

International Spring School Statistical Thermodynamics, Santiago de Chile
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Lecture 23

Treatment of quantum effects: hybrid QM/MM simulation

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Treatment of quantum effects in molecular simulation

Classical versus Quantum simulation

1. Quantum effects
2. Methods and applications

Quantum-mechanical (QM) or quantum-dynamical (QD) simulation

1. Hybrid QM/MD simulation
2. Car-Parrinello "ab initio" simulation
3. Path-Integral (PI) simulation
4. Hybrid QMD/CMD dynamic simulation: wave function propagation
5. Hybrid QMD/CMD dynamic simulation: density matrix evolution

Different levels of resolution in modelling

Coarse-graining from a finer-grained level to a coarser-grained level of resolution

Quantum (statistical) mechanics  Classical (statistical) mechanics

Level of resolution	I	II	III	IV	V
Particles	Sub-nuclear particles: nucleons + electrons	Sub-atomic particles: nuclei + electrons	Atomic particles	Supra-atomic particles	Supra-molecular particles
Mass of particle (amu)	$10^{-3} - 1$	$10^{-3} - 10^2$	$1 - 10^2$	$10 - 10^2$	$10 - 10^2$
Size of particle (nm)	10^{-6}	$10^{-6} - 10^{-5}$	0.03 – 0.3	0.5 – 1.0	0.5 – 1.0
Interactions	Strong, Coulomb, Pauli principle	Coulomb, Pauli principle	bonded terms, Coulomb, repulsive, van der Waals		Coulomb, repulsive, van der Waals
Scaling effort	$N_{nucleons}^{\geq 3}$	$N_{electrons}^{\geq 3}$	N_{atoms}^{1-2}	N_{beads}^{1-2}	N_{beads}^{1-2}
Reduction number of degrees of freedom from previous level		10 – 100	10 – 100	2 – 5	2 – 10
Reduction computational effort from previous level		$\geq 10^3$	$\geq 10^3$	2 – 25	2 – 100

Riniker et al. *Phys. Chem. Chem. Phys.* 14 (2012) 12423-12430
 Meier et al., *Angew. Chem. Intl. Ed.* 52 (2013) 2-17

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Quantum effects

- Quantisation of energy levels

→ vibrations with $\hbar\omega > k_B T$
zero point energy:
harmonic oscillator $\frac{1}{2}\hbar\omega$

Atomic degrees of freedom

bond vibrations	3700cm ⁻¹
angle vibrations	1600cm ⁻¹
water libration	500cm ⁻¹
$k_B T$	200cm ⁻¹

- Exchange
Bose-Einstein
Fermi-Dirac } statistics

liquid Helium
Boltzmann statistics generally O.K.

- Uncertainty
tunneling
no defined trajectory

proton transfer

Quantum effects

- Non pair additivity

- polarisation
- charge transfer

- • Change of chemical bonds

- • Relaxation processes

Types of quantities:

- thermodynamic
- structural
- dynamic

Electronic degrees of freedom

- metals
- semiconductors
- ionic crystals
- hydrated electron

- electron transfer reactions

Energy transfer from excited molecules

Essential quantum systems:

- spin
- liquid He

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Main differences between quantum and classical mechanics as applied to molecular systems

Quantum statistical mechanics (QM)	Classical statistical mechanics (CM)
<ul style="list-style-type: none"> time-dependent Schrödinger equation: $i\hbar \frac{\partial \Psi(\vec{r}^N, t)}{\partial t} = \widehat{H} \Psi(\vec{r}^N, t)$ with wave function Ψ 	<ul style="list-style-type: none"> Newton's equation: $\vec{f}_i = m_i \vec{a}_i \qquad \vec{f}_i = - \frac{\partial V(\vec{r}^N)}{\partial \vec{r}_i}$
<ul style="list-style-type: none"> Born-Oppenheimer approximation: nuclei and electrons decoupled 	<ul style="list-style-type: none"> interaction potential energy function $V(\vec{r}^N)$ is generally pair additive, but polarisation can be included
<ul style="list-style-type: none"> probabilistic nature of wave function: $\Psi(\vec{r}_i, t) ^2$, uncertainty principle, no trajectory 	<ul style="list-style-type: none"> phase space trajectory \vec{r}^N, \vec{p}^N
<ul style="list-style-type: none"> Bose-Einstein or Fermi-Dirac statistics (Pauli principle: anti-symmetry) 	<ul style="list-style-type: none"> Boltzmann statistics
<ul style="list-style-type: none"> Computing effort: (number of electrons)³⁻⁵ 	<ul style="list-style-type: none"> Computing effort: (number of atoms)¹⁻²

Theoretical molecular chemistry




Distinctions:

Quantum mechanics (QM)	↔	Classical mechanics (CM)
ground state	↔	excited state
equilibrium	↔	dynamics

Degrees of freedom:

atoms/nuclei	↔	electrons
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Classification of molecular simulation theory and methods

	Quantum statistical mechanics	Classical statistical mechanics	
	1. <i>One single configuration</i> : Static QM: time-independent Schrödinger equation $T = 0$ <ul style="list-style-type: none"> • ab-initio • density-functional • semi-empirical • empirical valence bond 	CM: energy minimization $T = 0$ <ul style="list-style-type: none"> • (empirical) force field 	Static modelling
	2. <i>Ensemble of configurations</i> : Equilibrium statistical mechanics QM: density matrices $T \neq 0$ <ul style="list-style-type: none"> • path-integral simulation 	CM: Boltzmann sampling $T \neq 0$ <ul style="list-style-type: none"> • force field • Monte-Carlo simulation • molecular dynamics simulation • stochastic dynamics simulation 	Equilibrium statistical mechanics
	2. <i>Trajectories of configurations</i> : Dynamics QD: time-dependent Schrödinger equation $T \neq 0 + \text{dynamics}$ <ul style="list-style-type: none"> • wave function propagation • density matrix evolution • real-time path integral • Bohmian dynamics • surface hopping 	CD: Newton, Lagrange, Hamilton, Langevin equations $T \neq 0 + \text{dynamics}$ <ul style="list-style-type: none"> • force field • molecular dynamics simulation • stochastic dynamics simulation 	Dynamics

Methods/Applications

	Atoms/Nuclei	Electrons
1. Conventional Quantum Chemistry (1960 →)	Fixed: $T = 0$ K no dynamics	QM: Schrödinger ground + excited equilibrium → no dynamics
2. Conventional Classical Simulation (1970 →)	CM: atoms Newton: $T = 300$ K dynamics	averaged out no reactions
3. `Ab-initio` Simulation (1985 →)	CM: nuclei Newton: $T = 300$ K dynamics	QM: ab initio density functional valence bond semi-empirical only ground state no dynamics

Methods/Applications

	Atoms/Nuclei	Electrons
4. Hybrid QM/MM Simulation (HIV-protease) (1990 →)	CM : nuclei + atoms Newton: $T = 300\text{K}$ dynamics	QM : as under 3. for few atoms only ground state no dynamics
5. Path-Integral Simulation (water) (1990 →)	QM : atoms equilibrium	Averaged out
6. Hybrid QMD/CMD Dynamic Simulation (proton transfer) (1993 →)	QM : few atoms Schrödinger: dynamics, ground + excited states CM : many atoms Newton: $T = 300\text{K}$ dynamics	Averaged out

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Hybrid Quantum/Classical Simulation

Combination:	Quantum	+	Classical
	few	+	many
			degrees of freedom
	semi-empirical	+	Newton
	QM: AM1 PM3 OM3 DFT		GROMOS force field

- 1. Quantum** Hamiltonian must include **long-range electric field** due to **classical** Hamiltonian
- 2. Classical** Hamiltonian must account for **changing charge distribution** of the **quantum** Hamiltonian

Combined QM/MM model

Hamiltonian:

$$\hat{H} = \sum_I^M \frac{P_I^2}{2m_I} + \sum_A^N \frac{P_A^2}{2m_A} + V_{\text{solvent/solvent}}(\{R_I\}) \\ + V_{\text{core/core}}(\{R_A\}) + V_{\text{solvent/core}}(\{R_I\}, \{R_A\}) \\ + \hat{H}_{\text{electron}}$$

I, J : solvent atoms

A, B : atomic cores = nuclei plus inner shell electrons

i, j : valence shell electrons

H. Liu et al., J. Chem. Phys., 102 (1995) 1722-1730
K. Meier et al., J. Comput. Chem. 33 (2012) 1153-1161

Combined QM/MM model

Solvent-solvent potential energy function:

$$V_{\text{solvent/solvent}}(\{R_I\}) = \sum_I^M \sum_{J>I}^M \frac{Q_I Q_J}{R_{IJ}} + \sum_I^M \sum_{J>I}^M 4\varepsilon_{IJ} \left(\frac{\sigma_{IJ}^{12}}{R_{IJ}^{12}} - \frac{\sigma_{IJ}^6}{R_{IJ}^6} \right)$$

Q_I, Q_J : partial charges

$\varepsilon_{IJ}, \sigma_{IJ}$: Lennard-Jones parameters

Interactions between the atomic cores of the solute:

$$V_{\text{core/core}}(\{R_A\}) = \sum_A^M \sum_{B>A}^M \frac{Z_A Z_B}{R_{AB}}$$

Z_I, Z_J : effective charges of the atomic cores

H. Liu et al., J. Chem. Phys., 102 (1995) 1722-1730

K. Meier et al., J. Comput. Chem. 33 (2012) 1153-1161

Combined QM/MM model

Interactions between the solvent atoms and the solute atomic cores:

$$V_{\text{solvent/core}}(\{R_I\}, \{R_A\}) = V_{\text{electrostatic}}(\{R_I\}, \{R_A\}) + V_{\text{van der Waals}}(\{R_I\}, \{R_A\})$$

van der Waals part:

$$V_{\text{van der Waals}}(\{R_I\}, \{R_A\}) = \sum_I^M \sum_A^N 4\epsilon_{IA} \left(\frac{\sigma_{IA}^{12}}{R_{IA}^{12}} - \frac{\sigma_{IA}^6}{R_{IA}^6} \right)$$

electrostatic part:

$$V_{\text{electrostatic}}(\{R_I\}, \{R_A\}) = \sum_I^M \sum_A^N \frac{Q_I Z_A}{R_{IA}}$$

H. Liu et al., J. Chem. Phys., 102 (1995) 1722-1730

K. Meier et al., J. Comput. Chem. 33 (2012) 1153-1161

Combined QM/MM model

Electronic part of the Hamiltonian:

$$\hat{H}_{\text{electron}} = -\sum_i^n \frac{\nabla_i^2}{2} + \sum_i^n \sum_{j>i}^n \frac{1}{r_{ij}} - \sum_i^n \sum_I^M \frac{Q_I}{R_{iI}} - \sum_i^n \sum_A^N \frac{Z_A}{R_{iA}}$$

Born-Oppenheimer approximation → motion of the solvent atoms and solute atomic cores can be described classically

Effective potential energy term due to the electrons:

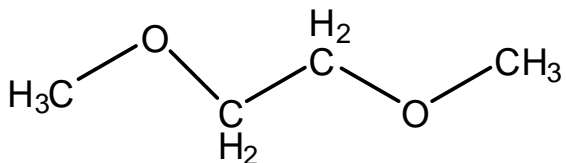
$$V_{\text{electron}} = \langle \Psi | \hat{H}_{\text{electron}} (\{R_I\}, \{R_A\}) | \Psi \rangle$$

H. Liu et al., J. Chem. Phys., 102 (1995) 1722-1730
K. Meier et al., J. Comput. Chem. 33 (2012) 1153-1161

Dimethoxyethane Conformations

Ab-initio QM

ttt



E (kJ mol⁻¹)

Gas phase

=0

Solution = + reaction field

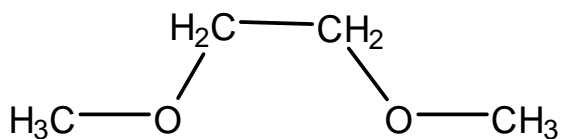
=0

μ (D)

0

0

tgt



E

+2.3

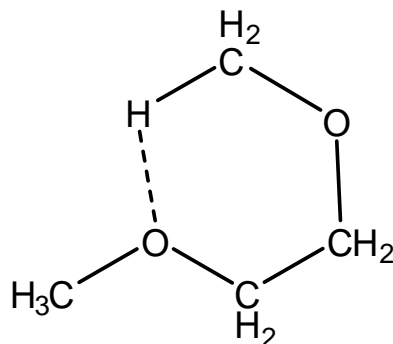
0

μ (D)

1.44

1.65

tg⁺g



E

+0.1

-3.3

μ (D)

1.72

1.97

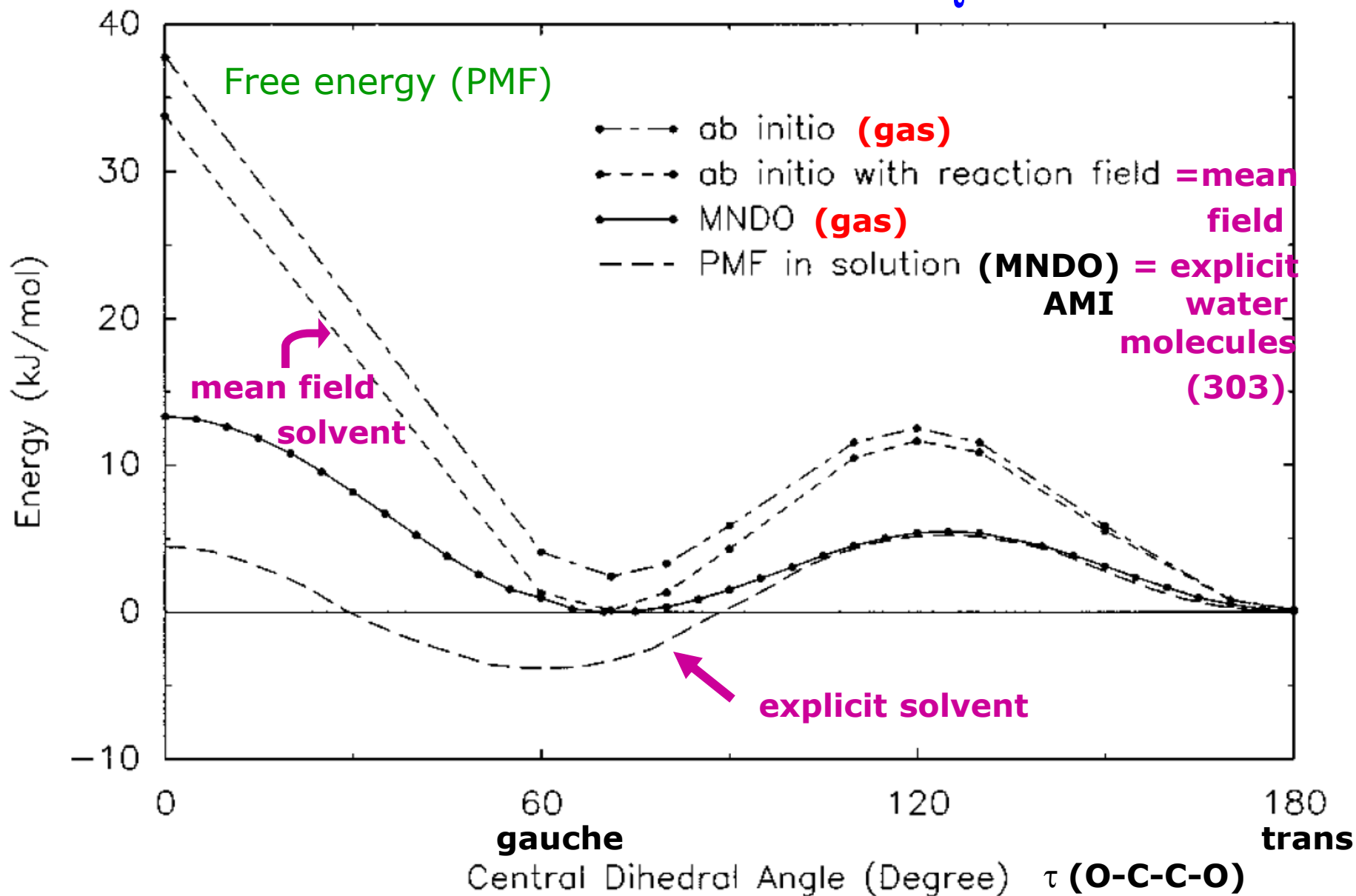
most stable?
internal H-bond?

Is the mean field continuum } approximation (for solvation) correctly predicting the lowest energy conformation?

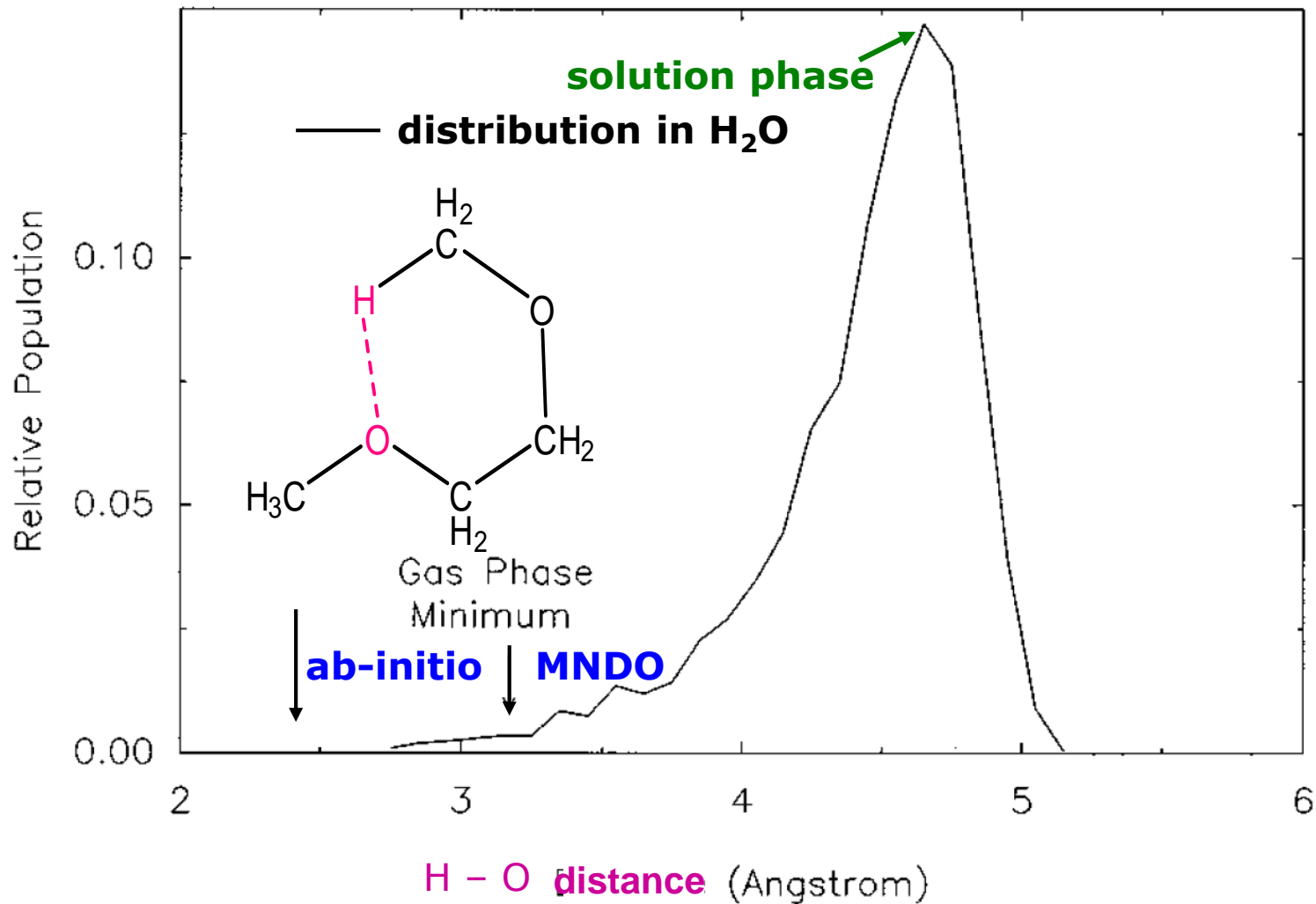
1.2-Dimethoxyethane $\text{CH}_3\text{-O-CH}_2\text{-CH}_2\text{-O-CH}_3$

H. Liu et al., J. Chem. Phys., 102 (1995) 1722-1730

↑
 τ



Dimethoxyethane, tg^+g^- conformer internal "hydrogen bond"



Without explicit solvent correct conformation is *not* found

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Quantum simulation: Car-Parrinello method

Remlen & Madden, Mol. Phys. 70 (1990) 921

Atomic (core) degrees of freedom: \vec{R}_i

- Velocities: $\dot{\vec{R}}_i = \frac{d}{dt} \vec{R}_i$
- Lagrangian: $L = T - V = \frac{1}{2} \sum_{i=1}^N M_i \dot{\vec{R}}_i^2 - V_{at}(\{\vec{R}_i\})$
- Equation of motion: $m_i \ddot{\vec{R}}_i = - \frac{\partial}{\partial \vec{R}_i} V_{at}(\vec{R}_1, \dots, \vec{R}_N)$

Electronic degree of freedom: c_β^α

- Basis: $\left. \begin{array}{l} \varphi_\beta(\vec{r}) \\ \psi_\alpha(\vec{r}) \end{array} \right\}$
- Occupied orbital: $\psi_\alpha(\vec{r})$
- Velocities: $\dot{c}_\beta^\alpha = \frac{d}{dt} c_\beta^\alpha$ $\psi_\alpha(\vec{r}) = \sum_\beta c_\beta^\alpha \varphi_\beta(\vec{r})$
- Lagrangian: $L = T - V = \frac{1}{2} \mu \sum_\alpha \sum_\beta (\dot{c}_\beta^\alpha)^2 - V_{el}(\{c_\beta^\alpha\}, \{\vec{R}_i\})$

Quantum simulation: Car-Parrinello method

Orthonormality condition for orbitals → constraint:

$$\begin{aligned}\sigma_{\alpha\alpha'} &= \frac{1}{\text{norm}} \int \psi_{\alpha}^*(\vec{r}) \psi_{\alpha'}(\vec{r}) d\vec{r} - \delta_{\alpha\alpha'} = 0 \\ &= \sum_{\beta} c_{\beta}^{\alpha*} c_{\beta}^{\alpha'} - \delta_{\alpha\alpha'} = 0\end{aligned}$$

Can be handled like a distance constraint: $\vec{R}_{ij} \cdot \vec{R}_{ij} - d_{ij}^2 = 0$

Lagrangian multipliers: λ_{ij}

- Constraint force: $-\lambda_{\alpha\alpha'} \frac{\partial \sigma_{\alpha\alpha'}}{\partial c_{\beta}^{\alpha}}$
- Equation of motion: $\mu \ddot{c}_{\beta}^{\alpha} = -\frac{\partial V_{el}}{\partial c_{\beta}^{\alpha}} - \sum_{\alpha'} \lambda_{\alpha\alpha'} c_{\beta}^{\alpha}$

Combine MD in both spaces:

- Lagrangian:

$$L = \frac{1}{2} \sum_{i=1}^N M_i \dot{\vec{R}}_i^2 + \frac{1}{2} \mu \sum_{\alpha} \sum_{\beta} \dot{c}_{\beta}^{\alpha 2} - V_{at}(\{\{\vec{R}_i\}\}) - V_{el}(\{\{c_{\beta}^{\alpha}\}, \{\{\vec{R}_i\}\})$$

Combine MD in both spaces: $\left. \begin{array}{l} \text{atomic} \\ \text{electronic} \end{array} \right\} \text{degrees of freedom}$

- Lagrangian:

$$L = \frac{1}{2} \sum_{i=1}^N M_i \dot{\vec{R}}_i^2 - \frac{1}{2} \mu \sum_{\alpha} \sum_{\beta} (\dot{c}_{\beta}^{\alpha})^2 - V_{at}(\{\vec{R}_i\}) - V_{el}(\{c_{\beta}^{\alpha}\}, \{\vec{R}_i\})$$

- Equations of motion:

$$\text{atomic: } m_i \ddot{\vec{R}}_i = - \frac{\partial}{\partial \vec{R}_i} V_{at} - \frac{\partial}{\partial \vec{R}_i} V_{el}$$

$$\text{electronic: } \mu \ddot{c}_{\beta}^{\alpha} = - \frac{\partial}{\partial c_{\beta}^{\alpha}} V_{el} - \sum_{\alpha'} \lambda_{\alpha\alpha'} c_{\beta}^{\alpha'}$$

- Hellmann-Feynman theorem:

If Ψ is a stationary wave function then:

$$\text{force } \vec{f}_i \equiv - \frac{\partial V_{el}}{\partial \vec{R}_i} = - \left\langle \Psi(\vec{r}, \vec{R}) \left| \frac{\partial \hat{H}}{\partial \vec{R}_i} \right| \Psi(\vec{r}, \vec{R}) \right\rangle$$

For non-stationary states: *Chem. Phys. Lett.* 219 (**1994**) 259-266

$$\text{force } \vec{f}_i = - \sum_{\alpha} \langle \Psi | \psi_{\alpha} \rangle \left\langle \psi_{\alpha} \left| \frac{\partial \hat{H}}{\partial \vec{R}_i} \right| \psi_{\alpha} \right\rangle \langle \psi_{\alpha} | \Psi \rangle - \sum_{\alpha} E_{\alpha} \frac{\partial}{\partial \vec{R}_i} \langle \Psi | \psi_{\alpha} \rangle \langle \psi_{\alpha} | \Psi \rangle$$

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Path-integral method

Consider one particle in one dimension:

Hamiltonian:

$$\hat{H} = -\frac{\hbar^2}{2m} \frac{d^2}{dx^2} + V(x)$$

\nearrow eigenvalues E_λ ,
 \nearrow eigenfunctions $\psi_\lambda(x)$
 complete, orthonormal set

Density matrix: $\rho(x, x'; \beta) = \sum_\lambda \psi_\lambda(x) e^{-\beta E_\lambda} \psi_\lambda^*(x')$ $\beta \equiv \frac{1}{k_B T}$

Partition function: 1 particle in volume V

$$Z(1, V, \beta) = \sum_\lambda e^{-\beta E_\lambda} = \int \rho(x, x; \beta) dx$$

Decomposition of the density matrix:

$$\begin{aligned} & \int \rho(x, x''; \frac{1}{2}\beta) \rho(x'', x'; \frac{1}{2}\beta) dx'' = \\ &= \int \left[\sum_\lambda \psi_\lambda(x) e^{-\frac{1}{2}\beta E_\lambda} \psi_\lambda^*(x'') \right] \left[\sum_{\lambda'} \psi_{\lambda'}(x'') e^{-\frac{1}{2}\beta E_{\lambda'}} \psi_{\lambda'}^*(x') \right] dx'' \\ &= \text{integral over } x'' \Rightarrow \delta_{\lambda\lambda'} \\ &= \sum_\lambda \psi_\lambda(x) e^{-\beta E_\lambda} \psi_\lambda^*(x') = \rho(x, x'; \beta) \end{aligned}$$

³M. J. Gillan, in *Computer Modelling of Fluids, Polymers and Solids*, edited by C. R. A. Catlow, S. C. Parker, and M. P. Allen (Kluwer, Dordrecht, 1990), pp. 155–188.

Path-integral method

Partition function with P decompositions:

$$Z_P(1, V, \beta) = \int \int \dots \int \rho(x_1, x_2; \beta/P) \rho(x_2, x_3; \beta/P) \dots \\ \dots \rho(x_{P-1}, x_P; \beta/P) \rho(x_P, x_1; \beta/P) dx_1 dx_2 \dots dx_P$$

A closed path integral: 

Derive an expression for $\rho(x, x'; \beta/P)$ for large P:

$$\rho(x, x'; \beta) = \sum_{\lambda} \psi_{\lambda}(x) e^{-\beta E_{\lambda}} \psi_{\lambda}^*(x')$$

Take derivative with respect to β :

$$\frac{\partial}{\partial \beta} \rho(x, x'; \beta) = - \sum_{\lambda} \underbrace{E_{\lambda} \psi_{\lambda}(x)}_{\hat{H} \psi_{\lambda}(x)} e^{-\beta E_{\lambda}} \psi_{\lambda}^*(x') = - \left[-\frac{\hbar^2}{2m} \frac{\partial^2}{\partial x^2} + V(x) \right] \rho(x, x'; \beta)$$

Assume $V(x) = 0$:

$$\frac{\partial}{\partial \beta} \rho(x, x'; \beta) = \frac{\hbar^2}{2m} \frac{\partial^2}{\partial x^2} \rho(x, x'; \beta)$$

This is a diffusion equation with:

$$\begin{aligned} \text{time} &= t = \beta \\ \text{diffusion constant} &= D = \frac{\hbar^2}{2m} \end{aligned}$$

Path-integral method

Solution:

$$\rho(x, x'; \beta) = \left[\frac{m}{2\pi\beta\hbar^2} \right]^{\frac{1}{2}} e^{-\frac{m}{2\beta\hbar^2}[x-x']^2}$$

Assume $V(x) = \text{constant}$:

$$\rho(x, x'; \beta) = \left[\frac{m}{2\pi\beta\hbar^2} \right]^{\frac{1}{2}} e^{\underbrace{-\frac{m}{2\beta\hbar^2}[x-x']^2 - \beta V(x)}}_{\text{Dominated for small } \beta}$$

So, $V(x) \approx \text{constant}$

Use mean of $V(x)$ and $V(x')$: $\frac{1}{2}[V(x) + V(x')]$

Single-particle, 1-dimensional density matrix for large P :

$$\rho(x, x'; \beta/P) = \left[\frac{mP}{2\pi\beta\hbar^2} \right]^{\frac{1}{2}} e^{-\frac{mP}{2\beta\hbar^2}[x-x']^2 - \frac{\beta}{2P}[V(x) + V(x')]}$$

Partition function in terms of path integrals

One particle, one dimension:

$$Z_P(1, V, \beta) = \left[\frac{mP}{2\pi\beta\hbar^2} \right]^{\frac{P}{2}} \int \int \dots \int e^{-\beta \sum_{s=1}^P \left[\frac{mP}{2\beta^2\hbar^2} [x_{s+1} - x_s]^2 + \frac{1}{P} V(x_s) \right]} dx_1 dx_2 \dots dx_P$$

One can show (Feynman, Statistical Mechanics):

$$Z(1, V, \beta) = \lim_{P \rightarrow \infty} Z_P(1, V, \beta)$$

Isomorphism:

Partition function of a **quantum particle** has the form of the configurational partition function of a cyclic chain of **P classical particles** (or **beads**) **coupled by harmonic springs** with spring constant $\frac{mP}{\beta^2\hbar^2}$

Each particle (bead) being acted on by the **true potential V(x) divided by P**.

N particles, 3 dimensions:

$$Z_P(N, V, \beta) = \left[\frac{mP}{2\pi\beta\hbar^2} \right]^{\frac{3NP}{2}} \int e^{-\beta \sum_{s=1}^P \left[\frac{mP}{2\beta^2\hbar^2} \sum_{i=1}^N [\vec{r}_{i,s+1} - \vec{r}_{i,s}]^2 + \frac{1}{P} V(\vec{r}_{1,s}, \dots, \vec{r}_{N,s}) \right]} \prod_{i=1}^N \prod_{s=1}^P d\vec{r}_{i,s}$$

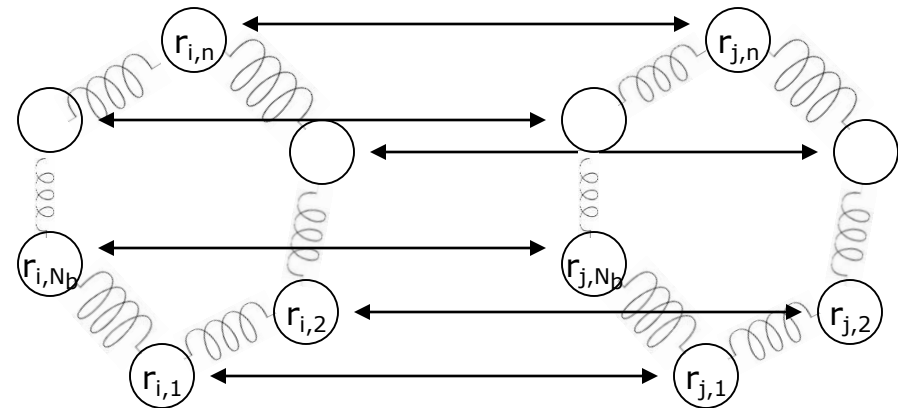
$\vec{r}_{i,s}$ = position vector of bead **s** on chain representing particle **i**

Quantum partition function

Quantum partition function:

$$Z_{N_b} = \left[\frac{k_B T N_b}{2\pi\hbar^2} \right]^{3N_Q N_b/2} \prod_{j=1}^{N_Q} (m_j)^{3N_b/2} \int \exp\left\{ -\sum_{n=1}^{N_b} \left[\frac{(k_B T)^2 N_b}{2\hbar^2} * \sum_{i=1}^{N_Q} m_i (\vec{r}_{i,n+1} - \vec{r}_{i,n})^2 + N_b^{-1} V(\vec{r}_{1,n}, \vec{r}_{2,n}, \dots, \vec{r}_{N_Q,n}; s) \right] / k_B T \right\} \prod_{i=1}^{N_Q} \prod_{n=1}^{N_b} d\vec{r}_{i,n}$$

Two quantum atoms i and j, represented by two rings of N_b beads. The position of bead n on ring i is denoted by $\vec{r}_{i,n}$. The **wiggly lines** represent the **harmonic interaction** between neighbouring beads on a ring. The **arrows** indicate the **scaled interaction** between beads on different rings having the same bead index n .



Harmonic springs:

$$\frac{1}{2} \frac{(k_B T)^2 N_b m_i}{\hbar^2} (\vec{r}_{i,n+1} - \vec{r}_{i,n})^2$$

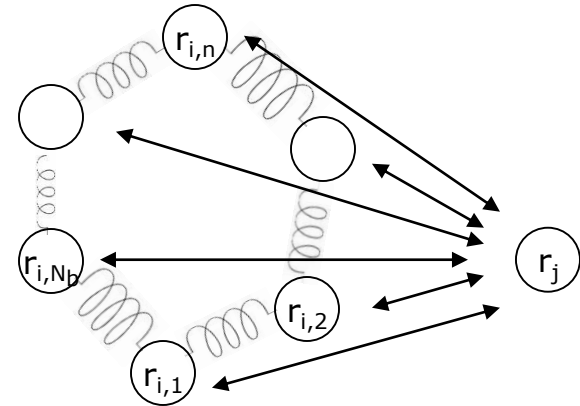
Scaled interaction:

$$N_b^{-1} V(\vec{r}_{1,n}, \vec{r}_{2,n}, \dots, \vec{r}_{N_Q,n}; s)$$

Quantum partition function

A **quantum atom i** represented by a ring of beads with positions

$\mathbf{r}_{i,n}$ ($n = 1, 2, \dots, N_b$) and a **classical atom j** with position \mathbf{r}_j . The **wiggly lines** represent the **harmonic interaction** between neighbouring beads on a ring. The **arrows** indicate the **scaled interaction** of the beads with the classical atom.



Classical limit:

- high temperature T
 - large masses m_i
 - small Planck's constant \hbar
- } **Chain shrinks**

Quantum limit:

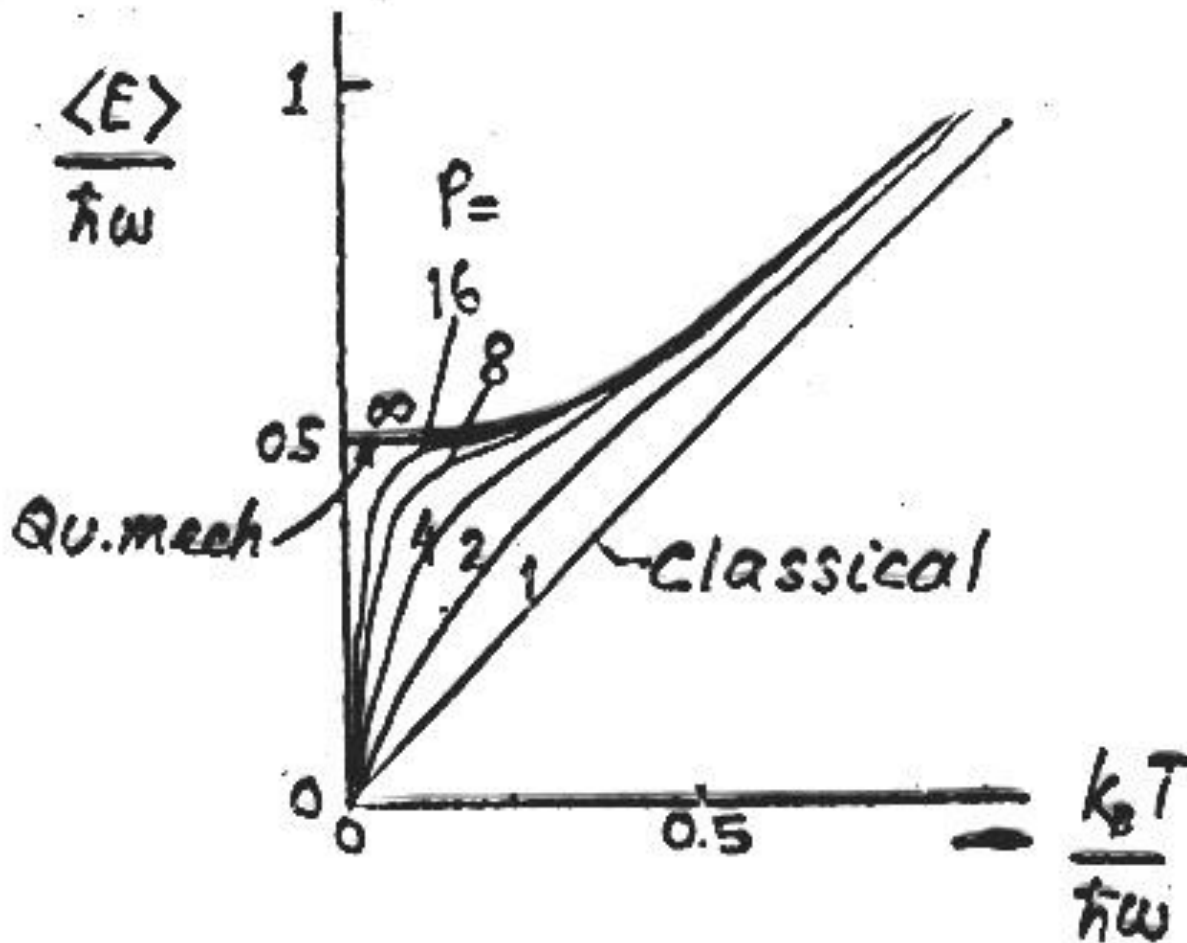
Chain spreads out

³M. J. Gillan, in *Computer Modelling of Fluids, Polymers and Solids*, edited by C. R. A. Catlow, S. C. Parker, and M. P. Allen (Kluwer, Dordrecht, 1990), pp. 155–188.

Path-integral approximation for a quantum-harmonic oscillator

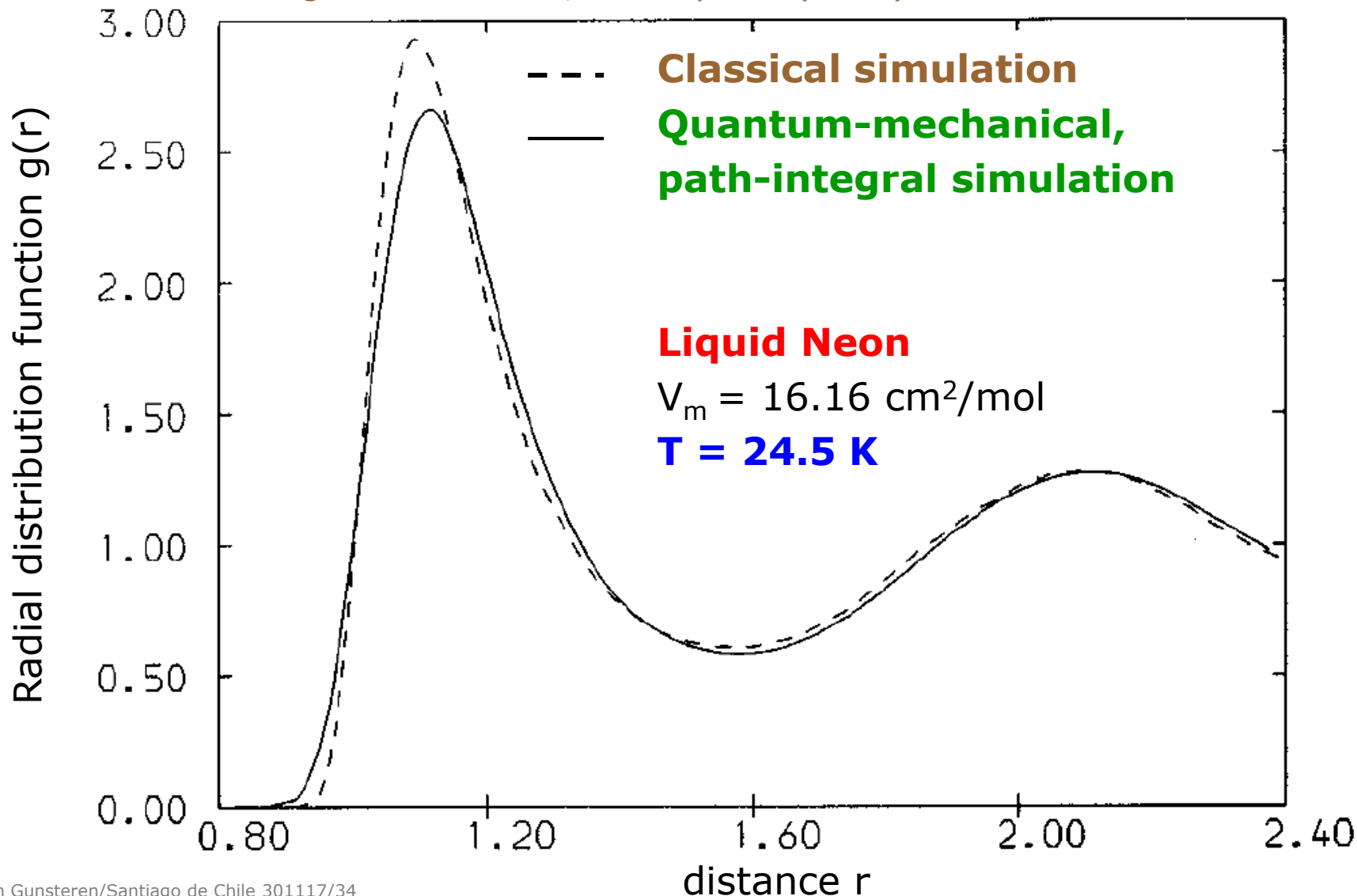
Energy as function of (low) temperature

Schweizer et al., *J. Chem. Phys.* 75 (1981) 1347



Radial distribution function for liquid Neon at low temperature

K. Singer and W. Smith, Mol. Phys. 64 (1988) 1215-1231



Cubic periodic box with 216 or 512 water molecules

S.R. Billeter et al., J.Chem.Phys. 100 (1994) 6692-6699

(N,P,T) SPC/E model

Path-integral:

N = 216, 50 + 400 "psecs"

Classical:

N = 512, 40 + 100 psecs

Methods:

1. Minimum volume in (N,P,T)
2. Minimum pressure in (N,V,T)
3. Energy-volume correlation:

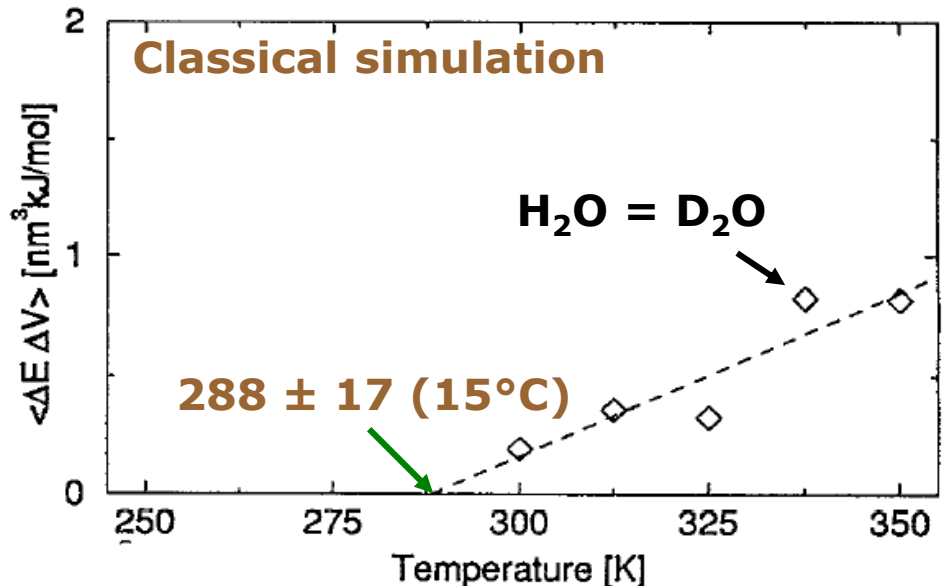
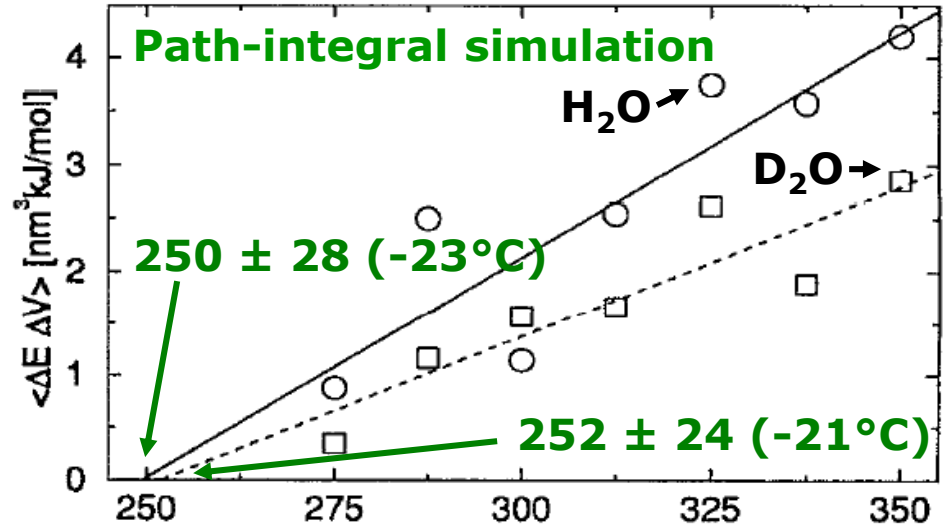
$$\langle \Delta E \Delta V \rangle_{T=T_{\max}} = 0$$

Experiment:

H₂O **277K** **(4°C)**

D₂O **284K** **(11°C)**

classical limit **291K** **(18°C)**



Treatment of quantum effects in molecular simulation

Classical versus Quantum simulation

1. Quantum effects
2. Methods and applications

Quantum-mechanical (QM) or quantum-dynamical (QD) simulation

1. Hybrid QM/MD simulation
2. Carr-Parrinello "ab initio" simulation
3. Path-Integral (PI) simulation
4. Hybrid QMD/CMD dynamic simulation: wave function propagation
5. Hybrid QMD/CMD dynamic simulation: density matrix evolution

Quantum-dynamical (QD) simulation

Why proton transfer simulation?

- Almost all biomolecules are protolytes
- Protein structure depends on pH
- A "local pH" is not measurable

Why QM for protons?

- De Broglie wavelength

$$\Lambda = \left[\frac{\hbar^2}{mk_B T} \right]^{1/2} \approx 1 \text{ \AA}$$

- Experiment: isotope effects

Why QD (dynamics) for protons?

- Excited states are accessible at room temperature
- Proton transfer very fast

Methods for quantum dynamical simulation

- **Wave function propagation**
- Density matrix evolution
- Surface hopping
- Bohmian dynamics
- ...

Quantum-dynamical simulation

Wave function propagation

the basic assumptions

- **Schrödinger dynamics:**

$$i\hbar \frac{\partial}{\partial t} |\psi_s(t)\rangle = \hat{H}_s(t) |\psi_s(t)\rangle$$

- **Separation of the state:**

$$\psi_s(X, x, t) = \psi(x, t) \cdot \psi_e(X, t)$$

proton(s)

environment:
protein & water

- **Schrödinger motion of the proton:**

$$i\hbar \frac{\partial}{\partial t} |\psi(t)\rangle = \hat{H}(X(t)) |\psi(t)\rangle$$

- **Newtonian motion of the environment:**

$$m_i \frac{d^2}{dt^2} X_i(t) = f_i(t)$$

Hybrid QD/MD simulation

S.R. Billeter & WFvG, Comp. Phys. Comm. 107 (1997) 61-91

1. Technical aspects

A. Propagation of the wave function

$$|\psi(t)\rangle = \hat{G}(t)|\psi(0)\rangle = \hat{T}e^{-\frac{1}{\hbar}\int_0^t dt' \hat{H}(t')} |\psi(0)\rangle$$

Compare 10 different methods

Best: Eigenstate expansion

Chebyshev series expansion

Time ordering operator



B. QD/MD time integration schemes

- Standard
- Guessed leap-frog
- Enhanced guessed leap-frog

C. Forces on classical atoms due to quantum subsystem

- Standard Hellmann-Feynman forces
- Simple extended HF forces
- Extended HF forces

D. Representation of the quantum subsystem

- **1** versus **3** dimensions
- Number of basis points
- Moving the classical reference frame

Hybrid QD/MD simulation

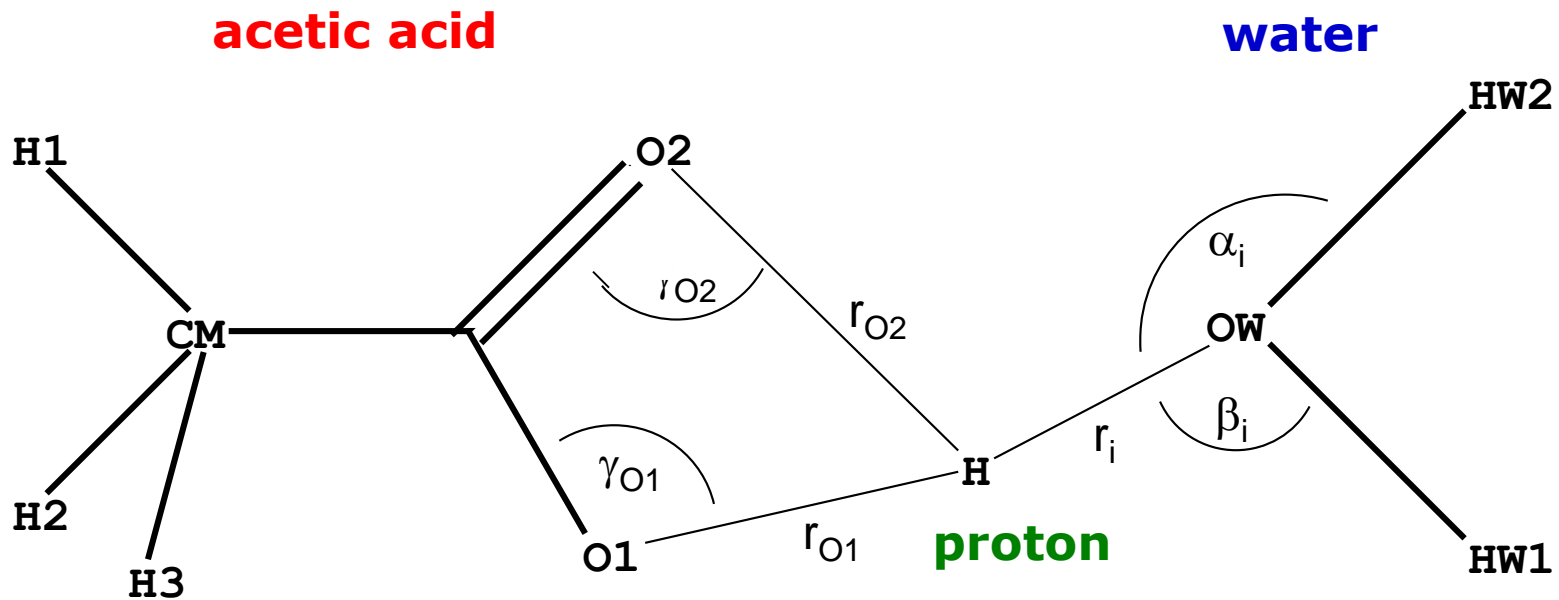
2. The potential function for a proton

- Direct proton-water/acid terms
- Lennard-Jones with configuration-dependent parameters ϵ and σ
- Polarisation terms
- Easily generalisable *S.R. Billeter & WFvG, J. Phys. Chem. A 102 (1998) 4669*

3. Results: proton transfer between acid and water

- Quantum dynamic effects
- Role excited states of the proton
- Transfer rates

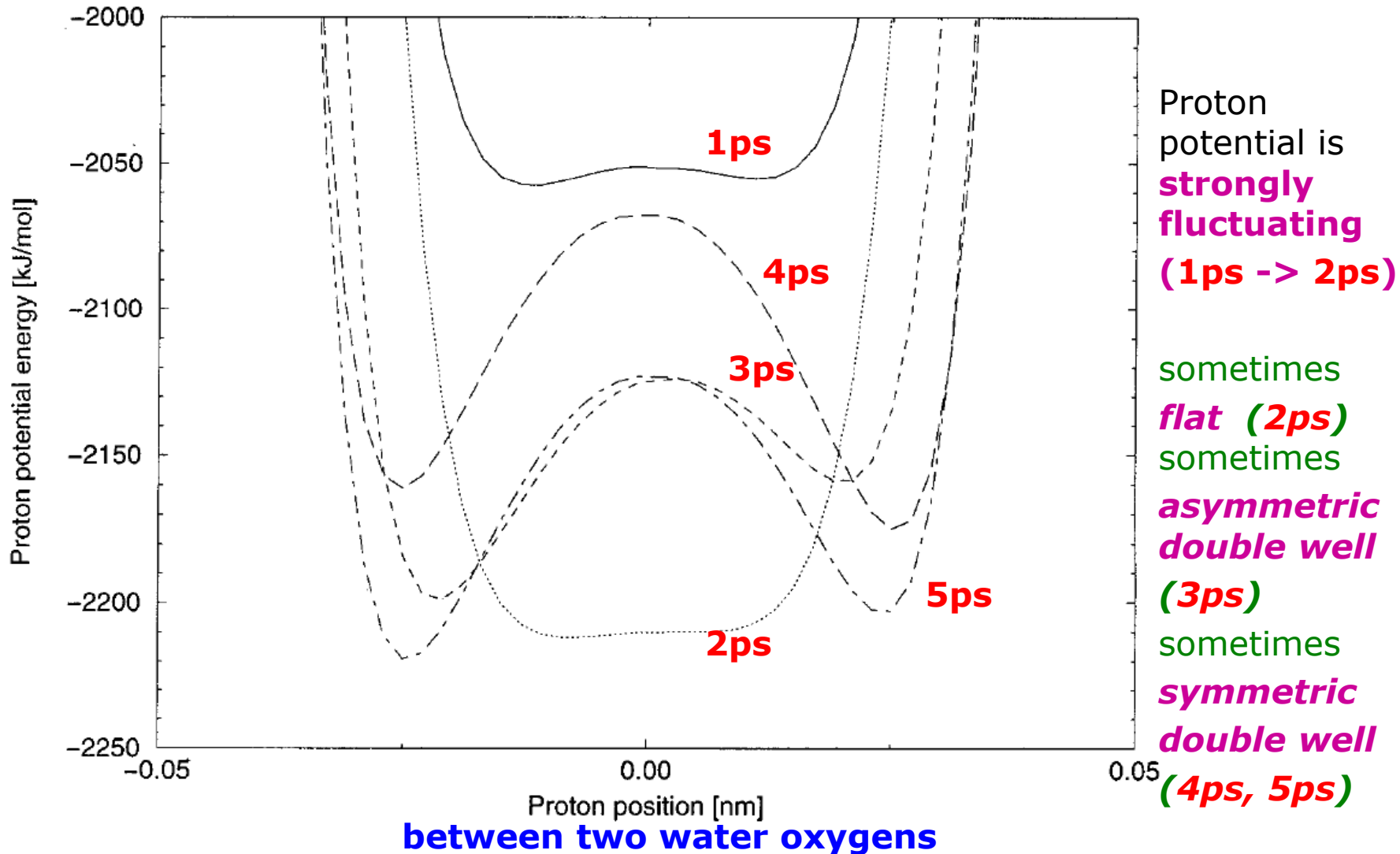
The proton and its neighbours



Proton potential energy operator

216 molecules

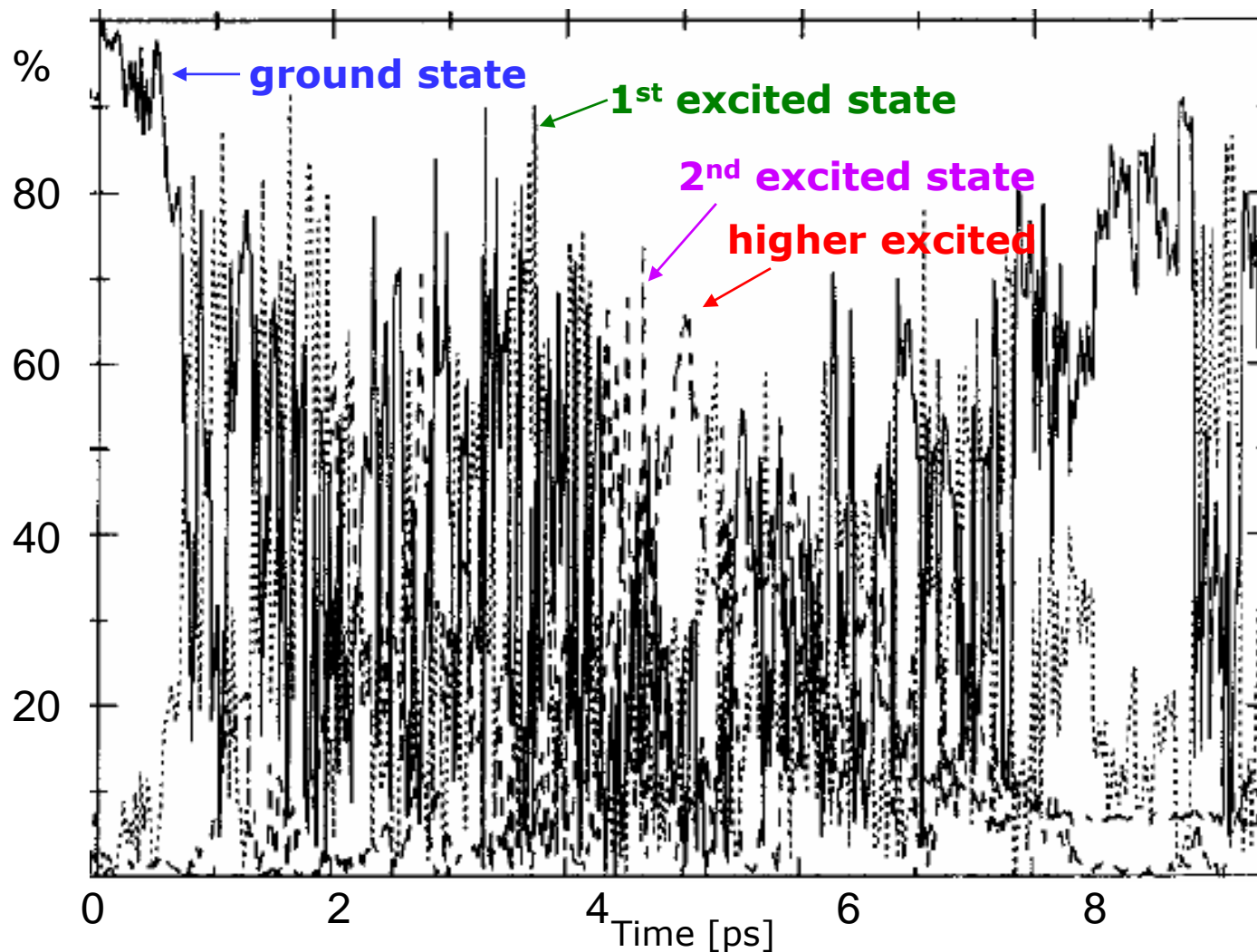
Protonated liquid SPC/E water, LJ force field, **snapshots**



QD/MD simulation of protonated liquid water

216 molecules

Population as function of time: occupation of states



S.R. Billeter & WFvG, *J. Phys. Chem. A* 102 (1998) 4669-4678

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- **Density matrix evolution**
- Surface hopping
- Bohmian dynamics
- ...

Quantum-dynamical simulation

Density matrix evolution method

Berendsen & Mavri, J. Phys. Chem. 97 (1993) 13464-13468

Phys. Rev. E 50 (1994) 198-204

Degrees of freedom

	QM	CM
Coordinates	$\hat{\xi}$	\vec{q}
Conjugate momenta	$\hat{\pi}$	\vec{p}

Hamiltonian

$$\left. \begin{array}{l} \hat{H}(\vec{p}, \vec{q}, \hat{\pi}, \hat{\xi}) \\ \text{QM basis (orthonormal): } \psi_{\alpha}(\xi) \end{array} \right\} H_{\alpha\alpha'}(\vec{p}, \vec{q}) = \langle \psi_{\alpha} | \hat{H}(\vec{p}, \vec{q}, \hat{\pi}, \hat{\xi}) | \psi_{\alpha'} \rangle$$

Solution time-dependent Schrödinger equation in terms of basis:

$$\Psi(\xi, t) = \sum_{\alpha} c_{\alpha}(t) \psi_{\alpha}(\xi) \rightarrow c_{\alpha} = \langle \psi_{\alpha} | \Psi \rangle$$

Density matrix:

$$\rho_{\alpha\alpha'} = c_{\alpha} c_{\alpha'}^*$$

Quantum-dynamical simulation: density matrix evolution


Time evolution or equation of motion:

$$\left. \begin{array}{l}
 \text{QM: } \frac{d\rho_{\alpha\alpha'}}{dt} = \frac{i}{\hbar} [\rho H(\vec{p}, \vec{q}) - H(\vec{p}, \vec{q})\rho]_{\alpha\alpha'} \\
 \text{CM: } \frac{d\vec{q}}{dt} = \text{Trace} \left(\rho \frac{\partial H(\vec{p}, \vec{q})}{\partial \vec{p}} \right), \quad \frac{d\vec{p}}{dt} = \text{Trace} \left(\rho \frac{\partial H(\vec{p}, \vec{q})}{\partial \vec{q}} \right)
 \end{array} \right\} \begin{array}{l} \text{integrate} \\ \text{numerically} \\ \text{QMD} \end{array}$$

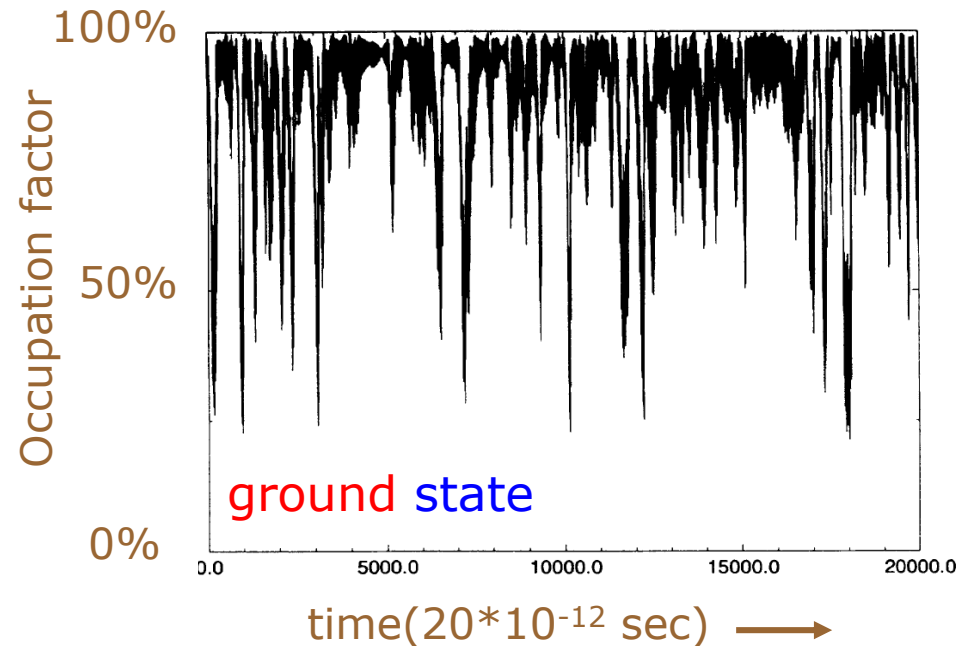
Expectation value of **observable \hat{A}** :

$$\text{QM: } \text{Trace}(\rho A) = \sum_{\alpha} (\rho A)_{\alpha\alpha}$$

$$\text{CM: } \langle \text{Trace}(\rho A) \rangle$$


 CM ensemble

(a)

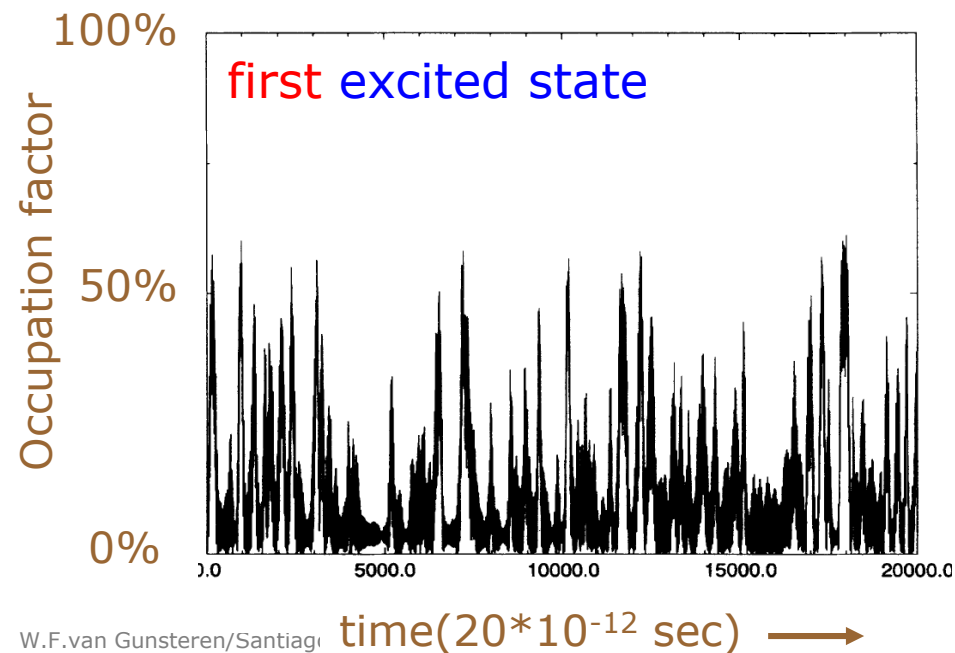


QD: N_2 in
 CD: 79 Argon atoms
 at $T = 1000\text{K}$

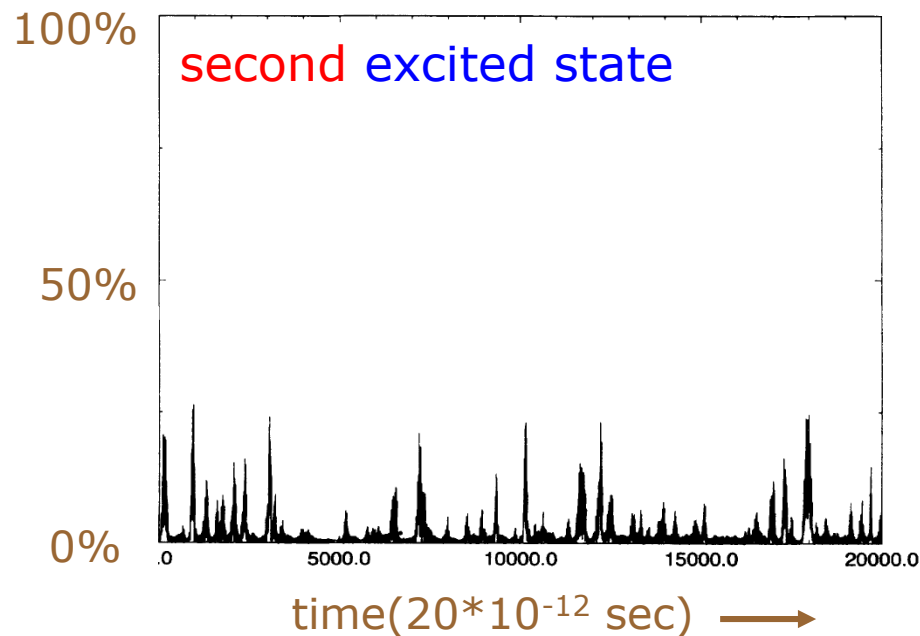
Berendsen & Mavri,
Phys. Rev. E50 (1994) 198-204

FIG. 2. Time evolution of the diagonal elements of the density matrix for a three level quantum harmonic oscillator in a dense Ar bath at 1000 K (79 Ar atoms in a simulation box of $15 \text{ \AA} \times 15 \text{ \AA} \times 15 \text{ \AA}$): ground state ρ_{00} (a), first excited state ρ_{11} (b), and second excited state ρ_{22} (c).

(b)



(c)



Classification of methods

A Quantum Mechanics

B Classical Mechanics

1. *One structure, state: Static*

QM: time-independent Schrödinger

$$T = 0$$

- ab initio
- density functional
- semi-empiric
- empirical valence bond

CM: energy minimization

$$T = 0$$

- empirical force field

2. *Ensemble of structures, states: Statistical Mechanics*

QM: density matrices

$$T \neq 0$$

- Fermi-Dirac
- Bose-Einstein
- **path-integral simulation**

CM: Boltzmann sampling

$$T \neq 0$$

- force field
- Monte Carlo
- molecular dynamics

Classification of methods

A Quantum Mechanics

B Classical Mechanics

3. Trajectories of structures, states: Dynamics

QD: time-dependent Schrödinger

T \neq 0 + dynamics

- wave function propagation
- density matrix evolution
- surface hopping
- real time path integral
- Bohmian dynamics

CM: Newton; Lagrange

T \neq 0 + dynamics

- force field
- molecular dynamics

Various combinations of techniques possible:

A1 (electrons) + **B3** (atoms, nuclei)

or

A3 (proton) + **B3** (molecules)

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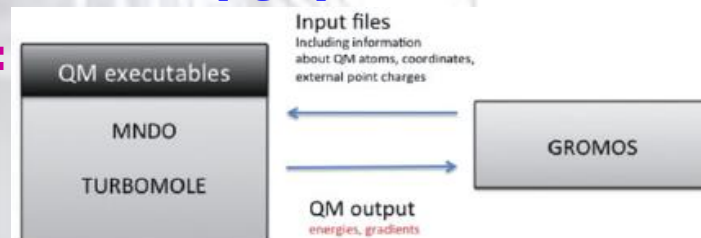
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1. Quantum effects
2. Methods and applications

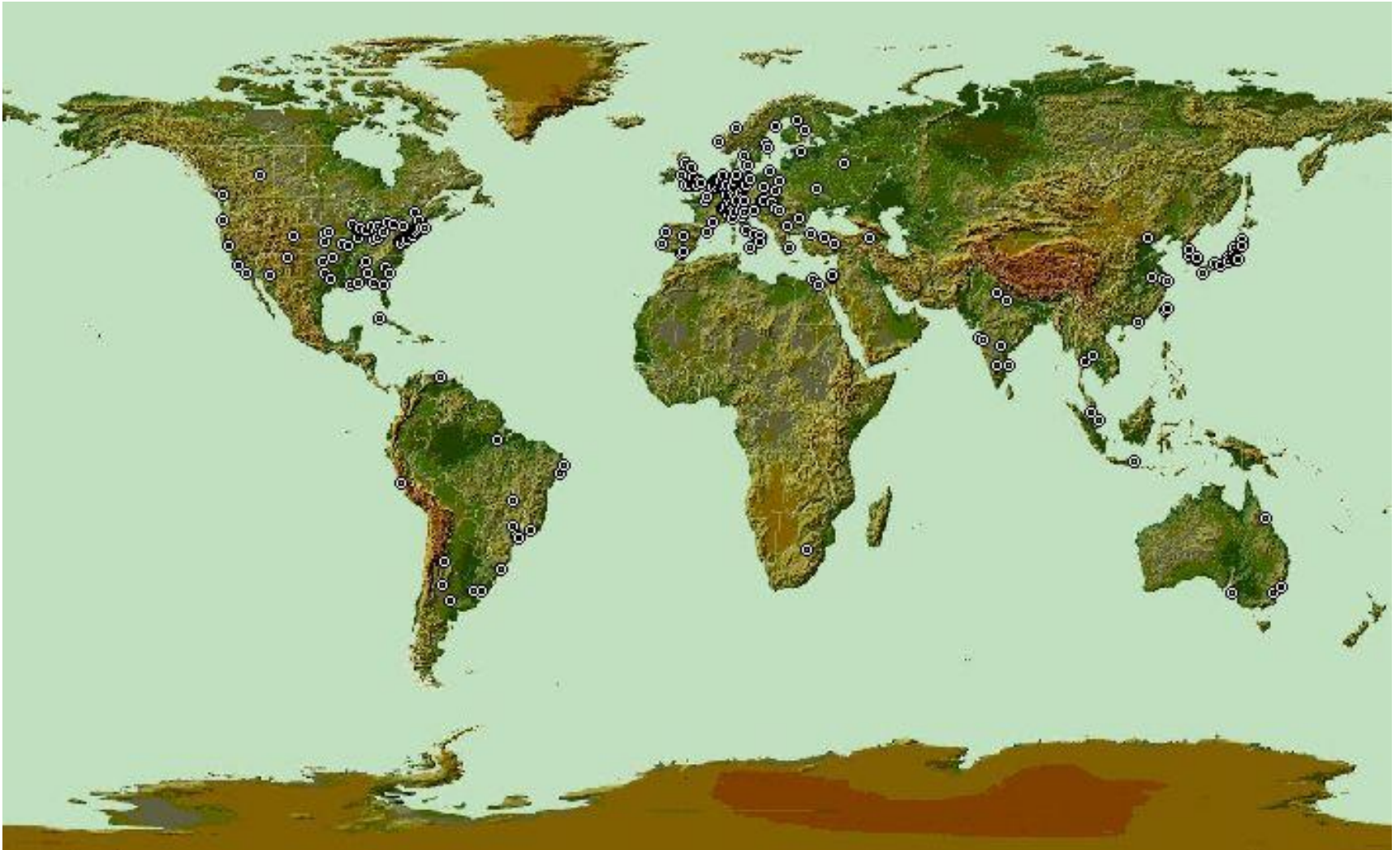
Quantum-mechanical (QM) or quantum-dynamical (QD) simulation

1. Hybrid QM/MD simulation with GROMOS:
2. Car-Parrinello "ab initio" simulation
3. Path-Integral (PI) simulation
4. Hybrid QMD/CMD dynamic simulation: wave function propagation
5. Hybrid QMD/CMD dynamic simulation: density matrix evolution



K. Meier et al., J. Comput. Chem. 33 (2012) 1153-1161

Spatial distribution of licences GROMOS biomolecular simulation software



GROMOS = Groningen Molecular Simulation + GROMOS Force Field

Generally available: <http://www.gromos.net>