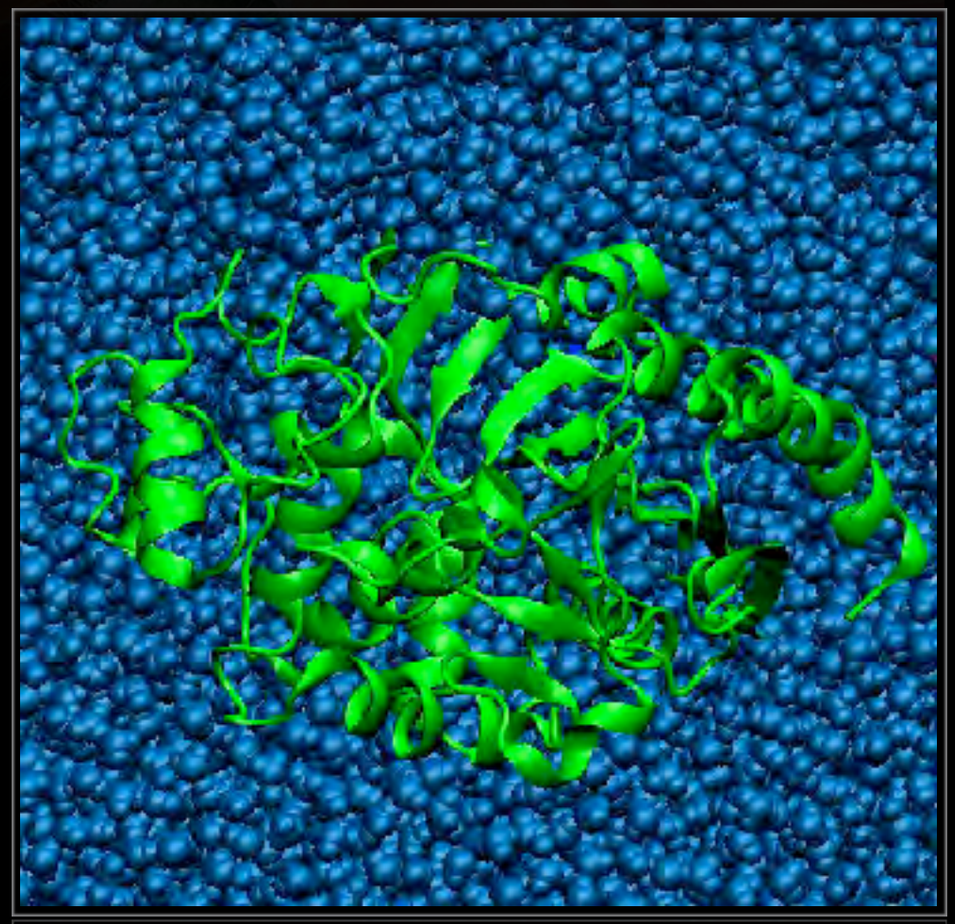
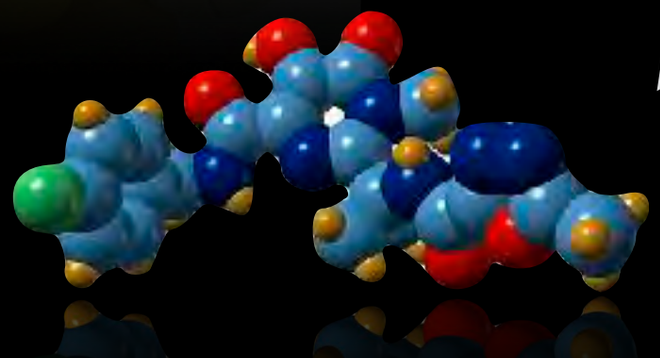
Lecture 1

Molecular Mechanics Force Field

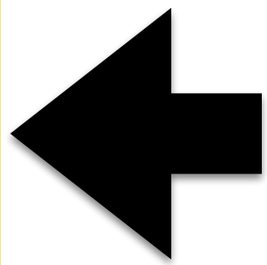




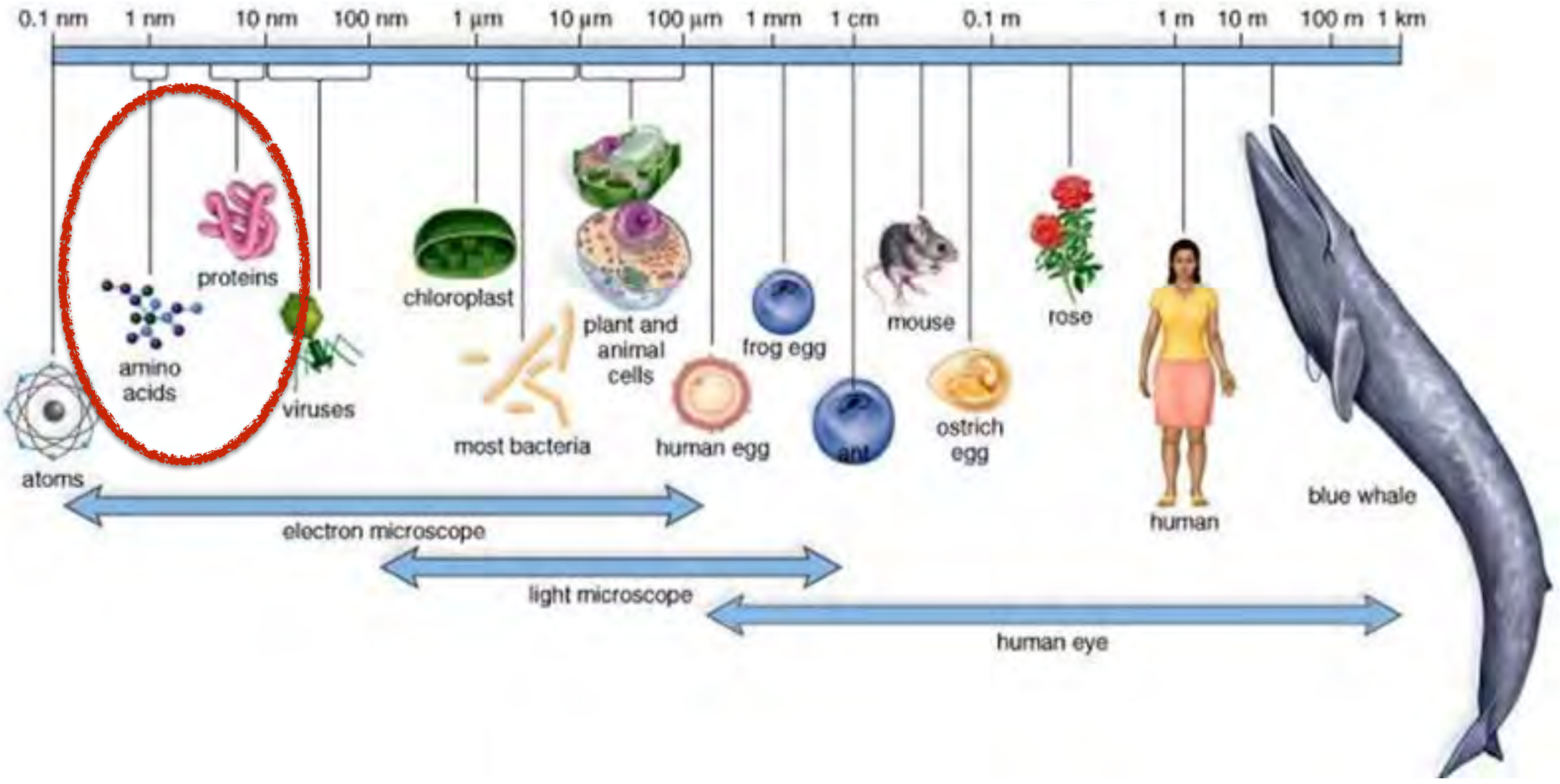
Understanding Molecular Systems!

- Biological functions - for e.g. of proteins
- Functions of materials - for e.g. photochemical properties of solids

Understanding the origin of properties
&
Predicting the properties



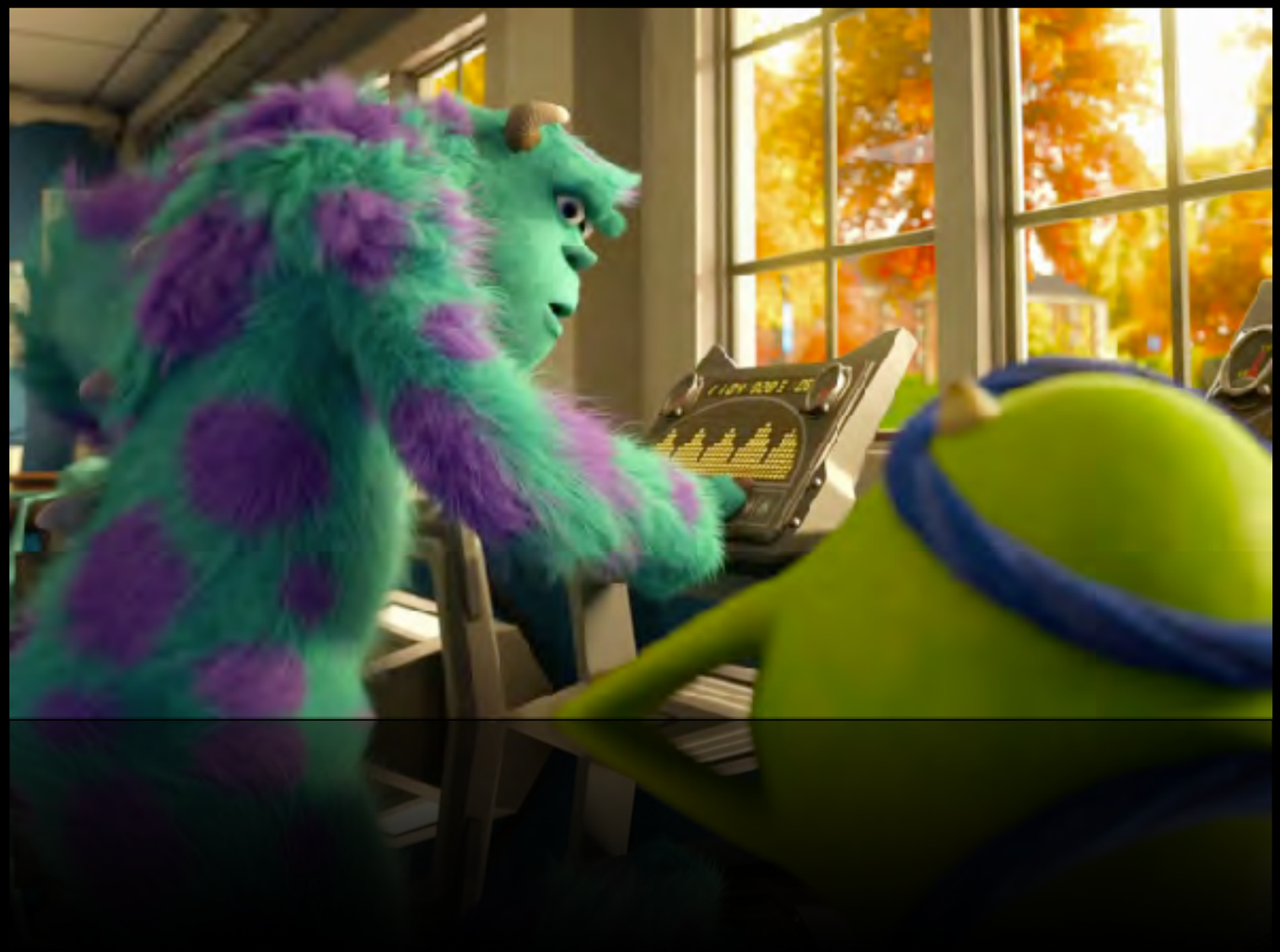
structure
&
dynamics
of molecules



Too small a size (compared to macroscopic size)

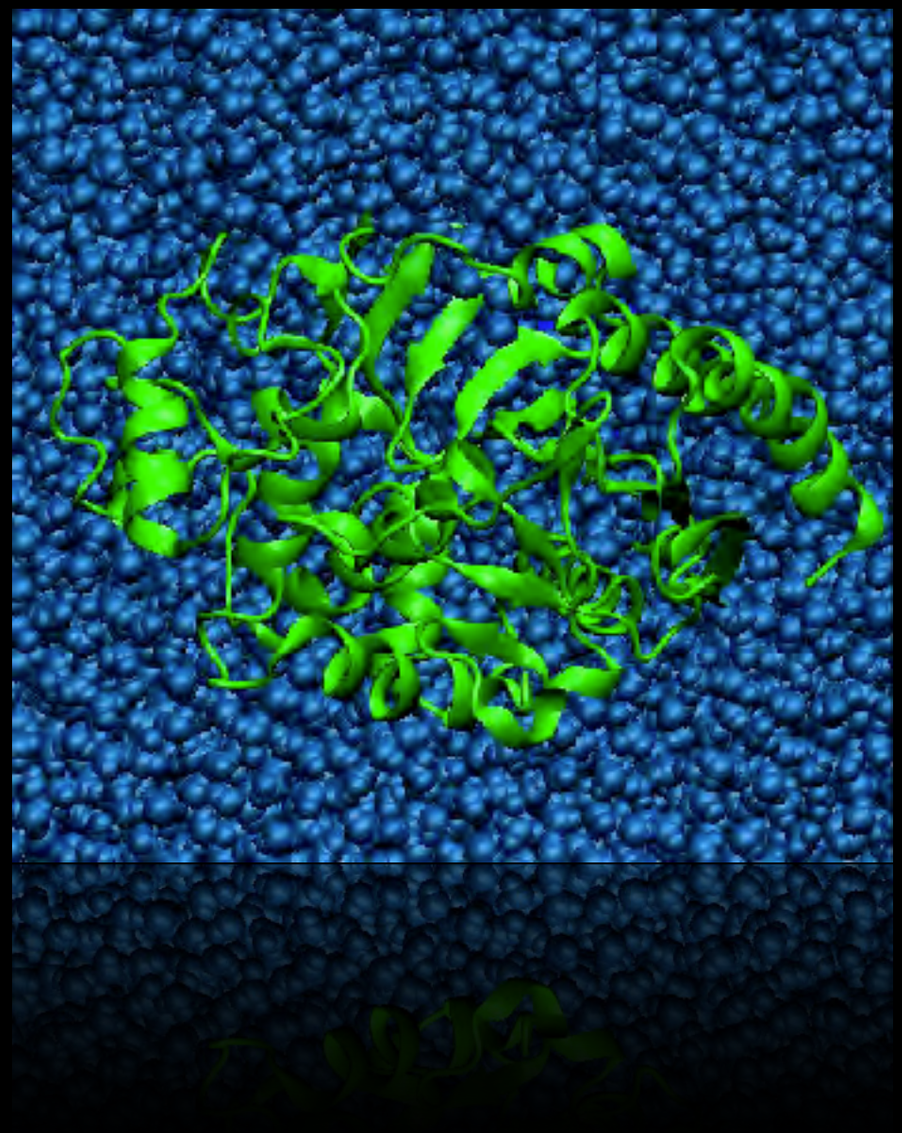
Dynamics: femtoseconds!

~1 frame per 0.1 seconds



Pixar/Disney Movies

~1 frame per 1×10^{-15} s



How to get structural informations at Angstrom Level?

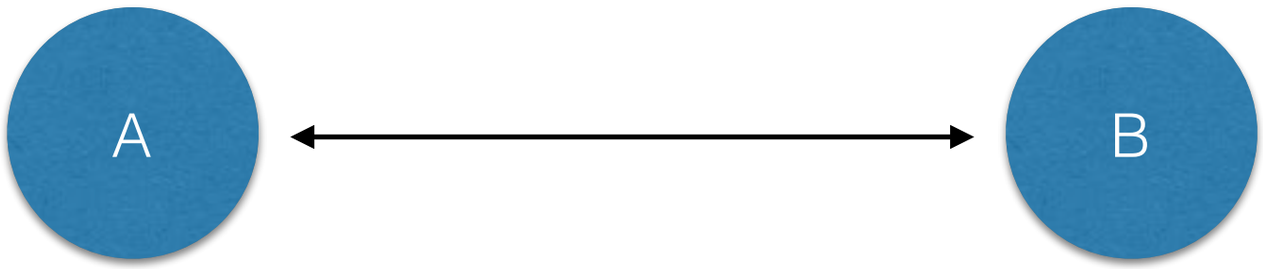
- X-ray crystallography (needs to crystalize)
- Nuclear Magnetic Resonance (NMR) Spectroscopy [not directly - need computer simulations]

How to get dynamic informations at femto second level?

- specialised spectroscopic techniques - but not applicable in general!

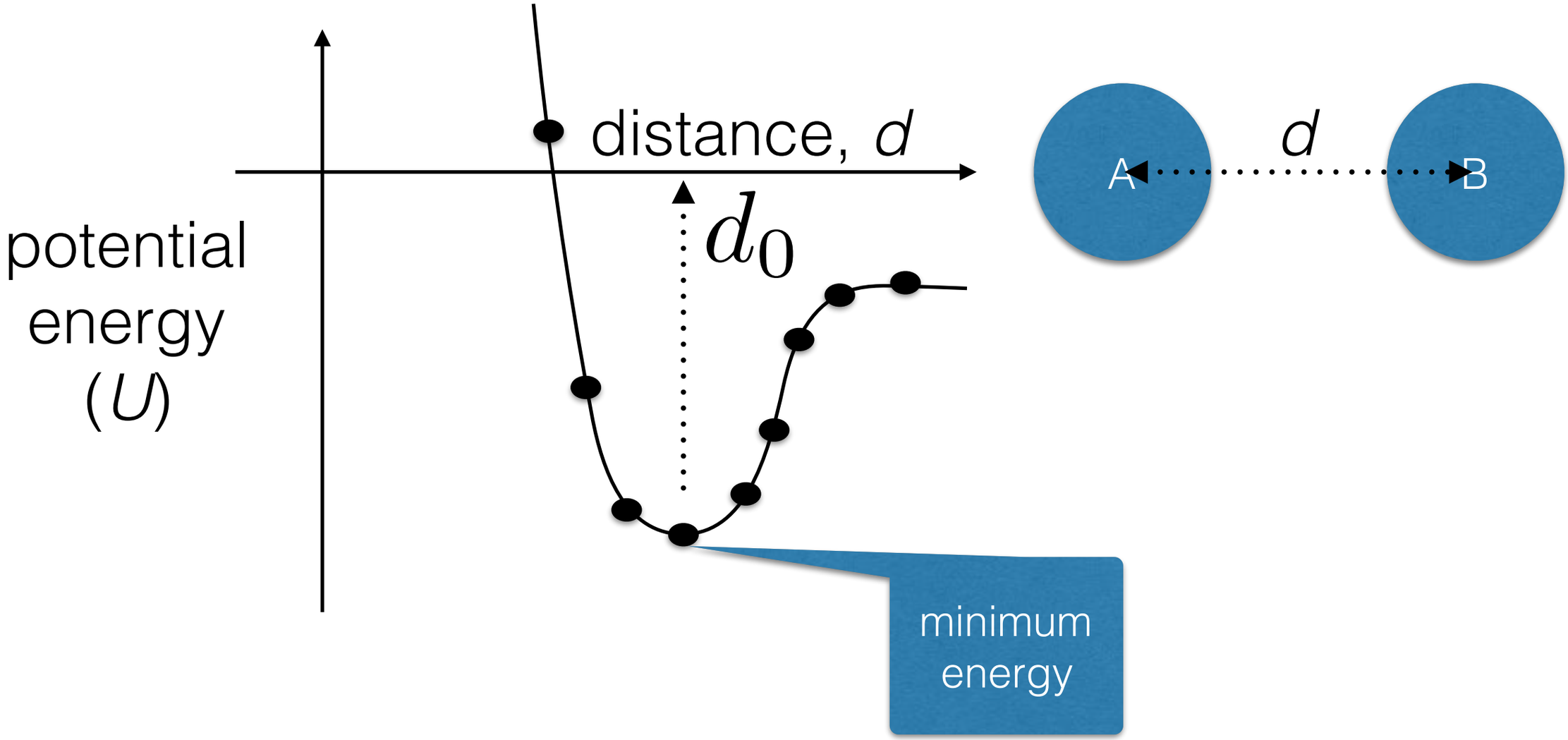
Computational Methods

- Can we predict the structure and dynamics of molecular systems by computations?



Stable structure has the lowest **potential energy**

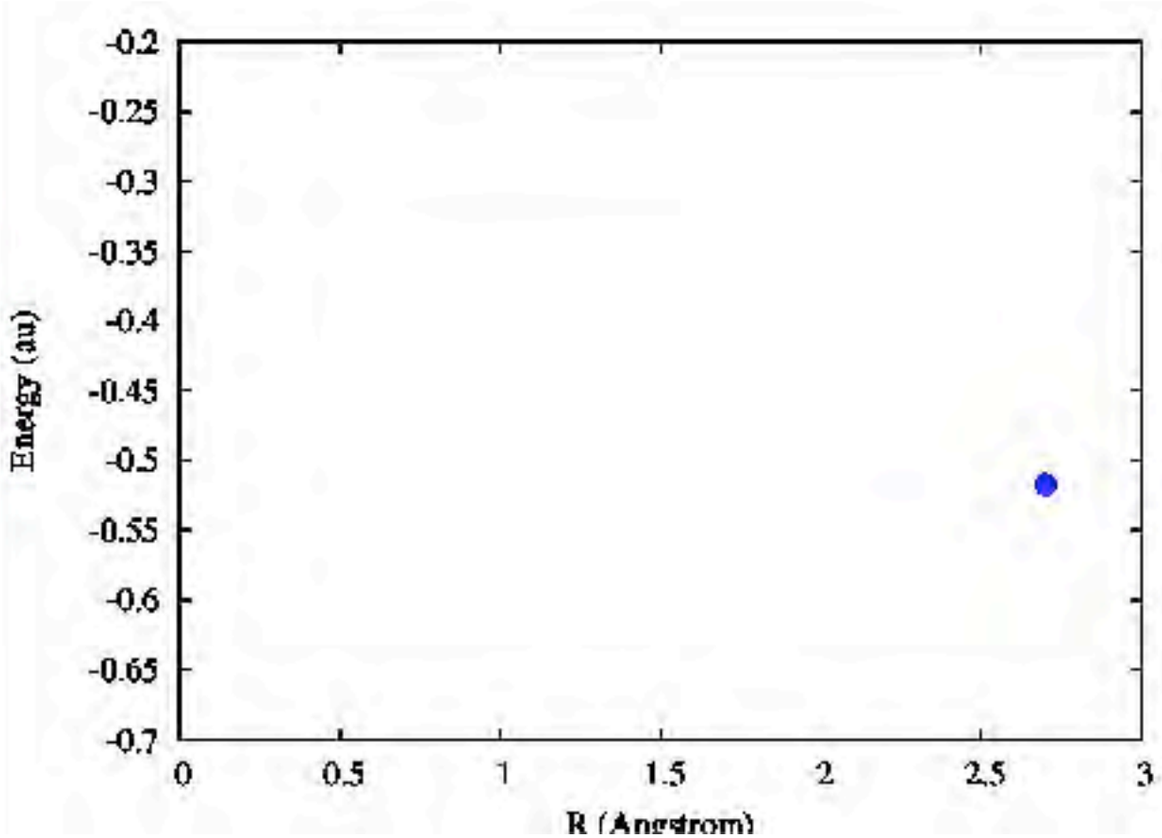
Total potential energy =
Potential energy of A +
Potential energy of B +
Energy due to A - B interaction



Computations predict that the most stable structure of A-B has a internuclear distance of d_0

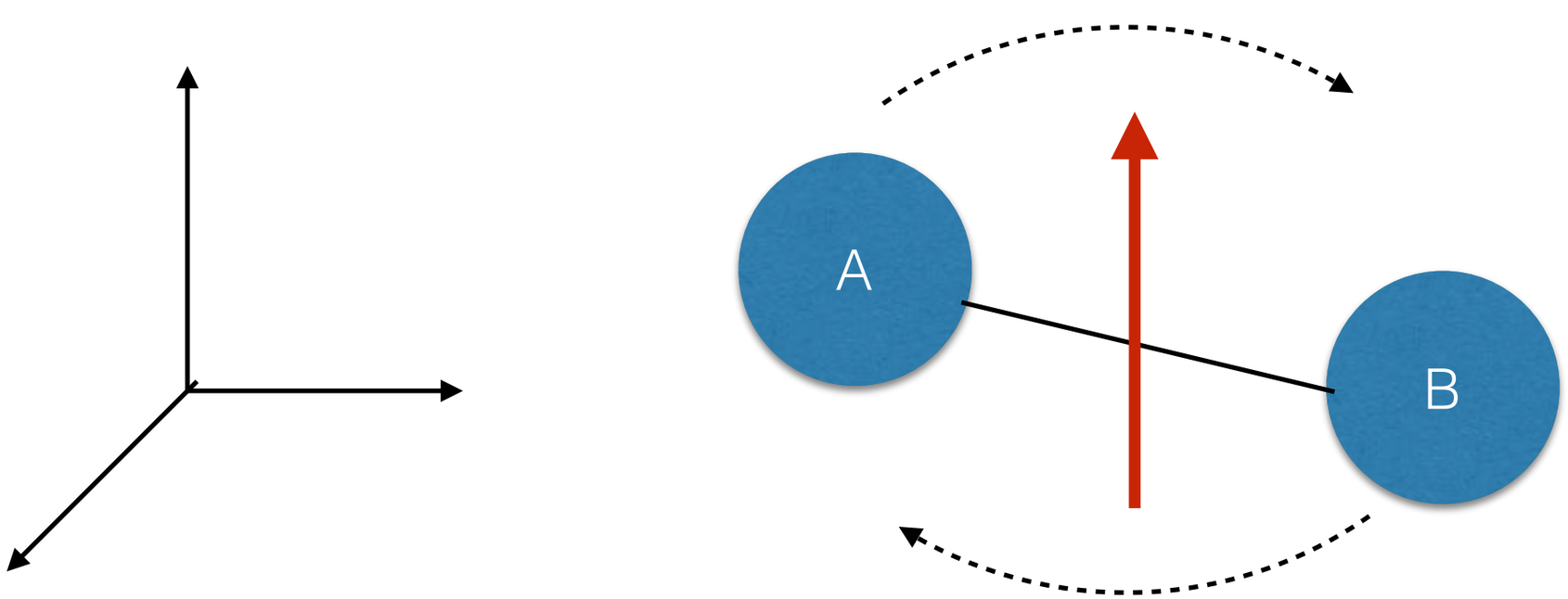
We know U can be computed by quantum mechanics

- By solving the Schroedinger equation: H_2^+ example from CHM102A lessons!

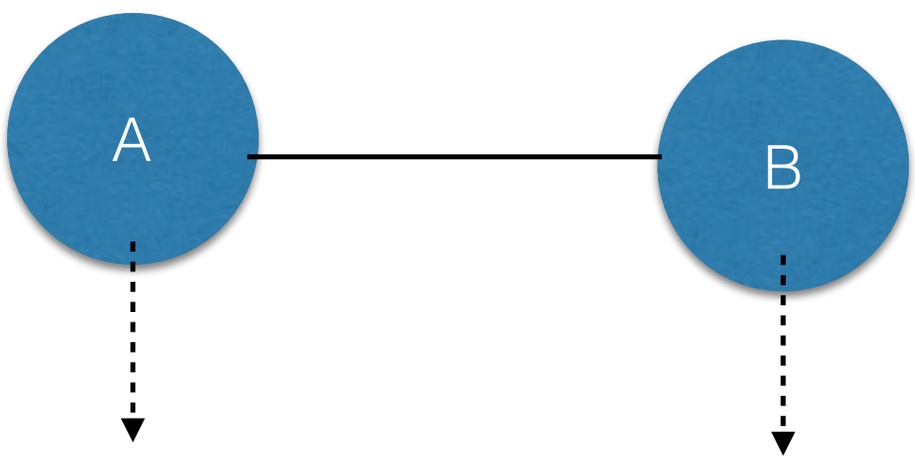


Question:

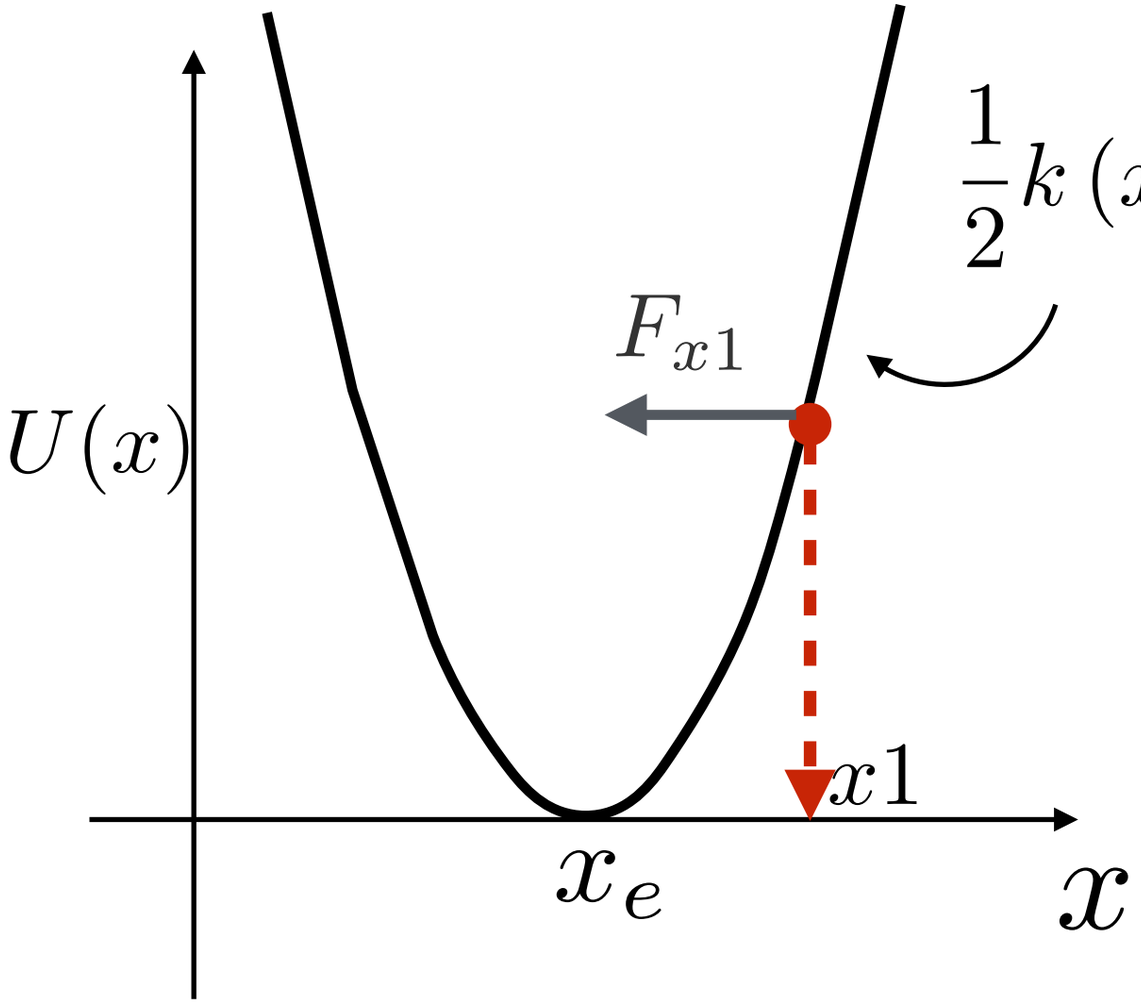
- Can the potential energy change if the molecule is rotating?



- Can the potential energy change if the molecule is translating?



Geometry Optimization



$$\left(\frac{dU}{dx}\right)_{x1} = k(x1 - x_e)$$

$$x_e = x1 - \frac{1}{k}\left(\frac{dU}{dx}\right)_{x1}$$

$$= x1 + \frac{1}{k}F_{x1}$$

- We generally don't know "k"
- Potential need not be harmonic

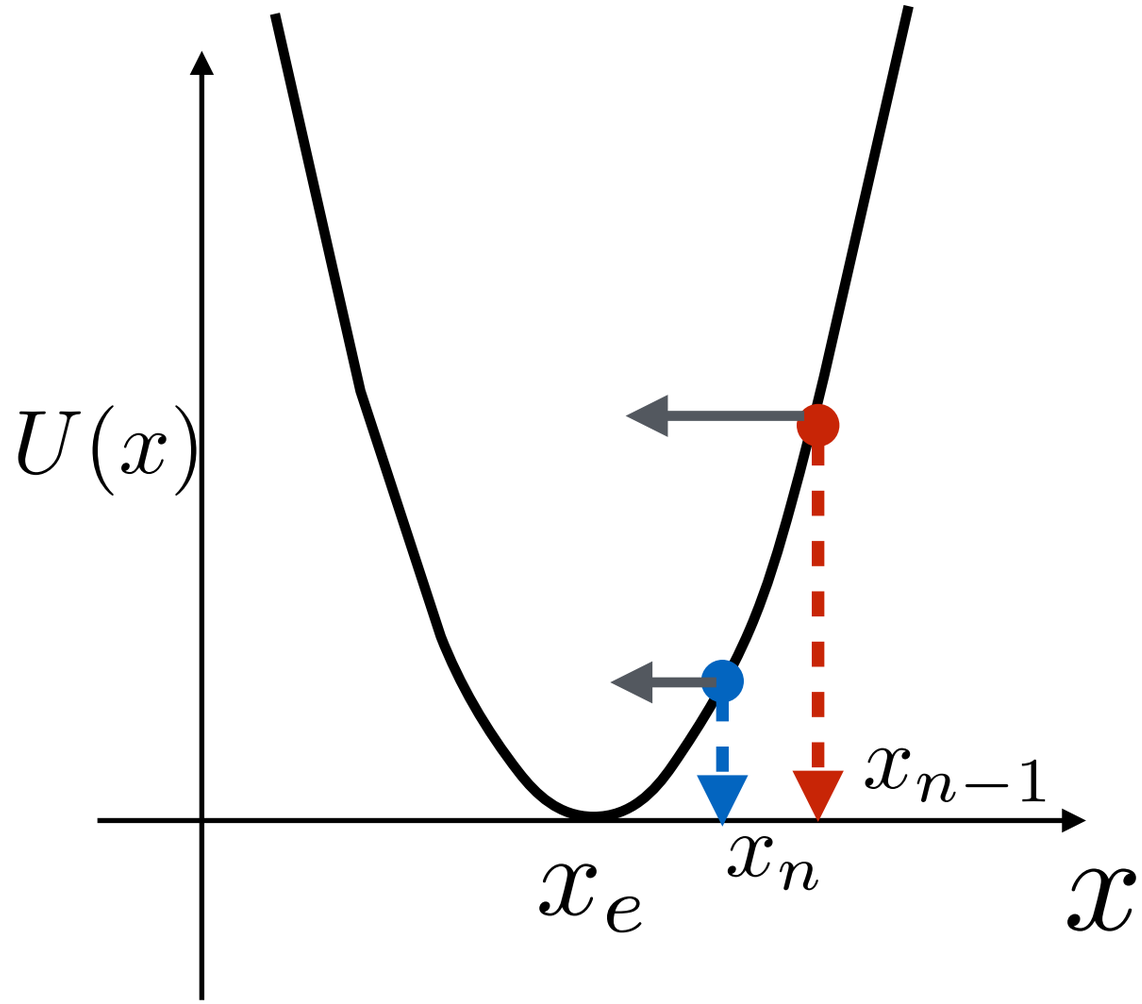
Steepest Descent

Iterative approach:

$$x_n = x_{n-1} - c\left(\frac{dU}{dx}\right)_{x_{n-1}}$$

Iterate this till

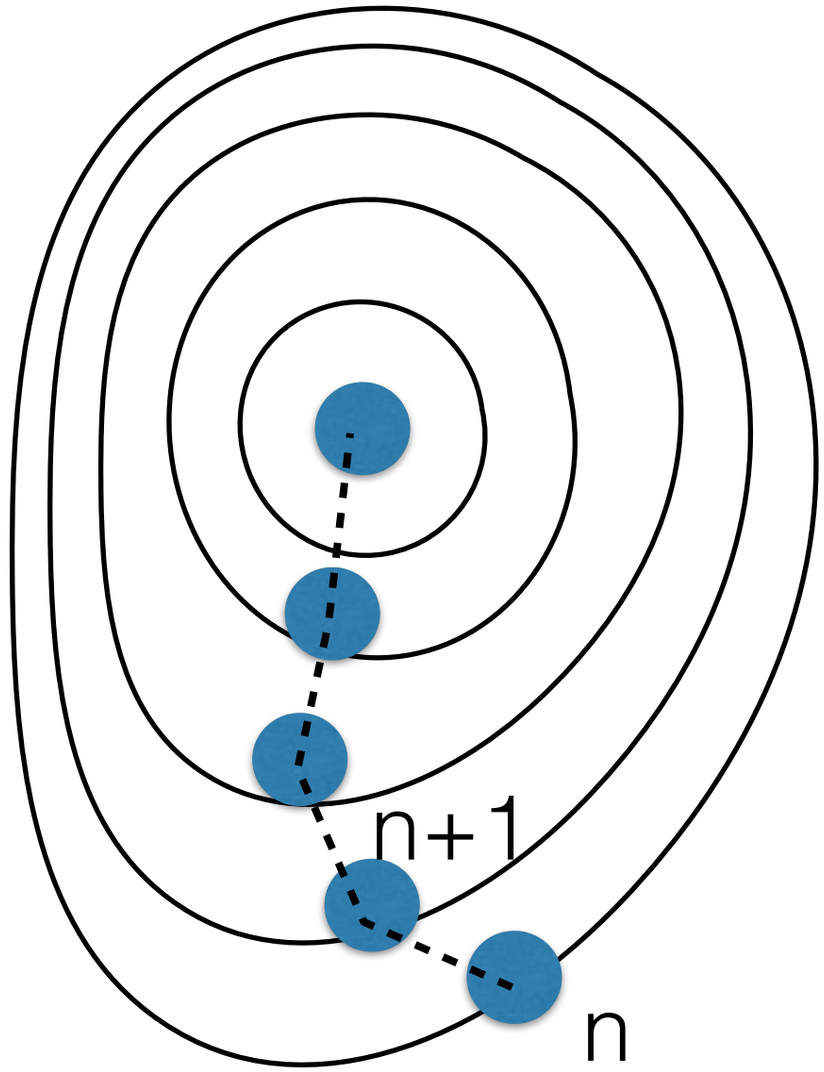
$$\left(\frac{dU}{dx}\right) \approx 0$$



If a potential is given, we can predict the minimum.

$$\mathbf{R}_{n+1} = \mathbf{R}_n - \gamma \nabla U(\mathbf{R}_n)$$

iterate till gradients
become very close to zero



Newton-Raphson Step

$$x_e = x_1 - \frac{1}{k}\left(\frac{dU}{dx}\right)_{x_1}$$

$$= x_1 - \left(\frac{d^2U}{dx^2}\right)^{-1}_{x_1}\left(\frac{dU}{dx}\right)_{x_1}$$

Iterative approach:

$$x_n = x_{n-1} - c\left(\frac{d^2U}{dx^2}\right)^{-1}_{x_{n-1}}\left(\frac{dU}{dx}\right)_{x_{n-1}}$$

In matrix form (for 3N coordiantes):

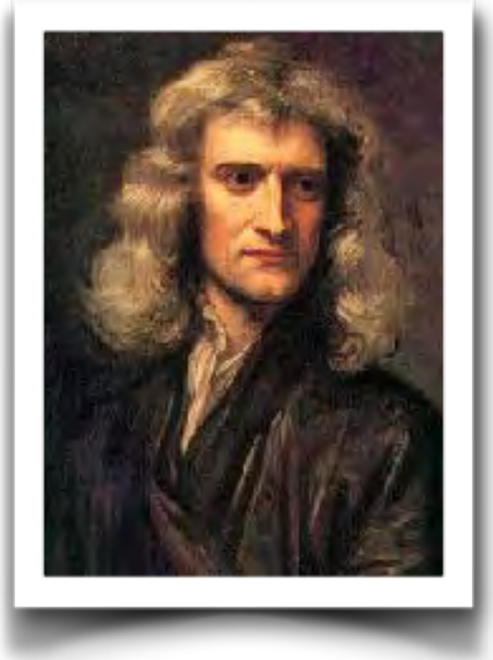
$$\mathbf{R}_n = \mathbf{R}_{n-1} - c\,\mathbf{H}^{-1}_{n-1}\,\mathbf{g}_{n-1}$$

Hessian

gradient

Computational methods could also predict dynamics

Classical Mechanics

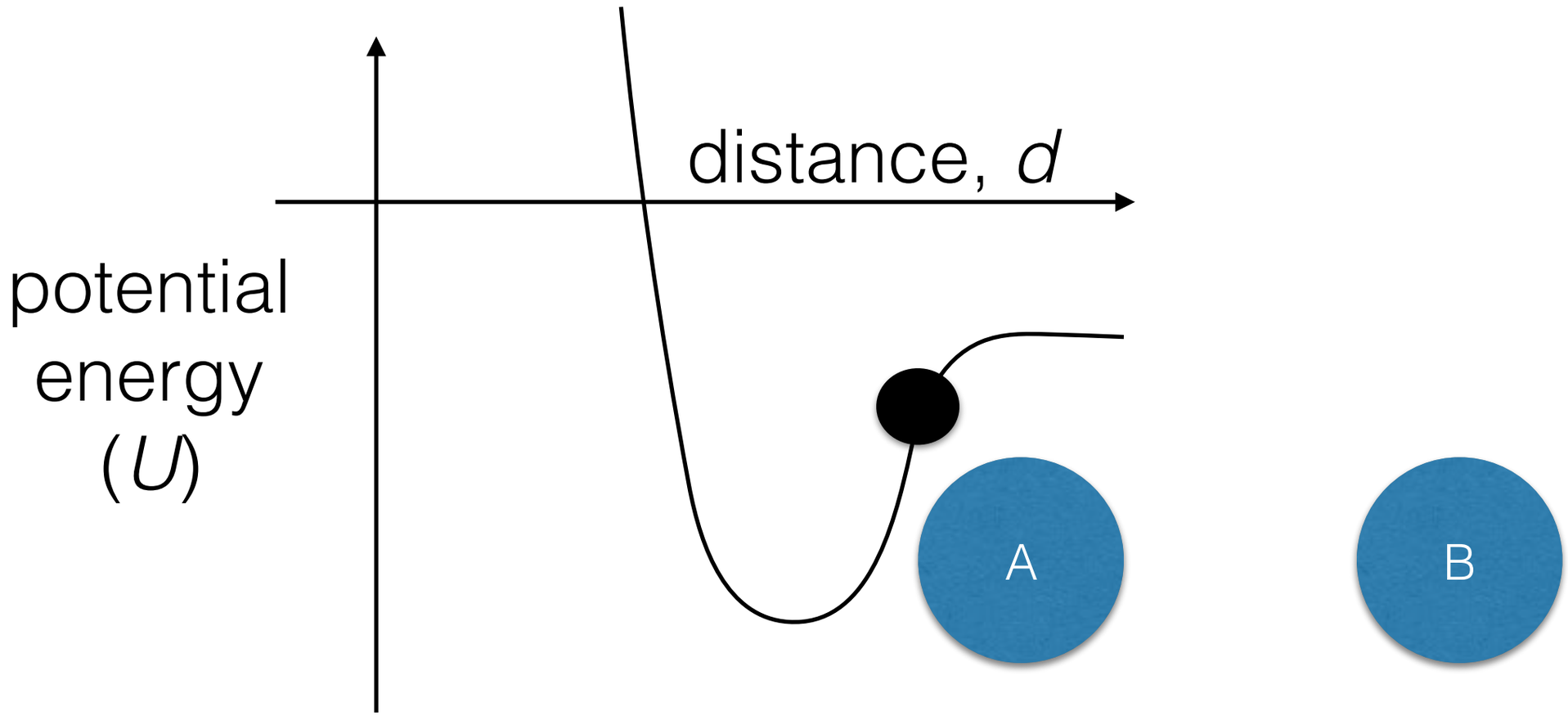


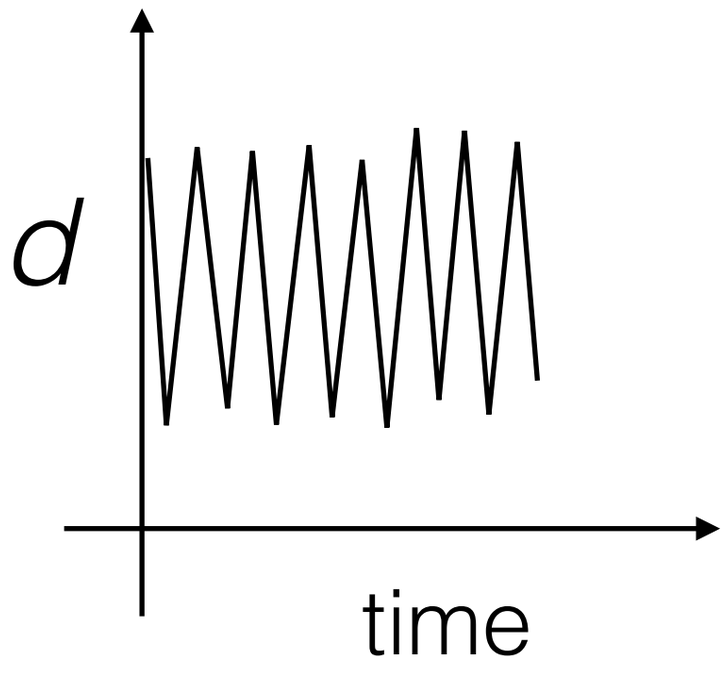
Equations of motion:

$$F = m\frac{d^2x}{dt^2} \qquad \& \qquad F = -\frac{dU}{dx}$$

Solving (integrating) the above differential equation to predict

$$x(t) \quad \dot{x}(t)$$


distance, d
potential
energy
(U)
A
B


d
time

Modeling a Protein

- We just need a description of the potential *U*
- How can we compute *U* for protein?

Solving Schroedinger Equation for Protein?

- No, that is not possible!

- Quantum mechanical calculations are limited to a few 100 of atoms (that too approximately!)

- How do we deal with proteins with 1000-100000 atoms?

Can we avoid quantum mechanics to compute the potential?

Nobel prize in chemistry 2013

Martin Karplus

Michael Levitt

Arieh Warshel

“for the development of multiscale models for complex chemical systems”

- Empirical ways to compute potential for molecular systems, in particular, bimolecular systems like proteins

- Quantum mechanics is not needed *per se*

- This empirical potential is **computationally cheap**

- This was a breakthrough, since now the structure of proteins, RNA, DNA can now be predicted. Also their equilibrium dynamics can be simulated.

These potentials are still used today in academics and industry!

How can one build an empirical potential for a complex system like protein?