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REVIEW ARTICLE

Multi-scale simulations of apatite–collagen composites: from molecules to materials

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ABSTRACT: We review scale-bridging simulation studies for the exploration of atomic-to-meso scale processes that account for the unique structure and mechanic properties of apatite–protein composites. As the atomic structure and composition of such complex biocomposites only partially is known, the first part (i) of our modelling studies is dedicated to realistic crystal nucleation scenarios of inorganic–organic composites. Starting from the association of single ions, recent insights range from the mechanisms of motif formation, ripening reactions and the self-organization of nanocrystals, including their interplay with growth-controlling molecular moieties. On this basis, (ii) reliable building rules for unprejudiced scale-up models can be derived to model bulk materials. This is exemplified for (enamel-like) apatite–protein composites, encompassing up to 10^6 atom models to provide a realistic account of the 10 nm length scale, whilst model coarsening is used to reach μm length scales. On this basis, a series of deformation and fracture simulation studies were performed and helped to rationalize biocomposite hardness, plasticity, toughness, self-healing and fracture mechanisms. Complementing experimental work, these modelling studies provide particularly detailed insights into the relation of hierarchical composite structure and favorable mechanical properties.

KEYWORDS: biocomposites; deformation; fracture; molecular simulation

Contents

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1 Introduction

Biogenic composites such as bone and teeth are fascinating materials that use organic soft matter and inorganic nanocrystals to combine several materials properties and thus optimally perform for their specific functions. While this optimization results from millions of years of evolution, biomimetic approaches aim at adopting features and mechanisms to provide novel materials in the lab. The success of such syntheses strategies clearly depends on a

profound knowledge of the involved principles of (typically) hierarchical structure formation [1]. Indeed, it is crucial to understand the relation of composite structure and its specific properties. The latter challenge not only involves the characterization of electric, magnetic or elastic properties, but also the understanding of the mechanisms of dynamical processes such as plastic deformation and fracture.

Teeth and bones represent a particularly prominent class of biominerals and are well-known for their exceptional mechanical properties [1–2]. While hardness stems from inorganic components like calcium phosphates or iron oxides, the 1–20 wt.% of organic constituents account for more subtle properties such as resilience, porosity and form control [1–9]. Among the wealth of experimental characterization studies, Swain and coworkers nicely demonstrated the 'steel-like' properties of enamel, namely creep and back-creep phenomena observed from indentation by atomic force microscopy [5–7]. Evidence for the role of the organic constituent (1–2 wt.% of amelogenin and enamelin) was derived from indenting at different locations of the hierarchical composite — which showed different stress–strain profiles the protein-rich and protein-poor domains of enamel.

To unravel the underlying molecular scale mechanisms, i.e. the interplay of apatite and proteins at the atomic level of detail, we are bound to reduce the complexity of living matter and focus on simpler, biomimetic compounds of more defined composition and structure. Within 2 decades of ongoing research, Kniep and coworkers established the reproducible synthesis of biomimetic apatite–collagen composites which in terms of its hierarchical structure and protein content (2 wt.%) is of striking similarity to enamel [10]. Using this simple and controllable syntheses route, the formation process of the biomimetic composite could be monitored from electron microscopy and X-ray diffraction (XRD) as functions of size [11]. This offers a level of in-depth understanding from experimental characterization which — to this extend — is rather unique in the field of biomineralization. Moreover, by the close collaboration of theory and experiment, this understanding was carried even further and by now includes atomic scale information from molecular simulation [11–12].

While in the beginning of developing our modelling and simulation approaches we used experimental evidence for benchmarking and validation [13], theory quickly evolved to an additional tool of investigation to provide insights that are hardly available from experiment. This journey started in the early 2000's from exploring individual ion–protein interactions and crystal–solvent interfaces [13–15] and by now spans the mechanisms of composite nucleation and growth as well as the analysis of the bulk materials properties — which is the subject of the present review.

In what follows, we outline the analysis of molecular simulation studies on apatite–collagen composite nucleation and the formulation of up-scale models encompassing up to millions of atoms. After characterizing the molecular mechanisms of hierarchical structure formation, plastic deformation, self-healing and fracture from atomic resolution models [16–19], post-molecular simulation approaches were derived from systematic coarsening. On this basis, the formation of electric fields and fracture mechanisms could be rationalized at length scales spanning the nm to μm length scale [20]. Indeed, scale-bridging is of critical importance for both modelling and heuristic understanding, as atomic reorganization at the organic–inorganic interface occurs at the nanometer scale, whilst the structural hierarchy of teeth and bone determines deformation and fracture at the 10–1000 nm scale. Despite operating at different length scales, these processes are closely linked, and the unprejudiced characterization of meso- and nano-scale processes requires insights from the molecular scale.

2 The interplay of proteins, ions, crystals and water as functions of pH

Thanks to the development of specific force-fields, all constituents relevant to the understanding of biominerals and their formation can adequately be modelled from classical molecular mechanics [21–26]. An important limitation to this is the role of proton transfer reactions which modelling requires at least a fundamental degree of quantum mechanical characterization. In the past 10 years, this challenge was addressed by developing suitable quantum mechanical/molecular mechanical (QM/MM) models. Considering the complexity of protein–ions/crystals–solvent systems, it appears crucial to focus the quantum calculations on the most critical degrees of freedom, whilst modelling most of the system classically [27]. Among the manifold of possible QM/MM implementations, here we shall only discuss a particularly simple consideration of the pH-dependence of the anionic species. The approach was inspired from a molecular simulation of zinc oxide nucleation from solution which required the modelling of hydroxide (de-)protonation during aggregate

formation [28] and crystal growth [27]. Quantum chemical calculations were only employed to assess the proton transfer between two hydroxide ions yielding a water molecule and an O^{2-} ion in vacuum. A particularly convenient feature of this model is that the difference in proton affinity of the isolated species remains constant and thus needs to be calculated only once. On the other hand, drastic changes are encountered for the role of the embedding solvent, crystal surfaces etc. during the nucleation and growth simulations. These interactions may however be modelled adequately by molecular mechanics. Thus, the question if the (de-)protonation of an anion at a given aggregate surface is exothermic or not, can essentially be probed by MM models, namely by comparing the energy of the possible reaction products with those of the educts [28].

The computational efficiency of this approach allows for the sampling of many possible proton transfer events and thus provides reasonable statistics also for complex systems. Even for an apparently simple process like the growth of zinc oxide surfaces from solution, we found a considerable manifold of possible protonation states [27] which would have been elusive to more sophisticated quantum calculations simply because of prohibitive computational costs. We argue that the complexity of biogenic and biomimetic crystal nucleation and growth is typically even larger, and hence suggest our approach as a reasonable compromise in accuracy of calculating individual interactions and the reduction of statistical errors.

While the use of QM/MM models is indispensable for studying the formation of bio(mimetic) composites based on oxides [27,29], also silicate, carbonate and phosphate based systems require the consideration of (de-)protonation events. However, for both calcium–carbonate and calcium–phosphate complexes, simulation studies revealed that the HCO_3^- and HPO_4^{2-} species in water change their proton affinity drastically upon association of a calcium ion [30–31]. Indeed, the aggregation of calcium carbonate and phosphate is typically modelled by anticipating anion deprotonation from the very beginning [12,32–33]. On the other hand, the specific role of pH was subject to studies focusing on the acid-induced dissociation of apatite [34] and the assessment of the 'local p*K*' of phosphate at the (001) apatite–water interface (Fig. 1). In the later study, the change of proton affinity of PO_4^{3-} in bulk water was related to that of phosphate at the crystal surface to interpret the pH-dependence of growth and dissociation processes in line with the experiment [35].

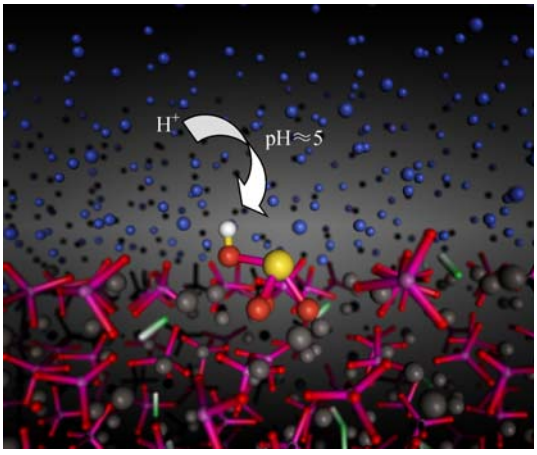

Fig. 1 Combined quantum/molecular mechanics calculation of the 'local' pK_A value of phosphonate at the (001) surface of hydroxyapatite (HAP) in contact with water. Experimental (5.5) and theoretical (4.3) estimates are within reasonable agreement [35]. Colors: blue, O (water); red, O (phosphate); green, O (hydroxide); grey, Ca^{2+}; white, hydrogen.

3 Composite nucleation and growth

To form a robust basis for the understanding of composites, including biomaterials, we feel that the profound investigation of the underlying mechanisms of nucleation and growth is of central importance. Indeed, the most unprejudiced route to simulation studies of complex nano-materials is to construct bulk models on the basis of detailed structural information obtained from studying composite nucleation and growth. However, this idealistic concept is in contrast to the much more common blend of empirical modelling and intuition [36].

The beforehand mentioned bio-mimetic apatite–collagen composites, first synthesized by Kniep and coworkers [10] however offer sufficient control of the composite constituents and favorable system simplicity to attempt unprejudiced composite structure prediction. Starting from the association of single calcium, (hydrogen) carbonate and (hydrogen) phosphate ions to collagen models, molecular simulation studies unraveled the formation of aggregates comprising hundreds of ions [12,33]. Figure 2 illustrates the formation of salt-bridges and hydrogen bonds for the tails domain and the triple-helix of the inner part of collagen, which 300 nm length correlates with the nano-mosaic structure of fluorapatite–collagen composites [10]. A striking observation of the molecular simulations related to this system is the close interplay of ion association and the formation of crystalline motifs, namely $[Ca_3F]$ triangles which are formed *within* the triple-helix. Indeed, collagen–

collagen hydrogen bonds are replaced by even stronger salt-bridges without compromising the overall triple-helical fiber arrangement (the phosphate ions are associated laterally, only). In other terms, we find an intergrowth of the two constituents of the composite. On the basis of these simulations, the experimentally observed structural hierarchy of the composite could be related to the molecular mechanism of [Ca_3F] motif incorporation and orientation by collagen [12].

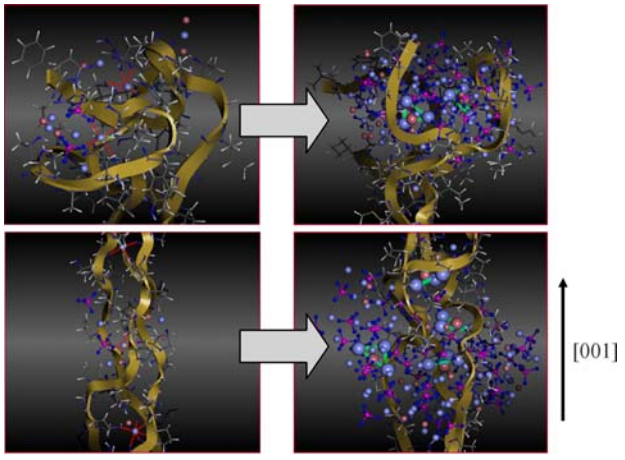

Fig. 2 Ion association (left) to a collagen triple-helix and nucleation of (fluor)apatite-type motifs (right) as assessed from molecular dynamics simulations [12]. The embedding of Ca_3F/$Ca_3(OH)$ motifs by salt-bridges with the back-bone of collagen leads to a structural alignment of the protein fiber and the *c*-axis of the forming apatite crystal. This correlation is critical for the observed nm-μm scale structural hierarchy of the composite [11]. Colors: yellow, protein backbone; light blue, Ca^{2+}; dark blue, O (phosphate); red, F^-; purple, P (phosphate).

While fluorapatite and collagen reflect a favorable match of composite constituents, even small amounts of carbonate ions may strongly distort structural hierarchy at the >10 nm scale. Within a few weight percentages of carbonate content, the 300 nm correlation length along the *c*-axis of the nano-mosaic structure of fluorapatite-based composites were found to reduce linearly to less than the detection limit of ~50 nm [37]. A possible explanation for this may be suggested from molecular simulations of (pure) calcium carbonate association to different collagen models [33]. Collagen types which include few or even no saccharide residues (as used in the beforehand mentioned modelling study) were found to embed carbonate aggregates at the cost of the triple-helical structure. This 'unfolding' may however be inhibited by saccharide residues which redirect calcium carbonate association to lateral binding with the biomolecule. We conclude that collagen types exhibiting a weak degree of glycolization are hence prone to local re-organization (nm-scale unfolding) during the formation of carbonated apatite composites. On the other hand, the particularly heavily glycolisated collagen species of otolin was shown to protect the triple-helical structure even at 100% carbonate content (i.e. formation of otolin–calcite composites) [33,38].

4 Model up-scaling: from aggregates to bulk apatite–collagen composites

A simple and intuitive route to preparing a bulk composite simulation system is to dock pre-defined apatite nanocrystals to collagen. This leads to a nanocomposite model in which the constituents exhibit hydrogen and electrostatic bonds at the interface and — if combined with energy optimization — also allows for a limited degree of structural relaxation. However, the beforehand described structural incorporation of ions *within* the triple-helix implies significant re-arrangements of both constituents when forming the composite. As a consequence, modelling the material in terms of proteins attached to crystal surfaces would fail to account for the intergrowth of collagen and apatite, thus missing key aspects of structural hierarchy and its implications on mechanical properties.

Buehler and coworkers addressed this issue in an approximate, yet very efficient manner [39]. Starting from a collagen fibril model, they performed a geometric search for cavities and collagen surfaces. Empty space was then filled by apatite nanoparticles which size and was adapted to the available volume. On this basis, induced-fit type of docking is hard to cover and we feel that this procedure should be considered as a lower estimate of collagen-ion intergrowth. However, it is reasonable to assume collagen fibrils (as characteristic in bone) to undergo much less re-folding as compared to single collagen triple-helices (which dominate enamel-like composites). While the former model indeed reproduced mechanical properties of bone [39], the latter type of composite requires a different simulation approach.

In principle, the most accurate description of apatite–collagen composites with low protein content is to model its actual nucleation and growth. Unfortunately, the evolution from aggregates comprising a few hundreds of ions to bulk composite models of hundred thousands of ions clearly exceeds the scope of ion-by-ion growth simulations. We therefore introduced a scale-up strategy based on the learnings from explicit modelling of the early

stages of composite formation [17]. To allow the incorporation of ions and thus full intergrowth, we must consider the replacement of protein–protein hydrogen bonds by salt-bridges. Using an artificial hyperspace coordinate η (i.e. by performing molecular dynamics in 4-dimensional (4D) space) a model of single-crystalline apatite and a collagen triple-helix were gradually merged. Along this line, interatomic distances r_{ij} were calculated according to Eq. (1):

$$r_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2 + (\eta_i - \eta_j)^2} \quad (1)$$

which reflects a mathematical trick to avoid singularities in force calculations, even during overlap in real space (x, y, z). The separation of the composite constituents along the 4th dimension $\Delta\eta$ was first reduced until a minimum in lattice energy $E(\Delta\eta)$ was reached. This procedure induced significant rearrangements of the protein, whilst the (much harder) apatite crystal remained practically unchanged. In other terms, at this stage protein refolding is fully exploited and ions that are still overlapping must be cut form the simulation box. This was implemented as a second step using a variety of geometric criteria for cutting ions. The two constituents were eventually merged into a 3-dimensional (3D) composite model, i.e. $\Delta\eta = 0$, and benchmarked in terms of the apatite–collagen interaction energy. The model of optimal interaction energy of the two composite components indeed nicely reflected the earlier discussed structural features, namely calcium triangles which incorporation into collagen is stabilized by salt-bridges. An illustration of the composite model is shown in Fig. 3. Note the strong correlation of the [001] direction of the apatite crystal with the alignment of the triple helix. Moreover, the overall distortion of the bulk crystal was found as surprisingly small. We interpret this phenomenon as a signature of the favorable interplay of collagen and apatite stemming from what we consider as a combination of flexible and rigid docking of apatite into collagen. To replace collagen–collagen hydrogen bonds by collagen-ion salt bridges, the protein undergoes local reorganization, whilst the overall protein backbone remains unchanged and thus implies the necessary rigidity to impose [001] crystal growth along the collagen fiber.

5 Molecular mechanisms of deformation, slip, fracture and self-healing

The enamel-like composite model was subjected to a series

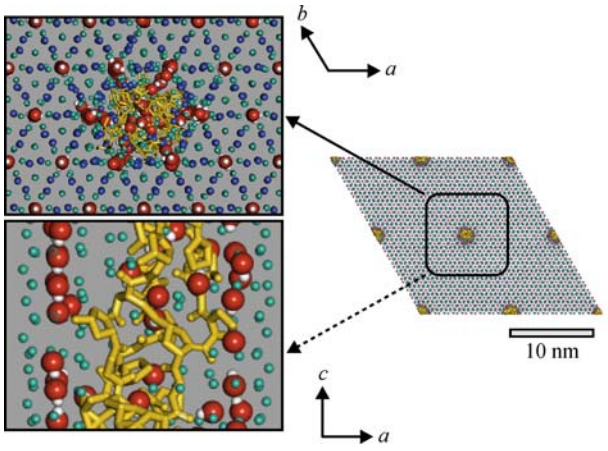

Fig. 3 Scale-up model of an apatite–collagen composite model comprising 212.340 atoms. In accordance with the nucleation study illustrated in Fig. 2 we find an intergrowth of both constituents of the composite, namely the embedding of oriented $Ca_3(OH)$ motifs that form salt-bridges with the back-bone of collagen. This leads to the structural alignment of the triple-helices with the c-axis of apatite and remarkably few distortions from the crystalline arrangement at the organic–inorganic interface [16–17]. Colors: yellow, protein backbone; cyan, Ca^{2+} ($Ca_3(OH)$ motifs, only); blue, remaining Ca^{2+} ions; red, O (hydroxide); white, H (hydroxide); green, P (phosphate).

of simulation studies to explore the molecular scale processes during mechanical loading and relaxation. Despite the simplicity of our simulation models compared to macroscopic polycrystals and biogenic composites, fundamental mechanical properties such as the elastic bulk moduli are reasonably well reproduced. Table 1 also shows the reduction of the bulk modulus in the course of 2 wt.% protein incorporation into the model composite and bovine enamel which was found as 14% and 28%, respectively [40]. Note that enamel does not contain collagen triple-helices, but much less ordered (amelogenins and enamelins) proteins. The latter tend to accumulate within protein-rich domains [5–7,41] whilst in the former composite the collagen is preferentially arranged periodically [10]. Nevertheless, the mechanism of hardness reduction of apatite by 2% protein incorporation is nicely demonstrated.

In both the biomimetic and the biogenic composites, the lowering of hardness caused by protein incorporation reflects a trade-off for the remarkable reduction of brittleness in these materials [5–7]. Indeed, it is this steel-like resilience — controlled by the different protein content of enamel, dentine and bone — that qualifies apatite-based composites for building teeth and skeletons [8–9,41]. While the composite hardness is assessed from deforma-

Table 1 Comparison of the bulk moduli of the HAP single crystal and the HAP–collagen composite model

Substance	B_0 /GPa	
	Simulation model	Experiment in Ref. [40]
HAP	101.2 (single crystal)	88.0 (synthetic polycrystal)
HAP–collagen composite	86.6 (single crystal + collagen)	63.1 (bovine enamel)

Note: Experimental data is provided for more complex HAP polycrystals and biogenic enamel samples (HAP polycrystals with various protein species). Compared with those of HAP, the bulk moduli of HAP–collagen composite have reductions of 14% and 28% in the simulation model and the experiment in Ref. [40], respectively.

tion simulations within the elastic regime, the understanding of resilience requires characterization of more complex processes as described in the following.

A first step beyond elastic deformation was performed for the beforehand discussed enamel-like composite model by implementing compression along the [001] direction along with volume relaxation within the (001) plane [16]. The choice of this process setup was motivated by its similarity to biting which implies [001] compression of biogenic HAP-based composites with similar protein content. Despite the comparable simple simulation models, we could still reveal a molecular mechanism of plastic deformation, followed by self-healing of the material [16]. In absence of collagen, deformation of single crystalline apatite beyond the yield load implies a catastrophic failure, i.e. amorphization of the entire system or brittle fracture. However, the composite was shown to avoid such failure by instead sacrificing local ordering whilst maintaining overall structural integrity (Fig. 4). Along this line, plastic deformation is initially localized in the softer domains of the composite — the collagen–apatite interface — whereas domains of pure apatite remain comparably unstrained. In the stress–strain profiles, this phenomenon is reflected by a constant force after loading beyond the elastic limit.

A particularly striking feature of the composite is however observed during unloading after plastic deformation. Apart from fast relaxation of the elastically deformed parts of the material, we found a secondary relaxation process on a much slower time scale. The latter was identified as the re-organization of the collagen–apatite interface which — supported by the adjacent domains of single crystalline apatite — exhibits an intrinsic mechanism of self-healing. In other terms, shock energy is first transferred into plastic deformation and then gradually released into heat whilst the composite recovers its original structure [16].

While the beforehand described study clearly shows a molecular scale mechanism accounting for the materials resilience, the hierarchical nature of the composite suggests that there may also exist a hierarchy of deformation mechanisms acting on different length scales. To explore this issue, an even larger model (yet still of atomistic resolution) was subjected to indentation. For this purpose, a $3\times3\times1$ super cell of the composite model, thus comprising 9 explicit collagen triple-helices, as illustrated in Fig. 5 was employed [18].

In this ~500 000 atoms simulation cell the outermost frame normal to the [001] direction was kept fixed to provide immobilization of the overall material during

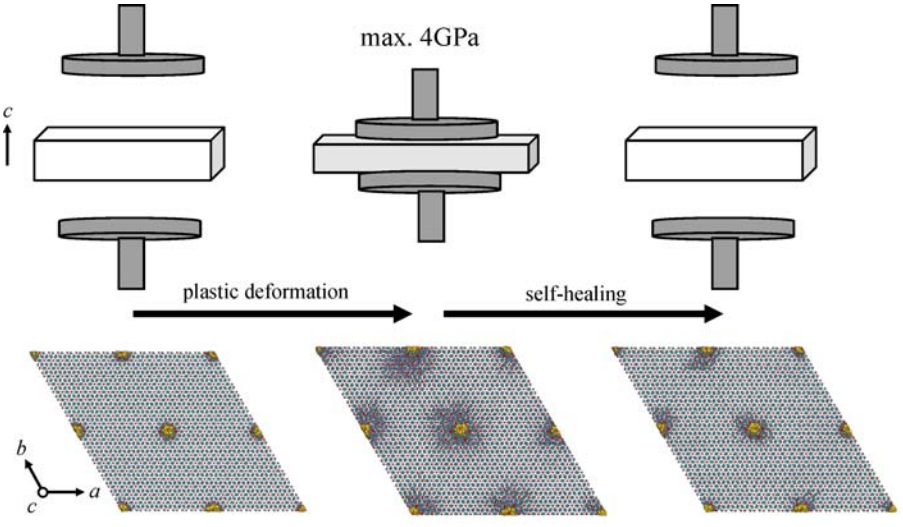

Fig. 4 Composite model as illustrated in Fig. 3 as explored for mechanical loading and relaxation. Stress applied along the *c*-axis leads to plastic deformation at the apatite–collagen interface region, whilst in-between domains of pure apatite remain intact. Upon stress release, re-organization of the damaged zones is facilitated by the crystalline regions and occurs on a ns scale [16].

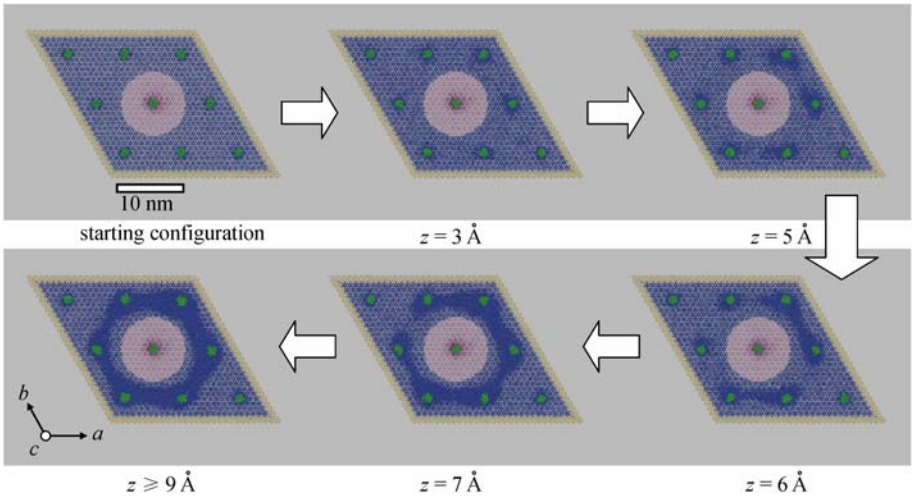

Fig. 5 Snapshots of the composite model used for indentation simulations showing only the calcium ions and the collagen molecules (green). Calcium ions are colored in yellow, red and blue to illustrate full position constrains (for fixing the outer frame of the simulation model), *z*-coordinate constrains (mimicking a cylindrical indenter) and unconstraint ions, respectively. In analogy to compression as illustrated in Fig. 4, indentation leads to localized plastic deformation and slipping starting at the protein–crystal interface (top left, $z = 5$ Å). The lower panel shows the gradual merging of the plastic deformation regions until a 'complete' slip zone is formed ($z = 9$ Å). Note that the resulting slip zone does not reflect the minimal surface area given by the cylinder subjected to displacement, but instead follows the hexagonal pattern of the collagen matrix. Reproduced with permission from Ref. [18].

indentation. The actual indenter was chosen as a cylindrical rod, mimicked by applying *z*-coordinate constraints to the composite atoms which *x*–*y* coordinates are within the cylinder radius. To avoid surface effects and thus focus on shearing in the bulk composite, periodic boundary conditions are applied in all directions (Fig. 5).

Much in analogy to the beforehand discussed mechanisms of bulk compression and plastic deformation, the organic constituent plays a crucial role also for indentation and shear of the composite. Beyond the elastic regime, we observe the formation of dedicated slip zones. These are pre-defined by the hierarchical arrangement of collagen in the composite, thus a hexagonal pattern of ~10 nm spacing [17]. The clear preference of this pattern for slip zone formation prevails the imposing of shear by an in principle much smaller domain, namely the cylinder highlighted in Fig. 5. Following the hexagonal matrix, dedicated slip zones accommodate shear without compromising the overall composite structure. Instead, we find the sliding of intrinsically defined hexagonal rods at roughly constant restoring force after passing the elastic limit. Moreover, in analogy to the beforehand discussed self-healing upon releasing load, also rod displacement is reversible and back creep is observed as gradual ionic rearrangement in the slip zones. The latter process was found to be subjected to an activation barrier of ~20 kJ/mol and thus occurs on a much slower pace as compared to elastic relaxation.

While enamel is too complex and structurally undefined to allow direct transfer of our simulation protocols, our findings may still be related to the biogenic materials on a qualitative basis. Indeed, also enamel comprises of a hexagonal pattern of protein-rich and protein-free domains, giving rise to shearing facilitated by the organic–inorganic interface, i.e. structure-inherent slip zones [18]. It is intuitive to expect the hierarchical pattern of softer and harder domains to also play a key role in fracture nucleation and its propagation. In particular for studying the latter process, it is crucial to assess the micrometer scale to explore issues like fracture bifurcation and the pinning of micro-cracks to avoid material failure. This calls for model coarsening as described in the following section.

6 From molecular insights to coarse-grained models: fracture up to the mm scale

The quality of coarse-grained models tremendously depends on the underlying parameterization strategy. To ensure adequate model reduction without losing potentially critical details, fracture mechanisms were first characterized for the atomistic HAP–collagen composite model as discussed in the previous section. Thus, using full atomistic resolution, we first characterized plastic deformation and fracture processes within simulation cells of a few tens of

nanometers [19]. As expected, fracture nucleation and propagation was found to be facilitated by the organic–inorganic interface. In other terms, the fracture curves follow the pattern defined by the arrangement of the collagen proteins. For loading in directions normal to the [001] direction, this implies fracture propagation on a hexagonal grid, i.e. as zic-zag curves rather than straight lines. As a consequence, the overall crack length increases thus considerably increasing the total crack energy for extended fracture curves. However, an even more striking observation is the tendency to fracture bifurcation stemming from non-linear crack propagation routes as illustrated in Fig. 6 [19].

To characterize the brittleness of composite fracture, it is useful to calculate the applied mechanical work and the observed potential energy as functions of the strain Δs — which are both shown in Fig. 7, respectively. In terms of potential energy, the material exhibits a parabolic curve within the elastic regime, whilst a roughly constant curve is observed during plastic deformation and fracture. In a somewhat similar fashion, unloading after stretching beyond the elastic limit leads to 'quasi-elastic' relaxation to a locally damaged system, exhibiting plastic deformation along the organic–inorganic interface [19].

Upon elongation by about 1 nm, the deformation mechanism changes from elastic to plastic. After stretching up to the fracture limit of 3.5 nm, relaxation is investigated by reversing the strain rate. The inset at the top left shows that the system does not immediately recover to the pristine configuration, but retains considerable plastic deformation. As a consequence, the corresponding potential energy profile (red curve) exhibits an offset in both energy and equilibrium geometry. Note that despite the limited dimensions of the atomistic model, the onset of fracture bifurcation (highlighted by yellow arrows) is — at least qualitatively — already observed.

Based on the learnings from the atomistic simulations, coarse-graining was implemented as a hexagonal array of building blocks [19]. The building blocks were taken to be "soft spheres", i.e. their interactions were modeled by distant-dependent potential energy functions. The latter were parameterized to reproduce the potential energy profiles assessed for the atomistic model as shown in Fig. 7. To account for the change in interaction energy upon composite damage, two species of building blocks were defined. For the loading of the undamaged, or fully relaxed, composite model building blocks denoted as "pristine (P)" were parameterized according to the blue curve in Fig. 7. On the other hand, "damaged (D)" building blocks were implemented to reproduce the red curve of the potential energy profiles shown in Fig. 7. This allows modelling the transition from elastic to plastic deformation by switching from 'pristine' to 'damaged' building blocks — which was implemented by a distance criterion. Accordingly, separation of two building blocks beyond the elastic limit leads to a change in the interaction potential, thus mimicking the loss in elastic energy as elaborated for the atomistic model (Fig. 7).

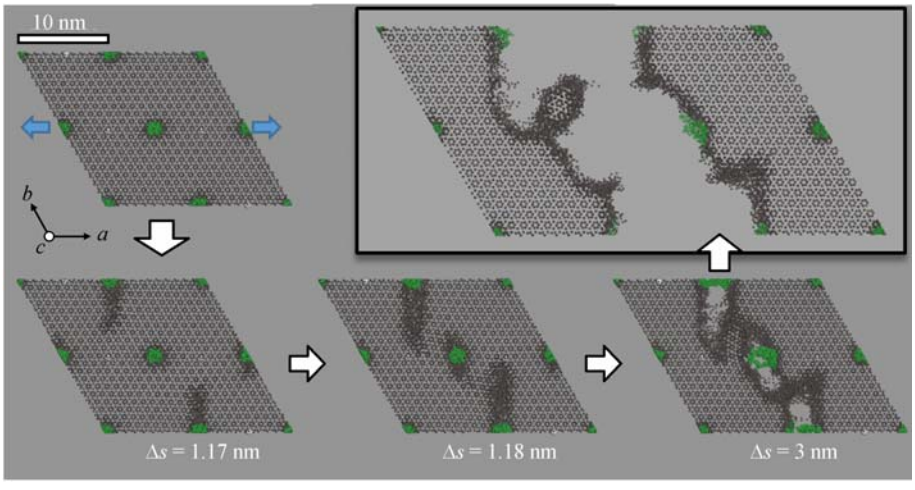

Fig. 6 Atomistic model mimicking the composite material at the 20 nm length scale, illustrating only calcium ions (grey) and the backbone of the collagen triple-helices (green). While applying 3D periodic boundary conditions, the system is stretched along the apatite *a*-axis (blue arrows) to induce fracture (which occurs at $\Delta s \approx 3.5$ nm). Plastic deformation and fracture nucleation is facilitated by organic–inorganic interface. Note that the hexagonal pattern of softer and harder domains opposes straight deformation/fracture curves and gives rise to rough fracture patterns. While the overall size of the simulation cell is too limited to allow the direct observation of fracture bifurcation, the underlying tendency is demonstrated quite clearly.

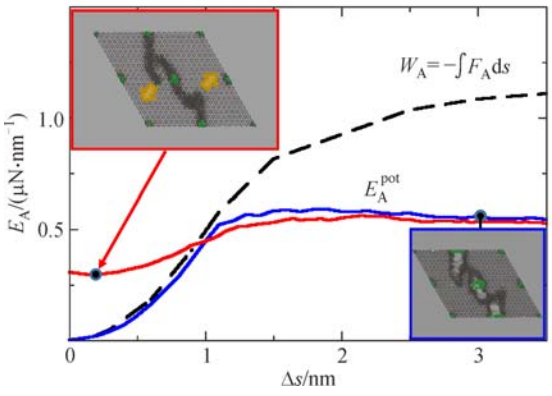

Fig. 7 Potential energy (blue curve) and mechanical work (black curve) per nm^2 as functions of model stretching Δs along the [100] direction. The deformation mechanism changes from elastic to plastic upon elongation by about 1 nm. This leads to a deviation of potential energy and mechanical work, and hysteresis effect during repeated loading/unloading cycles (red curve). As a consequence, two types of building block species are used for coarse-graining the composite to mimic the energy profiles of pristine and damaged composite, respectively. Despite the limited dimensions of the atomistic model, trends to fracture bifurcation (highlighted by yellow arrows) may clearly be related to the arrangement of the collagen fibers within the composite. Reproduced with permission from Ref. [19].

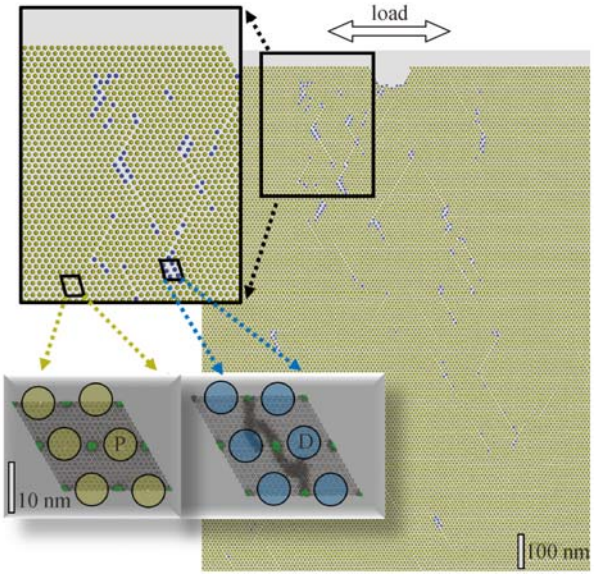

Fig. 8 Atomistic (lower left) and coarse-grained models mimicking the composite material, bridging the 10 nm and μm scale, respectively. The coarsened model comprises 90 000 building blocks and is shown for the early stage of relaxation upon loading. The later was implemented as 5% elastic deformation along the horizontal direction and running particle dynamics simulations of 100 000 time-steps (3.5 ns) whilst fixing the boundaries of the simulation cell to hold the imposed strain. Reproduced with permission from Ref. [19].

The use of such building blocks reduces the overall number of particles considerably — in the present case a single building block replaces 53085 atoms — and thus allows for assessing much larger length scales. Moreover, the large mass of the building blocks also allow for larger time-steps in dynamics simulations, thus also extending the accessibly time scales. Based on such model coarsening, a μm-sized simulation system as illustrated in Fig. 8 was subjected to loading analogous to the beforehand discussed atomistic model. Going beyond the 10 nm scale not only allows accessing fracture bifurcation and coexisting cracks within the simulation cell, but also paves the way to studying rough surfaces as clearly dominating the nature of real materials. To explore the relevance of surface roughness, a ~100 nm-sized kink was incorporated in the coarse-grained model as illustrated in Fig. 8.

Despite initially implementing elastic deformation (5% along the horizontal direction in Fig. 8) relaxation quickly evolves in favor of a heterogeneous pattern of plastic deformations and microcracks. Both processes lead to considerable stress reduction, hence stabilizing the material against failure. Indeed, the overall length summed up for all microcracks clearly exceeds the crack length needed for a sharp cut of the whole simulation model into two separated fragments. On the one hand side, the pinning of microcracks results from crack bifurcations. However, an even more dominant mechanism is given by coexisting crack nucleation events. A series of snapshots from particle dynamics simulations of composite relaxation whilst holding the 5% deformation (which was initially implemented as elastic) is shown in Fig. 9.

The simulations reveal exponential stress decay within the μs scale, ending at a moderate stress of ~0.2 $N \cdot m^{-2}$ that can be interpreted as the elastic limit of the model system. The key to withstanding strain that relate to stress levels exceeding the elastic limit by orders of magnitude is the materials ability to accommodate a large density of coexisting microcracks. The later were found to remain stable upon separation by ~100 nm or more, whilst nearby cracks tend to merge into branched fracture patterns. Both of these phenomena lead to non-percolating fracture curves, but a diffuse pattern of microcracks which extension barely exceeds 1 μm. This finding also applies to the initially prepared kink acting as a starting point to crack propagation upon loading. Indeed, crack propagation from this scratch implemented in the surface of the simulation model was found to compete with the nucleation of coexisting cracks that eventually terminate crack propagation according to the mechanisms discussed before [19].

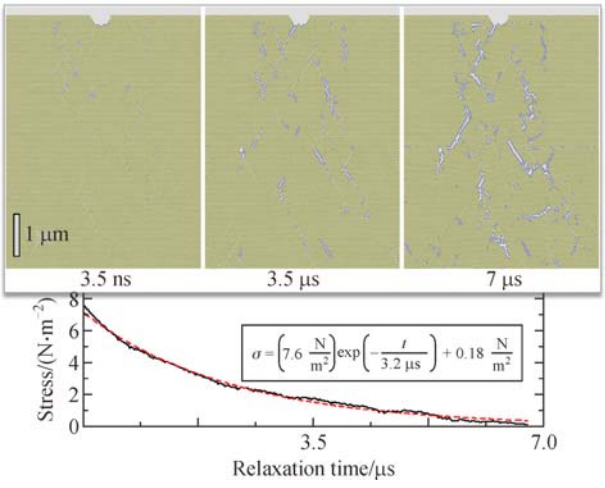

Fig. 9 Snapshots from particle dynamics simulations of the coarsened composite model after loading and holding 5% strain along the horizontal direction. While initially deformed according to an ideally elastic behavior, within μs time scales the simulation model evolves to a heterogeneous pattern of plastic deformation and microcracks. Reproduced with permission from Ref. [19].

7 Conclusions

Atomistic and post-atomistic simulations may provide a wealth of mechanistic insights for composite nucleation, structural hierarchy and materials properties. The modelling studies discussed in the present review largely focus on a biomimetic apatite–collagen composite [10]. This choice was motivated by the excellent starting points provided from in-depth experimental characterization performed over decades in the Kniep group [10–11]. While such limitation to a single, well-defined system is crucial for developing simulation techniques and approaches of model up-scaling and coarsening, the developed methods are widely transferrable. Indeed, ongoing applications involve silica and magnetite based composites comprising a range of organic constituents [12,24–25,29].

Molecular simulations are well established for revealing the interplay of ion association and crystal nucleation with the (macro-)molecular composite constituent. So far, studies have addressed the association of individual ions [12,26] and protein/macromolecule binding to a given crystal surface [23–24]. While the former refers to the initial steps to polymer/protein-induced composite nucleation, the latter corresponds to growth-control and/or the 'gluing' of already formed nanoparticles. To bridge between these two approaches, we suggest the preparation of scale-up models that mimic both types of composites — materials formed by direct composite nucleation and compounds obtained from binding nanoparticles into a molecular matrix. An example for the former class of composites is given by enamel and enamel-like composites.

In apatite–collagen composites of protein content similar to enamel, the observed intergrowth of the organic and the inorganic component calls for modelling approaches that offer particularly careful structural relaxation. This may be provided using molecular dynamics simulations extended to hyperspace as originally introduced by Roux et al. for calculating solvation free energies in liquids [42]. To study protein incorporation in solids, the original method was extended by geometric/energetic criteria for cutting ions which overlap despite structural relaxation [17]. In the following, the use of atomistic scale-up models was demonstrated for a series of mechanic properties and the characterization of molecular mechanisms accounting therefore.

Moreover, in going from ion-protein association studies to atomistic scale-up models, it is avoided to use experimental data as input to model preparation. Experiments are thus used for model confirmation rather than parameterization. In a similar fashion, model coarsening can be based purely on atomistic simulation data to avoid biasing simulations in favor of the experiments to be reproduced. Along this line, our coarse-grained model for studying deformation and fracture in enamel-like composites demonstrates the unbiased assessment of microcrack patterns and bifurcation mechanisms [19].

Despite the still considerable computational demand required for modelling composites by multi-scale simulation approaches, we argue that there are unique insights available from simulations justifying these efforts. This particularly applies to hierarchical materials for which it appears quite straightforward to expect cascades of mechanisms acting on different time and length scales. The example of collagen–apatite composites discussed in the present review might well reflect only one case out of many yet to follow.

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