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Concluding remarks

Herman J. C. Berendsen*

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1 Introduction

When a retired scientist is asked to present concluding remarks, the risk is high that he will treat you to a nostalgic survey of the past. I shall restrain myself and try to put the developments as witnessed in this conference into a proper future perspective, preceded by and interlaced with some reflections of the past.

For the past ten years I have had the opportunity to watch the development in a field that I have participated in from its conception in the early seventies of the last century: molecular simulation. I have seen the methodological development, but also the enormous expansion in applications to realistic systems. The latter has been largely the result of the incredible increase in available computer power, which has roughly maintained a growth rate of a factor of ten every five to six years. In the mean time, models have gone from descriptions that were, by computational necessity, very much simplified, to more end more detailed molecular descriptions, even including quantum details, to coarse-grained models that allow simulations to reach into the microsecond regime for systems of millions of particles.

This conference is a landmark in the development of multiscale modeling methods and applications. It has shown us where we are now in the field of multiscaling simulation of soft condensed matter, in particular polymers, membranes, proteins and colloids. These are the materials that exhibit self-organization: if properly functionalized they can assemble into organized structures that could form the basis of new classes of functional nanomaterials. Unfortunately, self-organization is—like any other phase change—a slow and highly cooperative process that requires very long simulations of a very large number of particles. Such simulations are still—and will be for a long time to come—far beyond the capabilities of atomistic simulations. They are the ideal playground for the development of coarse-grained methods that aim at describing the system on a coarser spatial and temporal scale. What this conference has not addressed is the important class of nanomaterials that have specific electrical, magnetic or optical properties. The latter invariably require an approach involving quantum mechanical methods in addition to molecular or coarse-grained simulations.

After a nostalgic dip into the first membrane simulations in Section 2, I shall focus in Section 3 on the coarse-graining methodology and classify the various multiscale methods according to their purpose and capabilities, and according to their place in a systematic hierarchy of models. Section 4 elaborates a bit on the effective potentials for reduced systems, while Sections 5 and 6 consider how dynamic and hydrodynamic details can be faithfully incorporated. Section 7 concludes with some trends in the development that emerge from the papers presented in this conference.

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2 Early membrane simulations

For someone who has struggled in the early 1980s to simulate simple lipid bilayers with the then available computer power of, say, 10 Mflop (compared to close to 100 Gflop for a modern PC and 1 Petaflop for a large cluster), the achievements today are astonishing. Papers by Voth *et al.*, Vattulainen *et al.* and Marrink *et al.*, are examples.[1–3] With proper coarse-graining, systems with millions of particles can be simulated over real times approaching 100 microseconds. But membrane processes are slow; as is shown in ref. 3, a 45 μs CG simulation did not reach equilibrium distributions for pore-forming peptides in bilayer membranes. Papers by Voth *et al.*[1] and Müller *et al.*[4] had to rely on a coarser description to meet the demands of long time-scale events. So did Smit *et al.*,[5] which simplifies membrane proteins to discs.

Fig. 1 shows two snapshots from a bilayer membrane, built from 2×16 C_{10} hydrocarbon chains with a head group. The chains were modeled as united atoms, but with proper dihedral interactions, as earlier used for hydrocarbon liquids.[6] The

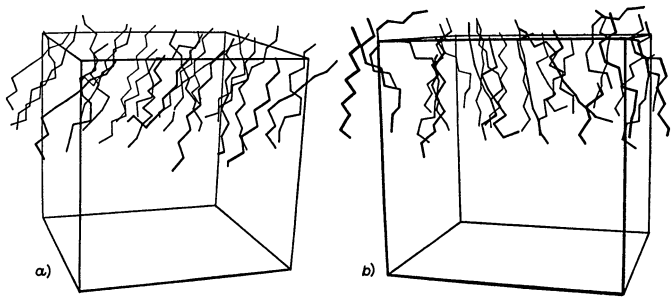

Fig. 1 Two snapshots taken from an ordered (*a*) and less ordered (*b*) state of a decane bilayer with effective head group interactions that restrain the head groups near a plane (reproduced with permission from Berendsen[10]). Copyright 1986, Società Italiana di Fisica.

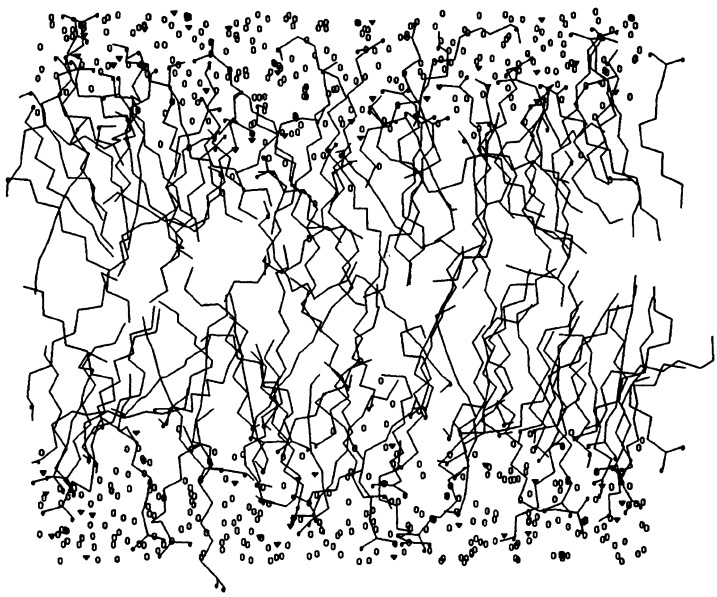

Fig. 2 Snapshot of a sodium decanoate/decanol/water bilayer.[12] Reproduced with permission from Egberts and Berendsen, *J. Chem. Phys.*, 1988, **89**, 3718. Copyright 1988, American Institute of Physics.

head groups were modeled in a coarse-grained fashion *avant la lettre* with a harmonic restraint with respect to the average of the head group positions. This was the first simulation of a realistic bilayer, published in 1980[7] and in 1982.[8] The small system exhibited transient ordering with tilted chains. A 2×64 molecule system was studied in more detail,[9] including the molecular tilt, order parameters, lateral pressure and diffusion. The total simulation time was 320 ps, requiring the better part of a PhD research period.

The next challenge was to go to full atomic detail including head groups and water. We studied the simple bilayer system decanol/decanoate/water which was known to form smectic liquid crystals. Fig. 2 shows a snapshot. This was published in 1986[11] and 1988.[12] It was soon followed by a phospholipid bilayer (DPPC) in atomic detail.[13] It appeared to be necessary to adjust details of the force field in order to obtain a gel-to-liquid crystal transition at the correct temperature. Fig. 3 shows a snapshot of the DPPC bilayer in the liquid-crystalline phase.

In the early nineties the emphasis was on enhancing resolution to atomic detail; the growing capabilities of MD were employed to refine the coarse models used before. Much effort was spent on the development of reliable force fields. But it was also realized that many realistic processes could not—and would never—be solvable by atomistic simulations. So coarse-graining in various forms was invented, and methods were developed to parameterize CG models.

I'll conclude the nostalgic part of this talk with an early example of extreme coarse-graining: reduce the system to motion in *one* "reaction coordinate." This was the main topic of the thesis of one of the organizers of this conference, Professor Siewert Jan Marrink. He studied the transport of a single water molecule through a lipid membrane.[15] The average force and the force fluctuation were both determined from simulations of a membrane with single water molecules constrained

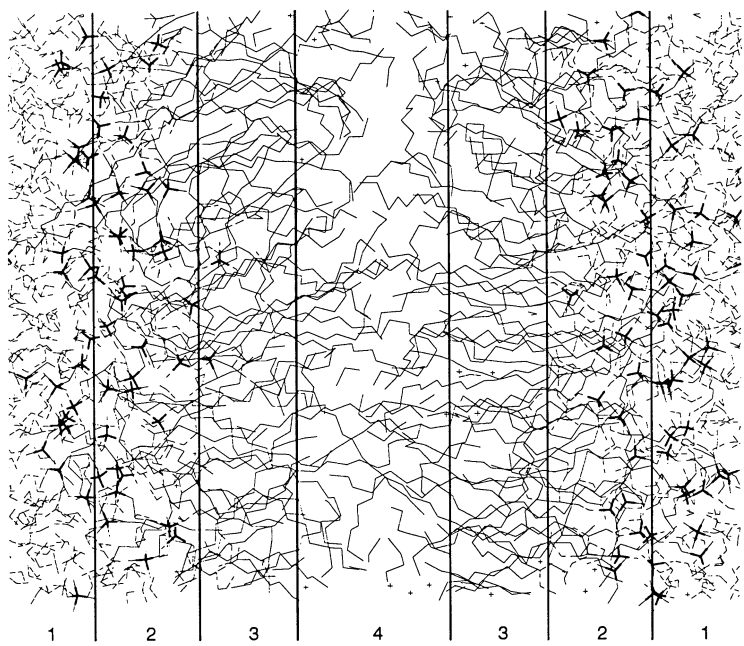

Fig. 3 Snapshot of a DPPC liquid-crystalline bilayer.[13] Reproduced with permission from *Pure Appl. Chem.*[14] (Copyright 1993, IUPAC). Membranes were characterized in four layers: 1. water/headgroups interface (polar, mobile), 2. headgroups/chains interface (dense, weakly polar), 3. ordered chains (dense, nonpolar), 4. disordered tails (open, nonpolar, mobile).

with their centers of mass at a given depth in the membrane. Thus both the potential of mean force and the friction coefficient could be determined along the path of a single water molecule through the bilayer. With these data a stochastic equation can be devised that describes the motion of a water molecule along a path through the membrane. Solving this equation for a steady state of constant difference in thermodynamic potential of water over the membrane yields the water flux and thus the permeability coefficient. We'll return to this example in the following sections.

3 A modeling hierarchy

The heart of any coarse-graining method is the *reduced* description of the system. One distinguishes *relevant* or *important* degrees of freedom from all other degrees of freedom, which are consequentially *irrelevant* or *unimportant*. The next step is to describe the dynamics of the reduced subsystem in such a way that it approaches as faithful as possible the *projection* of the motion of the complete system onto the reduced degrees of freedom. This is only possible when the time scales of the motion of the "relevant" degrees of freedom and of the "irrelevant" degrees of freedom are well-separated (the former being much slower than the latter). When there is overlap in time scales, one must give up on accuracy of the dynamical behavior, but one should at least conserve the probability distribution in configurational space, thus conserving thermodynamic properties of the system. Español *et al.*[16] gives a rederivation of Zwanzig's projection operator technique that gives a formal description of the dynamics in reduced space. The authors show clearly that the reduced description is only valid in the limit of well-separated time scales, in which case the stochastic dynamics in reduced space is Markovian, *i.e.* memoryless, and easy to implement.

The choice of the "relevant" degrees of freedom (d.o.f.) is made on an intuitive basis and depends on the properties one wishes to study. Note that "normal" molecular dynamics is already concerned with a reduced system of atomic coordinates; all electronic coordinates are considered "irrelevant" and a Born–Oppenheimer approximation is assumed (*i.e.*, electrons are infinitely fast with respect to nuclei). In addition, the usual *united atom* treatments which are viewed as accurate atomic reference models, consider the d.o.f. of the nonpolar hydrogen atoms as irrelevant and consider covalent bonds as constraints. Thus, a constrained united-atom model of butane has $3 \times 4 - 3 = 9$ degrees of freedom, which is a considerable reduction with respect to the 42 d.o.f. of the all-atom model and the 144 d.o.f. of the all-electron model. The step to a real coarse-grained model of the *superatom* type, lumping four methylene groups together in one superatom, is relatively moderate as it only reduces the d.o.f. further from 9 to 3. This is the level of coarse-graining that is most extensively used in many applications (*e.g.* 2, 3, 5, 18–21).

A substantial higher level of coarse-graining can be achieved by a continuum representation, such as the Navier–Stokes equations of fluid dynamics, or a density-functional description of the free energy as a functional of the density distribution of components of a composite material. The latter is often applied to block-copolymer melts; the free energy functionals are usually based on a simplified (*e.g.* Gaussian chain) intramolecular model plus a mean-field description for the intermolecular interactions. Dynamics are invoked by the inclusion of linear mobility relations to the gradients of thermodynamic potentials. The continuum equations are usually solved on a regular grid or using irregular finite elements, but they can also be solved by a system of particles obeying specified dynamical rules. The Lattice–Boltzmann method is a special case: the continuum equations are solved on a regular grid by updating attributes of the lattice points as a function of the attribute values at neighboring points. The resolution of these methods depends on the scale at which the simulated system shows structure: thus block-copolymers with structural features on a nanometre scale require nanometre resolution, but fluid flow in macroscopic objects may get away with resolution on a centimetre scale, comprising, say, 10^{22} atoms.

Multiscale modeling methods can be categorized in a modeling *hierarchy* ranging from detailed quantum treatment to macroscopic continuum descriptions. Precisely such a hierarchy is the subject of a book[17] that was published in 2007 entitled "*Simulating the Physical World, Hierarchical modeling from quantum mechanics to fluid dynamics*", from which I shall quote in the following.

Fig. 4 lists a number of approximations, ranging from a complete relativistic quantum-dynamical description to a macroscopic description of fluid dynamics. The former is unworkably complex and the latter has abstracted the system to the very basic level of the conservation laws, together with zero-order thermodynamic and first-order dynamic properties. In between are the practical levels of molecular dynamics and the coarse-grained approaches describing reduced systems of practical interest.

4 Effective potentials for coarse-graining

As mentioned above, it is essential that thermodynamical properties are retained on coarse-graining. This guarantees that equilibrium properties (average structure, free energies, solubilities, partition coefficients, *etc.*) are still validly predicted by the CG methods. Also non-equilibrium properties as driving forces for slow dynamics will be faithfully represented. What does this mean for the effective potential?

Consider a detailed system with (cartesian) coordinates $\{\boldsymbol{r}\} = \boldsymbol{r}_1,\ldots,\boldsymbol{r}_n$. Assume that we have good reasons to distinguish *relevant* coordinates $\boldsymbol{r}'$ and *irrelevant* coordinates $\boldsymbol{r}''$. So the full space consists of a set of coordinates $\{\boldsymbol{r}\} = \{\boldsymbol{r}',\boldsymbol{r}''\}$ and the reduced space consists of the set $\{\boldsymbol{r}'\}$. For simplicity we take the coordinates of the reduced space as a subset of the full space rather than a set of generalized coordinates. The Helmholtz free energy A for a given volume and temperature T is given by

$$A = -k_{\mathrm{B}}T\ln Q \tag{1}$$

$$Q = c\int e^{-\beta V(r)}\,\mathrm{d}\boldsymbol{r} \tag{2}$$

Here Q is the partition function and $\beta = (k_{\mathrm{B}}T)^{-1}$; c is a temperature-dependent constant containing the masses of the particles and $V(\boldsymbol{r})$ the conservative potential

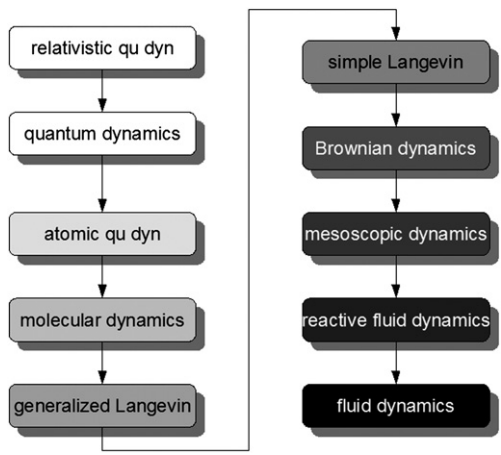

Fig. 4 Hierarchy of models for simulation,[17] ranging from very detailed (white background) to very coarse-grained (black background). Each level has its own description of the reduced system and its own simulation method. Each higher level loses some details of the preceding level.

of the full system. We wish to define an effective potential $V^{\mathrm{mf}}(\boldsymbol{r}')$ such that a Boltzmann distribution in $\boldsymbol{r}'$-space is maintained for the reduced system:

$$Q = c' \int e^{-\beta V^{\mathrm{mf}}(\boldsymbol{r}')} \, \mathrm{d}\boldsymbol{r}' \tag{3}$$

This is accomplished by defining the effective potential as follows:

$$V^{\mathrm{mf}}(\boldsymbol{r}') \stackrel{\mathrm{def}}{=} -k_{\mathrm{B}}T \ln\left[\int e^{-\beta V(\boldsymbol{r}',\boldsymbol{r}'')} \mathrm{d}\boldsymbol{r}''\right] + \text{constant} \tag{4}$$

as can be easily verified by inserting eqn (4) into eqn (3). Note that this effective potential is *not* the mean potential, *i.e.* the original potential averaged over the irrelevant degrees of freedom. But its derivative with respect to $\boldsymbol{r}'_i$, which is the *force* acting on $\boldsymbol{r}'_i$ in the reduced system, *is* a mean force, *i.e.* the average of the detailed force over the irrelevant degrees of freedom. This is seen by differentiating eqn (4) with respect to $\boldsymbol{r}'_i$:

$$\boldsymbol{F}_i^{\mathrm{mf}} \stackrel{\mathrm{def}}{=} -\frac{\partial V^{\mathrm{mf}}(\boldsymbol{r}')}{\partial \boldsymbol{r}'_i} = \frac{\int \left(-\dfrac{\partial V(\boldsymbol{r}',\boldsymbol{r}'')}{\partial \boldsymbol{r}'}\right) e^{-\beta V} \mathrm{d}\boldsymbol{r}''}{\int e^{-\beta V} \mathrm{d}\boldsymbol{r}''} = \langle \boldsymbol{F}_i \rangle_{\boldsymbol{r}''} \tag{5}$$

Thus the term *potential of mean force* (PMF) is quite appropriate for the effective potential V^{mf}. Note that it is not a potential in the Lagrangian or Hamiltonian sense; the potential of mean force is really a free energy with respect to an equilibrium distribution of the irrelevant degrees of freedom. It may (and will) depend on density, constitution and temperature. One has to take such dependencies into account when the normal thermodynamic derivatives are considered to derive thermodynamic quantities. For example, the internal energy U is no longer equal to the ensemble average of V^{mf}, but rather

$$U = \partial(\beta A)/\partial\beta = \left\langle V^{\mathrm{mf}} + \beta \frac{\partial V^{\mathrm{mf}}}{\partial \beta} \right\rangle \tag{6}$$

We see from eqn (5) that the mean force can be generated from an equilibrium simulation in which the relevant degrees of freedom are *constrained* (kept constant). Note that this is true irrespective of the overlap of time scales. When this is done at several values of $\boldsymbol{r}'$, the potential of mean force can be constructed—up to a constant—by numerical integration. In practice this is not as easy as it appears to be because in the multidimensional case many simulations are needed and statistical noise will soon spoil the accuracy. In one dimension (such as a single reaction coordinate that describes an essential event) there is in general no problem. In many dimensions the way to proceed is to devise the shape of a potential and adjust its parameters to minimize the difference between forces of the model and averaged forces from constrained simulations. In ref. 16 this approach has been used to derive a pair-additive potential of mean force for the interaction of star polymers in the melt. By assuming pairwise additivity one may miss essential attributes of the real potential of mean force; indeed, the recovered radial distribution function of the CG simulation is not exactly equal to the rdf of the detailed simulation.

In most cases the *bottom-up* reconstruction of V^{mf} from fine-grained simulations will not produce the precision one may require to predict the adequate thermodynamic properties from CG simulation. A *top-down* approach: adjusting model parameters on the basis of the required thermodynamic properties, will then be necessary. But be aware of a serious pitfall here: if the CG model does not predict any properties beyond the ones you have used for the parametrization, you have

achieved nothing! At best you have gained some understanding and insight. Always require your model to predict something yet unknown!

To end this section, we go back to Marrink's work on water permeation through a membrane in 1994.[15] Fig. 5 shows the potential of mean force for a single water molecule as a function of the depth z in a bilayer membrane. The curve has been constructed from three different kinds of simulation:

1. For regions with measurable water density, the PMF was evaluated directly from the local density $\rho(z)$:

$$V^{\mathrm{mf}}(z) = -\,k_{\mathrm{B}}T\ln(\rho(z)/\rho_0) \tag{7}$$

where ρ_0 is the bulk water density, and the PMF is referenced with respect to the bulk water phase (triangles in Fig. 5).

2. The curve was continued by integration of the average constraint force needed to keep a water molecule at a given depth z in the membrane (squares in Fig. 5).

3. In the middle region the density of hydrocarbon chains is much less than in other regions and it is possible to employ Widom's *particle insertion method*.[22] Water molecules are placed at random positions and in random orientations at a depth z in the membrane and their interaction energies with the environment $E_{\mathrm{int}}(z)$ are stored. The water molecules are *ghost particles* that do not influence the system. The potential of mean force $V^{\mathrm{mf}}(z)$ equals $-k_{\mathrm{B}}T\ln\langle\exp[-\beta E_{\mathrm{int}}(z)]\rangle$ plus a known constant[15] (circles in Fig. 5).

5 Dynamics in reduced space

The motion in reduced space (*i.e.*, the primed coordinates of the previous section) can be described in various approximations.[17] The equations of motion are no longer Hamiltonian: the forces depend not only on the present configuration, but also on the past. Forces proportional to velocities give a damping and are non-conservative (kinetic energy is lost). In order to maintain the average kinetic energy and temperature, a noise term must be added, consistent with the fluctuation–dissipation theorem.

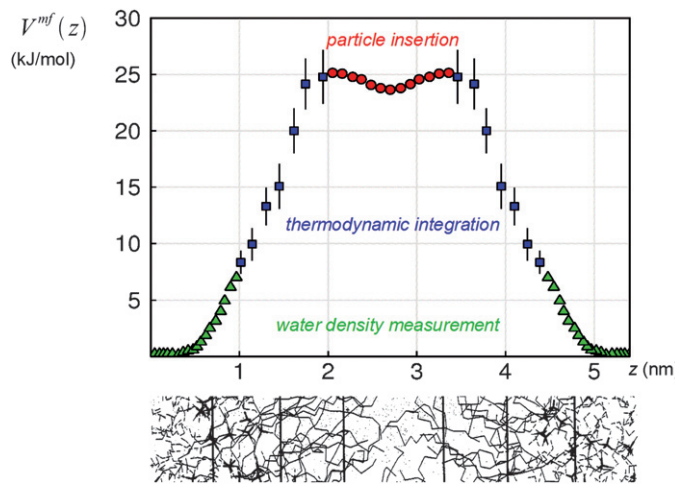

Fig. 5 Potential of mean force for transport of a single water molecule through a bilayer membrane. Triangles: from the water density; squares: from integration of the average constraint force; circles: from Widom's particle insertion method. The layer structure of the membrane (see Fig. 3) is pictured below the graph. Figure redrawn with permission from Marrink and Berendsen.[15] Copyright 1994 American Chemical Society.

The generalized Langevin equation

Taking time-dependent friction into account, the *generalized Langevin equation* is obtained:†

$$m_i\dot{\boldsymbol{v}}_i = -\frac{\partial V^{\mathrm{mf}}}{\partial \boldsymbol{r}_i} - \sum_j \int_0^\infty \zeta_{ij}(\tau)\boldsymbol{v}_j(t-\tau)\,\mathrm{d}\tau + \boldsymbol{\eta}_i(t) \tag{8}$$

where we have dropped the prime in the coordinates and write $\boldsymbol{v}$ for the time derivative of $\boldsymbol{r}$·$\boldsymbol{\zeta}_{ij}(\tau)$ is the time-dependent friction coefficient between particles i and j and $\boldsymbol{\eta}_i(t)$ is a "coloured" noise force characterized by:

$$\langle \boldsymbol{\eta}_i(t)\rangle = 0; \tag{9}$$

$$\langle \boldsymbol{\eta}_i(t)\boldsymbol{\eta}_j(t+\tau)\rangle = 2k_{\mathrm{B}}T\boldsymbol{\zeta}_{ij}(\tau) \tag{10}$$

The Markovian Langevin equation

The general Langevin equation is not without problems: the equation is not exact when there is overlap between the time range of friction correlation and the characteristic time for the motion due to the systematic force. Also, data on the time dependence of the friction are hard to obtain and algorithms to generate the required colored correlated noise are complicated. Only in the case that the correlation time for the friction is small compared to the characteristic time for the motion are reliable simulations possible. This is the case that the friction (and hence the noise) *has no memory*, usually called the *Markovian limit*. The resulting stochastic equation of motion is the *Markovian Langevin equation*:

$$m_i\dot{\boldsymbol{v}}_i = -\frac{\partial V^{\mathrm{mf}}}{\partial \boldsymbol{r}_i} - \sum_j \zeta_{ij}\boldsymbol{v}_j(t) + \boldsymbol{\eta}_i(t) \tag{11}$$

with

$$\langle \boldsymbol{\eta}_i(t)\rangle = 0; \tag{12}$$

$$\langle \boldsymbol{\eta}_i(t)\boldsymbol{\eta}_j(t+\tau)\rangle = 2k_{\mathrm{B}}T\boldsymbol{\zeta}_{ij}\delta(\tau) \tag{13}$$

A derivation based on Zwanzig's projection operator is given in ref. 16. The authors show that this equation is exact when the time scales of the relevant and irrelevant degrees of freedom are well-separated.

Galilean-invariant frictions

The authors of ref. 16 also point out—and this is a point that has been often overlooked—that the friction and noise forces must conserve the total momentum in order for the dynamics to be correct in the limit of large length and time scales. The validity of the Navier–Stokes equations in that limit requires conservation of

† For simplicity we take i as a selection of particles with cartesian coordinates. When the primed relevant degrees of freedom are generalized coordinates $q_k(\boldsymbol{r})$, the masses m_i should be replaced by the effective mass tensor $\mathbf{M}$, which is defined[17] as the inverse of a matrix $\mathbf{X}$ with elements $X_{kl} = \sum_i (1/m_i)(\partial q_k/\partial \boldsymbol{r}_i)\cdot(\partial q_l/\partial \boldsymbol{r}_i)$. For example, if the relevant coordinates are the centers of mass of a specified group of atoms, the effective mass tensor is diagonal and m_i must be replaced by the total mass of the i-th group.

linear momentum, or, equivalently, invariance under Galilean transformations.‡ This implies that

$$\boldsymbol{\zeta}_{ii} = -\sum_{j \neq i} \boldsymbol{\zeta}_{ij} \tag{14}$$

so that the Markovian Langevin equation can be rewritten as

$$m_i \dot{\boldsymbol{v}}_i = -\frac{\partial V^{\mathrm{mf}}}{\partial \boldsymbol{r}_i} - \sum_{j \neq i} \zeta_{ij} \{\boldsymbol{v}_j(t) - \boldsymbol{v}_i(t)\} + \boldsymbol{\eta}_i(t) \tag{15}$$

with $\boldsymbol{\zeta}_{ij} = \boldsymbol{\zeta}_{ji}$. The diagonal values of $\boldsymbol{\zeta}$ are positive; the off-diagonal elements are generally negative.

The Langevin dynamics in this form is related to dissipative particle dynamics (DPD)[23,24] which uses Galilean-invariant relative frictions as well. However, the DPD frictional and random forces between particle pairs are restricted to act in a direction *parallel* to the interparticle direction. There is no theoretical need for this restriction: forces acting in the *transverse* direction are allowed as well. There is also no theoretical need for having the same friction coefficient for the parallel and transverse components of the velocity differences, as (eqn (15)) seems to suggest (true if ζ_{ij} would be a scalar, but it isn't: ζ_{ij} is a 3-D tensor or else one can consider i and j to enumerate all components). Junghans *et al.*[25] have shown that transverse friction has a far stronger influence on diffusion and viscosity than parallel friction and can be used to fine-tune the dynamic properties of coarse-grained models. Español *et al.*[16] shows for the example of a star-polymer melt that the parallel friction (between the com's of star polymers) is much larger than the transverse friction.

Simple Langevin

A severe approximation of the Markovian Langevin equation is the assumption that the friction tensor is *diagonal*. The equation of motion then is, for one component of the velocities:

$$m_i \dot{v}_i = -\frac{\partial V^{\mathrm{mf}}}{\partial x_i} - \zeta_i v_i(t) + \eta_i(t) \tag{16}$$

with

$$\langle \eta_i(t) \rangle = 0; \tag{17}$$

$$\langle \eta_i(t) \eta_j(t + \tau) \rangle = 2 k_{\mathrm{B}} T \zeta_i \delta_{ij} \delta(\tau) \tag{18}$$

This is called the *simple Langevin equation*. The friction and noise are simple one-dimensional memoryless additions to the equations of motion, without any coupling between degrees of freedom. This makes implementation in a stochastic dynamics code rather straightforward§ But, of course, this equation is not Galilean-invariant and any velocity deviation tends to die out to zero. The equation makes sense only if the velocity is defined with respect to the center of mass, for example for the motion of a single colloidal particle in a stationary fluid, or for the motion of several particles in a stationary fluid with complete neglect of hydrodynamic interactions.

‡ Recall that a Galilean transformation is a transformation to a reference frame that moves with constant velocity. The laws of classical mechanics are invariant to such a transformation.
§ However: beware that the incorporation of friction and noise in a Verlet algorithm, such that the accuracy is preserved to the same order as the frictionless Verlet scheme,[26] is not trivial!

The simple Langevin equation can be used to act as a thermostat: as noise and friction are designed to maintain a given temperature, deviations from that temperature will be corrected with a first-order kinetics with decay time m_i/ζ_i. In that respect the Langevin thermostat is similar to weak coupling[27] but it introduces a damping that slows down the dynamics of the system.

In the absence of systematic forces, the friction also determines the diffusion constant. Writing $\gamma = \zeta/m$, we obtain the *pure Langevin equation*

$$\dot{v} = -\gamma v + \eta(t) \tag{19}$$

where $\eta(t)$ now is a Markovian random variable with

$$\langle \eta(t)\eta(t+\tau)\rangle = 2\gamma k_{\mathrm{B}} T\delta(t) \tag{20}$$

This stochastic equation¶ is exactly solvable by substituting $v(t)\exp(\gamma t)$ for a new variable. The result is

$$v(t) = v(0)\exp(-\gamma t) + \int_0^t \eta(\mathrm{t}-\tau)\exp(-\gamma\tau)\,\mathrm{d}\tau \tag{21}$$

From this the velocity autocorrelation function follows:

$$\langle v(0)\ v(t)\rangle = \langle v(0)^2\rangle\ \exp(-\gamma t) \tag{22}$$

The displacement $x(t)$ is characterized by a diffusion constant D, given by the integral of the velocity correlation function:

$$D = \int_0^\infty \langle v(0)v(t)\rangle\,\mathrm{d}t = \frac{k_{\mathrm{B}}T}{m\gamma} = \frac{k_{\mathrm{B}}T}{\zeta} \tag{23}$$

Note that this relation between diffusion constant and friction is strictly valid only in the force-less case.

Brownian dynamics

Return to the simple Langevin eqn (16). If the systematic force is constant or slowly changing and the friction is high enough, the *inertial term* $m_i\dot{v}_i$ can be neglected. We then obtain for any degree of freedom x the equation for *Brownian dynamics*:

$$\dot{x} = v = \frac{1}{\zeta}F^{\mathrm{sys}} + \frac{\eta(t)}{\zeta} \tag{24}$$

where

$$F^{\mathrm{sys}} = -\frac{\partial V^{\mathrm{mf}}}{\partial x} \tag{25}$$

Thus the mass and even the velocity drops out of the equation and we can make a time step simply as

$$x(t+\Delta t) = x(t) + \frac{D}{k_{\mathrm{B}}T}F^{\mathrm{sys}}(x) + \sqrt{2D\Delta t}\xi \tag{26}$$

¶ Purists will write the equation as $\mathrm{d}v = \gamma v\,\mathrm{d}t + \sqrt{(2\gamma k_{\mathrm{B}}T)}\mathrm{d}W$, where W is a Wiener process.

where ξ is a random number sampled from a normal distribution with zero mean and variance equal to 1.

The Brownian evolution (eqn (24)) implies[17] an equation for the evolution of the *density* $\rho(x, t)$, which in general is called the *Fokker-Planck equation* and in this special case the *Smoluchowski equation*:

$$\frac{\partial \rho}{\partial t} = \frac{D}{k_B T} \frac{\partial}{\partial x}\left(\rho \frac{\mathrm{d}V}{\mathrm{d}x}\right) + D\frac{\partial^2 \rho}{\partial x^2} \tag{27}$$

The equilibrium solution ($\partial\rho/\partial t = 0$) is the Boltzmann distribution

$$\rho(x) \propto \exp\left(-\frac{V}{k_B T}\right) \tag{28}$$

and steady-state non-equilibrium solutions are easily derived.

How to determine friction from simulations

The friction coefficient can be obtained from simulations with constrained $\boldsymbol{r}''$ by monitoring the constraint force F_c acting on the constraint variables. The friction constant ζ in eqn (16) is found from the integral of the correlation function of $\Delta F_c = F_c - \langle F_c \rangle$:

$$\zeta = \frac{1}{k_B T}\int_0^\infty \left\langle \Delta F_c(t) \Delta F_c(t+\tau) \right\rangle \mathrm{d}\tau \tag{29}$$

Instead of computing the friction coefficient, one can derive the diffusion constant from eqn (23):

$$D = \frac{(k_B T)^2}{\int_0^\infty \left\langle \Delta F_c(t) \Delta F_c(t+\tau) \right\rangle \mathrm{d}\tau} \tag{30}$$

This equation is derived in ref. 16, but it was already known and applied[28] almost twenty years ago. We end this section by quoting Marrink,[15] who has applied this equation to compute the friction a water molecule feels in the z-direction when its z-coordinate is constrained in a bilayer membrane. Fig. 6 shows the diffusion constant derived from the force autocorrelation function at various depths in the bilayer. In regions where the water concentration is measurable, the diffusion constant can be measured directly by monitoring the mean-squared displacement of water molecules in the z-direction. There is a smooth connection between the two types of determination, lending credit to the use of constraint forces for friction determination. The friction is high enough for the Brownian limit to be valid; therefore eqn (24) and eqn (27) apply. From the "measured" potential of mean force (Fig. 5) and diffusion constant (Fig. 6) the transport properties for single water molecules, such as the permeability coefficient, can be computed without the need to simulate the stochastic motion of a water molecule through a membrane. Here we give no details,[14,15] but mention that the results agree quite well with experimental values.

6 The importance of dynamics and hydrodynamics

Friction and noise can play various roles in the dynamics of reduced systems, such as providing a thermostat, introducing viscosity, or introducing thermal conductivity. The friction and noise can be tuned to obtain a desired effect. So, before

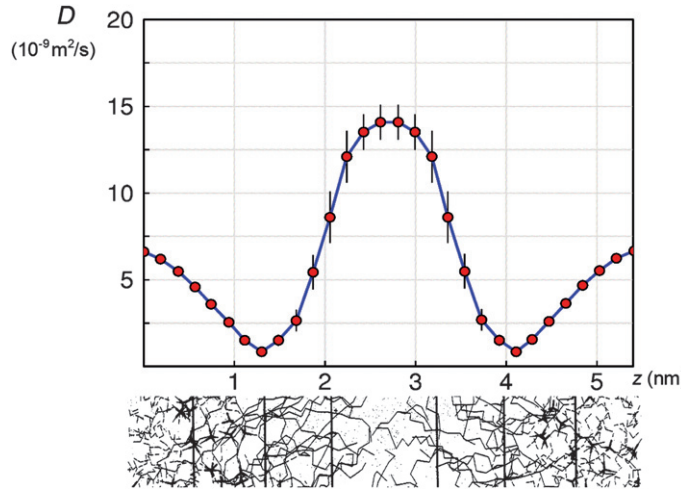

Fig. 6 Diffusion constant for a single water molecule moving through a bilayer membrane. Points without error bars: from mean square displacement; points with error bars: from integration of the autocorrelation function of the constraint force acting in the z-direction in simulations with water molecules at fixed depth z. The layer structure of the membrane (see Fig. 3) is pictured below the graph. Figure redrawn with permission from Marrink and Berendsen.[15] Copyright 1994 American Chemical Society.

introducing friction and noise, ask yourself *what is your purpose?* Let's examine some possibilities.

1. You wish to get the dynamics right

Incorporate friction and noise as accurately as possible. Analyze detailed MD on constrained systems to determine frictional parameters; fine-tune to obtain correct viscosities and/or diffusion constants.

2. You wish to get the hydrodynamics right

Hydrodynamical interactions, *i.e.*, interactions mediated through solvents, have a rather long range. The incorporation of long-range pair interactions, as the Oseen tensor, replacing an explicit solvent, is not very accurate. Better include solvent-like particles with proper DPD-type friction representing accurate viscosity, or else couple your system to a fluid of particles or to lattice points that have the proper limiting Navier–Stokes behavior. Use exclusively Galilean-invariant friction and noise. See below.

3. You are not interested in accurate dynamics, but want to explore configurational space quickly

Omit friction and noise altogether. Configurational probabilities are independent of friction and noise. Use the largest time step that conserves configurational distributions. Friction will generally slow down the dynamics, but noise may be essential to get any dynamics going. Appropriate friction and noise can be inserted to obtain proper thermostat behavior without increasing viscosity. Alternatively, use Monte Carlo sampling.

The *hydrodynamic coupling* to a fluid obeying the Navier–Stokes equations can be accomplished in various ways. The first question you should address is: *which solvent properties are essential for my problem?* Is it possible to mimic the solvent

interactions by some implicit model? If not, or if not accurately enough, you better include some coarse-grained model that exerts the essential interactions. Such a model you can augment with Galilean-invariant friction and noise to adjust the viscosity to a desired value. If you don't need other physical characteristics than those that determine hydrodynamic behavior, you can *couple* your solutes to a hydrodynamic fluid. The latter may be realized by *lattice points* or by *particles*. Neither are meant to represent real solvent particles, but they form a framework to solve the hydrodynamic, *i.e.*, the Navier–Stokes equations. The coupling itself will usually represent stick boundary conditions (see *e.g.* Padding *et al.*[29] how to do this).

1. Coupling to a lattice

The lattice points represent the local fluid velocity and possibly other hydrodynamic properties as density and pressure. They are either arranged on a 3D lattice or on a finite-element grid. The properties of the points are updated according to the Navier–Stokes equations. A popular method, used by Grass and Holm,[30] and Fenkel *et al.*,[31] is the *Lattice-Boltzmann* model,[32] which allows a limited range of velocities with a simple update scheme based on nearest neighbors.

2. Coupling to particles

Fluids of particles that interact *via* Galilean-invariant friction and noise will obey the macroscopic equations of fluid mechanics, more or less irrespective of the potential function used (if any) for the conservative inter-particle interactions. Many models are possible, but one particularly simple method,[33,34] invented in 1999, seems quite promising. It is called SRD (Stochastic Rotational Dynamics)‖ and it is used in ref. 35–37. The fluid particles have no conservative interactions (they form an ideal gas) and proceed a time step according to their velocities. After each time step they undergo a stochastic velocity change as follows: partition space into small cubes each containing a few particles. For each cube, subtract the average velocity $\bar{\boldsymbol{v}}$ of the particles in that cube from each velocity $\boldsymbol{v}_i$, yielding $\boldsymbol{v}'_i$. Now define a matrix $\boldsymbol{R}$ representing a rotation over a fixed angle around a randomly chosen axis. Rotate each velocity $\boldsymbol{v}'_i$ by $\boldsymbol{R}$, yielding $\boldsymbol{v}''_i = \boldsymbol{R}\boldsymbol{v}'_i$. Then add the average velocity to each of the $\boldsymbol{v}''_i$. It is easily shown that this procedure conserves both linear momentum and kinetic energy. The dynamics therefore obeys Navier–Stokes, but it does not act as a thermostat. The method is efficient and the viscosity can be adjusted by the choice of parameters.

7 Conclusion

To conclude I will summarize the preferential methods to which simulation methods for complex "soft materials" seem to converge. With complex soft materials I mean the condensed phase with structural inhomogeneities on the nanometre scale, including all biological macromolecular complexes and almost all of the rapidly developing nanomaterials. My summary is a very personally biased view, based on my conviction that simple methods that are easy to understand and to implement—provided they are correct and work—will always prevail over complex methods, even if the latter are more accurate.

1. Superatom models will be the coarse-grained models of choice. They are straightforward and connect naturally to the atomic scale. The alternative density descriptions on a lattice, using free energy density functionals to derive driving forces for the dynamics, are restricted to mean field approximations and include

‖ In ref. 35 SRD is named MPCD (multi-particle collision dynamics).

ad hoc dynamic variables. They are complex and not much more efficient as they require a density of lattice points comparable to the density of superatoms.

2. Parametrization of coarse-grained models will require a combination of *bottom-up* and *top-down* approaches. Bottom-up, *i.e.*, based on detailed atomistic simulations, is the ideal approach. However, the accuracy obtained, especially for multidimensional and non-pair additive interactions, will not be sufficient to determine thermodynamic quantities with the required precision. Therefore, top-down adjustments, based on experimental thermodynamic quantities, will be necessary. But be aware! If the CG simulation does not predict any other experimental quantities than have been used for parametrization, you have achieved nothing! Always test top-down models for predictive power beyond the realm of properties used for parametrization.

3. Thermostats based on DPD-like friction and noise will become more dominant. In general, the incorporation of adjustable Galilean-invariant friction and noise in order to achieve required dynamic properties will become common-place.

4. SRD (stochastic rotational dynamics) or similar variants will become popular for the provision of a hydrodynamic fluid environment. It will make lattice-based methods, including Lattice–Boltzmann schemes, obsolete.

5. Despite the large body of existing codes for fluid dynamics, it is likely that particle-based methods such as SRD will gain importance, even for macroscopic fluid dynamics applications.

References

1 G. S. Ayton, E. Lymon and G. A. Voth, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901996k.
2 T. Apajalahti, P. Niemelä, P. N. Govindan, M. S. Miettinen, E. Salonen, S.-J. Marrink and I. Vattulainen, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901487j.
3 A. J. Rzepiela, D. Sengupta, N. Goga and S. J. Marrink, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901615e.
4 Y. Norizoe, K. Ch. Daoulas and M. Müller, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901657k.
5 M. Yiannourakou, L. Marsella, F. de Meyer and B. Smit, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b902190f.
6 J. P. Ryckaert and A. Bellemans, *Faraday Discuss. Chem. Soc.*, 1978, **66**, 95.
7 P. Van der Ploeg and H. J. C. Berendsen, *Biophys. Struct. Mechanisms*, 1980, **6, Suppl.**, 106.
8 P. Van der Ploeg and H. J. C. Berendsen, *J. Chem. Phys.*, 1982, **76**, 3271.
9 P. Van der Ploeg and H. J. C. Berendsen, *Mol. Phys.*, 1983, **49**, 233.
10 H. J. C. Berendsen., in *Molecular-Dynamics Simulation of Statistical-Mechanical Systems*, eds G. Ciccotti and W. Hoover, Soc. Italiana di Fisica, Bologna. North Holland, Amsterdam, 1986, 496–519.
11 H. J. C. Berendsen and E. Egberts, in *Structure, Dynamics and Function of Biomolecules*, eds A. Ehrenberg et al., Springer Verlag 1986, 275–280.
12 E. Egberts and H. J. C. Berendsen, *J. Chem. Phys.*, 1988, **89**, 3718.
13 E. Egberts, S.-J. Marrink and H. J. C. Berendsen, *Eur. Biophys. J.*, 1994, **22**, 423.
14 H. J. C. Berendsen and S.-J. Marrink, *Pure Appl. Chem.*, 1993, **65**, 2513.
15 S.-J. Marrink and H. J. C. Berendsen, *J. Phys. Chem.*, 1994, **98**, 4155.
16 C. Hijón, P. Español, E. Vanden-Eijnden and R. Delgado-Buscalioni, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b902479b.
17 H. J. C. Berendsen., *Simulating the Physical World, Hierarchical modeling from quantum mechanics to fluid dynamics*, Cambridge University Press, 2007.
18 A. Lyubartsev, A. Mirzoev, L. Chen and A. Laaksonen, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901511f.
19 M. Schor, B. Ensing and P. G. Bolhuis, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901608b.
20 A. J. Crane and E. A. Müller, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901601e.
21 S. Baoukina, S. J. Marrink and D. P. Tieleman, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b905647e.
22 B. Widom, *J. Chem. Phys.*, 1963, **39**, 2808.
23 P. J. Hoogerbrugge and J. M. V. A. Koelman, *Europhys. Lett.*, 1992, **19**, 155.
24 P. Español and P. Warren, *Europhys. Lett.*, 1995, **30**, 191.
25 C. Junghans, M. Prapotnik and K. Kremer, *Soft Matter*, 2008, **4**, 156.

26 W. F. Van Gunsteren and H. J. C. Berendsen, *Mol. Simul.*, 1988, **1**, 173.
27 H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola and J. R. Haak, *J. Chem. Phys.*, 1984, **81**, 3684.
28 B. Roux and M. Karplus, *J. Phys. Chem.*, 1991, **95**, 4856.
29 J. T. Padding, A. Wysocki, H. Löwen and A. A. Louis, *J. Phys.: Condens. Matter*, 2005, **17**, S3393.
30 K. Grass and C. Holm, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b902011j.
31 B. Rotenberg, I. Pagonabarraga and D. Frenkel, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901553a.
32 J. M. Thijssen., *Computational Physics*, 2nd ed., Cambridge University Press, 2007.
33 A. Malevanets and R. Kapral, *J. Chem. Phys.*, 1999, **110**, 8605.
34 R. Kapral, *Adv. Chem. Phys.*, 2008, **140**, 89.
35 A. Wysocki, C. P. Royall, R. G. Winkler, G. Gompper, H. Tanaka, A. van Blaaderen and H. Löwen, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b901640f.
36 E. S. Boek, J. T. Padding, T. Headen and J. Crawshaw, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b902305b.
37 J. Sané, J. T. Padding and A. A. Louis, *Faraday Discuss.*, 2010, **144**, DOI: 10.1039/b905378f.