# Quantum mechanical free energy calculations using path integral molecular dynamics

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# Background

1. Free energy calculations
   - Free energy calculations are an integral part of chemistry
     - Provide insight into equilibrium structures, reaction rates, etc.
   - Helmholtz free energy directly related to partition function:

$$A = -k_B T \ln(Z)$$

   - In principle, easy to calculate. In practice, $Z$ is very difficult
2. Nuclear quantum effects
   - Important in molecular dynamics simulations[1]
   - Use Feynman path integrals

**What if we want to do free energy calculations on systems with non-negligible nuclear quantum effects?**

[1] M. Ceriotti, et al., Phys. Rev. Lett. **103**, 030603 (2009), M. Ceriotti, et al., Proc. Natl. Acad. Sci. **110**, 15591–15596 (2013).

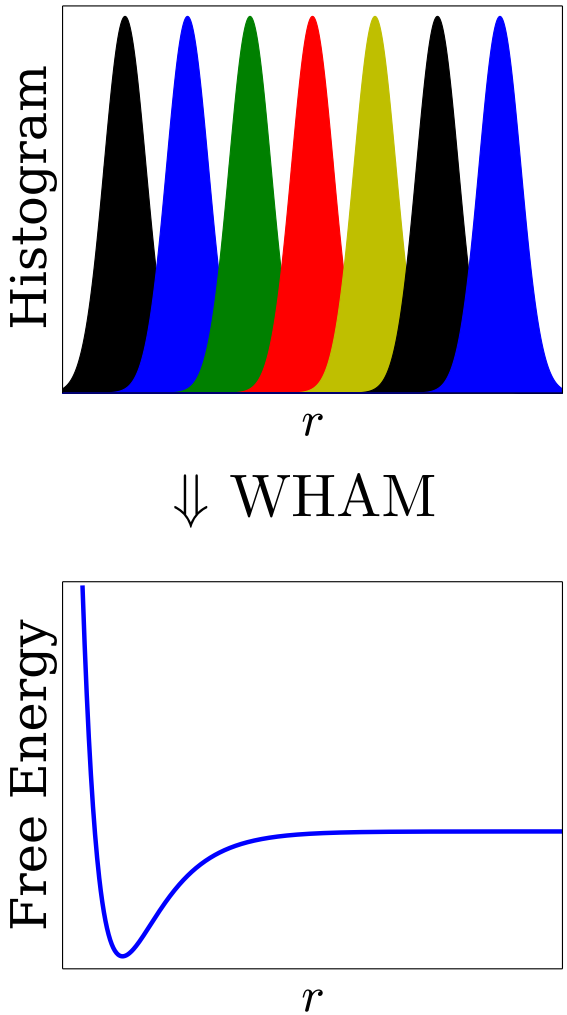
# Umbrella sampling with post-quantization restraints (PQR)

# *Classical* Umbrella sampling[1] and WHAM[2]

- Umbrella sampling introduces a biasing potential to the system

$$V_{\text{total}}(q) = V(q) + \frac{1}{2}k(q - q_{eq})^2$$

- Bias is required to sample desired configurations
  - Water dimer would evaporate at high temperature
- Unbias simulation *windows* using the Weighted Histogram Analysis Method (WHAM)




[1] G. M. Torrie, and J. P. Valleau, Chem. Phys. Lett. **28**, 578–581 (1974), G. Torrie, and J. Valleau, J. Comp. Phys. **23**, 187–199 (1977).

[2] S. Kumar, et al., J. Comp. Chem. **13**, 1011–1021 (1992).

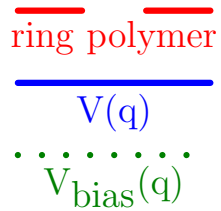
# Umbrella sampling for path integrals

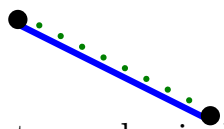
- Unbiased path integral definition

$$Z = \mathrm{Tr}\left[e^{-\beta\left(\hat{K}+\hat{V}\right)}\right]$$

$$= \lim_{P\to\infty} \int \mathrm{d}q_1 \ldots \mathrm{d}q_P \prod_{i=1}^{P} \rho_\tau(q_i, q_{i+1})$$

where $\rho_\tau(q_i, q_{i+1}) = e^{-\frac{\tau}{2}V(q_i)} \rho_0(q_i, q_{i+1}) e^{-\frac{\tau}{2}V(q_{i+1})}$



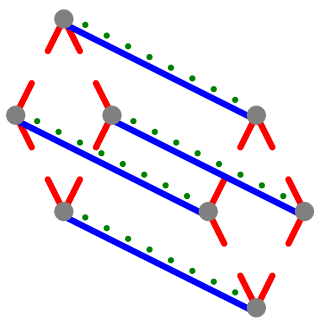



2 atoms classically

- Simple solution

$$Z_{\mathrm{bias}} = \mathrm{Tr}\left[e^{-\beta\left(\hat{K}+\hat{V}+\hat{V}_{\mathrm{bias}}\right)}\right]$$

$$= \lim_{P\to\infty} \int \mathrm{d}q_1 \ldots \mathrm{d}q_P \prod_{i=1}^{P} \rho_\tau^{\mathrm{bias}}(q_i, q_{i+1})$$



2 atoms with P=4,R=4

where

$$\rho_\tau^{\mathrm{bias}}(q_i, q_{i+1}) = e^{-\frac{\tau}{2}(V(q_i)+V_{\mathrm{bias}}(q_i))} \rho_0(q_i, q_{i+1}) e^{-\frac{\tau}{2}(V(q_{i+1})+V_{\mathrm{bias}}(q_{i+1}))}$$

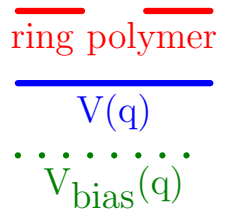
# Umbrella sampling for path integrals

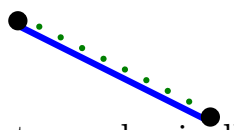
- Unbiased path integral definition

$$Z = \mathrm{Tr}\left[e^{-\beta(\hat{K}+\hat{V})}\right]$$

$$= \lim_{P\to\infty} \int \mathrm{d}q_1 \ldots \mathrm{d}q_P \prod_{i=1}^{P} \rho_\tau(q_i, q_{i+1})$$

where $\rho_\tau(q_i, q_{i+1}) = e^{-\frac{\tau}{2}V(q_i)} \rho_0(q_i, q_{i+1}) e^{-\frac{\tau}{2}V(q_{i+1})}$



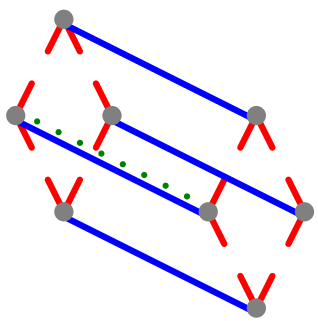



2 atoms classically

- Small change to simple solution

$$Z_{\mathrm{PQR}} = \mathrm{Tr}\left[e^{-\beta(\hat{K}+\hat{V})} e^{-\beta V_{\mathrm{bias}}}\right]$$

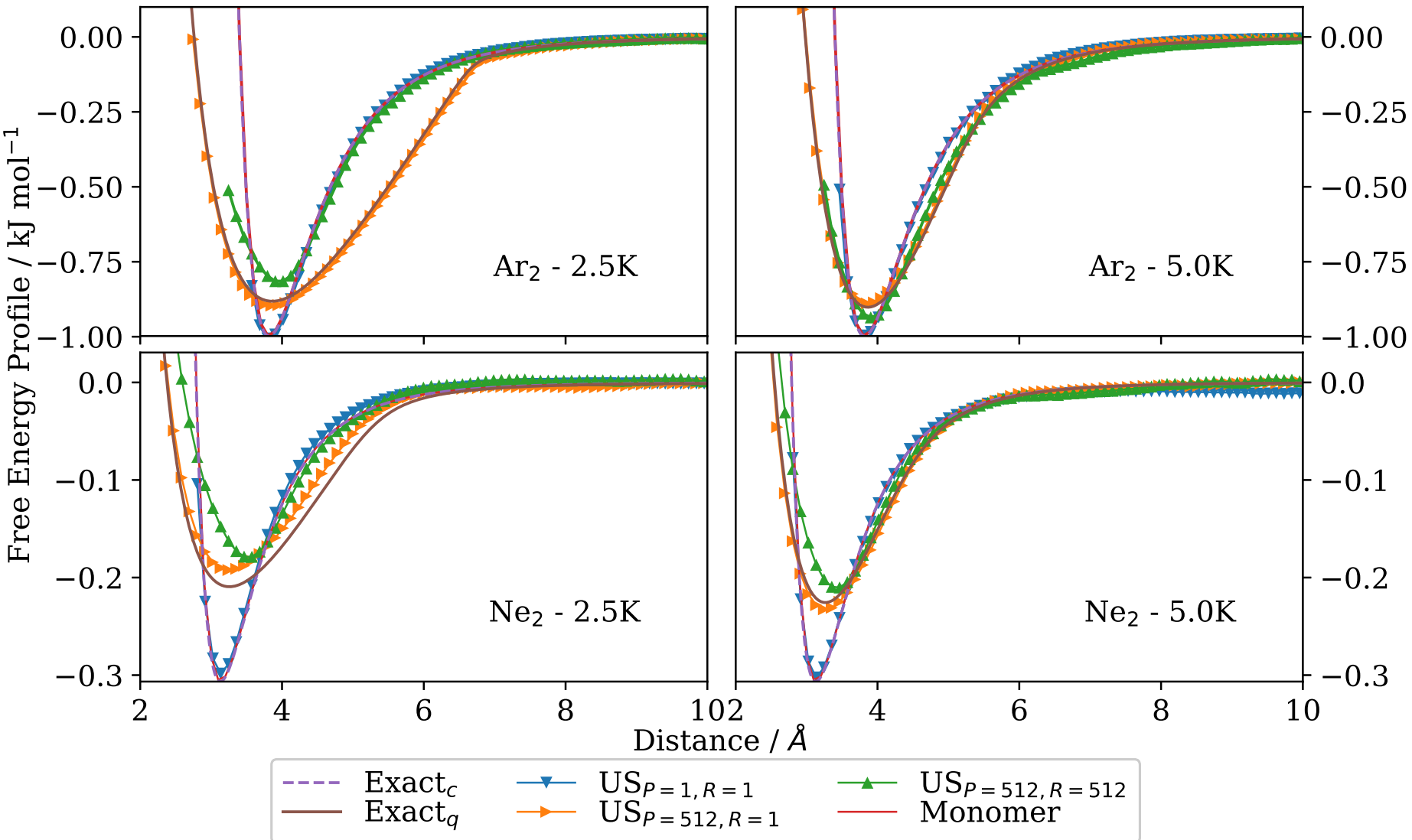
$$= \lim_{P\to\infty} \int \mathrm{d}q_1 \ldots \mathrm{d}q_P \, e^{-\beta V_{\mathrm{bias}}(q_1)} \prod_{i=1}^{P} \rho_\tau(q_i, q_{i+1})$$



2 atoms with P=4,R=1

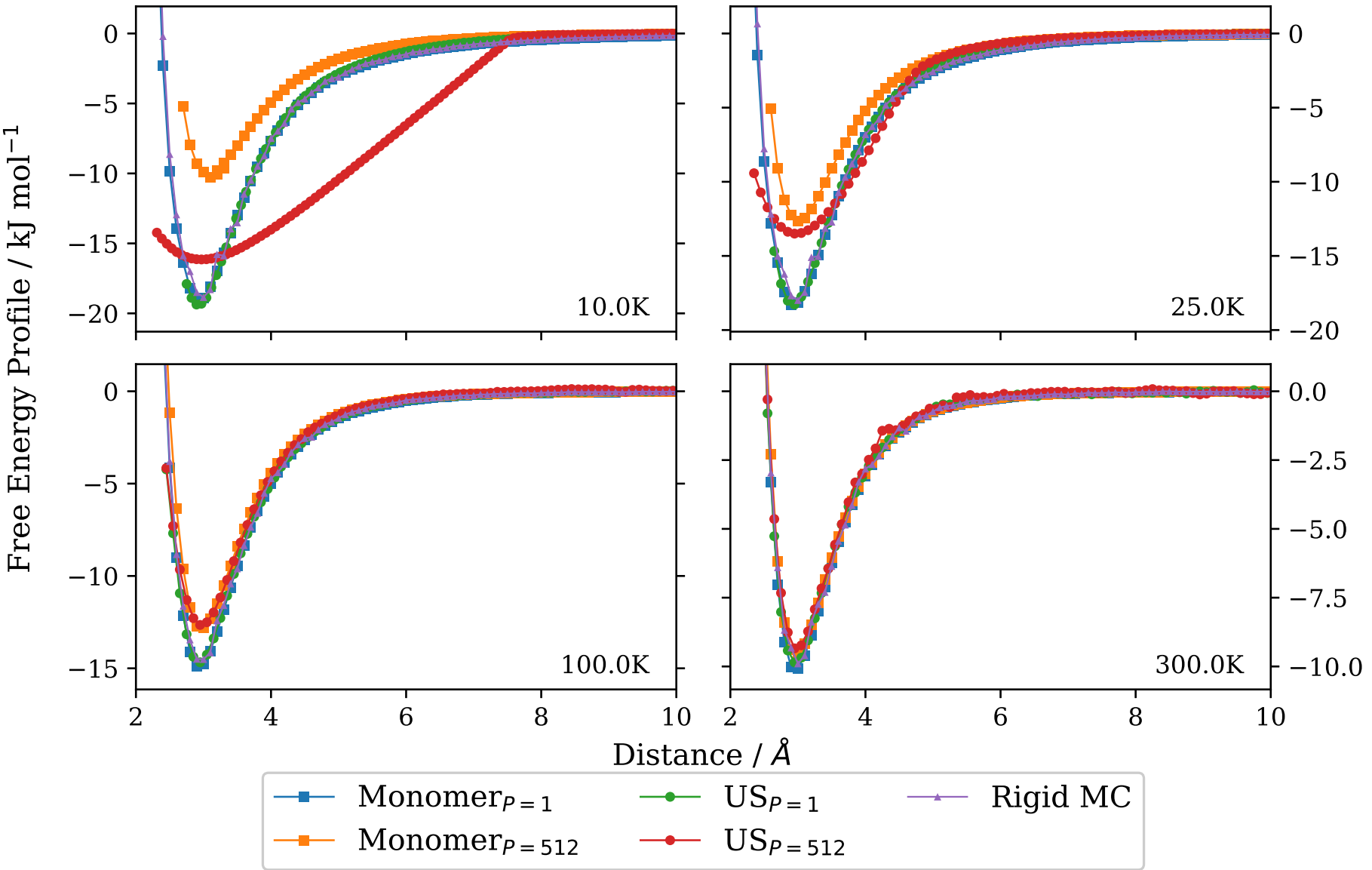
  - Only requires 1 $V_{\mathrm{bias}}$ term

# Test Method - $Ar_2$ and $Ne_2$[1]




[1] K. P. Bishop, and P.-N. Roy, J. Chem. Phys. **148**, 102303 (2018).

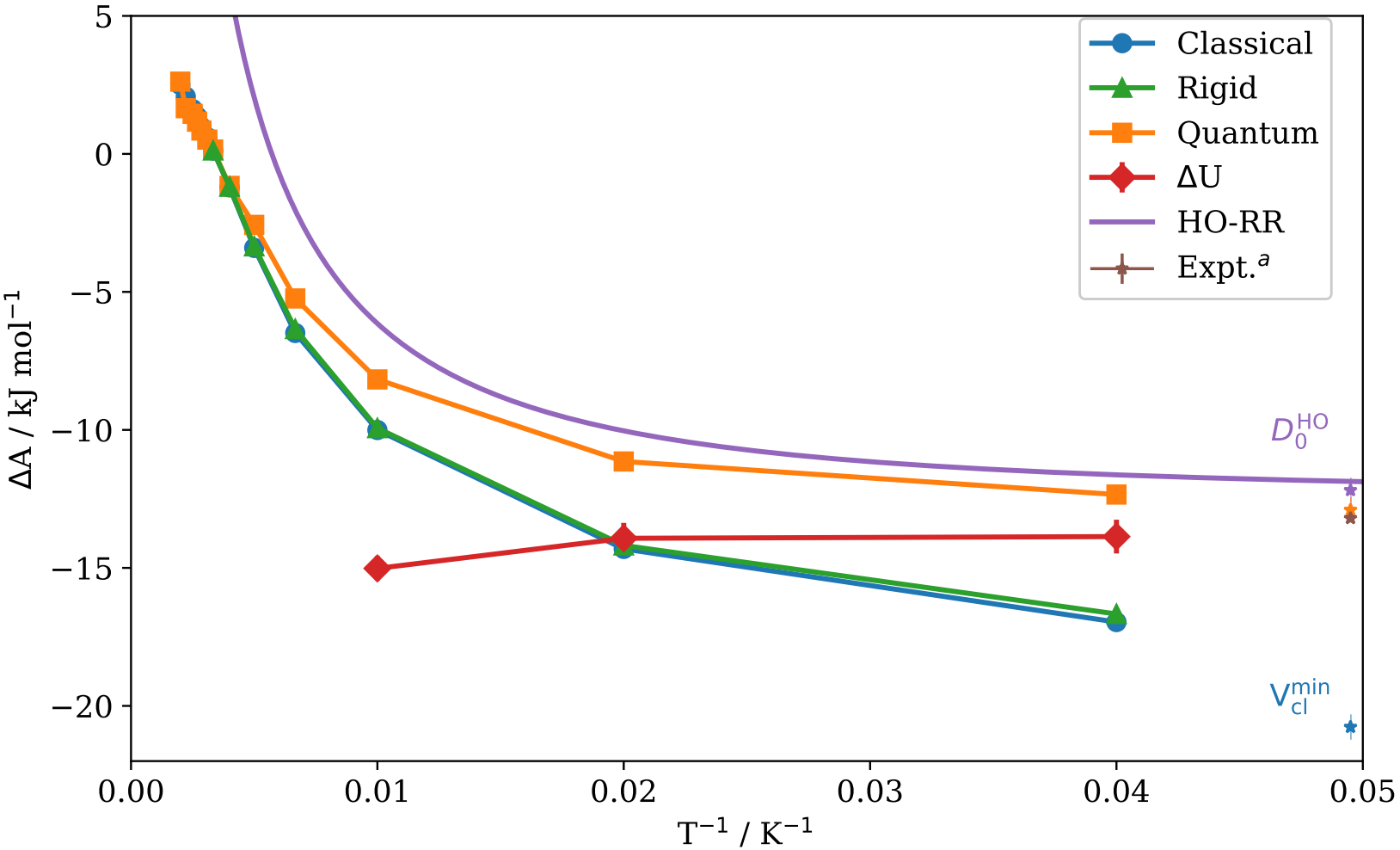
# Free energy profiles for MB-pol[1]




[1] K. P. Bishop, and P.-N. Roy, J. Chem. Phys. **148**, 102303 (2018).

# Free energy differences for MB-pol[2]

- $\Delta A$ = -12.90 ± 0.05 kJ/mol, Expt. value[1] = -13.2 ± 0.12 kJ/mol




[1] B. E. Rocher-Casterline, et al., J. Chem. Phys. **134**, 211101 (2011).

[2] K. P. Bishop, and P.-N. Roy, J. Chem. Phys. **148**, 102303 (2018).

Quantum mechanical free energy calculations using constrained path integral molecular dynamics

# Formalism

- Free energy for a specific value of a reaction coordinate, $\xi^*$

$$A(\xi^*) = -k_B T \ln \rho(\xi^*) = -k_B T \ln \langle \xi^* | \mathrm{Tr}_{\mathbf{X}}\, e^{-\beta \hat{H}} | \xi^* \rangle$$

- The derivative of the free energy is thus

$$A'(\xi^*) = \frac{\partial}{\partial \xi} A(\xi^*) = \frac{\partial}{\partial \xi}(-k_B T \ln \rho(\xi^*)) = -k_B T \frac{\rho'(\xi^*)}{\rho(\xi^*)}$$

  where $\rho(\xi^*) = \int \mathrm{d}\mathbf{q}\, \delta(\xi(\mathbf{q}_1) - \xi^*) \langle \mathbf{q} | e^{-\beta \hat{H}} | \mathbf{q} \rangle$

- The final component to evaluate is $\rho'(\xi^*)$ and Dmitri Iouchtchenko has formally derived 2 estimators:
  1. Evaluate derivative in operator representation and then discretize
  2. Discretize and evaluate derivative in path integral representation

# Estimator 1

The derivative of the density is given by

$$\rho'(\xi^*) \approx \int \mathrm{d}\mathbf{q}_1 \cdots \int \mathrm{d}\mathbf{q}_P \overbrace{\delta(\xi(\mathbf{q}_1) - \xi^*)\pi(\mathbf{q}_1, \ldots, \mathbf{q}_P)}^{\rho(\xi^*)} \times \left[ \frac{\partial}{\partial \xi} \ln |J(\mathbf{q}_1)| - \frac{\beta}{P} \sum_{i=1}^{f} \frac{\partial q_i(\mathbf{q}_1)}{\partial \xi} \boxed{\sum_{j=1}^{P} \frac{\partial V(\mathbf{q}_j)}{\partial q_i}} \right],$$

where $\pi(\mathbf{q}_1, \ldots, \mathbf{q}_P) = \langle \mathbf{q}_1 | e^{-\tau \hat{H}} | \mathbf{q}_2 \rangle \langle \mathbf{q}_2 | e^{-\tau \hat{H}} | \mathbf{q}_3 \rangle \ldots \langle \mathbf{q}_P | e^{-\tau \hat{H}} | \mathbf{q}_1 \rangle$ and $J(\mathbf{q}_1)$ is the Jacobian transformation between coordinates. The derivative of the free energy may then be evaluated using

$$A'_{\mathrm{Est1}}(\xi^*) = -k_B T \left\langle \frac{\partial}{\partial \xi} \ln |J(\mathbf{q}_1)| - \frac{\beta}{P} \sum_{i=1}^{f} \frac{\partial q_i(\mathbf{q}_1)}{\partial \xi} \sum_{j=1}^{P} \frac{\partial V(\mathbf{q}_j)}{\partial q_i} \right\rangle_{\xi^*, P}$$

# Estimator 2

An alternative for the derivative of the density is given by

$$\rho'(\xi^*) \approx \int \mathrm{d}\mathbf{q}_1 \cdots \int \mathrm{d}\mathbf{q}_P \overbrace{\delta(\xi(\mathbf{q}_1) - \xi^*)\pi(\mathbf{q}_1, \ldots, \mathbf{q}_P)}^{\rho(\xi^*)} \left[ \frac{\partial}{\partial \xi} \ln |J(\mathbf{q}_1)| \right.$$
$$\left. - \frac{\beta}{P} \frac{\partial V(\mathbf{q}_1)}{\partial \xi} - \sum_{i=1}^{f} \frac{m_i P}{\hbar^2 \beta} \frac{\partial q_i(\mathbf{q}_1)}{\partial \xi} \boxed{(2q_i(\mathbf{q}_1) - q_i(\mathbf{q}_2) - q_i(\mathbf{q}_P))} \right]$$

The derivative of the free energy may then be evaluated using

$$A'_{\mathrm{Est2}}(\xi^*) = -k_B T \left\langle \frac{\partial}{\partial \xi} \ln |J(\mathbf{q}_1)| - \frac{\beta}{P} \frac{\partial V(\mathbf{q}_1)}{\partial \xi} \right.$$
$$\left. - \sum_{i=1}^{f} \frac{m_i P}{\hbar^2 \beta} \frac{\partial q_i(\mathbf{q}_1)}{\partial \xi} (2q_i(\mathbf{q}_1) - q_i(\mathbf{q}_2) - q_i(\mathbf{q}_P)) \right\rangle_{\xi^*, P}$$

# Implementing the estimators within PIMD

- The reaction coordinate for the first bead needs to be fixed at $\xi^*$
  - Requires a *constraint*
  - Our implementation uses the CCMA[1] constraint of OpenMM[2]
- Implementation is initially benchmarked against Lennard-Jones dimers
  - Constraint between Lennard-Jones atoms
- Estimators are then used to evaluate free energy profile of water dimer and compared to PQR results
  - Constraint between oxygen atoms
  - q-SPC/Fw[3], q-TIP4P/F[4] and MB-pol[5]

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[1] P. Eastman, and V. S. Pande, J. Chem. Theory Comput. **6**, 434–437 (2010).

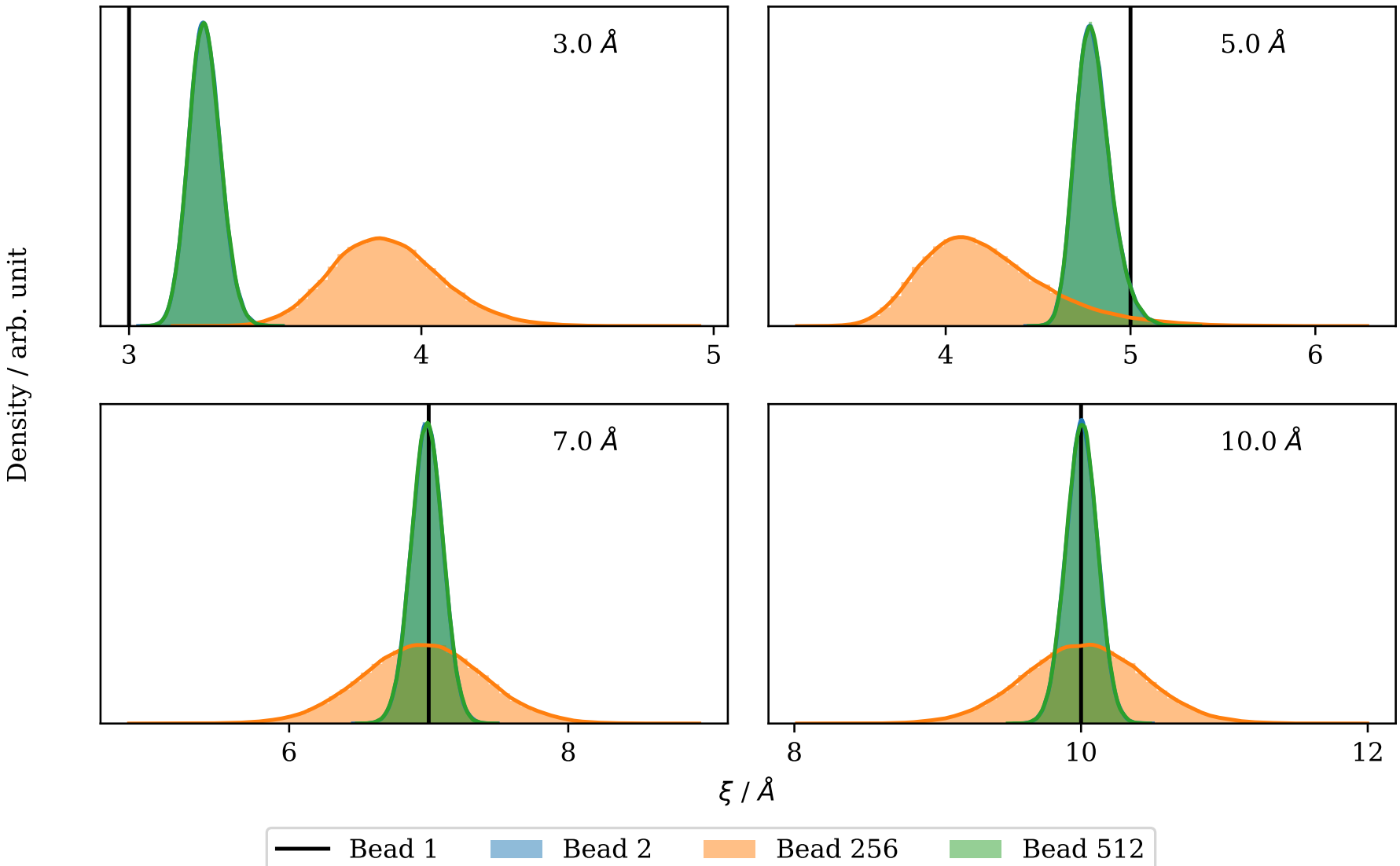
[2] P. Eastman, et al., PLOS Comput. Biol. **13**, 1–17 (2017).

[3] F. Paesani, et al., J. Chem. Phys. **125**, 184507 (2006).

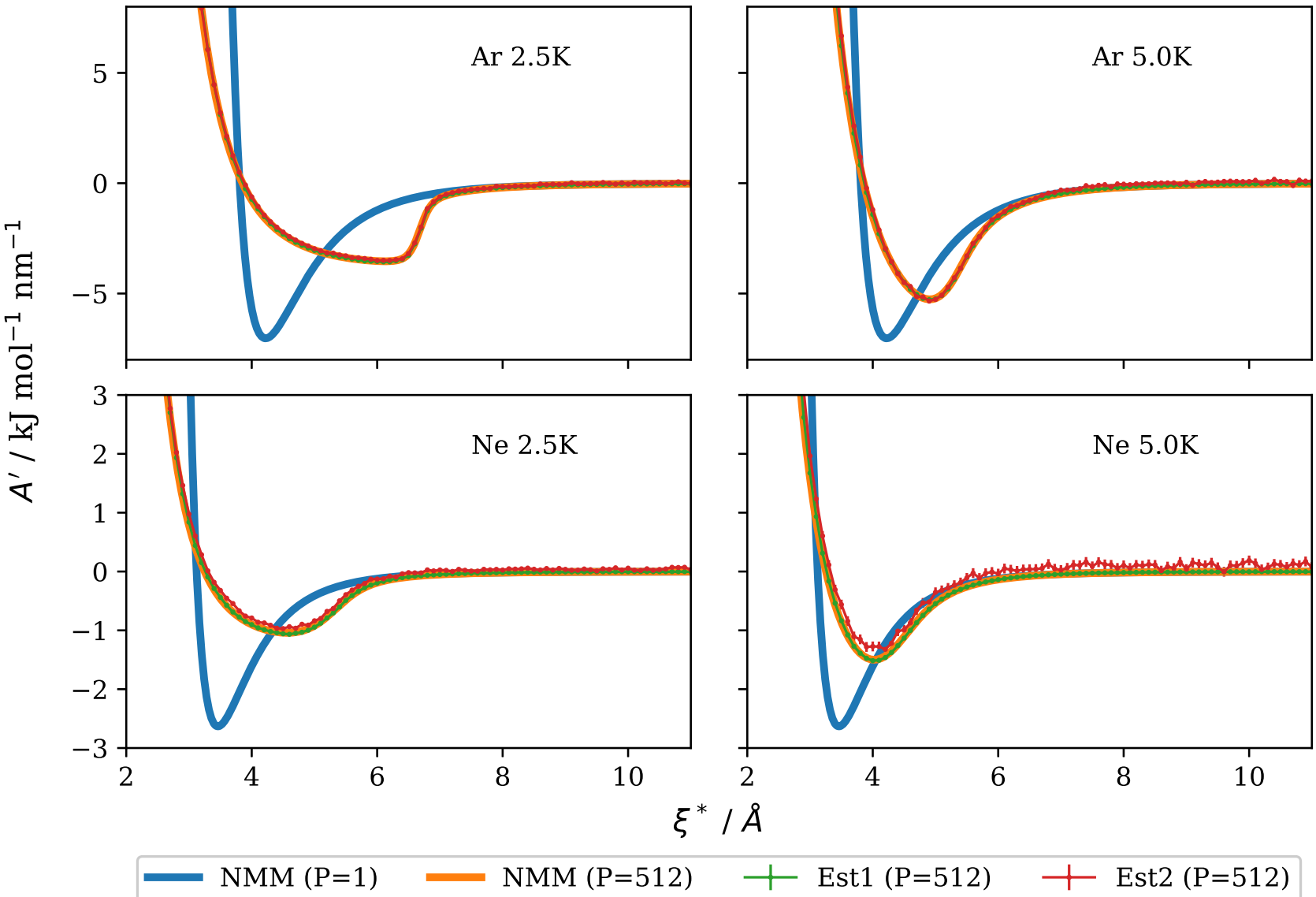
[4] S. Habershon, et al., J. Chem. Phys. **131**, 024501 (2009).

[5] V. Babin, et al., J. Chem. Theory Comput. **9**, 5395–5403 (2013), V. Babin, et al., J. Chem. Theory Comput. **10**, 1599–1607 (2014).

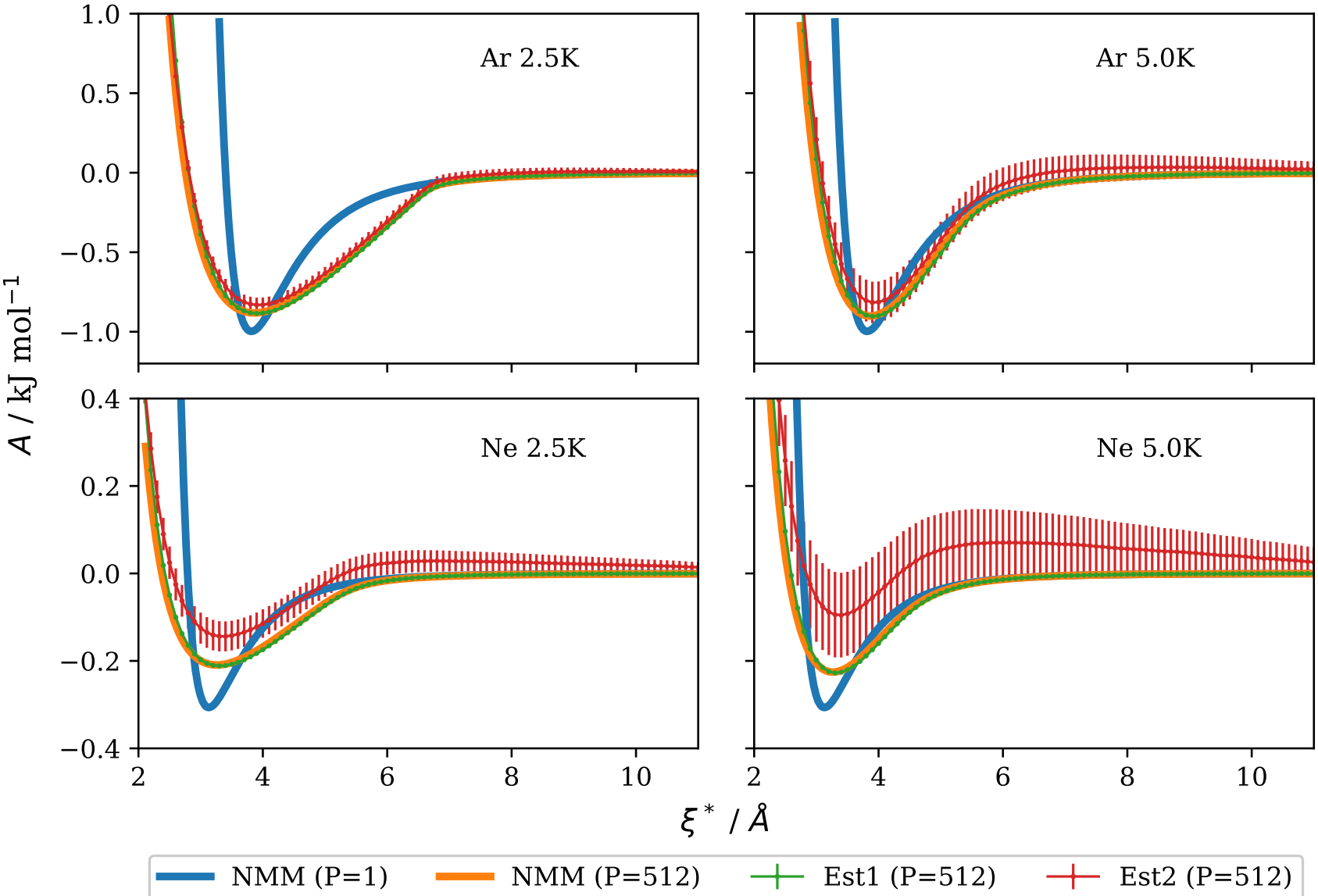
# Constrained PIMD simulations of $Ar_2$ at 10K



# Free energy derivatives of $Ar_2$ and $Ne_2$

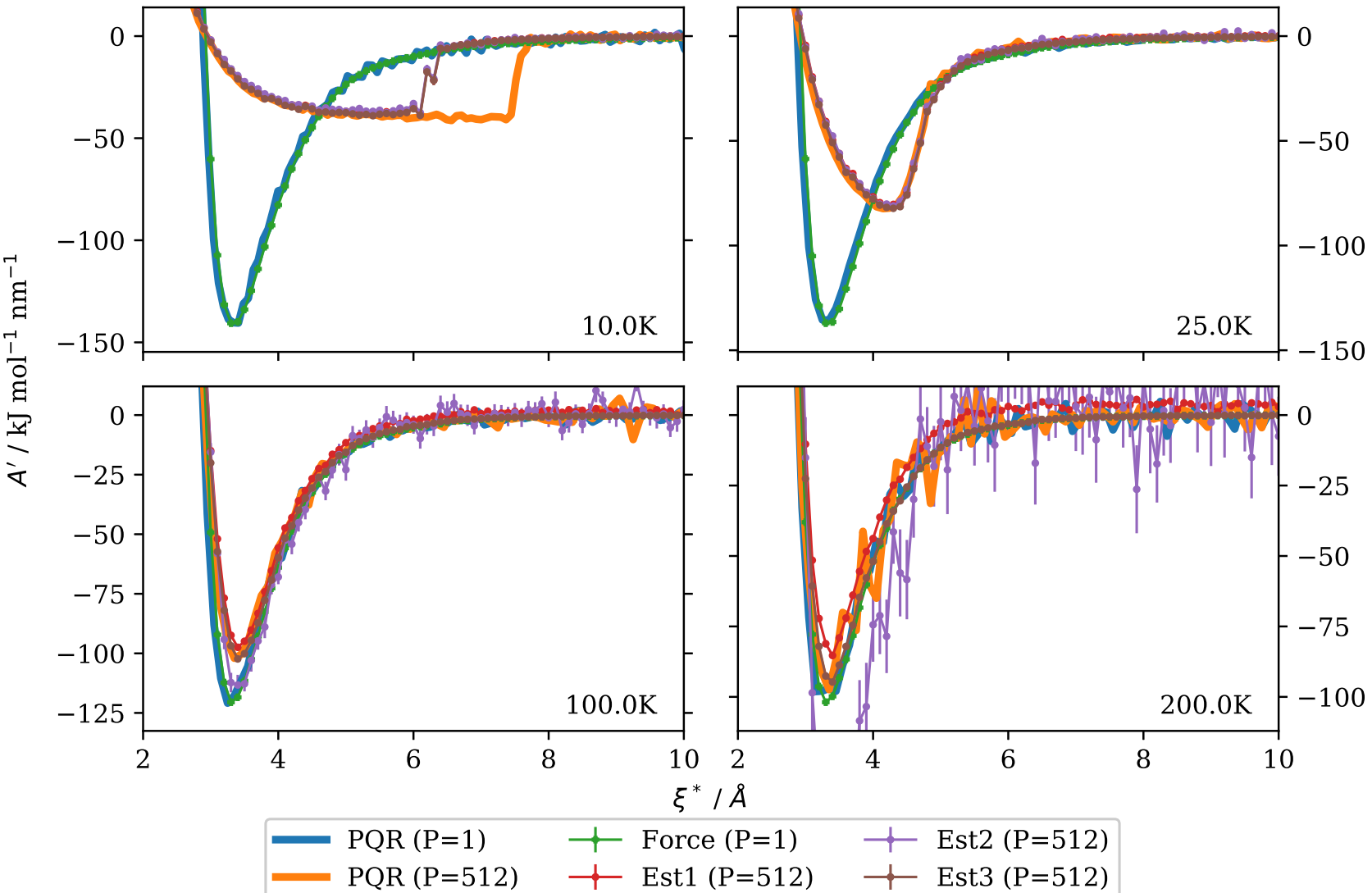


# Free energy profiles of $Ar_2$ and $Ne_2$



# Free energy derivatives of MB-pol

$$A'_{\mathrm{Est3}}(\xi^*) = -k_b T \left\langle -\frac{\beta}{P} \sum_{j=1}^{P} \frac{\partial V(\mathbf{q}_j)}{\partial \Xi_j} \right\rangle_{\xi^*,P} \quad , \quad \Xi \text{ is COM separation}$$



# Free energy profiles of MB-pol

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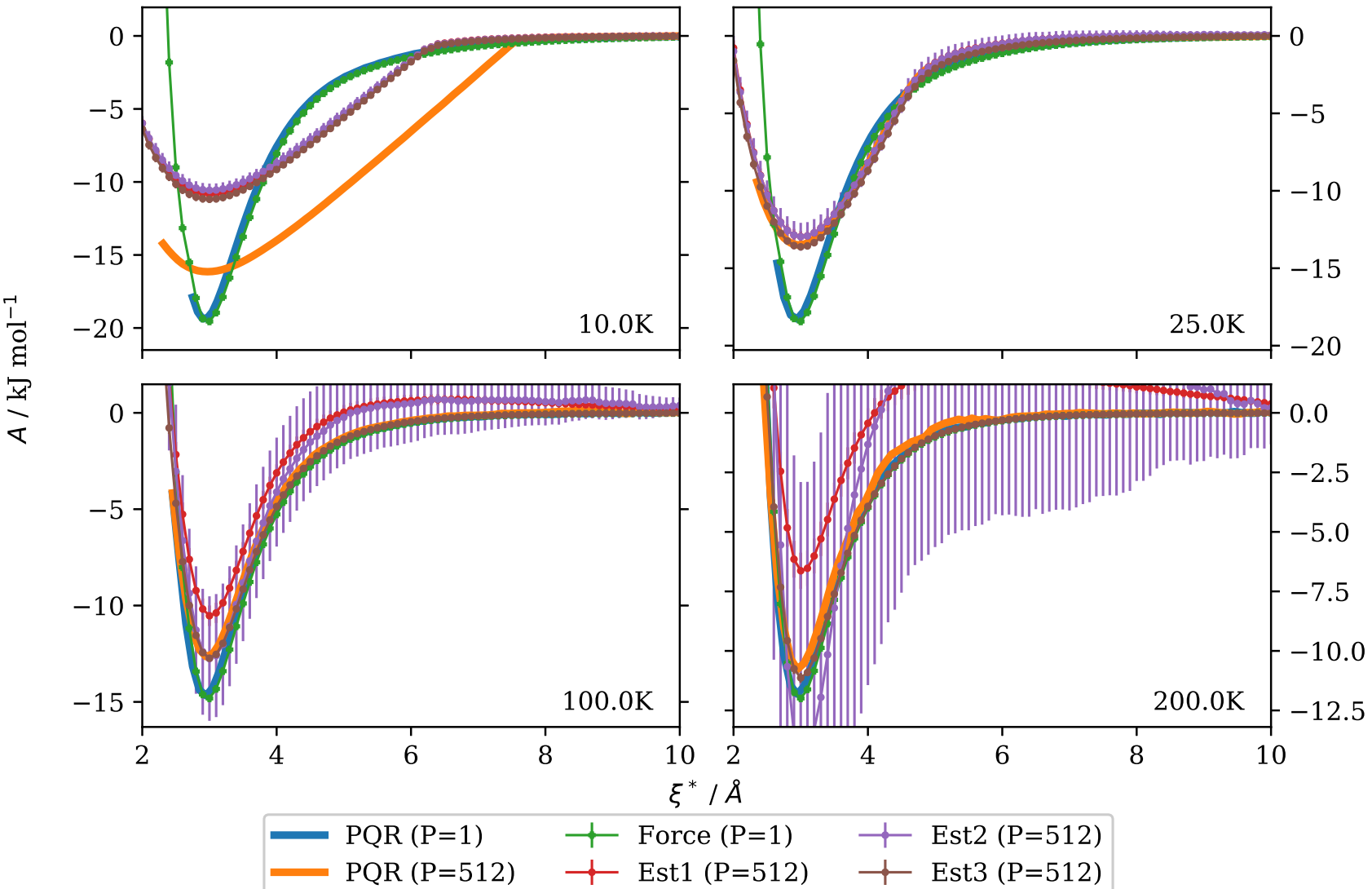
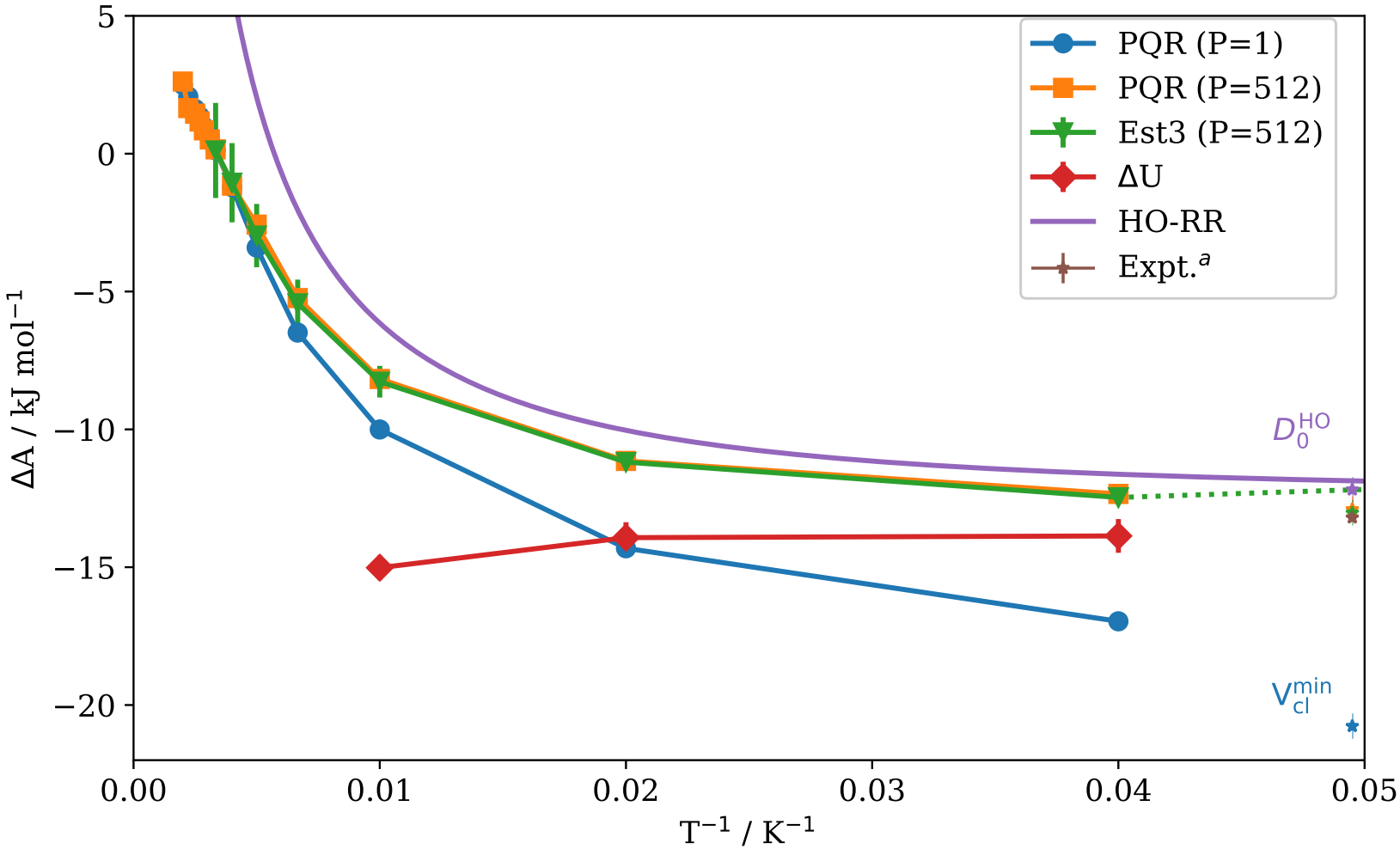


# ΔA for MB-pol

- ΔA = -13.03 ± 0.14 kJ/mol, Expt. value[1] = -13.2 ± 0.12 kJ/mol




[1] B. E. Rocher-Casterline, et al., J. Chem. Phys. **134**, 211101 (2011).

# Conclusions and future work

- PQR methodology works well down to 25 K
  - Optimization of Langevin friction
  - $\Delta A$ = -12.90 $\pm$ 0.05 kJ/mol
- Constraint methodology also works well down to 25 K
  - Currently only supports atom-atom distance constraints
  - Estimator 3 is the most stable estimator for the water dimer over a broad temperature range
  - $\Delta A$ = -13.03 $\pm$ 0.14 kJ/mol
- GPU implementation within OpenMM for constrained PIMD
- Systematic smoothing of free energy derivatives prior to integration
- Extensions to adaptive biasing methods such as metadynamics

# Acknowledgements

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Theoretical Chemistry Group

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PhD Advisory Committee

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- Wing-Ki Liu
- Marcel Nooijen

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