The bioactive mechanism, by which living tissues attach to and integrate with an artificial implant through stable chemical bonds, is at the core of many current medical applications of biomaterials, as well as of novel promising applications in tissue engineering. Having been employed in these applications for almost 40 years, soda-lime phosphosilicate glasses such as 45S5 represent today the paradigm of bioactive materials. Despite their strategical importance in the field, the relationship between the structure and the activity of a glass composition in a biological environment has not been studied in detail. This fundamental gap negatively affects further progress, for instance, to improve the chemical durability and tailor the biodegradability of these materials for specific applications. This paper reviews recent advances in computer modelling of bioactive glasses based on molecular dynamics simulations, which are starting to unveil key structural features of these materials, thus contributing to improve our fundamental understanding of how bioactive materials work.

Keywords: molecular dynamics simulations; bioactivity; silicate glasses; structural properties

1. Introduction

The discovery by Hench and co-workers that a range of compositions of modified phosphosilicate glasses has the ability to form a stable chemical bond with living tissues (bone, ligament and muscle) opened a completely new field in biomedicine, ca 40 years ago (Hench et al. 1971). Since then, many artificial biomaterials based on, or inspired by, Hench’s glasses have been developed and successfully employed in clinical applications for repairing and replacing parts of the human body. This field is continuously expanding; new processing routes have extended the range of applications towards new exciting directions in biomedicine (Hench & Polak 2002), many of which still rely on the original Hench’s base formulation, 45S5 Bioglass, which has now become the paradigm of bioactive materials. However, the growing technological importance of these materials has not been supported by a corresponding growth in fundamental
understanding of the nature of their bioactivity, and trial-and-error approaches still represent the most common way to systematically optimize new applications of bioactive glasses. The availability of increasingly more powerful computational methods and resources now makes computer simulations an attractive alternative to experimental techniques, to obtain an atomistic view into the bioactive behaviour of bioglasses and fill the gap in fundamental knowledge. In particular, molecular dynamics (MD) simulations can now effectively tackle complex multicomponent amorphous systems such as the Hench’s glasses, and provide an unprecedented high-resolution view into their atomistic structure (Takada & Cormack 2008).

The scope of the present short review is to illustrate the recent applications of MD simulations to study bioactive silicate glasses. First, the strategic role of bioactive glasses in the current generation of biomaterials is introduced, and the importance of investigating their structure is discussed; then, after a short description of computational methods commonly employed to model glasses, the main highlights of recent MD simulations are discussed, focusing on structural features which can have a direct impact on the special properties of bioactive glasses.

2. Biomaterial types: bioinert, resorbable and bioactive

Materials for repairing and replacing injured, deteriorated or defective parts of the human musculoskeletal system have considerably contributed to improve the quality of life over the last decades, thanks to huge technological advances in the development of orthopaedic and dental implants and devices. The demand for these biomaterials to repair bones, joints and teeth is continuously increasing, owing to longer life expectancy and increase in musculoskeletal pathologies in the modern society (Hench 1998; Kokubo et al. 2003; Vallet-Regí et al. 2003; Hertz & Bruce 2007; Cerruti & Sahai 2006). Synthetic biomaterials can be generally classified into three separate categories, on the basis of the strength of the response that the exposure of the implant to a biological medium elicits in the living environment (Hench 1998).

First-generation biomaterials, developed during the 1960s and 1970s, are metals or alloys (titanium, stainless steel, cobalt–chrome) and dense or porous ceramics (Al₂O₃ or alumina and ZrO₂ or zirconia). They are bioinert, owing to their absent or weak interaction with living tissues upon implant: in the past, the minimal response from the host was in fact considered a desirable feature of any biomaterial for use inside the human body. Following contact with biological fluids, inert biomaterials are encapsulated within a non-adherent, fibrous layer of variable thickness. The implant–tissue interaction is essentially of mechanical nature, as the material can be cast and pressed in place to yield a suitably tight fit: this results in a very thin fibrous layer, which is crucial for the success of inert implants, as it reduces relative movement at the implant–tissue interface. Interfacial movement under external stress leads to loosening and deterioration of the mechanical fit, which causes pain and eventually leads to clinical failure of bioinert implants (Hench 1998). While porous ceramics can achieve a better mechanical fit thanks to tissue ingrowth in the micropores (Hulbert 1993), the absence of a real chemical adhesion with the tissues, combined with the reduction in strength inherent to the porous structure, limits their long-term durability in porous ceramic implants as well, and they have found...
applications mostly as bone spacers and scaffolds. While several millions of successful implants made from inert biomaterials have played and still play an important role in biomedicine, the maximum lifetime of these implants is generally less than 20 years, which is no longer adequate in a modern society with increasingly longer life expectancy.

The opposite case of bioinert materials is represented by resorbable or completely biodegradable materials, such as calcium phosphates, either crystalline or amorphous, which are rapidly dissolved upon exposure to physiological fluids, and gradually replaced with living tissues (Bouler et al. 2000; Knowles 2003). This procedure is, in principle, ideal, being based on the natural ability of bone and muscles to self-heal and regenerate, but is complicated by the need to match the rates of implant dissolution and tissue growth; while the implant is being replaced by new tissue, its strength will progressively decrease, and a very unstable interface will result, requiring immobilization of the patient for long periods.

Surface-active or bioactive materials represent an ideal compromise between these two limits: after implant, a bioactive material rapidly forms a stable bond with the tissues through a reactive surface layer (see below). The chemical (as opposed to mechanical) nature of this bond considerably enhances the interfacial adhesion of the implant; at the same time, the reactivity of bioactive materials is limited to their surface, owing to progressive passivation by the surface layer, which does not allow further degradation to progress rapidly to the bulk material, and therefore a stable interface is maintained long enough to favour further cellular interaction and induce controlled growth of mature tissues. Several biomaterials belong to this category: the first bioactive materials were discovered by Hench et al. (1971) ca 40 years ago; they showed that specific compositions of melt-derived Na₂O–CaO–SiO₂–P₂O₅ glasses can form a strong bond with hard (bone) and in some cases soft (muscle and tendons) connective tissues, through a sequence of rapid chemical processes that follow their implant in vivo or the in vitro contact with a physiological test solution. The key feature, which leads to the bone-bonding ability of bioactive glasses (and of bioactive materials in general), is the formation of a film of crystalline hydroxyapatite (HA) on their surface: as HA is the mineral component of bone, its presence on the glass surface promotes further cellular steps, such as incorporation of collagen and interaction with other biomolecules and tissue growth factors, which then favour the development of a biological bond with the tissues (Hench & Paschall 1973; Hench & Andersson 1993; Hench 1998; Kokubo et al. 2003). The overall thickness of the bonding HA layer is approximately 100–200 μm in bioactive compositions (Hench & Andersson 1993); this layer creates a strong bridge between the natural tissues and the artificial implanted material, thus promoting the integration of the bioactive implant; at the same time, it passivates the glass surface against further degradation, which would otherwise extend to the rest of the glass. This crucial double role of the HA film explains the close correlation observed between the rate of HA formation and the bone-bonding ability of a glass composition: an exceedingly slow rate of HA formation will, in fact, result in no bonding to tissue (Ogino et al. 1980). On the other hand, the most bioactive composition of this class, the 45S5 Bioglass, containing 45 wt% SiO₂, crystallizes HA in few hours after implant, and achieves bonding to both hard and soft tissues in approximately a week (Hench & Andersson 1993; Hench 1998). Higher silica
compositions, up to 60 wt%, require a few days to form the HA film and only bond to bone, but not to soft tissues. Glasses containing more than 60 wt% SiO\textsubscript{2} do not form the HA surface layer and behave essentially as bioinert materials, with no bonding to bone and encapsulation in fibrous tissue. Given this close relationship, compositional and other effects on the bioactivity are often assessed by simply measuring the in vitro rate of HA crystallization, rather than the actual bone-bonding ability in vivo (Ogino et al. 1980; Pereira et al. 1994; Cho et al. 1996; Peitl et al. 2001; Kokubo et al. 2003; Cerruti et al. 2005a).

The high effectiveness of the bioactive fixation process, by which the implant is attached to the living tissues through the HA–collagen interface, reflects the high strength of adhesion between the interface and the implant and with the tissues; in fact, failure of bioactive implants in load-bearing application can occur in either the implant or the bone, but not at their interface. Failure in the implant reflects the weak mechanical strength (i.e. brittleness and limited fracture toughness) of bioactive glasses, whereas fracture in the bone is often related to stress-shielding effects (Hench 1998); owing to the lower elastic modulus of bone compared with 45S5 glass, the latter supports most of the applied loads whereas the bone is exposed to lower loads, leading to its progressive weakening. The relatively poor mechanical properties limit clinical uses of melt-derived bioactive glasses to low-load-bearing applications, such as otolaryngological, maxillofacial, dental and periodontal implants (Yamamuro 1990; Hench et al. 1991; Wilson & Low 1992; Wilson et al. 1993, 1995). These applications are generally based on the 45S5 composition; its unique ability to bond to both bone and soft connective tissue is of key importance in middle-ear replacement prostheses (Wilson et al. 1993, 1995), whereas the ability to induce a formation of new bone very shortly after implant is crucial in the most common clinical applications of 45S5, i.e. to treat periodontal disease (Wilson & Low 1992); moreover, even though compact bioactive glass cannot be directly employed in high-load-bearing orthopaedic implants, its excellent osteoconductive ability can still be exploited to stimulate bone regeneration, by filling bone defects with 45S5 Bioglass in powder form (Hench & West 1996).

Synthetic HA and glass-ceramics biomaterials also induce a similar bioactive response upon implant. Synthetic HA ceramics is employed in powder or porous form, mostly in dental applications, and as coating to provide bioactive bonding to metallic prostheses (Ducheyne et al. 1980). As for bioactive glasses, the poor mechanical performances of HA biomaterials limit their application to non-load-bearing implants only; the HA response in these applications can be less efficient, because of its faster resorption, which reduces the stability of the interface in the earlier stages of the implant. The use of nanotechnology is currently being explored to improve the mechanical toughness and bioactivity of HA (Kalita et al. 2007). Enhanced mechanical properties can be achieved by partial crystallization, as in bioactive glass ceramics where a tough ceramic phase reinforces the glass. For instance, A/W glass ceramics, composed of apatite and wollastonite crystals embedded in a calcium-silicate amorphous phase, has very good mechanical properties while still being able to form a strong bond with bone (Nakamura et al. 1985; Kokubo et al. 2003); therefore, it can be successfully used in bone repair prostheses (Yamamuro 1993), even though application to high-load cases such as femoral and tibial bones is still not possible, and processing of glass-ceramics biomaterials can be difficult and expensive.

In §3, we focus on Hench’s bioglasses, which represent the prototype of the class of bioactive materials.
3. Bioactive glasses

Melt-derived bioactive glasses are obtained by quenching a mixture of the oxide precursors (SiO$_2$, Na$_2$CO$_3$, CaCO$_3$ and Na$_3$PO$_4$) previously melted at high temperatures, followed by grinding and sieving the quenched glass to produce the desired particle size. The presence of network modifiers such as sodium and calcium cations, which open the silicate network by breaking Si–O–Si bridges (Greaves 1985; Greaves & Sen 2007), reduces the melting temperature of the initial mixture, but temperatures above 1300°C are still needed, which negatively affect the processing costs. Much lower processing temperatures (below 600°C) are accessible when the glass is produced by the sol–gel synthesis route, first introduced for bioactive glasses in 1991 (Li et al. 1991). This technique involves hydrolysis and polycondensation of tetraethylorthosilicate, tetraethylphosphate and calcium nitrate or methoxyethoxide precursors in an aqueous environment, followed by mild thermal treatment. No source of sodium is needed to reduce the melting temperature in this case: bioactive sol–gel glasses have been synthesized with SiO$_2$ : CaO : P$_2$O$_5$ or even SiO$_2$ : CaO binary compositions, containing between 60 and 90 per cent SiO$_2$ (Pereira et al. 1994; Martínez et al. 2000; Balas et al. 2001). In fact, besides lower processing temperatures, the sol–gel technique also permits to expand the relatively narrow bioactivity range of melt-derived glasses; while melt-derived compositions containing more than 60 per cent are no longer bioactive, the upper limit is shifted to 90 per cent SiO$_2$ for sol–gel glasses. The enhanced bioactivity of sol–gel glasses is due to the much larger surface area (more than 100 times larger than melt-derived glasses), which reflect their porous hydrated structure, and leads to faster HA deposition rates; a higher surface area is also known to enhance the adhesion of biomolecules to the glass surface (Levy et al. 2007). In the last years, these favourable features have encouraged a significant shift in the research on bioactive silicate glasses, towards highly porous materials. In particular, recent work has shown the high potential of bioactive glasses for third-generation tissue-engineering applications (Hench & Polak 2002), where a highly porous, biodegradable scaffold combined with tissue cells hosts the in vitro growth of immature bone-like material, which is then implanted in vivo, where the tissue-engineered construct adapts to the living environment and stable mature bone is formed (Hench & Polak 2002; Hing 2004; Jones et al. 2007).

It is remarkable that the base composition for many of these advanced applications is still the original Hench’s 45S5, which can be made into a porous scaffold by sintering of powders (Boccaccini et al. 2007): the 45S5 composition turns out to activate genes, which stimulate healing of living tissues and control cellular repair (Xynos et al. 2000). This could be related to the release of specific amounts of Si, P, Na and Ca ions, whose local concentration in the physiological environment can approach critical values needed to stimulate the cellular activity (Xynos et al. 2000, 2001; Hench & Polak 2002; Day 2005; Boccaccini et al. 2007).

These observations highlight the central role still played by the original glass compositions introduced by Hench in the bioactivity of many current biomaterials, and it is likely that this key role will be maintained in the future. In order to tackle new challenges in this field, fundamental research on biomaterials needs a major shift towards more rational investigations: the
structural relationship between glass composition and bioactivity, the nature of the interactions between the biomaterial and the biological environment and the effect of surface texture on the adhesion to living tissues are some of the basic issues whose investigation is needed to support further progress in this field (Anderson 2006; Levy et al. 2007). In other words, before turning to devise new materials with potential biological applications, it is essential to gain a more critical understanding of how current biomaterials work. Given the key role played by Hench’s glasses in current biomaterials, and the large amount of experimental data available on their bioactivity, they represent an excellent reference to support new fundamental investigations, whose conclusions will be transferable to most bioactive systems, not only those based on the 45S5 or related compositions, but also, in general, to any surface-active biomaterial with the ability to bond to bone via an HA layer.

In §4, we thus examine the current understanding on the properties of bioactive silicate glasses, and illustrate in detail how the results of recent atomistic simulations are starting to provide a new, more rational view of these systems.

4. The bioactive mechanism and its origin: key facts

Following contact with a physiological fluid, the deposition of HA on the surface of bioactive glasses occurs through a sequence of five consecutive stages (Clark et al. 1976): (i) Na\(^+\) ions are rapidly released and replaced by H\(^+\) from the solution, (ii) the corresponding increase in local pH promotes breaking of surface Si–O–Si bonds and release of soluble silica to the solution, (iii) some of the surface silanol groups formed in steps (i) and (ii) condense to form a hydrated silica-rich layer on the surface, depleted in modifier cations, (iv) calcium and phosphate ions are released through the surface silica layer, and incorporate other Ca\(^{2+}\) and PO\(_4^{3-}\) from solution to form an amorphous calcium phosphate phase deposited on the surface, and (v) the latter amorphous film incorporates additional carbonate ions from solution and crystallizes to hydroxycarbonate apatite. Incorporation of collagen molecules in the HA layer and further interaction with other biomolecules and cells then lead to the formation of new tissue (Hench 1998). The HA formation mechanism was originally identified through the surface compositional profiles measured by Auger electron spectroscopy (Clark et al. 1976), and fully confirmed by a large number of subsequent investigations with different analytical techniques, ranging from vibrational and X-ray photoelectron spectroscopies to characterize the dynamical changes in the surface of the sample exposed to a physiological solution (Ogino et al. 1980; Peitl et al. 2001; Cerruti et al. 2005a), to optical emission spectroscopy techniques to analyse the composition of the contact solution at different times (Sepulveda et al. 2002; Arcos et al. 2003), to scanning and transmission electron microscopy to study the morphology and composition of the sample particles after immersion in body fluids (Kokubo 1990; Padilla et al. 2005).

As mentioned earlier, because the rate of HA formation determines the bone-bonding ability of bioactive materials, fundamental investigations only need to focus on the initial stages leading to HA crystallization. Several important observations about this process have been reported: the fact that the HA layer can be formed by silicate glasses containing no calcium or phosphorus is especially meaningful, because it highlights the central role of the hydrated
silica-rich surface layer in attracting and steering the deposition of calcium phosphate from the solution (Ohura et al. 1991; Kokubo et al. 2003). A reduced ability to form this reactive layer, as a result of a slower dissolution rate, could be the main factor responsible for the loss of bioactivity in compositions containing more than 60 per cent SiO₂ (Ogino et al. 1980). Several authors have attributed the key role of the silica-rich layer to its high density of exposed surface silanol (Si–OH) groups, which are needed for HA formation in a physiological environment (Cho et al. 1998; Kokubo et al. 2003); the silanol groups will be deprotonated at physiological pH, and the negatively charged surface will attract Ca²⁺ ions, which has been proposed as the first step of the calcium phosphate deposition (Li & Zhang 1990; Sahai & Anseau 2005). Even though for some particular compositions containing a very low silica fraction, a high rate of calcium phosphate precipitation (steps (iv) and (v)) can result in no apparent formation of an intermediate silica-rich layer (Aguiar et al. 2008), the formation of this layer exposing silanol groups appears essential for most bioactive compositions. To sum up, a rapid HA formation must reflect a fast dissolution of the glass network, with partial degradation of the silicate network, hydrolysis of Si–O–Si bridges and release of soluble silica in solution. This conclusion is also corroborated by the possible direct participation of dissolved silica species in the overall bioactive mechanism, not only as nucleation centres for the precipitation of calcium phosphate (Pereira et al. 1994; Cerruti et al. 2005b), but also in activating genes that induce osteoblast proliferation (Xynos et al. 2001). The important role of released silicon also contributes to the higher bioactivity of bioactive glasses compared with synthetic, Si-free HA biomaterials (§2).

5. Computational methods: classical and ab initio molecular dynamics

Classical MD simulations using empirical force fields represent one of the most powerful techniques to probe the complex potential energy landscape of amorphous materials and silicate glasses in particular, as proven by many applications in the last three decades (Woodcock et al. 1976; Huang & Cormack 1991; Vessal et al. 1992; Smith et al. 1995; Horbach et al. 1998; Lammert & Heuer 2005; Mead & Mountjoy 2006; Tilocca et al. 2006). The fact that, despite their wide technological relevance, only a small fraction of these simulations concerned glasses including three or more base oxides (e.g. Cormack & Du 2001) reflects the intrinsic difficulty to model multicomponent compositions using empirical potentials. While standard force fields commonly used to model crystalline oxides, such as the BKS potential (van Beest et al. 1990), are adequate to model pure and binary silicate glasses (Vollmayr et al. 1996; Yuan & Cormack 2001; Machacek & Gedeon 2003), their application to ternary and quaternary glasses is generally not as straightforward. This difficulty is mainly related to the mixed character of Si–O and P–O bonds, whose ionic–covalent balance depends on their local environment, such as the composition and geometry of the coordination shell of network-modifying cations in close proximity to the oxygen, and the bridging/non-bridging nature of the latter. The effect of this diverse and often quite distorted local environment can hardly be reproduced by mean-field approaches using fixed partial charges, as in the BKS potential and in many other rigid-ion (RI) force fields. A practical and much more accurate way to take the molecular environment into account in classical MD
simulations is via a shell-model (SM) approach, where the atomic polarizability is explicitly incorporated in the model by replacing polarizable atoms (typically the oxide ions for silicates) with core-shell dipoles consisting of two opposite charges connected by a harmonic spring (Yu & van Gunsteren 2005). In this way, the charge distribution in silicate and phosphate groups is always consistent with the local electric field, and a more adequate description of distorted bonded and non-bonded geometries, as well as of dynamical fluctuations at finite temperature, can be achieved. Even though any empirical potential, typically fitted to crystalline structures, is, in principle, not suitable to reproduce defects and coordination environments significantly different from those found in the crystal, SM and polarizable force fields represent a consistent step forward from this perspective. In fact, an SM scheme has been successful in a large variety of condensed-phase systems, ranging from ionic solids and liquids and their interfaces, to aqueous solutions (O’Sullivan & Madden 1991; Kerisit & Parker 2004; Spangberg & Hermansson 2004; Rosen et al. 2007), and was recently extended to model silicate glasses (Tilocca et al. 2006) and calcium phosphates (Pedone et al. 2007).

A higher level of accuracy is achieved in ab initio (AI) MD simulations, where ionic forces are calculated using quantum mechanics methods: this parameter-free, first-principles approach clearly represents the best possible way to include polarization and other electronic effects in the MD model, and has a much wider applicability than classical MD (Marx & Hütter 2000). Starting with Sarnthein et al.’s (1995) pioneering study on amorphous silica, in the last two decades, efficient AIMD methods such as the Car–Parrinello approach (Car & Parrinello 1985) have enabled researchers to look at the properties of silicate glasses with very high accuracy (Ispas et al. 2001; Charpentier et al. 2004; Donadio et al. 2004; Pöhlmann et al. 2004; Tilocca & de Leeuw 2006a,b). Despite the limited time scale (10–100 ps) and system size (100–300 atoms) imposed by their high computational requirements, the parameter-free nature of AIMD simulations and the built-in explicit treatment of electronic structure make them extremely useful to tackle problems and systems which pose a serious challenge to empirical potentials, such as reactivity at surfaces or dynamical processes in melts.

A common approach in first-principles simulations of glasses is to obtain an initial structure through classical MD with an empirical potential and then switch to the ab initio treatment using the classical structure as ‘starting guess’ (Ispas et al. 2001; Donadio et al. 2004; Tilocca & de Leeuw 2006a; Malavasi et al. 2007). This allows a partial relaxation of the structure at the ab initio level, but some important structural features, such as the intertetrahedral connectivity and the composition of the ionic coordination shells, will hardly be changed upon switching to the ab initio treatment, and therefore will be completely determined by the quality of the empirical potential used to construct the initial structure. This limits the scope of these mixed classical/ab initio approaches to investigate short-range features, or properties which turn out to have mainly local character (at least for these systems), such as the electronic structure and the vibrational spectrum (Tilocca & de Leeuw 2006a,b; Malavasi et al. 2007; Corno et al. 2008). For instance, the vibrational (power) spectrum obtained from a Car-Parrinello (CP) MD trajectory has been employed to identify and assign specific vibrational features in the overall vibrational spectrum of the 45S5 glass, such as those pertaining to phosphate and silicate groups in different coordinations (Tilocca & de Leeuw 2006b); the excellent agreement found with the phonon frequencies
computed from the eigenvalues of the Hessian matrix in the harmonic approximation (Corno et al. 2008) shows that anharmonic effects (included in the CPMD power spectrum) are small for this system.

A completely ab initio approach (Sarnthein et al. 1995; Tilocca 2007), whereby the glass structure is produced by ab initio MD melt-and-quench, is more suitable to obtain an unbiased view of some structural and dynamical features of bioactive glasses, such as the role of coordination defects in the glass-forming process and the mechanism of interchange between $Q^n$ species, as well as to assess the actual occurrence of specific structural features such as Si–O–P bonds in the glass (Tilocca 2007). Compared with the mixed approach, the full ab initio procedure is clearly much more demanding in terms of computer resources, especially if the melt must be cooled down to room temperature at a reasonable rate of $10^{-2}$ to $20$ K ps$^{-1}$ (Vollmayr et al. 1996); this explains why these investigations have only started to appear very recently (Giacomazzi et al. 2007; Tilocca 2007). It can be anticipated that unbiased computational studies of glasses will become more common in the future, with the increasing availability of high-performance supercomputing resources, and the development/implementation of efficient computational methodologies in optimized codes.

6. The structure of bioactive glasses

Based on the observations discussed in §4, in order to achieve a deeper understanding of the biological activity of Hench’s glasses, we need to focus on those properties of the glass which may impact:

(i) the partial dissolution of the silicate network and
(ii) the reactivity of the glass surface.

The basic information needed to begin any rational study of these effects is the bulk structure of the glass; despite its obvious importance, and the relatively long history of successful applications of bioactive glasses, investigations on the atomistic structure of bioactive glasses have only started to appear very recently. This is undoubtedly related to the highly disordered and multicomponent nature of bioglass systems, which represents a serious challenge to standard experimental and computational techniques to unveil their atomistic structure. However, prompted by recent advances in experimental and computational methods and available resources, in the last few years, several groups have started to focus their investigations on the structure of these complex systems (FitzGerald et al. 2007; Tilocca et al. 2007a; Linati et al. 2008). These studies have produced interesting new insight on the medium-range arrangement and other structural features, which are discussed in the following sections, in relation to their possible impact on the dissolution and reactivity of bioactive glasses.

(a) Modified silicate glasses: general structural features

Silicate glasses (Shelby 2005) are amorphous solids, characterized by a network of covalent SiO$_4$ tetrahedral building blocks, linked together by bridging oxygen (BO) atoms, each BO shared by two Si. While the short-range order within the tetrahedra is similar to their crystalline counterparts, no long range
order is present; the high flexibility in the angle between linked tetrahedra and in their relative orientation determines a high degree of structural disorder beyond the short range. Amorphous SiO\textsubscript{2} is characterized by a continuous network, fully interconnected in three dimensions, with every tetrahedron linked by BOs to four adjacent tetrahedra. The addition of alkali or alkaline-earth metal cations (‘modifier’ cations) breaks the silicate network by replacing Si–BO–Si bonds with Si–NBO, where NBO is a non-BO. Ionic bonds between NBOs and the modifier cations ensure the local charge balance and the overall charge neutrality; while weaker than the covalent Si–O bonds, the ionic interaction between NBOs and modifiers is extremely important to stabilize ‘invert’ glasses containing low silica amounts, such as the bioactive glasses (figure 1). For instance, the 45S5 composition contains 45 per cent SiO\textsubscript{2}, 6 per cent P\textsubscript{2}O\textsubscript{5} and 24.5 per cent of both Na\textsubscript{2}O and CaO (weight percentages), with less than one-third of the oxygen atoms as BOs; owing to the low silica amount, the modifier–NBO interaction is crucial for the formation of a stable glass dominated by chain-like fragments, occasionally interconnected to each other (figures 1 and 2).

(b) Network connectivity

Earlier work has tried to identify suitable structural markers to predict and compare the bioactivity of different glass compositions; for instance, the network connectivity (NC), defined as the average number of BO atoms per glass-forming

\( \text{Proc. R. Soc. A (2009)} \)
species, was introduced to describe the structural basis of the bioactivity (Strnad 1992). For instance, NC\textsubscript{Z4} for pure silica glass with its full three-dimensional network, whereas NC\textsubscript{Z2} denotes chain-like structures, such as a linear polymer. By comparing the NC of glass compositions with different bioactivities (measured either as the rate of formation of the HA layer or as the bone-bonding ability), an empirical upper limit around NC\textsubscript{Z3} was proposed, separating bioactive (NC\textsubscript{Z}<3) from bio-inactive (NC\textsubscript{Z}>3) glasses (Kim \textit{et al}. 1992; Strnad 1992). The qualitative interpretation of this threshold is based on the correlation between solubility and NC; low NCs denote open and fragmented glass structures, whose rapid partial dissolution in an aqueous physiological environment will lead to HA formation and bone bonding in a shorter time, compared with glasses with a more interconnected network. The empirical observation that glasses with NC\textsubscript{Z}>3 are bio-inactive entails that the hydrolysis of silica units with an average of three or more BOs bears an excessively high energetic cost, which slows down the overall bioactive mechanism up to a point where bone bonding can no longer be achieved (figure 1). As a reference, the NC for the 45S5 composition would be 1.9 (Strnad 1992). However, while an useful qualitative guideline, a classification based on the NC is not always accurate, as its predictive power rapidly decreases when a wider range of compositions is considered (Hill 1996). The reason is that the NC estimated from the glass composition is based on the assumptions of regular coordination for all network-forming ions and of homogeneous glass structure, which do not necessarily hold true for these compositions (see below). A less crude estimate of the NC can be obtained by atomistic modelling, which enables the direct and unambiguous calculation of the average number of BOs per network-forming

Figure 2. The silicate network of 45S5 Bioglass as obtained from SM MD (Tilocca 2008); Na and Ca ions are not shown for clarity. Ball-and-stick visualization is used to highlight an individual silicate chain fragment, with Si atoms coloured in green, and its interconnections to other fragments, with Si atoms coloured in light blue.
atom, as well as the analysis of the different network-forming ability/role of different species (Tilocca & Cormack 2007). This kind of analysis is based on the premise that the theoretical framework (empirical potential and simulation set-up) is adequate and produces a reliable structural model of the glass, generally verified for the MD based on SM potentials. In fact, in the first attempt to model amorphous silicates using an SM approach, the comparison between the structural models of soda- and soda-lime silicate glasses obtained using RI and SM potentials did show a better agreement with the experiment of the inter-tetrahedral structure predicted using the SM (Tilocca et al. 2006); in particular, considerable improvements were obtained in the $Q^n$ distribution (where $Q^n$ is a network-forming atom bonded to $n$ BOs) of a common sodium silicate composition modelled with the SM potential. An accurate $Q^n$ distribution is crucial, particularly when bioactive glasses are the target of the simulations, because, as discussed above, the dissolution process and the bioactivity of these glasses are strongly affected by their structure in the medium range.

The application of the SM potential to model Hench’s soda-lime phosphosilicate glasses does confirm the reliability of this approach, which yields $Q^n$ distributions of both Si and P in closer agreement with the available experimental data, compared with RI potentials (Tilocca 2008). It should be remarked that the current experimental picture of the $Q^n$ speciation in 45S5 Bioglass is still somewhat incomplete; while a binary model with only $Q^2$ and $Q^3$ species is sometimes assumed (FitzGerald et al. 2007), a three-component model with $Q^1$, $Q^2$ and $Q^3$ silicates was proposed to fit very recent nuclear magnetic resonance (NMR) data (Linati et al. 2008), and the presence of more than two $Q^n$(Si) species in this glass had already been inferred from previous Raman spectra (Lin et al. 2005). Furthermore, given that the coexistence of several $Q^n$(Si) species in depolymerized alkali silicate glasses is well established (Maekawa et al. 1991; Zhang et al. 1996; Mysen 2003), and that the presence of other species besides $Q^1$, $Q^2$ and $Q^3$ in 45S5 is less likely, the ternary $Q^n$(Si) distribution as in the SM model of 45S5, centred on $n=2$, appears most adequate. While the 53 per cent fraction of $Q^2$(Si) in the SM structure may still be slightly on the lower side with respect to the experiments, there is a clear improvement with respect to other potentials; similar improvement is also obtained in the phosphate speciation (see below).

Having verified the accuracy of the model, one can confidently analyse properties that are relevant for the bioactivity. An effective computational strategy (Tilocca et al. 2007a,b) has involved comparing the MD structure of glass compositions of different (known) bioactivities, covering a range from very high (45S5), to intermediate (55S, containing 55% SiO$_2$) to bio-inactive (65S, with 65% SiO$_2$). The $Q^n$(Si) distribution of 45S5 denotes that the highest bioactivity for this class of biomaterials arises from a structure dominated by chains of $Q^2$ metasilicates, which are occasionally cross-linked through $Q^3$ units, whereas the $Q^1$ species terminate the chains (figures 1 and 2). The comparison with the $Q^n$(Si) distribution of less bioactive compositions (figure 3) shows that the transition from high bioactivity (45S) to bio-inactivity (65S), through a region of intermediate bioactivity (55S), is accompanied by a shift of the $Q^n$ distribution towards higher $n$ values, with the 55S and 65S compositions now dominated by $Q^3$ units. While this trend confirms the correlation between bioactivity and high network fragmentation, it is clear that other structural
effects should be taken into account to interpret the very different bioactive behaviour of compositions 55S and 65S, which are both predominantly $Q^3$. Following this route, two additional features have recently been identified to play an important role in the properties of bioactive glasses: the fraction and mobility of silicate chain fragments, and the formation of nanoscale inhomogeneities.

(c) Chain and ring nanostructures

The importance of a fast initial dissolution of silicate fragments in the bioactive process was quantitatively confirmed by Arcos et al. (2003), who showed that a higher bioactivity reflects a lower activation energy for silica release. It is therefore interesting to focus on structural features that reduce the energetic cost of releasing soluble silica from the bulk glass to the solution. Clearly, linear silicate chains such as the trimer marked in figure 1a, or the longer fragment identified in an MD model (Tilocca 2008) and shown in figure 2, have a higher mobility and can approach the glass–tissue interface faster, compared with more bulky features such as rings; in fact, when thermal treatment is used to promote the condensation of chains into rings of tetrahedra, the whole dissolution process is slowed down (Arcos et al. 2002). The classification of a glass in terms of its chain-like or ring-like structural character is therefore very convenient to further rationalize the properties of bioglasses. While some features of vibrational spectra can highlight the presence of small rings (Geissberger & Galeener 1983; West & Hench 1993), a direct experimental determination of chain-like nanostructures is not as straightforward (Goldstein & Davies 1955). On the other hand, quantitative identification of chains and rings in amorphous structures can be performed very effectively using specific search algorithms on the structures obtained by MD (Yuan & Cormack 2002; Tilocca et al. 2007b). The analysis of 45S, 55S and 65S MD structures (figure 4) unambiguously confirms the dominance of silicate chains in highly bioactive glasses, and of silica rings in bio-inactive structures. The models allow us to conclude that the presence of a significant fraction of silicate chains is a necessary condition for bioactivity; predominantly $Q^3$ structures as 55S can in fact be moderately bioactive, provided that chain fragments can still be formed, as shown in figure 4, but bioactivity is severely inhibited when the silica content is high enough that all chain fragments are fused into rings, as in glass 65S.

As schematically highlighted in figure 1, the migration, detachment and release of silicate units initially incorporated in a ring requires the breaking of a larger number of covalent Si–O bonds, compared with the release of a linear silicate chain; in fact, Si atoms incorporated in chains are, on average, less interconnected than Si atoms in rings (the average $n$ of BOs calculated from the MD models is between 2.7 and 3.4 for rings, and less than 1.9 for chains). The much lower energetic cost associated with the dissolution of silica in highly bioactive compositions is also clearly related to the significant fraction of $Q^1$ chain terminators, which are absent in 55S and 65S, and, in principle, can promote a fast and direct release in solution of highly mobile, non-cross-linked silica dimers and trimers, without breaking any Si–O bond. Moreover, the opening of stable (five- or six-membered) silica rings is energetically unfavoured, which further inhibits the release of soluble silica incorporated in ring-like structures.

Proc. R. Soc. A (2009)
The observed bioactivity of phosphorus-free compositions shows that apatite nucleation and crystallization can proceed by incorporating phosphate from the physiological contact solution (Ebisawa et al. 1990; Ohura et al. 1991; Andersson et al. 1992; Peitl et al. 2001). However, while not strictly necessary for bioactivity, the incorporation of a small P$_2$O$_5$ fraction in the glass does enhance its HA deposition and bone-bonding ability (Ebisawa et al. 1990; Andersson et al. 1992; Brink et al. 1997; Zhang et al. 2003; Vallet-Regí et al. 2005). Several interpretations of this effect have been proposed: the low connectivity of phosphorus incorporated in bioglasses (see below) facilitates the release of additional soluble phosphate species into the contact fluid, which not only will increase the local supersaturation and accelerate the HA precipitation from the solution (Ebisawa et al. 1990), but can also further work as a buffer, preventing excessive surface acidity which would prevent bone bonding (Karlsson et al. 1989). Furthermore, it has been observed that the presence of phosphate in the glass leads to the deposition of a more uniform HA film, which, in turn, determines a stronger bond with bone, compared with P-free compositions (Andersson et al. 1992; Brink et al. 1997). A different explanation of the higher bioactivity of P-containing glasses is based on the labile nature of surface P–O–Si bridges, whose fast hydrolysis is deemed to contribute to the surface hydrophilicity (Cerruti et al. 2003).

Most of these hypotheses can be tested by a detailed analysis of the structural role of phosphorus in bioactive glasses. While earlier investigations assumed that no other species than orthophosphate are present in 45S5 glass (Lockyer et al. 1995), recent MAS-NMR experiments indicate that a small fraction of pyrophosphate ($Q^1$ or Si–O–P($O_3$)) species, where one of the four tetrahedral oxygens forms a bridge to an adjacent Si, can coexist with the majority of orthophosphate ($Q^0$) species (FitzGerald et al. 2007; Linati et al. 2008). The deconvolution of NMR signals for this and similar compositions is complicated by the rather broad and featureless character of the bands (Elgayar et al. 2005; Linati et al. 2008), and two-dimensional NMR techniques would be needed to

Figure 3. The $Q^n$ distribution of 45S (squares), 55S (circles) and 65S (triangles) glasses, as obtained from SM MD (Tilocca et al. 2007a).

(d) The role of phosphorus

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improve the spectral resolution, especially with a very low P$_2$O$_5$ fraction present (Coelho et al. 2006), but no such investigations have concerned Hench’s bioglasses as yet. The prevalence of P–O–Si over P–O–P linkages in mesoporous bioactive glasses was very recently highlighted through cross-polarization NMR (Leonova et al. 2008); this may point out that Si–O–P linkages actually replace P–O–P in some of the signals assigned to pyro- and metaphosphate units in bioactive silicate glasses (Dupree et al. 1989). Therefore, while their exact amount is currently not known, the presence of a small fraction of non-orthophosphate species in Hench’s Bioglass appears now established.

How do the models describe this aspect? As already seen for the silicate, the SM potential also considerably improves the description of the phosphate speciation, compared with standard fixed-charge potentials (Tilocca 2008). Owing to the low total number of P tetrahedra in common Hench’s compositions,
the convergence of the \( Q^n(P) \) distribution with the modelled system size is slower than for the \( Q^n(Si) \). The latter is already well converged for \( N \sim 1500 \) atoms in the simulation box (Tilocca et al. 2007a), whereas a converged \( Q^n(P) \) distribution requires \( N \sim 10000 \) atoms (Tilocca 2008). With the latter system size, the SM MD yields a fraction of orthophosphate units in 45S5 approximately 82 per cent, whereas fixed-charge potentials lead to a much lower orthophosphate fraction, which are replaced by pyro- and even metaphosphate (\( Q^2 \)) species (Linati et al. 2008; Lusvardi et al. 2008; Tilocca 2008). An SM approach is thus required for a satisfactory description of the phosphate speciation and connectivity, so that one can confidently analyse other structural properties extracted from the SM structure to rationalize the role of phosphorus in these materials.

A systematic analysis of the structural changes induced by replacing \( \text{SiO}_2 \) by \( \text{P}_2\text{O}_5 \) in bioactive compositions (Tilocca & Cormack 2007) has highlighted that increasing the \( \text{P}_2\text{O}_5 \) fraction leads to repolymerization of the silicate network. This is in agreement with experimental evidence (Lockyer et al. 1995) that was interpreted on the basis of the higher affinity of Na and Ca cations for phosphate groups, which are able to strip the modifier cations out of the silicate network, thus inducing its repolymerization. While the MD models do confirm the latter effect, they also highlight an additional factor that leads to an increase in the silicate connectivity upon phosphate inclusion: phosphorus can replace \( \text{Na}^+ \) or \( \text{Ca}^{2+} \) in balancing \( \text{Si}–\text{NBO} \) bonds. Therefore, the silicate network repolymerization can occur through either \( \text{Si}–\text{O}–\text{Si} \) or \( \text{Si}–\text{O}–\text{P} \) new links. A similar effect was also highlighted by Lusvardi et al. (2008), whose MD simulations highlighted the formation of \( \text{Si}–\text{O}–\text{P} \) links when fluorine removes Na and Ca from the silicate network of bioactive glasses. Because a higher silicate NC inhibits the overall bioactive process, this would explain why substantial \( \text{P}_2\text{O}_5 \) fractions have a negative impact on the bioactivity (Hench 1998); however, the experiments discussed before also indicated that the inclusion of a small \( \text{P}_2\text{O}_5 \) amount enhances bioactivity. This remarkable inversion in the effect of phosphorus can be explained by taking into account that, while some of the added phosphorus forms \( \text{P}–\text{O}–\text{Si} \) links which reduce the bioactivity (negative effect), some other is found as free orthophosphate, whose relatively fast initial release accelerates the deposition of HA and boosts the bioactive process (positive effect). The balance between these opposite effects will ultimately determine the bioactivity of the P-containing composition. Based on the bioactivity data of the compositions modelled, Tilocca & Cormack (2007) concluded that the positive effect prevails for low \( \text{P}_2\text{O}_5 \) fractions, whereas the negative effect prevails for higher (above 10 mol\% \( \text{P}_2\text{O}_5 \)) fractions.

An additional feature highlighted by a statistical analysis of the MD simulations is the increasingly stronger affinity between Ca and phosphate groups in glasses containing an increasing \( \text{P}_2\text{O}_5 \) fraction (Tilocca & Cormack 2007; Tilocca et al. 2007a). The Ca–phosphate aggregation becomes increasingly stronger than the one between phosphate and Na ions, and for a 12 mol\% \( \text{P}_2\text{O}_5 \) glass (labelled P12) results in the formation of nanoscale calcium phosphate domains separated from the silicate network, shown in figure 5. Based on the low biological activity of this composition, this feature suggests a possible role of nanoscale inhomogeneities as additional inhibitors of the bioactivity.
The association between nanoscale inhomogeneity and a reduction in bioactivity is interesting, given the widespread interest in controlling the dissolution rate of these compositions in order to match the natural growth rate of tissues, as discussed earlier. A possible explanation of this association is the reduced mobility of calcium and phosphate enclosed in these domains: glass-in-glass phase separation of a silica-rich and a phosphate-rich phase is known to enhance the resistance to dissolution of modified silicate glasses, owing to the increased viscosity of the phase-separated glass (Wu et al. 1997; El-Ghannam et al. 2001). While realistic modelling of phase separation processes lies beyond the current capabilities of atomistic MD simulations, these models are still able to highlight a tendency of some compositions to develop local inhomogeneities (Huang & Cormack 1991; Lusvardi et al. 2005), which may well represent the precursor of a phase-separated glass. The clustering of non-network-forming ions in silicate glasses can be quantitatively explored by a statistical analysis based on the ion coordination numbers calculated by MD simulations (Mead & Mountjoy 2006; Tilocca & Cormack 2007; Lusvardi et al. 2008). Based on this kind of analysis, it can be shown that the distribution of modifier cations in bioactive 45S5 is rather uniform, whereas bio-inactive 65S is characterized by marked clustering and formation of small calcium phosphate nanoaggregates (Tilocca et al. 2007a), similar to the larger size inhomogeneities found in P12 glass. The presence of phosphorus appears important to induce the separation of nanoaggregates, owing to the very favourable interaction with calcium ions (Tilocca & Cormack 2007, in press): phosphorus further enhances the tendency of modifier cations to aggregate and concentrate in cluster regions, above what would be expected, for instance, on the basis of modified random network models of silicate glasses (Greaves 1985; Huang & Cormack 1991), which would predict clustering only for compositions containing a significantly lower fraction of modifier cations. In fact, recent MD simulations by Mead & Mountjoy (2006) have highlighted that calcium clustering does occur for P-free (CaO)$_x$(SiO$_2$)$_{1-x}$ glasses, but only for a silica fraction greater than 80 per cent, as opposed to only approximately 60 per cent SiO$_2$ for the P-containing glasses (Tilocca et al. 2007a).

A different driving force for nanosegregation in bioactive glasses has been proposed by Lusvardi et al. (2008); their MD simulations showed that the incorporation of fluorine, which has high affinity for Na and Ca modifier cations, determines the separation of a highly polymerized phosphosilicate matrix from an ionic phase rich in Na, Ca and F. While fluorine-free bioglasses favour the separation of a phosphate-rich phase from a silica-rich one, incorporation of F leads instead to enhanced P–Si interactions, which are found in the same phase, well separated from an ionic phase with low viscosity.

Clustering of mobile cations in glasses is known to affect ionic transport, which is thought to proceed through ion-conducting channels populated primarily by these cations (Lammert & Heuer 2005). In the case of Hench’s bioglasses, clustering does not seem to promote ion migration, given the known reduced bioactivity of compositions with marked clustering. However, it is hard to separate the possible contribution to this reduction owing to the more interconnected silicate network from the (presumed) lower ionic mobility in...
calcium phosphate clusters, and direct MD simulations of ionic migration would probably represent the only way to assess the relative weight of these effects.

Figure 5. Separation of nanoscale calcium phosphate domains in a 24.4 Na$_2$O–27.1 CaO–36.3 SiO$_2$–12.2 P$_2$O$_5$ system (red, oxygen; blue, silicon; green, phosphorus; white, sodium; black, calcium). Snapshot extracted from the MD simulation (Tilocca & Cormack 2007).

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(f) The bioactive interface

While establishing the relationship between bulk structure and bioactivity is a key starting point, it is at the glass surface that the bioactive process starts and is eventually completed, and a direct investigation of this region is therefore essential. As for the bulk, molecular simulations can not only assist in the interpretation of the results of surface analytical techniques (Cerruti & Sahai 2006), but also provide a high-resolution probe into the features of the surface. Adsorption and reactivity at surfaces involves significant structural rearrangements, bond breaking and shifts in electronic density, whose modelling requires ab initio techniques. While ab initio cluster models can offer some interesting insight into the local properties of hypothetical surface sites (Cerrutti et al. 2005b; Cerruti & Sahai 2006), the activity of a realistic, extended model of the 45S5 Bioglass dry surface has very recently been explored by CPMD, by examining the different ability of selected sites (such as two- and three-membered rings and coordinative defects) to adsorb and dissociate a water molecule (Tilocca & Cormack 2008). A very interesting finding of these calculations is that the opening and hydroxylation of small rings exposed on the glass surface, while thermodynamically favourable, is hindered by a significant kinetic barrier, which may result in a fraction of these rings to remain stable even after immersion of the glass in an aqueous environment. Therefore, the CPMD calculations fully support the possibility that small silicate rings can provide active sites for calcium phosphate nucleation and deposition in the early stages of the bone-bonding mechanism (Sahai & Anseau 2005).
7. Final remarks

The powerful combination of the atomistic insight provided by MD models with experimental data on structure, solubility and bone-bonding ability of selected compositions enables a much deeper understanding of the bioactivity. While important correlations have already been identified between bulk structural features and the glass performance in biological applications, much more work is needed towards a rationalization of the properties of these materials. A crucial shift in the focus of simulations, from the bulk glass to the processes occurring at the interface between the glass and the physiological environment, can be envisaged to lead to further progress. *Ab initio* models of gas-phase adsorption have already started to yield valuable information on the surface properties of 45S5 bioactive glass (*Tilocca & Cormack 2008*) and of HA (*Rimola et al. 2008*). As the available computational power steadily grows, it will become possible to further extend these *ab initio* approaches to study the interface of bioactive systems on a large scale, and thus complete the model with important effects such as full surface hydration and interactions with biomolecules.

A.T. is a Royal Society University Research Fellow. The author would like to acknowledge collaboration and interaction with Prof. A. N. Cormack (Alfred University, USA) and Prof. N. H. de Leeuw (UCL), as well as fruitful exchanges with Dr A. Pedone (University of Modena and Reggio Emilia, Italy).

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