UiT
THE ARCTIC UNIVERSITY OF NORWAY

Biomolecular modeling

Bjørn Olav Brandsdal

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A tentative definition

Molecular modeling is the science and art of studying molecular structure and function through model building and computation
(T.Schlick – Molecular Modeling and Simulation)

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Why simulations?

«everything that living things do can be understood in terms of the jiggling and wiggling of atoms»
(Feynman's lectures on physics, 1963)

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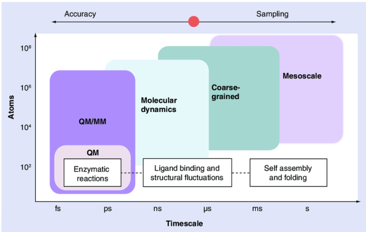
Time frames



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Modelling, how and what?

- modelling by deriving (semi-)empirical laws from data on observed phenomena
- modelling by following physical and chemical laws

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"The general theory of quantum mechanics is now almost complete. The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble"

Dirac, 1929

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Quantum mechanics

- Explicit description of the electrons
- Costly in terms of computer power
- Limited to systems containing a most a few hundred atoms

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Molecular mechanics

Ball and stick model: atoms are the smallest particle and are represented by spheres of a given radius

Component of the energy function:
- Deviations of bonds and angles from their reference values
- Rotation around bonds
- Interaction between non-bonded parts of the systems

Force fields are empirical, there is no "correct" energy function or parameters

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Thermodynamics

What does thermodynamics tell us?
- Every system seeks to achieve a minimum of free energy

- For complex formation:
  $\Delta G_{binding} = RT \ln K_a$ $(R = k_B N_A)$
- For conformational changes:
  $\Delta G_{conf} = k_B T \ln (P_{conf1}/P_{conf2})$

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Entropy and free energy

$G = U + pV - TS$

Gibbs (free) energy

entropy

enthalpy

Entropy

- *thermodynamic def.:* measure of the energy not available in the system for useful work in a thermodynamic process
- *statistical mechanics def.:* measure of the number of state a system can adopt, often taken as a measure of the number of disorder

$S = -k_B \times \sum (p_i ln p_i)$ $S = k_b ln\Omega$ (for Ω states equally likely)

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Entropy and free energy

$G = U + pV - TS$

Gibbs (free) energy

entropy

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Free energy

- engergy left once you have aid the price of entropy
- *statistical mechanics def.:*

$$G = -k_B T \ln(Z)$$

energy of each microstate

$$Z = \sum_i e^{-\beta E_i} \text{ (partion function)}$$

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Ergodic hypothesis

average over statistical ensemble = average over time

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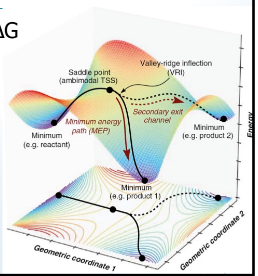
Potential energy surfaces

- states of high energy contribute to ΔG but are difficult to sample
- simulations most of the time limited to local minima
- sample the potential energy (E) is a function of all the coordinates in the system

E = f (positions of the nuclei)



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