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How to predict diffusion of medium-sized molecules in polymer matrices. From atomistic to coarse grain simulations

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Abstract The normal diffusion regime of many small and medium-sized molecules occurs on a time scale that is too long to be studied by atomistic simulations. Coarse-grained (CG) molecular simulations allow to investigate length and time scales that are orders of magnitude larger compared to classical molecular dynamics simulations, hence providing a valuable approach to span time and length scales where normal diffusion occurs. Here we develop a novel multi-scale method for the prediction of diffusivity in polymer matrices which combines classical and CG molecular simulations. We applied an atomistic-based method in order to parameterize the CG MARTINI force field, providing an extension for the study of diffusion behavior of penetrant molecules in polymer matrices. As a case study, we found the parameters for benzene (as medium sized penetrant molecule whose diffusivity cannot be determined through atomistic models) and Poly (vinyl alcohol) (PVA) as polymer matrix. We validated our extended MARTINI force field determining the self diffusion coefficient of benzene ($2.27 \cdot 10^{-9} \, \mathrm{m^2 s^{-1}}$) and the diffusion coefficient of benzene in PVA ($0.263 \cdot 10^{-12} \, \mathrm{m^2 s^{-1}}$). The obtained diffusion coefficients are in remarkable agreement with experimental data ($2.20 \cdot 10^{-9} \, \mathrm{m^2 s^{-1}}$ and $0.25 \cdot 10^{-12} \, \mathrm{m^2 s^{-1}}$, respectively). We believe that this method can extend the application range of computational modeling, providing modeling tools to study the diffusion of larger molecules and complex polymeric materials.

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Introduction

Molecular dynamics (MD) simulations are a powerful tool in the material science field as they provide material's structural and dynamics details that are difficult, cost- or time-consuming to be assessed with experimental techniques. In particular, MD simulations are a valid tool for the design of polymeric membranes with tuned permeability properties. Up to now, however, the design of barrier materials is based on trial and error experimental procedures, in which a large part of the effort is spent to synthesize and characterize materials and blends which finally turn out to be unsatisfactory.

Atomistic simulation have been successfully applied in the past to obtain the diffusion coefficients of small molecules (like oxygen, carbon dioxide or water) in polymeric membranes [1–7], polymeric blends [8, 9], biopolymers [10, 11] and organic-inorganic hybrid membranes [12]. However, despite the increasing computational power available to researchers and the improvements in the MD codes, atomistic simulations are still able to handle only systems with tens or hundreds of thousands of atoms and in the nanoseconds time scale. Several phenomena of interest at the material scale, however, cover time and space scales larger than those affordable with atomistic modeling. This is the case of normal diffusion regime. The diffusion coefficient D can be directly calculated from the motion of the particles extracted during a MD simulation, in particular from the mean square displacement (MSD) of the particles, using the Einstein equation [5]. This equation holds only in the case that the observation time (i.e., the simulation time) is large enough to allow the particles to show uncorrelated motion. This means that the MSD is linear with time, i.e., $MSD \sim t^n$ where n=1. Conversely, if $n < 1$ then the

diffusion is in the anomalous diffusion regime. Therefore, in order to assess an accurate diffusion coefficient, MD simulations must reach the normal diffusive regime which, depending on the membrane and diffusive molecule, can be on time scales higher than few nanoseconds. This regime is therefore often difficult to reach for molecules larger than diatomic molecules, like water or benzene, hindering molecular simulations to assess an accurate diffusion coefficient [12, 13].

Recently, the use of coarse grain (CG) modeling, in which a number of atoms are condensed into beads or interacting particles, has proven to be a suitable option to model large systems and long time scales, providing realistic results. The methods, assumptions and level of resolution greatly vary depending on the scope of the models and the properties of interests [14, 15]. CG models have been developed with particular focus on biomolecular systems, since biomolecules are often too large and their characteristic times too long to be treated with full atomistic simulations. However, there are no theoretical impediments to the application of CG methods to polymeric materials.

In this view, of particular interest is the coarse grain force field developed by Marrink and co-workers and called MARTINI force field. This CG force field was originally developed to model the lipid bilayers forming the cellular membranes and then extended to proteins [16–18]. Unlike other CG models, which focus on accurate modeling of a particular state or a particular molecule, the philosophy of the MARTINI force field is to accurately parameterize the basic building blocks of the system (e.g., the single amino acids for proteins), thus allowing a broad spectrum of applications without the need of reparameterization.

Relying on the same philosophy, in this work we present an atomistic-informed parameterization of the MARTINI force field for the modeling of penetrants diffusion in polymeric membranes. We used atomistic simulations to calculate the interaction free energy between the basic building blocks of the system, i.e., the penetrant molecule and the polymer monomers, and then we performed CG molecular dynamics simulations to assess the diffusion behavior. As a test case, we investigated the diffusion behavior of benzene in a matrix of Poly (vinyl alcohol), PVA. Benzene, an important industrial solvent and precursor in the production of drugs, plastics, synthetic rubber, and dyes, was chosen since it is a well known representative of medium-sized permeant molecules. On the other hand, the choice of PVA as the polymer matrix is based on the fact that this polymer is widely used in several fields and finds applications as membrane material due to its excellent chemical stability, film forming capacity, barrier properties and high hydrophilicity.

Methods

Coarse grain mapping

The original MARTINI mapping scheme is based on the four-to-one rule, i.e., on average four heavy (non-hydrogen) atoms are grouped into a bead or interaction center. Here we used a similar mapping, where the benzene molecule is represented by one bead and the vinyl alcohol (VA) monomers are represented by a different bead (see Fig. 1). The mass of the two types of beads are calculated as the sum of the masses of the atoms grouped into the bead.

Bonded and nonbonded interactions

The chemically bonded beads interact through a bond interaction modeled as a harmonic potential $V_{bond}(r)$:

$$V_{bond}(r) = \frac{1}{2} k_{bond}(r - r_0) \tag{1}$$

where r is the distance between two bonded beads, k_{bond} is the force constant of the bond interaction and r_0 is the equilibrium distance. In the system under investigation, only VA beads representing chemically bonded monomers along a PVA chain are subject to bond interactions.

The beads i and j that are not chemically connected interact via nonbonded interactions, which are described by a Lennard-Jones 12-6 potential:

$$V_{LJ}(r) = \varepsilon_{ij} \left[\left(\frac{r_{0ij}}{r} \right)^{12} - 2 \left(\frac{r_{0ij}}{r} \right)^{6} \right], \tag{2}$$

where r is the distance between the two nonbonded beads, ε_{ij} is the energy minimum depth (the strength of the interaction) and r_{0ij} is the distance at the minimum of the potential.

Parameterization

Given the mapping scheme and the type of interaction, we needed to calculate one set of bonded parameters (for bonded VA–VA beads) and three sets of nonbonded parameters (VA–VA, benzene–benzene and VA–benzene). For each set we run a full atomistic simulation of the two groups involved in the interaction and we calculated the free energy of interaction between the two groups. The free energy calculations are performed using the adaptive biasing force (ABF) framework [19] as implemented in the NAMD code [20, 21]. The atomistic MD simulations are carried out using the NAMD program and the all-atom CHARMM force field [22], for a simulation time of 40 ns (time step of 1 fs) at a temperature of 300 K. Nonbonded interactions are computed using a switching

Fig. 1 Overview of the CG modeling approach. Panel **a** shows the initial atomistic model of benzene in PVA matrix. The system is then coarse grained using the mapping scheme depicted in panel **b**: in the case of benzene each molecule is represented by one CG bead, while for PVA each monomer is modeled with a different bead. This leads to the CG packing model used for the subsequent molecular simulations (panel **c**)

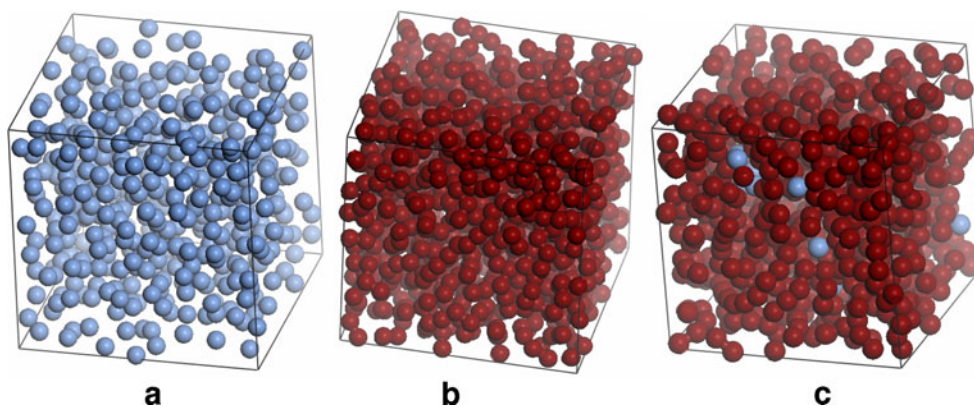(A)   (B)   (C)
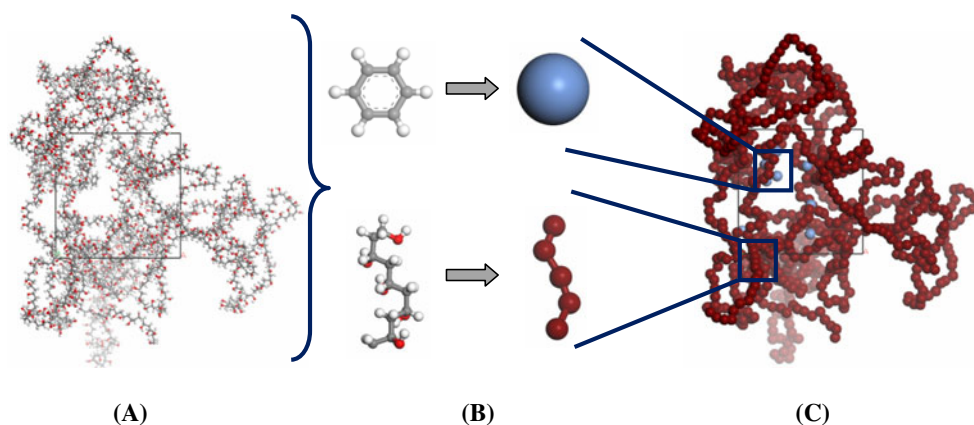
function between 20 and 22 Å. The free energy of interaction, computed *via* the ABF framework, is monitored between the two groups of atoms as a function of their center-of-mass distance, in the range 2–20 Å using windows of 0.01 Å.

Generation of the CG models

We generated three different molecular models: pure benzene, pure PVA and PVA with a small amount of benzene as penetrant molecule. All three systems were generated in the atomistic form using the *Amorphous Cell construction* tool of Materials Studio 4.4 (Accelrys, Inc.). The pure benzene system contained 500 benzene molecules in a cubic periodic box with initial density of 0.88 gcm^{-3}. For the pure PVA system we considered six atactic PVA molecules (consisting of 200 repeat units) in a cubic periodic box with initial density of 1.25 gcm^{-3}. Finally, the third system contained four PVA chains (of 200 repeat units) and 12 benzene molecules in a cubic periodic box with initial density of 1.25 gcm^{-3}. The three atomistic systems are then converted into CG systems using the *Coarse Grainer* tool of Materials Studio according to the mapping scheme described above (see Fig. 2).

CG simulations

CG molecular dynamics simulations are carried out using the Mesocite module and the MARTINI force field implemented in Materials Studio. Prior to the simulations, we modified the original force field including the parameters for bonded and nonbonded interactions between benzene and VA beads, as obtained from the ABF atomistic simulations. The CG systems are minimized for 1000 steps, then equilibrated for 1 ns (using a time step of 20 ps) at 300 K. Finally, production simulations are run for a simulated time of 10 ns (for pure benzene and pure PVA) and 200 ns (for benzene in PVA matrix). The diffusion coefficient D_i of a single permeant molecule i is calculated by the Einstein relation, starting from the diffusion trajectory $\vec{r}_i(t)$ which is determined during the production MD simulations:

$$D_i = \frac{\left\langle |\vec{r}_i(t) - \vec{r}_i(0)|^2 \right\rangle}{6t}, \qquad (3)$$

where $\left\langle |\vec{r}(t) - \vec{r}(0)|^2 \right\rangle$ represents the root mean square displacement (MSD) of the permeant molecule i averaged over all possible time origins and t represents the time. The computationally derived diffusion coefficient D for a given

Fig. 2 Overview of the three different CG systems considered in this study. The packing models of pure benzene (panel **a**), pure PVA (panel **b**) and benzene in PVA matrix (panel **c**) are represented. Each benzene bead model one benzene molecule, while each VA bead represents one VA monomer

a   b   c

kind of permeant molecule is then obtained as average over the diffusion coefficients for N permeant molecules:

$$D = \frac{\sum\limits_{i=0}^{N} D_i}{N}. \tag{4}$$

In this work the diffusion of all 500 benzene beads (for benzene self diffusion) and the 12 benzene beads (for benzene in PVA) was investigated during the CG simulations.

Results

The parameters of the CG force field, *i.e.* the bonded and nonbonded interactions between the beads, are calculated through full atomistic simulations and by applying the ABF framework. The ABF calculations provide the free energy profile as a function of the distance between the group of atoms, as shown in Fig. 3. The free energy profile of two bonded VA monomers (Fig. 3a) is interpolated with a harmonic potential, giving the equilibrium distance and the force constant (see Table 1). On the other end, from the interaction free energy profiles between nonbonded VA monomers, benzene molecules and VA-benzene molecules (Fig. 3b–d) we obtained the three sets of r_0 (energy minimum) and ε (energy minimum depth), used to feed the Lennard-Jones 12-6 potential of the CG force field (see Table 1).

We used the CG approach to investigate three different systems: pure benzene, pure PVA and benzene molecules in

a PVA matrix (see Fig. 2). The pure benzene system consisted of 500 benzene molecules, which were coarse grained into benzene beads. We measured the density of the system during the 1 ns equilibration obtaining a realistic value of 0.881 ± 0.001 g cm^{-3} (where the experimental value is 0.876 g cm^{-3}). After the equilibration we carried out a 10 ns simulation in which we monitored the MSD of the benzene molecules (see Fig. 4a) and, by applying Eq. 3, we determined the self diffusion coefficient of benzene, obtaining a value of $2.273 \pm 0.588 \cdot 10^{-9}$ m^2 s^{-1}, very close to the experimental value of $2.203 \pm 0.004 \cdot 10^{-9}$ m^2 s^{-1} [23]. In the case of pure PVA the system consisted of a periodic box with six chains of 200 monomers each. The coarse grained system was equilibrated for 1 ns and the density of the CG PVA box was measured, giving a value of 1.305 ± 0.011 g cm^{-3}, which lie in the experimental range (1.232–1.329 g cm^{-3}) [24]. Finally, the third system consisted of 12 benzene molecules diffusing in a PVA matrix. The density of the coarse grained system, measured at the end of 1 ns equilibration, was 1.293 ± 0.003, similar to that of pure PVA. The MSD of the benzene beads was monitored during a 200 ns MD simulation (see Fig. 4b), and from the derivative of the curve, we calculated the diffusion coefficient of benzene in PVA. We obtained a diffusion coefficient of $0.263 \pm 0.035 \cdot 10^{-12}$ m^2 s^{-1} which is in good agreement with the experimental value, that is $0.25 \cdot 10^{-12}$ m^2 s^{-1} [12]. The 200 ns simulation of the 4 nm × 4 nm × 4 nm CG box (with 812 beads representative of ≈6000 atoms) took 36 hours on a single CPU. The results of the simulations as well as the experimental data are shown in Table 2.

Fig. 3 Interaction free energy profile between the groups of atoms represented as beads in the CG simulations. Panel (**a**) represents the interaction between two VA monomers covalently connected in a PVA chain. The interaction profile was interpolated with a harmonic potential, giving the equilibrium distance r_0 and the force constant k_{bond}. From the free energy profiles between nonbonded groups (VA monomers, panel **b**; VA monomer and benzene molecule, panel **c**; benzene molecules, panel **d**) we extracted the energy minimum depth ε and the distance at the minimum r_0 to feed a Lennard-Jones 12-6 potential
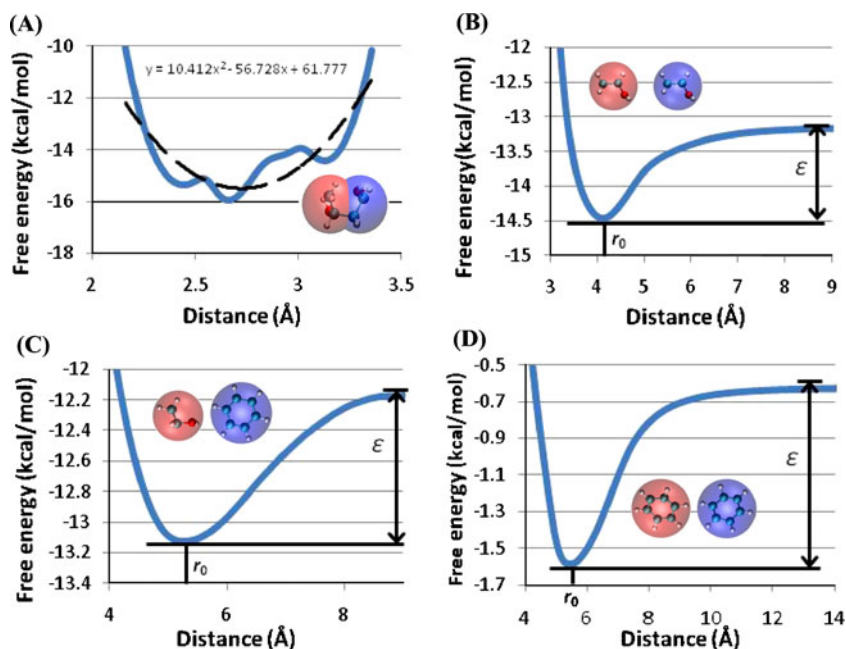
Table 1 Parameters of the CG force field, obtained from full atomistic free energy calculations. Within this approach bonded interactions (*i.e.*, VA beads covalently connected) are modeled through a harmonic potential, while nonbonded interactions are approximated with a Lennard-Jones 12-6 potential

Interaction	Bonded		Nonbonded	
	k_{bond} (kcal/mol/Å^2)	r_0 (Å)	ε (kcal/mol)	r_0 (Å)
VA–VA	40.36	2.76	1.306	4.115
VA–Benzene	–	–	0.957	5.51
Benzene–Benzene	–	–	0.9634	5.62

Discussion

In this work we present a multi-scale method for the parameterization of the MARTINI CG force field and its application for the calculation of the diffusivity of medium sized molecules in polymeric membranes. In the past, atomistic simulations have been already successfully applied for the calculation of diffusivity of small molecules in polymeric membranes. Nonetheless, the computational costs can hinder the ability of MD simulations to predict such a parameter. Indeed, the Einstein relation (Eq. 3) applied for the assessment of the diffusion coefficient can only be used when the simulation is in the regime of normal diffusion and this realm is reached when the slope of the function $\log[MSD(t)] = f[\log(t)]$ equals 1. In the case of very small molecules, like oxygen or hydrogen, the normal diffusion regime can be reached within few nanoseconds [5] while, in the case of medium sized molecules like benzene [12] or even water [13], it cannot be reached within the limit of atomistic simulations. In this view, the use of CG simulations, where a number of atoms are condensed into beads or interacting particles, can be a useful approach to overcome the limitations of atomistic simulations.

In order to test the feasibility of the CG approach, we investigated the self diffusion coefficient of benzene and its diffusivity in PVA matrix using an atomistic-informed CG force field (see Fig. 1). As shown in Table 2, the coarse graining reduces the number of interacting particles by a factor of ≈10. Furthermore, since the CG interactions are much smoother compared to atomistic interactions [16], it

is possible to use a time step of 20–40 fs, much larger than that typical of classical MD (1–2 fs). Thus, the CG approach leads to a total speed-up factor of 200–400 with respect to atomistic simulations.

In this work we did not rely on the standard MARTINI bead types but rather we defined two *ad hoc* bead types (one for benzene molecule and one for VA monomer) and we estimated the bonded and nonbonded parameters using atomistic free energy calculations.

The predicted parameters are then used to feed the MARTINI force field. The extended force field is then used to perform CG molecular dynamics simulations of three different systems: pure benzene, pure PVA and benzene in PVA (see Fig. 2). The coarse grain systems underwent1 ns equilibration dynamics, during which they reached a stable density very close to the experimental values (Table 2), thus confirming that the outcome of the atomistic free energy calculations are reasonable.

As a final validation of our approach, we ran longer CG simulations in order to assess the self diffusion coefficient of benzene and the diffusion coefficient of benzene in PVA. For the pure benzene, we ran a 10 ns simulations from which we estimated the diffusion coefficient. The calculated and the experimental values are shown in Table 2, and the comparison confirms that the CG model is able to predict the experimental value with good approximations. In the case of benzene diffusing in a PVA matrix, 10 ns of simulation were not enough to reach the normal diffusion regime, since the derivative of the function $\log[MSD(t)] = f[\log(t)]$ was lower than 1. This result is in agreement with the observations of Pan *et al.* [12], which showed that MD

Fig. 4 Mean square displacement (MSD) *vs.* time (straight lines) and linear interpolation (dashed lines) for the diffusion of benzene molecules in benzene (panel **a**) and in PVA (panel **b**). In the case of benzene diffusing in PVA matrix, the first 50 ns were excluded from the linear interpolation
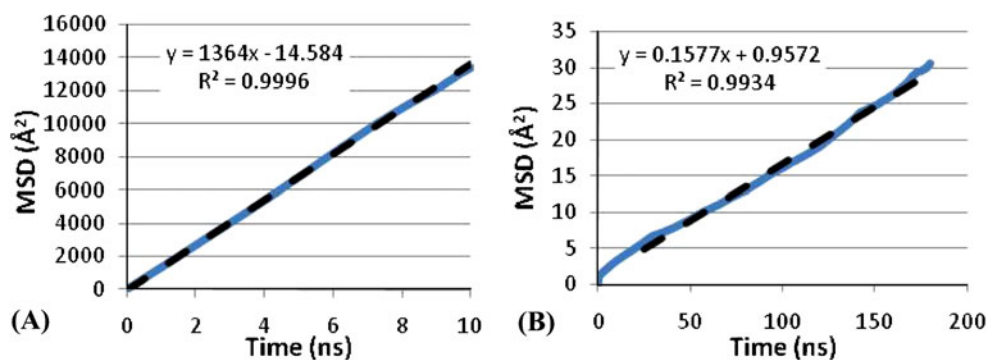
Table 2 Main results of the CG simulations. The conversion of the three systems under study from atomistic to coarse grain reduces the interacting particles by a factor between 7 and 12, depending on the specific system. Despite the loss of atomistic details, the CG models feature realistic densities and are able to predict benzene diffusion coefficient very close to the experiments

Systems	Total atoms	Total beads	Final density (g/cm^3)	Experimental density (g/cm^3)	Predicted $D_{benzene}$ (m^2/s)	Experimental $D_{benzene}$ (m^2/s)
500 benzene molecules	6000	500	0.881	0.876	$2.273 \cdot 10^{-9}$	$2.203 \cdot 10^{-9}$ [23]
6 PVA chains	8400	1200	1.305	1.23–1.32 [24]	–	–
4 PVA chains + 12 benzene	5744	812	1.293	–	$0.263 \cdot 10^{-12}$	$0.25 \cdot 10^{-12}$ [12]

simulations of a few nanoseconds are not long enough to reach the normal diffusion regime and provide a good estimation of benzene diffusivity in PVA. For this reason, we run a longer simulation of 200 ns, in order to reach the realm of normal diffusivity, as shown in Fig. 5. Indeed, the trajectory of this long simulation permitted us to obtain a diffusion coefficient very close to the experimental value (see Table 2). This result confirms the feasibility of the CG approach to reach the normal diffusion regime of medium sized molecules in polymer matrices and that our multi-scale approach is a valid method to treat this kind of problem.

The major limitation of atomistic computational techniques applied in the literature to solve diffusive problems is related to the restricted time scale and sample size which can be simulated, which are a few nanoseconds and a few nanometers, respectively. Thus, when the phenomena under investigation exceed these limits MD simulations fail to provide reliable values of the diffusivity. In order to overcome these limitations we developed a novel method, which consits of combining atomistic and coarse grain simulations in a multi-scale paradigm, where the parameters for the meso-scale model are derived from atomistic MD simulations. Similar techniques are increasingly applied for the study of biological problems, but to the best of our knowledge, have not been used for the investigation of

diffusion problems. Here we showed that this technique can be successfully applied to investigate the diffusion of penetrant molecules in polymer matrices, reliably predicting experimental data. A similar method as used in this paper could be applied to study the diffusion of larger molecules, which require a longer time to reach the normal diffusion regime, or the study of complex polymeric materials, for which representative volumes are larger than a few cubic nanometers.

Conclusions

In conclusion, the main focus of this work has been to develop and validate a novel multi-scale method for the prediction of diffusivity in polymer matrices. We demonstrated that atomistic-informed CG simulations can be a valid approach to treat problems where the computational limits of classical MD simulations are too restrictive while, at the same time, strictly atomistic details are not mandatory. Thus, the multi-scale approach presented in this work extends the application range of computational modeling and provide a useful tool to investigate phenomena at the micro-scale which determine macroscopic physical properties of polymeric materials. In this view, multi-scale paradigm here discussed can further help
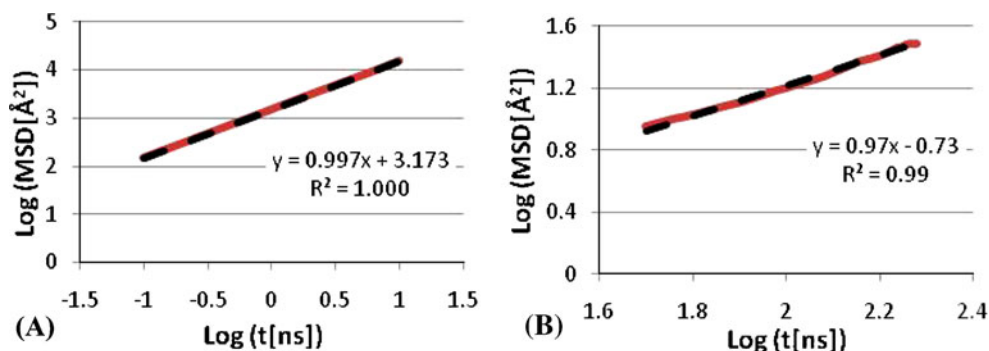

Fig. 5 Log(MSD) *vs.* log(t) plots (straight lines) and linear interpolation (dashed lines) for the self diffusion of benzene (panel **a**) and for the diffusion of benzene in PVA (panel **b**) obtained from CG simulations. The plots show that in the case of pure benzene the normal diffusion regime is reached, as indicated by the slope very close to 1, already in the range from 10^{-1} to 10^1 ns, while in the case of benzene in PVA (panel **b**) a longer simulation time is required since the normal diffusion regime is reached in the range from $10^{1.7}$ to $10^{2.3}$ ns (*i.e.*, from 50 to 200 ns)

computation aided molecular modeling to reduce the extent of the experimental trial-and-error approach during the design and investigation of new materials, thus resulting in a more cost and time efficient process.

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