Electronic Supplementary Material (ESI) for Nanoscale.
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Membrane Lipids Destabilize

Short Interfering Ribonucleic Acid (*siRNA)/Polyethylenimine Nanoparticles*

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S1: Structural parameters for the two types of NPs and two membranes.

In Section 3.3 of the main text, structural parameters of NPs have been discussed. Here, Table S1 summarizes the changes in the structural parameters for the two types of NPs and two membranes.

Table S1. Changes in structural parameters of PEI/siRNA NPs during four stages of membrane crossing process. Key differences between POPS and POPC membranes are shown in red color.

NP	MEMBRANE MODEL	PARAMETER	APPRAOCH	ATTACHMENT	EMBEDMENT	DETACHMENT
PEI NP	POPS	*Rg*	Relatively constant	Decrease	Decrease	Increase to 1.5 Å larger than initial value
	POPC		Relatively constant	Decrease	Decrease	Increase to initial value
PEI-LA NP	POPS		Relatively constant	Decrease	Decrease	Increase to initial value
	POPC		Relatively constant	Decrease	Decrease	Increase to 1 Å larger than initial value
PEI NP	POPS	COM distance between siRNAs	Relatively constant	Relatively constant	Relatively constant	Increase to much larger than initial value
	POPC		Relatively constant	Relatively constant	Decrease	Increase to initial value
PEI-LA NP	POPS		Relatively constant	Relatively constant	Relatively constant	Slightly decrease
	POPC		Relatively constant	Relatively constant	Slightly decrease	Relatively constant
PEI NP	POPS	Angle between siRNAs	Relatively constant	Relatively constant	Relatively constant	Increase to 15 degree more than initial value
	POPC		Relatively constant	Slightly increase	Slightly increase	Decrease to initial value
PEI-LA NP	POPS		Relatively constant	Relatively constant	Decrease	Decrease to almost parallel orientation
	POPC		Relatively constant	Slightly decrease	Decrease	Decrease to almost parallel orientation

S2. Number of hydrogen bonds (HBs) between siRNAs and PEI molecules

In section 3.3 of the main text, the number of PEI N atoms within 4 Å of any N/O atoms of siRNA as a function of COM position of NP have been discussed. Here, Fig. S1 and Fig. S2 show the number of HBs between PEIs and siRNA molecules as a function of COM position of NP for POPS and POPC membranes, respectively. Compared with Fig. 6 and Fig. 7 of the main text, the trend of the curves remain the same.

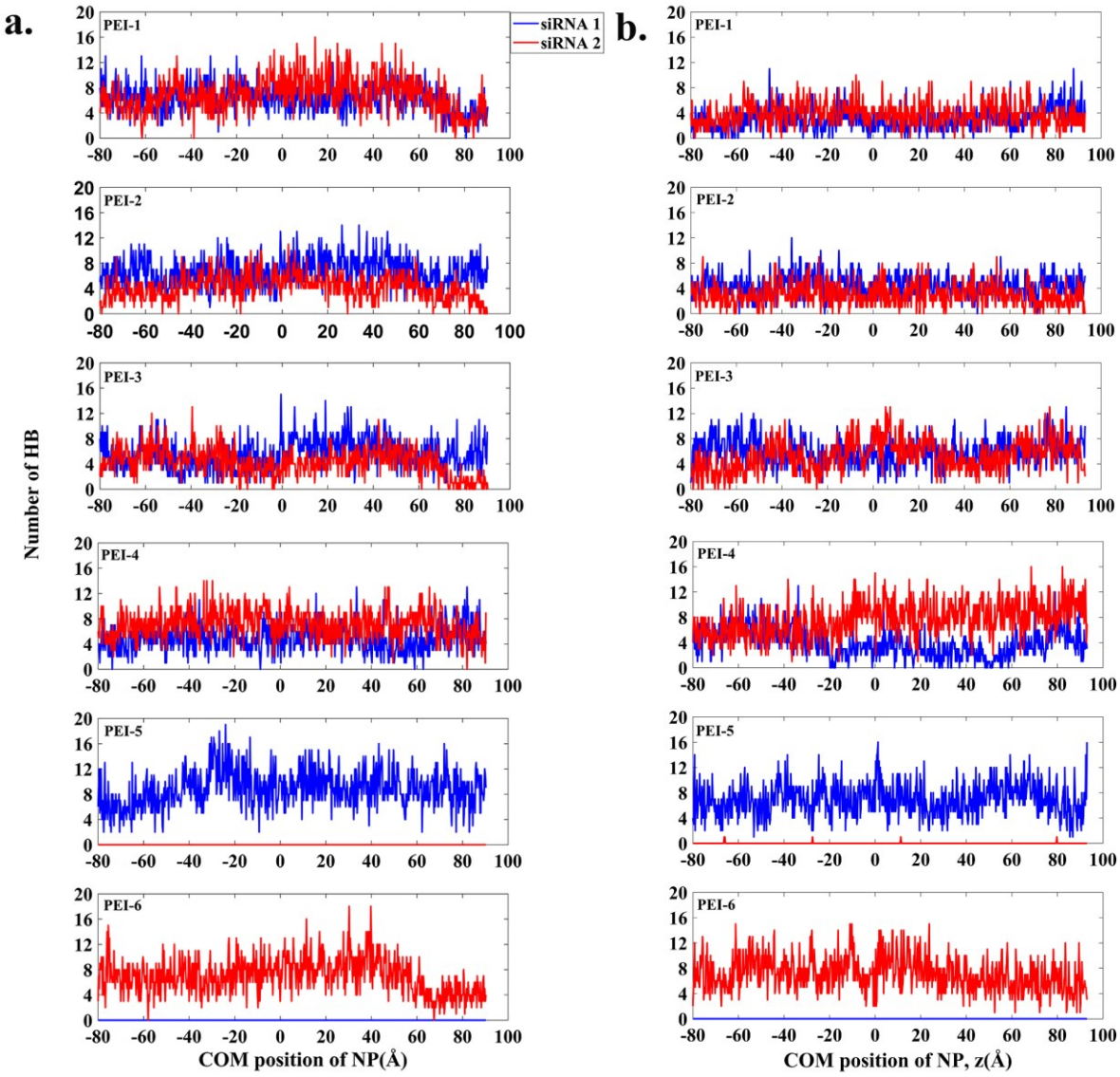

Fig S1. Number of HBs between PEIs and siRNA molecules as a function of COM position of NP while crossing the POPS membrane, (a) PEI NP and (b) PEI-LA NP.

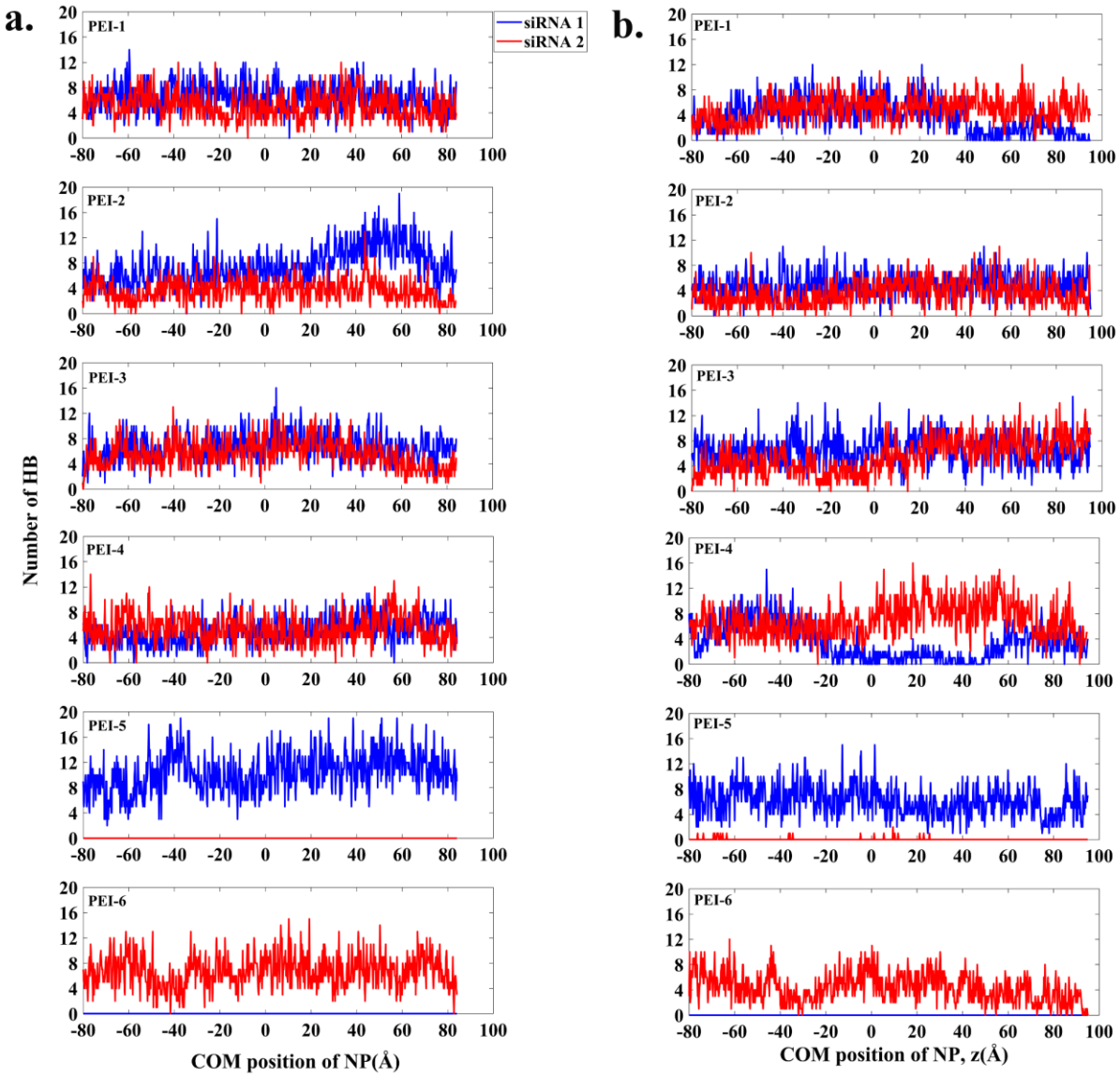

Fig S2. Number of HBs between PEIs and siRNA molecules as a function of COM position of NP while crossing the POPC membrane, (a) PEI NP and (b) PEI-LA NP.

S3: Number of membrane-NP hydrogen bonds (HBs)

In Section 4 of the main text, correlation between force profiles and HBs between NPs and membranes have been discussed. Here, Fig. S3 shows the number of HBs between each NP and membranes. For both NP and membranes, the number of HBs is zero during the approach stage. During attachment and embedment, the number of HBs between NP and membrane increases, and finally during detachment, the number of HBs display a decreasing trend. For both NPs, number of HBs formed between NP and the POPS membrane is higher than between NP and the POPC membrane, suggesting that interaction between NPs and the POPS in stronger than that of POPC membrane.

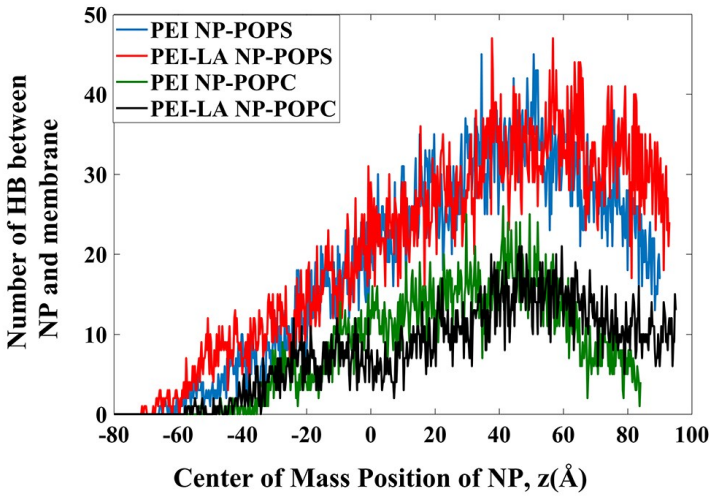

Fig S3. Number of HBs between NPs and membranes as a function of COM position of the NP.

S4: Lipid associations between PEIs of PEI-LA NPs

In Section 4 of the main text, lipid associations between the PEIs of PEI-LA NP have been discussed. Here, Fig. S4 shows the lipid associations between the PEIs of PEI-LA NP and membranes. Lipid associations is quantified based on the number of pairs of lipid Cs that are closer than 5 Å between each pair of PEIs. The 5 Å limit is based on the closest carbon-carbon distance within which the free energy for the association of two alkane molecules is negative, and therefore, association is energetically favorable[1]. Considering that the LA lipid has 18 carbons and each PEI of PEI-LA NP has 3 substitutions, all possible pairing of carbons between two PEIs would be 2916. During approach and attachment stage, the associations is stable for both membranes, followed by a decreasing trend during detachment, in which associations are completely lost in POPC membrane, while it is strongly weakened in the POPS membrane.

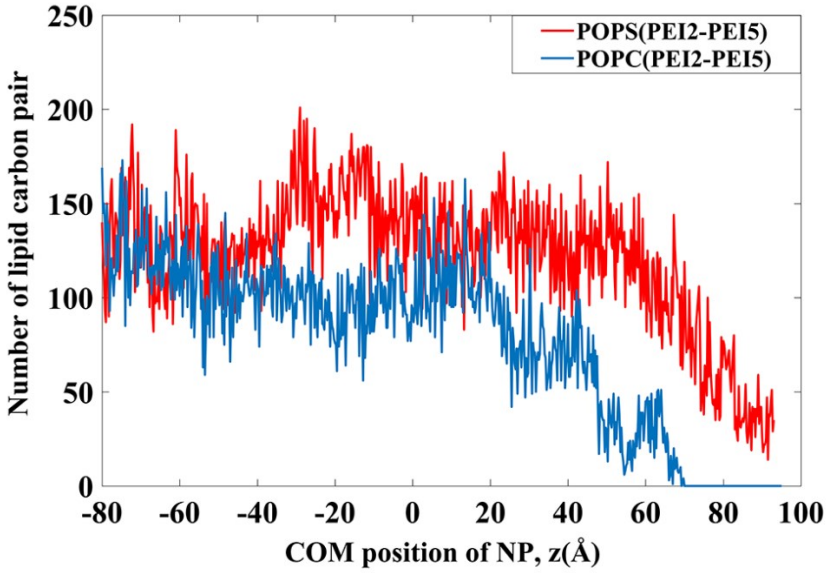

Figure S4. Number of LA lipid carbon pairs that are closer than 5 Å between PEI-2 and PEI-5 of PEI-LA NP as a function of COM position of NP.

Reference

1 C. Sun, T. Tang and H. Uludağ, *Biomacromolecules*, 2012, **13**, 2982–2988.