An introduction to Molecular Dynamics

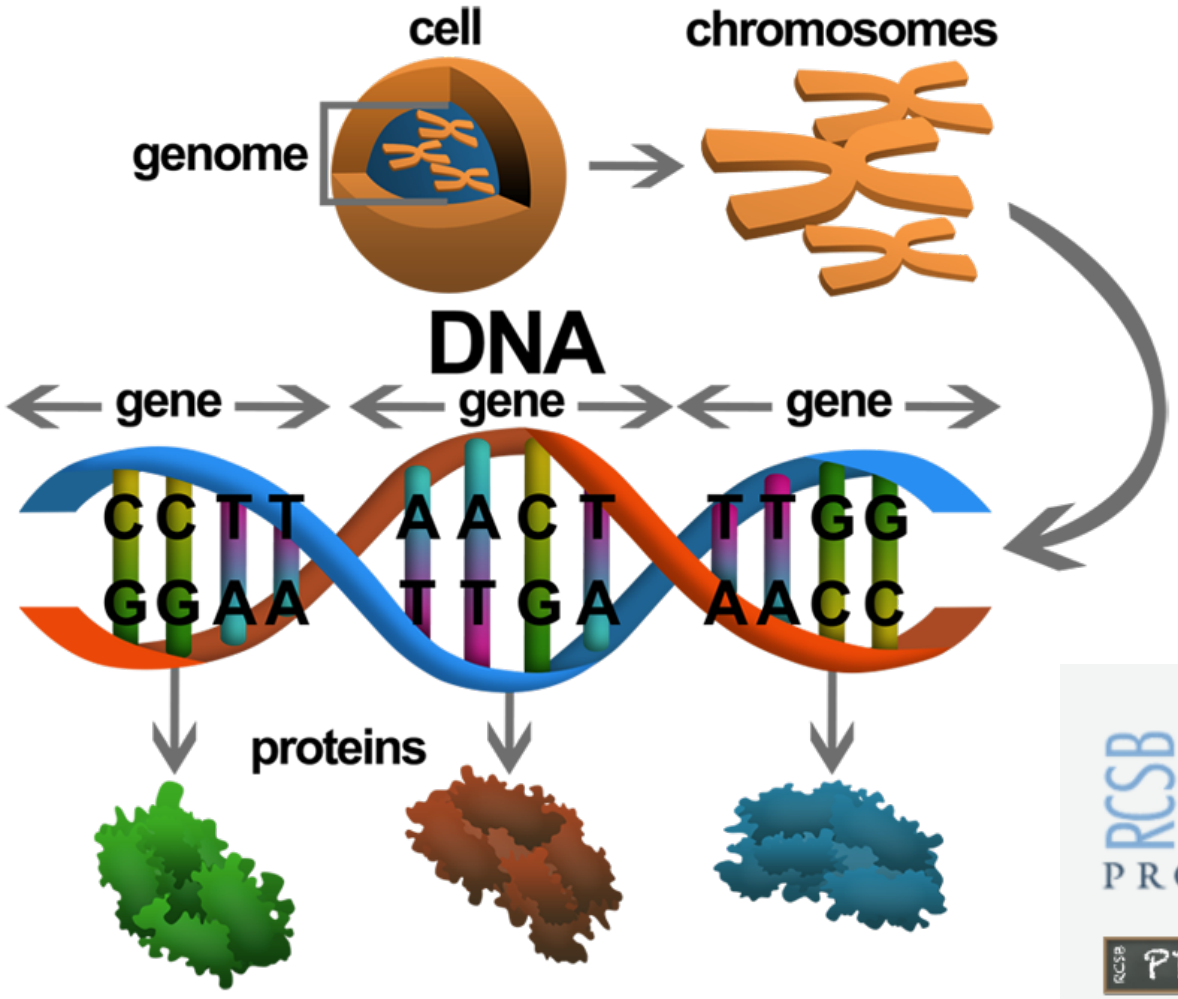
EMBO, June 2016

What is MD?


Loading Tables
• Nodes and edges can have data associated with them
– Gene expression data
Loading Networks
Loading Tables
• Nodes and edges can have data associated with them
– Gene expression data
– Mass spectrometry data
– Protein structure information
– Gene Ontology terms, etc
• Cytoscape supports multiple data types: Numbers, Text, Logical, Lists...


Loading Tables
• Nodes and edges can have data associated with them
– Gene expression data
Loading Networks
Loading Tables

Introduction to Molecular Dynamics



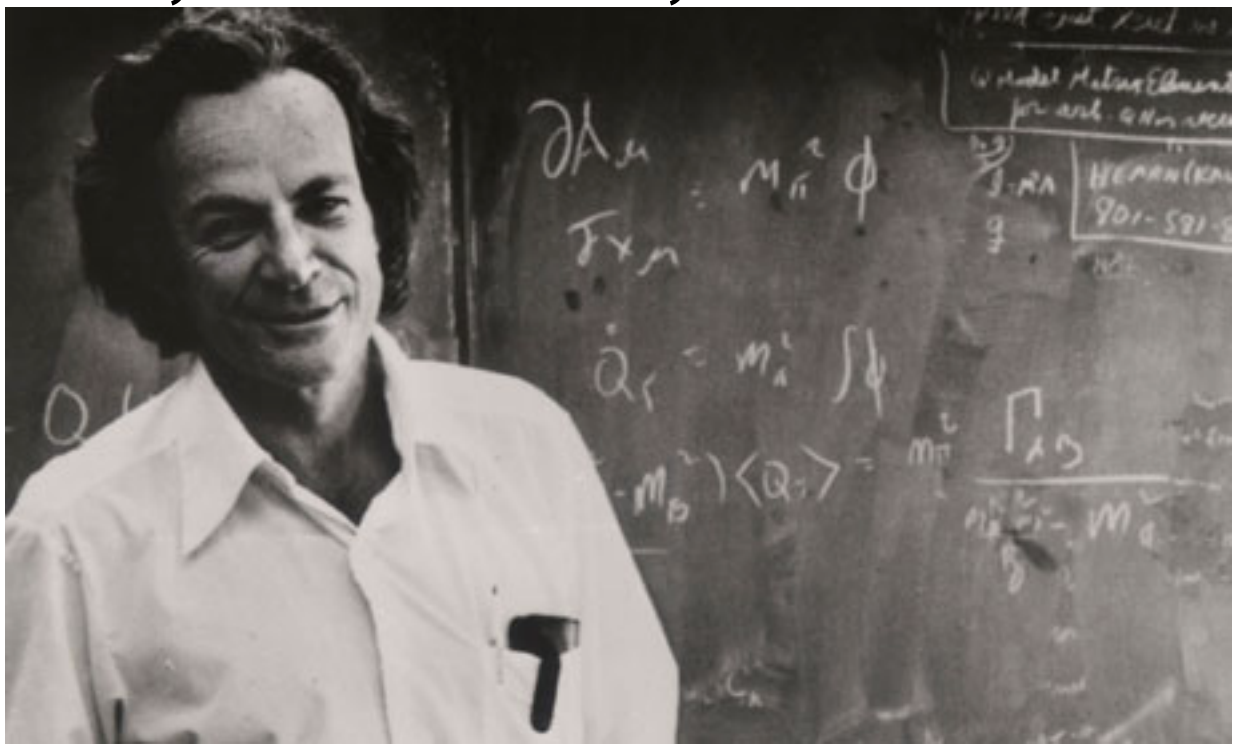
RCSB PDB
PROTEIN DATA BANK
An Information Portal to
119137 Biological
Macromolecular Structures

PDB-101 · WORLDWIDE PDB PROTEIN DATA BANK · EMDataBank Unified Data Resource for 3DEM · ndb NUCLEIC ACID DATABASE · StructuralBiology Knowledgebase

Introduction to Molecular Dynamics

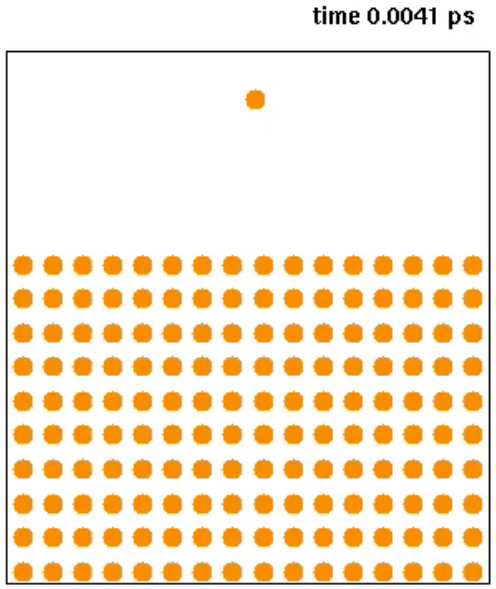
"everything that living things do can be understood in terms of the jiggling and wiggling of atoms."

The Feynman Lectures in Physics vol. 1, 3-6 (1963)



Introduction to Molecular Dynamics

- Molecular dynamics is a technique for computer simulation of complex systems, modelled at the atomic level.



- Example of a molecular dynamics simulation in a simple system: deposition of a single Cu atom on a Cu surface.

Introduction to Molecular Dynamics

- Dynamics
  - displacements from average structure - e.g., local sidechain motions that act as conformational gates in oxygen transport myoglobin, enzymes, ion channels

- Thermodynamics
  - equilibrium behaviour - e.g., energy of ligand binding

Simulations: Modelling Strategies

Ab initio QM Methods

Molecular Simulations

Force Field Methods

Quantum Mechanics

- postulates and theorems of quantum mechanics form the rigorous foundation for the prediction of observable chemical properties from first principles.
  - microscopic systems are described by wave functions that completely characterise all the physical properties of the system
  - operators applied to the wave function allow one to predict the probability of the system having a value or range of values.

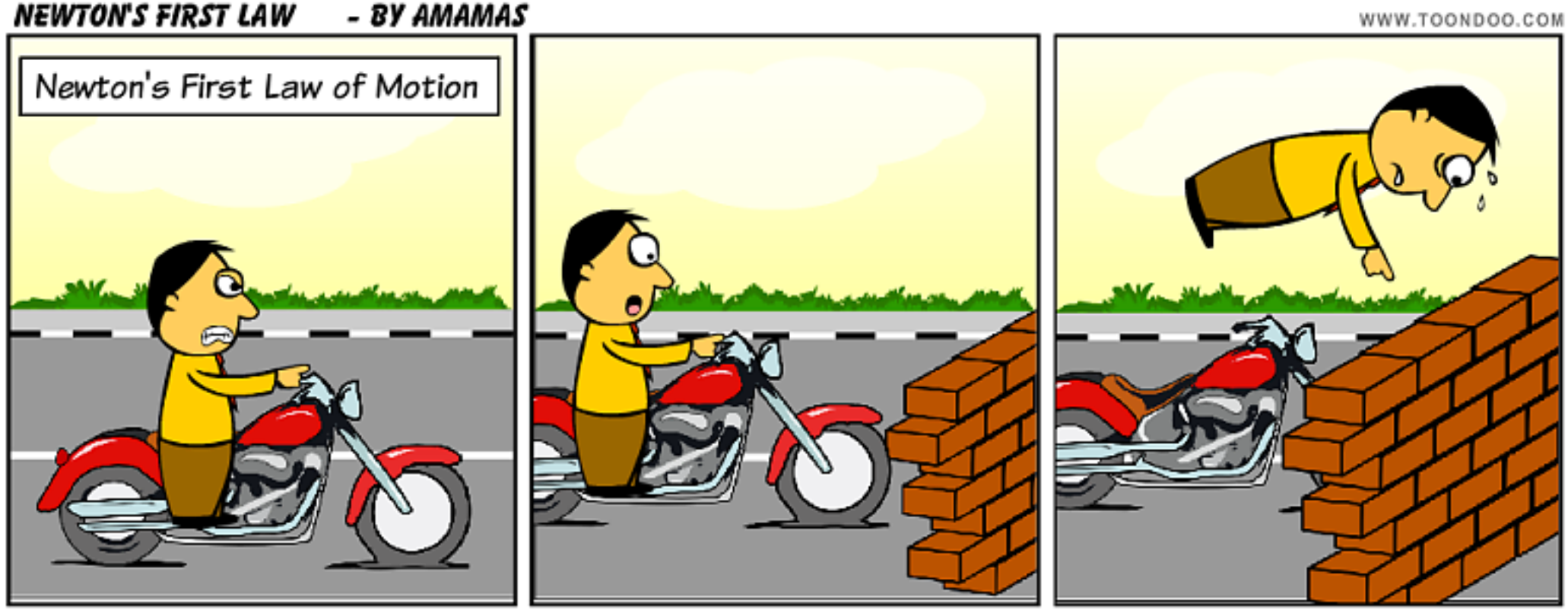
Quantum mechanics vs Force Field methods

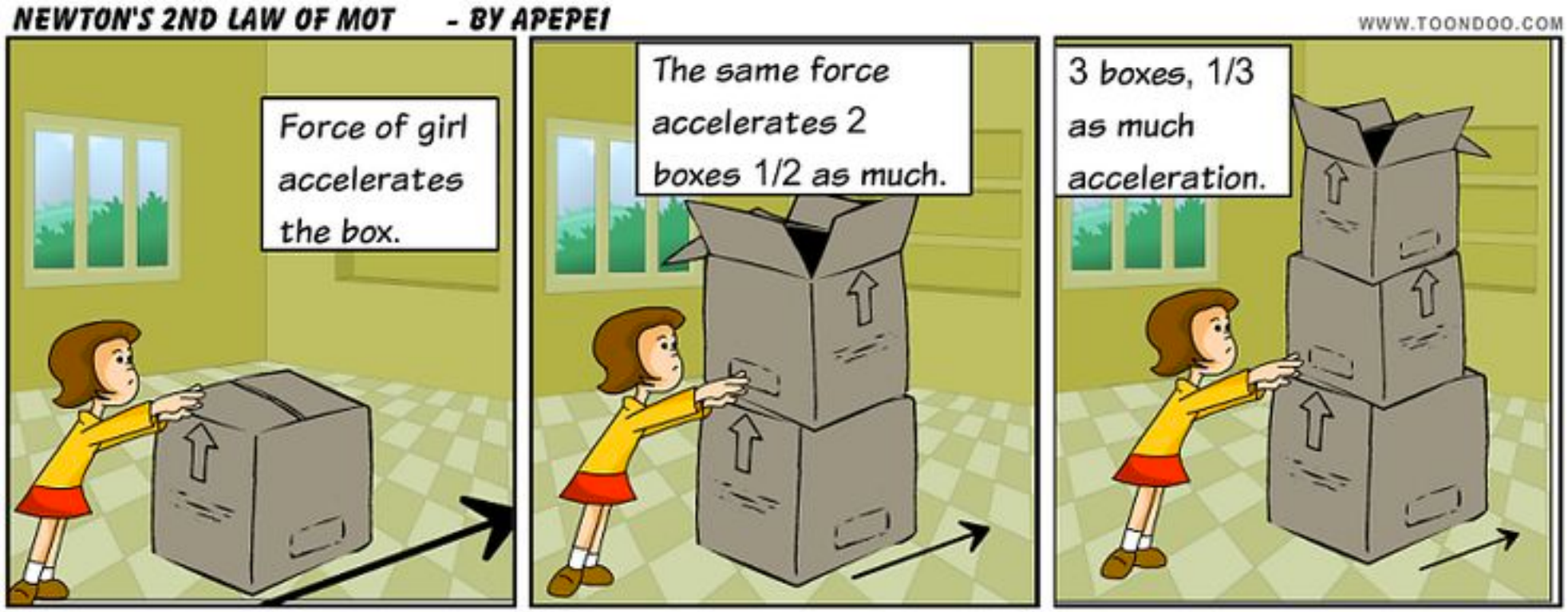
- QM deals with electrons in system
  - Accurate
  - Can deal with reactions (bond breaking etc.)
  - Often used to parameterise force fields
  - Large number of particles means infeasibly time-consuming for molecules as large as proteins
  - Static models only (no time)
- FF methods
  - Molecular mechanics
  - Cannot answer questions that depend on electron distribution in a molecule
  - But fast and surprisingly useful

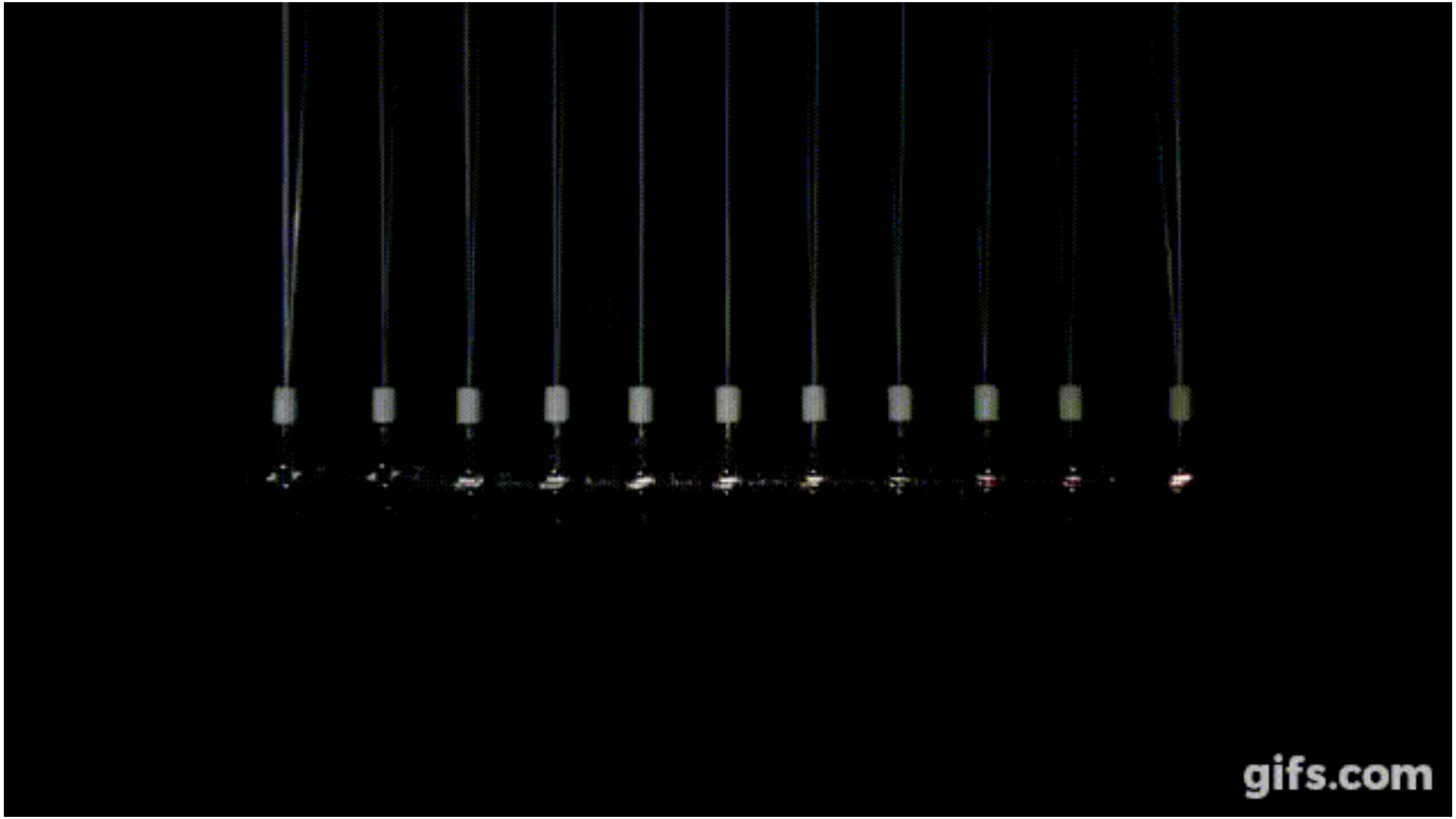
Introduction to Molecular Dynamics

MD simulations boil down to numerically integrating Newton's equations of motion

Newton's Laws of Motion


NEWTON'S FIRST LAW - BY AMAMAS
WWW.TOONDOO.COM
Newton's First Law of Motion


NEWTON'S 2ND LAW OF MOT - BY APEPE1
WWW.TOONDOO.COM
Force of girl accelerates the box.
The same force accelerates 2 boxes 1/2 as much.
3 boxes, 1/3 as much acceleration.


gifs.com

Introduction to Molecular Dynamics

MD simulations boil down to numerically integrating Newton's equations of motion

Newton's Laws of Motion

1. A body maintains its state of rest or of uniform motion in a straight line, unless acted upon by a force.
2. The applied force is equal to the rate of change of momentum.
3. For every action, there is an equal and opposite reaction.

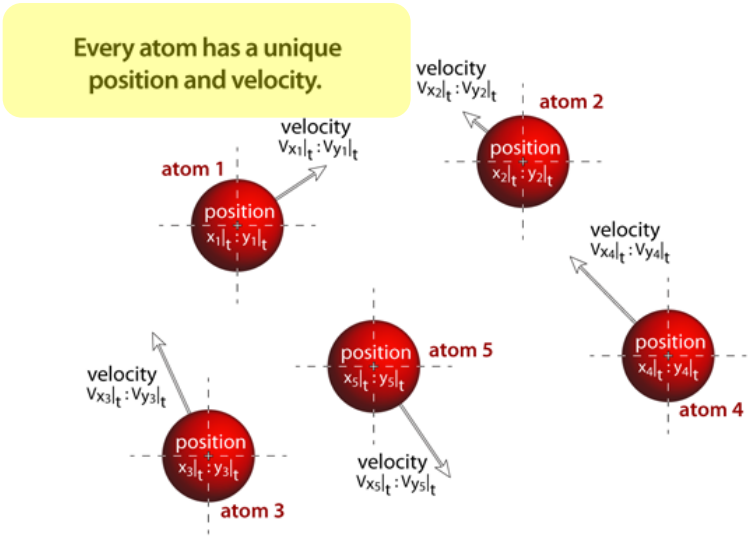
Introduction to Molecular Dynamics

- Use Newtonian mechanics to calculate the net force and acceleration experienced by each atom
- Each atom *i* is treated as a point with mass m_i and fixed charge q_i
- Determine the force F_i on each atom:

$$\vec{F}_i = m_i a_i = -\frac{\mathrm{d}V}{\mathrm{d}r_i}$$

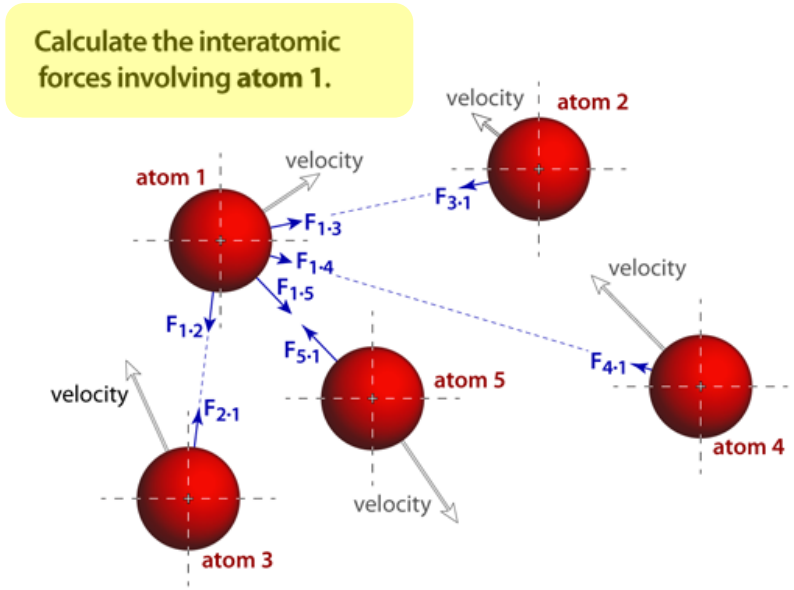
- Use positions and accelerations at time *t* to calculate new positions at time $t_n + t_{n+1}$

Introduction to Molecular Dynamics



$F = ma$

Forces are derived from interatomic potential functions (analytical approximations)



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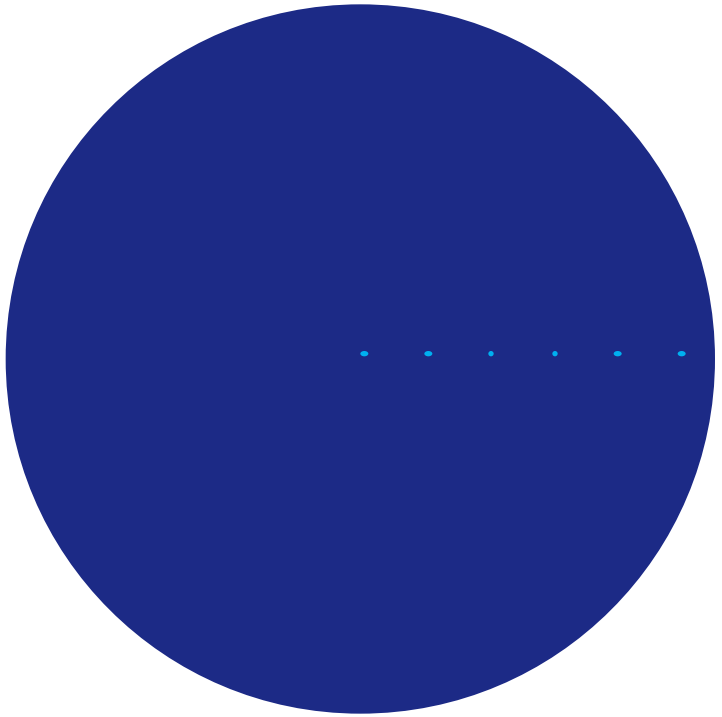

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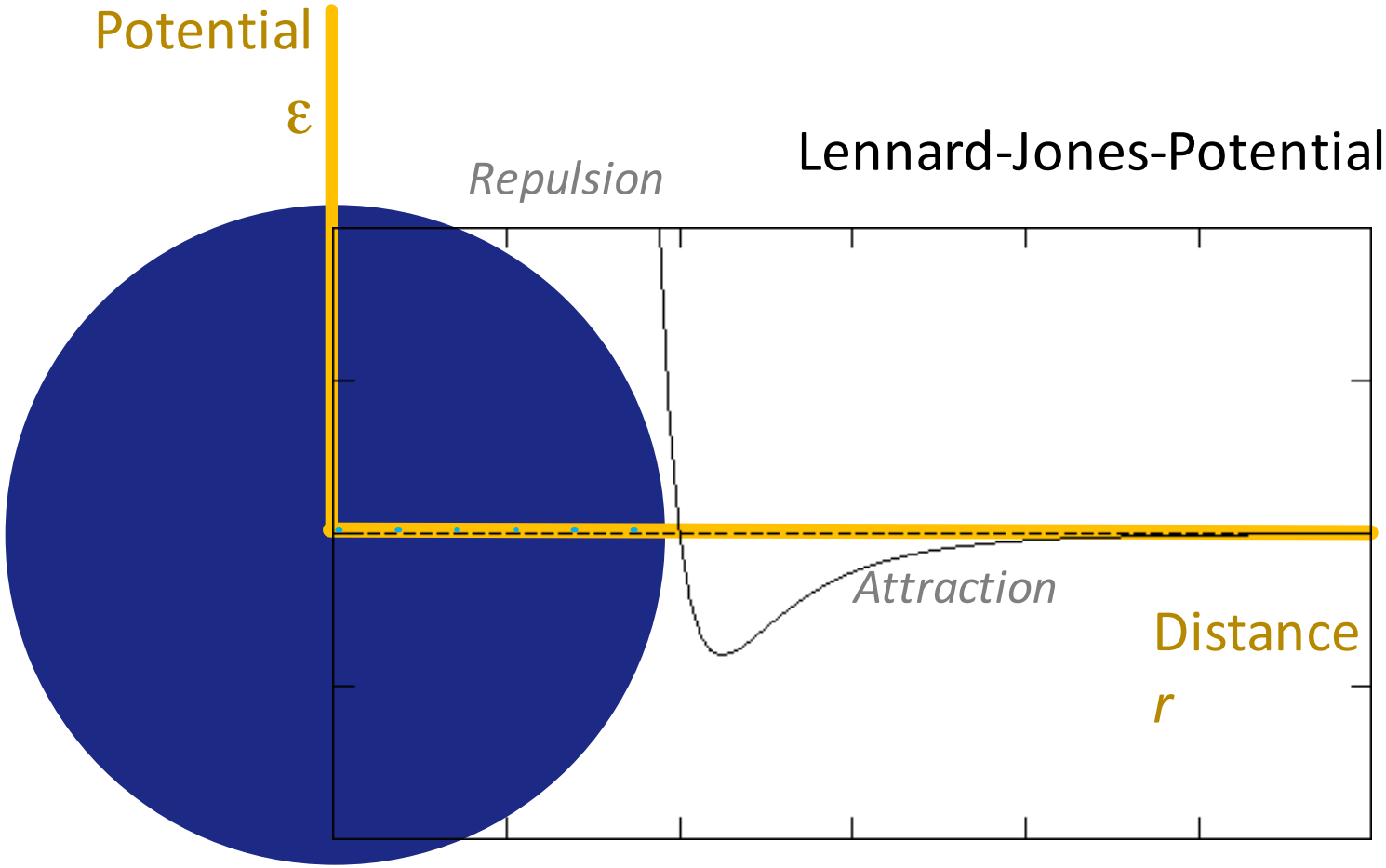

mathematically simple model that approximates the interaction between a pair of neutral atoms or molecules

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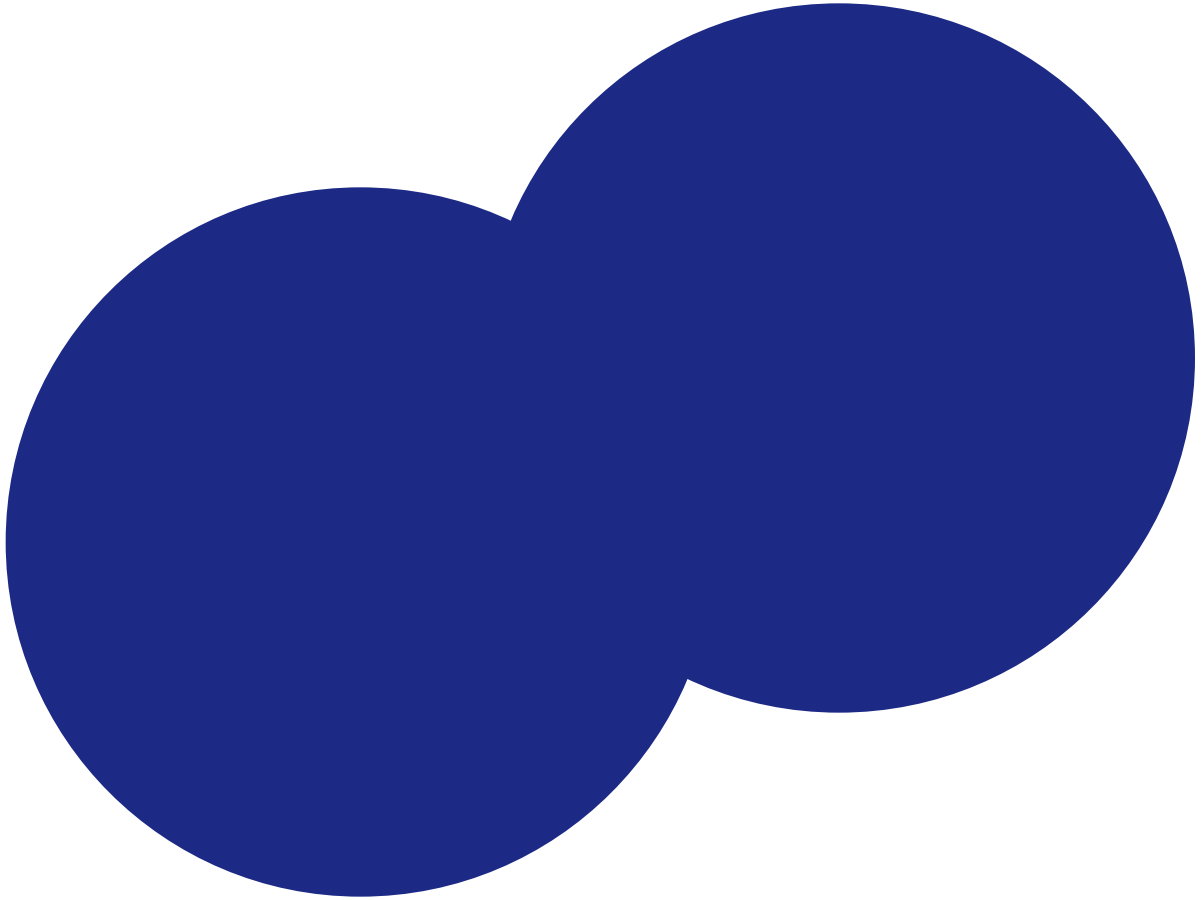

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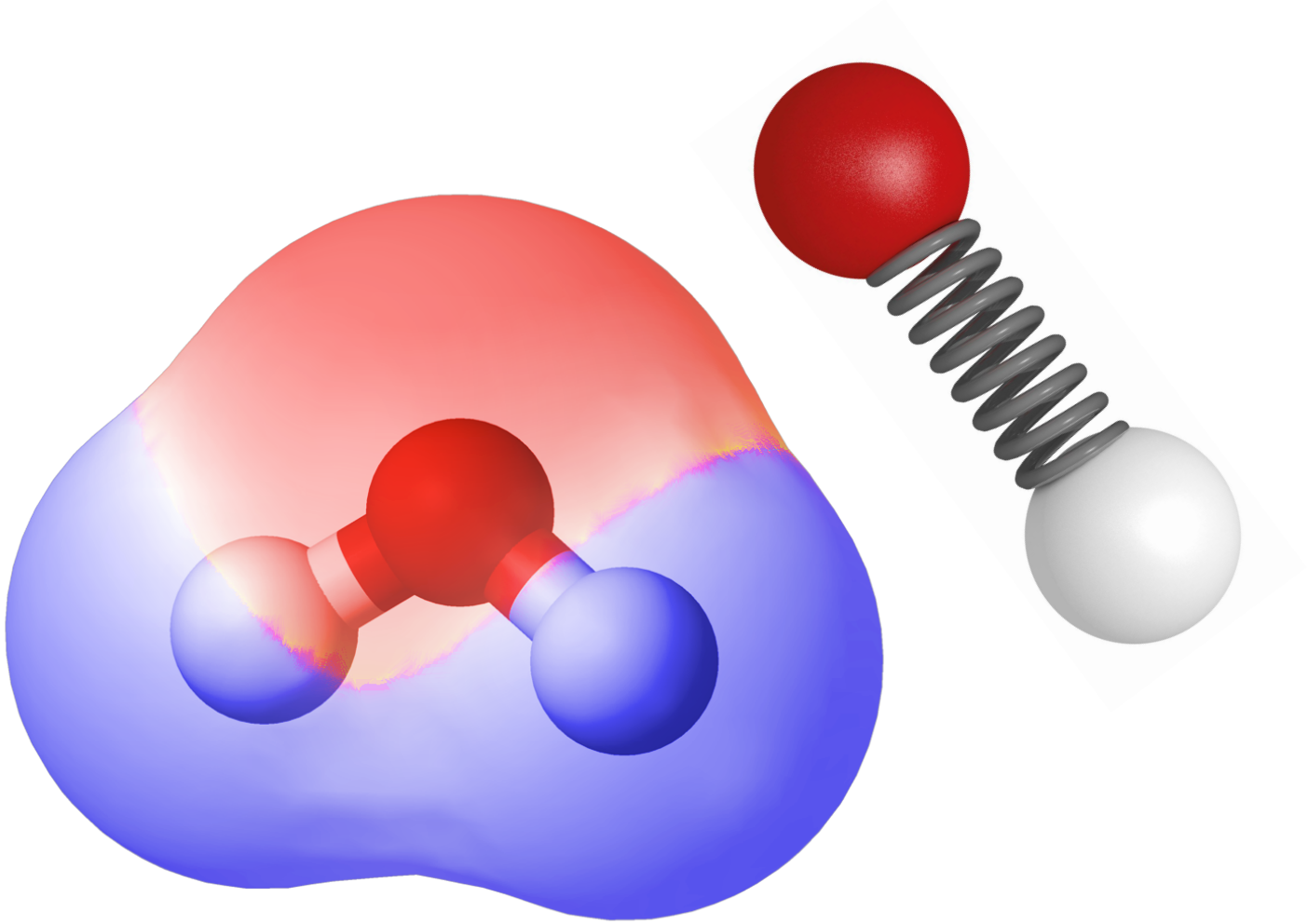

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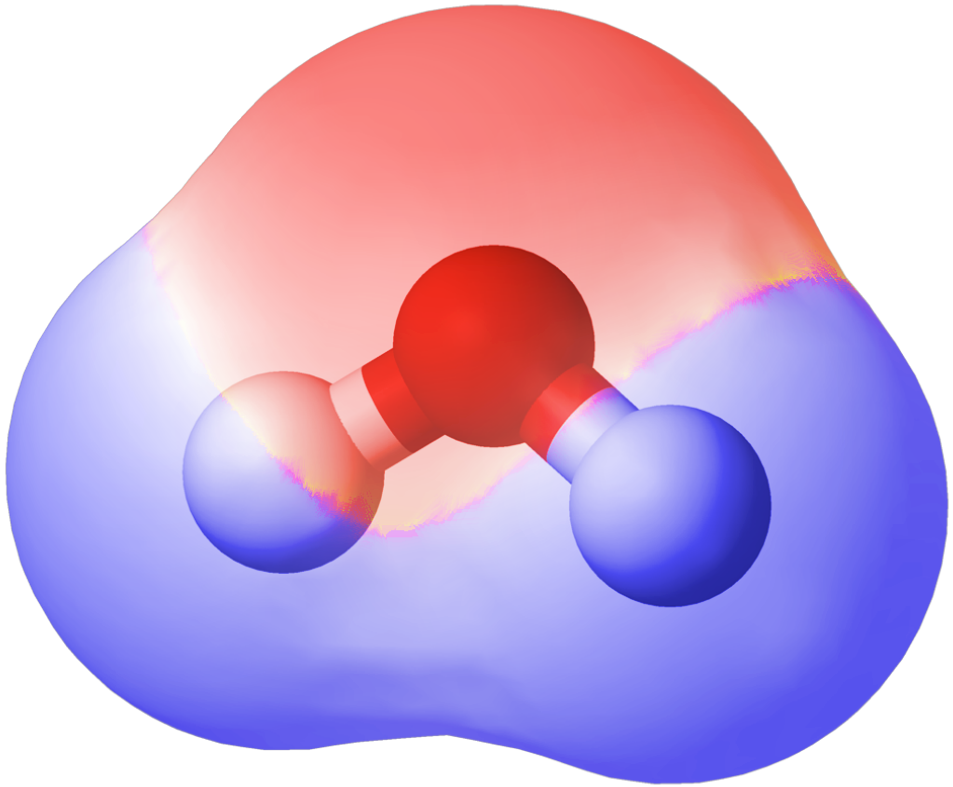
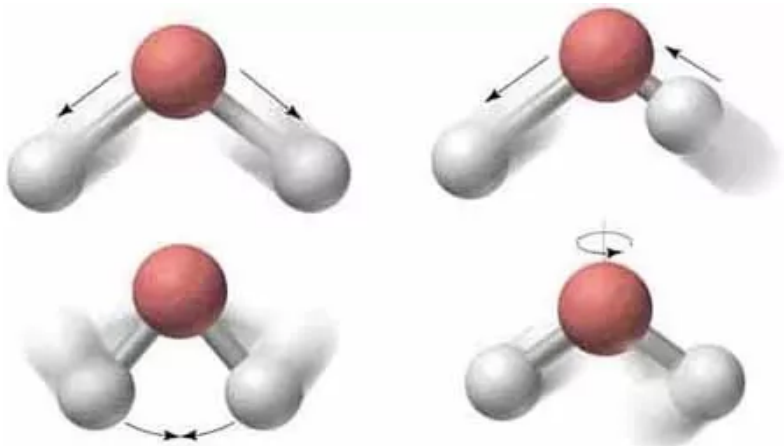
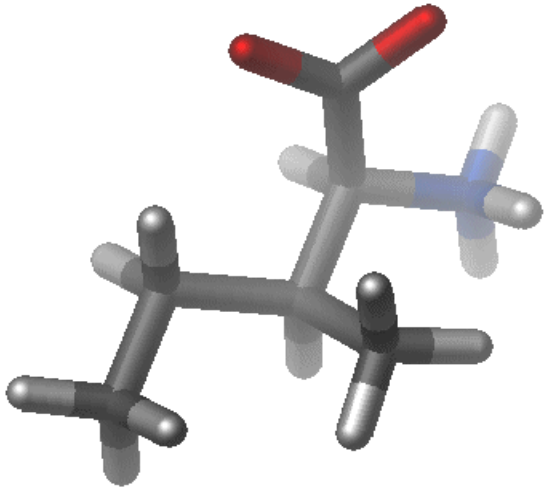




Introduction to Molecular Dynamics

A force field is made up by the contributions of many terms that represent the different types of interactions between the atoms of the protein molecule (energy function)

- van der Waals energy
- Electrostatic energy
- Hydrogen bond
- Bond energy
- Bond angle energy
- Dihedral angel energy



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$$E_{total} = E_{bonded} + E_{non\text{-}bonded}$$

$$E_{bonded} = E_{bond} + E_{angle} + E_{dihedral}$$

$$E_{electrostatic} + E_{van\,der\,Waals} = E_{non\text{-}bonded}$$

Example of a Single Step

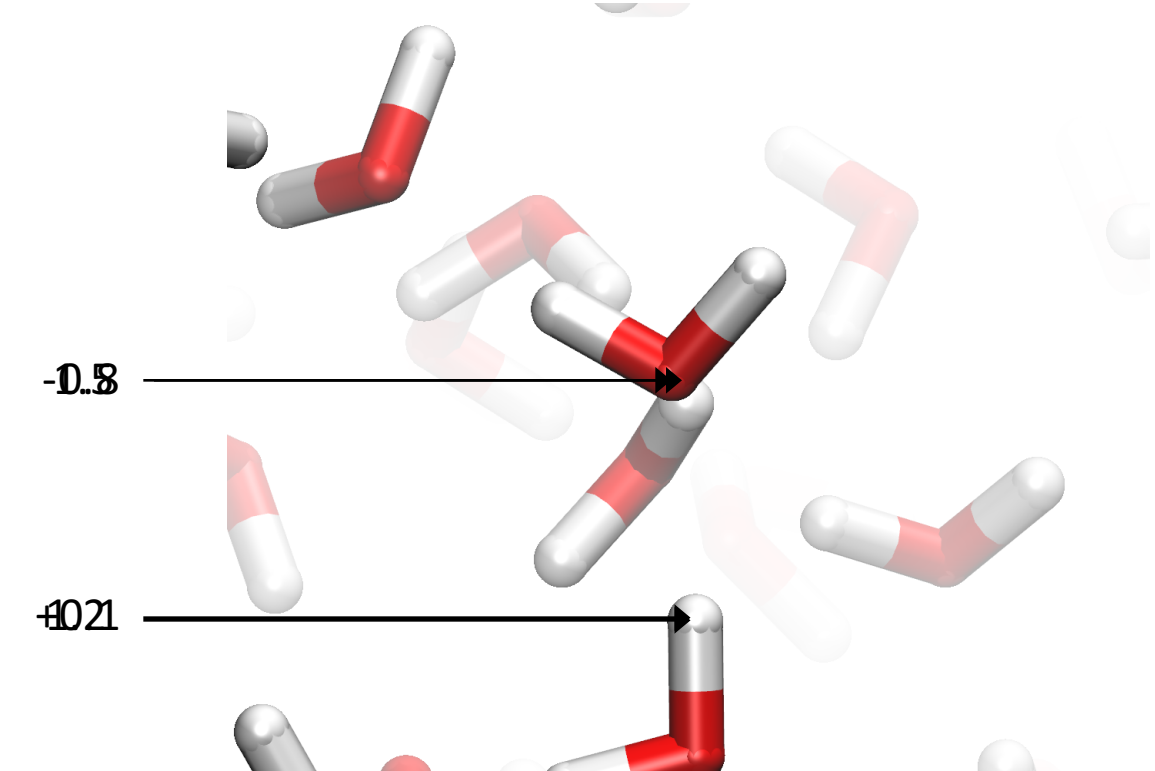
- Calculates forces acting on each atom
- Predicts new position after 2 fs (10^{-15})
- Takes single step and recalculates forces
- Repeat…

Coulomb's Law:

$$F = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

Lennard-Jones:

$$\left(\frac{r_{0ij}}{r_{ij}}\right)^{12} - 2\left(\frac{r_{0ij}}{r_{ij}}\right)^{6}$$



What is Molecular Dynamics

- Use force fields to describe molecular properties
  - These force fields are tuned to reproduce experimental observables
  - Specialised for particular molecules (e.g. Glycam)

- μs (10^{-6}) simulations of large (100k atoms) are now feasible
  - Exponential growth in computing speed

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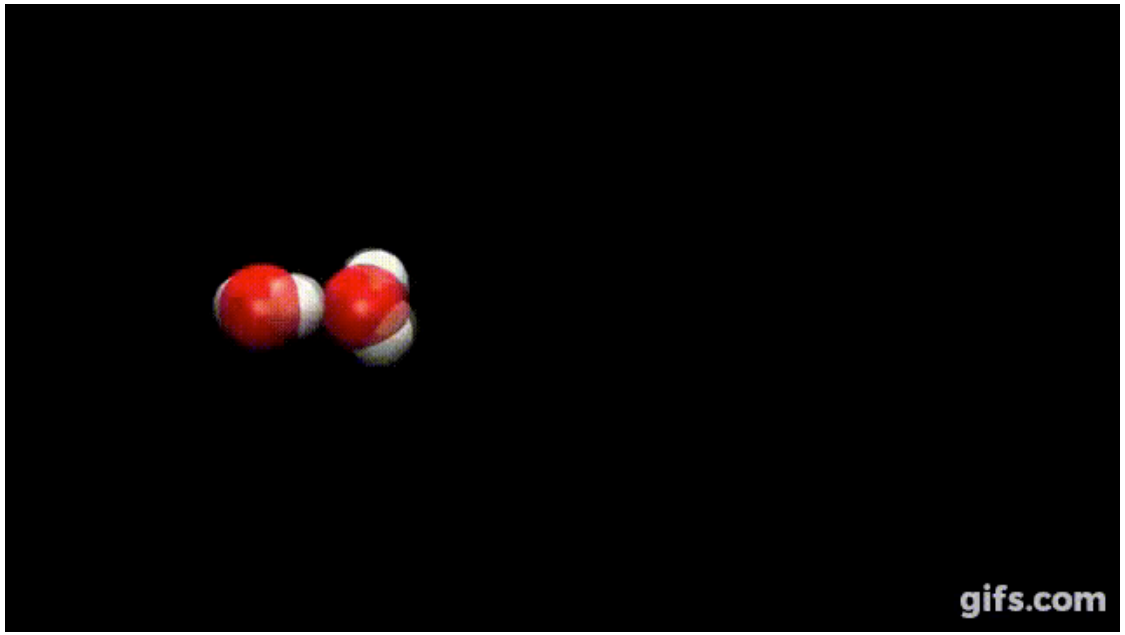

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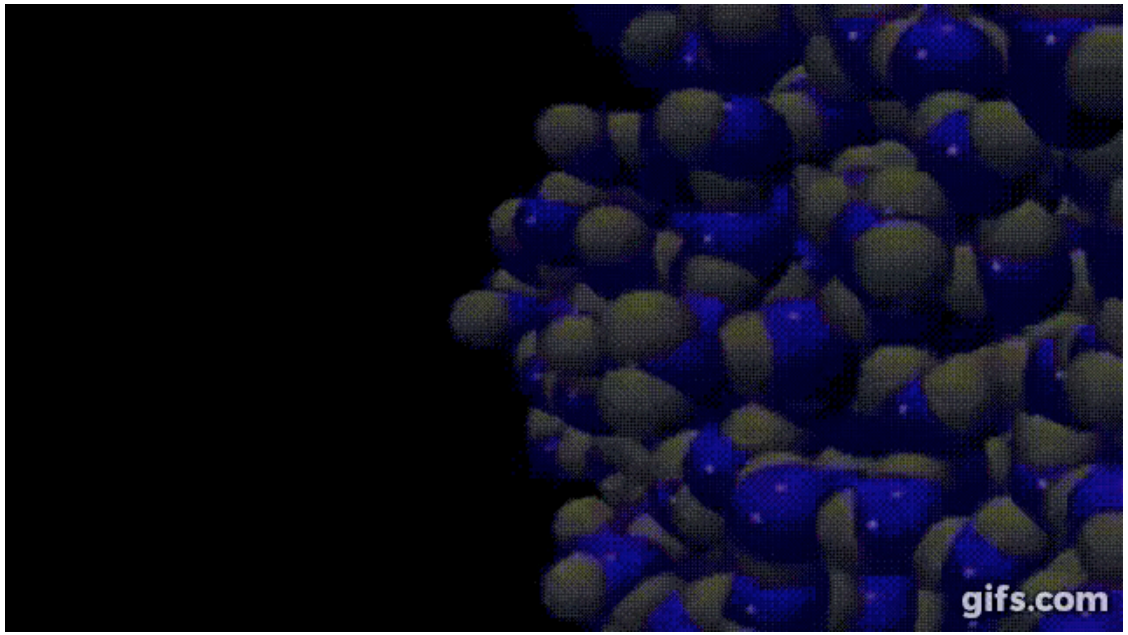

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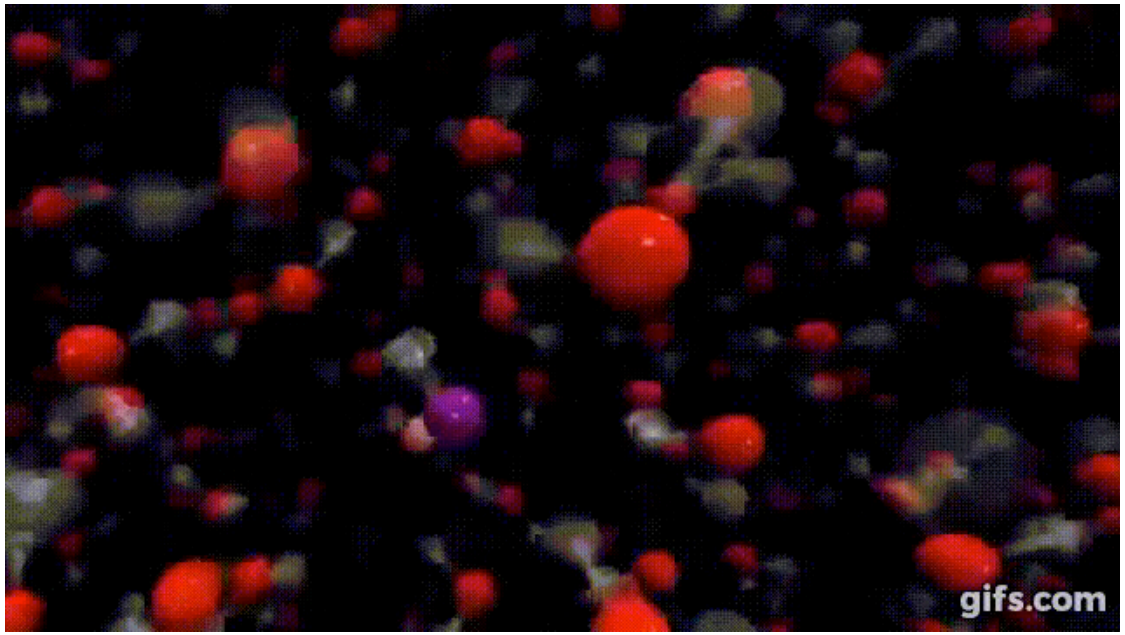
Radial distribution function



If we plot the average probability of finding an Oxygen in the space around a specific water molecule.

*Structure

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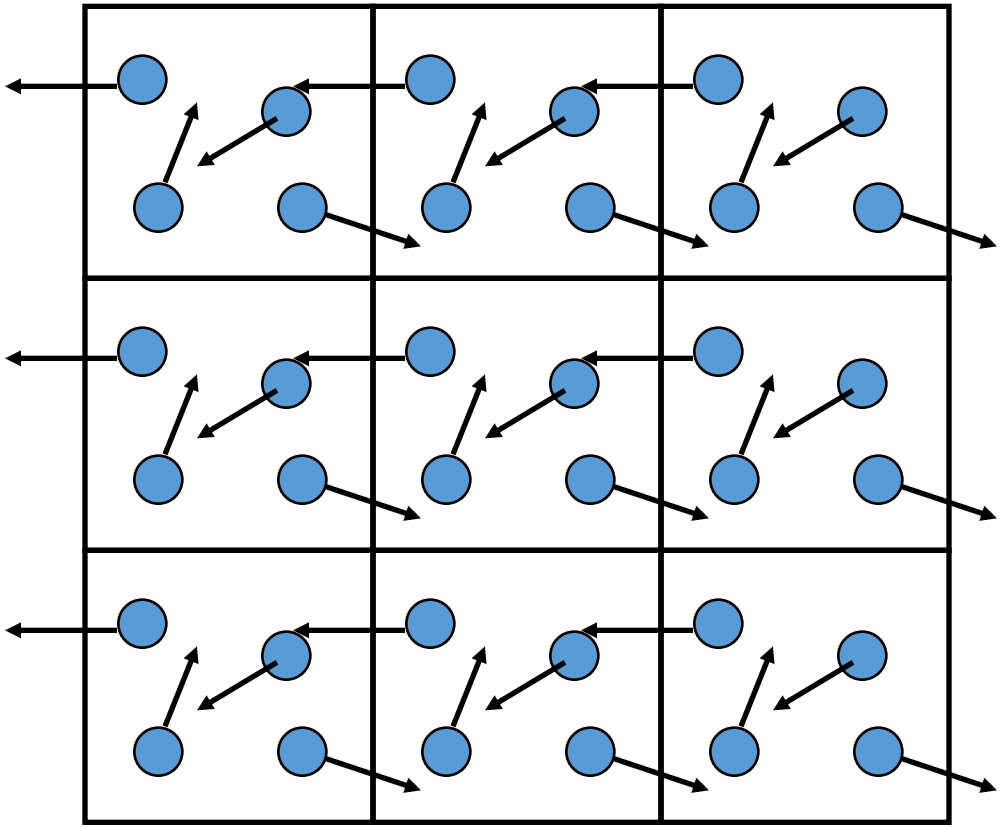

- *Periodic Boundary Conditions*
  - *your structure doesn't know that it's in a box (non-infinite space).*

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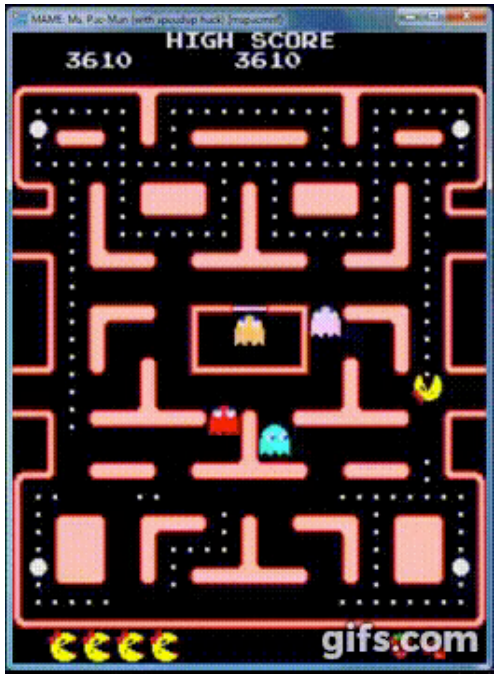

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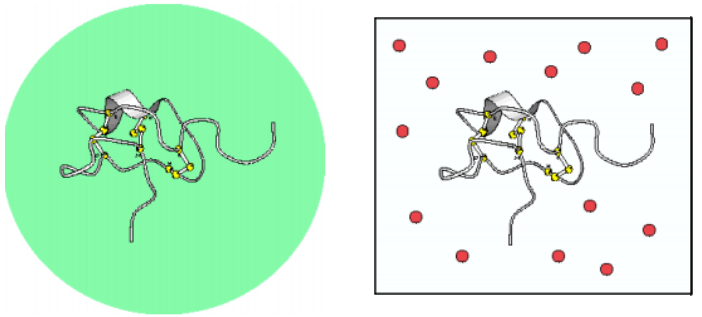
Introduction to Molecular Dynamics

- Protocol for an MD simulation
- Initial Coordinates
  - X-ray diffraction or NMR coordinates from the Protein Data Bank
  - Coordinates constructed by modeling (homology)
- Treatment of non-bonded interactions
- Treatment of solvent
  - implicit
  - explicit
- If using explicit treatment of solvent
  - Periodic boundary conditions (PBC)
  - Solvation sphere
  - Active site dynamics



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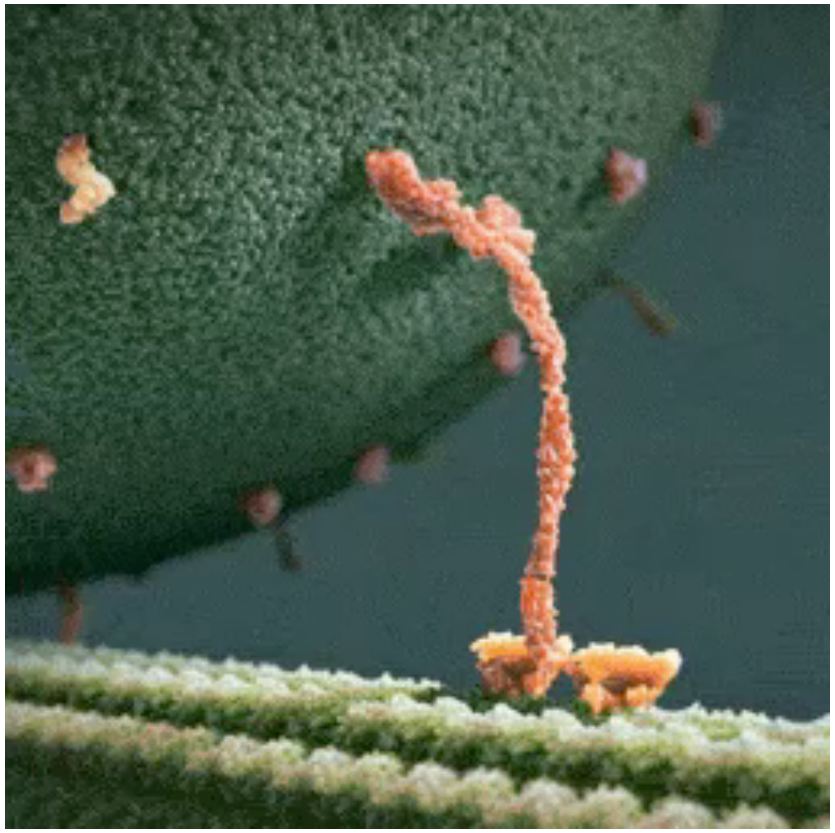

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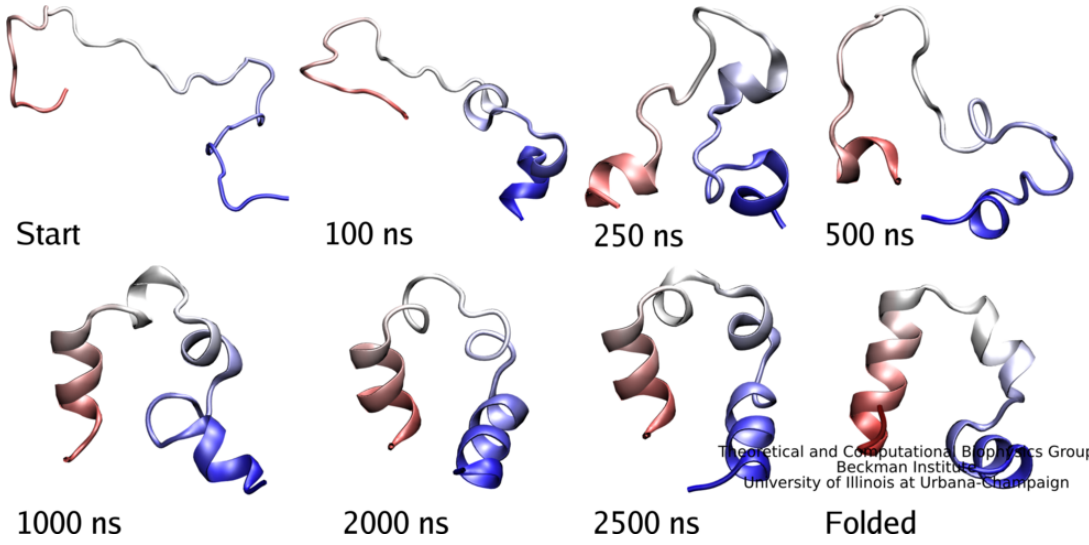
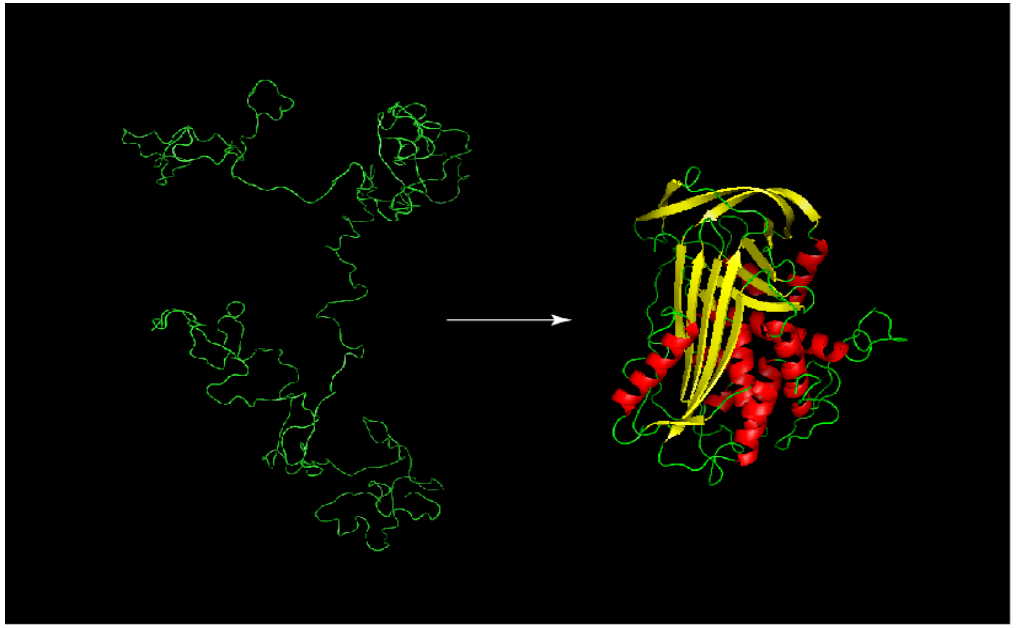
Folding pathways





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Protein Interactions

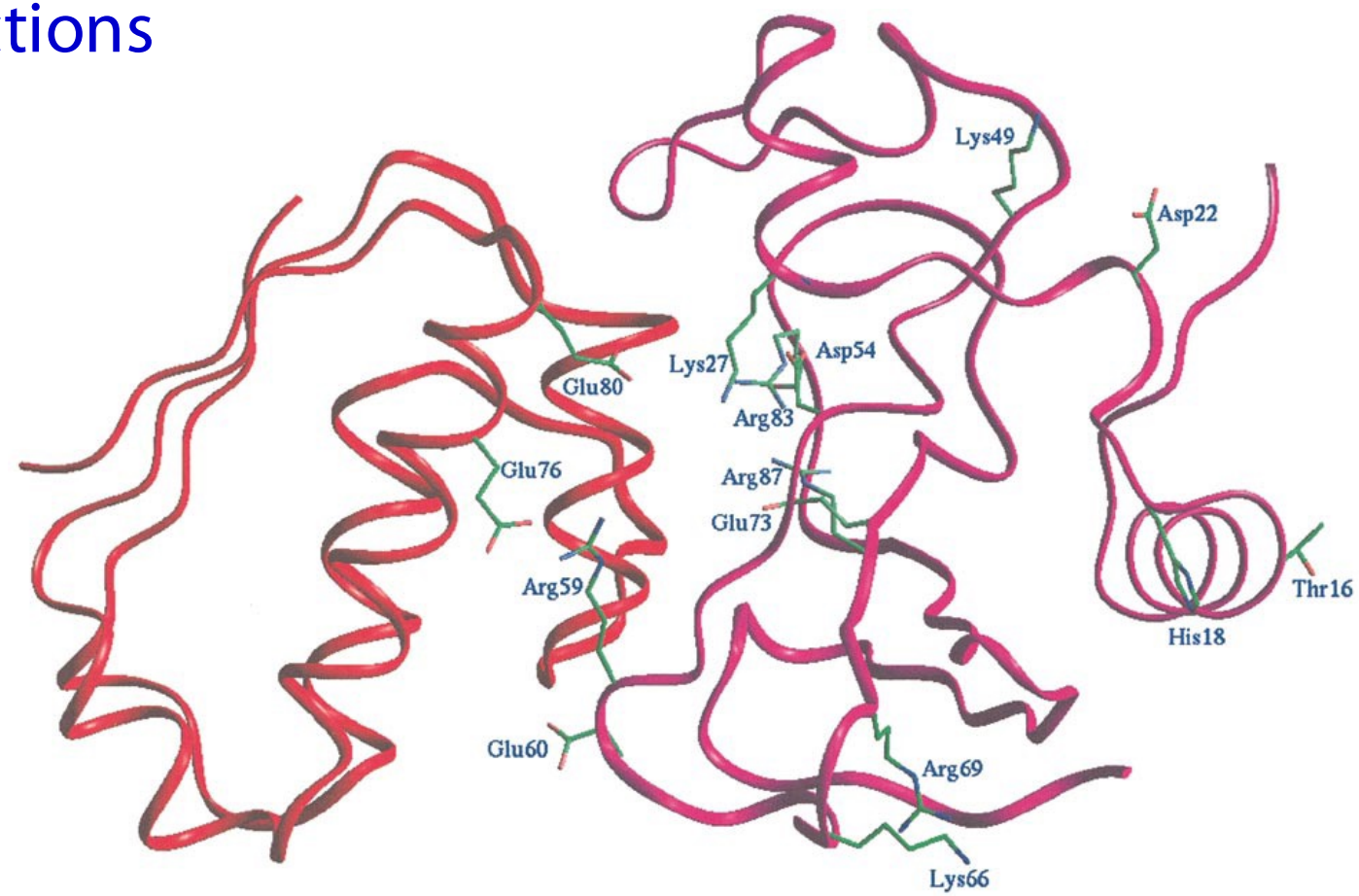

Image: Vijayakumar, et al., *J. Mol. Biol.* 278, 1015 (1998)

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Binding of Drugs to their Molecular Targets

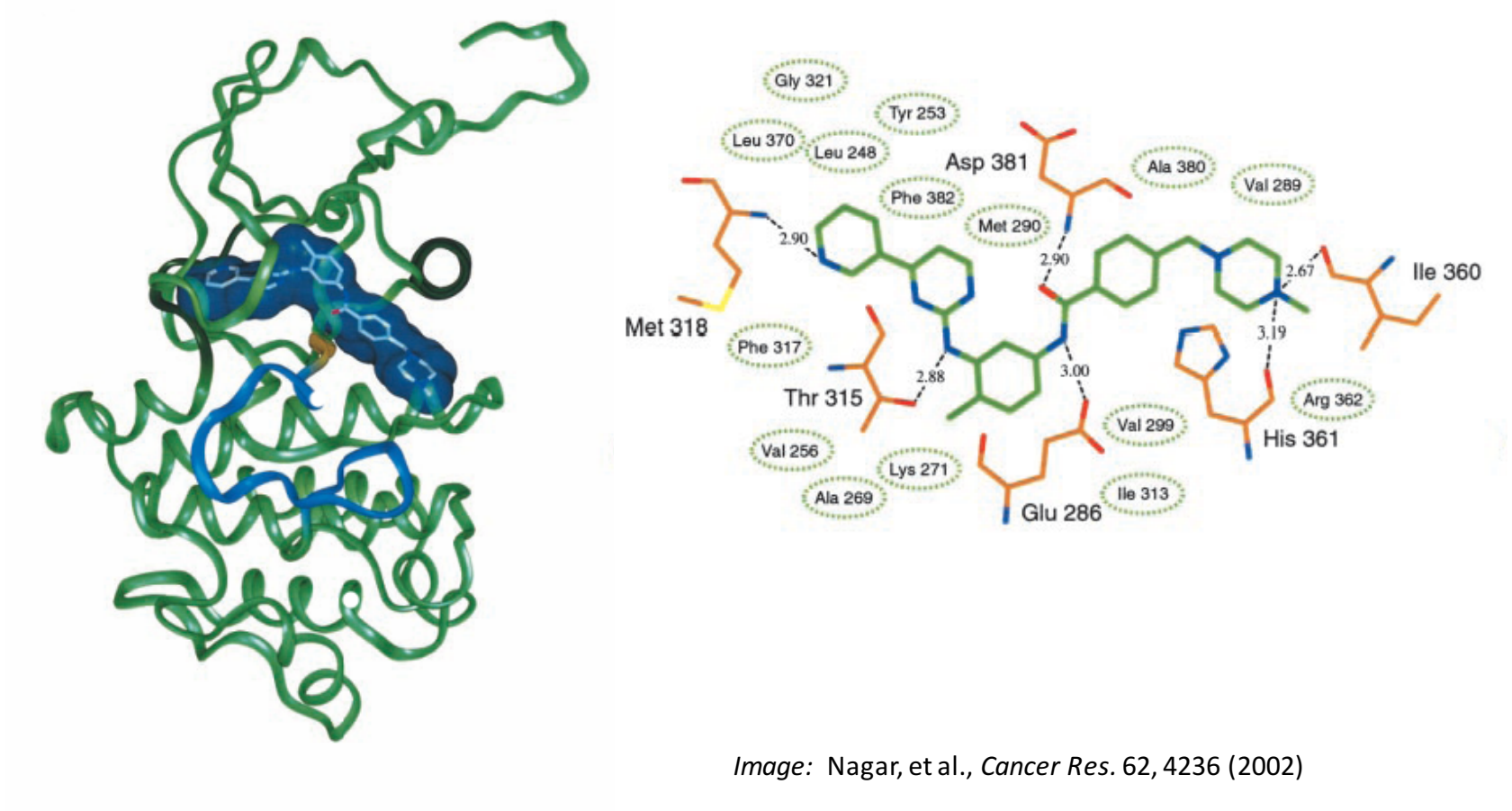

Image: Nagar, et al., *Cancer Res.* 62, 4236 (2002)

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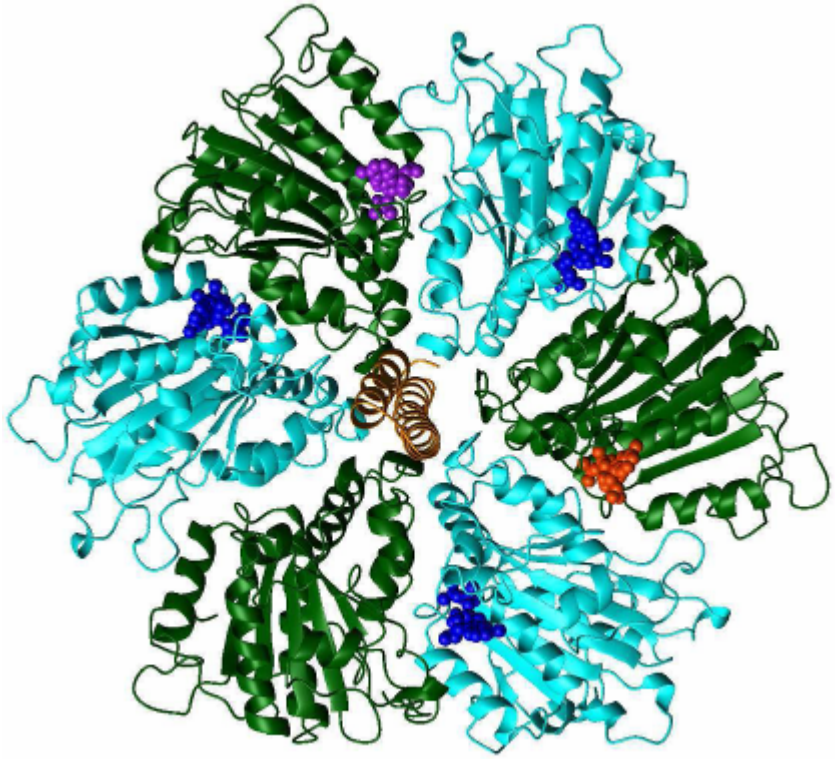
Mechanisms of Intracellular machines



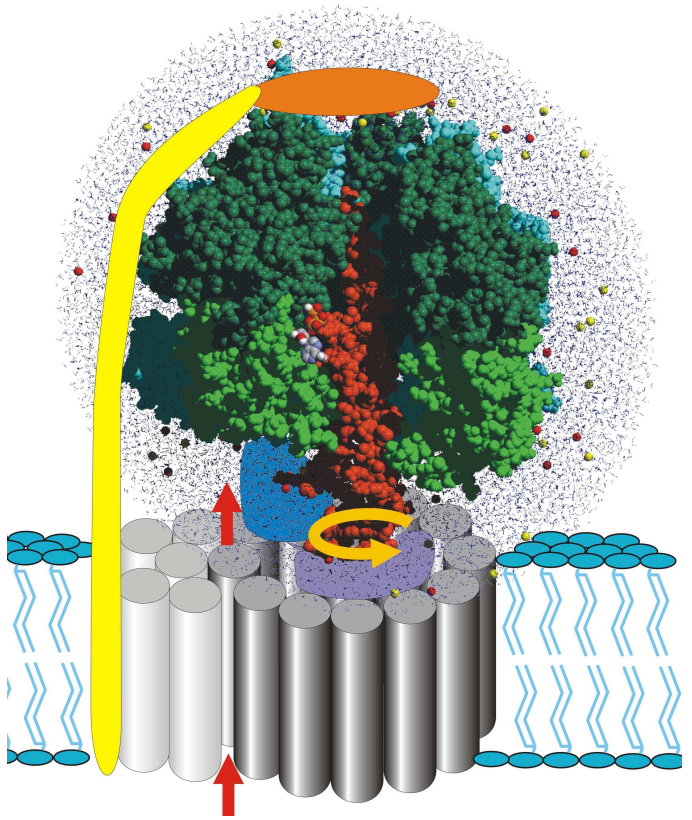


Image: H. Grubmüller, in Attig, et al. (eds.), *Computational Soft Matter* (2004)

"I... a universe of atoms, an atom in the universe."

Feynman