Molecular structures

Minimization, vibrational analysis, transition states

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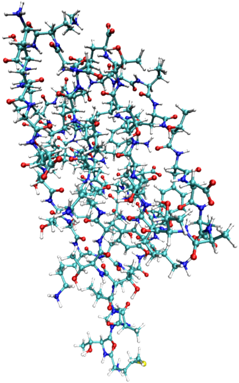
Modeling of biomolecules

Potential energy surface: $E_{\text{el}} = E_{\text{el}}(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N)$
(coordinates of atoms/nuclei $\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N$)

Approximations:

- Born–Oppenheimer approximations
  - separation of nuclei and electrons
  - energy obtained for fixed positions of nuclei
- Classical description of nuclei
  - Motion of nuclei not described with quantum mechanics
- Application of a force field
  - harmonic springs, point-charge electrostatics. . .



Energy with a force field

$$
\begin{aligned}
E_{\text{el}}(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N) = {} & \frac{1}{2} \sum_i^{\text{bonds}} k_i (r_i - r_i^0)^2 + \frac{1}{2} \sum_i^{\text{angles}} k_j^{\theta} (\theta_j - \theta_j^0)^2 \\
& + \frac{1}{2} \sum_n^{\text{torsions}} \cos(n_n \omega_n - \gamma_n) \\
& + \sum_I \sum_{J>I} \frac{1}{4\pi\varepsilon_0} \frac{q_I q_J}{|\boldsymbol{R}_I - \boldsymbol{R}_J|} \\
& + \sum_I \sum_{J>I} 4\varepsilon_{IJ} \left[\left(\frac{\sigma_{IJ}}{|\boldsymbol{R}_I - \boldsymbol{R}_J|} \right)^{12} - \left(\frac{\sigma_{IJ}}{|\boldsymbol{R}_I - \boldsymbol{R}_J|} \right)^{6} \right]
\end{aligned}
$$

Limitations of the force field approximation

The parameters have to be determined / fitted

- difficult for certain, or unusual elements (e.g., transition metals)

Conceptual limitations

- chemical bonds cannot be broken or created
- atom types are pre-determined
- atomic charges are pre-determined and constant
  – no change of electron density can be described

Electrons are not described explicitly, so no wave function

- only ground-state energy and forces are available
- no spectroskopic properties (interaction with light)
- no photochemistry (excited states)

Quantum chemistry vs. force fields

Quantum mechanics:
electronic wave functions: $\Psi_{\text{el}} = \Psi_{\text{el}}(\boldsymbol{r}_1, \ldots, \boldsymbol{r}_N)$
(coordinates of electrons $\boldsymbol{r}_1, \ldots, \boldsymbol{r}_N$)
solve the electronic Schrödinger equation

$$\hat{H}^{\{\boldsymbol{R}\}}\Psi^{\{\boldsymbol{R}\}} = E_{\text{el}}(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N)\Psi^{\{\boldsymbol{R}\}}$$

Quantum chemistry

- wave function theory (WFT)
- density functional theory (DFT)

→ calculation of energy is computationally intensive

Force field methods

- evaluate E_{el} ‘directly’, do not look for the electronic structure

→ calculation of energy is very quick and efficient

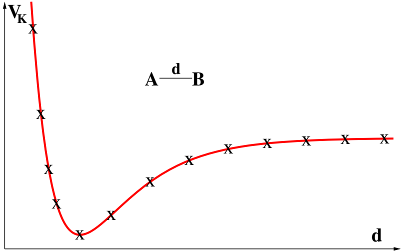
Potential energy surface

elektronic energy is a function of coordinates of nuclei $\{\boldsymbol{R}_I\}$

$$E = E(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N)$$

→ electronc energy defines the *potential energy surface (PES)*

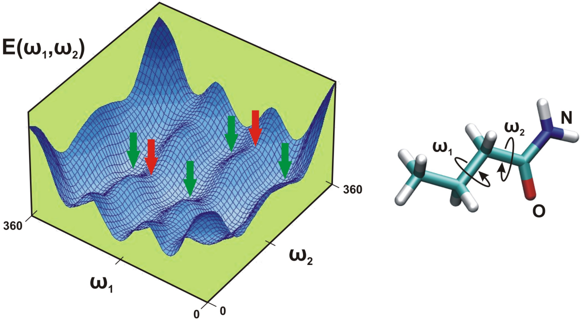
example: a diatomic molecule



→ all of the calculations only provide the PES point-wise

Sampling of the potential energy surface

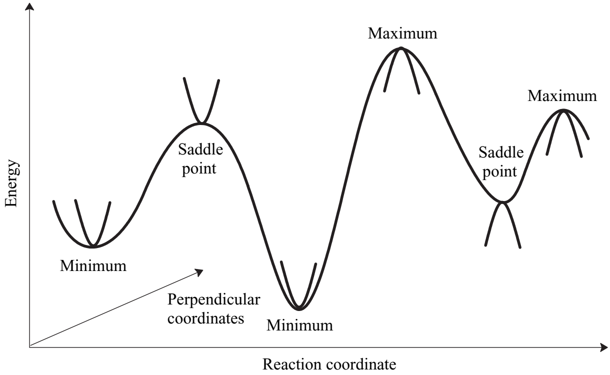
chemically interesting: stationary points on the PES



→ minimum:
stable conformation of a molecule, ‘equilibrium’ structure

→ saddle point of 1st order:
transition state (TS),
i.e. point of maximum energy along the direction of a ‘reaction’

Potential energy surface

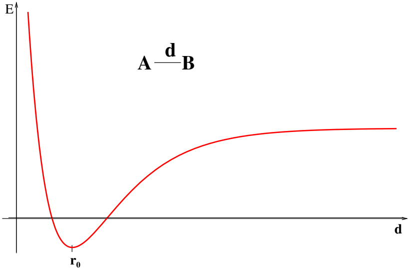


- **minimum**: every change of structure leads to an increase of energy
- **saddle point**: a maximum along reaction coordinate, while minimum along all other coordinates

Characterization of stationary points

How shall we find the interesting stationary points?

Example: Minimum of energy of a diatomic molecules



- condition for a stationary points: $\dfrac{\mathrm{d}E}{\mathrm{d}d} = 0$
- additional condition for a minimum: $\dfrac{\mathrm{d}^2E}{\mathrm{d}d^2} \geq 0$

Characterization of stationary points

How shall we find the interesting stationary points?

generally: $3M$ atom coordinates; $E = E(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N)$

Condition for stationary points:

$$\text{Gradient: } \boldsymbol{g} = \boldsymbol{\nabla} E = \left(\frac{\mathrm{d}E}{\mathrm{d}x_1}, \frac{\mathrm{d}E}{\mathrm{d}y_1}, \frac{\mathrm{d}E}{\mathrm{d}z_1}, \frac{\mathrm{d}E}{\mathrm{d}x_2}, \ldots, \frac{\mathrm{d}E}{\mathrm{d}z_N} \right)^T = 0$$

Second derivatives:

$$\text{Hessian: } \boldsymbol{H} = \begin{pmatrix} \frac{\mathrm{d}^2E}{\mathrm{d}x_1^2} & \frac{\mathrm{d}^2E}{\mathrm{d}x_1\mathrm{d}y_1} & \frac{\mathrm{d}^2E}{\mathrm{d}x_1\mathrm{d}z_1} & \frac{\mathrm{d}^2E}{\mathrm{d}x_1\mathrm{d}x_2} & \cdots \\ \frac{\mathrm{d}^2E}{\mathrm{d}y_1\mathrm{d}x_1} & \frac{\mathrm{d}^2E}{\mathrm{d}y_1^2} & \frac{\mathrm{d}^2E}{\mathrm{d}y_1\mathrm{d}z_1} & \frac{\mathrm{d}^2E}{\mathrm{d}y_1\mathrm{d}x_2} & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{pmatrix}$$

- **Condition for minimum**: all eigenvalues of $\boldsymbol{H}$ are positive
- **Condition for a saddle point of 1st order**: one eigenvalue of $\boldsymbol{H}$ is negative, all of the others are non-negative

Characterization of stationary points

How shall we find the interesting stationary points?

- Is it possible to sample the PES systematically?
    - Example: 10 atoms, 24 ($= 3N - 6$) coordinates

    → 10 points per coordinate → 10^{24} calculations of energy!

    → 100 points per coordinate → 10^{240} calculations!

⇒ finding the global minimum – very difficult problem

- chemical intuition – concentrate on meaningful structures

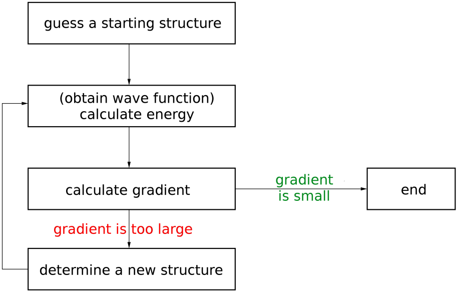
→ local minima, transition states between low-energy regions

What do we need now?

- calculation of gradients (and Hessian)
- algorithm
    - to optimize the geometry (search for a local minimum)
    - to search for transition states

Geometry optimization

→ search for a local minimum, starting from a suitable structure



- starting structure?
  → depending on the chemical problem
- convergence criterion? e.g.

$$|\boldsymbol{g}| = \left(\sum_{I,\alpha} g_{I,\alpha}^2 \right)^{1/2} < t$$

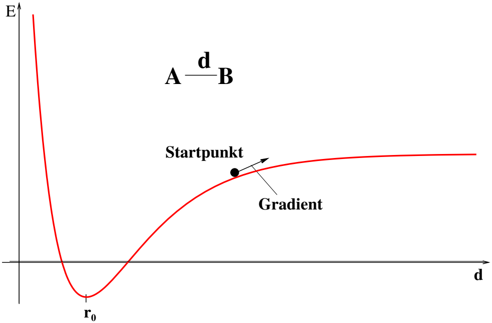
- how shall we determine the new structure?

- **Goal:** as few steps as possible
  (calculation of energy/gradients is expensive)
- calculation of Hessian shall be avoided
  (even more expensive)

Geometry optimization

How to make a step from the current structure towards a minimum?

Example: geometry optimization of a diatomic molecule

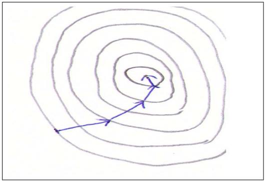


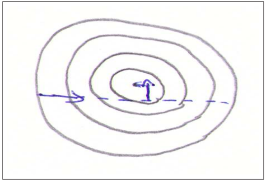
→ follow the negative of the gradient, i.e.,

$$\boldsymbol{R}_{i+1} = \boldsymbol{R}_i + \Delta\boldsymbol{R}_i = \boldsymbol{R}_i - \alpha\boldsymbol{g}_i$$

→ how can be the step length α determined?

Steepest descents optimization





- Step along the negative of gradient

$$\Delta \boldsymbol{R}_i = \alpha \boldsymbol{d}_i \qquad \boldsymbol{d}_i = -\boldsymbol{g}_i$$

- Choice of the step length α?
  - too short → too many steps needed
  - too long → overshoot the minimum

⇒ "*line search*":

choose α such that the energy in the direction of the gradient $\boldsymbol{d}_i = -\boldsymbol{g}_i$ is minimized

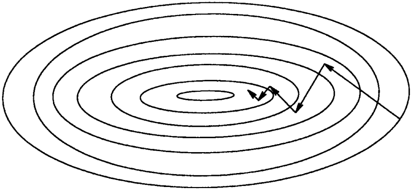
→ calculate the energy at several points along a line

→ the convergence is guaranteed

Steepest descents optimization

Problems

- too many steps in similar directions needed (problem with narrow valleys)



- convergence is getting slower when close to the minimum

Conjugate gradient optimization

Solution

- Idea: choose the direction of the step $\boldsymbol{d}_i$ such that it is orthogonal to previous ones

$$\boldsymbol{d}_i = -\boldsymbol{g}_i + \beta_i \boldsymbol{d}_{i-1} \qquad \beta_i^{\mathrm{FR}} = \frac{\boldsymbol{g}_i \cdot \boldsymbol{g}_i}{\boldsymbol{g}_{i-1} \cdot \boldsymbol{g}_{i-1}}$$

Newton–Raphson optimization

Taylor expansion of the PES around $\boldsymbol{R}_i$:

$$E(\boldsymbol{R}) = E(\boldsymbol{R}_i) + \boldsymbol{g}_i \cdot (\boldsymbol{R} - \boldsymbol{R}_i) + \frac{1}{2}(\boldsymbol{R} - \boldsymbol{R}_i)^t \cdot \boldsymbol{H}_i \cdot (\boldsymbol{R} - \boldsymbol{R}_i) + \cdots$$

minimum of this Taylor expansion up to the 2nd order:

$$0 = \frac{\mathrm{d}E}{\mathrm{d}\boldsymbol{R}} = \boldsymbol{g}_i + \boldsymbol{H}_i \cdot (\boldsymbol{R} - \boldsymbol{R}_i)$$

$$\Rightarrow \boldsymbol{H}_i \cdot (\boldsymbol{R} - \boldsymbol{R}_i) = -\boldsymbol{g}_i$$

$\Rightarrow$ **Newton–Raphson:**

calculate the step in direction of the minimum from this Taylor expansion:

$$\Delta\boldsymbol{R}_i = -\boldsymbol{H}_i^{-1} \cdot \boldsymbol{g}_i$$

→ for harmonic PES, this leads to the minimum directly

Problem: the calculation of Hessian in every step is expensive

Quasi-Newton optimization

Apply an approximated Hessian rather than the exact Hessian

- begin e.g. with a unit matrix (→ steepest-descents)
  - better starting Hessians are available
  - e.g. from certain simple rules or from a full calculation
- in every step, use the gradients $\boldsymbol{g}_i$
  to improve the approximated Hessian $\tilde{\boldsymbol{H}}_i$
- various update algorithms are possible, e.g. **BFGS**:

$$\tilde{\boldsymbol{H}}_i = \tilde{\boldsymbol{H}}_{i-1} + \frac{\Delta\boldsymbol{g}_i \Delta\boldsymbol{g}_i^t}{\Delta\boldsymbol{g}_i^t \Delta\boldsymbol{R}_{i-1}^t} \frac{\tilde{\boldsymbol{H}}_{i-1}\Delta\boldsymbol{R}_{i-1}\Delta\boldsymbol{R}_{i-1}^t\tilde{\boldsymbol{H}}_{i-1}}{\Delta\boldsymbol{g}_i^t \tilde{\boldsymbol{H}}_{i-1}\Delta\boldsymbol{R}_{i-1}^t}$$

- quasi-Newton algorithm often converges quickly and reliably

→ standard method in most quantum chemical packages

Choice of the coordinate system

⇒ Convergence of a quasi-Newton optimization is the better,
the closer to a quadratic form the PES is

→ depends on the choice of coordinate system strongly

Possible choices of coordinate system

- cartesian coordinates
  - simple, but not adjusted to a 'chemical' problem
  - → often slow convergence
- internal coordinates
  - use bond lengths, angles and torsional angles
  - → often good convergence
  - → but the definition of $3M - 6$ coordinates difficult
- redundant internal coordinates
  - use 'too many' internal coordinates
  - → mostly good convergence
  - → simple automatized definition is possible
- complexer coordinate systems possible

Geometry optimization: Summary

- starting point: a chemically meaningful structure
- minimization procedures:
  - *steepest descents:* converges always, but slowly
  - better: *conjugate gradients*, *quasi-Newton (e.g. BFGS)*

  → all of these avoid the calculation of Hessian
- biomolecules – often very difficult to find true minima
- in the quantum chemistry
  - calculations mostly limited to a single minimum
  - starting point for the calculation of molecular properties (spectra. . .)
- with the force field methods
  - starting point for MD simulation around a minimum (and beyond)
  - pre-optimization for quantum chemical calculations

Potential energy surface

What is going on with the energy of the atomic nuclei?

→ PES $E_{\mathrm{el},i}(\boldsymbol{R}_1, \ldots, \boldsymbol{R}_N)$ is the potential energy of the nuclei

- Is it possible, to calculate the entire potential energy surface?
    - Example: 10 atoms, 24 ($= 3N - 6$) coordinates
    - → 10 points per coordinate → 10^{24} calculations of energy!
    - → 100 points per coordinate → 10^{240} calculations!
- only concentrate on the relevant region close to a minimum

Search for a local minimum: geometry optimization

- requires a chemically meaningful starting structure
- calculation of electronic energy and its gradients
  in several (few) points of the coordinate space

In the region close to a local minimum

→ apply a Taylor expansion to the PES

Harmonic approximation

- let us move the origin of coordinates into the local minimum of PES:

$$\boldsymbol{R}_{I,0} = \boldsymbol{o} \quad \text{(null vector)}$$

→ the variables $\{\boldsymbol{R}_I\}$ determine the deviation from minimum

- Taylor expansion of energy

$$E_{\mathrm{el}}(\{\boldsymbol{R}_I\}) = \underbrace{E_{\mathrm{el}}(\{\boldsymbol{o}\})}_{const.} + \underbrace{\sum_{I=1}^{M}\sum_{\alpha=1}^{3}\left(\frac{\partial E_{\mathrm{el}}}{\partial R_{I,\alpha}}\right)_{\boldsymbol{R}_I=\boldsymbol{o}} R_{I,\alpha}}_{=0}$$

$$+\frac{1}{2}\sum_{I,J}^{M}\sum_{\alpha=1}^{3}\sum_{\beta=1}^{3} R_{I,\alpha}\left(\frac{\partial^2 E_{\mathrm{el}}}{\partial R_{I,\alpha}\partial R_{J,\beta}}\right)_{\substack{\boldsymbol{R}_I=\boldsymbol{o}\\ \boldsymbol{R}_J=\boldsymbol{o}}} R_{J,\beta} + \mathcal{O}(R_{I,\alpha}^3)$$

→ gradients in a local minimum of PES vanish

Harmonic approximation

- terminate the Taylor series after the second order
- the 2nd derivatives may be written in a matrix form
  Hessian:

$$\boldsymbol{H} = \{H_{ij}\} = \left\{ \frac{\partial^2 E_{\text{el}}}{\partial R_i \partial R_j} \right\} \rightarrow \text{coupling of coordinates of different nuclei}$$

- condense the atomic masses into the coordinates:

$$\begin{aligned} \boldsymbol{R}_I^{(m)} &= \sqrt{M_I}\boldsymbol{R}_I \\ \boldsymbol{H}^{(m)} &= \boldsymbol{M}^{-1/2} \cdot \boldsymbol{H} \cdot \boldsymbol{M}^{-1/2} \end{aligned}$$

- looking for: a linear combination of mass-weighted coordinates, which diagonalizes the Hessian → normal coordinates $\{q_i\}$

Harmonic approximation

- Normal coordinates $\{q_i\}$, normal modes $\{Q^{(i)}\}$:

$$q_i = \sum_{j=1}^{3M} Q_j^{(i)} R_j^{(m)} \qquad \frac{\partial^2 E_{\mathrm{el}}}{\partial q_i \partial q_j} = 0 \quad \forall \quad i \neq j$$

$$\boldsymbol{Q} = (\boldsymbol{Q}^{(1)}, \cdots, \boldsymbol{Q}^{(3M)})^T \qquad \boldsymbol{Q}^{(i)} = (Q_{1,x}^{(i)}, \cdots, Q_{3M,z}^{(i)})$$

$$\boldsymbol{H}^{(q)} = \boldsymbol{Q}^T \cdot \boldsymbol{H}^{(m)} \cdot \boldsymbol{Q} \qquad \boldsymbol{\nabla}^{(q)} = \boldsymbol{Q}^T \cdot \boldsymbol{\nabla}^{(m)}$$

- Eigenvalues of energy of the harmonic oscillator
  → the vibrational frequencies ω_i
  follow from the eigenvalues of the Hessian

$$\omega_i = \sqrt{H_{ii}^{(q)}}$$

- for molecules in the gas phase:

  translations+rotations are separated from the vibrations

Summary: vibrational analysis

- starting point: local minimum on the PES
- calculate the Hessian:

$$\boldsymbol{H} = \left\{ \frac{\partial^2 E_{\text{el}}}{\partial R_i \partial R_j} \right\}$$

  → the most computationally intensive step

- introduce mass weighting:

$$\boldsymbol{H}^{(m)} = \boldsymbol{M}^{-1/2} \cdot \boldsymbol{H} \cdot \boldsymbol{M}^{-1/2}$$

- diagonalize the mass-weighted Hessian:

$$\boldsymbol{H}^{(q)} = \boldsymbol{Q}^{\boldsymbol{T}} \cdot \boldsymbol{H}^{(m)} \cdot \boldsymbol{Q}$$

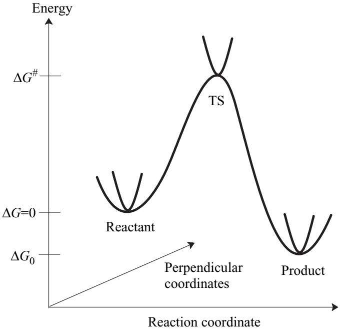
- calculate the vibrational frequencies from the eigenvalues:

$$\omega_i = \sqrt{H_{ii}^{(q)}}$$

Transition states

To describe a chemical reaction, or another process of interest:

- energies and structures of the reactant and the product
  → reaction enthalpy ΔH_r
- energy and structure of the transition state → rate of the process



- transition state theory (TST):

$$k = \frac{k_{\mathrm{B}} T}{h} \cdot \exp[-\Delta G^{\#}/k_{\mathrm{B}} T]$$

- free energy of the TS:

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$$

- from quantum chemistry:

$$\Delta H^{\#} = E_{\mathrm{TS}} - E_{\mathrm{Reactant}}$$

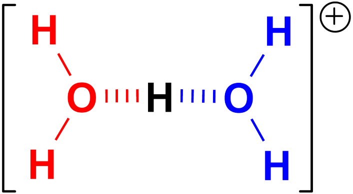
- entropy contribution $\Delta S^{\#}$:
  → from vibrational analysis

Optimization of transition states

TS search with one-structure methods

- geometry optimization of the reactant and the product
- search for a good starting structure
  - e.g. linear transit between the reactant and the product
- works only for simple reaction coordinates

  very symmetric systems, e.g. Zundelion $H_2O\ldots H^+\ldots OH_2$

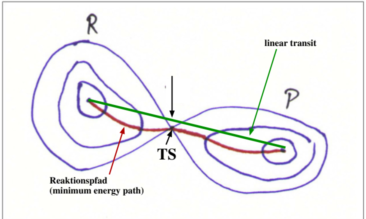


Optimization of transition states

How to find a suitable starting structure for the TS search?

- should be good – as close as possible to the true TS
- easiest way: follow a (guessed) reaction coordinate
  e.g. bond length / angle that is changing during reaction

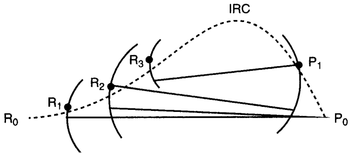
- linear transit: vary this/these coordinate/s in regular steps
- in every step, optimize all of the other coordinates
  ('constraint optimization' with the selected coordinate fixed)
- the maximum of energy along this path should be close to TS
  – this will be the starting structure



Optimization of transition states

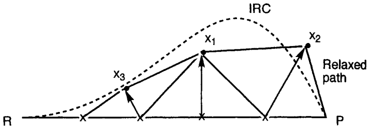
Alternative: ‘two-structure’ methods

- start from reactant and product; encircle the TS step-by-step



Alternative: ‘multiple-structure’ methods

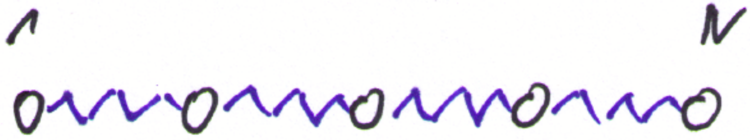
- start with a linear interpolation between reactant and product
- optimize structuren along the entire reaction path



Nudged Elastic Band (NEB)

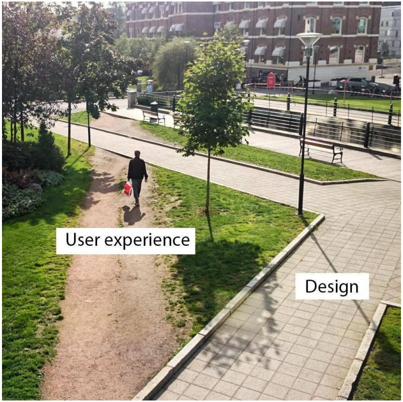
- Start with linear transit geometries, obtain N systems
- System: coordinates $\mathbf{x_i}$ and potential $V_i := V(\mathbf{x_i})$
- Connection between Systems: Springs $\frac{1}{2}k\left(\mathbf{x_{i+1}} - \mathbf{x_i}\right)^2$
- Goal: Minimize the energy function T^{NEB}

$$T^{\mathrm{NEB}} = \sum_{i=1}^{N} V_i + \sum_{i=1}^{N-1} \frac{1}{2}k\left(\mathbf{x_{i+1}} - \mathbf{x_i}\right)^2$$



Why Springs Are Dangerous

- Two big problems with the spring constants k:
    - k very small: Springs too weak, images slide down to product and reactand
    - k very large: Springs too strong, *cutting corners*



How to Nudge an Elastic Band

- Get tangent vector $\tau_{\mathbf{i}} = \mathbf{x_{i+1}} - \mathbf{x_{i-1}}$
  spring force only *parallel* to reaction path
  potential force only *perpendicular*

Parallel force from springs:

$$\left[\mathbf{F}_{\mathbf{i}}^{\mathrm{Spring}}\right]_{\parallel} = \left[k\left(\mathbf{x_{i+1}} - \mathbf{x_i}\right) - k\left(\mathbf{x_i} - \mathbf{x_{i-1}}\right)\right] \times \tau$$

Perpendicular force from the potential energy:

$$\left[\mathbf{F}_{\mathbf{i}}^{\mathrm{pot}}\right]_{\perp} = \left[\nabla V_i\right]_{\perp} = \nabla V_i - \nabla V_i \times \tau_i$$

Use known geometry optimizer for T^{NEB} with force

$$\mathbf{F}_{\mathbf{i}}^{\mathrm{tot}} = \left[\mathbf{F}_{\mathbf{i}}^{\mathrm{Spring}}\right]_{\parallel} + \left[\mathbf{F}_{\mathbf{i}}^{\mathrm{pot}}\right]_{\perp} .$$

Summary: transition states

- Optimization of TS is much more difficult
  than a normal optimization of an energy minimum
- *one-structure methods*:
  good starting structure and starting Hessian are essential
- *multiple-structure methods*:
  usually more robust, but not always available/applicable
- after the optimization of TS:
  always calculate the Hessian to check if it really is a TS!
- in quantum chemistry:
  - description of chemical reactions (→ activation energy)
  - *but 1:* reaction rates require very accurate energies
  - *but 2:* entropy contributions may require MD simulation
- with force field methods:
  - chemical reactions impossible, only conformational changes
  - then, not clear how meaningful it is to search for TS