MOLECULAR DYNAMICS SIMULATIONS

summary of seminar talk – Heidelberg University, December 2021 by Fabian Egersdoerfer

Molecular Dynamics (MD) simulations have developed as one of the most powerful tools in modern biochemistry over the last decades, driven by advances in both methodology as well as computer hardware. The remarkable thing about it is that the underlying physical understanding is rather simple. This is a summary of the simplifications made and the capabilities that result from them. Fig. 1 shows an overview.

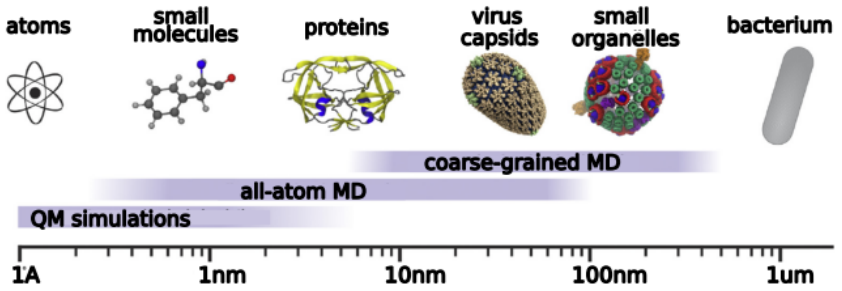

Figure 1: Characteristic length-scales currently associated with varying levels of description in biomolecular simulations. From [1].

1 QUANTUM MECHANICS

Approaching it from the perspective of a physicist, molecules are fundamentally described as quantum mechanical (QM) objects. Numerical solutions of QM systems are widespread in the field, especially since coupled systems of N particles have no analytical way of solving them. Applications include the study of interactions between molecules and light [2]. Despite these quantum mechanical simulations being able to deliver accurate results and reflecting our deepest level of understanding, scaling up these calculations to systems larger than a few dozen atoms becomes infeasible quickly. For example, the wavefunction of a system with $N = 100$ atoms, discretized on a three dimensional grid with $d = 1000$ grid points per dimension, already has a size of $N \cdot d^3 = 10^{11}$. Since most sophisticated methods for solving the time propagation involve diagonalizing the Hamiltonian matrix (e.g. [3]), which is of the appropriate size, the need for simplification is obvious.

2 AB INITIO MD

In an attempt to preserve the quantum mechanical properties of the system, one moves to a semi-classical approach, usually referred to as *ab initio MD* [4]. Here, the commonly used Born-Oppenheimer approximation serves as a helpful framework for efficient simplification. Assuming largely different timescales between electronic and nuclear motion, we can separate the two dynamics. Now, the nuclei are treated as classical particles that move in an effective potential formed by the electrons, which depends on the nuclear positions parametrically. The idea is to still derive the shape of these potentials from a stationary quantum problem, maintaining some level of quantum mechanical accuracy. This stationary problem usually needs to be solved for every set of parameters, i.e. nuclear configuration, individually. A seemingly impossible task for large systems.

However, recent applications of machine learning algorithms to solve the electronic structure have shown promising results [5, 6, 7], and are beginning to outperform established methods based on density functional theory.

3 ALL ATOM MD

The breakthrough in performance only comes when letting go of the QM description and replacing the derived potential energy surfaces by simple effective potentials V_{ij} that describe pairwise interactions between classical atoms at positions r_i. Examples include harmonic potentials, Lennard-Jones potentials, or the Coulomb potential. With this we finally arrived at what is usually referred to as *molecular dynamics simulations* [8, 9, 10, 11]. It is worth it here to pause for a second and acknowledge how simplistic of an approach this seemingly is:

$$m_i \ddot{r}_i = -\sum_j \frac{\partial}{\partial r_{ij}} V_{ij} \quad ; r_{ij} = r_j - r_i$$

The fact that it is still able to give us unprecedented insights into the structures and workings of large molecules and microbiological objects is a sign of the often underestimated value of simplicity and efficiency in science.

However, caution is necessary as there are limitations to the method. For example, a molecule whose chemical bonds are modeled as harmonic potentials will never exhibit bond breaking and therefore can not partake in chemical reactions. Carefully crafted, effective descriptions that faithfully capture the characteristics of lower lying levels of understanding do not simply follow from the fundamental principles. They are the result of their own scientific process, which constantly has to be reiterated and improved upon.

4 COARSE GRAINED MD

The last step to fully unlocking the potential of MD simulations lies in introducing a method of parallelization. In these so-called *coarse-grained* simulations [12, 1], atoms are combined into larger pseudo atoms, the interactions of which again require a clever effective description.

5 APPLICATIONS

The power of these methods was recently demonstrated in the extensive research efforts undertaken to tackle the COVID-19 pandemic. MD simulations proved to be highly valuable in understanding the chemical structure of the SARS-CoV-2 viral capsid. The findings made are influencing our understanding of viral transmission, drug design and immunisation. For more information, see references [13, 14].

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