

Supplementary information

Studies of interactions between polymer nanoparticles and cell membranes at atomistic levels

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Model set up and simulation methods

(1) Polymer Nanoparticles (PN).

Two polystyrene nanoparticles were initially set up as random coils using Chem3D [1]. The first one consists of a single chain of 100 monomers (PS-1), while the other consists of a lump of coil made up of four chains each with 25 monomers (PS-2). Both structures were independently collapsed in vacuum by carrying out molecular dynamics (MD) at 300 K using MM2 force field supplied within the Chem3D package. All structures were collapsed within 100 ps. After that, the structures were subjected to a cyclic process of heating and cooling to unlock any high energy conformations. The temperature was increased to 400 K for 100 ps and reduced to 300 K for 100 ps. The process was repeated for 1 ns. The same process was repeated for polyethylene nanoparticles, which were constructed by substituting the phenyl side groups with hydrogen atoms to produce the corresponding PE-1 and PE-2 nanoparticles.

After that, the DL_FIELD [2] program was used to set up larger models consist of polymer nanoparticles immersed in water for DL_POLY_4 [3] MD simulations. The coordinates were extracted from Chem3D package and CHARMM force field was used to describe the polymer models and TIP3P for the water model (See Section (4) for further details). For each model, a 2 ns simulation was carried out to unlock any high-energy conformations. After that, it was cooled to 300 K and equilibrated for a further 3 ns.

Figure 1 and Figure 2 show the variation of the radius of gyration, R_g , with respect to time for PS-1 and PE-1, respectively at 300 K. The time scales on the figures were adjusted so that the simulation models were initially at the temperature of about 400 K at time = 0 ns and began to cool to 300 K as the simulation progressed. Note that in both cases, the R_g values decreased and fluctuate around the mean values in less than 2 ns. This shows the equilibration time of 3 ns is sufficient as described in the main text. The resulting polymer structures adopt globular shapes with mean R_g values of $12.7 \pm 0.1 \text{ \AA}$ for PS and $8.7 \pm 0.1 \text{ \AA}$ for PE. The mean values were estimated from the MD simulation time of 2 ns onwards and indicate as the

horizontal lines in the figures. The molecular weights are ~10.4 kDa for PS and ~2.83 kDa for PE.

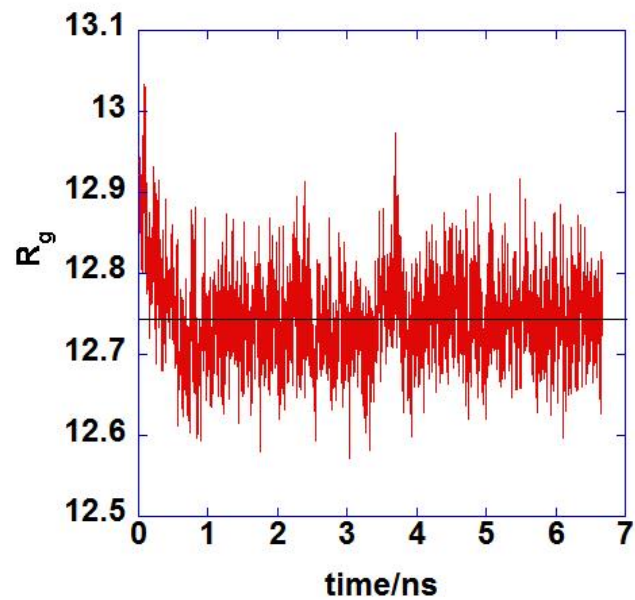


Figure 1 Variation of R_g for PS-1 in water with respect to time at 300 K. The horizontal line indicates the average value of R_g determined from 2 ns onwards.

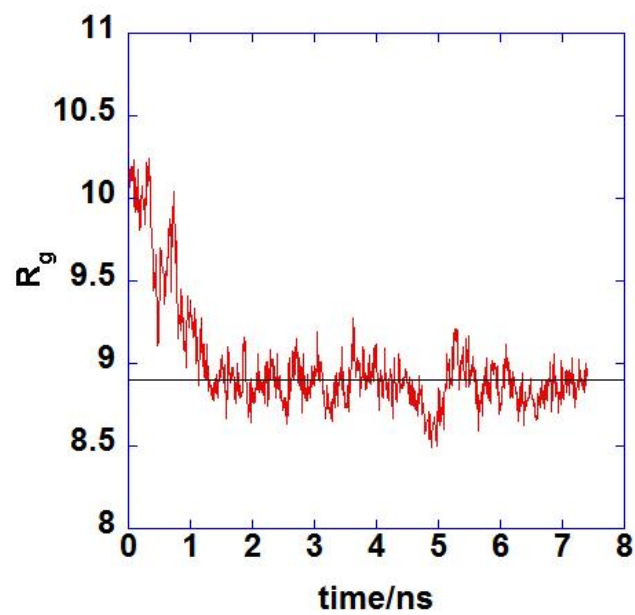


Figure 2 Variation of R_g for PE-1 in water with respect to time at 300 K. The horizontal line indicates the average value of R_g determined from 2 ns onwards.

(2) Solvated POPC membrane

The lipid membrane was constructed from VMD [4] package, which consists of 131 POPC molecules. The DL_FIELD program was used to solvate the structure and set up the force field model. The membrane model was centred at the zero origin with the surface plane oriented along the x - y direction and the surface normal parallel to the z -direction. The whole system was equilibrated using DL_POLY_4 for about 5 ns until there is no appreciable change to the simulation box size.

(3) The polymer-membrane models

MD simulations of nanoparticle interactions with membrane were carried out using the DL_POLY_4 package. The model consists of 131 POPC molecules with a nanoparticle placed on top of the surface in a fully solvated environment. Both POPC and the nanoparticle were pre-equilibrated as described in Section (1) and Section (2). This gives a total of about 84000 atoms.

The simulation conditions were maintained at the near-physiological conditions of 1 atmosphere and 300 K using Langevin thermostat [5] with the temperature and pressure relaxation constants set at 0.4 ps^{-1} and 1.0 ps^{-1} respectively. The simulation box was allowed to change isotropically in the x - y plane (the plane of the membrane surface) and independently scaled from the z -direction. Long-range interactions were calculated using smoothed particle mesh Ewald method [6]. Both the electrostatic real space cut-off and short-range non-bonded interaction cut-off were set to 9.0 \AA .

All bonds containing hydrogen atoms were constrained at their equilibrium length using SHAKE algorithm [7] with a tolerance level of 10^{-4} , while all water molecules were modelled as the rigid body TIP3P model. The removal of the fastest mode of vibrations involving hydrogen atoms means a timestep of 2 fs can be safely used without significant energy drift.

All simulations were carried out in Scientific Computing Application Resource for Facilities (SCARF) of STFC's Scientific Computing Department. Typically, a simulation time of 1 ns/day is achieved using 32 CPU nodes.

(4) Force field model

With the exception of the use of Chem3D in Section (1), all MD calculations were carried out in DL_POLY_4 using CHARMM36 force field [8] and TIP3P water model [9]. The CHARMM36 force field is particularly suited to model POPC lipid membrane in water. The target geometries such as butane and pentane were used to fit longer hydrocarbon chains contain within the POPC molecules. The PE and PS model constructions were based on target geometries using similar CHARMM formalism. In order to test the validity of the force

field models for PNs, the glass transition temperature, T_g , is estimated for the polystyrene models. Figure 1 shows the radius of gyration, R_g , of PS-1 over a range of temperature from 100 K to 480 K. For each temperature, the average R_g value was obtained over 30-40 ns. The samples were extracted at every 1000 MD steps and errors were determined using the block analysis [10] method. Figure 3 shows the R_g variation with respect to temperature. It can be seen R_g is small and remain rather constant at low temperature when the polymer is in a glassy state. As the temperature is increased, the R_g value also increases gradually. The value of T_g , which coincides with a rapid increase of R_g , is estimated to be about 362 K. This agrees reasonably well with the experimental estimates of 373-380 K [11]. Note that the discrepancy with the experimental value can be due to several factors such as the state of the initial configuration (sample history), finite size and also inadequate sampling of polymer configurations from the MD simulations.

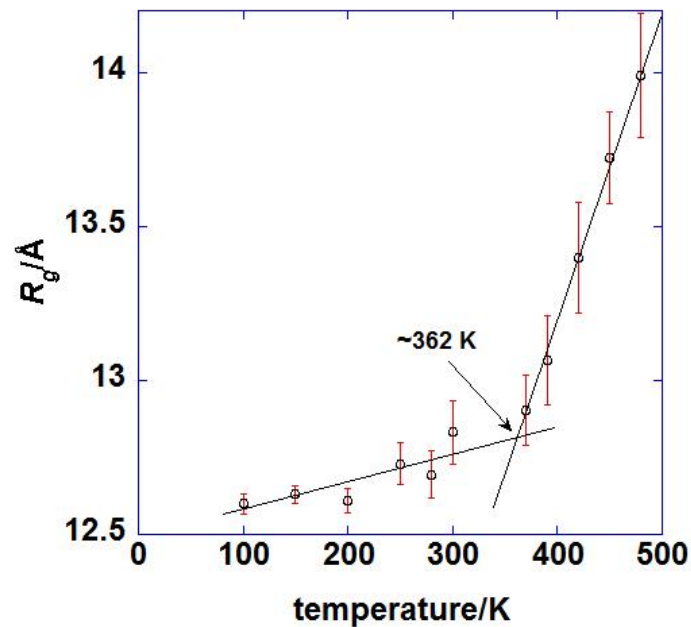


Figure 3 Variation of R_g for PS1 with respect to the temperature. Two lines are drawn as a guide to determine the T_g value, which is estimated to be ~362 K.

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