

Current challenges in atomistic simulations of glasses for biomedical applications

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Atomic-scale computer simulations have emerged as a powerful tool to probe at a very high resolution, the structural and dynamical properties of amorphous and crystalline biomaterials with a direct impact on their biological activity. In particular, bioactive glasses (BGs) represent a target of high strategic importance for the simulations, due to the central role that they play in the broad arena of materials for repairing and regenerating tissues. Simulations aimed at understanding the properties of bioactive glasses thus reveal the potential, and also the limitations, of computational approaches to support the rational development of biomaterials. This perspective article examines several key challenges that computer simulations of BGs are currently dealing with and that will need to be effectively tackled in order to achieve further substantial progress in this field. Relevant examples are the identification of new structural descriptors, the modelling of ion migration, and the simulation of nanosized samples, which are discussed in relation to the underlying issues, such as the limited space and time scales that can be probed using simulations.

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Introduction

Bioactive glasses (BGs) represent a key reference in the field of materials for biomedicine. Traditional clinical uses of BGs exploit the ability of the glass to form bonds with existing tissues, thus providing a stable matrix that promotes the

growth of new bone and supports bone repair.¹ Subsequent developments are attempting to capitalise on the ability of BGs to promote regeneration of tissues away from the implant interface, thanks to the osteogenic properties of the ionic products released at and around the implant site by the glass dissolution.^{2,3} Reflecting this shift of perspective, while *bioactivity* was sometimes associated only with the bone-bonding ability of a material, nowadays the term tends to be used in a broader context, to indicate materials capable of inducing a favourable response from the body.³ The bone bonding and tissue regeneration abilities both depend on the fast release of soluble species such as calcium, silica and phosphates from the implanted glass. This establishes critical concentrations of these species in the environment surrounding the implant, which are then capable of activating bone-bonding processes at the glass/tissue interface and also triggering osteogenic mechanisms at the cellular level.³ The proangiogenic and anti-osteoporotic properties of these glasses, recently emerged, also depend on the delivery and release *in situ* of other ions, such as nickel, cobalt and strontium from suitably doped bioglasses.^{4–6}

The key role of the glass dissolution in controlling its biological activity underpins current attempts at rationalising the performances of these materials based on structural and dynamical features with a direct impact on the dissolution process itself.^{7,8} The typical size and time scales of these features, involving structural units covering few Å and elementary dynamical events lasting few picoseconds, make atomistic computer simulations such as Molecular Dynamics (MD) particularly suitable to investigate them. Whereas promising

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His research is focused on rationalising the behaviour of materials at the atomic scale. He employs classical and *ab initio* simulations to model structure, dynamics, and reactivity of materials including crystalline and amorphous oxides with applications in biomedicine and (photo)catalysis.

1 progress has been made in some respects (for instance, the
identification of direct structure-bioactivity links⁹) progress has
been slower in other directions, such as in the explicit simula-
5 tion of dynamical transformation and reactivity at the
interface.^{10,11}

In this Perspective, several challenges faced today by atomistic
computer modelling approaches applied to rationalise the
behaviour of bioactive glasses are discussed, in relation to the
successes and limitations of the simulations in each case. Even
10 though the discussion is focused on BGs, the established role of
these systems in the field is such that many considerations
made here can be considered relevant in the broader area of
atomistic simulations of biomaterials.

15 Current challenges for atomic-scale simulations

The physicochemical behaviour of a bioactive glass following
20 its implant in a physiological environment can be investigated
and understood using computer simulations targeting different
aspects:

(1) *Bulk and surface structure.* The rationalisation of the
25 compositional dependence of several macroscopic properties
of glasses based on the underlying microstructure is a very
active field.^{12–15} In particular, several structural features of the
bulk glass have previously been associated with the glass
stability, solubility and bioactivity.^{16–18} The simulations can
30 directly determine these and other microscopic features, assess
their correlation with available experimental data on the
solubility, and extrapolate these findings to predict the
behaviour of new glasses.¹⁹ Furthermore, reactive models of
the surface region exposed to molecular probes such as water
35 and ammonia^{11,20,21} allow one to integrate the information
above with additional details about specific surface sites (not
necessarily stable in the bulk glass structure) that contribute to
the interaction of the biomaterial with the host.

(2) *Ion migration dynamics.* The release of a biologically active
40 ionic species (*e.g.*, a modifier cation, but also a soluble phos-
phate or a silicate chain, *etc.*) from the glass depends on the
rate at which the species itself can migrate through the bulk
and gain access to the interface region. Indirect conjectures
about the expected ion migration behaviour can be based on
45 the static local structure (coordination environment) of the
mobile species, which obviously influences its dynamical
behaviour.^{5,22,23} However, MD simulations also allow one to
directly observe the diffusive process with very high space and
time resolution, so that the diffusive mechanism of different
50 soluble species can be fully analysed and linked to the
biological behaviour.²⁴

(3) *Reduced size.* Once their effect on the glass behaviour has
been fully understood, adjusting the structural and dynamical
features mentioned above is the key to achieve specific resorp-
tion rates and bioreactivity, tailored to a specific application.
55 The emerging new behaviour exhibited by BG systems of sub-
micrometre dimensions, such as BG nanoparticles (NPs) and

nanofibres,^{25–28} points to the reduced size as a powerful way to
1 achieve this target. Simulations can provide answers to the
question of how shape and morphology of the glass substrate
affect the above properties and thus control its performance.

In the following, I will summarize the main findings of
5 recent simulations performed in the three areas above, and
discuss some important challenges that must be faced to make
further progress in each case.

10 Bulk structure

New structural descriptors

The largest fraction of computational work in the field of
15 bioactive glasses has been focused on their bulk structure. This
is because the computational methods to obtain a realistic
model of a bulk melt-derived glass are relatively well developed,
also for more complex, multicomponent compositions.^{7,30,31}

For instance, Reverse Monte Carlo (RMC) modelling enables
20 the constrained fitting of experimental neutron or X-ray diffrac-
tion patterns with an atomic-scale 3D structure, which can then
be used to isolate short-range features such as the local
coordination of a species.³² The quantitative reproduction of
medium-range features, however, is not necessarily as accurate,
and further independent experimental and theoretical data
25 may be needed for refining the RMC hypothetical structure,³³
which cannot then be completely unbiased. On the other hand,
MD simulations directly yield an unbiased structural picture of
the glass, which does not rely on the availability of additional
structural data, and whose reliability only depends on the
30 quality of the underlying force field. Accurate force fields are
now available that allow one to access quite large system sizes,
on the order of $\sim 10^4$ atoms, with a high level of accuracy.³⁴
Models of this size, spanning lengths between 2 and 10 nm, are
necessary to extract structural properties relevant for the glass
35 dissolution with a high statistical accuracy. In fact, ion dissolu-
tion rates of glasses indirectly reflect medium-range bulk
features such as network connectivity,¹⁶ ion clustering and
nanosegregation⁹ or organisation in chain and ring nano-
structures.¹⁷ Whereas the effect of these features on the bioactivity
40 is now relatively well established,⁷ it has also been emerging
that they cannot provide a complete description, allowing
accurate predictive estimates of the glass behaviour in different
cases. Further work is needed to discover additional structural
descriptors that exhibit significant correlation with the glass
45 durability and can then be employed to expand and comple-
ment the set of structural parameters discussed above. This
task requires experimental reference data on the compositional
trends of the glass biodegradation rate.³⁵ By fitting a suitable
predictive model to the experimental dataset, one can identify
50 new structural parameters whose inclusion in the set of
descriptors improves the fitting, and discard those descriptors
that do not. Following this approach, we were recently able to
identify a few new structural descriptors that affect the solubility
and thus the performances of glasses used as radioisotope
55 vectors for *in situ* radiotherapy,^{19,29} an application which also

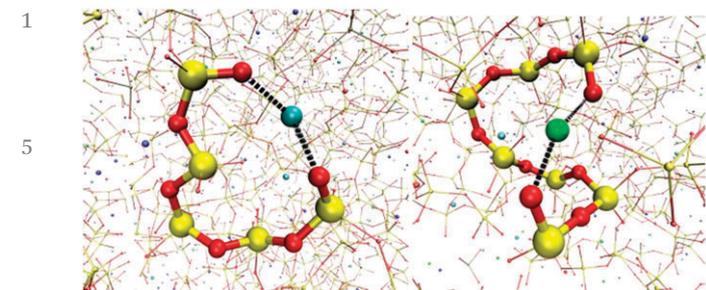


Fig. 1 Nanostructures taken from the model of a Y-doped bioglass, showing a modifier ion (the sphere at the centre of the loop, left: Ca, right: Y) cross-linking two tetrahedra belonging to the same chain fragment: the modifier ion can be thought as holding the whole $\text{O}_3\text{SiO}-(\text{SiO}_2)_n-\text{OSiO}_3$ unit in place and thus increasing the network durability by hindering its release. Adapted from ref. 29 with permission from The Royal Society of Chemistry.

critically depends on the glass durability. The additional structural descriptors that were identified complement standard parameters such as the network connectivity in quantitatively expressing the strength of the glass network and its resistance to dissolution. For instance, non-covalent cross-links between separate portions of the silicate network, bridged by a central modifier cation, play a key role in this context. Phosphosilicate chains whose end members are coordinated to the same modifier cation can be considered as held together (and thus, to some extent – depending on the specific strength of the cation-glass network interaction – prevented from dissolving) by that same cation^{29,36} (Fig. 1). It turned out that a higher ionic field strength (such as that of Y^{3+} , used as β -emitter in radiotherapy) increases the ratio of inter- to intra-tetrahedral linkages in the ion's coordination shell, and leads to a greater ability of the higher-field strength cation to bind together several spatially-separated fragments of the glass network (Fig. 1).^{29,37} Because these effects work together against the break-up and dissolution of the glass matrix, quantitative measurements of the corresponding features, extracted from the models, can be successfully included into the set of structural descriptors that a solubility-predictive model is built upon.¹⁹ The key challenges here are represented by the need to obtain experimental datasets covering the biodegradation of a wide range of relevant compositions, and the task of devising structural descriptors such as those above that can help to reproduce, and then eventually predict, the experimental trends.

Cooling-rate and size effects

A key issue to be assessed is the possible effect of the necessarily limited time and space scales common to all MD-based computational procedures to generate a model of a glass, on the accuracy of key structural descriptors such as those discussed above. The MD procedures typically involve a melt-and-quench approach that mimics the experimental one, but over much faster cooling rates and with much smaller samples. The thorough assessment of size and cooling rate effects is conceptually straightforward, but it represents a significant

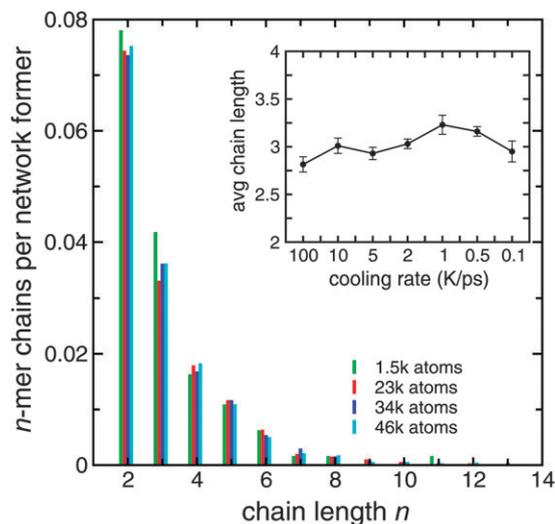


Fig. 2 Main panel: distribution of the lengths of (phospho)silicate chains identified in MD models of 45S5 Bioglass[®] of different sizes.³⁸ Inset: average chain length of models obtained at different cooling rates.

challenge in practice, because of the implicit difficulty in evaluating the convergence of the structure over simulation conditions varied over very different time and space scales, covering several orders of magnitude. For instance, the 10^3 time scaling factor involved when switching from a conventional (10 K ps^{-1}) to a considerably slower (0.01 K ps^{-1}) cooling rate leads to a corresponding massive increase in the simulation time required to complete the simulation.[†] This difficulty is vastly amplified for large sample sizes, with the result that even with powerful state-of-the-art computer resources at hand, combining large systems ($N > 10^5$ atoms) with slow cooling rates ($< 10^{-2} \text{ K ps}^{-1}$) still represents an arduous task.

However, recent investigations^{38,39} show that the weight of size and cooling rate effects is indeed small, not only for short-range properties (which is expected), but particularly for key structural properties such as Q^n speciation, chain/ring structure, and spatial distribution of modifier cations. For instance, Fig. 2 illustrates the chain structure of MD models of 45S5 Bioglass[®] obtained under different simulation conditions.³⁸ The 45S5 structure appears dominated by short silicate chains containing 2 to 4 monomers: the inset of Fig. 2 confirms that the average chain length is around 3, essentially unaffected by the cooling rate, besides statistical fluctuations. The distributions of chain lengths, shown in the main panel of the figure, retain a very similar trend in a range of system sizes varied by a factor of 32, the only apparent effect of a smaller size being a slightly higher fraction of the smallest (dimer and trimer) chain fragments. This is consistent with the essentially constant Q^n distribution recently found for sodium silicate glass models containing up to one million atoms (Fig. 3).³⁹

[†] For instance, a total of 270 ns, or > 1.3 billion MD time steps (a typical time step is 2×10^{-16} s in simulations performed with a shell model potential³⁰) would be needed to cool down to room temperature a melt pre-equilibrated at 3000 K, as done in common MD procedures.

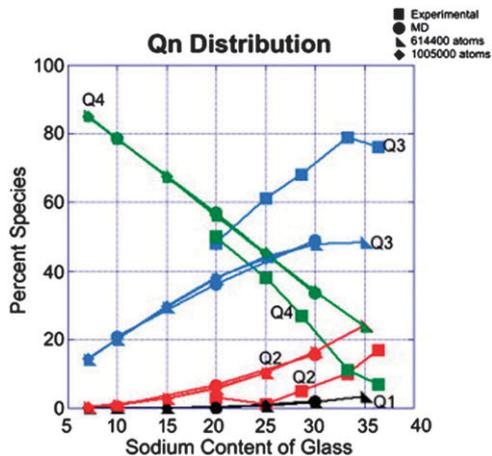


Fig. 3 Q^n distribution for several sodium silicate glasses, obtained from samples of different sizes, from 3000 to 10^6 atoms. Reprinted from ref. 39, with permission from Elsevier.

The important message, then, is that medium-range structural features extracted from models of silicate and phosphate glasses obtained through conventional MD setups^{40–43} are generally reliable, so that CPU-demanding procedures to access more challenging conditions are in most cases unnecessary. Essentially, the unrealistic (compared to practical synthesis) MD conditions employed to obtain the models do not appear to have a negative impact on the accuracy of the main structural features that affect the glass durability, and then on key conclusions based on the analysis of those features. It should be noted, however, that the different performances of polarisable vs. non-polarisable force fields (with the former generally leading to a more accurate description of the Q^n speciation^{34,44}) means that the convergence of medium-range structural features should ideally be evaluated on a case-by-case basis, especially for non-polarisable force fields whose convergence could be slower.

Dynamical properties

MD simulations are naturally suited to follow dynamical processes in condensed phases, and many MD studies have indeed investigated the migration of modifier ions in silicate and phosphate glasses.^{45–50} Not as many studies, however, have concerned ion migration in bioactive compositions. Even though some general features identified for conventional, bio-inactive glasses could also describe the migration of network-modifier cations in bioactive compositions, the same structural peculiarities that enhance the biological response of these glasses can also determine a different dynamical behaviour for an ion moving in the bioactive matrix, and this different behaviour can in turn further affect the activity of the bio-material. For instance, it is well known that the fast dissolution of highly bioactive compositions such as 45S5 Bioglass[®] arises from a highly fragmented, open silicate backbone.⁷ It turns out that this fragmentation enables ion migration pathways not favourable in the denser network of common higher-silica

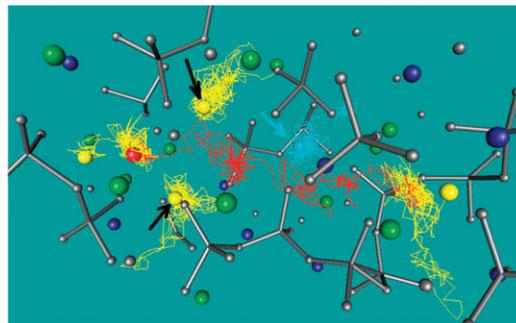


Fig. 4 3D traces of the MD trajectory of key Na and Ca ions, illustrating the migration of an individual Na^+ (red) and the correlated displacements of several other ions (Na, yellow and Ca, cyan). Reprinted with permission from ref. 24, Copyright 2010 American Institute of Physics.

(bio-inactive) glasses: recent simulations²⁴ have highlighted how an ion migrating in the fragmented 45S5 matrix can travel through vacant transient sites created by temporary displacements of another Na or a Ca cation (Fig. 4). The formation of these temporary sites, even if still possible, would not be as favourable in the more rigid network of a higher-silica common glass.⁴⁸

The main challenge to be faced in order to apply standard MD approaches to model ion migration in bioactive glasses has to do with the infrequent nature of the hopping events that compose the diffusive process. The “slow” (relative to typical MD time scales) character of ion migration in glasses entails that prohibitively long trajectories would be needed in order to gain a reasonably accurate sampling of the diffusive event at room temperature. Most MD studies of diffusion in glasses of biomedical interest to date have adopted an effective strategy to cope with this problem, wherein the simulations are run at a high temperature, below the glass transition.^{24,51,52} This approach should ensure (although this condition must be directly verified in each case) that the modifier ions move in a static silicate/phosphate network whose average configuration and energy landscape match the ones stable at room temperature, so that the description of the diffusive phenomenon at the higher temperature is still representative of practical conditions.

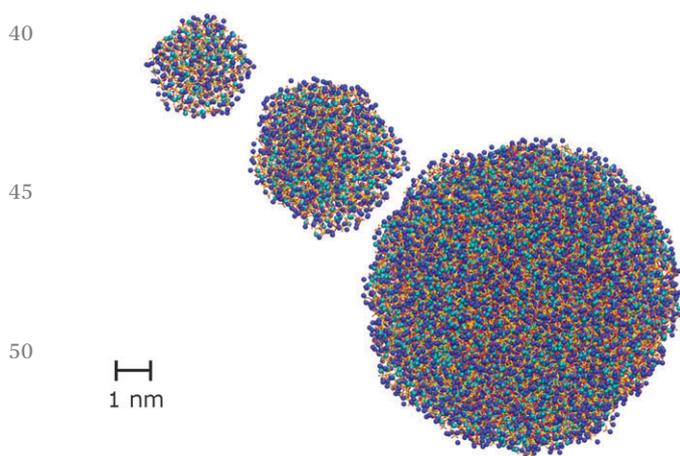
Another potential difficulty is represented by the possible inadequacy of force fields employed in classical MD runs: being normally parameterized by fitting structural and (less frequently) elastic properties of crystalline phases related to the target glass, a potential that provides a good description of the glass structure does not necessarily perform equally well in the reproduction of diffusive processes. Whereas classical potentials have been employed with good results to model diffusive processes in bioglasses,^{51,52} a safer solution would undoubtedly be represented by parameter-free *ab initio* MD (AIMD) approaches.⁵³ The higher computational demands of the latter, however, limit the AIMD trajectory length to below the nanosecond range, with the consequence that a straightforward investigation of the migration of slow-moving cations is complicated, even with the higher-temperature strategy described above. For instance, using AIMD it has been possible to characterise sodium migration in 45S5 Bioglass[®] (Fig. 4), but not enough calcium migration events

1 were observed during the simulation time to yield an equally
2 clear picture of the (slower) diffusive process of Ca.²⁴

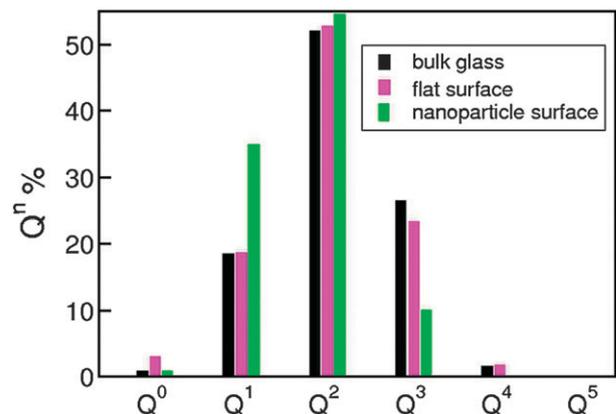
3 A more rigorous approach for tackling the timescale pro-
4 blem affecting MD simulations of migration in glasses could be
5 represented by enhanced-sampling methods.^{54–56} These have
6 been developed to accelerate the sampling of processes that,
7 due to high energy barriers or for other reasons, proceed too
8 slowly in configuration space to provide accurate statistics over
9 typical MD runs. Whereas the application of these methods to
10 study ion migration in crystalline solids, often characterised by
11 well-defined deep energy minima separated by high barriers,
12 does not present particular difficulties,^{57–59} the application of
13 AIMD combined with enhanced-sampling to the more complex
14 energy landscapes experienced by ions migrating in multi-
15 component bioactive glasses is less straightforward, and
16 represents an intriguing challenge for the future.

20 Reduced size

21 Several recent examples show the reliability of MD simulations
22 for modelling crystalline and amorphous nanoparticles
23 (NPs).^{60–62} The number of atoms contained, for instance, in
24 an isolated BG nanoparticle of 5–15 nm is of the order of 10^4 – 10^5 ,
25 a manageable size for classical MD simulations. The latter can
26 then provide, in a relatively straightforward way, an atomistic-
27 resolution picture of the actual nanosized substrates⁶³ (Fig. 5). A
28 suitable computational procedure in this case involves fast
29 quenching a liquid mixture constrained in an isolated sphere of
30 the desired size, roughly replicating the flame synthesis used to
31 prepare small BG nanoparticles in a high-temperature environ-
32 ment.⁶⁴ Models of a 45S5 particle obtained in this way recently
33 provided some preliminary indications about which structural
34 and dynamical effects of the reduced size can be relevant for the
35 biological behaviour.⁶⁰ It turns out that some of the key properties
36 of bioactive glasses most beneficial for their bioactive behaviour
37 are further enhanced when the size of the glass substrate is



38 Fig. 5 Models of 45S5 Bioglass[®] nanoparticles of 3–10 nm size, obtained
39 using Molecular Dynamics.⁶⁰ The largest particle contains ~40 000
40 atoms.



41 Fig. 6 Silicon speciation in the external region of 45S5 nanoparticles,
42 compared to the flat surface and to the bulk structure. Adapted from
43 ref. 60 with permission from The Royal Society of Chemistry.

44 reduced: the high fragmentation of the silicate network further
45 decreases on the surface of a 45S5 nanoparticle, compared not
46 only to the bulk glass but, most importantly, to the virtually flat
47 surface of a corresponding larger glass substrate (Fig. 6).
48 Moreover, the mobility of modifier cations and the density of
49 three-membered silicate rings – key features to support rapid
50 dissolution and bone bonding processes at the surface⁶⁵ – are also
51 enhanced at the nanoparticle surface compared to samples of
52 larger size.

53 Whereas models of dry nanoparticles are the necessary
54 starting point to gather information on these systems, they
55 do not take into account the additional perturbation induced
56 by the surrounding fluids that come into contact with the
57 particle in a biological environment. An important future step
58 thus must involve modelling of the explicit interface between
59 the nanoparticle and a suitable aqueous medium, and assess
60 the effects of this interaction on the properties discussed above.
61 The main challenges that will have to be faced concern: (i) the
62 need of accurate force fields to model the additional interac-
63 tions at the biomaterial interface (the considerable size of the
64 models prevents the straightforward application of AIMD
65 approaches in this case); (ii) the significantly increased
66 computational demands of the simulations of solvated systems
67 compared to the dry cases, especially for the largest NPs.

45 Conclusions

46 The direct observation, through computer simulations, of the
47 chemical processes that follow the implantation of a biomater-
48 ial in a biological environment is complicated by the character-
49 istic space and time scales that rule these phenomena. In
50 principle, a process such as the biodegradation of a bioactive
51 glass scaffold for tissue engineering can only be explicitly
52 modelled through very large-scale (coarse-grained, mesoscale
53 and Finite Elements) numerical approaches.^{66–68} The coarse-
54 grained nature of all these approaches, while allowing one to
55 reach more realistic space and time scales, averages out the
56 chemical details of the biomaterial and its biointerfaces, such

1 as short- and medium-range structural features and elementary
 dynamical (ion migration and reaction) steps. The latter aspects
 can only be modelled through the higher resolution of atomistic
 simulations. These atomic-level details provide the foundation
 5 for a rational design of the core biomedical materials, whose
 performances can be understood and optimised based on the
 insight extracted from the atomistic models. While there is some
 important degree of complementarity between very different
 information provided by the macroscopic and atomic-scale
 10 methods, an important future challenge will involve filling the
 substantial gap that separates them, for instance by further
 extending the space and time scales that can be accessed in
 atomistic simulations, but also in mapping the fundamental
 information provided by the latter to develop and refine the
 15 macroscopic approaches.

This is particularly important from the perspective of
 modelling nanosized biomaterials of practical sizes, and of
 simulating infrequent dynamical processes such as activated
 chemical reactions and ion migration on those substrates. The
 20 combined application of enhanced-sampling approaches with
 AIMD on high-end parallel supercomputers represents a very
 promising tool in this context.

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