



## The design of shape-tunable hairy vesicles



Fikret Aydin, Geetatha Uppaladadiam, Meenakshi Dutt\*

Department of Chemical and Biochemical Engineering, Rutgers The State University of New Jersey, Busch Campus, 98 Brett Road, Piscataway, NJ 08854, United States

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### ABSTRACT

Via the use of a mesoscopic simulation technique called dissipative particle dynamics, we design sterically stable biocompatible vehicles through the self-assembly of a binary mixture composed of amphiphilic molecular species, such as PEGylated lipids, and phospholipids. We examine the factors controlling the shape of the hairy vesicle, and report the shape to change with molecular stiffness, and dissimilarity in the hydrocarbon tail groups, along with the relative concentration of the species, and the functional group length. We also draw correspondence with experimental studies on the shape transformations of the hairy vesicles through phase diagrams of the reduced volume, the ratio of the minimum and maximum radii, and the interfacial line tension, as a function of the concentration of the hairy lipids and the hydrocarbon tail molecular chain stiffness. Results from our investigations can be used for the design and prediction of novel hybrid soft materials for applications in the encapsulation and delivery of therapeutic agents.

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### 1. Introduction

The plasma membranes of eukaryotic cells have been shown to protect the proteins and the lipid molecules in the non-cytosolic monolayer from the external environment by a coat of carbohydrate molecules. In addition, these molecules have been known to promote cell recognition, communication and adhesion processes which include sperm–egg interactions, blood clotting, lymphocyte recirculation and inflammatory responses. The carbohydrate chains on the surface of cells can inspire the design of biocompatible therapeutic agent carriers with longer circulation times and targeted delivery [1–5]. Our goal is to design interfacially stable delivery vehicles with shapes conducive for unhindered passage through the circulation system and efficient internalization by desired cell populations.

Earlier investigations [1–5] have demonstrated liposomes composed of end-functionalized lipids to have extended circulation due to enhanced stability promoted by its steric hindrance. A common route to designing sterically stable liposomes is via the grafting of polyethylene glycol (PEG) chains to the lipid head groups [6–8]. PEG chains have been shown to control the size [8–10], morphology [10–12], compressibility [9,13], encapsulation efficiency [8,14,15] and permeability of liposomes [8,14]. Experimental and

computational studies have investigated the morphology of binary mixtures of PEGylated and non-PEGylated lipids [10,11,13,16]; and their dynamics and stability [6,11,13], for species composed of the same hydrocarbon tail groups [8,10,14,17,18]. We are interested in understanding the factors which can be used to control the shape of hairy vesicles composed of species with different head group area and hydrocarbon tail groups. The specific system we examine is a binary mixture of phospholipids and end-functionalized or hairy phospholipids.

We have adopted a molecular dynamics (MD)-based mesoscopic simulation technique entitled dissipative particle dynamics (DPD) [19–23] which simultaneously resolves both the molecular and continuum scales, for the investigations presented in this paper. The DPD method has been used to investigate the dynamics and morphology of self-assembly, phase separation and phase transition in lipid systems [24,25], block co-polymers [26], dense colloidal suspensions [27], polymers in dilute solution or in a melt [28], and chains in microfluidic channels [29,30]. Where as the DPD method does not capture specific physical interactions such as electrostatics, these interactions can be effectively modeled via the use of suitable soft repulsive interaction parameters. For example, the DPD simulation technique has been shown to capture the static and dynamic properties of bilayers composed of zwitterionic lipid molecules [22,24].

Via self-assembly, we design hairy vesicle composed of hairy and non-hairy phospholipids, and examine the role of the relative concentration, molecular chain stiffness, and dissimilarity in the

\* Corresponding author. Tel.: +1 848 445 5612.

E-mail address: [meenakshi.dutt@rutgers.edu](mailto:meenakshi.dutt@rutgers.edu) (M. Dutt).

hydrocarbon tail groups of the species, and the hair length on the shape of the vesicle. Our results can be used to design novel effective drug delivery vehicles.

## 2. Materials and methods

DPD is a mesoscopic simulation technique that uses soft-sphere coarse-grained models to capture both the molecular details of the nanoscopic building blocks and their supramolecular organization while simultaneously resolving the hydrodynamics of the system over extended time scales [19,23,31]. In order to capture the dynamics of the soft spheres, the DPD technique integrates Newton's equation of motion via the use of similar numerical integrators used in other deterministic particle-based simulation methods [23,32]. The force acting on a soft sphere  $i$  due to its interactions with a neighboring soft sphere  $j$  ( $j \neq i$ ) has three components: a conservative force, a dissipative force and a random force, which operate within a certain cut-off distance  $r_c$  from the reference particle  $i$ . These forces are pairwise additive and yield the total force acting on particle  $i$ , which is given by  $\mathbf{F}_i = \sum_{j \neq i} \mathbf{F}_{c,ij} + \mathbf{F}_{d,ij} + \mathbf{F}_{r,ij}$ . The soft spheres interact via a soft-repulsive force ( $\mathbf{F}_{c,ij} = a_{ij}(1 - r_{ij}/r_c)\hat{\mathbf{r}}_{ij}$ , for  $r_{ij} < r_c$  and  $\mathbf{F}_{c,ij} = 0$ , for  $r_{ij} \geq r_c$ ), a dissipative force ( $\mathbf{F}_{d,ij} = -\gamma\omega^d(r_{ij})(\hat{\mathbf{r}}_{ij} \cdot \mathbf{v}_{ij})\hat{\mathbf{r}}_{ij}$ ) and a random force ( $\mathbf{F}_{r,ij} = -\sigma\omega^r(r_{ij})\theta_{ij}\hat{\mathbf{r}}_{ij}$ ), where  $\omega^d(r) = [w^r(r)]^2 = (1 - r)^2$  (for  $r < 1$ ),  $\omega^d(r) = [w^r(r)]^2 = 0$  (for  $r \geq 1$ ) and  $\sigma^2 = 2\gamma k_B T$ .  $a_{ij}$  is the maximum repulsion between spheres  $i$  and  $j$ ,  $\mathbf{v}_{ij} = \mathbf{v}_i - \mathbf{v}_j$  is the relative velocity of the two spheres,  $\mathbf{r}_{ij} = \mathbf{r}_i - \mathbf{r}_j$ ,  $r_{ij} = |\mathbf{r}_i - \mathbf{r}_j|$ ,  $\hat{\mathbf{r}}_{ij} = \mathbf{r}_{ij}/r_{ij}$ ,  $r = r_{ij}/r_c$ ,  $\gamma$  is the viscosity related parameter used in the simulations,  $\sigma$  is the noise amplitude,  $\theta_{ij}(t)$  is a randomly fluctuating variable from Gaussian statistics,  $\omega^d$  and  $\omega^r$  are the separation dependent weight functions which become zero at distances greater than or equal to the cutoff distance  $r_c$ . Since the local linear and angular momentum is conserved by all of these three forces, even the small systems exhibit hydrodynamic behavior [23]. The constraints imposed on the random and dissipative forces by certain relations ensure that the statistical mechanics of the system conforms to the canonical ensemble [23,32]. The relation between the pair repulsion parameter  $a_{ij}$  and the Flory interaction parameter  $\chi$  for a bead number density  $\rho = 3r_c^{-3}$  is given by  $\chi = (0.286 \pm 0.002)(a_{ij} - a_{ii})$  [23]. Groot et al. [23] have provided a detailed explanation on the relationship between the Flory's  $\chi$  parameter and the DPD interaction parameters.

As shown in Fig. 1(a), the individual phospholipid molecules are represented by bead-spring models, and are modeled by a head group comprised of three hydrophilic beads and two hydrocarbon tails represented by three hydrophobic beads each. The hairy lipids, as shown in Fig. 1(b) and (c), encompass an identical architecture for the phospholipid, with hydrophilic tethers grafted to one of the hydrophilic head beads. The hairs or tethers are modeled by three and six hydrophilic beads. Two consecutive beads in a chain are connected via a bond that is described by the harmonic spring potential  $E_{\text{bond}} = K_{\text{bond}}((r - b)/r_c)^2$ , where  $K_{\text{bond}}$  is the bond constant and  $b$  is the equilibrium bond length. The constants,  $K_{\text{bond}}$  and  $b$  are assigned values of  $64\epsilon$  and  $0.5r_c$ , respectively [19,20]. The three-body stiffness potential along the lipid tails has the form  $E_{\text{angle}} = K_{\text{angle}}(1 + \cos\theta)$  where  $\theta$  is the angle formed by three adjacent beads. The coefficient  $K_{\text{angle}}$  is set to be  $20\epsilon$  in our simulations. The three-body stiffness term increases the stability and bending rigidity of the bilayers. Similar bond and angle potential functional forms and parameters are used for the tethers.

In this paper, we design shape-tunable hairy vesicles encompassing phospholipids and hairy lipids through variation in the relative concentrations of each species and tether lengths. Experimental examples of the tethers are polyethylene glycol chains with degrees of polymerization  $n$  given by 6 and 12. We examine the role

of the relative concentration, molecular stiffness and the effective dissimilarity of the hydrocarbon chains of the phospholipid species, along with the tether length, on the shape of the hairy vesicle.

The soft repulsive pair potential parameters for the lipid molecule head and tail beads were selected to capture its amphiphilic nature. In addition, the tether beads are considered to be hydrophilic in nature. The interaction parameters between the like components,  $a_{ij}$ , are based on the property of water [23]. The repulsion parameter between two beads of the same type is set at  $a_{ii} = 25$  (measured in units of  $k_B T/r_c$ ) which is based upon the compressibility of water at room temperature [23] for a bead density of  $\rho = 3r_c^{-3}$ . The soft repulsive interaction parameter  $a_{ij}$  between hydrophobic and hydrophilic beads is set at  $a_{ij} = 100k_B T/r_c$ , and is determined by using the Flory–Huggins interaction parameters,  $\chi$ , as  $a_{ij} = a_{ii} + 3.496\chi$ , for  $\rho = 3r_c^{-3}$  [23].

The soft repulsive interaction parameters between the tethers ( $T$ ), head ( $h$ ), and tail ( $t$ ) beads of lipid types 1 and 2, and the solvent ( $s$ ) beads are assigned the following values (in units of  $k_B T/r_c$ ):  $a_{ss} = 25$ ,  $a_{TT} = 25$ ,  $a_{Ts} = 25$ ,  $a_{h1h1} = 25$ ,  $a_{t1t1} = 25$ ,  $a_{h2h2} = 25$ ,  $a_{t2t2} = 25$ ,  $a_{h1t1} = 100$ ,  $a_{h1s} = 25$ ,  $a_{t1s} = 100$ ,  $a_{h2t2} = 100$ ,  $a_{h2s} = 25$ ,  $a_{t2s} = 100$ ,  $a_{h1T} = 25$ ,  $a_{t1T} = 100$ ,  $a_{h2T} = 25$ ,  $a_{t2T} = 100$ ,  $a_{h1t2} = 100$ ,  $a_{h2t1} = 100$  and  $a_{h1h2} = 25$ . The values of the inter-specie tail–tail soft repulsive interaction parameter  $a_{t1t2}$  will span values ranging from 31 to 50, to mimic mixtures of amphiphilic species with different tail group properties. These parameters are selected to model the effective distinct chemistry of the molecular species, thereby capturing the differences in the melting temperature of the individual species [21,22,33].

In our simulations, the respective characteristic length and energy scale are  $r_c$  and  $k_B T$ . As a result, our characteristic time scale can be described as  $\tau = \sqrt{mr_c^2/k_B T}$ . Finally,  $\sigma = 3$  and  $\Delta t = 0.02\tau$  are used in the simulations along with the total bead number density of  $\rho = 3r_c^{-3}$  and a dimensionless value of  $r_c = 1$  [20]. The mass of all the beads is set to unity [19,20,22–24,31].

We draw a correspondence between our model and physical systems via the experimental properties of biological lipid bilayers [31]. The characteristic length scale is  $r_c = 0.76$  nm, and is obtained through the comparison of experimental measurements of the interfacial area per lipid of a DPPC bilayer with similar measurements from our simulations. The time scale  $\tau$  was calculated to be 6.0 ns by comparing the experimental measurement of the diffusion coefficient of DPPC bilayer, which is given by  $5 \times 10^{-12}$  m<sup>2</sup>/s [20], with that obtained from the simulations. Using a temperature of 50 °C, the energy scale is calculated to be  $\epsilon = k_B T = 4.5 \times 10^{-21}$  J.

## 3. Results and discussion

### 3.1. Self-assembly of hairy vesicle

We design the hairy vesicles via self-assembly of the hairy and non-hairy amphiphilic species in a hydrophilic solvent. For the initial setup, a 9:1 mixture of phospholipids and short tether hairy lipids are randomly positioned in a simulation box of dimensions  $30r_c \times 30r_c \times 30r_c$ , along with the solvent beads. The simulation box has periodic boundaries along the three axes, and a 5.6% bead concentration of amphiphilic species. The unfavorable enthalpic interactions between the hydrophobic and hydrophilic species drives the self-assembly of the two species to form a stable hairy vesicle, as shown in Fig. 1. The simulations are run for a time interval of  $60,000\tau$ . In the early times of the aggregation process, the amphiphilic molecules diffuse in the solvent, collide and coalesce to form small size clusters. At later times, the self-assembly process proceeds via the diffusion, collision and coalescence of the small clusters to form medium to large clusters. We examine the role of the tether length and the relative concentrations of the two

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