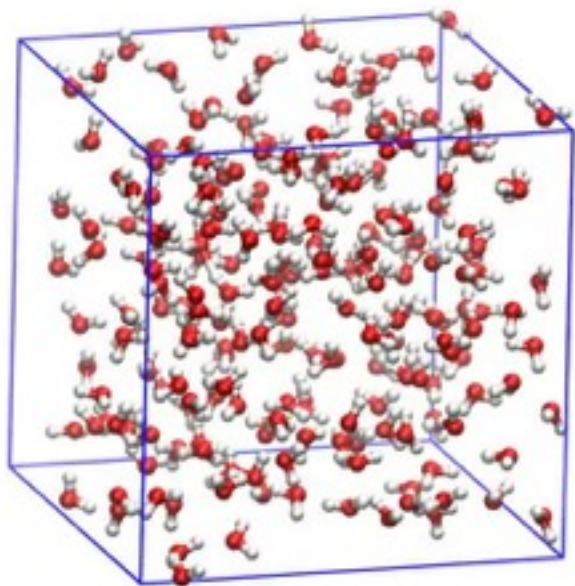# Molecular Dynamics: Methods

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Overview

What: Molecular Dynamics (MD) offers a general framework to study the movement of molecular structures over time *in silico*.

Why: MD allows us to calculate properties associated with a sample material that would be difficult or even impossible to compute through experiment alone.

How: Models of materials are represented as a set of n particles. At each time step the position and velocity of each particle is updated according to a potential function. The process is repeated for a desired number of iterations.

A molecular dynamics simulation of water at 298 K and 1 atm pressure. Credit: Christopher Rowley

Potential Functions

One of the most important components of a MD simulation is the choice of potential function used. The choice of function is dependant on the structure and composition of the material. For non-bonded interactions a pair potential, such as the **Lennard–Jones** potential is common. For bonded molecules additional terms can be included to account for the effects of covalently bonded atoms such as the dihedral and torsion angles.
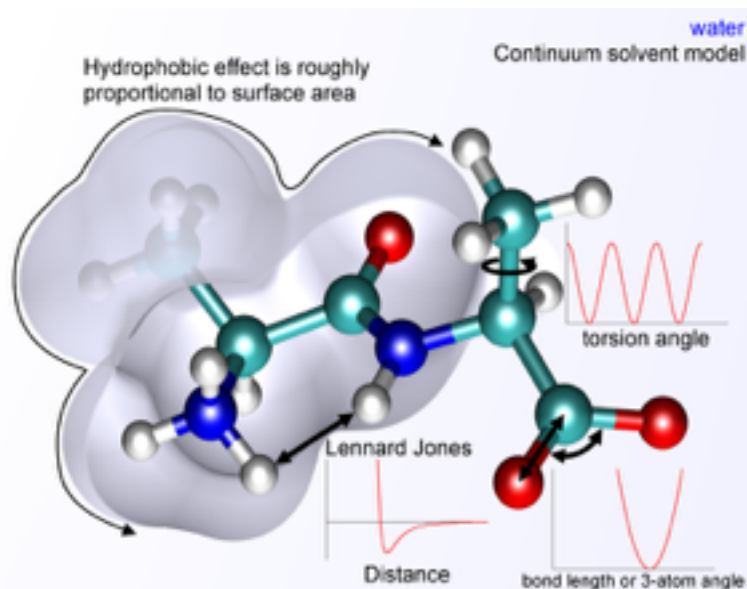

Potential functions for the molecule *alanine dipeptide*.
Image Credit: Boas F.E. and Harbury P.B. (2007)

Integrators

The results of a MD simulation will be heavily effected by the choice of integration method. There is a trade off between the time complexity of the integrator and the accuracy of the results. Common choices include **leapfrog** methods and **predictor-corrector** (PC) methods. PC methods are typically better suited to complex, high accuracy problems. Leapfrog methods have lower memory usage and are suitable for very large scale problems.

Computing Interactions

In order to compute the potential energy and therefore update the system, the interactions between particles must be computed. The naive approach is to use the **all pairs** method. Better performance can be achieved through approaches such as **cell subdivision** which splits the domain into cells proportional to the interaction range and **neighbourhood lists** which caches a list of neighbours for a particular particle. All three approaches are illustrated (right) taken from ref. [1].
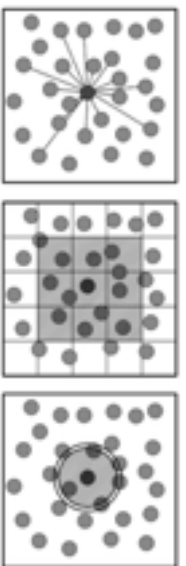
Parallelisation & Specialised Hardware

Due to the computational intensity of MD methods calculations are often performed on specialised hardware and often involve the use of supercomputers. The ability to parallelise the update calculation for a given time step using **domain decomposition** is key. The simulation domain is split in several regions whose interactions can be computed independently of other regions.

Simplified schematic of the molecular dynamics algorithm

Give atoms initial $r^{(i=0)}$ and $v^{(i=0)}$, set a = 0.0, t = 0.0, i = 0, choose short Δt

Predictor stage: predict next atom positions:
Move atoms: $r^p = r^{(i)} + v^{(i)} \Delta t + \frac{1}{2} a \Delta t^2$ + more accurate terms
Update velocities: $v^p = v^{(i)} + a \Delta t$ + more accurate terms

Get forces $F = -\nabla V(r^p)$ or $F = F(\Psi(r^p))$ and $a = F/m$

Corrector stage: adjust atom positions based on new a:
Move atoms: $r^{(i+1)} = r^p$ + some function of $(a, \Delta t)$
Update velocities: $v^{(i+1)} = v^p$ + some function of $(a, \Delta t)$

Apply boundary conditions, temperature and pressure control as needed

Calculate and output physical quantities of interest

Move time and iteration step forward: $t = t + \Delta t$, $i = i + 1$
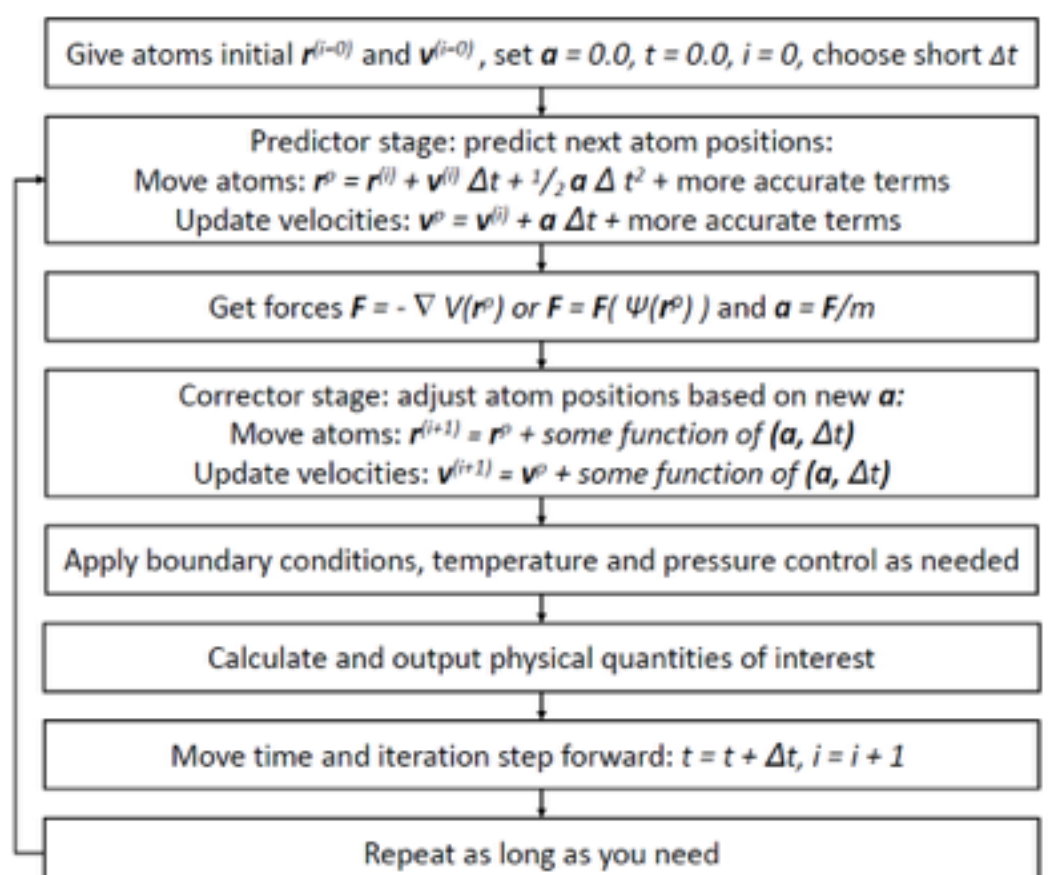
Repeat as long as you need

Diagram Credit: Kai Nordlund

Molecular Dynamics: Applications

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Overview

Molecular Dynamics was originally developed to solve problems in computational physics. One of the first notable applications was the simulation of liquid Argon using the Lennard-Jones potential by Rahman in1964. Since then the technique has developed to have a broad range of application across the sciences. Here are two example applications, one each from the Bioinformatics and Physics domains, are discussed.

RNA Tertiary Structure Prediction

Predicting the tertiary structure of RNA molecules from a sequence of nucleotides is still an open problem in the field of Bioinformatics. Various approaches have been suggested that attempt to produce an accurate 3D model of folded RNA for both the primary and secondary structure.

Attempts to determine the 3D structure make use of MD in a variety of different forms [3]. Several techniques take a fully atomistic approach where an accurate model of nucleotides is used. These are often limited by their time and space complexity to short sequences of RNA. Other approaches make use of a coarse-grained model to simplify the problem. Here chains of nucleotides are often represented as a simple "bead on a string". MD is also used in combination with other approaches, such as fragment assembly. RNA motifs are "stitched" together using fragment assembly and the final model is further refined using either a fully atomistic or coarse-grained MD simulation.
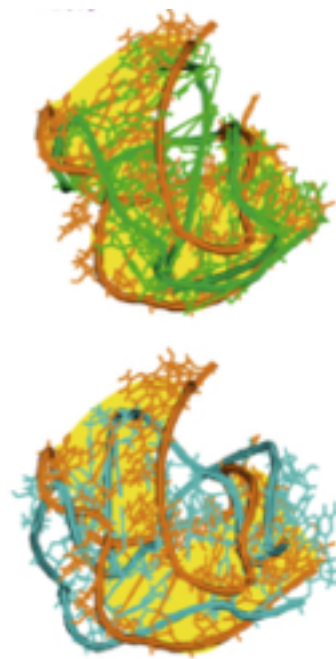
RNA molecule (top) and the prediction by NAST (bottom). Image source: ref [3]
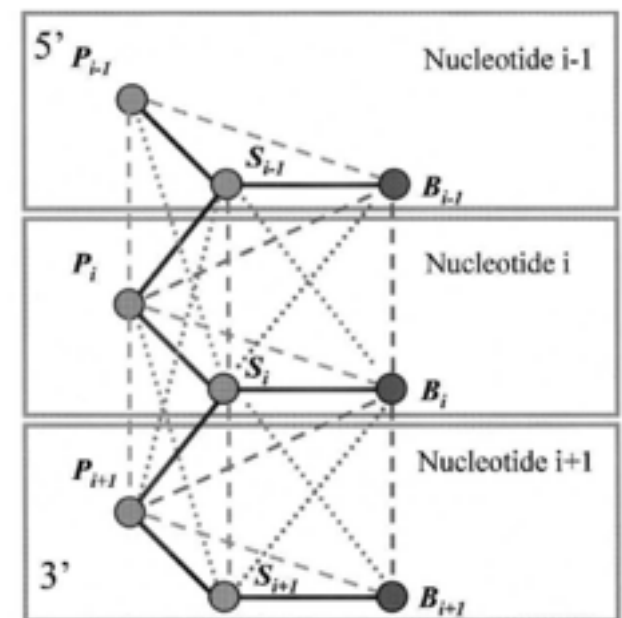
Coarse grained "bead on a string" model.
Image source: ref [4]
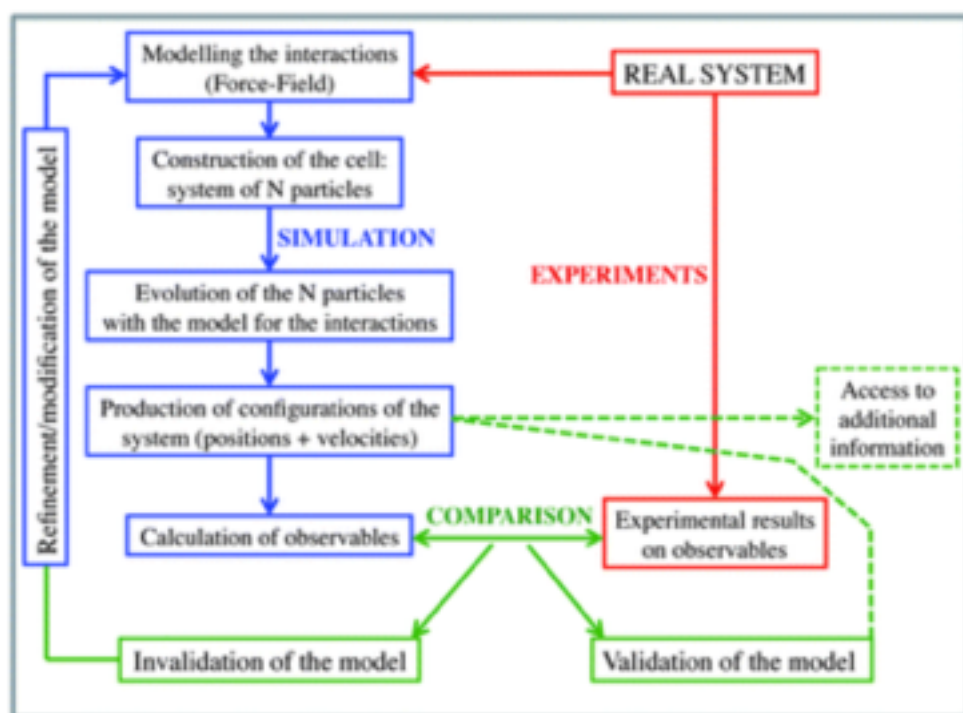
MD as a complement to neutron scattering experiments. Image source: ref [2]

A Complement to Neutron Scattering

Neutron scattering is an experimental technique for examining the structure and dynamics of matter at the atomistic level. The pattern of neutrons scattering in a diffraction or spectroscopic experiment produces a characteristic signal from which properties of interest can be computed.

Sadly the technique is limited by a number of factors including instrument resolution, cost and access to instruments, the differentiation of atoms of the same isotropic species, and having to work in reciprocal space.

MD simulations can complement neutron scattering experiments. The results of a scattering experiment can be compared with the same quantities calculated by a MD simulation of the material to verify its accuracy. Then quantities unobtainable from direct experimentation can be computed via the verified simulation.

References

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3. Laing, Christian, and Tamar Schlick. *"Computational approaches to 3D modeling of RNA."* Journal of Physics: Condensed Matter 22.28 (2010): 283101.
4. Ding, Feng, et al. *"Ab initio RNA folding by discrete molecular dynamics: from structure prediction to folding mechanisms."* Rna 14.6 (2008): 1164-1173.