



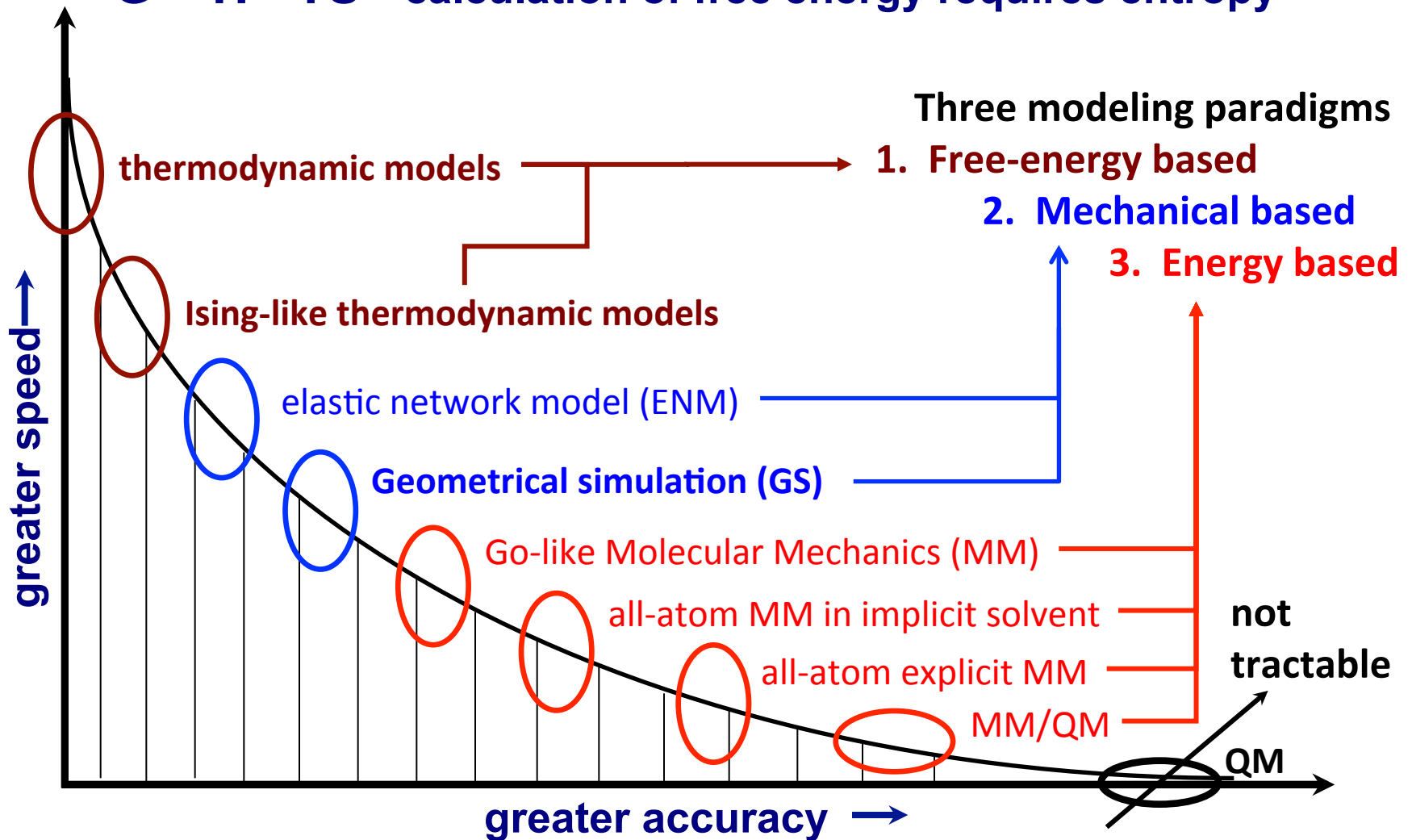
# **Interrelationships Between Protein Stability, Flexibility and Dynamics**

**Donald Jacobs**, Associate Professor  
Department of Physics and Optical Science

# Computational Methods Applied to Proteins

## A comparison of speed versus accuracy tradeoffs

$G = H - TS$  calculation of free energy requires entropy



# Computational Methods Applied to Proteins

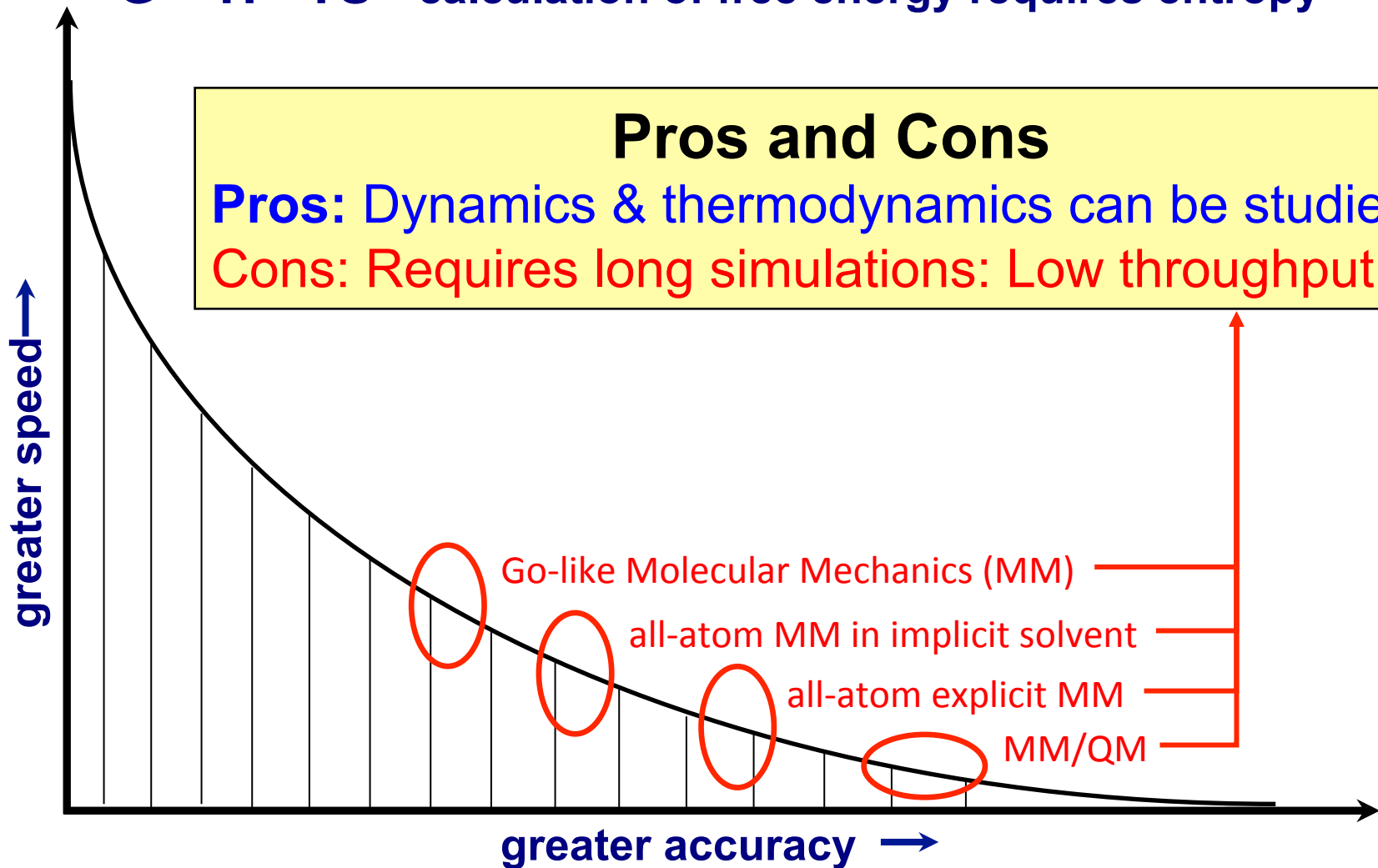
## A comparison of speed versus accuracy tradeoffs

$G = H - TS$  calculation of free energy requires entropy

### Pros and Cons

**Pros:** Dynamics & thermodynamics can be studied

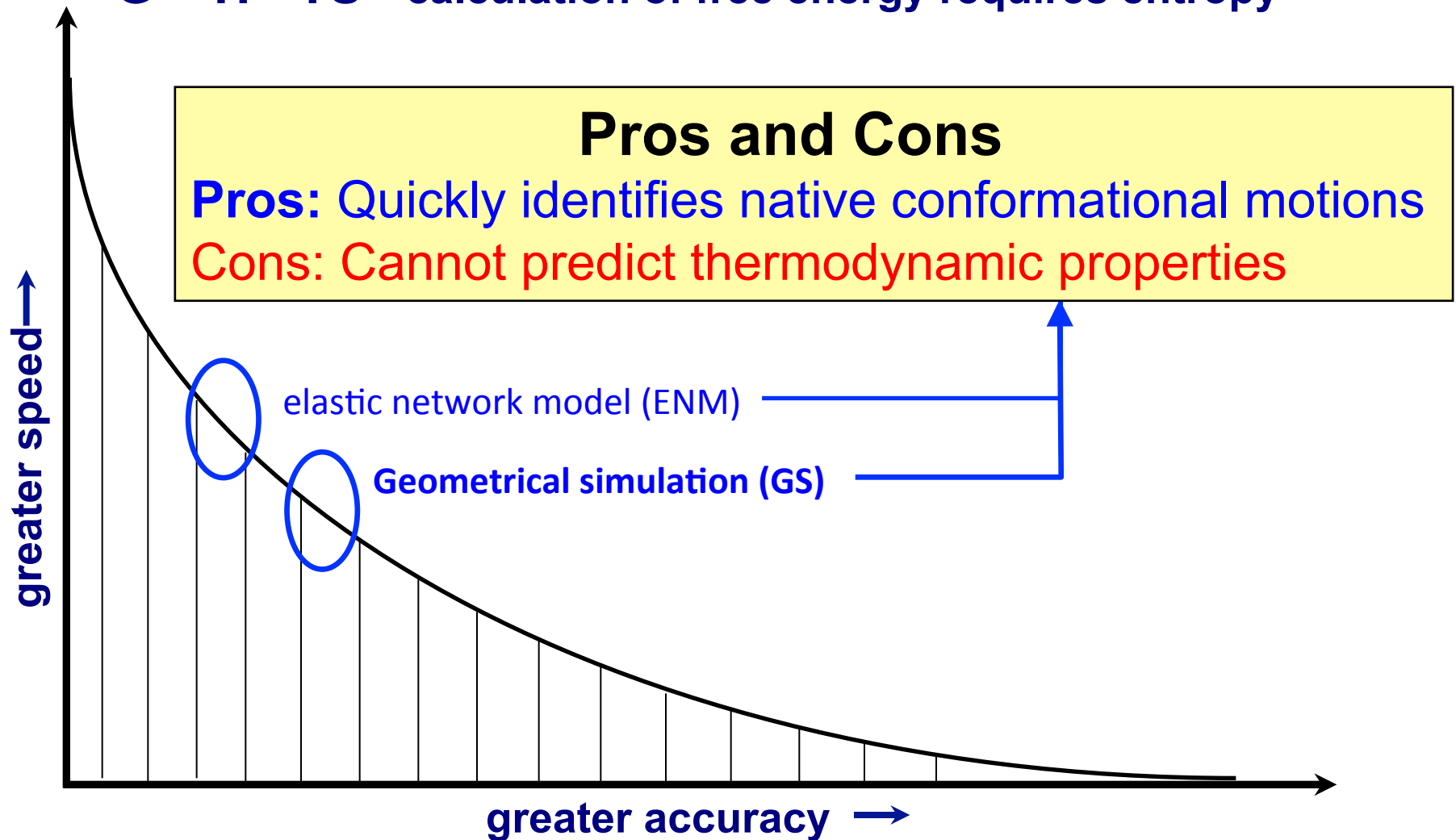
**Cons:** Requires long simulations: Low throughput



# Computational Methods Applied to Proteins

## A comparison of speed versus accuracy tradeoffs

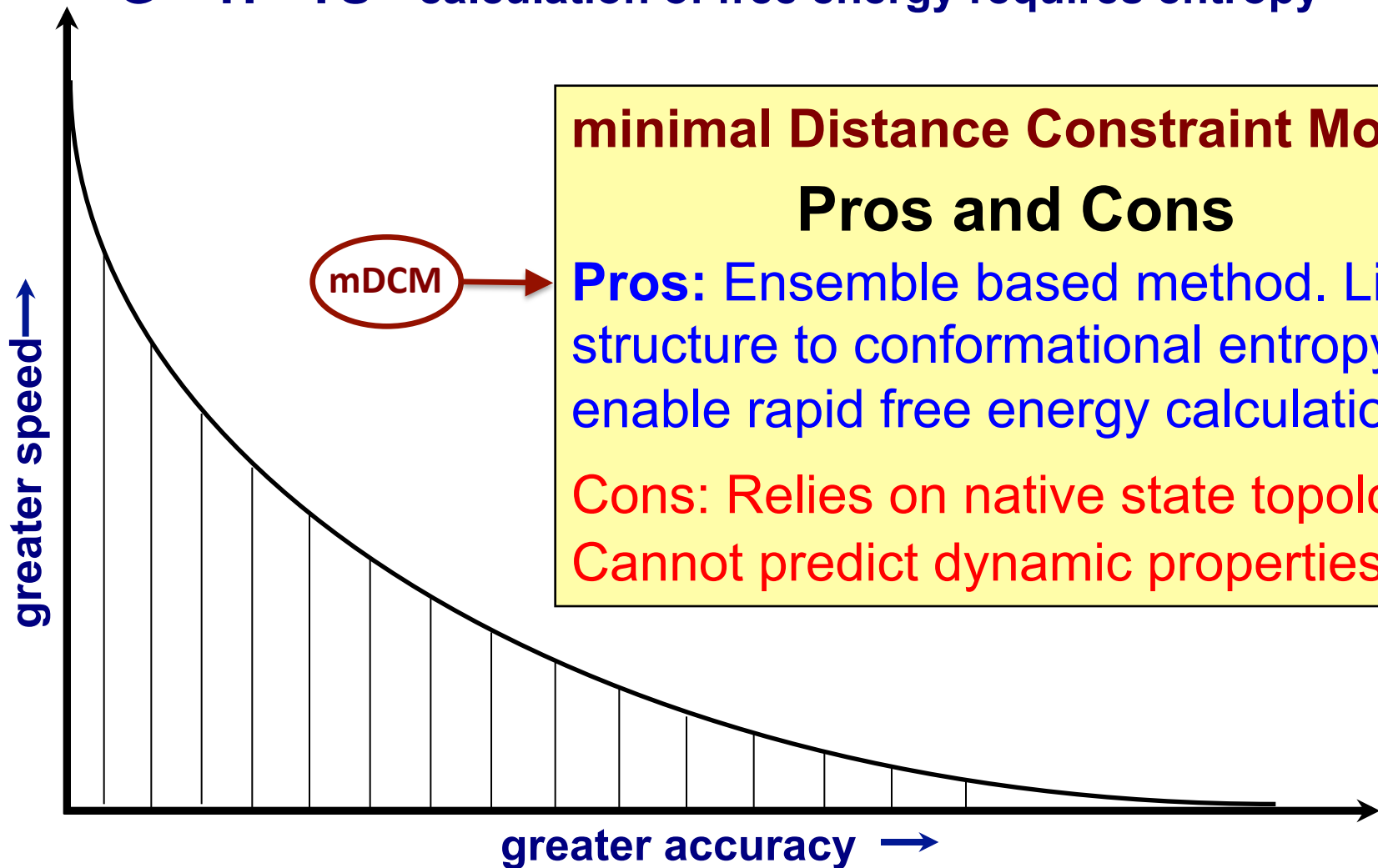
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# Computational Methods Applied to Proteins

## A comparison of speed versus accuracy tradeoffs

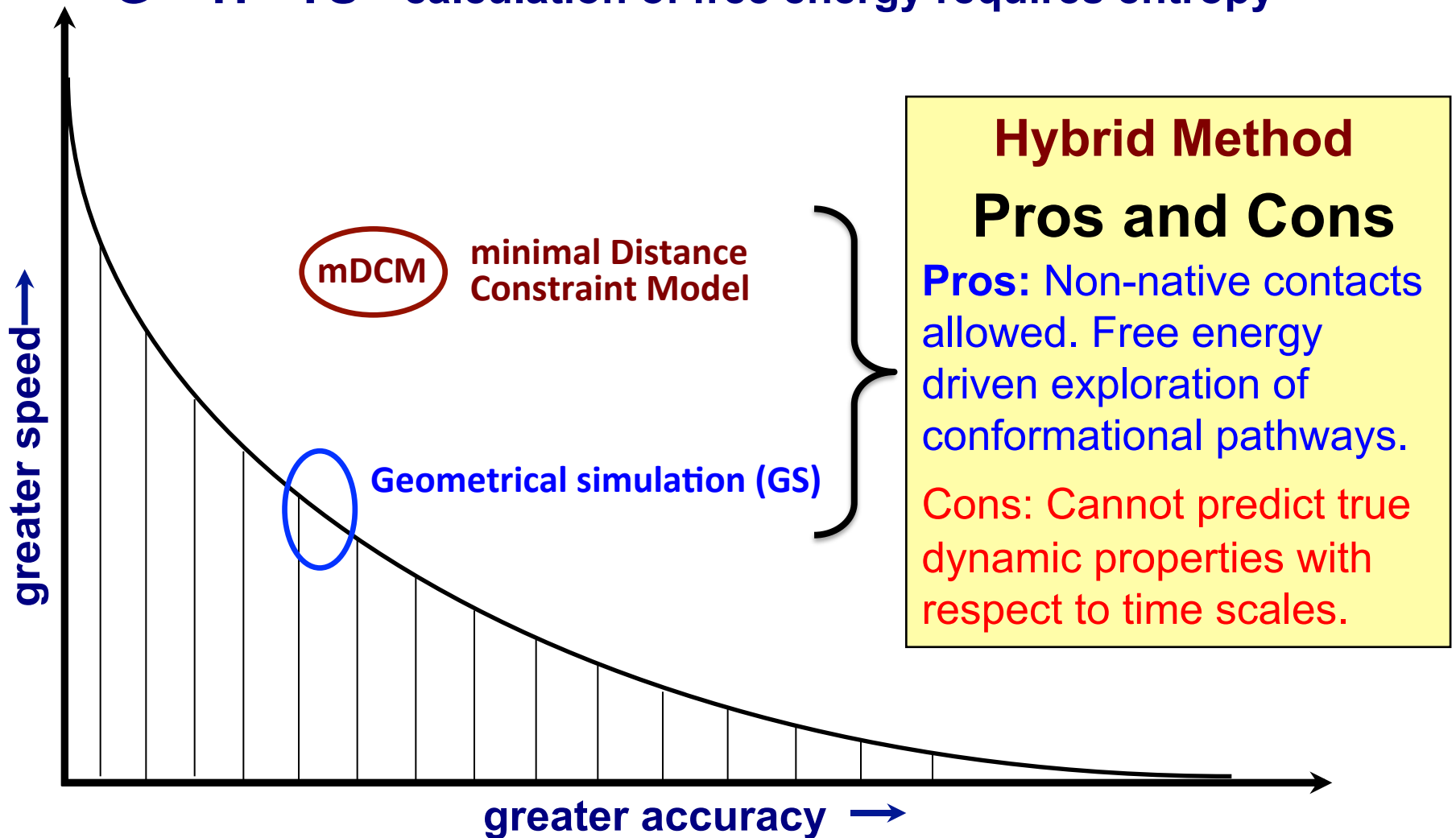
$G = H - TS$  calculation of free energy requires entropy



# Computational Methods Applied to Proteins

## A comparison of speed versus accuracy tradeoffs

$G = H - TS$  calculation of free energy requires entropy



**Protein Dynamics is Linked to Rigidity and Stability**

**Merging geometrical and topological properties**

**Free Energy Driven  
Geometrical Simulation  
of Protein Dynamics**

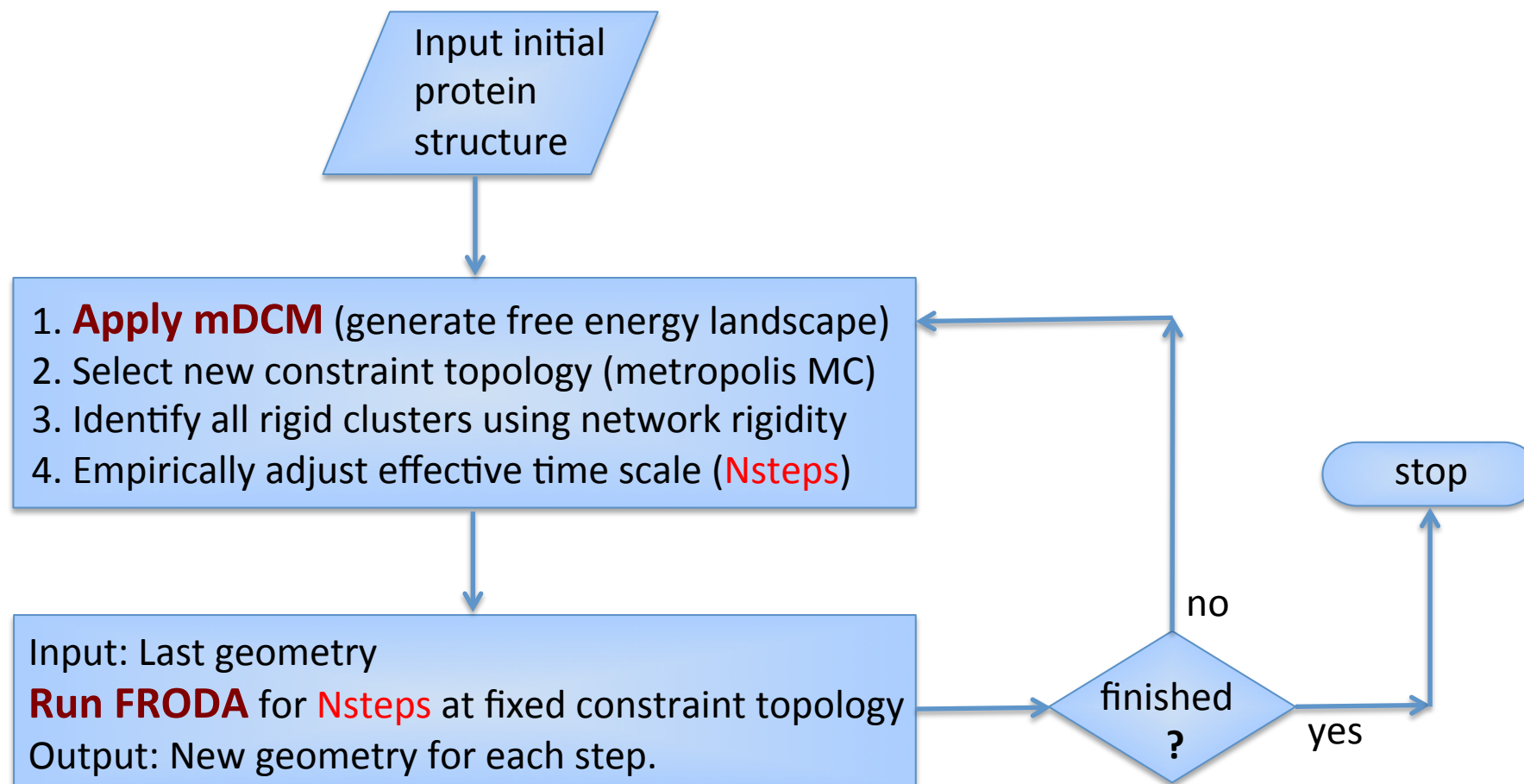
**Geometrical Simulation compared to Molecular Dynamics and Elastic Networks:**

C. David and D.J. Jacobs, *Characterizing protein motions from structure*,  
J. Mol. Graph Model, **31**:41-56 (2011)

# New Hybrid Model

## Combining mDCM with GS

### High Level Overview

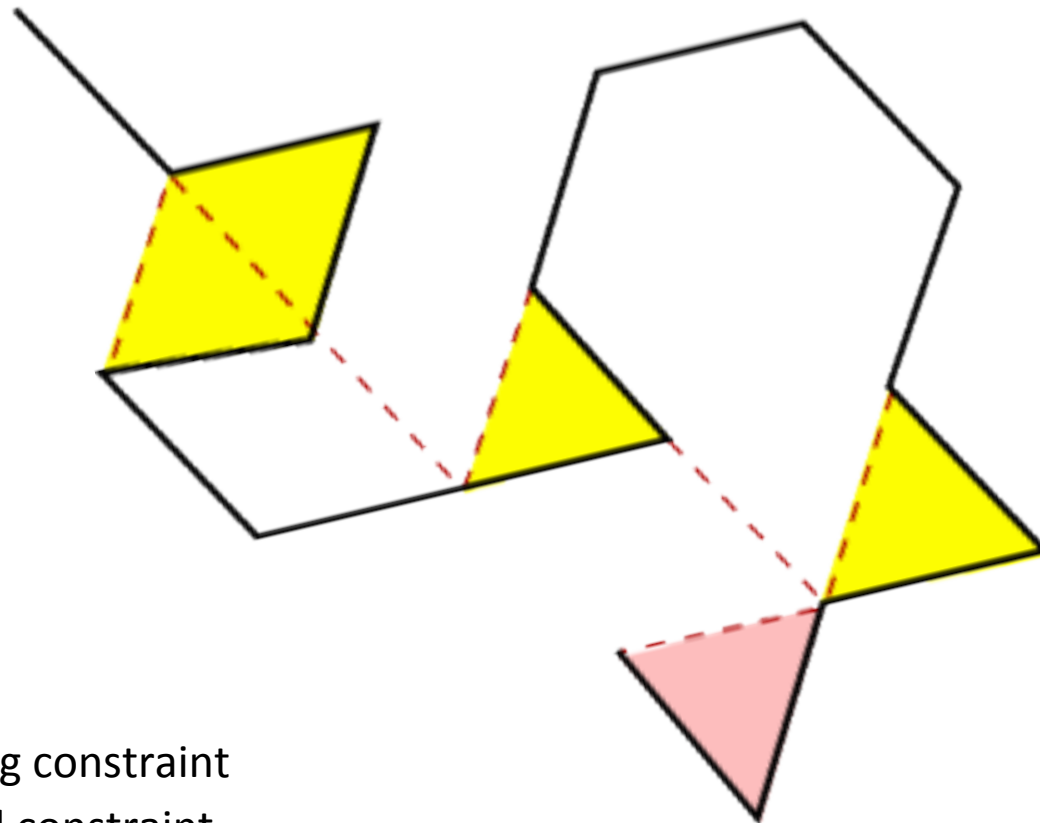




# New Hybrid Model

## Two dimensional example

**mDCM:** Determines **new constraint topology** for **fixed geometry**



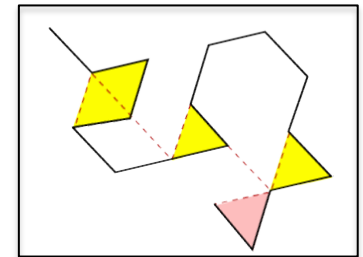
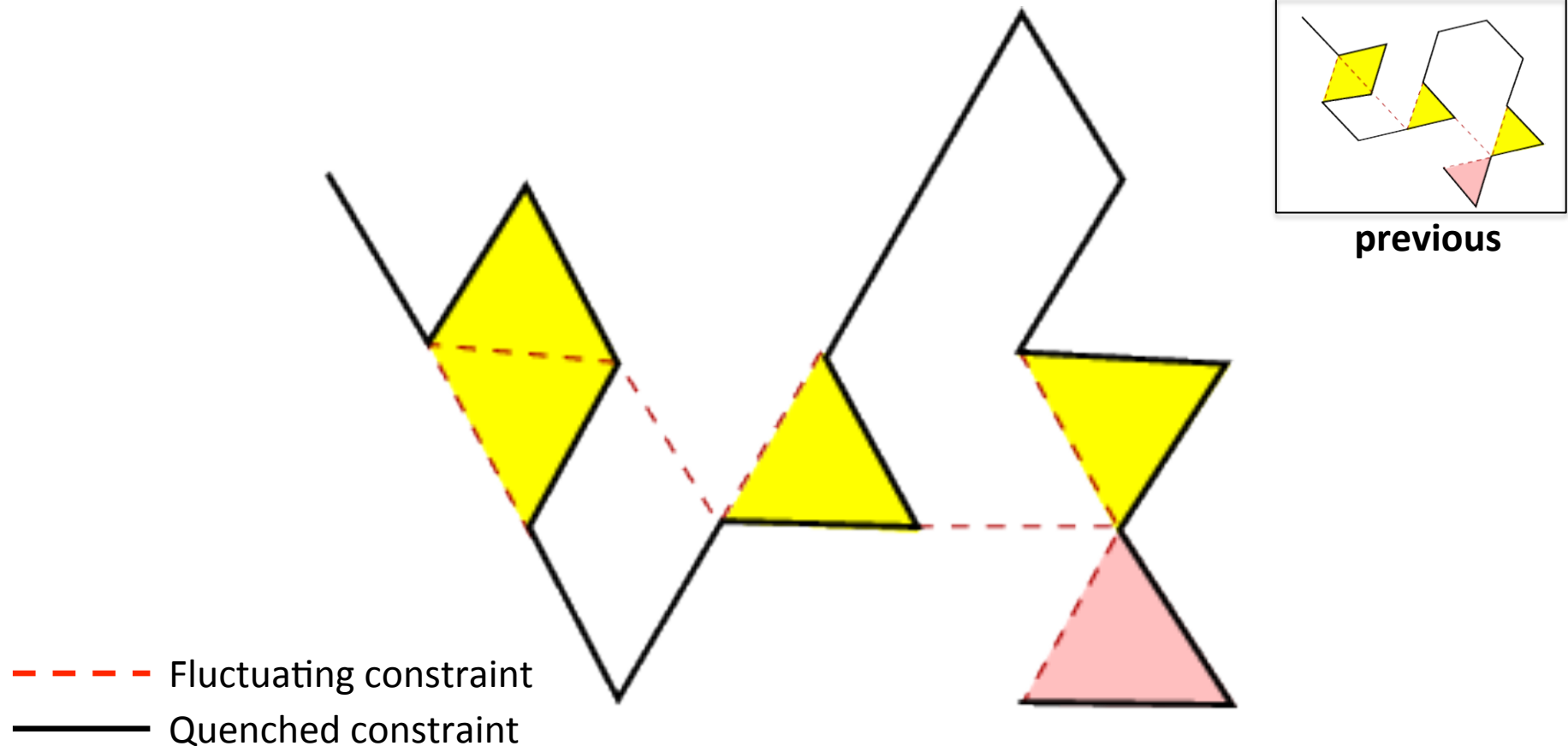
- - - - Fluctuating constraint
- Quenched constraint

**Pink** and **yellow** shaded regions highlight rigid clusters with 3 atoms or more.

# New Hybrid Model

## Two dimensional example

**GS:** Determines **new geometry** for **fixed constraint topology**



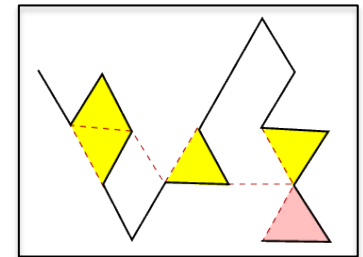
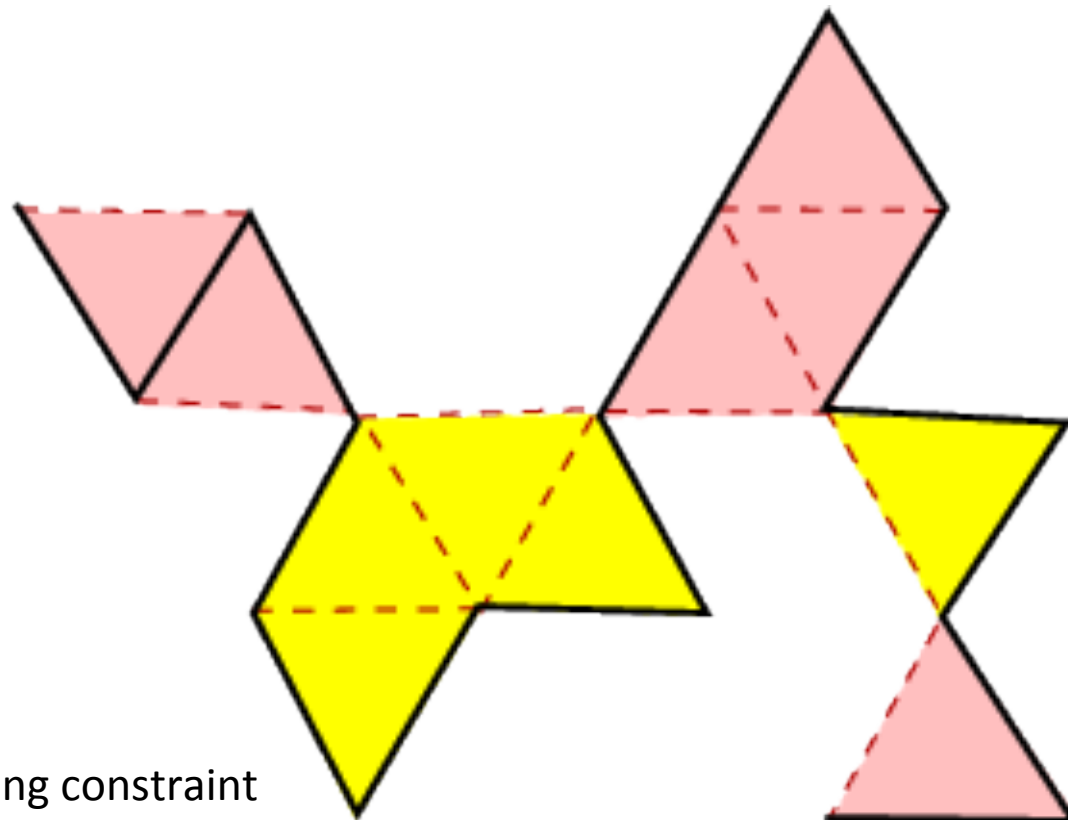
previous

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# New Hybrid Model

## Two dimensional example

**mDCM:** Determines **new constraint topology** for **fixed geometry**



previous

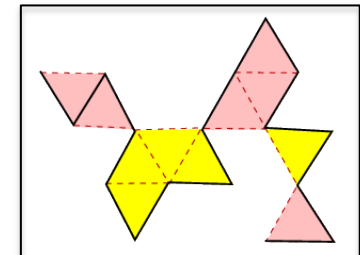
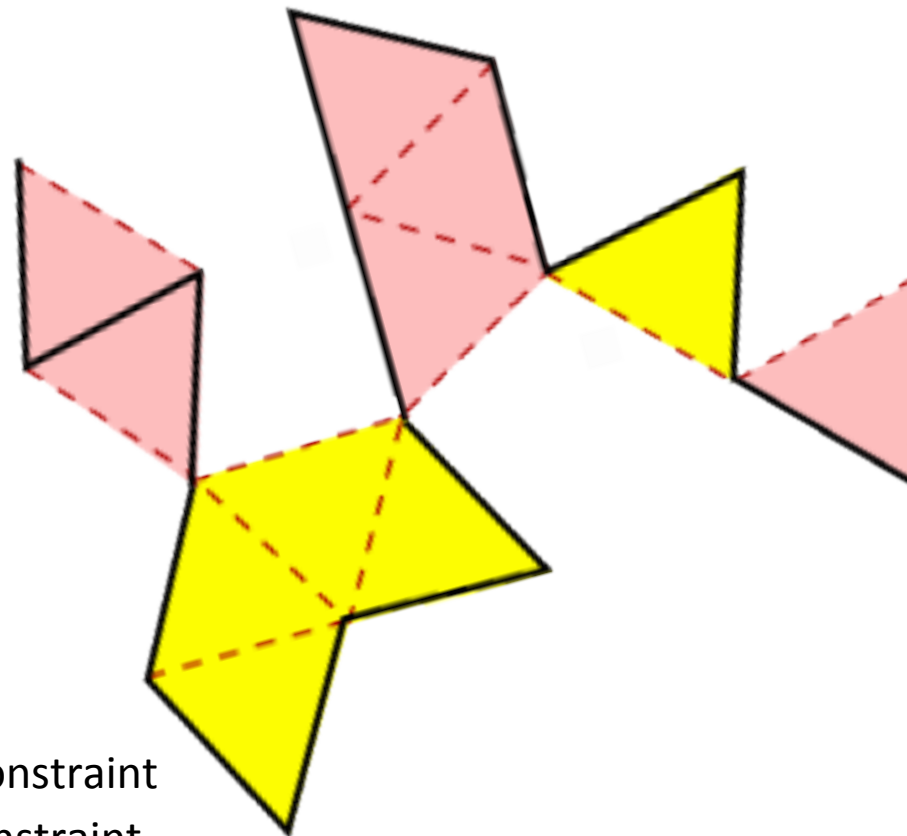
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# New Hybrid Model

## Two dimensional example

**GS:** Determines **new geometry** for **fixed constraint topology**



previous

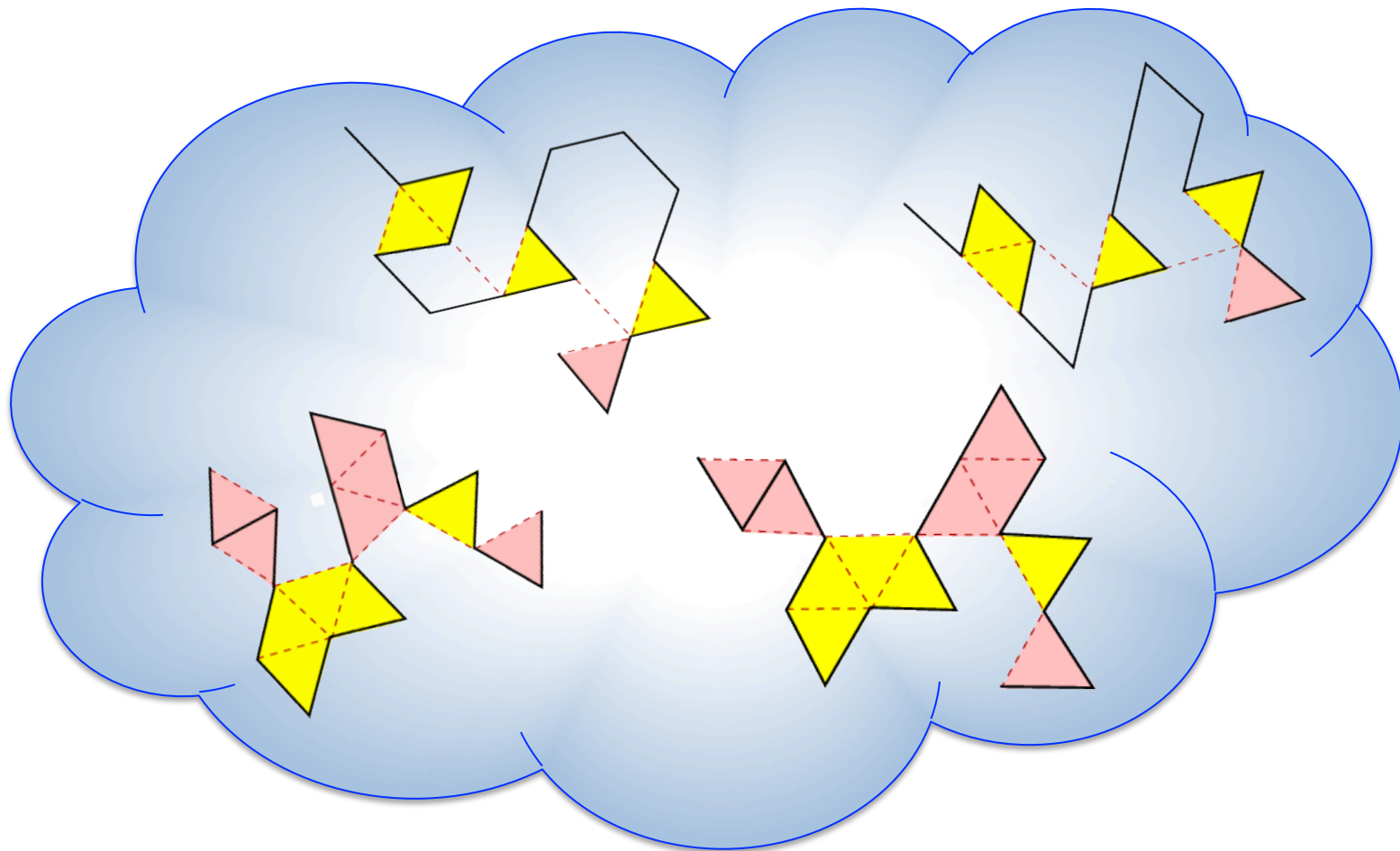
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# New Hybrid Model

## Two dimensional example

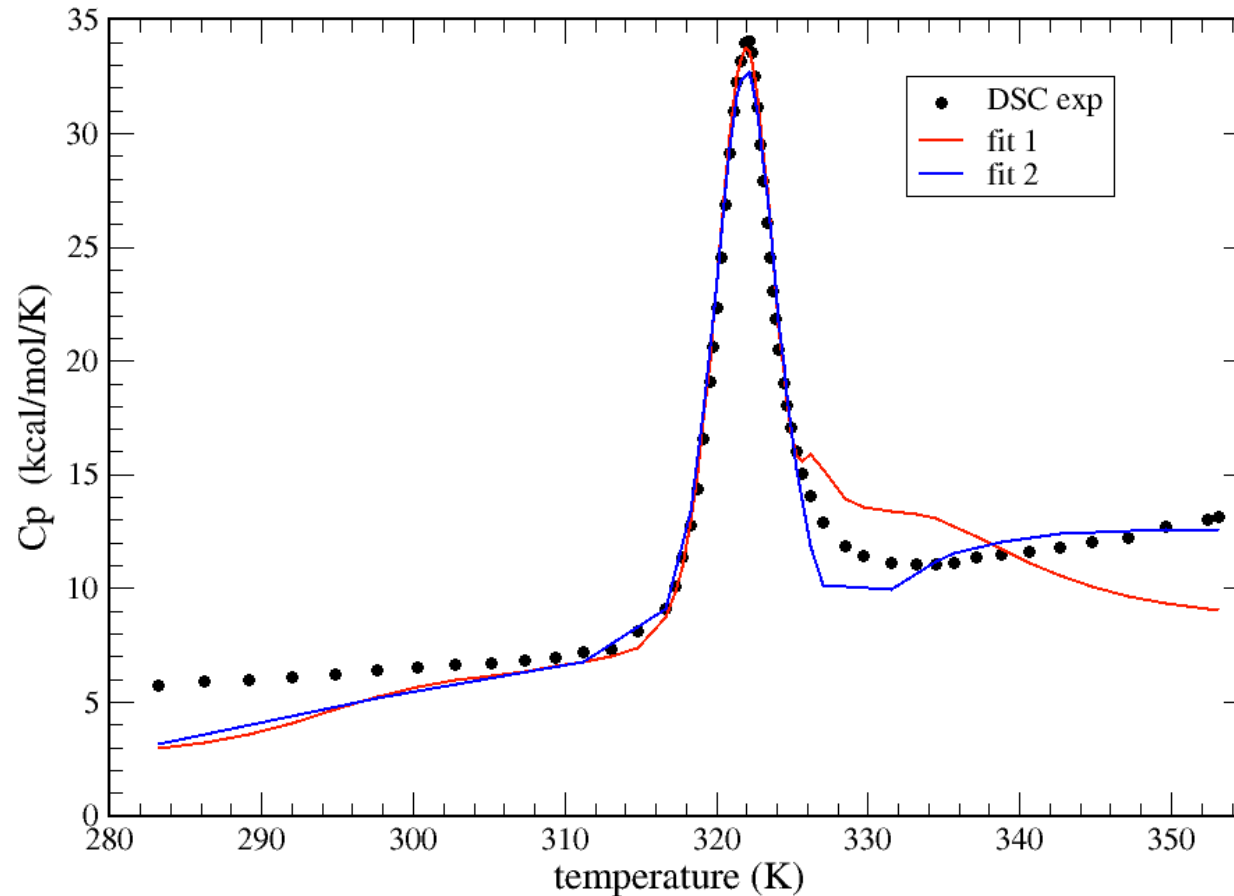
An ensemble over constraint topology and conformation is generated that contains native and non-native contacts, driven by free energy!



# Results

Protein example: (adenylate kinase: 1ake.pdb)

## Thermodynamic Properties



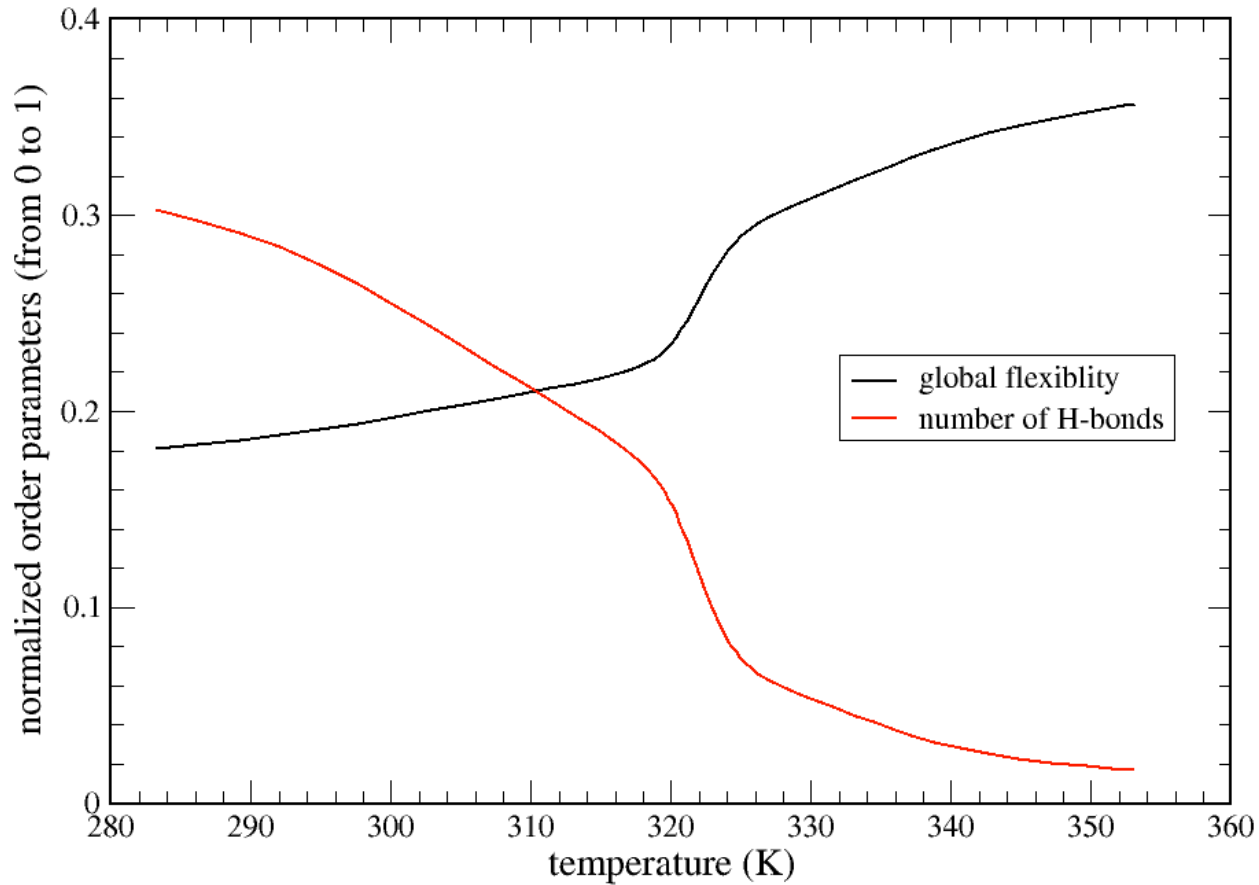
Both fits result in virtually the same parameterization.

Heat capacity curve measured by Jorg Rösgen, Penn State University, College of Medicine

# Results

Protein example: (adenylate kinase: 1ake.pdb)

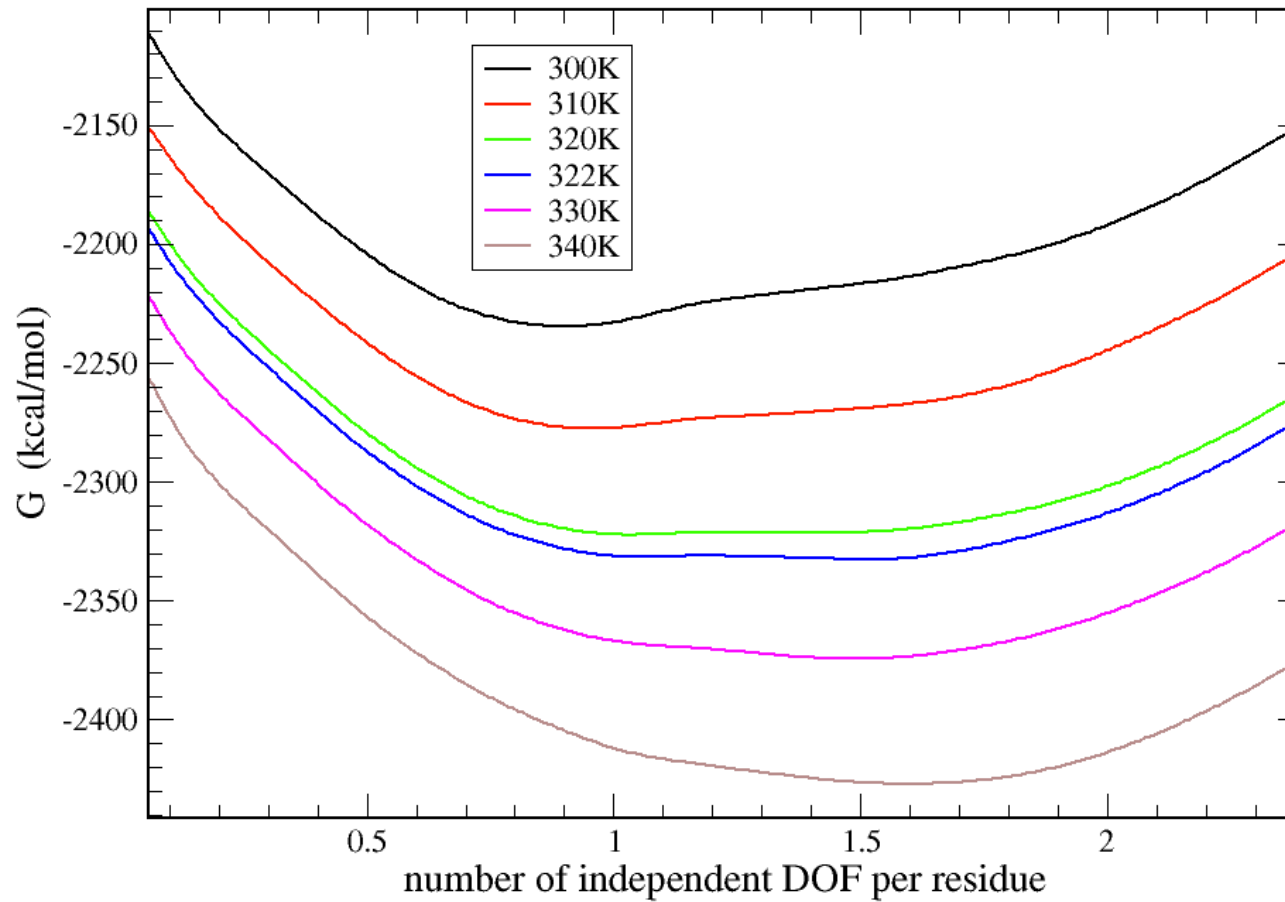
## Thermodynamic Properties



# Results

Protein example: (adenylate kinase: 1ake.pdb)

## Thermodynamic Properties

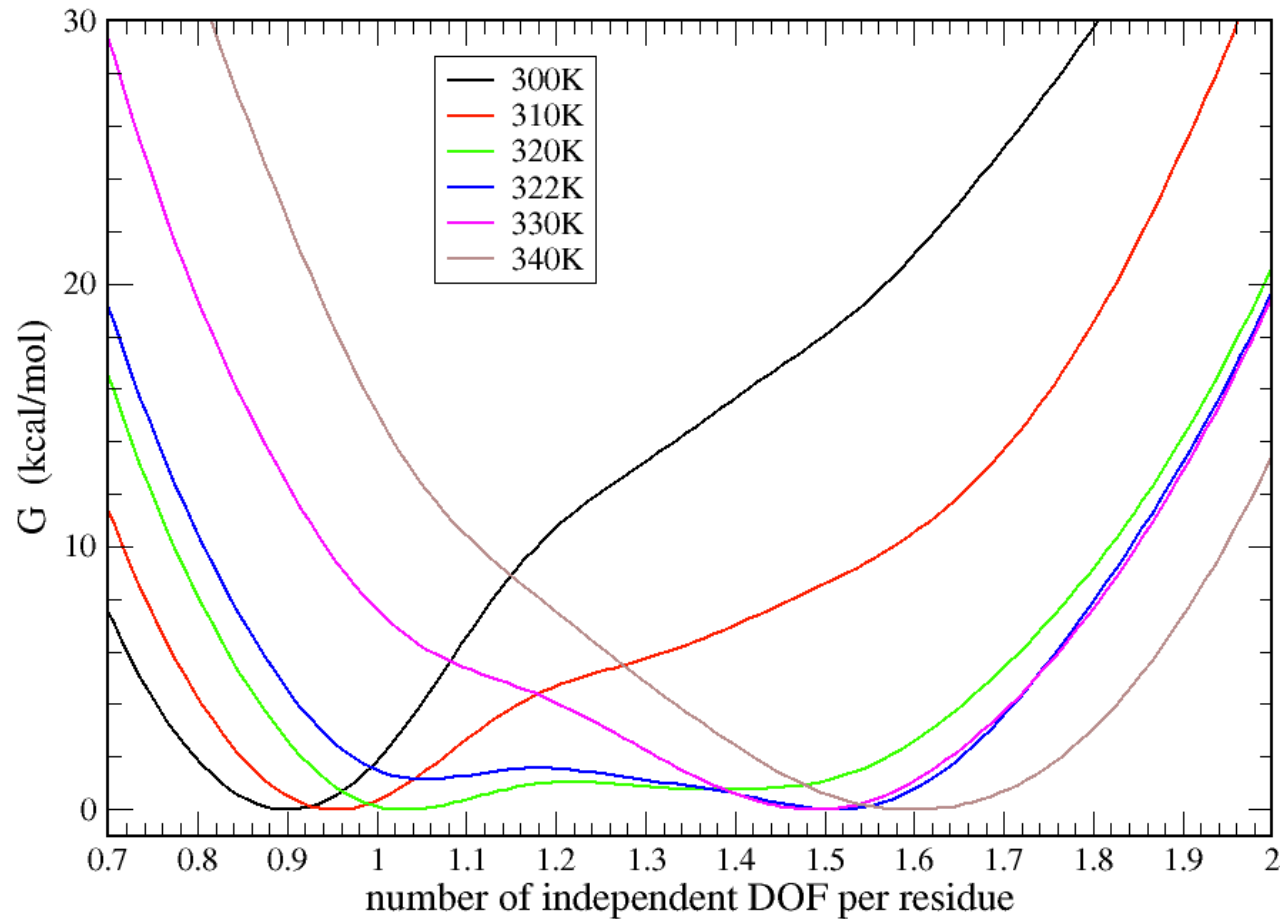




# Results

Protein example: (adenylate kinase: 1ake.pdb)

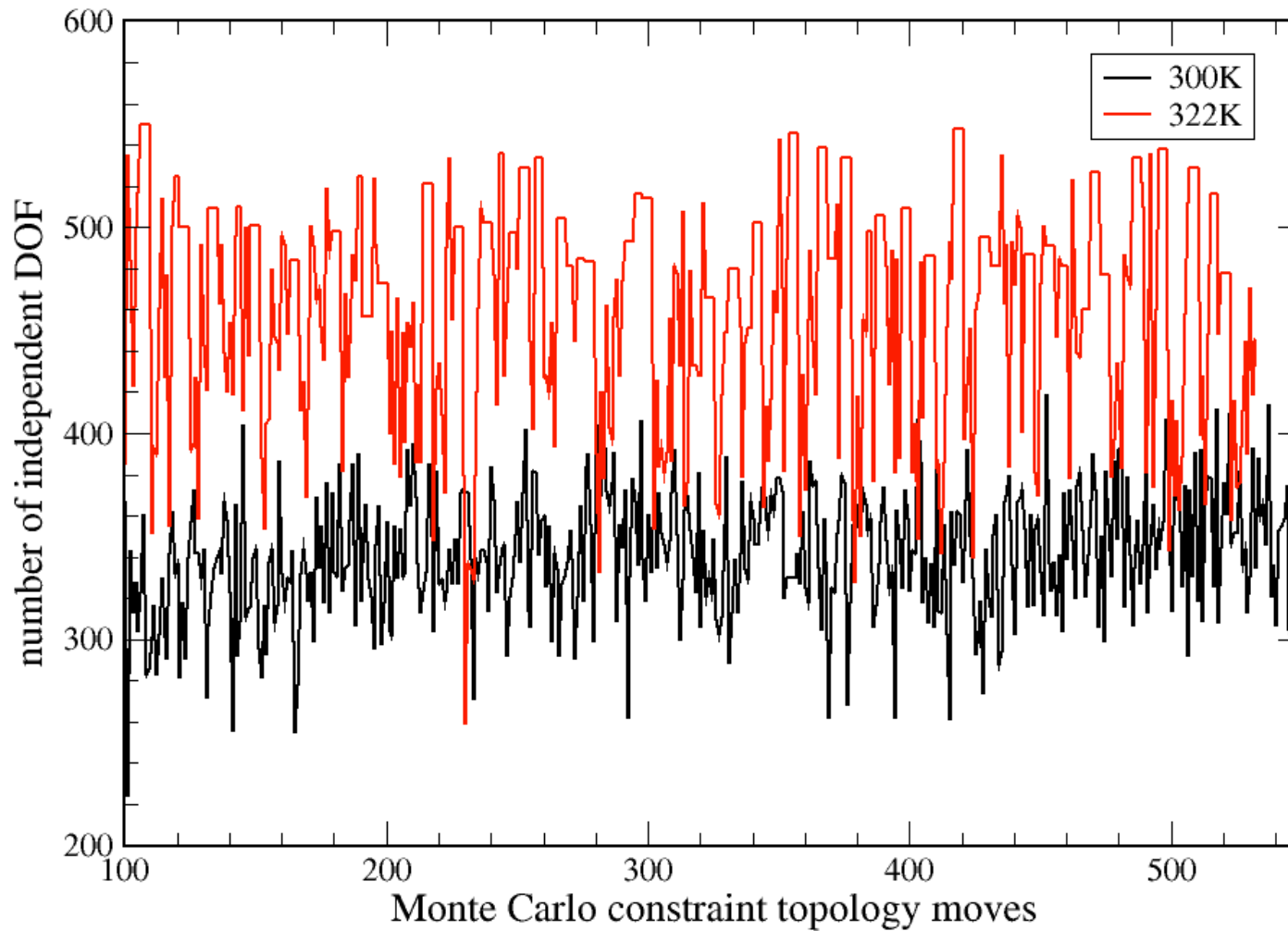
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# Results

Protein example: (adenylate kinase: 1ake.pdb)

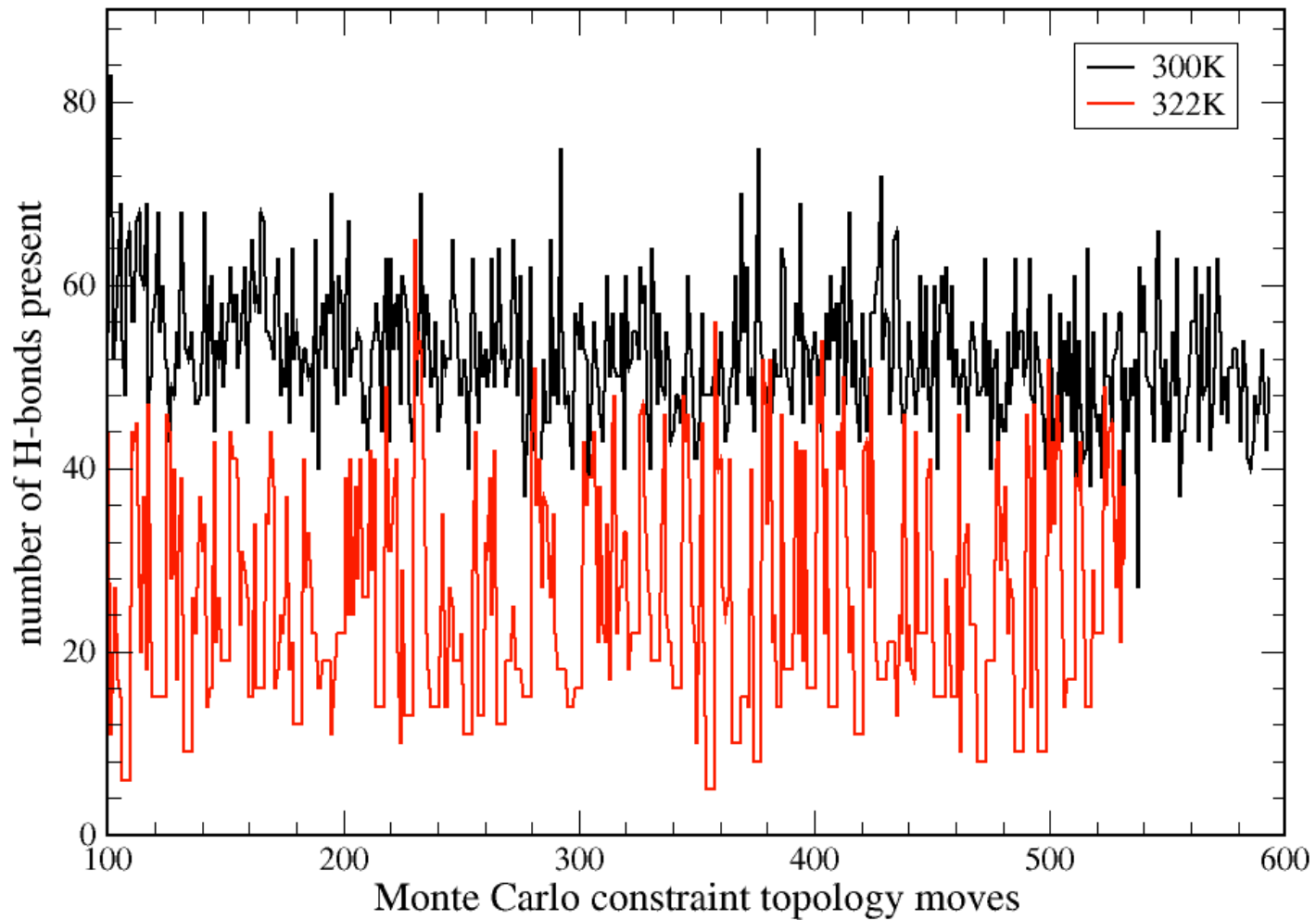
## Dynamic Properties



# Results

Protein example: (adenylate kinase: 1ake.pdb)

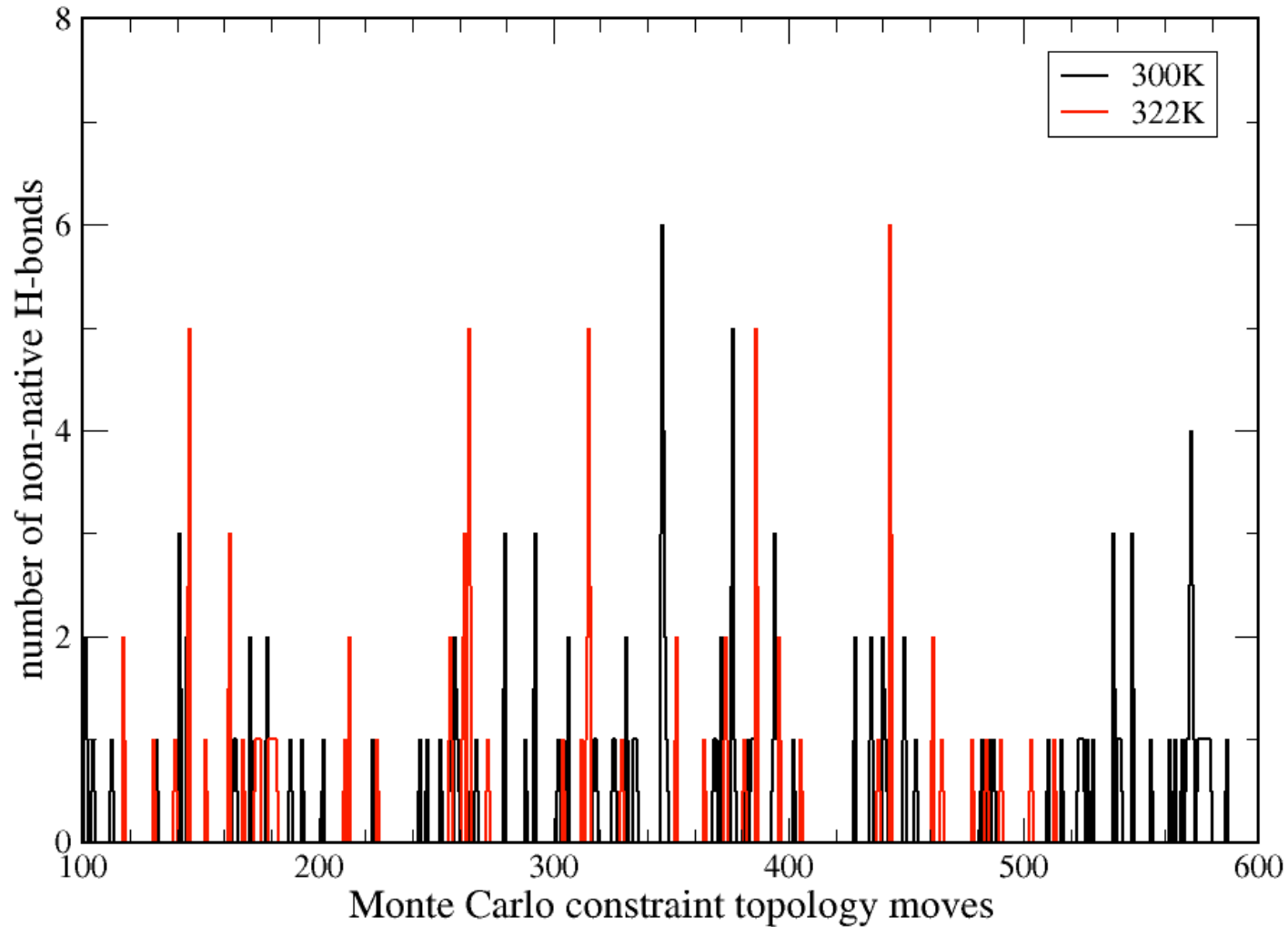
## Dynamic Properties



# Results

Protein example: (adenylate kinase: 1ake.pdb)

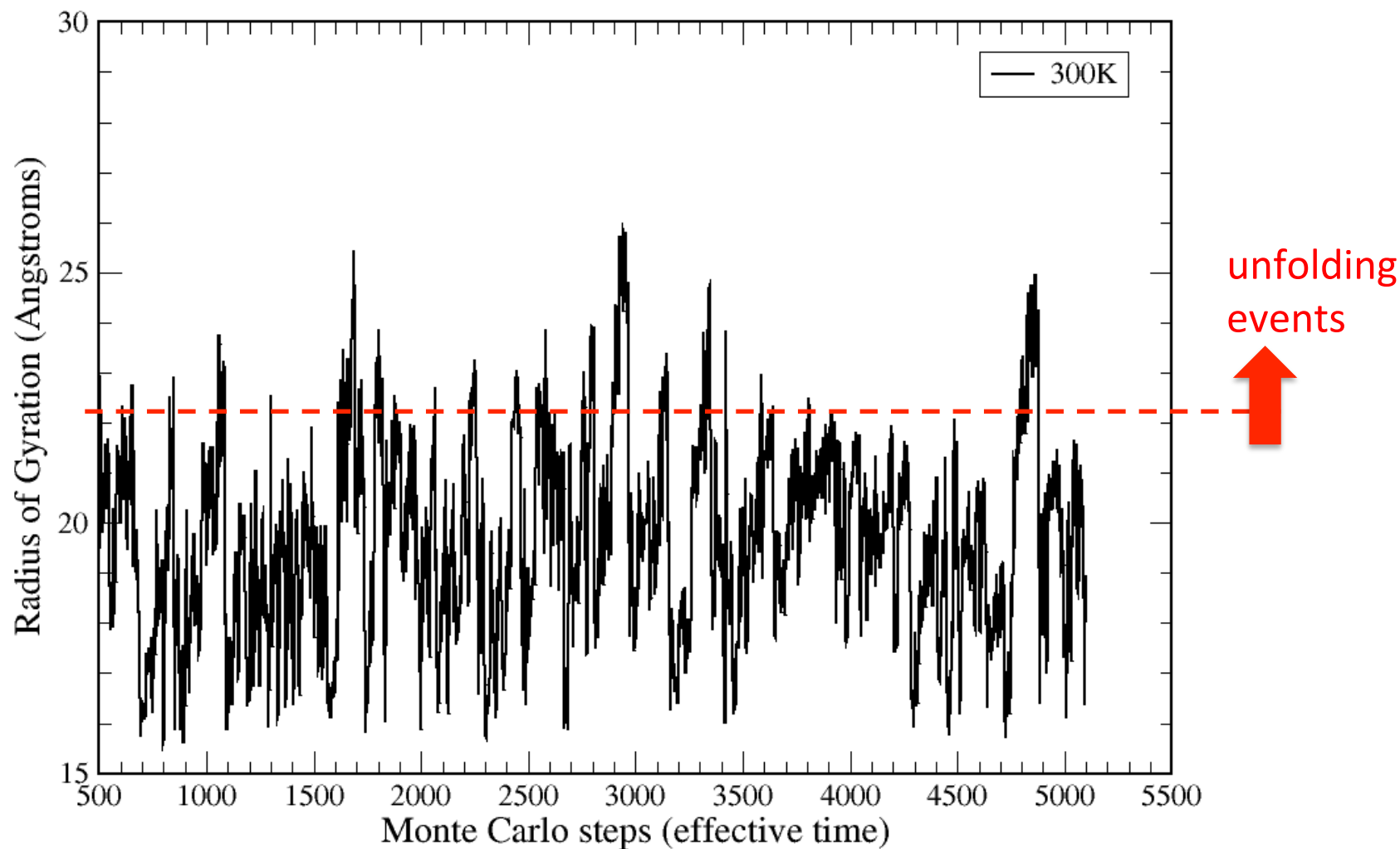
## Dynamic Properties



# Results

Protein example: (adenylate kinase: 1ake.pdb)

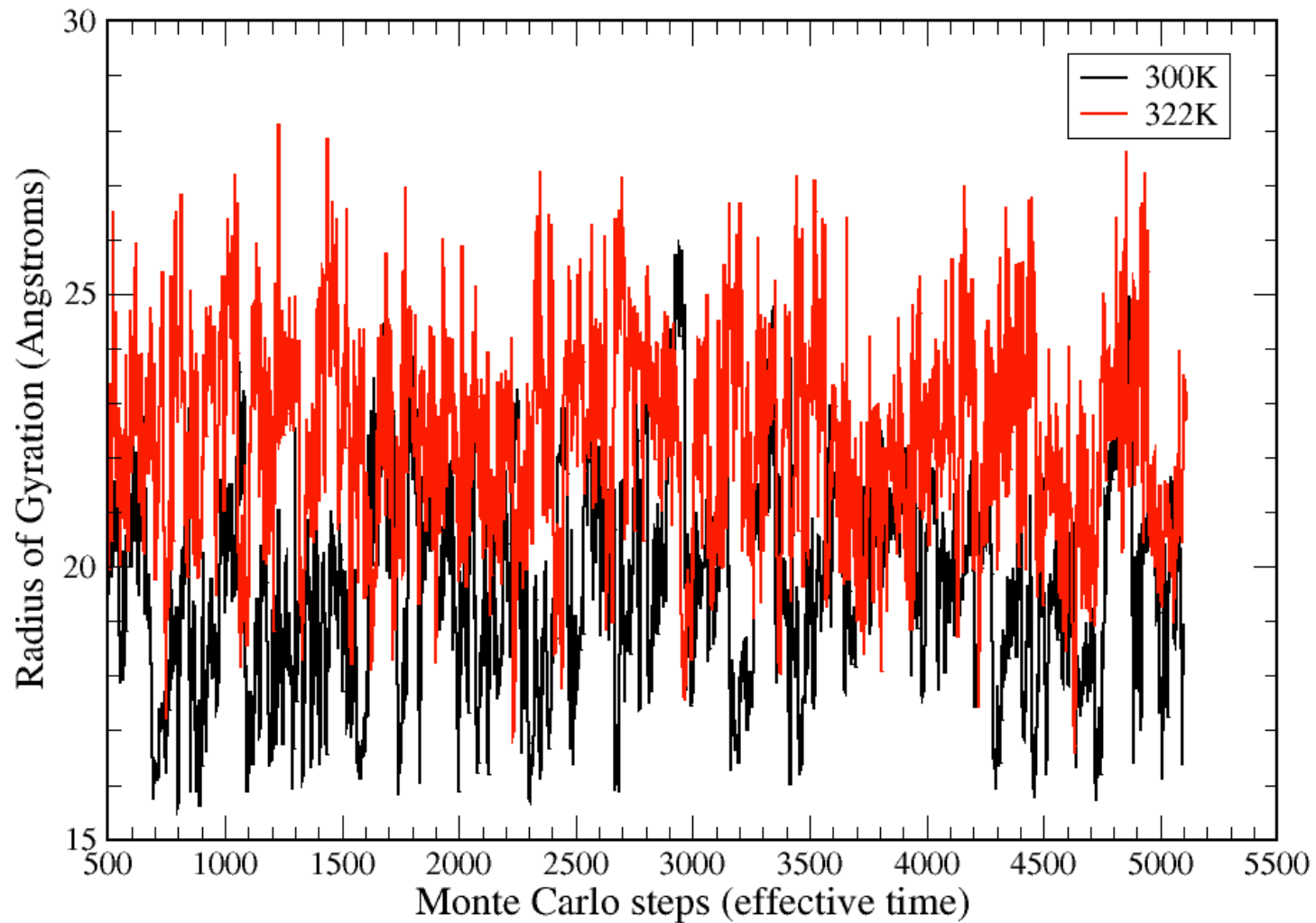
## Dynamic Properties



# Results

Protein example: (adenylate kinase: 1ake.pdb)

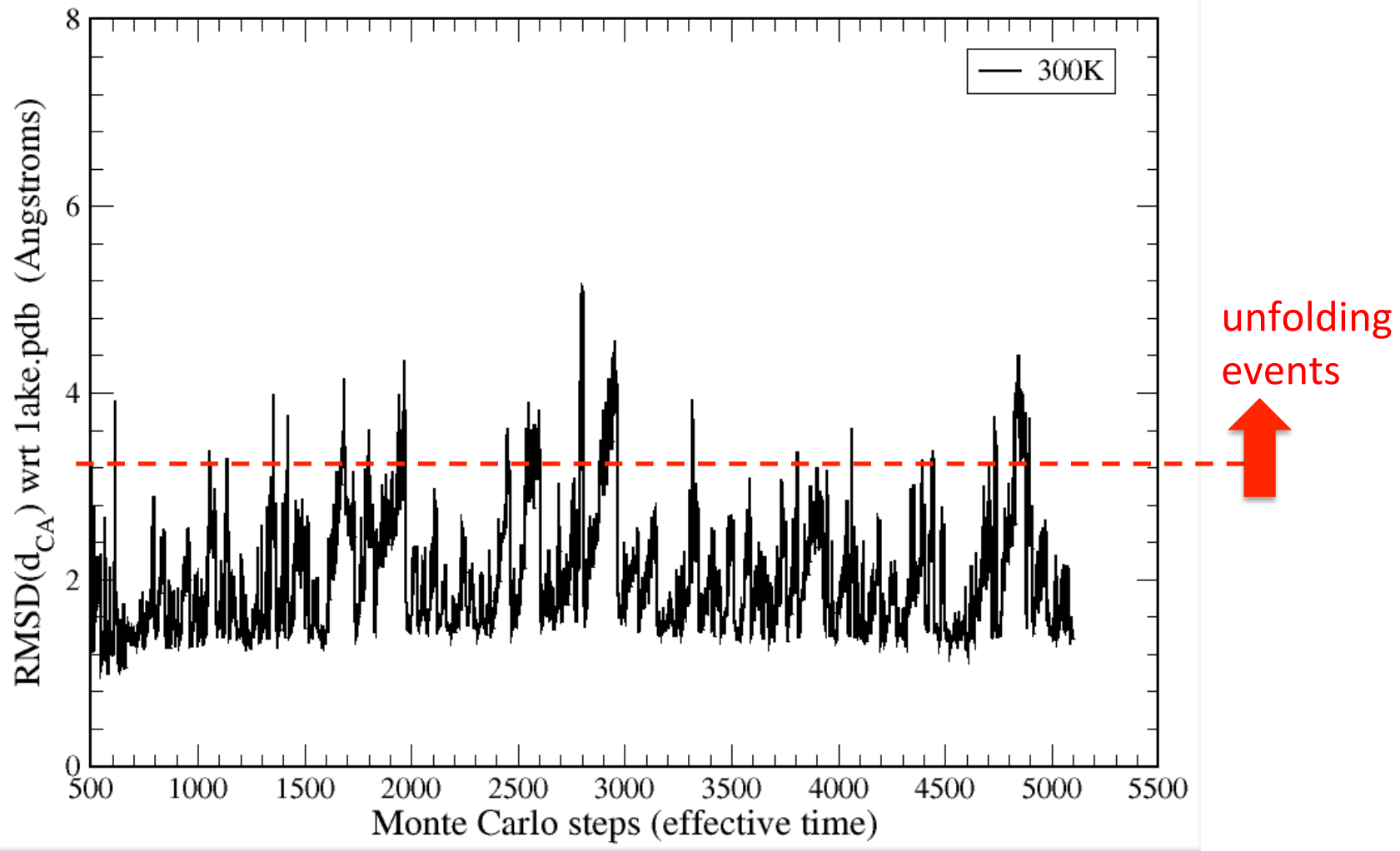
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## Dynamic Properties

