The use of molecular dynamics simulations in structural biology and biophysics has come of age. Indeed, computational modeling is going beyond classical static tasks such as structure refinement for x-ray and NMR spectroscopy, or docking of small molecules against rigid protein surfaces in search of new drugs. Nowadays, whole ribosomes are subjects of serious studies represented by numerical setups with approximately a few million atoms, and experimental data such as transition rates of the ribosome’s internal clockwork can be addressed (1). The combination of advanced sampling strategies, intelligent use of computing resources, and the latest generation of adapted hardware makes an aggregate sampling timescale of milliseconds possible, even at full atomistic resolution (2). However, comprehensive insight into a system often requires reduced or coarse-grained (CG) models that computationally are much more efficient and allow for scanning the space of relevant parameters in a systematic manner (3). The enlarged parameter space accessible to CG models permits to clarify conceptual issues such as, e.g., the interplay between tension and shape fluctuations of lipid bilayers (4). The computational protocol developed in CG simulations may then be employed in atomistic simulations as well.

Superficially, CG strategies are all very similar because they make use of so-called superatoms or CG beads, each representing a whole group of atoms. In general, this will smooth the energy landscape and reduce its dimensionality. For lipid membranes, the acceleration of diffusive processes is advantageous because the redistribution of single lipid molecules proceeds much faster on the timescale of a CG simulation as compared to an all-atom setup. Different CG models often use different computational schemes to derive interaction parameters between CG sites. One may directly project the atomistic model onto the CG variables; alternatively, knowledge- or structure-based techniques can be used or a combination thereof (5). In most cases, CG models are closely tied to specific, invariable systems. Staying close to a template clearly facilitates the detection and removal of possible artifacts that may arise during the CG procedure. To some extent, it limits versatility and transferability, although these features would be highly desirable—especially for representing biologically relevant lipid membrane or monolayer systems. Corresponding computational models ideally should reflect the interplay of a number of different components such as charged/uncharged lipids, ions, and proteins to address important pending questions that can only be answered if molecular scales are taken into account.

The intriguing behavior of pulmonary lung surfactant (PS) represents the kind of computational challenge just described. In principle, the same type of monolayer, formed from different lipid types and small proteins, covers the pulmonary alveoles in all mammals. PS maintains their dynamic stability under expansion or retraction (6). To achieve this, PS has to support a broad range of surface pressures. This requires some well-regulated collapse mechanism whereby (mostly unsaturated) lipids from liquid-phase domains are removed from the monolayer and expelled into the water subphase (squeeze-out mechanism) or stored in bilayer folds and stacks connected to the monolayer (modified squeeze-out mechanism), allowing for a reversible spreading of the layer.

In this issue of the Biophysical Journal, Baoukina et al. (7) present a numerical study on the collapse of heterogeneous lipid monolayers that, in some respects, mimic the situation in a realistic PS film. They employ a mixture of different saturated and unsaturated lipids, cholesterol, and ions (7) to generate coexisting liquid-expanded/liquid crystalline as well as liquid-ordered/liquid-disordered domains. To represent these systems computationally, they make use of the MARTINI force field developed by Marrink et al. (8). In principle, it represents a transferrable, standalone CG framework, that is, a force field of its own designed to model soft matter at mesoscopic scales. Within this methodology, the mutual interactions of CG sites may be determined quite independently from any specific structure or all-atom force field. The idea is to break down a biomolecule into suitable fragments that can be represented by small organic molecules, for which a large body of experimental data such as relative solvation free energies is available to calibrate the force-field parameters.

From their simulations, Baoukina et al. (7) are able to draw a number of interesting conclusions. Some of them are directly relevant to conjectures about the functionality of PS monolayer systems, for instance:

1. That percolating solid domains considerably slow down the kinetics of collapse;
2. That on collapse, liquid phases rich in unsaturated lipids are transferred to forming folds and wrinkles, which become bilayer regions (i.e., a modified squeeze-out mechanism); and
3. The general observation that the composition of the monolayer...
finally in equilibrium with bilayers bears a modified distribution and composition of phase compared to a flat monolayer.

Together with their previous work, the authors have clearly shown the usefulness of the CG setup. Nevertheless, it is important to ask to what extent the simulation results can be directly corroborated by experimental studies. On the one hand, the size and complexity of the problem might already have left the realm of what could be run concurrently in a fully atomistic setting. On the other hand, high-resolution microscopy techniques that have been introduced to the study of lipid mono- and bilayers are steadily being improved.

Indeed, today’s state-of-the-art microscopy techniques are targeting micron- or even submicron lengthscales to address the distribution and effects of surface proteins or to elucidate the very concept of lipid rafts. The dynamics of fluorescently labeled lipids and proteins, as of this writing, can be resolved down to tenths of nanometers by high-resolution optical microscopy (9). AFM imaging allows for lateral resolution on the nanometer scale: in DPPC/POPC/POPG-model PS monolayers that were transferred to solid supporting substrates, scanning areas of ~1 μm² sufficed to characterize the size- and shape distribution of nanodomains (6). These systems can be investigated further, with respect to lateral chemical composition with time-of-flight secondary ion-mass spectrometry (ToF-SIMS) measurements (10). The contemporary resolution limit of ToF-SIMS experiments is ~100 nm; a pixel of a corresponding composition map would roughly cover the entire simulation box containing a surface patch of 80 nm². That is, increasing the size of the simulation box by an order of magnitude would, for well-defined cases, already give access to results from a series of experimental techniques. The currently available computational power for molecular dynamics simulations should make this step possible, which appears crucial for the further development of this CG methodology.

REFERENCES