

Emerging methods for multiscale simulation of biomolecular systems

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Three multiscale computational methodologies for biomolecular systems are described: the force-matching method for developing coarse-grained models directly from atomistic simulations; the quasi-particle approach of simulating field theory representations at the mesoscopic scale; and the multiscale-coupling method for direct information transfer between mesoscopic and atomistic scales on the fly. The statistical mechanical background for each of the methods is described in a comprehensive manner in order to highlight their theoretical foundations. Examples of various applications of these methods to model different biophysical processes are given. Combining with atomistic-level MD simulations, these three methods compose a powerful tool for bridging and spanning the multiple spatial and temporal domains that are present in many biological assemblies. Future directions of the methodology developments are also discussed.

1. Introduction

The functionalities of complicated biological assemblies such as cell membranes, chromosomal DNA, and protein complexes, contain processes that occur at multiple length- and time-scales. Describing how various properties at these different scales are coupled is thus critical in order to understand the molecular mechanisms that ultimately sustain the life of a cell. Molecular modelling and simulation has become an indispensable tool to study biological systems [1–16]; however, integrating theoretical approaches and physical models at different scales (ranging from atomistic to almost macroscopic spatial/temporal domains) remains a fundamental challenge [7–21].

In order to overcome the multiscale challenge mentioned above, an intermediate coarse-grained (CG) scale, in which fewer details than the actual number of atoms are used to represent the molecules in a system, can be very useful, if not necessary, in order to bridge information across different scales [10, 14, 16, 21–29]. Although the morphology and resolution at the CG scale can be modulated for different systems and problems, the possibly arbitrary nature of the exact

choice of CG description, along with the lack of theoretical underpinning for developing CG models has made the interpretation and reproducibility of CG scale simulations difficult.

However, it is possible to formally derive a statistical mechanics for coarse-graining, and such a derivation for the multiscale force-matching method is presented here. The multiscale coarse-graining (MS-CG) method based on the force-matching (FM) [1, 26] approach systematically utilizes the force data obtained from atomistic molecular dynamics (MD) simulations to develop CG force-fields. The MS-CG method has been successfully applied to CG scale simulations of different bio- and nano-systems. [1–3, 26–29]

As an alternative to the ‘bottom-up’ FM approach to developing reduced models directly from the atomistic scale, a more ‘top-down’ field theory based approach can extend the spatial/temporal domains that are required to fully model many complex bioassemblies [17–21]. In a field theory formulation, order parameters describing the fields that are involved in a process are first defined, and the response of order parameters to external excitations such as thermal fluctuations is then described by a phenomenological mesoscopic Hamiltonian [30, 31]. The material properties that act as key parameters in the mesoscopic Hamiltonian can be directly computed from atomistic scale simulations using non-equilibrium molecular dynamics

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(NEMD) [32], thus allowing the information transfer across different scales. This field theory approach is particularly useful for self-assembled structures composed of distinct length-scales such as cell membranes and chromosomal DNA. Computational methodologies that can be used to model biological systems based on field theories with complicated geometries and compositions are also described in this work and used to model different biophysical properties of lipid bilayers.

Of course, one obvious drawback to an essentially continuum-level field theory picture is the complete lack of atomistic details. As such, it is not possible to, for example, examine the atomistic response of a biological assembly (e.g. a membrane-bound protein) to mesoscopic-level phenomena (e.g. mesoscopic stress fields). However, we have recently shown that it is possible to effectively ‘embed’ an atomistic-level system into a field theory-based model [19, 20, 33]. This scheme is denoted multiscale coupling (MSC) and has been applied to both pure bilayers [19] as well as bilayers with membrane-bound proteins [20, 33]. MSC couples the effects of mesoscopic perturbations such as plane stress fields into synthetic and spatially distributed fields at the MD level via the equations of motion at the atomistic scale. The MSC method will also be described in this paper. Results for the coupling of a membrane-bound influenza A virus M2 proton channel at the atomistic scale to the mesoscopic undulations of the surrounding lipid bilayer will be given to illustrate the application of this method.

In the following sections, each of the three methods mentioned above will be described in a comprehensive manner with the results of implementation/application reported. Finally, concluding remarks are drawn.

2. The development of CG models from atomistic simulations: the multiscale coarse-graining approach

‘Coarse-graining’ (CG) is a procedure for reducing the number of degrees of freedom that are used to represent a system. For example, in an all-atom model, the CG procedure begins by grouping several atoms together via a mapping expressed as:

$$\vec{R}_\alpha = \sum_{i=1}^N c_{\alpha i} \vec{r}_i, \quad \text{with} \quad \sum_{i=1}^N c_{\alpha i} = 1 \text{ for each } \alpha. \quad (1)$$

In equation (1), $c_{\alpha i}$ s are the coefficients used for determining the positions of CG sites from the coordinates of atoms. The summation index i is the atom index for an N atom system, and α is the index for an M site CG representation of the same system. After a mapping as in

equation (1) is defined, the configurational Helmholtz free energy, $A(\vec{R})$, of the system can be partitioned according to the CG site coordinates:

$$\exp(-\beta A(\vec{R})) = \frac{1}{V^M} \int d\vec{q} \exp(-\beta U(\vec{R}, \vec{q})) \quad (2)$$

so that the thermodynamic Helmholtz free energy A is given by:

$$\exp(-\beta A) = \frac{1}{V^M} \int d\vec{R} \exp(-\beta A(\vec{R})). \quad (3)$$

In equations (2) and (3), the boldfaced letter \vec{R} denotes a $3M$ -dimensional vector recording the positions of all CG sites, \vec{q} denotes the remaining $3(N - M)$ internal coordinates in addition to the M \vec{R}_α (position of a CG site α) that are needed to fully describe an atomistic configuration \vec{r} of dimension $3N$, $U(\vec{R}, \vec{q})$, or $U(\vec{r})$, is the atomistic potential energy, V is the volume, $\beta = 1/k_B T$, and $A(\vec{R})$ is the configuration free energy of the atomistic system as a function of CG site coordinates and is defined as the exact CG effective potential energy that a CG force field should ideally reproduce. Although $A(\vec{R})$ is directly related to $U(\vec{r})$ as indicated in equation (2), the very large number of degrees of freedom makes the direct determination of $A(\vec{R})$ extremely difficult in practice.

On the other hand, it can be shown that the effective forces on the CG sites due to derivatives of $A(\vec{R})$ can be related to the ensemble averages of the forces on the CG sites due to $U(\vec{r})$ (see Note at the end of this paper):

$$\vec{F}_\alpha^{CG}(\vec{R}) = - \frac{\partial A(\vec{R})}{\partial \vec{R}_\alpha} \quad (4)$$

Equation (4) is the key equality for the MS-CG approach. The RHS of equation (4) can be directly computed from an atomistic MD simulation, and a CG force field can then be obtained by matching the forces on CG sites. This matching is done by first defining an residual function, \mathfrak{R}^2 , as the following:

$$\mathfrak{R}^2 = \frac{1}{3M} \sum_{\alpha=1}^M \left(\vec{F}_\alpha^{CG}(\vec{R}) - \vec{F}_\alpha(\vec{r}) \right)^2 \quad (5)$$

where $\vec{F}_\alpha^{CG}(\vec{R})$ is the force on a CG site α given \vec{R} determined by a CG force field, and $\vec{F}_\alpha(\vec{r}) = \sum_{i \in \alpha} \vec{f}_i(\vec{r})$ is the force on α due to $U(\vec{r})$. By applying the variational principle, the force field that minimizes \mathfrak{R}^2 is determined.

Although the exact CG potential can be obtained via equation (5), the high dimensionalities that are involved in this problem preclude its practical use. Usually, the following assumptions are almost always assumed in a CG force field:

1. The local interaction approximation:

$$\vec{F}_{\alpha\beta}^{CG} \approx \vec{F}_{\alpha\beta}^{CG}(\vec{R}_{\alpha}, \vec{R}_{\beta}) \quad \text{and} \quad (6)$$

2. the radial force approximation:

$$\vec{F}_{\alpha\beta}^{CG}(\vec{R}_{\alpha}, \vec{R}_{\beta}) = F_{\alpha\beta}^{CG}(R_{\alpha\beta})\hat{u}_{\alpha\beta}. \quad (7)$$

Equation (6) suggests that the interactions between two CG particles depend only on the position of these two particles but not on those of other sites. Even though local interaction is usually assumed in $U(\vec{r})$, the configuration integrals in equation (2) or (4) can introduce non-local correlations. Equation (6) is the local interaction approximation for pair-wise interactions, and the generalization to many-body interactions is straightforward. Equation (7) ignores the potential orientational dependence that may be caused by reducing the number of degrees of freedom, and may be considered to be the major source of deviation in the behaviour of a CG model from that of the underlying atomistic model. With both the local interaction and central force approximations, the dimensionality in a CG force field can be greatly reduced to the point where it can be efficiently implemented in a simulation methodology.

The FM approach of developing CG models starts from an atomistic-level MD simulation of the system. FM then utilizes the forces and coordinates from the MD trajectory to determine the force field that minimizes equation (5). Since a sum of squares form is used in equation (5), applying a variational principle results in a least squares problem. By representing the CG force field in a tabulated form, the least square problem becomes linear (i.e. a linear least square problem results). Moreover, using tabulated force coefficients not only avoids the iterations that would be required for solving a nonlinear least square problem, it is also not required to assume any specific functional form for the CG force field. In this way, the emergent form of site-site interactions at a CG scale can be captured directly from the atomistic scale. Therefore, given a set of assumptions such as equations (6) and (7), using the FM approach combined with a tabulated form of force coefficients is a general and systematic way to propagate the information obtained at the atomistic scale to a CG scale.

As an example, if an atomistic model of liquid water is coarse-grained into a one site per water model with the centre of mass of the water being the position of the CG site, the emergent site-site interactions of such a CG model in the liquid phase cannot be found *a priori*; however, FM can be used to resolve the emergent behaviour of site-site interactions from an atomistic MD simulation. For the case where the TIP3P all-atom water model is used to describe the interactions among 125 water molecules in a cubic box of 15.2 Å under periodic boundary conditions with full electrostatics, the emergent site-site interactions for an one-site CG water model (see figure 1) is shown in figure 2. It can be seen that the pair interactions between CG water is not a simple functional form and cannot be represented by a small set of inverse power potentials that are

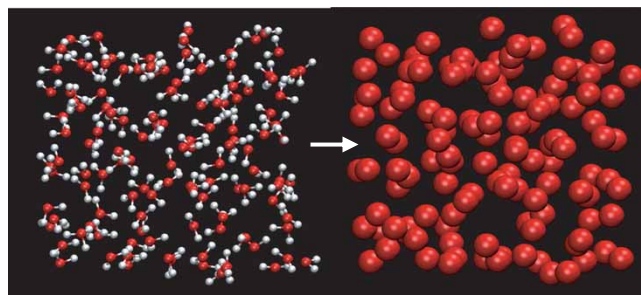


Figure 1. Atomistic and CG representations of liquid water; 125 water molecules under periodic boundary conditions are shown. The left panel is the all-atom representation, and the right panel is a CG representation with one CG site corresponding to each water molecule.

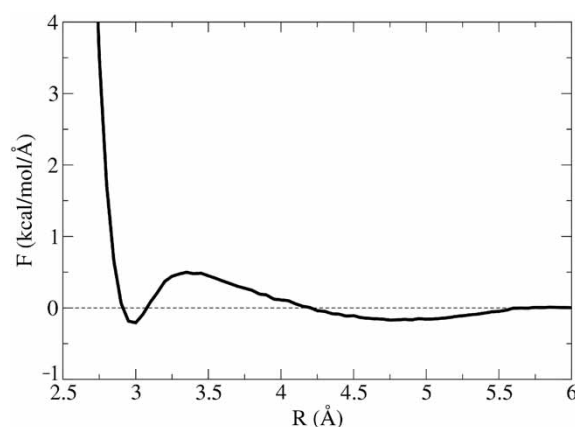


Figure 2. Pair wise force between one-site CG water molecules in the unit of kcal/mol/Å as a function site-site distance in the unit of Å. The CG pair wise force is determined by the force-matching approach and an atomistic MD simulation of liquid water based on the TIP3P model.

typically used in atomistic force fields. Again, by using a multiscale method such as FM, the information at the atomistic scale can be propagated into the CG scale. More details of the numerical implementations and applications of FM can be found elsewhere [1–3, 26–29, 34].

3. The development of computational methodologies for modeling and simulation at mesoscopic scale

The CG scale models that were discussed in the previous section are generally reduced representations of a molecular entity, but the general characteristics such as shape, length, and size, etc., of a molecule are still preserved. However, as the degree of a coarse-grained mapping such as equation (1) becomes larger and the resulting molecular details become blurred, ‘fields’, such as density, strain, pressure, and velocity become the variables that characterize a system. Continuum mechanics are usually employed in this case to describe the dynamics associated with field theories at the mesoscopic scale. For example, the Helfrich free energy functional [30, 31] describes the undulation of an elastic membrane by using continuous strain and bending fields. Except for extremely simplified scenarios, the formal field theory representation of a complicated biological system is generally too complicated to allow for analytical solutions. The development of flexible computational methods that can be used to analyse complicated biological systems at a mesoscopic scale is thus extremely valuable. Moreover, since the emergent properties of biological processes at a mesoscopic scale originate from the underlying atomistic scale as previously discussed, the ability to bridge information between atomistic and mesoscopic scales is also required.

The challenges of mesoscopic scale simulations of biological systems have led to the development of a particle-based methodology [8, 18, 35, 36], originating from the fields of non-equilibrium molecular dynamics (NEMD) [32], Smooth Particle Applied Mechanics (SPAM) [37–40] and Smoothed Particle Hydrodynamics (SPH) [41, 42]. The approach is to take the complex continuum field theory representations of biological membranes and other assemblies and formally re-cast them into new ‘quasi-particle’ representations [35]. The resulting dynamics of the system is then transformed into a form similar to that employed in NEMD [32]. This approach can easily incorporate multiple highly inhomogeneous components into the scheme (e.g. transmembrane proteins embedded in the bilayer), and the non-local hydrodynamics [43, 44] can also be

automatically included via an explicit mesoscopic solvent.

Developing a robust multiscale mesoscopic membrane/solvent simulation methodology that is ultimately capable of coupling to atomistic-level models has also been an ongoing project [18, 19, 33, 36, 45, 46]. The mesoscopic component of this multiscale simulation methodology consists of two interacting parts: an elastic membrane and a viscous solvent. The mesoscopic membrane model is denoted EM2 [21] and it is a discretized solution to the Helfrich Hamiltonian for a membrane [30, 35]. This is expressed as

$$F_H = \int dA \frac{k_c}{2} [2H]^2 + \int dA \frac{\lambda h}{2} [2\varepsilon]^2 \quad (8)$$

where dA is an area element, k_c is the bending modulus, H is the mean curvature, h is the membrane thickness, λ is the bulk modulus, and 2ε is the plane strain.

The term ‘discretized’ refers to the fact that the EM2 membrane consists of free energy ‘quasi-particles’ that interact in such a way that the behaviour of the governing field theory model is recovered above a critical discretization length-scale. The EM2 quasi-particle interactions employ parameterizations that are based on properties calculated at the atomistic scale (i.e. the bending modulus, k_c , bulk modulus, λ) [33, 36, 45, 47] as well as structural information (density and thickness). The discretization of a continuum-level field theory model into an interacting set of quasi-particles can remove the restrictions due to the boundary conditions, and thus forms a general scheme for treating complex geometries (i.e. vesicles [35, 36] domain formation (with Cahn–Hilliard or Landau–Ginzburg dynamics) [48] and explicit hydrodynamic effects [48]).

The remaining component of the mesoscopic model is an explicit mesoscopic solvent denoted BLOBs, and again this is composed of a new set of interacting quasi-particles that are characterized by very strong random/drag forces whose magnitude/character can also be found from atomistic-level MD simulations of small fluid droplets. More details concerning the quasi-particle mesoscopic simulation methodology can be found elsewhere [35, 45, 48].

When the elastic mesoscopic EM2 membrane is brought into contact with the explicit mesoscopic BLOBs solvent, the critical hydrodynamic dampening behaviour of a bilayer in a viscous solvent is recovered [35]. In fact, the observed undulation dynamics of the EM2 membrane in the BLOBs solvent agree with hydrodynamic theory, and it was also found that the shear viscosity of the BLOBs solvent plays a key role in the membrane undulation dynamics.

The EM2/BLOBs mesoscopic model, by virtue of its quasi-particle decomposition, can be employed to examine large length-scale and long time-scale phenomena that would be difficult to resolve by tackling the underlying continuum-level equation directly, such as the structures and dynamics of lipid bilayers in confined geometries (e.g. smectic membranes [31, 49] bilayers against surfaces [31, 50–52] and close bilayer pairs [31, 53–55]). For example, in the case of two bilayers separated by a small distance d , an entropic repulsion that scales like $1/d^2$ has been predicted theoretically [31, 54] and has also been observed experimentally by reflection interference contrast microscopy [56]. An undulation coupling between the two membranes, including the narrow channel of solvent separating them [31, 53], starts to appear as the separation d decreases.

In figure 3, the free energy scaling for two EM2 membranes with explicit mesoscopic solvent is shown; the $1/d^2$ scaling as the membranes are brought closer is indeed apparent. What is interesting is to examine a snapshot of the two EM2 membranes. In figure 4, simulation snapshots at a separation of 3 nm (top image) and 1.5 nm (bottom image) show a distinct lack of spatial correlation between the two membranes. In other words, the two membranes do not elect to adopt a ‘lasagna-like’ structure, but rather exist in a state of dampened undulations. The origin of the entropic repulsion is in fact the dampened undulation magnitudes of one membrane due to the other. The free energy difference, ΔF , can be compactly expressed as [21, 48]

$$\Delta F = N_q k_B T \ln \frac{k_c^{eff}}{k_c} \quad (9)$$

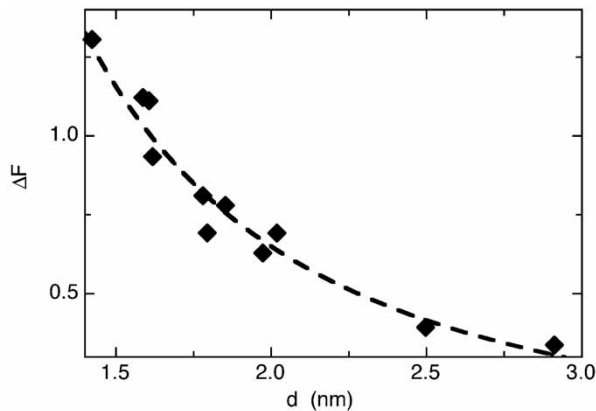


Figure 3. Free energy change, ΔF , as a function of the separation, d , for two EM2 membranes. The dashed line gives the $1/d^2$ fit to the data.

where N_q is the number of wavevectors sampled and k_c^{eff} is the measured *effective* bending modulus due to the dampened undulation magnitudes.

The EM2 approach can be further extended to examine lipid domain formation by superimposing a Landau model for phase coexistence on the EM2 membrane and then employing Cahn–Hilliard (CH) or Landau–Ginzburg (LG) dynamics to resolve the domain dynamics. In keeping with the free-energy quasi-particle discretization of the problem, the composition dynamics component of the methodology are further decomposed via Smooth Particle Applied Mechanics (SPAM) into another set of interacting composition quasi-particles. In this case, the SPAM particles move about the surface of the EM2 membrane; they contain a host of ‘particle properties’, for example, the local composition of the EM2 membrane, ϕ as well as local composition-dependent material properties. The SPAM approach removes any reliance on boundary conditions, and allows the system at the mesoscale to explore complex geometries and to respond to a variety of deformations/perturbations that could occur in the real system.

In the case of domain formations arising from ternary mixtures of lipids in Giant Unilamellar Vesicles (GUV), a Landau model capable of describing phase separations can be expressed as [35, 46, 57, 58]

$$F_T[\phi, H] = F_H + \int dA \left[\frac{\xi^2}{2} |\nabla \phi|^2 + V(\phi) + \Lambda \phi H^2 \right] \quad (10)$$

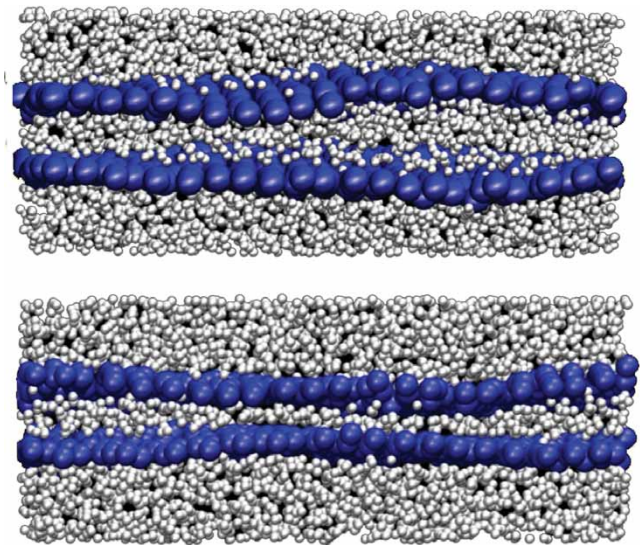


Figure 4. Simulation snapshot of the EM2/BLOBs system for two different values of the separation. The upper panel has $d = 3$ nm while the lower panel has $d = 1.5$ nm.

where ζ gives the non-local strength of the gradient of ϕ the composition, $V(\phi)$ is a double-well potential, and Λ is the coupling strength between the curvature and composition [35, 46, 57, 58]. In this case, the entire membrane and composition dynamics can be formulated with SPAM. The resulting expressions appear complicated, but are easily implemented within a pairwise additive algorithm similar to that employed in MD simulations. In this discretized form, equation (10) takes on the form of

$$F_T[\phi, H]\rho_N = \sum_{j=1}^N \left(\frac{\zeta^2}{2} |\nabla \phi_j|^2 + V(\phi_j) + \Lambda \phi_j H_j^2 \right) \quad (11)$$

where ρ_N is a surface area number density, and the summation goes over all N SPAM quasiparticles.

In figure 5, the change in domain structure due to an external deformation on a 20 μm GUV is shown.

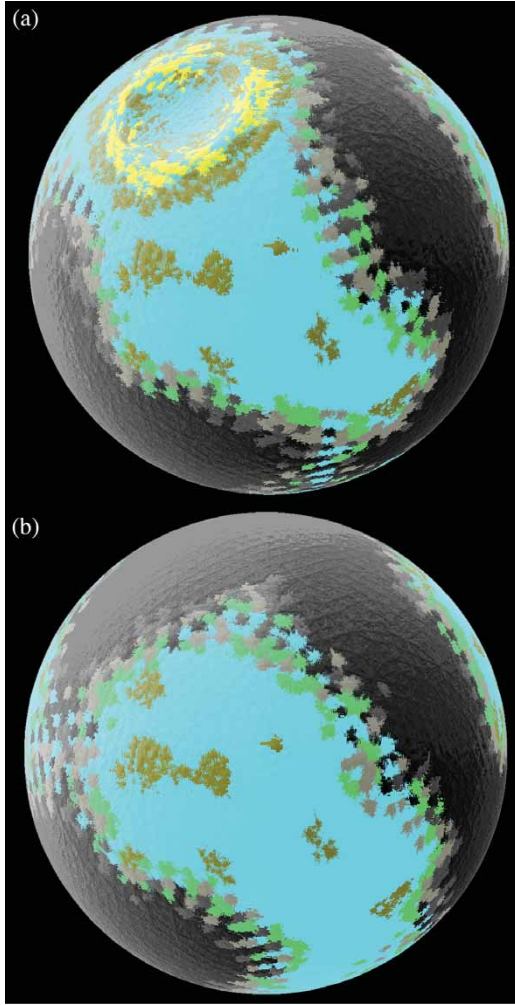


Figure 5. Composition dynamics for a GUV using SPAM. The externally imposed dint is shown in the upper panel. The color coding is explained in the text.

The two domains are shown in black and green (where the green domain favors regions of higher curvature due to its smaller bending modulus, k_c); the GUV is shown in exactly the same orientation in both panels, but in figure 5(a) an external ‘dint’ is imposed (i.e. mirroring a micromanipulation experiment) while in figure 5(b) the GUV is unperturbed. The dint in figure 5(a) is shown by the yellow ring of high curvature, and it is observed that the domain favouring higher curvature regions (the green domain) encompasses the external dint. Furthermore, the domain structure far away from the dint is also altered; it is not just a localized event.

By superimposing composition dynamics over the deformation dynamics of a bilayer, another component in the overall multiscale simulation methodology is created. When composition-dependent material properties are allowed to modulate the governing interactions of the EM2 membrane, a feedback scenario can be constructed, and complex multicomponent systems can thus be modelled. When combined with specially selected atomistic-level ‘windows’ via a multiscale-coupling (MSC) scheme that will be described in the next section, the atomistic-level response to a mesoscopic phenomenon such as the ‘dint’ described above can be captured and fed back to the atomistic scale, thus completing the process of bridging these two scales.

4. Coupling between atomistic and mesoscopic scales

In the previous two sections, methods for systematically developing models at CG and mesoscopic scales were presented. At both scales, different ways of extracting atomistic scale information can be devised, such as the FM approach to define the force field of a CG model and NEMD to obtain the material properties for a field theory formulation at the mesoscopic scale. After a reduced model is developed, simulations can then be performed to explore the system at larger length-scales and longer time-scales. However, due to the fewer number of parameters in a reduced representation, the detailed behaviour of a complicated molecular system cannot be fully captured at CG or mesoscopic scales (e.g. the example of strain-dependent material property of a GUV mentioned earlier). Therefore, the capability of coupling CG and/or mesoscopic scales to the underlying atomistic scale directly is highly desirable for modelling certain biological processes, especially when large-scale structural motions are involved.

Such direct coupling between atomistic and mesoscopic scales can be achieved by embedding an atomistically detailed ‘window’ or ‘patch’ in the mesoscopic model. This multiscale methodology has recently

been developed and is denoted as Multiscale Coupling (MSC) [19, 33]. With MSC, a detailed atomistic-level model is ‘embedded’ into a field theory-based mesoscopic model of the same system [19, 33, 35, 36, 45, 46, 48]. The approach allows a specific region of interest to retain a full degree of atomistic-level resolution, while the details at very long spatial dimensions are smoothed into a continuum representation. However, the coupling has to be implemented carefully; when done properly [33], the coupling can be shown to be formally exact. Earlier attempts of coupling different scales involve adding ‘buffer regions’ that try to alleviate the discontinuities caused by mixing models at different scales [59–61]; as a result, important interactions such as long-range electrostatics for biological systems are difficult to incorporate by this kind of coupling.

The above difficulty can be avoided by MSC. One of the novel aspects of MSC is that the atomistically detailed system is never explicitly embedded in the mesoscopic model. Rather, it remains bound within the periodic boundaries in the atomistic MD simulation. This approach alleviates difficulties associated with long-range electrostatics, as well as lipid diffusion. The explicit mixing of different scales is avoided because the coupling to mesoscopic fields can be translated into spatially distributed fields in the equations of motion at the atomistic scale. Propagating the effective fields back and forth thus achieves the bridging between the two different scales.

The MSC approach can allow membrane-bound proteins, for example, to sample long wavelength mesoscopic stress modes originating from both long wavelength membrane undulations as well as membrane-solvent couplings. For example, in the case of a membrane-bound influenza A virus M2 proton channel in the open state [62] embedded in a dimyristoylphosphatidylcholine (DMPC) bilayer, small, but distinct, variations in the structure of the two His³⁷ residues can be observed as a result of the mesoscopic-level perturbations [20]. Figure 6 shows the M2 proton channel embedded in the bilayer; the location of the His³⁷ residues is shown in figure 6(b). Under MSC, the protein is subjected to very slowly varying plane stress fields as generated from the surrounding EM2/BLOBS mesoscopic environment. These stress fields are then propagated down to an ensemble of MD simulations that follow the slowly varying mesoscopic plane stress field. The result, over the course of 4 ns, is that the local structure of the M2 protein is slightly altered and the density near the His³⁷ residue is slightly reduced due to the effects of mesoscopic stresses. In figure 6(c), it can be seen that the orientation of the His³⁷ residues is altered; the His³⁷ residue next to the protonated one is pushed into the channel wall slightly. This effect was observed

in all members of the atomistic-level ensemble. On the other hand, without coupling to the mesoscopic EM2 membrane this effect was not observed, as seen in the result of an isolated constant pressure MD simulation of the M2 channel, figure 6(d), where all four residues are directed towards the channel pore.

The above result indicates that certain variations in the protein structure can be traced back to the external mesoscopic stress fields. This observation suggests that membrane-bound proteins are not only affected by phenomena occurring at close range (i.e. lipid–protein interactions) but also by phenomena occurring at very long range (i.e. long wavelength membrane undulations).

5. Concluding remarks

The interplay of phenomena at multiple length- and time-scales makes a systematic and detailed study of complicated biological systems extremely difficult. In this article, three categories of multiscale computational methodologies that aim to overcome this multiscale challenge are introduced. It is shown that these methods can be developed rigorously based on the principles of equilibrium and non-equilibrium statistical mechanics. With a multiscale method such as force-matching (FM), atomistic scale information can be systematically propagated to the CG scale so that the emergent mesoscopic behaviour can be captured. Alternatively, material properties of bioassemblies can also be computed directly at the atomistic scale based on the NEMD formulation and then used in a field theory representation of the system at the mesoscopic scale. The multiscale coupling (MSC) between atomistic and mesoscopic scales through effective fields, rather than having multiple different models present simultaneously, avoids the difficulties caused by boundary condition discontinuities. In this way, the molecular properties responsible for certain functionalities and activities of interest can be elucidated. Future research directions in overcoming the multiscale challenge include investigating the transferability of CG force fields, analysing the effects of different assumptions such as equation (6) and (7) on the quality of a CG model, examining the time-scales corresponding to CG simulations, establishing a connection between the field theory representation and CG models, and developing general methods for exchanging information at different scales in a simulation designed to overcome the multiple time-scale issue. With such ongoing advancement of computational methodologies and computer power, multiscale modelling and simulation is expected to play an increasingly

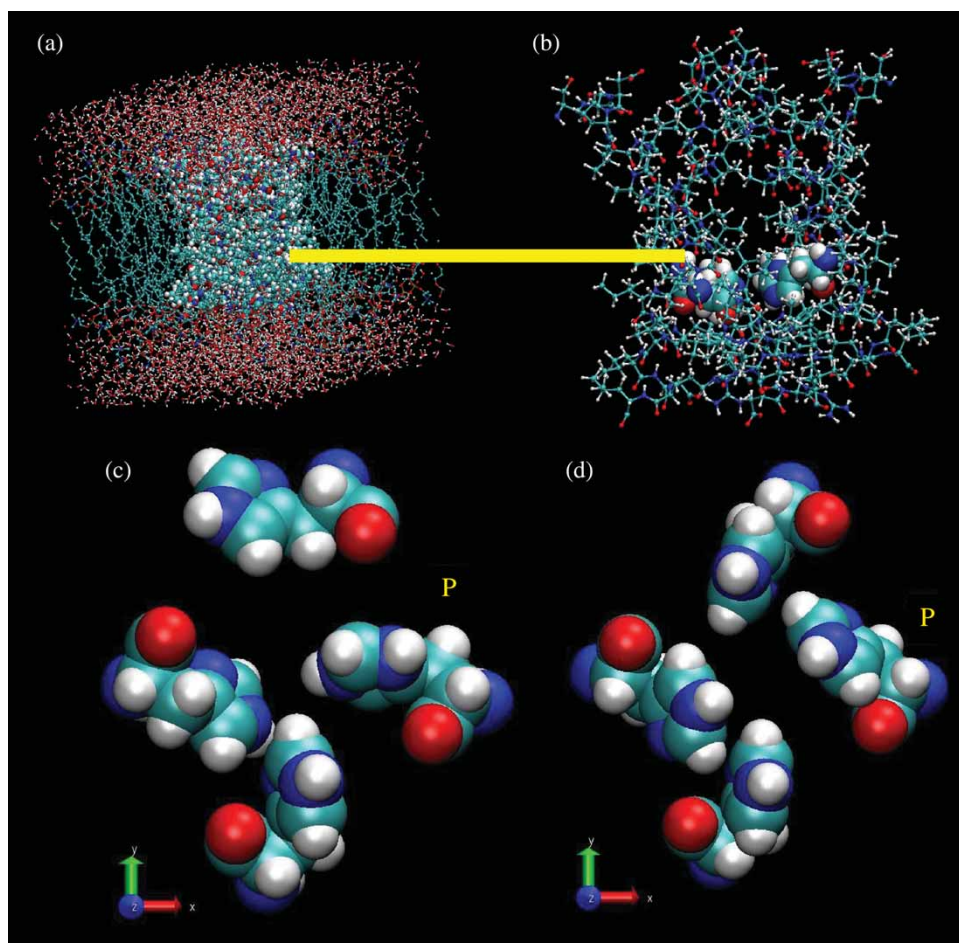


Figure 6. MSC simulation of an influenza A virus proton channel in a DMPC bilayer. Panel (a) shows the full proton channel embedded in the bilayer, panel (b) shows the location of the His³⁷ residues (which form the PMF barrier to proton transport), panel (c) shows a top down view of the His³⁷ residues in the open state under MSC, while panel (d) shows the same residues under an uncoupled constant pressure MD simulation. The 'P' designates the protonated residue.

more important role in the fields of molecular biology, biophysics, and systems biology.

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Note

See W. G. Noid, J.-W. Chu, G. S. Ayton and G. A. Voth, *J. Chem. Phys. B.* (2007), in press, for further details.

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