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Simulation of the dynamics of protein chains using metropolis Algorithm

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1. Metropolis Algorithms

- Metropolis Algorithm performs a sample of the configuration space starting from a random conformation and repeat a large number of steps.
- Each step consists of attempting a transition to a new conformation x' choosing among a set allowed moves, accepting the attempt with probability

$$\min[1, \exp(- (U(x') - U(x)) / T)]$$

where U is the potential energy and T the absolute temperature in units of Boltzmann's constant.

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Proposition 1.1 *For any temperature schedule (T_n) decreasing to 0 and satisfying*

$$T_n \geq \frac{c}{\ln(n)} \text{ for large } n,$$

if c large enough, the probability that x_n is global minimum tends 1 as $n \rightarrow +\infty$.

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2. Masters Equation

This is equivalent to solving the master equation

$$\frac{\partial p(x, t)}{\partial t} = \int [p(x'w(x' \rightarrow x) - p(x, t)w(x \rightarrow x'))] dx'$$

where the transition rates are

$$w(x' \rightarrow x) = w_0 \cdot p_{ap} \cdot \min \left[1, \exp \left(-\frac{U(x) - U(x')}{T} \right) \right],$$

where w_0 sets the time scale of the transitions and

$$p_{ap}(x' \rightarrow x) = p_{ap}(x \rightarrow x')$$

and allows the system to visit the whole space, the algorithm provides a probability which converges to the Boltzmann distribution.

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3. Proteins

- We metropolis algorithm investigate properties of proteins, particularly enzymes.
- The master equation describe a tailor-made dynamics which in principle, has nothing to do with actual dynamics of the protein.

4. Langevin's Equation

- Actual dynamics of the protein is described by Langevin's Equation

$$\frac{dp}{dt} = F - \frac{\gamma}{m}p + \eta,$$

where p is the momentum of the given particle, F is the force acting on it, γ is the friction coefficient, m the mass and η a stochastic variable describing the interaction of the solvent.

- $\langle \eta(t) \rangle = 0$ and $\langle \eta(t)\eta(t') \rangle = D\gamma^2\delta(t - t')$, where the brackets indicate the average over the realizations of η and D is the diffusion coefficient.

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Implementing the Metropolis algorithm

- One is free to choose any kind of fancy move, with the only goal of speeding up the sampling of the confirmation space.
- If the chosen move allows enormous jumps across the conformation space, it is clear that the resulting dynamics has nothing to do with the actual dynamics of the protein.
- However, set moves chosen for protein models is usually quite realistic, involving mainly local moves of the atoms.
- Thus, one ask whether the trajectories obtained with the Metropolis algorithm and small moves have some degree of realism, in the sense that they provide approximation to the solution of the Langevin's Equation.

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Stochastic

- Both Langevin's equation and the Metropolis algorithm are stochastic, containing some randomness.
- What makes physical sense is not a single trajectory but trajectories averaged over the force η exerted by solvent with the trajectories generated by the Metropolis algorithm, averaged over independent runs.

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Approximated by Metropolis algorithm for protein-like chains

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- Under what conditions the average solution of Langevin's equation is approximated by Metropolis algorithm for proteins
- Under the assumption that p_{ap} allows only small transitions $\delta x = x' - x$, the master equation solved by the Metropolis algorithm approximates a diffusive Fokker-Planck equation,

$$\frac{\partial p(x, t)}{\partial t} = -\frac{\partial A(x)p(x, t)}{\partial x} + \frac{1}{2} \frac{\partial^2 B(x)p(x, t)}{\partial x^2}$$

where

$$A(x) = \int \delta x w(x, \delta x) d(\delta x) \text{ and } B(x) = \int (\delta x)^2 w(x, \delta x) d(\delta x)$$

which is equivalent to Langevin's equations.

The theory

- We define the small number R as the maximum displacement allowed to the coordinate x in a single move.

- $$A(x) = -w_0 \frac{U'(x) \cdot R^2}{6T} \text{ and } B(x) = w_0 \frac{R^2}{3}$$

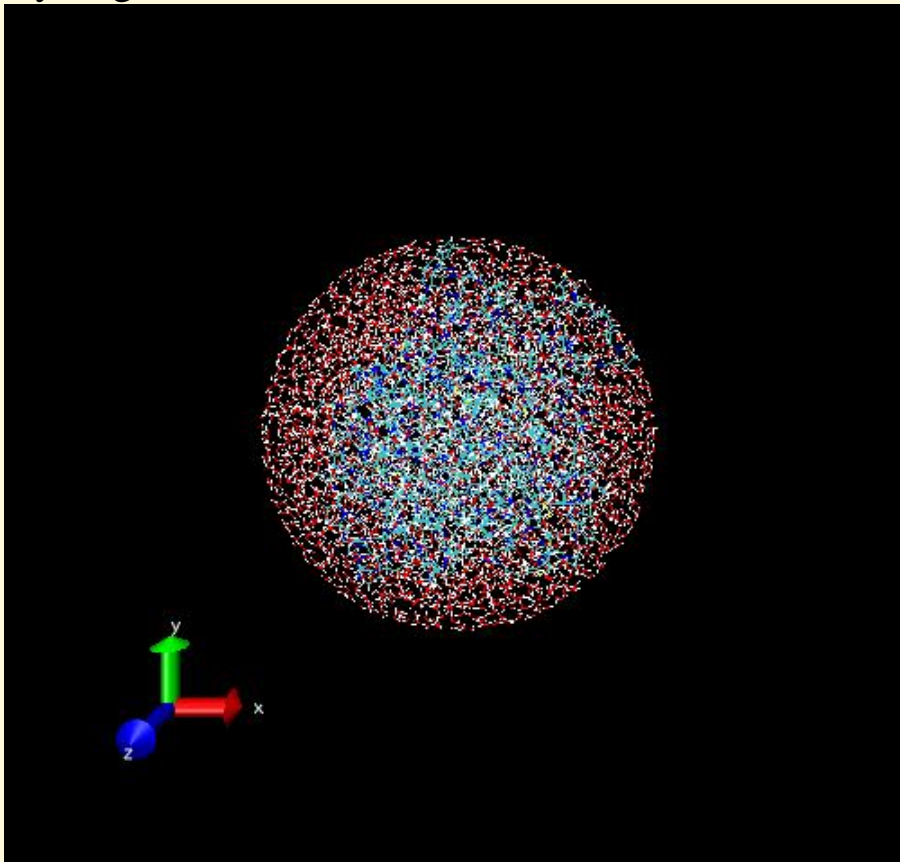
- Then the Fokker-Planck equations corresponds to Langevin dynamics with

$$\gamma = \frac{6T}{w_0 R^2} \text{ and } D = w_0 \frac{R^2}{6}$$

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static: Solvating the RIHC in the sphere

- Hydrogen atoms are colored black for contrast



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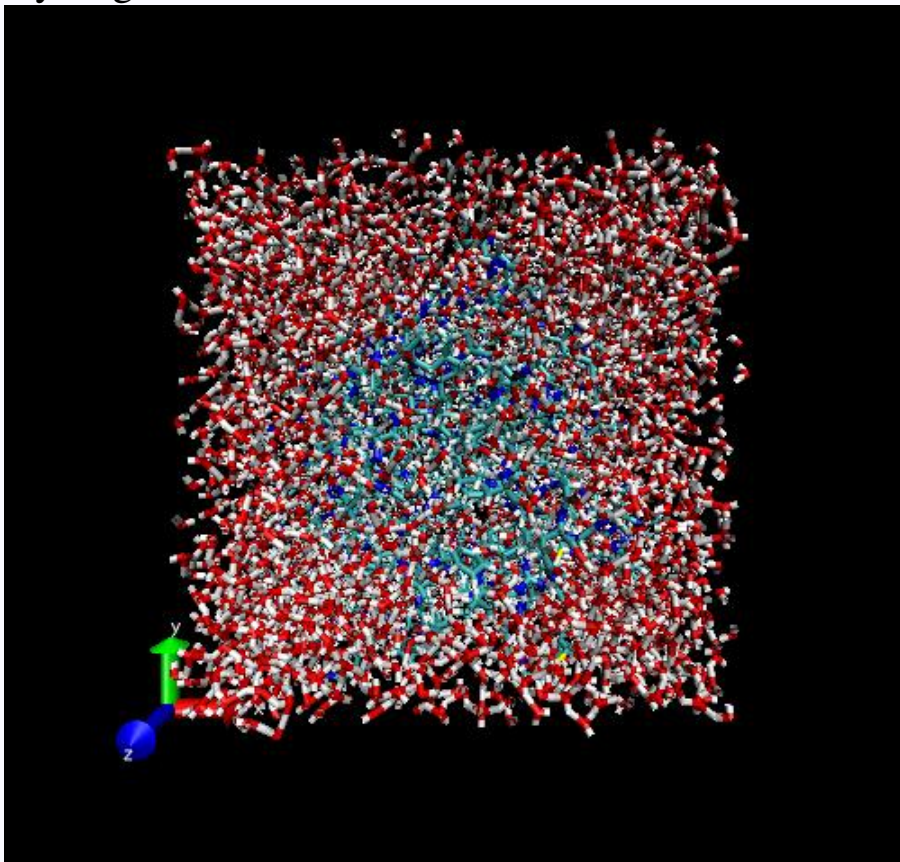
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Static: RIHC in the water box

- Hydrogen atoms are colored black for contrast.



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static: rihc in the water system

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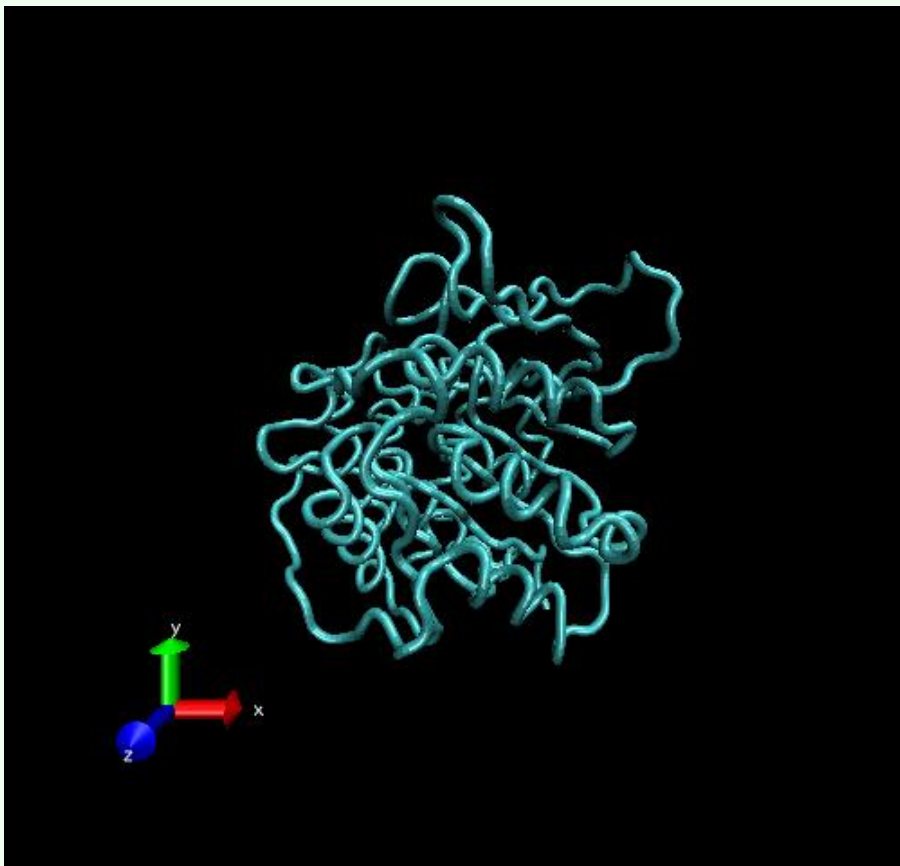
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Analysis of RIHC enzyme equilibration in water sphere using RMSD

- RMSD(Root Mean Square Deviation) characterizes the amount by which a given selection of our molecule deviates from a defined position in space
- RMSD is define as:

$$RMSD_{\alpha}(t_j) = \sqrt{\frac{\sum_{\alpha=1}^{N_{\alpha}} (\mathbf{x}_{\alpha}(t_j) - \langle \mathbf{x}_{\alpha} \rangle)^2}{N_{\alpha}}},$$

$$\langle \mathbf{x}_{\alpha} \rangle = \frac{1}{N_t} \sum_{j=1}^{N_t} \mathbf{x}_{\alpha}(t_j)$$

N_{α} is the number of atoms, N_t is the number of steps over which atomic positions are being compared, and $\mathbf{x}_{\alpha}(t_j)$ is the position of the atom α .

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RMSD versus simulation time for a RIHC system equilibrating

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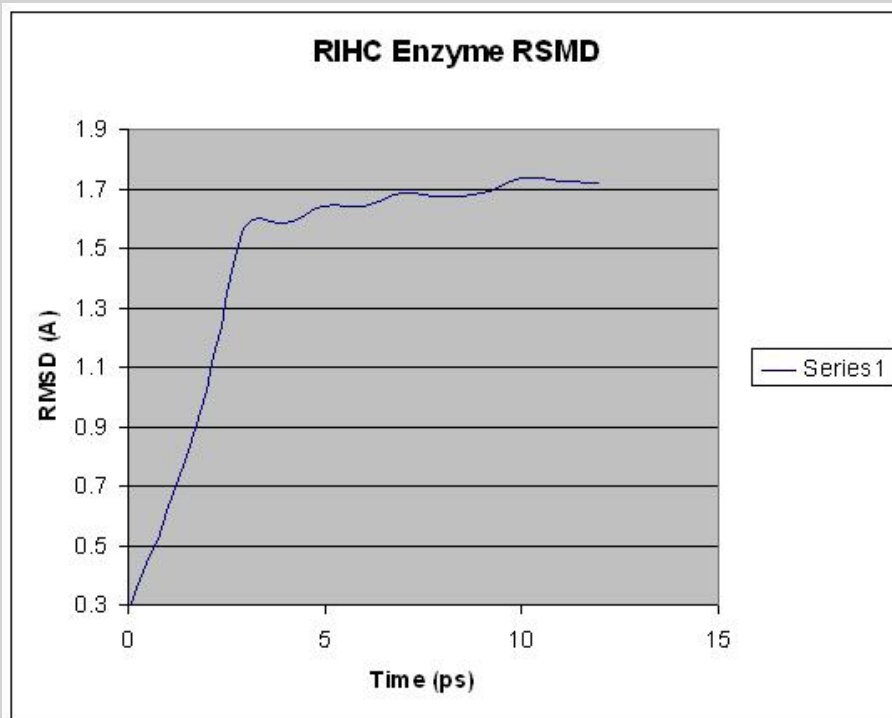
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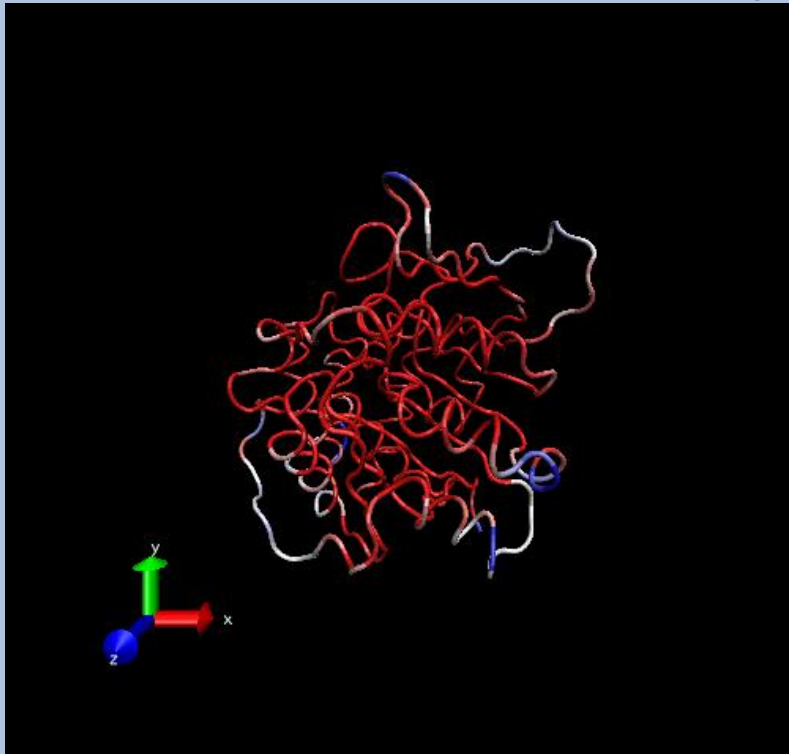
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RMSD for individual residues of RIHC

- RIHC colored by the average RMSD per residue. Red denotes more mobile residues, and blue residues which move less during equilibration.



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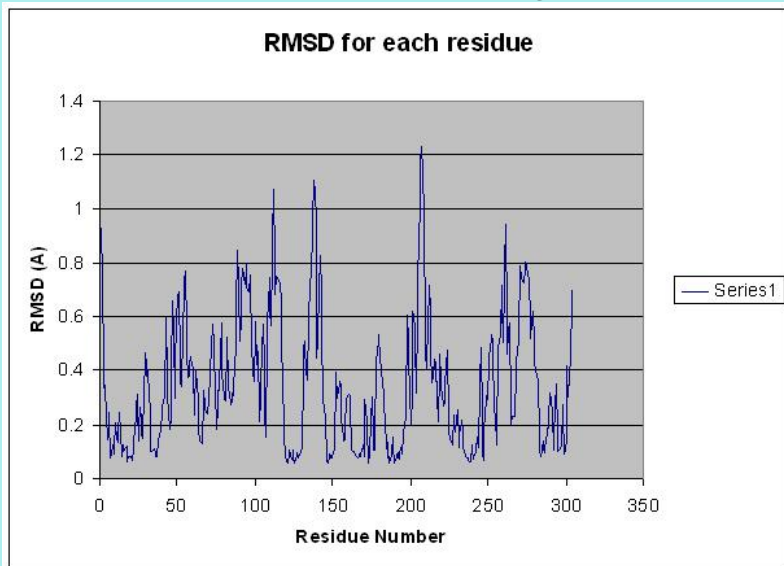
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Analysis: Distribution of RMSD of RIHC

- Take a look at RMSD distribution. You can see regions where a set of residues show less mobility. There is a correlation between the location of these regions and secondary structures.

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Analysis: Maxwell-Boltzmann Energy Distribution

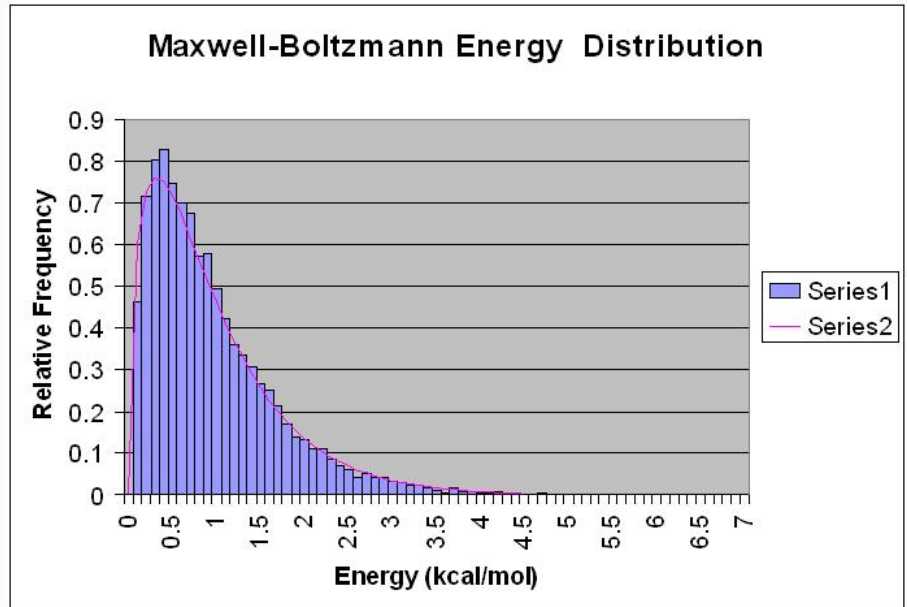
- Maxwell distribution for kinetic energy

$$f(\epsilon_k) = \frac{2}{\sqrt{\pi}} \frac{1}{(k_B T)^{\frac{3}{2}}} \sqrt{\epsilon_k} \exp\left(-\frac{\epsilon_k}{k_B T}\right)$$

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Analysis: Maxwell-Boltzmann Energy Distribution

- Maxwell-Boltzmann distribution for kinetic energy of RIHC



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Heat Diffusion: Cooling of RIHC in a water sphere

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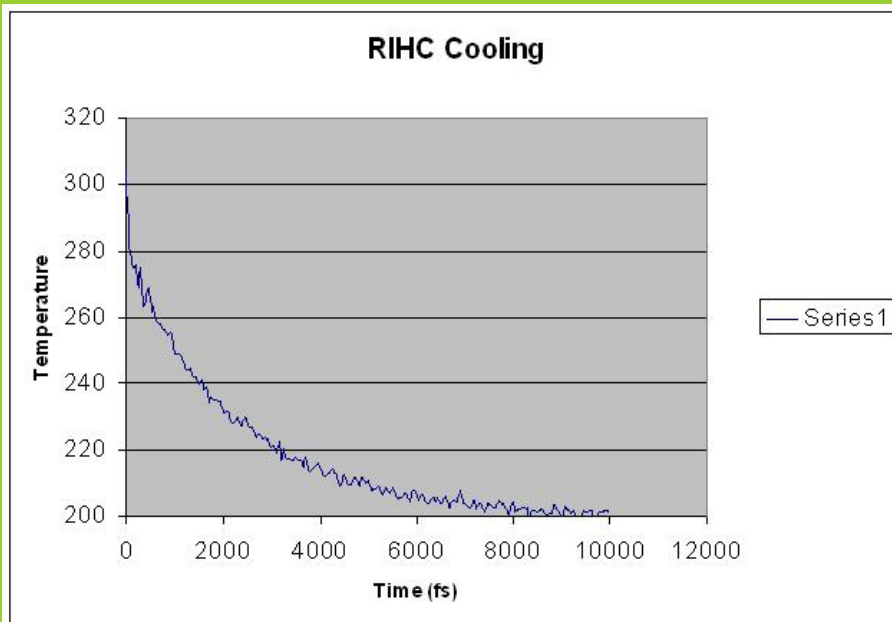
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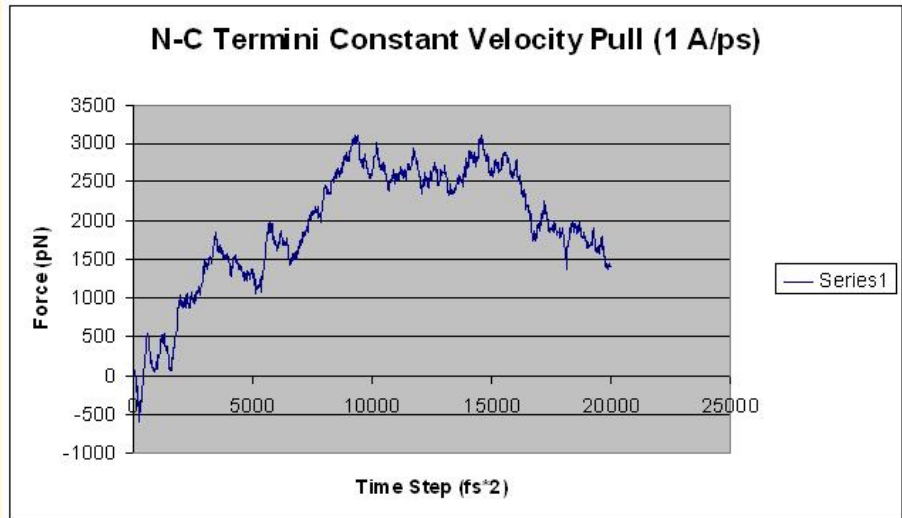
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Force analysis of RIHC enzyme: Graph

- The first peak in the force is associated with the breaking of hydrogen bonds between two β strands



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