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Supercomputing in the biological sciences: Toward Zettascale and Yottascale simulations

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Molecular simulations of biological systems tend to be significantly more compute-intensive than those in materials science and astrophysics, due to important contributions of long-range electrostatic forces and large numbers of time steps (>1E9) required. Simulations of biomolecular complexes of microseconds to milliseconds are considered state-of-the-art today. However, these time scales are miniscule in comparison to physiological time scales relevant to molecular machine activity, drug action, and elongation cycles for protein synthesis, RNA synthesis, and DNA synthesis (seconds to days). While an exascale supercomputer has simulated an entire virus for nanoseconds, this supercomputer would need to be 10 billion times faster to simulate that virus for 3 hours of physiological time, demonstrating the insatiable need for computing power. With growing interest in computational drug design from the pharmaceutical sector, the biological sciences are positioned to be an industry driver in computing.

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Introduction

Biological systems present some of the most demanding, compute-intensive high-performance computing applications. For example, mechanistic understanding of viruses and molecular machines, as well as computational drug-design efforts, often requires calculations of free energies. Free-energy calculations require enormous amounts of conformational sampling to achieve equilibrium thermodynamics [1]. Even modest amounts of sampling (e.g. 1 ms of physiological time) require 10^{12} time steps. Due to the electrostatic charges present, long-range electrostatic forces play important roles (e.g. every nucleotide of DNA and RNA is charged) [2]. Thus, biological simulations are often much more intensive than material science applications, which typically do not include long-range electrostatic interactions. While cosmological calculations have long-range gravitational forces, biological simulations require orders of magnitude more time steps. Additional factors of complexity in biological systems, such as the fact that many processes are far from equilibrium and that chemical reactions can be critical (requiring quantum mechanical calculations), further complicate these systems. If we neglect chemical reactions and nonequilibrium effects, we estimate that simulating 1 s of physiological time for the human genome (in the case of 23 chromosomes) would require at least 10^4 yottaFLOPs (1 YF = 10^{24} FLOPs) or 10^{10} exaFLOPs. While these calculations are far beyond the scope of current platforms, they provide a roadmap for the way forward in biomolecular simulation and demonstrate that the biological sciences have an insatiable demand for computing and will continue to do so for the coming decades (Figure 1). In Figure 1, system sizes are taken from actual all-atom simulations (protein, ribosome, virus, gene) or from the length scale of coarse grained simulations (chromosome, nucleus, cell). FLOP values are extrapolated from actual values (protein) or from high performance computing (HPC) platforms on which molecular dynamics simulations were performed (ribosome, gene). With growing interest in computational drug design from large pharmaceutical companies, it is reasonable to suggest that biomolecular computation may drive the computing industry in the future.

As we do not currently have 10 billion exascale supercomputers at our disposal, many have adopted an integrated biology approach, using constraints from a wide variety of experimental data to dramatically expand the accessible time scales. This approach is not ab initio and limits the scope of predictions that can be made. However, as the accuracy of free-energy calculations is directly related to the amount of conformational sampling achieved, which we know is inadequate by many orders of magnitude today, today's ab initio approaches

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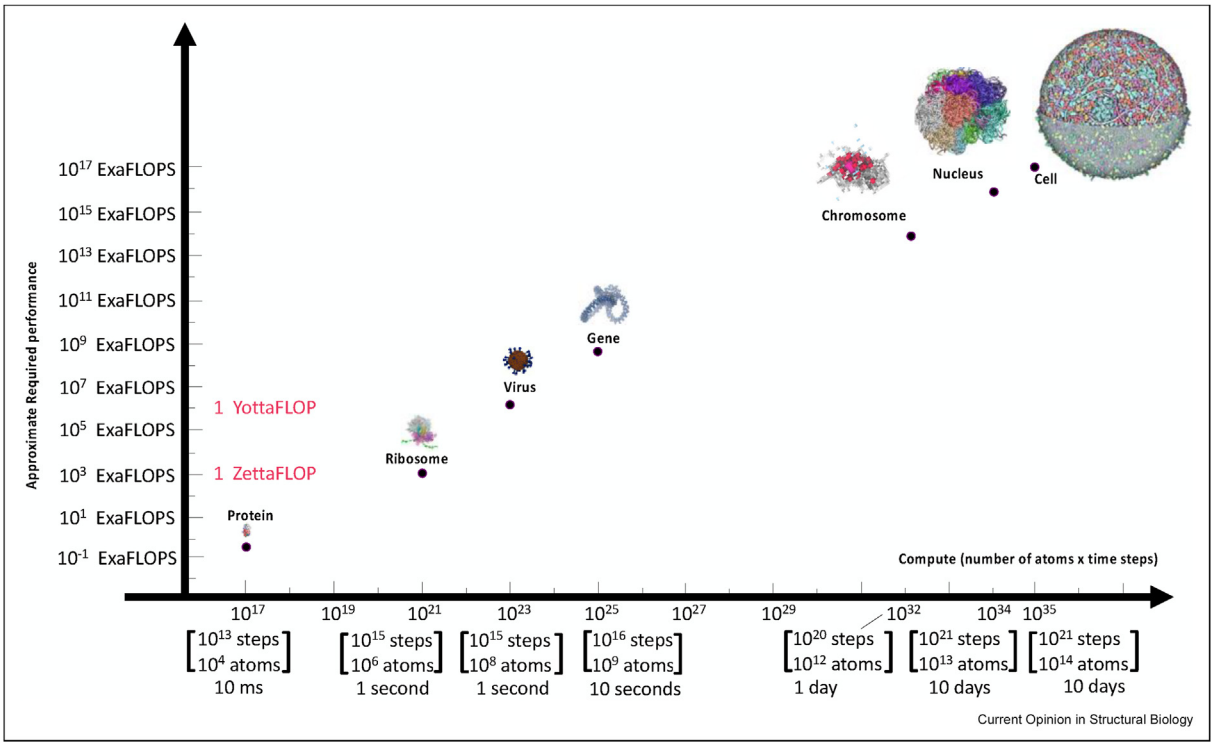
Figure 1



Approximate required performance vs. compute, in units of time steps multiplied by the number of atoms. Simulating 10 days of physiological time of a cell in atomistic detail in explicit solvent would take a 10 ExaFLOPS supercomputer approximately 10^{16} years, or 10^{6} times the lifetime of our Sun.

are also severely limited due to limitations in compute power, even using the world's most powerful supercomputers, as detailed earlier. Thus, in many situations, an integrated biology approach, which incorporates experimental data as constraints, represents the most accurate and descriptive approach available. A variety of computational tools have been used to characterize large biological systems, including all-atom explicit solvent simulations, long-time-scale simulations, enhanced sampling simulations, and coarse-grained and reduced-model simulations. In the following, we review efforts in each of these areas. This review is by no means comprehensive and due to limited space, does not mention many important studies in the field. The review uses a few illustrative examples to highlight methods and topics that have emerged in the push toward larger and larger systems and simulations.

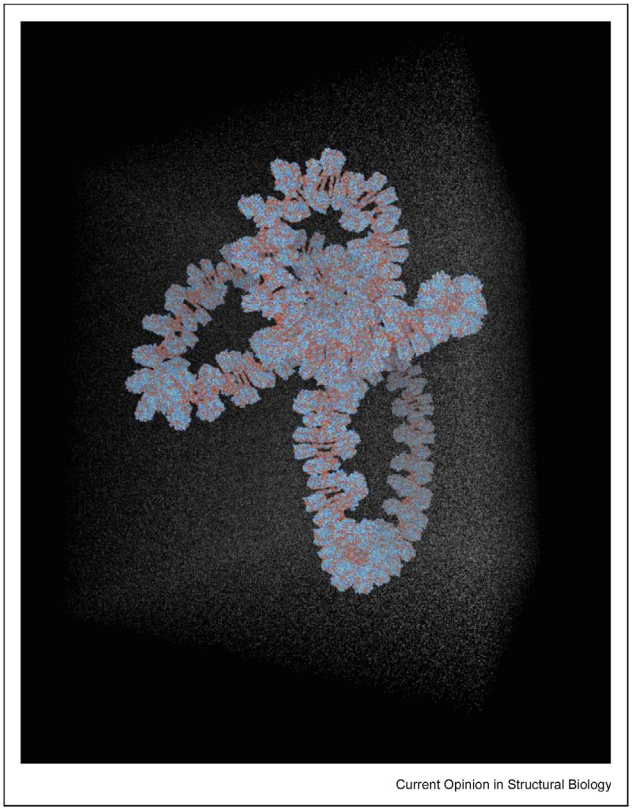
Structural biology studies are the basis of atomistic molecular dynamics simulations of macromolecular complexes

Molecular dynamics simulations often use high-resolution structures of large biomolecular complexes generated by X-ray crystallography or cryogenic electron microscopy (cryo-EM). There are too many examples to name in this review. A few specific examples of such systems include virus particles, the ribosome, chromatin complexes, and membrane-receptor complexes, such as RyR1, glutamate, and STRA6 [3–9]. While crystallographic structures were predominantly used in molecular dynamics simulations since their inception into the 2000s, the resolution revolution in cryo-EM made a large number of structures of large macromolecular complexes available in the 2010s to the present day.

Equilibrium-explicit-solvent molecular dynamics simulations of large biomolecular systems

Equilibrium molecular dynamics simulations in explicit solvent produce information about short-time-scale fluctuations (hundreds of nanoseconds to milliseconds), hydrogen-bond networks, solvent structure, ion distributions, electrostatic potentials, and ligand interactions. Schulten et al. and Grubmuller et al. were pioneers of large-scale biomolecular simulations, performing simulations of over 100,000 atoms of fibronectin and F1-ATP synthase [10,11]. Since these early studies, successive landmarks were established by simulations of over a million atoms of the ribosome, flagellum, and satellite tobacco mosaic virus [12–16]. Most recently, the first simulations over a billion atoms have been performed of a chromatin system (GATA4 gene, 427 nucleosomes), the SARS-CoV-2 particle, and large swaths of cytoplasm, including hundreds of proteins [17–19] (Figure 2). As

Figure 2



Explicit solvent simulation of GATA4 gene including 83 kb and 427 nucleosomes requires 1 billion atoms.

discussed in the following, the challenges involved in simulating large systems are compounded by the fact that larger systems require more sampling than do smaller systems for equilibration.

Long-time-scale simulations

Long-time-scale simulations represent another important frontier of molecular simulation. Here, simulations of single proteins are performed for longer time scales (milliseconds) to characterize fluctuations on these time scales and help validate short-time-scale (hundreds of nanoseconds to microseconds) simulations. The first microsecond simulation was performed by Duan et al. [20], in which a single protein was simulated. Later, with the aid of the Anton platform, millisecond simulations were performed [21], where a single protein was simulated. More recently, simulations exceeding milliseconds have been performed. As the simulation time scale increases by significant leaps, different behaviors are observed, underscoring the challenges involved in assessing convergence and establishing equilibrium. For example, suppose one performs a simulation of 10 ms, but the relevant physiological timescale is 10 min. One could then perform 100 more 10 ms simulations, and obtaining consistency between the 100 simulations, conclude that the simulations have converged according to various metrics. However, if 10 years later, a new supercomputer is developed capable of performing simulations of 10 s, these new simulations may produce results that conflict with the 10-ms simulations. This pattern of declaring convergence could proceed until 100 simulations of 10 min can be performed, decades in the future. In short, with limited compute power, and correspondingly limited conformational sampling and time scales, it is difficult to assess ergodicity and whether one has truly achieved thermodynamic equilibrium.

Enhanced sampling methods

A key area of development in molecular simulation has been enhanced sampling algorithms. Typically, conformational sampling is artificially enhanced in very specific ways, such as careful heating by small amounts of heat in specific circumstances or by lowering force-field interaction energies of very specific interactions at specific times [22]. These artificial enhancements are carefully quantified, followed, and tracked. At the end of the study, the additions of heat, temperature, or energy are often subtracted, yielding equilibrium free-energy landscapes [1].

Some of the earliest work in enhanced sampling originated in the spin-glass community in condensed-matter physics, with seminal papers from Hansmann and Okamoto, who applied these techniques to applications in protein folding [23–28]. Hansmann, Okamoto and Sugita pioneered replica-exchange simulations, a technique widely used today, where many replicate simulations are performed at slightly different temperatures, and small temperature jumps are given to each replicate by exchanging temperatures with its neighbor in the temperature space [22,23]. This gives a ~25-fold boost in conformational sampling and Boltzmann equilibrium sampling and easily folds small proteins and peptides [29]. The method has also been applied to RNA systems such as ribosome–antibiotic complexes, single-stranded RNA, and riboswitches [30–32]. Many variants of this algorithm have been developed that do not melt the system and are more suitable for large biomolecular complexes. These include Replica exchange umbrella sampling (REUS), Hamilton replica, resolution replica, protonation replica, and sparse replica [33–38]. In one case, a multiscale study was produced with a smart-resolution replica-exchange technique [37]. More recently, weighted histogram methods and artificial intelligence (AI) methods have been used [39,40].

Metadynamics is another popular and useful technique, made convenient in the PLUMED framework [41–43]. Here, basins in the energy landscape are gradually filled by Gaussians, which are carefully tracked. In the end, the Gaussians are subtracted, giving the free-energy landscape. A key aspect of many of these methods is

determining the most useful collective variable or order parameter to describe a conformational change of interest that best characterizes a transition. Another emerging area is that of enhanced-sampling kinetic approaches [44—46].

While enormous resources in the pharmaceutical community have been devoted to accurately characterizing the enthalpic component of the free energy of drug binding, much less attention has been paid to the entropic component, which critically depends on obtaining tremendous amounts of conformational sampling [47,48]. The free energy consists of the difference between the enthalpic and entropic terms. These terms are often large and opposite in sign, nearly canceling. Thus, to obtain an accurate free energy of binding, one must absolutely obtain an accurate entropic component of the free energy. Conformational sampling and accurate entropy estimation remains a key challenge in drug design today.

While significantly less expensive than conventional molecular dynamics simulations, these methods are nonetheless quite expensive, complex, and difficult to implement for very large systems. One of the open areas in large-scale simulation is to apply these very useful methods to very large systems.

Coarse-grained simulations

Molecular dynamics simulations of biomolecules considered 'more accurate' are often those that are considered the 'most realistic' and include the most effects possible, such as atomistic detail, explicit water, electrostatics, polarization, explicit ions, the buffer closest to the biochemical experiment, and the most physiologically relevant complex. However, these are sometimes not the most useful simulations as they are (i) very limited in their access to relevant time scales and (ii) have corresponding inaccurate free-energy estimates due to the lack of conformational sampling, especially for very large systems (equilibrium conformational sampling is required for the entropic component of the free energy). The current state-of-the-art for explicit solvent atomistic molecular dynamics simulations for relatively large systems grossly undersamples their dynamics, even using the fastest supercomputers available. For a million-atom system such as the ribosome (2—5 million atoms, depending on the specific ribosome complex), the state-of-the-art is at best 1 ms of physiological time. As relevant rates are 100—800 ms, at least 1 s of aggregate sampling is required to have a minimum number of replicates for statistics. As shown in Figure 1, this would require a 1 ZettaFLOP supercomputer (1000 ExaFLOPS). Since the fastest machine available is $\sim$ 1—2 exaFLOPS, even a one-millisecond simulation of the ribosome would be 1000-fold undersampled, yielding grossly inaccurate free energies. Even assuming a 25-fold boost for enhanced sampling algorithms, the system would still be 40-fold undersampled. This problem is compounded when simulating even larger systems. Not only do these have correspondingly more atoms but they require much longer time scales to equilibrate (e.g. the GATA4 and COVID billion-atom simulations sample only a few nanoseconds but likely require much longer than 1 s for equilibration).

These examples underscore the advantages of using coarse-grained and reduced-model simulations (protein shown in Figure 1 was simulated using reduced-model simulations to achieve agreement with single-molecule Forster resonance energy transfer (FRET) [49]). For example, native-contact-based simulations of tRNA accommodation into the ribosome during transfer RNA (tRNA) selection are able to simulate events with rates slower than 100 ms with excellent statistics (hundreds of trajectories to one thousand trajectories of accommodation) [50,51]. While these simpler models lack the complexities included in explicit-solvent atomistic molecular dynamics simulations, they have vastly superior sampling and assessments of conformational sampling and entropy. Coarse-grained strategies follow a fundamental tenet of theoretical physics: the best practice is to understand zeroth-order effects first, and only after this, move on to more complicated higher-order effects. A good physicist must know how to neglect what is unimportant and focus on what is important by making the most effective approximations and simplifications. One should be reminded that Newton obtained quite accurate approximations of the Earth's orbit around the Sun by neglecting the Earth's ocean, atmosphere, asymmetry, all life on Earth, and approximating the Earth as a single pseudo particle, a very coarse-grained model indeed [52—54]. Newton's highly simplistic model (a very coarse-grained model with simplistic force field, in molecular dynamics simulation parlance) could predict the orbital periods and relative distances of planets from the Sun to within a fraction of a percent and accurately predicted eclipses and the return of Halley's Comet. Once these fundamental zeroth-order effects are understood, perturbation theory can be used to model higher-order effects, such as tidal effects of the Moon and variations in orbits. These examples highlight the approach of choosing the most appropriate level of coarse-graining for the task at hand and for the particular question of interest. In biological and biomedical applications, time scales range from femtoseconds to weeks, and length scales range from angstroms to meters, spanning more than ten orders of magnitude. To deal with this complexity, an appropriate level of coarse-graining must be chosen.

In addition to saving vast amounts of compute time, coarse-grained simulations have the advantage of being very amenable to the incorporation of experimental data as they can access much longer time scales and much larger systems that are more relevant to experimental studies. This makes these approaches ideal for integrated biology studies. For example, many conformational changes of the ribosome occur with rates of hundreds of milliseconds. A

proper study with excellent statistics might require a hundred of these hundred-millisecond trajectories (e.g. as in single-molecule FRET studies), summing to aggregate sampling of 10 s, at least four orders of magnitude longer than a millisecond simulation of the ribosome. However, with proper coarse graining, such simulations are possible [55—57]. These simulations use force fields that are 'less accurate' in the conventional sense, with pseudo particles that represent several or many atoms, corrections to compensate for lack of explicit water molecules, and less accurate electrostatics. However, these same coarse-grained simulations are, in a certain specific sense, more accurate than all-atom explicit-solvent simulations, in that the coarse-grained simulations obtain vastly more conformational sampling than explicit solvent simulations and therefore yield more accurate entropic components of the free energy, which critically depends on the amount of conformational space sampled. These methods obtain much more conformational sampling relative to explicit-solvent approaches, especially for large systems [58—60]. Several coarse-grained simulations of virus particles have been performed, including the SARS-CoV-2 virion [61—65]. Coarse-grained approaches to chromatin have also explored very large systems with various levels of coarse-graining, describing nucleosomes and linker DNA with various levels of detail [66—72].

Most importantly, many coarse-grain and reduced-model simulations are 'top-down' and use experimental data as constraints, guaranteeing consistency with experimental data from the outset. The approach is often used in integrated structural biology studies, where molecular simulations bring together disparate types of experimental data into a coherent study of mechanism [73—76]. This approach is often more of an interpolation between experimental data points than an extrapolation into unknown parameter regimes. While a naïve observer might ask, "what can one learn from such a simulation where the 'answer' is hardwired into the simulation?" such interpolative simulations do not suffer from concerns about experimental validation (as the validation is designed into the simulation from the outset) and yield interesting and useful insights related to transitions between states, such as energy landscapes, transition pathways, and transition intermediates, as well as information about mechanism such as order of events. The approach also allows the testing of different possible mechanisms while maintaining consistency with experimental data.

A key area of "top-down" simulations that use experimental data from the outset are called structure-based simulations, also known native-contact models or as Go-like models, after the pioneer of the method, Professor Nobuhiro Go [77,78]. Here, the potential is based on the native contacts present in a known structure. These potentials were used by Onuchic et al. to work out the protein-folding-funnel free-energy landscape [79,80], where simulations beginning with a completed disordered protein could be rapidly folded into the native folded state. These approaches have been modernized in atomistic, off-lattice versions with electrostatics and ions. They have also been repurposed to study large-scale conformational changes of macromolecular complexes, using the final state in a conformational change as the native state and beginning with a known conformation preceding the conformational change, such as a PRE to POST conformational change [50,51,81]. In the case of the ribosome, structure-based approaches have been used to investigate accommodation of tRNA into the ribosome during tRNA selection for cognate and near-cognate tRNAs, integrating an X-ray crystallography, cryo-EM, single-molecule FRET, and single-molecule FRET data [50,51]. There have been several top-down, integrative structural biologies related to COVID-19 [61,82].

In the direction of very coarse-grained simulation, a new area of simulation has emerged, inspired by simulations in polymer physics and the invention of a high-throughput sequencing method called Hi-C, which experimentally obtains contact maps of chromosomes by crosslinking, digestion, and sequencing. Here, beads-on-springs polymer models are used to approximate chromosomes, with a single bead typically representing 100 kb of DNA (in explicit solvent, simulating a single bead would require approximately one billion atoms). Mirny et al. performed ab initio block copolymer simulations [83,84]. Onuchic, Wolynes, and Zhang applied maximum-entropy techniques to produce three-dimensional (3D) models and gain insight [85,86].

Lappala developed a top-down method (4DHiC) to directly incorporate large amounts of experimental data to directly visualize the Hi-C data in 3D, revealing compartment mixing during various states of X-inactivation (shown in Figure 1 as 'Chromosome') [87]. The nucleus model shown in Figure 1 was produced by Ankush Singhal using a similar method.

Toward whole-cell simulations

A final area of coarse graining includes efforts to simulate an entire cell (image shown in Figure 1 as 'Cell' published previously [88]). Starting in the 1990s with simple zero-dimension models based on reaction kinetics, the field has evolved to 3D models of the cell with time evolution [89,90]. Several efforts are making great progress in this area [88,91—93].

Conclusions

Molecular simulations of biological systems tend to be significantly more compute-intensive than those in material science and astrophysics, due to important contributions of long-range electrostatic forces and large numbers of time steps ($>10^9$) required for microsecond simulations of proteins, DNA, RNA, and macromolecular complexes, including viruses, chromatin, ribosomes, and

other molecular machines. Although simulation durations ranging from microseconds to milliseconds are often considered the state-of-the-art for explicit-solvent molecular dynamics simulations today; these time scales are miniscule in comparison to physiological time scales relevant to molecular machine activity, drug action, and elongation cycles for protein synthesis, RNA synthesis, and DNA synthesis, ranging from hundreds of milliseconds to days. AI is being implemented in molecular dynamics simulations to improve sampling of biologically relevant events, enhancing collective variable selection or optimizing force-field potentials. However, for AI to yield necessary gains of many orders of magnitude, we first need to provide such enormously long simulation trajectories of large systems to train on, which will likely not be accessible for many decades. While the largest and fastest supercomputers on Earth can simulate a virus for nanoseconds on an exascale supercomputer, these platforms are at least twelve orders of magnitude away from performing a single simulation of a virus for 10 s, not to mention the requirement for statistical replicates. These issues are compounded by the fact that larger systems require much more conformational sampling to reach equilibrium, making the task of scaling up to full chromosomes, nuclei, and cells formidable. With growing interest in computational drug design from the pharmaceutical sector, the biological sciences are positioned to be an industry driver in computing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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