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EDITORIAL

Editorial

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This is the first Special Issue in the short history of *Biophysical Reviews.* The unifying concept of this new venture is to illustrate how computation can be used to solve a diverse range of significant biological problems. Why choose computational methods rather than conventional biophysical techniques like fluorescence and NMR spectroscopy? The answer is that computational biophysics (CB) does not need complex infrastructure (synchrotron facilities, spectrometers, X-ray or neutron beams) or even simple things like a stable power supply that cannot be taken for granted in many countries. We assume that highly talented computational people are not confined to the developed world, but how can they be located and encouraged to enter the field of CB? Thanks to the internet, CB can be done virtually anywhere by any talented computational biologist/biophysicist provided an appropriate mentor is available to provide feedback, advice and sometimes even access to higher level computing via the Cloud. Each contributor to this Special Issue, as well as some who could not make our production deadline, have agreed to be available as mentors.

White paper

Wriggers W, Olson W and dos Remedios CG "Computational opportunities for Remote Collaboration and Capacity Building Afforded by Web 2.0 and Cloud Computing". This contribution is a White Paper, defined as: *An authoritative report or guide that helps solve a problem White papers are used to educate readers and help people make decisions.* The expectation in this contribution is authoritative and achieves the objectives of education and decision-making. The White Paper provides details on Cloud computing and discusses ways by which CB can be used to solve the problem of performing high quality research in the absence of significant infrastructure. Their audience includes "garage" scientists as well as early career biophysicists in both the developed and the developing worlds. For the latter, one "problem" is the so-called brain-drain which tends to permanently take young talented computation-oriented people out of their native country. Many of them develop bright ideas and may wish to return home but are concerned about limited research opportunities such as limited access to resources, small research budgets, and little contact with experienced mentors.

The term Computational Biophysics is not defined in Wikepedia, so the White Paper attempts to define while discussing many of its potential pros and cons including the need for mentors to be selective with their time and efforts, and the need for sources of funding. Below we have grouped the contributions into (1) Computational Methods, and (2) Applications of Computational Biophysics.

Computational methods

Electrostatic macromolecular interactions Fukuda and Nakamura "Non-Ewald Methods: Theory and Applications to Molecular Systems". This review focuses on the importance of electrostatic interactions that are essential determinants of macromolecular simulations of structure and function. The authors discuss potential artifacts, limitations and advantages of the Reaction Field method, the Pre-Averaging method, the Wolf method, and their recent Zero-Dipole Summation method.

Nuclear DNA structure Olson et al. "Insights into Gene Expression and Packaging from Computer Simulations". This

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review deals with the structure of unfathomably long, twisted, and intricately coiled molecular segments that comprise the genes that provide the instructions that a cell needs to operate. Crucial questions remain about how the physical arrangement of this DNA affects the way genes work such as how the nucleus stores genetic information while maintaining accessibility to DNA for genetic processing. The authors have developed new methodologies to simulate the dynamic, three-dimensional structures of long, fluctuating, protein-decorated strands of DNA. Their a priori approach allows a determination of the effects of individual proteins and their chemical modifications on overall DNA structure and function. They review the communication between regulatory proteins attached to precisely constructed stretches of chromatin. They use simulations that account for the enhancement in communication detected experimentally on chromatin compared to protein-free DNA of the same chain length. They also discuss the critical roles played by the cationic 'tails' of the histone proteins in this signaling. Their simulations of the states of chromatin offer new insights into the ways that the DNA, histones, and regulatory proteins contribute to long-range communication along the genome.

Molecular dynamics of glycans Re et al. "Conformational flexibility of N-Glycans in Solution Studied by REMD Simulations". This focuses on the conformational diversity of glycans. These structures are apparently incompatible with specific binding to receptor proteins that regulate a wide range of biological processes. However, the labile nature of glycans makes it difficult to characterize their conformational states. All-atom molecular dynamics (MD) simulations can provide atomic details of glycan structures in solution but extensive sampling is required. This limits conventional MD simulations to di- and tri-saccharides. Replica-exchange molecular dynamics (REMD) simulation, which one of the authors originally developed, with extensive sampling of structures in solution, can identify families of glycan conformers and reveal new insights into their conformation, their equilibria, and their chemical modifications. The results support the concept of "conformer selection" in protein–glycan recognition.

The need for experimental data in CB Alison "Assessing and Refining Molecular Dynamics Simulations of Proteins with Nuclear Magnetic Resonance Data". This author points out that, regardless of the increasing sophistication of the methods used for molecular dynamics (MD) simulations of proteins, it is essential to compare the sampled structures in a simulation with quantitative experimental data. She emphasizes the value of nuclear magnetic resonance (NMR) data in checking the quality of protein simulations because it provides both structural and dynamic temporal and spatial information. She outlines features and implications of using NMR data to validate and bias MD simulations including an overview of the different types of NMR data. She focuses on how to account for conformational averaging, particularly in the context of the assumptions inherent in the relationships that link the NMR data to protein structure.

Applications of computational biophysics

Amyloid disease Edskes and Hall "Computational Modeling of the Relationship of Amyloid's Structure to Disease". Computational modeling permits testing of hypotheses on the relationship between amyloid structure and a wide range of amyloid-based diseases including Alzheimers and type 2 diabetes. This review addresses the relationship between structural commonalities of amyloid aggregates and progression of amyloid diseases. Rather than "artificially" studying di- and tri-saccharides over very short timescales, it focuses on simulations of amyloid aggregation as they occur in the human body, over periods of months to years.

Removing the noise from cryo-electron microscopy Starosolski et al. "Developing a Denoising Filter for Electron Microscopy and Tomography Data in the Cloud". The low radiation conditions and phase-object image of cryo-EM result in images with extremely high noise levels and low contrast. Single particle or tomographic 3D reconstruction does not completely eliminate this noise and can even introduce new noise. The authors evaluate the performance of the new Digital Paths Supervised Variance (DPSV) denoising filter using simulated and experimental data from cryo-EM and tomography in two and three dimensions. They also assessed the benefit of filtering reconstructions for visualization and or enhancing the accuracy of feature detection. The DPSV filter eliminates high-frequency noise artifacts that normally preclude accurate segmentation of tomography reconstructions or the detection of α-helices in single-particle reconstructions. This collaborative software development project was carried out remotely by virtual interactions among the authors who have never met. They used publicly available development and file-sharing tools. This is an example of how CB can add value to experimental technology.

CB and cardiovascualr research Bazan et al. "Contractility Assessment in Enzymatically Isolated Cardiomyocytes". Isolated cardiac myocytes are widely used in modern cardiovascular research because their contractions closely parallel the responses of intact tissue. Much of our understanding regarding the processes underlying heart function can be attributed to single-cell stimulation. Here, the authors survey the most popular published methods used to assess adult and neonatal mammalian cardiomyocyte contractility. They are divided into those employing optical (image)-based systems and those using transducer-based technologies. These techniques are constantly evolving and hold great promise for the next generation of

developments in the prevention, treatment, and cure of cardiovascular diseases.

System biology and CB Ho "Application of a Systems Approach to Study Developmental Gene Regulation". All cells in a multicellular organism contain the same genome, yet different cell types express different sets of genes. Recent advances in high throughput genomic technologies have opened up new opportunities to understand the gene regulatory network in diverse cell types in a genome-wide manner. Ho reviews the recent advances in experimental and computational approaches for the study of gene regulation in embryonic development from a systems perspective. This review is written for computational biologists who have an interest in studying developmental gene regulation using an integrative analysis of gene expression, chromatin landscape, and signaling pathways. Dr Ho highlights the utility of publicly available data and tools, as well as some common analytical approaches.

CB produces surprises when studying olfactory receptors Launay et al. "Modeling of Mammalian Olfactory Receptors and Docking of Odorants". This review deals with the in silico methodologies used to model the three-dimensional (3D) structure of olfactory receptors (ORs) and to dock ligands into these 3D structures. ORs belong to the super-family of G protein-coupled receptors (GPCRs). These constitute the second largest class of genes, accounting for about 3 % of the mammalian genomes. ORs are present in all multicellular organisms and represent more than half the GPCRs in mammals (e.g., the mouse OR repertoire contains more than 1,000 functional genes). ORs are mainly expressed in the olfactory epithelium where they detect odorant molecules. However, they are also expressed in a number of other cells. Recently, it was reported that ORs are present in tumors, and are expressed at different levels than in healthy tissues. A specific OR is over-expressed in prostate cancer cells and its activation inhibits their proliferation. Even though their biological roles are not elucidated, they might constitute new targets for diagnosis and therapeutics. It is important to understand the activation mechanism of these receptors at a molecular level. CB provides insights into which ligands are likely to activate a particular receptor ("deorphanization") and may help design antagonists for a given receptor.

Membrane protein structure and CB Bastug and Kuyucak "Molecular Dynamics Simulations of Membrane Proteins". These proteins control the traffic across cell membranes and thereby play essential roles in cell functions from transport of various solutes to immune responses via molecular recognition. Because it is very difficult to determine the structures of membrane proteins experimentally, computational methods are increasingly used to study their structure and function. Here, they focus on two classes of membrane proteins—ion channels and transporters—that are responsible for the action potentials in nerves, muscles, and other excitable cells. They describe how CB is used to construct models for these proteins and study the transport mechanism using molecular dynamics (MD). Their simulations can refine structures using free energy calculations of transport channels such as gramicidin, potassium channels, and aspartate transporters. CB is used to construct models for these proteins and study their transport mechanisms.

Conflicts of interest None.