

Molecular simulation of self-assembly

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15.1 Introduction

Molecular self-assembly is a ubiquitous process in biology that underlies essential aspects of the most important phenomena that generate and sustain life, such as the formation of cellular membranes and the folding of proteins [1]. The principles of self-assembly are also being increasingly exploited for technological applications, especially in the areas of nanotechnology, drug delivery, and biomaterials [2,3]. In terms of physical bases, self-assembly is a phenomenon that is mostly driven by generic thermodynamics and kinetic factors [4]. In biological systems, where the solvent is universally water, the key driving factor for self-assembly at the molecular scale is the hydrophobic effect, that is, the spontaneous separation of hydrophobic (“water-hating”) and hydrophilic (“water-loving”) substances [5].

In recent decades, the exponential increase in computer power has made it possible for traditional experimental investigation of self-assembly to be compounded by various computer modeling and simulation approaches, which can give access to a level of detail that is unattainable in real experiments, typically because of the small (subnanometer) scale and high complexity of the relevant materials and interactions. The existing usefulness and future potential of computer simulation in the field of self-assembly is now well recognized, and computer modeling represents an increasingly popular way to guide and understand experimental observations. In general, computer simulations can reveal quantitative details of self-assembly phenomena by decomposing individual contributions of energetic, dynamic, and kinetical nature and by connecting a range of various length scales and timescales through multiscale modeling methods [6–9]. This chapter focuses on recent computational studies of self-assembly conducted using the molecular dynamics method. After an introduction to the main methodological aspects, the available literature is categorized, summarized, and critically discussed.

15.2 The molecular dynamics method

Molecular dynamics (MD) is a generic computer simulation technique typically used to calculate equilibrium and transport properties for collections of discrete particles. Since its inception several decades ago, MD has proved to be an especially effective tool to study matter at the molecular scale; MD has indeed been applied widely

in science and engineering for simulating a numerous and diverse range of systems, from the most basic gases and liquids [10–15] to many complex materials including proteins [16–18], lipid membranes [19–21], polymers [22–24], carbon nanostructures [25–27], and soil substances [12,13].

Among the many existing MD software packages, popular options include LAMMPS [28], GROMACS [29], AMBER [30], GROMOS [31], and CHARMM [32].

This section summarizes the key components of the MD method; more details can be found in dedicated books [33–36] and review articles [17,37–39].

The core stages of the main MD algorithm are depicted in Fig. 15.1.

The first stage normally requires initializing the calculation by providing the computer program with the coordinates of all particles in the system of interest (\mathbf{x}), together with the mathematical models (V) that determine how the particles interact with each other; such models are characterized by analytic functions that are typically called *potentials* or *force fields*.

It should be noted that the focus of this chapter is general and this MD summary in particular is on fixed-charge biomolecular/organic force fields, as these are most frequently used in the simulation of molecular self-assembly. However, it must be borne in mind that several other types of force fields exist, as documented extensively in the literature; in particular, significant progress has been recently made on polarizable models [40–43].

The usual form of a force field is

$$V = V_{bonded} + V_{nonbonded} \quad (15.1)$$

where V_{bonded} defines the (intramolecular) interactions between atoms covalently bonded to each other and $V_{nonbonded}$ defines the intermolecular interactions. In most force fields, V_{bonded} typically contains simple harmonic functions, whereby, for example, a covalent bond is modeled with the simple potential that represents an elastic mechanical spring:

$$V(l) = \frac{1}{2} k (l - l_{eq})^2 \quad (15.2)$$

with k the spring rigidity constant, l the actual spring (bond) length, and l_{eq} the equilibrium spring (bond) length. Additional similar functions are employed to model the angles within groups of three consecutively bonded atoms and torsions involving groups of four bonded atoms. Rigidity constants and equilibrium values are typically optimized to reproduce vibrational and conformational properties from experimental measurements or ab initio quantum mechanics calculations.

The nonbonded functions of a force field normally describe van der Waals and electrostatic intermolecular interactions. In particular, the van der Waals interaction between each pair of particles a distance r apart is modeled with the Lennard-Jones potential function:

$$V(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] \quad (15.3)$$

with σ characterizing the collision distance and ϵ the attractive energy.

Atoms interacting through the Lennard-Jones potential are akin to spheres that repel each other at short range (a feature that mimics the overlap between electron clouds) and attract each other at long range (corresponding to attractive dispersion forces). The Lennard-Jones parameters σ and ϵ are usually optimized to reproduce thermodynamic data from experiment, including liquid densities and enthalpies of vaporization. Electrostatic forces between each pair of atoms i and j located a distance r apart are modeled with the Coulomb potential function:

$$V(r) = \frac{Q_i Q_j}{4\pi\epsilon_0 r} \quad (15.4)$$

with Q_i and Q_j the corresponding charges and ϵ_0 the permittivity of free space. In most force fields, charges are assigned empirically to match experimental observables such as electric multipole moments or thermodynamic properties.

The second stage in Fig. 15.1 refers to the main computational routine of a molecular dynamics simulation. The first part of the loop involves evaluating the force on each atom, which is equal to the negative gradient of the potential V . The second part of the loop involves using the forces to update the atom positions by moving each atom forward in time; this is achieved by solving numerically Newton's equations of motion. For example, considering one of the most widely used algorithms [44], given the force $\mathbf{f}(t)$ and velocity $\mathbf{v}(t)$ at the current time t , each atom moves, over one timestep Δt , from position $\mathbf{x}(t)$ at time t to position $\mathbf{x}(t + \Delta t)$ at time $t + \Delta t$, according to the equation

$$\mathbf{x}(t + \Delta t) = \mathbf{x}(t) + \Delta t [\mathbf{v}(t) + \Delta t \mathbf{f}(t) / 2m] \quad (15.5)$$

where m is the atom's mass. Each iteration of this second stage makes the system move forward in time by a single timestep, which is typically on the order of 10^{-15} s.

The third stage in Fig. 15.1 involves the generation of the simulation output. The main output data are the simulation *trajectory*, which consists of consecutive

Molecular dynamics algorithm

- Stage (1) Input data:
 - Starting positions of atoms: \mathbf{x}
 - Model ("force field") of interactions between atoms: V



- Stage (2) Main calculation loop:
 - (i) Compute force on every atom: $\mathbf{f} = -\nabla V$
 - (ii) Use force to move atoms by a single timestep
 - Repeat (i)–(ii) for the required number of timesteps



- Stage (3) Output data:
 - Trajectory of atom positions through time: $\mathbf{x}(t)$
 - Properties of interest: energy, density, etc.

Fig. 15.1 Basic workflow of a typical molecular dynamics simulation.

snapshots of the system coordinates taken at regular time intervals during the simulation. The output trajectory is then normally analyzed using statistical mechanics to calculate a wide range of thermodynamic and dynamic properties of interest, such as energies, densities, diffusion and viscosity coefficients, mechanical parameters, and electric potentials. In fact, the amount of information that can be obtained from a molecular dynamics simulation is potentially vast and typically much greater than what is accessible by experiment.

15.3 Simulations of molecular self-assembly

In this section, a selection of prominent molecular dynamics studies of self-assembly reported in the recent literature are reviewed. The investigations considered are organized into three different subsections corresponding to three different categories of systems, namely, lipids, peptides, and proteins. Previous reviews of different aspects of molecular self-assembly simulation are available in the literature [6,45–53].

15.3.1 Lipids

The self-assembly of lipids in aqueous environments is one of the most important processes in biology, resulting in the spontaneous formation of the plasma bilayer membrane and other fundamental structures such as micelles and vesicles.

The first simulations of the self-assembly of lipids into bilayers were carried out using a so-called united-atom model, where aliphatic hydrogens are treated implicitly to lower the computational cost [54]. In later years, simpler and still cheaper *coarse-grained* models, in which collections of nearby atoms are represented by single (macro-) particles, have been used to study the aggregation of different lipid types on larger temporal and spatial scales [55–59]. On the other hand, thanks to the most recent improvements in computer power and architectures, it is now possible to simulate lipid bilayer self-assembly with full atomistic resolution [60]. Reassuringly, all these studies provide a consistent picture regarding the main aspects of the self-assembly process. In particular, a first stage showing a relatively fast phase separation between lipids and water is followed by the formation of proto-bilayers comprising transient water pores (lined by lipid headgroups) that eventually reorganize to yield a stable, defect-free bilayer.

Simulations have also been carried out to investigate the formation of non-lamellar inverse phases, which are relevant to key cellular processes (such as membrane fusion) and can be exploited for technological applications [61]. In particular, using coarse-grained models, it has been possible to simulate the spontaneous phase transition from lamellar to inverse hexagonal phases in response to a temperature increase [62–64].

More complex systems have also been simulated, where extra molecules were included in addition of the usual lipid and water components. For example, Wallace and Sansom [65] simulated the self-assembly of different lipid types and a carbon

nanotube; depending on the lipid type, the carbon nanotube would adsorb to either cylindrical micelles or hemimicelles. Orsi et al. [66] studied the effect of antimicrobial molecules on the self-assembly of phospholipids (Fig. 15.2). It was found that the self-assembly process was not perturbed at low antimicrobial concentrations, whereas at high concentration (above 33 mol%), long-lived defects prevented the formation of a bilayer over the entire simulation time. In combination with an analysis of curvature elastic properties from preassembled bilayers, the results obtained suggested a possible nonspecific antimicrobial mechanism of action. The interaction between antimicrobials and self-assembled lipid membranes was also studied by Khatami et al. [67]; in their simulations, a special focus was placed on the strong peptide preference to associate with bilayer pores. A study of the binding of capsaicin (the active ingredient of red-hot chili peppers) to ion channels in a lipid membrane was carried out by Hanson et al. [68]; in particular, it was shown that capsaicin was capable of flipping from the extracellular to the intracellular lipid bilayer leaflet and eventually access the protein binding site.

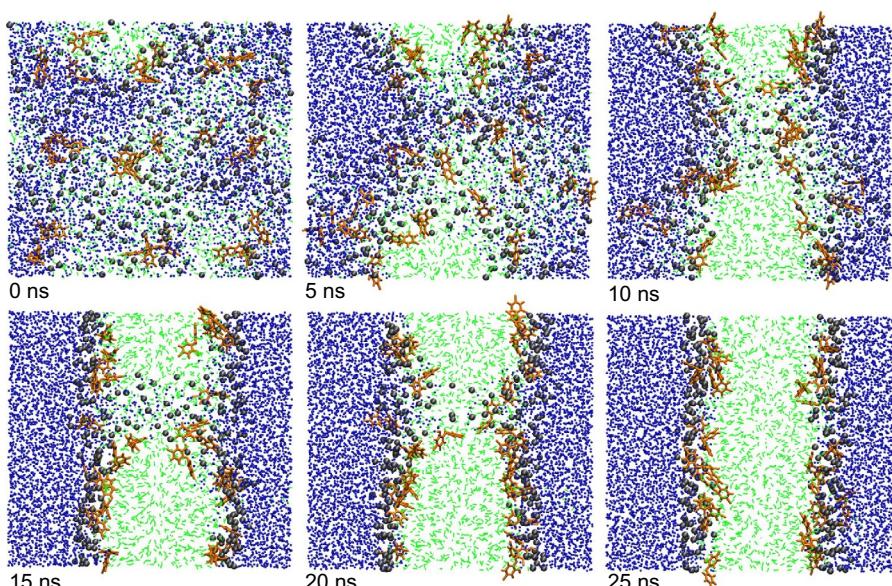


Fig. 15.2 Simulation snapshots from the self-assembly of a system comprising 27 triclosan antibacterial molecules, 128 phospholipids, and 5760 water molecules. Triclosan is *orange*; the lipids heads and tails are *black* and *green*, respectively; and water is *blue*. Images prepared with VMD [68a].

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15.3.2 Peptides

Peptides are characterized by key features of particular advantage in the context of self-assembly. A practically unlimited number of different peptides can be designed by combining the individual building blocks (amino acids), and large quantities can then be synthesized relatively easily and cheaply. Moreover, additional chemical groups can be added to functionalize and tailor different peptides for a variety of applications. Importantly, peptides are inherently biocompatible.

Colombo et al. [47] published an earlier review on peptide self-assembly from both a computational and experimental perspective. Pioneering applications were surveyed especially in the fields of biomedicine and biosensors. More generally, it was recognized that the potential of peptide self-assembly could greatly benefit from theoretical and simulation studies, which promised to provide fundamental understanding and ultimately guide the design of novel sequences [47].

A more recent review, by Frith [69], focused on the application of peptide self-assembly to form gels, especially in the context of the foods, home, and personal care industry.

Significant work in the field has been recently conducted at Northwestern University by the Schatz and Stupp groups. In particular, Lee et al. [70] used atomistic simulations to obtain molecular-level details on the fluctuations of supramolecular assemblies of peptide amphiphiles (Fig. 15.3).

Computational studies have also been coupled to experiments, shedding light on the nature of the complex dynamics of self-assembled nanofibers at the molecular scale [71] and on the corresponding intermolecular forces [72]. An interesting and ambitious application involved the use of molecular simulations to predict self-assembled structures starting from only the sequence of the constituent peptides. Specifically, Frederix and coworkers simulated series of systems containing all possible di- and tripeptides, amounting to 400 and 8000 combinations, respectively [73,74]. The systems were then analyzed in terms of their propensity to self-assemble, yielding a set of design rules that were used to discover new hydrogel-forming tripeptides [73]. The formation of hydrogels was also simulated by Fu et al. [75], using a novel coarse-grained model; in this study, the self-assembly of peptides was investigated under different conditions of temperature and hydrophobicity.

15.3.3 Proteins

Investigating the self-assembly of multiple proteins in the same simulation is a challenging task, due to the required system size and associated large computational cost.

A number of studies focused on the self-assembly of proteins forming virus capsids [76]. In particular, the satellite tobacco mosaic virus was the first to be simulated using atomistic molecular dynamics [77]; that study yielded insights into a range of basic physical properties including electrostatic potentials and density distributions. More recently, simulations have been performed on the human immunodeficiency virus-1 (HIV-1) capsid [78]; in this investigation, simulations proved crucial to the structural determination of the HIV-1 core, thus providing novel drug targets (Fig. 15.4).

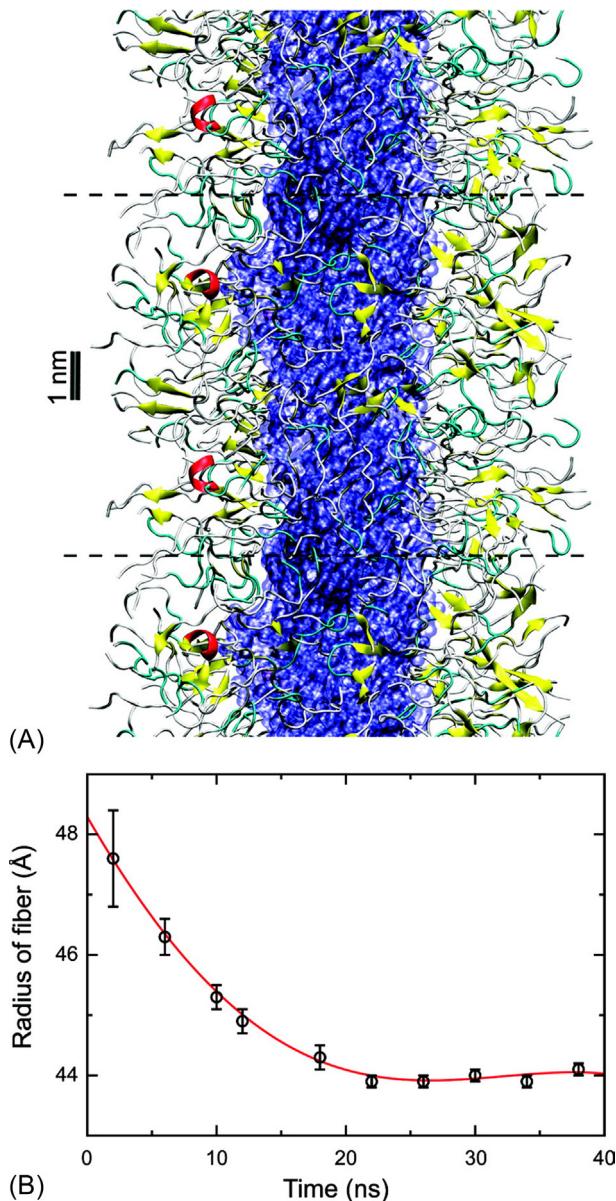


Fig. 15.3 (A) Simulation snapshot of self-assembled peptide amphiphiles. (B) Radius of the self-assembled fiber as a function of the simulation time.

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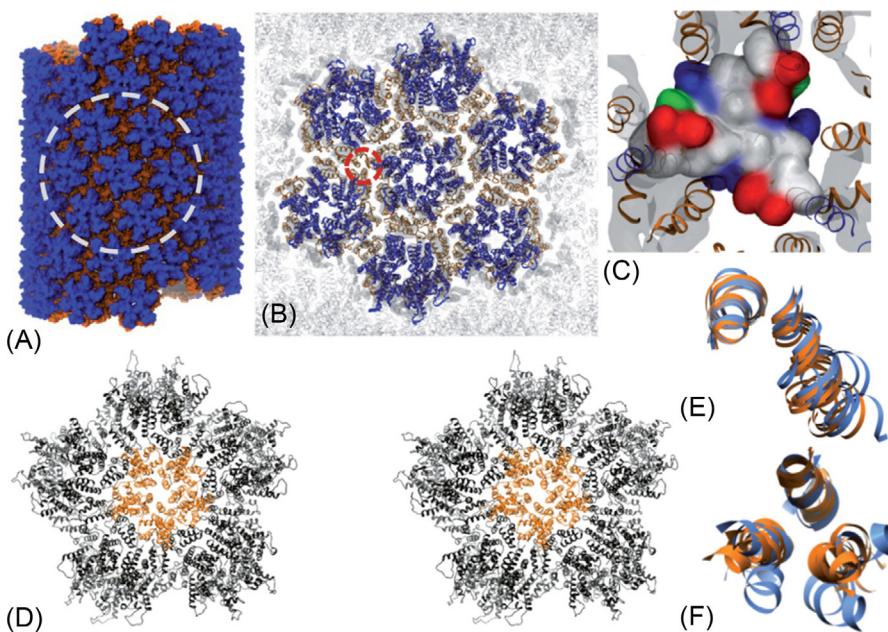


Fig. 15.4 (A and B) Molecular model of tubular assembly comprising 71 capsid protein hexamers. (C) Close up of trimer interface (area in red circle from B). (D) Stereo view of a pentamer-of-hexamer model. (E and F) Superposition of relevant dimer and trimer from hexamer-of-hexamer (blue) and pentamer-of-hexamer (orange) motifs.
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Molecular simulation can also reveal how different self-assembled protein structures can affect, and respond to, mechanical properties. For example, Simunovic and Voth [79] investigated the interplay between Bin/Amphiphysin/Rvs (BAR) protein assemblies and membrane mechanics. BAR proteins, which are known to regulate the curvature of cell membranes, were shown to aggregate differently as a consequence of changes in the surface tension of the surrounding membrane environment [79].

A remarkable application of molecular simulation was reported by Zhong et al. [80], who used modeling data to design novel self-assembling multiprotein nanofibers with unprecedented underwater adhesion strength. In particular, the adhesives were developed by fusing mussel foot proteins with subunits of *Escherichia coli* amyloid curli fibers.

15.4 Conclusion and future trends

The self-assembly of molecules is a multifaceted process emerging from a subtle balance of various intermolecular interactions involving a range of timescales and length

scales. To tackle the complexity of self-assembly, it is now recognized that molecular simulation represents a powerful approach that can be used effectively to better interpret traditional experiments, make quantitative predictions, and guide new lines of investigation. This chapter presented a selection of recent studies in which the popular molecular dynamics computational method was used to simulate self-assembly processes involving lipids, peptides, and proteins.

While molecular simulation can provide unparalleled atomic-level insights into molecular self-assembly processes and structures, a number of issues and limitations should be borne in mind. First of all, the models used are empirical, in that they comprise (typically many) parameters that are optimized to reproduce specific properties of specific systems under specific conditions, without any intrinsic guarantee of transferability [81]. This issue is especially severe for coarse-grained models, due to their simplicity, whereas more detailed atomistic models prove more reliable. In fact, multiscale approaches have been developed that involve a first simulation stage where coarse-grained models are used to efficiently simulate the self-assembly process, followed by a second stage where the structure obtained is backmapped to atomistic models, in order to make more reliable predictions on the properties of interest [82–85].

Another limitation is that systems characterized by low concentrations are difficult to study, due to the large computational cost required by the simulation of large amounts of solvent. For this reason, computer simulation typically can only be used for studying the self-assembly of solutes at high concentrations (in the 0.1–1 M range). Alternatively, the system of interest is preassembled, thus saving the computation time required to reproduce the (typically slow) self-assembly process; obviously, this is a sensible approach only when a self-assembled structure is available (typically from experiment) and when the self-assembly process itself is not of interest.

Regarding future prospects, there is a general expectation that computer power will continue to grow at the rates observed over past decades, thus allowing simulations to continue pushing the temporal and spatial limits of the systems that can be studied under the “computational microscope.” However, some caution may be in order, due to possible physical boundaries that computer hardware may run into in the near future, especially in terms of hardware constraints on heat generation [69]. In this context, the development of multiscale modeling techniques, which strive to optimize computational power by simplifying some aspects of the models while maintaining accuracy where most important, may turn out to be even more useful than they already appear to be [7,85–91].

In more general terms, it is not unreasonable to predict that, in the foreseeable future, the investigation and application of molecular self-assembly will have increasingly greater relevance in key scientific and technological areas, including for instance medicine and energy, as already shown by pioneering studies [92,93].

In combination with the more traditional experimental research approaches, it is expected that molecular simulation will increasingly play key roles in the field of self-assembly, especially with regard to interpretation of existing experiments, inspiration for new ones, and prediction of properties not readily accessible in the laboratory.

References

- [1] Mendes AC, et al. Self-assembly in nature: using the principles of nature to create complex nanobiomaterials. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2013;5(6):582–612.
- [2] Capito RM, et al. Self-assembly of large and small molecules into hierarchically ordered sacs and membranes. Science 2008;19(5871):1812–6.
- [3] Ferreira DS, et al. Molecularly engineered self-assembling membranes for cell-mediated degradation. Adv Healthc Mater 2015;4(4):602–12.
- [4] Wang J, et al. Peptide self-assembly: thermodynamics and kinetics. Chem Soc Rev 2016;45:5589–604. Available at: <http://xlink.rsc.org/?DOI=C6CS00176A>.
- [5] Chandler D. Interfaces and the driving force of hydrophobic assembly. Nature 2005;437(7059):640–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16193038>.
- [6] Glotzer SC, Solomon MJ, Kotov NA. Self-assembly: from nanoscale to microscale colloids. AIChE J 2004;50(12):2978–85.
- [7] Kamerlin SCL, Warshel A. Multiscale modeling of biological functions. Phys Chem Chem Phys 2011;13(22):10401–11. Available at: <http://pubs.rsc.org/en/Content/ArticleHTML/2011/CP/C0CP02823A>.
- [8] Orsi M, Essex JW. Permeability of drugs and hormones through a lipid bilayer: insights from dual-resolution molecular dynamics. Soft Matter 2010;6(16):3797. Available at: <http://pubs.rsc.org/en/content/articlehtml/2010/sm/c0sm00136h>.
- [9] Wassenaar TA, et al. Mixing MARTINI: electrostatic coupling in hybrid atomistic-coarse-grained biomolecular simulations. J Phys Chem B 2013;117(13):3516–30.
- [10] Adams DJ, Adams EM, Hills GJ. The computer simulation of polar liquids. Mol Phys 1979;38(2):387–400. <https://doi.org/10.1080/00268977900101751>.
- [11] Ding W, Palaiokostas M, Orsi M. Stress testing the ELBA water model. Mol Simul 2016;42(4):337–46.
- [12] Orsi M. Comparative assessment of the ELBA coarse-grained model for water. Mol Phys 2014;112(11):1566–76.
- [13] Orsi M. Molecular dynamics simulation of humic substances. Chem Biol Technol Agric 2014;1(1):10. Available at: <http://www.chembioagro.com/content/1/1/10>.
- [14] Stoddard SD, Ford J. Numerical experiments on the stochastic behavior of a Lennard-Jones gas system. Phys Rev A 1973;8(3):1504–12. Available at: <http://journals.aps.org/prabSTRACT/10.1103/PhysRevA.8.1504>; Accessed January 10, 2017.
- [15] Vega C, Abascal JL. Simulating water with rigid non-polarizable models: a general perspective. Phys Chem Chem Phys 2011;13(44):19663.
- [16] Deriu MA, et al. Anisotropic elastic network modeling of entire microtubules. Biophys J 2010;99(7):2190–9.
- [17] Mackerell AD. Empirical force fields for biological macromolecules: overview and issues. J Comput Chem 2004;25(13):1584–604.
- [18] Soncini M, et al. Mechanical response and conformational changes of alpha-actinin domains during unfolding: a molecular dynamics study. Biomech Model Mechanobiol 2007;6(6):399–407.
- [19] Ding W, et al. Effects of lipid composition on bilayer membranes quantified by all-atom molecular dynamics. J Phys Chem B 2015;119(49):15263–74.
- [20] Ding W, et al. Effects of high pressure on phospholipid bilayers. J Phys Chem B 2017;121(41):9597–606.
- [21] Orsi M, Michel J, Essex JW. Coarse-grain modelling of DMPC and DOPC lipid bilayers. J Phys Condens Matter 2010;22(15):155106.

- [22] Fritz D, et al. Multiscale modeling of soft matter: scaling of dynamics. *Phys Chem Chem Phys* 2011;13(22):10412–20.
- [23] Di Pasquale N, Gowers RJ, Carbone P. A multiple time step scheme for multiresolved models of Macromolecules. *J Comput Chem* 2014;35(16):1199–207.
- [24] Varnik F, Baschnagel J, Binder K. Molecular dynamics results on the pressure tensor of polymer films. *J Chem Phys* 2000;113(10):4444. Available at: <http://link.aip.org/link/?JCPA6/113/4444/1>.
- [25] Cohen-Tanugi D, Grossman JC. Water desalination across nanoporous graphene. *Nano Lett* 2012;12(7):3602–8.
- [26] Corry B. Designing carbon nanotube membranes for efficient water desalination. *J Phys Chem B* 2008;112(5):1427–34.
- [27] Izvekov S, Violi A, Voth GA. Systematic coarse-graining of nanoparticle interactions in molecular dynamics simulation. *J Phys Chem B* 2005;109(36):17019–24.
- [28] Plimpton S. Fast parallel algorithms for short-range molecular dynamics. *J Comput Phys* 1995;117(1):1–19.
- [29] Hess B, van der Spoel D, Lindahl E. GROMACS user manual version 4.6.7., www.gromacs.org; 2014.
- [30] Wang J, et al. Development and testing of a general amber force field. *J Comput Chem* 2004;25(9):1157–74.
- [31] Chandrasekhar I, et al. Molecular dynamics simulation of lipid bilayers with GROMOS96: application of surface tension. *Mol Simul* 2005;31(8):543–8. <https://doi.org/10.1080/08927020500134243>.
- [32] Zhu X, Lopes P, MacKerell A. Recent developments and applications of the CHARMM force fields. *Wiley Interdiscip Rev: Comput Mol Sci* 2012;2(1):167–85.
- [33] Allen MP, Tildesley DJ. Computer simulation of liquids. Oxford, UK: Oxford University Press; 1989.
- [34] Berendsen HJC. Simulating the physical world. Annals of Physics, Cambridge, UK: Cambridge University Press; 2007:624.
- [35] Rapaport DC. The art of molecular dynamics simulation. 2nd ed. Cambridge, UK: Cambridge University Press; 2004.
- [36] Schlick T. Molecular modeling and simulation: an interdisciplinary guide: an interdisciplinary guide. New York: Springer Science & Business Media; 2010.
- [37] Cheung DL, et al. Computer simulation of liquids and liquid crystals. *Comput Phys Commun* 2008;179(1–3):61–5.
- [38] Van Gunsteren WF, et al. Computer simulation of biomolecular systems: where do we stand? *Syst Biol* 2008;40:49–56.
- [39] Schlick T, et al. Biomolecular modeling and simulation: a field coming of age. *Q Rev Biophys* 2011;44(2):191–228. Available at: http://journals.cambridge.org/article_S0033583510000284%5Cnhttp://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8259348&fileId=S0033583510000284.
- [40] Baker CM. Polarizable force fields for molecular dynamics simulations of biomolecules. *Wiley Interdiscip Rev: Comput Mol Sci* 2015;5(2):241–54. Available at: <http://doi.wiley.com/10.1002/wcms.1215>; Accessed January 10, 2017.
- [41] Peter EK, Pivkin IV. A polarizable coarse-grained water model for dissipative particle dynamics. *J Chem Phys* 2014;141(16):164506.
- [42] Ponder JW, et al. Current status of the AMOEBA polarizable force field. *J Phys Chem B* 2010;114(8):2549–64. <https://doi.org/10.1021/jp910674d>.
- [43] Wick CD, et al. The effect of polarizability for understanding the molecular structure of aqueous interfaces. *J Chem Theory Comput* 2007;3(6):2002–10.

- [44] Swope WC. A computer simulation method for the calculation of equilibrium constants for the formation of physical clusters of molecules: application to small water clusters. *J Chem Phys* 1982;76(1):637. Available at: <http://link.aip.org/link/?JCPA6/76/637/1>.
- [45] Adler-Abramovich L, Gazit E. The physical properties of supramolecular peptide assemblies: from building block association to technological applications. *Chem Soc Rev* 2014;43(20):6881–93. <https://doi.org/10.1039/C4CS00164H>.
- [46] Allen DT, Lorenz CD. Molecular scale simulations of the self-assembly of amphiphilic molecules: current state-of-the-art and future directions. *SAME* 2015;2015(1):01–38. Available at: http://riverpublishers.com/journal_thematic_article.php?j=JSAME/2015/004.
- [47] Colombo G, Soto P, Gazit E. Peptide self-assembly at the nanoscale: a challenging target for computational and experimental biotechnology. *Trends Biotechnol* 2007;25(5):211–8.
- [48] Cui H, Webber MJ, Stupp SI. Self-assembly of peptide amphiphiles: from molecules to nanostructures to biomaterials. *Biopolymers* 2010;94(1):1–18.
- [49] Dehsorkhi A, Castelletto V, Hamley IW. Self-assembling amphiphilic peptides. *J Pept Sci* 2014;20(7):453–67. Available at: <http://doi.wiley.com/10.1002/psc.2633>.
- [50] Larson RG. Simulations of self-assembly. *Curr Opin Colloid Interface Sci* 1997;2(4):361–4. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S1359029497800775>.
- [51] McCullagh M, et al. Modeling self-assembly processes driven by nonbonded interactions in soft material. *J Phys Chem B* 2008;112(34):10388–98.
- [52] Rajagopalan R. Simulations of self-assembling systems. *Curr Opin Colloid Interface Sci* 2001;6(4):357–65. Available at: <http://www.sciencedirect.com/science/article/pii/S1359029401001030>.
- [53] Svenson S. Controlling surfactant self-assembly. *Curr Opin Colloid Interface Sci* 2004;9(3):201–12. Available at: <http://www.sciencedirect.com/science/article/pii/S1359029404000676>.
- [54] Marrink SJ, et al. Simulation of the spontaneous aggregation of phospholipids into bilayers [23]. *J Am Chem Soc* 2001;123(35):8638–9.
- [55] Cooke IR, Kremer K, Deserno M. Tunable generic model for fluid bilayer membranes. *Phys Rev E Stat Nonlinear Soft Matter Phys* 2005;72(1):2–5.
- [56] Ingólfsson HI, et al. The power of coarse graining in biomolecular simulations. *Wiley Interdiscip Rev: Comput Mol Sci* 2014;4(3):225–48.
- [57] Lopez CF, et al. Self-assembly of a phospholipid Langmuir monolayer using coarse-grained molecular dynamics simulations. *J Phys Condens Matter* 2002;14(14):9431–44. Available at: <http://iopscience.iop.org/0953-8984/14/40/327>.
- [58] Orsi M, et al. A quantitative coarse-grain model for lipid bilayers. *J Phys Chem B* 2008;112(3):802–15.
- [59] Orsi M, Essex JW. The ELBA force field for coarse-grain modeling of lipid membranes. *PLoS One* 2011;6(12):e28637.
- [60] Skjevik ÅA, et al. All-atom lipid bilayer self-assembly with the AMBER and CHARMM lipid force fields. *Chem Commun (Camb)* 2015;51(21):4402–5. Available at: <http://pubs.rsc.org/en/content/articlehtml/2015/cc/c4cc09584g>.
- [61] Tresset G. The multiple faces of self-assembled lipidic systems. *PMC Biophys* 2009;2(1):3.
- [62] Corsi J, et al. DNA lipoplexes: formation of the inverse hexagonal phase observed by coarse-grained molecular dynamics simulation. *Langmuir* 2010;26(14):12119–25.
- [63] Marrink S-J, Mark AE. Molecular view of hexagonal phase formation in phospholipid membranes. *Biophys J* 2004;87(6):3894–900. Available at: [http://www.ncbi.nlm.nih.gov/entrez/fcgi?artid=PMC1304900](http://www.ncbi.nlm.nih.gov/pubmed/15377528%5Cnhttp://www.ncbi.nlm.nih.gov/entrez/fcgi?artid=PMC1304900).

- [64] Orsi M, Essex JW. Physical properties of mixed bilayers containing lamellar and non-lamellar lipids: insights from coarse-grain molecular dynamics simulations. *Faraday Discuss* 2013;161:249–72.
- [65] Wallace JE, Sansom MSP. Carbon nanotube self-assembly with lipids and detergent: a molecular dynamics study. *Nanotechnology* 2009;20(4):45101. Available at: <http://stacks.iop.org/0957-4484/20/i=4/a=045101>.
- [66] Orsi M, Noro MG, Essex JW. Dual-resolution molecular dynamics simulation of antimicrobials in biomembranes. *J R Soc Interface* 2011;8(59):826–41. Available at: <http://rsif.royalsocietypublishing.org/content/8/59/826.long>.
- [67] Khatami MH, et al. Molecular dynamics simulations of histidine-containing cod antimicrobial peptide paralogs in self-assembled bilayers. *Biochim Biophys Acta Biomembr* 2014;1838(11):2778–87. Available at: <http://www.sciencedirect.com/science/article/pii/S0005273614002570>.
- [68] Hanson SM, et al. Capsaicin interaction with TRPV1 channels in a lipid bilayer: molecular dynamics simulation. *Biophys J* 2015;108(6):1425–34. Available at: <http://www.sciencedirect.com/science/article/pii/S0006349515001757>.
- [68a] Humphrey W, Dalke A, Schulter K. VMD—visual molecular dynamics. *J Mol Graphics* 1996;14:33–8.
- [69] Frith WJ. Self-assembly of small peptide amphiphiles, the structures formed and their applications. (A foods and home and personal care perspective). *Philos Trans A* 2016;374(2072):20150138, <https://doi.org/10.1098/rsta.2015.0138>.
- [70] Lee OS, Stupp SI, Schatz GC. Atomistic molecular dynamics simulations of peptide amphiphile self-assembly into cylindrical nanofibers. *J Am Chem Soc* 2011;133(10):3677–83.
- [71] Ortony JH, et al. Internal dynamics of a supramolecular nanofibre. *Nat Mater* 2014;13(May):1–5. Available at: <http://www.nature.com/doifinder/10.1038/nmat3979%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/24859643>.
- [72] Newcomb CJ, et al. Cell death versus cell survival instructed by supramolecular cohesion of nanostructures. *Nat Commun* 2014;5:3321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24531236>.
- [73] Frederix PWJM, et al. Exploring the sequence space for (tri-)peptide self-assembly to design and discover new hydrogels. *Nat Chem* 2014;7(1):30–7. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25515887%5Cnhttp://www.nature.com/doifinder/10.1038/nchem.2122>.
- [74] Frederix PWJM, et al. Virtual screening for dipeptide aggregation: toward predictive tools for peptide self-assembly. *J Phys Chem Lett* 2011;2(19):2380–4. Available at: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3688361&tool=pmcentrez&rendertype=abstract>.
- [75] Fu IW, et al. Role of hydrophobicity on self-assembly by peptide amphiphiles via molecular dynamics simulations. *Langmuir* 2014;30(26):7745–54. Available at: <http://pubs.acs.org/doi/abs/10.1021/la5012988>.
- [76] Perilla JR, et al. Molecular dynamics simulations of large macromolecular complexes. *Curr Opin Struct Biol* 2015;31:64–74. <https://doi.org/10.1016/j.sbi.2015.03.007>.
- [77] Freddolino PL, et al. Molecular dynamics simulations of the complete satellite tobacco mosaic virus. *Structure* 2006;14(3):437–49.
- [78] Zhao G, et al. Mature HIV-1 capsid structure by cryo-electron microscopy and all-atom molecular dynamics. *Nature* 2013;497(7451):643–6. <https://doi.org/10.1038/nature12162>.
- [79] Simunovic M, Voth GA. Membrane tension controls the assembly of curvature-generating proteins. *Nat Commun* 2015;6(May):7219. <https://doi.org/10.1038/ncomms8219>.

- [80] Zhong C, et al. Strong underwater adhesives made by self-assembling multi-protein nano-fibres. *Nat Nanotechnol* 2014;9(10):858–66. <https://doi.org/10.1038/nnano.2014.199>.
- [81] Louis AA. Beware of density dependent pair potentials. *J Phys Condens Matter* 2002;14(40):9187–206. Available at: http://apps.isiknowledge.com/InboundService.do?product=WOS&action=retrieve&SrcApp=Papers&UT=000179052100012&SID=X2hPfKiMI41Oe93ndHk&SrcAuth=mekentosj&mode=FullRecord&customersID=mekentosj&DestFail=http://access.isiproducts.com/custom_images/wok_failed_aut.
- [82] Ayton GS, Noid WG, Voth GA. Multiscale modeling of biomolecular systems: in serial and in parallel. *Curr Opin Struct Biol* 2007;17(2):192–8.
- [83] Lombardi LE, Martí MA, Caperce L. CG2AA: backmapping protein coarse-grained structures. *Bioinformatics* 2016;32(8):1235.
- [84] Machado MR, Pantano S. SIRAH tools: mapping, backmapping and visualization of coarse-grained models. *Bioinformatics* 2016;32(10):1568.
- [85] Sherwood P, Brooks BR, Sansom MS. Multiscale methods for macromolecular simulations. *Curr Opin Struct Biol* 2008;18(5):630–40.
- [86] Chavent M, Duncan AL, Sansom MS. Molecular dynamics simulations of membrane proteins and their interactions: from nanoscale to mesoscale. *Curr Opin Struct Biol* 2016;40:8–16. Available at: <http://www.sciencedirect.com/science/article/pii/S0959440X16300641>.
- [87] Michel J, Orsi M, Essex JW. Prediction of partition coefficients by multiscale hybrid atomic-level/coarse-grain simulations. *J Phys Chem B* 2008;112(3):657–60.
- [88] Orsi M, Ding W, Palaiokostas M. Direct mixing of atomistic solutes and coarse-grained water. *J Chem Theory Comput* 2014;10(10):4684–93.
- [89] Orsi M, Sanderson WE, Essex JW. Permeability of small molecules through a lipid bilayer: a multiscale simulation study. *J Phys Chem B* 2009;113(35):12019–29.
- [90] Riniker S, Van Gunsteren WF. Mixing coarse-grained and fine-grained water in molecular dynamics simulations of a single system. *J Chem Phys* 2012;137:44120.
- [91] Voth GA. A multiscale description of biomolecular active matter: the chemistry underlying many life processes. *Acc Chem Res* 2017;50(3):594–8. Available at: <http://pubs.acs.org/doi/abs/10.1021/acs.accounts.6b00572>.
- [92] Hendsbee AD, et al. Synthesis, self-assembly, and solar cell performance of N-annulated perylene diimide non-fullerene acceptors. *Chem Mater* 2016;28(19):7098–109. <https://doi.org/10.1021/acs.chemmater.6b03292>.
- [93] Inostroza-Brito KE, et al. Co-assembly, spatiotemporal control and morphogenesis of a hybrid protein-peptide system. *Nat Chem* 2015;7(11):897–904. <https://doi.org/10.1038/nchem.2349>.