C7790 Introduction to Molecular Modelling

TSM Modelling Molecular Structures

C9087 Computational Chemistry for Structural Biology

Lesson 20

Potential Energy Surface - IV (Transition States)

JS/2022 Distant Form of Teaching: Rev1

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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

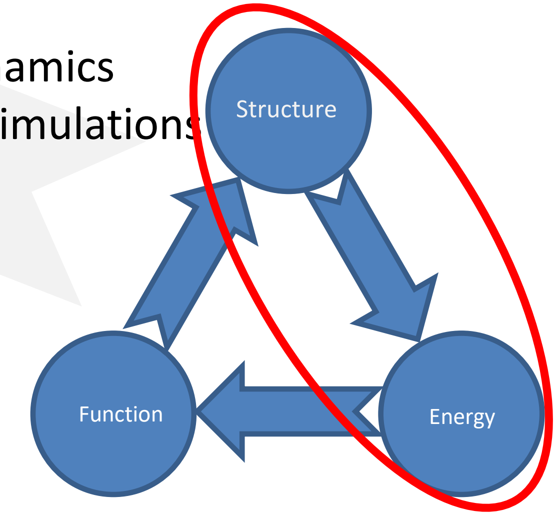
(mechanical properties, E)

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: Activation energy and modelling

$$\boldsymbol{aA + bB \xrightarrow[\text{via } \textbf{TS}]{k} cC + dD}$$

Eyring equation

$$k = \kappa \frac{k_B T}{h} e^{-\frac{\Delta G^{\neq}}{RT}}$$

rate constant

activation free energy

$$\Delta G^{\neq} = \Delta G_{f,TS} - (a\Delta G_{f,A} + b\Delta G_{f,B})$$

A

B

TS

We only need to know the **properties of individual components** involved in the reaction at standard conditions (or at different conditions, which are well defined).

easier for modelling

TS transition state

Revision: Partition function and modelling

Canonical partition function:

$$Q = \sum_{j=1}^{K} e^{-\beta E_j}$$

Helmholtz energy F:

$$F = -k_B T \ln Q$$

approximation

Consider only the most important microstate

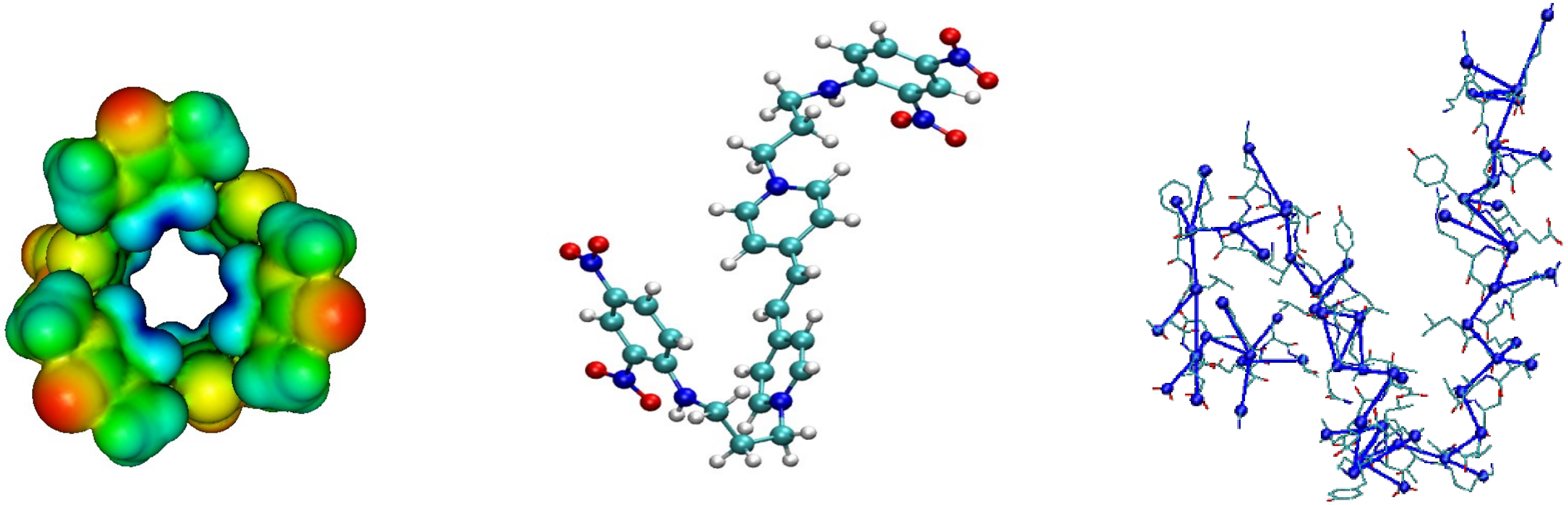
E_1, ~~E_2, E_3, ...~~

$$F = E_1$$

The most important microstate is the microstate with the lowest energy.

It is very often used for qualitative consideration or when computationally demanding methods are employed (typically quantum chemical calculations).

Revision: Potential energy calculations



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

$$\boxed{E(\mathbf{R})} \xrightarrow{\text{approximations}} \boxed{E(\mathbf{R})} \xrightarrow{\text{approximations}} \boxed{E(\mathbf{R})}$$

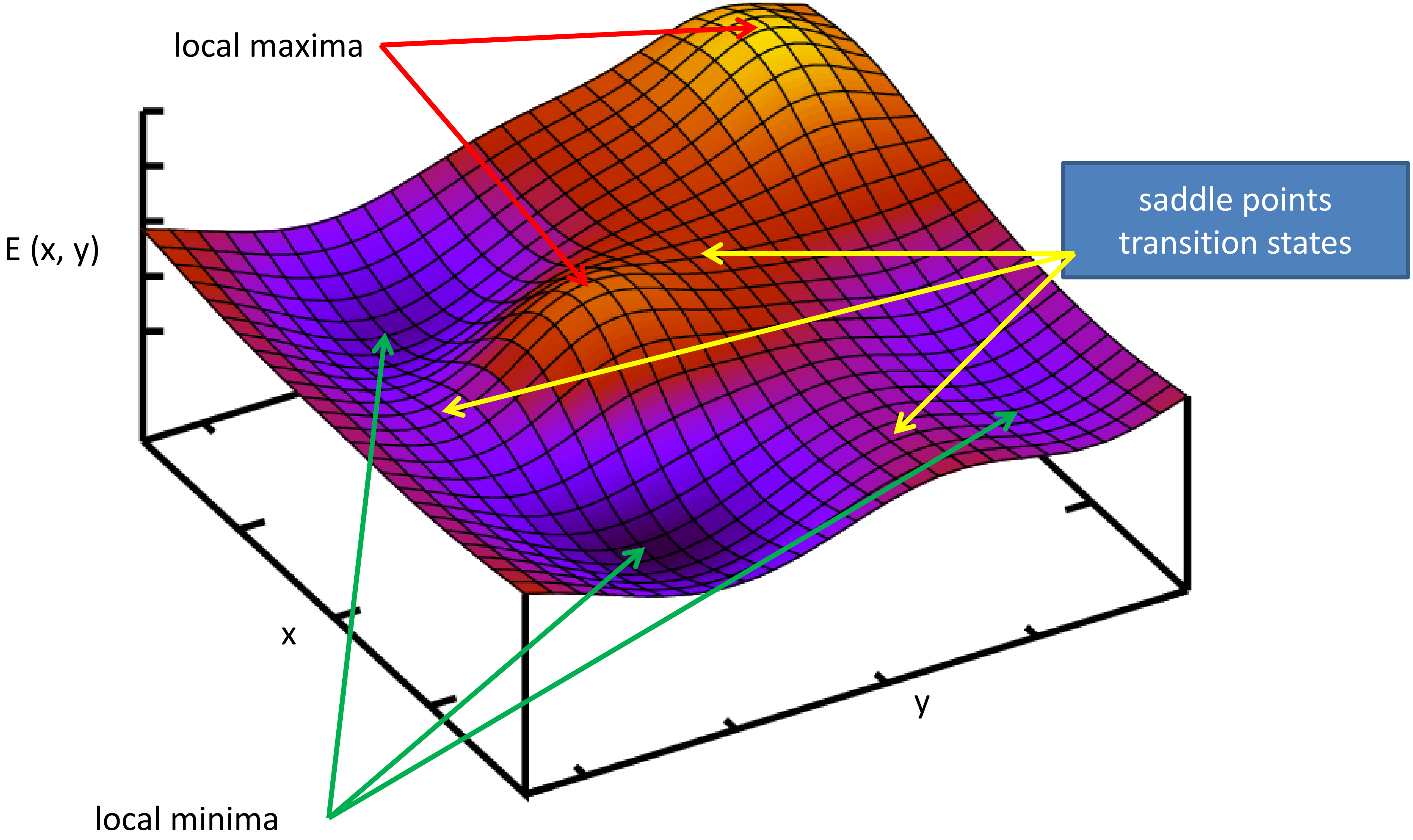
R - position of atom nuclei

R - position of atoms

R - position of beads

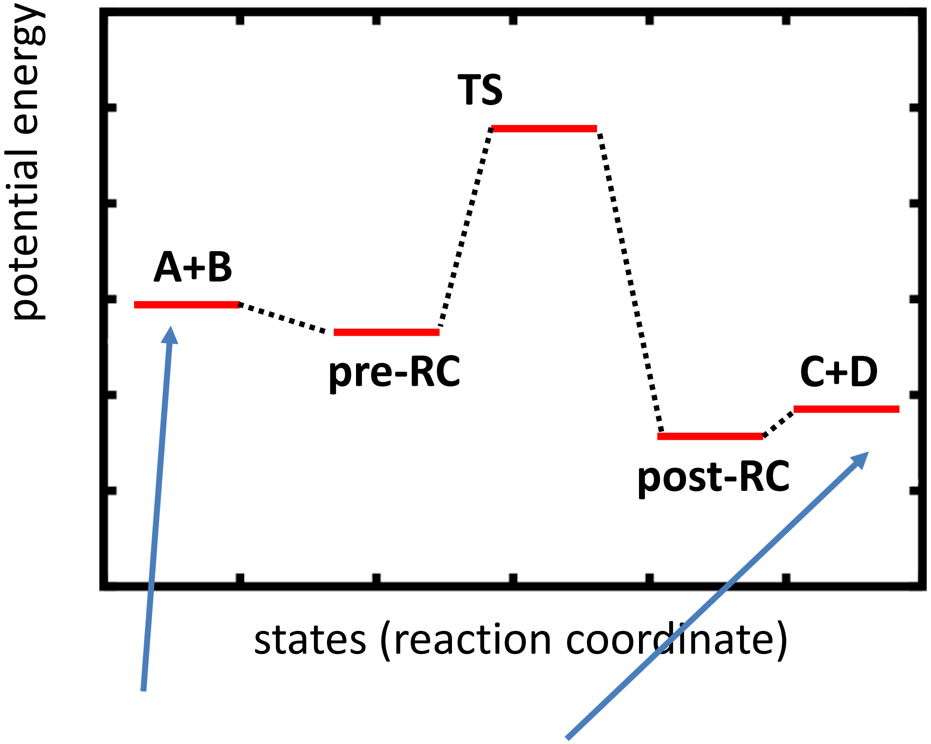
Potential energy surface can be calculated by various method (model chemistry)!

Revision: Transition State on PES



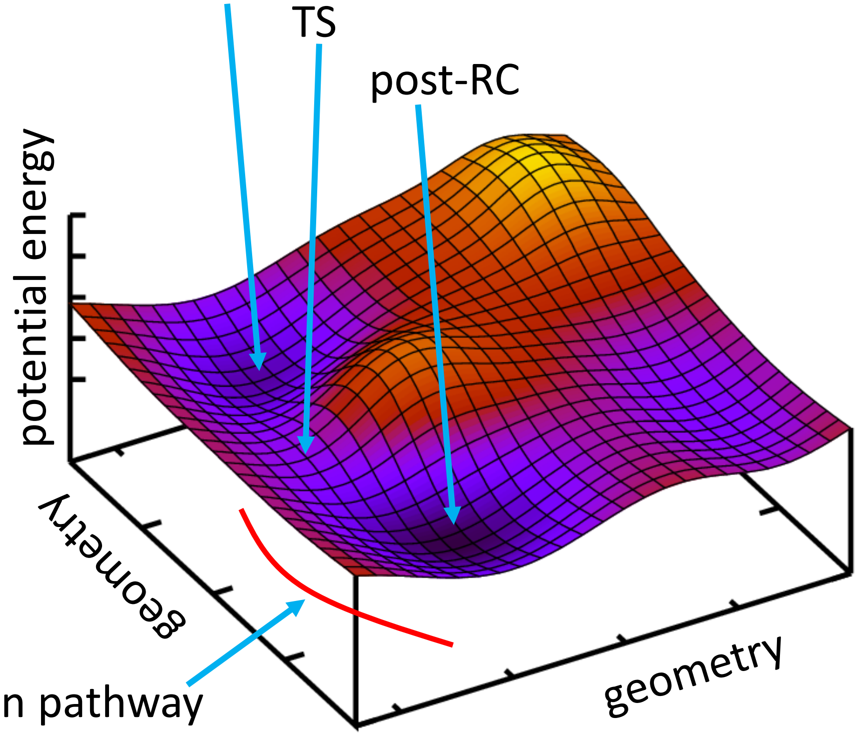
Elementary reaction and PES

Elementary reaction is the transformation of reactants and products represented by **pre-reaction** and **post-reaction complexes separated by just one transition state**.



individual non-interacting components at standard state

stationary points on PES
pre-RC (reaction complex)



Finding Transition States on PES

If the initial geometry is already close to searched transition state:

- local optimalization methods

If the reactants, products or both are known:

- semi-global optimization methods
  - Single Coordinate Driving Method
  - Synchronous Transit Methods
  - Nudged Elastic Band Methods

Reaction Coordinate

- The **reaction coordinate** describes the geometrical changes, which are necessary for transforming reactants into products via the transition state and vice versa.
- Its correct form is not a priori known.
- Approximate reaction pathways can be obtained by:
  - nudged elastic band method
  - string method

- If the transition state is known, then the **intrinsic reaction coordinate (IRC)** can be calculated.
  - IRC describes geometrical changes resulting from going "downhill" from TS in both directions in such a way that the energy gradient in all perpendicular directions is zero.

Since the potential energy is a state function, the exact knowledge of reaction pathway is not needed. Only proper characterization of states (reactants, products, transition states) is necessary.

However, at least some crude representation of reaction pathway is necessary to find transition state.

Locating Transition Structures

Local Methods

Local Methods

- **Transition state (TS)** is a **saddle point** on PES.
- The saddle point is a **stationary point**:

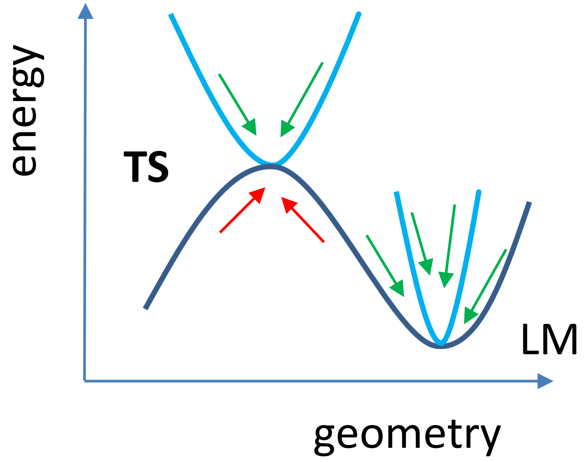
$$\frac{\partial E(\mathbf{R})}{\partial \mathbf{R}} = 0$$

- PES curvature at the saddle point provides **one negative Hessian H eigenvalue**:

$$\mathbf{H}\mathbf{c}_k = \lambda_k \mathbf{c}_k$$

all positive λ_k - local minimum (LM)
one negative, other positive λ_k - **first order saddle point transition state - TS**

- Searching for a transition state structure is more complex procedure than searching for a local minima because:



LM geometry optimizers:

- move geometry "downhill" only

TS geometry optimizers:

- move geometry "uphill" along negative eigenvector
- at the same time, move geometry "downhill" along the other degrees of freedom

Local Methods, cont.

Transition state geometry optimizers:

- pseudo-second order methods (quasi-Newton methods) need to be employed
- **starting geometry (structure) must be very close to the saddle point**
- **initial Hessian must be of high quality**
  - empirical Hessians employed in local geometry optimization are not usable
  - **Hessian calculated at the same level theory** as used during geometry optimization is good choice. However, this is computationally very demanding.
- for difficult cases, Hessian need to be recalculated at the same level of theory at each geometry optimization step (quasi-Newton -> full Newton method). This is extremely computationally demanding and suitable only for small molecular systems.

Starting structure for SP (TS) search can be found by **pseudo-global optimalization methods**:

  - single coordinate driving method
  - linear and quadratic synchronous transit methods
  - nudged elastic methods
  - string methods
  - others ....

Local Methods - Practical Realizations

Transition structure search in Gaussian

request optimization of the transition state

```
%Chk=ts.chk
# PM3 Opt(CalcFC,TS,NoEigenTest,MaxCycle=25)

transition state optimization

XX
X .... ..... .....
```

do not waste computational time on bad structures

skip very tight requirements on starting structures
if the starting structure is not of good quality, the optimization can fail

CalcFC	force constants (Hessian) are calculated on the input geometry
CalcAll	force constants (Hessian) are calculated on each geometry during optimization (full Newton-Raphson method)

Validation of TS

- It is necessary to validate the nature of stationary state representing the transition state employing vibrational analysis.
- Only ONE normal mode must be imaginary, the other normal modes must be represented by frequencies, which are real numbers.
- Atom movement along imaginary vibrational mode must follow the intended reaction change (formation/breaking bonds).

Locating Transition Structures

Semi-global Methods

Single Coordinate Driving (SCD) Method
Synchronous Transit (ST) Methods
Nudged Elastic Band (NEB) Methods

Single Coordinate Driving Method

Single coordinate driving (SCD) method is a simple approach for finding initial structures for the transition state geometry optimization.

SCD is a special case of potential energy surface scan methods (limited to a single geometry parameter).

Driven geometry parameter should represent the geometry change occurring during the reaction. Suitable coordinates can be:

- distance of formed bond
- distance of broken bond
- dihedral angle representing rotation around bond during a conformational change
- others …

- The SCD method can suffer from **driving hysteresis**. Two different driving pathways can be observed when driving from the reactant or product state.

Synchronous Transit Methods

Linear synchronous transit (LST) method

- Geometry parameters (Cartesian or internal coordinates) vary linearly between initial (reactants) and final (products) states:
- The order of atoms in $\boldsymbol{R}_{reactants}$ and $\boldsymbol{R}_{products}$ must be the same!

$$\boldsymbol{R}_i = \frac{N-i}{N}\boldsymbol{R}_{reactants} + \frac{i}{N}\boldsymbol{R}_{products} \qquad i \text{ - } 0, 1, 2, \ldots, N$$

- The guess of transition state geometry is taken as a geometry with the maximum energy.
- The structure with maximum energy is usually far away from the correct transition state.
- Thus, the geometry obtained by LST must be optimized using a local method.

Improved versions:

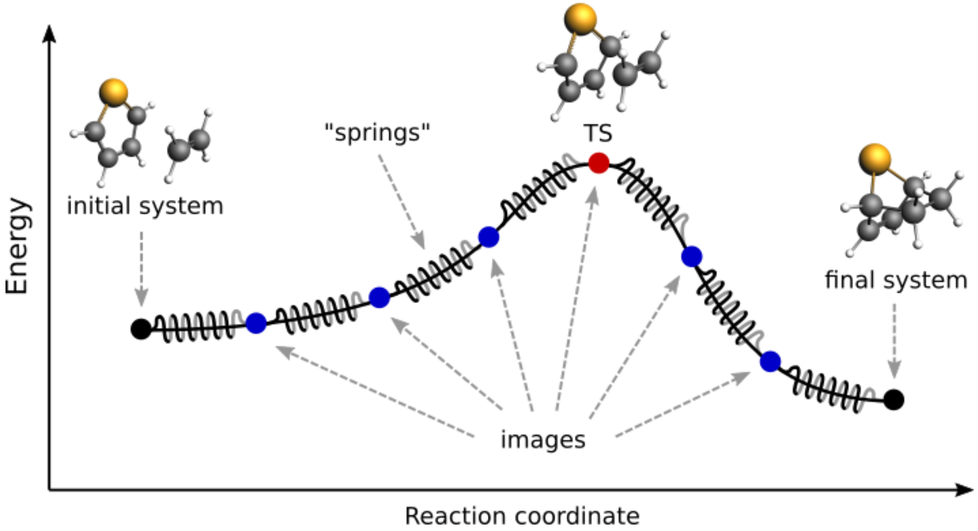
  - QST2 - quadratic synchronous transit between reactants and products
  - QST3 - quadratic synchronous transit between reactants and products via crude approximation of transition state

Nudged Elastic Band Method

Nudged elastic band (NEB) method is an approach for finding reaction paths and transition structures.

- Reaction path is represented by beads. Each bead represent a specific system geometry.
- NEB ensures equidistant spacing between beads by springs.
- Potential energy is minimized in all perpendicular degrees of freedom.
- Due to path discrimination, only guess of transition state geometry is obtained, which need to be refined by local optimization.

The **string method** (SM) is similar as NEB. SM uses splines to achieve equidistant bead separation.



https://www.scm.com/doc/AMS/Tasks/NEB.html

Summary

- Finding transition states is necessary step for quantification of reaction kinetics.
- Broad range of methods is available to locate either correct TS or at least its estimate.
- In comparison with characterization of reactants and products, finding transition structures is much difficult task.
- Nature of found transition states needs to be verified by vibrational analysis.
- Transition state must be a stationary state with only one imaginary molecular vibrations.