C7790 Introduction to Molecular Modelling
TSM Modelling Molecular Structures

Lesson 22
Large Models - Ensembles Averages

PS/2021 Present Form of Teaching: Rev2

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Context

macroworld **microworld**

states

(thermodynamic properties, G, T,…)

phenomenological thermodynamics

equilibrium (equilibrium constant)
kinetics (rate constant)

free energy
(Gibbs/Helmholtz)

partition function

statistical thermodynamics

microstates

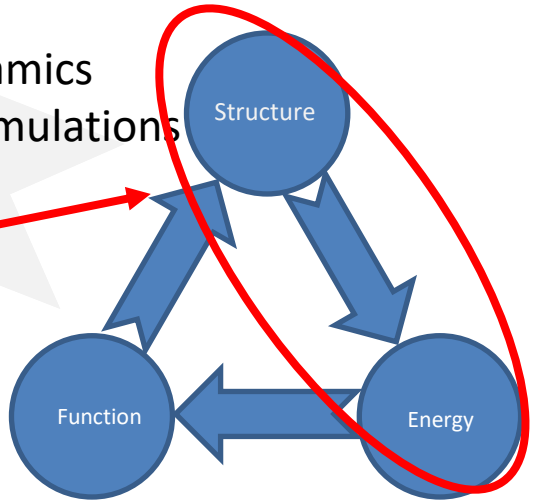
(mechanical properties, E)

Description levels (model chemistry):

- quantum mechanics
  - semiempirical methods
  - ab initio methods
  - post-HF methods
  - DFT methods
- molecular mechanics
- coarse-grained mechanics

Simulations:

- molecular dynamics
- Monte Carlo simulations
- docking
- …



microstate ≠ microworld

Revision: Statistical thermodynamics

Statistical approach:

Statistical physics (statistical mechanics) relates two levels of description of physical reality, namely the macroscopic and microscopic levels. In a more traditional sense, it deals with the study of the properties of macroscopic systems or systems, considering the microscopic structure of these systems (**statistical thermodynamics**). The founders were Ludwig Boltzmann and Josiah Willard Gibbs.

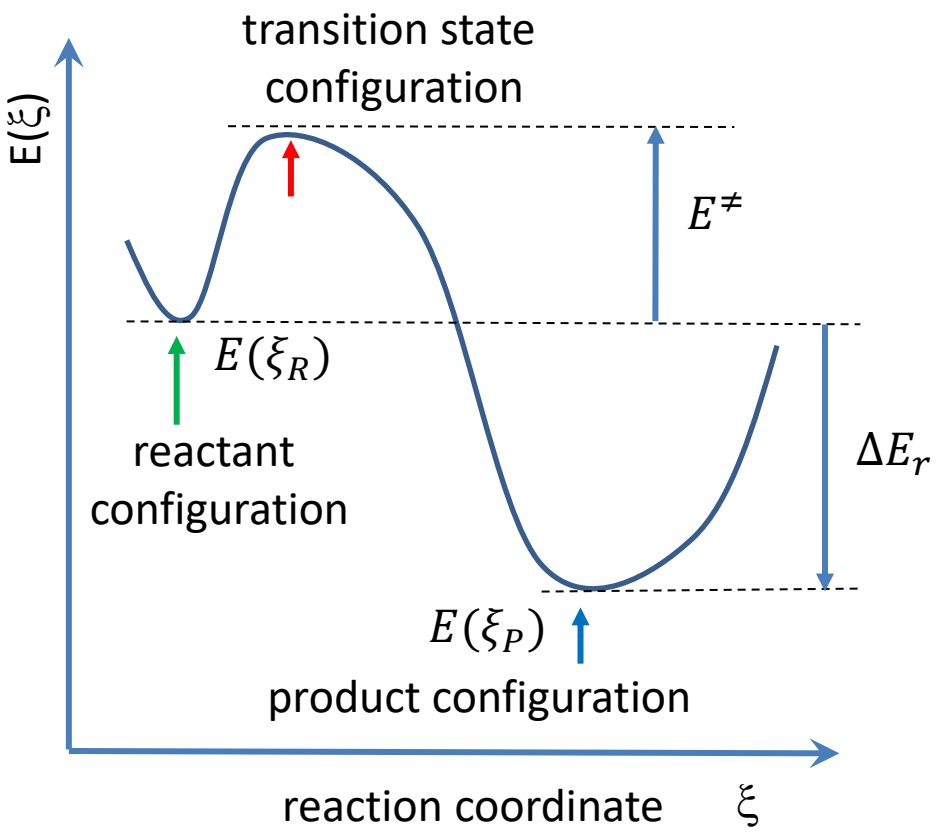
Level of description:

- particles and interactions between them
- equations of motions

wikipedia.cz, simplified

Revision: PES

Small models

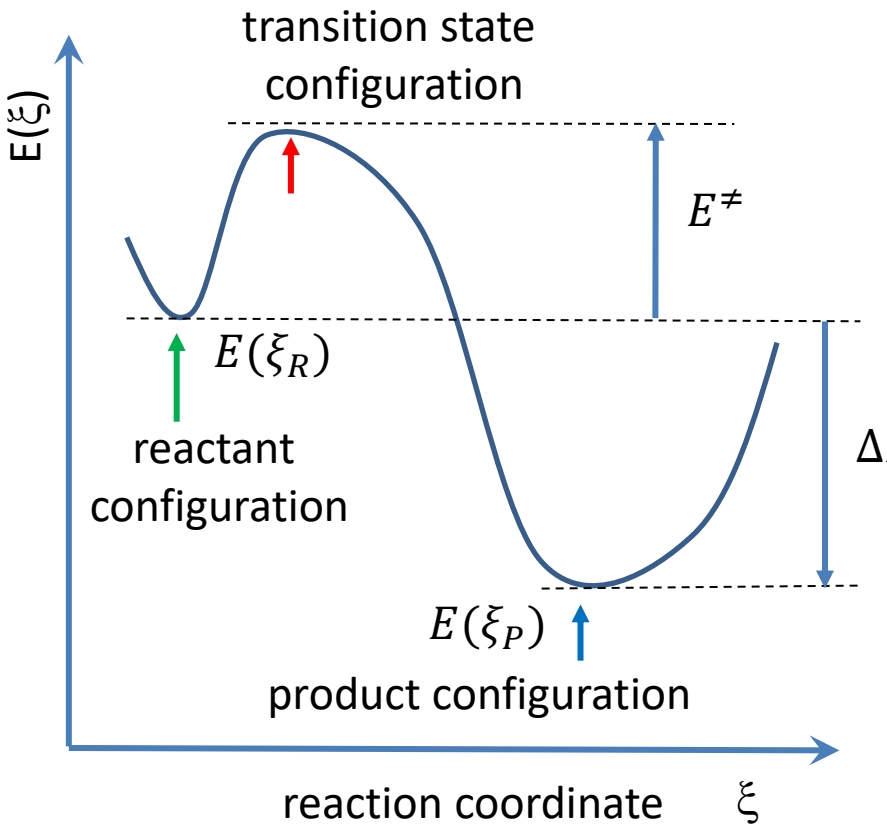


This is a **single point approach**. Each state is characterized by only ONE configuration.

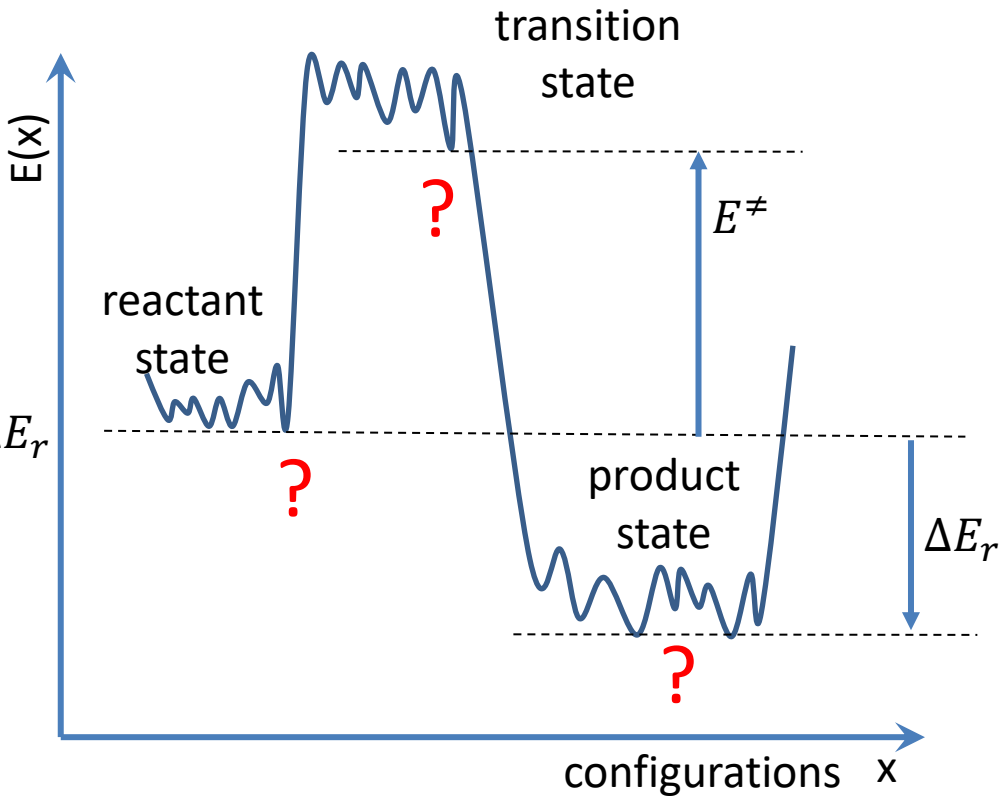
- Increasing degrees of freedom (model size) result in increased roughness of PES.
- The only reasonable description of large models is to use statistical weighting using right sampling technique.

Revision: PES

Small models



Large models



- Increasing degrees of freedom (model size) result in increased roughness of PES.
- The only reasonable description of large models is to use statistical weighting using right sampling technique.

Revision: System properties

The observable value ($\bar{M}$) of the property M can be determined by two approaches:

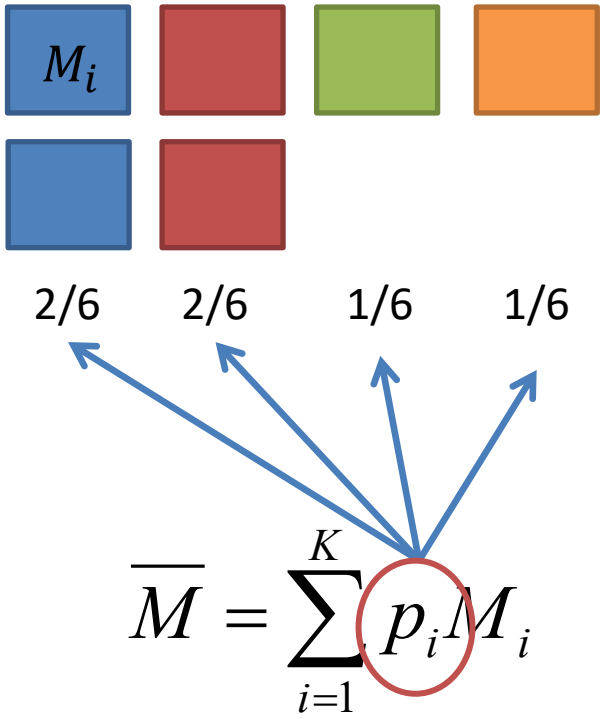
Time average:

snapshot of the system at time *t* is called a microstate

$$\overline{M} = \frac{1}{t_{tot}} \int_{o}^{t_{tot}} M(t)dt$$

We can run **molecular dynamics simulations** to get value of property by molecular modelling.

Ensemble average:



We can run **Monte Carlo simulations** to get value of property by molecular modelling.

Ergodic Hypothesis

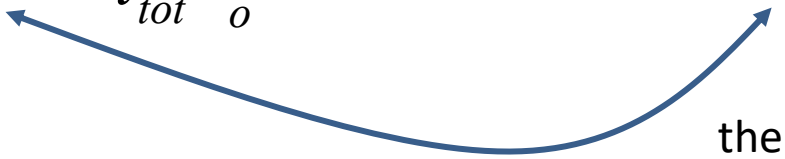
The **ergodic hypothesis** is often assumed in the statistical analysis of computational physics. It postulates that the average of a process parameter **over time** and the average over the **statistical ensemble** are the same.

Time average:

$$\overline{M} = \frac{1}{t_{tot}} \int_{o}^{t_{tot}} M(t)dt$$

Ensemble average:

$$\overline{M} = \sum_{i=1}^{K} p_i M_i$$



the same outcome

In special cases: However, this assumption—that it is as good to simulate a system over a long time as it is to make many independent realizations of the same system—is not correct for all physical systems.

https://en.wikipedia.org/wiki/Ergodic_hypothesis

Two sampling approches

Time average:

$$\overline{M} = \frac{1}{t_{tot}} \int_{o}^{t_{tot}} M(t)dt$$

Ensemble average:

$$\overline{M} = \sum_{i=1}^{K} p_i M_i$$

Molecular dynamics simulations

Monte Carlo simulations

Typically, a very large number of microstates (> 10^6) is needed in BOTH approaches to get converged thermodynamical properties.

Simplified models are needed

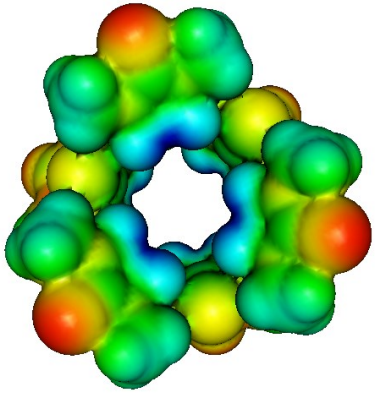
Solution of **Schrodinger equation (SE)** can provide mechanical properties (for example, potential energy) describing microstates.

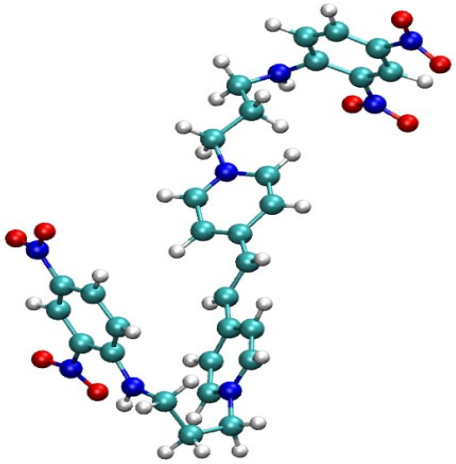
$$\hat{H}\psi_k^{\mathbf{R}}(\mathbf{r}_e) = E_k(\mathbf{R})\psi_k^{\mathbf{R}}(\mathbf{r}_e)$$

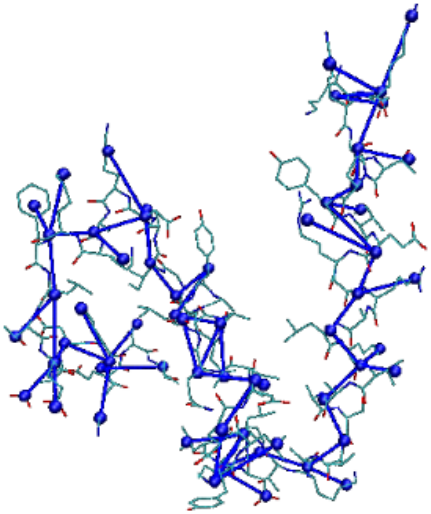
However, solution of SE is too computationally expensive to provide a suitable number of microstates for converged thermodynamical properties.

We need simplified computational models (chemistry models)!

Chemistry Models







QM (Quantum mechanics)	MM (Molecular mechanics)	*CGM (Coarse-grained* mechanics)

$E(\mathbf{R})$ —approximations→ $E(\mathbf{R})$ —approximations→ $E(\mathbf{R})$

R - position of atom nuclei

R - position of atoms

R - position of beads

Potential energy surface can be calculated by various method (model chemistry)!

Summary

- Microstates of macrosystems are too large to model. Two levels of simplifications is necessary:
  - model (small systems containing enough atoms to represent the studied phenomenon)
  - theory (chemistry model)
- Altogether, they must provide enough information about the system in reasonable computational time.