Control Performance and Biomembrane Disturbance of Carbon Nanotube Artificial Water Channels by Nitrogen-Doping

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ABSTRACT To establish ways to control the performance of artificial water channels is a big challenge. With molecular dynamics studies, we found that water flow inside the water channels of carbon nanotubes (CNTs) can be controlled by reducing or intensifying interaction energy between water molecules and the wall of the CNTs channel. A way of example toward this significant goal was demonstrated by the doping of nitrogen into the wall of CNTs. Different ratios of nitrogen doping result in different controllable water performance which is dominated mainly through a gradient of van der Waals forces created by the heteroatom doping in the wall of CNTs. Further results revealed that the nitrogen-doped CNT channels show less influence on the integrality of biomembrane than the pristine one, while the nitrogen-doped double-walled carbon nanotube exhibits fewer disturbances to the cellular membrane integrality than the nitrogen-doped single-walled carbon nanotube when interacting with biomembranes.

KEYWORDS: N-SWCNT · N-DWCNT · artificial water channel · water flow control · molecular dynamics simulation

Water transportation is an important biological function for designing novel molecular devices, machines, and sensors. The artificial water channels of carbon nanotubes (CNTs)[1] have been attracting significant interests[2−6] since Hummer and his co-workers found that water can transmit through a (6,6) CNT forming a single file.[7] One knows that an osmotic, hydrostatic pressure gradient, or chemical potential can drive water flow in a channel.[8−10] When a system has an imbalance of surface tension,[11] of chemical[12] or thermal gradients,[13] the movement of water can be changed. For practical uses of the artificial water channel, two aspects of their performance are of great significance, which also play key roles in maintaining the functions of biological water channels. The first is to control the on/off states of water when entering the channel (gating), and the second is to control the flow of water when moving along the channel. So far, two ways have been proposed for gating water permeation in artificial channels. Fang *et al*. designed the artificial channel under a continuous deformation to create a nanopore switch between empty and filled states,[14]which hence created an on/off gating of water. Later, Zhou *et al*. introduced a single external charge to create on/off gating states of nanopores,[15] which has made significant progress on the manipulation and the realization. A lot of experimental[16−18] and theoretical[19−23] papers are focused on the characteristics and the mechanism of water flow in confined channels. Fang *et al*.[24] designed a molecular water pump using a combination of charges positioned adjacent to a nanopore. Later, Joseph and Aluru found that rotation−translation coupling could pump confined water in a CNT.[25]

So far, most of the water channel studies focused on single-walled carbon nanotubes (SWCNTs). However, experimental data indicated that the multiwalled carbon nanotubes exhibit less cytotoxicity than SWCNTs.[26] This is important for CNT applications in biomedicine and biotechnology fields,[27−32] in which better functions and less influence on cellular membrane integrality of CNT-based systems are crucial factors. Recently, we proposed a systematic chemistry for surface modifications of carbon nanotubes in biomedical applications in order to achieve safe carbon nanomaterials in life science uses.[33] Inspired by all these previous studies, we designed and examined the performance of artificial water channels based on surface modification of double-walled carbon nanotubes (DWCNTs)

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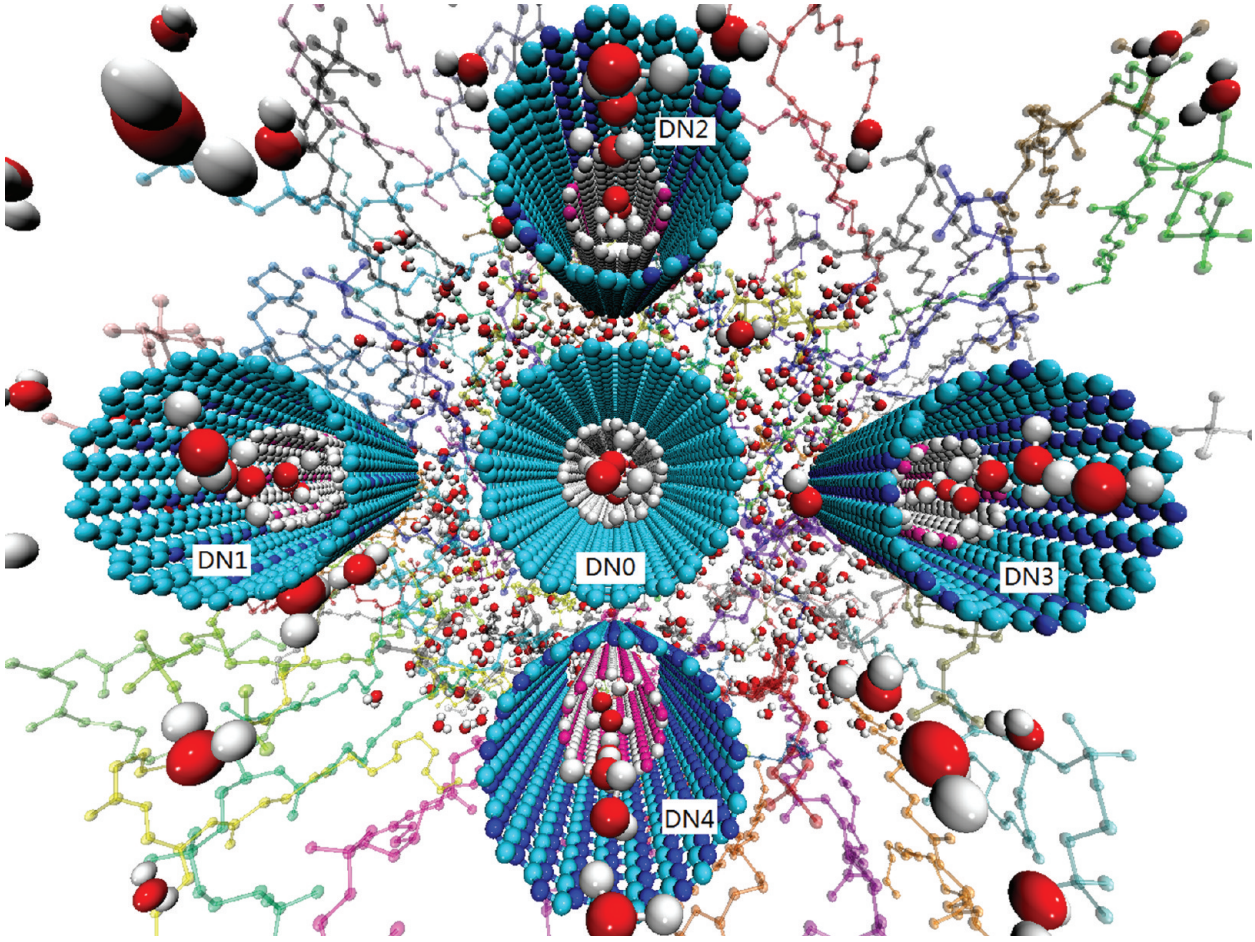

Figure 1. Full view of the models: N-DWCNT with armchair type (11,11) as the outer tube and (6,6) as the inner tube in the DMPC bilayer membrane. Carbon and nitrogen atoms are colored by cyan and blue in the outer tube and by white and magenta in the inner tube, respectively. From models DN0 to DN4, the doping proportions of N atoms in CNTs are 0% (DN0), 11% (DN1), 18% (DN2), 26% (DN3), and 50% (DN4).

with nitrogen doping. Here, we report a novel and simple way to drive and control the water flow inside the artificial channels of carbon nanotubes embedded in biomembranes. With nitrogen doping, the hetero-CNTs can create a controllable gradient in van der Waals interactions between the wall of CNT and the water molecules, which not only control the flow speed of water inside the CNT channel but also largely improve the performances of CNT-based devices in biomembranes.

RESULTS AND DISCUSSION

Model Design. As shown in Figure 1, we designed a N-doped double-walled carbon nanotube (N-DWCNT) with armchair type (11,11) as the outer tube and (6,6) as the inner tube. The diameter of the inner tube is around 8 Å, and the space between the tubes is around 3.4 Å. There are two types of C−N bonds that can occur in carbon nanotubes: the two- and three-coordinated N.[34] The three-coordinated N atom within the sp2-hybridized network was used in our model. Then, the model channel was embedded into the dimiristoylphosphatidylcholine (DMPC) bilayer membrane. We changed the doping concentration of nitrogen in N-DWCNTs and tested the different type of artificial channels with different doping proportions. The designed proportions of N atoms in N-DWCNTs are 0% (DN0), 11% (DN1), 18% (DN2), 26% (DN3), and 50% (DN4), respectively (Figure 1). For comparison, we designed an N-doped single-walled carbon nanotube (N-SWCNT) as a control system, denoted as SN, with 50% of N atoms. All the tubes are uncapped with a length of 33 Å, and two equivalent charges (+0.25e) were assigned to a pair of next-nearest-neighboring carbon atoms roughly at the middle of the inner tube to mimic a asparagine−proline−alanine (NPA) region of aquaporin (AQP) proteins.[35,36]

Theoretical Investigation of Cellular Membrane Integrality When Interacting with Artificial Water Channels of CNTs. Biocompatibility is an important factor in evaluation of the biological safety of artificial biodevices,[37−41] but its theoretical determination is difficult. Instead, we evaluated the influence of CNTs on the cellular membrane integrality by calculating how the inserted CNT water channels altered the structure of the individual lipid molecule as well as the organization of lipid molecules. Generally,

conformations of individual DMPC molecules fluctuate with time. When the nanotube was inserted into the bilayer membrane, each individual lipid molecule would adjust its conformation to accommodate the nanotube. The conformational fluctuations of lipid molecules with inserted nanotubes should be different from that of pure lipids. We investigated the conformational fluctuation of each individual DMPC molecule by the root-mean-square deviation (rmsd). Rmsd is a numerical measure of the difference between two structures and reveals the average conformational evolvement over time. It is defined as

$$\mathrm{rmsd} = \sqrt{\frac{\sum_{i=1}^{N_{\mathrm{atoms}}} (r_i(t_1) - r_i(t_2))^2}{N_{\mathrm{atoms}}}} \quad (1)$$

where N_{atoms} is the number of atoms whose positions are being compared, and $r_i(t)$ is the position of atom i at time t.

Rmsds were calculated by the rmsd trajectory tool in VMD[42] with a frame span of 1 ps and the average structure as the reference. The rmsd of lipid molecules in pure DMPC, DN4, and SN is 1.44, 1.43, and 1.28 Å, respectively. The results of rmsd indicate that the N-SWCNT (SN) diminishes the conformational fluctuations of lipid molecules. However, the rmsd value for N-DWCNT is very close to that of the pure DMPC. This implies that the lipid molecules become more rigid when the N-SWCNT was inserted into the membrane and that the N-DWCNT produces less influence on the conformational fluctuations of lipid molecules.

We further investigated the influence of the inserted CNT channels on the organization of membranes. We first characterize the packing density of the membrane in our model by calculating the area per molecule (APM). APM is one of the fundamental features used to structurally characterize a lipid membrane and is also a useful measure to monitor the equilibration process in the molecular dynamics study of a membrane assembly. The average APM of a membrane can be calculated as

$$A_{\mathrm{mol}} = A_{\mathrm{total}}/N$$

where A_{mol} is the average APM, A_{total} is the area in the bilayer xy plane, and N is the number of lipid molecules.

The APM of lipid molecules in pure DMPC, DN4 and SN are 48.93, 48.30, and 43.29 Å^2, respectively. The result suggested that the insertion of N-SWCNT constricts the packing of membranes. The lipid molecules of DMPC in DN4 show nearly same organization to the pure DMPC.

Both the rmsd and APM values indicated that the N-SWCNT made more influences on the lipid molecules when inserted into the membrane than N-DWCNT. This implied that the N-DWCNT exhibits fewer disturbances to the integrality of cellular membranes than that of the N-SWCNT, which is consistent to the experimental results,[26] in which they indicated that the SWCNT exhibits more cytotoxicity than multiwalled CNT. Thus, N-DWCNT is a more promising artificial water channel in biological systems than N-SWCNT.

Controllable Performance of Water Flow Inside N-DWCNT Water Channels. It has been reported[7,43,44] that the initially empty central channel of the nanotube could be rapidly filled by water from the surrounding reservoir and remains occupied during the entire simulation time. In our simulations, water molecules can also readily fill in the tube and form a single file (Figure 2a). Statistical results of water density verify that the channel of the nanotube is occupied by about 12 water molecules during the entire 30 ns (Figure 2b). In addition, Hummer *et al.*[7] found that a tight hydrogen-bond network inside the nanotube and water fluctuations outside the nanotube lead to highly concerted, yet rapid, drift-like motions of the water molecules along the nanotube axis, resulting in bursts in the water flow. These characters were also observed in our previous study[44] and in the present simulations, as shown in Figure 2c and d.

The water movement has been characterized by a continuous-time random walk (CTRW).[9,45] We first calculated the key parameter, permeation rate of water, and its change with the doping concentration of nitrogen. We found that the permeation rate of water showed a proportional nature to the percentage of doped nitrogen atoms in the N-DWCNT channel (Figure 3a). At the same time, one sees that the diffusion coefficients (D_T) of water molecules in the N-DWCNT channels increase with the increase of the nitrogen proportion (Figure 3b). These results indicate that the water flow in the nitrogen-doped CNT channels is controllable by a simple design of the proportion of doped nitrogen atoms in DWCNT.

To find the intrinsic force that can dominate the permeation rate of water inside the channel, we calculated the van der Waals interaction energy between the wall of N-DWCNT and the water molecules for all the models and found that the forces of van der Waals interactions change regularly with the change in doping concentrations of nitrogen in N-DWCNTs (Figure 3c). We see that the van der Waals energy is inversely proportional to the percentage of doped nitrogen atoms in CNTs. The interaction force between water molecules and nitride atoms ($\varepsilon_{N-O} = 0.365$ kJ/mol) is weaker than that between water molecules and carbon atoms ($\varepsilon_{C-O} = 0.4312$ kJ/mol). The results in Figure 3d clearly demonstrated that the decrease of van der Waals interaction energy between the water molecules and the CNT wall results in the increase of permeation rates of water inside the CNT channel. To further confirm this finding, we counted the average life of hydrogen bonds among water molecules when flowing through the water chan-

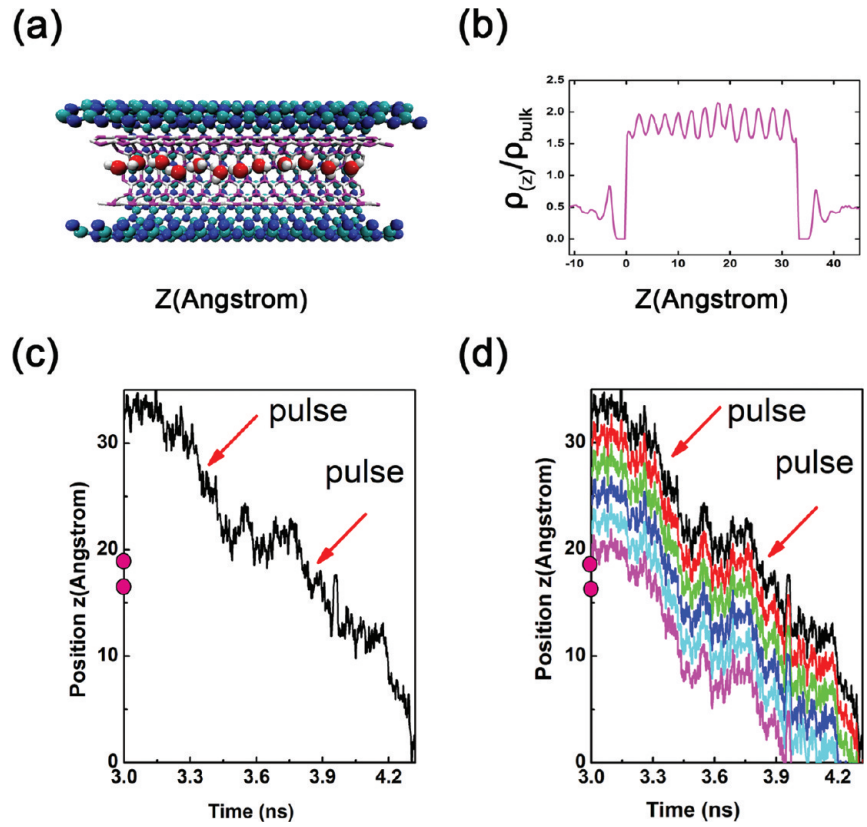

Figure 2. Representative results (DN4). (a) A snapshot in the simulation of model DN4. (b) Statistical results of water density inside the N-DWCNTs of model DN4. (c) Traced permeation trajectories of one water molecule in model DN4. (d) Pulse-like concerted motion of six water molecules through the water channel.

nel of N-DWCNT. Very interestingly, the average lives of hydrogen bonds are inversely proportional to the amount of doped nitrogen atoms (Supporting Information). It suggests that the diminished van der Waals interactions between the water molecule and the wall of artificial channels improved the activity of water diffusion so that the hydrogen bonds among water molecules become weaker and less stable in the nitrogen-doped CNTs. Recently, Striolo *et al.*[46] reported that the oxygenated CNT showed a slower water diffusion compared to that of pristine CNTs. This observation is consistent with the present results: The water permeation rate relates to the intensity of interaction between the water molecules and the tube. Though there is a big difference between the oxygenated CNTs and the nitrogen-doped of CNTs, the oxygenation of CNT enhanced the interaction force between the wall of CNT and the water molecules, which slows down the water flow in the tube, while the nitrogen doping reduced the interaction forces between CNT and water, speeding up the water flow in the tube.

In addition, in the work of Striolo *et al.*, the water-diffusion rate inside the O-doped CNTs was found to be strongly dependent on the number of water molecules inside the tube, indicating a water concentration effect on diffusion rates. Striolo's model adopted the (8,8) CNT, in which water molecules formed a multilayer but not a single-file chain, thus the water concentration naturally affects their diffusion rates. However, (6,6) CNT was used in the present model as an inner tube, in which water forms only a single-file chain passing through the channel; the water concentration here is less changed, and their observation might not be applicable to the present model.

It should be pointed out that carbon and nitrogen atoms in all our model CNTs were treated as Lennard-Jones particles only, similar to previous studies with molecular dynamics (MD) simulations.[47] The electrostatic interactions do not contribute to the total force between water and nanotubes. This makes the calculation results reflecting only the van der Waals interactions. So all the results indicate that we can control the flow process of water in CNT-based artificial water channels by weakening or intensifying the interaction energy between water molecules and the wall of the channel, no matter whether we achieve this goal by nitrogen doping or oxygen modifying.

As the thermodynamic force possibly contributes to the water flow, we hence calculated the free energy profiles of water permeation inside the channel. However, the free energy barriers for all the models studied here are lower than 1.6 K_BT, which is too low to make any contribution to the water flow process. Accordingly, the speed of water permeation inside the nanochannel is not dominated by thermodynamic properties.

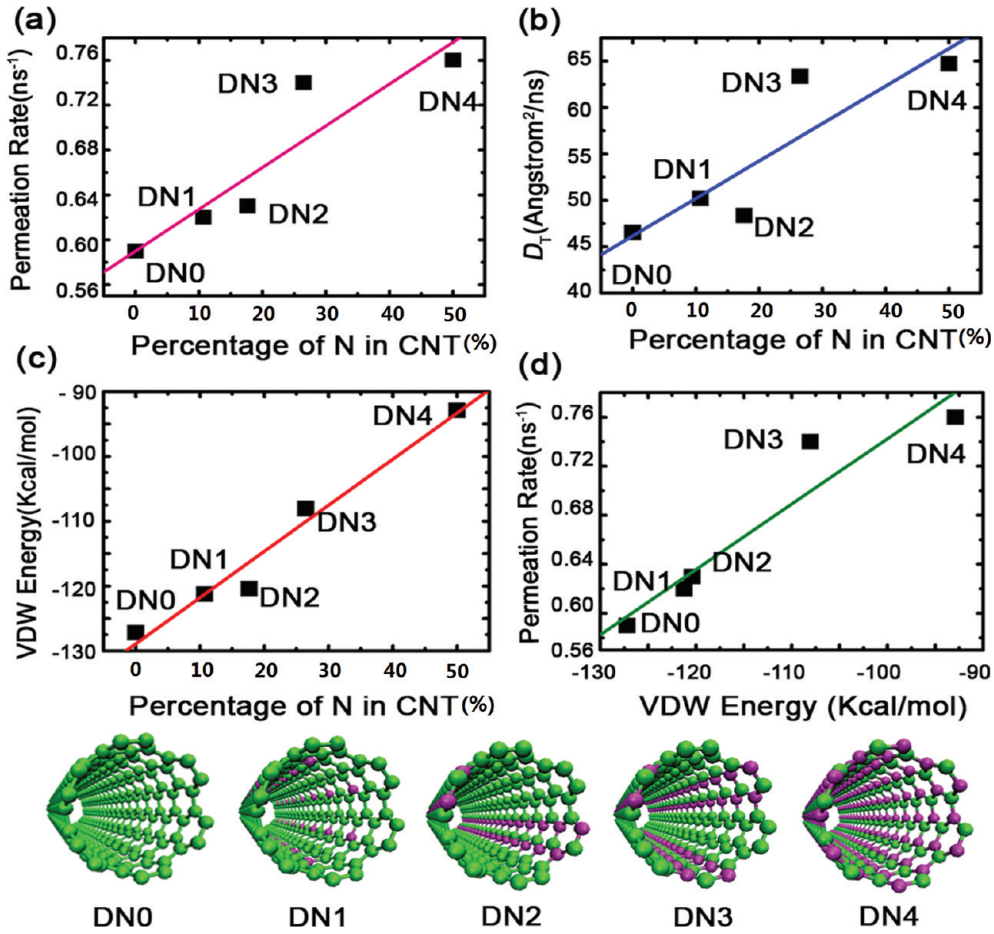

Figure 3. Controllable performance of water permeation across the N-DWCNTs channels with changing proportions of doped nitrogen atoms in DWCNTs. (a) Linear correlation between permeation rate of water and nitrogen proportions. (b) Linear correlation between the diffusion coefficients (D_T) of water permeation across the channels and the nitrogen proportions. (c) Linear correlation between van der Waals interaction energy and nitrogen proportions. (d) Linear correlation between the permeation rate and the van der Waals energy. At the bottom, carbon and nitrogen atoms in each model are colored by green and magenta, respectively.

We also calculated the permeation rate of water in the model SN. It is 0.35 ns^{-1}, almost half of the permeation rate in DN4 (0.76 ns^{-1}) and even smaller than DN1 (0.62 ns^{-1}). This result indicates that if we need to slow the flow of water, then the N-SWCNT is maybe preferred.

Influences of DWCNTs and N-DWCNTs on Cellular Membrane Integrality Monitored by Theoretical Simulations. As descrbed in the previous section, we defined and evaluated the influence of CNT channels on the integrality of biomembranes by calculating how the inserted CNT water channels altered the structure of individual lipid molecules as well as the organization of lipid molecules. Table 1 summarized the average rmsds and APM for all DWCNT models.

TABLE 1. Influence of Inserted Channels on Biomembranes

	rmsd (Å)	APM (Å^2)	Δr (Å)
DN0	1.33	51.71	0.88
DN1	1.51	51.31	0.45
DN2	1.35	51.09	0.61
DN3	1.39	51.41	0.55
DN4	1.43	48.30	0.52
pureDMPC	1.44	48.93	—

The rmsd results show that the pristine DWCNT (DN0) diminishes the conformational fluctuations of lipid molecules, indicating that lipid molecules become more rigid when the pristine DWCNT was inserted into the membrane. However, the rmsd values for models DN1−DN4 are closer to that of the pure DMPC (the intact membrane). They suggest that the N-CNTs produce less influence on the conformational fluctuations of lipid molecules than the pristine CNT without the doping of nitrogen.

The APM of lipid molecules in DN0 increases compared to that of pure DMPC, suggesting that the insertion of pristine DWCNT relaxed the organization of membranes (Table 1). The lipid molecules of DMPC in N-DWCNT show nearly the same organization to the pure DMPC.

A snapshot of the top view of DMPC−CNT assembly could give us a visual impression on how they are organized. As shown in Figure 4, the packing of DMPC molecules around the nanotube could be character-

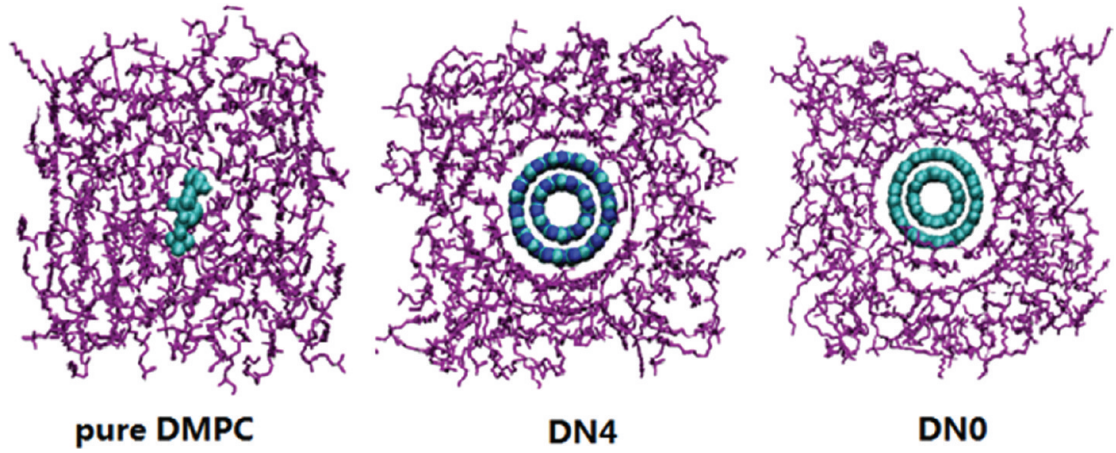

Figure 4. Top views of different models. The center DMPC is shown in cyan in the pure DMPC. Carbon and nitrogen atoms of DWCNT are colored by cyan and blue, respectively, in DN4. Carbon atoms of DWCNT are colored by cyan in DN0.

ized by a nearly unoccupied cylindrical ring, which is in contrast to the packing of the DMPC molecules about one another in the absence of the nanotube.

Apparently, inserted CNT reduces the entropy of DMPC molecules because of its rigid and unaccommodating structure, which leads to fewer conformational states available to DMPC molecules adjacent to the channel. On the contrary, the flexible DMPC molecules can accommodate one another in many conformations, which makes the high plasticity available to the phospholipids membrane.

To quantify the magnitude of the vacant cylindrical ring, we introduce the minima distances (Δr) between the center of mass of the lipid molecules and the tube walls. The results of minima distance (Δr) also indicate that the lipid molecules pack closer to the N-DWCNT than the pristine DWCNT (Table 1).

CONCLUSIONS

We found that the flow performance of water inside the artificial water channel of carbon nanotubes (CNTs) can be controlled by reducing or intensifying the interaction energy between water molecules and the wall of the artificial channel. A simple chemistry toward this significant aim is the doping of nitrogen into the wall of CNTs. Correlations among the water permeation rate, the water diffusion coefficients, the van der Waals energy, and the nitrogen-doping proportion demonstrated that the performance of water inside the CNT-based water channels is controllable by tuning the interaction energy between water and the nanotube wall, such as heteroatom doping which dominates the water performance mainly through a gradient in van der Waals interactions created by the doping.

We also compared the water flow in N-doped single-walled (N-SWCNT) and double-walled (N-DWCNT) carbon nanotubes. The permeation rate of water in N-SWCNTs is almost half of that in the corresponding N-DWCNT. So if we need slow the flow of water, then the N-SWCNT may be preferred. However, we further found when the N-SWCNT was inserted into the membrane, the lipid molecules became more rigid, which largely constricted the packing of membrane, while the insertion of N-DWCNT produced less influence on the conformational fluctuations of lipid molecules, showing that the original organization is nearly the same as the pure DMPC. Thus, the N-DWCNT shows less influence on the cellular membrane integrality (namely, more friendly or less toxic) than N-SWCNT. Meanwhile N-DWCNTs exhibit fewer disturbances to the cellular membrane integrality than the pristine one. Therefore, the surface modification with N-doping reduced the toxic response of CNTs to biosystem.

METHODS

Simulations were performed using the program NAMD (version 2.6)[48] with the CHARMM force field[49,50] and the TIP3P water model[51] at NPT ensemble (310 K and 1 atm) with periodic boundary conditions. The parameters of carbon atoms for benzene in CHARMM general force field were used for those of carbon atoms in pristine DWCNT. The parameters of atoms for C_5H_5N pyridine were used for DWCNT in model DN1. The parameters for the carbon atoms bonded with the nitrogen atom in DN2−DN4 and SN were those of type CG2R64, and the corresponding nitrogen atoms were those of type NG2R62, which were designed for 1,3,5-triazine.[50] The carbon and nitrogen atoms in all CNTs were modeled as uncharged Lennard-Jones particles.[47] Sodium and chloride ions were added into the system to keep their concentration at 0.15 M (physiological condition). The long-range electrostatic interactions were computed by the particle mesh Ewald (PME) method,[52] and the short-range van der Waals forces were calculated within a cutoff distance of 12 Å. Bonds to all hydrogen atoms were kept rigid, and multiple time steps were used. A 30 ns MD run was carried out after equilibrations and data were collected every 1 ps. The DMPC membrane was downloaded from the Web site of Klauda's group.[53] Then more water molecules were added to reach a fully hydrated state: 54 water molecules/lipid. The membrane water assembly was subjected to 30 ns equilibration at 1 atm, 310 K without any restraint.[54] The details of creating the cylinder hole in the DMPC membrane

and embedding the CNTs into the holes have been described in our previous work.[44]

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Supporting Information Available: Details of calculations of water permeation and variations of hydrogen bonds between water molecules inside channels with changing amounts of doping nitrogen atoms in DWCNTs. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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