Chaos in Protein Dynamics

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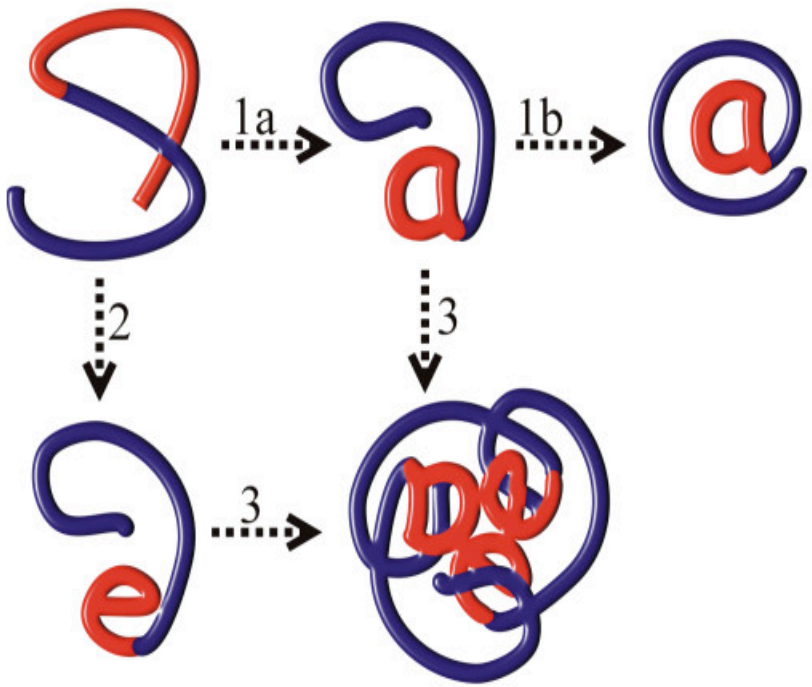
Presented by: Trilce Estrada

Folding Pathways

- Protein folding must follow a pathway from any unfolded conformation to the native conformation

- To what extent the events along the folding pathway are invariant?



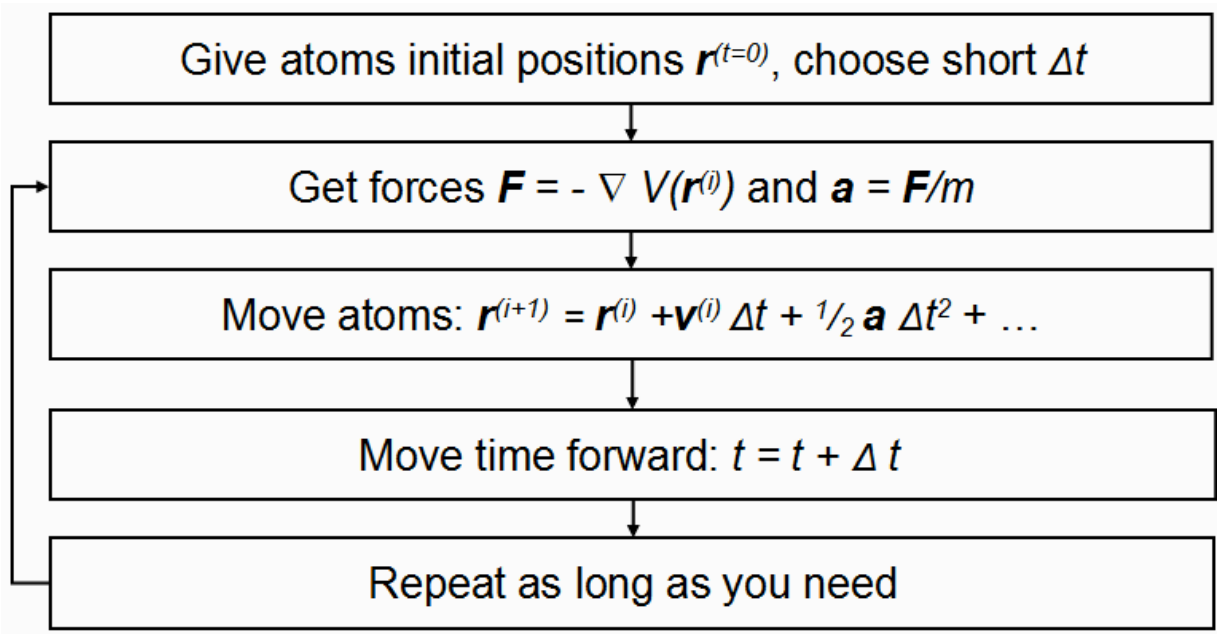
Folding Pathways (2)

- Difficulty to characterize experimentally:
  - Transient folding events
  - Partially folding intermediates

- Early folding events seem to occur locally in small regions of the polypeptide chain
- Study of small regions is more tractable than the study of complete proteins

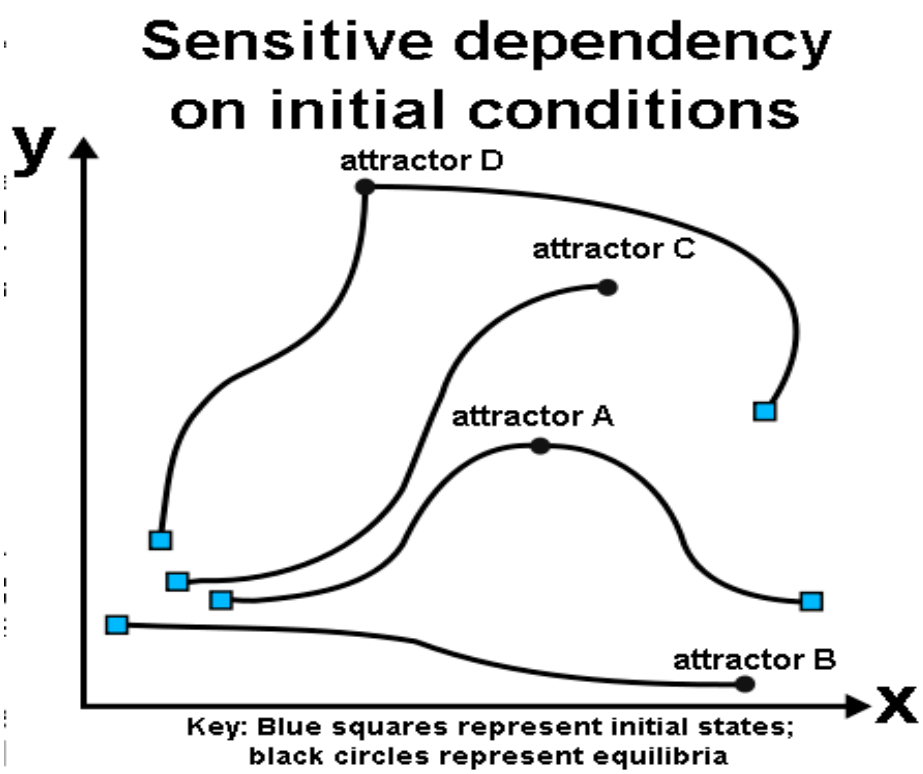
MD algorithm

- MD simulations consist on iteratively solve systems of nonlinear differential equations.
- Many such systems are known to exhibit chaotic behavior



Chaotic systems

A system is defined as **chaotic** if small perturbations in its initial configuration are amplified exponentially with time

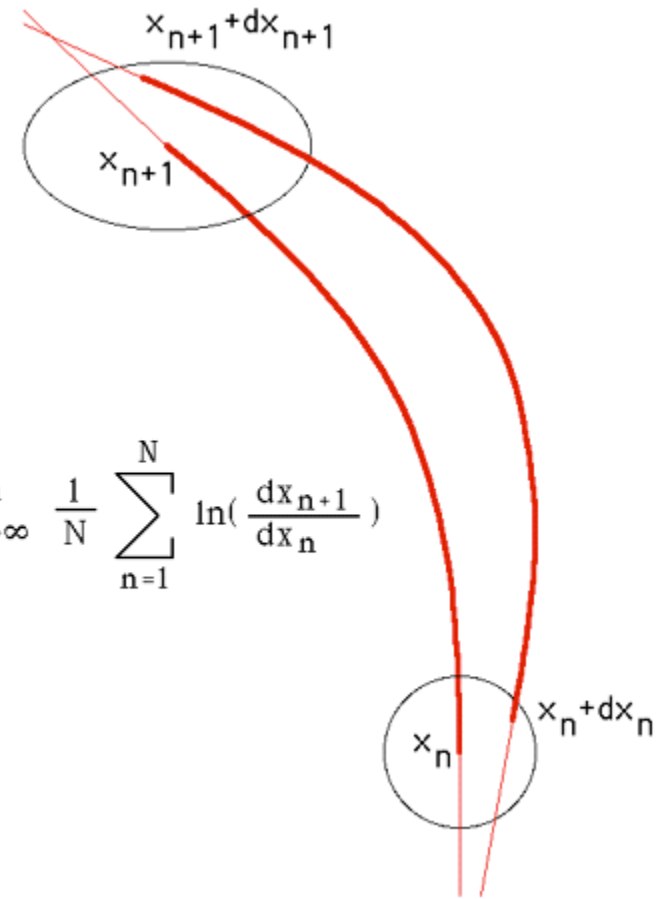


Three objectives for this paper

- Show that MD simulations of protein folding exhibit chaotic behavior
- Calculate the divergence rate of the system at different stages of the folding process
- Study the effect of this chaotic behavior on the occurrence of certain folding events

Measurement of chaos in MD simulations

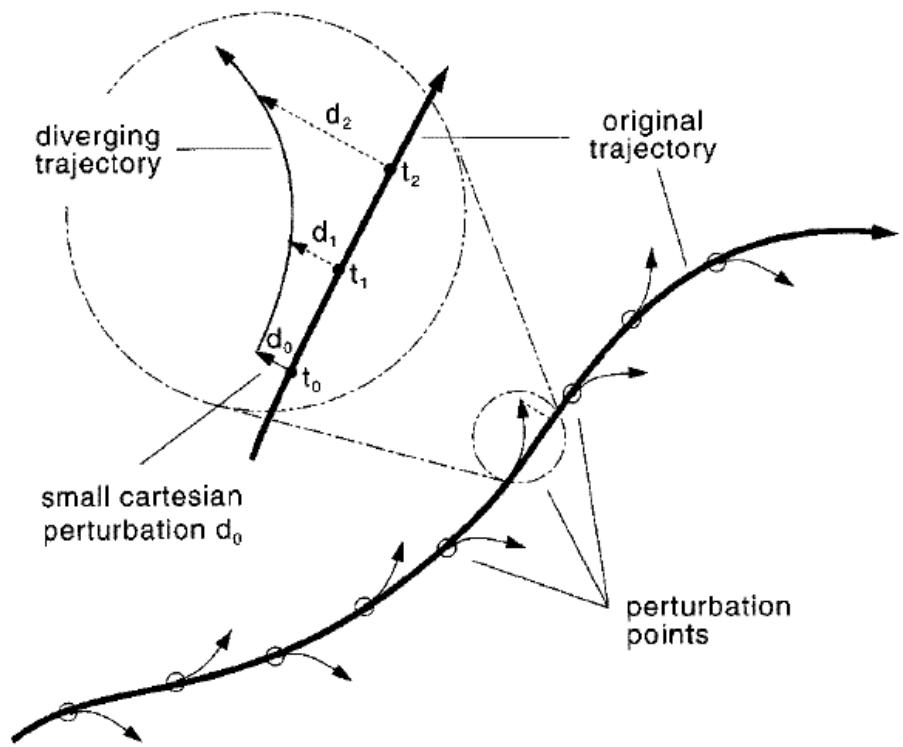
- The standard measure for determining whether or not a system is chaotic is the Lyapunov exponent
- There are as many Lyapunov exponents as degrees of freedom in the system
- A system is chaotic if it has at least 1 positive Lyapunov exponent



$$\lambda = \lim_{N \to \infty} \frac{1}{N} \sum_{n=1}^{N} \ln\left(\frac{dx_{n+1}}{dx_n}\right)$$

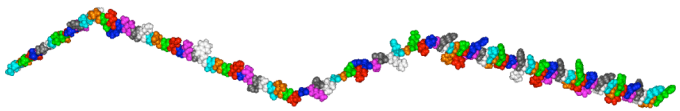
Proving that MD simulations of protein folding are chaotic

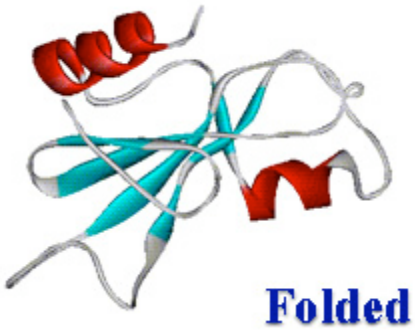
- Calculate the maximum Lyapunov exponent in the MD folding simulations by introducing small perturbations at many points along the trajectory

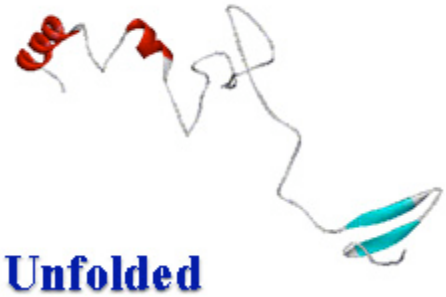


MD simulations (1)

- 13-residue barnase fragment. Explicit solvent treatment
  - 1000 ps MD simulation starting from the folded state
  - 600 ps MD simulation starting from a representative unfolded conformation

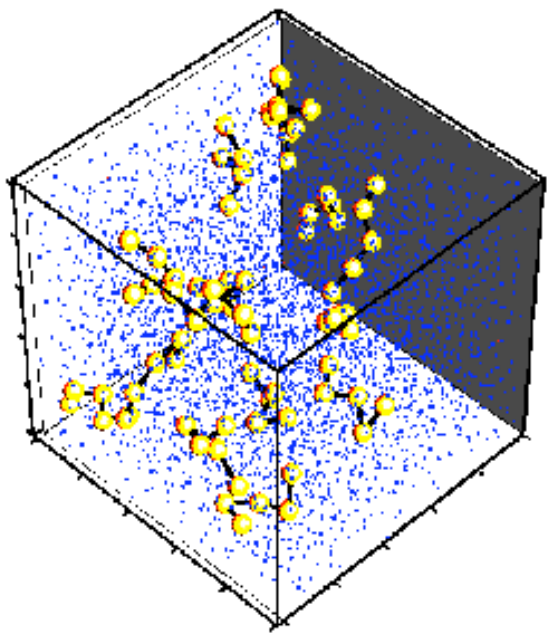






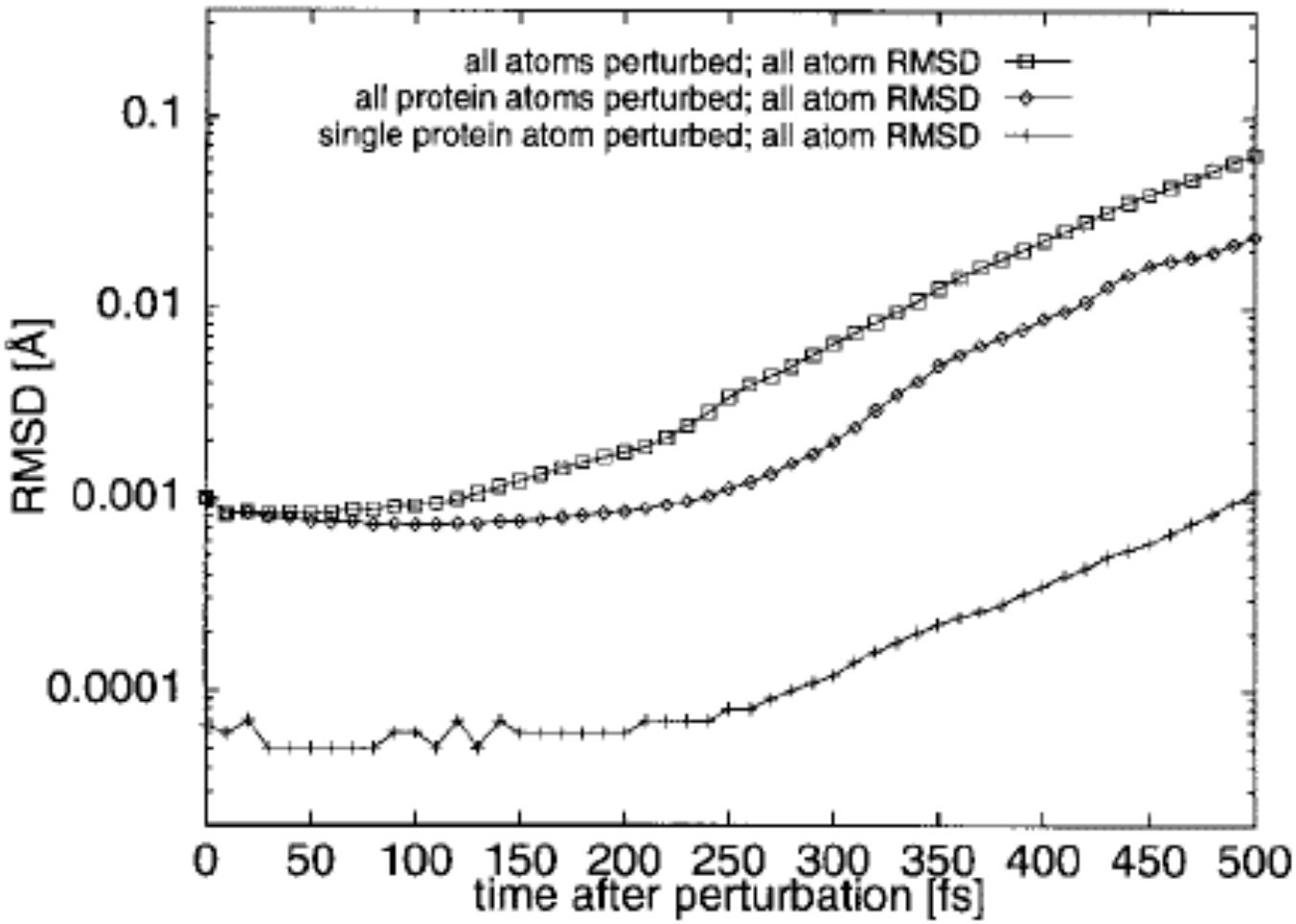
MD simulations (2)

MD simulations were executed using the program **DISCOVER**



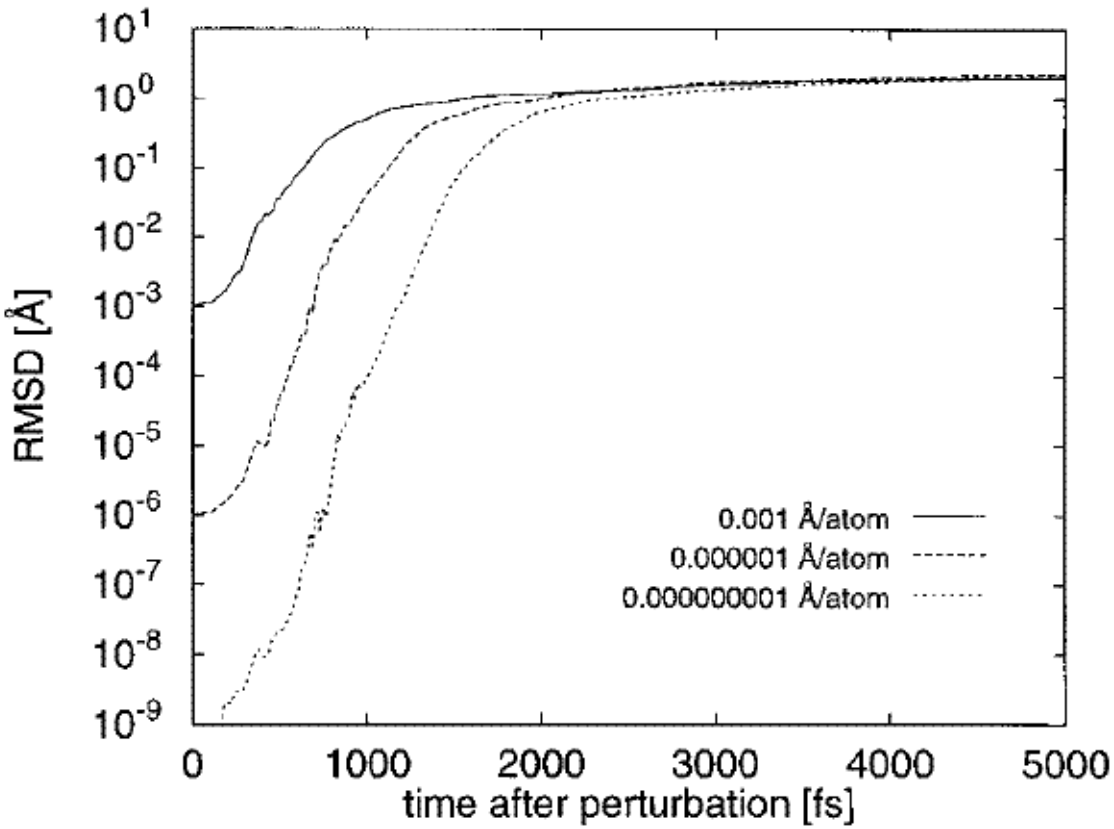
- Native-like system
  - 1598 water molecules in a box of 37x37X37 A^3
- Denatured system
  - 2042 water molecules in a box of 40x40x40 A^3
- Both systems were equilibrated
- Restart files were saved every 10ps

Chaotic behavior of MD simulations



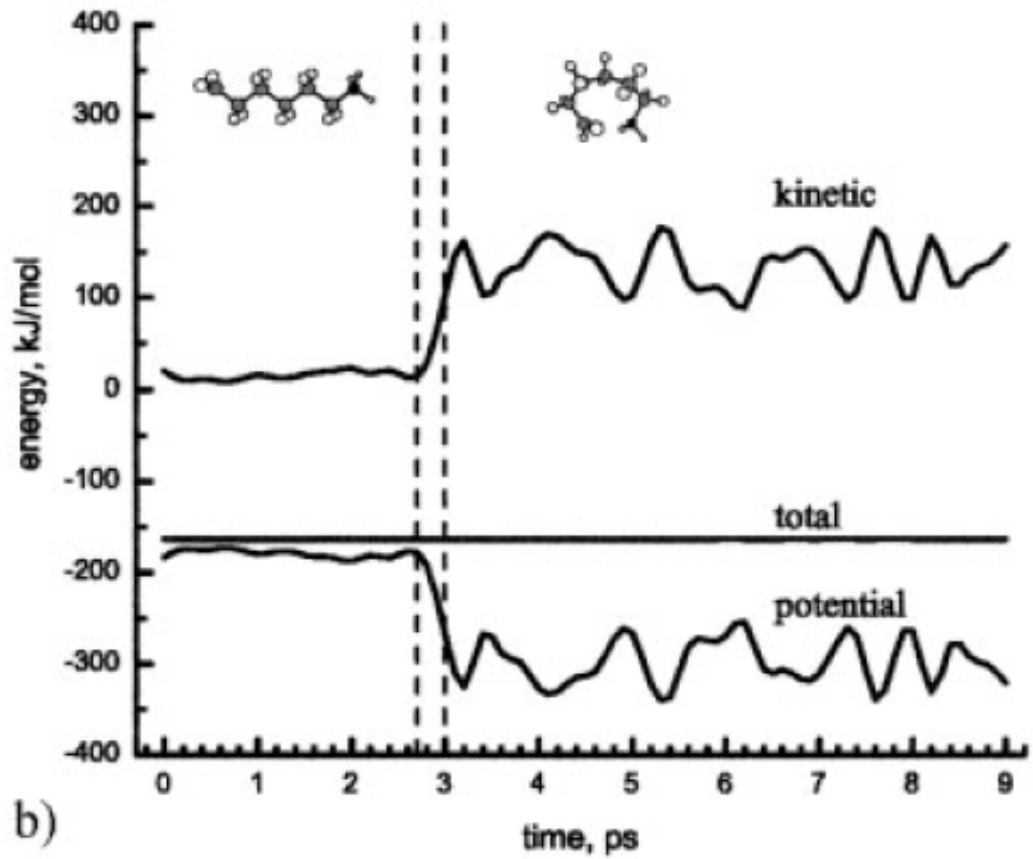
Effect of Magnitude of Perturbation

Exponential growth with similar slopes.
The plateau is reached at a constant RMSD

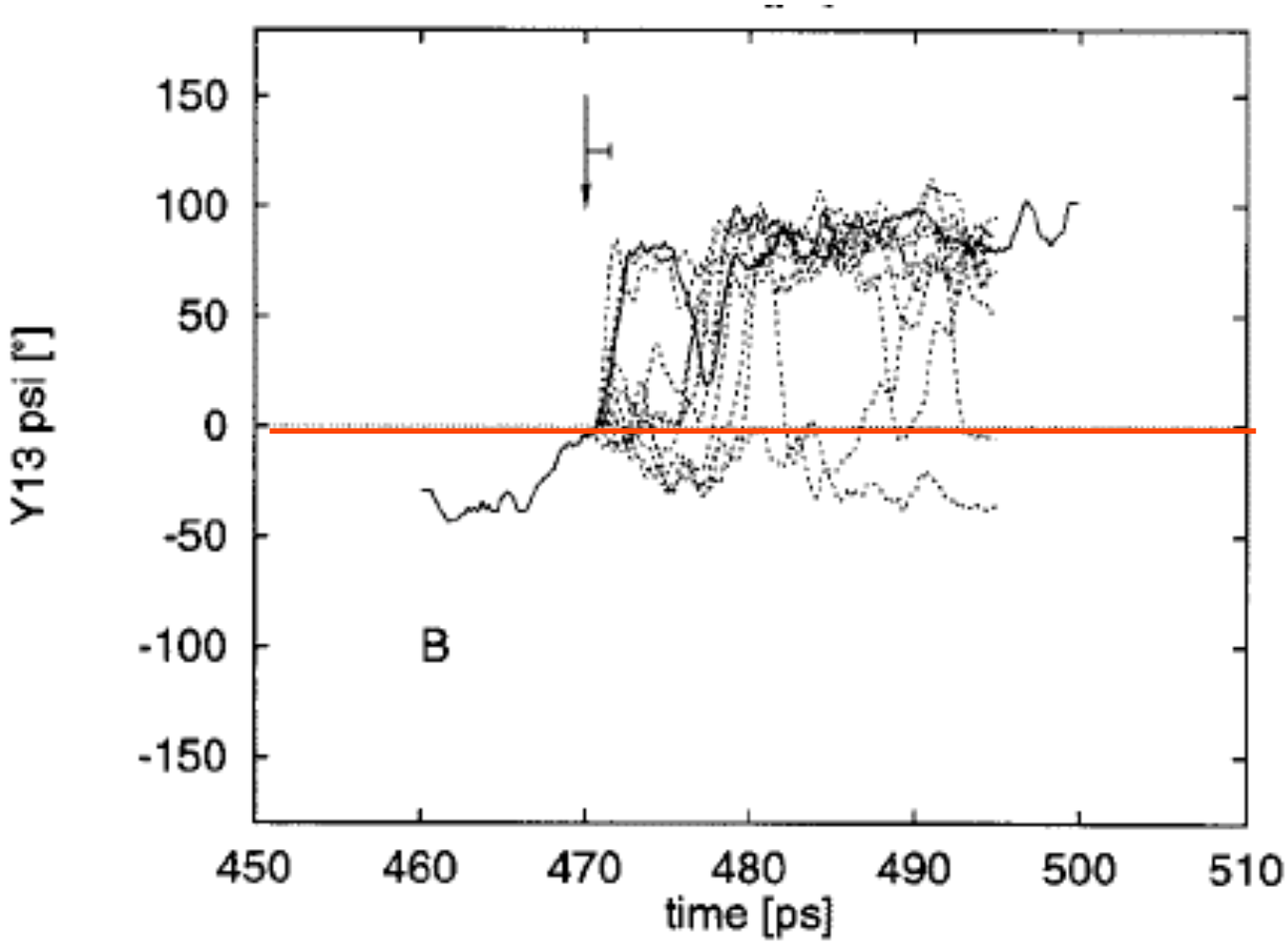


Behavior at Different Stages of Folding

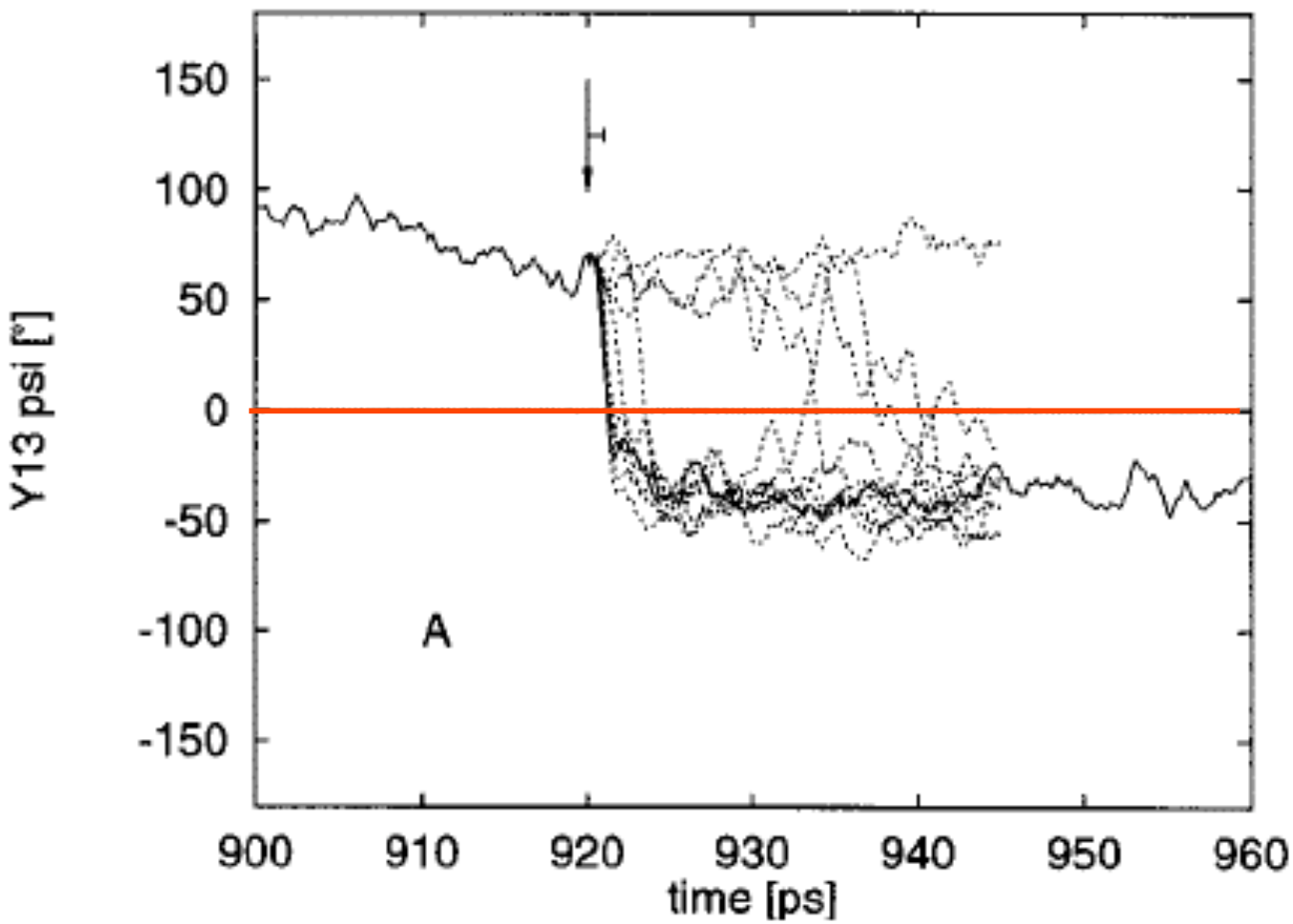
Can major folding events be avoided if the simulation is slightly perturbed just before they occur?



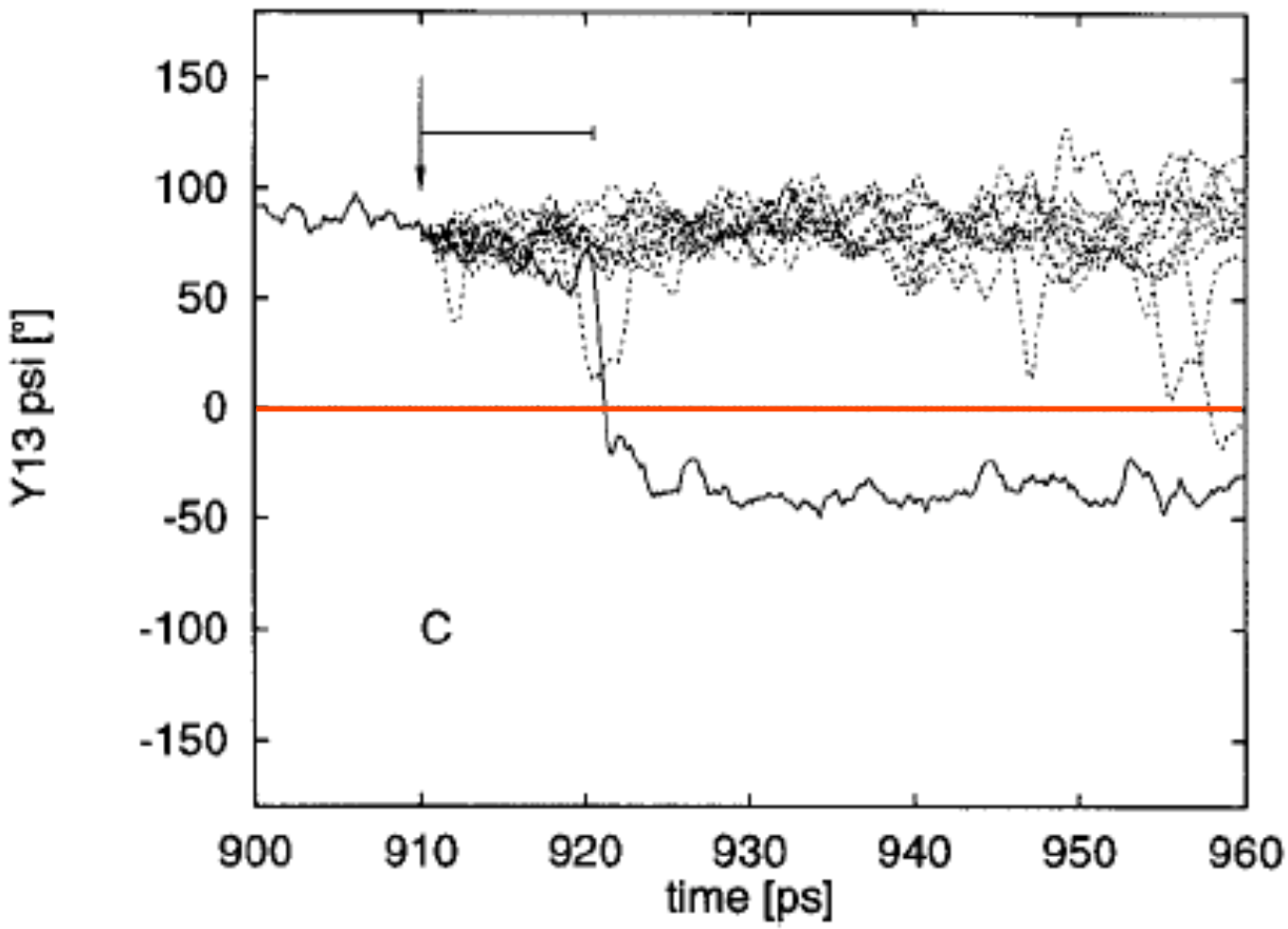
Distance from the transition: 1.5 ps



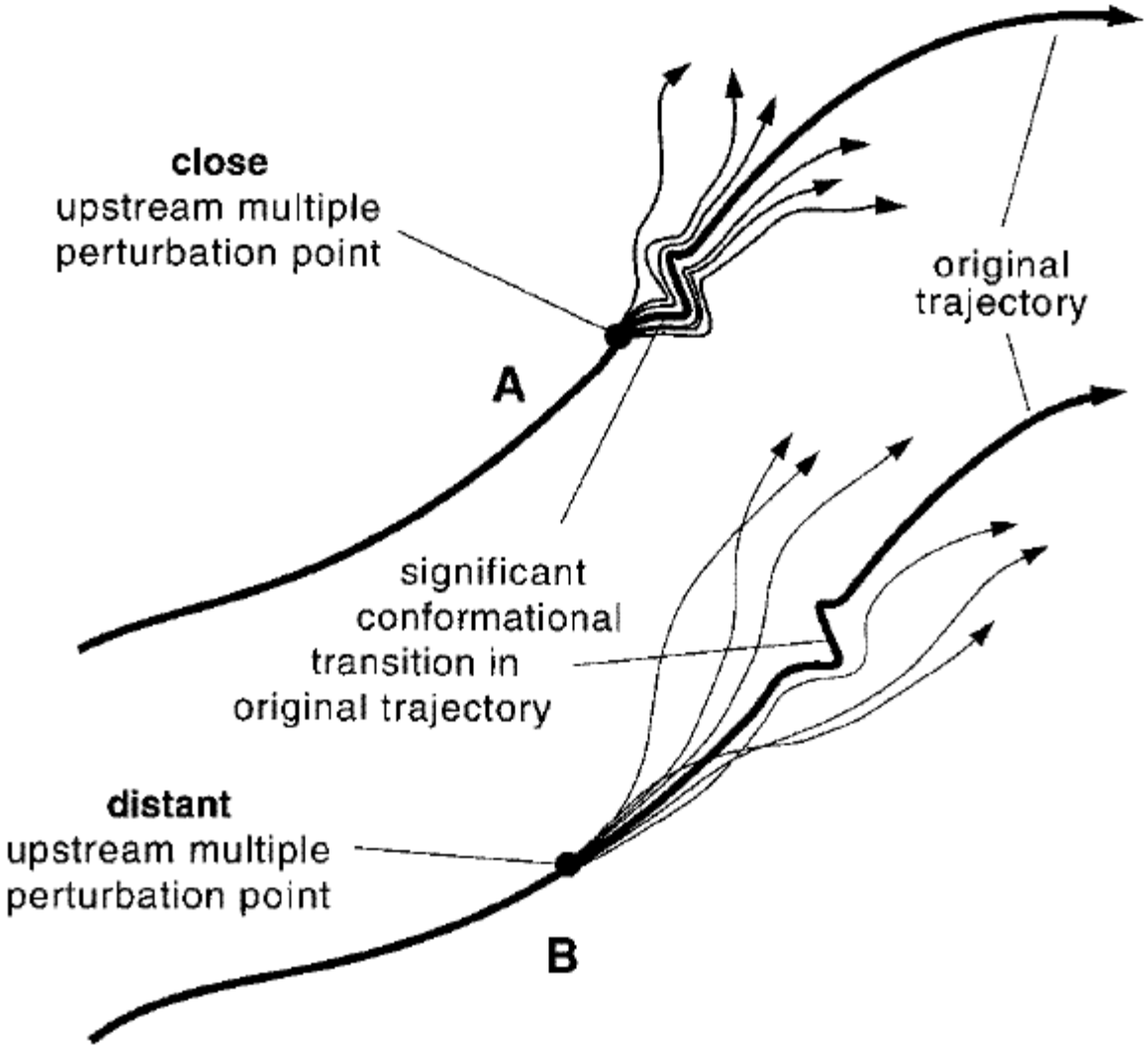
Distance from the transition: 0.8ps



Distance from the transition: 10.8ps



Effects of Chaotic Behavior on Folding Events

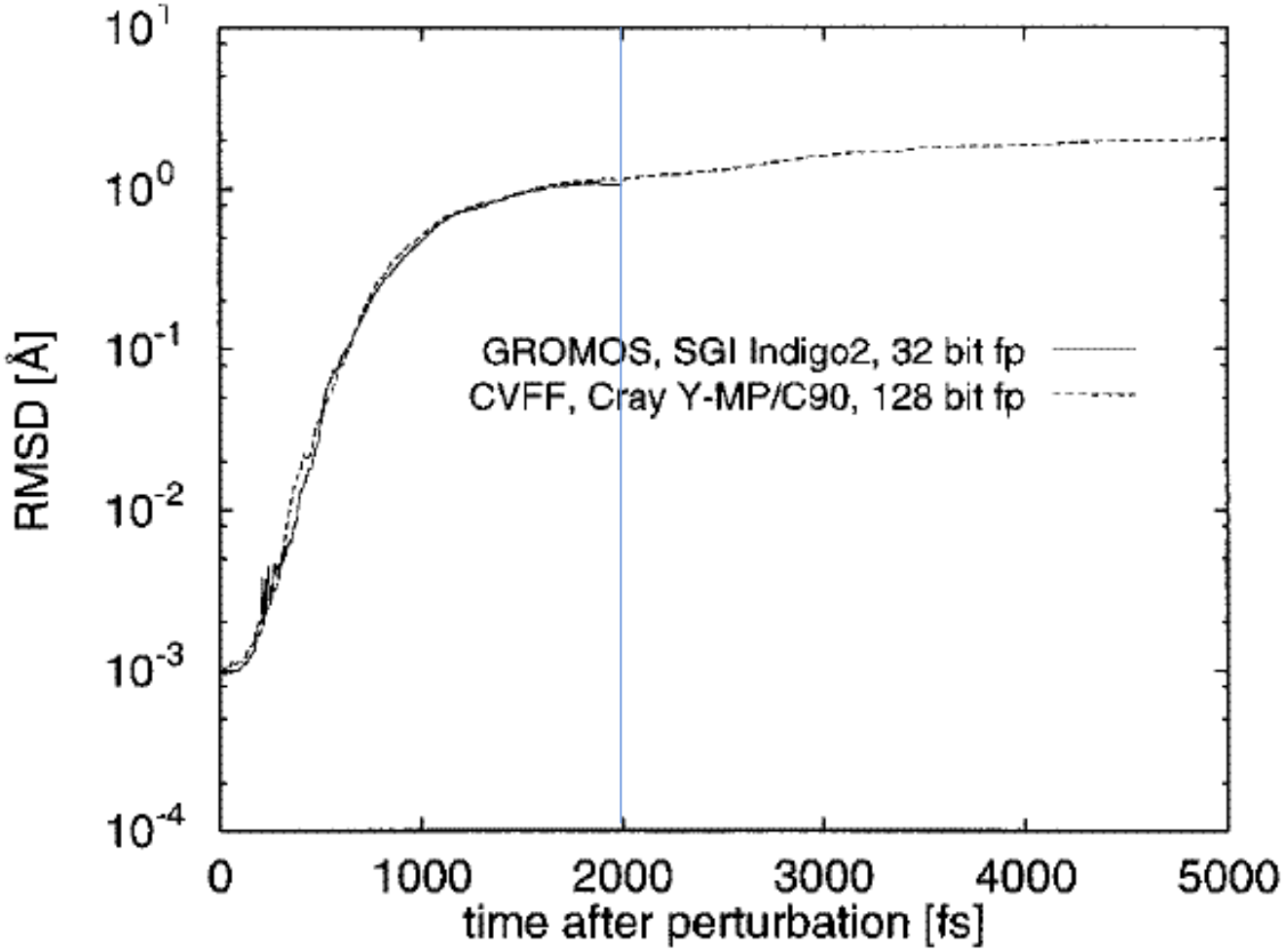


Numerical Stability (1)

- Experiment 1
  - Cray Y-MP
  - Double precision
  - DISCOVER CVFF force field
  - A cutoff radius for non bonded interactions of 8.5 Å in a water box
  - All atom representation

- Experiment 2
  - SGI Indigo2 workstation
  - Single precision
  - GROMOS software and force field
  - Instead of an all-atom representation the GROMOS force field uses a united atom representation for non polar CHx groups.

Numerical Stability (2)



Is MD really numerically Stable?

- It has been a common frustrating experience that **when a computer or a compiler has been slightly changed**, trajectories of MD cannot be reproduced. The chaotic behavior of our system offers an explanation for these experiences.

- Is a simulation of 2ps enough to conclude the stability of MD simulations?

Discussion (1)

1.- Show that MD simulations of protein folding exhibit chaotic behavior

- Individual MD trajectories of folding are too sensitive to small perturbations to have significant predictive quality.
- Single trajectories may provide insight into the type of events possible in a system, but averaging over a number of independent runs is essential to obtain data on event likelihood.

Discussion (2)

2.- Calculate the divergence rate of the system at different stages of the folding process

- Observed a rate of exponential divergence of 1A RMSD

Discussion (3)

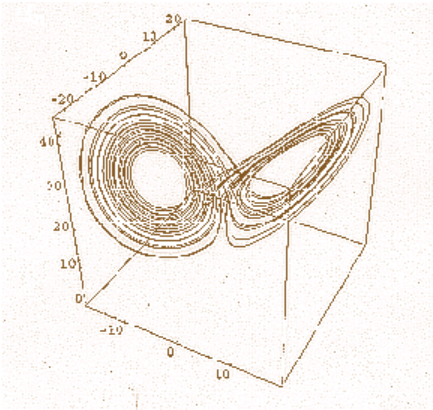
3.- Study the effect of this chaotic behavior on the occurrence of certain folding events

- Given two identical polypeptide chains start to fold at the same time from the same initial conformation, except for one atom differing in position by 10^{-9} Å
- The results of the paper suggest that along the way the folding pathways will rapidly diverge and become significantly distinct.

Transient chaos

- How can reconcile the chaotic nature of the folding trajectory and the fact that all trajectories end at essentially the same folded functional conformation?

- This combination of properties can be found in dissipative systems and is known as *transient chaos.*



Thank you!!