

## Supporting Information for

### Theoretical and computational studies of dendrimers as delivery vectors

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#### 1. Discussion of some techniques that deal with electrostatic interactions

##### 1.1 Debye–Hückel approximation<sup>1</sup>

Debye and Hückel developed a theory to calculate the mean ionic activity coefficient of the solution,  $\gamma_{\pm}$ :

$$\log \gamma_{\pm} = - \frac{1.824 \times 10^6}{(\epsilon T)^{3/2}} |z_+ z_-| \sqrt{I}, \quad (1)$$

where  $\epsilon$  is the dielectric constant,  $z_+$  and  $z_-$  are the charges of the cation and anion, respectively, and  $I$  is the ionic strength of the solution. The theory is based on three assumptions of how ions act in solution. The first one is that electrolytes completely dissociate into ions in solution. The second one is that solutions of electrolytes are very dilute. The last one is that each ion is surrounded by ions of the opposite charge, on average. It is obvious that the Debye–Hückel approximation is valid only in the limit of low concentrations as well as the complete dissociation of electrolytes. The theory/approximation breaks down when the concentration of the electrolyte is greater than about 100 mM, or when ions with a higher charge are in solution, where the ion association may take place. In addition, the role of solvent such as water is ignored in the theory.

##### 1.2 Ewald summation and reaction field methods<sup>2</sup>

The Ewald summation is a method for calculating the electrostatic potential under periodic boundary conditions. The method rewrites the electrostatic interaction potential as the sum of two terms,

$$\varphi(\mathbf{r}) \stackrel{\text{def}}{=} \varphi_{sr}(\mathbf{r}) + \varphi_{lr}(\mathbf{r}), \quad (2)$$

where  $\varphi_{sr}(\mathbf{r})$  represents the short-range term that sums quickly in real space and  $\varphi_{lr}(\mathbf{r})$  represents the long-range term that sums quickly in Fourier space. The advantage of this approach is the rapid convergence of the Fourier-space summation compared to its real-space equivalent when the real-space interactions are long-range, thus it reduces the computational load.

The reaction field method is used to treat the effect of long-range dipole-dipole interactions in molecular simulations with periodic boundary conditions. It is assumed that any given molecule is surrounded by a spherical cavity of finite radius. Inside the cavity, the electrostatic interactions are calculated explicitly, while outside the cavity, a dielectric continuum of the system is used. The molecule leads to polarization in this media which in turn can create a reaction field. The method allows us to calculate the dipole-dipole interactions, instead of the infinite Coulomb sum, by a finite sum plus the reaction field.

For many quantities of interest, both the Ewald summation method and the reaction field technique can yield the equivalent results. But, the latter shows a considerable reduction in the computer time required. It should be pointed out that for the non-isotropic systems, such as large biomolecules systems and liquid-solid

coexistence systems, the application of reaction field method should be careful. Sometimes, the application becomes complicated or impossible.<sup>3</sup>

## 2. Molecular dynamics simulations<sup>2</sup>

Molecular dynamics (MD) simulations are based on Newton's equation of motion, which is given by,

$$-\frac{dV}{dr_i} = m_i \frac{d^2 r_i}{dt^2}, \quad (3)$$

where  $V$  is the potential energy of the system,  $m_i$  is the mass of particle  $i$ , and  $r_i$  is the coordinate of particle  $i$ . The equation of motion can relate the potential energy to the changes in position of particles as a function of time. Integration of the equations of motion then yields a trajectory that describes the positions and velocities of the particles as they vary with time. From the trajectory, the average values of properties can be determined based on the statistical mechanics. In addition, Brownian dynamics (BD) and dissipative particles dynamics (DPD) actually are the MD with the temperature control by Langevin thermostat and DPD thermostat, respectively.

The interacting potential of a system can be described by a serial of force field functions and parameters. There are many types of force fields such as AMBER, CHARMM, OPLS, and Dreiding. Different force fields have different force field function and parameter sets. The force field functions and parameter sets are derived from both experimental work and/or high-level quantum mechanical calculations. Different force fields can be derived from dissimilar types of experimental data, such as enthalpy of vaporization (OPLS), enthalpy of sublimation, dipole moments, or various spectroscopic parameters. Especially, Dreiding uses general force constants and geometry parameters based on simple hybridization considerations, rather than individual force constants and geometric parameters that depend on the particular combinations of atoms involved in the bond, angle, or torsion terms. Also, different force fields are designed for different purposes. For example, AMBER is designed for organic molecules such as organic ligands, nucleic acids, and proteins; CHARMM is widely used for both small molecules and macromolecules; GROMOS has been developed for the study of the aqueous or apolar solutions of proteins, nucleotides and sugars and the isolated molecules in a gas phase. Generally speaking, one chooses a suitable force field in dependence of the applicable scope of the force field. There is a detailed description of these force fields on Wikipedia ([http://en.wikipedia.org/wiki/Force\\_field\\_\(chemistry\)](http://en.wikipedia.org/wiki/Force_field_(chemistry))).

There are about four steps when we perform MD simulations: construction of models (including the number of particles in the system, their interactions, their positions and velocities, etc.), relaxations (including the energy minimization, a long time for equilibrium state, etc.), collecting data, and analysis of your data such as RDF, velocity correlation. There are many methods to generate an initial configuration that the authors needed. Different authors may adopt the different methods. At beginning of the simulations, in general, one needs do the energy minimization firstly. This depends on the initial configuration of the system. To check whether the system reaches an equilibrium state or a steady state, the easiest property of the simulated system to follow is energy conservation if one does not use a thermostat. There are other properties that should be preserved as well such as the average volume in variable cell, the average pressure, the individual forces for a given, identical conformation, the distribution of forces over time, radial distribution functions, and velocity auto-correlation functions. The above properties can be used to judge the correctness of your performances. For the estimation of simulation length, one can track the  $R_g$  of target

molecules, or calculate the time correlation, etc. The correctness of simulation results can be checked through comparing with experimental data or/and the correct physical intuitions.

### 3. Discussion of pKa, sizes, and shapes of some dendrimers

A molecule, or an atom group in a molecule, may lose or gain a proton as the molecule is placed in an aqueous solution. The exact probability that a molecule will be protonated or deprotonated depends on the pKa of the molecule and the pH of the solution. Half of molecules will lose protons if they are in a solution with  $\text{pH} = \text{pKa}$  ( $[\text{A}^-] / [\text{AH}] = 10^{(\text{pH} - \text{pKa})}$ ). The higher the pH value, the more likely a molecule will lose a proton. The difference of pKa will influence the charges of dendrimers at different pH values. For PAMAM dendrimers, the primary amines at the surface groups have a pKa value ranging from 9 to 11, while the tertiary amines at the interior of dendrimer have a value of 5. The pKa values lead to the buffering action of dendrimers, thereby preventing the DNA degradation within the endosomes/lysosomes. Similar to PAMAM dendrimers, PPI has acidic (pKa~5-8) internal ammonium functionalities and basic amine peripheral groups (pKa~9-11).<sup>4</sup> The evaluated pKa values (8.3-8.5) for dendritic poly(L-lysine) dendrimers were found to be significantly lower than those (9.2-9.4) for the corresponding linear poly(L-lysine)s probably due to steric effects.<sup>5</sup>

The size and shape of these dendrimers will change as their generations increase or when the pH and salt environments change. For PAMAM dendrimers, the diameter increases from 1.5 nm to 4.5 nm with the increase of generation from G0 to G4. The diameter of PPI dendrimers increases from 0.9 nm to 2.8 nm as the generation increases from G0 to G4. Generally, the dendrimers at low generations are usually flexible and open. The asphericity decreases from low to high generations. Dendrimers at higher generations usually show a more and more compact spherical structure.

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