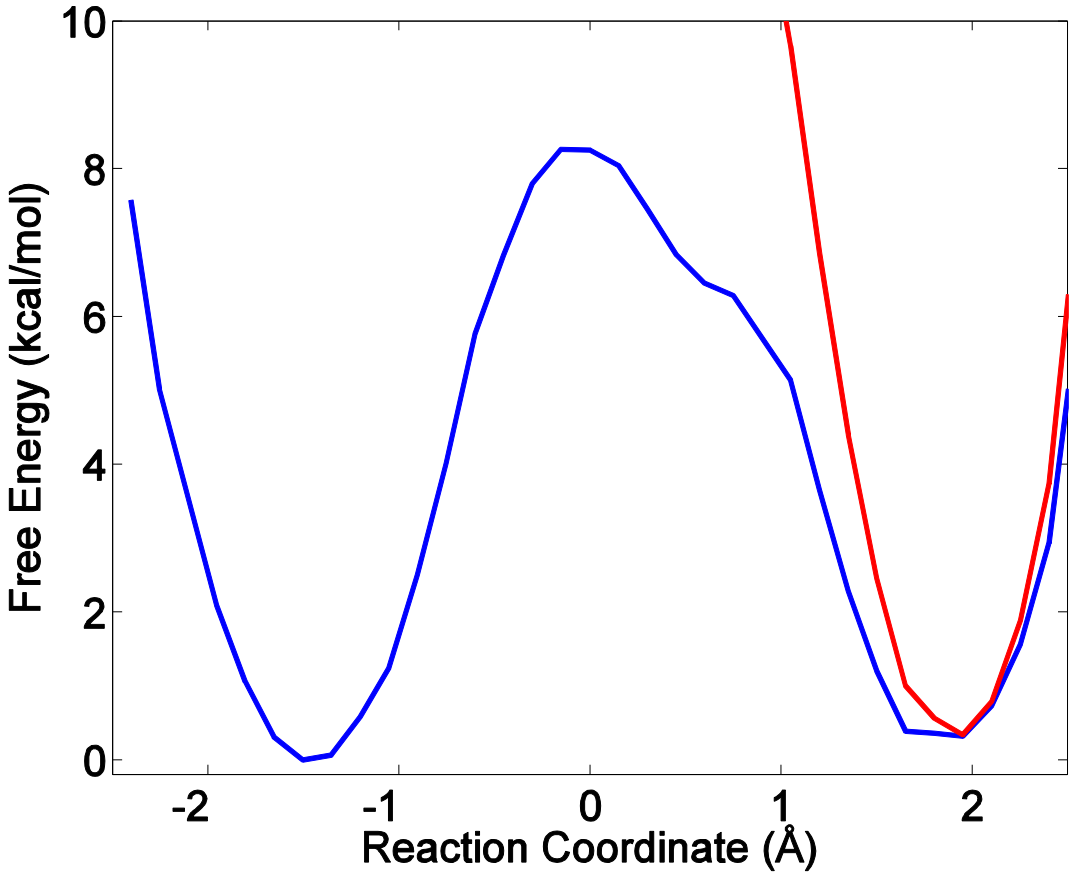
Umbrella Sampling

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

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

Harmonic bias

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



Ferrenberg, Swendsen; Phys. Rev. Lett. 1989
Kumar, Rosenberg, Bouzida, Swendsen, Kollman; *J. Comput. Chem.* 1992 (cited over 2500 times)

WHAM

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

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

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

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

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

$$c_i^{(k)} = e^{\frac{-U_i^{(k)}}{k_B T}}$$

Boltzmann factor for biasing energy

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

Normalizing factor for the equilibrium probability

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

WHAM

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

$\tilde{L}$

Lagrange multipliers for normalization

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

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

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

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

Free Energy Simulations Using the String Method

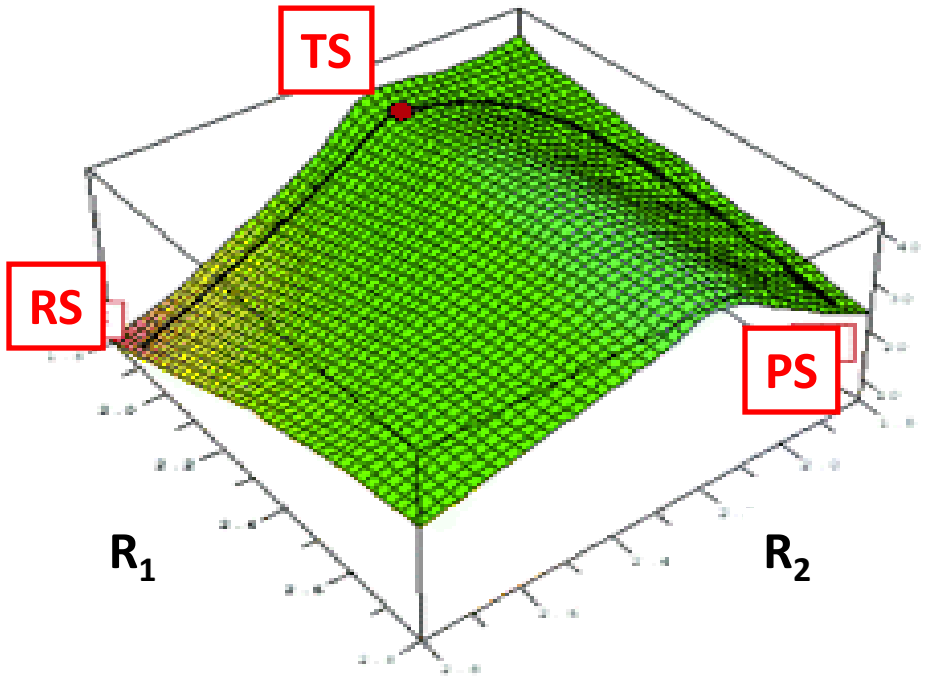
- String-type methods have become highly successful in recent years

  Henkelman, Jonsson, W. Yang, Brooks, …

- Optimized a 1D string in the multidimensional space of the internal reaction coordinates to obtain minimum free energy path

  E, Ren, Vanden-Eijnden, *Phys. Rev. B*, 2002

- Hamiltonian replica exchange between string images



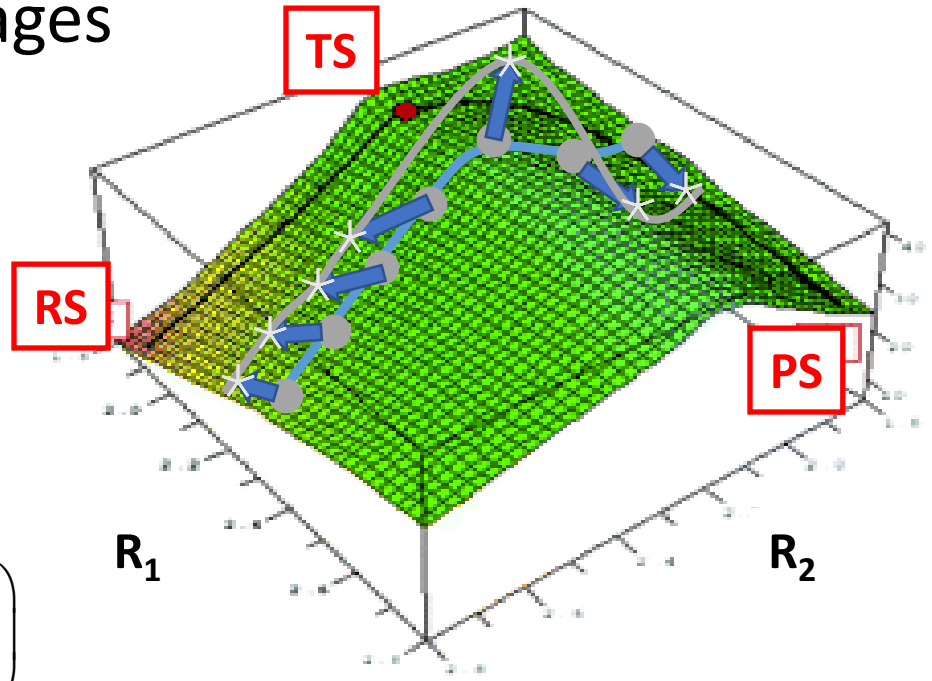
Rosta, Nowotny, Yang, Hummer, *J. Am. Chem. Soc.*, 2011

Free Energy Simulations Using the String Method

- Start with a guess for the string
- Run Umbrella Sampling simulations
- Determine forces for the images along the string
- Fit new string

$$K_{ij}^{k} = \max\left(\min\left(K_{\max}, \frac{\Delta_{ij}^{k-1}}{\delta_i} K_{ij}^{k-1} \right), K_{\min} \right)$$

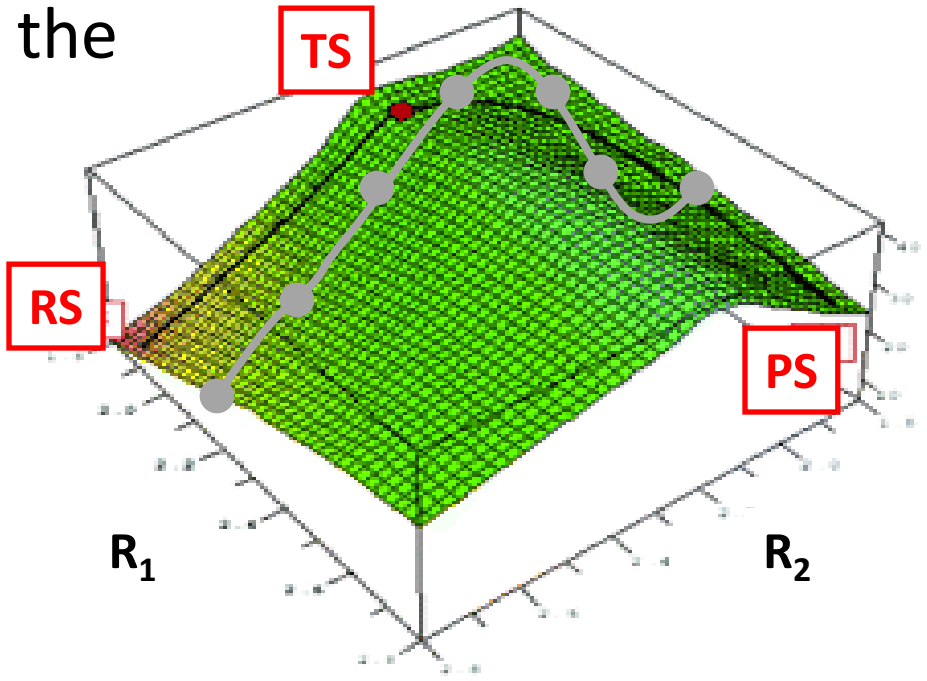
$$p_{j \leftrightarrow j+1}^{k} \approx \exp\left(-\beta \sum_{i=1}^{M} \frac{K_{i\,j}^{k} + K_{i\,j+1}^{k}}{2} \left(c_{i\,j}^{k} - c_{i\,j+1}^{k} \right)^2 \right)$$



Rosta, Yang, Hummer, *J. Am. Chem. Soc.*, 2014

Free Energy Simulations Using the String Method

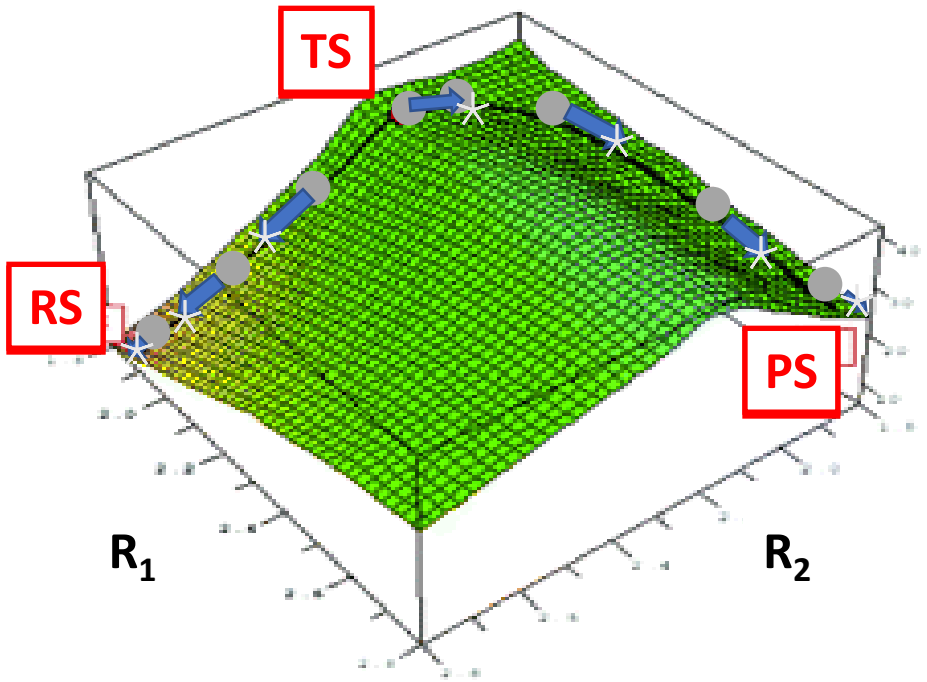
- Start with a guess for the string
- Run Umbrella Sampling simulations
- Determine forces acting on the images along the string
- Fit new string
- Redistribute images
- Run next iteration



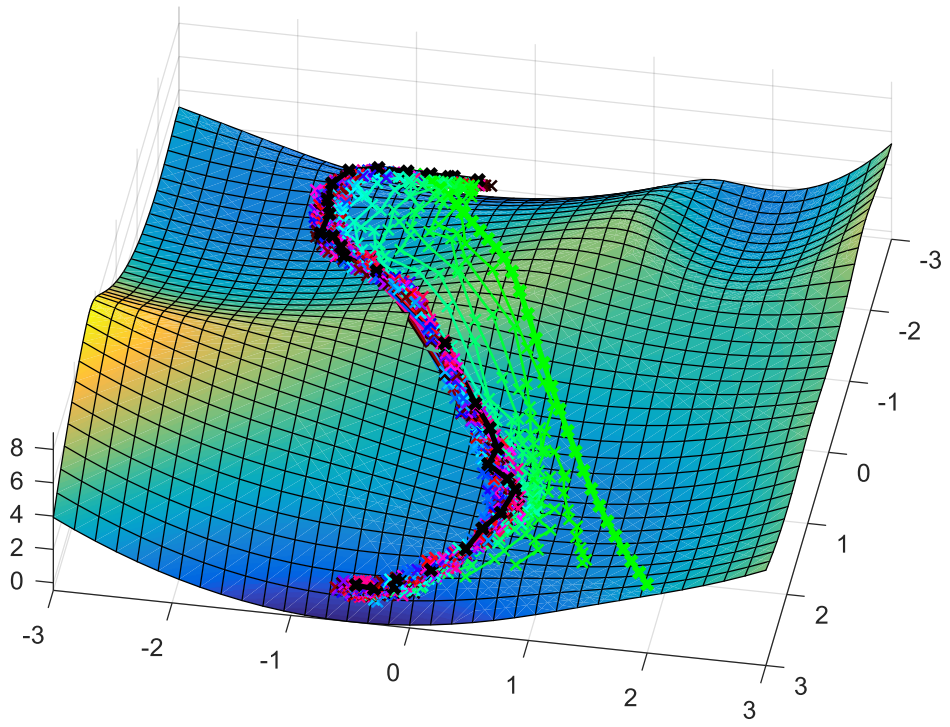
Free Energy Simulations Using the String Method

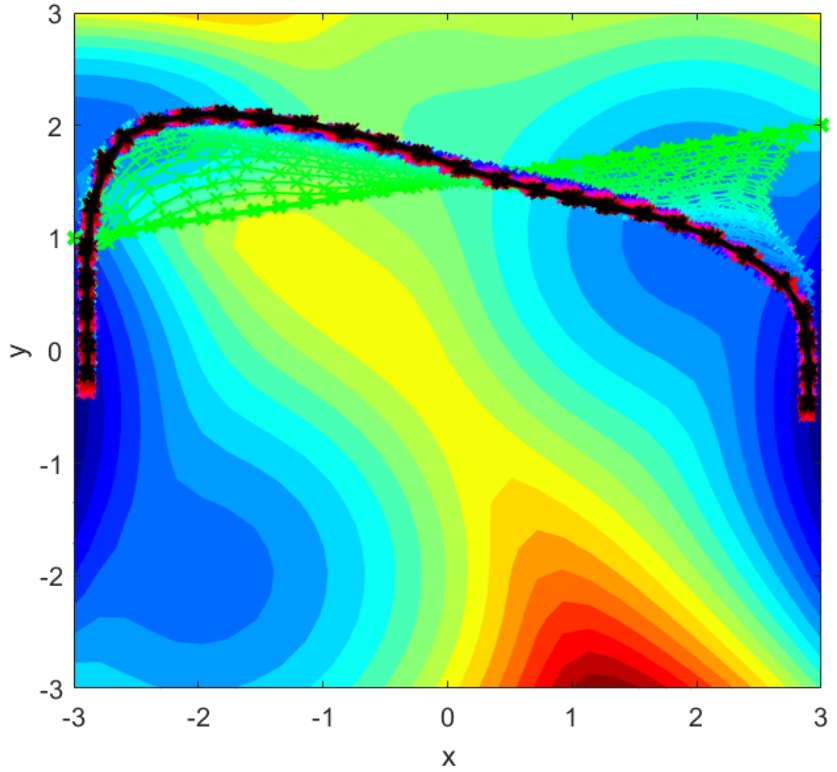
- Converged string:
  - Forces are parallel to string
- We use all data from all string simulations with **Histogram Free** implementation of WHAM: works with **very high dimensionality**

$$\frac{1}{f^{(k)}} = \sum_{k=1}^{NSim} \sum_{A \in NSim} \frac{c^{(k)}\left(\xi_A^k\right)}{\sum_{l=1}^{NSim} N^{(l)} f^{(l)} c^{(l)}\left(\xi_A^k\right)}$$

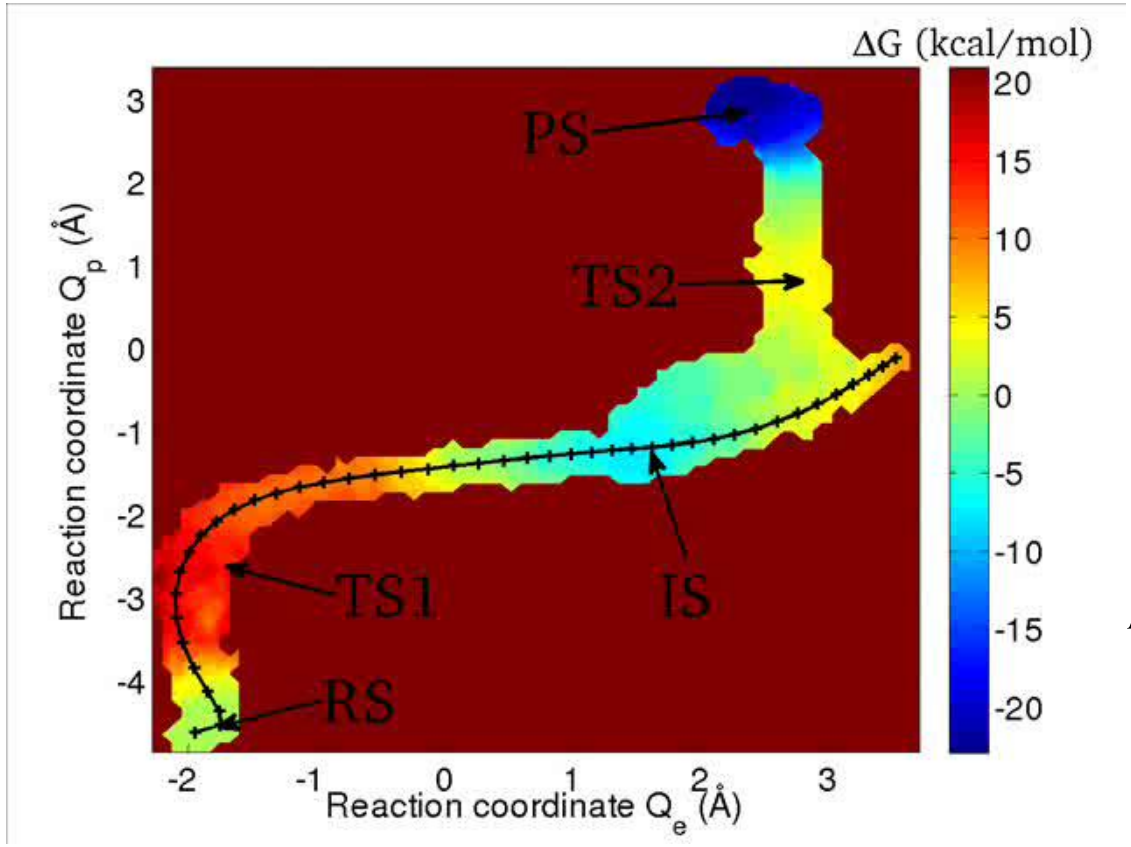


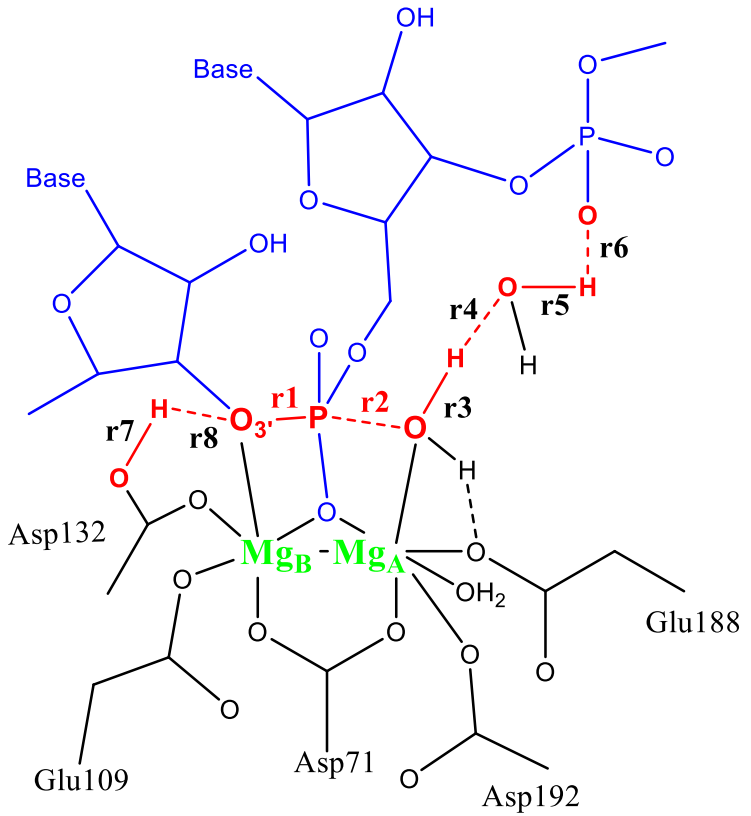
Free Energy Simulations Using the String Method





RNase H: Free Energy Surface





$Q_e=r_1-r_2$

$Q_p=r_3-r_4+r_5-r_6+r_7-r_8$