysis in F- (left) and G-actin (right) PMF from non-tempered MetaD simulations as described in the main text (data from *J. Am. Chem. Soc.* **2014**, 136, 13053−13058). The unit of energy is kcal/mol.

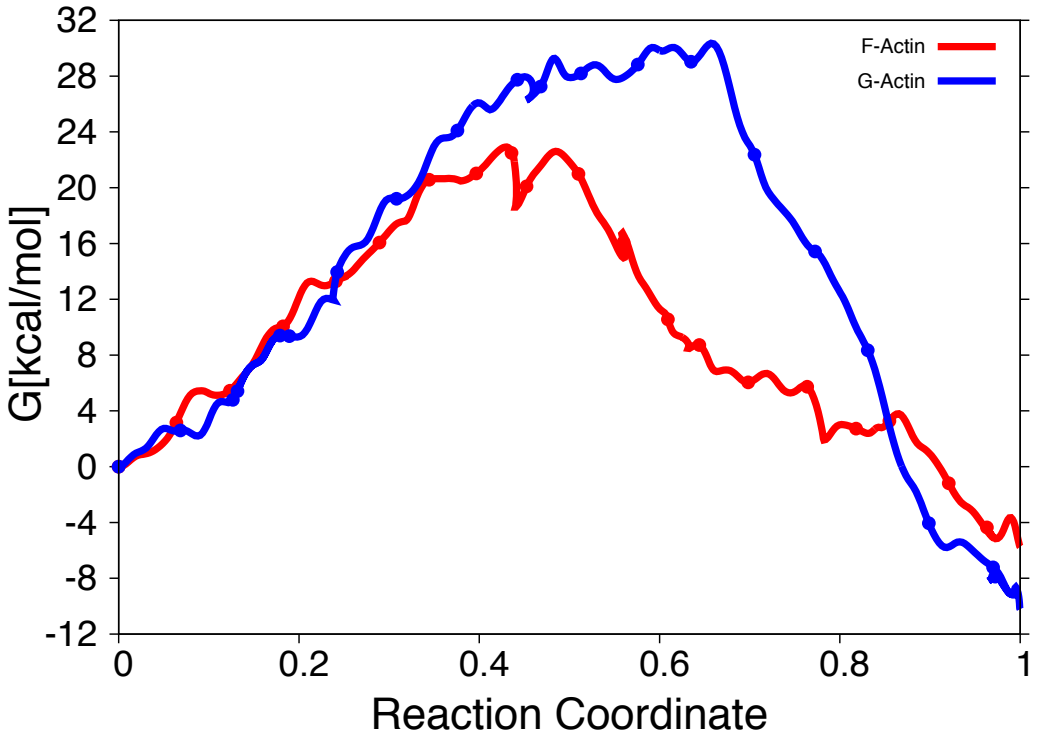

Figure S3. The minimum free energy path from the 2D free energy surfaces (Fig. S2) for ATP hydrolysis in F- and G-actin. The reaction coordinate represents the hydrolysis reaction progress along the minimum free energy path, i.e. "0" being ATP and "1" being ADP + Pi. (data from *J. Am. Chem. Soc.* **2014**, 136, 13053−13058). The unit of energy is kcal/mol.