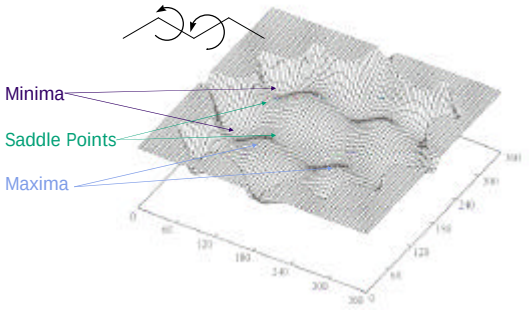
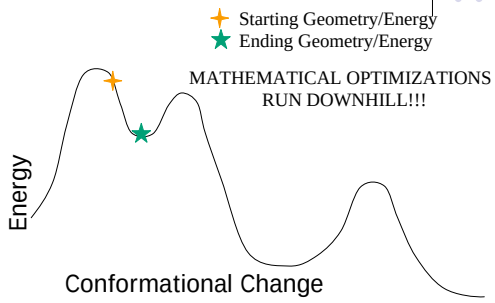
# Conformational Search Methods

## CHEM 8711/7711

## Potential Energy Surfaces




## Potential Energy Surfaces II




## Conformational Analysis

- Goal: to explore the energy surface of a molecule
- Needed:
  - A definition of conformational space
  - A search method
  - An energy determination method (force field)

## Conformational Space

- Cartesian coordinates (**x, y, z**)
- Internal coordinates (bond lengths, angles, **torsions**)
- Templates with a joining scheme (cyclohexane can appear as a chair, or two enantiomeric half-chairs, etc)

## Conformational Search Methods

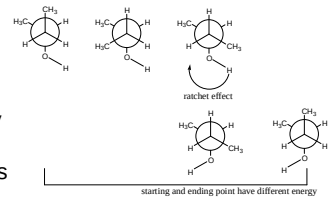
- Torsion angle driving
- Monte Carlo
- Artificial Intelligence
- Simulated Annealing
- Poling
- Etc.

## Torsion Angle Driving

- Called ‘Conformational Search’ in MOE (or ‘Systematic Search’ in newer versions)
  - Compute -> Conformations -> Conformational Search
- Steps a torsion angle from a starting to an ending point by a given increment
  - can be minimized completely at each step to give minima
  - other coordinates can be minimized to derive potential energy surface for torsional rotation
- Benefit: exhaustive

## Torsion Driving Limitations

- Not good for highly flexible molecules (too many torsions requires generation of a large number of conformations for evaluation)
- Explores large regions with high energy
- Ratcheting while exploring PES may result in different start and end points




## Class Exercise 1

- Build an alkane with 5 rotatable torsions and save it
  - Perform 2 torsion angle conformational searches with angle increments of 10º for only 1 dihedral angle, with and without optimization of the conformations
  - Take note of how many conformations are generated, and how many you end up with after minimization
  - Plot the energy for the search done without minimization
  - Perform conformational searches with angle increments of 10º for each dihedral angle, with and without optimization
  - Take note of how many conformations are generated, and how many you end up with after minimization

## Monte Carlo

- Uses a random kick of coordinates followed by minimization to find new minima
  - More effective on highly flexible molecules
  - Not exhaustive -> heuristics used to define end point:
    - if each of the lowest energy conformations has been found ~10 times, the search has probably found all the interesting ones
    - if duplicate conformations are found ~20 times in a row, the interesting conformations have probably all been found
    - (actual numbers to use depend on the flexibility of the system and your interest in a nearly exhaustive search!)
- In MOE there are two methods that include this
  - Compute -> Conformations -> RIPS Conformational Search
  - Compute -> Conformations -> Hybrid Monte Carlo

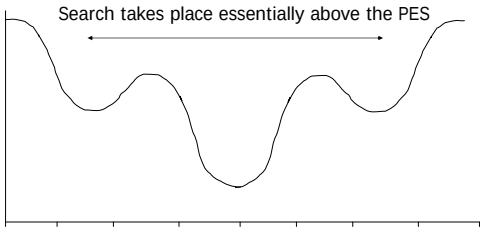
## Class Exercise 2

- Perform a RIPS conformational search on the molecule you built for the previous exercise
  - Take note of how many conformations are generated and how many are actually unique
- Perform a Hybrid Monte Carlo conformational search on the same molecules
  - Take note of how many conformations are generated and how many are unique

## Simulated Annealing

- Variant of molecular dynamics
  - Provides kinetic energy to the atoms
  - Recalculates atomic positions after a small time step (needs to be more frequent than molecular vibrations to prevent dissociation)
  - Higher temperatures generally used to give molecules sufficient energy to cross energy barriers
  - Cooling cycles used to minimize molecules
- Initially proposed as a way to drive the conformational search to the global minima

## Simulated Annealing II

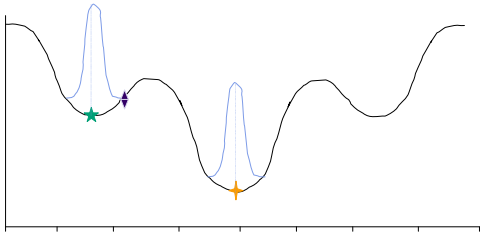



## Poling

- Goal: to sample accessible conformations, not necessarily only minima
- Justification: interactions between drug molecules and their biological target involve conformational changes in both the drug molecule and the target to generate the COMPLEX structure of lowest free energy – this is not necessarily identical to the lowest energy isolated structure

## Poling II

Once a minima is found, an energy penalty (pole) is added at that geometry, new minima are created



## Reading

- Chapter 8 through the end of 8.8 in Leach (First Edition – probably add one chapter for the Second Edition)