Final Draft

of the original manuscript

Hoffmann, F.; Machatschek, R.; Lendlein, A.:

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In: MRS Advances. Vol. 5 (2020) 52 - 53, 2737 - 2749.

First published online by Cambridge University Press: 22.10.2020

https://dx.doi.org/10.1557/adv.2020.386

Understanding the impact of crystal lamellae organization on small molecule diffusion using a Monte Carlo approach

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ABSTRACT

Many physicochemical processes depend on the diffusion of small molecules through solid materials. While crystallinity in polymers is advantageous with respect to structure performance, diffusion in such materials is difficult to predict. Here, we investigate the impact of crystal morphology and organization on the diffusion of small molecules using a lattice Monte Carlo approach. Interestingly, diffusion determined with this model does not depend on the internal morphology of the semi-crystalline regions. The obtained insight is highly valuable for developing predictive models for all processes in semi-crystalline polymers involving mass transport, like polymer degradation or drug release, and provide design criteria for the time-dependent functional behaviour of multifunctional polymer systems.

INTRODUCTION

General introduction

The diffusion of small molecules through polymer matrices is of great relevance for medical applications [1, 2]. In biomaterials, small molecule diffusion drives material functions such as polymer degradation [3] and drug release [4]. The functional behaviour of these materials strongly depends on the diffusion characteristics of small molecules such as water, bioactive molecules or oligomeric fragments. The diffusion of small molecules is typically associated with a random walk behaviour, and in case of water, diffusion rate constants are available from the literature [5-7]. However, it is questionable whether the hypothesis of a random walk behaviour still holds in non-isotropic materials like semi-crystalline polymers. Here, amorphous regions are flexible and can take up small molecules from the environment, while crystalline regions are characterized by stacks of repeating lamellae, which are stabilized by van der Waals forces and reject small molecules from entering into these regions [8]. The effect of crystallinity on the diffusion of small molecules through semi-crystalline polymers has been studied with experimental [9, 10], analytical [11] and modelling approaches [12, 13]. The experimental investigations show

that the diffusion coefficient of small molecules decreases with increasing crystallinity. The modelling approaches investigated the influence of the crystallites in semi-crystalline polymers on the diffusion of small molecules. The internal morphological structure of these crystalline regions, which consist of stacks of sheet like crystal lamellae, has been mainly ignored in these studies.

The substructure of lamellar stacks can vary in many ways, for example in the number of lamellae within a stack, the area of the lamellae, the distance between lamellae and the orientation of the stack within the polymer. Each lamella has an orientation defined by the surface normal of the crystal lamellae. However, the orientation of the different stacks depends on the processing conditions, and can range from anywhere between completely random to fully aligned. Measuring the dependence of the diffusion of small molecules on the size and orientation of the crystalline regions requires a homogenous orientation and controlled size distribution of the crystalline lamellae in a semi-crystalline polymer, which is difficult to achieve. Semi-crystalline samples typically exhibit distributions in the organisation of crystalline orientations, which are influenced by its surface properties, kinetics of chemical reactions and transitions around the critical temperature T_{crit} [14]. Measuring the local concentration of small molecules in a semi-crystalline region requires analytical methods capable of a spatial resolution in the dimension of few nanometers, which relates to the distance between crystal lamellae [15]. Most available methods that can differentiate between water and other molecules do not provide such precision. For example, Nuclear Magnetic Resonance (NMR) can detect polymer morphologies on length scales of several μm [16] and neutron scattering can be used to estimate length scales of the radius of gyration R_g of long polymer chains if these chains are properly labelled. Yet, understanding how the number, size, and orientation of crystallites affect the diffusion behaviour of small molecules on a length scale of a few nm is not possible with these experimental techniques. However, understanding this behaviour is a prerequisite for predicting the functional behaviour of established semi-crystalline biomaterials like poly(ε-caprolactone) (PCL), poly(glycolide) (PGL), poly(*L*-lactic acid) (PLLA) and poly(p-dioxanone) as well as advanced materials like shape-memory polymers [17]. Hence, a modelling approach is required.

Several approaches have been used in the past to study the diffusion of small molecules through polymers. Knopp et al. [18] and Nick et al. [19] calculated the chemical potential of small molecules in dense polymer systems with molecular dynamics simulations using thermodynamics integration and estimated the equilibrium water content and the water sorption behaviour in amorphous polymers of various materials. Although the simulation time of several ps and force field accuracy at this time were rather limited, the authors could successfully distinguish between different sorption behaviours for different polymer systems. Following simulations were able to calculate the diffusion constants of gas molecules through polymers [20-22]. With increasing computational power, it is now possible to determine the diffusion of bigger molecules through polymers. For example, Forrey et al. [23] calculated the diffusion constant of the drug tetracycline (TAC) in poly(styrene-*co*-isobutylene-*co*-styrene) (SIBS) with solvent tetrahydrofuran (THF) using simulations of about 1 μs. Their molecular dynamics simulations are based on all-atomistic force fields. While they are able to describe diffusion constants of small molecules in polymers accurately, they are limited to amorphous polymers, thereby excluding many materials of high technological relevance.

Here, we use Monte Carlo (MC) calculations to simulate the diffusion of small molecules in a semi-crystalline polymer. Monte Carlo calculations are not limited to the characteristics of a specific force field. Random moves allow to explore the phase space without the risk of getting trapped in few low energy conformations. We assume that the diffusive molecules do not react with or bind to the polymers on time scales similar or faster than their diffusion time, do not aggregate and are small in comparison to the size of a polymeric lamella. Furthermore, we assume that there are no attractive potentials

between small molecules and polymers and that repulsion is described with a lattice gas model. A sphere in a lattice model represents a small volume element of the polymer matrix. Such models have been used in the past to successfully model the diffusion and release of molecular drugs [22, 24-26]. However, the influence of the semi-crystalline morphology has so far been neglected because crystalline regions, if present in these models, have been represented as square shaped blocks distributed randomly through the polymer matrix. Here, we hypothesize that the impact of polymer crystallinity on the diffusion of small molecules can be assessed by inserting stacks of sheet-like structures into the lattice model.

Starting point is a completely amorphous system, in which small molecules diffuse into the polymer from specific directions. We use a spherical system for our simulation because a complete analytical solution for the diffusion equation of a sphere is available. The uptake of small molecules is simulated for spheres with different radii R, to determine the minimum size of the sphere, which can represent normal diffusion without finite size effects. Then, we determine the minimum amount of Monte Carlo steps needed to reach an equilibrated structure with constant concentration c of small molecule clusters. Here, a small molecule cluster contains about 10^5 small molecules (see Supplementary Information). The volume elements in our model can contain either one such cluster or no clusters at all. The concentration is the number of occupied amorphous volume elements divided by the total number of amorphous volume elements. The final distribution of the molecules in this simulation is used as a starting distribution for the following simulations, in which we simulate the diffusion of small molecules through a sphere without and with parallel crystalline lamellae, which are impenetrable for these molecules. Hereby, the number, size and orientation of the lamellae are varied to represent different types of semi-crystalline morphologies. We further extend our simulations to extremely spacious lamellae to look for deviations from the observations drawn from more regular morphologies.

METHODS

The diffusion of small molecules through an amorphous and a semi-crystalline polymer is modeled with a Monte Carlo approach on a three-dimensional lattice. In short, relative diffusion constants parallel and perpendicular to the direction of entry of small molecules into an amorphous polymer and in dependence of the orientation, size a, distance d and number n of crystalline lamella are calculated. The lamellae have the shape of cuboids with height 1 and a quadratic base of side length $2a + 1$. All spatial and temporal quantities are reported in lattice unit length l_u and MC time l_t. Concentrations are reported relative to the maximum concentration ($c_{max} = 1$), which corresponds to a sphere where every amorphous volume element of the sphere is occupied with a cluster of small molecules. An experimental validation of these dimensions is not performed because the model with one experimental input parameter (diffusion constant D) and two unknown quantities (l_u and l_t) is underdetermined. Figure 1A shows a schematic description of the parameters of the simulation. A detailed description about the methods incl. the estimation of the statistical error can be found in the Supplementary Information.

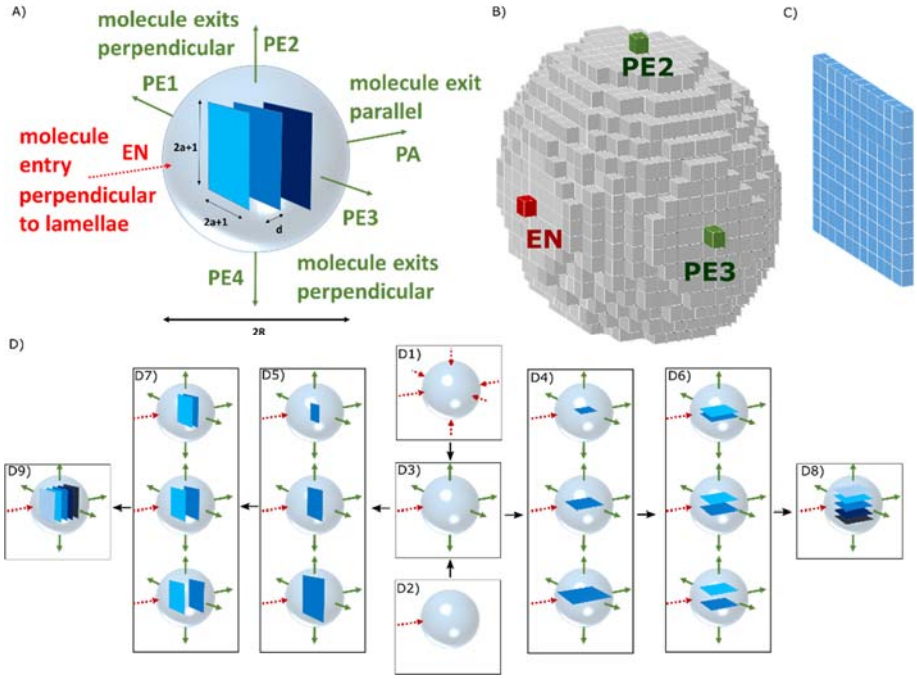

Fig. 1 Schematic visualization of the Monte Carlo model. A) Sphere with three lamellae oriented perpendicularly and exits parallel (PA) and perpendicular (PE1-4) to the direction of small molecule entry. B) Lattice model for sphere with radius R = 9 and positions of small molecule entry (EN) and two exits (PE2 and PE3). C) Lamella with a = 5 in lattice representation. D) Cascade of simulations: D1) Small molecule uptake from 6 opposing directions, D2) Small molecule uptake from one direction, D3) Small molecule diffusion through amorphous sphere, D4-9) Small molecule diffusion through semi-crystalline sphere with lamellae orientations parallel (D4, D6, D8) and perpendicular (D5, D7, D9) to the direction of small molecule entry, D4/5) One Lamella of different size a, D6/7) Two Lamellae with different distances d, D8/9) 5 Lamellae. Directions of small molecule entry and exit are marked with red, dotted and green, solid arrows, respectively.

RESULTS AND DISCUSSION

Theory of diffusion in a sphere

Here, we describe the diffusion of small molecules through amorphous and semi-crystalline parts of a polymer, which are represented by a sphere of cubic volume elements. Fick's law describes normal diffusion in homogenous media. The solution for this law for a sphere is:

$$\frac{c_t}{c_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}e^{-n^2\pi^2\frac{D}{R^2}t}$$

The equation describes the release of small molecules from a sphere with concentration c or the sorption of small molecules into an empty sphere. The individual contributions of this multi-exponential function decrease very rapidly with increasing n and the function is dominated by its first term ($n = 1$). The function is usually approximated by a stretched exponential function:

$$\frac{c_t}{c_\infty} = 1 - e^{-(\frac{t}{\tau})^b}$$

Here, b and τ are fitting parameters, which describe the physics of the sorption of small molecules. The latter is the reduced time, measured in units of R^2/D. For an infinitely big sphere, fitting the exact solution of Fick's law with the stretched exponential function gives $b_{fit} = 0.68$ and $\tau_{fit} = 0.054$ R^2/D [24].

Uptake of small molecules from 6 directions

In a first step, the uptake of small molecules from specific points of entry is simulated (see Fig. 1D1). This is different from the theoretical case because the points of entry are not homogenously distributed around the center of the sphere. We model a completely amorphous sphere. This means that all volume elements of the sphere are penetrable for clusters of small molecules with the same probability. Monte Carlo calculations have been performed for small molecules entering the sphere from 6 opposite directions via its outer volume element. This corresponds to a symmetric, but inhomogeneous sorption of small molecules. Fig. 2A shows the concentration of the sphere as a function of the Monte Carlo time for the simulation of a sphere with radius $R = 7$ up to a maximum concentration of $c = 0.9$. It can be seen that the increase follows a stretched exponential function.

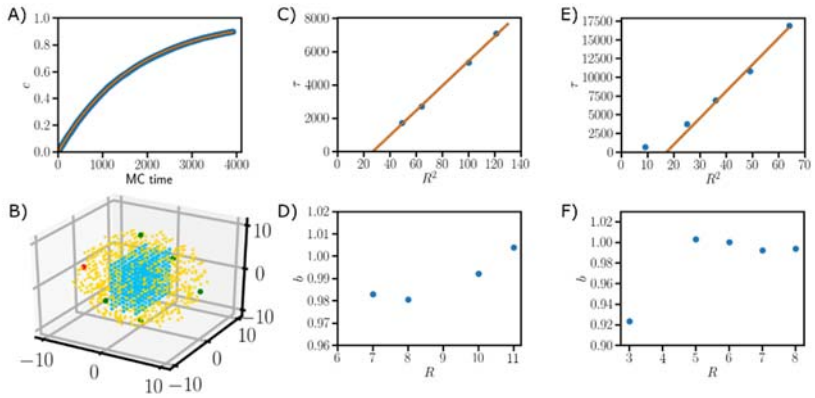

Fig. 2 A) Concentration c as a function of the MC time for R = 7 and filling the sphere from 6 directions. B) Starting configuration of clusters of small molecules (gold dots) for following simulations with R = 10. Position of small molecule entry (red triangle) and exits (green stars) and of 3 lamellae with a = 5 and d = 2 (deep sky blue squares) are shown for illustration. C-F) Fitting parameter τ and b as a function of sphere radius R for simulations of sphere filling from 6 (C, D) and from 1 directions (E, F). Data shown as blue dots and linear fit for all data (C) and R ≥ 6 (E) shown as orange line.

Monte Carlo runs have been performed for different radii R of the sphere up to a concentration $c = 0.5$ and fitted with a single exponential. Figs. 2C and 2D represent the values of the fitting parameters τ and b as a function of sphere radius R.

The reduced time τ depends on the square of sphere radius R and the slope is 74.4. Homogenous diffusion in three dimensions with 6 degrees of freedom would correspond to an increase of f $\tau_{fit} = 0.324$ with $f = 6$ the number of degrees of freedom per molecule and τ_{fit} the value of the fitting parameter of the homogenous solution. One should keep in mind that the slope of τ vs. R^2 is the inverse of the diffusion constant D, i.e. the

greater the slope, the slower the diffusion. The quadratic approximation reaches steady state ($\tau = 0$) for a sphere radius of $R = 5.2$ which means that there is a transition from a retarded diffusion due to finite size effects for $R < 5.2$ to normal diffusion for $R > 5.2$. Fig. 2D shows that the parameter b has values around 1. Higher values than $b = 0.61$ are connected to a slower filling of the sphere in comparison to the homogenous case. As the sphere is filled from specific locations on its surface, diffusion is retarded to the limited accessible volume, which only allows moves within the sphere. The results show that the simulated filling of the sphere is described by a normal, retarded diffusion.

Uptake of small molecules from 1 direction

After modelling diffusion from 6 directions, diffusion within the sphere is modeled for an entry of small molecules from only one direction (see Fig. 1D2). This represents the situation that diffusion is not random, but has a preferred orientation, and prepares the following simulations with crystals below. The results of Monte Carlo calculations with different sphere sizes are visualized in Figs. 2E and 2F. Fig. 2E shows that normal diffusion starts for sphere sizes $R > 6$. The deviation for smaller sphere sizes points to a retarded diffusion. Smaller spheres have a higher surface area to volume ratio. As a result, the fraction of random moves outside the sphere increases with decreasing sphere size. Since these moves are rejected, this leads to a retarded diffusion. The slope of 355.5 in the τ-R^2-Plot for $R > 6$ is about 5 times bigger than the slope of the same plot in the homogenous case (Fig. 3C). The diffusion is therefore 5 times slower because the slope is inversely proportional to the diffusion constant.

Diffusion through an amorphous polymer

After having established that filling a sphere with Monte Carlo calculations follows normal, retarded diffusion for sphere sizes with a radius $R > 5$, directional diffusion is investigated. Monte Carlo calculations are performed for a sphere under variation of the radius, in which the small molecules enter from one direction and can leave the sphere in the other 5 directions, one of them opposite to the direction of entry and the other four perpendicular to the direction of the entry (see Fig. 1D3). This system is used to measure the influence of lamella orientation on the diffusion behavior of small molecules in the next sections. Here, we focus on an amorphous polymer without lamellae. In order to describe the relative diffusion of small molecules in detail, it is important to start with an equilibrated system. Tables S1 and S2 show the number of clusters of small molecules, which leave spheres of different radii R parallel or perpendicular to the direction of entry after 10^6 and after 10^7 MC steps, respectively.

It can be concluded that 10^6 MC steps are not enough to reach a ratio of 20%, corresponding to the ratio of small molecule entries to exits, between clusters of small molecules entering and leaving the sphere for $R > 8$, but 10^7 steps are enough for $R = 10$. We therefore used the distribution of small molecules from the simulation with $R = 10$ after 10^7 MC steps, shown in Figure 1B, as starting configuration for all following simulations of semi-crystalline elements and perform simulations of similar length with the same sphere size. Furthermore, one can see that the ratio of clusters of small molecules leaving the sphere parallel to the direction of entry to the clusters of small molecules leaving the sphere perpendicular to the direction of entry is about 22-26%, corresponding to the number ratio of small molecule exits (1:4). In other words, the direction of small molecule exit is statistically distributed, as it should be in an amorphous system.

Diffusion through a semi-crystalline polymer

In the previous step, a purely amorphous polymer has been modeled and it was shown that the diffusion of small molecule clusters parallel and perpendicular to the direction of molecule entry are similar, which is reflected by the ratio of 1:4 between the number of exits parallel and perpendicular to the direction of entry (see Fig. 1). In the next step, the model is extended to represent semi-crystalline volume elements. Therefore, stacks of impenetrable lamellae are inserted into the sphere. Here, quadratic lamellae are considered, which are located around the center of the sphere, either parallel or perpendicular to the direction of the entry of small molecules. The height of the lamellae is one unit length l_u and the length of the quadratic area is 2a+1. Table 1 shows the number of small molecule clusters leaving the sphere parallel and perpendicular to the direction of entry for different lamellae orientations and different values of *a* (see Figs. 1D4 and 1D5), *d* (see Figs. 1D6 and 1D7) and *n* (see Figs 1D8 and 1D9).

Table 1. *n* number of lamellae, *a* size of a lamella, *d* distance between two lamellae, N_e clusters of small molecules within sphere at the end of the simulation, N_{par} clusters of small molecules leaving sphere parallel to its entry, N_{per} clusters of small molecules leaving sphere perpendicular to the direction of entry, f_{parper} fraction of small molecule clusters leaving parallel vs perpendicular to the direction of entry. The error is the standard deviation from 8 independent MC runs.

Orientation [a]	*n*	*a*	*d*	N_e	c_e	N_{par}	N_{per}	f_{parper} [%]
[b]	0	-	-	781.7 ± 15.3	18.9	248.6 ± 9.5	1052.7 ± 27.8	23.6 ± 1.5
Parallel	1	3	-	766.0 ± 27.1	18.7	265.6 ± 17.1	1075.3 ± 35.6	23.6 ± 2.4
Parallel	1	5	-	759.1 ± 18.6	18.9	270.0 ± 11.6	1072.4 ± 22.1	25.2 ± 1.6
Parallel	1	7	-	749.0 ± 16.5	19.1	259.4 ± 14.0	1083.9 ± 21.5	23.9 ± 1.8
Perpendicular	1	3	-	772.4 ± 14.3	18.9	251.4 ± 15.4	1074.1 ± 39.0	23.4 ± 2.3
Perpendicular	1	5	-	771.6 ± 23.1	19.2	263.4 ± 16.6	1059.1 ± 36.1	24.9 ± 2.4
Perpendicular	1	7	-	748.7 ± 24.9	19.1	263.3 ± 17.1	1090.7 ± 12.6	24.1 ± 1.8
Parallel	2	5	2	743.7 ± 16.7	19.1	269.7 ± 10.7	1106.3 ± 33.6	24.4 ± 1.7
Parallel	2	5	3	743.3 ± 19.8	19.0	267.6 ± 8.2	1108.4 ± 34.1	24.1 ± 1.5
Parallel	2	5	4	731.1 ± 30.2	18.7	265.1 ± 13.0	1116.1 ± 36.1	23.8 ± 1.9
Perpendicular	2	5	2	748.0 ± 14.6	19.2	262.0 ± 16.4	1102.6 ± 36.5	23.8 ± 2.3
Perpendicular	2	5	3	745.4 ± 19.9	19.1	265.6 ± 10.2	1111.9 ± 42.0	23.9 ± 1.8
Perpendicular	2	5	4	748.0 ± 14.6	19.2	262.0 ± 16.4	1102.6 ± 36.5	23.8 ± 2.3
Parallel	5	5	2	746.0 ± 15.3	21.1	257.4 ± 13.5	1130.3 ± 10.7	22.8 ± 1.4
Perpendicular	5	5	2	745.6 ± 29.0	21.1	267.9 ± 14.6	1118.0 ± 47.9	24.0 ± 2.3
Parallel [c]	1	5	-	769.7 ± 19.7	19.1	251.4 ± 10.6	1073.3 ± 28.2	23.4 ± 1.6
Parallel [d]	1	6	-	443.4 ± 15.5	19.4	370.4 ± 21.0	1773.9 ± 34.8	20.9 ± 1.6

[a] Orientation of lamellae with respect to orientation of small molecule entry
[b] Amorphous sphere
[c] Simulation with corrected MC time
[d] Simulation with thick lamella (h=11)

The number of clusters of small molecules within the sphere N_e decreases from the amorphous case to the situation with lamellae due to the reduced available volume. However, this is not just an effect of the replacement of clusters by lamellae in the starting configuration, because the number of clusters leaving the sphere increases. Introducing stacks of lamellae in an amorphous sphere introduces an additional pressure on the remaining clusters between the lamellae. The effect increases with increasing number of lamellae per stack. As a result, the concentration c_e at the end of the simulation, calculated with respect to the available volume of the sphere by subtraction the volume of the lamellae, is in most of the cases higher with lamellae than without lamellae. The directional

diffusion is marginally influenced by the size of the lamellae. One small lamella with a = 3 does not influence f_{parper}, but larger lamellae seem to increase the diffusion in the direction of entry in comparison to its perpendicular direction independent of the orientation of the lamellae. This effect could be explained by the negative pressure on the side of the stack of lamellae opposite to the direction of entry, which leads to a removal of the clusters in this area.

The orientation of one lamella within the sphere does not seem to have an influence on the directional diffusion of small molecules. This seems to be different if two lamellae are introduced in the sphere. If these two lamellae are orientated parallel to the direction of small molecule entry, f_{parper} is always higher than for a perpendicular orientation between lamellae and small molecule entry. Crystalline lamellae embedded in an amorphous environment represent an obstacle included in a lamellar flow field of diffusing clusters of small molecules. The main direction of the flow field is defined by the direction of entry of these molecules into the sphere. If a thin obstacle is orientated parallel the flow field, the lamellar flow field is only marginally influenced by the obstacle because the molecules diffuse around without changing their general direction. If the obstacle is orientated perpendicular to the flow field, all molecules have to diffuse around the edges of the obstacle. This increases the local concentration of clusters close to the edges and increases the size of the obstacle perpendicular to the lamellar flow field, therefore reducing the flow of small molecules in this direction.

The value of f_{parper} for simulations of two lamellae with a = 5 is about 23.8% for different distances d between the lamellae for a perpendicular orientation of the lamellae with respect to the direction of small molecule entry and only slightly varies between 23.8% and 24.4% for a parallel orientation. The data suggest that the distance between two lamellae has an influence on the directional diffusion of small molecules around it.

As directional diffusion is only marginally influenced by the insertion of a stack of lamellae around its center, we estimate the magnitude of the diffusion constant in such a semi-crystalline volume element with respect to a completely amorphous element. For free diffusion, small molecules move according to the following law:

$$< \Delta x >^2 = 6D < \Delta t >$$

We calculated Δx (in length of l_u) and Δt (in MC times l_t) for every cluster of small molecules, which did not enter or leave the sphere during the simulation. Fig. 3A and B show the normalized distribution of Δx and $(\Delta x)^2$, respectively, for the amorphous sphere and for a sphere with a stack of 5 lamellae, which represents a volume element of high crystallinity.

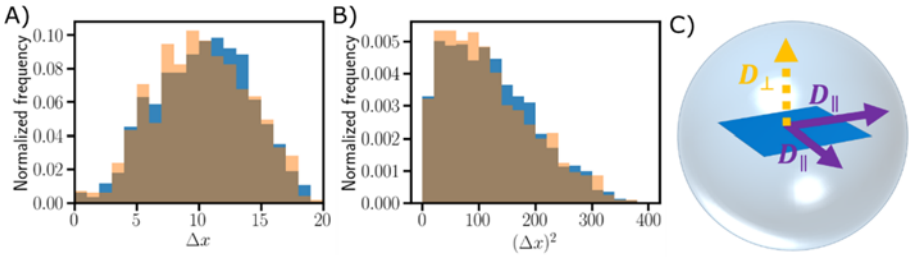

Fig. 3 Normalized distribution of distances Δx (A) and square of distances $(\Delta x)^2$ (B). The data belong to the simulations of the amorphous sphere (blue opaque background) and of the sphere with n = 5 lamellae with a = 5 and d = 2 perpendicular to the entry of small molecules (light orange transparent background). The overlapped area is visualized with a mixed colour. (C) Description of the direction of diffusion with respect to the orientation of the lamella. Parallel and perpendicular orientation are represented with violet solid and yellow dashed arrows, respectively.

The distributions of distances without lamella and with a stack of 5 lamellae nearly overlap. This means that clusters of small molecules, which stay in the sphere through the full duration of the simulation, walk similar distances. The diffusion constants calculated for all of these clusters are very similar: $D_{amorph} = 0.001592\ l_u^2/l_t$ for the amorphous sphere and $D_{crystalline} = 0.001545\ l_u^2/l_t$ for the sphere with a stack of 5 lamellae. The ratio of $D_{crystalline} / D_{amorph} = 0.97$ shows that the insertion of a stack with 5 lamellae decreases the diffusion rate constant of small molecules by only 3%. The results for other crystal morphologies and orientations are similar.

Diffusion through multiple stacks of crystalline lamellae

The previous results show that the diffusion of small molecules through a semi-crystalline polymer that contains one stack of parallel lamellae embedded in an amorphous environment is independent of the internal characteristics of the lamella. This is even the case if a stack of lamella is modeled, which represents the ratio of height to base side length of a lamella in the real world (see Supplementary Information). A typical semi-crystalline polymer contains multiple domains with stacks of crystalline lamella. If the distance between these stacks is big in comparison to the size of the lamella, they represent independent obstacles for the diffusion of small molecules and the stacks of lamellae do not influence the diffusion of small molecules. If the distance between the stacks is small in comparison to the size of the stacks, molecules diffuse preferably along the base of the stacks because the space between stacks is limited. To mimic this effect, we simulated the diffusion around a thick lamella with height $h = 11$. Furthermore, we chose a lamella with $a = 6$ which ensures that the distance between the sides of the lamella and the end of the sphere ($<= 4\ l_u$) is markedly smaller than the height of the lamella. Here, the end of the sphere represents a second lamella perpendicular to the direction of the entry of clusters of small molecules because moves outside the sphere are rejected (except at the positions where they can diffuse out of the sphere). In this case, the ration $f_{parper} = 20.9$ is lower than for the thin lamellae. This means that the number of molecules diffusing perpendicular out of the sphere with respect to the direction of entry is higher than the number of molecules diffusing parallel out of the sphere. This shows that the small molecules preferably diffuse around multiple stacks of lamella, which are close to each other instead of diffusing between them.

The result shows that the diffusion of small molecules through semi-crystalline polymer with separated stacks of semi-crystalline polymers is independent of the internal morphology of the crystalline region. If the distance between multiple stacks of lamellae is small in comparison to the size of the lamella, diffusion between these stacks is reduced. This can happen for crystals, which grow from the melt to large spherulites. The result adds additional information to current implementations of Monte Carlo calculations on diffusive molecules in the vicinity of polymer chains, which are focused on amorphous polymers [27, 28]. The model does not include interactions of polymers with small molecules, which could be studied with molecular dynamics simulations [29, 30]. The outcome of this study shows that the diffusion constants determined for the amorphous state in MD simulations have the potential to be converted to the semi-crystalline state independent of its morphology, if the crystalline content of the polymer is considered [31].

CONCLUSION AND OUTLOOK

In this paper, the diffusion of small molecules through amorphous and semi-crystalline polymers was investigated *via* Monte Carlo calculations of a sphere on a lattice

model. It has been shown that differences in the diffusion of small molecules through an amorphous and a semi-crystalline region are less than 3%. The internal morphology in terms of size and density of a single stack of lamellae does not change the time or direction of the small molecule diffusion. Small changes are detected for the relation of the direction of diffusion and the orientation of the lamellae with respect to the entry of small molecules. Overall, our simulations suggest that crystallites influence the diffusion of small molecules through polymers only by reducing the available volume. However, if the crystalline region contains multiple stacks of crystalline lamellae, whose inter-stack distance is small in comparison to the size of the stack, diffusion through the crystalline region is reduced. This finding greatly facilitates the development of predictive models describing kinetic processes such as hydrolysis or drug release in semi-crystalline polymers, which are highly relevant for the design of multifunctional materials.

If the orientation of the crystallites does not influence the diffusion of small molecules, they can be used for other functions, which are then independent from diffusion. One example are shape-memory polymers (SMP) [32]. These polymers have the capability to change their shape upon application of an external stimulus. The change in shape is often connected to a transition of the microscopic substructure. If such a SMP switches from an amorphous phase to a glassy phase, it changes its diffusion and the properties are not independent from diffusion. However, if the switching domains in SMP changes to a semi-crystalline state, but always leaves an amorphous, viscoelastic subphase, the shape-memory effect could be designed to be almost independent from diffusion. This consideration is also relevant in SMP actuators. These actuators have an additional phase, a reshapeable internal skeleton, which implements or adjusts the alignment of actuation domains on the nm length scale. In case of thermally controlled SMP actuators, the skeleton has to maintain the alignment over multiple heating and cooling cycles, while being sufficiently elastic to allow shape changes. The current study suggests that the functions of this skeleton phase are also independent of diffusion if the distance of the stacks of crystalline lamella is sufficiently big.

SUPPLEMENTARY INFORMATION

Number of molecules per volume element; Description of the methods incl. statistical error estimation; Tables S1 and S2 with statics about the simulations for the estimation of the number of MC steps required to achieve an equilibrium distribution; Diffusion through a semi-crystalline polymer with modified MC time.

DATA AVAILABILITY

Data and source code of the MC program can be required upon reasonable request by the authors.

ACKNOWLEDGMENTS

This work was financially supported by the Helmholtz Association through programme-oriented funding.

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