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Short Commentary

Accessing Drug Delivery Mechanism by Coarse-Grained Simulation

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Commentary

Extensive researches on controlled drug delivery systems and nanomedicines, such as lipid-based nanoparticles [1] and dendrimers [2], have been carried out in past decades, although limited number of drugs have been approved [3]. To rationalize the development of new drug delivery systems, a combination of experimental and computational studies might be necessary. Examples of such investigations on lipid membranes and liposomes have been reviewed by A. Bunker et al. [4]. Due to the extremely expensive computations, the atomistic simulations of drug delivery systems are usually limited to hundreds of nanoseconds [5], during which the complicated transitions of the drug delivery process might not take place. Thus, a more promising approach to study this complex biophysical process is Coarse-Grained (CG) simulation. One most successful coarse-grained model for biomolecules is the MARTINI force field [6] which has been widely used in investigating drug delivery systems.

In MARTINI force field, four heavy atoms are treated as one bead that the overall biomolecular simulations have been sped up significantly, which allows people to study the mechanism of pore formation on lipid bilayers by PAMAM dendrimers [7]. And one very recent work [8] employs the SDK model [9] to study the peptide-based drug amphiphile filaments structure. These coarse-grained models which group several heavy atoms and freeze the internal degrees of freedom of those grouped atoms allow researchers to perform long simulations with simulation time up to microseconds. However, molecular dynamics simulations based on these coarse-grained models are still limited to a relatively small system, as a huge number of solvent molecules are modeled explicitly. Cooke et al. [10] developed a coarser model for lipid bilayers which only uses 3 beads to represent one lipid molecule and model the solvent implicitly (Figure 1(a)). Due to the degrees of freedom of the system have been reduced dramatically, large vesicles formation can be studied using this model

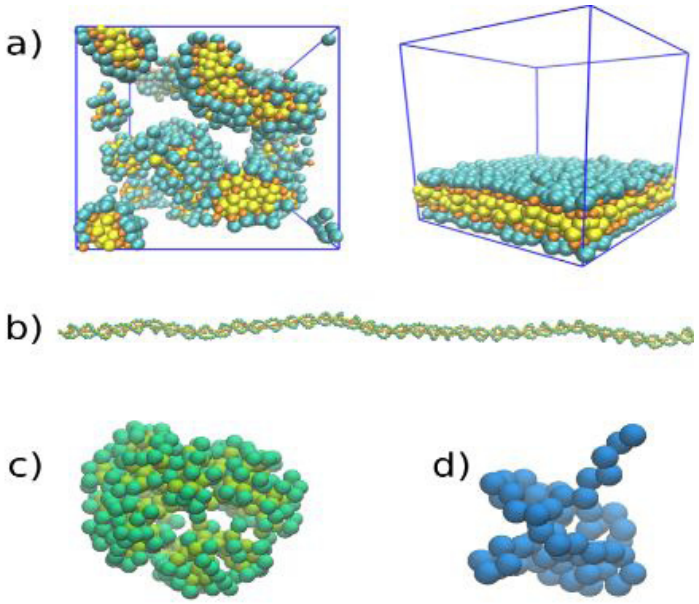

Figure 1(a-d): (a) Snapshots of lipids simulations in solution (left) and on surface (right) based on a tunable generic coarse-grained model for bilayer membranes [10]. (b) A snapshot of dsDNA simulation based on 3SPN.2 force field [11]. (c) A bead-spring, united atom model for a dendrimer molecule [12]. (d) A coarse-grained model for protein G generated by CafeMol software [13].

One big advantage of this generic model is that the parameters of this model can be varied that the aggregates of the lipid molecules can change from fluid to gel. So, this coarse-grained model can be mapped to different kinds of lipid membranes. Coarse-grained models of nucleic acids as well as proteins at similar coarse-graining levels have also been developed. Sambriski et al. [11] developed a mesoscopic 3SPN model which uses 3 beads to represent a single nucleotide (Figure 1(b)), allowing people to simulate long DNA molecules up to hundreds of base pairs. And

the mechanical properties of both dsDNA and ssDNA can be correctly predicted by the revision of this model. United atom model of dendrimer [12] which only considers the terminal groups and branching points as well as the coarse-grained model of protein [13] which models one amino acid as one bead are shown in (Figure1(c,d)) respectively. Note that the 3SPN model of nucleoid acids and various CG models of proteins can be combined into one forced field and have been implemented by a simulation package, CafeMol [14]. Moreover, C. Tan et al. [14] successfully obtained the dynamics of various proteins binding, sliding on DNA using this coarse-grained molecular dynamic simulation recently.

Therefore, a combination of coarse-grained models of lipids, nucleic acids, proteins, and dendrimers discussed above (Figure 1) can be a coarser analogy of the MARTINI force field. Since the lipids model [10] can be tuned easily, the combination of the such coarse-grained models can be mapped to the MARTINI force field readily. And this combination of coarse-grained models of biomolecules can be used to simulate the big drug delivery system which even includes cytoplasm. Hence, the slower transitions in drug delivery process which cannot be obtained by atomistic molecular dynamics or MARTINI/SDK force fields might be revealed using this CG model.

Various drug delivery systems like Solid Lipid Nanoparticles (SLN), liposomes, dendrimers can easily be implemented in this CG force field, for the lipids model can be modified to simulate lipid membranes in different phases. And because dsDNA, ssDNA, and RNA models are already included in the Cafemol package [13] and modeled nucleic acids can be conjugated to simulated dendrimer or encapsulated by lipids vesicles in the combined force field, this CG model can be used for gene delivery simulations too. Hopefully, this CG model can provide more useful information of drug delivery process which can help people design new drug delivery systems. As solvent molecules are considered implicitly in those CG models, many details of the systems are lost. In addition, since the electrostatic interactions among different biomolecules cannot be perfectly computed by Debye-Huckel theory which is being used in this CG model, the dynamics of those simulated biomolecules might be inaccurate. Therefore, to improve this combined coarse-grained model its predictions should be verified by MARTINI CG simulations or atomistic molecular dynamics simulations.

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