Anisotropic diffusion of water molecules in hydroxyapatite nanopores

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Abstract New insights into the dynamical properties of water in hydroxyapatite (HAP) nanopores, a model system for the fluid flow within nanosize spaces inside the collagen-apatite structure of bone, were obtained from molecular dynamics simulations of liquid water confined between two parallel HAP surfaces of different sizes (20 Å $\leq H \leq$ 240 Å). Calculations were conducted using a core-shell interatomic potential for HAP together with the extended simple point charge model for water. This force field gives an activation energy for water diffusion within HAP nanopores that is in excellent agreement with available experimental data. The dynamical properties of water within the HAP nanopores were quantified in terms of the second-order water diffusion tensor. Results indicate that water diffuses anisotropically within the HAP nanopores, with the solvent molecules moving parallel to the surface twice as fast as the perpendicular direction. This unusual dynamic behaviour is linked to the strong polarizing effect of calcium ions, and the synergic interactions between the water molecules in the first hydration layer of HAP with the calcium, hydroxyl, and phosphate ions, which facilitates the flow of water molecules in the directions parallel to the HAP surface.

Keywords Hydroxyapatite · Water confinement · Molecular dynamics · Hydrogen bonding · Anisotropic diffusion

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Introduction

The macroscopic properties of bone tissue are tightly coupled to molecular processes taking place at the interface between Hydroxyapatite minerals (HAP, molecular unit formula $[CA_{10}(PO_4)_6(OH)_2]$) and water within the lacuno-canalicular network (Sansalone et al. 2013) . In particular, the formulation of theoretical models for the prediction of tissue behaviour under the influence of time-dependent external stress inducing internal remod-elling requires a detailed understanding of the dynam-ics of water and its interaction with the surface of HAP surfaces. Mechanics modelling to describe the mechani-cal behaviour of bone at the macroscopic scale are based on homogenization and micromechanical methods which are powerful tools not only to obtain the overall behav-iour of the material via the determination of the over-all properties, but also to obtain information about the microfields which are defined at the microscale and are associated with the local distribution of the macrofields. Macroscopic predictions of either part or all of the elastic modulus tensor have been given by many authors (Yoon

and Cowin 2008; Sansalone et al. 2012 ; Hellmich and Katti 2015). In this context, bones with different forms of water will display differences in stiffness and strength.

HAP scaffolds constitute a prototypical model of biomaterial-based surfaces (Kandori et al. 2000b; Rimola et al. 2012; Corno et al. 2010) and have been used in several studies of bone repair (Oddou et al. 2011). These substitutions HAP-based materials allowed the investigation of the interactions between HAP surfaces with biomolecules (Almora-Barrios et al. 2009; Katti et al. 2010; Kandori et al. 2000a; Hernandez et al. 2015; Lukasheva and Tolmachev 2015), water (Zhao et al. 2014), ions (de Leeuw 2004a , b; Sakhno et al. 2010), and gases (Chi-atti et al. 2013). Water plays a crucial role during bone mineralization and in the protein interaction (Corno et al. 2010; Qin et al. 2012; Nair et al. 2014; Lemaire et al. 2015a) as they can act as a prominent charge carrier, transporting ions (Prakash et al. 2009; Prakash and Subramanian 2011) and maintaining the pH of the medium. When considering cells nanopores of transmembrane proteins (Hille 2001) or bone nanopores (Pham et al. 2015), the interactions between water molecules and the polar groups of HAP (calcium (Ca^{2+}), phosphate ($PO^{3}_{4}^{-}$), and hydroxyl (OH^{-}) ions) may affect the local environment of the interface, modifying the diffusion of water mole-cules, which tend to be reduced when compared with the bulk (Bhide and Berkowitz 2005; von Hansen et al. 2013; Lemaire et al. 2015b).

The unusual dynamics of water and other molecules under confinement has been subject to several experimen-tal and theoretical studies (Tan et al. 2005; Sendner et al. 2009; Su and Guo 2011; Nguyen and Bhatia 2012; Bourg and Steefel 2012; Srivastava et al. 2012; Xu et al. 2013; Planchais et al. 2014; Prakash et al. 2015; Han et al. 2015; Qiu and Huang 2015; Nie et al. 2016). In particular, nuclear magnetic resonance (NMR) techniques showed that water diffuses anisotropically inside nanoporous systems (Cleve-land et al. 1976; Thomsen et al. 1987; Wei et al. 2011; Salles et al. 2011) and two different self-diffusion coef-ficients of water were measured in sheep Achilles tendon using pulsed-field-gradient stimulated-echo NMR (Fechete et al. 2005). However, the molecular-level details regarding the diffusion mechanism of water molecules in the vicin-ity of the HAP bone surface, the origin of this anisotropic diffusion behaviour, and the interactions at the interface responsible for the preferential movement of water mole-cules towards a particular direction, remain unclear.

Owing to advances in theoretical models and techniques, atomistic simulation methods are particularly suited to obtain a molecular-level characterization of the solid-water interface (Kirkpatrick et al. 2005; Kubicki 2016), including a direct exploration of the structure and dynamics of water in contact with a mineral (Parvaneh et al. 2016).

In this study, we present classical molecular dynamics (MD) simulations of liquid water in hydroxyapatite nanopores of different pore sizes. The aim of this work is to investigate the dynamical properties of water, and changes therein with varying pore sizes. In particular, the concept of self-diffusion tensor originally introduced by Kubo (1957) has been applied to compute all nine Cartesian components of the three-dimensional diffusion. As the diffusion coeffi-cient is a scalar quantity and cannot, therefore, quantify the preferential movement of water molecules in a particular direction, in this work, we computed the anisotropic diffu-sion of water within HAP nanopores in order to determine the effect of confinement on its dynamic behaviour.

Theoretical models and methods

HAP surface and water models

Hydroxyapatite (HAP given by $CA_{10}(PO_4)_6(OH)_2$) is viewed as an hexagonal primitive cell with $P6_3/m$ space group. The nanopore is represented by a face-to-face configuration of parallel HAP platelets. Its size corresponds to the narrowest pore diameters measured in bones by Holmes et al. (1964). This geometrical configuration is motivated by the fact that, in bone tissue, hydroxyapatite is present in the form of thin micro-plates with dimensions ($L \times \times e$), where L = 250−500 Å (in 1-direction), = 150−250 Å (in 2-direction) and e = 25 Å (in 3-direction) (Weiner and Traub 1986). Cell parameters and crystallographic data of Sudarsanan and Young (1969) were used for the initial configuration of the HAP structure. The dimensions of the parallelepipedic-shaped simulation box were adjusted to contain 3 × 3 × 4 such micro-plates. The position of each atom in the box is given using the vector position whose the cartesian coordinates are denoted by (r_1, r_2, r_3) in the orthogonal frame (1, 2, 3) (see Fig. 1).

The HAP platelets and water layers constituted the elementary unit cell for our simulations. HAP nanopores were generated by varying the *c*-axis of the crystal from H = 20 Å to H = 240 Å. The resulting surface corresponds to the (0001) basal plane, which is the dominant surface in the thermodynamically-stable morphology (Mkhonto and de Leeuw 2002) and is important in biological systems, as the elongation of the bone platelets along the *c*-direction of the apatite crystal results in the expression of this sur-face (Rohanizadeh et al. 1999). In addition, experimental evidence shows that these faces act as the binding site for many adsorbates (Wierzbicki and Cheung 2000).

For all pore sizes, the atomic configuration editor Aten (Young 2016) was used to fill the resulting vacuum with water molecules corresponding to the experimental density of 1 g cm^{-3}.

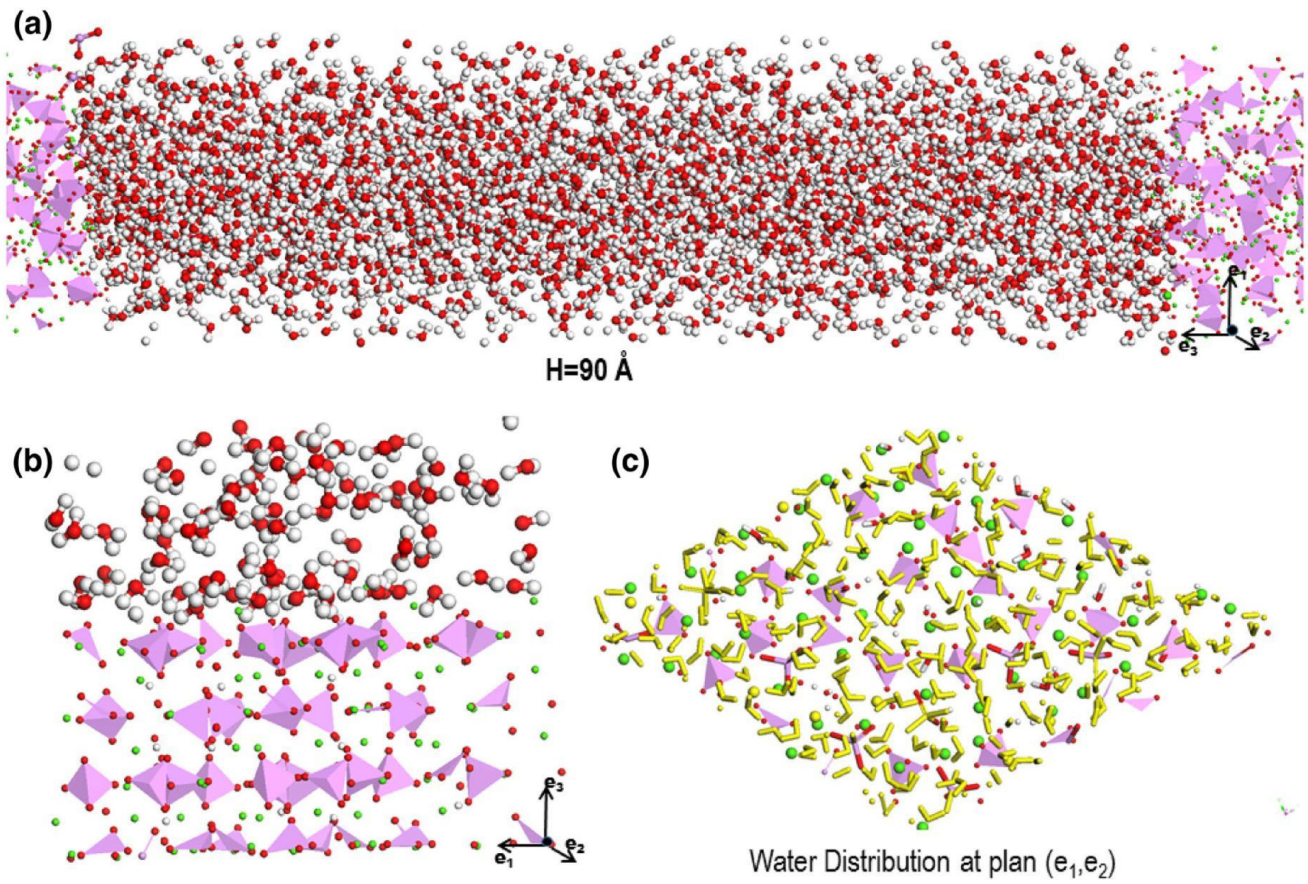

Fig. 1 HAP-water system (Ca-*green*, $PO^{3}_{4}{}^{-}$-*pink*, O-*red*, and H-*white*) with a pore size of 90 Å. **a** Unit cell of the HAP nanopore—water used in the simulations. **b** Side view of the HAP-water interface. **c** Top view of the HAP-water interface

Molecular dynamics

All MD simulations were performed using the DL_POLY 4.05.1 code (Todorov et al. 2006). Interatomic potentials for HAP and its interaction with water are the ones developed by de Leeuw (2004a) and de Leeuw and Parker (1998). The water molecules were represented using the extended sim-ple point charge (SPC/E) potential (Berendsen et al. 1981). The potential parameters used in this work are reported in electronic supporting material (see Tab. S1).

Each system considered in the present study was first equilibrated for 50 ps in the microcanonical (NVE) ensemble. This was followed by an equilibration period in the isothermal–isobaric (NPT) ensemble (P = 1 atm. and T = 300 K) during which the volume was monitored to confirm the system reached equilibrium. The behaviour of the volume for the nanopores with H = 20, 60 and 110 Å is reported in Fig. S2 of electronic supporting information. This was followed by 2 ns of production period in the NPT ensemble. All simulations used the Nosé–Hoover algorithm with 0.5 and 0.5 ps as the thermostat and barostat relaxa-tion times, respectively. To mimic the in vivo human bone environment, simulations were performed at temperature of 310 K unless otherwise stated. The Verlet leapfrog scheme with a time step of 0.1 fs was used to integrate the equa-tions of motion. Periodic boundary conditions were applied in all three directions of the unit cell. The long range elec-trostatic interactions between the charges of all species were computed using the Smoothed Particle Mesh Ewald (SPME) method with a relative error of 10^{-6} (Essmann et al. 1995). Table 1 lists the number of atoms in HAP (N_{HAP}), which included core-shell atoms, number of water molecules N_O , duration of each simulation T_D, and initial H and equilibrated H^* values of the pore sizes. Notice that the equilibrium height of the pore size is close to the initial one, which justifies the use of the NPT ensemble instead of NVT for our simulations. The structure of the HAP nanopore-water systems considered in the present study is reported in Tab. S3 of electronic supporting material.

To verify if HAP nanopores and the surface retained the crystalline structure, we computed the phosphorous–phos-phorous (P–P) radial distribution functions (RDFs) of the hydroxyapatite crystal, and of the bulk and surface of the HAP (H = 110 Å) nanopore in contact with water (see

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Table 1 Details of the molecular dynamics simulations of the HAP nanopores-water systems: number of atoms in HAP N_{HAP}, number of water molecules N_{Ow} , duration of each simulation T_D (in ns), initial H (in Å), and equilibrated H^* (in Å) pore sizes

H (in Å)	N_{HAP}	N_{H_2O}	T_D (in ns)	H^* (in Å)
20	2520	455	2	21.6
30	2520	682	2	32.8
40	2520	910	2	41.3
50	2520	1138	2	52.7
60	2520	1363	2	64.1
70	2520	1593	2	71.4
80	2520	1820	2	82.7
90	2520	2048	2	92.4
100	2520	2276	2	103.9
110	2520	2506	2	112.6
120	2520	2732	2	124.6
130	2520	2960	2	135.3
160	2520	3650	1	167.3
200	2520	4550	1	196.8
240	2520	5300	1	228.1

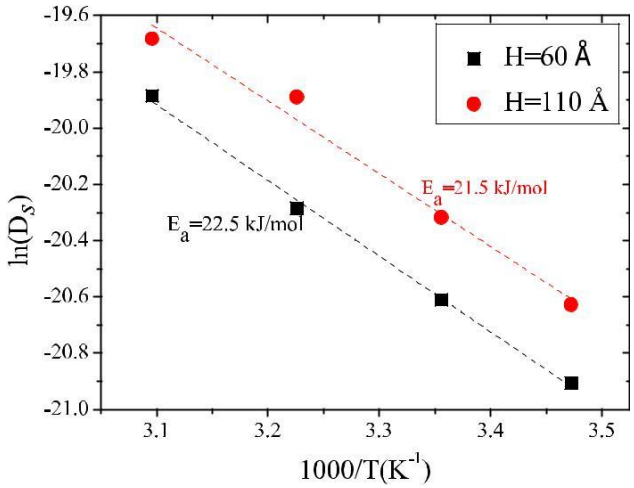

Fig. 2 Arrhenius plots of the average diffusion coefficient of water versus the inverse of the temperature for the HAP-water systems with pore sizes equal to 60 and 110 Å, where H is the initial height of the nanopore

Fig. S4 of electronic supporting material). The P–P RDF profile of the nanopore is very similar to that of the crystal, which indicates that HAP nanopores remain crystalline. The P–P RDF profile of the HAP surface shows some deviations compared with that of HAP nanopore, suggesting some restructuring of the surface but not to an extend to indicate amorphousization of the surface (Tian et al. 2016). This agrees with the previous MD work by de Leeuw, which showed that HAP surfaces maintain its crystalline structure (de Leeuw 2004a, b).

Validation of the theoretical methodology

We have used the SPC/E water model, because it gives a density, radial distribution functions, and self-diffusion coefficient for water in good agreement with experiment (Berendsen et al. 1987). In particular, the value of self-diffusion coefficient D_S for bulk SPC/E water obtained from a molecular dynamics simulation of 729 water molecules (NPT ensemble, 2 ns of production period) is 2.58×10^9 m^2 /s, in good agreement with the experimental value of 2.999×10^9 m^2/s (Holz et al. 2000). Moreover, comprehen-sive calculations of the activation energy of diffusion E_A of water in bulk liquid water also concluded that using the SPC/E model, the value of E_A is 14.8 kJ/mol, which is only 2.6 kJ/mol lower than the experimental value E_A = 17.4 kJ/ mol (Holmboe and Bourg 2014). To validate the combina-tion of force fields, molecular models, and computational techniques used in the present work, we compared the acti-vation energy denoted E_A for the diffusion of water within HAP nanopores with the experimental values measured for cortical bone and inter-tubular dentine (Fernández-Seara et al. 2002). MD simulations were conducted at the temperatures of 288, 298, 310, and 323 K to determine the activation energy for water diffusion in HAP nanopores with H = 60 ¯ and H = 110 ¯ (see Fig. 2), which are representative of typical nanopores in bones (50 < H < 125 Å) (Holmes et al. 1964). The activation energies were obtained from the linear fit of the points in Fig. 2 using Arrhenius equation $\ln(D_S) = \ln(D_0) - E_A/(RT)$, and the values of E_A are 22.5 ± 0.7 kJ/mol for H = 60 Å and 21.5 ± 2.0 kJ/mol for H = 110 Å, which are very close to NMR measure-ments in cortical bone (E_A = 26.6 kJ/mol) and inter-tubular dentine E_A = 29.5 kJ/mol (Fernández-Seara et al. 2002). This result validates the molecular models and interac-tion potentials used in the present work to represent fluid flow within bone sub-micrometer pores. A related point to consider is that the activation energies for water diffu-sion within the HAP nanopores are higher than in bulk E_A = 17.4 kJ/mol (Holmboe and Bourg 2014), which sug-gests that diffusion of water is hindered by the interaction between water molecules and the polar groups at the HAP surface.

Results and discussion

Self-diffusion coefficient

The self-diffusion coefficient of water, denoted by D_S , is a key property when studying the flow of fluid. From an MD simulation diffusion coefficients can be calculated using Einstein relation:

$$D_S = \frac{1}{d_S}\frac{1}{2}\frac{d\,[\,(t) - (0)]^2}{Dt} \quad . \tag{1}$$

where d_S is the dimension of the space (in this paper $d_S = 3$), (0) and (*t*) are the position vectors at times $t = 0$ and *t*, respectively, and the angled brackets · indicate the average over the number of times origin spanned by *t* and the number of water molecules. However, this scalar quantity cannot describe the differential diffusion of water in directions parallel or perpendicular to the HAP surface (see Fig. 1).

To quantify the anisotropic diffusion of water in the HAP nanopores, we introduce the second-order water self-diffusion tensor , which is defined as follows:

$$\begin{matrix} D_{11} & D_{12} & D_{13} \\ D_{13} & D_{23} & D_{33} \end{matrix} \tag{2}$$

whose components D_{ij} represent the anisotropic diffusion coefficients and are computed using the following expression which was derived from Kubo (1957):

$$D_{ij} = \frac{1}{2}\frac{d\,\langle r_i(t) - r_i(0)\rangle \cdot \langle r_j(t) - r_j(0)\rangle}{dt}, \quad i, j = 1, 2, 3. \tag{3}$$

In Eq. (3), r_i (0) and r_i (*t*) are the components of the position vectors along the *i*-direction (*i*, *j* = 1, 2, 3) of the Cartesian frame shown in Fig. 1. The anisotropic diffusion coefficients D_{ij} were computed by modifying the DL-POLY code. This new utility accurately determines the anisotropic self-diffusion coefficients by computing the mean square displacement (MSD) for the different atomic species in the simulation using multiple time origins as defined by Eq. 3. The mean square displacements associated with the diagonal elements of the anisotropic self-diffusion tensor D_{ii} for $i = 1, 2, 3$ are plotted in the Fig. 3.

Without attempting an exhaustive list on a subject beyond the scope of this paper, Cummings et al. (1991) have presented different methods for calculating certain self-diffusion coefficients in a non-Newtonian fluid subject to a couette strain field. Furthermore, Liu et al. (2004) have introduced a Einstein–Smoluchowski-like method for calculating the parallel and perpendicular components of the self-diffusion to a surface. Boţan et al. (2011) have used this previous method for studying the self-diffusion in clay nanopores.

The anisotropic diffusion tensor can be decomposed into its so-called spherical and deviatoric parts:

$$= \frac{1}{3}(\mathrm{TRA}\ ) + \mathrm{DEV}\ , \tag{4}$$

where is the identity tensor, TRA is trace operator that gives the sum of the diagonal elements of , and the deviatoric part is given by $\mathrm{DEV} = -(1/3)(\mathrm{TRA}\ )$. Any tensor of the form , where is a scalar, is known as a spherical tensor, while DEV is known as a devia-tor of . Note that an important property of the deviatoric tensors is TRA (DEV) = 0. This decomposition decou-ples the "volumetric" from the "distortional" properties

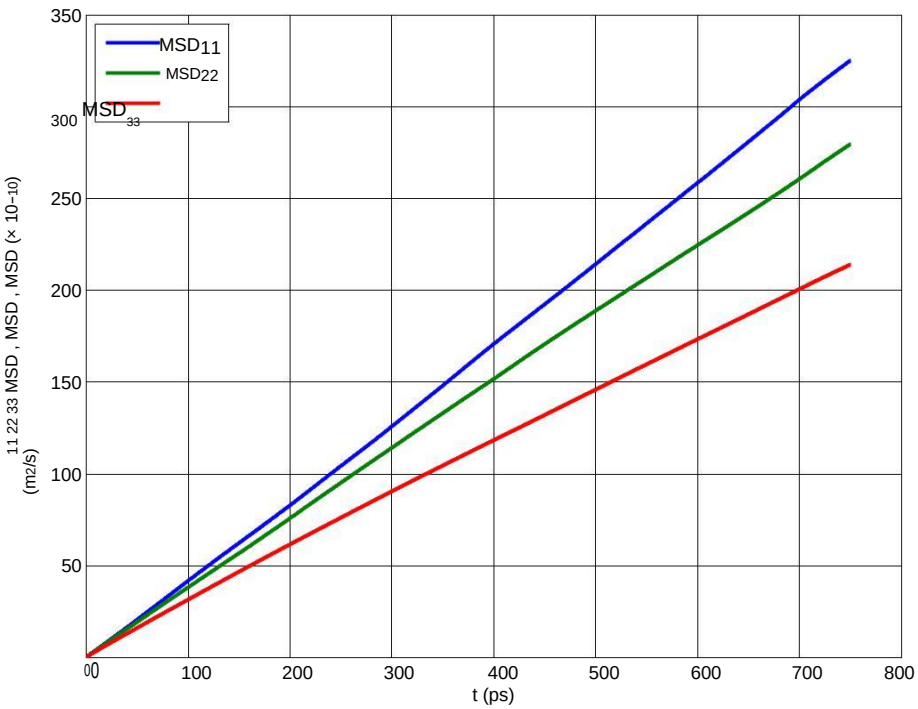

Fig. 3 Mean square displacements associated with the three interest quantities describing the diffusion coefficients D_{ii} for $i = 1, 2, 3$ for $H = 90$ Å

which can be interpreted as a decoupling of the "mean" part from the "fluctuation" part because of the underly-ing orthogonality of the spherical and deviatoric partitions $\mathrm{TRA}(\mathrm{S} \times \mathrm{DEV}) = 0$, where $\mathrm{S} = (1/3)(\mathrm{TRA})$. This decomposition mimics the ones of the vectors that can be decomposed uniquely as a sum of two vectors, one tangent to a surface, called the tangential component of the vec-tor, and another one perpendicular to the surface, called the normal component of the vector. As a result, due to the geometry of the HAP nanopores, the matrix representation of the self-diffusion tensor should be diagonal. This was first confirmed by the quasi-nullity of the off-diagonal elements, and then by computing the spherical part of in Eq. (4), which does, indeed, correspond to the standard diffusion coefficient of water calculated using Eq. (1).

The anisotropic diffusion coefficients of water as a function of the pore size are reported in Fig. 4. Our calculations show that the transport properties of water depend significantly on the size of the HAP nanopore (Pham et al. 2015), but also quantify the marked anisotropic behaviour of liq-uid water when confined within nanosize volumes.

In Fig. 4, for small-to-medium nanopores (20 Å < H < 70 Å), the coefficients D_{11} and D_{22} associated with the diffusion along the 1 and 2 directions correspond to the movement of particles parallel to the HAP surface (see Fig. 1), and their values are similar to the isotropic self-diffusion coefficient D_S. For nanopores larger than >70 Å, D_{11} is about 15% higher than D_S, whereas $D_{22} \sim D_S$. On the other hand, for all nanopores, the coefficients D_{33}, which correspond to the normal direction to the HAP surface, are significantly lower than both the isotropic coefficient D_S, and the coefficients D_{11} and D_{22} associated with the diffu-sion parallel to the HAP surface. For example, in the HAP nanopore with $H = 110$ Å, $D_{33} = 1.5 \times 10^{-9}$ m^2/s, and D_{11} and D_{22} are equal to 3.0×10^{-9} and 2.2×10^{-9} m^2/s, respectively. This signifies that water molecules preferentially diffuse along the HAP surfaces rather than towards the bulk of the aqueous solution in contact with the nanopore. In Fig. 4, the spherical part of the diffusion tensor corresponds to the standard isotropic diffusion coefficient.

This in-plane confinement effect is visually represented in Fig. 5 by the trajectory of a water molecules that is part of the first hydration layer of the HAP nanopore with H = 110 Å. A water molecule was considered to be part of the first hydration layer of HAP if the distance between the calcium atoms (Ca) at the HAP surface and the oxygen atoms (O_W) of the water molecules is less than 3.0 Å. This distance corresponds to the position of the first minimum in the $Ca^{2+} - O_W$ pair distribution function (e.g., Di Tommaso et al. 2014) as well as the position of the minimum in the number density profile of the oxygen atoms that are closer to the HAP surface. Figure 5 shows that during the dynamics, the tagged water molecule moves approximately parallel to the surface of HAP. A similar conclusion was obtained from the visualization of the trajectories of water molecules that were part of the second hydration layer of HAP. Moreover, the analysis of the motion of the tracer molecule from its initial (t = 0 ns) to its final (t = 2 ns) MD

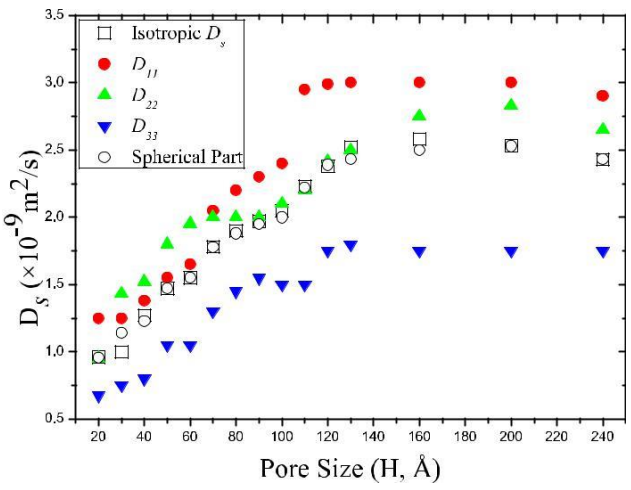

Fig. 4 Anisotropic diffusion coefficients D_{II} (I = 1, 2, 3), standard iso-tropic diffusion coefficient D_S, and spherical part of the diffusion ten-sor of water molecules within the HAP nanopores

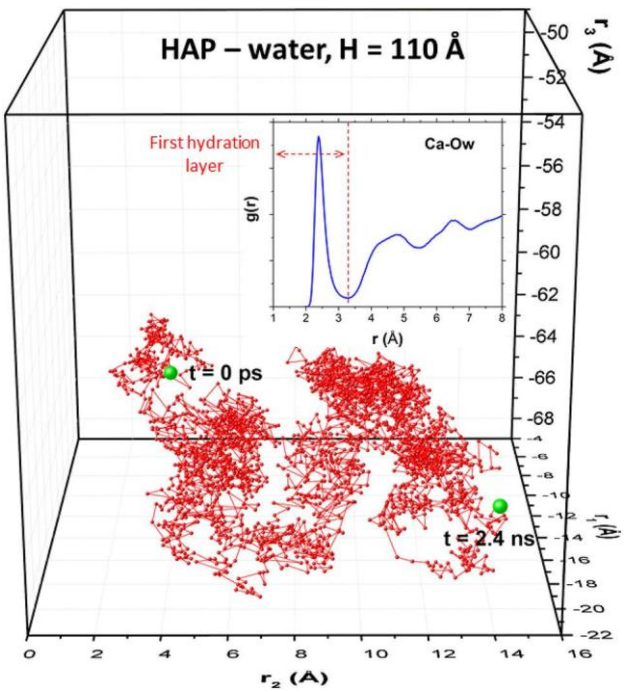

Fig. 5 Motion of a randomly chosen tracer molecule that is part of the first hydration layer of the HAP nanopore with H = 110 Å. The *inset* reports the radial distribution function [$g(r)$] of calcium ions at the surface and oxygen water atoms (Ca–Ow)

steps indicates that the 1 and 2 components of the position vector change by twice as much as the 3 component. This agrees with the values of the anisotropic diffusion coefficients D_{11} and D_{22} being larger than D_{33} (see Fig. 4). The polarization effect of the calcium ions at the HAP surface, which can extend up to four layers of water (Bolis et al. 2012), can be used to rationalize the slow diffusion of water along the 3-direction observed in our MD simulations.

The time-dependent MSD of the oxygen atoms of water molecules (O_W) close to the HAP-water interface, and further away from it, was also computed using the following expression:

$$^2(t) \qquad _{OW,n} = [\ (t) - \ (0)]^2 \quad ,$$

where (0) and (t) are the position vectors at times $t = 0$ and t, respectively, and the angled brackets $\cdot$ indicate the average over the number of times origin spanned by t and the number of water molecules. The subscript $O_{W,n}$ denotes the oxygen atoms that are part of the n-th "layer" of water in the HAP nanopore. For example, a water molecule was considered to be part of the first hydration layer if $d(CA^{2+} - O_W) < 3.0$ Å. The (water) oxygen atoms used to compute the MSD of a specific hydration layer were deter-mined from the configuration of the first MD step of the production period, and by selecting those O_W atoms such that $d(CA^{2+} - O_W)$ was within a specific threshold. The MSD of O_W in the hydroxyapatite nanopores with $H =$ 60 and 110 Å for the hydration layers defined by $d(CA^{2+} - O_W)$ equal to 6 Å (first and second layer), 20, 30, and 40 Å are reported in Fig. S5 of electronic supporting material. The results indicate that as we move further away from the interface, water molecules diffuse more slowly and this effect becomes more pronounced with the size of the nanopore. However, it is important to notice that several water exchanges were counted between the different hydration layers during the MD trajectories, and consequently, the MSD in Fig. S4 cannot be unambiguously associated to a specific hydration layer of the HAP nanopore.

Hydrogen bonding at the HAP-water interface

Hydrogen-bonding (H-bonding) interactions play a vital role in the movement of water molecules on the HAP surface. Figure 6 shows the molecular arrangement of water molecules on the HAP surface. In particular, Fig. 6a gives a closer view of the orientation of water molecules on the surface and the H-bonded interaction with hydroxyl and phosphate groups of HAP. Visualization of the trajectories revealed a peculiar "rolling" motion for the water molecules. This is illustrated in Fig. 6b–e, where the molecular arrangement of a selected water molecule at four MD steps shows that the H-bonding interactions with the HAP surface influence the translation and rotation motions of water and facilitate the anisotropic diffusion of water. Figure 7 reports a schematic representation of the rolling motion of water, which occurs via H-bonding interactions, determining a preferential diffusion of water molecules on the (1, 2)-plane.

The H-bonding structure greatly influences the dynamical properties of water (Chandra 2002). The effect of confinement on the distribution of the number of H-bonds was, quantified by scanning the MD trajectories of bulk water and water within HAP nanopores in order to determine the existence of an H-bond between two water molecules based on the following geometrical criteria: (1) the donor–acceptor inter-oxygen distance is less than 3.5 Å; (2) the donor–acceptor inter hydrogen-oxygen distance is less than 2.45 Å; (3) the hydrogen-donor–acceptor angle is less than 30° (Chandra 2000).

The average number of H-bonds n_{HB} is about 3.5 in bulk liquid water and in the HAP nanopore with $H = 110$ Å, but n_{HB} decreases to 3.4 for $H = 60$ Å, 3.3 for $H = 40$ Å and 3.0 for $H = 20$ Å, that is, as the degree of confinement increases. This is linked with the increasing influence of the HAP surface on H-bonding network. In fact, the dis-tribution of the number of H-bonds between water mole-cules coordinated to the HAP surface and the surrounding water molecules (see Table 2) shows that, in liquid water, the majority of water molecules (51%) have a local tetrahe-dral network, whereas in the first hydration layer of HAP, more than 60% of water molecules have two, one, or zero H-bonds (HBs). In an aqueous environment, the motion of water molecules occurs via the breaking and reform-ing of H-bonds and the reduction in water diffusion within HAP nanopores can be explained in terms of the lack of water–water H-bonds through which a water molecule can diffuse from the surface to the bulk. Given that water mol-ecules coordinated to the surface form, on average, less than two HBs per molecule with the surrounding water molecules, this implies that they interact with the hydroxyl group and diffuse preferentially along the surface rather than towards the bulk solution.

Conclusion

We conducted classical molecular dynamics simulations of liquid water within hydroxyapatite nanopores of different sizes (20 Å $\leq H \leq$ 240 Å) to determine the effect of confinement on the dynamical properties of water. We showed that our core-shell potential for hydroxyapatite together with the standard SPC/E water model gives an activation energy for water diffusion have a local tetrahedral network that is in very good agreement with available experimental data. We identified an anisotropic diffusive behaviour

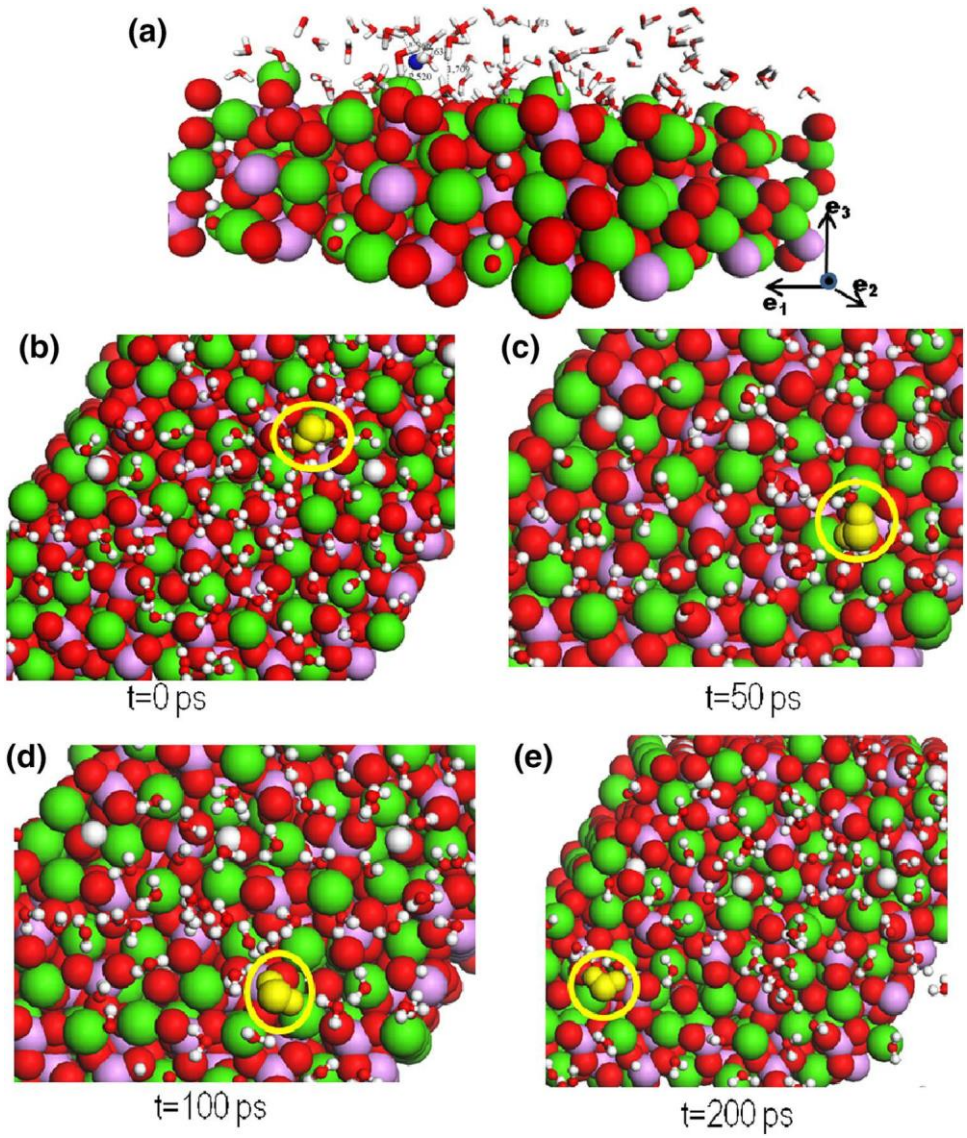

Fig. 6 Molecular arrangement of water molecules on the HAP surface with *H* = 70 Å (Ca-*green*, P-*pink*, O-*red*, H-*white*, and hydroxyl O in *blue*): **a** H-bonding between hydroxyl ion (HAP) and water molecules: **b**–**e** motion of selected water molecule (in *yellow color circle*) on the HAP surface at selected times (in ps)

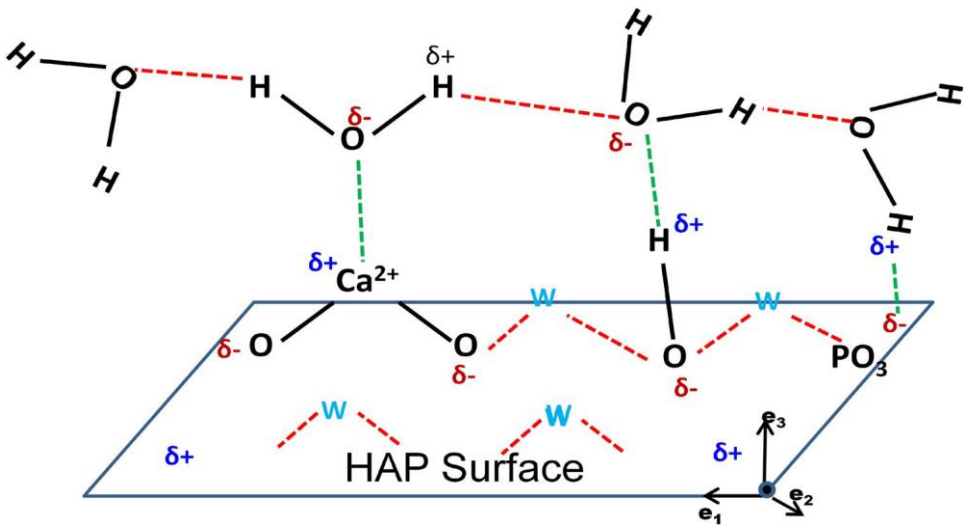

Fig. 7 Schematic representation of the HAP-water interface showing the water adsorption sites and the mechanism of water rolling motion on the HAP surface

Table 2 Distribution of the number of hydrogen bonds for the water molecules coordinated to the calcium surfaces

	0	1	2	3	4	5	Average
Bulk water	0.0	0.9	0.8	33.0	51.3	5.9	3.53
HAP-water							
110 Å	22.3	22.4	22.0	19.7	12.5	1.0	1.81
60 Å	22.7	22.5	22.0	19.4	12.3	1.0	1.79
40 Å	24.5	23.6	21.4	18.3	11.2	1.0	1.71
20 Å	26.8	27.9	21.2	15.0	8.3	0.7	1.52

Results obtained from molecular dynamics simulations of bulk water and water within HAP nanopores of different sizes (20 Å ≤ H ≤ 110 Å). The values given are percentages of molecules with the given number of hydrogen bonds and the average number of hydrogen bonds per water molecule

for the molecules, which was quantified by defining a self-diffusion tensor, , and computing the anisotropic diffu-sion coefficients of water, Dij (i, j = 1, 2, 3). As a result of the strong interactions between water molecules and the functional groups of HAP, which become dominant in such confined environments, the motion of water molecules in the direction parallel to the surface is significantly faster than in the direction perpendicular to it, where the polar-izing effect of Ca^{2+} sites reduces the diffusion of water molecules. On the other hand, solvent molecules can move preferentially along the 1-direction (characterized by ani-sotropic diffusion coefficient $D11$) as a result of synergic interactions of the water molecules at the interface with the calcium, hydroxyl, and phosphate ions of the HAP surface.

Our study demonstrates and quantifies the anisotropic behaviour of fluid in bone nanostructures, which is an important area of bone biophysics (Lemaire et al. 2015a; Abdalrahman et al. 2015) and, therefore, gives new insights into the mechanisms controlling the motion of solvent mol-ecules in confined spaces.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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