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Editorial

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Biophysics at the dawn of exascale computers

We are happy to present the special issue titled Biophysics at the Dawn of Exascale Computers to commemorate the BPS Thematic Meeting held in Hamburg, Germany, in May 2022. Through the talks and extensive discussions, molecular and cellular biologists, chemists, physicists, mathematicians, and computer scientists worked to find common ground about sharing innovations and debate on future needs—and to move forward as a community to take advantage of leading-edge resources. Such interdisciplinarity in the discourse was reinforced by the choice of the venue, namely the site of the European X-Ray Free-Electron Laser Facility, where the physics of light-matter interactions is harnessed to learn biology from molecules up to cells and tissues. The special issue epitomizes this multidisciplinary spirit of the conference and a holistic multiscale view of biophysical computations arranged in 16 contributions, bringing together experimentalists and theoreticians to look about the exciting possibilities that exascale computing will enable in the field of biophysics.

The issue covers a breadth of biological systems ranging from simple proteins and nucleic acids to their oligomeric complexes used for molecular recognition and locomotion. Concomitantly, methodological developments of realistic solvation and membrane models have been reported that probe a multitude of spatiotemporal scales (mesoscopic to atomistic), while concomitantly melding biophysical, computational, and quantitative experimental insights. We brought together experimentalists and theoreticians working in the broad areas of protein folding and assembly, dissection of allosteric pathways, macromolecular interactions, and bottom-up structure of cells, wherein large-scale computing is expected to bring forth major discoveries. Some exemplary findings are now highlighted.

Computational biophysics helps to identify possible mechanisms of action that would otherwise be difficult to identify by experiments alone. Such synergies can be seen in the work of Khandelia and co-workers (1) in which they rationalize the effect of protein association on membrane curvature and use this knowledge to engineer peptide sequences that increase association. Access to exascale computing will further enhance cross talk between experimental and computational communities (2). Gumbart and co-workers present a new and notable computational effort using enhancing sampling tools to reconcile a folding mechanism for pertactin that is compatible with known experimental data (3). Protein unfolding is investigated by using accelerated molecular dynamics simulations with adaptive approaches (4). By bridging molecular cues with phenotypic outcomes, parameters from molecular dynamics simulations are used to set up Brownian and population dynamics of studies on the origins of antibiotic resistance (5) and the role of missense polymorphisms (6). Solvation (7) and nucleic acids were also represented in this conference, with studies ranging from the importance of atomistic force fields to represent their structure and dynamics (8) to the more coarse-grained level to understand how molecular condensates form (9) or how chromatin fibers behave (10).

Computations also help untangle the mechanisms that underlie complex molecular processes ranging from the permeation of small substrates across membranes (11) to the intricate catalytic rotary steps of $F_O F_1$-ATP synthase (12). Although exascale computing offers the promise of pushing back the current limits of molecular dynamics simulations to ultimately tackle organelle-to-cell-scale systems over realistic timescales, investigation of very large biological assemblies at this time imposes compromises in terms of either resolution or timescale. Much effort has been devoted to increasing the granularity of molecular simulations, allowing phenomena spanning longer timescales to be explored (13).

Although the thematic meeting was conceived and approved for 2020, it was postponed to 2022 because of the COVID pandemic. Interestingly, this very pandemic brought together the broader community to contribute computer time to finding solutions, resulting in the first distributed exascale supercomputer (Folding@home) (14). It also spearheaded exciting research aimed at better apprehending how the SARS-CoV-2 virus responds to its environment, in particular by examining its different components, like the spike protein (15) or the nonstructural protein 1 (16), turning to advanced sampling schemes. At the time of release of this issue, three exascale supercomputers have been deployed for academic use (Fugaku in Japan and Aurora and Frontier in the USA), with others in development. We are excited by the impact and possibilities that these supercomputers will bring to the biophysical community.

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Altogether, molecular biophysics over the next decade will be dominated by a marriage of structural biology and imaging with molecular dynamics and machine learning. Taking us a step closer toward capturing bimolecular assemblies in action, these methods are delivering not only static structures but movies of cellular functions. Thus, a clear theme emerged on how to incorporate these experimental data with molecular modeling. However, work is needed to simultaneously model complexity at different spatio-temporal scales. This need will propel the creation, implementation, and scaling of new hybrid multiresolution methodologies, for example, in transition-state sampling, studying molecular recognition in crowded and confined environments, and reaching timescales required to monitor cellular interactions—themes that we hope to revisit in future theme meetings.

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