Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supporting information: Molecular insights into MXene destructing cell membrane as a “nano thermal blade”

Daxin Wu,‡[a] Ruixuan Zhao,‡[a] Yu Chen,[b] Ying Wang[a], Jiebo Li*[a], Yubo Fan[a]

[a] *Institute of Medical Photonics, Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing 100191, P.R. China*

[b] *School of Mechanical Engineering and Automation, Beihang University, Beijing, 100191, P. R. China*

* jiebo39@buaa.edu.cn;

‡ These authors contribute equally to this work.

Including Fig. S1-4, NOTE S1-2.

The selection of loading rate

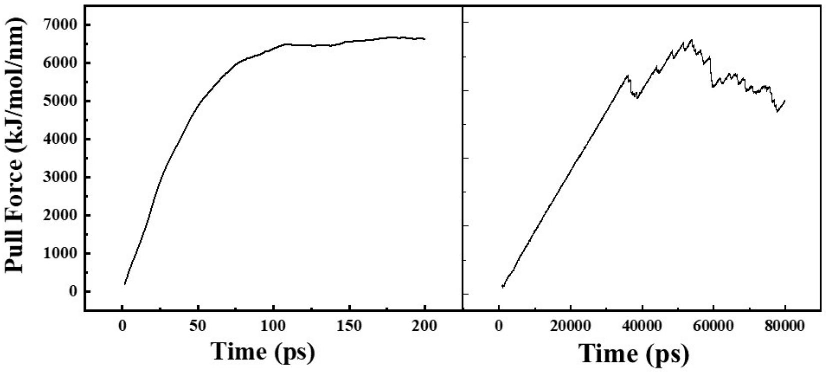

Fig. S1 Comparison of different loading rate imposed on Ti_3C_2 nanosheet during penetration into plasma memrbane. The left was 0.13 nm/ps and the right was 0.0001 nm/ps.

As shown in Fig. S1, both pulling process with different loading rate all converged to almost the same force (about 6000 kJ/mol/nm), which indicated that the descrepency of the loading rate (0.13 nm/ps and 0.0001 nm/ps) would not have a siginificant impact on the critical force required for the penetration in our model. Furthermore, we could see that as force started to converge, the force-time curve influcturated relatively intensively in small loading rate (0.0001 nm/ps) so that it was more difficult to search the critical force . Consequently, to obtain a more stable pulling process and save the computational resources, we chose the pulling rate of 0.13 nm/ps to achieve the penetration process.

Pull force curve versus time for different penetration patterns

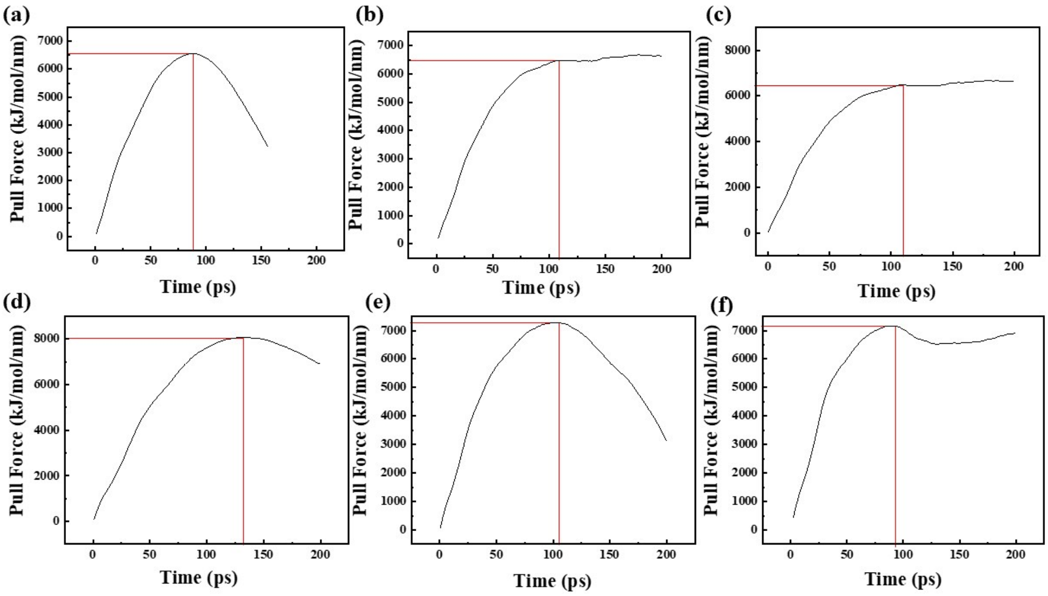

Fig. S2 Pulling force-time curve of (a) 30 degrees, corner site; (b) 60 degrees, corner site; (c) 90 degrees, corner site; (d) 30 degrees, smooth site; (e) 60 degrees, smooth site and (f) 90 degrees, smooth site Ti_3C_2 entering cell membrane. In each panel. The red line corresponds to the point of minimum force for Ti_3C_2 penetration.

From the force-time curve, it could be found that pull force built up until reached a turning point, which meant Ti_3C_2 broke the energy barrier and inserted into the plasma membrane. So, we consider the turning point as the minimum force Ti_3C_2 required to penetrate into the lipid bilayer.

Analysis of order parameter

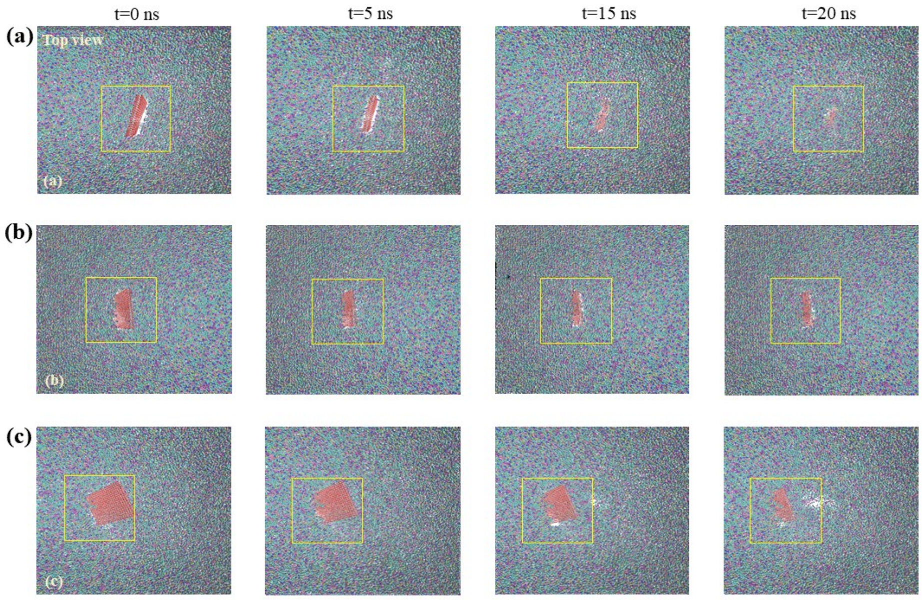

Fig. S3 analysis of local disturbance to plasma membrane, with Ti_3C_2 insertion of (a) $\Phi = 90°$, (b) $\Phi = 60°$, (c) $\Phi = 30°$.

As shown in Fig. S3, the snapshots of Ti_3C_2 flake with smooth site towards membrane were presented here. (Ti_3C_2 flake with corner site looked almost the same as smooth site from top view) We chose a rectangular area (10 nm×10 nm, the yellow rectangular in the Fig. S3) around the pore induced by Ti_3C_2 penetration to calculate the order parameters. The analyzing time of order parameters were all set to be 15 ns.

The penetrating pattern of multilayer Ti_3C_2 into cell membrane

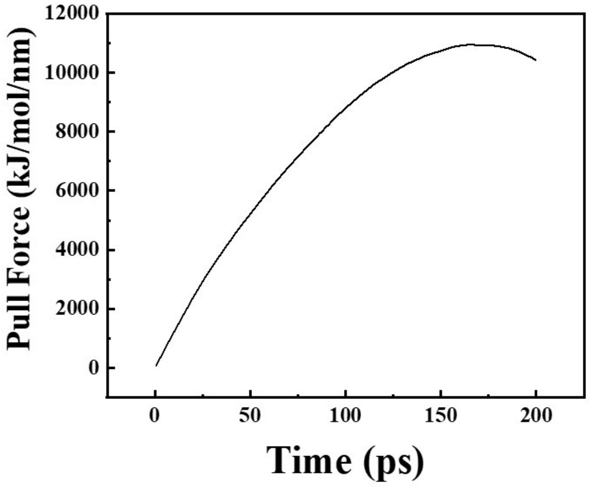

Fig. S4 Pulling force of multilayer vertical Ti_3C_2 entering plasma membrane.

As shown in Fig. S4, the pulling time force of multilayer vertical Ti_3C_2 entering plasma membrane was the same as single layer Ti_3C_2. More than that, we calculated the

Order parameter of POPC lipids before and after Ti_3C_2 went through cell membrane. The value turned out to be 0.236 and 0.137. Such a change in order parameter further confirmed that the pattern of multilayer Ti_3C_2 entering into plasma membrane was the same as single layer ones. Therefore, it is reasonable to simulate heat conduction with POPC lipids using multilayer Ti_3C_2.

Note S1. The calculation of the relative velocity

In our model, the Ti_3C_2 nano sheet had 1200 coarse-grained beads. When force-time curve reached the turning point, Ti_3C_2 nanosheet (with sharp corner site towards membrane, $\Phi=90°$) had a penetration depth of 3 nm. However, considering the physical truth, the size of a single-layered Ti_3C_2 sheet is about 1 um × 1 um, so we supposed an enormous Ti_3C_2 fake (1 um × 1 um) applied in our calculation to approximate the real situation. We employed the theorem of kinetic energy to obtain the relative velocity that the upright Ti_3C_2 required to pierce into the lipid membrane. According to the formula, $Fx = \frac{1}{2}mv^2$, *F* represents the resultant of all the external forces, *x* stands for the penetration depth, *m* indicates the mass of Ti_3C_2 sheet and *v* denotes the relative velocity. In our coarse-grained model, the minimal force called for the penetration of upright corner site Ti_3C_2 was 6200 kJ/mol/nm (about 10.29 nN), and *x* was set to be 5 nm. The mass of Ti_3C_2 sheet (1 um × 1 um) was about 1.771×10^{-18} kg (the mass of each bead in Martini force field is 72 amu, and Ti_3C_2 flake (1um × 1 um) possesses about 14814804 beads. As a result, the relative velocity of Ti_3C_2 sheet should be 5.89 m/s – 6.69 m/s (as *F* ranges from 6200 kJ/mol/nm to 8000 kJ/mol/nm).

As for graphene (GN) and carbon nanotubes (CNT), the situation is different. Ascribing to the hydrophobic interactions between lipid tails and hydrophobic surface of GN and CNT, the critical force could distinctly decrease as hydrophobic force could aid materials to break the energy barrier during the penetration process[1]. Therefore, as long as the initial penetration is accomplished, it would become much easier for GN and CNT to achieve deeper penetration. Accordingly, we set *x* to be 1 nm (a critical distance that hydrophobic interactions could take effect[1]) to calculate the relative initial velocity of GN and CNT. Furthermore, considering the practical applications and coordination with Ti_3C_2 flake, we set the length of CNT to be 1 um and a comparable size of GN (1.85 um × 1 um). Consequently, the mass of a GN sheet was estimated to be 1.408×10^{-18} kg, CNT to be 3.108×10^{-21} kg (diameter equals to 1.3 nm). According to previous simulation works, CNT (diameter, 1.3 nm) required about 600 pN to accomplish penetration[2], while GN called for 2.21 nN[3]. As a result, the relative initial velocity was calculated to be 19.6 m/s for CNT, and 1.77 m/s for GN. With regard to a 100 nm (diameter) gold nanoparticle, the mass could be estimated to be 8.092×10^{-17} kg. As the needed penetration force was about 250 pN[4], the initial relative velocity was about to be 0.078 m/s (x set to be 1 nm).

NoteS2. Thermal conductivity for Ti_3C_2 layers

We calculated the thermal conductivity of Ti_3C_2 flakes using nonequilibrium molecular dynamics (RNEMD)[5&6]. This method is accomplished by dividing Ti_3C_2 into slabs. We exchange velocities of the "hottest" atom in cold area and the "coldest" atom in hot area to transfer energy. Heat flux is generated by this way and the formula is[7]:

$$J = \frac{1}{2tA} \sum_{N_{transfer}} \frac{m}{2}(v_{hot}^{2} - v_{cold}^{2})$$

J is the heat flux, t is the time of simulation, A is the area of cross-sectional that is perpendicular to the direction of heat flux, m is the atom mass, v_{hot} and v_{cold} are the velocities of the hottest atom in the cold slab and the coldest atom in the hot slab, and $N_{transfer}$ indicates the number of exchanges during time t.

When the system reaches the steady state, a temperature gradient is produced. And the thermal conductivity can be calculated from Fourier's law:

$$K = -\frac{J}{dT/dx}$$

At the same time, there is a jump (ΔT) in the temperature across the boundary of Ti3C2 layers, the jump characterized the boundary conductance (Kapitza conductance) G_k through formula[8]:

$$G_k = -\frac{J}{\Delta T}$$

Our simulation is accomplished by LAMMPS. The timestep is set to be 1 fs. At first, the system is relaxed in NVE simulation at 300K by berendsen thermostat over 200 ps. Then, we conducted NPT ensemble to release the stress for 200 ps. Finally, we conducted simulation in NVE ensemble. Berendsen thermostat was used to keep the temperature at 300K. After relaxing for 100 ps, RNEMD simulation are performed in NVE ensemble. The simulation box is separated into 81 slabs. Fix thermal command was used in LAMMPS to create heat flow by exchanging the velocities of atoms per 20 steps. The system spent 1.5 ns reaching a steady state. The heat conductivity of Ti_3C_2 was calculated to be 0.215658.

References

(1) Li, Y.; Yuan, H.; von dem Bussche, A.; Creighton, M.; Hurt, R. H.; Kane, A. B.; Gao, H. Graphene microsheets enter cells through spontaneous membrane penetration at edge asperities and corner sites. *PNAS*. **2013**, 110, 12295-12300.

(2) Gangupomu V K , Capaldi F M . Interactions of Carbon Nanotube with Lipid Bilayer Membranes. J. Nanomater. **2011**, 99-110.

(3) Raczyński, P.; Górny, K.; Bełdowski, P.; Yuvan, S.; Dendzik, Z. Application of Graphene as a Nanoindenter Interacting with Phospholipid Membranes—Computer Simulation Study. J. Phys. Chem. B. ***2020***, 124, 6592-6602.

(4) Jameson, C.; Oroskar, P.; Song, B.; Yuan, H.; Murad, S. Molecular Dynamics Studies of Nanoparticle Transport Through Model Lipid Membranes. **2019**, pp 109-165.

(5) F. Muller-Plathe, A simple nonequilibrium molecular dynamics method for calculating the thermal conductivity, *J. Chem. Phys.*, 1997, **106**, 6082–6085.

(6) Müller-Plathe, F.; Reith, D., Cause and effect reversed in non-equilibrium molecular dynamics: an easy route to transport coefficients. *Comput. Theor. Polym. Sci.* **1999**, *9, 203-209.*

(7) Bagri, A.; Kim, S. P.; Ruoff, R. S.; Shenoy, V. B. Thermal transport across twin grain boundaries in polycrystalline graphene from nonequilibrium molecular dynamics simulations. *Nano Let*. **2011**, *11*, 3917

(8) Schelling, P. K.; Phillpot, S. R.; Keblinski, P., Kapitza. conductance and phonon scattering at grain boundaries by simulation. *J. Appl. Phys.* **2004**, *95*, 6082-6091.