2.3- Dynamics

Biophysics – Bioinformatics

Outline

- Conformational ensembles
- Obtaining ensembles
  - Experiment
  - (Molecular mechanics)
  - Monte-Carlo simulations
  - Molecular dynamics simulations
- Using ensembles

Conformational ensembles

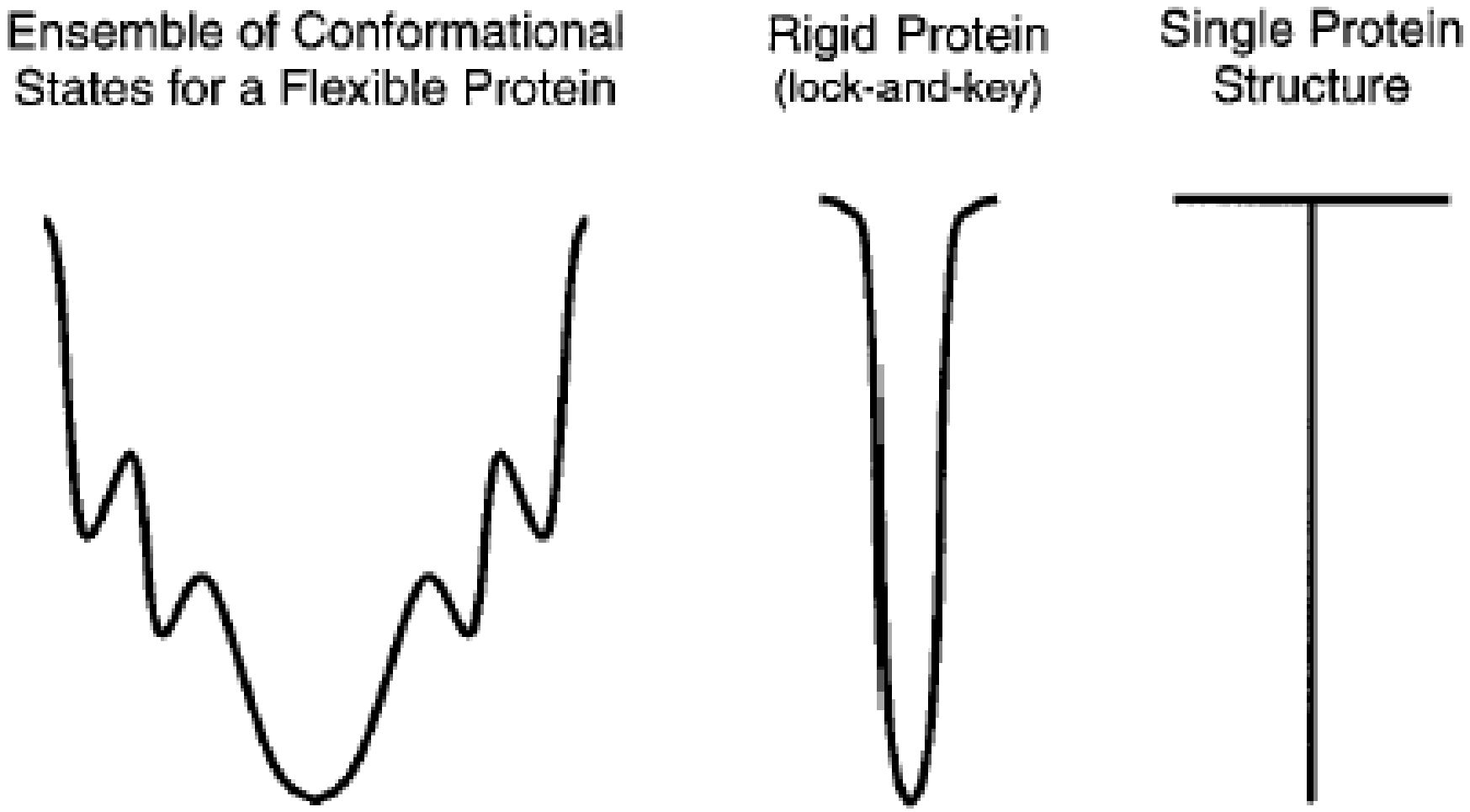
- "Ensemble": set of structures that represents ALL possible microscopic states of the system

- Thermodynamics can be deduced from the average of "ensemble" properties.

- Ensembles help to understand macromolecules behaviour
  - Induced fit *vs* conformational selection

- Types of ensembles
  - Microcanonical ensemble (NVE)
  - **Canonical ensemble (NVT)**
  - **Isothermal-isobaric ensemble (NPT)**
  - Isoenthalpic-isobaric ensemble (NPH)
  - Grand canonical ensemble (μVT)

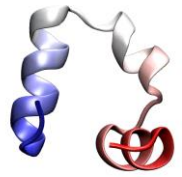
N: Constant Number of particles
P: Constant Pressure
T: Constant Temperature



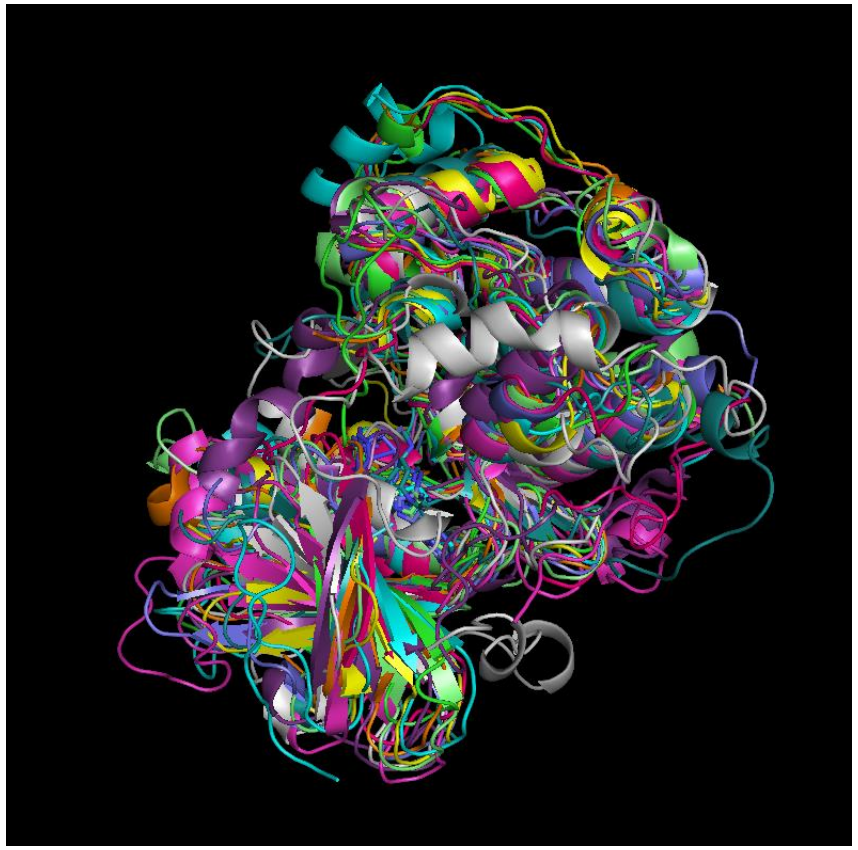
Carlson H.A. & McCammon J.A. (1999) Mol. Pharmacol. 57, 213-218

Obtaining ensembles

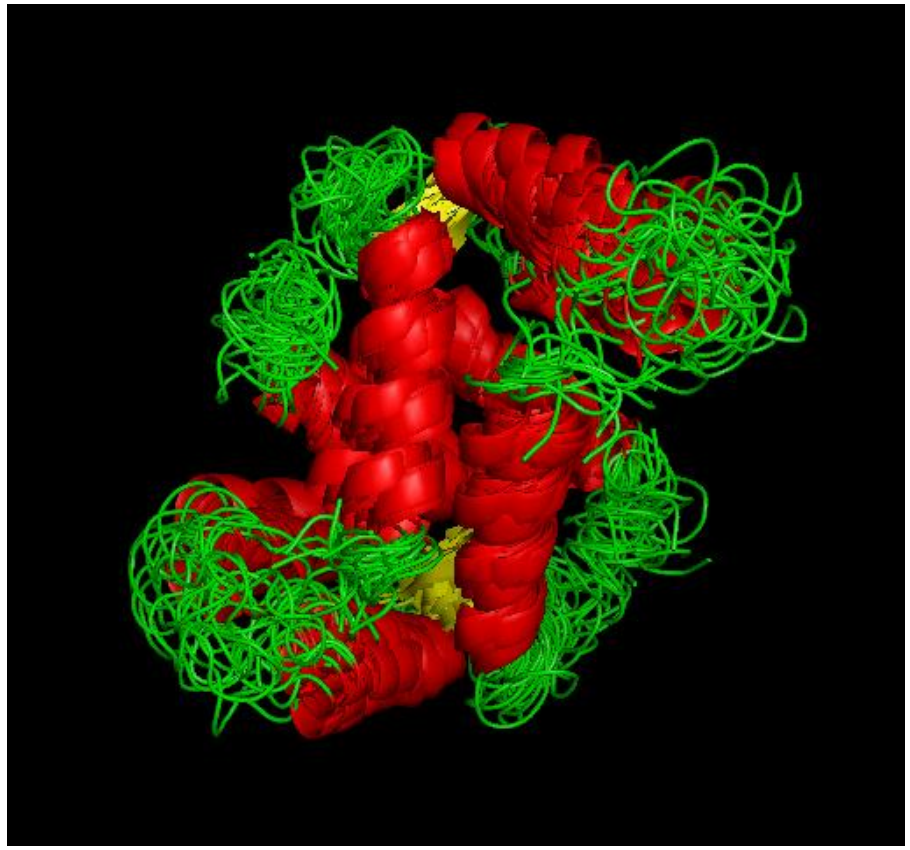
- Experimental
  - PDB analysis
  - RMN, SAXS
  - Protein Ensemble Database
- Theoretical
  - Simulation
    - Molecular dynamics
    - Monte-Carlo



Experimental ensembles



Xray: 1CM8 and other Prot. Kinases



RMN: 1A03. Ca^{2+} Binding protein

PED

Browse Help About Feedback Deposition

Welcome to the **Protein Ensemble Database**

The Protein Ensemble Database (PED) is an open access database for the deposition of structural ensembles, including intrinsically disordered proteins (IDPs). Manually curated data of structural ensembles measured with nuclear magnetic resonance spectroscopy, small-angle X-ray scattering, fluorescence resonance energy transfer are annotated in PED. The deposition of structural coordinates can be used for the evaluation of the ensembles, thus supporting the evolution of new modeling methods leading to much improved skills of connecting the characteristic "lack of structure" of IDPs with function. Each entry in PED corresponds to the primary experimental data and to the structural ensembles associated with these data.

To deposit new structural ensembles into PED, please read the info for data owners.

Search in PED ... Search

Examples Yeast SIC1 MeV Nucleoprotein

How to cite

PED in 2021: a major update of the Protein Ensemble Database for intrinsically disordered proteins Lazar et al., (2021) *Nucleic Acids Research*, 49 (D1) pp. D404-D411. **PubMed**, **NAR**

Info

Funding

This database is part of a project that has received funding from the

Statistics

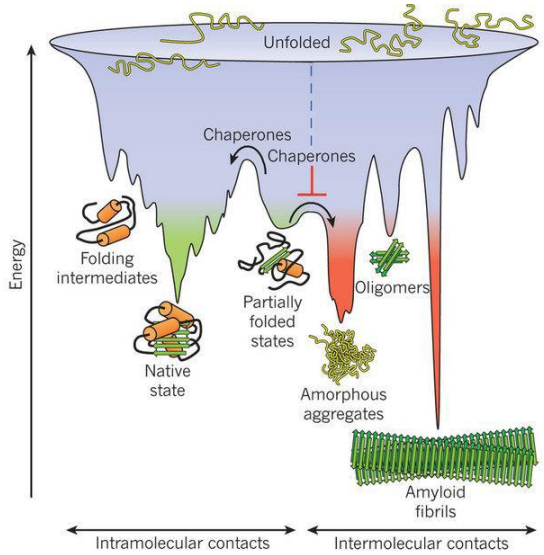
Social media

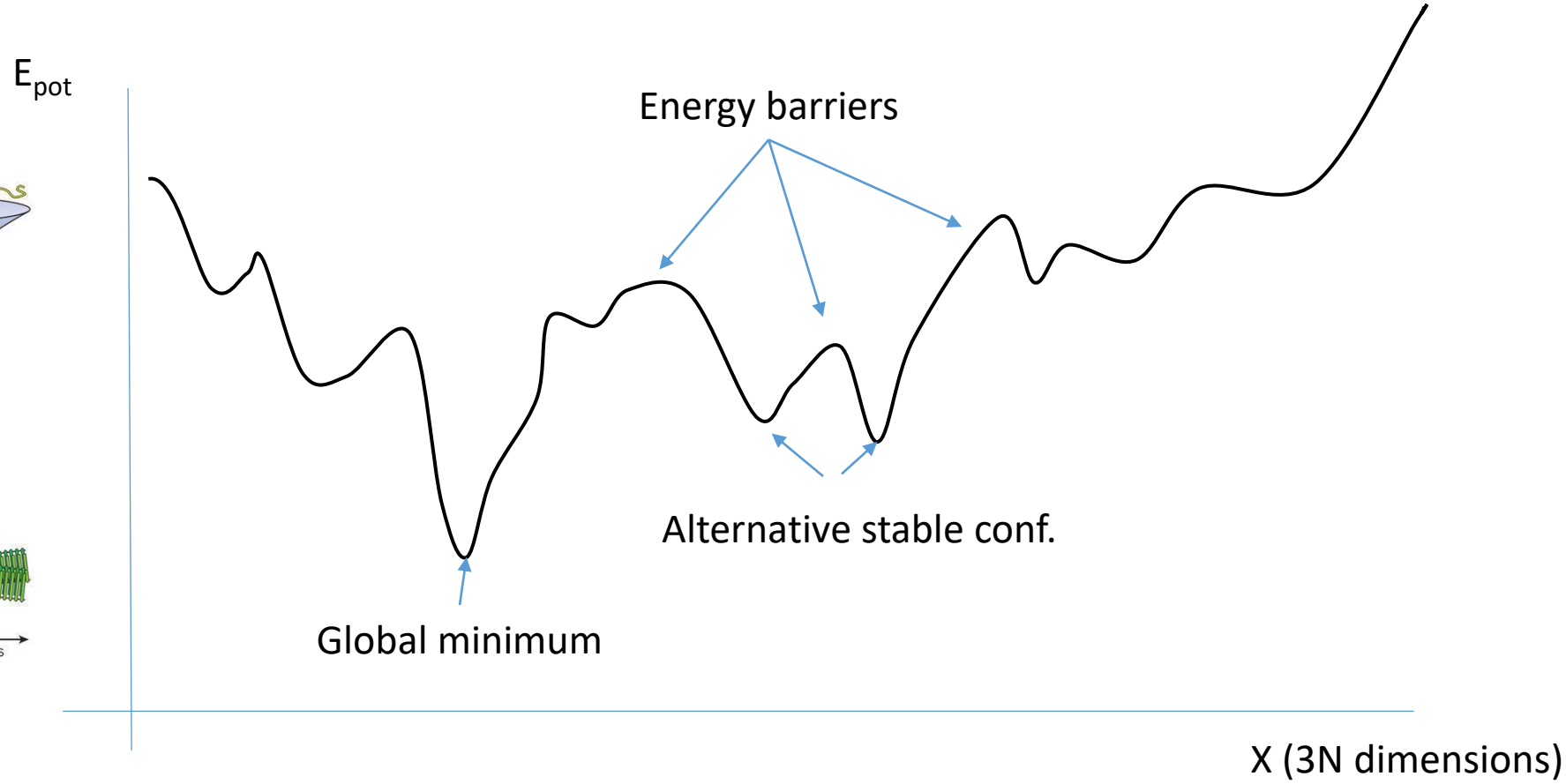
@proteinEnsemble

PED

https://proteinensemble.org/

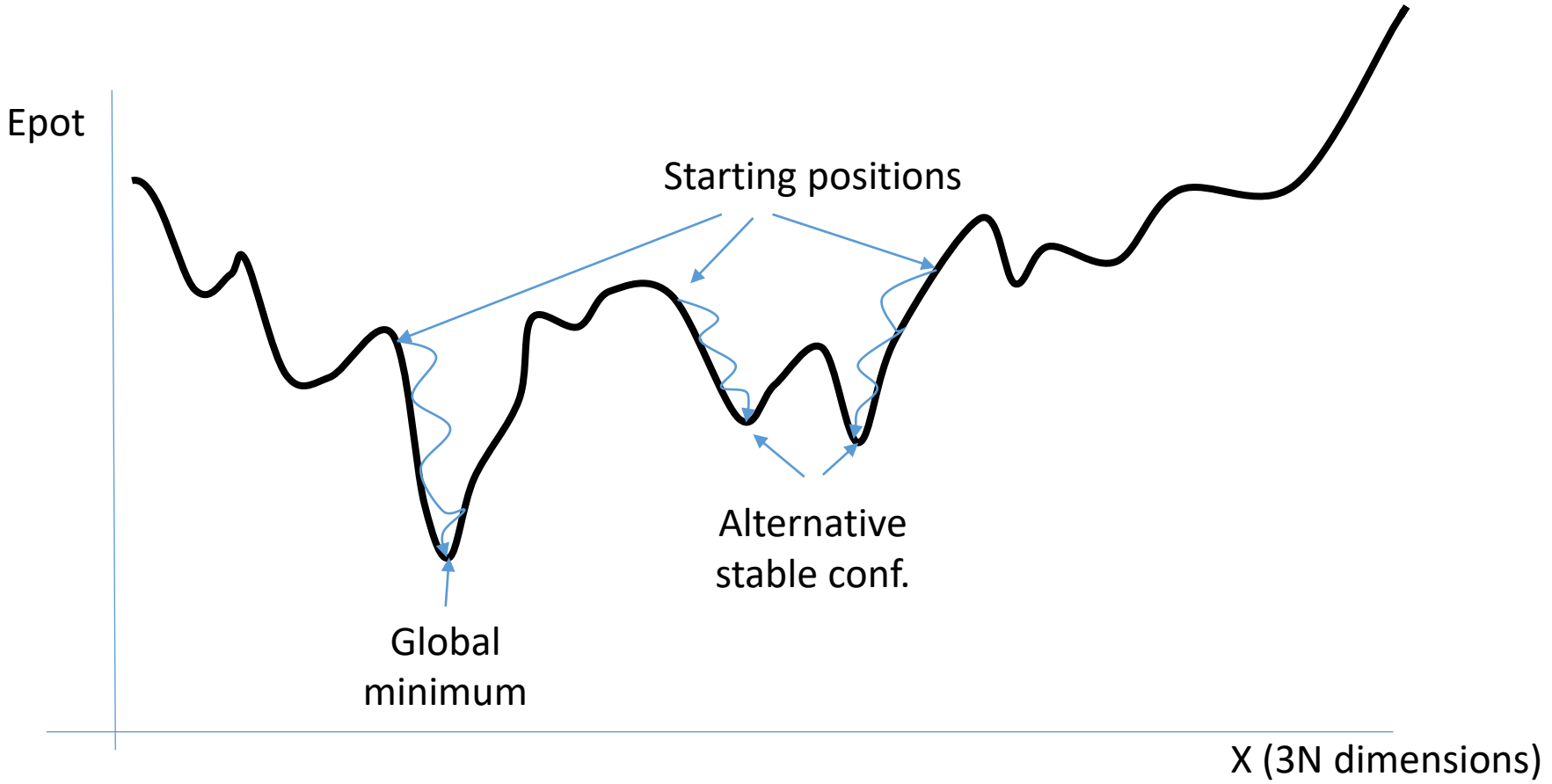
Lazar et al., (2021) *Nucleic Acids Research*, 49 (D1) pp. D404-D411





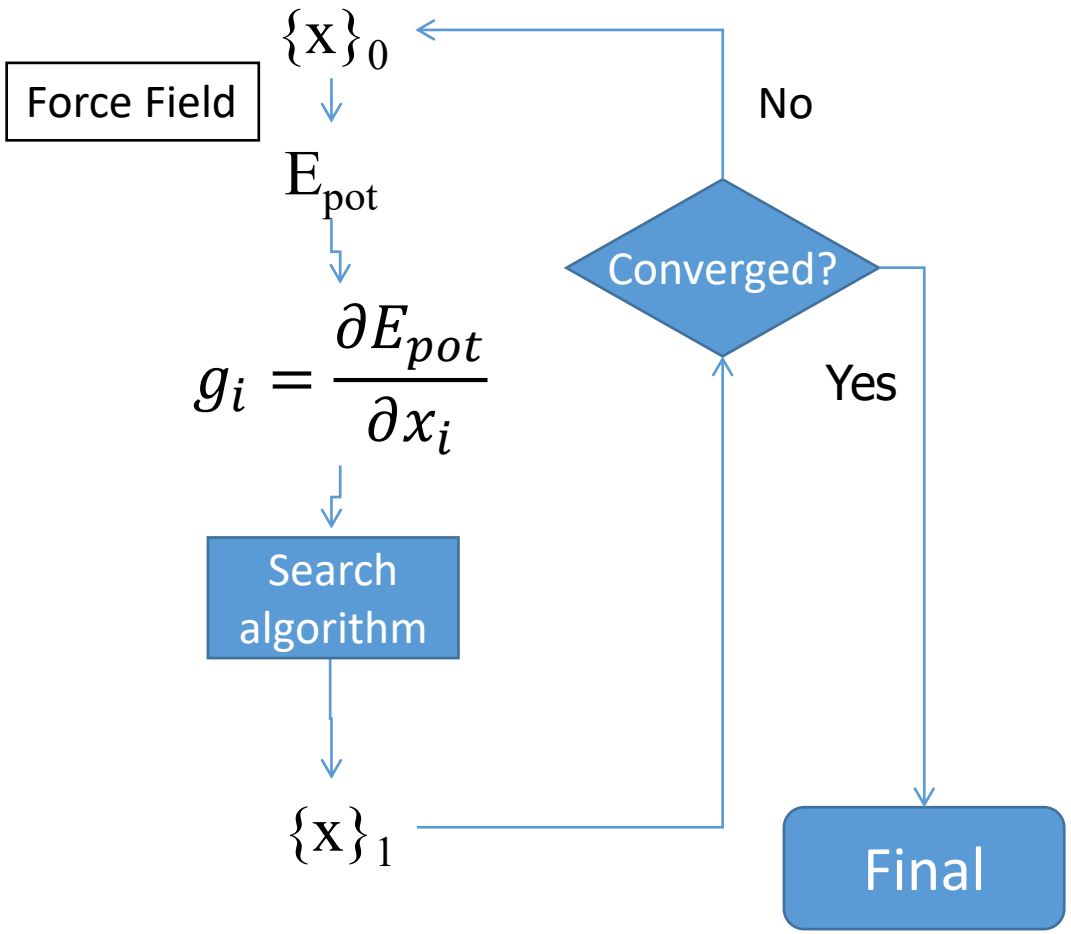
- The initial structure corresponds only to a single point in the hypersurface
- Landscape can be discovered by conformational sampling
  - Simple algorithms: Molecular Mechanics / Monte Carlo / Molecular Dynamics
  - Enhanced sampling algorithms aims to improve coverage (SBIO)

Molecular mechanics



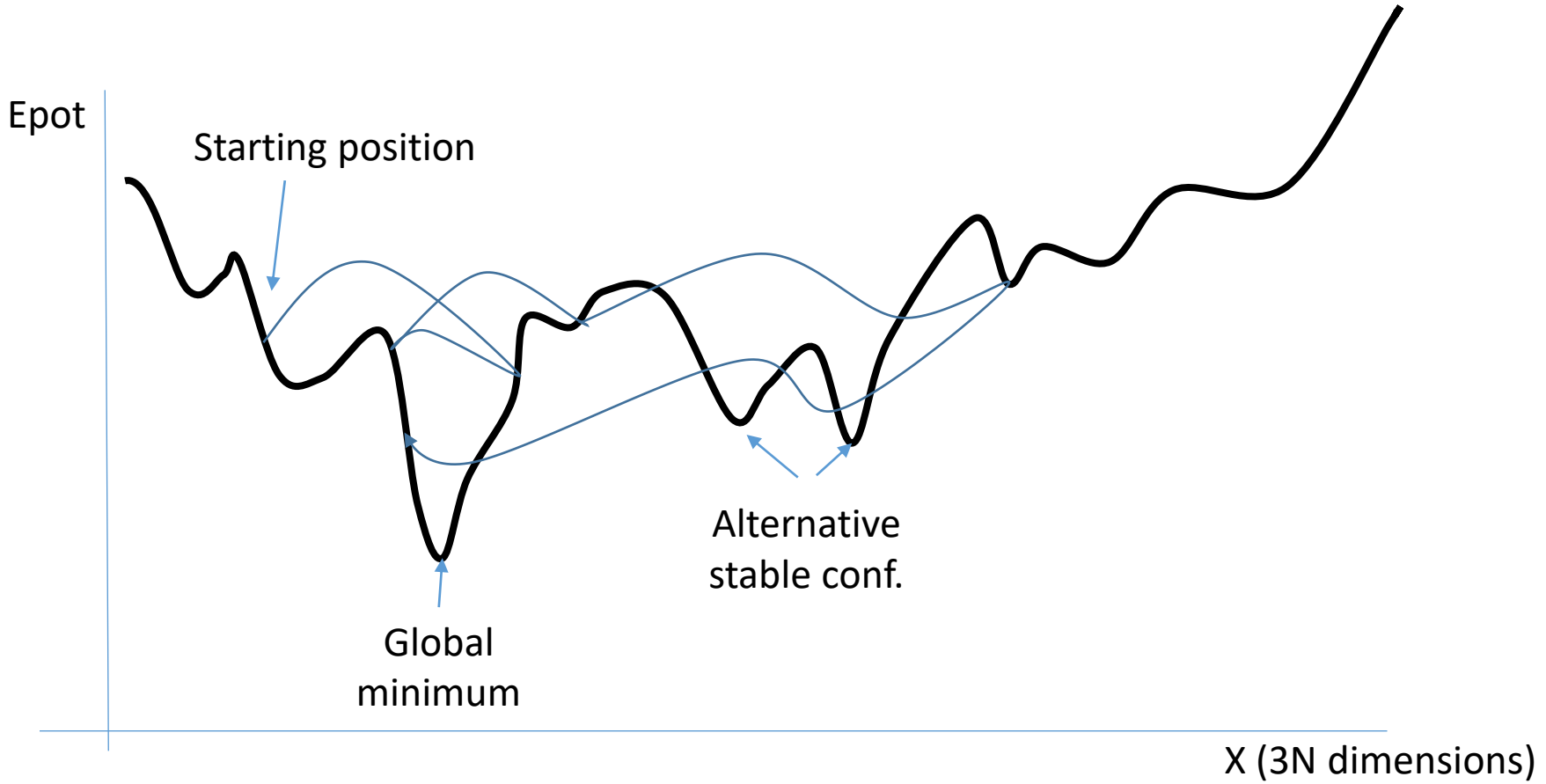
Molecular mechanics moves to conformations with lower energy values

Molecular mechanics



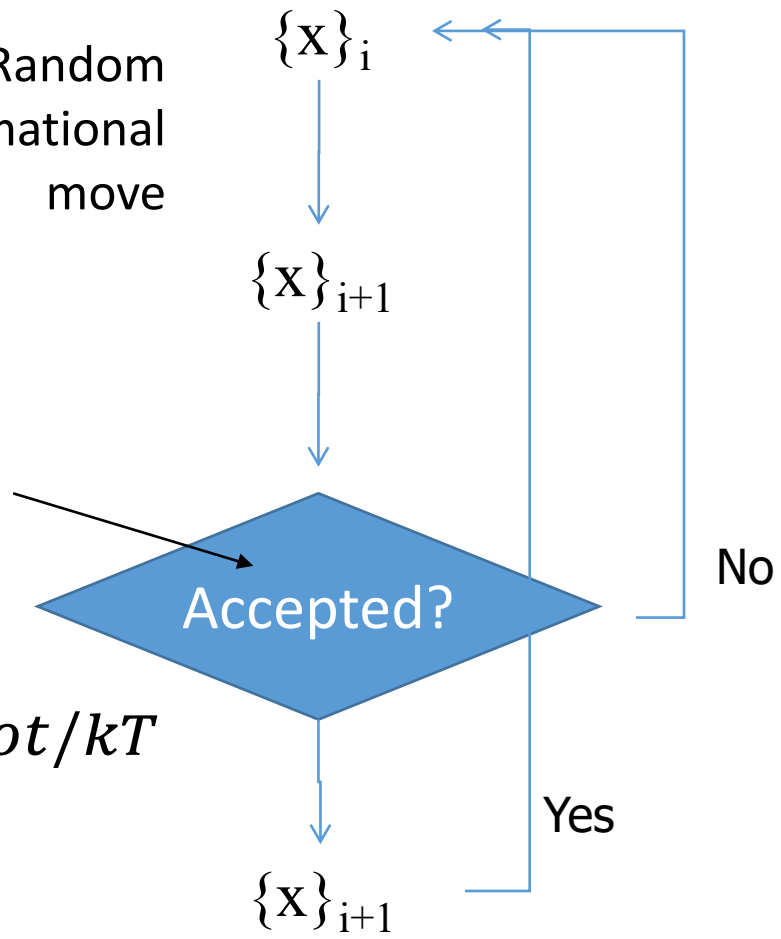
- Fast and cheap
- Finds local minima. Result always depends on the initial conformation
- Used before simulations to “relax” the system

Monte-Carlo Simulation



Monte-Carlo jumps randomly and accepts changes to lower or to slightly higher energies (considering temperature).

Monte-Carlo Simulation



$$p = e^{-\Delta Epot/kT}$$

- Very efficient in exploring large changes (no stopping barriers)
- Can include "non-physical" transitions in combination with MD simulations
  - pH const. dynamics
  - chemical transformations
- "time" is not considered (no "movie" is produced)
- Monte Carlo simulators are less optimized than MD ones

Molecular Dynamics Algorithm

$$v = \sqrt{\frac{3\,k_b T}{m}}$$

0: Energy added to the system (T: v_i)

Force-Fields calculation

$$E_{pot}\{x_i\}$$

Forces (gradients) calculation

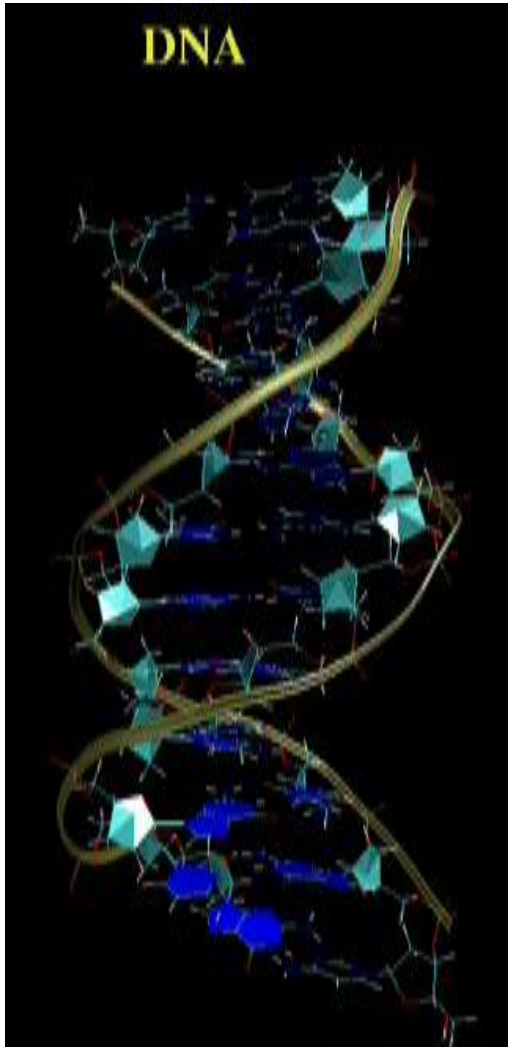
$$F_i = -\frac{\partial E_{pot}}{\partial x_i}$$

Classical mechanics Integration

$$a_i = \frac{F_i}{m_i}$$

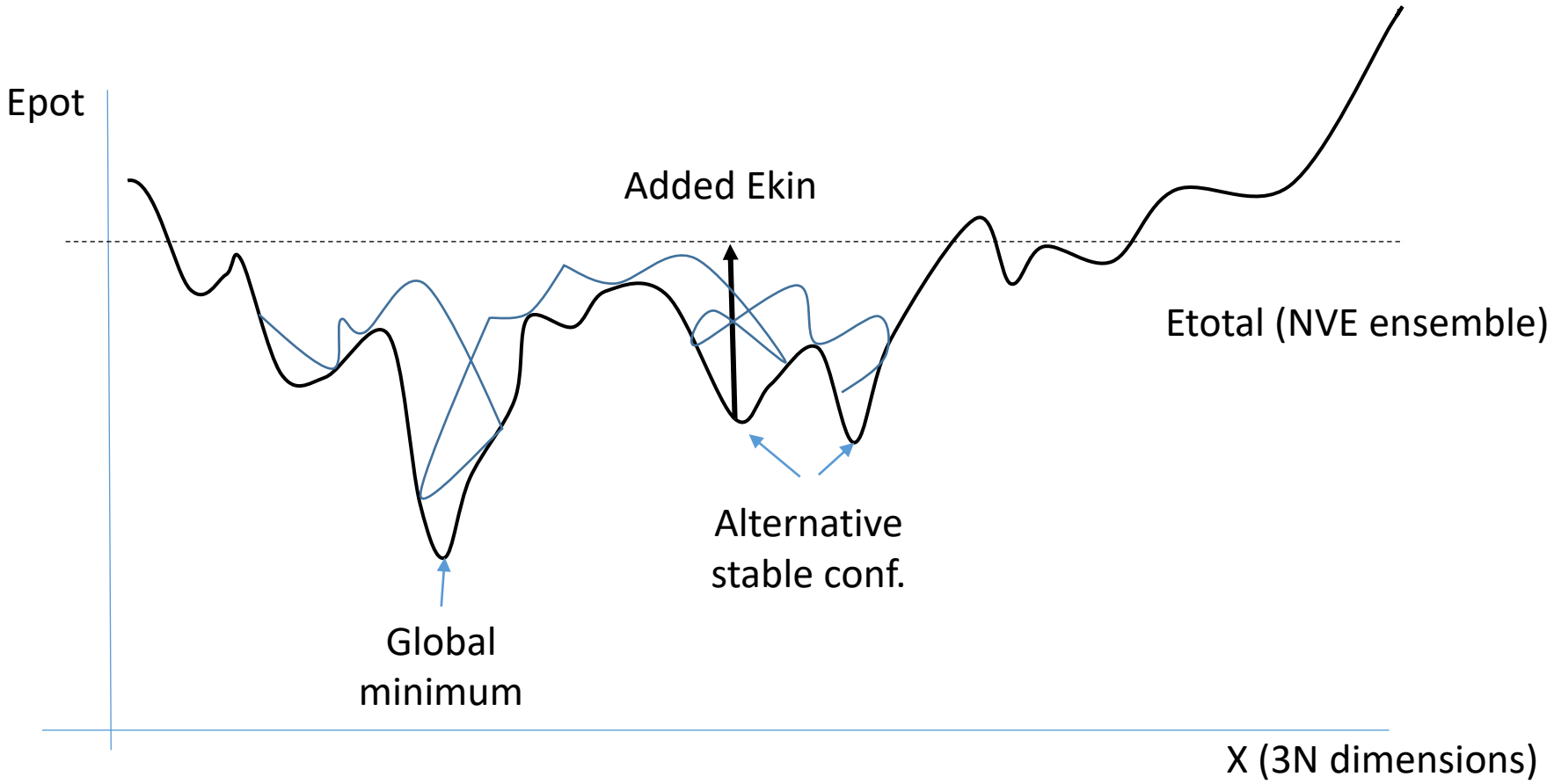
$$v_i\,(t + dt) = v_i(t) \quad + \; a_i\; dt$$

$$x_i\,(t + dt) = x_i(t) \quad + \; v_i\; dt$$



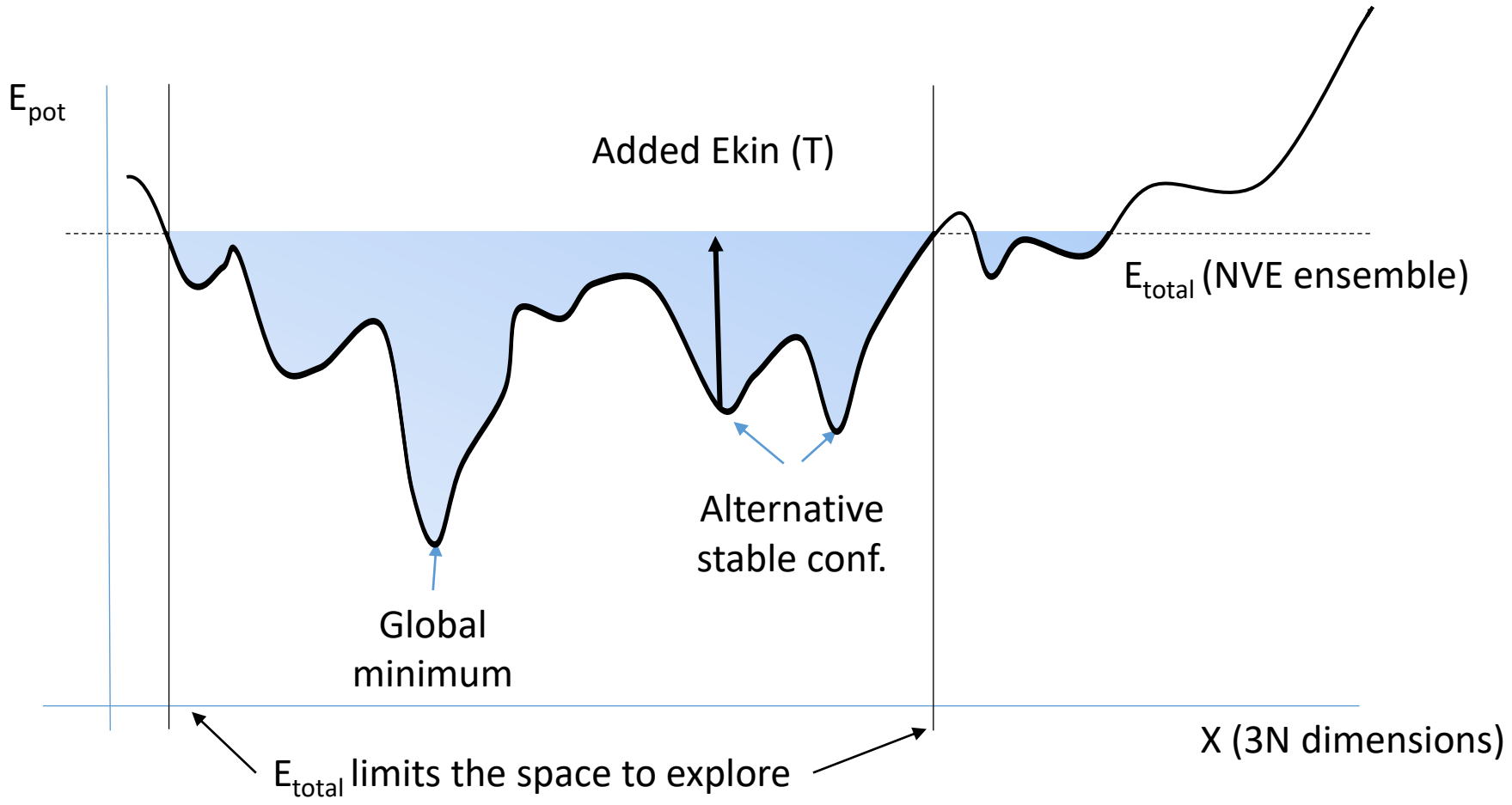
dt ≈1 fs = 10^{-15} s

Molecular Dynamics



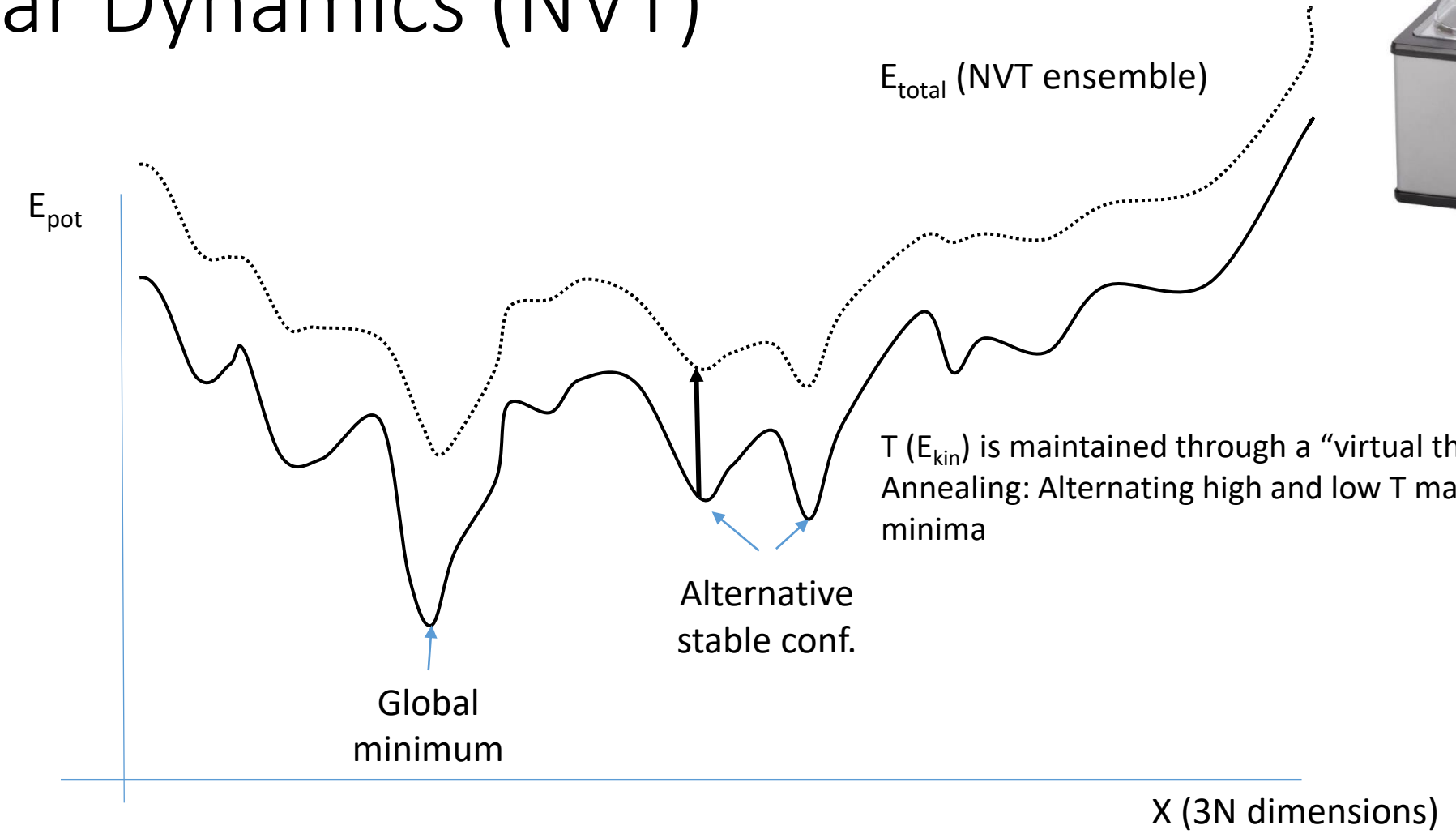
Molecular Dynamics uses extra (kinetic) energy to jump over energy barriers

Molecular Dynamics (NVE)



Molecular Dynamics uses extra (kinetic) energy to jump over energy barriers

Molecular Dynamics (NVT)



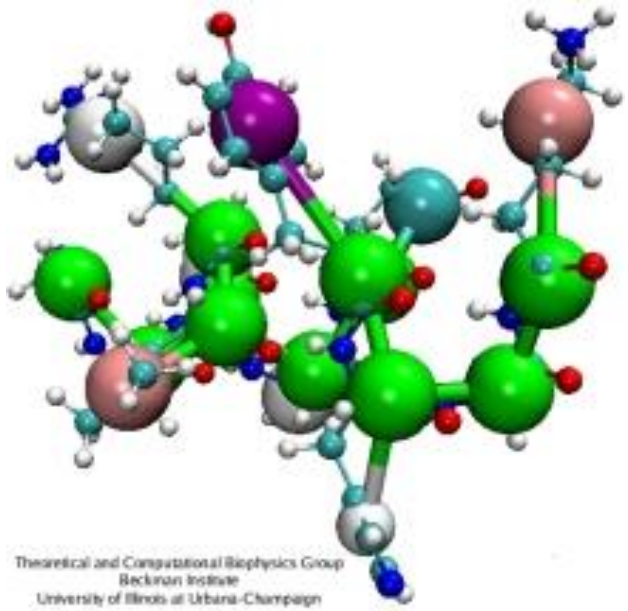
Molecular Dynamics uses extra (kinetic) energy to jump over energy barriers

Which algorithm?

- Molecular mechanics:
  - Mostly used for the initial minimization of the system (“relaxation”) to assure a mathematical minimum on the energy surface
- Monte Carlo
  - Efficient conformational sampling
  - Mostly used in combination with MD to sample alternative systems (ionization states, etc)
- Molecular dynamics:
  - Behavior of the systems along time.
    - Folding/unfolding
    - Conformational dynamics
  - Advanced optimization
  - Flexibility analysis

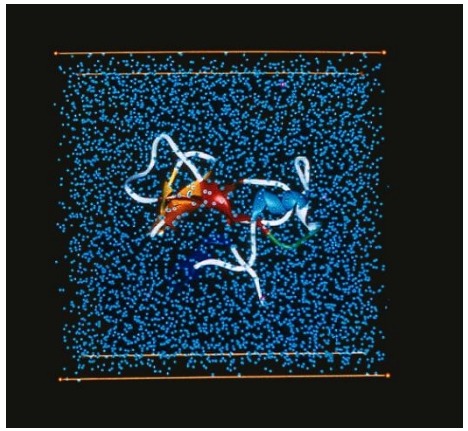
MD Strategies (-> SBIO)

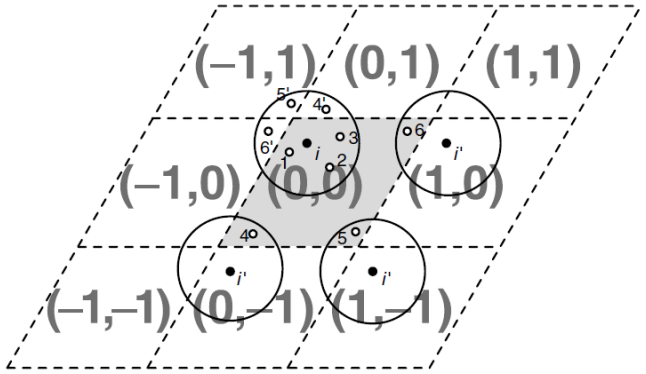
- System representation
  - Atomistic
  - Coarse-Grained
- Solvent
  - **Explicit (PBC)**
  - Implicit (GB)
  - None

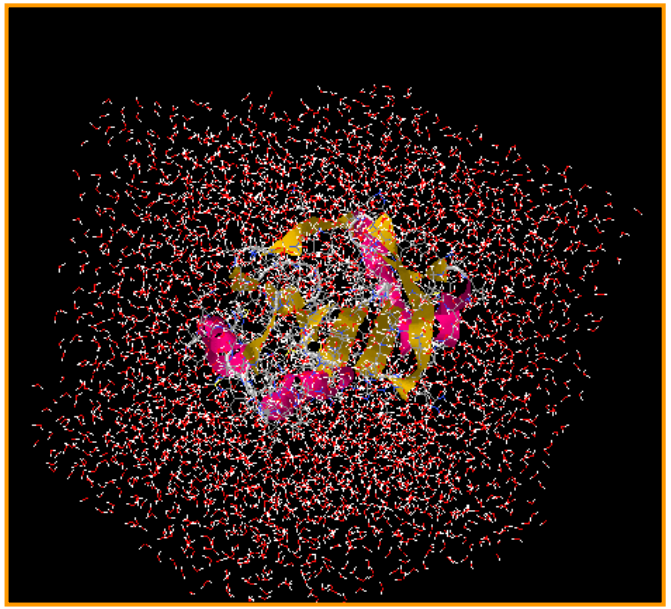


Usual settings :

- Explicit Solvent
- Periodic boundary conditions (PBC)
- NTP

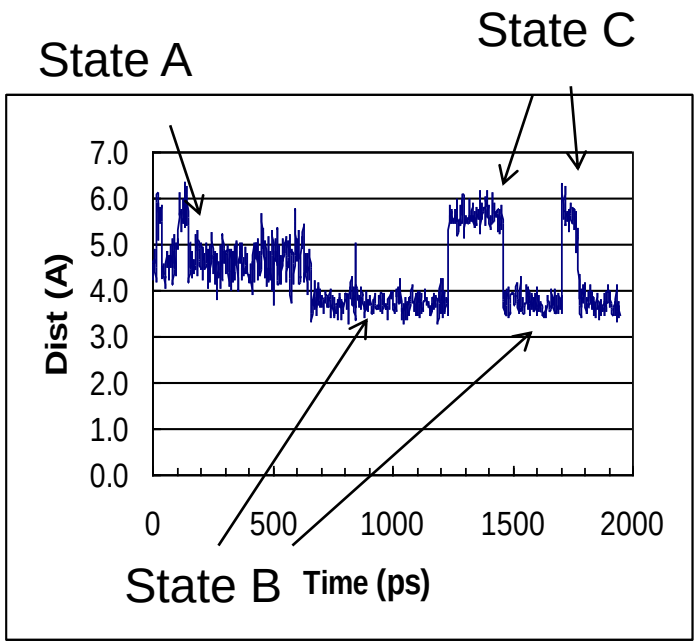




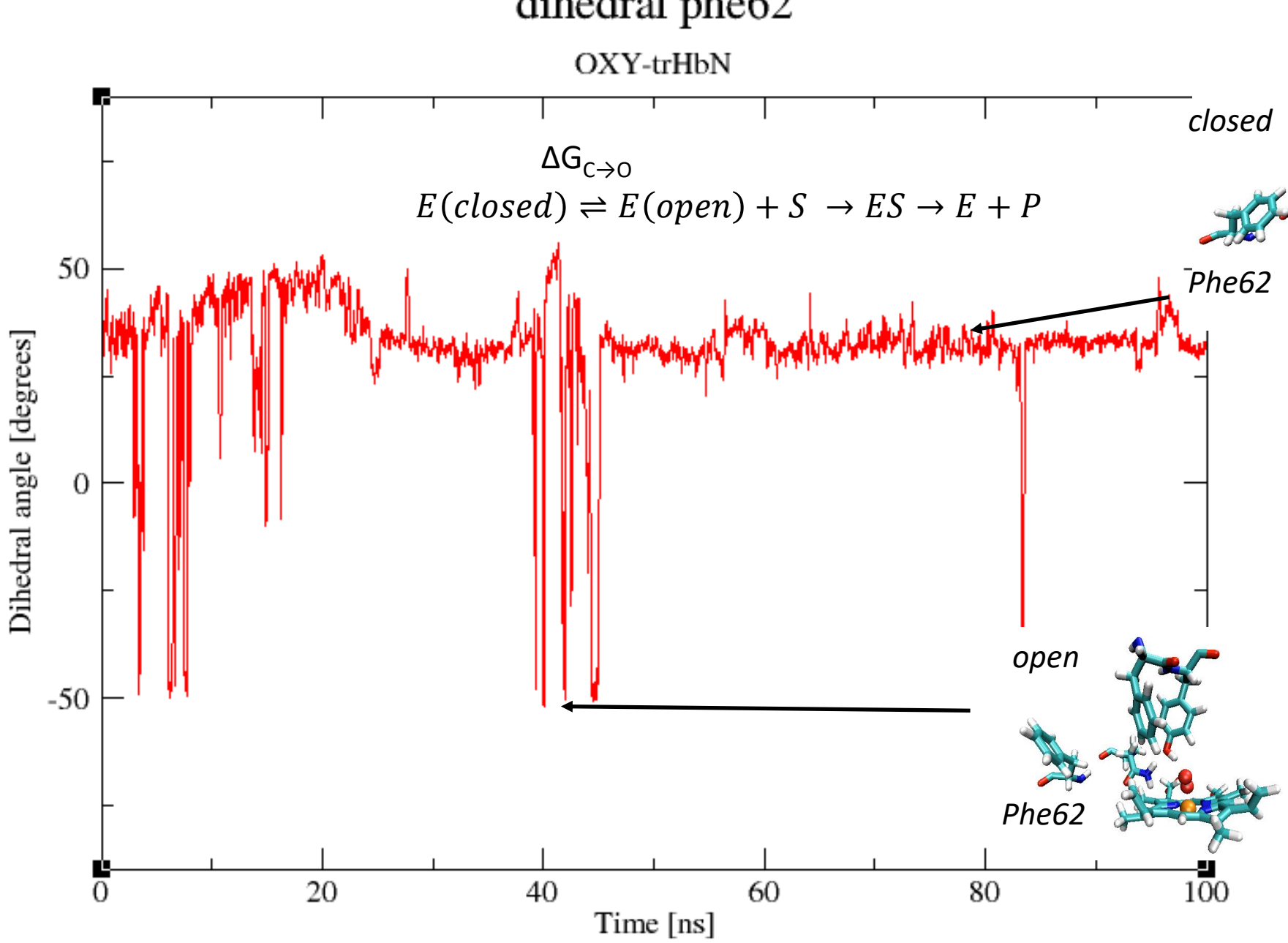


Using ensembles

- Analysis of a single system along time is equivalent to the analysis of many copies of the same system (*ergodic principle*)
  - Simulation snapshots considered as individual states
- Statistical thermodynamics allows to obtain ΔS and ΔG

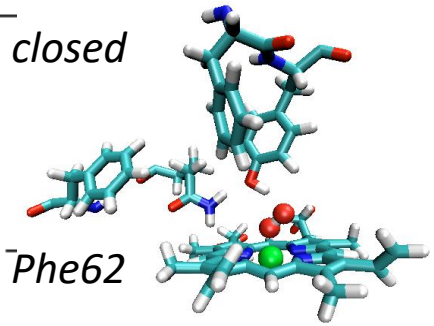


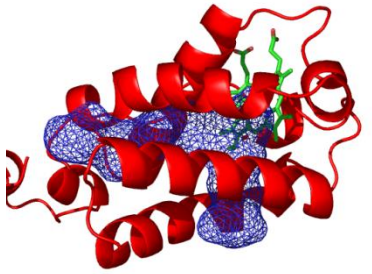
$$\Delta G_{A\to B} = -RT \ln \frac{N_B}{N_A}$$

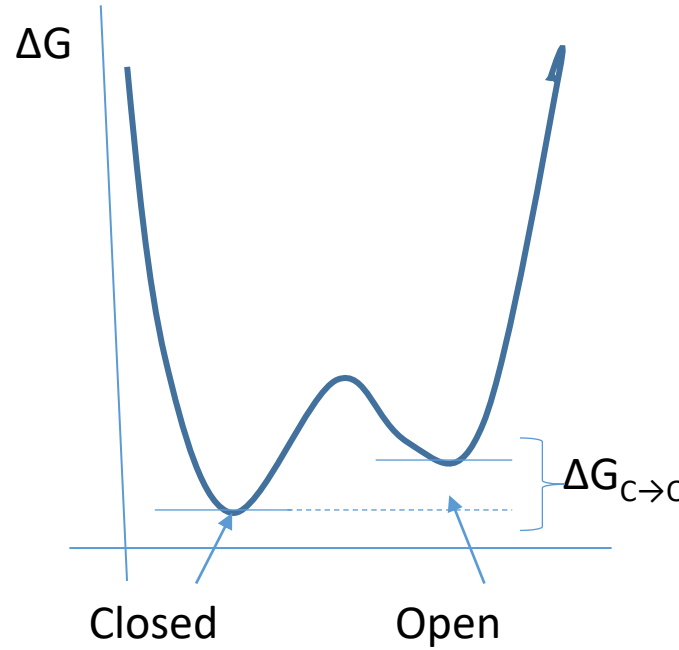


$\Delta G_{C\rightarrow O}$

$$E(closed) \rightleftharpoons E(open) + S \rightarrow ES \rightarrow E + P$$







$$\Delta G_{C\rightarrow O} = -RT \ln \frac{N_O}{N_C}$$

Summary

- Conformational ensembles are the true representation of a macromolecule
  - Particularly relevant on IDPs
- Macroscopic properties are best obtained by averaging ensemble properties
  - Statistical thermodynamics
- Simulation methods allow to explore the conformational space and build a valid ensemble