

Scaling Behaviors of Polymers on Lipid Membranes: Coupling of Polymer Chain Dynamics and Surface Thermal Fluctuations

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 Electronic Supplementary Information

Abstract Despite extensive researches on the motion of polymer chains on lipid membranes, the effect of membrane fluctuations on polymer chain dynamics remains poorly understood. Here we report single molecule tracking experiments that allow for comparable measurements of polymer chain diffusion dynamics on nanotubular and planar phospholipid membranes. We observe a super-diffusion behavior and no apparent chain-length-dependent mobility of polymer chains on nanotubular membranes, while a Brownian motion and apparent chain-length-dependent mobility of polymer chains on planar membranes. We suggest the super-diffusion nature of polymer chains may be due to the thermal-fluctuations of lipid nanotubes, which can be described from a statistical thermodynamic phenomenon coupling of polymer chain dynamics and surface thermal fluctuations. We suggest that the existence of surface environment fluctuations should influence the dynamics of the adsorbed polymer chains. This study provides previously uncharacterized insights into polymer diffusion dynamics on thermal-fluctuating flexible surfaces, which is essential to understanding the effect of environment fluctuations on polymer chain behaviors.

Keywords Polymer diffusion; Lipid membrane; Scaling behavior

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INTRODUCTION

The motion of polymer chains at surfaces plays a significant role in a wide range of chemical and biological processes. To understand this phenomenon, how the surface diffusion coefficient D of the single adsorbed polymer chains scales with the chain molecular weight M is considered in the $D \sim M^{-\alpha}$ relation. For example, $\alpha \approx 1$ (Rouse-like dynamics) was observed for single chains dragged by surface friction on a smooth surface.^[1,5] Stronger and weaker scalings of $\alpha \approx 3/2$ (caterpillar-like dynamics) and $\alpha \approx 3/4$ (Zimm-like dynamics) were also found for single chains diffusing between variable corrugations on an attractive surface^[5,10] and translating parallel to an ideal smooth surface,^[11,13] respectively. These heterogeneous scalings are obvious physically as the intramolecular conformations of polymer chains at surfaces are significantly correlated to the attraction of chain segments to the surface, which may be further influenced by the topographical and chemical heterogeneity of the surface^[5–19] as well as the architectures of the polymer chains.^[20–23]

Unlike previously reported works, the aim of this work is to study the motion of polymer chains on fluidic membrane sur-

faces. Not like solid surfaces, fluidic membrane surfaces exhibit extraordinary flexibilities, such as surface thermal fluctuations. Thermal fluctuations are able to induce additional out-of-plane fluctuations of flexible surfaces.^[24] The non-equilibrium surface fluctuation effect can be further amplified by the presence of other nearby flexible surfaces.^[25,26] Theory works have pointed to the enhancement of the diffusion rate of proteins and particles on fluctuating surfaces.^[27,28] Strikingly fast diffusion dynamics of peptides^[29] and nanoparticles^[30] have been also observed to be coupled to the out-of-plane fluctuations of phospholipid nanotubes (PNTs). With this in mind, one would expect a correlation of polymer surface dynamics to surface thermal fluctuations, and such correlation is not yet clear. To the best of our knowledge, no literature shows the scaling behaviors of single polymer chains on thermal-fluctuating surfaces.

Thermal-fluctuating flexible surfaces are ubiquitous to biological systems. Exemplified are PNTs.^[31–35] These nanowire structures, on the order of tens of nanometers in diameter and micrometers in length, are crucial structures in biological systems as many protein/peptide transports and propagations occur along them. Statistical thermodynamics show that the flatness and straightness of PNTs are strongly affected by thermal fluctuations due to the decrease of the nanowire dimension compared with the two-dimensional planar membrane surface.^[24] With this in mind, we expect a correlation of

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polymer dynamics to PNT fluctuations. To study this problem, we herein used single molecule tracking (SMT) to quantify the surface diffusion dynamics of poly(*N*-isopropylacrylamide) (PNIPAM) chains along 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) PNTs. These PNTs were generated by drying a suspension of DOPC liposomes followed by rehydration in water and sandwiched between two glass coverslips. This method has been widely used to generate PNTs with diameter of ~100 nm and lengths of several hundred microns.^[36] As a control system, an adsorbed DOPC bilayer with suppressed thermal fluctuations was also prepared on a glass coverslip.^[37] By comparing the scaling behaviors of single PNIPAM chains on DOPC PNTs and supported bilayers, we observed that nanotubular lipid membranes were able to speed up polymer surface diffusion and influence the scaling behaviors of polymers at surfaces.

EXPERIMENTAL

Materials

1,2-Dioleoyl-*sn*-glycero-3-phosphocholine (DOPC), 1,2-dipalmitoyl-*sn*-glycero-3-phospho-ethanolamine-*N*-(biotinyl) (biotinyl-PE) and cholesterol were purchased from Avanti Polar Lipids Inc. (USA). *N*-hydroxysuccinimide-ester-Alexa555 probe was purchased from Thermo Fisher Scientific Inc. (USA). Amino-terminated poly(*N*-isopropylacrylamide) (PNIPAM) polymers were purchased from Polymer Source Inc. (Canada). The number-average molar masses M_n of PNIPAM were 5, 28, 61 and 171 kDa. The polydispersity index of all PNIPAM samples were ~1.5. Hydrogen peroxide (H₂O₂) and concentrated sulfuric acid (H₂SO₄) were purchased from Energy-Chemical Inc. (China). Avidin and chloroform were purchased from Sigma-Aldrich Inc. (USA). All chemicals were used as received without further purification.

Dye-labeled PNIPAM Polymer Preparation

The reaction of amino-terminated PNIPAM with *N*-hydroxysuccinimide-ester-Alexa555 (NHS-Alexa) in pH 8 PBS buffer at room temperature for 1 h led to fluorescent dye-labeled PNIPAM chains. This method generated one polymer chain having only one fluorescence dye linked to the end of the polymer chain. First, a 5-fold molar excess of NHS-Alexa was added into 2 mg/mL PNIPAM PBS buffer solution at pH 8 for reaction for 1 hour to enhance the labeling efficiency. Then, the resultant dye-labeled PNIPAM solution was passed through a dye removal column (22858, Thermo Fisher Scientific, USA) five times to remove the non-reacted dye molecules. Finally, the dye-labeled PNIPAM PBS solution was dialyzed against deionized water for 7 days to ensure the removal of PBS salts. No existence of fluorescent molecules in the solution outside of dialysis tube by direct single molecule tracking experiments demonstrated the complete removal of non-reacted fluorescent dye molecules.

Glass Surface Preparation

To prepare DOPC nanotubes (PNTs) and supported DOPC bilayers, the glass substrates were freshly cleaned as follows. First, the ultra-flat glass cover slips were put into a 500 mL beaker. Then, 5 mL of H₂O₂ and 15 mL of concentrated H₂SO₄ were sequentially added into the beaker with pipettes, followed

by shaking slowly on a shaking table for 1 h. Finally, the glass cover slips were washed with plenty of Milli-Q water for 3 times and dried with nitrogen. The freshly cleaned glass cover slips were used for the following PNT and bilayer preparation.

Phospholipid Nanotubes (PNTs) Preparation

PNTs were prepared as follows. First, the freshly cleaned glass cover slips were coated with avidin by immersing the glass coverslips in a water solution of 1 mg/mL avidin for 1 h followed by rinsing with plenty of water. Then, a stock CHCl₃ solution of 1 mg/mL DOPC and biotinyl-PE (0.01 mol%) was made. 50 μ L of this solution was added into a small vial and dried under vacuum at the bottom of the vial followed by rehydrated with 300 μ L of Milli-Q water at room temperature for 5 h. Finally, 1 μ L from the above suspension was sandwiched between the above prepared avidin-coated coverslip and another freshly cleaned glass cover slip by using a home-made flow cell. After 30 min, the PNTs were formed in the flow cell for the following experiments. All the PNTs surfaces were freshly prepared for the single molecule tracking experiments.

Supported Lipid Bilayer Preparation

The supported DOPC bilayers on glass substrates were generated on freshly cleaned glass cover slips mounted with a home-made holder apparatus as follows. First, DOPC was prepared in CHCl₃, dried, and re-suspended in PBS buffer to a concentration of 1.0 mg/mL. Then, the DOPC suspension after pre-filtration was forced through a polycarbonate filter with 100 nm pores 11 times to yield a small unilamellar vesicles (SUVs) solution with nominal diameters of ~200 nm. Finally, the SUVs solution was deposited onto the freshly cleaned glass substrates and incubated for one hour at room temperature under controlled humidity. The excess vesicle above the SLBs were removed from the glass substrates by extraction with fresh Tris buffer 10 times from the holder apparatus. The preparation temperature for DOPC bilayers was 25 °C. The fluidity of the bilayer was verified by tracking the 2D diffusivity of dye-PC molecules in the sea lipids through single molecule tracking experiments.

Single Molecule Tracking Experiments

The single molecule tracking experiments were carried out through total internal reflection fluorescence microscopy (TIRFM) at 25 °C on a commercial instrument based on a Nikon inverted microscope. A 532 nm laser was shined into a 100 $\times$ oil immersion objective lens with 1.45 numerical aperture to generate an evanescent wave that illuminates the fluorescence dye-labeled PNIPAM polymer chains within ~100–200 nm from the surface-water interface. The fluorescence images were acquired on an Andor EM-CCD. A series of fluorescence images were acquired. We obtained single PNIPAM chain trajectories (positions versus time) from the time-dependent images using an algorithm developed by MATLAB. The time-dependent fluorescence images (55 μ m $\times$ 55 μ m) are shown in movie formats, with time steps per frame of 40 ms on each surface. Polymer chains that existed since the first and the last frames were discarded due to the uncertainty in assigning their residence time and diffusivities. To calculate polymer chain positions, the closest objects in sequential frames were linked with the threshold to link polymer chains between sequential frames set at 2 μ m.

RESULTS AND DISCUSSION

We probed the surface diffusion dynamics of initially adsorbed PNIPAM chains by distinctly tracking the trajectories of single PNIPAM chains on DOPC bilayers and PNTs via total internal reflection fluorescence microscopy (TIRFM) in aqueous solution at room temperature. This condition provides a “good solvent” environment for PNIPAM chains to exhibit a flexible and swollen conformation.^[38] In each TIRFM measurement, a large number of $\sim 10^4$ single molecule trajectories were statistically analyzed to exactly assess the surface diffusion dynamics of single polymer chains. As shown in Fig. 1, the motions of single PNIPAM chains on DOPC bilayer and PNT can be distinctly differentiated and tracked. PNIPAM chains moved slowly within smaller local areas on DOPC bilayers while appeared highly mobile with larger displacements on DOPC PNTs.

To quantify the motion of PNIPAM chains on surfaces, we considered the mean squared displacement (MSD), $\langle r^2 \rangle = \langle |r(t + \Delta t) - r(t)|^2 \rangle$ where r distance and t time, as a function of the time interval (Δt) in the relation of $\langle r^2 \rangle = 4D_{\text{eff}}(\Delta t)^\beta$, where D_{eff} the effective 2D-diffusion coefficient of the polymer chains. Figs. 2(a) and 2(b) show the MSD plots for one typical PNIPAM sample (number average molecular weight M_n , 5 kDa) on DOPC bilayers and PNTs, respectively. As can be seen, the linear dependence of MSD on Δt , $\langle r^2 \rangle = 4D_{\text{eff}}(\Delta t)^\beta$ with $\beta=1.0$, indicates the classical Brownian motion of PNIPAM chains on DOPC bilayers with $D_{\text{eff}}=0.8 \mu\text{m}^2/\text{s}$ (Fig. 2a). While on DOPC PNTs, the β value of 1.3 implies an abnormal super-diffusion motion of adsorbed PNIPAM chains with $D_{\text{eff}}=21 \mu\text{m}^2/\text{s}$ (Fig. 2b). This diffusivity is strikingly fast, ~ 25 times faster than the diffusion on planar lipid bilayer. This diffusivity is also ~ 15 times faster than the diffusion of DOPC molecules in the bilayer,^[18] which indicates that the observed super-diffusion of PNIPAM chains unlikely arises from the local fluidity of lipids in the PNTs.

To study the abnormal super-diffusion motion of PNIPAM chains on DOPC PNTs, we analyzed the van Hove correlation function $G_s(\Delta x, \Delta t)$ = describing the probability for a single polymer chain to move a displacement Δx along the x or y co-

ordinate during time Δt . This method allows to distinguish the slow and fast dynamics of the diffusing polymer chains. Figs. 2(c) and 2(d) show the $G_s(\Delta x, \Delta t)$ functions for four types of PNIPAM chains with different M_n on DOPC bilayers and PNTs, respectively. As shown in Fig. 2(c), one can see that $G(\Delta x, \Delta t)$ function of each diffusion mode possesses a large Gaussian peak (i.e., $G(\Delta x, \Delta t) \sim \exp[-(\Delta x/\sigma)^2]$) with a short extended non-Gaussian tail. The dominant Gaussian distribution in each mode is associated with adsorbed chains undergoing normal Brownian motion at the interface, despite the rare occurrence of longer displacement. Moreover, on DOPC bilayers, the narrowing of $G_s(\Delta x, \Delta t)$ with increasing the M_n qualitatively indicates a chain-length-dependent mobility of PNIPAM chains on DOPC bilayers, where the D_{eff} values were further calculated and found in the relation of $D_{\text{eff}} \sim M_n^{-0.5}$ (Fig. 3). Even more interesting is that, on DOPC PNTs, there is no apparent chain-length-dependent mobility of PNIPAM chains (Fig. 2d) and the corresponding D_{eff} were found in the $D_{\text{eff}} \sim M_n^0$ relation (Fig. 3). We are very interested in such abnormal diffusion of single polymer chains on PNTs. We did this experiments for many times and made sure that such super-diffusion dynamics of polymer chains on PNTs are real. We are trying to figure out the mechanism of such super-diffusion dynamics on PNT surfaces. One of the possible reasons for these abnormal diffusion dynamics is the existence of surface environment fluctuations, particularly for flexible lipid surfaces, that is not considered in conventional theory and simulations of polymer surface diffusion.

Conventional theory assumes an in-plane model for adsorbed polymer chains and predicts the scaling $D_{\text{eff}} \sim M_n^{-\alpha}$ in the range $3/4 < \alpha < 3/2$ that depends on the bound segments and conformations of the polymer chains.^[1–13] If the polymer chains are weakly bound on the surface and adopt conformations similar to those expected in bulk solution, a desorption-mediated mechanism of polymer surface diffusion dominates and weaker scalings have been observed, i.e., $\alpha \sim 0.6$ for a coiled chain^[39] and $\alpha \sim 0.3$ for a collapsed globular chain.^[23] These models do not consider the effect of surface environment fluctuations. We can describe the out-of-plane fluctuations of PNTs with a continuum free energy functional based on the Helfrich^[25] equation as:

$$F = \int dS \left[\frac{1}{2} \kappa (\nabla^2 h)^2 + \frac{1}{2} \gamma (\nabla h)^2 \right] \quad (1)$$

where κ and γ are the bending modulus and surface tension of the PNT system, respectively, h is the fluctuation displacement from the average position, S is the system area. With the usual Fourier expansion $h(\mathbf{r}) = \sum_{\mathbf{q}} h(\mathbf{q}) \exp(i\mathbf{q} \cdot \mathbf{r})$, the thermal fluctuation spectrum has the standard form implied as the energy equipartition theorem:

$$\langle h^2(\mathbf{q}) \rangle = S \frac{k_B T}{\gamma q^2 + \kappa q^4} \quad (2)$$

where k_B is the Boltzmann constant and T is the temperature. Fourier transformation of Eq. (2) yields the correlation function that describes the height fluctuations of the system as:

$$\langle h^2(\mathbf{r}) \rangle = \frac{1}{(2\pi)^2 S} \int d\mathbf{q} \langle h^2(\mathbf{q}) \rangle \quad (3)$$

With the integral range $\pi/L < q < \sqrt{\gamma/\kappa}$, Eq. (3) yields the mean surface height fluctuations as:

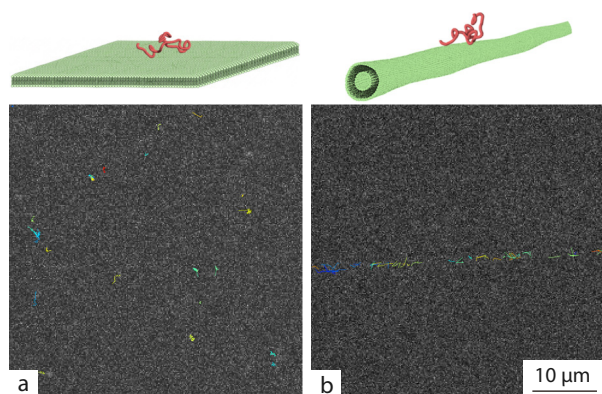


Fig. 1 The single molecule trajectories (marked by different color) extracted from TIRFM images of a time series (0.04 s per step) showing ~ 30 single PNIPAM polymer chains adsorbed to DOPC bilayer (a) and PNT (b). Illustrations of one single polymer chain adsorbed on DOPC bilayer and PNT are also included.

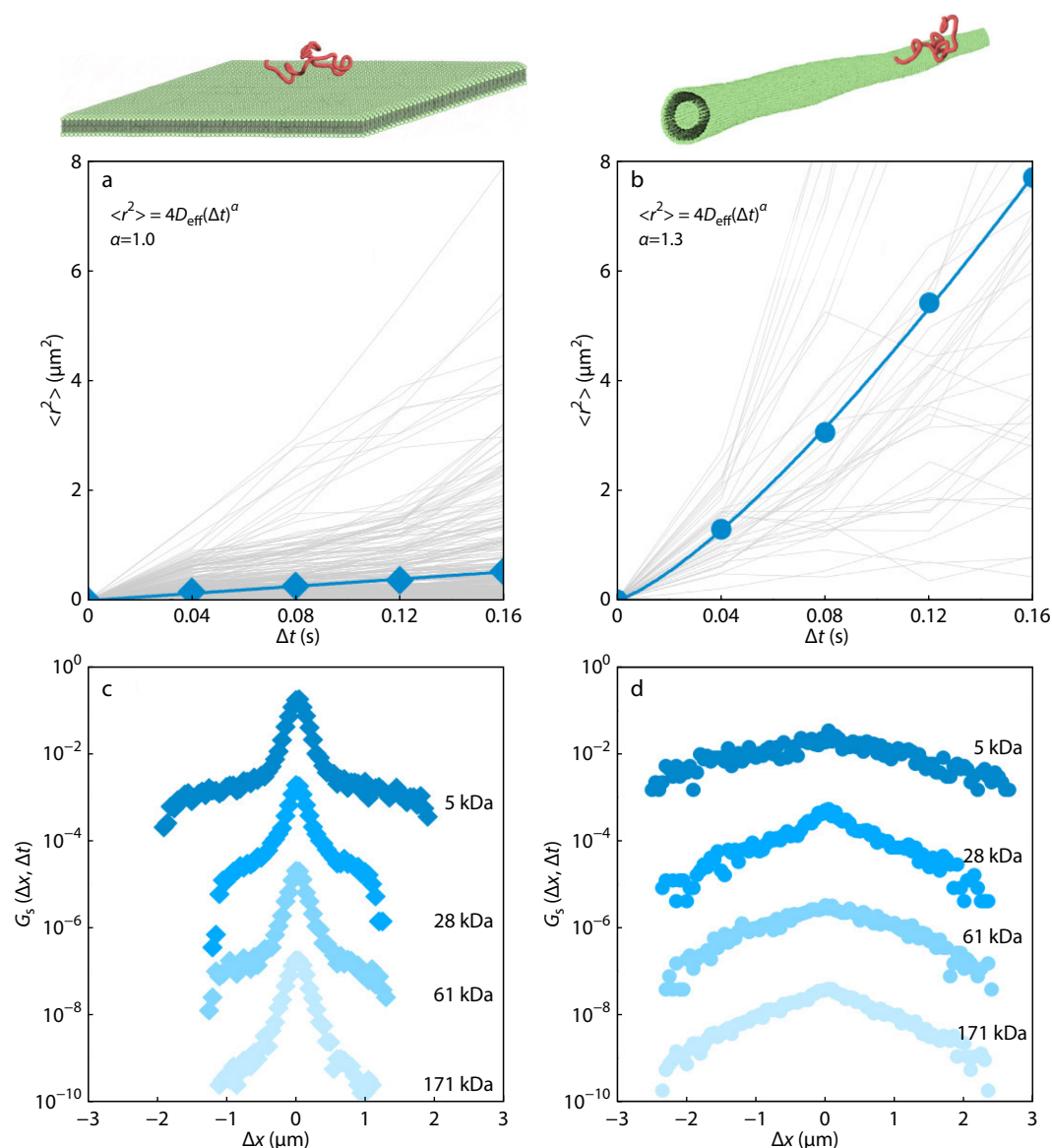


Fig. 2 (a, b) The mean squared displacement (MSD, $\langle r^2 \rangle$) as a function of time interval (Δt) for single PNIPAM chains (M_n , 5 kDa) on DOPC bilayers and PNTs, respectively. French gray lines represent for each of more than 50 trajectories. Symbols are the average MSD over all trajectories. Solid blue lines are the fittings to the model $\langle r^2 \rangle = 4D_{\text{eff}}(\Delta t)^\alpha$, where D_{eff} is the effective 2D-diffusion coefficient. (c, d) The van Hove functions ($G_s(\Delta x, \Delta t)$) describing the distributions of the surface displacements Δx for single PNIPAM chains (M_n , 5, 28, 61 and 171 kDa) on DOPC bilayers and PNTs, respectively. To allow easier interpretation, the curves were shifted downward by factors of 10^{-2} , 10^{-4} , 10^{-6} for PNIPAM with M_n of 28, 61, 171 kDa, respectively. Illustrations of one single polymer chain adsorbed on DOPC bilayer and PNT are also included.

$$\langle (\Delta h)^2 \rangle = \frac{2k_B T}{(2\pi)^2} \int \frac{2\pi q dq}{\gamma q^2 + \kappa q^4} = \frac{k_B T}{\gamma \pi} \ln \left(\frac{L}{\pi} \sqrt{\frac{\gamma}{\kappa}} \right) \quad (4)$$

For $\gamma \approx 5 \times 10^{-5} \text{ J/m}^2$, $\kappa \approx 10^{-19} \text{ J}$ and $L \approx 50 \mu\text{m}$ in our case, the surface fluctuations of PNTs is $\approx 13 \text{ nm}$, which means that the PNT surface is roughening and wandering in aqueous solution. This fluctuation can modulate PNT surface over long-length scales along the PNT contour. The fluctuation quantity is larger compared with the hydrodynamic size of $\sim 1\text{--}5 \text{ nm}$ of PNIPAM chains and, thus, the bumps on the surface resulting from the thermal fluctuations are able to push the polymer chains and speed up their diffusion dynamics. Moreover, the relaxation frequency of surface fluctuation modes dragged by

hydrodynamic interactions is given as:^[40]

$$\omega(q) = \frac{\langle z \rangle^3 q^2}{12\eta} (\kappa q^4 + \gamma q^2) \quad (5)$$

where $\eta \approx 10^{-3} \text{ Ns/m}^2$ is the viscosity of water and $\langle z \rangle \approx 100 \text{ nm}$ is the average diameter of PNTs. In our case, the smallest $q \approx 10^6 \text{ m}^{-1}$ and Eq. (5) yields the relaxation of PNT fluctuations $\approx 0.24 \text{ s}$, which is consistent with the time scales of PNIPAM diffusion on PNTs as shown in Fig. 2(b). The above phenomenological analysis highlights the possible coupling of the observed super-diffusion nature of PNIPAM chains and the surface thermal fluctuations that eventually lead to no apparent chain-length-dependent mobility of PNIPAM chains on PNTs as demonstrated

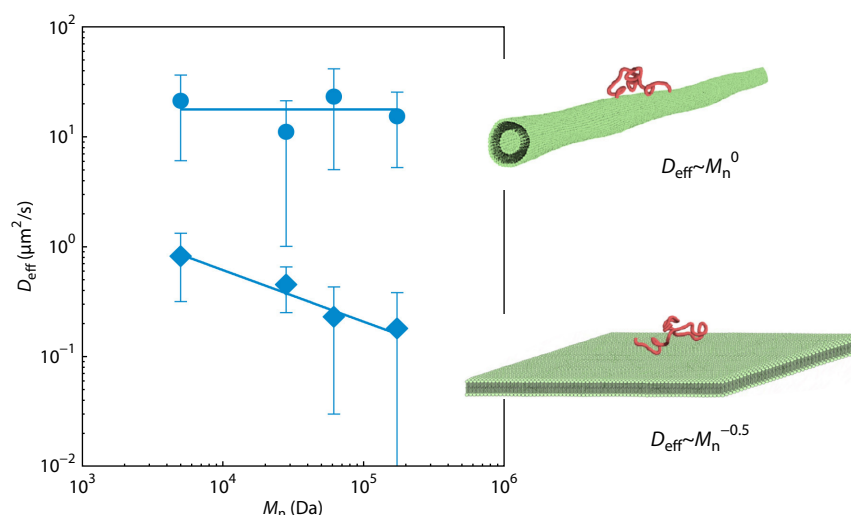


Fig. 3 The effective surface diffusion coefficient D_{eff} for PNIPAM diffusing on DOPC bilayers and PNTs are plotted against molecular weight M_n . Solid lines are power fittings as $D_{eff} \sim M_n^{-0.5}$ and $D_{eff} \sim M_n^0$ for PNIPAM diffusing on DOPC bilayers and PNTs, respectively.

by the above SMT experiments. In contrast, on DOPC bilayers supported on glass substrate, the surface thermal fluctuations were suppressed and, thus, PNIPAM chains exhibited classical Brownian motion on the surface without additional driving forces. The observed chain-length-dependent mobility of PNIPAM chains on DOPC bilayers appears the same dependence on M_n as their three-dimensional chains in a θ -solvent ($D \sim M_n^{-0.5}$). This suggests that the PNIPAM chains in our experiments, even as in contact with the DOPC bilayer surface, adopted conformations similar to those expected in bulk solution rather than strictly two-dimensional conformations. In another control experiment, we mixed 20 mol% cholesterol into PNTs to stiffen the tube structure. While SMT experiments showed that PNIPAM surface diffusion slowed down by half, no strong chain-length-dependent mobility of PNIPAM chains in the $D_{eff} \sim M_n^{-0.1}$ relation were observed (Fig. S1 in the electronic supplementary information, ESI). This implies that 20 mol% cholesterol molecules can enhance the PNIPAM-PNT interactions but cannot effectively suppress the thermal fluctuations of PNTs. PNT nanowire structures are much more sensitive to the effects of thermal fluctuations than planar bilayer systems.

The above analysis from statistical thermodynamics is qualitative and deserved to be demonstrated through both experiments and simulations. We suggest that the existence of surface environment fluctuations should influence the dynamics of the adsorbed polymer chains. The future work can be focused on how energy transfer from PNT surfaces to adsorbed polymer chains through both experiments and simulations to find out the real mechanism of the coupling between polymer chain dynamics and surface fluctuations.

With the discoveries of enhanced super-diffusion modes of polymers, proteins, peptides, enzymes, bacteria and active colloids,^[41,42] scientist begin to pay attention to the impact of non-equilibrium systems on object dynamics and functions. The non-equilibrium environments are able to induce additional out-of-plane fluctuations of flexible surfaces, which are ubiquitous to biological systems. These fluctuating surfaces were sometimes observed as “active” membranes.^[43] Surface fluctuations could play a role in the diffusive process. To mo-

dulate polymer functions, one must understand the effects of surface as well as environment fluctuations^[44] on polymer chain behaviors.

CONCLUSIONS

Our work presented here provides previously uncharacterized insights into polymer diffusion dynamics on fluidic nanotubular membrane surfaces. Not like on the more usual planar solid surfaces, single polymer chains on lipid nanotubes exhibit a super-diffusion nature and no apparent chain-length-dependent mobility that could be facilitated by the thermal fluctuations of the nanotube structures. We suggest that the super-diffusion nature of polymer chains may be due to the thermal-fluctuations of lipid nanotubes, which can be described from a statistical thermodynamic phenomenon coupling of polymer chain dynamics and surface thermal fluctuations. We further suggest that the importance of non-equilibrium system can also induce additional out-of-plane fluctuations of flexible surfaces and further influence the dynamics of adsorbed polymer chains. This study is essential to understanding the effect of environment fluctuations on polymer dynamics.

NOTES

The authors declare no competing financial interest.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-022-2848-4>.

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