Title

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Abstract

1 Introduction

First synthesized in 2004[11], graphene has since experienced an explosive growth in interest[14]. For pristine graphene, it's interactions with other particles are mainly due to Van der Waals forces and $\pi - \pi$ stacking.[22] As pristine graphene is chemically inert[6] a classical description of it is expected to suffice in simulations. Multiple molecular dynamics studies on the interactions between proteins and carbon based nanoparticles (CBNs) –such as graphene– have been published[1,4,5,7,8,10,13,19,21,22]

2 Methods

2.1 Free Energy Methods

2.1.1 Umbrella Sampling

2.1.2 Well-Tempered Multiple Walker Metadynamics

2.2 Molecular Dynamics Simulation

MD simulations were performed using the GROMOS11[16,18] and the NAMD 2.14 simulation packages[12]. Details of the simulations will be presented separately for each program.

2.2.1 GROMOS

The SHAKE algorithm[17] was employed to constrain all bonds to their reference values with a relative tolerance of 10^{-4}, allowing for a time-step of 2 fs using the leapfrog algorithm[9]. For water, the SPC model was used[2]. Non-bonded interactions were computed using a triple range cut-off. Interactions within the short-range cut-off of 0.8 nm were computed every time-step, from a pair-list that was generated every 5 steps. At these time points, interactions between 0.8 and 1.4 nm were also computed which were kept constant between these updates. A reaction-field contribution was added to electrostatic interactions approximating for a homogeneous medium outside the 1.4 nm long-range cut-off, employing the relative permittivity of SPC water (61)[20]. All interactions were calculated using the GROMOS 54a8 potential energy function, with all graphene atoms modeled as neutral sp^2 carbons[15]. After a steepest-descent minimization to remove bad contacts, all velocities were randomly assigned from a Maxwell-Boltzmann distribution at 298 K. All simulations were run coupled to thermostats using the weak-coupling algorithm[3]. The solute, graphene and solvent atoms were independently coupled to different heat baths. Additionally, the graphene layer was coupled to separate baths for regulation of its center of mass motion and its rotational and internal degrees of freedom. This totaled 4 heat baths.

2.2.2 NAMD

3 Results

3.1 Adsorption Free Energy

3.2 Adsorption Entropy

3.3 Adsorption Energy

3.4 Diffusion

4 Conclusions

Acknowledgements

This work was partially supported by grant no. ICM-Economia grant no. P09-022-F Centro Interdisciplinario de Neurociencia de Valparaiso, Universidad de Valparaiso; FONDECYT 1180987 (to J.A.G.), PAI grant no. 77170045 (to J.A.G.) and a doctoral scholarship from CONICYT–PFCHA/DOCTORADO BECAS NACIONAL/2020–21201020. Access to the supercomputing infrastructure of the National Laboratory for High-Performance Computing was supported through grant no. ECM-02 (Powered@NLHPC).

References

[1] Mohammed N. Al-Qattan, Pran Kishore Deb, and Rakesh K. Tekade. Molecular dynamics simulation strategies for designing carbon-nanotube-based targeted drug delivery. *Drug Discovery Today*, 23(2): 235–250, Feb 2018. ISSN 1359-6446. doi: 10.1016/j.drudis.2017.10.002. URL `http://dx.doi.org/10.1016/j.drudis.2017.10.002`.

[2] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, and J. Hermans. Interaction models for water in relation to protein hydration. *Intermolecular Forces*, page 331–342, 1981. ISSN 0924-4875. doi:

10.1007/978-94-015-7658-1_21. URL http://dx.doi.org/10.1007/978-94-015-7658-1_21.

[3] H. J. C. Berendsen, J. P. M. Postma, W. F. van Gunsteren, A. DiNola, and J. R. Haak. Molecular dynamics with coupling to an external bath. *The Journal of Chemical Physics*, 81(8):3684–3690, Oct 1984. ISSN 1089-7690. doi: 10.1063/1.448118. URL http://dx.doi.org/10.1063/1.448118.

[4] Yu Chong, Cuicui Ge, Zaixing Yang, Jose Antonio Garate, Zonglin Gu, Jeffrey K. Weber, Jiajia Liu, and Ruhong Zhou. Reduced cytotoxicity of graphene nanosheets mediated by blood-protein coating. *ACS Nano*, 9(6):5713–5724, Jun 2015. ISSN 1936-086X. doi: 10.1021/nn5066606. URL http://dx.doi.org/10.1021/nn5066606.

[5] Guangxin Duan, Seung-gu Kang, Xin Tian, Jose Antonio Garate, Lin Zhao, Cuicui Ge, and Ruhong Zhou. Protein corona mitigates the cytotoxicity of graphene oxide by reducing its physical interaction with cell membrane. *Nanoscale*, 7(37):15214–15224, 2015. ISSN 2040-3372. doi: 10.1039/c5nr01839k. URL http://dx.doi.org/10.1039/C5NR01839K.

[6] Ali Eftekhari and Hermenegildo Garcia. The necessity of structural irregularities for the chemical applications of graphene. *Materials Today Chemistry*, 4:1–16, Jun 2017. ISSN 2468-5194. doi: 10.1016/j.mtchem.2017.02.003. URL http://dx.doi.org/10.1016/J.MTCHEM.2017.02.003.

[7] C. Ge, J. Du, L. Zhao, L. Wang, Y. Liu, D. Li, Y. Yang, R. Zhou, Y. Zhao, Z. Chai, and et al. Binding of blood proteins to carbon nanotubes reduces cytotoxicity. *Proceedings of the National Academy of Sciences*, 108(41):16968–16973, Oct 2011. ISSN 1091-6490. doi: 10.1073/pnas.1105270108. URL http://dx.doi.org/10.1073/pnas.1105270108.

[8] Michael González-Durruthy, Amal Kanta Giri, Irina Moreira, Riccardo Concu, André Melo, Juan M. Ruso, and M. Natália D.S. Cordeiro. Computational modeling on mitochondrial channel nanotoxicity. *Nano Today*, 34:100913, Oct 2020. ISSN 1748-0132. doi: 10.1016/j.nantod.2020.100913. URL http://dx.doi.org/10.1016/j.nantod.2020.100913.

[9] R W. Hockney. *The potential calculation and some applications*, volume 9 of *Methods in Computational Physics*, pages 136–211. Academic Press, 1977.

[10] Baoyu Li, Yuanzhao Zhang, Xuan-Yu Meng, and Ruhong Zhou. Zipper-like unfolding of dsdna caused by graphene wrinkles. *The Journal of Physical Chemistry C*, 124(5):3332–3340, Jan 2020. ISSN 1932-7455. doi: 10.1021/acs.jpcc.9b08778. URL http://dx.doi.org/10.1021/acs.jpcc.9b08778.

[11] K. S. Novoselov. Electric field effect in atomically thin carbon films. *Science*, 306(5696):666–669, Oct 2004. ISSN 1095-9203. doi: 10.1126/science.1102896. URL http://dx.doi.org/10.1126/science.1102896.

[12] James C. Phillips, David J. Hardy, Julio D. C. Maia, John E. Stone, João V. Ribeiro, Rafael C. Bernardi, Ronak Buch, Giacomo Fiorin, Jérôme Hénin, Wei Jiang, and et al. Scalable molecular dynamics on cpu and gpu architectures with namd. *The Journal of Chemical Physics*, 153(4):044130, Jul 2020. ISSN 1089-7690. doi: 10.1063/5.0014475. URL http://dx.doi.org/10.1063/5.0014475.

[13] Elle Puigpelat, Jordi Ignés-Mullol, Francesc Sagués, and Ramon Reigada. Interaction of graphene nanoparticles and lipid membranes displaying different liquid orderings: A molecular dynamics study. *Langmuir*, 35(50):16661–16668, Nov 2019. ISSN 1520-5827. doi: 10.1021/acs.langmuir.9b03008. URL http://dx.doi.org/10.1021/acs.langmuir.9b03008.

[14] Edward P. Randviir, Dale A.C. Brownson, and Craig E. Banks. A decade of graphene research: production, applications and outlook. *Materials Today*, 17(9):426–432, Nov 2014. ISSN 1369-7021. doi: 10.1016/j.mattod.2014.06.001. URL http://dx.doi.org/10.1016/j.mattod.2014.06.001.

[15] Maria M. Reif, Philippe H. Hünenberger, and Chris Oostenbrink. New interaction parameters for charged amino acid side chains in the gromos force field. *Journal of Chemical Theory and Computation*, 8(10):3705–3723, May 2012. ISSN 1549-9626. doi: 10.1021/ct300156h. URL http://dx.doi.org/10.1021/ct300156h.

[16] Sereina Riniker, Clara D. Christ, Halvor S. Hansen, Philippe H. Hünenberger, Chris Oostenbrink, Denise Steiner, and Wilfred F. van Gunsteren. Calculation of relative free energies for ligand-protein binding, solvation, and conformational transitions using the gromos software. *The Journal of Physical Chemistry B*, 115(46):13570–13577, Nov 2011. ISSN 1520-5207. doi: 10.1021/jp204303a. URL http://dx.doi.org/10.1021/jp204303a.

[17] Jean-Paul Ryckaert, Giovanni Ciccotti, and Herman J.C Berendsen. Numerical integration of the cartesian equations of motion of a system with constraints: molecular dynamics of n-alkanes. *Journal of Computational Physics*, 23(3):327–341, Mar 1977. ISSN 0021-9991. doi: 10.1016/0021-9991(77)90098-5. URL http://dx.doi.org/10.1016/0021-9991(77)90098-5.

[18] Nathan Schmid, Clara D. Christ, Markus Christen, Andreas P. Eichenberger, and Wilfred F. van Gunsteren. Architecture, implementation and parallelisation of the gromos software for biomolecular simulation. *Computer Physics Communications*, 183(4):890–903, Apr 2012.

ISSN 0010-4655. doi: 10.1016/j.cpc.2011.12.014. URL http://dx.doi.org/10.1016/j.cpc.2011.12.014.

[19] Sergey Shityakov, Giorgia Pastorin, Carola Foerster, and Ellaine Salvador. Blood-brain barrier transport studies, aggregation, and molecular dynamics simulation of multiwalled carbon nanotube functionalized with fluorescein isothiocyanate. *International Journal of Nanomedicine*, page 1703, Mar 2015. ISSN 1178-2013. doi: 10.2147/ijn.s68429. URL http://dx.doi.org/10.2147/IJN.S68429.

[20] Ilario G. Tironi, René Sperb, Paul E. Smith, and Wilfred F. van Gunsteren. A generalized reaction field method for molecular dynamics simulations. *The Journal of Chemical Physics*, 102(13):5451–5459, Apr 1995. ISSN 1089-7690. doi: 10.1063/1.469273. URL http://dx.doi.org/10.1063/1.469273.

[21] Ming Zheng, Anand Jagota, Ellen D. Semke, Bruce A. Diner, Robert S. Mclean, Steve R. Lustig, Raymond E. Richardson, and Nancy G. Tassi. Dna-assisted dispersion and separation of carbon nanotubes. *Nature Materials*, 2(5):338–342, Apr 2003. ISSN 1476-4660. doi: 10.1038/nmat877. URL http://dx.doi.org/10.1038/nmat877.

[22] Guanghong Zuo, Seung-gu Kang, Peng Xiu, Yuliang Zhao, and Ruhong Zhou. Interactions between proteins and carbon-based nanoparticles: Exploring the origin of nanotoxicity at the molecular level. *Small*, 9(9-10):1546–1556, Oct 2012. ISSN 1613-6810. doi: 10.1002/smll.201201381. URL http://dx.doi.org/10.1002/smll.201201381.