Novel approaches to multiscale modelling in materials science

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Computational modelling techniques are now widely employed in materials science, due to recent advances in computing power and simulation methodologies, since they can enable rapid testing of theoretical predictions or understanding of complex experimental data at relatively low cost. However, many problems at the leading edge of materials science involve collective phenomena that occur over a range of time and length scales which are intrinsically difficult to capture in a single simulation. This review summarises some of the latest developments in multiscale modelling techniques over the past decade, as applied to selected problems in materials science and engineering, thereby motivating the reader to explore how such techniques might be applied in their own area of specialty. Methods for accelerating molecular dynamics by enhancement of kinetic barrier crossing, such as hyperdynamics and metadynamics, are discussed alongside mesoscale simulation techniques, such as dissipative particle dynamics or adaptive coarse graining, for enabling larger and longer simulations. The applications are mainly focused on simulations of microstructure and mechanical properties, and examples of surface diffusion in metals, radiation damage in ceramics, strengthening of nanocrystalline metals and alloys, crack propagation in brittle solids, polymer chain relaxation in nanocomposites and the control of nucleation in biomimetic materials are discussed.

Keywords: Multiscale computer simulation, Materials modelling, Molecular dynamics, Monte Carlo, Finite element analysis, Hierarchical/hybrid models, Density functional theory, Review

Introduction

The last 10 years have seen a rapid expansion in the use of computer modelling techniques in materials science, with the number of relevant articles indexed on ISI's Web of Knowledge between 2000 and 2010 more than tripling in comparison to the preceding decade. As noted by the late Robert Cahn in his account of 'The Coming of Materials Science',[1] computational modelling is now a well established technique in virtually all areas of mainstream materials science, including polymers,[2] ceramics,[3] semiconductors[4] and metals.[5] It is also a major driving force in relatively new avenues of research, such as pharmaceutical materials science,[6] nanotechnology and engineering,[7] biomimetic materials[8] and solid-state ionics,[9] to name just a selection. This review seeks to summarise some of the latest developments in multiscale modelling techniques as applied to selected problems in materials science and engineering,[10–14] thereby motivating the interested reader to explore how such techniques might be applied in their own area of specialty. The applications are mainly focused on simulations of microstructure and mechanical properties,

although some discussion of electrical percolation in polymer nanocomposites and the control of nucleation in biomimetic materials is also given.

Many researchers in materials science consider computer modelling to be a theoretical technique, since the algorithms and methods involved are often expressed in highly mathematical terms, and also perhaps because theoretical groups tend to make heavy use of numerical simulations. However, this is somewhat of a misconception, since modelling may better be considered as a form of numerical experimentation. Of course, numerical experiments cannot in themselves explain the occurrence of a physical phenomenon, any more than a real experiment can, without a theoretical interpretation of the results. Therefore, modelling, theory and physical experimentation have a rather more complex and subtle interdependence that might be thought of diagrammatically in the form of a triangle, with each vertex a necessary and important part in the full elucidation of a scientific or engineering problem. In other words, it should be emphasised that computer modelling will never replace, nor was it ever intended to replace, direct experimentation in the development of new scientific theories or technologies. At its best, using appropriate physical models and the minimum of *ad hoc* assumptions, computer simulation can be used as a powerful predictive tool to guide novel experimental programmes in a fraction of the time and cost of trial-and-error

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approaches.[15] Furthermore, with the increasing use of three-dimensional imaging techniques such as X-ray micro- or nanotomography[16] (and similar electron or ion beam based methods), it is now possible to undertake microstructurally faithful materials modelling in which multiscale structural information can be used directly for property prediction.[17–20]

There have been a number of important driving forces for the increased use of computer modelling in materials science. The first is the availability of inexpensive commodity processing power, driven in part by Moore's law[21] which, in its original form, related to the doubling of the transistor density in integrated circuits every 18 months. In practice, this has led to a rapid decrease in the unit price of CPU power, physical memory and hard disk space as machines suitable for scientific calculations have found their way onto the mass market. As well as improvements in hardware, there now exist many commercially available integrated modelling software packages; a selection of notable examples include: GAUSSIAN[22] (mainly for quantum chemical calculations), Materials Studio[23] (for quantum, classical and mesoscale calculations) and ABAQUS[24] [for finite element (FE) calculations]. There has also been a passage of codes, such as CASTEP[25,26] (Cambridge Serial Total Energy Package) and VASP[27] (Vienna Ab initio Simulation Package), from specialised academic groups to industrial users and experts, and development of multiscale modelling protocols, e.g. the OCTA project[28] and the VOTCA (Versatile Object-oriented Toolkit for Coarse-graining Applications) toolkit,[29] to enable real materials science and engineering problems to be addressed. The combined result of these dramatic changes over the last decade has been a greatly increased usage of modelling techniques by the materials community, usually in combination with experimental or theoretical work.

The diverse outputs of these simulation enabled studies are reflected in a number of recent reviews covering various aspects of materials modelling. In 2002, as part of a general survey of techniques for modelling of structural materials, Porter[30] discussed the requirement for a very wide range of length scales to be considered in tackling materials problems, and briefly described some of the most commonly used methods for doing so, together with some case studies of their application. Since that time, there have been two further review articles in this journal that have considered some specific topic explicitly involving the use of a multiscale approach, including the study of radiation damage processes in metals[31] and sintering processes in powder compacts.[32] Since the number of different modelling methods and their possible applications are almost bewildering large, it has until recently been difficult to find a comprehensive source of reference for the specialist, or for the non-specialist to obtain a balanced perspective. However, this situation has been somewhat improved by the publication of a 'Handbook of Materials Modelling', edited by Sidney Yip (MIT) in 2005,[33] which was recently reviewed by the present author.[34] Based loosely in the concept of the CRC Press's 'Handbook of Chemistry and Physics', this volume involved the efforts of 18 subject editors coordinating submissions from over 260 authors to produce a two-volume reference that attempted both to define the broad area of 'computational materials science' and help stimulate its continuing growth. Although largely successful in its aim to become the defining reference volume in its area, the Handbook is inevitably rather unwieldy in both its physical bulk and the sheer conceptual scope of the endeavour. An earlier text by Raabe[35] provides a somewhat leaner treatment of microstructural and mesoscopic techniques, although is missing a full discussion of quantum mechanical (QM) methods and is not able to take into account more recent developments. More recently, there have been several books focusing on hierarchical[36] and coarse grained modelling techniques,[37] which will be discussed further in the section on modelling approaches below.

Perhaps the best way to obtain the most up-to-date perspective on the field is to consider the recent International Conferences on Multiscale Materials Modelling (MMM), which were held in 2002 (at Queen Mary, University of London, UK), 2004 (at University of California, Los Angeles, CA, USA), 2006 (at University of Freiburg, Germany) and 2008 (at University of Florida, Gainesville, FL, USA). The most recent meeting was held in Freiburg in 2010. The proceedings from the 2002 MMM meeting were published in *Materials Science and Engineering A*,[38] to which further reference will be made later in this article. Also of relevance are the Foundations of Molecular Modelling and Simulation (FOMMS) meetings held in 2000, 2003 (Keystone, CO, USA) and 2006 (Blaine, WA, USA), whose proceedings were published in the journal *Molecular Physics*,[39,40] again to which more specific reference will be made later. These conference series, and others like them, have helped to define the scope and development of materials modelling in an international context. The profile of this discipline was further raised by the devotion of an entire issue of the *Annual Review* to 'Computational Materials Research', with a selection of articles chosen by LeSar and Rickman in 2002.[41] There have also been several symposia of the Materials Research Society (MRS) devoted to this topic, notably including 'Multiscale modeling of materials', in 1999[42] and 2001,[43] and 'Multiscale phenomena in materials: experiments and modeling' in 2000[44] and 2003,[45] in addition to regular symposia at the American Physical and American Chemical Society meetings. de Pablo and Curtin also reviewed several applications of 'Multiscale modeling in advanced materials research' in a recent special issue of *MRS Bulletin*.[46]

To a certain extent, the recent surge in activity in materials modelling, together with the drive towards a multiscale approach, can be attributed to a series of funding reports conceived in the mid-nineties and early in the new millennium. The Technology Foresight review in 1995 highlighted materials modelling as one of the key areas for development.[47] The UK based Institute of Materials (now IoM[3]) initiated a study, supported by the Office of Science and Technology, to report on the state of materials modelling in UK.[48] These reviews urged for substantial investment from government research councils, and several materials modelling initiatives have recently been funded in the areas of radiation damage in steels, alloys by design, and the organic/inorganic interface in biomaterials. Furthermore, on the pedagogical side, there have been a number of Master's and other graduate courses set up
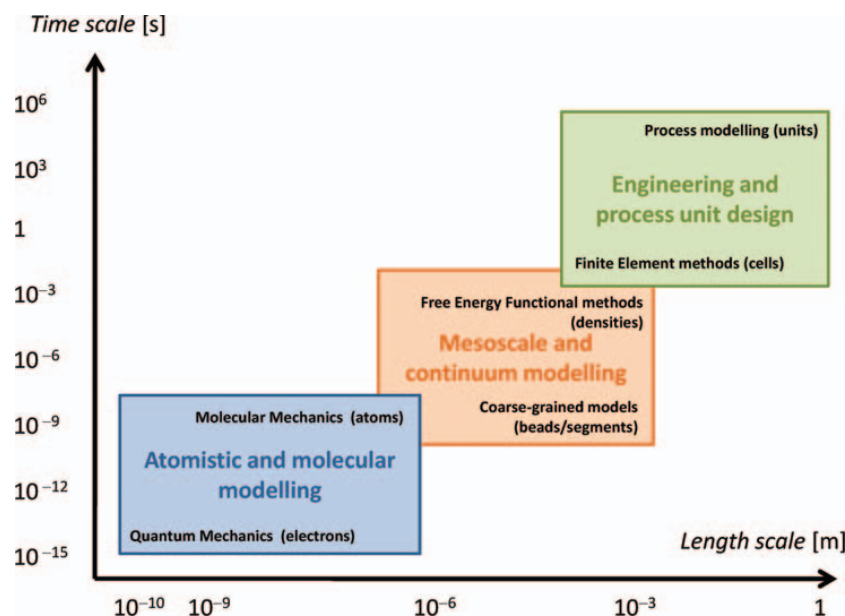
1 **The hierarchy of multiscale modelling techniques, showing approximate range of temporal and spatial scales covered by different categories of methods. Areas of overlap permit 'mapping' or 'zooming' from one scale to the next, which often required for parameterisation of higher scale methods or for obtaining a finer scale resolution of selected parts of the larger system**

in the UK to teach the principles of material modelling to physical science graduates, including an MPhil in Cambridge that resulted in an introductory textbook on this subject.[49]

Approaches for MMM

By definition, multiscale modelling entails the application of modelling techniques at two or more different length and times scales, which are often, but not always, dissimilar in their theoretical character due to the change in scale. A distinction is made between the hierarchical approach,[10,36,50] which involves running separate models with some sort of parametric coupling, and the hybrid approach,[51–54] in which models are run concurrently over different spatial regions of a simulation. The relationships between different categories of methods commonly used in the multiscale modelling hierarchy are shown in Fig. 1. Although some techniques have been known for a long time and are now widely used, such as molecular dynamics (MD) and Monte Carlo (MC) methods, others such as mesoscale modelling and some more advanced methods for accelerating atomistic simulations are not as common, and we therefore include here a technical summary for the benefit of non-specialists.

Summary of modelling techniques
Atomistic and molecular modelling
The first applications of MD and MC methods to atomistic systems using classical potentials are now over 50 years old, and detailed descriptions of these techniques can be found in a number of recent textbooks.[55–58] Furthermore, recent advances in electronic density functional theory (DFT),[59,60] and related tight binding (TB) approximations,[59] have now made first principles based QM calculations – both static and dynamic – feasible for large systems where previously only classical molecular mechanics (MM) simulations were possible.

Some researchers have developed hybrid QM–MM methods,[54] which can accurately reproduce interatomic potentials in atomistic simulations 'on-the-fly' without the expense of a full QM treatment, while others have strived to reduce the steep increase of computational cost with system size, e.g. linear scaling DFT using the ONETEP (Order-N Electronic Total Energy Package) code.[61] A distinction is sometimes made between first principles or '*ab initio*' methods (e.g. the Hartree–Fock method), in which the variational principle guarantees an approximate solution whose energy is an upper bound to the ground state energy, and empirical or semiempirical methods (e.g. DFT or MM) where experimental parameterisation is required, and whose accuracy is less systematically controlled. However, in practice, this difference is not very significant for materials modelling because, for any system of reasonable complexity, both approaches lead to approximate solutions, and those obtained *ab initio* are not necessarily more accurate than those obtained empirically. Nevertheless, *ab initio* and DFT calculations are commonly regarded as the benchmark for comparison against empirical interatomic potentials for complex systems with mixed bonding character,[62] or where radically new structures are found under extreme conditions.[63]

However, a problem of concern to materials scientists is the great mismatch in length and time scales that can be reproduced in simulations – perhaps typically of tens of nanometres or nanoseconds, and exceptionally tens of micrometres or microseconds – compared to the scales required to describe the relevant phenomena. Some pertinent examples, which will be discussed in more detail in the following section on applications, are surface diffusion, radiation damage, crack propagation and nanocomposite property prediction. Furthermore, problems in materials science often tend to involve first order (i.e. discontinuous) phase transitions, free energy calculations and non-equilibrium phenomena, which are
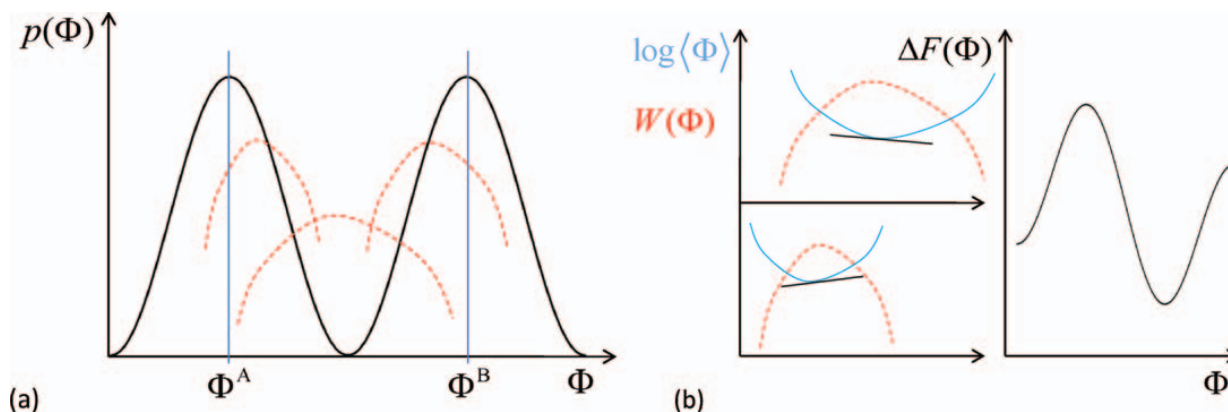
2 Advanced statistical sampling methods for MC, showing *a* umbrella sampling of two-phase (A/B) region as function of order parameter Φ and *b* reconstruction of full free energy profile (right) from local variations of free energy deduced from each umbrella simulation (left)

not easily studied by conventional techniques. In order to address these needs, some researchers have pioneered advanced statistical sampling methods for MC, such as umbrella sampling[56,64] and multicanonical[65] or Wang–Landau methods,[58,66] and accelerated dynamics schemes for MD, such as metadynamics[67,68] or hyperdynamics[69,70] that can overcome limitations of standard techniques. While a full account of these is beyond the scope of this review, it is appropriate to include a brief description here, in order to illustrate their general flavour and advantages and disadvantages over conventional methods, as a preamble to the discussion of specific case studies in later sections. A key point in common with all the methods covered is their focus on enhancing the probability of rare events, i.e. those that would occur with only vanishingly small probability over the time scale of a canonical MD simulation under normal conditions of temperature and pressure. A good example is the diffusion of atomic silver on a flat Ag(100) surface, where the real time between each hopping event is of order 10 μs,[71] which may take around one week of CPU time! The artificial acceleration of rare events allows the extension of atomistic modelling time scales up to the micro- or even millisecond range, whereas the extension of length scales is better handled by mesoscale methods described in a later section to follow.

The concept of 'umbrella sampling' was originally developed by Torrie and Valleau[64] in order to calculate free energy differences in systems undergoing large changes in configuration, such as a first order phase transition (if the changes are not too large, more straightforward methods such as thermodynamic integration[56] or Widom particle insertion[56,72] can be used instead). It should be emphasised that it is not possible to do this using standard canonical MD or MC simulations, since entropies and free energies cannot be computed as averages over configurations or time as they are related to the volume of phase space accessible to the system. Moreover, the conventional methods sample only sparsely from unstable regions of configuration space, such as near to a transition point, giving rise to large statistical errors in the free energy differences calculated by comparing simulations of the two phases separately in thermal equilibrium. By introducing an additional weighting function to bias the Boltzmann distribution used in standard MC, the

system can be guided to sample more frequently from the normally unstable regions, resulting in a more accurate estimate of the free energy. This process is illustrated schematically in Fig. 2, where Fig. 2*a* shows the probability density of states (DOS) as a function of some order parameter Φ, which tracks the progress of the phase transition. The two maxima in $p(\Phi)$ correspond to the stable phases A and B, and the intervening minimum corresponds to the two-phase region. Normally, the system would exist in either state A or B, with only a small probability of being found in between. However, with the additional of biasing functions, the probability distributions can be shifted as shown by the dashed red curves, which illustrate the overlapping distributions obtained from three separate simulations using a harmonic constraint on the order parameter. Notice that the simulations, particularly the second, now sample extensively in the two-phase region, and that they form a set of overlapping 'umbrellas' that bridge from phase A to phase B (the greater the number of umbrellas, the more accurate the calculation). As illustrated in Fig. 2*b*, since the free energy can be computed from logarithm of the order parameter distribution averaged over each simulation $\log\langle\Phi\rangle$ (shown as solid blue line), plus the bias potential $W(\Phi)$ (shown as dashed red line), then the variation in free energy over each umbrella simulation (shown as solid black line) can be transformed to give the variation of free energy over the whole range.[64] Although umbrella sampling is a very powerful method in general, its efficiency for a particular system depends greatly on the choice of bias function, which constrains the system to a fixed region of phase space and must be updated manually, and so other 'adaptive' techniques have since evolved from it that rely less on trial-and-error construction. We review some atomistic techniques that implement some of the above sampling methods using dynamical approaches, before returning to consider adaptive MC based techniques in the following section on mesoscale modelling.

Time acceleration in dynamical simulations can be achieved using some of the ideas of umbrella sampling in combination with either a bias potential or transition state theory (TST),[73–75] which gives a simple Arrhenius form for the transition rate if the energy is assumed to vary harmonically near the minimum and barrier regions for all the degrees of freedom other than the
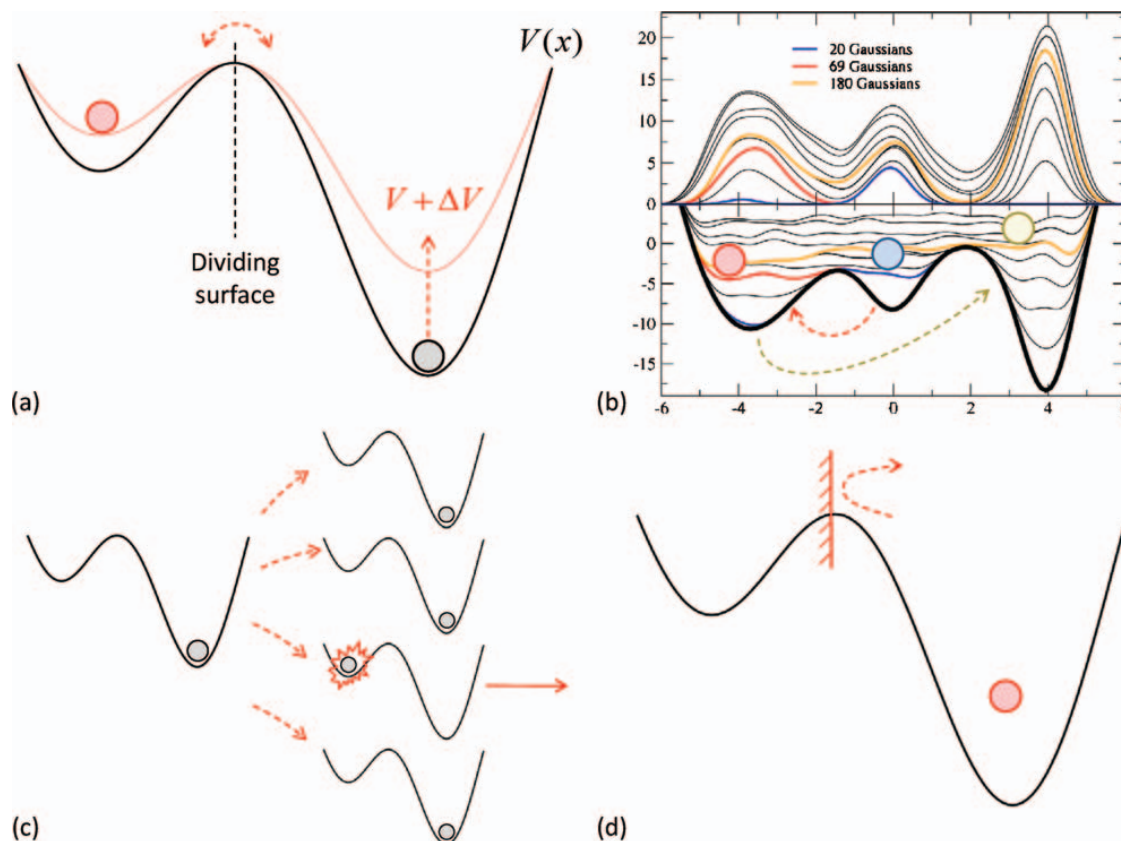
3 Accelerated dynamics methods, illustrating differences between *a* hyperdynamics, *b* metadynamics (adapted with permission from Fig. 1 in Ref. 68), *c* parallel replica dynamics and *d* temperature accelerated dynamics

reaction coordinate direction.[76] This is illustrated in Fig. 3, which shows schematically the behaviour of a single atom moving in a series of simple one-dimensional potential energy surfaces (PES) denoted by solid black lines. For example, in the hyperdynamics scheme conceived by Voter,[69] shown in Fig. 3*a*, the original PES, $V(x)$, is augmented by a bias potential ΔV, which is zero at the dividing surface between the two energy minima, and acts to increase the frequency of barrier crossing by 'filling in' the areas of low energy. In the regions where the bias potential is non-zero, the effective simulation time passes more quickly by a factor of $\exp(\Delta V/k_B T)$. The ratio of accumulated hypertime to the standard MD clock time is known as the 'boost', and can be as large as 10^6 if an appropriate form of biasing potential is chosen. It follows that the boost drops off considerably as rare events become more frequent. Unfortunately, in common with umbrella sampling, it is not easy to find a general method of specifying the bias potential, and this area still is a topic of ongoing research.[77] However, particularly convenient forms have been devised, such as the 'bond-boost method' of Miron and Fichthorn,[78] and also the bias potential dynamics (BPD) method by Hamelberg *et al.*,[79] the latter of which is implemented in the DL_POLY code[80–83] (version 2·20), available under academic license from Daresbury Laboratory in the UK.

A technique related to hyperdynamics is the metadynamics method of Laio and Parinello,[67,68] in which a series of Gaussian functions are added to the PES in order to flatten it and force the atom to explore other regions of phase space, as shown in Fig. 3*b*. Metadynamics enables the rapid exploration of free

energy surfaces in some chosen set of coordinates, but there is no direct connection to a timescale and so any dynamics is largely fictitious. Laio and Gervasio[68] give the analogy of a walker trapped in an empty swimming pool at night who, from time to time, drops packets of sand on ground as they wander in the darkness. Given a sufficient supply of sand, they will eventually escape and, if they are able to remember where they dropped the sand, be able to reconstruct a negative image of the pool. Figure 3*b* shows the time evolution of the total potential (at negative y values) and repulsive bias potential (at positive y values) for an atom as it is displaced from the central minimum (blue curve) by the addition of 20 Gaussian functions, and so on for the left-hand minimum (red curve, after 69 Gaussians) and finally right-hand minimum (yellow curve, after 180 Gaussians). The advantages of the metadynamics method over hyperdynamics or BPD are that it requires no *a priori* knowledge of the bias potential, and that the sum of Gaussians deposited up to a particular time provides an unbiased estimate of the free energy in the region explored during the simulation.[68]

Two other accelerated dynamics methods also developed by Voter and co-workers that do not rely on biasing the PES are parallel replica dynamics (PRD) and temperature accelerated dynamics (TAD).[84,85] Parallel replica dynamics is illustrated schematically in Fig. 3*c*, where the canonical dynamics of a single system is replicated on a number (say, M) of processors running in parallel. Having allowed the replicas to become locally uncorrelated (i.e. randomised within the original basin of attraction), the dynamics of all M systems are then monitored until, it is hoped, a transition occurs in a

single one corresponding to a rare event. The simulation clock is then advanced by the elapsed time summed over all M replicas, and the replication process is continued from the replica which made the transition, allowing for a short period in which correlated dynamic events could occur. TAD, on the other hand, can be thought of as very similar to 'on-the-fly' Kinetic Monte Carlo (KMC),[58] in which the barriers are constructed during the course of the simulation, and is also implemented in the DL_POLY code[83] (version 2·20) in addition to BPD. As illustrated in Fig. 3d, TAD is based on the concept of raising the temperature of the system to enable rare events to occur more frequently, while at the same time preventing the system from evolving along diffusion pathways only accessible at high temperatures. At first sight, these two aims may appear mutually contradictory, but if the high temperature system is arrested just after making a transition then harmonic TST can be used to extrapolate the appropriate low temperature rate for the transition by finding the appropriate barrier height from the two end point minima using a technique such as the nudged elastic band method.[86,87] By confining the system to its local basin of attraction, the TAD method essentially tries to find all possible escape routes at high temperatures, and then selects the one with the shortest time to occur at low temperatures. This raises the question of how long the high temperature simulation should be run in order to ensure that all reasonable escape routes have been found, and Voter[85] gives an empirical prescription based the criterion of a high confidence that no shorter transition will be seen at the lower temperature. Compared to other accelerated dynamics methods, TAD is the most approximate, relying heavily on the assumption of harmonic TST, whereas PRD is the most accurate. On the other hand, TAD can yield large boost factors when energy barriers are high, whereas PRD is dependent on the number of available processors to achieve a given boost. Parallel replica dynamics is implemented in the Large-scale Atomic/Molecular Massively Parallel Simulator (LAMMPS) code available from Sandia National Laboratories.[88,89]

It is clear that the future development of materials modelling will depend on finding ever more sophisticated physical shortcuts to the computational bottlenecks found in 'brute force' applications of standard methods.[90] One remaining difficulty is that the sheer amount of information (e.g. atomic positions, wave functions, electronic densities) generated from large scale atomistic simulations rapidly overwhelms the ability to process and extract meaningful conclusions from it. For that reason, considerable effort has been made towards reducing the number of degrees of freedom in simulations which, as well as reducing the complexity of the variable space to a manageable level, can enable orders of magnitude increases in the length scale of simulations that are possible.

Mesoscale and continuum modelling

Until relatively recently, a somewhat neglected level of description in materials modelling has been the mesoscopic regime, lying between discrete atomic particles and FE representations of a continuum, and covering characteristic length scales of 0·1–10 μm as shown in Fig. 1. At this scale, the system is still too small to be regarded as a continuum, yet too large to be simulated effectively using atomistic methods. More precisely, a mesoscale can be defined as any intermediate length scale at which the phenomena at the next level below (e.g. particle motions) can be regarded as having been equilibrated, and at which new phenomena emerge with their own characteristic time scales (e.g. Brownian motion of a solute particle,[91,92] or the diffusive path of a crack tip through an elastic continuum[93]). Of course, this does not imply that the system as a whole must be in equilibrium – in fact, the behaviour of entire classes of materials systems, such as steels, is determined by non-equilibrium trajectories through the phase diagram. The concept of an evolving mesostructure, and its effect on materials properties, was reviewed elsewhere by Stoneham and Harding,[94] but we focus here on how to get from the atomistic to the mesoscale. This is performed by a process of integrating out redundant degrees of freedom, known as 'coarse graining', which can be achieved either by forcing atoms onto a lattice or by grouping them into larger particles (often know as 'mapping'). Conversely, the process of 'reverse mapping' refers to the restoration of full atomistic detail. In general, there is no systematic procedure for coarse graining that is applicable across all classes of material, but many groups have developed methods for particular systems,[37,95–103] and semi-automated tools are available in commercial software, such as Materials Studio referred to above.

An example of a polymer chain coarse grained onto a face centred cubic lattice is used in Fig. 4a and b. The processes of mapping and reverse mapping enables the calibration of a generic lattice chain to a particular system, with specific molecular chemistry, by matching of the densities, end-to-end distance and radial distribution functions.[2,97,104] Furthermore, owing to the greatly reduced size of conformational space, the lattice chain provides a much more computationally convenient framework for simulating larger systems[105] or bulk phase behaviour. This can be achieved using an alternative form of adaptive umbrella sampling, recently developed by Wang and Landau,[66] and related to the multicanonical method of Berg and Neuhaus[65] in which the histogram of sampled states is first flattened (similar to summing the red curves in Fig. 2a) and then reweighted[106,107] to enable the correct Boltzmann distribution to be deduced at any temperature within the sampled range. However, the objective of the Wang–Landau method is to determine the full DOS by performing a random walk in configurational space with a probability proportional to the reciprocal of the DOS. The thermodynamic reweighting method is illustrated in Fig. 4a for an isolated lattice polymer chain of length 100 segments, where the log(DOS) is shown as a function of the number of polymer–polymer nearest neighbour contacts, and each contact contributes an energy ε. The five dashed black lines show canonical histograms for the system at five difference temperatures, and the dashed coloured line shows the total histogram taking into account the appropriately reweighted contributions from all temperatures. Once the DOS distribution is known to sufficient precision, all other thermodynamic quantities can easily be derived, and the inset to Fig. 4a shows a plot of heat capacity versus reduced temperature showing transitions (i.e. peaks in the heat capacity) from an extended coil at high temperatures to a compact 'crystal' at low
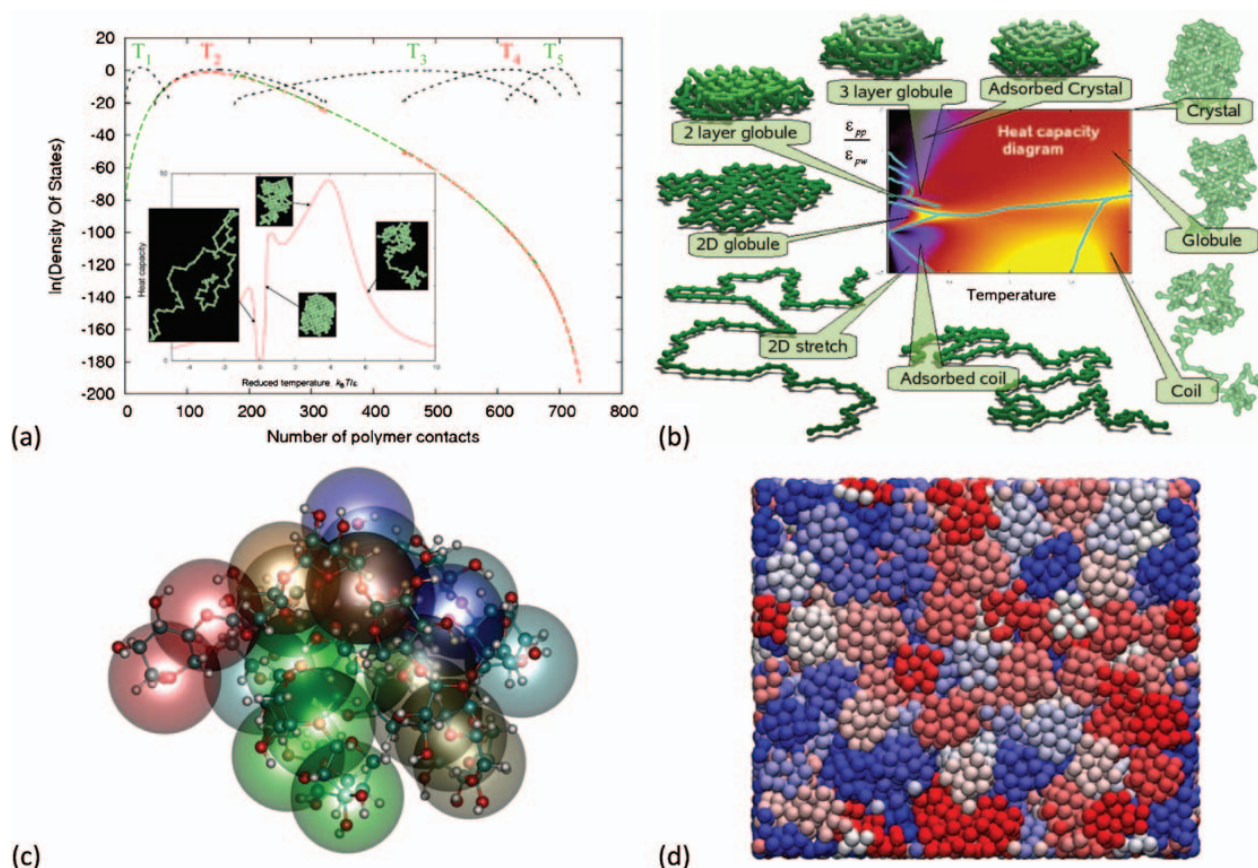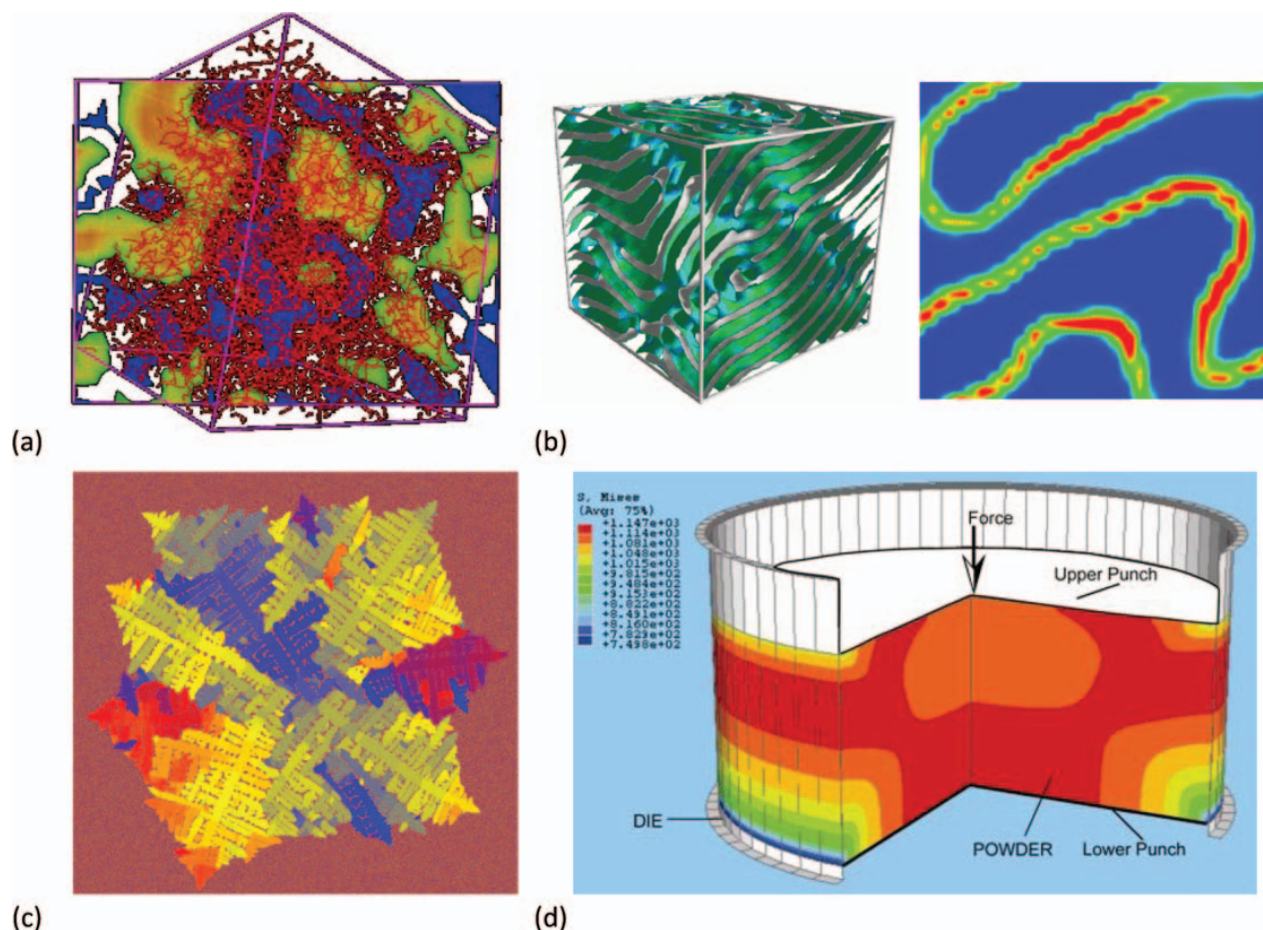
4 Examples of mesoscale modelling in coarse grained systems *a* reconstruction of DOS for a lattice chain polymer by histogram reweighting, with heat capacity versus reduced temperature shown as inset, and *b* heat capacity for lattice chain adsorbed on flat surface, showing surface induced crystallisation and multilayer coil–globule transitions, *c* off-lattice representation of oligosaccharide (larger semitransparent spheres) superimposed on corresponding atomic configuration and *d* model for granular material composed of assembly of cohesive spheres (those in each granule coloured identically)

temperatures.[108] Negative temperatures, corresponding to a repulsive interaction between polymer beads, give rise to an expanded coil conformation. Figure 4*b* shows the Wang–Landau method applied to a more complex system, where the lattice chain is adsorbed to a flat surface or wall. A 'phase diagram' of the system, as a function of relative polymer–polymer (ε_{pp}) to polymer wall (ε_{pw}) contact energies and reduced temperature, shows the existence of distinct adsorbed phases (i.e. separated by maxima in heat capacity, shown by the blue lines on the phase diagram). This phenomenon has been discussed in more detail by several groups,[109,110] and similar methods have been used to study mobile nanoparticles dispersed in a polymer.[111]

Although the Wang–Landau method is a powerful method to study phase behaviour for lattice based systems, the efficiency of the algorithm is limited when applied to off-lattice models due to the greatly increased number of degrees of freedom. An alternative means of coarse graining is shown in Fig. 4*c*, which illustrates an oligosaccharide molecule represented by a series of 'beads' centred on the positions of oxygens connecting glucosidal rings that define the chain conformation.[112] The advantage of this 'off-lattice' approach is that it gives a much greater flexibility in describing the conformations of each molecule, and allows the use of soft interactions between beads,[98,113] at the expense of some computational efficiency compared to lattice models. Of course,

such coarse graining methods are not restricted to polymeric systems, and have also been applied to liquid systems,[101] including ionic liquids,[114] and solute motion.[115] Moreover, Kremer and co-workers have recently developed an Adaptive Resolution Scheme (AdResS) for coarse graining specific regions of a simulation 'on-the-fly', which shows great promise for dealing with the simulation of macromolecules, free surfaces and nanoparticles in solution.[103,116] The length scale of mesoscopic simulations can now even be extended to model powders through the use of discrete (or distinct) element modelling,[117,118] in which each particle is considered to be either a whole or part constituent of a granular medium, interacting via elastic and dissipative force contact laws.[119,120] Figure 4*d* shows a model for an assembly of cohesive particles, where each agglomerate (identified by its individual colour) is made up of 'glued' spheres, fused by normal and tangential bonded potentials with a maximum threshold fracture strength, in order to simulate large scale plastic deformation and fracture. Such models are now providing insights into the constitutive behaviour of cohesive and crushable particle assemblies at the macroscopic scale.[17,121–124]

A popular mesoscale method for simulating soft materials, such as polymer and liquids, is dissipative particle dynamics (DPD), first developed by Hoogerbrugge and Koelman[125,126] for modelling the flow of hard spheres in suspension, and reformulated on a

5 **Examples of mesoscale and continuum models:** *a* **two-dimensional water bead density (yellow/blue) derived from three-dimensional DPD simulation**[133] **of coarse grained PFSA ionomer (red lines),** *b* **three-dimensional isosurface and two-dimensional density fields for block copolymers in the lamellar phase from a MesoDyn calculation,** *c* **phase field model of dendrites with particulate induced disorder (reproduced with permission from Ref. 147) and** *d* **FE model of a flat faced cylindrical tablet under uniaxial compaction (colours denote von Mises stress)**

rigorous thermodynamic basis by Groot and Warren[127] and Español and Warren.[128] It is closely related to the Brownian dynamics method,[36,129] in which standard canonical MD is augmented by dissipative and random forces between particles, representing the integrated effects of a coarse grained fluid medium, in addition to a soft repulsive force which can be deduced from experiments or molecular simulations via Flory–Huggins theory.[130] However, unlike in Brownian dynamics, the forces in DPD are always pair wise acting, which guarantees the emergence of true hydrodynamic behaviour in the limit of large system size.[131] In this extended sense, DPD can be thought of simply as local, hydrodynamics conserving Langevin thermostat for MD. Dissipative particle dynamics is implemented in the Extensible Simulation Package for Research on Soft matter (ESPResSo) code available from the Max Planck Institute in Mainz,[132] and also in the commercial software Materials Studio referred to above. As an example, Fig. 5a shows a cross-section of the density distribution of water beads (with yellow corresponding to high density, and blue to low density) from a DPD simulation of hydrated perfluorsulphonic acid (PFSA) ionomer, superimposed on a coarse grained representation of the polymeric component (with red segments denoting pairs of connected beads).[133] It is important to note that the size scale of the simulation box is just over 32 nm cubed,

with each DPD bead representing 13 atoms on average, corresponding to 2·5 million effective atoms in total. An equivalent fully atomistic simulation would be at least an order of magnitude more costly in time and computational power. Such simulations are helping to understand the connection between the morphology of membranes used for hydrogen fuel cell applications and their ionic conductivity.[134–136]

Moving increasingly towards the continuum regime, a popular category of techniques include free energy functional methods, such as the dynamic density functional theory (DDFT) approach implemented in the MesoDyn package,[137,138] more advanced field theoretic methods developed by Fredrickson and co-workers,[139] or the particle based approaches of Müller, de Pablo, Nealey and co-workers.[140–142] In the DDFT approach, rather than solve explicitly for the positions of the mesoscopic particles, their density distributions in three dimensions are evolved under the influence of a slowly varying external potential in which the particles are in instantaneous equilibrium, and for which the free energy of the system is minimised. At each time step, a density distribution is found which minimises the free energy in the external field, and the system evolves dynamically in a stochastic fashion according to a series of coupled Langevin equations. In contrast to DDFT, the local densities in the particle
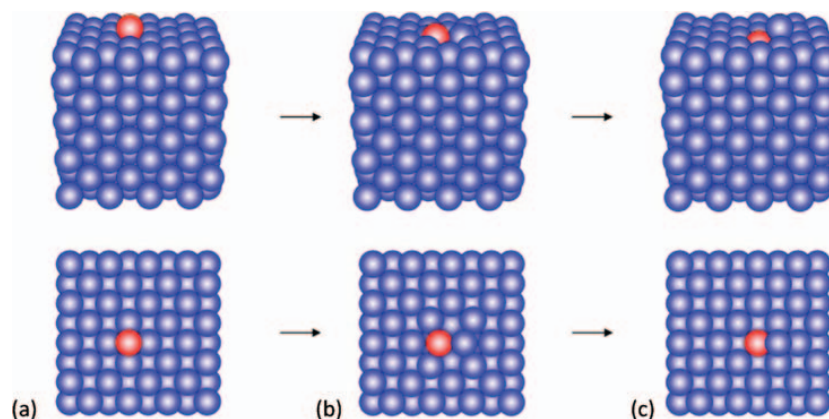
6   Diffusion of Ag adatom (red) on Ag fcc(100) surface studied by hyperdynamics, showing surface layer exchange step in *b* with a barrier of 0·64 eV and relaxation time of 1 ms at 300 K. Both plan (bottom) and oblique (top) views are shown in each case, to highlight the surface profile

based methods are defined from the bead positions by a particle mesh smoothing procedure, which relaxes the assumption that the chain conformations are always in equilibrium with the fields.[140] Examples of the types of density distributions (both two- and three-dimensional) produced by MesoDyn simulations are illustrated in Fig. 5*b* – both images show a lamellar morphology for block copolymer, with a spacing between lamellae of approximately 25 nm. A closely related technique is phase field modelling,[143,144] based on a free energy functional of the crystalline order parameter including bulk and gradient energy terms, which has been applied extensively to solidification[145,146] and nucleation[146] in metallic systems. An example of a dendritic microstructure brought about by particulate induced disorder is shown in Fig. 5*c*.[147] Of great importance for modelling defects in crystalline systems are cell structured methods such as dislocation dynamics,[148,149] which have contributed greatly to the understanding of microstructural evolution in metals and ceramics.

This brings us finally almost to the top of the hierarchy of modelling techniques shown in Fig. 1, making contact with the finite element method (FEM)[150,151] commonly used for stress analysis and heat or mass transfer problems in engineering. Figure 5*d* shows an example of the FE analysis of the uniaxial compaction of a flat faced cylindrical tablet used in the pharmaceutical industry, which is described in more detail in the following section. Although it is not our intention to discuss FEM at any great length here, we will mention briefly that much effort has been devoted to devising coupling or parameterisation schemes to link atomistic or discrete element simulations with FEM via constitutive relationships.[51,152–154] This is motivated by the desire to reduce the number of degrees of freedom of the full discrete particle model to a set of fields carried by nodes of the FE mesh. However, this is an intrinsically difficult problem in principle due to the fact that there is no systematic mapping from the fundamentally 'correct' discrete particle description to the nodal fields. Therefore, if one is not careful, spurious forces or displacements can be introduced when traversing from one model to the other. It would be much better if degrees of freedom could be added or removed seamlessly, leaving the overall behaviour of the system

unchanged. One method by which this can be achieved is the quasi-continuum method,[155–157] which is based on the ideas of renormalisation group theory in that the Hamiltonian of the system retains a constant form over all scales.[3] This entails calculating the energy of each cell in the FE model from the underlying atomistic Hamiltonian, and allows seamless remeshing down to the atom (or particle) level without the introduction of artefacts. At present, the quasi-continuum method has been applied successfully to models of interface structure and deformation under conditions of zero temperature and static equilibrium.[158,159]

Selected applications of MMM

Having reviewed some of the main developments in techniques for MMM over the last decade, we now consider in more detail some specific case studies for particular material systems that make use of the methods described above. Although there is only space to discuss a selection of cases from the published literature, the aim is to highlight particular examples that have moved the field forward, and that may offer new ideas that could be applicable in the reader's own fields of expertise.

Diffusion and radiation damage in metals

The accelerated dynamics and hybrid methods described in the previous section provide a powerful method for probing long time scale processes, such as surface diffusion or bulk defect relaxation in crystalline metals following irradiation. Although a quantitatively correct prediction of diffusion rate or relaxation time is often the desired aim, even the qualitative features emerging from such simulations can be illuminating. This is because systems often behave in surprising ways, exhibiting transition pathways that are unexpected, as discussed by Uberuaga and Voter.[71] This occurs, for example, even for the extremely simple case of a Ag adatom on a Ag fcc(100) surface modelled using an embedded atom potential.[160] For this isolated adatom in a fourfold hollow, with four available ⟨011⟩ directions for hopping to an adjacent site, the exchange of adatom with a surface layer atom is substantially favoured over hopping. This exchange process is illustrated in Fig. 6, where the initial, transition and final configurations of the system containing adatom (shown in red) are shown. Although the net effect is equivalent to surface hopping,

the identity of adatom in Fig. 6*a* and *c* has changed and the activation barrier for surface exchange is lower than for straightforward hopping process. Indeed, it has since been found that such exchange events are dominant in providing a low energy pathway for surface smoothing, diffusion over step edges and surface mixing.[161] It follows that for an accurate description of long time scale diffusion behaviour, such exchange events must be included in KMC simulations. This demonstrates the importance of including unexpected rare events into a dynamical simulation, which until recently relied mainly on the physical intuition of the practitioners for their inclusion.

Another important metallurgical area where multiscale simulations are having a great impact is on the understanding of mechanisms of hardening and embrittlement in metals irradiated by neutrons or heavy ions in the nuclear industry.[31] Following collision with an energetic particle, the primary knock-on atom (PKA) generates a cascade of atomic displacements that results in single and clustered interstitial and vacancy defects (Frenkel pairs).[162] Although the time and length scales of the primary collision cascade process are within the range of conventional MD simulations, secondary processes such as multiple overlapping cascades and thermalisation of the energy released in primary cascade can lead to clustering and annihilation of defects. For example, Flewitt[5] modelled the number of Frenkel pairs forming during a sequential binary cascade as a function of separation of their centres of gravity at two different energies, 5 keV and 400 eV, corresponding to collisions with fast and thermal neutrons, respectively. It was found that pre-existing damage from low energy impacts generally assists the recombination of vacancies and interstitials, whereas, for a higher energy initial impact, the damage depends greatly on the degree of overlap. Gao *et al.*[163] modelled the effect of temperature on defect production in bcc iron using a hybrid MD model in which the irradiation temperature was controlled via a boundary layer of atoms enclosing the MD simulation. They found a small but statistically significant effect of irradiation temperature on the production of Frenkel pairs, with a reduction of between 20 and 30% for a temperature increase of 100 to 900 K. Since the mobility of clustered defects is relatively high in metals, then it may be possible to study the relaxation processes adequately with MD. However, in ceramic materials, the cluster mobilities are much lower, and this situation is discussed in more detail in the section on fracture behaviour of ceramics below.

### Mechanical properties of nanocrystalline metals and alloys

Nanocrystalline metals and alloys,[164] with mean grain sizes below 100 nm, are currently of great interest to materials scientists since they offer the potential to circumvent the compromises of mechanical properties normally found in traditional bulk systems, e.g. between hardness and toughness[165] or strength and ductility.[166] Kumar *et al.*[167] reviewed the mechanical properties of nanocrystalline metals and alloys, including computational results of studies on deformation, damage evolution, fracture and fatigue, and nucleation and kinetics of defects in response to mechanical loading. In particular, the use of large scale classical MD simulations has revealed detailed structural information concerning the deviation from the Hall–Petch strengthening relationship
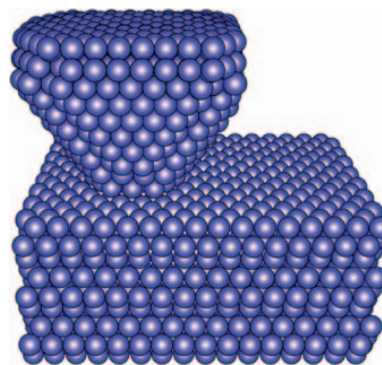
7 Atomistic configuration of a Cu/Cu interface mimicking the contact of an elastically compliant Cu(111) terminated friction force microscope tip with an infinite Cu(111) surface, as used in Ref. 172. During the simulation, the tip is dragged at constant velocity parallel to the surface (along $\langle \bar{1}01 \rangle$ direction) and the resulting friction force is recorded

at sub-100 nm grain sizes, and the nucleation of defects under nanoindentation at free surfaces. More recently, continuum modelling studies on nanotwinned copper carried out by Dao *et al.*[168] have shown why metals with nanoscale twins can provide the same level of yield strength, hardness and strain rate sensitivity as a nanostructured counterpart without twins (but with grain size similar to the twin spacing), and why nanotwinned Cu with high strength does not experience diminished ductility after microstructural size reduction, unlike in conventional nanocrystalline Cu after grain refinement. In order to circumvent the limitations of both large scale MD and continuum techniques used independently, Shilkrot *et al.*[169] have developed a two-dimensional coupled atomistic and discrete dislocation method, which is capable of supporting discrete dislocations in the continuum region and includes algorithms to automatically detect and convert dislocations between the two domains. Applications to nanoindentation, atomic scale void growth under tensile stress, and fracture were demonstrated, but extension of the model into three dimensions is complicated by the possibility of dislocation loops that span the atomistic/continuum interface.

Of prime importance in the design of nanomechanical devices is the control of the tribological behaviour of various nanoscale interfaces. Indeed, given their large surface to volume ratio, the performance of these devices is very sensitive to friction and wear. Simulation studies of interfaces sliding with respect to one another are, however, hampered by the low speeds (of order 10 nm s^{-1}) at which these experiments are typically conducted. Artificially raising the sliding speed into the MD accessible regime (of order 1 nm ns^{-1}) can introduce artefacts that obscure the relevant low speed physics and make extrapolation to experimental conditions extremely difficult. The accelerated dynamics techniques reviewed above show a promising route to overcome that difficulty, as illustrated by the grain boundary sliding simulations of Mishin *et al.*[170] and by the friction force microscopy simulations of Martini and Perez *et al.*[171,172] shown in Fig. 7. In both these cases, the extended timescales provided by the methods enabled velocities hundreds to thousands of times slower than standard MD which allowed the unambiguous
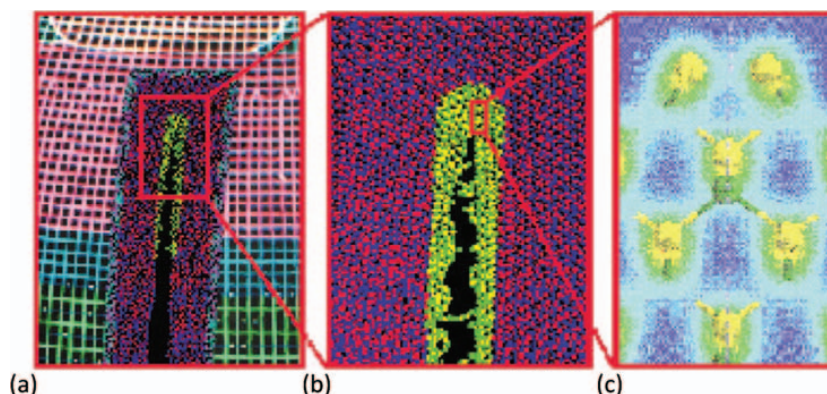
8 Illustration of a hybrid FE, MD, and QM simulation of fracture *a* system described by FEM outside region of crack tip, whereas in *b* the non-linear region near the crack is handled with the MD method, and *c* a QM approach is used around the crack tip region where bonds break or reform. Reproduced with permission from Fig. 20 in Ref. 174

identification of scaling relations obeyed by the interfacial stresses, and hence extrapolation to experimental conditions. These same tools are now being applied to model other mechanical deformation processes, such as plasticity in nanowires and void growth in bulk metals, and may soon yield new insights into the atomistic failure mechanisms in grain and twin boundaries in nanocrystalline metals and alloys.

Large scale fracture behaviour of ceramics

As part of an early review article on MMM, Rudd and Broughton[3] presented results from coarse grained MD and FE/MD/TB coupled length scale simulations on crack propagation in ceramic materials. As well as being of great practical relevance for the understanding of fast fracture in brittle materials,[173] the phenomenon of crack propagation is an excellent example of the need for multiscale simulations due to the strong coupling between different length scales. This is illustrated by Fig. 8, taken from a review by Rountree *et al.*[174] of the atomistic aspects of dynamic fracture in a variety of brittle crystalline, amorphous, nanophase and nanocomposite materials. Figure 8*a* shows the region surrounding the crack tip, where an FE model is used to deal with stress and strain fields for the majority of the sample where linear elasticity can be applied. Figure 8*b* shows the transition to the region where lattice distortions become large enough to require explicit calculation of atomic positions using MD, and Fig. 8*c* shows the fracture process zone, very close to the crack tip, where bonds are being broken and reformed by the passage of the crack. According to the Griffith criterion,[175] the critical stress for crack propagation is determined by the rate at which elastic strain energy is released relative to the consumption of energy required to create new surfaces in the fracture zone. Hence, in order to obtain a quantitatively correct description of this process, energy must flow seamlessly through the transition or 'handshaking' regions in the simulation, which relies on accurate coupling as discussed in methods section earlier. In a hybrid FE/MD/TB simulation (representing over 11 million atoms) of the brittle fracture of a slab of silicon containing a microcrack under uniaxial tension, Rudd and Broughton[3] reported no visible reflection of stress waves at the FE/MD or MD/TB interfaces, thus confirming that the coupling was seamless. Although it is not trivial to extend such methods to include bifurcation or multiple cracks, they show promise as an alternative means for large scale simulations of impact damage.[176] Rafii-Tabar and co-workers[93] have also pioneered a novel approach to crack propagation that couples the crack dynamics at the macro- and nanoscales via an intermediate mesoscale continuum, which allows stochastic diffusion of the crack tip.

Another example where MMM has been applied to ceramic materials is radiation damage in metal oxide materials for use as host materials for storing nuclear waste, which is related to the irradiation of metals previously discussed above. In this case, the objective was to study the evolution of damage profile using accelerated dynamics techniques to overcome the high barriers to reconstruction of the crystal lattice, which is a particular issue for ceramics where the mobility of defects is more limited. Uberuaga *et al.*[177,178] performed collision cascade simulations on pristine MgO (described by pair potential and long range Coulombic term) using MD over a picosecond time scale for several PKA energies, ranging from 400 eV to 5 keV, and then studied the subsequent evolution and mobility of clusters of interstitials with vacancies using TAD over a much longer time scale, up to several seconds. They showed that the number of Frenkel pairs increased with higher PKA energy immediately following the cascade, but the defects produced were dominated primarily by mono-interstitials and mono-vacancies. However, after several seconds had elapsed (up to 10^{12} times longer than the period of initial cascade), they found that the defects aggregated into larger clusters, some of which (six- and eight-atom interstitial clusters) were highly mobile. Using a chemical rate theory, they were able to predict an enhancement in the interstitial dislocation loop size, and hence concluded that such long time scale relaxations are important in understanding the effect of radiation damage on embrittlement in ceramics. A remaining difficulty is the incorporation of multiple cascade events within the long relaxation period, which could be achieved using the hybrid methods discussed earlier.

Macromolecular materials

One of the challenges of simulating polymeric systems is the very wide range of time scales between fast atomistic events, such as bond vibrations or rotations (0·1–10 ps), and slower meso- or macroscopic events, such as the relaxation of the main chain (>10 µs) or phase separation and crystallisation (>1 ms).[2,179,180] These

motions are normally tightly coupled, but since the focus of interest is usually on microstructural evolution, then a coarse grained simulation method, such as a lattice model or DPD discussed earlier, can be utilised as part of a hierarchical framework involving parameterisation by MM or QM simulations. As an example of this process, Elliott and Paddison[133] recently reviewed the application of MMM techniques to PFSA ion-containing polymers (ionomers) used as membrane separators in reduction–oxidation applications such as hydrogen fuel cells.[181] The function of the membrane is to prevent physical mixing of the electrolytes (e.g. oxygen and hydrogen gases) while allowing transport of protons between the electrodes. At the atomistic scale, proton conduction in the polymer first requires the transfer of protons from the sulphonic acid groups in the polymer to the aqueous phase, which has been studied in detail using DFT[182–184] and multiscale simulations.[185] However, effective proton transport also requires the existence of a connected network of sulphonic acid groups over a much larger scale and, although the precise details of the morphology remain controversial, there is a broad consensus that this is achieved by ion clustered domains with a characteristic spacing of 3–5 nm.[186] Despite strenuous efforts, reviewed elsewhere,[133] this is too large to simulate effectively using fully atomistic MD. However, Wu et al.[134,135] have recently carried out extensive DPD simulations (an example of which is shown in Fig. 5a) to investigate the dependence of PFSA morphology as a function of ion content, water content and chemical structure of the polymer phase. These have shown that the size and shape of ion clustered domains depend on the length of sulphonic acid side chain and molecular weight of the main chain, which can help to guide experimental research on new materials. It is hoped in future that such simulations will help lead to a full morphological characterisation of PFSA ionomers.

Polymer nanocomposites,[187,188] in particular those containing carbon nanotubes (CNTs),[189] also offer another promising application area for MMM.[190] In the early stages of CNT–polymer composite research, it was anticipated that the inclusion of CNTs into thermoplastic polymers would inevitably lead to enhancement of mechanical properties, such as tensile strength and stiffness, and electrical and thermal conductivity. Unfortunately, such hopes have as yet been only partially realised due to the complex relationship between filler–matrix interactions at the nanoscale and dispersion or orientation of CNTs at the macroscale.[191–193] An example is the electrical percolation of multiwall CNTs dispersed in an epoxy resin matrix, where the addition of as little as 0·01 wt-% CNTs has been found to produce bulk conductivities of up to 10^{-3} S m^{-1}.[194] However, the results depend strongly on process variables such as the stirring rate, resin temperature and curing temperature. Moreover, the critical percolation thresholds obtained by experiment do not agree with classical percolation theory for rigid rods based on an excluded volume approach,[195] which has been attributed to aggregation of the CNTs during processing. Motivated by these issues, Rahatekar et al.[196] carried out mesoscale simulations of electrical percolation in fibre filled systems using a DPD approach with a coarse grained representation of CNTs to generate large assemblies of rigid fibres with varying aspect ratio and degree of uniaxial alignment. Having established an equilibrium network structure, its electrical impedance was then determined using an MC method, and the results showed a good agreement with classical percolation theory when the fibres interacted only via excluded volume. The same approach was recently extended to model binary mixtures of fibres and spheres (as a model for mixed systems of CNTs and carbon black) and mixtures of short and long fibres,[197] showing that in the case of uniaxially oriented systems, the addition of small amounts of low aspect ratio filler helps to achieve a low critical percolation threshold. In future, such simulations can take into account van der Waals, Coulombic or other cohesive interactions, in combination with shear forces, to investigate the effects of fibre aggregation and de-aggregation on conductivity.

Another example of the use of coarse grained mesoscale modelling in CNT–polymer composites is in the prediction of mechanical properties. Since the Young's modulus of a defect free single wall CNT is more than two orders of magnitude higher than that of a typical thermoplastic polymer, it might be expected from the rule-of-mixtures that significant enhancement of the composite tensile modulus could be achieved by the addition of CNTs.[198] However, once again, the CNT–polymer interactions play a crucial role in determining the actual property enhancement observed by affecting polymer structure shear stress transfer at the interface.[190,192,193] In order to investigate this effect, Han and Elliott carried out MD simulations of a model composite system consisting of an isolated single wall CNT embedded in an amorphous polymer matrix.[199] As mentioned above, the relaxation time for large conformational changes in polymer melts can easily exceed the nanosecond MD time scale, and so the composite models were initially constructed at very low densities, before being slowly compressed to their true densities. By using this procedure, Han and Elliott were able to relax any residual stresses around the CNT inclusion and, from calculations of the low strain elastic properties for resulting composite, they found positive deviations from rule-of-mixtures behaviour for the tensile modulus parallel to tube axis as function of CNT volume fraction. This effect was attributed to local ordering of the polymer around the CNT, which gave rise to a higher effective modulus for the matrix. However, due to the procedure for constructing the models, the CNT volume fractions were restricted to being greater than 10%. In order to study lower CNT loadings, requiring larger amounts of polymer and even longer relaxation times, MMM must be used.[112] An example is shown in Fig. 9, using a lattice model to construct a relaxed coarse grained model which is then reverse mapped onto an atomistic structure from which elastic property calculations can be made. Figure 9a and b show the lattice and atomistic structures for an amorphous melt of 16 $C_{101}H_{204}$ chains (representing polyethylene) at 500 K, corresponding to a density of 0·73 g cm^{-3}. Using a similar method, Haire et al.[105] showed that the lattice model representation can reproduce the centre-of-mass diffusion coefficients observed experimentally and in MD, but with a factor of 10^4 increase in simulation time per unit of CPU time. Figure 9c shows the lattice model with a cylindrical inclusion at the
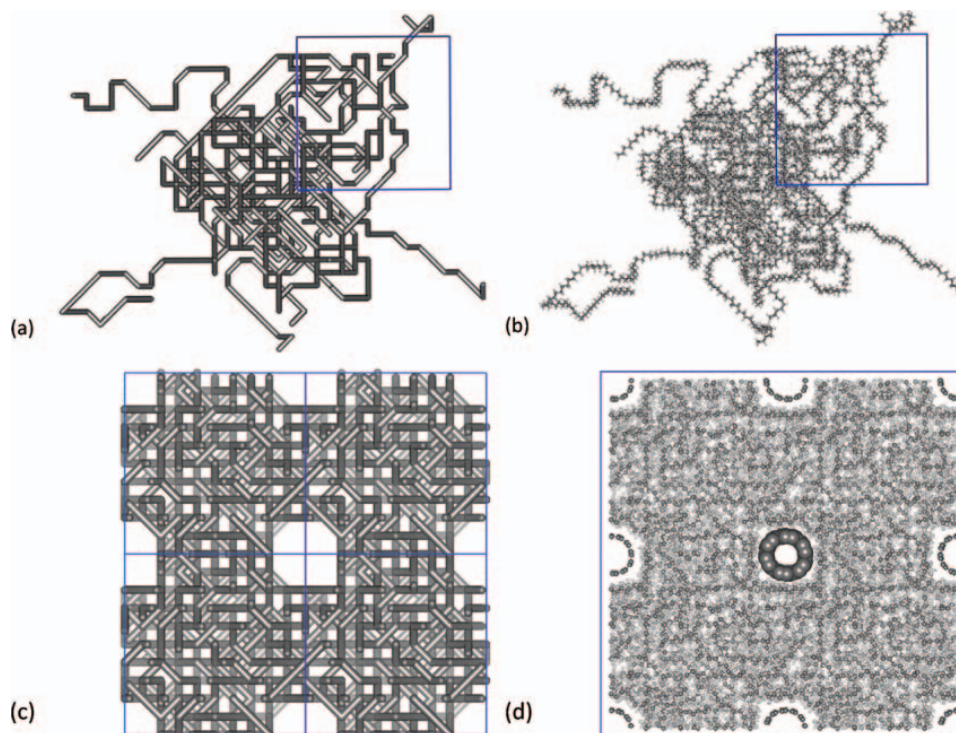
9 Lattice coarse graining of linear homopolymer: *a* 16 independent chains on fcc lattice (blue box indicates extent of periodic bounding box, polymer chains represented without imposition of boundary conditions for clarity), *b* corresponding reverse mapped atomistic structure for 'polyethylene' ($C_{101}H_{204}$), *c* lattice model with cylindrical inclusion, represented modulo cell (4 unit cells, with periodic boundaries indicated in blue) and *d* reverse mapped polyethylene–(6,6) CNT composite following 1 ns MD relaxation

origin, into which lattice segments are forbidden from entering. In Fig. 9*d*, following reverse mapping of the atomistic chains, a (6,6) single wall CNT has been inserted into the inclusion, and the whole structure relaxed by MD. Using this method, composite models with as low as 1 vol.-% CNT loading have been prepared, and the results support positive deviations from rule-of-mixtures found earlier by Han and Elliott.

Biomimetic materials

The final application area covered in this review is the use of MMM to understand how biological and synthetic materials can be fabricated systematically over a wide range of size scales, from the nano- to the macroscale, by adapting the principles found in naturally occurring systems for use in the field of nanotechnology.[200] This field was christened 'molecular tectonics' by Mann,[201] and is also known as 'molecular biomimetics'[202] due to the inspiration drawn from biological processes, such as biomineralisation, to produce complex, hierarchical structures, such as bone[203] or nacre,[204] using synthetic materials. Although there have been some attempts to describe structure–property relationships in such systems using hierarchical models,[205] recent attention has focused on the organic/inorganic interface as being of particular importance in controlling the nucleation, growth and assembly of biomineral nanoparticles in the early stages of fabrication. These efforts have been reviewed elsewhere,[206] but we focus here on a particular application of metadynamics by Freeman *et al.*[207] to study the role of the protein ovocleidin-17 on the crystallisation of calcium carbonate in eggshell formation. This particular challenge requires MMM, since the time scales of nucleation of the

inorganic phase far exceed that which can be simulated with standard MD. Previous simulation work has shown that, for small clusters at constant volume, amorphous calcium carbonate is energetically stable,[208,209] and becomes metastable with respect to calcite as the cluster grows in size. Freeman *et al.*[207] therefore performed simulations of amorphous calcium carbonate nanoparticles in aqueous solution together with an ovocleidin-17 molecule whose initial structure was determined from X-ray crystallography. At first, simulations were carried out with conventional MD in order to establish 'docked' configurations with low potential energy and high protein-nanoparticle contact area. Then, long metadynamics simulations were run, consuming over two million CPU hours in total, during which 8 to 12 spontaneous crystallisation or re-amorphisation events were observed.

Figure 10 shows projections of the free energy hypersurface for a nanoparticle containing 192 units of $CaCO_3$ in aqueous solution, both in isolation (Fig. 10*a*) and in the presence of ovocleidin-17 (Fig. 10*b*). The axes denote order parameters relating to the arrangement of carbon or oxygen atoms around the calcium ions,[209] and distinguish between amorphous calcium carbonate and two of its crystalline polymorphs: calcite and vaterite.[210] Although Fig. 10*a* shows that, even in the absence of the protein, the most stable structure for the nanoparticle is calcite, there is a large free energy barrier (~ 350 kJ mol^{-1}) which means that the amorphous state will persist for a long time. However, in the presence of ovocleidin-17, Fig. 10*b* shows that the free energy barrier and intervening minimum (similar to vaterite structure) are absent, resulting in rapid transformation to the calcite structure and providing strong evidence to
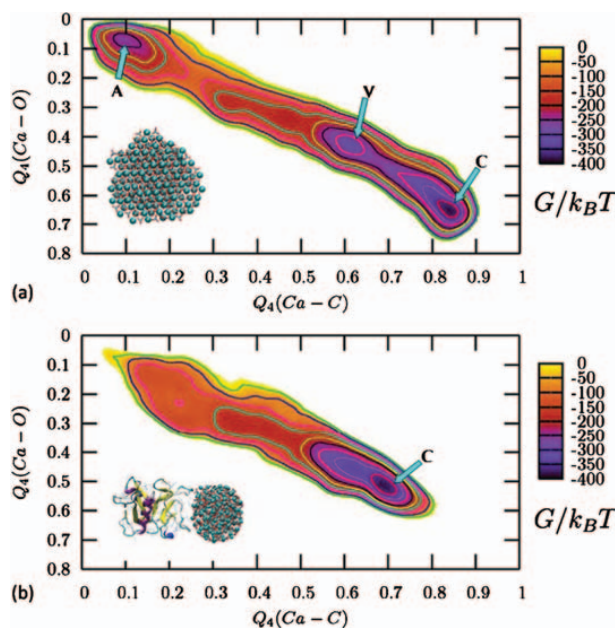
10 Two-dimensional projection of free energy hypersurfaces for 192 CaCO₃ nanoparticle determined by metadynamics simulations for *a* isolated particle in aqueous solution and *b* particle bound to ovocleidin-17 protein. Insets show snapshots of typical configurations in each case, and annotations correspond to the stability regions for amorphous (A) calcium carbonate, calcite (C) and vaterite (V). Reproduced with permission from Fig. S2 in Ref. 207

support the important role of protein action in eggshell formation. Although these simulations required massive computational resources, and focused on just a single protein taking part in one of many different biomineralisation processes, they nevertheless point to the fact that it is becoming increasingly possible to determine mechanisms of biomimetic control in molecular detail. It is hoped that in future the understanding gained from studying biomimetic systems can be transferred to the control of crystallisation in other areas, such as of inorganic crystals by self-assembled monolayers,[211,212] or the structural prediction of organic crystals for pharmaceutical applications.[213]

Conclusions

The objective of this review has been to summarise recent innovations in the area of MMM in the last decade, illustrated by selected case studies from the literature covering a wide range of materials systems, from metals and ceramics through to polymer and biomimetic systems. In this way, it has been demonstrated that that MMM is now very widely used in the materials science community, not just by specialists, and is capable of tackling much more than just small 'model' systems with no practical relevance. Previous investment in research initiatives, scientific training and development of computer codes is paying high dividends in terms of the value that modelling can now deliver to materials science. For example, the simulation of crystal nucleation via the use of accelerated dynamics techniques that allow fast barrier crossing is allowing more stringent tests of classical theories of nucleation and growth, possibly leading in future to new avenues for the

self-assembly of synthetic hierarchical materials that rival the complexity of bone. Powerful statistical sampling techniques, such as the multicanonical and Wang–Landau methods, now offer a route to simulate the phase behaviour of even relatively large systems and, in combination with coarse graining methods for polymers and solvents, can allow rapid 'electronic prototyping' of the putative performance of novel materials.

Although the simulation of macroscopic scale systems is still a grand challenge, requiring significant input of resources and a skilled set of practitioners, applications such as modelling the large scale fracture and long-time evolution of radiation damage in ceramics now show that it can be done with sufficient effort. Furthermore, given that only 50 years ago the MD of just a few hundred hard spheres was considered to be state of the art,[214] history suggests that such simulations may soon become routine. Indeed, if the current state of technological progress in digital computing continues, it is not beyond the bounds of possibility that, in the next 50 years, it could actually become quicker to carry out an atomically detailed simulation than an equivalent physical experiment. However, it would be well not to get carried away with such a digital fantasy, since the aim of computational modelling is not to replicate reality but to help understand it. The greatest benefit, and at the same time ultimate bane, of MMM will always be the total control that the practitioner exerts over the system under study. By creating their very own model universe, the computational materials scientist is no longer subject to the restrictions imposed by experimental methods; however, without incorporation of all the relevant physical mechanisms, any results generated will ultimately be meaningless.

In conclusion, it is possible to tentatively identify what might be the most fertile areas for the development of MMM over the next decade. In the author's opinion, the development of a general framework for transforming seamlessly from particle based to continuum based representations of materials will enable large scale simulations of failure in granular and monolithic systems to become almost routine. On-the-fly coarse graining will permit use of explicit solvent in the vicinity of solute molecules or particles, whilst still allowing the interaction of many thousands or even millions of them, facilitating the study of self-assembly in nanocomposite or biomimetic systems. Furthermore, the inclusion of unexpected rare events into dynamical simulations will yield new insights into atomistic failure mechanisms in nanocrystalline materials, and open up the possibility of studying very long time scale relaxations in systems containing full molecular detail. However, these developments must be tempered by the need to advance hand in hand with theoretical and experimental science, and thus the most likely scenario for the development of MMM in the near future is its continued incremental growth. The author hopes that this review, and the work described herein, may inspire the reader to consider how their own area of expertise may benefit from the application of such modelling techniques.

Acknowledgements

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