

The challenge of biominerals to simulations

J. H. Harding*^a and D. M. Duffy^b

Received 16th August 2005, Accepted 24th October 2005

First published as an Advance Article on the web 14th November 2005

DOI: 10.1039/b511650c

Biomaterials are hierarchical systems whose structure and properties represent a major challenge to simulation. We briefly discuss the remarkable experimental data now available both on the structure, formation and properties of biominerals. In the light of this we discuss current attempts to simulate biomaterials at atomic and meso length scales and timescales and the range of physical effects that are important in producing biomaterials. We emphasise the importance of obtaining robust forcefields for these systems and the sensitivity of simulations to the forcefields used. We conclude by suggesting future directions for the field and remaining problems to be solved.

Introduction

Biominerals and the process of biomineralization present a major challenge to simulation. This is because they are often hierarchical materials; with significant behaviour on many length scales and timescales. For example, the structure of bone can be considered on a hierarchy of at least seven separate scales¹ and thus calls on theories ranging from quantum mechanics and atomistic simulation to continuum mechanics and theories of composites² depending on the scale that one is working at. There are equally formidable problems of timescale. Organic arrays and scaffolds can control the shape and orientation of minerals that grow on them.³ If this involves a nucleation process, the timescale may be of the order of seconds or more. Moreover, the growth of biominerals is often a multi-stage process,⁴ and involves the self-assembly of complex nanoscale units. Faced with this, traditional molecular dynamics simulations can only be run for nanoseconds, perhaps approaching microseconds in some

favourable cases. New methods to speed up such simulations, usually given the collective label of hyperdynamics,⁵ can significantly increase the simulation timescale. However, the most effective of these, temperature-accelerated dynamics, requires high-temperature simulations, which may not be practical for these systems. The technique most likely to be applicable here, parallel replica dynamics, scales linearly with the number of processors available. This gives a useful boost to the simulation speed, but not the factors required to solve the timescale problems in biomineralization. This impasse suggests that the simulators of biominerals should turn to coarse-grained or other mesoscale methods. These must be parametrised; either in terms of the atomistic-scale processes they are supposed to represent⁶ or by the judicious use of experimental data.⁷ The prize for success is very great; if we could understand *how* these self-assembly processes work, it would open new vistas for nanotechnology; we could make nanostructures make themselves rather than having to assemble them piece by piece. One final problem is that biominerals are (literally) at the interface of two different simulation communities. Much work has been published on traditional “hard materials” (such as ceramics, metals and glasses) and “soft materials” have also received much attention, particularly in recent years. However, the two subjects are rarely discussed together. Thus the recent review

^aDepartment of Engineering Materials, University of Sheffield, Mappin St, Sheffield, UK S1 3JD. E-mail: j.harding@sheffield.ac.uk; Fax: 0114 222 5943; Tel: 0114 222 5957

^bDepartment of Physics and Astronomy, University College London, Gower St, London, UK WC1E 6BT. E-mail: d.duffy@ucl.ac.uk; Fax: 020 7679 1360; Tel: 020 7679 7850



John Harding

John Harding is Professor of Materials Simulation at Sheffield and Visiting Professor of Physics at University College London. His main research interests are the simulation of the behaviour of complex materials and interfaces, particularly those involving ceramics and minerals. He is also involved in developing methods for long timescale simulations.



Dorothy Duffy

Dorothy Duffy is a lecturer at University College London. Her main research interests are the simulation of organic inorganic interfaces and radiation damage of materials for fusion power-plants.

of Redondo and LeSar,⁸ which gives a thorough discussion of computational methods used in biomaterials, is clearly intended for simulators of “soft materials” and only briefly mentions hard biomaterials and biominerals. Rather more work has been done on the specific problem of the interaction of organic molecules and biomolecules with substrates.⁹ This is a convenient place to begin since it focuses attention on the atomistic scale. We shall then consider the more complex case of attempting to nucleate minerals on organic arrays and scaffolds before moving on to consider self-assembly and the simulation of biominerals at the larger scale.

Organic molecules on mineral surfaces

The simulation of organic molecules on minerals arises in two contexts. First, there is the issue of how the presence of a substrate affects the conformation and properties of biomolecules. This leads to discussion of the bio-reactivity of surfaces and ultimately to the design of bio-sensors.¹⁰ Second, there is the question of how the presence of organic molecules can control surface features of minerals such as edges and steps.¹¹ This is a basic process in growth inhibition.¹² In both cases, there is almost always the problem of water to consider.¹³ A common approach is to use an implicit solvent model, using dielectric and/or implicit area models to mimic the effects of the solvent.¹⁴ This gives a great saving in computational effort, but necessarily ignores detailed structural changes at an interface. In addition to the obvious point that the absorption of ions or molecules implies the displacement of individual water molecules, the modifications of water structure induced by a mineral surface change the local water properties and hence control the absorption behaviour of ions and molecules.^{15–17}

Much work has been done on the absorption of organic molecules on graphite, from simple oligomers¹⁸ through molecular arrays¹⁹ to sizeable biomolecules.²⁰ Ref. 20 shows how even a simple model of water is enough (and essential) to obtain the conformations of the organic molecules, although a detailed understanding of the hydration requires explicit water simulations. There is also considerable experimental interest in large organic molecules on metals,²¹ particularly on the properties of “Lander” molecules.²² There is a significant amount of work on the properties of self-assembled monolayers of organic thiols on metals like copper, silver and gold. Here the ordering is often simplified by the strong bonding between the sulfur of the thiol and the metallic surface.^{23–25} However almost all the simulations (and indeed the experiments) have been performed on systems *in vacuo* and are thus of limited relevance to simulations of biomaterials. Detailed experimental data are sometimes available on the conformation and dynamics of large molecules on minerals (for example statherin on hydroxyapatite²⁶). Some calculations have been reported on the interaction of organic molecules with ceramics. However, before we discuss these simulations in detail we need to address the issue of obtaining a suitable forcefield.

Forcefield models for the organic/inorganic interface

If the molecules are reasonably small, it is possible to calculate the absorption behaviour using *ab initio* methods. This

approach has been adopted by de Leeuw and coworkers for molecules on minerals^{27–29} and studies of molecules such as glycine and cysteine on titania.³⁰ Such calculations can give the relative absorption of molecules (with respect to water)²⁷ and configurations of the absorbed species. For larger molecules it is necessary to resort to constructing forcefields. As with all atomistic modelling, reliable interatomic potentials are essential if reliable estimates for interfacial energies are to be obtained, and the difficulties in obtaining and validating such models should not be underestimated. It is particularly risky to use “black-box” solutions and simple approximations when attempting to simulate complex interfaces. Carefully derived and tested interatomic potentials exist for many minerals³¹ and there are a number of well-established potential sets for organic molecules.^{32,33} However the situation is not as simple for the interactions between the mineral and the organic substrate. A natural approach is to attempt to extend (or even simply apply) the standard forcefields used in organic systems such as CHARMM³² or CVFF³³ using the Lorentz–Berthelot mixing rules as necessary to supply any missing interactions. Despite its appeal, this strategy does not work. The two studies that have investigated the matter in detail^{34,35} have both concluded that this procedure seriously overestimates the binding at the interface. An alternative approach, employed by de Leeuw and coworkers,³⁶ is to use Schroder³⁷ type mixing rules, which were originally derived for zeolite potentials. This method seems to eliminate some of the problems associated with the Lorentz–Berthelot procedure and, when calibrated against *ab initio* calculations, gives reasonable results for interfacial energies. An example of the differences involved is shown in Table 1. The current situation is that, as there is no well-tested potential set for organic/inorganic interfaces, each system should be validated carefully, by comparison with an appropriate set of *ab initio* (which is not necessarily density functional) calculations, before adsorption or interfacial simulations can be considered reliable.

Previous simulations on molecule–surface interactions

Experimental data that can be used to validate simulations of the growth and dissolution of calcite have been given by Teng *et al.*¹¹ These authors also show the drastic reorganisation of the growth steps close to a screw dislocation that can be induced by organic peptides. The presence of organic residues of this kind may not be obvious. The work of Stipp³⁸ shows that the presence of organics in almost undetectable amounts can control the surface properties of calcite.

Table 1 The interaction energy between an HCOOH molecule and a CaCO₃ cluster calculated using Hartree–Fock and with DL_POLY using the Lorentz–Berthelot rules and Schroder mixing rules

	Hartree–Fock	Lorentz–Berthelot	Schroder
Interaction energy/kJ mol ⁻¹	112.7	146.9	114.4
Distance (O in carbonate from H in carboxyl group)/Å	1.66	1.58	1.63
Distance (Ca to O in carboxyl group)/Å	2.44	2.17	2.27

A considerable amount of work has been done on X-ray studies and molecular dynamics simulations using the simple Dreiding forcefield have been used to investigate calcite inhibition by large molecules.³⁹ The results are interesting, suggesting that the flexibility of the protein is an important contributor to its ability to block a step. However the simplicity of the forcefield used, the inadequacy of the tests employed⁴⁰ and the absence of water from the simulation greatly limits the reliability of the results obtained. Similar problems, together with the neglect of the relaxation of the mineral surface, reduce the usefulness of three other studies of macromolecules on apatites.^{41–44} Calculations that attempt to model a surface using a cluster are also of little value.⁴⁵ The studies^{46–48} of the orientation of macromolecules on inorganic surfaces, although plausible for ice, suffer from the same problem with potentials when the methods are used for calcite.

There is a need for further work in this area, using properly validated potential forcefields to understand the related problems of how a surface can control the properties of an absorbed molecule by affecting its conformation and how molecules can control the morphology of surfaces by blocking kinks, pinning steps and so on. Monte Carlo procedures have demonstrated step blocking by impurities⁴⁹ and blocking of step growth on different faces is likely to play a crucial role in shaping bio-crystals. This has not yet been explored in detail but a combination of molecular dynamics simulations, to determine step/molecule interactions, and Monte Carlo growth models could help to establish the conditions necessary to shape growing crystals.

Controlling morphology: templates and scaffolds

The control of crystallisation by biological processes can be considered as the combination of two distinct components, the control of nucleation and the control of growth.⁵⁰ A striking example showing both kinds of control is the plates that make up the coccoliths grown by certain plankton.⁵¹ Here the control of the orientation of the basal plate is presumably due to nucleation, but the complex resulting shape must be due to subsequent control by organic molecules acting on the growing crystal. In this case polysaccharides appear to play a crucial role as they have been observed attaching preferentially to surface steps of calcite.⁵²

One of the remarkable characteristics of many biominerals is the precise control of the crystallographic orientation, with the implication that the organic layer or scaffold strongly favours the production of a specific crystal face on the mineral side. The usual explanation for this control is templating, where the spacing and orientation of the functional groups of the substrate somehow “match” the structure of the selected crystal face.⁵³ Experiments performed on growing crystals using either Langmuir monolayers^{54–56} or self-assembled monolayers^{57–59} have used this mechanism to guide the work. However some experiments do not support these ideas.⁶⁰

The templating explanation implicitly assumes that the control of orientation is due to the lowering of the energy of a specific organic/mineral interface. The obvious context whereby this could control subsequent mineral growth is classical nucleation theory. We shall discuss this later, but it is

important to note at the start that this is not the only possibility. If an amorphous phase were formed in the solution which subsequently crystallised at the surface, this would still result in morphology control by templating although there need be no clearly defined work of nucleation. We therefore begin by considering how such interfacial energies should be calculated. Modelling interfaces between organic molecules and inorganic crystals is not without its challenge and some of the issues that require careful consideration are outlined below.

1. Definition of the reference state

Perhaps the most fundamental question to be addressed when calculating interfacial energies is the identification of the reference state, that is the atomic configuration that is considered to have zero energy. The interfacial energy between two bulk materials (A and B) is straightforward, the reference (zero energy) state is two blocks of pure material (AA and BB) and the final state is two mixed blocks (AB and BA, Fig. 1a). The interfacial energy is calculated from the difference between the energies of the final state and the reference state. In the case of an interface between a mineral surface and an organic substrate, initially covered by water, there is no bulk phase associated with the substrate. The reference state can be defined as a block of mineral and an organic substrate in contact with a half block of water. The final state is the organic substrate in contact with a half crystal block plus a block of water (Fig. 1b). From these quantities it is possible to obtain the adhesion energy, β , which is needed for classical nucleation theories. (This quantity can also be obtained by a pair of calculations (Fig. 1c)). Extra care must be taken for polar crystal directions, where charged crystal surfaces form interfaces with ionised organic substrates. In this case the negative charge of organic substrate in the reference state must be

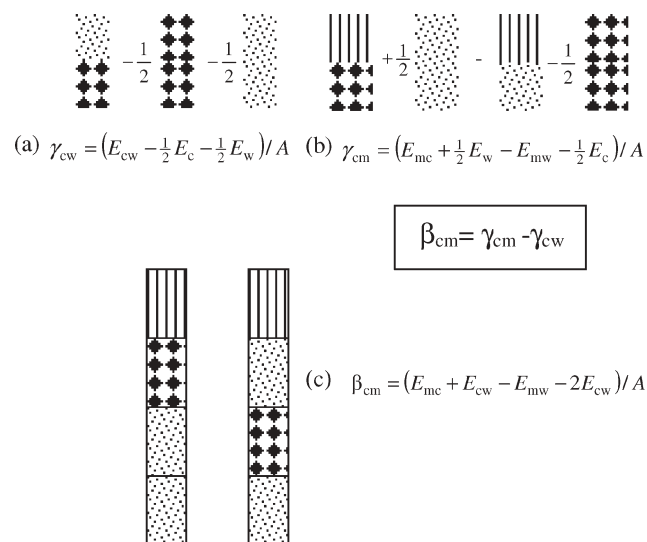


Fig. 1 Schematic representation of (a) the crystal/water interfacial energy, (b) the crystal/monolayer interfacial energy and (c) the adhesion energy calculations. The chequerboard pattern represents a crystal block, the lines represent the monolayer and the dots represent a water block.³⁴

compensated by an appropriate density of mineral cations and the crystal blocks must be terminated by a reduced charge layer, in order to cancel the dipole induced by the alternating charge layers.

Almost all the simulations carried out to date on organic/mineral interfaces have calculated the energy component of the free energy and neglected the entropy term. Entropy is notoriously difficult to calculate and usually involves a large number of simulations as the system is gradually changed from a reference state to the final state. However Kerisit *et al.*¹⁵ have demonstrated that the strong ordering of water molecules close to a mineral surface makes a significant contribution to the mineral/water interfacial free energy. It is evident, therefore, that accurate comparison with experiment will only be possible for simulations in which a realistic estimate of the entropy is included in the free energy calculation.

2. Lattice mismatch

Another issue to be addressed when modelling organic/inorganic interfaces is that of lattice mismatch. This arises from the periodic boundary conditions generally employed in simulations in order to extend the effective size of the model systems. The two-dimensional periodicity of the substrate and the periodicity of the mineral surface must both be commensurate with the periodicity of the simulation cell. A small amount of lattice misfit can be accommodated by introducing misfit dislocations, arrays of lines at the interface where there is strong distortion from the ideal interfacial structure. However an additional complication arises for interfaces involving polar directions. In this case, not only does the structural mismatch have to be accommodated, but the conditions of charge neutrality and zero dipole moment must be satisfied. This requires either a modification of the charge density, hence the atomic density, of the mineral surface or the modification of the charge density of the organic substrate. The organic monolayer of the self-assembled monolayer/(01 $\bar{1}$ 2) calcite interface has a lower charge density than the inorganic crystal surface. This mismatch can be accommodated either by reducing the atomic density of the crystal surface⁶¹ or by introducing negatively charged (bicarbonate) ions into the organic monolayer.⁶²

3. Electrostatics

Some of the issues with electrostatics (involving polar crystal directions) have already been considered, however, other effects, such as the pH of the solution and mineral surface charge, require comment. Crystal nucleation is known to be strongly pH dependent, an effect which can largely be attributed to the variation in the degree of ionisation of the organic functional groups. The surface charge is determined both by the local equilibria at the surface (controlled by the binding constants of protons and ions to the monolayer) and by the Gouy–Chapman–Stern solutions for the double layer. These calculations⁶³ have demonstrated that, above a particular pH, doubly charged cations form a condensed layer on the monolayer and this could form the basis for crystal nucleation. This approach gives good agreement with experiment results obtained from weighing the amount of ion that

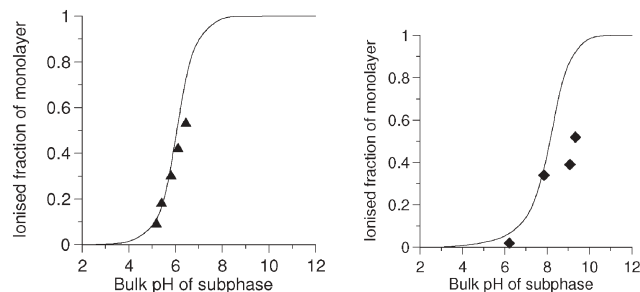


Fig. 2 Dependence of the ionised fraction of molecules on subphase pH for Ca^{2+} (left) and Na^{+} (right). Symbols are the experimental points,⁵⁵ lines are the calculation

binds to the film as a function of subphase pH⁶⁴ and also with the direct measurement of the fraction of ionised carboxylate in the monolayer using infra-red⁶⁵ (see Fig. 2; $\text{p}K_{\text{a}}$ values obtained from ref. 66, adjusted for high concentrations). When these methods are applied to carbonate solutions, it is also necessary to take the speciation of the solution into account. The data required for the solution equilibria are given in ref. 67. Most experimental protocols assume that the solution is saturated with CO_2 . The shape of the curve is similar to the left-hand curve in Fig. 2; the point where the sigmoid behaviour occurs varies from solution to solution, but is usually controlled by the $\text{p}K_{\text{a}}$ values.

Nucleation and nucleation theory

Modelling nucleation processes at an atomistic level is only possible for simple systems^{68,69} because of the strong mismatch between timescales attainable in simulations (a few nanoseconds) and nucleation timescales (seconds to days). Crystal nucleation from undercooled liquid water⁷⁰ and Si⁷¹ has been observed in simulations but such simulations tend to be prohibitively expensive. The method devised by ten Wolde and Frenkel⁷² allows nucleation from moderately undersaturated solution but it is difficult to apply to general systems. Some information about preferred nucleation directions can be obtained by modelling interfaces between organic substrates and mineral surfaces. Classical nucleation theory predicts that the volume of the critical nucleus, and hence the nucleation barrier, is reduced at a surface, k , by factor which depends on the ratio of the adhesion energy, β_{ks} to the surface energy, γ_{k} ⁷³ (for a definition of the adhesion energy see Fig. 1)

$$\frac{\Delta V_{\text{s}}}{\Delta V} = \frac{\Delta G_{\text{s}}^*}{\Delta G^*} = 1 + \frac{\beta_{\text{ks}}}{2\gamma_{\text{k}}} \quad (1)$$

where $(\Delta V_{\text{s}} / \Delta V)$ is the ratio of the volume of a critical nucleus at the interface to that in free space and $(\Delta G_{\text{s}}^* / \Delta G^*)$ is the ratio for the nucleation barrier.

An alternative approach, due to Liu and Lim,⁷⁴ gives a different expression since it assumes a different shape for the critical nucleus, but agrees that the important physical quantity is $\beta_{\text{ks}}/\gamma_{\text{k}}$. Therefore, crystallographic directions with low interfacial energies should have low nucleation barriers and growing crystals should be oriented along them.

This argument assumes the validity of classical nucleation theory. Despite its well-known shortcomings (particularly for

low contact angles and large undercoolings), the approach is still the basic framework for thinking about nucleation issues,⁷⁵ although a number of other models are now available that show considerable promise.⁷⁶ We shall discuss later some trial simulations that consider the case where the mechanism is not nucleation at the interface and subsequent growth.

Crystal growth simulations

Living organisms not only control crystal nucleation but they can also, in some cases, control the shape of growing crystals with remarkable precision. We must therefore put together the ideas of the two major preceding sections; organic molecules can control not only the basic orientation of a crystal, but also the specific shape (and it need not be the same molecules that do each part).

The growth of real biominerals has not, to our knowledge, been modelled but experimental systems, where mineral crystals are nucleated on Langmuir monolayers or self-assembled monolayers (SAMs), have been studied using simulation techniques. Interfaces between a range of faces of calcite crystals and Langmuir monolayers with carboxylic acid headgroups were modelled and it was found that the degree of ionisation of the head groups strongly influenced the favoured nucleation face.⁷⁷ Experiments in which calcite crystals were nucleated from a supersaturated solution on top of alkylthiols with carboxylic acid head groups, self-assembled on gold substrates, found a strong tendency to nucleate on the (01 $\bar{1}$ 2) calcite face.⁷⁸ They also noted an “odd-even” effect, where selective orientation was found for thiols with an even number of carbon atoms but random nucleation⁷⁹ or nucleation on a different face⁸⁰ was found on thiols with odd numbers of carbon atoms.

Simulations of interfaces between SAMs and calcite surfaces suggest that the (0001) face should be preferentially nucleated as this face is strongly commensurate with the substrate. The (01 $\bar{1}$ 2) face exhibits a strong lattice mismatch in one direction, which must be accommodated by charged defects. When these defects take the form of missing ions the resulting structure has a high interfacial energy.⁶¹ However it has recently been demonstrated that bicarbonate ions absorbed into the plane of the monolayer head groups can also provide the extra charge required to neutralise the charge and cancel the dipole moment.⁶² The resulting structure is strongly ordered and has a low interfacial energy, marginally lower than the (0001) interfacial energy. The structure of such an interface is shown in Fig. 3. Calcite crystals are normally grown in a supersaturated solution of bicarbonate ions therefore this model gives a very plausible explanation for the growth of (01 $\bar{1}$ 2) orientated crystals on SAMs. The simulations have demonstrated that simple templating arguments are not sufficient, as these would favour (0001) crystal nucleation. Additional effects, such as ion concentration, must be taken into account.

Direct simulations of calcite crystal growth on fixed SAMs have demonstrated that, in the absence of an aqueous environment with charged ions, templating arguments do select the correct nucleation face.⁸¹ In this case the (0001) face nucleates, as a simple templating would favour since it is an excellent epitaxial match (see Fig. 4). The direct simulations

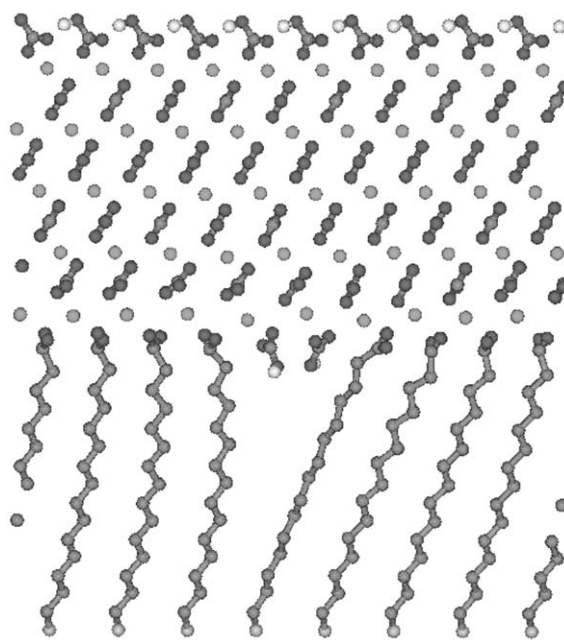


Fig. 3 Interface between the (01 $\bar{1}$ 2) face of calcite and a SAM. The lattice mismatch is accommodated by rows of bicarbonate ions⁷⁸

also show a limited odd/even effect as the order parameter increases more rapidly for growth on the even monolayer (Fig. 5a) than on the odd monolayer (Fig. 5b).

Mesoscale modelling of biominerals

Control of crystal morphology does not occur only at the atomic scale. The brief review of Adair and Suvaci⁸² discusses the effects of flow rate of the solution, shear rate, and ageing time as well as solution chemistry. Simple confinement can produce particular shapes as shown in a long series of papers by Meldrum⁸³ and coworkers. The experimental position for self-assembly on the nanoscale is discussed in detail by Colfen and Mann.⁸⁴

Most atomistic and mesoscale simulations of self-assembly are directed towards soft materials. Reviews of mesoscale methods and their relation to atomistic simulations (the problem of coarse graining) can be found in ref. 6,85.

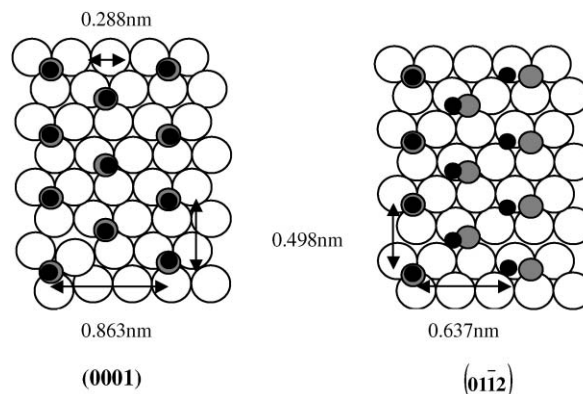


Fig. 4 Lattice mismatch for the (0001) and (01 $\bar{1}$ 2) directions (after ref. 79)

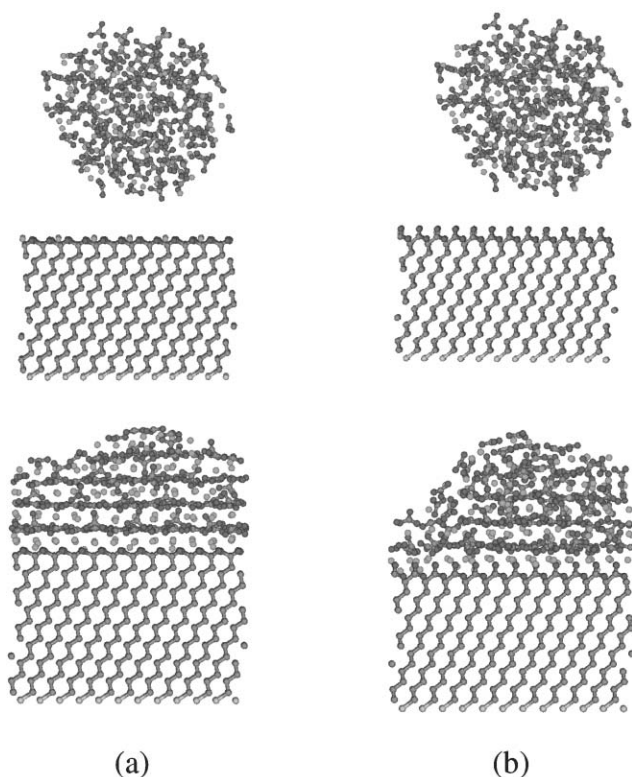


Fig. 5 Initial and final configurations for simulations of the crystallisation of amorphous calcite clusters on (a) an even SAM and (b) an odd SAM⁸¹

However some work on surfactants, particularly work on detergent particles, is relevant here. Tobias and Klein,⁸⁶ and later Beardsell and coworkers,^{87,88} have discussed the structures that consist of calcite nanoparticles (either crystals or amorphous) surrounded by organic surfactant molecules. Including water in the simulation is essential if the correct structure of the surfactant sheath is to be obtained. The later work⁸⁷ discusses the overall shape of the molecules and its dependence on the presence of co-surfactants. The interest here is that these structures are similar to the building blocks of the self-assembled materials reviewed by Colfen and Mann.⁸⁴

The recent work of Glotzer's group⁸⁹⁻⁹¹ which uses lattice Monte Carlo to study the self-aggregation of nanoparticles joined by biological linkers, is closer to the problem of the formation of biominerals in that we not only have the crucial combination of hard and soft material in a single system, but also self-assembly. However, the organic component only links existing nanoparticles, it does not control their growth. Nevertheless, the demonstration of the importance of nanoparticle shape and the location of the organic links on the nanoparticles⁸⁹ together with the effects of the length of the links^{90,91} are of considerable interest for our problem. It is clear that the manner and organisation of the self-assembly can be related to basic geometrical and topological properties of the nanoparticles. Work on the interaction of polymer chains with hard spheres⁹² is also likely to be relevant here. Recent work using reduced models of self-assembly dynamics⁹³ may also be helpful in mapping out the kinds of behaviour that might be expected. At a pictorial level, the kind

of mechanism is agreed; the hard particles are the basic structural elements and the soft matter glues them together. This remark, however, cannot be dignified with the term "explanation". We need detailed simulations to make sense of the considerable amount of existing experimental data, and suggest new directions for research. Once again, the problem is that while there is much work on self-assembly of soft materials, and also a fair amount on the interaction of hard particles (for example rods and spheres⁹⁴ and the increasing amount of interest in granular dynamics⁹⁵), there is little work yet on dynamical, self-assembling systems where both soft and hard particles are present. A recent example of simulating nanocomposites of this kind can be found in ref. 96 (and an alternative approach using continuum composite theory in ref. 97). The application of these methods is another review in itself. An introduction to the issues can be found in ref. 1 and an example of the application to bone in ref. 98.

Conclusions

Biominerals and biomineralization are areas where much remains to be started, let alone completed. Most progress has probably been at the level of atomistic simulation and we have concentrated on that work here. However, all too often the work is not as useful as it might be because insufficient attention has been paid to the problem of obtaining robust, reliable interatomic potentials. At this scale, simulations have suggested many effects that are important in the control of growth of these systems in addition to geometrical templating. There remains a daunting variety of types of system to be tackled. For example, the experimental evidence that complex molecules can control growth by electrostatic effects,^{99,100} However, most progress is needed at the mesoscale and the development of coarse-graining techniques to link the atomic and mesoscales (and also the mesoscale and continuum). Here the reviews of Mann⁸⁴ and Meldrum¹⁰¹ (to name but two) set an agenda that will keep simulators busy for a long time. It may be, as Stoneham suggests,¹⁰² that what is really needed is simple models that capture the essence of what is going on. If so, they will at some stage require more detailed simulations to back up their claims.

Acknowledgements

JHH and DMD acknowledge funding from EPSRC under grants GR/R25484 and GR/S80103. Some of the calculations were performed on the HPCx machine as part of the Materials Chemistry Consortium (headed by Prof. Richard Catlow) and on the Mott machine funded under the JREI initiative.

References

- 1 S. Wiener and H. D. Wagner, *Annu. Rev. Mater. Res.*, 1998, **28**, 271.
- 2 B. Ji and H. Gao, *J. Mech. Phys. Solids*, 2004, **52**, 1963.
- 3 S. Mann, *Biomineralization, Principles and Concepts in Bioinorganic Materials Chemistry*, Oxford, 2001.
- 4 S. Mann, S. A. Davis, S. R. Hall, M. Li, K. H. Rhodes, W. Shenton, S. Vaucher and B. Zhang, *J. Chem. Soc., Dalton Trans.*, 2000, 3753.
- 5 A. F. Voter, F. Montalenti and T. C. Germann, *Annu. Rev. Mater. Res.*, 2002, **32**, 321.

- 6 S. O. Nielsen, C. F. Lopez, G. Srinivas and M. L. Klein, *J. Phys.: Condens. Matter*, 2004, **16**, R481.
- 7 G. Srinivas, J. C. Shelley, S. O. Nielsen, D. E. Discher and M. L. Klein, *J. Phys. Chem. B*, 2004, **108**, 8153.
- 8 A. Redondo and R. LeSar, *Annu. Rev. Mater. Res.*, 2004, **34**, 279.
- 9 R. A. Latour, *Curr. Opin. Solid State Mater. Sci.*, 1999, **4**, 413.
- 10 B. D. Ratner and H. Q. Shi, *Curr. Opin. Solid State Mater. Sci.*, 1999, **4**, 395.
- 11 R. K. Tang, M. Durragh, C. A. Orme, X. Y. Guan, J. R. Hoyer and G. H. Nancollas, *Angew. Chem., Int. Ed.*, 2005, **44**, 3698; C. A. Orme, A. Noy, A. Wierzbicki, M. T. McBride, M. Grantham, H. H. Teng, P. M. Dove and J. J. DeYoreo, *Nature*, 2001, **411**, 775.
- 12 M. M. Reyhani, A. Oliveira, G. M. Parkinson, F. Jones, A. L. Rohl and M. I. Ogden, *Int. J. Mod. Phys. B*, 2002, **16**, 25.
- 13 The literature of simulating water is too large even to summarise here; see: G. W. Robinson, S. B. Zhu, S. Singh and M. W. Evans, *Water in Biology, Chemistry and Physics*, World Scientific, Singapore, 1996; for a recent test of potentials, see: M. W. Mahoney and W. L. Jorgensen, *J. Chem. Phys.*, 2001, **114**, 363.
- 14 A brief review of the state of the art is given in M. Feig and C. L. Brooks, *Curr. Opin. Struct. Biol.*, 2004, **14**, 217.
- 15 S. Kerisit, D. J. Cooke, D. Spagnoli and S. C. Parker, *J. Mater. Chem.*, 2005, **15**, 1454.
- 16 S. Kerisit and S. C. Parker, *J. Am. Chem. Soc.*, 2004, **126**, 10152.
- 17 D. Zahn and O. Hochrein, *Phys. Chem. Chem. Phys.*, 2003, **5**, 4004.
- 18 A. M. Yoney and Y. Iwakabe, *Surf. Sci.*, 1995, **11**, 3516.
- 19 R. Hentschke, *Macromol. Theory Sim.*, 1997, **6**, 287.
- 20 G. Raffaini and F. Ganazzoli, *Langmuir*, 2003, **19**, 34032004, **20**, 3371.
- 21 F. Rosei, M. Schunack, Y. Naitoh, P. Jiang, A. Gourdon, E. Laegsgaard, I. Stensgaard, C. Joachim and F. Besenbacher, *Prog. Surf. Sci.*, 2003, **71**, 95.
- 22 R. Otero, F. Hummelink, F. Sato, S. B. Legoas, O. Thstrup, E. Laegsgaard, I. Stensgaard, D. S. Galvao and F. Besenbacher, *Nat. Mater.*, 2004, **3**, 779.
- 23 I. Siepmann and I. R. MacDonald, *Thin Solid Films*, 1998, **24**, 205(Academic Press).
- 24 A. Ulman, *Chem. Rev.*, 1996, **96**, 1533.
- 25 F. Schreiber, *Prog. Surf. Sci.*, 2000, **65**, 151.
- 26 P. S. Stayton, G. P. Drobny, W. J. Shaw, J. R. Long and M. Gilbert, *Crit. Rev. Oral Biol. Med.*, 2003, **14**, 370.
- 27 T. G. Cooper and N. H. de Leeuw, *Langmuir*, 2004, **20**, 3984.
- 28 N. H. de Leeuw and T. G. Cooper, *Cryst. Growth Des.*, 2004, **4**, 123.
- 29 T. G. Cooper and N. H. de Leeuw, *Mol. Simul.*, 2002, 28539.
- 30 W. Langel and L. Menken, *Surf. Sci.*, 2003, **538**, 1.
- 31 A large selection of potentials is given on the website www.rigb.ac.uk/potentials but there is no recent critical review. Models for calcite have been derived by A. Pavese, M. Catti, S. C. Parker and A. Wall, *Phys. Chem. Miner.*, 1996, **23**, 89; D. K. Fislser, J. D. Gale and R. T. Cygan, *Am. Mineral.*, 2000, **85**, 217; for BaSO₄ and for apatite by N. H. de Leeuw, F. A. Wahlid, G. B. Thomson, G. M. Graham and R. A. Jackson, *J. Mater. Chem.*, 2002, **12**, 3799.
- 32 A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, D. Joseph-McCarthy, L. Kuchnir, K. Kuczera, F. T. K. Lau, C. Mattos, S. Michnick, T. Ngo, D. T. Nguyen, B. Prodhom, W. E. Reiher, B. Roux, M. Schlenkrich, J. C. Smith, R. Stote, J. Straub, J. M. Watanabe, J. Wiorkiewicz-Kuczera, D. Yin and M. Karplus, *J. Phys. Chem. B*, 1998, **102**, 3586.
- 33 W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, Jr., D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell and P. A. Kollman, *J. Am. Chem. Soc.*, 1995, **117**, 5179.
- 34 D. M. Duffy and J. H. Harding, *Langmuir*, 2004, **21**, 7630.
- 35 A. N. Cormack, J. L. Raymond and A. H. Goldstein, *J. Phys. Chem. B*, 2004, **108**, 20408.
- 36 N. H. de Leeuw, S. C. Parker and K. H. Rao, *Langmuir*, 1998, **14**, 5900.
- 37 K. P. Schroder, J. Sauer, M. Leslie, C. R. A. Catlow and J. M. Thomas, *Chem. Phys. Lett.*, 1992, 188.
- 38 S. L. S. Stipp, *Mol. Simul.*, 2002, **28**, 497.
- 39 V. Gerbaud, D. Pignol, E. Loret, J. A. Bertrand, Y. Berlan, J. C. Fontecilla-Camps, J. P. Canselier, N. Gabas and J. M. Verdier, *J. Biol. Chem.*, 2000, **275**, 1057.
- 40 That a forcefield gives the bulk energy to within 5% of experiment is not a good test of its ability to model a complex interface.
- 41 N. L. Huq, K. J. Cross and E. C. Reynolds, *J. Mol. Model.*, 2000, **6**, 35.
- 42 A. Wierzbicki, C. S. Sikes, J. D. Madura and B. Drake, *Calcif. Tissue Int.*, 1994, **54**, 133.
- 43 A. Wierzbicki and H. S. Cheung, *J. Mol. Struct. (THEOCHEM)*, 2000, **529**, 73.
- 44 S. Dahlin, J. Angstrom and A. Linde, *Eur. J. Oral Sci.*, 1998, **106**, 239.
- 45 J. Gordejev and P. Hirva, *Surf. Sci.*, 1999, **440**, 321.
- 46 Y. Dai and J. S. Evans, *J. Chem. Phys.*, 2000, **112**, 5144.
- 47 W. J. P. van Enkevort, A. C. J. F. van der Berg, K. B. G. Kreuwel, A. J. Derksen and M. S. Couto, *J. Cryst. Growth*, 1996, **166**, 156; W. J. P. van Enkevort and A. C. J. F. van den Berg, *J. Cryst. Growth*, 1998, **183**, 441.
- 48 S. R. Qiu, A. Wierzbicki, C. A. Orme, A. M. Cody, J. R. Hoyer, G. H. Nancollas, S. Zepeda and J. J. De Yoreo, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 1811.
- 49 J. J. De Yoreo and P. G. Vekilov, *Rev. Mineral. Geochem.*, 2003, **54**, 57.
- 50 S. Mann, D. D. Archibald, J. M. Didymus, T. Douglas, B. R. Heywood, F. C. Meldrum and N. J. Reeves, *Science*, 1993.
- 51 H. A. Lowenstam and S. Weiner, *On Biomineralization*, Oxford U.P. 1975.
- 52 K. Henriksen, J. R. Young, P. R. Bown and S. L. S. Stipp, *Palaeontology*, 2004, **47**, 725; K. Henriksen, S. L. S. Stipp, J. R. Young and M. E. Marsh, *Am. Mineral.*, 2004, **89**, 1709.
- 53 B. R. Heywood, in *Biomimetic Materials Chemistry*, ed. S. Mann, VCH Publishers, Weinheim, 1996, ch. 6.
- 54 B. R. Heywood, S. Rajam and S. Mann, *J. Chem. Soc., Faraday Trans.*, 1991, **87**, 727–735.
- 55 B. R. Heywood and S. Mann, *Adv. Mater.*, 1992, **4**, 278.
- 56 B. R. Heywood and S. Mann, *Chem. Mater.*, 1994, **6**, 311.
- 57 J. Küther and W. Tremel, *Chem. Commun.*, 1997, **21**, 2029.
- 58 J. Küther, R. Seshadri, W. Knoll and W. Tremel, *J. Mater. Chem.*, 1998, **8**, 641.
- 59 J. Küther, R. Seshadri, G. Nelles, W. Assenmacher, H. J. Butt, W. Mader and W. Tremel, *Chem. Mater.*, 1999, **11**, 1317.
- 60 E. diMasi, M. J. Olszta, V. M. Patel and L. B. Gower, *CrystEngComm*, 2003, **5**, 346.
- 61 D. M. Duffy and J. H. Harding, *Langmuir*, 2004, **21**, 7637.
- 62 D. M. Duffy, A. M. Travaille, H. van Kempen and J. H. Harding, *J. Phys. Chem. B*, 2005, **109**, 5713.
- 63 M. J. Lockhead, S. R. Letellier and V. Vogel, *J. Phys. Chem. B*, 1997, **101**, 10821.
- 64 M. R. Lovell and S. J. Roser, *J. Phys. Chem.*, 1995, **99**, 14058.
- 65 E. Le Calvez, D. Blaudez, T. Buffeteau and B. Desbat, *Langmuir*, 2001, **17**, 670. Note that the claim by these authors that their results disagree with Gouy–Chapman theory is correct only if the simplified linearised equations are used. The agreement with the full Grahame theory is entirely acceptable.
- 66 A. E. Martell and R. M. Smith, *Critical Stability Constants*, 1977, Plenum, p. 3; the adjustment for high concentrations is given in J. M. Bloch and W. Yun, *Phys. Rev. A: At., Mol., Opt. Phys.*, 1990, **41**, 844.
- 67 D. Langmuir, *Aqueous Environmental Geochemistry*, Prentice-Hall, New Jersey, 1997.
- 68 J. Anwar and P. K. Boateng, *J. Am. Chem. Soc.*, 1998, **120**, 9600.
- 69 K. K. Tanaka, K. Kawamura, H. Tanaka and K. Nakazawa, *J. Chem. Phys.*, 2005, **122**, 184514.
- 70 M. Matsumoto, S. Saito and I. Ohmine, *Nature*, 2002, **416**, 6879.
- 71 P. Beaucage and N. Mousseau, *Phys. Rev. B: Condens. Matter*, 2005, **71**, 094102.
- 72 P. R. ten Wolde, M. J. RuizMontero and D. J. Frenkel, *Chem. Phys.*, 1996, **104**, 9932.
- 73 B. Mutafschiev, *The Atomistic Nature of Crystal Growth*, Springer, 2001 ch. 12.
- 74 X. Y. Liu and S. W. Lim, *J. Am. Chem. Soc.*, 2003, **125**, 888 (note that this paper uses the opposite sign convention for β_{ks} to the one used here. Also, the reference state for the substrate is the

- substrate/vacuum interface, not the substrate/water interface as used here).
- 75 See the papers and discussion in the recent Royal Society Discussion Meeting "Nucleation and Control" published in *Philos. Trans. R. Soc. London, Ser. A*, 2003, **361**(1804).
- 76 I. H. Leubner, *Curr. Opin. Colloid Interface Sci.*, 2000, **5**, 151.
- 77 D. M. Duffy and J. H. Harding, *J. Mater. Chem.*, 2002, **12**, 3419.
- 78 A. M. Travaille, J. J. J. M. Donners, J.W. Gerritsen, N. A. J. M. Sommerdijk, R. J. M. Nolte and H. van Kempen, *Adv. Mater.*, 2002, **14**, 492.
- 79 A. M. Travaille, PhD Thesis, Radboud University, Nijmegen, 2005.
- 80 Y. J. Han and J. Aizenberg, *Angew. Chem., Int. Ed.*, 2003, **42**, 3668.
- 81 D. M. Duffy and J. H. Harding, *Surf. Sci.*, 2005, **595**, 151.
- 82 J. A. Adair and E. Suvaci, *Curr. Opin. Colloid Interface Sci.*, 2000, **5**, 160.
- 83 R. J. Marks and F. C. Meldrum, *J. Mater. Chem.*, 2004, **14**, 2291.
- 84 H. Colfen and S. Mann, *Angew. Chem., Int. Ed.*, 2003, **42**, 2350.
- 85 R. Rajagopalan, *Curr. Opin. Colloid Interface Sci.*, 2001, **6**, 357.
- 86 D. J. Tobias and M. L. Klein, *J. Phys. Chem.*, 1996, **100**, 6637.
- 87 C. A. Bearechell, D. M. Heyes, D. J. Moreton and S. E. Taylor, *Phys. Chem. Chem. Phys.*, 2001, **3**, 4771.
- 88 C. A. Bearechell and D. M. Heyes, *Mol. Simul.*, 2002, **28**, 517.
- 89 M. H. Lamm, T. Chen and S. C. Glotzer, *Nano Lett.*, 2003, **3**, 989.
- 90 Z. Zhang, M. A. Horsch, M. H. Lamm and S. C. Glotzer, *Nano Lett.*, 2003, **3**, 1341.
- 91 T. Chen, M. H. Lamm and S. C. Glotzer, *J. Chem. Phys.*, 2004, 121.
- 92 J. Klos and T. Pakula, *J. Chem. Phys.*, 2003, **118**, 1507–1513; J. Klos and T. Pakula, *J. Chem. Phys.*, 2003, **118**, 7682–7689.
- 93 D. C. Rapaport, *Phys. Rev. E: Stat. Phys., Plasmas, Fluids, Relat. Interdiscip. Top.*, 2004, **70**, 051905.
- 94 D. Antypov and D. J. Cleaver, *J. Chem. Phys.*, 2004, **120**, 10307.
- 95 P. Richard, M. Nicodemi, R. Delannay, P. Ribiere and D. Bideau, *Nat. Mater.*, 2005, **4**, 121.
- 96 S. Marceau, *Architecture Multiechelle et Propriete Mecaniques de Nanocomposites*, PhD Thesis, University of Savoie 2003 (obtainable from the website www.univ-savoie.fr/labos/mops/people/smarceau) see also D. Brown, P. Mele, S. Marceau and N. D. Alberola, *Macromolecules*, 2003, **36**, 1395.
- 97 G. M. Odegard, T. C. Clancy and T. S. Gates, *Polymer*, 2005, **46**, 553.
- 98 C. Hellmich, J. F. Bathelemy and L. Dormieux, *Eur. J. Mech. A*, 2004, **23**, 783.
- 99 D. Volkmer, M. Fricke, C. Agena and J. Mattay, *J. Mater. Chem.*, 2004, **14**, 2249.
- 100 D. Volkmer, M. Fricke, M. Gleiche and L. F. Chi, *Mater. Sci. Eng., C*, 2005, **25**, 161.
- 101 F. C. Meldrum, *Int. Mater. Rev.*, 2003, **48**, 187.
- 102 A. M. Stoneham, *Mater. Sci. Eng., C*, 2003, **23**, 2.