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DNA-Polycation Condensation by Coarse-Grained Molecular Dynamics

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Abstract : Many modern gene-delivery protocols rely on condensed complexes of DNA with polycations to introduce the genetic payload into cells by endocytosis. In particular, polyethyleneimine (PEI) stands out by a high buffering capacity (enabling the efficient condensation of DNA) and relatively simple fabrication. Realistic computational studies can offer essential insights into the formation process of DNA-PEI polyplexes, providing hints on efficient designs and engineering routes. We present comprehensive computational investigations of solvated PEI and DNA-PEI polyplexes involving calculations at three levels: ab initio, all-atom (AA), and coarse-grained (CG) molecular mechanics. In the first stage, we developed a rigorous AA CHARMM (Chemistry at Harvard Macromolecular Mechanics) force field (FF) for PEI on the basis of accurate ab initio calculations on protonated model pentamers. We validated this atomistic FF by matching the results of extensive molecular dynamics (MD) simulations of structural and dynamical properties of PEI with experimental data. In a second stage, we developed a CG MARTINI FF for PEI by Boltzmann inversion techniques from bead-based probability distributions obtained from AA simulations and ensuring an optimal match between the AA and CG structural and dynamical properties. In a third stage, we combined the developed CG FF for PEI with the standard MARTINI FF for DNA and performed comprehensive CG simulations of DNA-PEI complex formation and condensation. Various technical aspects which are crucial for the realistic modeling of DNA-PEI polyplexes, such as options of treating electrostatics and the relevance of polarizable water models, are discussed in detail. Massive CG simulations (with up to 500 000 beads) shed light on the mechanism and provide time scales for DNA polyplex formation independence of PEI chain size and protonation pattern. The DNA-PEI condensation mechanism is shown to primarily rely on the formation of DNA bundles, rather than by changes of the DNA-strand curvature. The gained insights are expected to be of significant help for designing effective gene-delivery applications.

Keywords : DNA condensation, gene-delivery, polyethylene-imine, molecular dynamics.
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