Instanton theory simulation of nuclear quantum effects

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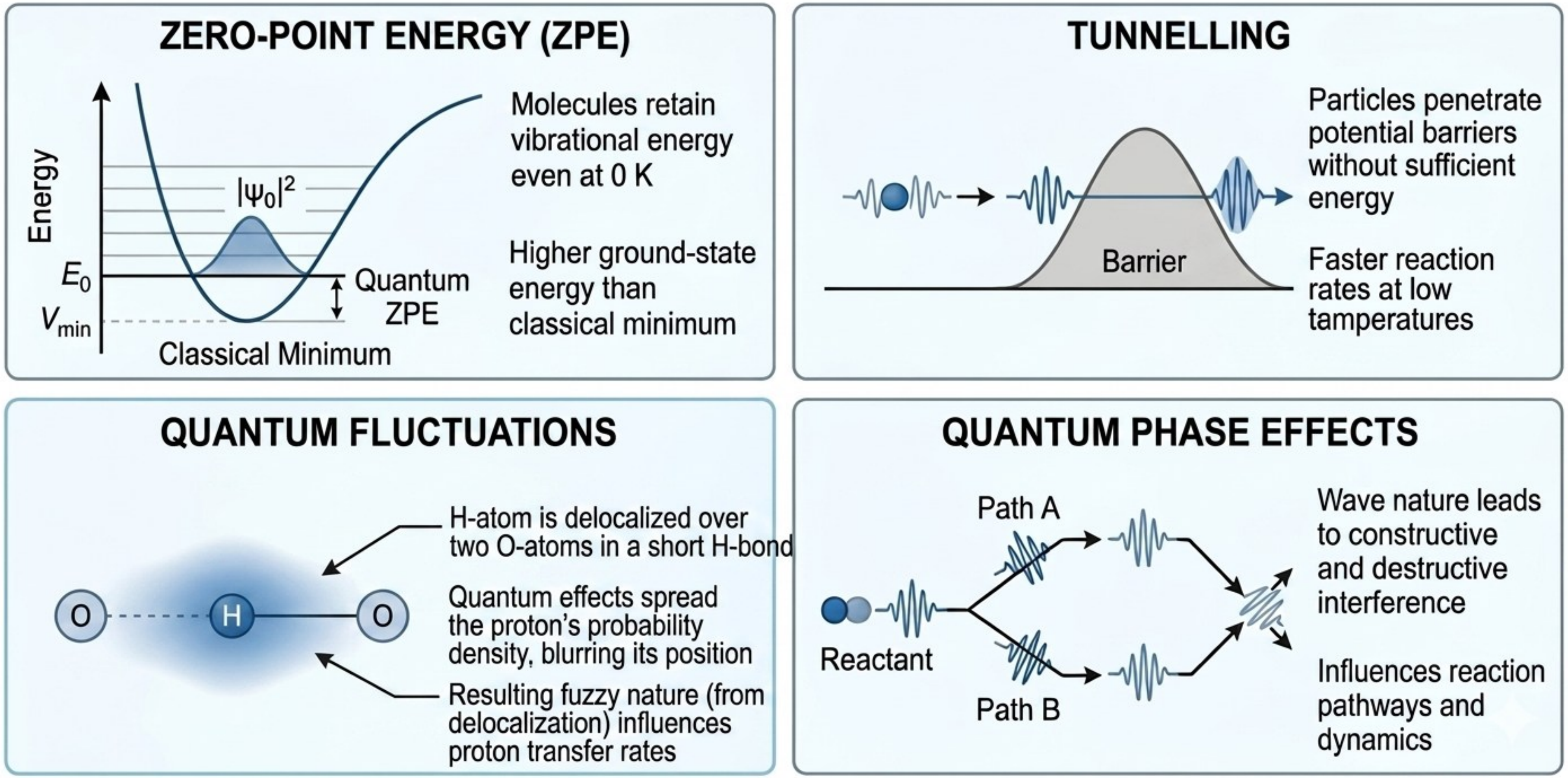
Nuclear Quantum Effects

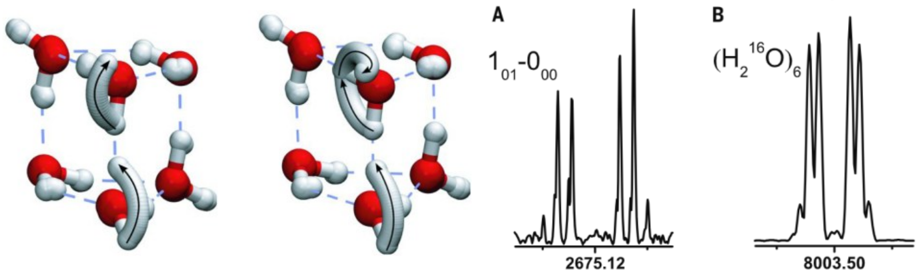
- NQEs mainly includes zero-point energy, tunnelling, quantum fluctuations, phase effects, etc.



Nuclear Quantum Effects

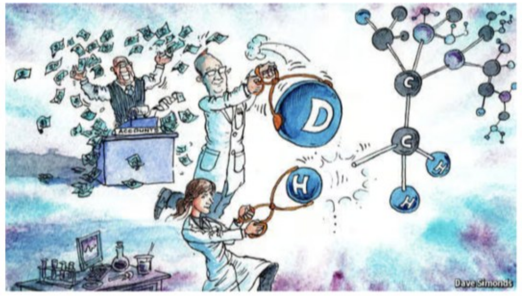
- Important manifestation & application of NQEs

Spectroscopy



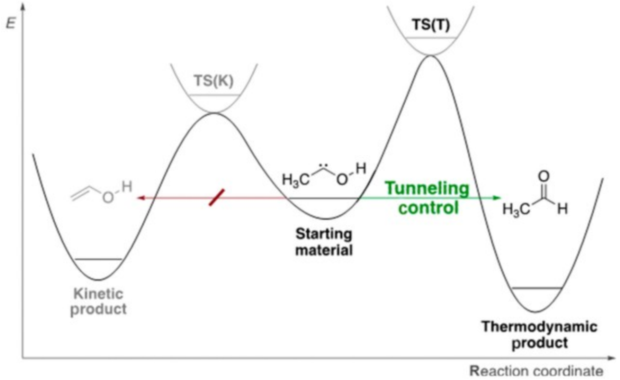
J. O. Richardson, et al. *Science* **2016**, *351*, 1310

Deuterated drugs



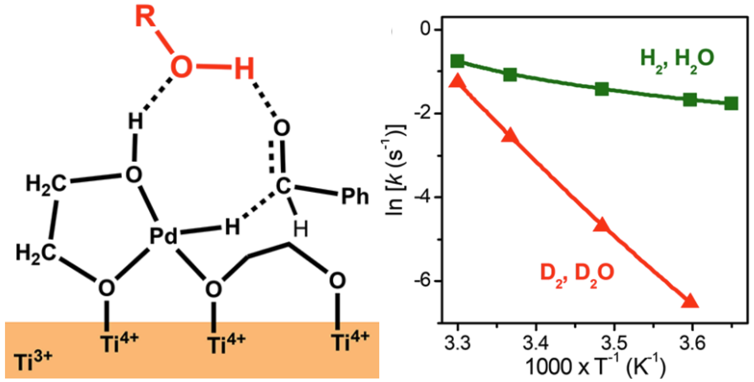
T. Pirali, *Nat. Rev. Drug Discov.* **2023**, 22, 562

Reaction kinetics



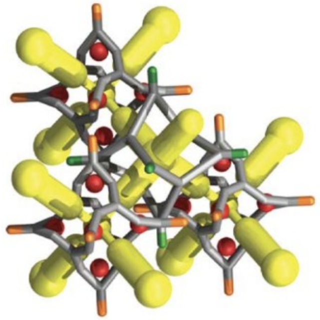
W. D. Allen, et al. *Science* **2011**, *332*, 1300

Catalysis



ACS Cent. Sci. **2025**, 11, 2180

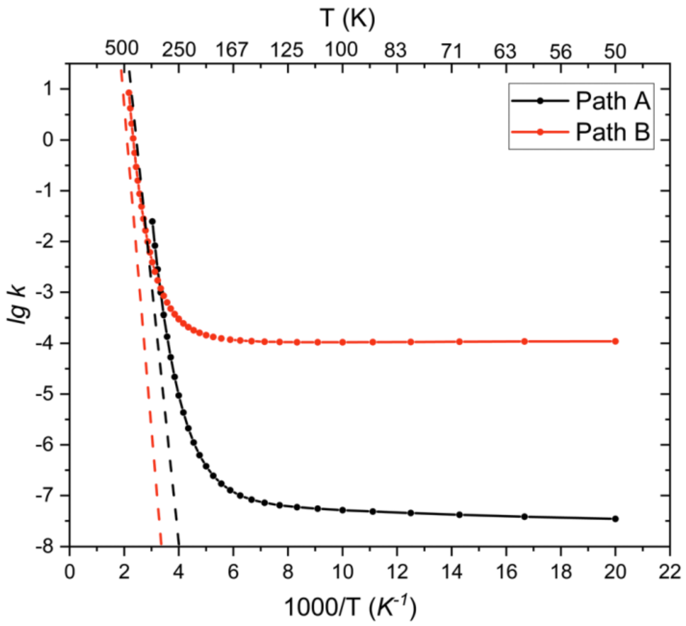
Hydrogen isotope separation

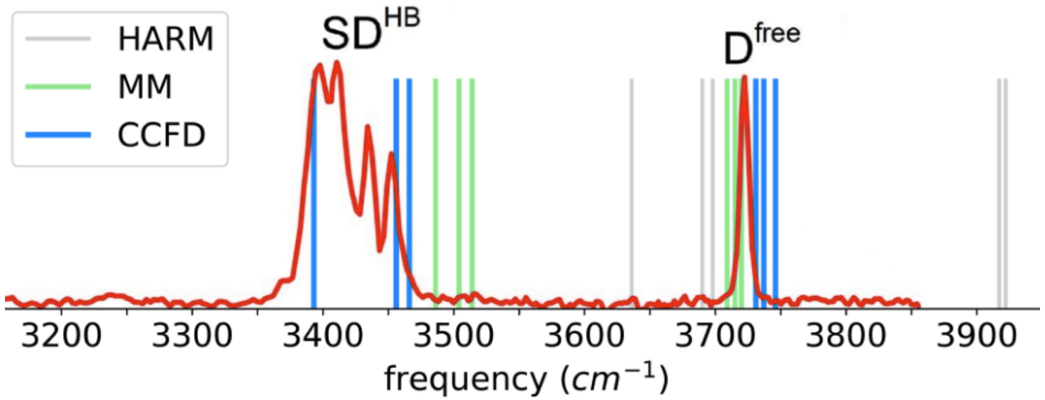


A. I. Cooper et al. *Science* **2019**, *366*, 613

Nuclear Quantum Effects

- Molecular simulation of commonly employ classical nuclei → unable to predict **isotope effects** and **non-Arrhenius** behaviour, and leads to systematic errors in **thermodynamics** and **spectroscopy** simulations, etc.





- How can we accurately and efficiently account for NQEs in simulations?

Table of Contents

- Semiclassical instanton theory for tunnelling kinetics
- Entropic path integral coarse graining for quantum spectra and thermodynamics

Imaginary Time Path Integral

- Wavefunction *vs* path integral, equivalent forms of quantum mechanics
- Wick rotation

$$\langle x'|\mathrm{e}^{-i\hat{H}t/\hbar}|x\rangle = \int \mathrm{e}^{iS[\mathbf{x}(t)]/\hbar}\mathcal{D}\mathbf{x}(t) \xrightarrow{it=\tau} Z(\beta) = \mathrm{Tr}\left[\mathrm{e}^{-\beta\hat{H}}\right] = \int \mathrm{d}x\ \langle x|e^{-\beta\hat{H}}|x\rangle$$

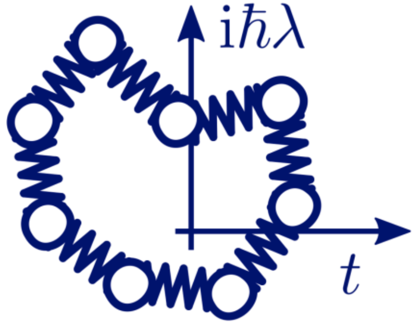
Real time path integral

Imaginary time path integral

- Ring-Polymer represents a closed imaginary time path

Euclidean action:

$$S[\mathbf{x}(\tau)] = \lim_{N\to\infty}\sum_j\left[\frac{m}{2}\left(\frac{x_{j+1}-x_j}{\mathrm{d}\tau}\right)^2 + \frac{V(x_{j+1})+V(x_j)}{2}\right] i\mathrm{d}\tau$$

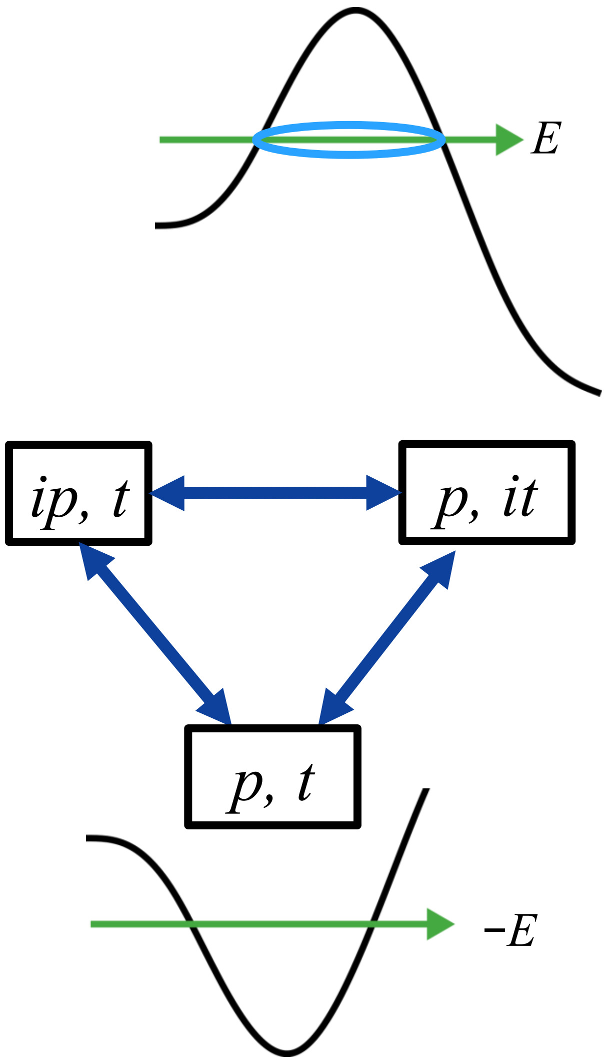


Imaginary Time Path and Tunnelling

- Consider a 1D potential, with a particle incidenting at energy E and tunnelling through the barrier
- To maintain energy conservation, it must have negative kinetic energy when tunnelling under the barrier, therefore having imaginary momentum
- Imaginary momentum is equivalent to travelling in imaginary time, also equivalent to travelling on the inverted potential
- With the semiclassical approximation (WKB), the tunnelling probability is

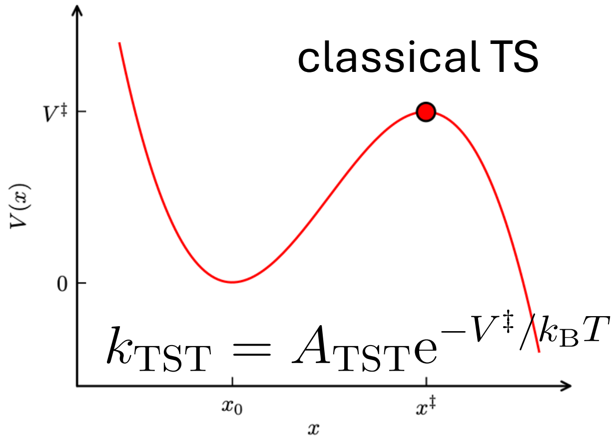
$$P(E) \sim \mathrm{e}^{-W(E)/\hbar}, \quad W(E) = \oint \sqrt{2m\,[V(x) - E]}\,\mathrm{d}x$$

- This shows that the **tunnelling probability is determined by the action of a periodic path in imaginary time**

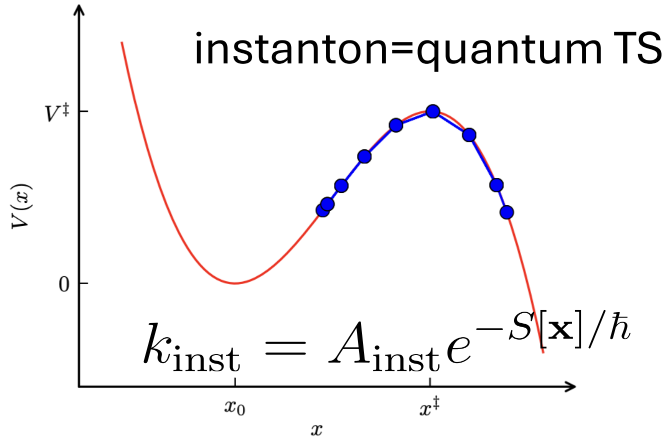


Semiclassical Instanton Theory

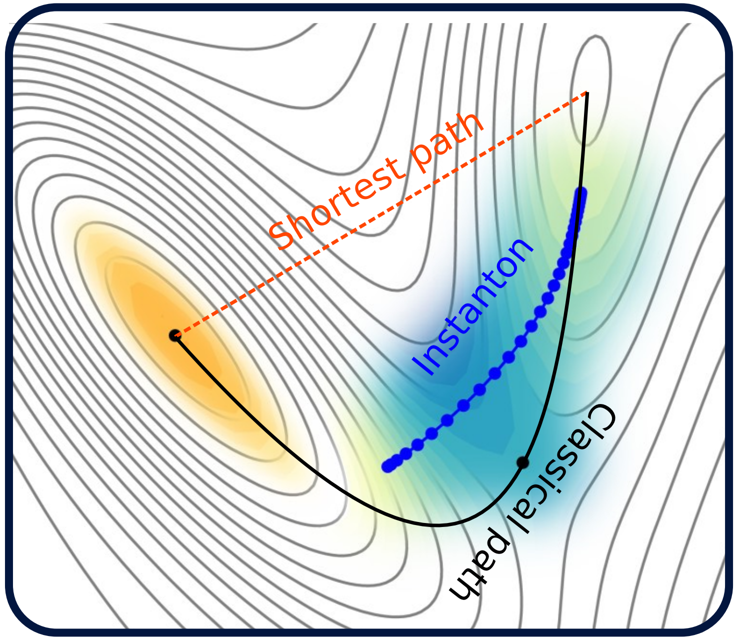
- **Periodic imaginary time paths** that minimizes the Euclidean action are called **instantons**
- Instanton rate theory is **rigorously derived**[1] from the semi-classical approximation to the quantum mechanical rate, and is **deeply related to RPMD rate theory**[2]
- **"Quantum transition state theory"**



Classical TST rate: mainly determined by the reaction barrier, the TS has the lowest barrier



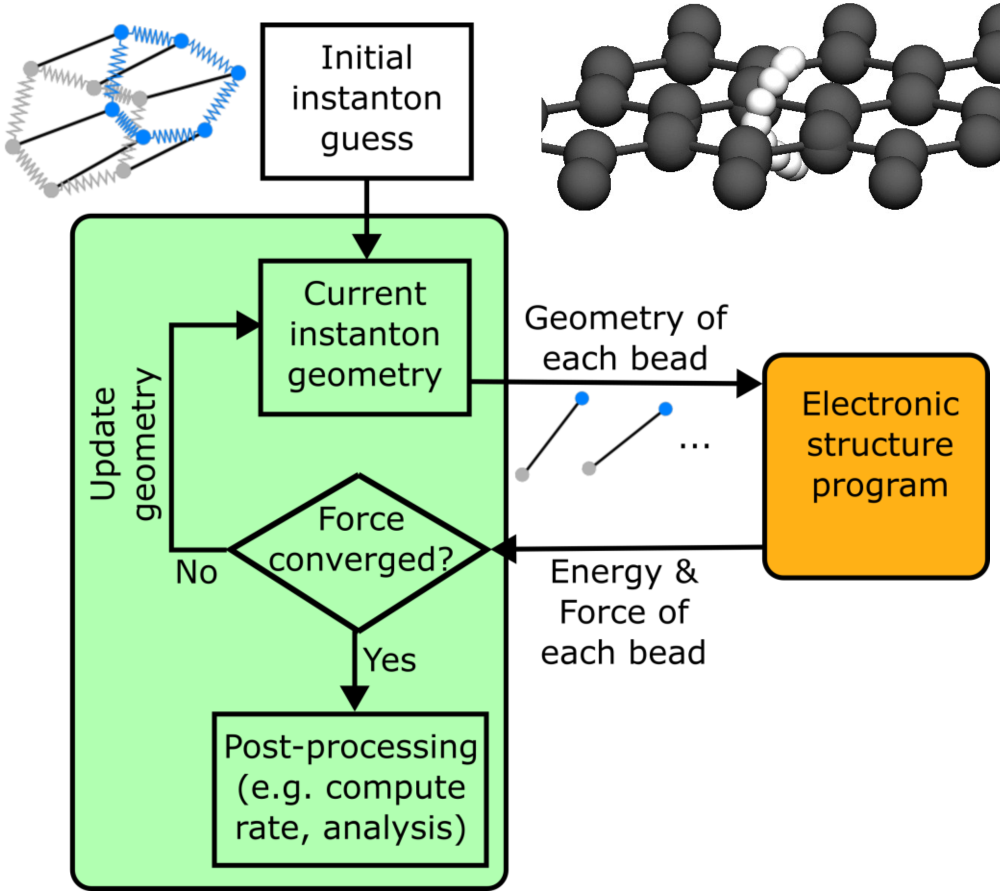
Instanton rate: mainly determined by the Euclidean action S of the instanton, which has the least action



[1] J. O. Richardson, *Int. Rev. Phys. Chem.* 37, 171 (2018)
[2] J. O. Richardson, S. C. Althorpe, *J. Chem. Phys.* 131, 214106 (2009)

Semiclassical Instanton Theory

- *Ab initio* calculations in practice:

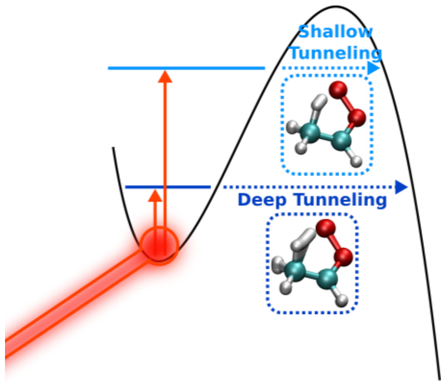


- Advantages of instanton theory:
  - ✓ Has good balance between cost and accuracy
  - ✓ Captures **corner-cutting effects** and other multidimensional tunnelling effects
  - ✓ **No tuneable parameters**
  - ✓ Instanton theory **framework can be extended** to simulate a wide range of tunnelling phenomena: microcanonical rate, tunnelling splittings, nonadiabatic tunnelling, etc.
- We applied instanton theory to various surface processes and gas-phase reactions

Phys. Rev. Lett. 119, 126001 (2017); *Nat. Commun.* 11, 1689 (2020); *J. Phys. Chem. Lett.* 13, 3173 (2022); *J. Am. Chem. Soc.* 146, 20494 (2024); etc.

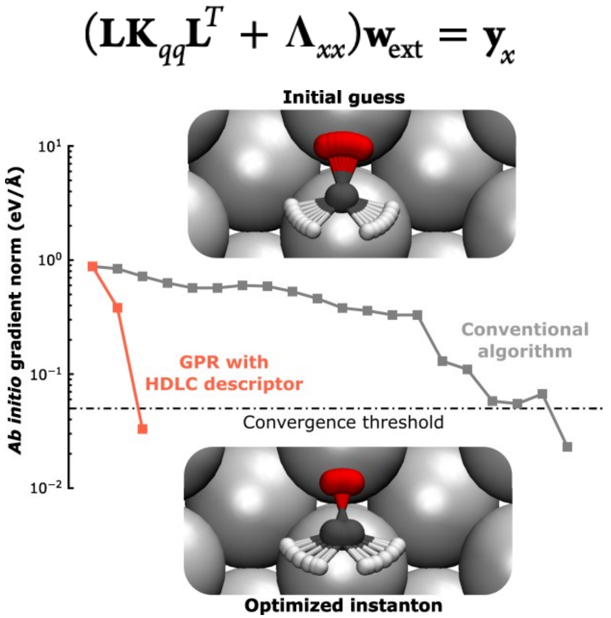
Recent Developments of Instanton Theory

- In the past years, we have been developing instanton theory



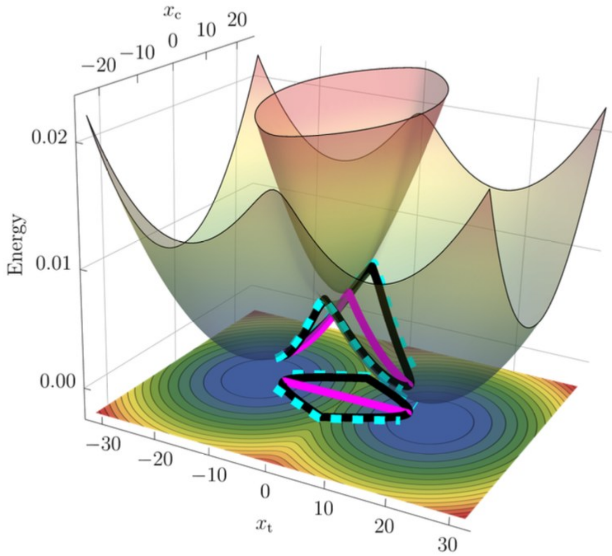
Microcanonical tunnelling theory

J. Chem. Theory Comput. 17, 40 (2021)



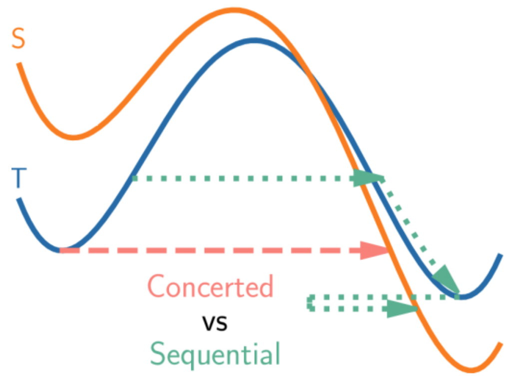
GPR framework speeding up instanton optimisation by one order of magnitude

J. Chem. Theory Comput. 20, 3766 (2024)



FGR instanton theory for tunnelling near conical intersection

Chem. Sci. 14, 10777 (2023)



Competing tunnelling pathways in near-barrier crossing

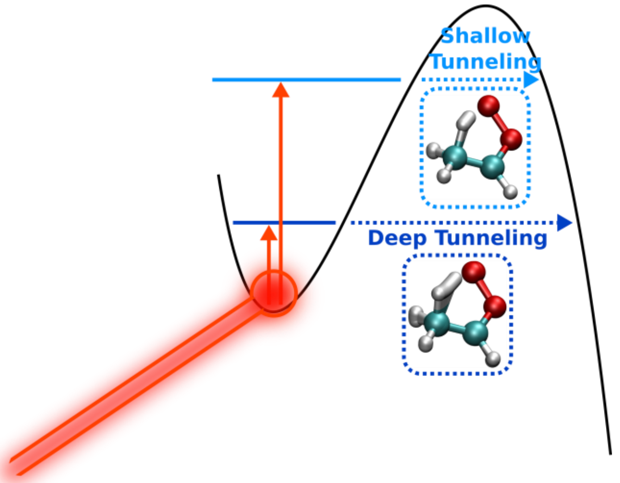
J. Chem. Theory Comput. 21, 10086 (2025)

Microcanonical Instanton Theory

- Microcanonical rates have significant relevance in spectroscopy
- Microcanonical rate and its relation with thermal rate

$$k_{\text{uni}}(\beta) = \frac{1}{Z_{\text{r}}(\beta)} \int_0^{\infty} \mathrm{d}E\, k(E)\rho_{\text{r}}(E)\mathrm{e}^{-\beta E}$$

$$k(E) = \frac{1}{2\pi\hbar}\frac{N(E)}{\rho_{\text{r}}(E)}$$



- The standard RRKM theory makes the separable approximation and ignores tunnelling
- Miller proposed the first microcanonical instanton theory[1], formally resembling RRKM

RRKM

$$N^{\text{vib}}_{\text{RRKM}}(E) = \sigma \sum_{\mathbf{n}} P_{\text{cl}}(E - \mathcal{E}^{(\mathbf{n})}_{\text{TS}})$$

$$\mathcal{E}^{(\mathbf{n})}_{\text{TS}} = \sum_{j=1}^{f-1}\left(n_j + \frac{1}{2}\right)\hbar\omega_j^{\ddagger}$$

Miller

$$N^{\text{vib}}_{\text{SC-sum}}(E) = \sigma \sum_{\mathbf{n}} P_{\text{SC}}(E^{(\mathbf{n})}_{\text{I}}) \qquad P_{\text{SC}}(E) = \begin{cases} [1 + \mathrm{e}^{W(E)/\hbar}]^{-1}, & E < V_{\text{TS}} \\ [1 + \mathrm{e}^{W_{\text{pb}}(E)/\hbar}]^{-1}, & E \geq V_{\text{TS}} \end{cases}$$

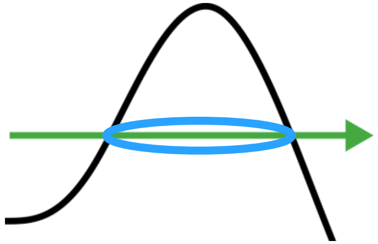
$$E^{(\mathbf{n})}_{\text{I}} = E - \sum_{j=1}^{f-1}\left(n_j + \frac{1}{2}\right)\hbar\omega_j(E^{(\mathbf{n})}_{\text{I}})$$

[1] Chapman, S.; Garrett, B. C.; Miller, W. H. *J. Chem. Phys*. 63, 2710 (1975)

Microcanonical Instanton Theory

- Instantons can be viewed as **pseudoparticles**
- E_I is the energy of the instanton[1]

$$E_\mathrm{I} = \frac{\partial S}{\partial \tau}$$



- Z_I is the partition function of the instanton[1], defined with stability parameters u_j (describe how a trajectory respond to perturbations)

$$Z_\mathrm{I}(\beta; E_\mathrm{I}) = Z_\mathrm{I}^{\mathrm{vib}}(\beta; E_\mathrm{I}) Z_\mathrm{I}^{\mathrm{rot}}(\beta; E_\mathrm{I})$$

$$Z_\mathrm{I}^{\mathrm{vib}}(\beta; E_\mathrm{I}) = \prod_{j=1}^{f-1} \frac{1}{2\sinh(\beta\hbar\omega_j(E_\mathrm{I})/2)} \qquad \omega_j(E_\mathrm{I}) = u_j(E_\mathrm{I})/\tau$$

[1] Miller, W. H. *J. Chem. Phys*. 62, 1899 (1975)

Microcanonical Instanton Theory

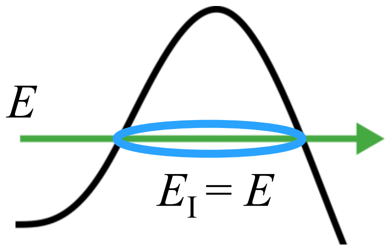
- Miller's direct summation approach is impractical for realistic systems
- We propose to change direct summation → integration over density of states (DoS)[1]

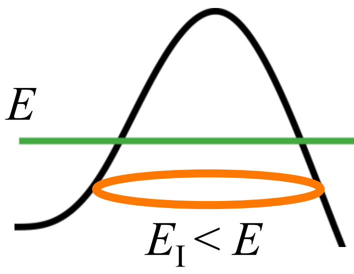
$$N^{\text{vib}}_{\text{SC-sum}}(E) = \sigma \sum_{\mathbf{n}} P_{\text{SC}}(E_{\text{I}}^{(\mathbf{n})}) \longrightarrow N_{\text{DoS}}(E) = \sigma \int_{E_{\text{I}}^{\text{min}}}^{\infty} \mathrm{d}E_{\text{I}}\, P_{\text{SC}}(E_{\text{I}})\rho_{\text{I}}(E;\, E_{\text{I}})$$

- For an instanton with energy E_{I}, its DoS relates to its partition function via Laplace transform

$$\int_{E_{\text{I}}}^{\infty} \mathrm{d}E\, \rho_{\text{I}}(E;\, E_{\text{I}})\mathrm{e}^{-\beta E} = Z_{\text{I}}(\beta;\, E_{\text{I}})\mathrm{e}^{-\beta E_{\text{I}}}$$

- An instanton with energy E_{I} not only contributes to $N(E_{\text{I}})$, but also contributes to $N(E)$ for all E above E_{I}, because tunnelling can occur via a ro-vibrationally excited instanton





[1] **W. Fang**, P. Winter, J. O. Richardson, *J. Chem. Theory Comput.* 17, 40 (2021)

Microcanonical Instanton Theory

- Miller's direct summation approach is impractical for realistic systems
- We propose to change direct summation → integration over density of states (DoS)[1]
- No free lunch! Computing inverse Laplace transform (ILT) is not trivial
- We employ the stationary phase approximation (SPA) to ILT:

$$\rho_{\mathrm{I}}(E;E_{\mathrm{I}}) = \left(2\pi \frac{\partial^2 \ln[Z_{\mathrm{I}}(\beta;E_{\mathrm{I}})\mathrm{e}^{-\beta E_{\mathrm{I}}}]}{\partial \beta^2}\right)^{-\frac{1}{2}}_{\beta=\beta_{\mathrm{sp}}} \mathrm{e}^{\beta_{\mathrm{sp}}E} Z_{\mathrm{I}}(\beta_{\mathrm{sp}};E_{\mathrm{I}})\mathrm{e}^{-\beta_{\mathrm{sp}}E_{\mathrm{I}}},$$

$$E \equiv E(\beta_{\mathrm{sp}};E_{\mathrm{I}}) = -\left(\frac{\partial \ln[Z_{\mathrm{I}}(\beta;E_{\mathrm{I}})\mathrm{e}^{-\beta E_{\mathrm{I}}}]}{\partial \beta}\right)_{\beta=\beta_{\mathrm{sp}}}$$

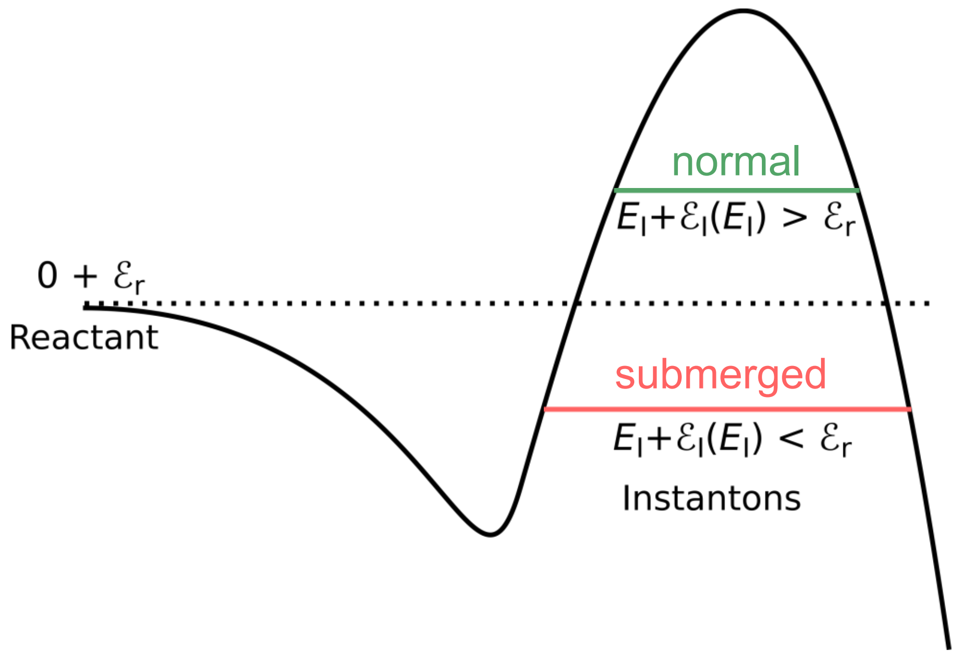
$$= E_{\mathrm{I}} + \bar{\mathcal{E}}_{\mathrm{I}}(\beta_{\mathrm{sp}};E_{\mathrm{I}}) + \frac{f^{\mathrm{rot}}}{2\beta_{\mathrm{sp}}}, \quad \beta_{\mathrm{sp}} \in \mathbb{R}^+$$

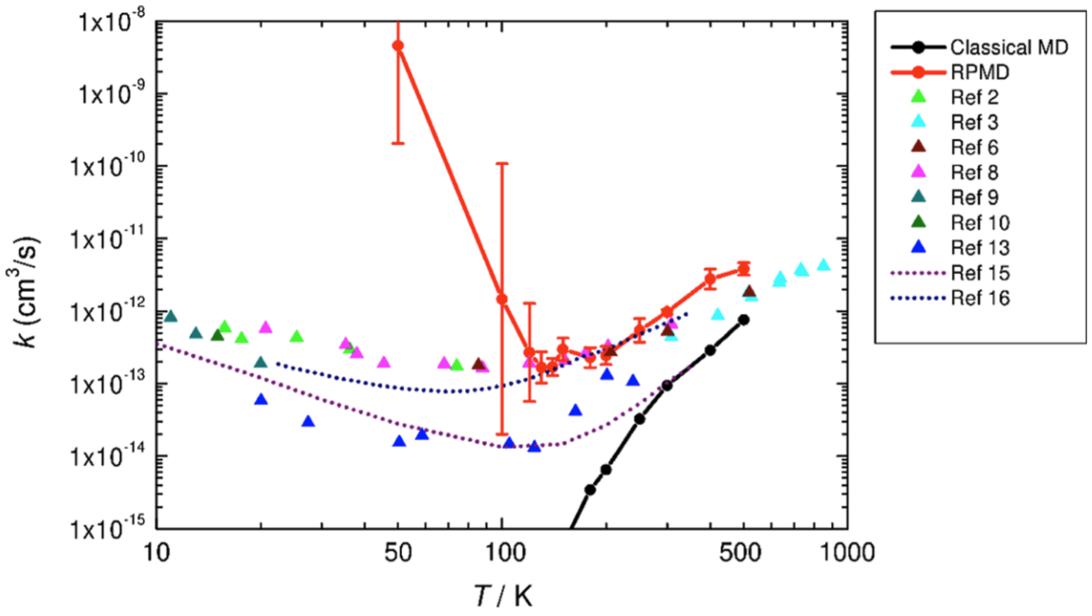
- For a system of harmonic oscillators, the DoS obtained via SPA-ILT recovers the well-known continuum approximation (Thomas–Fermi approximation) to the DoS when $E >> \hbar\omega$

[1] **W. Fang**, P. Winter, J. O. Richardson, *J. Chem. Theory Comput.* 17, 40 (2021)

Understanding Pre-reactive Minimum

- Many biomolecular reactions for pre-reactive complexes bound by weak interactions
- This feature causes problems from RPMD, predicting a drastic rate increase with decreasing T
- From the microcanonical instanton perspective, there are two types of instantons:

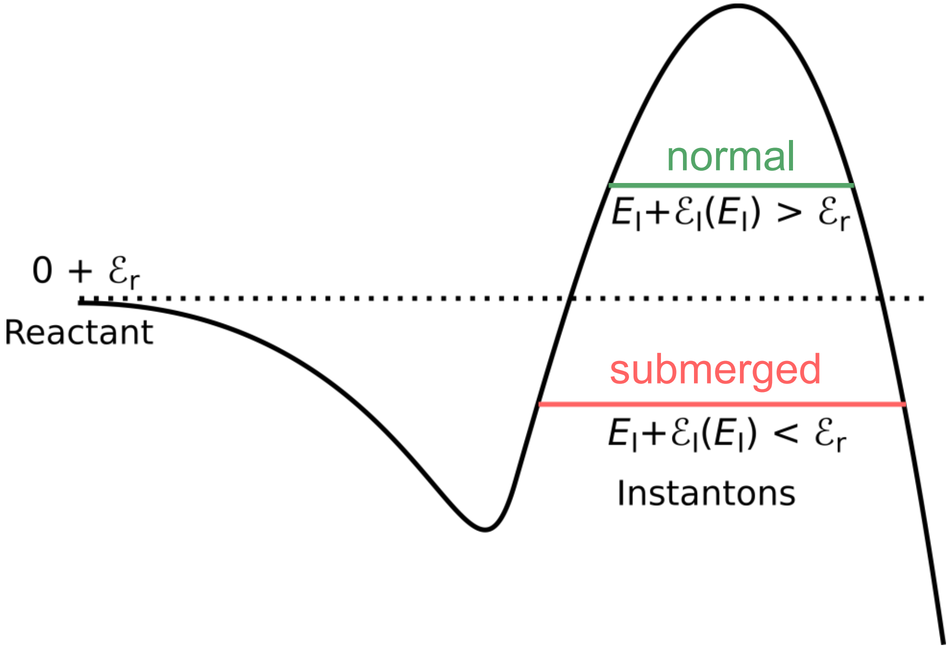




Y. Hashimoto, T. Takayanagi, T. Murakami, *ACS Earth Space Chem.* 7, 623 (2023)

Understanding Pre-reactive Minimum

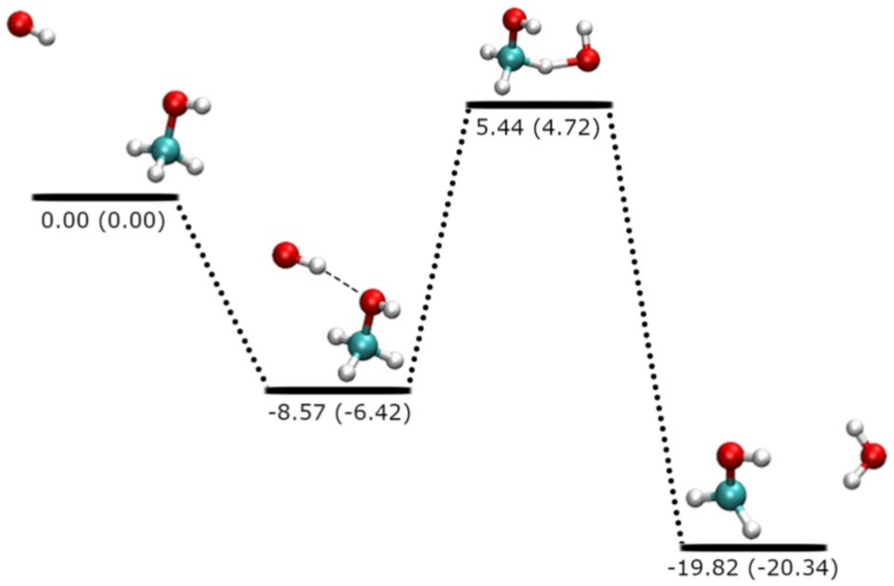
- Thermalised microcanonical instanton (TMI) rate
- Both normal and submerged instantons contribute to the thermal rate

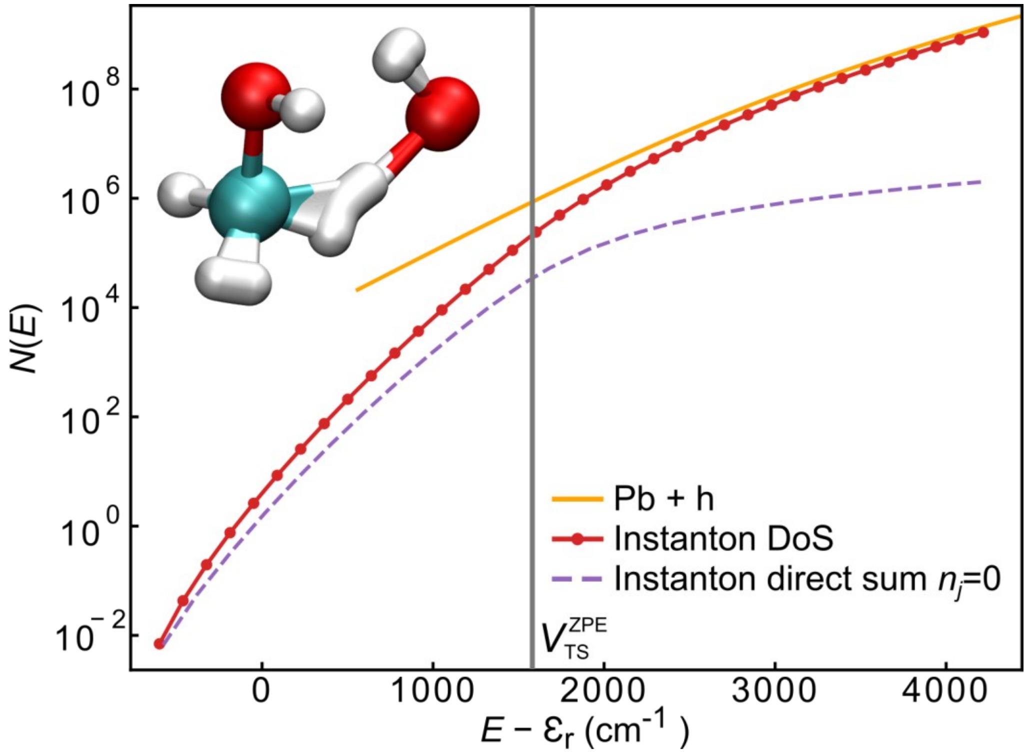


$$\begin{aligned} k_{\mathrm{TMI}}(\beta) &= \frac{\sigma}{2\pi\hbar}\frac{1}{Z_{\mathrm{r}}(\beta)}\int_{\mathcal{E}_{\mathrm{r}}}^{\infty}\mathrm{d}E\ \mathrm{e}^{-\beta E}\int_{E_{\mathrm{I}}^{\min}}^{\infty}\mathrm{d}E_{\mathrm{I}}\ P_{\mathrm{SC}}(E_{\mathrm{I}})\rho_{\mathrm{I}}(E;E_{\mathrm{I}}) \\ &= \frac{\sigma}{2\pi\hbar}\frac{1}{Z_{\mathrm{r}}(\beta)}\int_{E_{\mathrm{I}}^{\min}}^{\infty}\mathrm{d}E_{\mathrm{I}}\ P_{\mathrm{SC}}(E_{\mathrm{I}})\int_{\mathcal{E}_{\mathrm{r}}}^{\infty}\mathrm{d}E\ \rho_{\mathrm{I}}(E;E_{\mathrm{I}})\mathrm{e}^{-\beta E} \\ &= \frac{\sigma}{2\pi\hbar}\frac{1}{Z_{\mathrm{r}}(\beta)}\left[\int_{\tilde{E}_{\mathrm{I}}}^{\infty}\mathrm{d}E_{\mathrm{I}}\ P_{\mathrm{SC}}(E_{\mathrm{I}})Z_{\mathrm{I}}(\beta;E_{\mathrm{I}})\mathrm{e}^{-\beta E_{\mathrm{I}}} + \mathcal{T}(\beta;\tilde{E}_{\mathrm{I}})\right] \end{aligned}$$

Understanding Pre-reactive Minimum

- Methanol + OH reaction[1,2]
- Computed the $N(E)$ using DoS instanton theory[3]

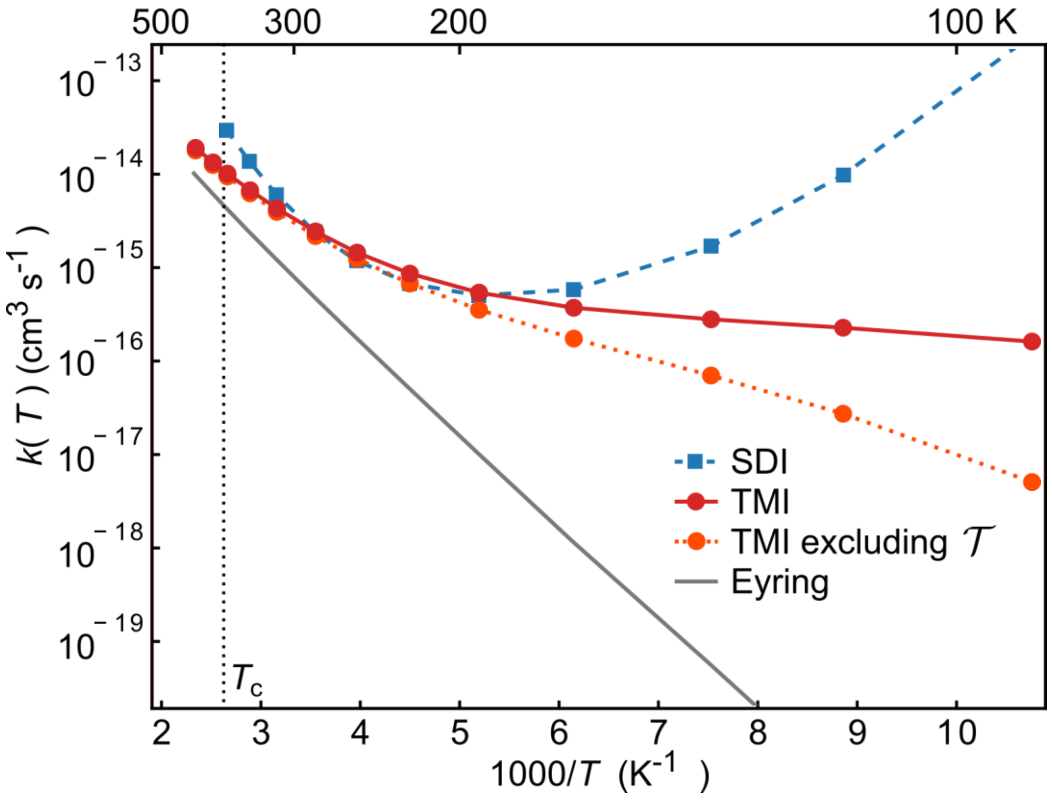




[1] Antinolo, M.; Agundez, M.; Jimenez, E.; Ballesteros, B.; Canosa, A.; Dib, G. E.; Albaladejo, J.; Cernicharo, J. Astrophys. J. 823, 25 (2016)
[2] Gao, L. G.; Zheng, J.; Fernandez-Ramos, A.; Truhlar, D. G.; Xu, X. J. Am. Chem. Soc. 140, 2906 (2018)
[3] **Fang, W.**; Winter, P.; Richardson, J. O. *J. Chem. Theory Comput.* 17, 40 (2021)

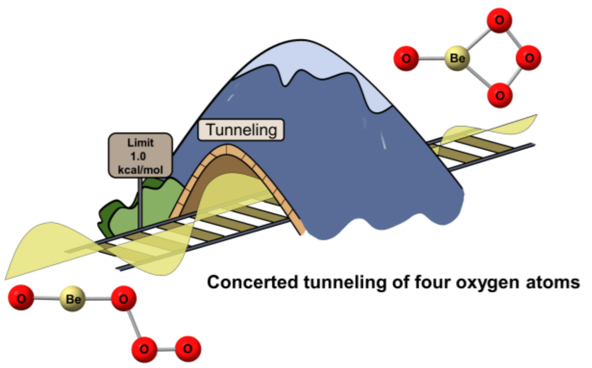
Understanding Pre-reactive Minimum

- Thermal rates for Methanol + OH reaction in the low pressure limit (LPL)
- Standard instanton theory (SDI) predicts **tunnelling dominated by submerged instanton**, which **is the behaviour when full thermalization occurs in the pre-reactive complex (HPL)**
- RPMD suffers from the same issue
- Excluding the $\mathcal{T}$ term results in under-estimating tunnelling at low temperatures
- Correctly accounting for the submerged instantons gives a near temperature independent rate



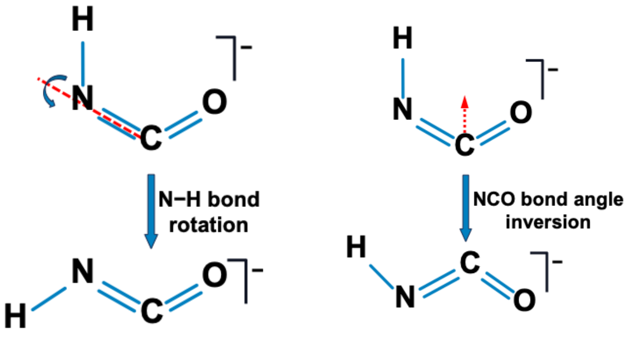
Understanding Mass-effects in Tunnelling

- We have applied instanton theory to understand the underlying mechanism of intriguing mass-dependence of tunnelling phenomenon observed in spectroscopy experiments

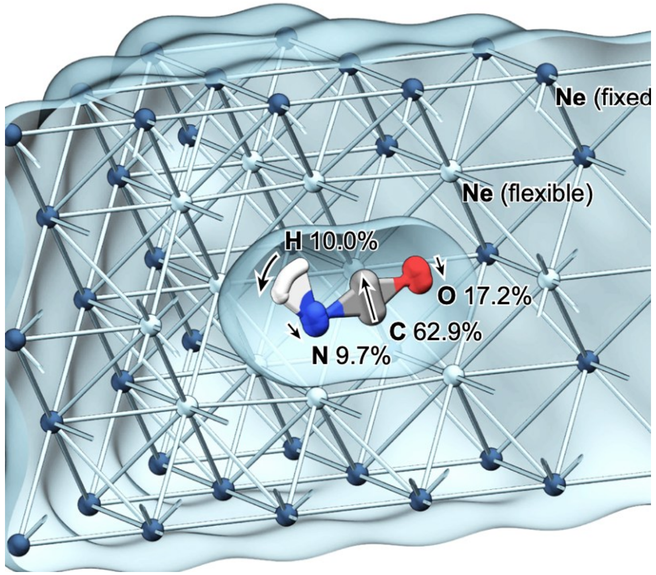


Concerted **oxygen tunnelling** mechanism in the isomerization reaction of beryllium oxide

J. Am. Chem. Soc. 145, 8817 (2023)
J. Am. Chem. Soc. 146, 26719 (2024)



KIE	Exp.	Inst.
$^{12}C/^{13}C$	1.7	1.9 – 2.4
$^{14}N/^{15}N$	1.1	1.1 – 1.1
H/D	9.9	13.2 – 15.2

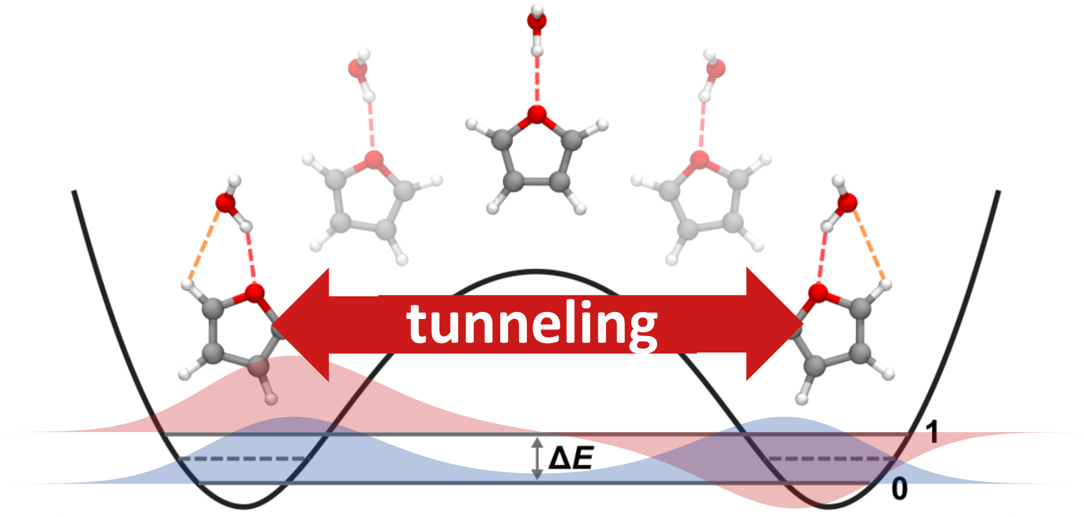


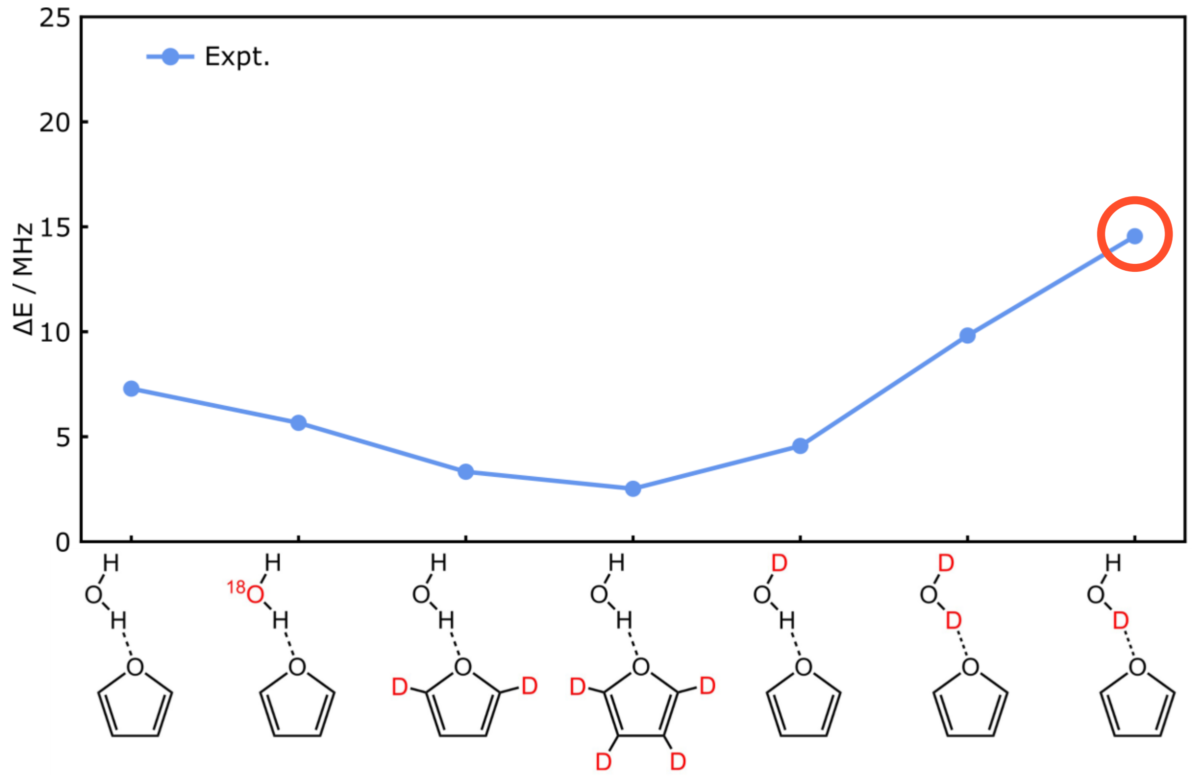
Uncovering **anomalous mass effect** in which heavy-atom tunneling competes with and dominates hydrogen-atom tunneling in the $HNCO^-$ isomerization reaction

Nat. Commun. 16, 10687 (2025)

Understanding Mass-effects in Tunnelling

- Tunnelling in the Furan-H_2O cluster can result in observable splittings in the rotational spectrum, and extensive isotope substitution experiments were performed
- Shockingly, experiments found deuterating the hydrogen-bond drastically **increases** tunnelling

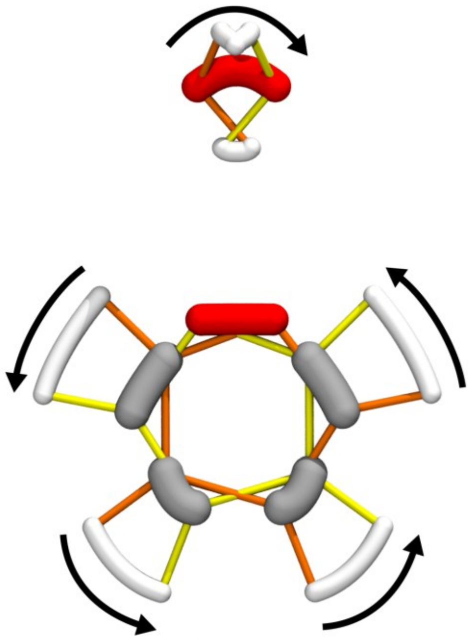




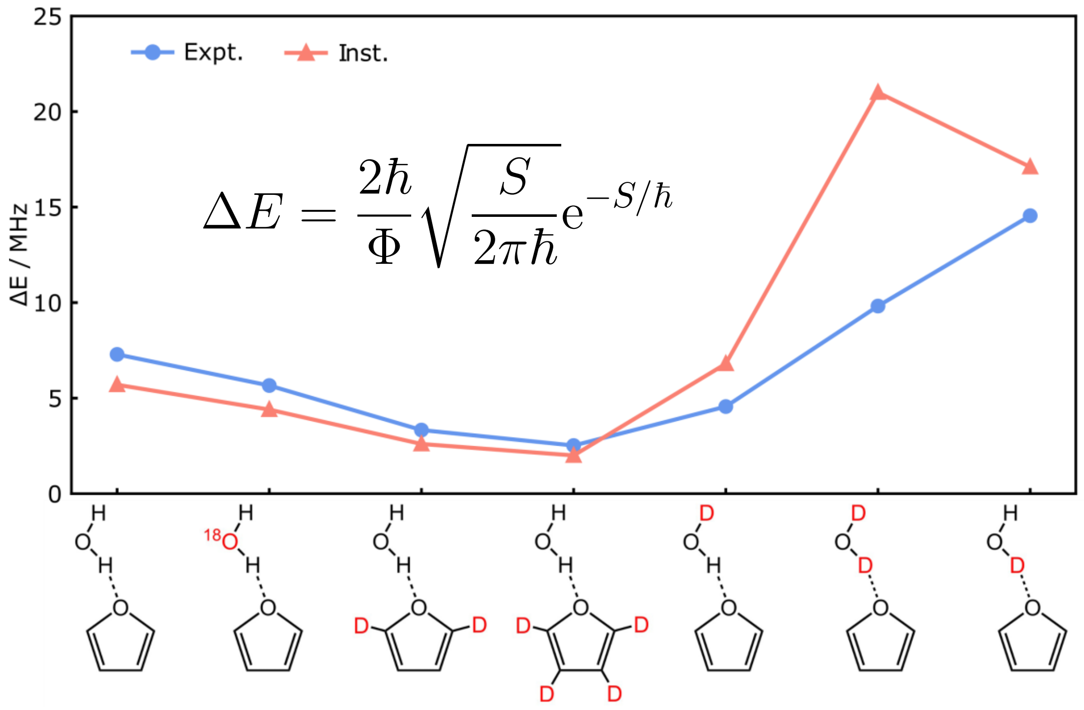
J. Phys. Chem. Lett. 16, 7773 (2025)

Understanding Mass-effects in Tunnelling

- Instanton theory calculations at the CCSD(T)-F12a/AVTZ // XYGJ-OS/AVTZ level
- Semi-quantitatively reproduce the experimental splittings

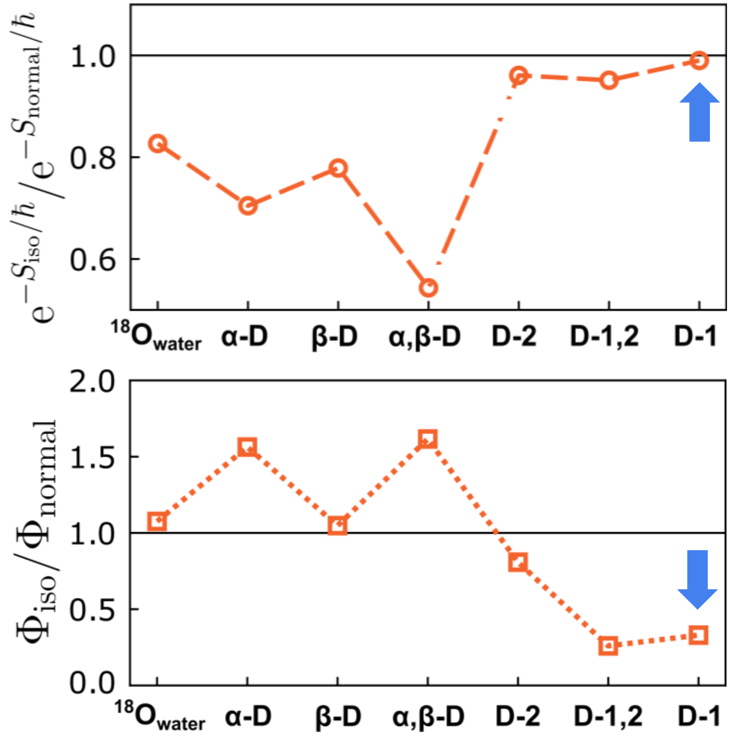


J. Phys. Chem. Lett. 16, 7773 (2025)



Understanding Mass-effects in Tunnelling

- Analysing the instanton reveals the physical origin of the inverse isotope effects
- The inverse isotope effect is caused by Φ , which can be understood as an effective ZPE effect



J. Phys. Chem. Lett. 16, 7773 (2025)

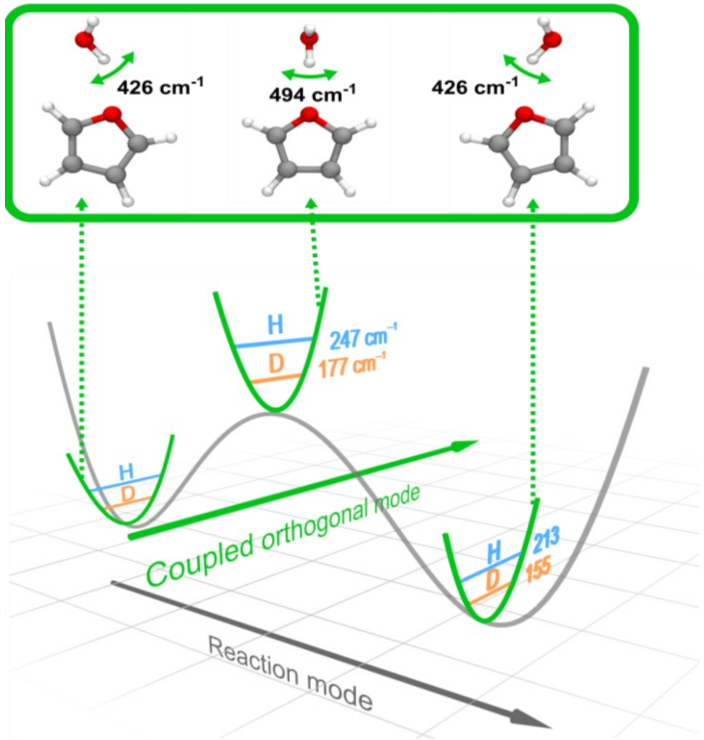
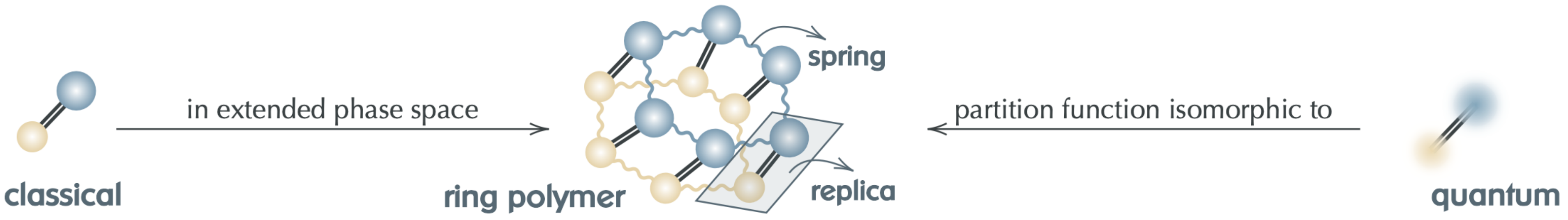


Table of Contents

Path Integral Molecular Dynamics

- Path integral molecular dynamics (PIMD): isomorphism between quantum Boltzmann statistics and the classical statistics of a ring polymer, which represents a closed imaginary time path

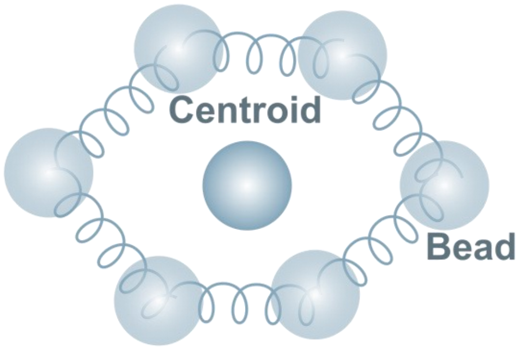


- Sampling ring-polymer carries a substantial computational overhead, typically an order of magnitude higher than classical MD, and increases to several orders for H at low temperatures
- Simulation of NQEs in complex large systems is impractical, urgently needing methodological developments

Centroid Formulation of Quantum Mechanics

- The quantum mechanical partition function can be formulated in terms of the RP centroid[1,2]

$$Z = \left(\frac{m}{2\pi\beta_P\hbar^2}\right)^{Pf/2} \int \mathrm{d}\boldsymbol{x}_1 \cdots \int \mathrm{d}\boldsymbol{x}_P \; \mathrm{e}^{-\beta_P U_{\mathrm{RP}}(\boldsymbol{x}_1,\ldots,\boldsymbol{x}_P)}$$
$$= \lambda^{-f} \int \mathrm{d}\boldsymbol{x}_\mathrm{c} \left[\frac{P^{Pf/2}}{\lambda^{(P-1)f}} \int \mathrm{d}\boldsymbol{x}_1 \cdots \int \mathrm{d}\boldsymbol{x}_P \; \delta_\mathrm{c}\, \mathrm{e}^{-\beta_P U_{\mathrm{RP}}}\right]$$
$$\equiv \lambda^{-f} \int \mathrm{d}\boldsymbol{x}_\mathrm{c} \; \mathrm{e}^{-\beta A_\mathrm{c}(\boldsymbol{x}_\mathrm{c};\beta)}$$



- A_c is the centroid free energy, its derivative is the centroid force

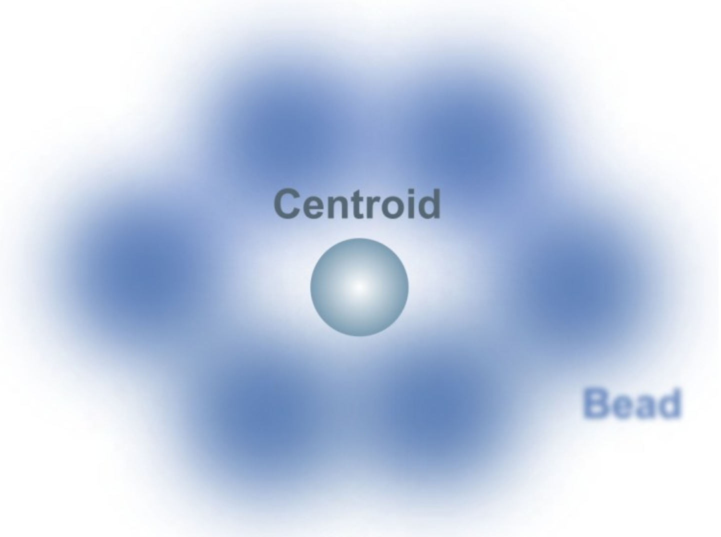
$$\boldsymbol{f}_c = -\frac{\partial A_\mathrm{c}}{\partial \boldsymbol{x}_\mathrm{c}} = \langle -\nabla_{\mathbf{x}_\mathrm{c}} U_{RP}(\boldsymbol{x}_1, \ldots, \boldsymbol{x}_P) \rangle_{U_{\mathrm{RP}},\boldsymbol{x}_\mathrm{c}}$$

- Since $\boldsymbol{f}_\mathrm{c}$ is accessible, MD performed using $\boldsymbol{f}_\mathrm{c}$ corresponds to the widely recognised Centroid Molecular Dynamics (CMD) method[2]

[1] Feynman, R. P.; Hibbs, A. R. Quantum Mechanics and Path Integrals; McGraw-Hill, 1965
[2] Voth, G. A. Path-integral centroid methods in quantum statistical mechanics and dynamics. *Adv. Chem. Phys.* 93, 135 (1996)

Path Integral Coarse-Graining

- CMD closely resembles classical MD, therefore offering the prospect of incorporating NQEs at classical cost
- A significant advance towards this is the machine learning of $\boldsymbol{f}_c$, known as the path integral coarse-graining (PIGS) framework[1-3]
- This coarse-grained the ring polymer into its centroid and the effective force acting on the centroid
- However, due to the lack of knowledge of A_c , PIGS predicts unreliable A_c , and undermines system & size transferability for A_c
- Therefore, PIGS cannot rigorously recover quantum thermodynamic quantities
- In addition, PIGS cannot capture the temperature dependence of the CMD effective potential



[1] Musil, F.; Zaporozhets, I.; Noé, F.; Clementi, C.; Kapil, V., *J. Chem. Phys.* 157, 181102 (2022)
[2] Loose, T. D.; Sahrmann, P. G.; Voth, G. A., *J. Chem. Theory Comput.* 18, 5856 (2022)
[3] Wu, C.; Li, R.; Yu, K., *Front. Mol. Biosci.* 9, 851311 (2022)

Instanton Free Energy Perturbation

- The most efficient approach to compute free energy is via free energy perturbation (FEP), which computes the free energy relative to a reference system:

$$A_{\mathrm{c},b} - A_{\mathrm{c},a} = -\frac{1}{\beta} \ln \left\langle \mathrm{e}^{-\beta_P (U_b - U_a)} \right\rangle_{U_a, \boldsymbol{x}_\mathrm{c}}$$

- Inspired by instanton theory, since instantons are pseudoparticles, we use **instanton-like** ring-polymers **x*** as the reference (RPI-FEP)

$$U_{\mathrm{RPI}}(\mathbf{x}) = U_{\mathrm{RP}}\big|_{\mathbf{x}^*} + \frac{1}{2}(\mathbf{x} - \mathbf{x}^*)^{\mathrm{T}} \left. \widetilde{\mathbf{H}}_{\mathrm{RP}} \right|_{\mathbf{x}^*} (\mathbf{x} - \mathbf{x}^*)$$

- The instanton-reference free energy can be computed *analytically*:

$$A_{\mathrm{c,RPI}}(\boldsymbol{x}_\mathrm{c}; \beta) = -\frac{1}{\beta} \ln \left[P^{f+1} \sqrt{\frac{B_P}{2\pi \beta_P \hbar^2}} \prod_{k=2}^{(P-1)f} \frac{1}{\beta_P \hbar \eta_k} \right] + \frac{U_{\mathrm{RP}}|_{\mathbf{x}^*}}{P}$$

$$B_P = \sum_{i=1}^{P} \sum_{j=1}^{f} m_j \left(x^*_{i+1,j} - x^*_{i,j} \right)^2$$

J. Shen, Z. Ye, M. Du, S. He, D. H. Zhang, J.-X. Zeng, V. Kapil, **W. Fang**, submitted, https://arxiv.org/abs/2602.18821

Instanton Free Energy Perturbation

- With the instanton reference, the centroid free energy can be computed via path integral Monte Carlo (PIMC) with the Gaussian sampling protocol:

$$A_{\mathrm{c}} = A_{\mathrm{c,RPI}} - \frac{1}{\beta} \ln \frac{\int \mathrm{d}q_2 \cdots \mathrm{d}q_{(P-1)f}\, w\, \mathrm{e}^{-\beta_P (U_{\mathrm{RP}} - U_{\mathrm{RPI}})}\, \mathrm{e}^{-\beta_P U_{\mathrm{RPI}}}}{\int \mathrm{d}q_2 \cdots \mathrm{d}q_{(P-1)f}\, \mathrm{e}^{-\beta_P U_{\mathrm{RPI}}}}$$

- The weight term w arises from Jacobian determinant of the transformation to a permutational invariant coordinate:

$$w = \frac{1}{B_P} \sum_{i=1}^{P} \sum_{j=1}^{f} m_j \left(x_{i+1,j} - x_{i,j}\right) \left(x^*_{i+1,j} - x^*_{i,j}\right)$$

- The instanton reference describes tunnelling through barriers, enabling applications to chemical reactions

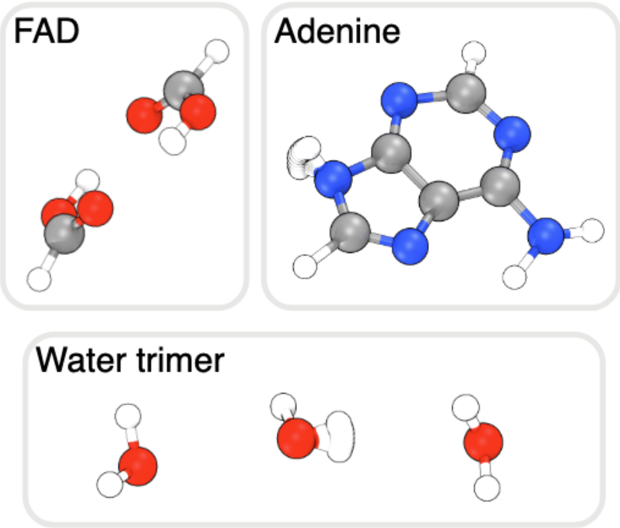
- If the vibrational modes at the centroid satisfy $\mathrm{Im}\, \omega_j < \frac{2\pi}{\beta\hbar}$, the "instanton" collapses and $A_{\mathrm{c,RPI}}$ returns to the P-bead RP free energy for a harmonic oscillator with the centroid constrained:

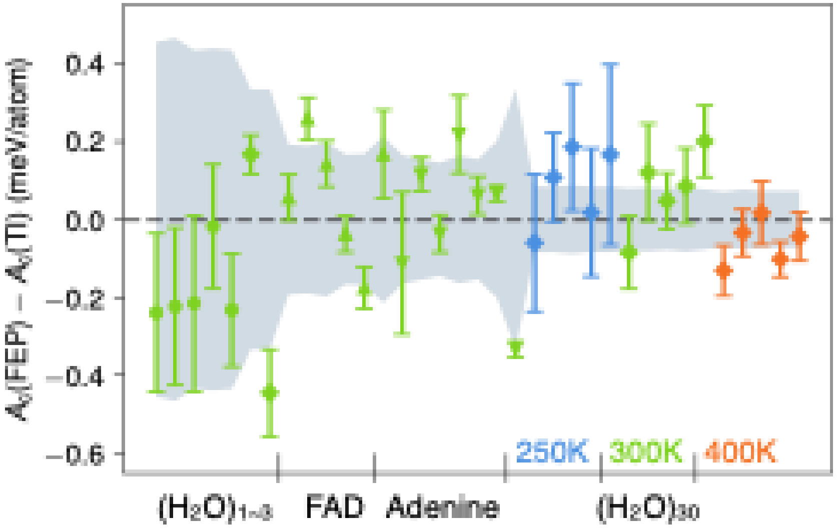
$$A_{\mathrm{c,HO}}\left(\boldsymbol{x}_{\mathrm{c}}; \beta\right) = \frac{1}{\beta} \sum_{j=1}^{f} \ln \frac{\sinh\left[P \sinh^{-1}\left(\beta_P \hbar \omega_j / 2\right)\right]}{\beta \hbar \omega_j / 2} + V(\boldsymbol{x}_{\mathrm{c}})$$

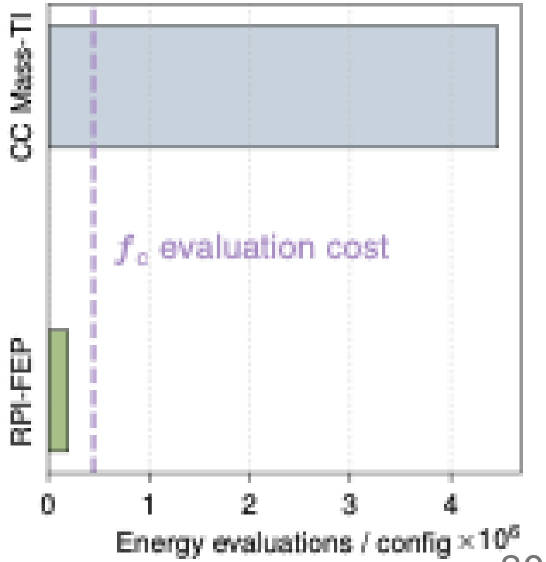
Instanton Free Energy Perturbation

- RPI-FEP calculation in practice:
  1. Optimization instanton with the centroid constrained
  2. Calculate instanton hessian and its eigenvalues η_k and eigenvectors $\mathbf{e}_k$
  3. Perform PIMC to obtain A_c

- Benchmark of RPI-FEP:
  - Test performance on molecules and clusters
  - All simulations employ the MACE-OFF23 foundation model, which is further fine-tuned for each system
  - Achieves quantitative agreement with reference calculations, demonstrating that **RPI-FEP can accurately and efficiently compute A_c**







Entropic Path Integral Coarse-Graining

- Entropic path integral coarse-graining (**EPIGS**) leverages **machine learning to construct a size- and temperature-transferable PES that encodes NQEs**
- The centroid **entropy** is the temperature derivative of the centroid free energy A_c, therefore it serves as the key quantity for learning the temperature dependence of A_c
- Centroid entropy is obtained from the same centroid-constrained PIMD simulation which we obtain $\boldsymbol{f}_c$ from:

$$TS_c = \beta \frac{\partial A_c}{\partial \beta} = \left\langle \widehat{K} + \widehat{V} \right\rangle_{U_{RP}, \boldsymbol{x}_c} - \frac{f}{2\beta} - A_c$$

- **EPIGS Dataset structure**: We employ a Δ-learning strategy: training on the difference between the centroid free energy surface and the PES

$$\Delta A_c(\boldsymbol{x}_c; \beta) \equiv A_c(\boldsymbol{x}_c; \beta) - V(\boldsymbol{x}_c) \qquad \Delta \boldsymbol{f}_c(\boldsymbol{x}_c; \beta) \equiv \boldsymbol{f}_c(\boldsymbol{x}_c; \beta) - \boldsymbol{f}(\boldsymbol{x}_c)$$

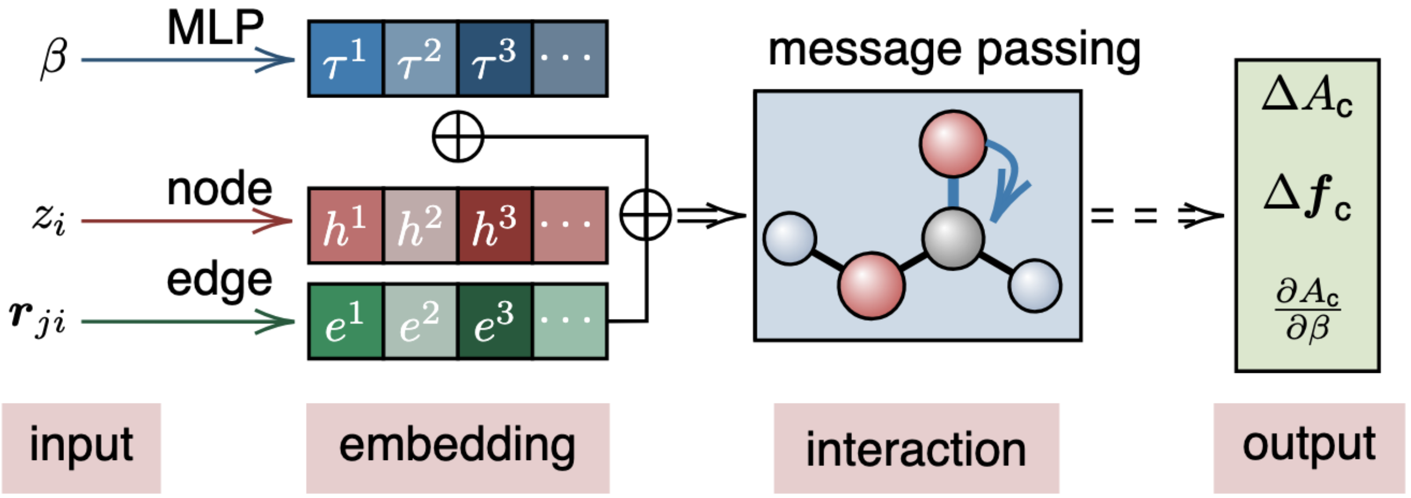
- The training data consists of **centroid potential**, **centroid forces**, and **centroid entropy**:

$$\mathcal{D} = \left\{ \left(\boldsymbol{x}_c^{(j)}, T^{(j)}, \Delta A_c^{(j)}, \Delta \boldsymbol{f}_c^{(j)}, S_c^{(j)} \right) \right\}_{j=1}^{M}$$

J. Shen, Z. Ye, M. Du, S. He, D. H. Zhang, J.-X. Zeng, V. Kapil, **W. Fang**, submitted, https://arxiv.org/abs/2602.18821

Entropic Path Integral Coarse-Graining

- **Architecture:** We modify the MACE graph neural network to serve as the machine-learning framework for EPIGS
- EPIGS takes in the pair-wise distances of a centroid geometry, atom type, and the inverse temperature as input and predicts ΔA_c , $\Delta \boldsymbol{f}_\mathrm{c}$, and S_c



- **Training:** An entropic term contribution is included in the loss function

$$\mathcal{L} = w_A \mathcal{L}_A + w_f \mathcal{L}_f + w_S \mathcal{L}_S$$

Entropic Path Integral Coarse-Graining

- **Inference:** EPIGS transforms the classical potential energy and forces into the centroid free energy and centroid forces, and provides the entropy needed for thermodynamic estimators
- EPIGS enables **CMD to be rigorously performed at the cost of classical MD,** achieving **efficient quantum dynamics** and **rigorous quantum thermodynamics** simulations
- The quantum mechanical internal energy can be computed from an EPIGS-MD simulation:

$$U^{\mathrm{q}} = -\frac{\partial \ln Z}{\partial \beta} = \frac{\int \mathrm{d}\boldsymbol{x}_{\mathrm{c}} \left(A_{\mathrm{c}} + \beta \frac{\partial A_{\mathrm{c}}}{\partial \beta}\right) \mathrm{e}^{-\beta A_{\mathrm{c}}(\boldsymbol{x}_{\mathrm{c}};\beta)}}{\int \mathrm{d}\boldsymbol{x}_{\mathrm{c}}\, \mathrm{e}^{-\beta A_{\mathrm{c}}(\boldsymbol{x}_{\mathrm{c}};\beta)}} + \frac{f}{2\beta}$$

- The classical-to-quantum free energy difference can be computed via EPIGS-TI simulation:

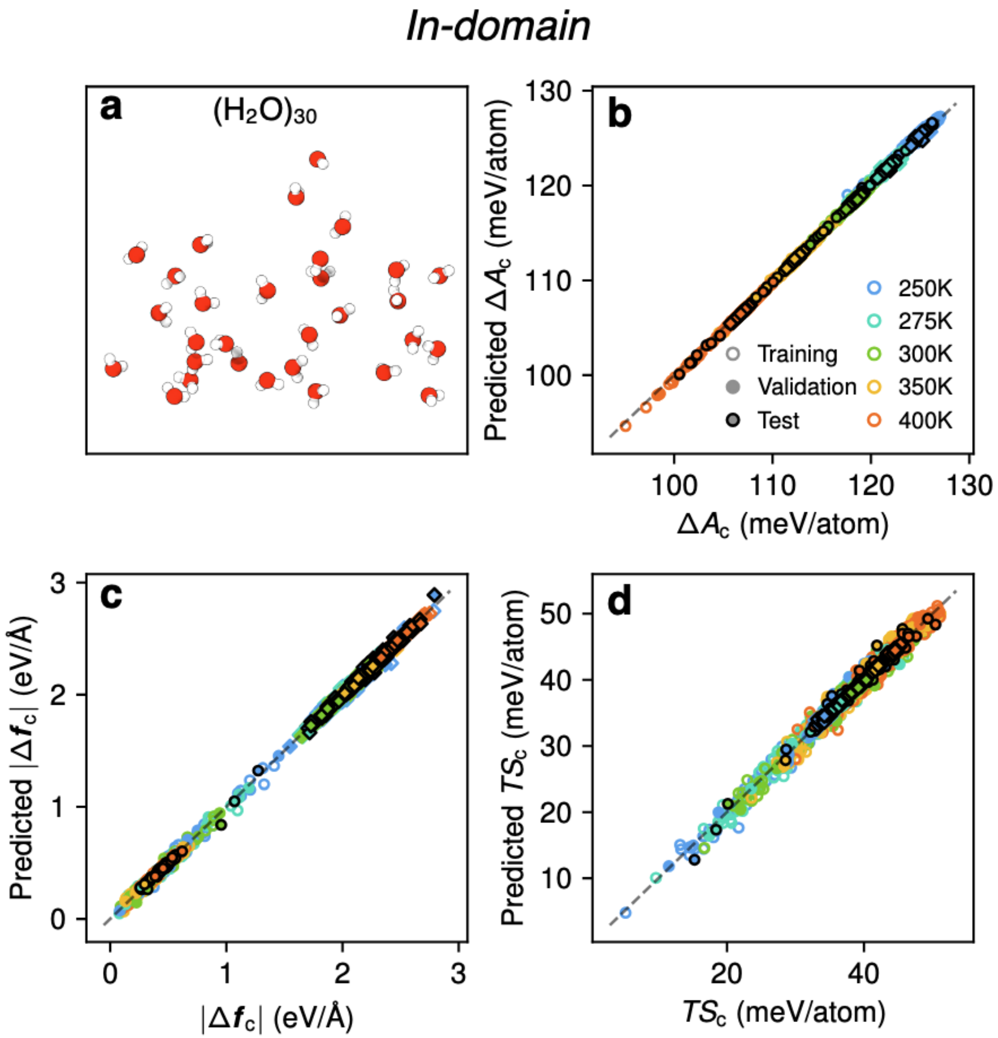
$$A^{\mathrm{q}} - A^{\mathrm{cl}} \equiv \Delta A^{\mathrm{q}\leftarrow\mathrm{cl}} = \int_0^1 \mathrm{d}\lambda \frac{\int \mathrm{d}\boldsymbol{x}_{\mathrm{c}}\, \Delta A_{\mathrm{c}}\, \mathrm{e}^{-\beta V_{\lambda}(\boldsymbol{x}_{\mathrm{c}};\beta)}}{\int \mathrm{d}\boldsymbol{x}_{\mathrm{c}}\, \mathrm{e}^{-\beta V_{\lambda}(\boldsymbol{x}_{\mathrm{c}})}}$$

$$V_{\lambda} = V + \lambda\left(A_{\mathrm{c}} - V\right)$$

- Enthalpy and Gibbs free energy can be computed similarly

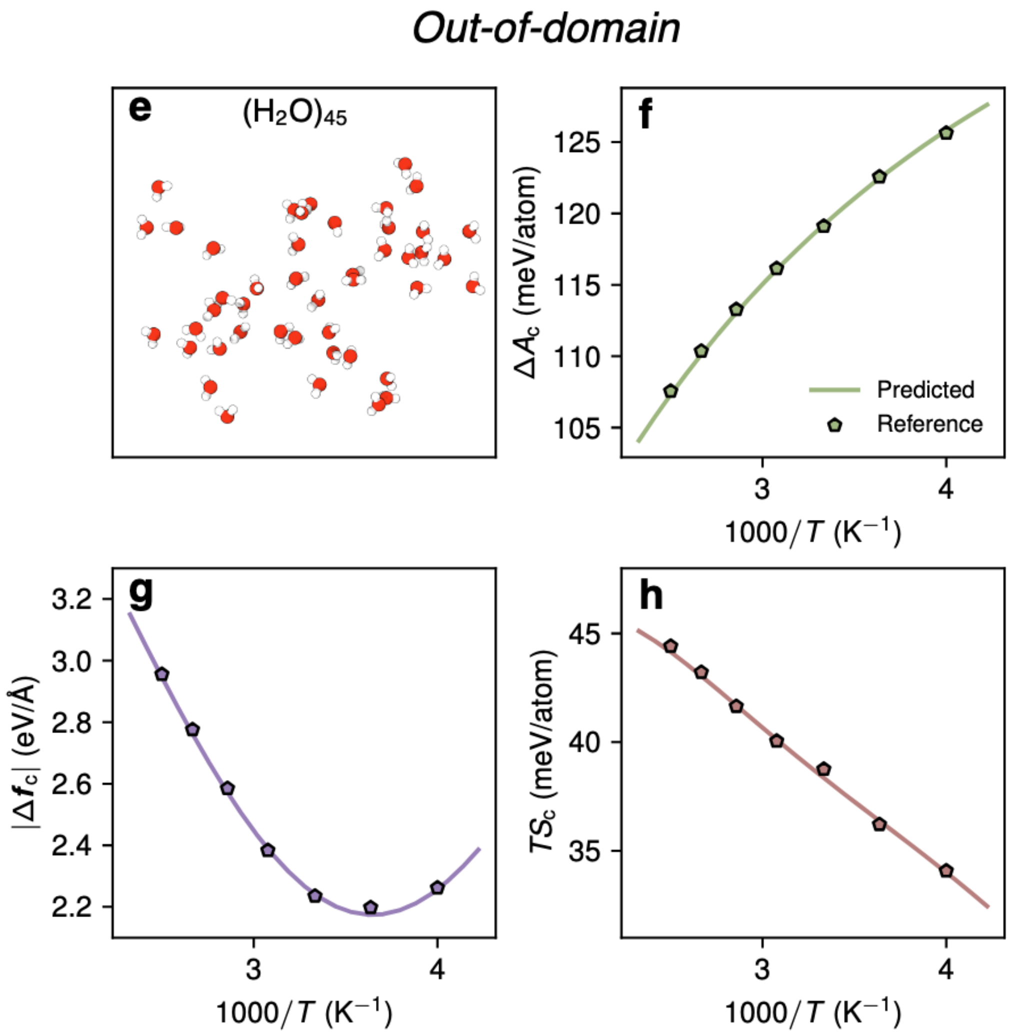
Temperature Transferability of EPIGS

- Train EPIGS on 132 $(H_2O)_1$ and 209 $(H_2O)_{30}$ configurations, with ΔA_c , $\Delta \boldsymbol{f}_c$, and TS_c data obtained at temperatures from 250 – 400 K
- EPIGS predicts ΔA_c with small RMSEs of ~0.2 meV/atom **across all temperatures**
- Similarly strong performance is observed for TS_c, with RMSE below 0.7 meV/atom (~2% relative error)
- Small validation and test errors indicate minimal overfitting



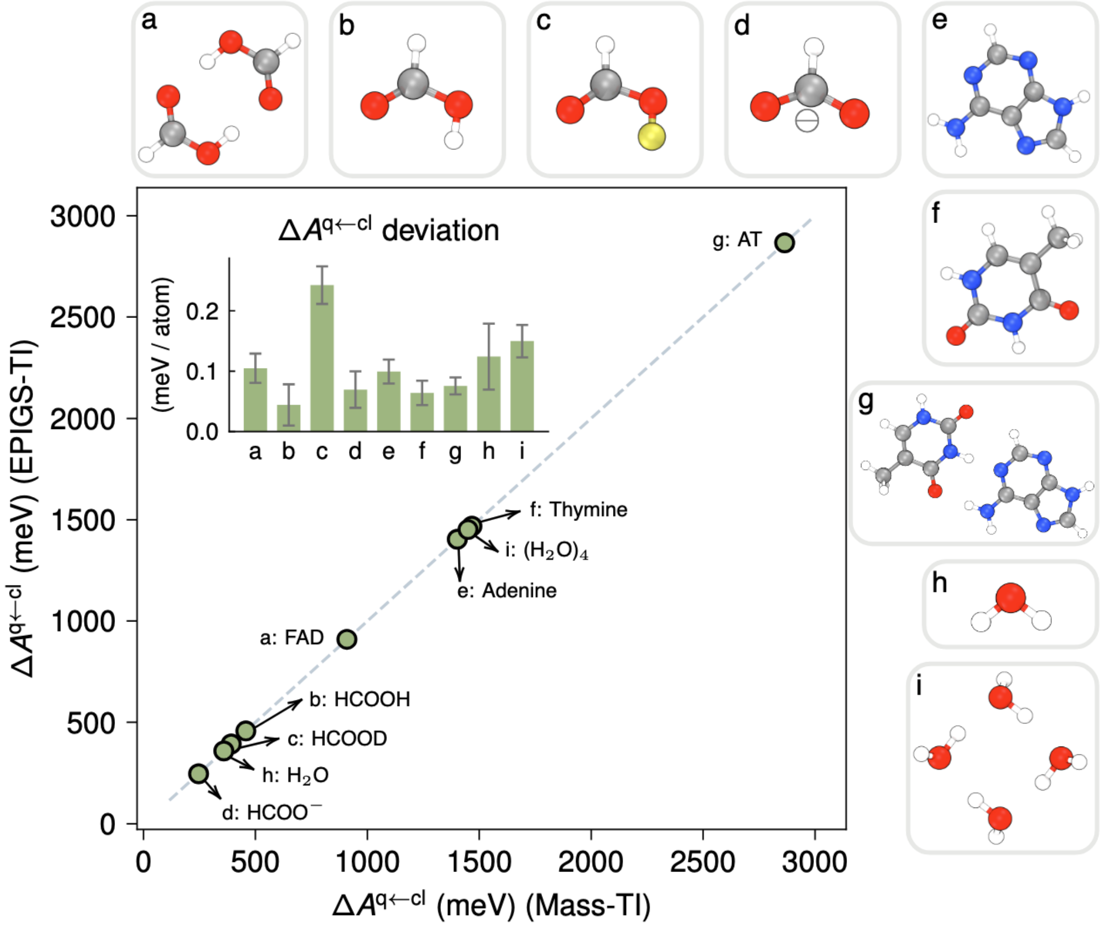
Size Transferability of EPIGS

- We test the performance of EPIGS on an unseen $(H_2O)_{45}$ cluster
- Achieves quantitative agreement with reference calculations for ΔA_c , $\Delta \boldsymbol{f}_c$, and TS_c across the full temperature range
- Demonstrating robust size transferability of the learned quantum thermodynamic
- **Learn small and predict big**



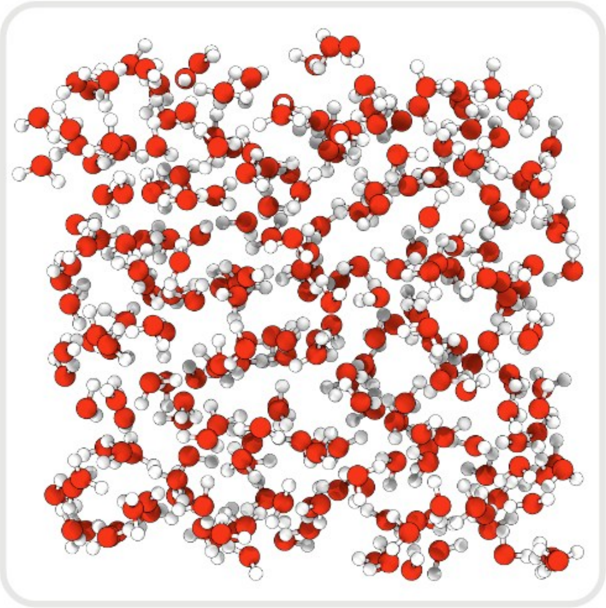
Quantum Free Energy from EPIGS

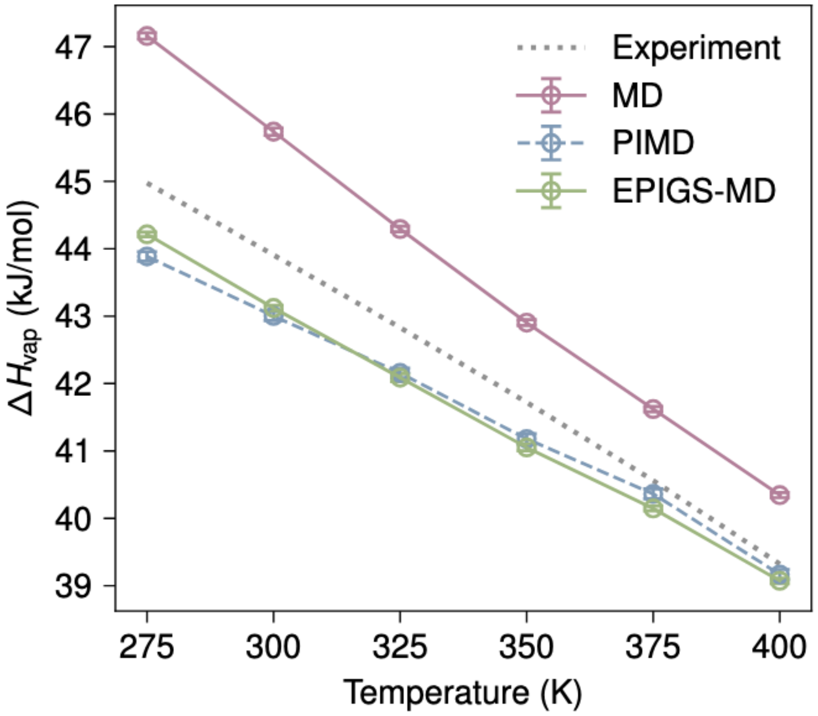
- Benchmark across nine representative gas-phase systems
- Classical-to-quantum free energy differences $\Delta A^{\mathrm{q}\leftarrow\mathrm{cl}}$ computed via EPIGS-TI quantitatively agree with reference results within ~0.1 meV/atom (relative error ~0.1%)
- Consistent good performance across all systems tested

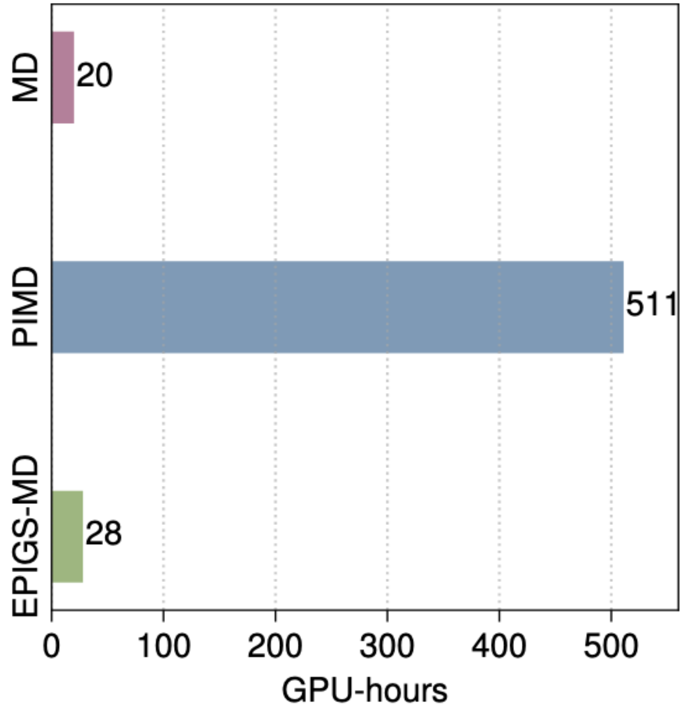


Quantum Enthalpy of Liquid Water

- EPIGS-MD prediction of the enthalpy of vaporization of liquid water from 275 to 400 K
- EPIGS Achieves **quantitative agreement** with PIMD despite trained only on water monomer and $(H_2O)_{30}$ clusters
- Costs **over 20 times cheaper than PIMD**

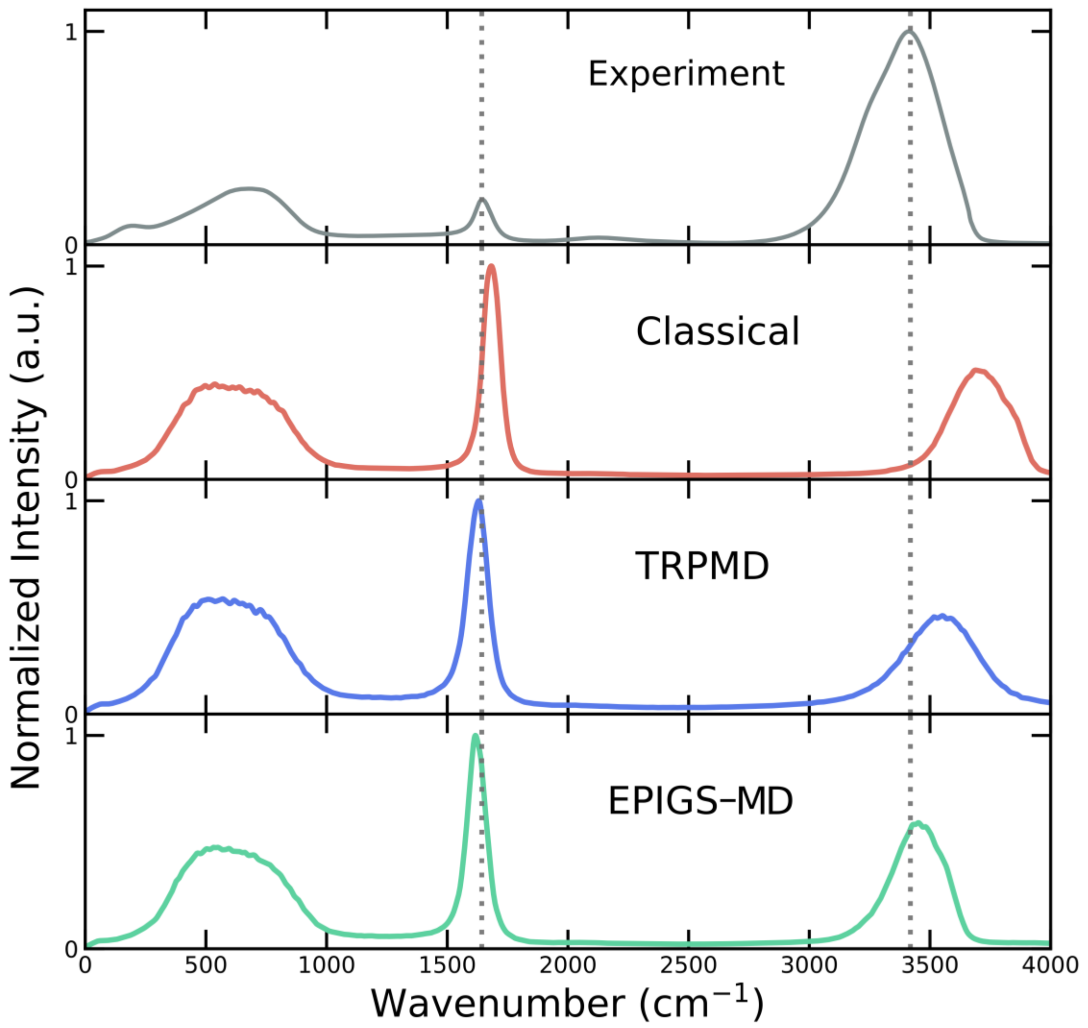






IR Spectrum from EPIGS

- EPIGS-MD prediction of the IR spectrum of liquid water at 300 K
- Classical MD predict severe blue shifts in the H-bond vibration peaks compared to the experimental results due to the lack of NQEs
- TRPMD reaches closer agreement in the peak position with the experiment, but at a computational overhead of ~20
- EPIGS-MD achieves the best agreement with experiment, while paying only ~40% of extra cost compared to classical MD



Summary

- Semiclassical instanton theory is a powerful framework for understanding tunnelling phenomena
- Instanton FEP made the centroid free energy feasible to compute
- Utilizing the centroid free energy and entropy, we developed EPIGS method that can rigorously simulate quantum thermodynamics at the cost of classical MD

PyRInst

Quantum Reaction Dynamics Platform
Based on Ring-Polymer Instanton Theory

INST

Instanton Rate

- **Optimizers:** eigenvector-following, LBFGS, stream-bed walking
- **GPR** accelerated instanton optimization
- Instanton rate for deep quantum tunneling reactions
- **Post-processing tools**: thermodynamic analysis, instanton analysis, dual-level correction, Wigner correction
- **Kinetic isotope effects** (KIE)

RPI-FEP

- **Instanton reference**: collapsed RP reference for stationary structure, fixed-centroid instanton optimization for imaginary-frequency structure
- **FEP**: PIMC with Gaussian sampling protocol
- Path integral centroid free energy and entropy evaluation

PES Interface

- *Ab initio* software: Gaussian / ORCA / VASP
- Machine learning potential: MACE
- Custom PES interface

Official Repo:
https://github.com/WeiFang-Lab/pyrinst

復旦大學

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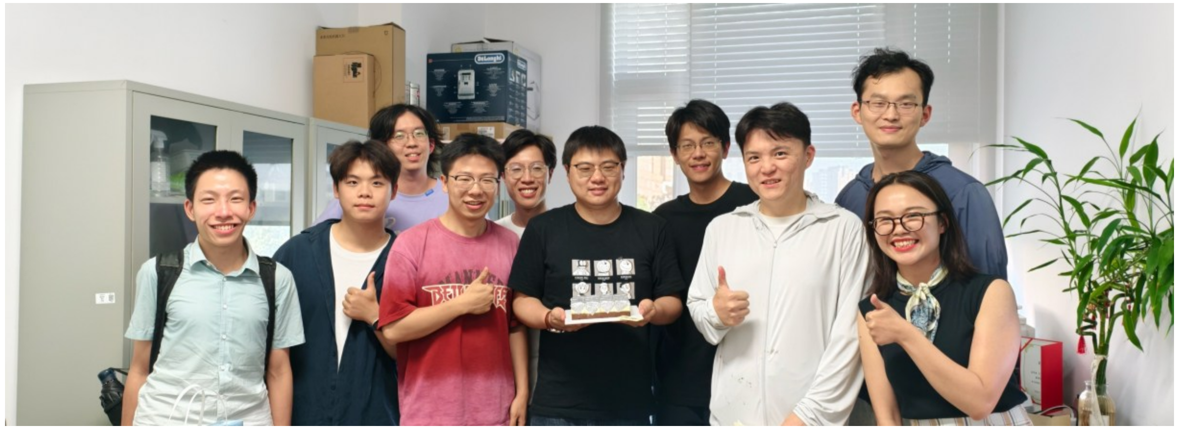

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THANK YOU!

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