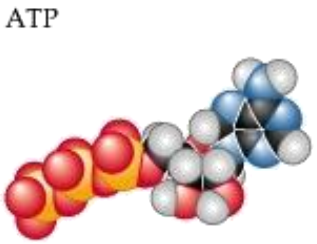
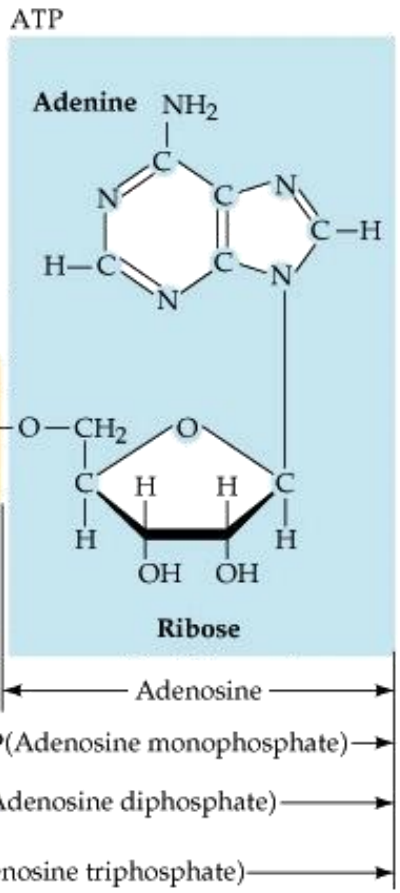
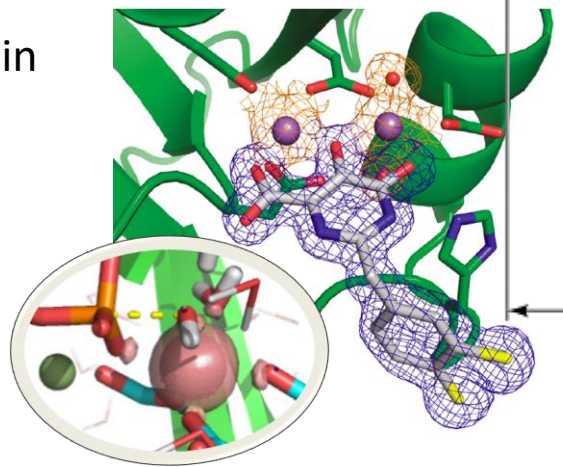
Why Nature Chose Phosphates?

- **Biological importance**:
  - **Reproduction of genetic material**:
    DNA and RNA hydrolysis, synthesis
    Regulation of gene expression
  - **Energy storage and transfer**:
    ADP/ATP equilibrium provides energy for reactions in the cells
  - **Signaling**:
    Phosphorylation activates or deactivates proteins in regulatory processes
  - **Metabolism:**
    Energy from ATP is used in biosynthetic pathways







- **Theoretical importance**:
  - **Reaction mechanism**
  - Highly charged species
  - Metal ions in enzymes

Nobel Prize in Chemistry 1998

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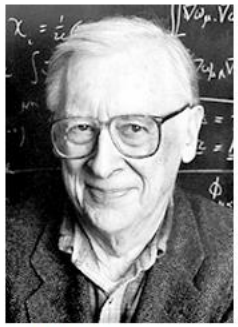
The Nobel Prize in Chemistry 1998
Walter Kohn, John Pople

The Nobel Prize in Chemistry 1998

Walter Kohn



John A. Pople

The Nobel Prize in Chemistry 1998 was divided equally between Walter Kohn *"for his development of the density-functional theory"* and John A. Pople *"for his development of computational methods in quantum chemistry"*.

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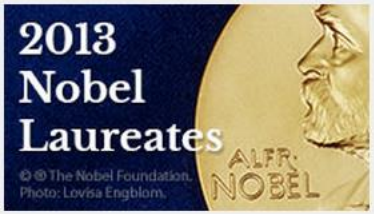


2013 CHEMISTRY PRIZE QUESTION

Did you know that computer models are used to study everything from molecules of life to industrial chemical processes?

Yes
No
Submit

Greetings to the 2013 Nobel

The recipients

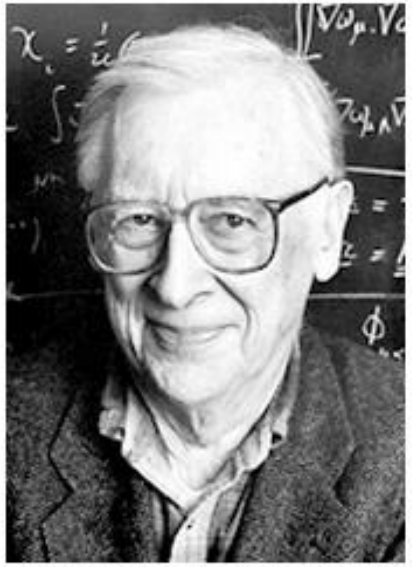
- Walter Kohn

Developed the Density Functional Theory (DFT), which became the most widely used quantum chemistry method due to its efficiency and accuracy.

- John Pople

Developed numerous algorithms for quantum chemistry methods. Main founder behind the currently most widely used quantum chemistry software, Gaussian.

Walter Kohn



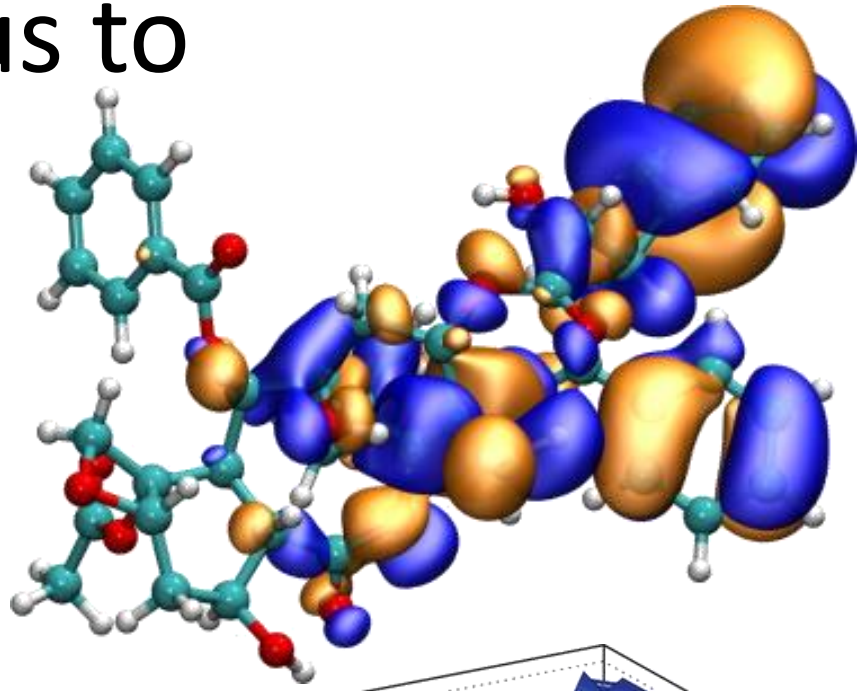
John A. Pople

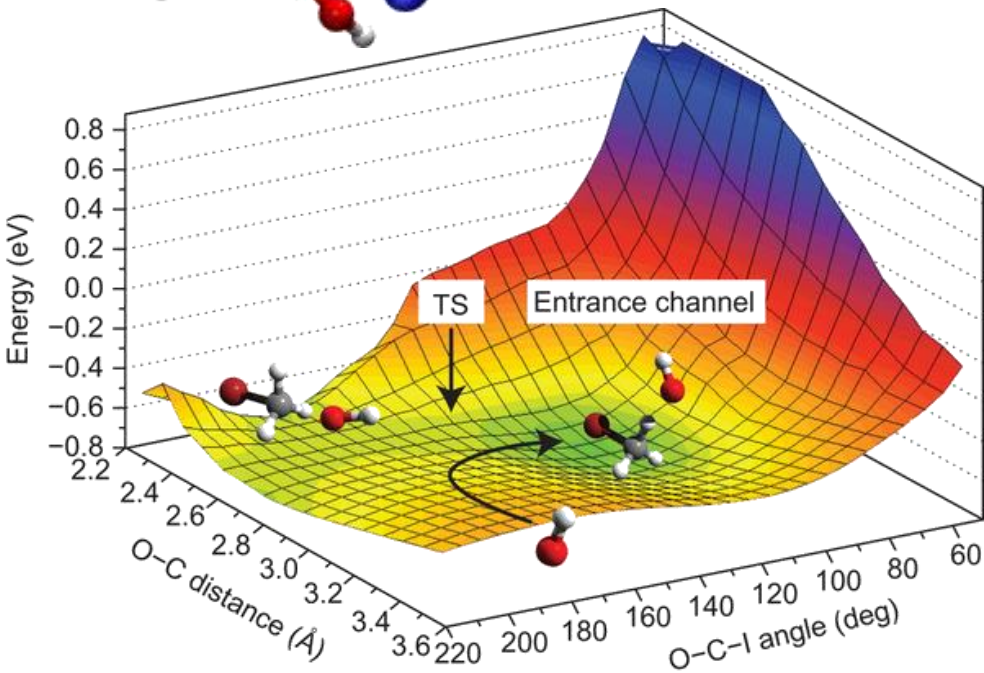
Their work enables us to

- Obtain the solution of the Schrödinger equation using approximate methods

$$H\Psi = E\Psi$$

- Find energies and wave functions of small to medium sized molecules
- Provide accurate models of **chemical structure** and **reactivity**
- Determine **molecular properties**





Nobel Prize in Chemistry 2013

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The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013

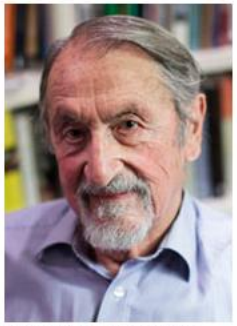
© Harvard University
Martin Karplus


Photo: © S. Fisch
Michael Levitt


Photo: Wikimedia Commons
Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

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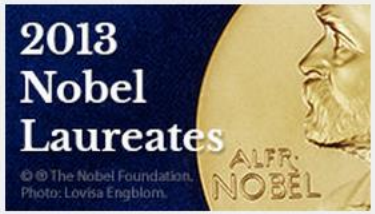


2013 CHEMISTRY PRIZE QUESTION

Did you know that computer models are used to study everything from molecules of life to industrial chemical processes?

Yes
No
Submit

Greetings to the 2013 Nobel

The recipients

Arieh Warshel

- Worked on force field development for molecular mechanics in Shneior Lifson's group at the Weizmann Institute.
- Developed Quantum Chemistry/Molecular mechanics (i.e., QM/MM) method together with Michael Levitt (1976).
- Performed the first molecular simulations of enzymatic reactions in proteins (1976).
- Performed the first protein folding simulation together with Michael Levitt (1976).

The recipients

Michael Levitt

- Worked on force field development for molecular mechanics in Shneior Lifson's group at the Weizmann Institute.
- Developed Quantum Chemistry/Molecular mechanics (i.e., QM/MM) method together with Arieh Warshel (1976).
- Wrote the first software to perform molecular dynamics simulations of DNA and proteins.
- Performed the first protein folding simulation together with Arieh Warshel (1976).

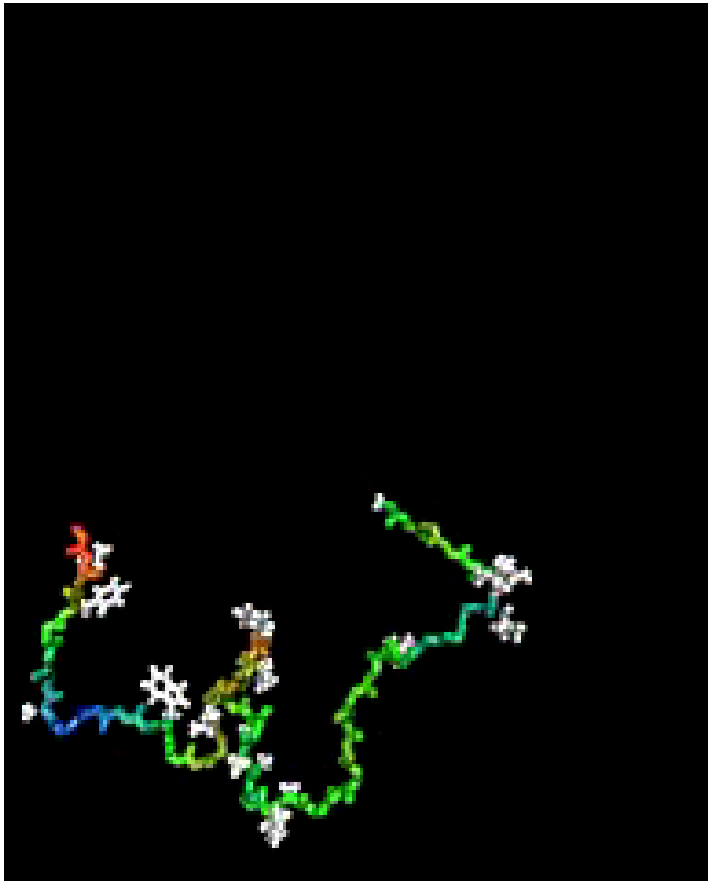
The recipients

Martin Karplus

- Force field development for molecular mechanics collaborating with Shneior Lifson's group at the Weizmann Institute.
- One of the first computational studies of biological systems.
- Main founder behind CHARMM (Chemistry at HARvard Macromolecular Mechanics)
- Pioneered QM/MM simulations, and developed numerous methods for computational modelling of biological systems.

Their work enables us to

- Find the structures of complex biomolecules by calculating their Newtonian dynamics
- Find reaction mechanisms of enzymes
- Model and predict structure and function of biological systems



MM and MD and QM/MM

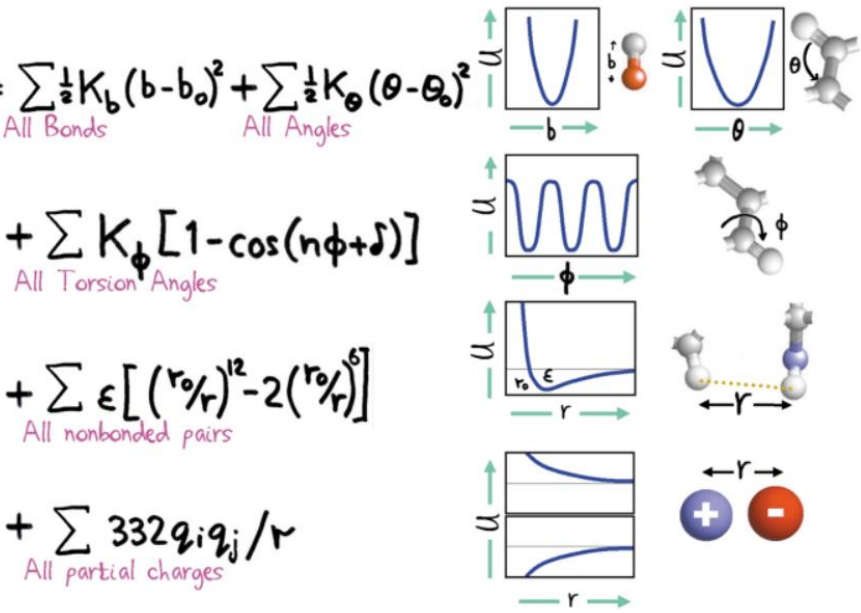
- **Molecular Mechanics** (MM) describes an empirical potential energy function (U) that allows us to calculate the approximate energy given as a function of the atomic positions.
- Each atom is represented explicitly, together with its partial charge (q_i), radius (r_0), and the list of all other atoms it is bonded to (with b_0 bond length).
- Bonds cannot break and cannot form.
- **Molecular Dynamics** (MD) defines the movements of the atoms classically, using Newton's equation of motion on a given potential energy surface.
- The potential energy surface for MD can be defined by MM, (which is an approximation of the quantum mechanical energy of the system), or by the approximate solution of the Schrödinger equation using quantum mechanics (QM) methods.
- The potential energy can also be a combination of QM and MM by defining two sets of atoms, a QM region and an MM region, and accounting for the electrostatic coupling between the two subsystems. In the QM region bonds can break and form.

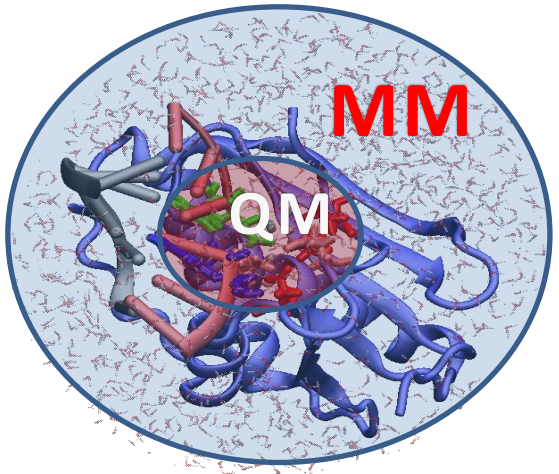
$$U = \sum_{\text{All Bonds}} \tfrac{1}{2}K_b(b-b_0)^2 + \sum_{\text{All Angles}} \tfrac{1}{2}K_\theta(\theta-\theta_0)^2$$

$$+ \sum_{\text{All Torsion Angles}} K_\phi[1-\cos(n\phi+\delta)]$$

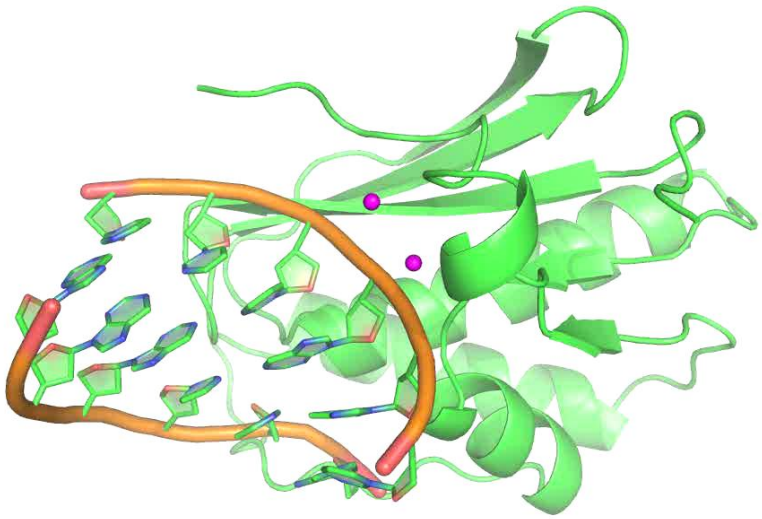
$$+ \sum_{\text{All nonbonded pairs}} \epsilon\left[\left(r_0/r\right)^{12} - 2\left(r_0/r\right)^{6}\right]$$

$$+ \sum_{\text{All partial charges}} 332 q_i q_j / r$$





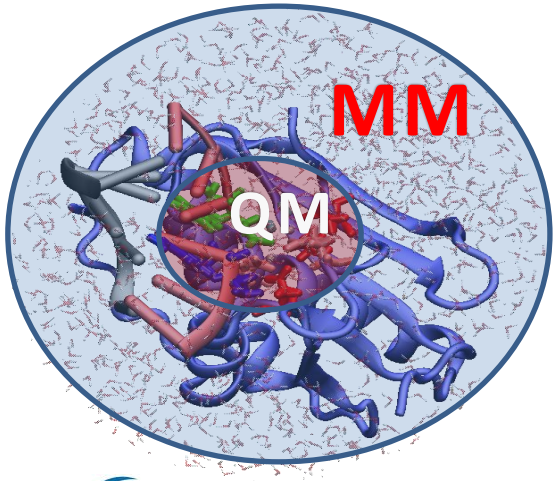
Computational Methods



- QM/MM implementation with Q-Chem +CHARMM using full electrostatic embedding

  Woodcock et al., *J. Comp. Chem.*, 2007

- DFT B3LYP method (6-31+G* basis)
- Free energy calculations of the reaction with **enhanced sampling** methods: Hamiltonian replica exchange coupled with finite temperature string method



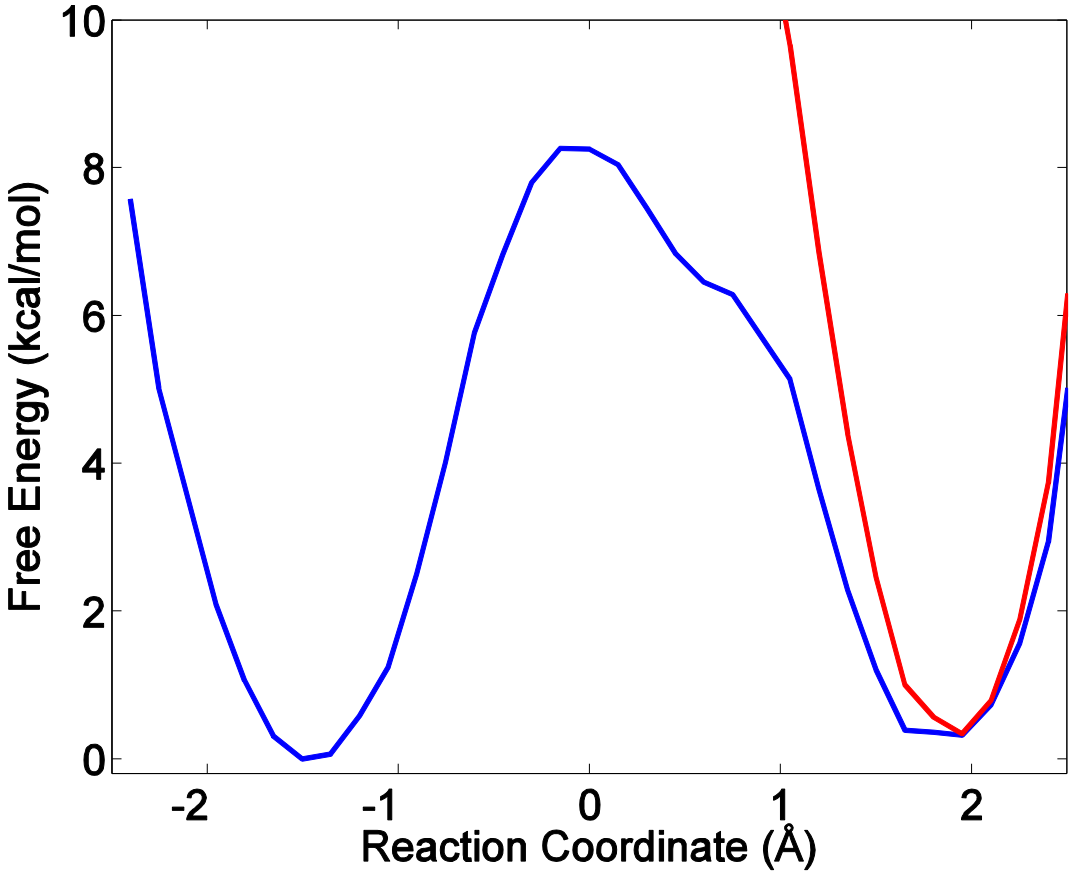
Q-CHEM

Shao, Rosta, et al., *Phys. Chem. Chem. Phys.*, 2006

Umbrella Sampling

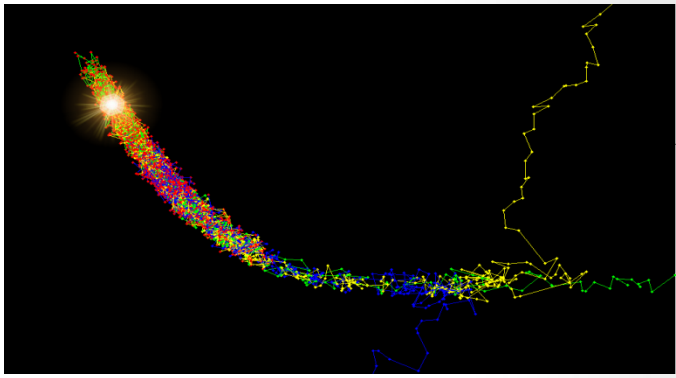
$$E_i(q_A) = U_{pot}(q_A) + \frac{1}{2} k_i (\xi_A - \xi_i)^2$$

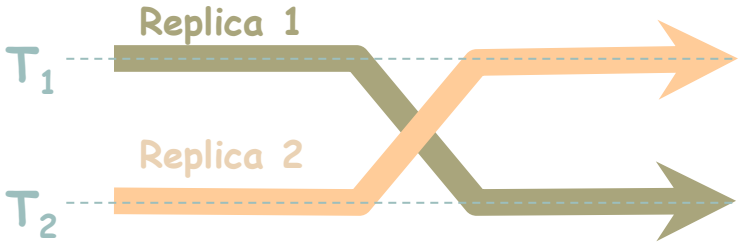
- Run parallel simulations with harmonic constraints moving along the reaction coordinate
- Recover the unbiased free energy surface from combined data using e.g., WHAM

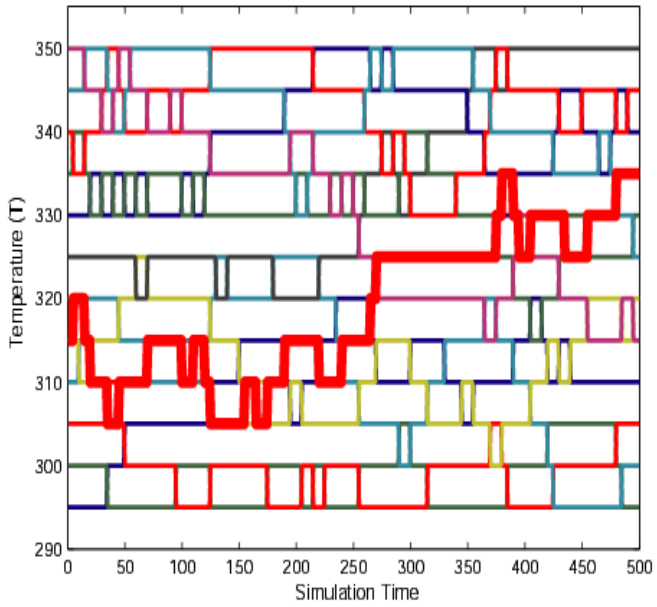


Monte Carlo Methods

- Stochastic methods for enhanced sampling
- Using replica exchange (REMD) and simulated tempering (ST)
  - How does it work?
  - How to use it best?
  - How to interpret results?
  - How useful/efficient is it?







E. Rosta and G. Hummer, JCP, 2009
E. Rosta and G. Hummer, JCP, 2010

Statistical sampling

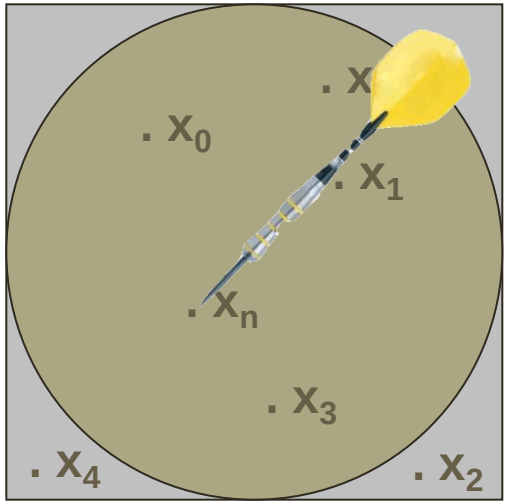
- Generate a random walk (throwing darts):

$$\{x_0, x_1, \ldots, x_n\}$$

- Average property of interest:

$$\langle A \rangle = \frac{1}{n} \sum_{i=1}^{n} A(x_i)$$

$$A(x_i) = \begin{cases} 1 & \text{if inside circle} \\ 0 & \text{if outside circle} \end{cases}$$



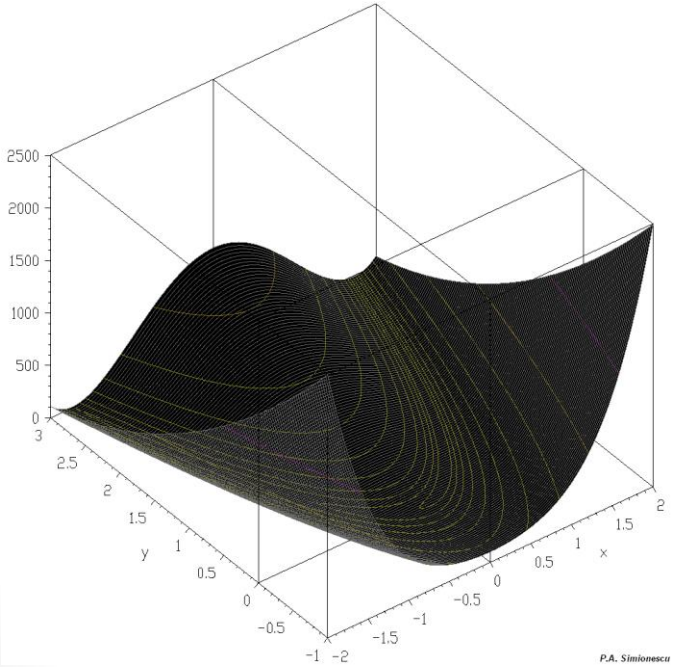
- Obtain the area within the circle (<A>) from random walk!

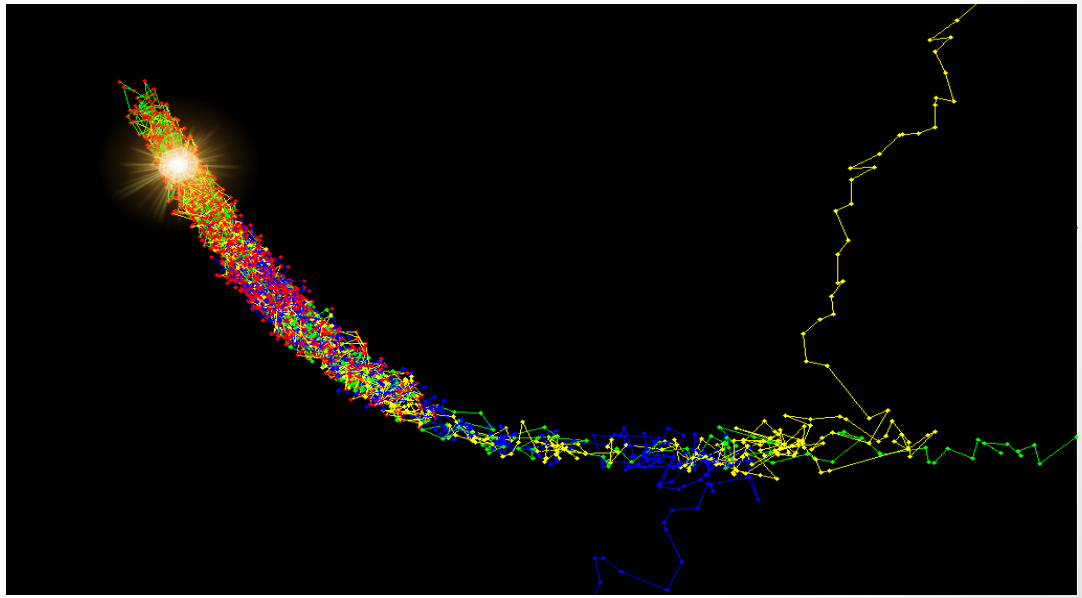
Metropolis Monte Carlo

A way to evaluate multidimensional integrals, such as partition functions and thermodynamic properties:

$$Z = \int d\tau \, e^{-U/k_B T}$$

$$\langle A \rangle = \frac{\int d\tau \, A e^{-U/k_B T}}{\int d\tau \, e^{-U/k_B T}} = \int d\tau \, A \left(\frac{e^{-U/k_B T}}{\int d\tau \, e^{-U/k_B T}} \right)$$





N. Metropolis, A.W. Rosenbluth, M.N. Rosenbluth, A.H. Teller, and E. Teller. Journal of Chemical Physics, 21(6):1087-1092, 1953

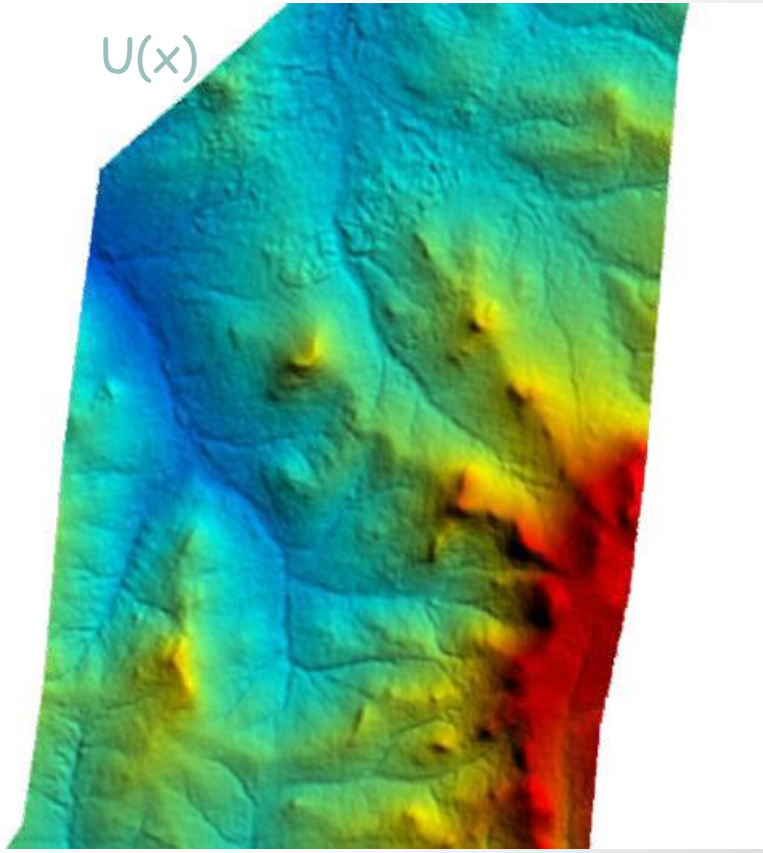
Metropolis Monte Carlo Algorithm

I. Randomly generate a new configuration.

II. Accept or reject the new configuration based on the Metropolis criterion:

$$T(x \to x') = \begin{cases} 1 \quad \text{for} \quad \Delta \le 0 \\ \exp(-\Delta) \quad \text{for} \quad \Delta > 0 \end{cases}$$

where $\Delta = \frac{1}{k_B T}(U(x') - U(x))$



Stochastic methods: Transition rule

- Generate random walk:

$$\{x_0, x_1, \ldots, x_n\} \qquad ? \qquad p(x) = \frac{e^{-U(x)/k_BT}}{\int e^{-U(x)/k_BT} d\tau} = \frac{e^{-U(x)/k_BT}}{Z}$$

- Transition rule for $T(x \to x')$
  - Time reversible
  - Conserves equilibrium probabilities ($p(x)$)
  - $T(x \to x')$ has to be between 0 and 1 (probability)

$$p(x)T(x \to x') = p(x')T(x' \to x) \quad \text{detailed balance condition}$$

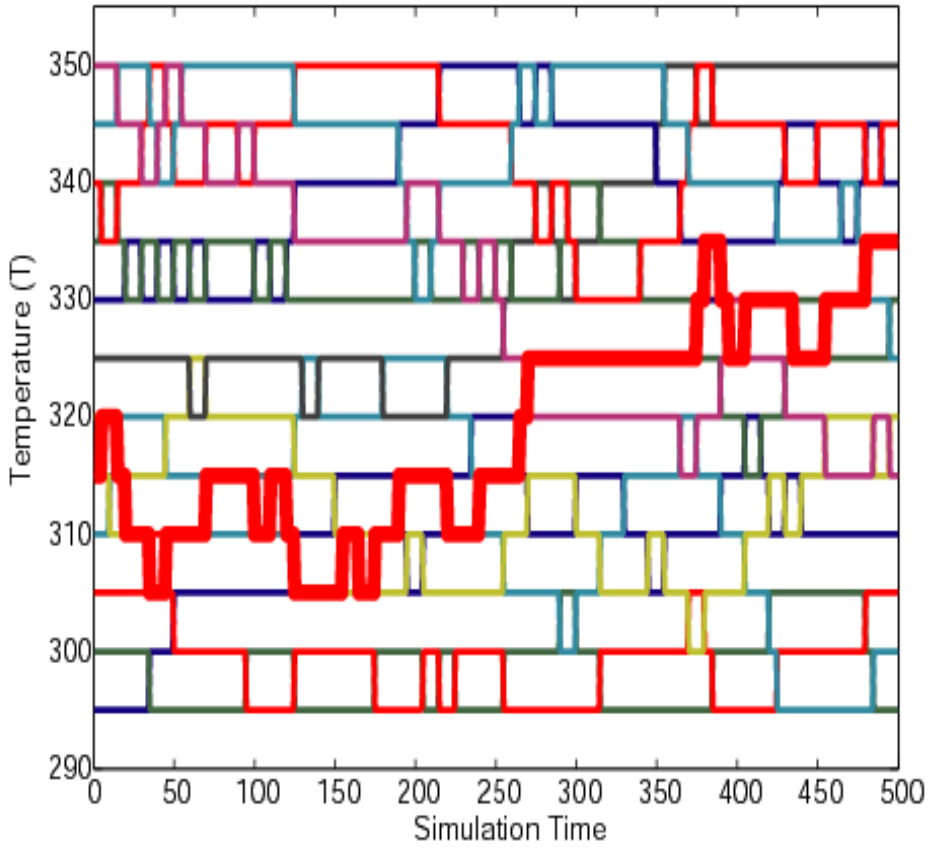
$$\frac{T(x \to x')}{T(x' \to x)} = \frac{p(x')}{p(x)} = e^{-[U(x')-U(x)]/k_BT} \quad \overset{e.g.\Delta U>0}{\Rightarrow} \begin{cases} T(x' \to x) = 1 \\ T(x \to x') = \exp(-\Delta U / k_BT) \end{cases}$$

Results in maximum number of transitions

- Modify random walk according to transition rule & obtain averages:

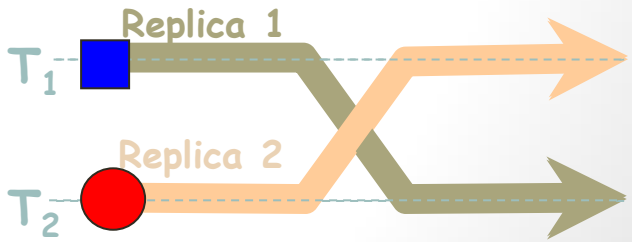
$$x_{i+1} := \begin{cases} x' & \text{if the transition is accepted} \\ x & \text{if the transition is rejected} \end{cases} \quad \Rightarrow \quad \langle A \rangle = \frac{1}{n} \sum_{i=1}^{n} A(x_i)$$

Replica exchange



K. Hukushima and K. Nemotto, J. Phys. Soc. Japan, 1996

- Running MD at different temperatures in parallel
- Couple the runs in order to speed up lowest temperature's dynamics
- Preserve P_{eq} at each temperature
- Detailed balance condition has to be satisfied



Replica Exchange Procedure

- Each replica is simulated simultaneously and independently for a certain number of MD or MC steps
- Pick some pairs of the replicas at neighboring temperatures and exchange the configurations according to the following acceptance rule:

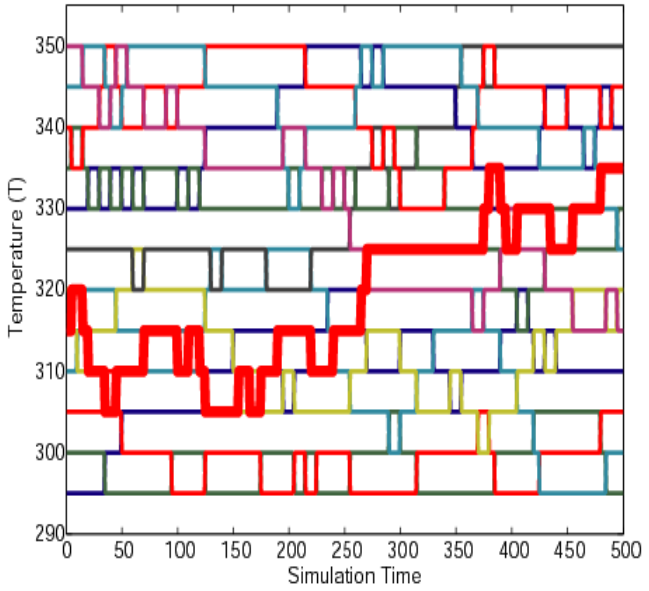
$$T(x_T, x'_{T'} \rightarrow x'_T, x_{T'}) = \begin{cases} 1 & for \quad \Delta \le 0 \\ \exp(-\Delta) & for \quad \Delta > 0 \end{cases}$$

where $\Delta = (1/k_B T - 1/k_B T')[U(x') - U(x)]$

$$\frac{T(x_T, x'_{T'} \rightarrow x'_T, x_{T'})}{T(x'_T, x_{T'} \rightarrow x_T, x'_{T'})} = \frac{p_T(x')p_{T'}(x)}{p_T(x)p_{T'}(x')} = e^{-[U(x')-U(x)]/(1/k_B T - 1/k_B T')}$$

Simulated tempering (ST)

- Only a single replica
- Changes the temperature of the simulation stochastically
- Preserves P_{eq} at each temperature
- Obtain partition functions (Z) iteratively



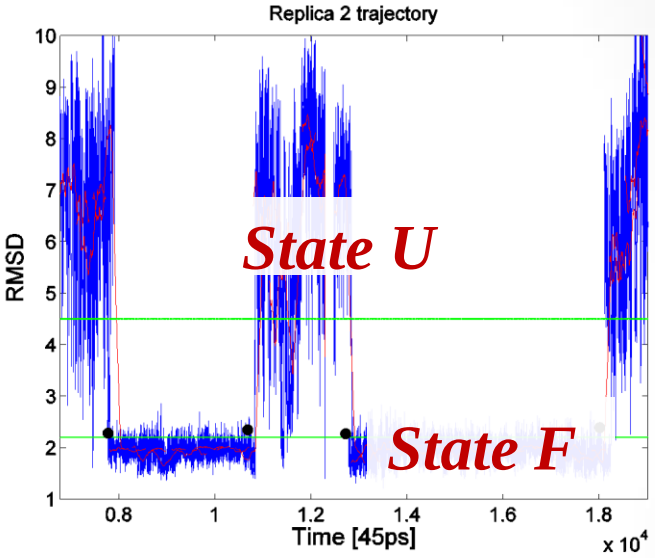
$$\frac{T(x,T \to x,T')}{T(x,T' \to x,T)} = \frac{p_{T'}(x)}{p_T(x)} = \frac{e^{-U(x)/k_B T'}}{Z'} \frac{Z}{e^{-U(x)/k_B T}}$$

A. P. Lyubartsev, A. A. Martsinovski, S. V. Shevkunov, and P. N. Vorontsov-Velyaminov, JCP, 1992
E. Marinari and G. Parisi, Europhysics Letters, 1992

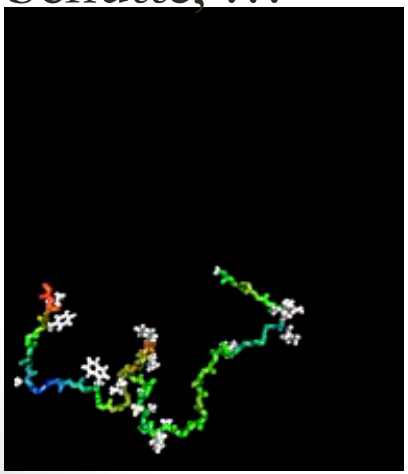
State Assignment in Protein Folding Simulations

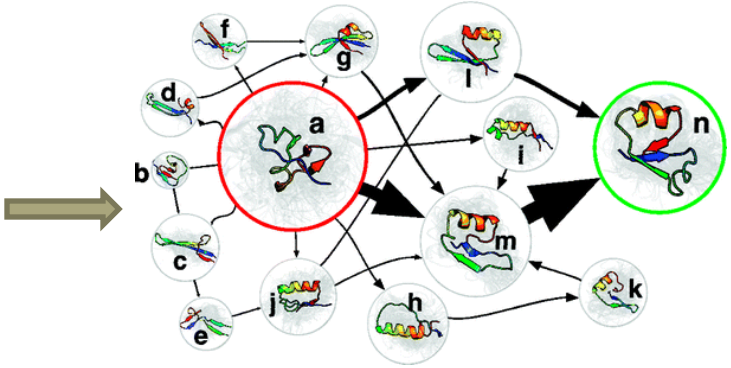
Master equation

$$\frac{dP_i}{dt}(t) = \sum_{\substack{j=1 \\ (j \neq i)}}^{N} k_{i \leftarrow j} P_j(t) - \sum_{\substack{j=1 \\ (j \neq i)}}^{N} k_{j \leftarrow i} P_i(t)$$



Hummer, Noe, Pande, Schutte, …





Levy PNAS, 2007

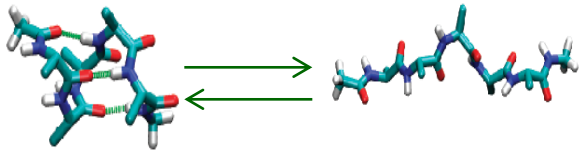
$$F \underset{k_F(T)}{\overset{k_U(T)}{\rightleftharpoons}} U$$

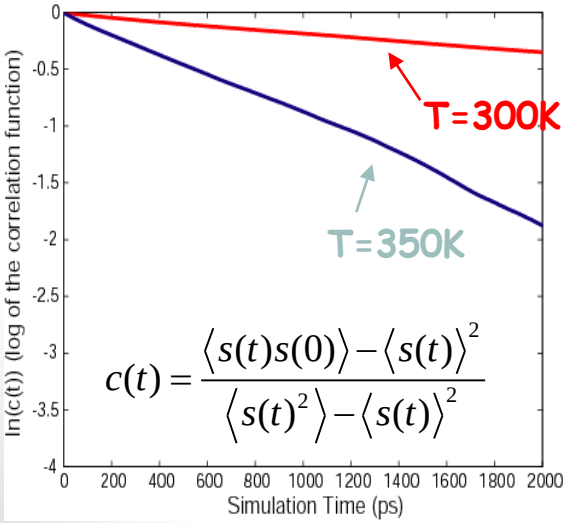
Voelz, Bowman, Beauchamp and Pande, *J. Am. Chem. Soc.*, 2010

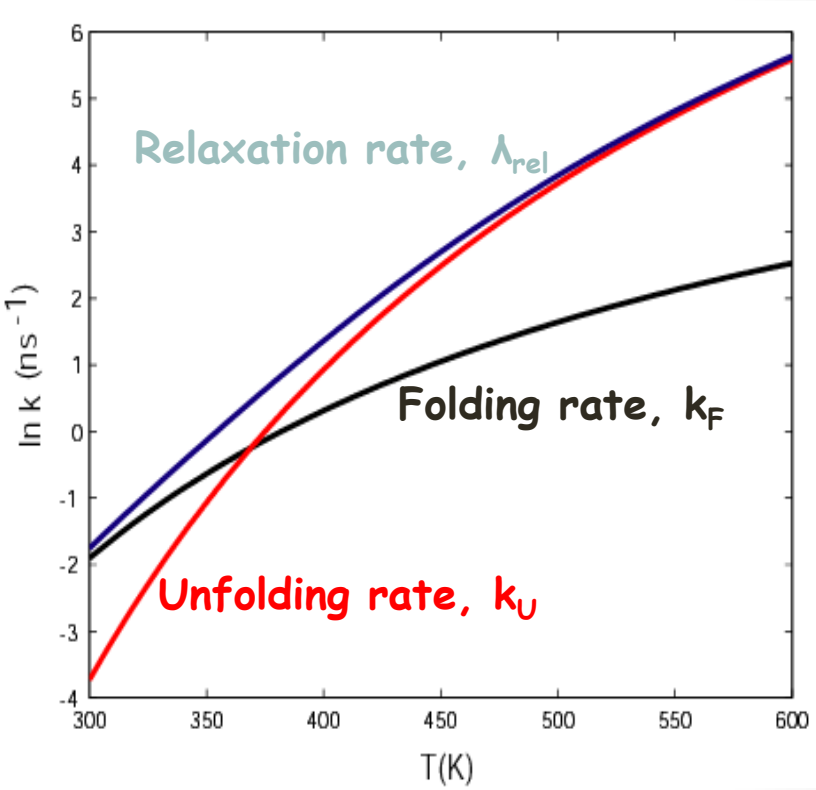
Kinetic model

Single Temperature:

$$F \underset{k_F(T)}{\overset{k_U(T)}{\rightleftharpoons}} U$$

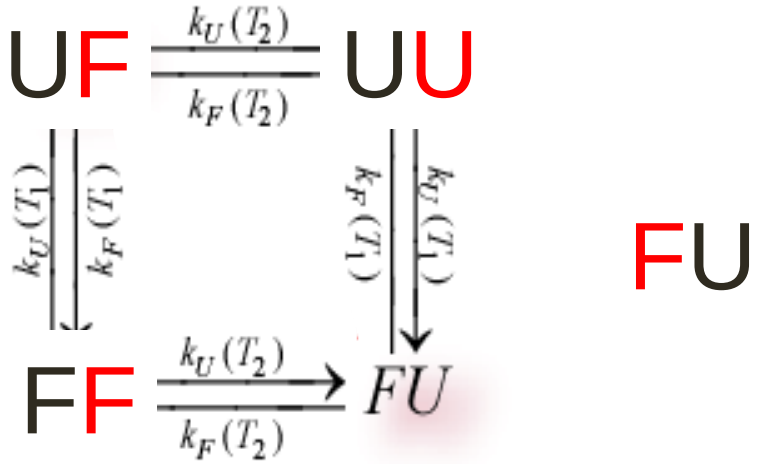


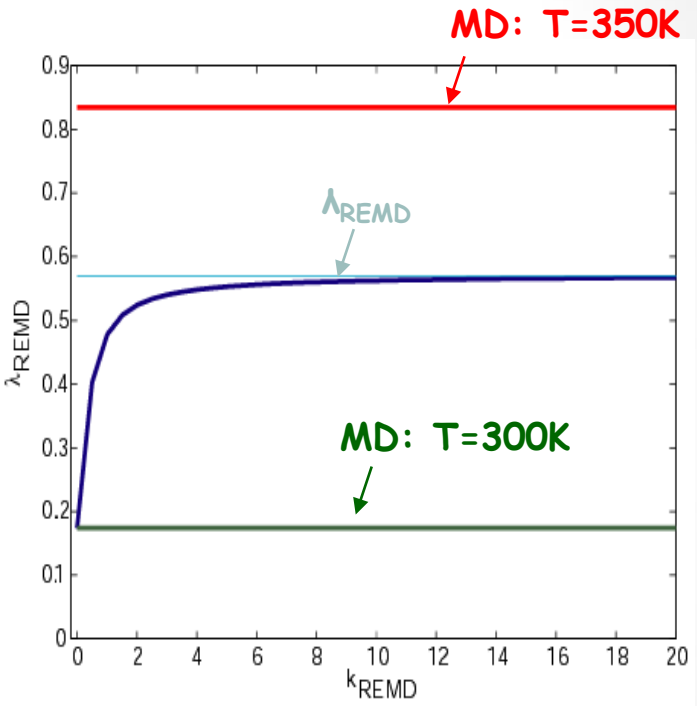




$$K = \begin{bmatrix} -k_U & k_F \\ k_U & -k_F \end{bmatrix} \Rightarrow \frac{1}{\tau_{rel}} = \lambda_{rel} = k_U(T) + k_F(T)$$

Replica Exchange Rate

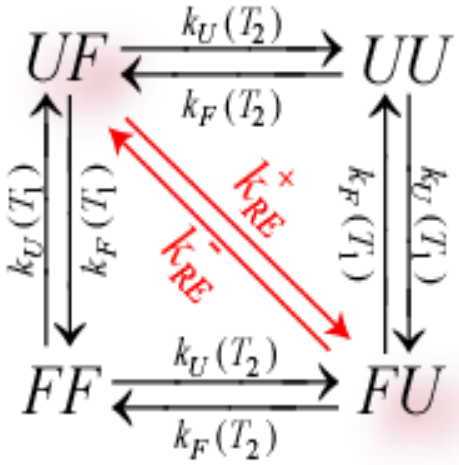




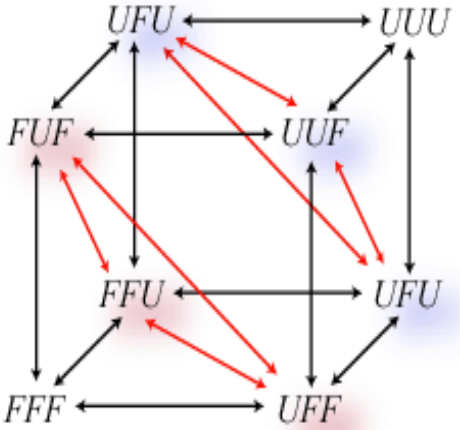
$$k_{RE}\ U_iF_j \rightarrow U_jF_i\ = \frac{p_{acc}\ U_iF_j \rightarrow U_jF_i}{\delta t_{xc}}$$

$$K = \begin{bmatrix} -k_U(T_1)+k_U(T_2) & k_F(T_1) & k_F(T_2) & 0 \\ k_U(T_1) & -k_F(T_1)+k_U(T_2)+k_{RE}^{+} & k_{RE}^{-} & k_F(T_2) \\ k_U(T_2) & k_{RE}^{+} & -k_U(T_1)+k_F(T_2)+k_{RE}^{-} & k_F(T_1) \\ 0 & k_U(T_2) & k_U(T_1) & -k_F(T_2)+k_F(T_1) \end{bmatrix}$$

Collective replica exchange coupled states



(N=2)



(N=3)

… *N* temperatures
(2^N microstates)

$$FF \rightleftarrows \begin{pmatrix} UF \\ FU \end{pmatrix} \rightleftarrows UU$$

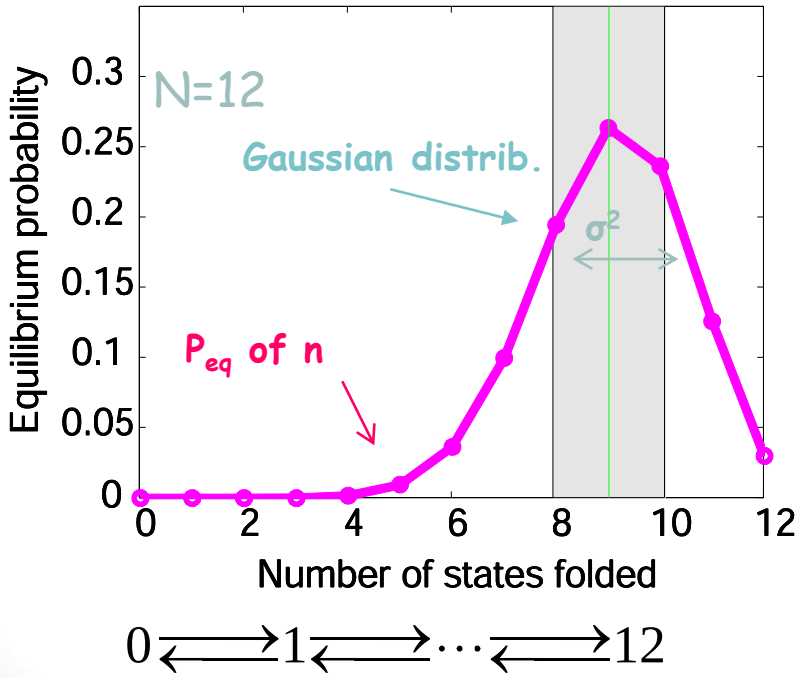
$$FFF \rightleftarrows \begin{pmatrix} FFU \\ FUF \\ UFF \end{pmatrix} \rightleftarrows \begin{pmatrix} FUU \\ UFU \\ UUF \end{pmatrix} \rightleftarrows UUU$$

$$\Sigma_0 \rightleftarrows \Sigma_1 \rightleftarrows \cdots \rightleftarrows \Sigma_N$$

How to solve the eigenproblem of the rate matrix & find the eigenvalue λ ?

Kinetic Theory: Continuum Limit

- Smoluchowski equation for diffusion in a one-dimensional harmonic potential



- Analytic solution for the slowest relaxation rate of the system:

$$\lambda = \frac{D}{\sigma^2} = \frac{K_{n_{\max}-1,n_{\max}}}{\sigma^2}$$

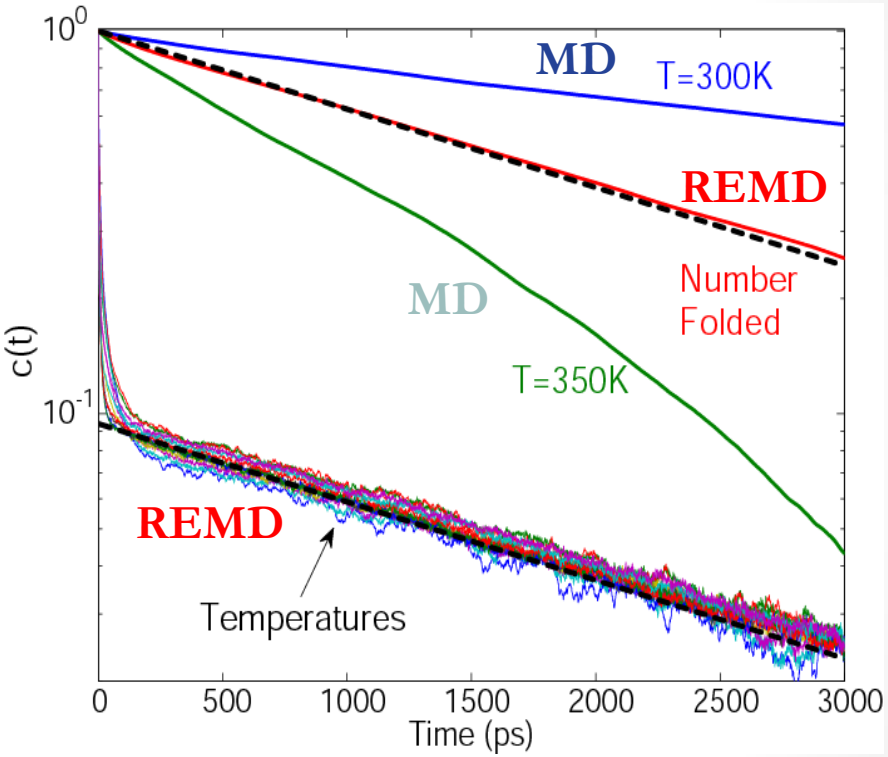
$$\lambda_{REMD} = \frac{\sum_{i=1}^{N} \lambda(T_i)\, p_F(T_i)\, p_U(T_i)}{\sum_{i=1}^{N} p_F(T_i)\, p_U(T_i)}$$

Exact for $N \to \infty$ and $k_{RE} \to \infty$.

Folding/Unfolding of Ala_5

- All-atom simulations of Ala_5 in explicit water
- State correlation function of all temperatures:

$$c(t) = \frac{\langle s(t)s(0)\rangle_T - \langle s(t)\rangle_T^2}{\langle s(t)^2\rangle_T - \langle s(t)\rangle_T^2}$$



- Fit for λ matches the prediction perfectly using the corresponding folding/unfolding rates!

$$\lambda_{REMD} = \frac{\sum_{i=1}^{N} \lambda(T_i)\, p_F(T_i)\, p_U(T_i)}{\sum_{i=1}^{N} p_F(T_i)\, p_U(T_i)}$$

Efficiency of Replica Exchange

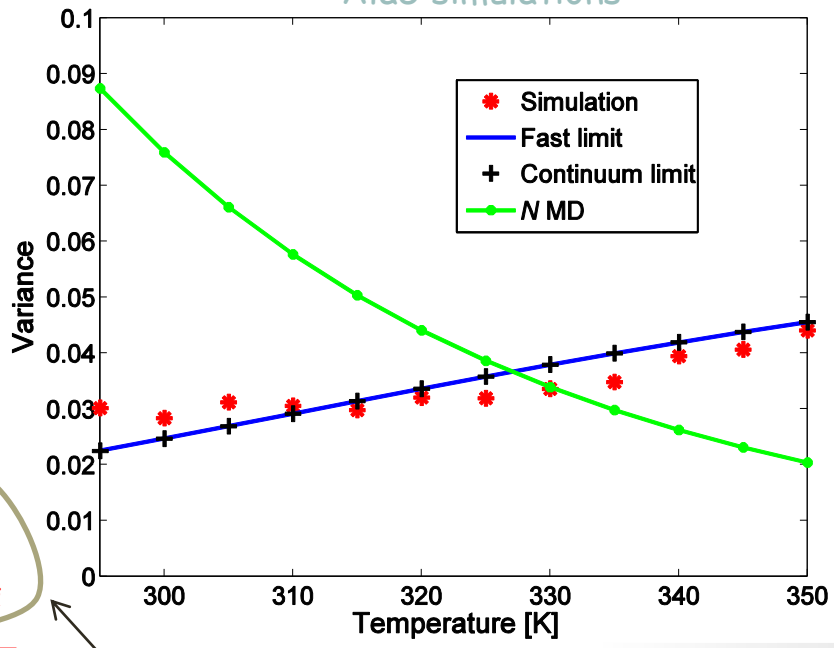
$$\eta = \frac{\sigma^2_{MD}\left(Nt_{sim}\right)}{\sigma^2_{REMD}\left(t_{sim}\right)} = \frac{\sigma^2_{MD}\left(t_{sim}\right)}{N\sigma^2_{REMD}\left(t_{sim}\right)}$$

$$\sigma^2_{MD}\left(t_{sim}\right) = \frac{2}{t_{sim}}\frac{p_{F_1}p_{U_1}}{\lambda_1}$$

$$\sigma^2_{REMD}\left(t_{sim}\right) = \frac{2}{t_{sim}}\frac{p^2_{F_1}p^2_{U_1}}{\sum_{i=1}^{N} p_{F_i}k_{U_i}}$$

$$\eta_1 = \frac{\sum_{i=1}^{N} p_{F_i}k_{U_i}}{N p_{F_1}k_{U_1}}$$

Ala5 simulations

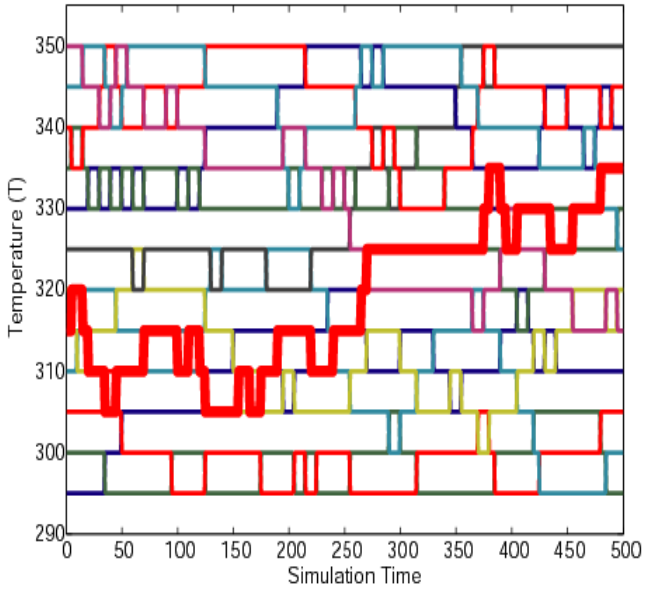


Average number of transitions over all temperatures

Number of transitions at target temperature (T_1)

Simulated tempering (ST)

- Only a single replica
- Changes the temperature of the simulation stochastically
- Preserves P_{eq} at each temperature
- Obtain partition functions (Z) iteratively

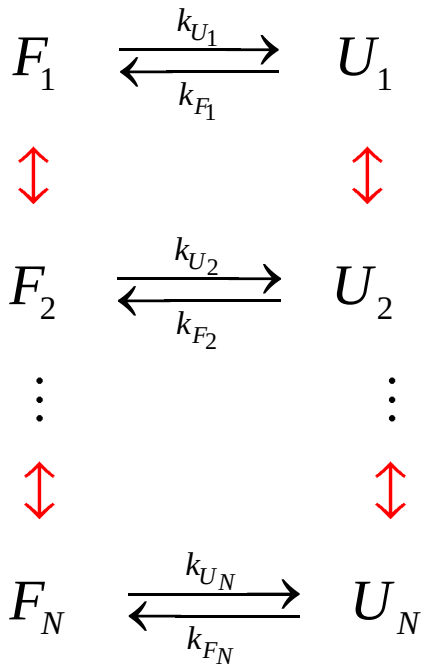


$$\frac{T(x,T \to x,T')}{T(x,T' \to x,T)} = \frac{p_{T'}(x)}{p_T(x)} = \frac{e^{-U(x)/k_B T'}}{Z'} \frac{Z}{e^{-U(x)/k_B T}}$$

A. P. Lyubartsev, A. A. Martsinovski, S. V. Shevkunov, and P. N. Vorontsov-Velyaminov, JCP, 1992
E. Marinari and G. Parisi, Europhysics Letters, 1992

Kinetic model of ST

- Full kinetic scheme



- With appropriate ST rates between temperatures that preserve detailed balance and achieve the desired Q_i-s, the average relative time spent at T_i:

$$Q_i = p\left(T_i\right)$$

- Coarse grained kinetic scheme in the limit of fast temperature changes:

$$F_{eff} \underset{k_F^{eff}}{\overset{k_U^{eff}}{\rightleftarrows}} U_{eff} \qquad \lambda^{eff} = k_F^{eff} + k_U^{eff}$$

- With previous notations for p_{F_i}, using local equilibrium approximation:

$$k_F^{eff} = \frac{\sum_{i=1}^{N} k_{F_i} Q_i p_{U_i}}{\sum_{i=1}^{N} Q_i p_{U_i}} \qquad k_U^{eff} = \frac{\sum_{i=1}^{N} k_{U_i} Q_i p_{F_i}}{\sum_{i=1}^{N} Q_i p_{F_i}}$$

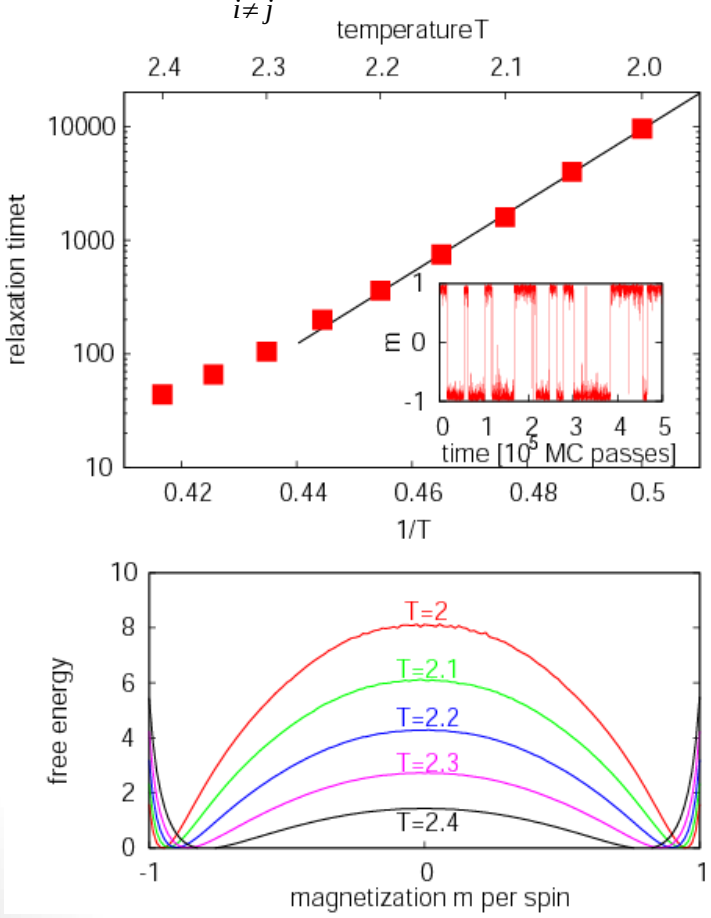
$$\sigma_{ST}^2 = \mathrm{var}\left(\frac{\bar{p}_{F_1}}{\bar{p}_{F_1} + \bar{p}_{U_1}}\right) = \sigma_{MD}^2 \sum_{i=1}^{N} \frac{1}{Q_i} \frac{k_{F_1}^{-1} + k_{U_1}^{-1}}{k_{F_i}^{-1} + k_{U_i}^{-1}}$$

- **Identical efficiency with the corresponding RE!**

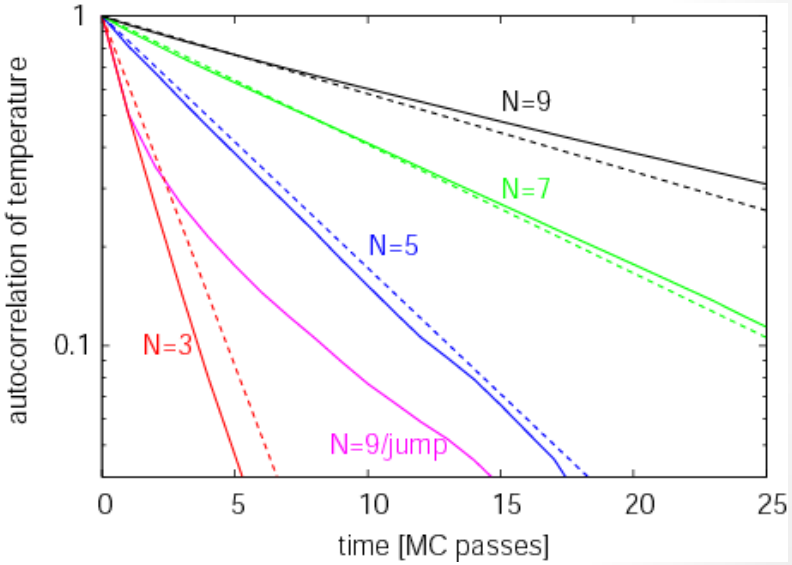
Application to 2D Ising model

- 2D Ising model using MC simulations:

$$H = -\sum_{\substack{i,j \\ i \neq j}} \sigma_i \sigma_j \quad (\sigma_i = \pm 1)$$



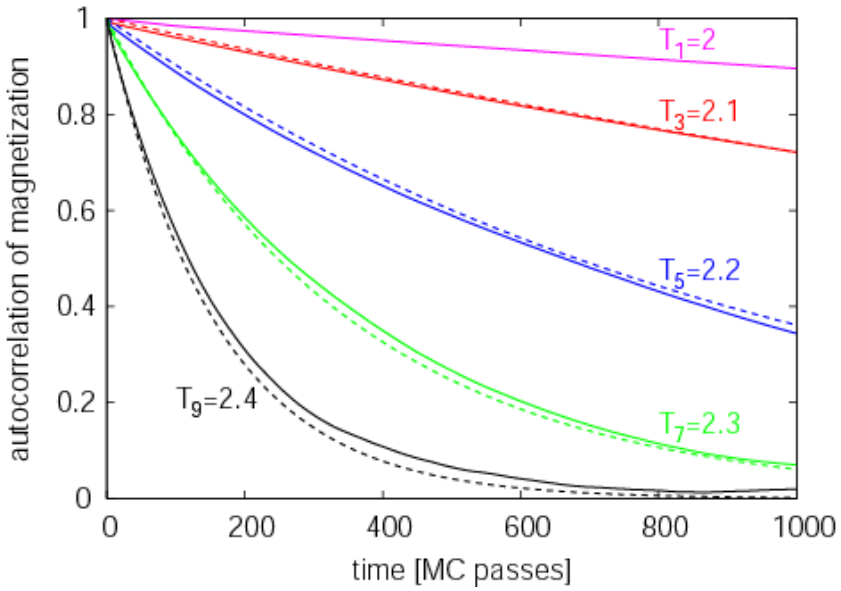
- Temperature autocorrelation functions using predicted (dashed lines) and actual (solid lines) relaxation rates. ST simulations with N temperatures and constant temperature spacing.



$$c(t) = \exp\left(-t/\tau_T\right) \qquad \tau_T \approx \frac{N^2}{10}\frac{\delta t_{xc}}{p_{acc}}$$

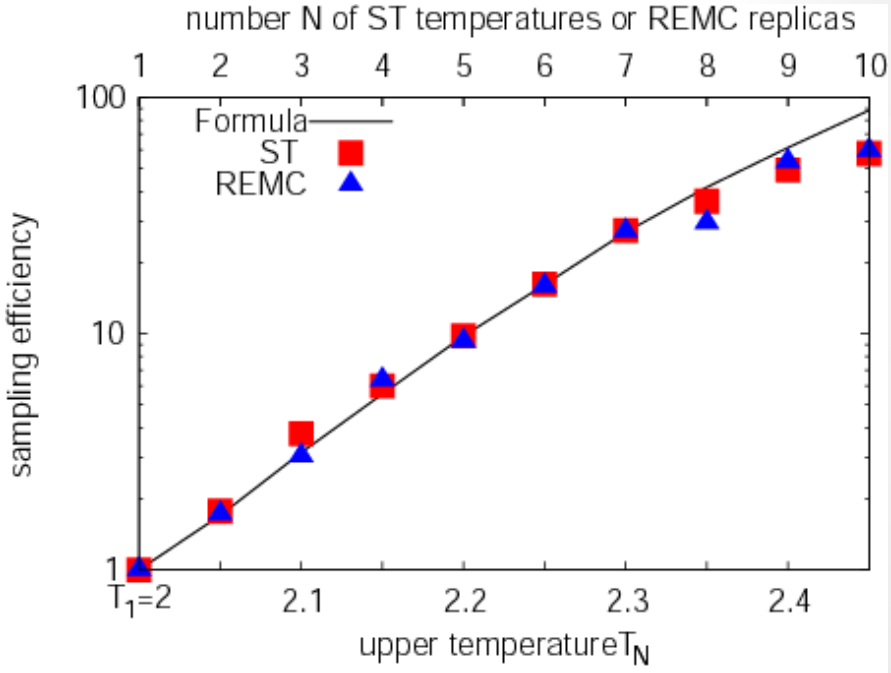
Application to 2D Ising model

- Autocorrelation function of the magnetization (solid lines) compared with the effective relaxation rate from the fast limit (dashed lines).
- T_N represents ST simulations using *N* temperatures with upper temperature T_N.



$$c(t) = \exp\left(-\lambda^{eff} t\right)$$

- The error of estimating the folded populations quantitatively agrees with the formula for the fast limit for both RE and ST.

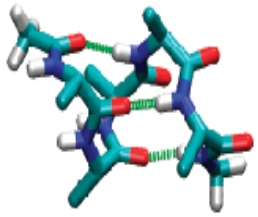


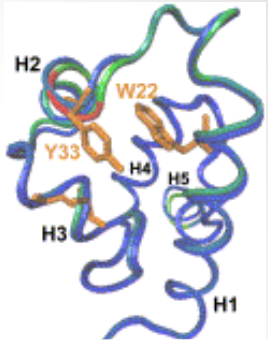
$$\eta_1 = \sum_{i=1}^{N} \frac{1}{Q_i} \frac{{k_{F_1}}^{-1} + {k_{U_1}}^{-1}}{{k_{F_i}}^{-1} + {k_{U_i}}^{-1}}$$

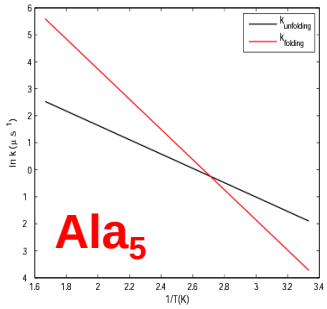
Optimal protocol

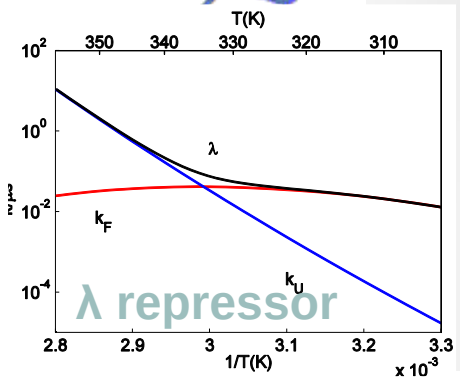
- For optimal RE/ST:
  - ***Target temperature should be the lowest***
  - ***Highest temperature should be where number of transitions is the highest, if applicable***
  - ***Use as many replicas as can be afforded, but still be in fast exchange limit***
  - ***Exchange should be fast, attempts should be as often as possible***
  - ***Well chosen nonuniform temperature distribution is more efficient***

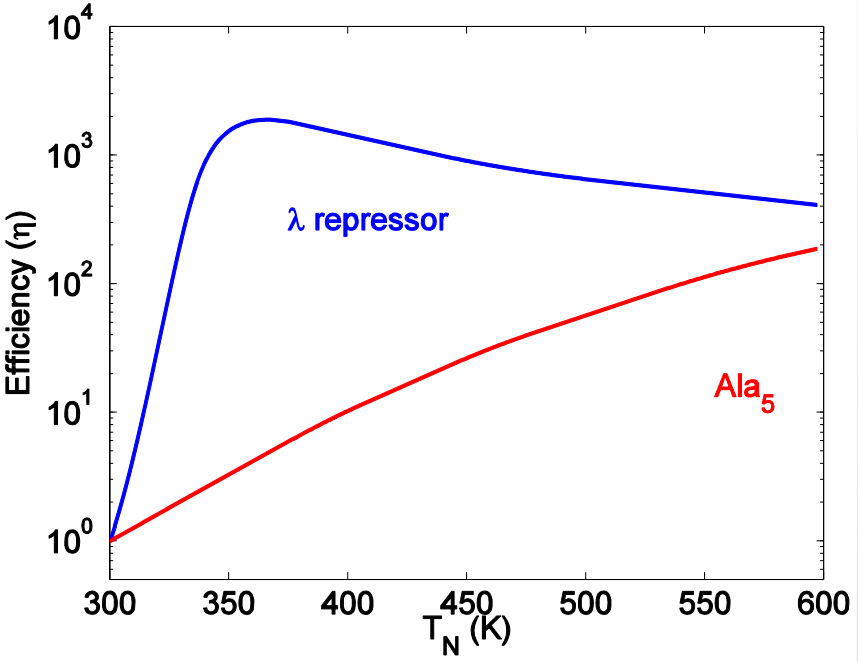
- If $k_F(T)$ and $k_U(T)$ are known, the kinetic matrix can be solved and the temperature range can be optimized for exact numerical solution.





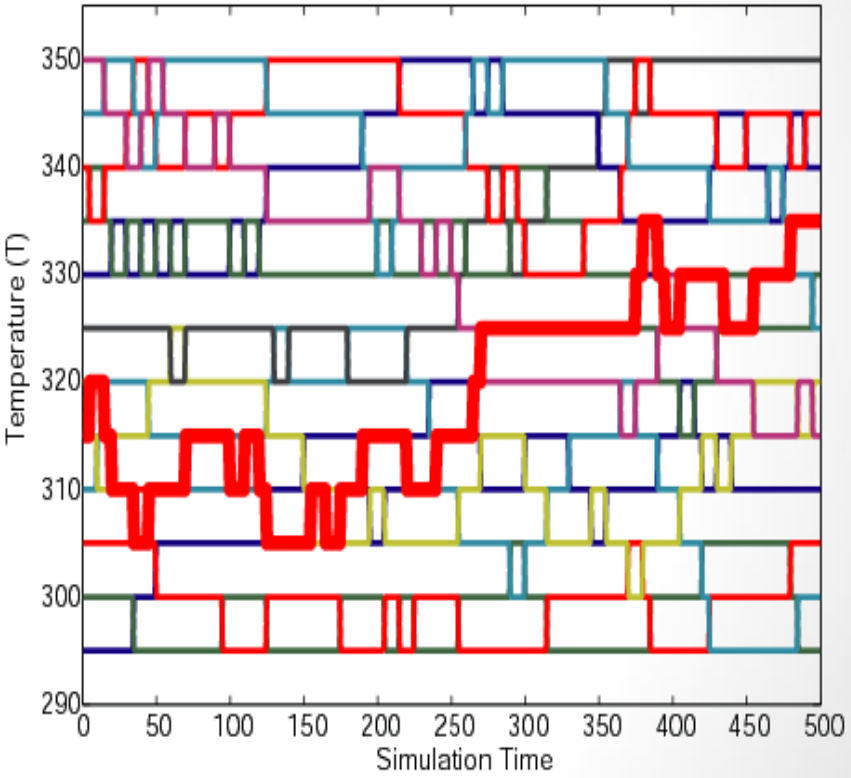






Questions?

- Monte Carlo methods to sample phase space
- Enhanced sampling methods with MC-based algorithms to enable faster sampling
- Hamiltonian is not modified, no artificial forces besides temperature – this is also a limitation and Hamiltonian-based H-REMD methods can be powerful in many cases



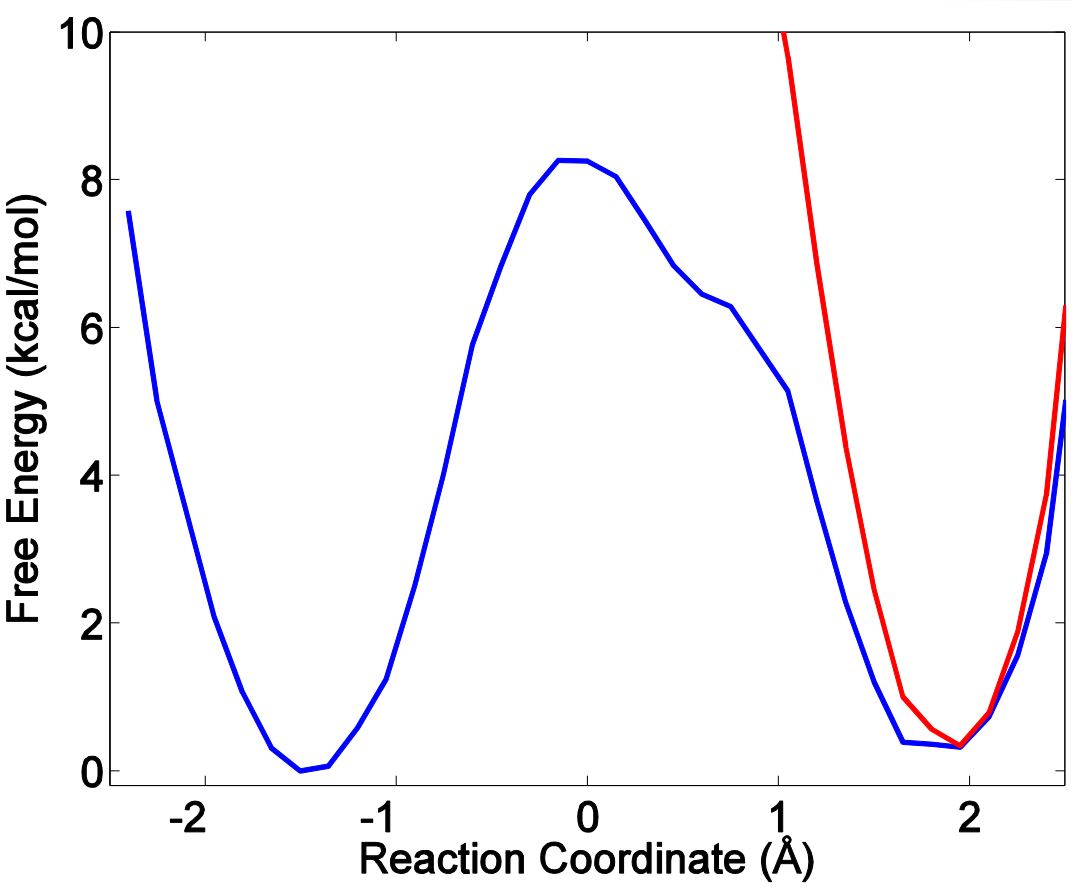
Umbrella Sampling

$$E_i(q_A) = U_{pot}(q_A) + \frac{1}{2} k_i (\xi_A - \xi_i)^2$$

- Run parallel simulations with harmonic constraints moving along the reaction coordinate

Torrie and Valleau; *J. Comp. Phys.* 1977

- Recover the unbiased free energy surface from combined data using e.g., WHAM



Ferrenberg, Swendsen; *Phys. Rev. Lett.* 1989
Kumar, Rosenberg, Bouzida, Swendsen, Kollman; *J. Comput. Chem.* 1992

WHAM

$$\Pr^{(k)} \propto \prod_{i=1}^{Nbin} \left(p_i^{(k)} \right)^{n_i^{(k)}}$$

$$\tilde{L} = \ln \prod_{k=1}^{NSim} \prod_{i=1}^{Nbin} \left(p_i^{(k)} \right)^{n_i^{(k)}}$$

$$p_i^{(k)} = f^{(k)} c_i^{(k)} p_i = \frac{c_i^{(k)} p_i}{\sum_{j=1}^{N_{bin}} c_j^{(k)} p_j}$$

$$c_i^{(k)} = \exp\left(-u_i^{(k)} / k_B T \right)$$

Probability of observing a trajectory in the *k*-th simulation.

$p_i^{(k)}$ Equilibrium probability for bin *i*

$n_i^{(k)}$ Histogram count in bin *i*

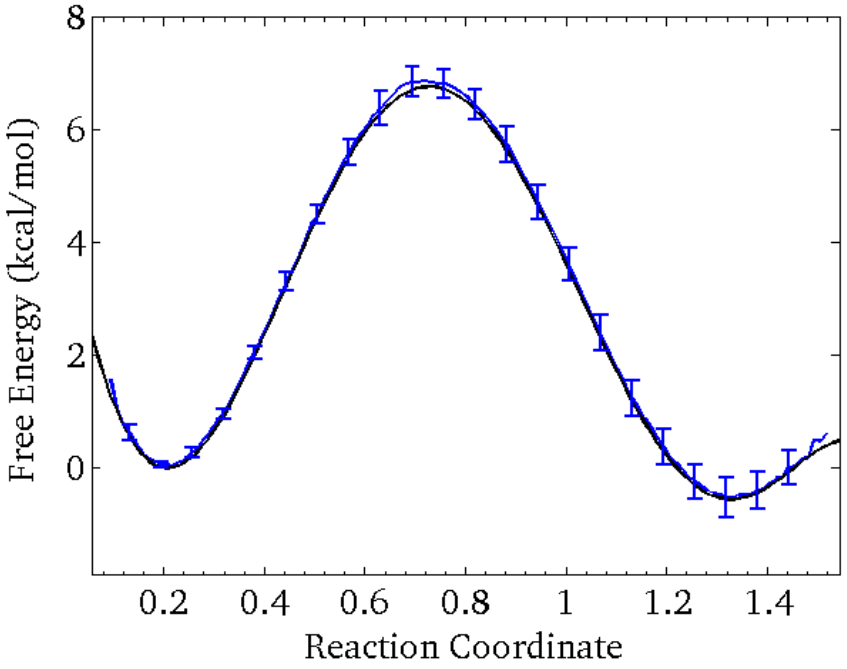
$$\frac{\partial L}{\partial f^{(k)}} = 0$$

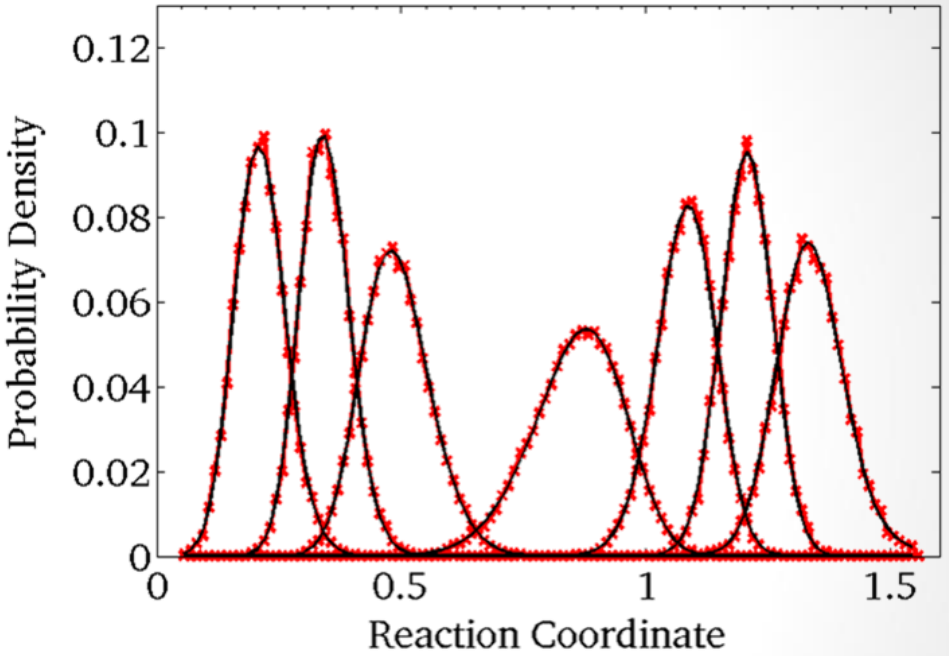
$$\frac{\partial L}{\partial p_i} = 0$$

$$p_i = \frac{\sum_{k=1}^{Msim} n_i^{(k)}}{\sum_{l=1}^{Msim} N^{(l)} f^{(l)} c_i^{(l)}}$$

$$L = \ln \prod_{k=1}^{NSim} \prod_{i=1}^{Nbin} \left(f^{(k)} c_i^{(k)} p_i \right)^{n_i^{(k)}} + \sum_{k=1}^{NSim} \lambda^{(k)} \left(1 - \sum_{i=1}^{Nbin} f^{(k)} c_i^{(k)} p_i \right)$$

Umbrella Sampling Simulations & WHAM

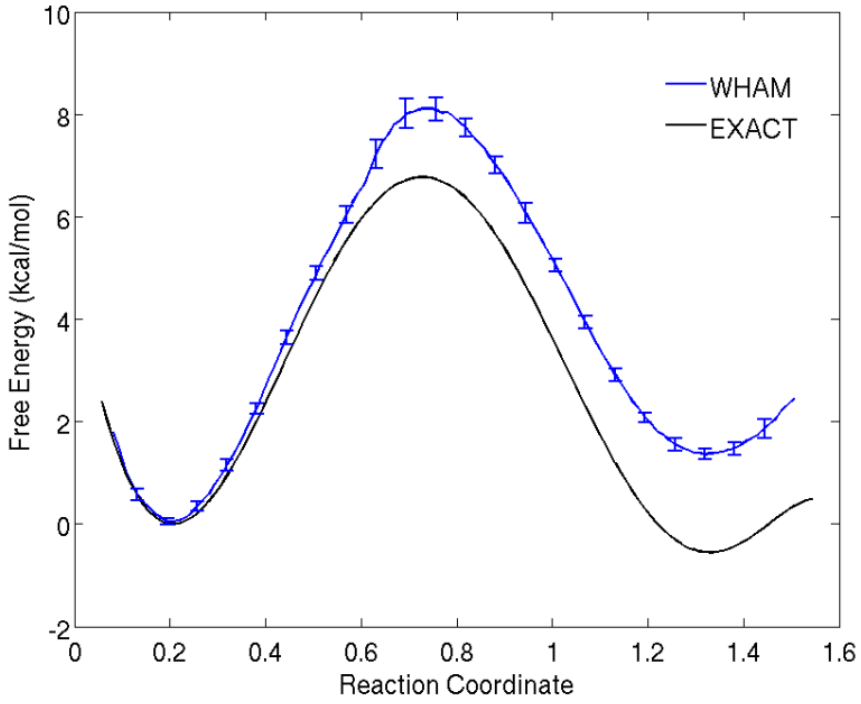


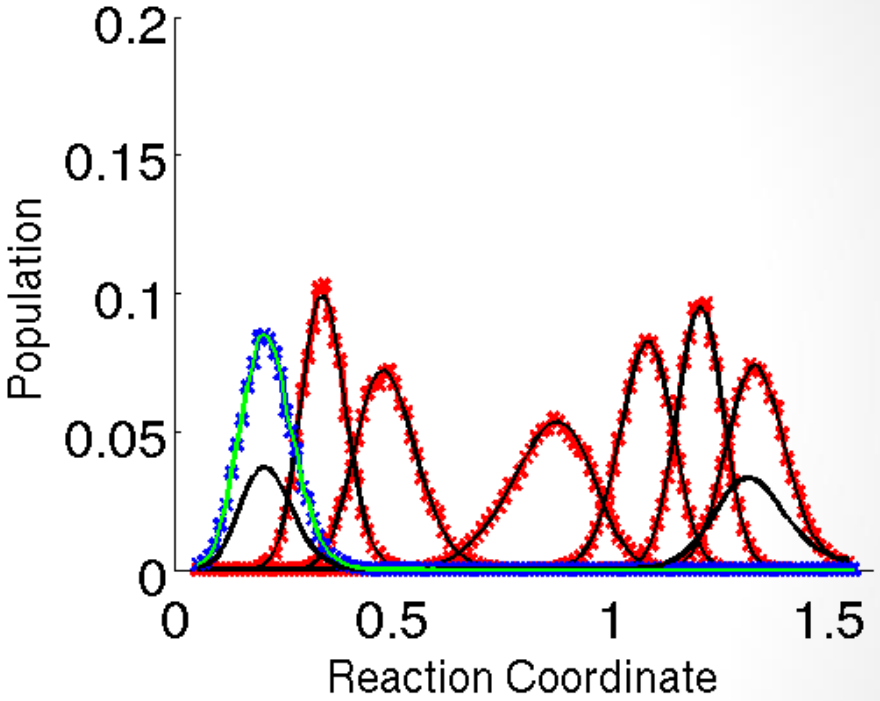


- MC simulations
- 7 Umbrellas with 50 kcal/mol biasing force each

Rosta, Hummer, *JCTC*, 2015

Systematic error when using WHAM in conjunction with small biasing force





- 6 Umbrellas with 50 kcal/mol biasing force each
- 1st Umbrella with 1 kcal/mol biasing force

Rosta, Hummer, *JCTC*, 2015

DHAM: Dynamic Histogram Analysis Method

$$\Pr^{(k)} \propto \prod_{i=1}^{Nbin} \prod_{j=1}^{Nbin} \left(M_{ji}^{(k)} \right)^{T_{ji}^{(k)}}$$

$$\tilde{L} = \ln \prod_{k=1}^{NSim} \prod_{i=1}^{Nbin} \prod_{j=1}^{Nbin} \left(M_{ji}^{(k)} \right)^{T_{ji}^{(k)}}$$

$$M_{ji}^{(k)} = f_i^{(k)} c_{ji}^{(k)} M_{ji} = \frac{c_{ji}^{(k)} M_{ji}}{\sum_{l=1}^{N_{bin}} c_{li}^{(k)} M_{li}}$$

$$M_{ji} = \frac{\sum_{k=1}^{Msim} T_{ji}^{(k)}}{\sum_{k=1}^{Msim} n_i^{(k)} f_i^{(k)} c_{ji}^{(k)}}$$

Biased Dynamical Trajectories

↓

Histogram of Transitions

↓

Markov Model

↓

Free Energy & Kinetics

Rosta, Hummer, *JCTC*, 2015

DHAM: Dynamic Histogram Analysis Method

$$\frac{M_{ji}^{(k)}}{M_{ji}^{(0)}} = \frac{p\left(x_i \to x_j\right)^{(k)}}{p\left(x_i \to x_j\right)^{(0)}} = \frac{\exp\left(-\left(\left(x_j - x_i\right) + \gamma\tau \dfrac{u_j^{(k)} - u_i^{(k)} + u_j^{(0)} - u_i^{(0)}}{x_j - x_i}\right)^2 / 4D\tau\right)}{\exp\left(-\left(\left(x_j - x_i\right) + \gamma\tau \dfrac{u_j^{(0)} - u_i^{(0)}}{x_j - x_i}\right)^2 / 4D\tau\right)}$$

$$\frac{p\left(x_i \to x_j\right)^{(k)}}{p\left(x_i \to x_j\right)^{(0)}} = \exp\left(-\frac{\left(u_j^{(k)} - u_i^{(k)}\right) + \dfrac{\gamma\tau\left(u_j^{(k)} - u_i^{(k)}\right)^2}{2\left(x_j - x_i\right)^2} + \dfrac{\gamma\tau\left(u_j^{(k)} - u_i^{(k)}\right)\left(u_j^{(0)} - u_i^{(0)}\right)}{\left(x_j - x_i\right)^2}}{2D/\gamma}\right)$$

$$\frac{M_{ji}^{(k)}}{M_{ji}^{(0)}} = f_i^{(k)} c_{ji}^{(k)} \approx \exp\left(-\left(u_j^{(k)} - u_i^{(k)}\right) / 2k_B T\right)$$

Rosta, Hummer, *JCTC,* 2015

DHAM: Dynamic Histogram Analysis Method

$$M_{ji} = \frac{\sum_{k=1}^{Msim} T_{ji}^{(k)}}{\sum_{k=1}^{Msim} n_i^{(k)} f_i^{(k)} c_{ji}^{(k)}}$$

$$\frac{M_{ji}^{(k)}}{M_{ji}^{(0)}} = f_i^{(k)} c_{ji}^{(k)} \approx \exp\left(-\left(u_j^{(k)} - u_i^{(k)}\right)/2k_BT\right)$$

$$\frac{M_{ji}^{(k)}}{M_{ij}^{(k)}} \frac{p_i^{(k)}}{p_j^{(k)}} = \frac{f_i^{(k)} c_{ji}^{(k)} M_{ji}}{f_j^{(k)} c_{ij}^{(k)} M_{ij}} \frac{p_i^{(k)}}{p_j^{(k)}} = \frac{f_i^{(k)} c_{ji}^{(k)} M_{ji}}{f_j^{(k)} c_{ij}^{(k)} M_{ij}} \frac{p_i^{(0)} \exp\left(-u_i^{(k)}/k_BT\right)}{p_j^{(0)} \exp\left(-u_j^{(k)}/k_BT\right)} = 1$$

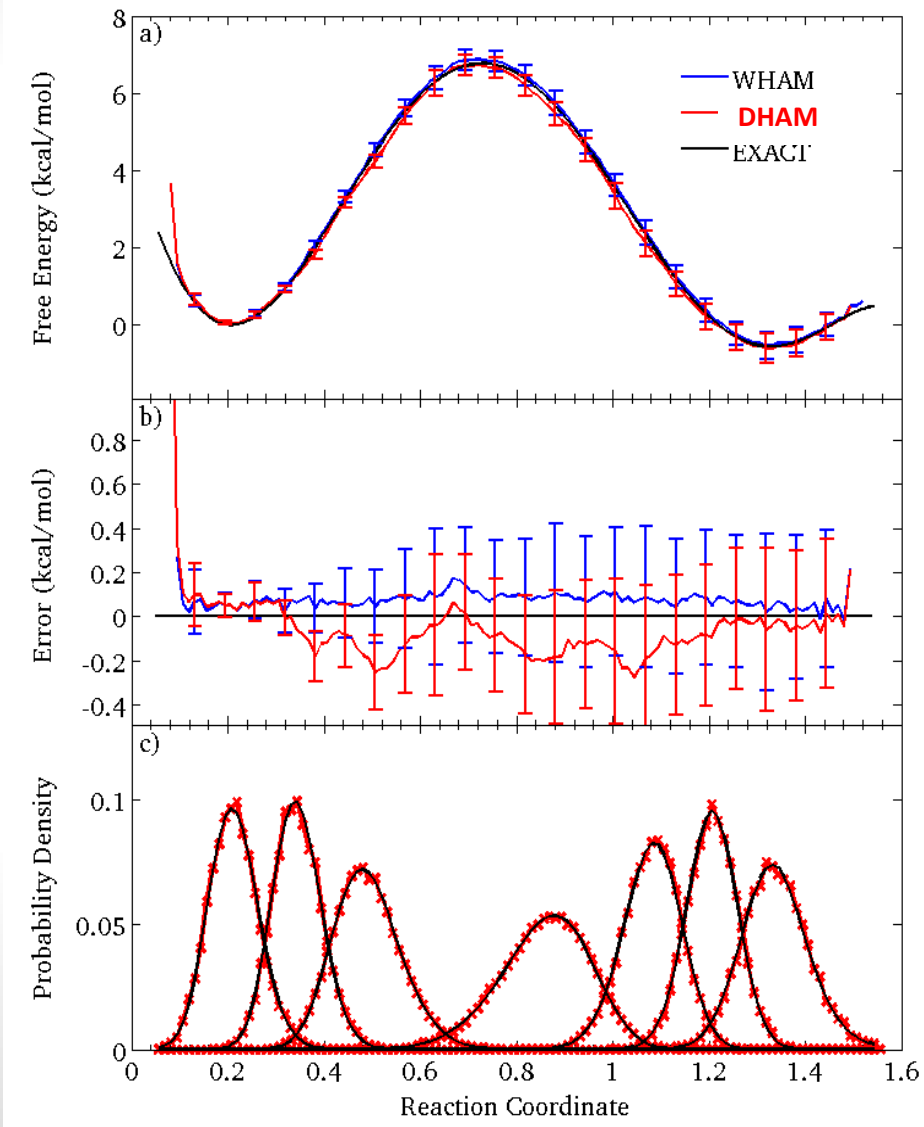
$$M_{ji}^{unnorm} = \frac{\sum_{k=1}^{Msim} T_{ji}^{(k)}}{\sum_{k=1}^{Msim} n_i^{(k)} \exp\left(-\left(u_j^{(k)} - u_i^{(k)}\right)/2k_BT\right)}$$

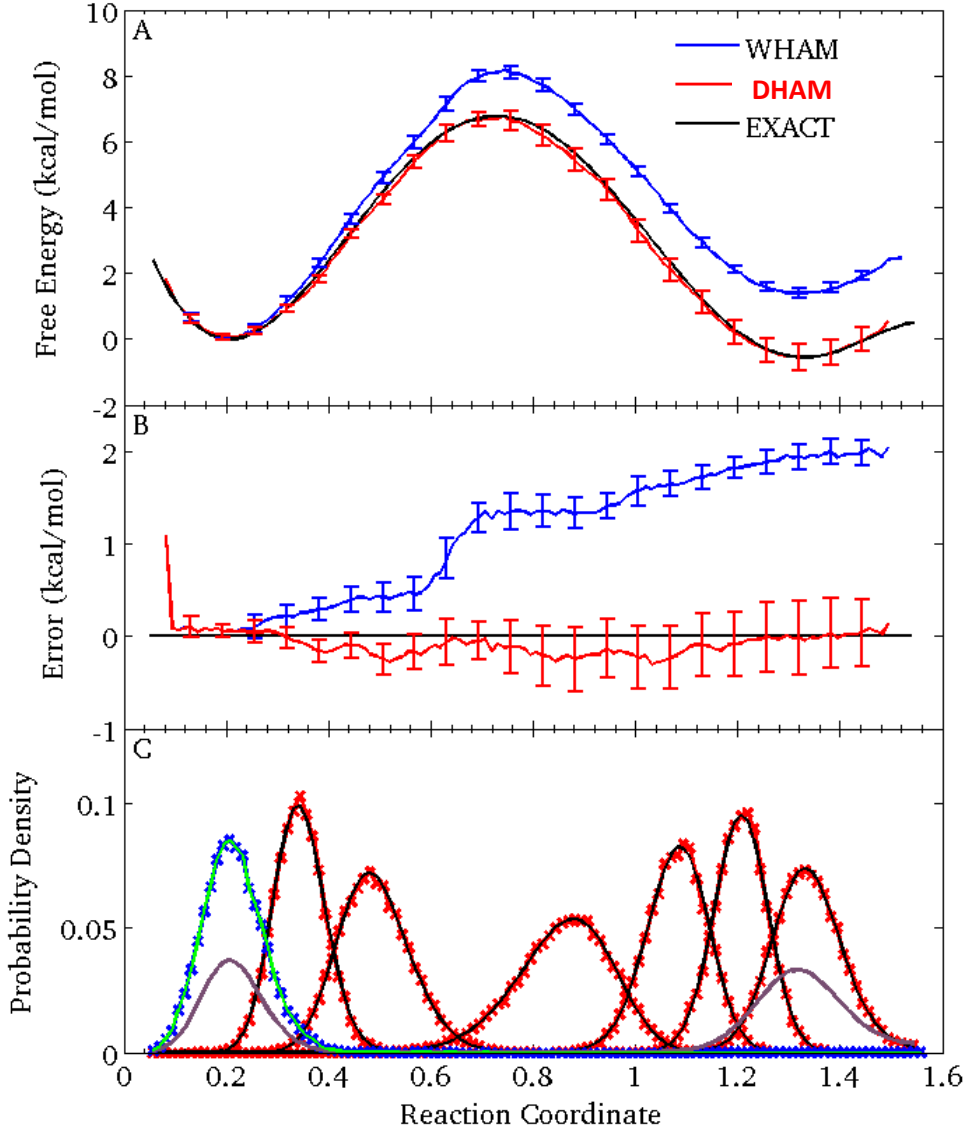
$$\sum_{j=1}^{Nbin} M_{ij} p_j = p_i$$

$$\tau = -1/\ln \lambda_2$$

Rosta, Hummer, *JCTC*, 2015

Umbrella Sampling with small biasing force

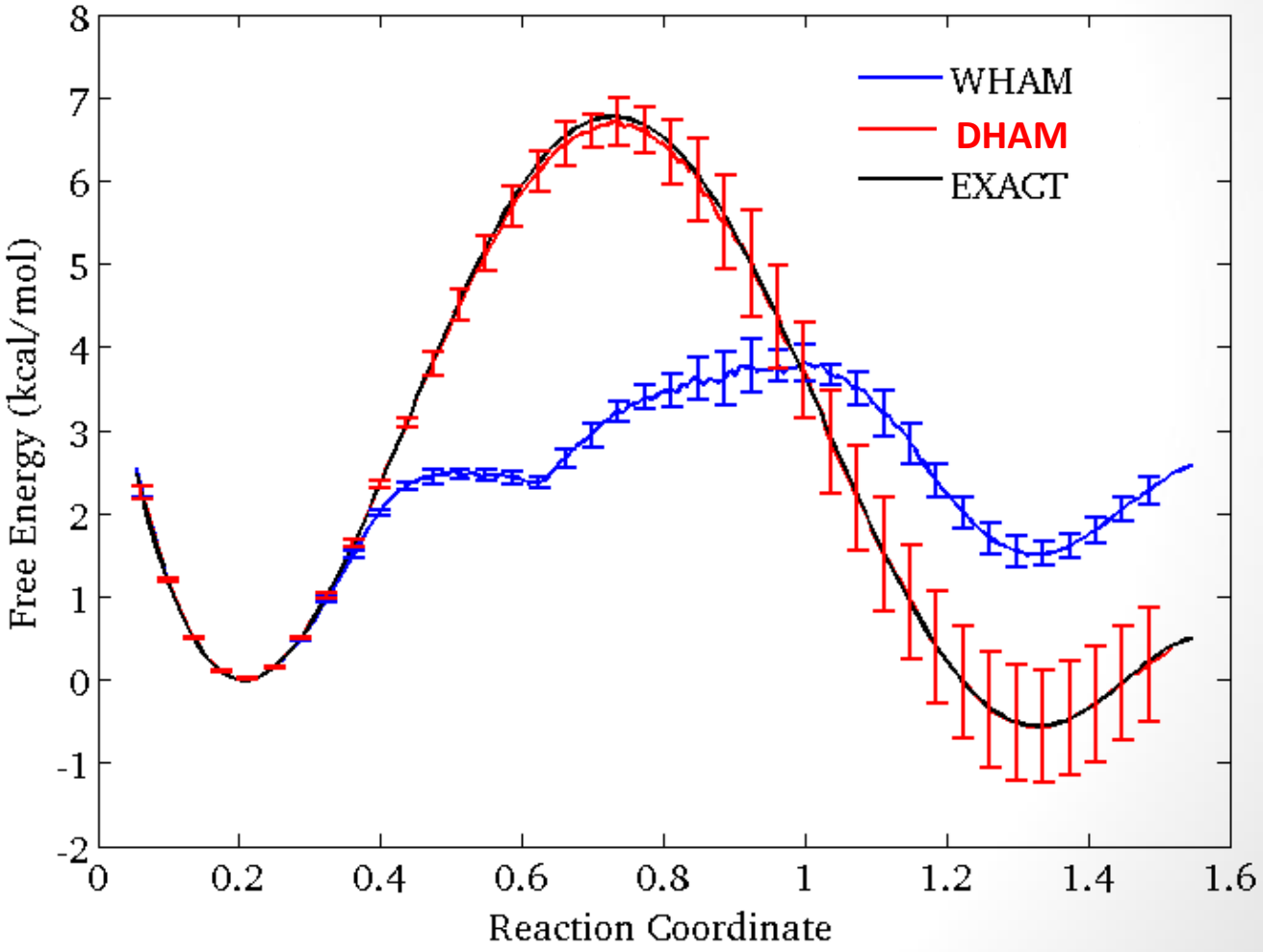




“Downhill” unbiased non-equilibrium trajectories

$$M_{ji} = \frac{\sum_{k=1}^{Msim} T_{ji}^{(k)}}{\sum_{k=1}^{Msim} n_i^{(k)}}$$

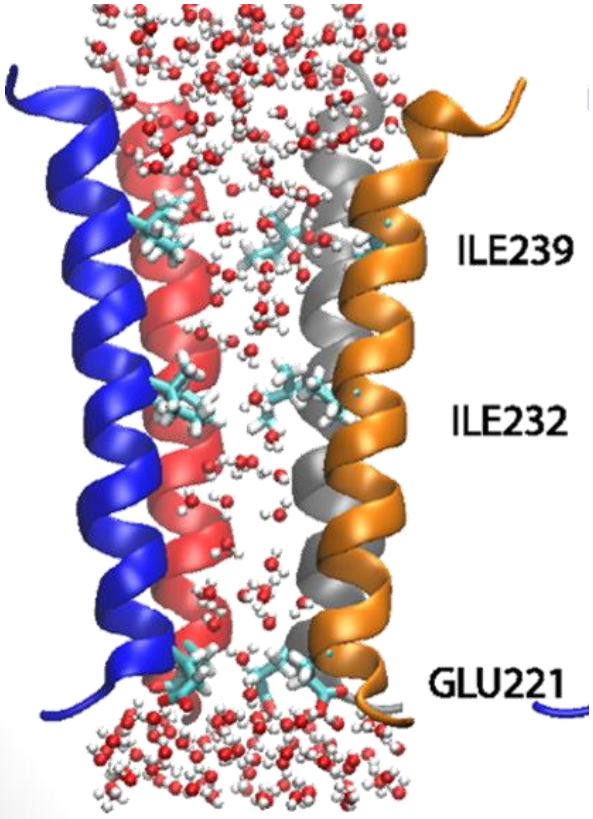
$$\sum_{j=1}^{Nbin} M_{ij} p_j = p_i$$



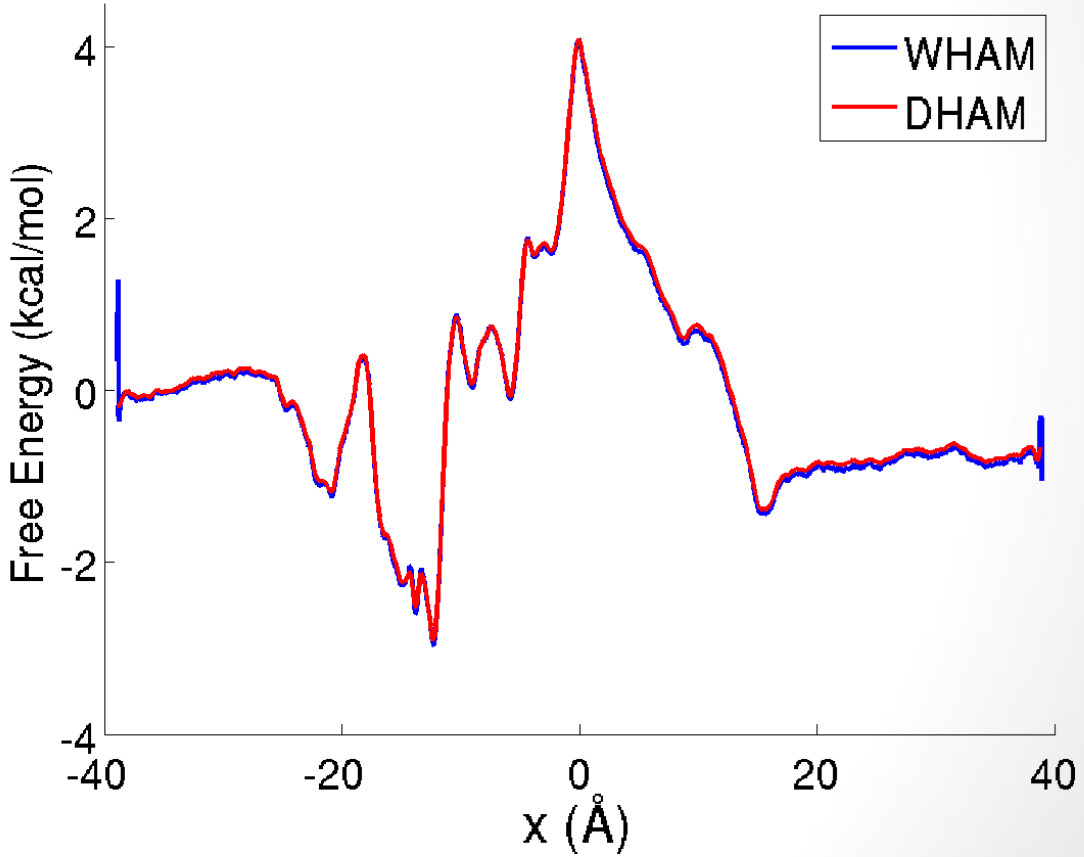
Rosta, Hummer, *JCTC*, 2015

MD simulations of a Na^+ in an ion channel

Langevin dynamics MD simulations of the passage of Na^+ through the transmembrane pore of the GLIC channel.

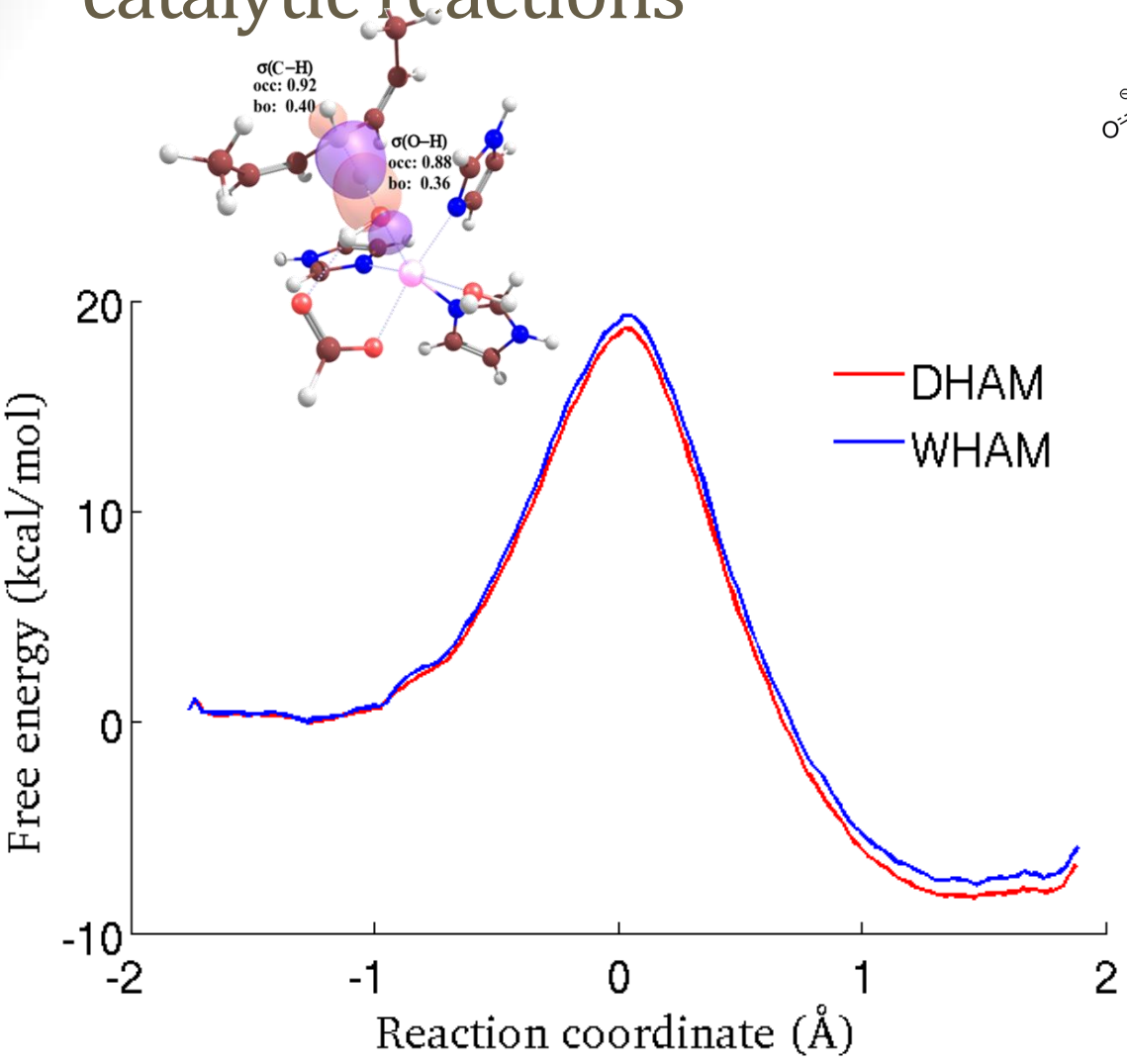


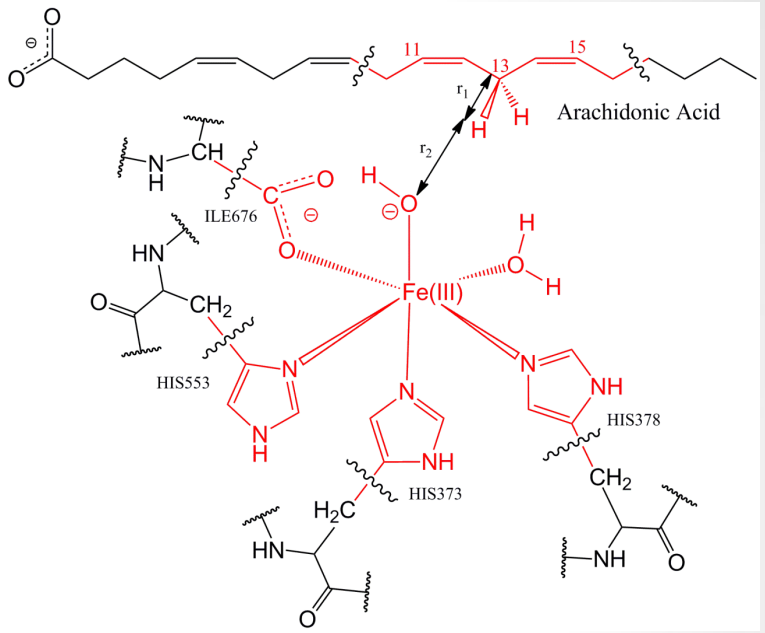
Open



Simulation data from: Zhu and Hummer, *PNAS* 2010, *JCC* 2012

Umbrella sampling QM/MM simulations of catalytic reactions

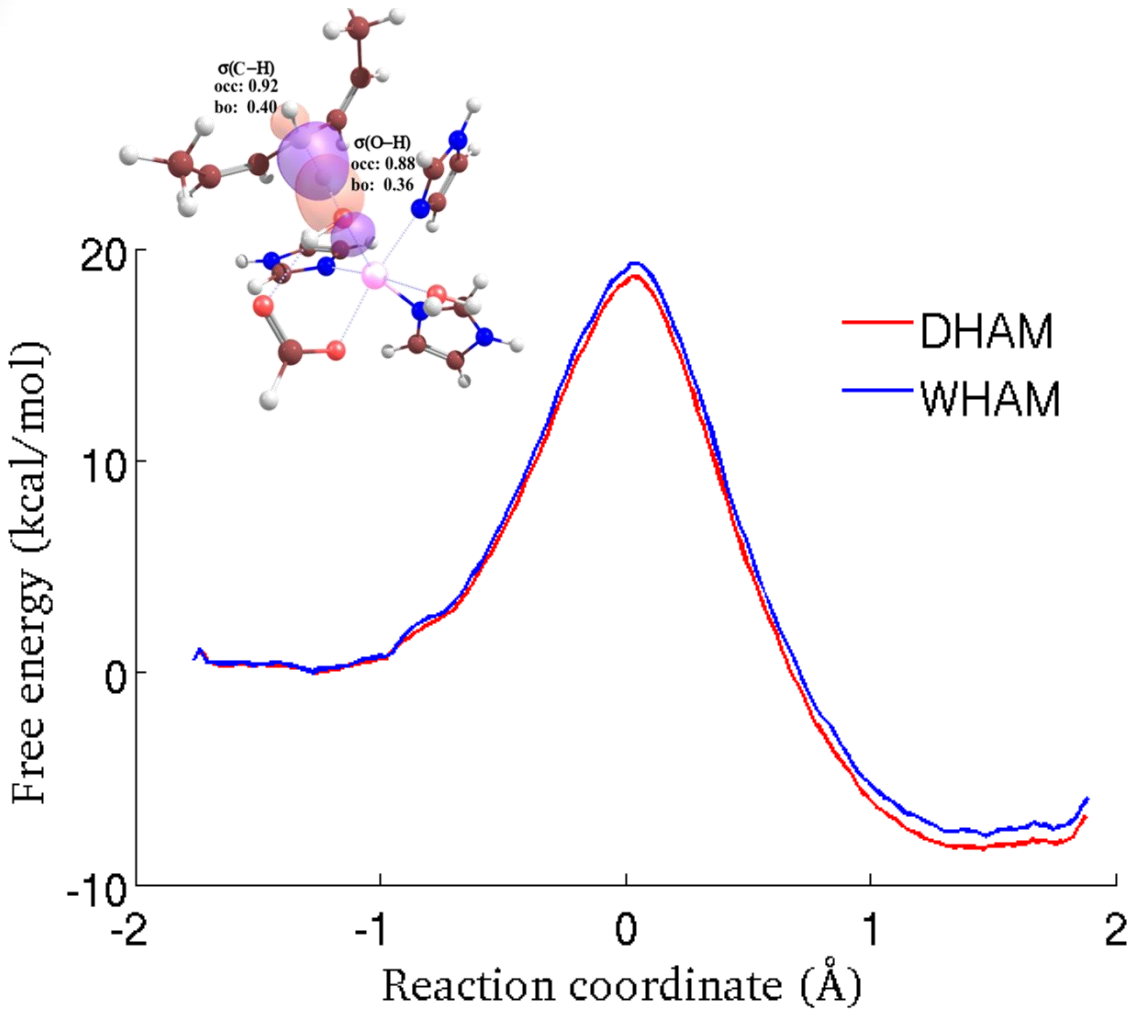




Hydrogen abstraction from arachidonic acid in the catalytic reaction of human 15-LOX-2 lipoxygenase.

R. Suardiaz, P. G. Jambrina, L. Masgrau, A. Gonzalez-Lafont, E. Rosta, J.M. Lluch, *JCTC*, 2016

Umbrella sampling QM/MM simulations of catalytic reactions



Lag time	Rate
1 fs	0.24 s^{-1}
10 fs	0.17 s^{-1}
50 fs	0.29 s^{-1}

Experimental k_{cat} = 0.7 s^{-1}

$$k = Ae^{-\Delta G^{\ddagger}/k_B T}$$

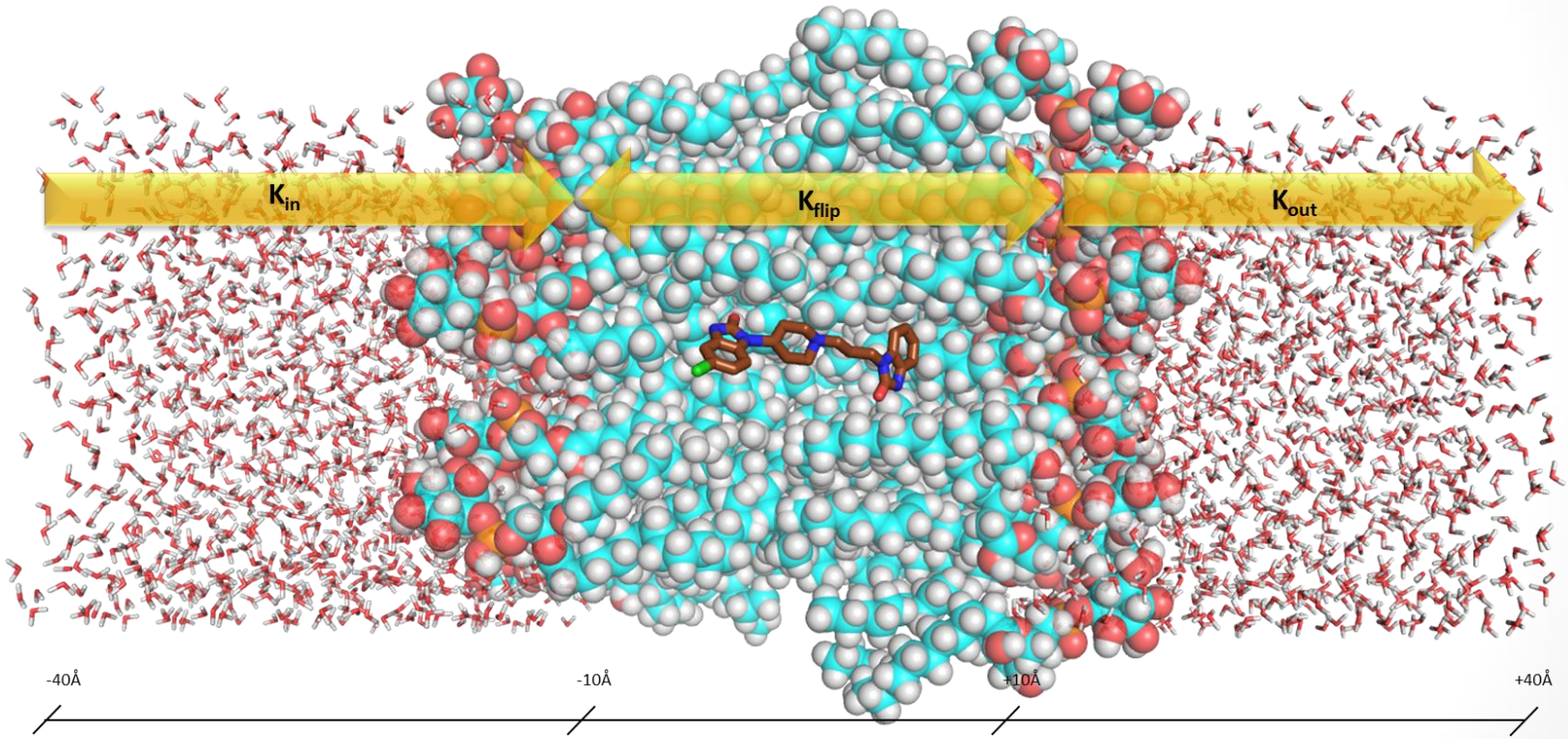
k=0.22 s^{-1} @T=300K
Calculated prefactor using a barrier of 18.7 kcal/mol:

A = 8.6×10^{12} s^{-1}

$k_B T/h = 6.3 \times 10^{12}$ s^{-1}

R. Suardiaz, et al, *JCTC*, 2016

Membrane Permeability

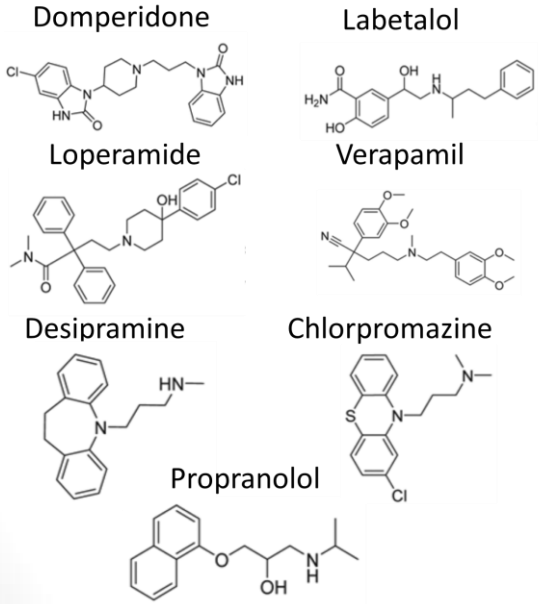


NOVARTIS PHARMACEUTICALS

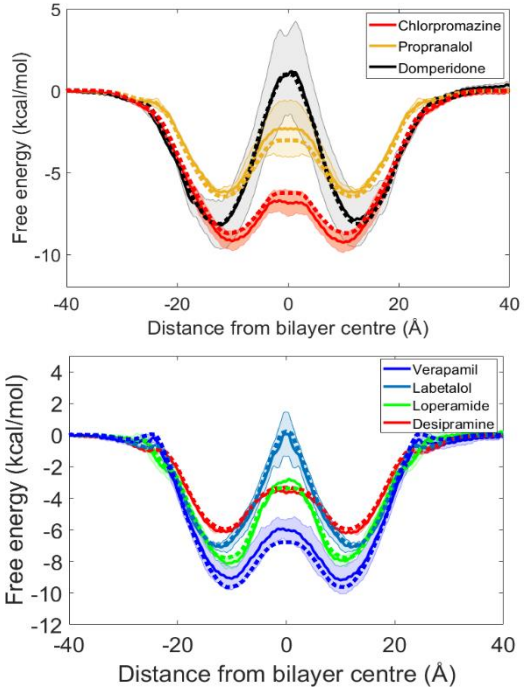
Dickson, Hornak, Pearlstein, & Duca, *JACS*, 2017

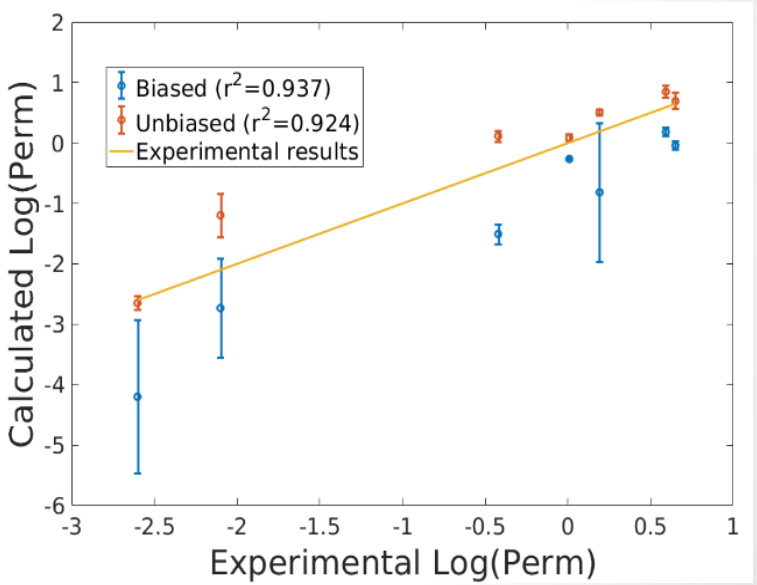
Membrane Permeability

- Umbrella sampling simulations for 7 drugs
- Calculated rates for entering, crossing and exiting the membrane match unbiased MD
- Matching the experimental permeabilities closely as well



$$k = Ae^{-\Delta G^{\ddagger}/k_B T}$$





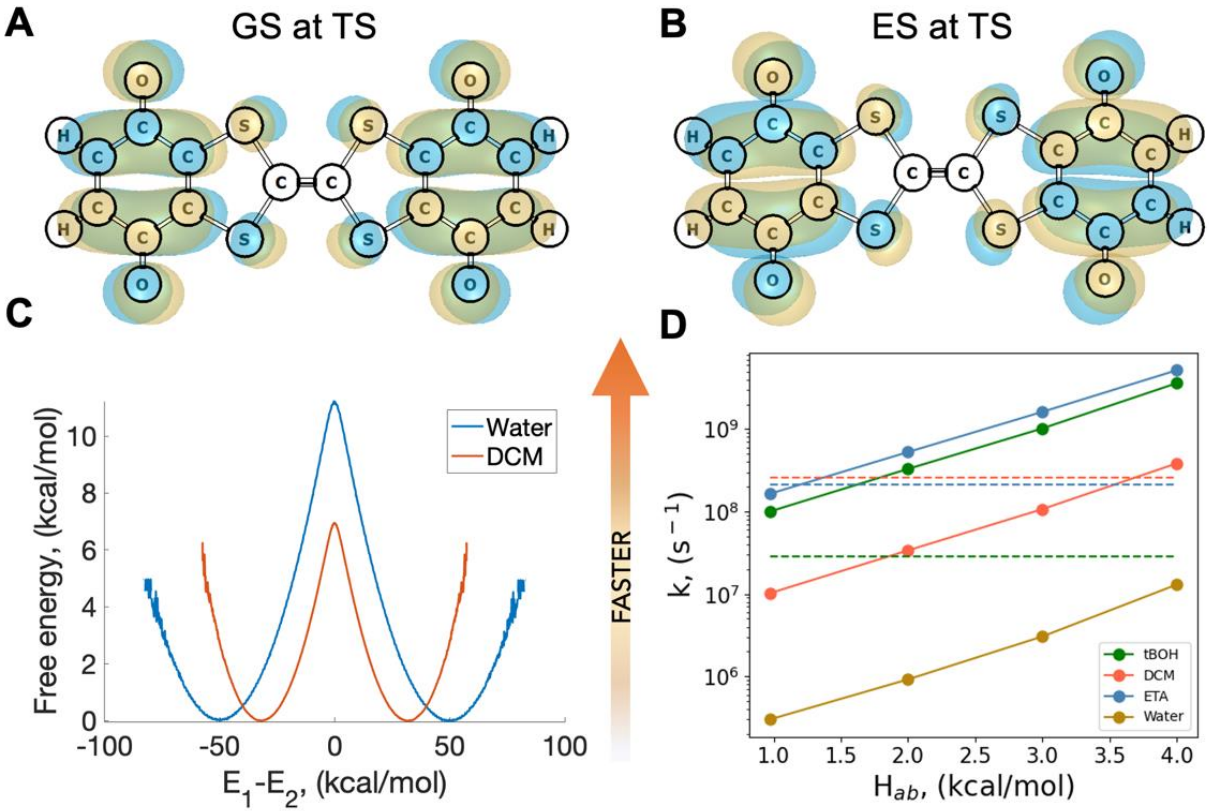
A = ~10^8 s^{-1} vs. k_BT/h = 6.3x10^{12} s^{-1}

Badaoui et al, *JPC*, 2018

Intramolecular electron transfer

- $(Q\text{-}TTF\text{-}Q)^{-}$: radical anion of the benzoquinone–tetrathiafulvalene–benzoquinone triad
- Calculated rates match the experimental permeabilities closely
- No need for nuclear tunnelling, TST seems valid

	calculated rate (s-1)	experimental rate (s-1)
tBOH	9.97E+07	2.89E+07
ETA	1.69E+08	2.10E+08
DCM	1.03E+07	2.58E+08
Water	3.00E+05	n/a



$$k = Ae^{-\Delta G^{\ddagger}/k_B T}$$

$A = 1.2 – 6.6 \times 10^{12}\ s^{-1}$ vs. $k_B T/h = 6.3 \times 10^{12}\ s^{-1}$

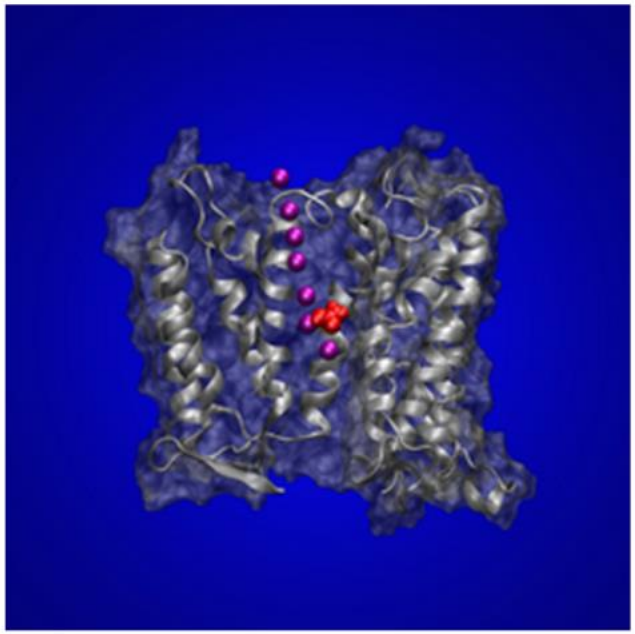
Koczor-Benda, Mateeva, Rosta, JPCL, 2023

Career Options

- D. E. Shaw & Co. assets of USD 40 billion
- PhD Stanford
- Assistant Professor at Columbia (1980)
- Works for Morgan Stanley (1986)
- Founds the hedge fund company D. E. Shaw & Co. (1988)
- Founds his own research company: D. E. Shaw Research

David E. Shaw

D E Shaw Research



About D. E. Shaw Research

D. E. Shaw Research ("DESRES") is engaged in scientific research in the field of c

- The design of novel algorithms and machine architectures for high-speed n of proteins and other biological macromolecules. In particular, we have des supercomputer called Anton, which executes such simulations orders of ma possible, along with a number of software tools and techniques that facilita
- The use of long MD simulations to study the structural changes underlying time scales far in excess of those previously accessible to computational st significantly advancing the process of drug development. We have been inv mechanisms of certain cellular receptors, transport proteins, and enzymes potential treatment of cancer, diabetes, and other diseases.

Members of the lab include computational chemists and biologists, computer scie and computer architects and engineers, all working collaboratively under the dire Scientist, David Shaw.

Career Options

- "Extending the Generality of Molecular Dynamics Simulations on a Special-Purpose Machine,"*Proceedings of the 27th IEEE International Parallel and Distributed Processing Symposium* (IPDPS '13), Boston, MA: IEEE Computer Society, 2013, pp. 933–945.
- "Structural Basis for Modulation of a G-Protein-Coupled Receptor by Allosteric Drugs," ***Nature***, vol. 503, no. 7475, 2013, pp. 295–299.
- "Architecture and Membrane Interactions of the EGF Receptor," ***Cell***, vol. 152, no. 3, 2013, pp. 557–569.
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- *Proceedings of the 50th Annual Design Automation Conference* (DAC '13), Austin, TX, June 2–6, 2013.
- "*The Journal of Physical Chemistry B*, vol. 117, no. 42, 2013, pp. 12935–12942.
- "Her2 Activation Mechanism Reflects Evolutionary Preservation of Asymmetric Ectodomain Dimers in the Human EGFR Family," *eLife*, vol. 2, 2013, pp. e00708.
- "Transitions to Catalytically Inactive Conformations in EGFR Kinase," ***Proceedings of the National Academy of Sciences of the United States of America***, vol. 110, no. 18, 2013, pp. 7270–7275.
- "The Dynamic Process of β_2-Adrenergic Receptor Activation," ***Cell***, vol. 152, no. 3, 2013, pp. 532–542.
- "Atomic-Level Simulation of Current–Voltage Relationships in Single-File Ion Channels," *The Journal of General Physiology*, vol. 141, no. 5, 2013, pp. 619–632.
- "Preconfiguration of the Antigen-Binding Site During Affinity Maturation of a Broadly Neutralizing Influenza Virus Antibody," ***Proceedings of the National Academy of Sciences of the United States of America***, vol. 110, no. 1, 2013, pp. 264–269.
- "Molecular Determinants of Drug–Receptor Binding Kinetics," *Drug Discovery Today*, vol. 18, no. 13–14, 2013, pp. 667–673.
- ***Proceedings of the National Academy of Sciences of the United States of America***, vol. 110, no. 15, 2013, pp. 5915–5920.
- *The Journal of Physical Chemistry B*, vol. 117, no. 42, 2013, pp. 12898–12907.
- ***Journal of the American Chemical Society***, vol. 135, no. 25, 2013, pp. 9465–9474.

Career Options

- Ron O. Dror, Thomas J. Mildorf, Daniel Hilger, Aashish Manglik, David W. Borhani, Daniel H. Arlow, Ansgar Philippsen, Nicolas Villanueva, Zhongyu Yang, Michael T. Lerch, Wayne L. Hubbell, Brian K. Kobilka, Roger K. Sunahara, David E. Shaw, "Structural Basis for Nucleotide Exchange in Heterotrimeric G Proteins," ***Science***, vol. 348, no. 6241, 2015, pp. 1361–1365. Text
- Alpan Raval, Stefano Piana, Michael P. Eastwood, and David E. Shaw, "Assessment of the Utility of Contact-Based Restraints in Accelerating the Prediction of Protein Structure Using Molecular Dynamics Simulations," ***Protein Science***, 2015. Text
- Hoi Sung Chung, Stefano Piana, David E. Shaw, and William A. Eaton, "Structural Origin of Slow Diffusion in Protein Folding," ***Science***, vol. 349, no. 6255, 2015, pp. 1504–1510. Text
- Huafeng Xu, Aaron G. Schmidt, Timothy O'Donnell, Matthew D. Therkelsen, Thomas B. Kepler, M. Anthony Moody, Barton F. Haynes, Hua-Xin Liao, Stephen C. Harrison, and David E. Shaw, "Key Mutations Stabilize Antigen-Binding Conformation during Affinity Maturation of a Broadly Neutralizing Influenza Antibody Lineage," ***Proteins: Structure, Function, and Bioinformatics***, vol. 83, no. 4, 2015, pp. 771–780. Text
- Zachariah H. Foda, Yibing Shan, Eric T. Kim, David E. Shaw, and Markus A. Seeliger, "A Dynamically Coupled Allosteric Network Underlies Binding Cooperativity in Src Kinase," ***Nature Communications***, vol. 6, no. 5939, 2015, pp. 1–10.
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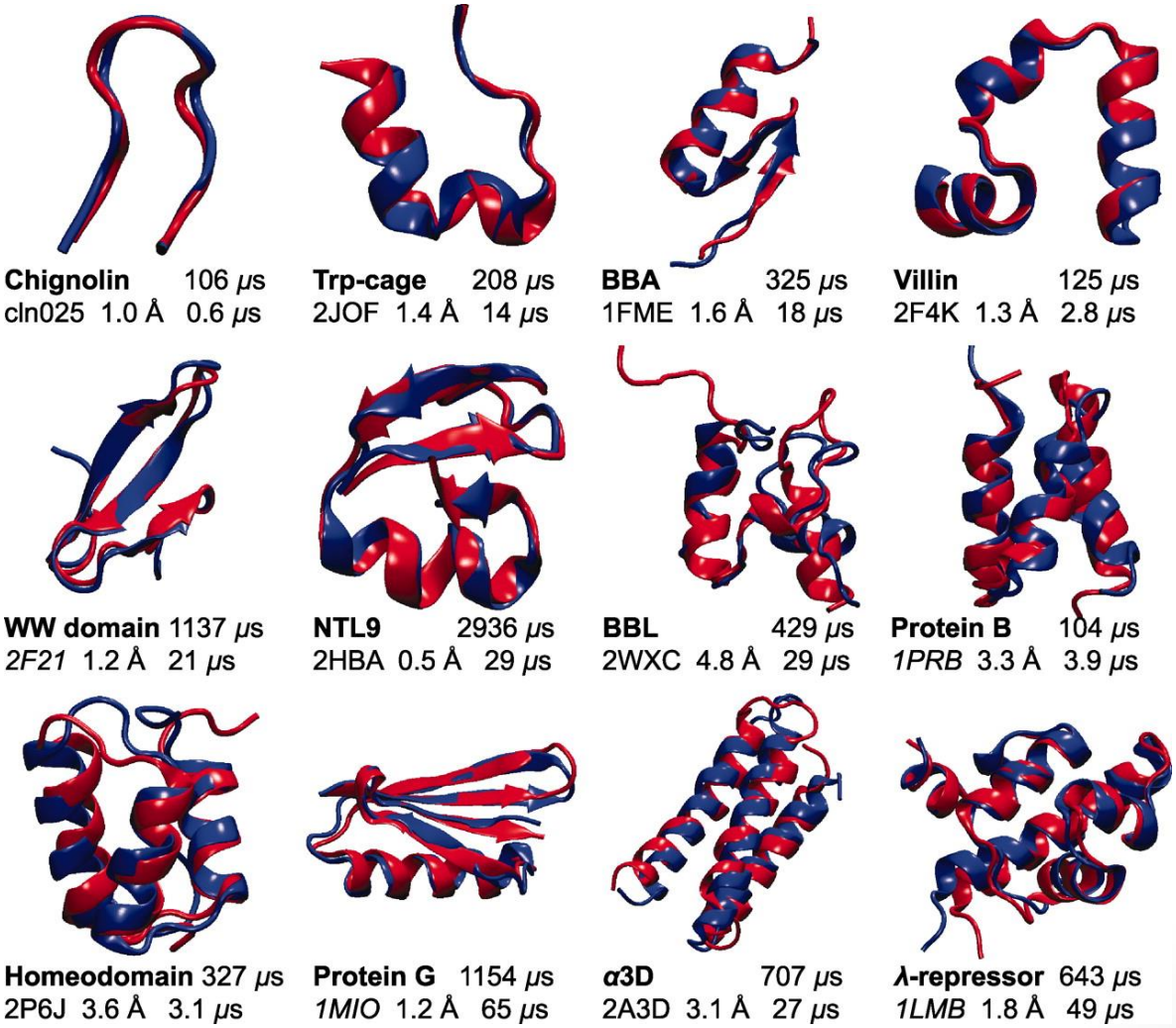
- Lorenzo Sborgi, Abhinav Verma, Stefano Piana, Kresten Lindorff-Larsen, Michele Cerminara, Clara M. Santiveri, David E. Shaw, Eva de Alba, and Victor Muñoz, "Interaction Networks in Protein Folding via Atomic-Resolution Experiments and Long-Timescale Molecular Dynamics Simulations," ***Journal of the American Chemical Society***, vol. 137, no. 20, 2015, pp. 6506–6516. Text

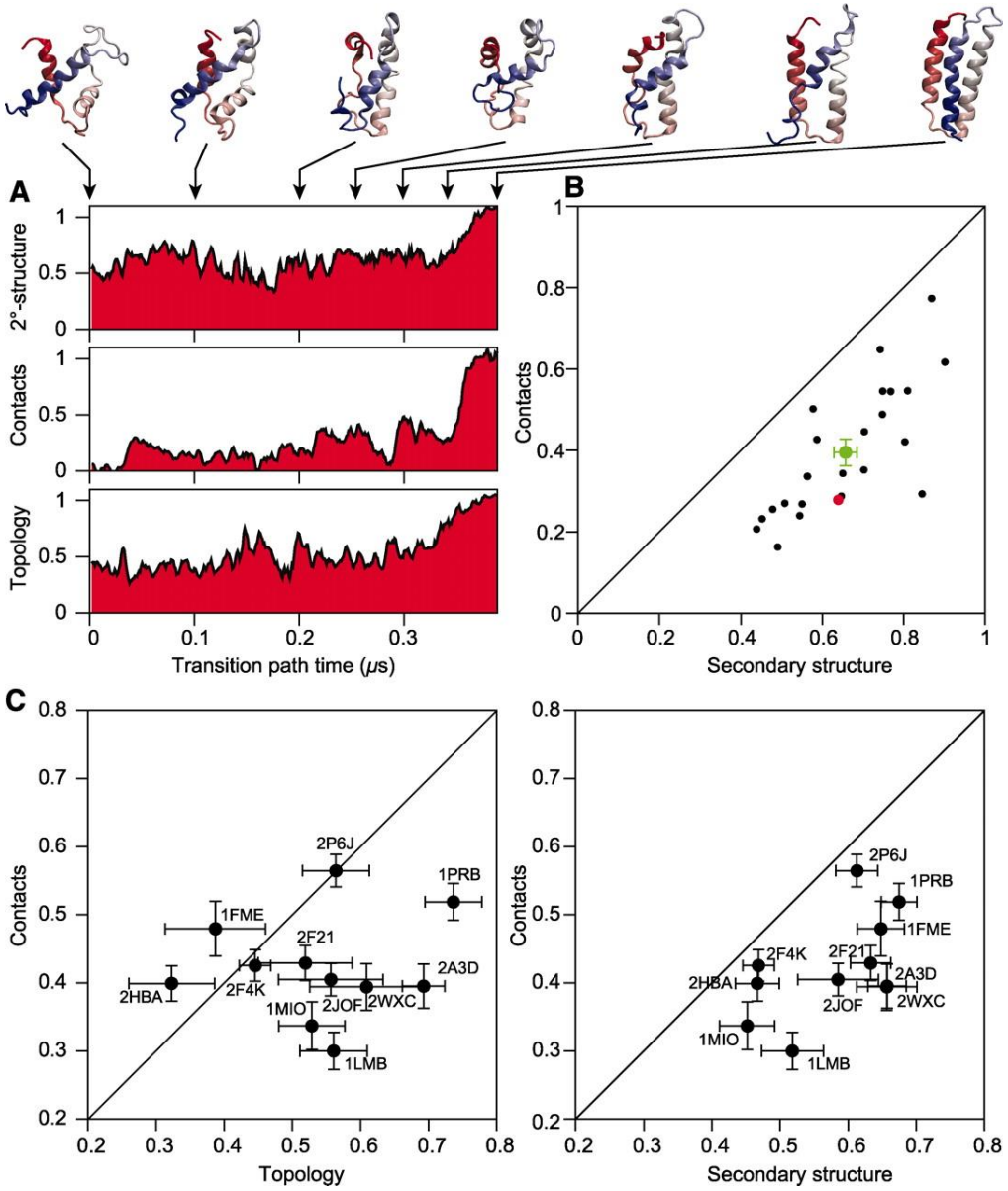
Molecular Dynamics simulations

Fig. 1 Representative structures of the folded state observed in reversible folding simulations of 12 proteins.



K Lindorff-Larsen et al. Science 2011;334:517-520

Fig. 2 Formation of topology, native contacts, and secondary structure during protein folding.



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