DOI: 10.25205/978-5-4437-1691-6-130

RECENT ADVANCEMENTS IN COARSE-GRAINED SIMULATIONS OF BIOMOLECULAR SYSTEMS *

M. E. Bozdaganyan, P. S. Orekhov

Shenzhen MSU-BIT University, China

✉ orekhov_p@smbu.edu.cn

Abstract

Over recent decades, computer simulations of proteins and other biological molecules have become a powerful tool, providing high-resolution insights into the dynamics of biological systems. The demand for simulations on larger time and length scales has led to the development of coarse-grained techniques, which simplify models by substituting groups of atoms with single particles, or 'beads'. These methods enable comprehensive exploration of complex phenomena, such as membrane dynamics and protein interactions, while reducing computational costs compared to all-atom simulations. This talk will highlight recent advancements in coarse-grained simulations, illustrated by diverse examples and discuss the limitations and challenges of popular coarse-grained models, proposing potential strategies for improvement.

Particularly, we will discuss the application of coarse-grained techniques at the early stages of drug development. Binding site prediction is one of critical area, which can be enhanced by coarse-grained simulations. We have recently proposed a cloud-based approach, Colabind [1], employing coarse-grained molecular dynamics simulations with molecular probes mimicking drug-like fragments for identification of potential binding sites of small molecular weight compounds. Colabind demonstrates high effectiveness across diverse biological targets, successfully identifying orthosteric binding sites and known druggable allosteric or PPI sites in both experimentally determined and AI-predicted protein structures. These findings provide valuable insights for pharmacophore hypothesis development, illustrating the potential of CG simulations in identifying and optimizing therapeutic targets.

Exploring the mechanical properties of cellular components such as microtubules and microtubule-associated proteins (MAPs) under mechanical loads offer another fascinating application of CG simulations. MAPs play crucial roles in linking microtubules with other cellular structures, and understanding their mechanical properties is vital for insights into cellular processes. Using CG molecular dynamics and Brownian dynamics simulations, we have investigated the asymmetric unbinding of the NDC80 complex from microtubules under directional load. The stiff stalk of NDC80, tilted toward the plus-end, creates a lever arm critical for asymmetric unbinding, unlike EB-proteins, PRC1, and kinesins, which lack pronounced unbinding asymmetry. These findings highlight design principles of MAPs, explaining how their distal parts modulate unbinding under external loads and informing the design of synthetic protein systems with predefined mechanical characteristics [2].

In the realm of membrane biophysics, the study of amphiphilic copolymers composed of styrene/maleic acid (SMA) monomers and diisobutylene/maleic acid (DIBMA) monomers [3] showcases another significant application of coarse-grained simulations. These copolymers have revolutionized membrane protein research by directly releasing phospholipids and membrane proteins from lipid bilayers, yielding stable water-soluble discoidal SMA/lipid particles (SMALPs) [4, 5]. Using a CG molecular model, molecular dynamics simulations revealed that SMA copolymers aggregate into clusters further interacting with membranes. The clusters of polymers with different ratio of styrene and maleic acid units interact with membranes in different fusion, with the polymers of 3:1 ratio extracting lipid patches to form SMALP-like structures. These results suggest that copolymer molecules with a sufficient number of sequential styrene monomers are necessary for SMALP formation, aligning with experimental data.

CG simulations can also provide critical insights in addressing public health challenges. In another recent publication [6], we have investigated interactions of common antiseptics with bacterial membranes. Cationic antiseptics are essential for combating bacterial and viral infections, and their mechanisms of action are crucial for developing effective treatments remaining elusive. CG molecular dynamics simulations revealed distinct patterns of membrane alterations induced by different antiseptic compounds. While none caused bilayer disintegration, their adsorption increased membrane vulnerability to poration under an external electric field and, plausibly, other types of external stress. This enhanced pore formation likely contributes to their cytotoxic action, offering valuable information for designing more effective antimicrobial agents.

* P. Orekhov is a member of an innovative drug development team based on structural biology and bioinformatics at Shenzhen MSU-BIT University #2022KCXTD034.

Lastly, the ongoing threat of coronaviruses, especially SARS-CoV-2, underscores the importance of detailed investigations aimed at understanding viral protein functions. Using CG molecular dynamics simulations, we analyzed the structure and dynamics of the SARS-CoV-2 envelope (E) protein [7]. The hydrophobic transmembrane domain (TMD) and amphiphilic helices H2 and H3 display specific orientations influenced by palmitoylation and glycosylation. The E protein generates and senses membrane curvature, localizing to convex regions, which may facilitate oligomer assembly and viral particle budding. These results enhance our understanding of structure-function relations for E protein and other viroporins, aiding efforts to combat COVID.

Despite the significant advancements and applications of coarse-grained simulations, several limitations and challenges remain, such as the loss of detailed atomic interactions, limitations in modeling specific molecular interactions, and potential inaccuracies in kinetics predictions. Addressing these challenges requires ongoing development of more sophisticated CG models, integration with all-atom simulations, and validation against experimental data.

In conclusion, coarse-grained simulations have become indispensable in molecular biophysics, enabling the exploration of complex biological systems with reduced computational costs. The examples discussed demonstrate the versatility and power of CG approaches in studying protein structure, binding site prediction, load-bearing properties of MAPs, polymer interactions with membranes, mechanisms of action of antiseptic compounds, and viral protein dynamics. Continued advancements and refinements in CG models will further enhance our understanding of biological processes and support the development of new therapeutic strategies.

References

1. Andreev G., Kovalenko M., Bozdaganyan M., Orekhov P. Colabind: A Cloud-Based Approach for Prediction of Binding Sites Using Coarse-Grained Simulations with Molecular Probes // The Journal of Physical Chemistry B. 2024. Vol. 128(13). P. 3211–3219.

2. Kovalenko I. B., Kholina E. G., Fedorov V. A. et al. Control of the force-bearing properties of microtubule-associated proteins via stalk/linker regions: insights from the NDC80 complex // Under review.

3. Orekhov P. S. et al. Mechanisms of Formation, Structure, and Dynamics of Lipoprotein Discs Stabilized by Amphiphilic Copolymers: A Comprehensive Review // Nanomaterials. 2022. Vol. 12(3). P. 361.

4. Voskoboynikova N., Orekhov P. S., Bozdaganyan M. E. et al. Lipid dynamics in diisobutylene-maleic acid (DIBMA) lipid particles in presence of sensory rhodopsin II // International Journal of Molecular Sciences. 2021. Vol. 22(5). P. 2548.

5. Orekhov P. S. et al. Styrene-maleic acid copolymers form SMALPs by pulling lipid patches out of the lipid bilayer // Langmuir. 2019. Vol. 35(10). P. 3748-3758.

6. Kholina E. G., Kovalenko I. B., Bozdaganyan M. E. et al. Cationic Antiseptics Facilitate Pore Formation in Model Bacterial Membranes // The Journal of Physical Chemistry B. 2020. Vol. 124(39). P. 8593–8600.

7. Kuzmin A., Orekhov P. S., Astashkin R. et al. Structure and dynamics of the SARS-CoV-2 envelope protein monomer // Proteins: Structure, Function, and Bioinformatics. 2022. Vol. 90(5). P. 1102–1114.