SUPPLEMENTARY INFORMATION

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

Falk Hoffmann1, Rainhard Machatschek1, Andreas Lendlein1,2

1Institute of Biomaterial Science and Berlin-Brandenburg Center for Regenerative Therapies, Helmholtz-Zentrum Geesthacht, Kantstraße 55, 14513 Teltow, Germany  
2Institute of Chemistry, University of Potsdam, Karl-Liebknecht-Straße 24-25, 14476 Potsdam, Germany  
\*Correspondence to: Andreas Lendlein   
E-mail: [andreas.lendlein@hzg.de](mailto:andreas.lendlein@hzg.de)

NUMBER OF MOLECULES PER VOLUME ELEMENT

A crystalline lamella has a typical lateral size of 1-25 m and a thickness of 5-50 nm [1]. Based on the dimensions, the number of small molecules in an occupied volume element of the sphere can be estimated. A sphere with radius *R* = 10 has a size of *V* = 4/3  *R*3 ~ 104 volume elements. A lamella with *a* = 5 has a volume of *V*lamella = *l*lamella2 *h*lamella = (2 *a* + 1)2 *h*lamella ~102 volume elements. That means that the sphere has a volume of about *V*sphere = 104/102 \* 10 nm \* (1 m)2 ~ 1 m3 and a single volume element accounts for *V*element = 10-4 m3. In equilibrium, 18-19 % of these volume elements are occupied, which means that the occupied volume of small molecules is on average *V*molecule = 2\*10-5 m3. Using water as an example, this directs to *N*molecules = water *V*molecule / *M*water *N*A = 6.7\*105 molecules. Here, the density of water water = 1 kg/m3, its Molar mass *M*water = 18 g/mol and Avogadro constant *N*A = 6.022 \* 1023 mol-1 are used. A move from one volume element to another, therefore, belongs to the diffusion of a cluster of ~105 molecules from the previous to the new volume element.

METHODS

The diffusion of small molecules into a sphere of radius *R* is simulated with a Monte Carlo approach on a three-dimensional cubic lattice of size *L*3 with *L* = 2 *R*. The sphere is included in the lattice. Fig 1B illustrates the lattice model used in the simulation for a sphere of radius *R* = 9. With *x*, *y* and *z* as the coordinates of a three dimensional Cartesian coordinate system centered around the origin of the lattice, the interior of the sphere contains all volume elements with positive integer coordinates (*ax*, *ay*, *az*) which fulfill *ax*2 + *ay*2 + *az*2 ≤ *R*2. Uptake of small molecules is simulated by filling the volume elements over time via one or six points of entry. A volume element is either occupied or not occupied with a cluster of small molecules. Occupation means that a volume element has reached a concentration *c*max. To achieve a constant entry of small molecules from a specific direction, the volume element with the coordinates (-*a*max, 0, 0) is always occupied with a cluster of small molecules. Here, *a*max is the maximum allowed integer value within the sphere: *a*max = *R*. This volume element is the only element occupied at the beginning of the Monte Carlo calculation. At every Monte Carlo step, a random occupied volume element within the interior of the sphere is chosen and the containing cluster is tried to be moved to a randomly selected nearest neighbor element. The move is accepted if the new volume element is empty and within the sphere and rejected otherwise. This ensures that excluded volume effects are explicitly taken into account. The outer volume elements with coordinates (-*a*max, 0, 0), (*a*max, 0, 0), (0, -*a*max, 0), (0, *a*max, 0), (0, 0, -*a*max) and (0, 0, *a*max) are called EN, PA, PE1, PE2, PE3 and PE4 in the following. If a cluster at EN is moved successfully, EN is filled with a new cluster to model the entry of small molecules from this direction. Filling the sphere from all directions includes the same for all 6 positions EN, PA, PE1, PE2, PE3 and PE4. The exit of small molecules from the sphere is modeled depending on the direction of the entry of small molecules. In this case, moves from PA, PE1, PE2, PE3 and PE4 outside the sphere are considered while EN is the position of small molecule entry. The Monte Carlo time is the time, which a cluster needs in average to move one unit length *l*u. This time is incremented by 1/*N*par at every Monte Carlo step. Here, *N*par is the number of particles present in this system after the Monte Carlo move. The first simulation is performed for an uptake of small molecules from all 6 directions with a sphere of *R* = 7 until a final concentration *c*e= 0.9 of occupied volume elements is reached. Then, uptake of small molecules from 6 and 1 directions is modeled for different radii *R* = [7, 8, 10, 11] and [3, 5, 6, 7, 8], respectively, until a final concentration *c*e= 0.5 is reached and the corresponding concentration curves are fitted with a stretched exponential function. Following simulations are stopped after a number of MC steps have been modelled. Simulations with radii *R* = 3-10 are performed up to 106 and 107 MC steps with an entry of small molecules at EN and no exit. All these simulations are performed once. The final snapshot after 107 MC steps for the simulation with *R* = 10 is used as the starting configuration for all following simulations.

All following simulations are stopped after 107 MC steps and are repeated 8 times. The number of small molecule clusters entering at EN and leaving at PA (parallel direction to its entry) or at PE1, PE2, PE3 and PE4 (perpendicular direction to its entry) are counted. To model the uptake of small molecules in a crystalline region, the same procedure is repeated with the exception that volume elements representing lamellae are not penetrable for clusters of small molecules. First, a simulation without lamella stacks is performed to model an amorphous polymer. Then, the dependence of the diffusion behavior of small molecules on the direction of a stack of lamellae is investigated by blocking all volume elements with coordinates (±*a*0, ±*a*0, 0) and (0, ±*a*0, ±*a*0) from occupation. Here *a*0 ≤ *a*, which means that this corresponds to the lamella parallel and perpendicular to the orientation of small molecule entry with length *l*lamella = 2 *a* + 1 and height *h*lamella = 1. Fig. 1C shows such a lamella with *a* = 5 in a lattice representation. This simulation is performed for *a* = 3, *a* = 5 and *a* = 7 which represent different sizes of lamellae. Next, the effect that most of the crystalline regions contain multiple parallel lamellae per stack is considered. Therefore, volume elements with coordinates (±*a*0, ±*a*0, *b*) and (*b*, ±*a*0, ±*a*0) with *a*0 ≤ *a* = 5 are blocked. Here we investigate two cases: In the first case, the dependency on the distance between lamellae is modeled by blocking the coordinates with *b* = (-1, 1), *b* = (-1, 2) and *b* = (-2, 2). In the second case, the dependency of the number of lamellae per stack is simulated by blocking all elements with *b* = (0, ±2, ±4) which corresponds to a stack of 5 lamellae with distance *d* = 2 between them. Finally, a simulation is performed in which the ratio of the spatial dimensions, width (*l*lamella = 1 m) and thickness (10 nm), of a crystal lamella, are matched to the real world situation. This is achieved by different Monte Carlo times: A successful move parallel to the lamellae adds 10/*N*par to the Monte Carlo time while a successful move perpendicular to the lamella adds 1/*N*par to the Monte Carlo time. Here, the length difference of 100 is modelled by a 10 times slower diffusion along a 10 times longer length (for *a* = 5) parallel to the lamella than perpendicular to the lamella. In all of these cases, the direction of diffusion parallel and perpendicular to the entry of small molecules is estimated by monitoring the number of clusters leaving the sphere in the corresponding directions. The concentration *c*e at the end of the simulation is calculated from the number of volume elements occupied at the end of the simulation *M*e and the total number of volume elements within the sphere *V*sphere while excluding the volume elements belonging to crystal lamellae *V*lamella: *c*e = *N*e/(*V*sphere - *V*lamella). Diffusion constants are calculated from the distance *x* and the MC time *t* of all clusters, which did not enter and leave the sphere during the simulation.

Statistical error estimation

The simulations for the uptake of water are modeled once. The error is estimated from the diagonal of the covariance matrix of the fitting parameter during the fitting process of the data with the stretched exponential function. The error is of the order of *O*(10-4) for *b* and *O*(100) for ** Simulations for the diffusion of small particles through an amorphous sphere of different radii started from an empty sphere for the determination of the required MC steps and equilibrium distribution are performed once and the reported values do not contain a statistical error. Simulations for the diffusion of small particles through an amorphous and semi-crystalline sphere of radius *R* = 10 up to 107 MC steps started from the equilibrium distribution are performed 8 times. The reported values are the mean of the 8 individual iterations and the error is the standard deviation.

ADDITIONAL TABLES

**Table S1.** *R* Radius, *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 its entry, *f*e fraction of volume elements occupied with clusters of small molecules at the end of simulation, *f*parper fraction of clusters of small molecules leaving parallel to its entry vs perpendicular to its entry direction.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *R* | *N*e | *N*par | *N*per | *f*e | *f*parper |
|  |  |  |  | [%] | [%] |
| 3 | 27 | 848 | 3700 | 27.2 | 22.9 |
| 4 | 49 | 398 | 1803 | 19.1 | 22.1 |
| 5 | 100 | 219 | 869 | 20.4 | 25.2 |
| 6 | 183 | 121 | 450 | 20.3 | 26.9 |
| 7 | 246 | 64 | 303 | 17.9 | 21.1 |
| 8 | 319 | 43 | 215 | 15.1 | 20.0 |
| 9 | 363 | 43 | 146 | 12.2 | 29.5 |
| 10 | 418 | 27 | 88 | 10.1 | 30.7 |

**Table S2.** *R* Radius, *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 direction of entry, *N*per clusters of small molecules leaving sphere perpendicular to its direction of entry, *f*e fraction of volume elements occupied with clusters of small molecules at the end of simulation, *f*parper fraction of clusters of small molecules leaving parallel to its entry vs perpendicular to its entry direction

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *R* | *M*e | *M*par | *M*per | *f*e | *f*parper |
|  |  |  |  | [%] | [%] |
| 3 | 19 | 8507 | 36548 | 19.2 | 23.3 |
| 4 | 44 | 4013 | 17096 | 17.1 | 23.5 |
| 5 | 104 | 2087 | 8624 | 21.2 | 24.2 |
| 6 | 172 | 1158 | 4843 | 19.1 | 23.9 |
| 7 | 279 | 711 | 3093 | 20.4 | 23.0 |
| 8 | 401 | 465 | 2067 | 19.0 | 22.5 |
| 9 | 550 | 319 | 1423 | 18.5 | 22.4 |
| 10 | 726 | 260 | 1006 | 17.5 | 25.8 |

Diffusion through a semi-crystalline polymer with modified MC time

The experimentally determined ratio of width to height for a typical polymer crystal lamella is about *r*1 = 102 [1]. A modelled lamella with *a* = 5 has a size ratio of *r*2 = (2 *a* + 1) / 1 = 11~101. This means that a modelled lamella with *a* = 5 does not represent the dimensions of a real lamella. A model for a lamella with height *h* = 1 which represents the dimensions of a lamella in real world would have a base with side length *a* = 50. Modeling such a lamella requires a simulation of a sphere with *R* = 100. However, such a simulation is computationally infeasible. To mimic the diffusion of small molecules through a polymer crystal layer of typical size, the simulation with *n* = 1 lamella of size *a* = 5 and parallel orientation with respect to the entry of small molecules has been repeated with a different counting of the MC time. Here, the MC time for MC moves perpendicular to the crystal lamellae (3C) is counted by adding *t*1 = 1/*N*par as in the previous simulations, but steps in parallel direction (3C) are slowed down by adding 1/(*r*2/*r*1 *N*par) = 10/*N*par per step to the MC time. The results for the number of MC clusters (Tab. 1) and for the distance distribution (not shown) are similar to the simulation without correction, but the diffusion constant of 0.000220 *l*u2/*l*t is by a factor of 7 smaller. This corresponds to the weighted average of time counting: *p*1 *t*1 + *p*2*t*2 = 7/*N*par = 7 *t*1. Here, *p*1 = 1/3 and *p*2 = 2/3 are the probabilities that a move is chosen perpendicular and parallel to the orientation of the lamella, respectively. The result shows that small molecules diffuse with the same diffusion constant in parallel and perpendicular direction to the lamella, but it takes more time to diffuse in parallel direction than in perpendicular direction because the distance is longer.

References

1. J.-I. Wang and I. R. Harrison, in *Methods in Experimental Physics*, edited by R. A. Fava (Academic Press, New York, London, 1980), Vol. 16, pp. 128-184.