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In Honor of Larry Hench

Reactive molecular dynamics: an effective tool for modelling the sol–gel synthesis of bioglasses

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ABSTRACT

Unlike melt-derived bioactive glasses, obtaining realistic models of sol–gel glasses represents a significant challenge for current simulation methods, due to the need to accurately reproduce the dynamical evolution in an aqueous solution starting from the precursors. Here we discuss the advantages of using reactive molecular dynamics in this context, by reviewing recent studies where the approach has been applied to examine the initial transformation of realistic precursor solutions. Moreover, we discuss additional results illustrating the gradual formation of clusters and rings in the presence of calcium, which corroborate our recent analysis and further highlight the importance of reactive molecular dynamics for guiding future computational studies of sol–gel biomedical glasses.

Introduction

Bioactive glasses have come a long way since Hench first introduced Bioglass®, which was produced by the traditional melt and quench technique [1]. This method requires elevated temperatures to form the initial molten state; however, there are now a number of applications for which such high temperatures must be avoided. One low-temperature glass preparative route is the sol–gel route, and this is now widely used in glass engineering, including the preparation of bioactive glasses [2]. However, it has been found that the detailed chemistry of the sol precursors can have a dramatic effect on the viability of the sol–gel process. For example, in forming calcium silicate bioactive glasses, it has been found that the nature of the calcium precursor is absolutely critical: using the "wrong" precursor, the glass cannot be formed without heating the gel to such high temperatures as to render the approach invalid [3].

Thus, investigating and understanding at the atomic scale the evolution of sol–gel particles from their precursors will lead to more effective materials and has been the subject of numerous computational studies [4–12]. The objective of these studies, by and large, is to understand at a fundamental level the dynamical processes that occur in solution, involving a series of hydrolysis and condensation reactions.

In this paper, we review recent simulations of the polycondensation of silicic acid from realistic precursor mixtures, that is, systems representative of conditions used in the sol–gel synthesis of bioactive

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silicate-based glasses [13, 14]. We discuss the present computational capability to model this key process, which is obviously the essential requisite for an accurate modelling of the synthesis of sol–gel biomedical glasses.

Computational approaches

Dynamical reactive processes, by their very nature, must be modelled with techniques that permit the dissociation of molecular species: bond-breaking and charge transfer. The obvious approach is to use quantum mechanical methods, in which the behaviour of electrons is implicitly included [15]. However, a major drawback is the size of the systems that can be modelled in this way. Ab initio simulations are restricted to a few hundred atoms, because of the computational expense of the quantum mechanical approach [16].

Such size constraints do not apply to classical simulations, where the systems can reach many thousands of atoms, following trajectories of hundreds of nanoseconds in molecular dynamics simulations [12]. However, other limitations exist in the application of classical simulations to reactive systems, such as sol–gel solutions. These are to be found in the nature of the interatomic potential models used to calculate the forces between atoms. Classical simulations do not explicitly include electronic structure effects, which rules out the possibility of modelling reactions involving electron transfer and in general processes where the molecular bonding connectivity is not fixed but changes dynamically. Recently, however, a number of force fields have been developed to overcome this limitation.

The most—and probably only—suitable class of classical MD force fields to tackle systems controlled by chemical reactions involving breaking and formation of covalent bonds are reactive force fields [17–20]. By taking into account the bonding environments instead of pre-defining all bonds a priori, they are able to describe covalent bond formation or breaking during the MD run, whereas in standard force fields the initial covalent bond connectivity is fixed: for instance, no water dissociation or formation of new O–H bonds, different from those in the starting structure, is possible. Moreover, with reactive force fields the description of every element remains the same across different phases, so, for example, the oxygen atoms in silicic acid and those in water are treated with the same mathematical formalism. For this reason, even though reactive force fields are computationally more expensive than non-reactive ones, they give a better description of the various processes, including the typical oligomerization reactions in sol–gel systems, than any other classical MD potential.

Here, we describe the use of the ReaxFF reactive force field, developed by van Duin et al., [21] which is a bond-order, variable-charge potential, and show that it can successfully reproduce the condensation reactions controlling the overall formation of bioactive sol–gel glasses, with a relatively low computational cost.

Reactive force fields

Ab initio DFT models [22] could provide the most accurate description of glass formation, due to the first-principles nature of their evaluation of interatomic forces. In practice, however, even with methods such as Car–Parrinello MD, [23] which is able to tackle relatively larger systems, the system size remains an issue due to the high computational costs involved in the first-principles treatment of the forces. A few hundred atoms—even using parallel supercomputing facilities—are not enough to produce accurate statistics for the glass network, even though they are suitable for obtaining accurate short-range and local vibrational properties [24, 25].

A common approach has been to combine classical and quantum mechanical MD, first creating a quenched structure with classical MD, and then using DFT to optimize its structure [26]. This means that the medium-range structural features of the modelled material will essentially reflect the quality and accuracy of the classical interatomic potential used to create the initial structure. There have been several efforts to create more accurate classical force fields, especially using shell-model polarizable potentials that represent better the medium-range structure of melt-derived bioactive glasses [27]; however, they are not adequate for reproducing the changing bonding environments and chemical reactions involved in sol–gel processes. While the glass network is being formed by condensation in solution, covalent bonds break and form continuously, and these fast and frequent changes in bonding patterns necessitate a

different description of the potential that includes variable, connection-dependent terms describing chemical bonds, as well as a flexible description of charges.

This is the gap that reactive potentials like ReaxFF can fill. ReaxFF employs a bond order-dependent approach, where bond orders are calculated and modified at every iteration, based on specific relationships between the bond distance and the bond order. Furthermore, the atomic charges are determined from the local bonding environment. Changes in bond order coincide with changes in electron densities. The partial charges of atoms therefore adapt to the changing local environment as the reactions in solution progress. More specifically, ReaxFF incorporates the charge equilibration technique (Qeq) introduced by Rappé and Goddard [28], which minimizes the electrostatic energy by assigning partial charges based on ionization potentials, electron affinities, and atomic radii. All atomic charges are thus assigned dynamically, and the charge of an individual atom depends on its environment. Compared to other reactive potential, ReaxFF has the additional advantage of being implemented in highly efficient parallel MD codes such as LAMMPS [29].

The total energy of the ReaxFF system is separated into several components, and all the covalent interactions are a function of the bond order:

$$E_{\text{system}} = E_{\text{bond}} + E_{\text{over}} + E_{\text{under}} + E_{\text{lp}} + E_{\text{val}} + E_{\text{pen}} + E_{\text{torsion}} + E_{\text{conj}} + E_{\text{vdW}} + E_{\text{coulomb}} \quad (1)$$

The system energy in Eq. (1) includes bond, over-coordination, under-coordination, lone electron pairs, valence angle, penalty, torsion, conjugation, van der Waals, and Coulomb contributions. A detailed description of these terms can be found in Ref [30]. ReaxFF has been shown to provide accurate estimates for both reaction energies and reaction barriers [31].

The parameterization of the ReaxFF force field involves fitting many parameters per atomic species to a reference data set (training set), through an optimization procedure [31]. Due to the complexity of the ReaxFF functional form (Eq. 1) and the large size of a typical training set, the initially developed parabolic search method [32] tends to get trapped in energy minima; therefore, more advanced parameter sampling methods such as Monte Carlo [33] and genetic algorithms [34] are being developed. The available parameters for a certain atom are not always transferable across different phases and systems, and even the most recent potentials are not always able to reproduce the energy landscapes obtained by DFT [8]: hence, it is important to assess how a ReaxFF approach can perform in the context of sol–gel biomedical glasses, before using it in large-scale studies.

Models of silica polymerization using reactive force fields

The key reactions required for the formation of sol–gel silicate glasses are the condensation of silanol (Si–OH) groups from the silicic acid monomers or *n*-mers, and its reverse (hydrolysis) process, specifically:

$$\equiv\text{Si--OH} + \text{HO--Si}\equiv \leftrightarrow \equiv\text{Si--O--Si}\equiv + \text{H}_2\text{O}. \quad (2)$$

The condensed products continue to polymerize forming additional siloxane bonds and removing silanol groups, leading to extended structures [35].

The ReaxFF potential has proven very useful in modelling complex systems with mixed bonding states, such as glasses. A previous study of the decomposition reaction in a combined silica and hydrocarbon system, by Chenoweth et al. [7], demonstrated that ReaxFF can successfully reproduce the chemical stability of silica at various temperatures and pressures. Deetz and Faller [6] used ReaxFF with their own optimized potential to model alkoxysilane polycondensation at different temperatures and calculate condensation and hydrolysis reaction energies, as well as activation energies for silane condensation. Rimsza et al. [5] used ReaxFF to simulate organosilicate glasses by generating structures of nanoporous amorphous silica with subsequent addition of organic methyl groups. Relaxing the structures with ReaxFF allowed them to develop models that included the randomized porosity and organic content critical to the microstructure of nanoporous silica and organosilicate glasses, while still generating experimentally accurate structures. More recently, Chowdhury et al. [36] performed a ReaxFF simulation of anhydrous silica glass to study the stress–strain response under variable tensile strain at different temperatures.

These previous simulations attest the strength of ReaxFF in supporting MD simulations of silica

polymerization from a variety of precursors. For applications to sol–gel synthesis of biomedical glasses, however, one has to carefully assess its capabilities in the case of aqueous solutions of calcium hydroxysilicates. ReaxFF was initially developed to simulate hydrocarbon-based systems, but the method was later extended to other elements. van Duin et al. [30] fitted the reactive force field parameter set to simulate silicon and silicon oxide systems. Fogarty et al. [37] then extended that parameterization to model the H_2O/SiO_2 interface, by fitting the parameters of the proton transfer reactions at the interface to DFT data. Larsson et al. [38] further improved the parameter fitting procedure using genetic algorithms. There have been further parameterizations for silicon oxide systems [4, 39, 40], but our extensive testing showed that the Si/O/H parameters of Larsson et al. are the most suitable to model the formation of sol–gel glasses, as they give the best description for liquid water compared to experiments. In fact, since the sol–gel processes occur in aqueous solutions, a very accurate representation of the liquid water structure is crucial. Figure 1 shows the different oxygen–oxygen radial distribution functions (rdfs) for pure liquid water obtained with different ReaxFF potentials: only the Larsson et al. parameters give an rdf in agreement with the experimental curve, obtained by X-ray and neutron diffraction data [41].

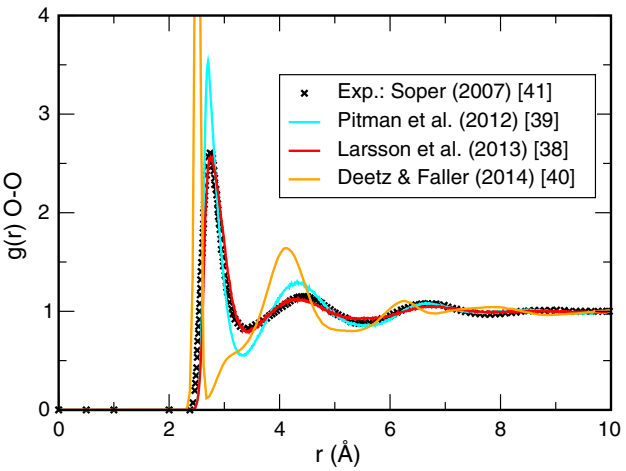

Figure 1 O–O radial distribution function at 300 K calculated with different ReaxFF force fields, compared with the experimental curve [41]. While the Ref. [40] potential accurately reproduces Si–O interactions, it fails to provide a reliable description of liquid water.

Reactive MD models of sol–gel bioactive glasses

The studies discussed above provided strong indications that ReaxFF is capable of modelling the fundamental interactions controlling the sol–gel synthesis of bioglasses. In order to directly check this possibility, we recently assessed its efficiency in reproducing the condensation/hydrolysis processes in an aqueous solution including silicon and calcium precursors typical of sol–gel bioactive glass compositions, [42] and with relative ratios corresponding to standard experimental values used in the synthesis of calcium silicate sol–gel bioactive compositions [3]. The simulations were started from the hydrolysis products of the TEOS precursors used in the experiments, that is, orthosilicic acid $Si(OH)_4$ monomers.

Molecular dynamics calculations of several nanoseconds were conducted using LAMMPS [29], an open-source classical MD code distributed by Sandia National Laboratories, which includes a ReaxFF module. The calculations were run in parallel on a cluster of 64 dual core Intel L5630 processors with a low latency, fast throughput infiniband interconnection. Although the relatively small number of CPUs in comparison with those that would be needed for a corresponding quantum mechanical calculation, classical MD with the ReaxFF force field allowed the calculations to be completed within a reasonable timescale.

In order to accelerate the hydrolysis and condensation processes, a high temperature of 2000 K was used, a procedure commonly applied to model silica polymerization on time scales affordable to MD simulations [12].

Simulations with variable-charge force fields require, as an input, the frequency of updating the atom charges. In this study, the atom charges were updated every time step, which, although computationally expensive, provided more accurate results by ensuring that the charges are always optimized for each configuration. Updating them less frequently decreases the computational time, but compromises the energy conservation, as demonstrated by Cowen and El-Genk [43].

This computational framework was shown to provide a realistic representation of the initial stage of the silica polycondensation in the presence of calcium [42]. Below we discuss additional results that extend

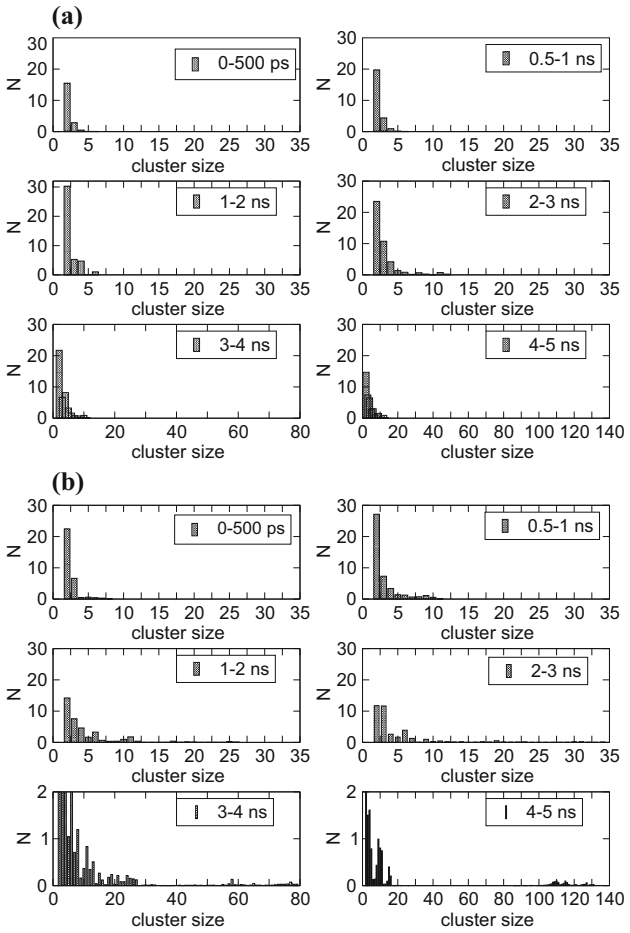

Figure 2 Cluster size distributions for **a** the calcium-free and **b** calcium-containing systems. Notice the different *y*-axis scale to highlight the formation of clusters of large size in the last two frames of (**b**).

the overall picture, confirming the suitability of ReaxFF for these systems.

We monitored the gradual change in the distribution of Si clusters and rings formed by condensation, with or without calcium in solution. Figure 2 shows that only small clusters are formed in the Ca-free system during 5 ns, whereas in the same time much larger silica clusters, reaching up to 100 atoms at the end of the simulation, are formed when Ca ions are present in the initial solution.

Cluster formation is accompanied by the formation of closed –(Si–O–Si–O)– rings of different sizes, which according to the above effect are predominantly observed when Ca is present in solution. The rings were identified by calculating the shortest path between two of the nearest O neighbours of a Si atom [44]. Figure 3 shows snapshots extracted from the simulation of the system containing calcium, where rings of size 5 can already be seen after 500 ps; most rings are not stable, that is, they open and reform several times, so that their total number stays constant up until 4 ns, after which a rapid increase in both ring size and number is observed, with large rings containing >30 Si atoms formed (Fig. 3, right panel).

The ring and cluster analysis highlights two different mechanisms controlling silica polymerization in these systems, promoted by the presence of calcium: the initial mechanism is based on monomer and then oligomer aggregation, and this process is gradually replaced by a different mechanism

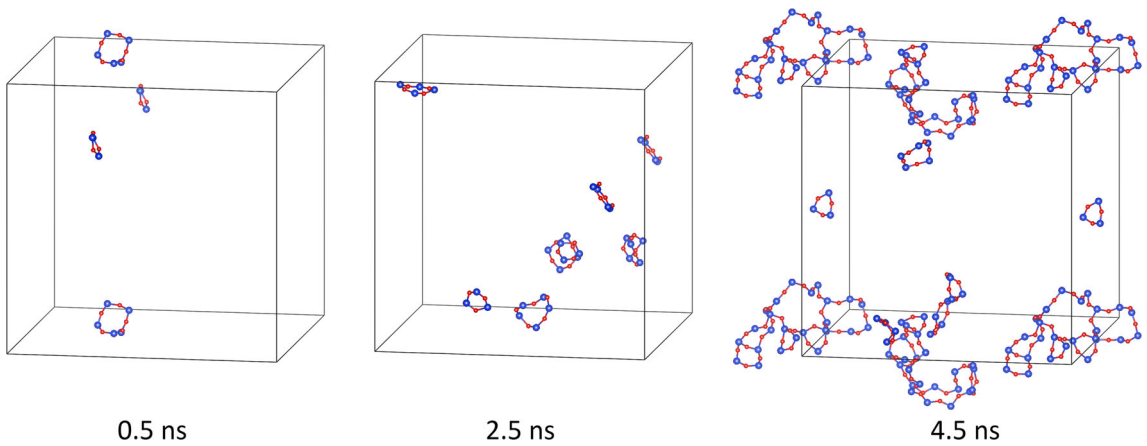

Figure 3 Snapshots from the MD run of the Ca-containing system in the simulation cell. For clarity only the –(Si–O–Si–O)– closed rings present in the system are shown (whereas water molecules, Ca and H atoms are omitted). Silicon atoms are depicted in *blue*, oxygen atoms in *red*.

involving internal rearrangements of the formed clusters leading to increased cross-linking with corresponding enhanced formation of silica rings. These data provide further support to the basic mechanisms controlling the initial polymerization of the silica network in solution that were hypothesized mainly on the basis of the evolution of the silica speciation in our previous work [42]. The important aspect is that the ReaxFF simulations predict an enhanced rate of formation of the initial pure silica nanoparticles in the presence of calcium hydroxide. This effect can be linked to the failure of Ca to enter the silica network already at the early stage of the sol–gel process, which as noted before is the key challenge to overcome in order to produce more effective sol–gel bioglasses [45]. The purpose of this review was to highlight the reliability of a computationally affordable approach such as ReaxFF in modelling the key features of the sol–gel solution chemistry of bioglasses. This tool can now be confidently applied to explore different conditions and identify those that may enhance Ca incorporation in the glass particles.

Conclusions

We discuss how reactive force fields can effectively model the polycondensation of silicic acid in aqueous solution, which is at the basis of the sol–gel synthesis of biomedical glasses. This allows realistic molecular dynamics simulations of the condensation and hydrolysis reactions, something that classical non-reactive potentials are unable to capture, and that ab initio approaches can capture in principle but cannot model in practice due to their prohibitively high computational requirements when applied to solution systems of suitable size. Therefore, reactive potentials, if correctly parameterized, are arguably the best way at present to accurately perform large-scale MD simulations of sol–gel biomedical glasses involving thousands of atoms, in a feasible time scale. The key aspect highlighted in this review is that the ReaxFF simulations provide accurate results for the process of silica polymerization from Ca and other (e.g. organic) precursors [6, 9, 42]. This is an essential prerequisite in order to use the same approach to model different initial conditions as well as the effects of the subsequent (drying and stabilization) stages of the sol–gel process.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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