PATH INTEGRAL MOLECULAR DYNAMICS: APPLICATIONS & NEW ALGORITHMS.

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IPAM CCS Workshop
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Outline

- Introduction to Path Integrals (PI)
- Double proton transfer in DNA base pair models
- Development of free energy methods in PIMD
- Improving the convergence of PIMD
- Summary

Outline

Introduction to Path Integrals

Double proton transfer in DNA base pair models

Development of free energy methods in PIMD

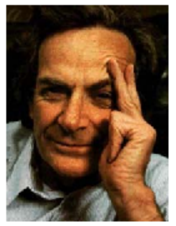
Improving the convergence of PIMD

Summary

Quantum Mechanics in Nature

What can PI do for you?

- Delocalization
- Zero Point Energy (ZPE)
- Tunneling
- Theory development (QCD)
- quantum dynamics?



R. P. Feynman

`www.wikipedia.org` JCP **130**, *184105* (2009).

PI Formulation of Canonical Partition Function

The canonical density matrix operator

$$\boxed{\rho\left(\beta\right) = \exp\left(-\beta\mathcal{H}\right)},$$

where $\mathcal{H} = T + U$ and $[T, U] \neq 0$.

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[1] Tuckerman, *Stat. Mech.: Theory & Molecular Simulation*, **Oxford**, 2010

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The canonical density matrix operator

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where $\mathcal{H}=T+U$ and $[T,U]\neq 0$.

$$Z\left(\beta\right)=Tr\left(e^{-\beta\mathcal{H}}\right)=\int dx_1\langle x_1|e^{-\beta(T+U)}|x_1\rangle=\lim_{\mathrm{P}\rightarrow\infty}\int dx_1\langle x_1|\Omega^{\mathrm{P}}|x_1\rangle,$$

where $\Omega=e^{-\frac{\beta}{2\mathrm{P}}U}e^{-\frac{\beta}{\mathrm{P}}T}e^{-\frac{\beta}{2\mathrm{P}}U}$, which follows from Trotter theorem[1]

$$e^{-\beta(T+U)}\quad=\quad\lim_{\mathrm{P}\rightarrow\infty}\left[e^{-\frac{\beta}{2\mathrm{P}}U}e^{-\frac{\beta}{\mathrm{P}}T}e^{-\frac{\beta}{2\mathrm{P}}U}\right]^{\mathrm{P}}.$$

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Inserting $(\mathrm{P}-1)$ completeness relations $I = \int dx|x\rangle\langle x|$

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$$\begin{aligned} Z(\beta) &= \lim_{P\to\infty} \int dx_1 dx_2 \cdots dx_P \langle x_1|\Omega|x_2\rangle\langle x_2|\Omega|x_3\rangle \cdots \langle x_P|\Omega|x_1\rangle \\ &= \lim_{P\to\infty} \int \prod_{i=1}^{P} dx_i \langle x_i|\Omega|x_{i+1}\rangle|_{x_{P+1}=x_1}. \end{aligned}$$

Inserting $(\mathrm{P}-1)$ completeness relations $I = \int dx|x\rangle\langle x|$

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\end{aligned}
$$

Need to compute

$$
\begin{aligned}
\langle x_i|\Omega|x_{i+1}\rangle &= \langle x_i|e^{-\frac{\beta}{2\mathrm{P}}U} e^{-\frac{\beta}{\mathrm{P}}T} e^{-\frac{\beta}{2\mathrm{P}}U}|x_{i+1}\rangle \\
&= e^{-\frac{\beta}{2\mathrm{P}}\left[U(x_i)+U(x_{i+1})\right]} \langle x_i|e^{-\frac{\beta}{\mathrm{P}}T}|x_{i+1}\rangle.
\end{aligned}
$$

What can we do...?

Introduce complete set momentum eigenstates $I = \int dp |p\rangle\langle p|$

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$$\langle x_i|e^{-\frac{\beta}{\mathrm{P}}T}|x_{i+1}\rangle = \int dp\langle x_i|p\rangle\langle p|e^{-\frac{\beta}{\mathrm{P}}T}|x_{i+1}\rangle = \int dpe^{-\beta p^2/2m\mathrm{P}}\langle x_i|p\rangle\langle p|x_{i+1}\rangle.$$

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Now use $\langle x|p\rangle = \frac{1}{\sqrt{2\pi\hbar}}e^{ipx/\hbar}$ in previous equality

$$\frac{1}{2\pi\hbar}\int dp\ e^{-\frac{\beta}{2m\mathrm{P}}p^2}\ e^{ip(x_i-x_{i+1})/\hbar} \quad = \quad \sqrt{\frac{m\mathrm{P}}{2\pi\beta\hbar^2}}e^{-\frac{m\mathrm{P}}{2\beta\hbar^2}(x_{i+1}-x_i)^2},$$

where we have completed the square in the last expression.

Then, we obtain

$$\langle x_i|\Omega|x_{i+1}\rangle = \sqrt{\frac{m\mathrm{P}}{2\pi\beta\hbar^2}}\, e^{-\frac{m\mathrm{P}}{2\beta\hbar^2}(x_{i+1}-x_i)^2-\frac{\beta}{2\mathrm{P}}[U(x_i)+U(x_{i+1})]}.$$

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Path integral representation of canonical quantum PF

$$Z(\beta) = \lim_{\mathrm{P}\to\infty}\left(\frac{m\mathrm{P}}{2\pi\beta\hbar^2}\right)^{\mathrm{P}/2}\int_{x_{\mathrm{P}+1}=x_1} dx_1\cdots dx_{\mathrm{P}}\; e^{-\beta U_{eff}},$$

where $U_{eff} = \sum_{i=1}^{\mathrm{P}}\left[\frac{m\mathrm{P}}{2\beta^2\hbar^2}(x_{i+1}-x_i)^2 + \frac{1}{\mathrm{P}}U(x_i)\right]$.

Each quantum particle is mapped onto a collection of P interacting quasi-particles.[1]

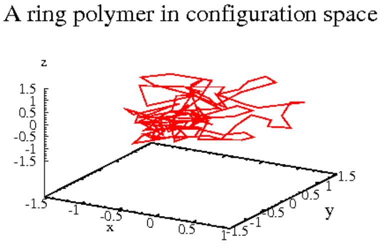
[1] Chandler & Wolynes, JCP **74** *4078* (1981).

The ring-polymer isomorphism

Analytical solutions to path integrals are limited:
devise numerical techniques for complex systems.
Discretized version of the path integral quantum PF:

$$Z(\beta) = \lim_{\mathrm{P}\to\infty} \left(\frac{m\mathrm{P}}{2\pi\beta\hbar^2} \right)^{\mathrm{P}/2} \int dx_1 \cdots dx_{\mathrm{P}}\, e^{-\beta \sum_{i=1}^{\mathrm{P}} \left[\frac{m}{2}\omega_{\mathrm{P}}^2 (x_i - x_{i+1})^2 + \frac{U(x_i)}{\mathrm{P}} \right]},$$

where $\omega_{\mathrm{P}}^2 = \mathrm{P}/\left(\beta\hbar\right)^2$ and $x_{\mathrm{P}+1} = x_1$.


A ring polymer in configuration space

A quantum particle is mapped onto a collection of **P** "*beads*" coupled via harmonic springs & each under external potential U/P.

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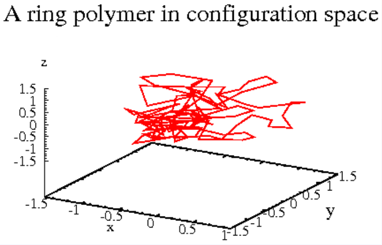
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centroid $x_c = \frac{1}{\mathrm{P}} \sum_{i=1}^{\mathrm{P}} x_i$

The ring-polymer isomorphism

Introducing nuclear quantum effects with the ring polymer.

zero-point energy

tunneling

`www.telluridescience.org/TullyLectures/tully.pdf`

PIMD Implementation

Assuming ergodicity, sampling can be effected using MD. Introduce a set of uncoupled Gaussian integrals to enable sampling of phase space (fictitious m'_k)

$$Z(\beta) \approx \mathcal{N} \int dp_1 \cdots dp_\mathrm{P}\; dx_1 \cdots dx_\mathrm{P}\; e^{-\beta \sum_{k=1}^{\mathrm{P}} \left[\frac{p_k^2}{2m'_k} + \frac{m}{2}\omega_\mathrm{P}^2 (x_k - x_{k+1})^2 + \frac{1}{\mathrm{P}} U(x_k) \right]}.$$

- Remember: Time is only a parameter for the exploration of phase space (**unphysical dynamics**).
- *Naive* PIMD implementation suffers from non-ergodicity & multiple time scales issues[1].

---

[1] Hall & Berne, JCP **81** *3641* (1984).

Efficient PIMD Implementation

Solution M. Tuckerman *et al.* JCP **99** *2796* (1993).

- Transformation coordinates:
  normal modes $u_k = \frac{1}{\sqrt{\mathrm{P}}} \sum_{j=1}^{\mathrm{P}} x_j e^{2\pi i (j-1)(k-1)/\mathrm{P}}$ (centroid is u_1)
  or staging $u_1 = x_1, u_k = x_k - \frac{(k-1)x_{k+1}+x_1}{k}, k = 2, \cdots, \mathrm{P}$.

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$$\tilde{H}(\mathbf{u},\mathbf{p}) = \sum_{k=1}^{\mathrm{P}} \left[\frac{p_k^2}{2m_k'} + \frac{m_k}{2}\omega_{\mathrm{P}}^2 u_k^2 + \frac{1}{\mathrm{P}} U\left(x_k(\mathbf{u})\right) \right],$$

  where $m_1 = 0$. $m_k = \frac{k}{k-1} m$ for staging and
  $m_k = 2m\mathrm{P}\left[1 - \cos\left(2\pi(k-1)/\mathrm{P}\right)\right]$ for normal modes.
- Fictitious masses chosen to collapse all time scales
  $m_1' = m, \ m_k' = m_k$
- Massive thermostats

Although computationally intensive, PIMD can be parallelized extremely well.

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Proton transfer reactions

Ubiquitous and crucial process in nature

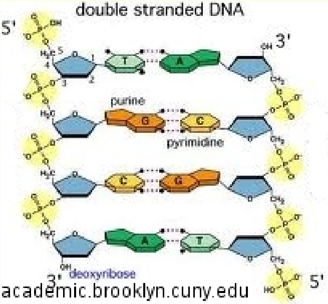
$$\boxed{S_1 - \mathrm{H}^* \cdots S_2 \Longleftrightarrow S_1 \cdots \mathrm{H}^* - S_2}$$

- Quantum Effects can be important even at room temperature![1]
- Rearrangement of chemical bonds calls for *ab initio* description of the electronic part

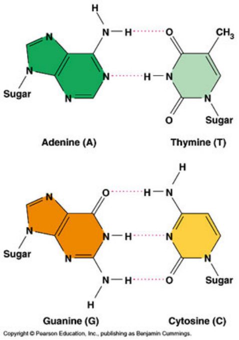
[1] Tuckerman & Marx, PRL **86** *4946* (2001).

Intermolecular proton transfer

DNA base pairs



academic.brooklyn.cuny.edu



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Intermolecular proton transfer

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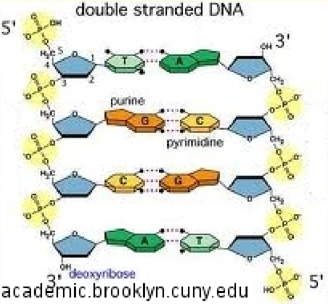

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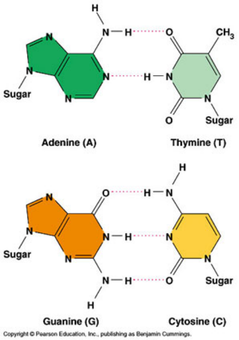

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- “Rare” tautomers implicated in **DNA mutations**
- Proton **tunneling** was hypothesized to favor “rare” tautomers[1]
- Experimental evidence only for analogues (large **KIE**)[2]

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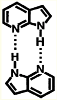
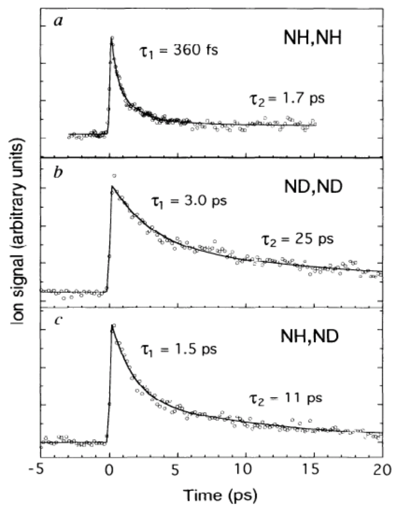
[1] Löwdin, RMP **35** *724* (1963). [2] Zewail *et al.*, Nature **378** *260* (1995).

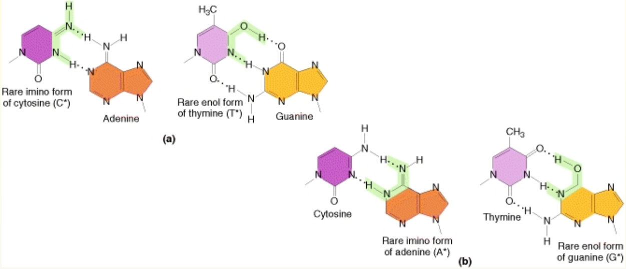
Experiment on 7-azaindole dimer(g)





Douhal, Kim, & Zewail *et al.*, Nature **378** *260* (1995).

Rare tautomers of DNA bases



http://www.ncbi.nlm.nih.gov/

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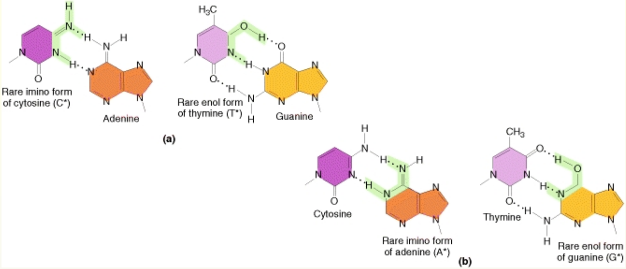

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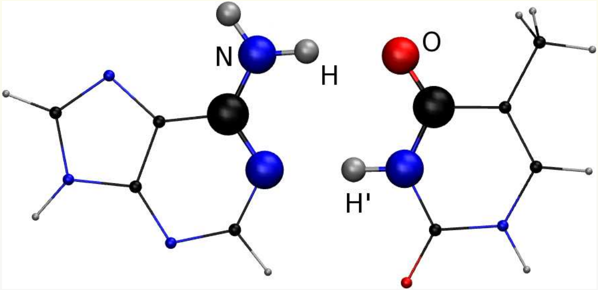
Intermolecular double proton transfer

Formamidine-Formamide (FIFA) tautomer complex[1]

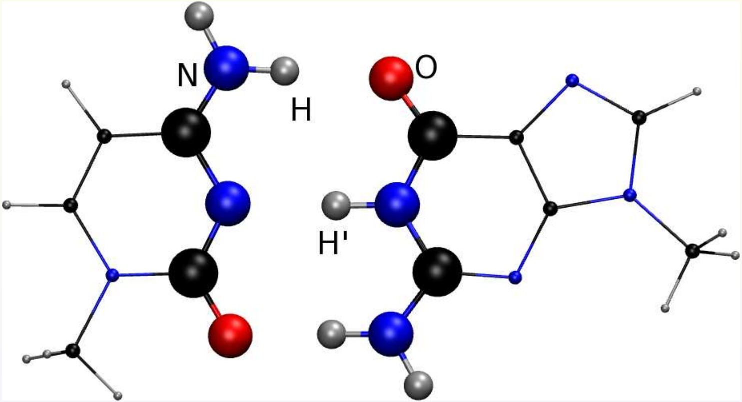


- Model system for A-T DNA base pair
- Concerted mechanism.

[1] J. Leszczynski *et al.*, JPCA **106** *12103* (2002)

Intermolecular double proton transfer

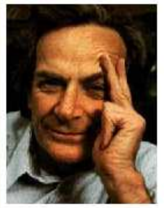
Model for G-C DNA base pair



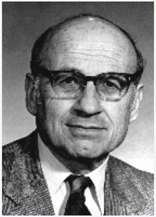
Forces from “First Principles”

Combining the best of two worlds...

- The quantum nature of nuclei is described using the **PI** formalism



- The electronic part (governing interaction between nuclei) is approximated using **DFT**



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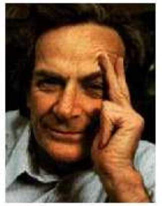

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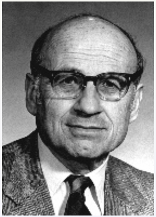


Car & Parrinello Molecular Dynamics (`CPMD`), PRL **55** 2471 (1985).

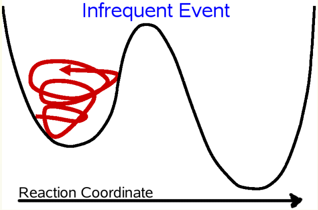
Choice of DFT XC functional

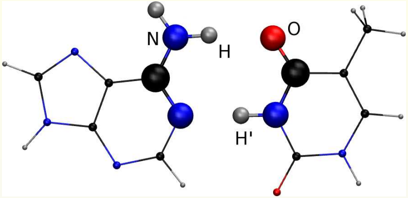
Energetics (kcal/mol) from `TURBOMOLE` code/**TZVPP** basis set. Structures correspond $\approx$ to reactants (R), the transition state (TS), and products (P)

	GC model			AT model		
method	$\Delta E_{\mathrm{P-R}}$	$\Delta E_{\mathrm{TS-P}}$	$\Delta E_{\mathrm{TS-R}}$	$\Delta E_{\mathrm{P-R}}$	$\Delta E_{\mathrm{TS-P}}$	$\Delta E_{\mathrm{TS-R}}$
RHF	13.50	14.65	28.15	11.80	9.47	21.27
MP2	9.37	4.04	13.41	8.62	4.37	12.99
CC2	**10.24**	**2.67**	**12.91**	**9.24**	**3.08**	**12.32**
PBE0	10.95	3.00	13.95	8.93	2.81	11.74
PBE	10.63	0.55	11.18	8.56	1.19	9.75
B3LYP	11.39	4.78	16.17	9.47	3.52	12.99
BLYP	**11.16**	**3.15**	**14.31**	**9.30**	**2.44**	**11.74**

BLYP represents best compromise between accuracy and cost!

Free energy methods & rare events





- Reaction coordinate: $\xi(\mathbf{r}) = d_{\mathrm{HN}} - d_{\mathrm{HO}}$
- Umbrella sampling[1] and WHAM technique[2]
- Drive system along reaction coordinate using harmonic bias potential (**centroid**)[3] $\xi_c = \frac{1}{\mathrm{P}} \sum_{i=1}^{\mathrm{P}} \xi_i$

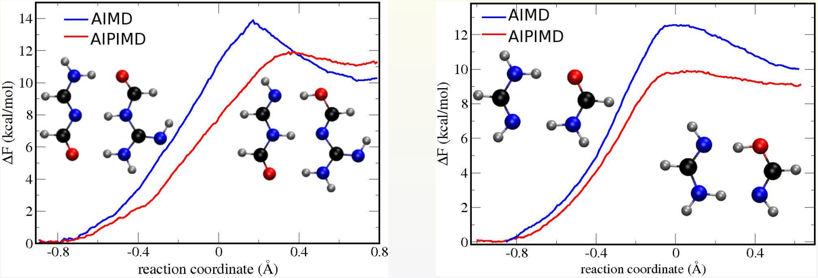
[1] Torrie & Valleau, Chem. Phys. Lett. **28** *578* (1974)

[2] Ferrendberg & Swendsen, Phys. Rev. Lett. **61** *2635* (1988)

[3] Gillan, PRL **58** *563* (1987). Voth, JCP **97** *8365* (1993).

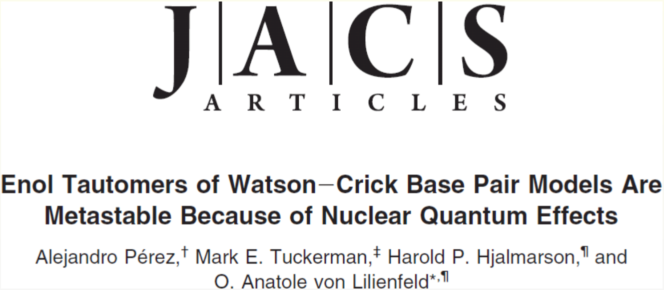
Free Energy Profiles Double Proton Transfer

Nuclear quantum effects have a dramatic impact on free energy profiles.



Rare tautomers predicted dynamically unstable: therefore, not involved in mutations!

Free Energy Profiles Double Proton Transfer



JACS

ARTICLES

Enol Tautomers of Watson–Crick Base Pair Models Are Metastable Because of Nuclear Quantum Effects

Alejandro Pérez,[†] Mark E. Tuckerman,[‡] Harold P. Hjalmarson,[¶] and
O. Anatole von Lilienfeld*,[¶]

J. AM. CHEM. SOC. **132**, *11510* (2010).

`www.youtube.com`

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Computing Thermodynamic Quantities: Estimators

An estimator: function whose average approximates a physical observable.

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An estimator: function whose average approximates a physical observable. Example: $E(\beta) = -\frac{\partial}{\partial\beta} \ln Z(\beta)$

$$\langle E \rangle \approx \frac{1}{Z_{\mathrm{P}}} \left(\frac{m\mathrm{P}}{2\pi\beta\hbar^2} \right)^{\mathrm{P}/2} \int dx_1 \cdots dx_{\mathrm{P}} \; \epsilon_{prim} \; e^{-\beta \sum_{k=1}^{\mathrm{P}} \left[\frac{m}{2}\omega_{\mathrm{P}}^2 (x_k - x_{k+1})^2 + \frac{U(x_k)}{\mathrm{P}} \right]},$$

where the *primitive* estimator for energy is

$$\epsilon_{prim} \quad = \quad \frac{\mathrm{P}}{2\beta} + \sum_{k=1}^{\mathrm{P}} \left[\frac{U(x_k)}{\mathrm{P}} - \frac{m}{2}\omega_{\mathrm{P}}^2 (x_k - x_{k+1})^2 \right]_{x_{\mathrm{P}+1} = x_1} .$$

Use MC, MD to sample this configuration integral.
A more efficient estimator (**virial**) was proposed:

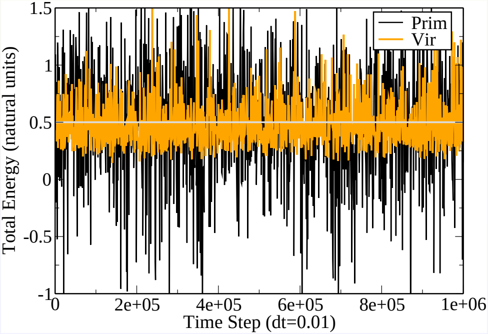
Herman *et al* JCP **76** *5150* (1982).

Internal Energy: Virial vs Primitive Estimators

There is a more efficient estimator for the internal energy called the "virial". Standard Deviation: 0.522(prim); 0.220(vir).

$$\epsilon_{vir} = \frac{1}{2\mathrm{P}} \sum_{k=1}^{\mathrm{P}} x_k \partial V / \partial x_k + \frac{1}{\mathrm{P}} \sum_{k=1}^{\mathrm{P}} V(x_k),$$

Instantaneous values of virial (orange) and primitive (black) estimators for $V(x) = x^2/2$ at $\beta = 10, \mathrm{P} = 64$.



Isotope Effect via Thermodynamic Integration (TI)

Motivation: No PI method to study Isotope Effect (IE).
Enzyme catalysis: proton transfer is the rate limiting step in many enzymatic reactions (**dehydrogenases**): large IE.
Acid dissociation, etc.
Typically, Site–H reacts faster than Site–D.

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$$\Delta F = F\left(m_f\right) - F\left(m_i\right) = \int_0^1 d\lambda \left(\frac{dF}{d\lambda}\right),$$

where $F = -\frac{1}{\beta}\ln Z$ is the (quantum) free energy.
For a linear path $m\left(\lambda\right) = \lambda m_f + \left(1-\lambda\right) m_i$.

Isotope Effect via Thermodynamic Integration (TI)

$$Z(\beta) \approx \prod_{i=1}^{n} \left(\frac{m_i \mathrm{P}}{2\pi\beta\hbar^2} \right)^{3\mathrm{P}/2} \int d^{n\mathrm{P}}\mathbf{r}\; e^{-\beta \sum_{i=1}^{n} \sum_{s=1}^{\mathrm{P}} \left[\frac{m_i}{2} \omega_{\mathrm{P}}^2 \left(\mathbf{r}_{i,s} - \mathbf{r}_{i,s+1} \right)^2 + \frac{U(\{\mathbf{r}_s\})}{\mathrm{P}} \right]}.$$

Isotope Effect via Thermodynamic Integration (TI)

$$Z(\beta) \approx \prod_{i=1}^{n} \left(\frac{m_i \mathrm{P}}{2\pi\beta\hbar^2} \right)^{3\mathrm{P}/2} \int d^{n\mathrm{P}}\mathbf{r}\; e^{-\beta \sum_{i=1}^{n} \sum_{s=1}^{\mathrm{P}} \left[\frac{m_i}{2}\omega_{\mathrm{P}}^2 \left(\mathbf{r}_{i,s} - \mathbf{r}_{i,s+1} \right)^2 + \frac{U(\{\mathbf{r}_s\})}{\mathrm{P}} \right]}.$$

Two PI estimators for $\frac{dF}{d\lambda}$:
primitive

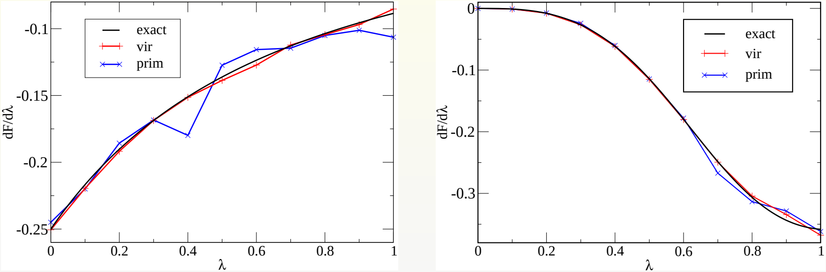
$$\left(\frac{dF}{d\lambda} \right)^{prim} \quad = \quad -\sum_{I=1}^{N} \left(\frac{m_I'}{m_I} \right) \left[\frac{3\mathrm{P}}{2\beta} - \left\langle \frac{m_I}{2} \omega_{\mathrm{P}}^2 \sum_{s=1}^{P} \left(\mathbf{r}_{I,s} - \mathbf{r}_{I,s+1} \right)^2 \right\rangle_{\lambda} \right],$$

and the **virial**

$$\left(\frac{dF}{d\lambda} \right)^{vir} \quad = \quad -\sum_{I=1}^{N} \left(\frac{m_I'}{m_I} \right) \left[\frac{3}{2\beta} + \left\langle \frac{1}{2\mathrm{P}} \sum_{s=1}^{\mathrm{P}} \mathbf{r}_{I,s} \cdot \partial_{\mathbf{r}_I} V\left(\mathbf{r}_s \right) \right\rangle_{\lambda} \right].$$

Isotope Effect via PIMD

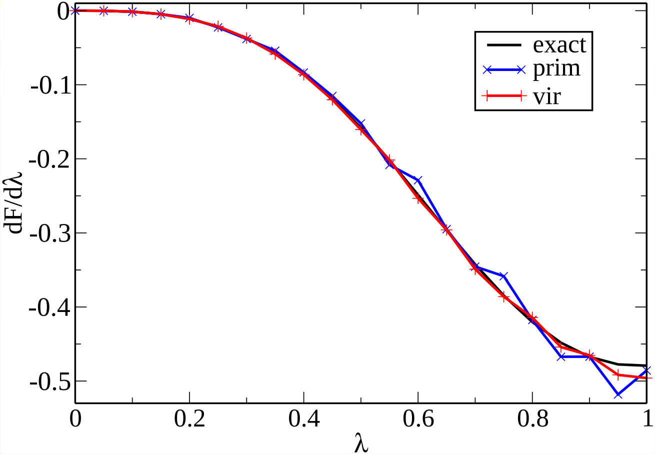
Results for an analytically solvable system (harmonic potential)



First derivative of quantum free energy with respect to mass.
Left: $m(\lambda) = \lambda m_f + (1-\lambda) m_i$.
Right: $m(\lambda) = \lambda^4 m_f + \left(1-\lambda^4\right) m_i$
Black: exact result. Red: virial and Blue: primitive estimators.

Isotope Effect via TI-PIMD

Two-oscillator model for $O - H(D) \cdots O$. (Antisymmetric Mode)
Useful to compute IE & understand **Ubbelohde** effect.

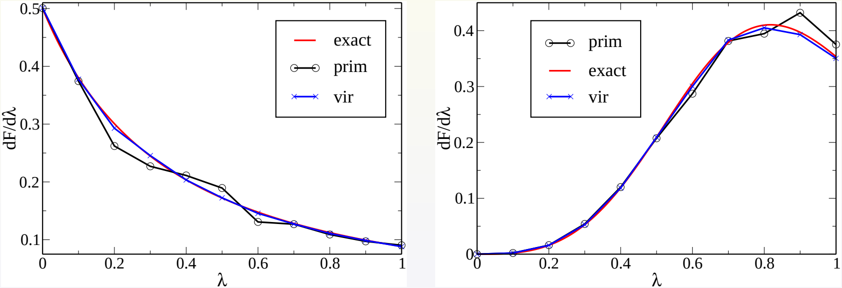


100,000 PIMD steps/window: prim=-0.2035, vir=-0.2052, exact=-0.2042.

Simultaneous change in mass and potential

Change of identity/interaction potential: Useful to study H binding to active sites.

$$\left(\frac{dF}{d\lambda}\right) = \frac{\hbar}{4\sqrt{(\kappa/m)}}\coth\left(\frac{\beta\hbar}{2}\sqrt{\kappa/m}\right)\left[\frac{m\kappa' - m'\kappa}{m^2}\right].$$



First derivative of the quantum free energy with respect to mass & force constant for harmonic potential.

Left: Linear path. Right: quartic path.

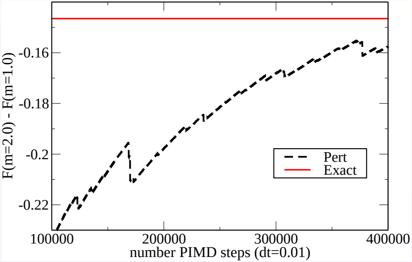
Black: primitive result. Red: exact and Blue: virial estimators.

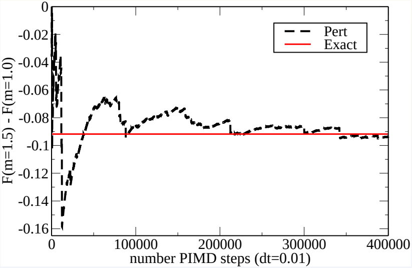
Perturbation Theory

Motivation: PI calculations are expensive!

$$\Delta F = -\frac{1}{\beta}\left[\frac{3NP}{2}\ln\left(\frac{m_f}{m_i}\right) + \ln\left\langle e^{-\beta\left(m_f-m_i\right)\frac{\omega_P^2}{2}A}\right\rangle_i\right],$$

where $A = \sum_{I=1}^{N}\sum_{s=1}^{P}\left(\mathbf{r}_{I,s} - \mathbf{r}_{I,s+1}\right)^2$.
Full PT for free energy difference due to isotope transformation using single PIMD simulation.





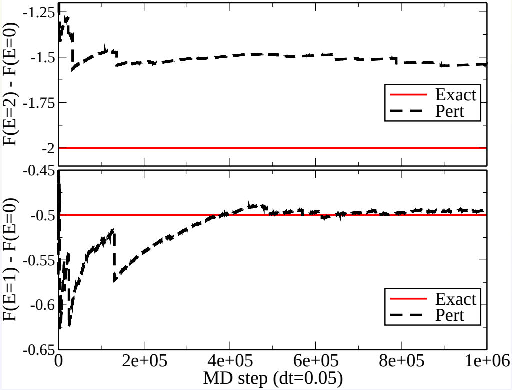
Left: $m_i = 1 \to m_f = 2$. Right: $m_i = 1 \to m_f = 1.5$.
Exact: red horizontal line.
PT works provided change is small $\cdots$ **Multistage-PT**.

Perturbation Theory (II)

Effect of a static electric field:

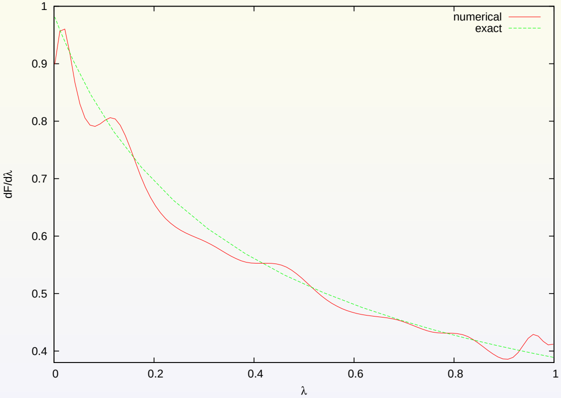
$$\Delta F \quad = \quad -\frac{1}{\beta} \ln \left\langle \exp\left[-\beta \left(q\mathbf{E} \cdot \bar{\mathbf{r}}\right)\right]\right\rangle_{\mathrm{E=0}}.$$

Useful to understand ferro/paraelectric hydrogen-bonded solids (KDP), Stark Effect.



λ-dynamics PIMD

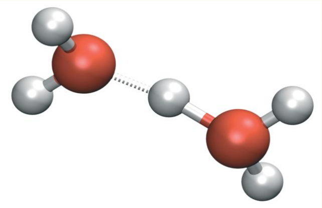
Allow λ to vary in a continuous way using single PIMD simulation.
Example: transmutation of diatomics $H_2 \rightarrow$HCl at 300 K.



$\Delta F = F\left(\mathrm{HCl}\right) - F\left(\mathrm{H}_2\right) = -0.00332$ a.u. (exact), -0.00332 a.u. (numerical).

Isotope effects in the Zundel cation

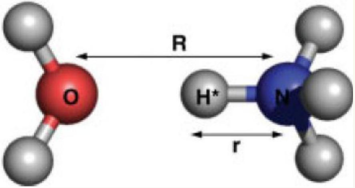
Important in hydrogen-bonded liquids & in enzymatic reactions.



`CPMD` Details: *Ab initio* PIMD ($H_2 \rightarrow D_2$).
BLYP/100 Ry, Cubic Box 12^3 Å^3, $P = 32$, T=300 K.
Numerical (PT) $\approx$ 4 kcal/mol.
CPL **329**, *36* (2000).

Goal: change of identity in PIMD simulations

Feasible in force fields-PIMD, harder in *ab initio* PIMD (pseudos).



Example: protonated water/ammonia complex

$\mathrm{H_2O} \cdots \mathrm{H}^+ \cdots \mathrm{OH_2} \rightarrow \mathrm{H_2O} \cdots \mathrm{H}^+ \cdots \mathrm{NH_3}$

Towards predicting changes in free energy barriers heights?

Predict kinetic isotope effect $k_H/k_D \approx e^{-\beta\left(\Delta F_H^\ddagger - \Delta F_D^\ddagger\right)}$.

Outline

Introduction to Path Integrals

Double proton transfer in DNA base pair models

Development of free energy methods in PIMD

Improving the convergence of PIMD

Summary

Higher-order methods to improve PIMD averages

Higher-order methods to improve PIMD averages

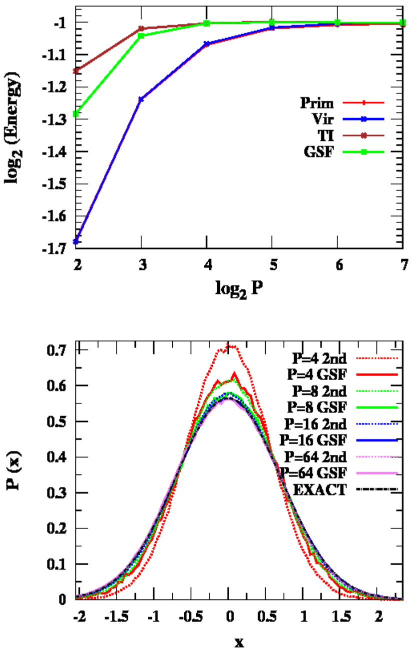
IDEA Why not to use the classical forces to improve averages?

$$\left\langle \hat{O} \right\rangle \approx \frac{\langle O(\mathbf{r}_1)\, w(\mathbf{r}_1, \cdots, \mathbf{r}_\mathrm{P})\rangle}{\langle w(\mathbf{r}_1, \cdots, \mathbf{r}_\mathrm{P})\rangle}.$$

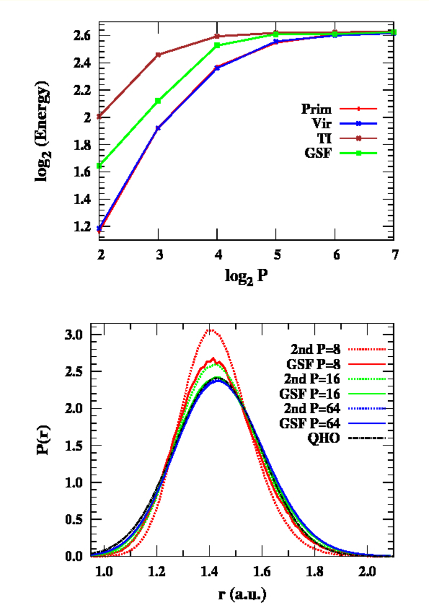
$w(\{\mathbf{r}\}; \beta)$ weighting function constructed using classical forces. In some cases, fourth-order convergence can be attained **without** additional overhead!

G. Voth et al, JCP 115, 7832 (2001).
A. Perez & M. Tuckerman, JCP (in review).

Harmonic potential at $\beta\hbar\omega = 10$

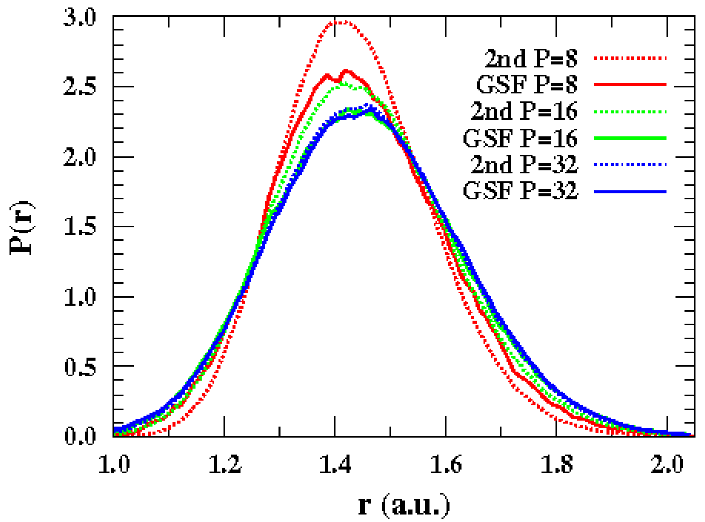


Hydrogen molecule at 300K: $D\left[1-\exp\left(-a\left(x-x_{eq}\right)\right)\right]$



Hydrogen molecule: *Ab initio* PIMD

Details: T=300K, `CPMD` BLYP/75 Ry, Cubic Box 9^3 Å^3.



High order PIMD methods

Liquid water at ambient temperature (q-SPC/Fw force field[1])

P	2nd	4th
4	-0.2778	0.5989
8	0.0400	0.3911
16	0.2699	0.3892
32	0.3688	0.4055
64	0.3968	0.4067

Energy values in a.u.

- Useful to converge faster averages in quantum simulations of bulk phases.
- Very easy to implement in existing *ab initio* PIMD codes.
- No overhead associated.

[1] JCP **125**, *184507* (2006).

Outline

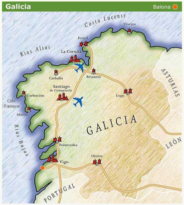
Summary

- The Feynman's path integral formalism was reviewed & applied to several systems
- Nuclear quantum effects are important even at room temperature
- "Rare" tautomers dynamically unstable & not implicated in mutations
- New estimators were derived & implemented to investigate alchemical transformations
- Higher-order algorithm to improve convergence of PIMD estimators

Acknowledgments

Acknowledgments

The beautiful town of Baiona



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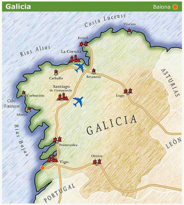

Thanks for your attention! Questions?