Bending models of lipid bilayer membranes: Spontaneous curvature and area-difference elasticity

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Abstract

We present a computational study of bending models for the curvature elasticity of lipid bilayer membranes that are relevant for simulations of vesicles and red blood cells. We compute bending energy and forces on triangulated meshes and evaluate and extend four well established schemes for their approximation: Kantor and Nelson (1987), Jülicher (1996), Gompper and Kroll (1996) and Meyer et al. (2003), termed A, B, C, D. We present a comparative study of these four schemes on the minimal bending model and propose extensions for schemes B, C and D. These extensions incorporate the reference state and non-local energy to account for the spontaneous curvature, bilayer coupling, and area-difference elasticity models. Our results indicate that the proposed extensions enhance the schemes to account for shape transformation including budding/vesiculation as well as for non-axisymmetric shapes. We find that the extended scheme B is superior to the rest in terms of accuracy, and robustness as well as simplicity of implementation. We demonstrate the capabilities of this scheme on several benchmark problems including the budding-vesiculating process and the reproduction of the phase diagram of vesicles.

MSC: 74S30; 53Z05

Keywords: Area-difference elasticity; Bending force; Lipid bilayer; Red blood cell; Triangulated mesh; Vesicle

1. Introduction

Lipid bilayers are fundamental structural elements in biology. Vesicles are compartments enclosed by lipid bilayer membranes and they have been studied extensively over the last four decades [1–4]. Notably vesicles have been the subject of investigations that were awarded the 2013 Nobel prize in the physiology or medicine (James Rothman, Randy Schekman and Thomas Südhof). A vesicle has a relatively simple structure when compared to other entities at cellular level and they have been the subject of several detailed theoretical [5–12] and experimental studies [13,14]. Models of vesicles are readily transferable to more complex structures, as lipid bilayer membranes enclose most cells and their nuclei as well as many viruses. Importantly, a lipid bilayer and a spectrin network constitute a red blood cell (RBC) membrane [15,16].

Lipid membranes are a few nanometers thin, but they span surfaces that are in the order of micrometers. The bending elasticity of the quasi two-dimensional structures is caused by relative extension/compression of outer/inner
surface, which can be expressed as a function of the membrane curvature [2–4]. Canham proposed the first form of membrane bending energy, that depends quadratically on the two principal curvatures of the surface [5]. This representation, along with constraints on total area and volume, constitutes the minimal model for a vesicle. Helfrich formulated a bending energy that includes a Gaussian curvature as well as a "spontaneous" curvature $2H_0$ [6] that is attributed to chemical differences in two lipid layers. This is the spontaneous curvature (SC) model and by setting $H_0 = 0$, it is equivalent to the minimal model. In turn, Sheetz & Singer [7] and Evans [8] accounted for the density difference of the two lipid layers. Their work led to the bilayer couple (BC) model [9] that introduces a constraint on the area difference so that $\Delta A = \Delta A_0$, where $\Delta A$ and $\Delta A_0$ are the instantaneous and targeted area differences between the two lipid layers. A few years later three groups [10–12] proposed that the non-local bending energy has a quadratic form $(\Delta A - \Delta A_0)^2$. Here $\Delta A_0$ reflects reference of the area difference between the two layers. This is area-difference elasticity (ADE) model, which degenerates to the minimal, SC or BC model as a special case. The ADE model has been validated experimentally on vesicles [17,18].

Despite the well established formulation of these membrane models, simulations of vesicles and red-blood cells remain a challenging task. The key difficulty lies in the evaluation of the resulting forces. The bending force depends on the Laplace–Beltrami operator $\nabla^2 s$ on the mean curvature, which further relates to $\nabla^2 s$ of the coordinates on a surface. Hence, the evaluation of the bending force requires approximations of the fourth derivatives of the surface coordinates. A recent review showcased how computation of the bending energy and especially the force remain elusive, even for the minimal model [19]. These computations have similar difficulties as those met when calculating Willmore flow in differential geometry [3,19], which are of particular interest to the computer graphics community [20].

One approach has focused on axi-symmetric shapes that reduces the calculations to solving Ordinary Differential Equations (ODEs) [1,4,21,22]. Recent works have employed either spherical harmonic expansions/quadratic approximation to represent the surface [23–26] or phase field [27] models. We note in particular level set methods for the description of the membrane surface [28–30] thus allowing for volume based calculations of the membrane dynamics and large deformations even with topological changes.

In this work, we represent the surface as a triangulated mesh, which has been used extensively to model vesicle and RBC membranes and they have been coupled to fluid solvers [31–36]. However, the majority of vesicle and RBC simulations have employed only the minimal model. Exceptions are Monte Carlo simulations from groups of Seifert [37] and Wortis [38] and the finite element method from Barrett et al. [39]. We examine and extend four established schemes for the discretization of the general bending model on a triangulated mesh [40–43]. We perform a number of benchmark problems to compare their accuracy, robustness and stability.

The paper is structured as follows: we describe energy functionals of the minimal, SC, BC and ADE models in Section 2 and present an expression for the force density. In Section 3, we present the four discretization schemes (A, B, C, D) which have been previously applied to the minimal model [40–43]. We extend schemes B, C, D to incorporate the spontaneous curvature and non-local bending energy thus accessing the SC, and BC/ADE models. The details of the derivations on Sections 2 and 3 can be found in Appendices A–G. In Section 4.1, we evaluate the proposed schemes on shapes with known analytical expressions for the energy and force. In Section 4.2 we compute the phase diagrams for oblate–stomatocyte, oblate–discocyte, prolate–dumbbell, prolate–cigar shapes described by the minimal model with the four discretization schemes, from different initial shapes such as prolate, oblate and sphere. Thereafter, we generate slices of phase diagrams of SC, BC and ADE models. We compare our results with solutions obtained by axi-symmetric ODEs, spherical harmonic as well as results from the program “Surface Evolver” and experiments. In Section 4.4 we present results from dynamic simulations. We summarize our findings in Section 5.

2. Continuous energy and force

2.1. Energy functionals

The primary model for the two-dimensional membrane elasticity is based on an extension of one dimensional beam theory by Canham [5] with an energy functional:

$$E^C = \frac{k_h}{2} \int (C_1^2 + C_2^2) dA,$$

(1)
where $\kappa_b$ is the bending elastic constant, $C_1$ and $C_2$ are the two principal curvatures\(^1\) and the integral is taken over a two-dimensional parametric surface embedded in three-dimensional space.

The *Canham energy functional* is scale-invariant, with smaller vesicles corresponding to larger curvatures. This energy functional is known as the *minimal model* of a vesicle membrane. Its phase diagram is determined by the reduced volume between a vesicle and a sphere $v = 3V/(4\pi R^3)$, with the same area and $R$ is the sphere’s radius.

A few years later, inspired by research in liquid crystals, Helfrich [6] developed an alternative free energy functional for lipid bilayers

$$E^H = 2\kappa_b \int (H - H_0)^2 dA + \kappa_g \int GdA,$$

(2)

where $H = (C_1 + C_2)/2$ is the mean curvature and $2H_0$ is the *spontaneous curvature*, reflecting the asymmetry in the chemical potential on the two sides of the lipid bilayer. $G = C_1C_2$ is the Gaussian curvature, and $\kappa_g$ is a bending elastic constant. According to Gauss–Bonnet theorem $\int GdA = 4\pi (1 - g)$, where $g$ is the genus of the surface. For the spherical topologies considered here, $g = 0$ and the energy term $\kappa_g \int GdA$ is omitted. The remaining term in Eq. (2) constitutes the *spontaneous curvature* (SC) model [6]. We note that for $H_0 = 0$, Eq. (1) has the same dynamics as that of Eq. (2). The Helfrich energy with $H_0 = 0$ is also scale-invariant. However, a non-zero $H_0$ introduces a length scale and we define $h_0 = H_0/R$.

It is important to remark that most simulations of vesicles or RBCs [34–36] use $H_0 = 0$, thus assuming no chemical differences between the two sides of the lipid bilayer. However it has been noted [2] that such an assumption lacks a physical realization. We denote the energy due to spontaneous curvature as

$$E^S = E^H - E^H_{H_0=0} = 2\kappa_b \int H_0^2 dA - 2\kappa_b \int H H_0 dA.$$

(3)

The first term resembles surface tension energy encountered in models of multiphase flow [44] with $2\kappa_b H_0^2$ being a “surface tension” constant.\(^2\)

In the early 90s, three groups [10–12] proposed an additional term to the energy functional that reflects the area difference between the outer and inner leaflets of the lipid membrane. This non-local term is *area-difference elasticity* (ADE) and it is expressed as:

$$E^{AD} = \frac{\alpha \kappa_b \pi}{2AD^2} (\Delta A - \Delta A_0)^2.$$

(4)

Here $\alpha\kappa_b$ is a bending elastic constant due to area difference and $D$ is the thickness of the bilayer. The ratio $\alpha$ is in the order of unity [10,11,22,38,45] and depends on the properties of the lipid.

In summary, the Helfrich model extended by the ADE terms, is the so called *ADE model* [2] that can be expressed as:

$$E = E^H + E^{AD} = 2\kappa_b \int (H - H_0)^2 dA + \frac{\alpha \kappa_b \pi}{2AD^2} (\Delta A - \Delta A_0)^2.$$

(5)

Setting $H_0 = 0$ in the ADE model and constrain $\Delta A = \Delta A_0$ we obtain the *bilayer-couple (BC) model* [9] that includes the area difference as a constraint. We simplify the formulation by introducing the zero, first and second moments of the mean curvature $H$

$$\mathcal{M}_0 = A = \int dA, \quad \mathcal{M}_1 = \int H dA, \quad \mathcal{M}_2 = \int H^2 dA.$$

(6)

We rewrite the total energy as

$$E = 2\kappa_b \mathcal{M}_2 + \frac{2\alpha \kappa_b \pi}{A} \mathcal{M}_1^2 - 4\kappa_b H_0 \mathcal{M}_1 - \frac{2\alpha \kappa_b \pi}{A} \frac{\Delta A_0}{D} \mathcal{M}_1 + 2\kappa_b H_0^2 A + \frac{\alpha \kappa_b \pi}{2A} \left( \frac{\Delta A_0}{D} \right)^2. \quad (7)$$

Here the “

\[\]"

indicates that the terms originate from either $E^H$ or $E^{AD}$, and we have used the expression $\Delta A = 2D\mathcal{M}_1$.

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\(^1\) We take a convention that $C_1$ and $C_2$ are positive for a sphere. With this convention, the surface unit normal vector points inwards.

\(^2\) Ideally, a lipid membrane is incompressible and the total area $A = \int dA$ of the neutral surface is constant. However, numerically we treat the constraint on area as penalization and therefore, we also consider the energies and forces due to total area arising from SC and ADE models.
2.2. Force from calculus of variation

We use the energy functional and the calculus of variations to derive (details are shown in Appendix A) the force magnitude corresponding to each moment as

\[ F_0 = 2H, \quad F_1 = G, \quad F_2 = -2H(H^2 - G) - \nabla_s^2 H. \]  

(8)

Here \( \nabla_s \) is the surface gradient operator and \( \nabla_s^2 = \nabla_s \cdot \nabla_s \) is the Laplace–Beltrami operator.

We use the above expressions to write the magnitude of force density acting along the normal \( n \) as

\[
\begin{align*}
 f^H &= 2\kappa_b F_2 + \frac{4\alpha\kappa_b\pi}{A} M_1 F_1 - \frac{2\alpha\kappa_b\pi}{A^2} M_1^2 F_0 - \frac{4\kappa_b H_0 F_1}{f^H} \\
 f^{AD} &= -\frac{2\alpha\kappa_b\pi}{A} \frac{\Delta A_0}{D} F_1 + \frac{2\alpha\kappa_b\pi}{A^2} \frac{\Delta A_0}{D} M_1 F_0 + \frac{2\kappa_b H_0^2 F_0}{f^H} - \frac{\alpha\kappa_b\pi}{2A^2} \left( \frac{\Delta A_0}{D} \right)^2 F_0.
\end{align*}
\]

(9)

These terms can be rearranged to show the components of the force density corresponding to the energy functionals as

\[
\begin{align*}
 f^H &= -2\kappa_b \left[ 2(H - H_0)(H^2 + H_0 H - G) + \nabla_s^2 H \right], \\
 f^{AD} &= \alpha\kappa_b\pi \left[ 2M_1 - \frac{\Delta A_0}{D} \right] \frac{2G}{A} - \left( 2M_1 - \frac{\Delta A_0}{D} \right)^2 \frac{H}{A^2}. \quad \tag{10}
\end{align*}
\]

3. Discretization schemes

We represent the membrane as a triangulated mesh and use the following notation (see Fig. 1):

- \( i, j, k, l \) are indices for vertices
- \( e : (i, j) \) is index for the edge connecting vertices \( i \) and \( j \).
- \( t : (i, j, k) \) is index for the triangle connecting vertices \( i, j \), and \( k \).
- \( \theta_e \) is the angle between the normal vectors of two triangles sharing edge \( e \).
- \( \phi_k, \phi_l \) are angles associated with vertices \( k \) and \( l \). \( \phi_k \) is the angle associated with vertex \( k \) within triangle \( t : (i, j, k) \).
- \( N_v, N_e, N_t \) are the numbers of vertices, edges and triangles.
The total energy is

\[ E = E^H + E^{AD} = 2\kappa_b \sum_i (H_i - H_0)^2 A_i + \frac{\alpha \kappa_b \pi}{2AD} \left( 2D \sum_i H_i A_i - \Delta A_0 \right)^2. \]  

(11)

where \( \Delta A = 2D \sum_i H_i A_i \) is the area difference. We note that the summation of total energy runs over each vertex. Following this convention, we may define energy for each vertex \( E_i \) as \( E_i \), and its density as \( \frac{E_i}{A_i} \). For example, \( E_i = 2\kappa_b H_i^2 \) for vertex \( i \) in the minimal model. Similar discrete definitions of \( E_i \) apply to SC and ADE models.

We introduce the discrete moments as

\[ M_0 = A = \sum_i A_i, \quad M_1 = \sum_i H_i A_i, \quad M_2 = \sum_i H_i^2 A_i. \]

(12)

so that the total energy becomes

\[ E = 2\kappa_b M_2 + \frac{2\alpha \kappa_b \pi}{A} M_1^2 - \frac{2\pi \alpha \kappa_b \Delta a'_0}{D} M_1 + 2\kappa_b H_0^2 A \frac{\Delta A_0}{2A} + \frac{\alpha \kappa_b \pi}{2A} \left( \frac{\Delta A_0}{D} \right)^2, \]

(13)

where \( \Delta a'_0 = \frac{2D H_0}{\alpha} + \frac{\Delta A_0}{A} \) is non-dimensional.

It is apparent that \( H_0 \) from Helfrich energy and \( \Delta A_0 \) from ADE energy may compensate each other’s mechanic effects, although the origins of the two are different. Therefore, we take their combined effect represented by \( \Delta a'_0 \) [24,38]. We assume \( H_0 = 0 \) and \( \Delta a'_0 = \frac{\Delta A_0}{A} \) in the ADE model so that the resultant \( \Delta A \) from a simulation of the ADE model can be non-dimensionalized as \( \Delta a' = \Delta A/A \). Therefore, for a given area \( A \), we have three parameters \( v, \alpha, \) and \( \Delta a'_0 \). Other work have adopted \( \Delta a_0 = \Delta A_0/(4\pi RD) \) and \( \Delta a = \Delta A/(4\pi RD) \) to non-dimensionalize the area differences, where the denominator corresponds to the area difference of a sphere [21,46]. This approach has the advantage of eliminating the membrane thickness \( D \). To compare with different references, we keep both means of non-dimensionalization and they are related as \( \Delta a = \Delta a'R/D \) and \( \Delta a_0 = \Delta a'_0R/D \).

We consider four discretization schemes which have been applied to the minimal model in the past. Note that scheme A defines the energy without defining \( H_i \) and \( A_i \). In turn, for schemes B, C, and D, there are explicit definitions of \( H_i \) and \( A_i \). In the present work we extend these three schemes to account for all energy terms in Eq. (13) and their corresponding forces.

### 3.1. Discrete force

For schemes A, B, and C, the force at a vertex \( x_m \) is

\[ F_m = -\frac{\partial E}{\partial x_m}. \]

(14)

We may convert between force and force density associated with each vertex as

\[ f_m = F_m/A_m, \quad F_m = f_mA_m, \]

(15)

where \( A_m \) is the area associated with vertex \( m \). The former is used by scheme A, B, and C, to convert force to force density for comparison with calculus of variation in Section 2.2. For scheme D, the force density is computed directly and converted to force to use in the energy minimization process. A summary of the discretization schemes is shown in Table 1 and we elaborate each scheme in the following.

### 3.2. Scheme A

This scheme was invented by Kantor & Nelson [40] to simulate planar polymeric network in Monge form. This model was later broadly adopted to model generally curved membranes, in particular for red blood cells.

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3 We do not differentiate continuous and discrete symbols if they are clear from the context.
The energy depends on each angle $\theta_e$ formed by the normal vectors of two triangles, which share the same edge $e: (i, j)$ (Fig. 1(a)). The total energy is

$$E = 2\tilde{k}_b \sum_{e: (i, j)}^{N_e} \left[ 1 - \cos (\theta_e - \theta_0) \right],$$

where $\tilde{k}_b$ is the bending modulus. We split the local energy evenly onto the four vertices $i, j, k, l$, has marginal differences. There is no difference on the force between the two ways of splitting. $\theta_0$ is the spontaneous angle, that is, for $\theta_e \equiv \theta_0$, $E \equiv 0$. If $\theta_e - \theta_0 \approx 0$, by Taylor expansion $\cos(\theta_e - \theta_0) \approx 1 - (\theta_e - \theta_0)^2/2$. Therefore, the approximation of the energy reads [50]

$$E^{1st} = \tilde{k}_b \sum_{e: (i, j)}^{N_e} (\theta_e - \theta_0)^2.$$  (17)

A few notes are in order; for a triangulated cylinder surface, $\tilde{k}_b = \sqrt{5}k_b/3$ was derived [51] while for a triangulated sphere surface, $\tilde{k}_b = \sqrt{5}k_b/2$ was obtained [42]. Based on these results, it was also noted that $\tilde{k}_b$ and $k_b$ have no general relation for other shapes [42]. Following Cauchy–Born assumption, a recent work obtained a continuous limit of energy for scheme A as $2\sqrt{3}\tilde{k}_b/3 \int (3H^2 - 2G) dA$, which is supposed to be universal for an arbitrary shape [52]. With $\tilde{k}_b = \sqrt{3}k_b/3$, the limit of total energy from scheme A is $2\tilde{k}_b \int (H^2 - 2G/3) dA$ [52]. We shall adopt this latest limit to validate scheme A. According to this limit scheme A has the same dynamics as the minimal model, as the integral of Gaussian curvature is constant for a fixed topology.

In general, there is no correspondence between $\theta_0$ and $H_0$. Furthermore, there is no definition of $H_i$ or $A_i$ in this scheme. Therefore, it is ambiguous to extend it to include SC and ADE. We will consider scheme A in its original form without $\theta_0$ and also consider its approximation. The expression for the discrete force is given in Appendix B and the only primitive derivative to compute is $\frac{\partial \theta_e}{\partial \kappa_{im}}$.

3.3. Scheme B

This scheme was proposed by Jülicher [41,53] to calculate bending energy of a vesicle with topological genus more than zero. To motivate the scheme we consider two triangles parallel to the original two neighboring triangles as sketched on Fig. 2. Each parallel triangle is separated from its counterpart with $h$ distance in the normal direction. The shared edge $e_{ij}$ of the two triangles and the two neighboring edges of the imaginary triangles form a fraction of a cylinder, as indicated on Fig. 2. We define the first moment of mean curvature on the fraction of the cylinder as

$$\mathcal{M}_i^e = \frac{1}{2} \left( 0 + \frac{1}{h^2} \right) h\theta_i l_e = \frac{1}{2} l_e \theta_e.$$  (18)

The two principal curvatures of the cylinder are 0 and $1/h$. The surface area for the fraction of the cylinder is $h\theta_i l_e$, where $l_e$ is the length of the edge $e_{ij}$ and $\cos \theta_e = n_i \cdot n_j$ as indicated on Fig. 1(a). We note that $\mathcal{M}_i^e$ does not depend on $h$ and has a proper limit as $h \to 0$. On the contrary, if we had defined local mean curvature or second...
moment of mean curvature directly instead, they would both behave singular as $1/h$. The total first moment of mean curvature reads

$$\mathcal{M}_1 = \frac{1}{2} \sum_{e:\langle i,j \rangle} l_e \theta_e.$$  \hfill (19)

For the local first moment associated with a vertex instead of edge we have

$$\mathcal{M}_1 = \sum_i N_i \mathcal{M}_i^l = \frac{1}{4} \sum_i l_e \theta_e,$$  \hfill (20)

where the prefactor is $1/4$ to account for the total summation. For each vertex $i$, we have relation $\mathcal{M}_i^l = H_i A_i$. This leads to a definition of $H_i$ as

$$H_i = \frac{1}{4A_i} \sum_{e:\langle i,j \rangle} l_e \theta_e,$$  \hfill (21)

where summation runs over all $N_i^e$ neighboring edges around vertex $i$. The local area associated with vertex $i$ is based on the barycentric centers of the surrounding triangles as sketched on Fig. 3(a) and it reads

$$A_i = \frac{1}{3} \sum_{t:\langle i,j,k \rangle} A^t,$$  \hfill (22)

where $A^t$ is the area of a neighboring triangle $t: \langle i, j, k \rangle$. This means that each triangle $t$ splits its area evenly onto its three vertices. The summation runs over all $N_i^t$ neighboring triangles around vertex $i$.

With the definitions of local mean curvature and area in Eqs. (21) and (22), we may calculate the three moments defined in Eq. (12). The expression for the discrete force is given in Appendix C and it consists of three primitive derivatives

$$\frac{\partial l_e}{\partial x_m}, \quad \frac{\partial \theta_e}{\partial x_m}, \quad \frac{\partial A^t}{\partial x_m}.$$  \hfill (23)

3.4. Scheme C

This scheme was proposed by Gompper & Kroll [42] to simulate a triangular network of fluid vesicles and later applied to model general membranes [31]. Its discrete definition of Laplace–Beltrami operator reads [43,54,55]:

$$(- \nabla^2_i w)_i = \frac{\sum_{e:\langle i,j \rangle} (\cot \phi_k + \cot \phi_l) \left( w_j - w_i \right)}{2 A^{vor}_i},$$  \hfill (24)
where \( w \) is an arbitrary function. The Voronoi area associated to vertex \( i \) indicated on Fig. 3(b) and is defined as

\[
A_{voro}^i = \frac{1}{8} \sum_{e \ni (i,j)} (\cot \phi_k + \cot \phi_l) |x_i - x_j|^2.
\]

If we consider the discrete counterpart of an expression for mean curvature known from differential geometry, that is,

\[
H_i = \frac{1}{2} \left( \nabla_s^2 x_i \right) \cdot n_i,
\]

and take function \( w \) as the surface coordinate \( x \) in Eq. (24), we have an explicit discrete definition of \( H_i \).

However, for the general energy/force in the SC and BC/ADE models considered in this work, we need an explicit discrete definition of \( n_i \). We consider a discrete \( n_i \) [36,57,58], where the unit normal vector for vertex \( i \) is the sum of neighboring normal vectors weighted by incident angles [57,58].

\[
n_i = \frac{\sum_{t \ni (i,j,k)} \phi'_t u'_t}{|\sum_{t \ni (i,j,k)} \phi'_t u'_t|},
\]

where \( \phi'_t \) is the angle at vertex \( i \) of triangle \( t \ni (i,j,k) \), \( u'_t \) is the unit normal vector of triangle \( t \).

With the definitions of local mean curvature and area in Eqs. (26) and (25), we calculate the three moments in Eq. (12), and the total energy in Eq. (13). The expression of the force is given in Appendix D.

### 3.5. Scheme D

This scheme was derived from an effort of developing a “unified and consistent set of flexible tools to approximate important geometric attributes, including normal vectors and curvatures on arbitrary triangle meshes” [43]. It has been adopted by several groups to study the bending mechanics of the minimal model for vesicles and RBCs [34,36,59]. The definition of the discrete Laplace–Beltrami operator reads as [43],

\[
(-\nabla_s^2 w)_i = \frac{\sum_{e \ni (i,j)} (w_i - w_j)}{2A_{mix}^i},
\]

which has almost identical expression as the one from scheme C, except that the area for vertex \( i \) is calculated as a mixture of two approaches [43] (see Fig. 3(c)). If the triangle \( t \ni (i,j,k) \) is non-obtuse then local areas \( A_i, A_j, \) and \( A_k \) on three vertices take the contribution from Voronoi tessellation of \( A' \); If the triangle \( t \ni (i,j,k) \) is obtuse
Fig. 4. Helfrich energy from four discretization schemes with $\kappa_b = 1$ and $h_0 = 0$. (a) sphere; (b) biconcave–oblate. For scheme A, $\bar{\kappa}_b = \sqrt{3} \kappa_b / 3$ and due to the contribution of Gaussian curvature, its results are added $16\pi/3$. Solid squares are from the simplified scheme A with first-order approximation.

then the tessellation relies on the middle point of each edge. Therefore, the triangle $t : (i, j, k)$ contributes $A'_t/2$ to $A_i$, and $A'_t/4$ to $A_j$ and $A_k$ each [43].

The key difference of scheme D from the other three schemes is in terms of the force calculation. The force density of scheme D relies on the variational expression in Eq. (9) or (10). Once the discrete mean curvature $H_i$ is calculated at each vertex, we apply Eq. (28) second time on discrete values of $H_i$ to get $(\nabla^2 s H_i)^i$. Furthermore, only scheme D needs a discrete definition of Gaussian curvature at vertex $i$ [60]

$$G_i = \frac{1}{A'_i} \left( 2\pi - \sum_{i:(i,j,k)} \phi_i^t \right),$$

which employs all incident angles around vertex $i$ and its area definition. Therefore, each discrete force density in Eq. (8) is readily available and thereafter the total force density can also be obtained.

4. Results

We present the results of the comparative study for all four schemes and the proposed extensions. We distinguish applications on prescribed shapes and on dynamically equilibrated shapes.

4.1. Prescribed configurations: sphere and biconcave–oblate

We first examine the performance of the four schemes on the calculation of the Helfrich energy for a sphere and a biconcave–oblate described by an empirical function [61] (Appendix E) using $\kappa_b = 1$ and $h_0 = 0$. The sphere with radius $R = 1$ is approximated with an icosahedron and higher resolutions are obtained by applying Loop’s subdivision scheme [62] for triangulated meshes with $N_t = 80, 320, 1280, 5120, 20480, 81920$. The same resolutions are obtained for a biconcave–oblate by transforming the surface coordinates of the sphere to the empirical function of the biconcave shape. We present the results in Fig. 4 verifying the total energy of each scheme converges (albeit to different values!) with increasing the number of triangles. Given the curvature of a sphere being 1, the continuum limit for scheme A is $2 \kappa_b \int (1 - 2/3) dA = 8\pi - 16\pi/3$ while for scheme B, C and D is $2 \kappa_b \int dA = 8\pi$. Therefore, the results of scheme A are added $16\pi/3$ for comparison with other schemes on Fig. 4(a). Schemes B, C and D converge to the reference solution with increasing $N_t < 320$ when the angle $\theta$ between two neighboring triangles is not small.

For the biconcave–oblate configuration we compute the reference solution analytically (see Appendix E) and the continuum limit is 48.47. We find that schemes B, C, D converge to the reference solution with increasing...
Fig. 5. Total Helfrich and area-difference elasticity (ADE) energy from three discretization schemes with $\kappa_b = 1$, $h_0 = -0.5$, $\alpha = 2/\pi$ and $d = D/R = 0.001$. $E^H$: Helfrich energy; $E^{AD}$: ADE energy. (a) sphere with $\Delta a_0 = (\Delta A_0/(4\pi R D)) = -1$; (b) biconcave–oblate with $\Delta a_0 = (\Delta A_0/(4\pi R D)) = -0.698$.

number of triangles (Fig. 4(b)). According to Gauss–Bonnet theorem, the contribution from Gauss curvature in the continuum limit of scheme A is again $16\pi/3$, by which we add onto the results of scheme A to compare with other schemes. However, scheme A and its simplified version converge to a lower value ($\sim 36.97$) than the one given by the reference solution. The value of the total energy for the prescribed shapes does not depend on the details of the triangulated mesh, as long as the mesh is regular. We note that the results from the first-order approximation for scheme A deviate significantly from those of the complete scheme A for $N_t < 1280$.

Subsequently, we compute Helfrich and ADE energy with $\kappa_b = 1$, $h_0 = -0.5$ and $\alpha = 2/\pi$ for a sphere ($\Delta a_0 = -1$) and a biconcave–oblate ($\Delta a_0 = -0.698$) using scheme B, C and D, respectively. The analytical value of the Helfrich energy on the sphere is $2\kappa_b \int (1 + 0.5)^2 dA = 18\pi \approx 56.55$. The analytical value of the ADE energy on the sphere is

$$\frac{\alpha \kappa_b \pi}{2AD^2} (\Delta A - \Delta A_0)^2 = \frac{\alpha \kappa_b \pi}{2AD^2} (4\pi R D)^2 \left(\frac{2D}{4\pi R D} \int H dA - \frac{\Delta A_0}{4\pi R D}\right)^2 = 4\kappa_b \pi (2 + 1)^2 = 36\pi \approx 113.1,$$

where we have used the facts $H = 1$, $\alpha = 2/\pi$ and $\Delta a_0 = (\Delta A_0/(4\pi R D)) = -1$. For the biconcave–oblate configuration we compute the reference solution analytically with Maxima (see Appendix E), where Helfrich and ADE energy are 74.25 and 103.73, respectively. All three schemes converge with increasing the number of triangles to the reference values, as shown in Fig. 5 For low resolution $N_t < 320$, scheme B deviates much less than schemes C and D from the reference values.

Furthermore, for the biconcave–oblate configuration we plot energy density versus the radial distance from the axis of symmetry (Fig. 6). Results from scheme B, C and D with $N_t = 1280$ coincide with the reference line except a few discrepancies, which disappear with high resolution $N_t = 5120$. Scheme A and its simplified version show no difference, but deviate from the reference values for $r_{xy} \gtrsim 0.6$, which accounts for the mismatch of the total energy on Fig. 4(b). Increasing the resolution from $N_t = 1280$ to 5120 does not improve the results of scheme A or those of its simplified version. The results indicate that scheme A is not an effective discretization of the Helfrich-type energy, consistent with the findings of two recent works [34,36].

Finally, we examine the energy density for the Helfrich energy with $h_0 \neq 0$, as computed by schemes B, C and D. We present the results in Fig. 7. All three schemes capture accurately the profile of the reference line. Some outliers showing for $N_t = 1280$ also disappear for higher resolution $N_t = 5120$. Note that the ADE energy is non-local and has only one global value, which was already presented in Fig. 5.

We defer the results of force calculations for the prescribed configuration in Appendix H.
Fig. 6. Energy density versus radial distance of vertices from axis of symmetry for a biconcave–oblate with $\kappa_b = 1$ and $h_0 = 0$. For scheme A and its simplified version $\tilde{\kappa}_b = \sqrt{3}\kappa_b/3$. (a) $N_t = 1280$; (b) $N_t = 5120$ and plotted for clarity with every 16 vertices in arbitrary order. Solid lines are analytical values of $2\kappa_b H^2$ while dashed lines are analytical values of $2\kappa_b(H^2 - 2G/3)$.

Fig. 7. Energy density versus radial distance of vertices from axis for a biconcave–oblate with $\kappa_b = 1$ and $h_0 = -0.5$. (a) $N_t = 1280$; (b) $N_t = 5120$ and plotted for clarity with every 16 vertices in arbitrary order.

4.2. Numerical results on equilibrium shapes

Here we consider the equilibrium shapes of a closed membrane of area $A = 4\pi$. The energy minimization process is initialized from prescribed shapes such as a sphere, prolate and oblate ellipsoids, or from another equilibrium shape (e.g. stomatocyte) of an optimization using different parameters. The minimization process relies on the calculation of the forces corresponding to the associated energy. The energy and the force are both calculated on the triangulated mesh. We set $\kappa_b = 0.01$ and $\alpha = 2/\pi$ [24,38]. We penalize the constraints on global area with $\kappa_{ag} = 2$ (Appendix F) and volume with $\kappa_v = 1$ (Appendix G) [27,32,33,48]. We also add an in-plane viscous damping force between any two neighboring vertices connected by an edge in order to dampen the kinetic energy. To explore the energy landscape efficiently, we also add a stochastic force of white noise between any two neighboring vertices connected by an edge. The pair of viscous and stochastic forces between vertices resemble the pairwise thermostat of dissipative particle dynamics (DPD) [63], which conserves momenta and has a proper thermal equilibrium. More specific, the following expressions are adopted

$$
\mathbf{F}_{ij}^D = -\gamma (\mathbf{v}_{ij} \cdot \mathbf{\hat{r}}_{ij}) \mathbf{\hat{r}}_{ij},
$$

$$
\mathbf{F}_{ij}^R = \sigma \delta_{ij} \mathbf{\hat{r}}_{ij},
$$

(31)
where \( \gamma \) and \( \sigma \) are coefficients for the dissipative and random forces, respectively. Between two neighboring vertices, velocity difference is \( v_{ij} = v_i - v_j \) and relative position is \( r_{ij} = r_i - r_j \). Furthermore, \( \dot{r}_{ij} = r_{ij}/|r_{ij}| \) is a unit vector and \( \theta_{ij} \) is a Gaussian noise with Delta correlations in pair, space, and time [63]. In addition, the two coefficients satisfy the fluctuation–dissipation relation as \( \sigma = \sqrt{2\gamma k_B T/\Delta t} \), with \( \Delta t \) being the time step. Note that we do not employ a weight function of relative distance between particles and both types of forces act only on neighboring vertices connected directly by an edge so that they act in the plane of the triangulated surface. The time integration is performed by the explicit velocity Verlet method. For a typical minimization process with \( N_t = 1280, \gamma = 100, k_B T = 0.01, \) and \( \Delta t = 0.01 \).

As the minimization evolves, the configuration of the triangulated mesh may deteriorate, e.g., elongate in one direction or generate obtuse angles. We remedy this mesh distortion by introducing two regularization schemes: by introducing a constraint on the local area with \( \kappa_{al} = 1 \) as penalization (Appendix F) [32,33,48] or by triangle equiangulation [64], also named as T2 bond flipping [65]. We note that as we perform multiple runs from different initial shapes we may reach different local minima of the energy landscape. Thereafter, we select the smallest among all available local minima as the global minimum, that is, the ground state.

### 4.2.1. The minimal model

We first consider the minimal model described by Helfrich energy with \( h_0 = 0 \). As the equilibrium shapes are axisymmetric, the referenced computations were reduced to solving two-dimensional Euler–Lagrangian ODEs [1,21]. We aim to reproduce the known phase-diagram with configurations and energies, in particular for small reduced volumes [66]. Furthermore, as the minimal model is widely used to simulate vesicles and RBCs we examine the performance of all four schemes in this situation.

We present the phase diagram generated by scheme B on Fig. 8, which shows the normalized energy of the vesicles versus the reduced volume \( v \). Results from schemes A, C and D are quite similar to those obtained from scheme B, so in the following we only emphasize their discrepancies. We adopt the reference lines from the work of Seifert et al. [21] and denote our results with symbols. Each symbol corresponds to the energy minima as obtained from our minimization procedure.

The reference lines correspond to three types of configurations. With decreasing \( v \) in the prolate branch, the shape changes from sphere to prolate, dumbbell, and long caped cylinder. With decreasing \( v \) in the oblate branch the shape changes from a sphere to a famous biconcave—oblate shape at around \( v = 0.6 \). For \( v = 0.51 \) the oblate branch bifurcates to form two stomatocyte sub-branches. One sub-branch has constant energy for \( 0 < v < 0.66 \) while the other has energy which depends on volume.

The simulation results denoted by symbols in Fig. 8, are obtained by three initial shapes: sphere, prolate and oblate ellipsoids. The volume for the initial prolate and oblate ellipsoids are the same as that of the target \( v \). However,
the prolate and oblate branches generated in this work are different from the reference work [21]. The reference restricts the prolate branch to only prolate-like shapes and the oblate branch to oblate-like shapes. Here, we do not impose such constraint on the shape during the minimization procedure. More specific, all the squared symbols are from initial shape of prolates and they all stay on the prolate branch when reaching the local energy minimum. Similarly, all the circle symbols are from initial shapes of oblates, with the corresponding \( v \), that stay on the oblate branch for \( v \lesssim 0.75 \) and jump onto the prolate branch for \( v \gtrsim 0.75 \). This result corroborates an earlier finding [37] where the oblate branch is only locally stable for \( v \lesssim 0.75 \). For the minimization from a spherical initial shapes (up triangle symbols), the energy minima are found on the prolate branch for \( v \gtrsim 0.65 \), on the oblate branch for \( v \lesssim 0.65 \) and scatter between prolate and oblate branches for \( 0.65 \lesssim v \lesssim 0.75 \).

For the constant energy sub-branch of the stomatocyte, we cannot explore a partial \( (v \gtrsim 0.51) \) energy landscape directly. Therefore, we take two final shapes of stomatocyte, which are obtained by minimization with initial shapes of oblates. One final shape is from \( v = 0.4 \) and the other is from \( v = 0.45 \). We use these two shapes as initial shapes to run minimization procedure with targeted reduced volume \( v_r \) ranging from 0.45 to 0.66. The results started from \( v = 0.4 \) are denoted with solid down triangles while from \( v = 0.45 \) are solid diamonds.

We demonstrate the convergence of the minimization process for the calculated energies, by examining the results in \( 0.55 < v < 0.7 \), as this range contains the regime of oblate-like biconcave shapes \( (0.59 < v < 0.65) \) that is relevant for the simulations of RBCs. We present results from schemes B, C and D with two resolutions \( N_t = 1280 \) and 5120 in Fig. 9. It is apparent that scheme B is superior, as it already captures the reference values with \( N_t = 1280 \), whereas schemes C and D reproduce the same results with \( N_t = 5120 \). Moreover, the energies at delimiting points, that is, 2 for \( v = 0.59 \) and 1.83 for \( v = 0.65 \) are reproduced quite well by all three schemes. The minimal energies computed by scheme A are removed, as they are completely out of range. This should not be surprising, given its poor performance on the prescribed biconcave configuration in Section 4.1. Nevertheless, we present the equilibrium shapes by scheme A along with the other three schemes, as it is supposed to have the same dynamics as other schemes, therefore the same equilibrium shapes from energy minimizations.

We select four equilibrium configurations in the prolate-like/dumbbell/cigar regime with \( 0.65 < v < 1 \) generated by the four schemes with \( N_t = 1280 \) in Table 2. We find very small differences in the shapes obtained by the four schemes. However, in the biconcave—oblate regime for \( 0.59 < v < 0.65 \) (Table 3), shapes obtained by scheme A are different from those of the other three schemes, consistent with recent work [56]. With an oblate-like biconcave shape as initial shapes, we reproduce the same sequence of shapes by scheme A as those shown in the supplementary movie of [56]. However, the run time of [56] is too short to observe the equilibrium configurations. Moreover, the final (local) equilibrium shape by scheme A is also dependent on the initial shapes. Each shape by scheme A in Table 3 is selected as the smallest energy among steady states of three minimizations, each of which has one initial shape among sphere, prolate and oblate. The equilibrium shapes by scheme A are always prolate-like/dumbbells/cigars, which are completely different from the results in the reference study [21]. Schemes B, C, and D all produce the biconcave oblates with no distinct differences among them.
Table 2
Equilibrium shapes of the minimal model: comparison among four schemes for $0.65 < v < 1$ with $N_t = 1280$.

<table>
<thead>
<tr>
<th>$v$</th>
<th>0.67</th>
<th>0.75</th>
<th>0.85</th>
<th>0.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="image" alt="Shape A" /></td>
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<tr>
<td>C</td>
<td><img src="image" alt="Shape C" /></td>
<td><img src="image" alt="Shape C" /></td>
<td><img src="image" alt="Shape C" /></td>
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<td><img src="image" alt="Shape D" /></td>
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</tbody>
</table>

At smaller reduced volume $v < 0.59$, scheme A does not generate stomatocyte, but always ends up with vesiculations, that is, two sphere—like shapes connected via thin tubes (not shown here). Schemes B and C generate equilibrium shapes consistent with what is expected by the reference study as shown in Table 4 for two and three different resolutions. Scheme B is stable even at low resolution of $N_t = 320$, although the equilibrium shapes are not as accurate. Especially for $v = 0.25$ and 0.3, scheme B with $N_t = 320$ does not lead to the proper stomatocyte. Instead the two spheres are connected externally via a line segment, which can be seen from two orthogonal views (the first two entries in the first row of Table 4). These two shapes are caused by the under-resolved neck connecting the two spheres at this low resolution. All equilibrium shapes generated by scheme B with $N_t = 1280$ are accurately axi-symmetric stomatocyte and show virtually almost no difference from the results of $N_t = 5120$. These results are comparable to the two-dimensional contours reported in the Ref. [21]. The results of scheme C are shown in the last two rows of Table 4 for $N_t = 1280$ and 5120. Especially for the most challenging case of $v = 0.25$ considered here, scheme C leads to unphysical shapes. Even for $v \geq 0.3$, scheme C cannot separate the inner sphere from the outer sphere with a reasonable distance, due to poor resolution at the neck. The results of scheme D are very similar to those of scheme C as the minimization procedure evolves for each target $v$. However, once scheme D reaches quasi-steady state with a proper stomatocyte shape, the overall configuration oscillates and the shape becomes unstable. We tried to employ regularization and smoothing to stabilize scheme D, but we were unsuccessful. We speculate that since scheme D does not enforce the conservation of momentum or energy this may cause this instability. To the best of our knowledge, there are no reports from previous work using triangulated mesh to simulate such low volumes. The exact reason why scheme D is unstable remains obscure.
4.2.2. Spontaneous curvature model

We compute the minimal energies determined by the SC model and the corresponding equilibrium configurations. In particular, we consider two spontaneous curvature values $h_0 = 1.2$ and 1.5 so that we can compare with results of Seifert et al. [21]. The possible shapes generated by the SC model are still axi-symmetric. However, the SC model enables quite a few more configurations that are numerically challenging. These include pear-like shapes which
break the up-down symmetry, budding transition with a narrow neck connecting the neighboring compartments of the same size, budding transitions with the neighboring compartments of different sizes, vesiculation where connection between the neighboring compartments of the same size is lost. There are also discontinuous transitions for \( h_0 \neq 0 \), but the minimization procedure of exploring the energy landscape is quite similar to the case of \( h_0 = 0 \) and we do not elaborate on this procedure here.

### 4.2.3. \( h_0 = 1.2 \)

We first consider \( h_0 = 1.2 \) and present the energy diagram in Fig. 10(a) and the representative equilibrium shapes in Table 5. The references are adapted from Seifert et al. [21]. For the regime \( v < \sqrt{2}/2 \approx 0.71 \), all three schemes...
accurately capture the shapes of necklace (with two necks) at $v = 0.53$, dumbbells at $v = 0.6$ and budding at $v = 0.69$, as shown in the first three columns of Table 5. The minimum energies in this regime computed by the three schemes are also quite close to the reference line. Especially scheme B accurately reproduces the energy line with $N_t = 1280$ as shown in the left part of Fig. 10(a). For the regime $v \gg 0.75$, we expect prolate/dumbbell shapes as suggested by the reference. All three schemes B, C and D are able to get the minimum energies accurately as shown in the right part of Fig. 10(a), and to generate the expected shapes comparable to the reference (see figure 12 of Ref. [21]) as shown in the last two columns of Table 5. The most challenging regime resides in $0.71 \lesssim v \lesssim 0.75$, since there are multiple local minima and the energy diagram bifurcates. However, all three schemes are able to produce the budding, where there is only one very thin neck connecting the two compartments of different sizes. For this very extreme regime, we do not expect accurate computation on the minimum energy. However, the energies by scheme B and D are still surprisingly close to the reference, whereas the scheme C is completely off due to the poor representation of the narrow neck with only a couple of triangles.

### 4.2.4. $h_0 = 1.5$

Computations for the case of $h_0 = 1.5$ are even more challenging as, besides budding transitions, vesiculations are also expected. For the regime $v \lesssim 0.58$, all three schemes are able to generate necklaces as shown in the first two columns in Table 6 and compute minimum energy accurately as shown on the left part of Fig. 10(b). There is notable discrepancy for the equilibrium shape generated by scheme C at $v = 0.56$, as it cannot sustain the axis-symmetry due to its inability to resolve the narrow necks of the budding shapes. For the regime $0.6 \lesssim v \lesssim 0.71$, all three schemes can generate dumbbell shapes at equilibrium, for example, at $v = 0.65$. However, only scheme B can generate vesiculation of two spheres of equal size expected from the reference [21], as shown by one example of $v = 0.7$ on Table 6. Scheme C at $v = 0.7$ may generate vesiculation, but the two compartments do not have equal size and the energy differs from the reference. Perhaps the regime of $v \gtrsim 0.75$ is the most challenging one, since the two compartments are expected to have up-down symmetry breaking for the vesiculation. We find that neither schemes C nor D can run stably in this regime of vesiculations. On the contrary, scheme B delivers the correct results with a satisfactory accuracy on both the energy values and configurations.

### Table 6

<table>
<thead>
<tr>
<th>$v$</th>
<th>0.52</th>
<th>0.56</th>
<th>0.65</th>
<th>0.7</th>
<th>0.76</th>
<th>0.78</th>
</tr>
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<tbody>
<tr>
<td>C</td>
<td>![Image]</td>
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</table>
To summarize this section, scheme B with \( N_t = 1280 \) is able to generate the whole spectrum of equilibrium shapes including dumbbells, necklaces, even buddings and vesiculations where only a couple of triangles are connecting different compartments. Furthermore, the corresponding energy value for each equilibrium shape is very accurate in comparison with the reference value. Both schemes C and D with \( N_t = 1280 \) run into troubles when budding or/and vesiculations are expected. With higher resolutions \( N_t = 5120 \), neither scheme C nor D show significant improvement (results not presented herein).

4.2.5. Bilayer-couple model

We consider the phase diagram of the BC model which can be realized by taking \( \alpha \rightarrow \infty \) in Eq. (5) so that the area-difference elasticity becomes a quadratic penalization. A typical value employed numerically is \( \alpha = 1000 \). In this model, there are two non-dimensional parameters \( v \) and \( \Delta \alpha \). We consider the BC model before presenting results from the complete ADE model for a few reasons: 1. The BC model has only continuous phase transitions [9,21]. 2. The equilibrium shapes and possible resultant \( \Delta \alpha \) in BC model contains those of the ADE model [2]. 3. The phase diagram of BC has two controlling parameters, one less than that of ADE model. 4. With \( h_0 = 0 \), we can focus on examinations of the area-difference elasticity.

We consider the same parameter ranges of \( v \) and \( \Delta \alpha \) as in Ref. [46], where the program Surface Evolver was used [64]. We present our phase diagram by scheme B in Fig. 11, where almost each individual shape has one-to-one correspondence to the shape on Fig. 1 of Ziherl and Svetina [46]. As in the SC model, we obtain similar axisymmetric shapes such as stomatocytes, prolate-like/dumbbells, budding necklaces. Different from the SC model, we obtain in addition many non-axisymmetric shapes from the constraint of the area difference between outer and inner leaflets. These shapes include elliptocytes (e.g., the fourth one at \( v = 0.7 \) or 0.65), rackets (e.g., the fifth one at \( v = 0.65 \) and sixth one at \( v = 0.6 \)), triangle oblates with equal sides (e.g., the sixth one at \( v = 0.55 \)), and triangle oblates with unequal sides (e.g., the seventh one at \( v = 0.5 \)). All these shapes have been recently validated by experiments on self-assembled vesicles combined with image analysis [18].

Furthermore, we verify the corresponding energy values as shown in Fig. 12, where the reference values are adapted from Ziherl and Svetina [46]. We observe that energies computed by scheme B with \( N_t = 1280 \) and 5120 exhibit negligible discrepancies and they both follow closely the reference values. Therefore, we omit the equilibrium configurations generated with \( N_t = 5120 \).

We have also computed the same phase diagram by scheme C and D with \( N_t = 1280 \) and 5120. However, scheme C and scheme D become unstable for certain values of \( \Delta \alpha \). We speculate that the vulnerability of scheme C is due to the definition of the discrete normal vector, which is not compatible with the discrete definition of the
Laplace operator. We maintain that the instability of scheme D is due to its lack of conservation properties. We consider that a more rigorous investigations on scheme C and D are beyond the scope of this work.

4.3. Area-difference-elasticity model

Here we compute the total energy and force in the ADE model. For comparison, we consider as reference the work of Khairy et al. [24], which employs spherical harmonics to represent the surface and calculate the total energy. Therefore, we take the same reduced volume $v \approx 0.642$ and $\alpha = 2/\pi$, which represent the parameters of a normal RBC [24,38].

We present the energy versus reference area difference $\Delta a_0$ on Fig. 13(a), where we include results of all three schemes and each with two resolutions of $N_t = 1280$ and 5120. For each $\Delta a_0$ considered from 1 to 3.5, there is only small discrepancy between the schemes with a proper resolution, that is, scheme B with $N_t = 1280$ and 5120 and scheme C and D with $N_t = 5120$. We present the resultant $\Delta a$ versus $\Delta a_0$ on Fig. 13(b) and observe that $\Delta a$ increases as $\Delta a_0$ for smaller $\Delta a_0 \lesssim 1.75$. It stays almost at one plateau for $1.75 \lesssim \Delta a_0 \lesssim 2.5$ and at another plateau for $\Delta a_0 \gtrsim 2.6$. Correspondingly, we plot again the energy versus the resultant $\Delta a$ on Fig. 13(c). We observe that the associated energies span among possible area differences for $\Delta a \lesssim 1$ and cluster at two discrete states of area differences for $\Delta a \gtrsim 1$. These characteristics of area differences and minimal energies reflect the possible equilibrium configurations of the vesicles, which will be presented next.

We present equilibrium configurations from scheme B, C and D with $N_t = 1280$ and 5120 in Table 7, where values of both $\Delta a_0$ and $\Delta a'_0$ are considered, as the latter corresponds to the parameter in Fig 3c of Khairy et al. [24]. With resolutions of $N_t = 1280$, all schemes B, C and D resemble closely the results of the reference. As $\Delta a_0$ decreases, we observe axi-symmetric stomatocytes with smaller height, as exemplified by the first two columns of Table 7. In the last regime, $\Delta a$ stays flat and we observe prolate–dumbbells as shown for example in the last column of Table 7. These configurations of $N_t = 1280$ agree with the work of Kairy et al. [24]. However, with $N_t = 5120$ the anisotropy of elliptocytes with $0.21 \lesssim \Delta a'_0 \lesssim 0.23$ tends to disappear and the final configurations are less elongated. We note that the difference between computed energies for $N_t = 1280$ and 5120 is very small as shown in Fig. 13. The results from the three different schemes are consistent with each other, which leads us to suspect that the number of terms in the spherical harmonics of the reference could be insufficient to resolve this subtle difference.

4.4. A dynamic simulation of area-difference-elasticity model

Finally, we present dynamic simulations of lipid bilayer membranes using the ADE model discretized by scheme B. We consider the same parameters ($v \approx 0.642$) as in Section 4.3, that correspond to mechanics activities of a
Fig. 13. Minimal energies and area differences from ADE model: $\alpha = 2/\pi$. Solid line on (c) is adapted from Fig. 12 for $v = 0.65$ in the BC model to serve as a guide of the scale of energy variations.

RBC. We start with a stomatoctye shape, which takes the final shape of the previous minimization procedure (see results of $\Delta a_0 = 1.11$ or $100\Delta a'_0 = 0.1$ on Table 7). We set the reference area-difference as $\Delta a = 0.585, 0.648, 0.96, 1.046, 1.179, 1.293, 1.305, 1.307, 1.312, 1.321, 1.325$.

We report the dynamic trajectories of local energy, non-local energy, area-difference and corresponding shapes on Fig. 14. The in-plane viscous damping force is orthogonal to the normal direction of the membrane surface and
Table 7
Equilibrium shapes of the ADE model: comparison among three schemes for $N_t = 1280$ and 5120, $\alpha = 2/\pi$.
Both values of $\Delta a_0$ and $\Delta a'_0$ are listed to compare with Khairy et al [24]. The results on the fourth column of elliptocytes are slightly controversial to that of Khairy et al [24], but consistent among the three schemes: B: $N_t = 1280$ with $100\Delta a'_0 = 0.22$ and $N_t = 5120$ with $100\Delta a'_0 = 0.21$; C: $N_t = 1280$ with $100\Delta a'_0 = 0.22$ and $N_t = 5120$ with $100\Delta a'_0 = 0.22$; D: $N_t = 1280$ with $100\Delta a'_0 = 0.23$ and $N_t = 5120$ with $100\Delta a'_0 = 0.21$.

| $\Delta a_0$ | 1.11 | 1.34 | 1.78 | 2.34 – 2.56 | 3.34 |
| $100\Delta a'_0$ | 0.1 | 0.12 | 0.16 | 0.21 – 0.23 | 0.3 |

B: $N_t = 1280$

B: $N_t = 5120$

C: $N_t = 1280$

C: $N_t = 5120$

D: $N_t = 1280$

D: $N_t = 5120$ NA

has negligible effects on the dynamic trajectories. However, a larger viscous force is needed to stabilize simulations with a higher resolution and therefore demands a smaller time step. The dynamic simulation arrives at the prolate–dumbbell shape, as shown on Fig. 14 in agreement with results on Figs. 13(a) and 13(b) and on Table 7, respectively, which are obtained from independent minimization procedures. From Fig. 14(a), we observe that the local energy does not change significantly over time, whereas the non-local energy decreases around ten fold. This confirms that the ADE is primarily responsible for the transformation of shapes. Comparing Fig. 14(b) with 13(b), we notice that the accessible states of $\Delta a$ are more abundant and even continuous in the dynamic simulation. Accordingly, there is a rich range of shapes including triangle oblates, curved-prolate-like shapes, and prolate–dumbbells, as represented
on Fig. 14(b). These intermediate configurations are dynamic (non-equilibrium) and do not have a correspondence for the intermediate $\Delta a_0$ values on Table 7. Further comparing with the phase diagram of the BC model on Fig. 11, we also do not find corresponding equilibrium shapes for the same values of reduced volume and $\Delta a$. The small discrepancy between the energy trajectories of $N_i = 1280$ and 5120 are not surprising, as they start from slightly different values.

5. Summary

We have presented a comparative study of four bending models for lipid bilayer membranes and their respective discretization on triangulated meshes. The physical models are the minimal, spontaneous curvature (SC), bilayer-couple (BC) and area-difference elasticity (ADE) models and the four schemes are termed as scheme A, B, C, and D respectively.

We find that the total energies computed by scheme A on a prescribed sphere and biconcave–oblate differ significantly from the analytical values. The energy computed by scheme A cannot be tuned to match the Helfrich-type energy for an arbitrary shape. For reduced volume $v > 0.75$, scheme A is able to generate prolate–dumbbells at equilibrium, although the corresponding energies are inaccurate. However, for $0.59 < v < 0.65$, scheme A does not result in biconcave oblates as equilibrium shapes and it does not sustain the shape if it is given a biconcave–oblate as the initial shape. Below $v < 0.59$, scheme A has numerical artifacts of budding transitions and vesiculations. Finally, due to the lack of direct definition of mean curvature and local area, scheme A cannot be directly extended to discretize the SC, BC, or ADE models.

The energies computed by scheme B, C and D on prescribed sphere and biconcave–oblate match well the analytical values. However, the accuracy of the three schemes has a varying dependence on their resolution. On the phase diagram of the minimal model, for $v > 0.59$, all three schemes produce prolate dumbbells and biconcave oblates as the equilibrium configurations. They also resolve well the critical energy values at $v = 0.75$ and 0.65 and 0.59, with scheme B at $N_i = 1280$ but scheme C and D at $N_i = 5120$. However, for $v < 0.59$, Scheme B produces stomatocytes as equilibrium configurations accurately with $N_i = 1280$, where the inner sphere separates clearly from the outer sphere. Scheme C generates acceptable equilibrium configurations, but cannot maintain a clear physical separation between the inner and outer spheres. For the most challenging case of $v = 0.25$, scheme C is in trouble to generate a physically correct configuration. A higher resolution of $N_i = 5120$ does not help scheme C significantly on the overall equilibrium shape. Scheme D has stability issues in the regime of stomatocytes that may be attributed to its lack of explicit energy and momentum conservation.

We have also computed two slices ($h_0 = 1.2$ and 1.5) of the phase diagram for the SC model. These are challenging benchmarks, as $h_0 = 1.2$ includes the budding transitions at equilibrium, while $h_0 = 1.5$ include both buddings and vesiculations. We observe that schemes B, C and D all capture accurately the budding process, but scheme C and D have difficulties to generate vesiculations. Furthermore, with the same resolution of $N_i = 1280$ scheme B computes the energy more accurately than scheme C and D. Moreover, the energies computed by scheme C at budding transitions are completely off the reference values due to the poor representation of the configuration necks.

As a special case of the ADE model, we considered the BC model, where a constraint is imposed on the area difference between the two layers of lipid. We focus on the results of scheme B and reproduce the phase diagram for different resolutions. We find that results of scheme B are comparable to the reference on the equilibrium shapes and energy values, which were calculated by Surface Evolver. We have also considered the complete energy functional of the ADE model. We reproduce the sequence of stomatocytes, biconcave oblates, biconcave ellipotocytes and prolate dumbbells by all three schemes, except for the extreme case of stomatocyte where scheme D runs into instability again. As the last demonstration, we consider a dynamic trajectory of the ADE model from stomatocyte to prolate–dumbbell. The values of local energy, non-local energy, and area-difference along the dynamic trajectory may also serve as reference for other researchers.

Our results indicate that it is a challenging task to compute accurately the bending energy and in particular forces on a triangulated mesh. However, due to its generality it is still a very promising path to pursue. At the same time we note the level set formulations introduced in [28] which incorporates some of the energy models presented in this work. We believe that this is a very promising direction to account for large membrane deformations and topological changes. Future work could be directed in comparing level set and triangulated surface representations.
In summary, the relatively simple formulation of scheme B, which bypasses definitions of Laplace–Beltrami operator and unit normal vectors, and instead defines the integral of mean curvature with respect to area, exhibits excellent accuracy, robustness, stability. Moreover as the implementation of scheme B is also almost as simple as that of scheme A we suggest that it deserves to be more broadly investigated as an alternative for vesicle and RBC simulations. While scheme B is readily applicable to the minimal model, in this work we promote and extend its potentials to further resolve SC, BC and ADE models. With ADE model as the most accurate model for lipid bilayer membrane, we envision many numerical applications on vesicles and RBCs in a dynamic context.

Acknowledgments

This work is supported by European Research Council Advanced Investigator Award 341117. X.B. benefits from discussions with Prof. Jülicher on scheme B. There is no numerical detail in Lim et al. [38]. However, after we have finished this work, X. B. learned via a private communication with Prof. Wortis that they also applied scheme B in the context of Monte Carlo simulations, and details of which are presented in a book [67].

Appendix A. Force from variational calculus of energy

In differential geometry, the Cartesian coordinates $x$ of a point on a surface may be expressed in terms of two independent parameters $u_1$ and $u_2$ as $x = x(u_1, u_2)$. For further derivations, we introduce some definitions [4,68]

$$x_i = \frac{\partial x}{\partial u_i}, \quad x_{ij} = \frac{\partial^2 x}{\partial u_i \partial u_j}, \quad g_{ij} = x_i \cdot x_j,$$

$$g^{ij} = (g_{ij})^{-1} \quad \text{or} \quad g^{ij}g_{jl} = \delta^i_l, \quad g = \det(g_{ij}),$$

(A.1)

where free index $i$ or $j$ is either 1 or 2, and summation convention applies to repeated index. Index $i$ after “,” denotes the partial derivative with respect to $u_i$. $g_{ij}$ is the covariant metric tensor and $g$ is its determinant. $g^{ij}$ is the contravariant metric tensor. An infinitesimal area is then

$$dA = g^{1/2}du_1du_2.$$  

(A.2)

The parameterizations of $u_1$ and $u_2$ are chosen in such a way that the normal direction

$$n = \frac{x_1 \times x_2}{|x_1 \times x_2|},$$

(A.3)

points inwards of a closed surface. Therefore, $H = \nabla \cdot n/2$ is positive for a sphere.

For a small and continuous perturbation $\psi(u_1, u_2)$ along the normal direction $n(u_1, u_2)$, the new position of the point on the parametric surface is given as

$$x'(u_1, u_2) = x(u_1, u_2) + \psi(u_1, u_2)n(u_1, u_2).$$

(A.4)

Thereafter, the variations for $dA$ and $H$ are given as

$$\delta(dA) = 2H\psi g^{1/2}du_1du_2 = 2H\psi dA,$$

(A.5)

$$\delta H = -(2H^2 - G)\psi - \frac{1}{2}g^{ij}(\psi_{,ij} - \Gamma^k_{ij}\psi_{,k}) = -(2H^2 - G)\psi - \frac{1}{2}g^{ij}\nabla_i\psi_{,j},$$

(A.6)

where $\Gamma^k_{ij}$ is the Christoffel symbol and $\nabla^2_s$ is the Laplace–Beltrami operator on the surface. We note a different sign convention used [4].

To have an explicit expression of $\delta E$, we need variational expressions for each moment. The variation of the zero moment simply reads as

$$\delta M_0 = \delta A = \int \delta(dA) = \int 2H\psi dA.$$  

(A.7)

However, to calculate variations of the first and second moments we need some fundamental equalities. For any function $f(u_1, u_2)$ we have

$$\int f\psi_{,i}du_1du_2 = -\int f_{,i}\psi du_1du_2, \quad \int f\psi_{,ij}du_1du_2 = \int f_{,ij}\psi du_1du_2,$$

(A.8)
which can be readily proven via integration by parts. We further notice

\[
(g^{1/2}g^{ij}f)_{ij} = \left[ (g^{1/2}g^{ij})_j f \right]_i + (g^{1/2}g^{ij}f)_j, \tag{A.9}
\]

\[
\left[ (g^{1/2}g^{ij})_j f \right]_i = -g^{1/2}g^{ij} (\Gamma^k_{ij} f)_k, \tag{A.10}
\]

\[
g^{-1/2} \left[ g^{1/2}g^{ij}f \right]_j = \nabla^2 f. \tag{A.11}
\]

Therefore,

\[
\int f g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) \, dA = \int f g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) g^{1/2} du_1 du_2
\]

\[
= \int \left[ (g^{1/2}g^{ij}f)_{ij} + (g^{1/2}g^{ij}\Gamma^k_{ij} f)_k \right] \psi du_1 du_2
\]

\[
= \int \left\{ \left[ (g^{1/2}g^{ij})_j f \right]_i + (g^{1/2}g^{ij}f)_j - \left[ (g^{1/2}g^{ij})_j f \right]_i \right\} \psi du_1 du_2
\]

\[
= \int (g^{1/2}g^{ij}f)_{ij} \psi du_1 du_2
\]

\[
= \int \nabla^2 f g^{1/2} du_1 du_2 = \int \nabla^2 f \, dA, \tag{A.12}
\]

Eq. (A.8) is applied from the second to the third line. Eqs. (A.9) and (A.10) are applied from the third to the fourth line. Eq. (A.11) is applied from the fifth to the sixth line.

The variation of the first moment is readily obtained as

\[
\delta M_1 = \int \left[ 8H dA + H \delta (dA) \right]
\]

\[
= \int \left[ -2(H^2 - G) \psi - \frac{1}{2} g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) + 2H^2 \psi \right] \, dA
\]

\[
= \int \left[ G \psi - \frac{1}{2} g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) \right] \, dA
\]

\[
= \int \left( G - \frac{1}{2} \nabla^2 \psi \right) \, dA = \int G \psi \, dA, \tag{A.13}
\]

where Eq. (A.12) is applied from the third to the fourth line. The variation of the second moment is also readily derived as

\[
\delta M_2 = \int \left[ 2H \delta H dA + H^2 \delta (dA) \right]
\]

\[
= \int \left[ -2H(2H^2 - G) \psi - H g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) + 2H^3 \psi \right] \, dA
\]

\[
= \int \left[ -2H(2H^2 - G) \psi - H g^{ij} (\psi_{ij} - \Gamma^k_{ij} \psi, k) \right] \, dA
\]

\[
= \int \left[ -2H(2H^2 - G) - \nabla^2 \psi \right] \, dA, \tag{A.14}
\]

where Eq. (A.12) is applied from the third to the fourth line.

Since the perturbation \( \psi \) is continuous, small and arbitrary, the integrand must be the density of virtual work along the normal direction. Therefore, the magnitudes of the virtual force density due to the three moments read as

\[
\mathcal{F}_0 = 2H, \quad \mathcal{F}_1 = G, \quad \mathcal{F}_2 = -2H(2H^2 - G) - \nabla^2 \psi, \tag{A.15}
\]
and they all act along the normal direction \( \mathbf{n} \). These results also corroborate another two recent derivations following different routes \([39,69]\).

The variation of energy of Eq. (7) read as

\[
\delta E = 2k_b \delta M_2 + \frac{4\sigma \kappa_b \pi}{A} M_1 \delta M_1 - \frac{2\sigma \kappa_b \pi}{A^2} M_1^2 \delta A - 4k_b H_0 \delta M_1
\]

\[
- \frac{2\sigma \kappa_b \pi}{A} \frac{\Delta A_0}{D} \delta M_1 + \frac{2\sigma \kappa_b \pi}{A^2} \frac{\delta A}{D} M_1 \delta A + 2k_b H_0^2 \delta A - \frac{\sigma \kappa_b \pi}{2A^2} \left( \frac{\Delta A_0}{D} \right)^2 \delta A. \tag{A.16}
\]

Given the variations of the zero, first and second moments in Eqs. (A.7), (A.13), and (A.14), we have readily an explicit expression for the variation of the energy and omit the repetitious details here. Accordingly, the magnitude of force density due to the energy Eq. (7) reads as

\[
f = \frac{2k_b \delta F_2 + \frac{4\sigma \kappa_b \pi}{A} M_1 \delta F_1 - \frac{2\sigma \kappa_b \pi}{A^2} M_1^2 \delta F_0 - 4k_b H_0 \delta F_1}{f^H} - \frac{2\sigma \kappa_b \pi}{A} \frac{\Delta A_0}{D} \delta F_1 + \frac{2\sigma \kappa_b \pi}{A^2} \frac{\delta A}{D} M_1 \delta F_0 + 2k_b H_0^2 \delta F_0 - \frac{\sigma \kappa_b \pi}{2A^2} \left( \frac{\Delta A_0}{D} \right)^2 \delta F_0, \tag{A.17}
\]

where geometric evaluations of \( F_0, F_1 \) and \( F_2 \) are given in Eq. (A.15), and \( f \) acts along the normal direction \( \mathbf{n} \). We may also obtain the force density according to the historical development of each energy term as

\[
f^H = 2k_b \left( F_2 - 2H_0 \delta F_1 + H_0^2 \delta F_0 \right) = -2k_b \left[ 2(H - H_0)(H^2 + H_0H - G) + \nabla_i^2 H \right],
\]

\[
f^C = -2k_b \left[ 2H(H^2 - G) + \nabla_i^2 H \right],
\]

\[
f^S = 4k_b H_0 \left( H_0H - G \right),
\]

\[
f^{AD} = \alpha \kappa_b \pi \left( \frac{4M_1 \delta F_1}{A} - \frac{2M_1^2 \delta F_0}{A^2} - \frac{2\Delta A_0 \delta F_1}{AD} + \frac{2\Delta A_0 \delta M_1 \delta F_0}{A^2 D} - \frac{1}{2A^2} \left( \frac{\Delta A_0}{D} \right)^2 \delta F_0 \right)
\]

\[
= \alpha \kappa_b \pi \left[ \left( 2M_1 - \frac{\Delta A_0}{D} \right) \frac{2G}{A} - \left( 2M_1 - \frac{\Delta A_0}{D} \right)^2 \frac{H}{A^2} \right]. \tag{A.18}
\]

where the superscripts “\( C, H, S, \) and \( AD \)” correspond to the forces of Canham, Helfrich, spontaneous curvature and ADE, respectively. They all act along the normal \( \mathbf{n} \) direction. \( f^C \) is just degenerated from \( f^H \) by setting \( H_0 = 0 \). Finally, given the total energy of Eq. (7), the total force density is simply \( f = (f^H + f^{AD}) \mathbf{n} \) or equivalently \( f \mathbf{n} \).

**Appendix B. Discrete force from scheme A**

The force on vertex \( m \) is

\[
\mathbf{F}_m = -\frac{\partial E}{\partial \mathbf{x}_m} = -2\kappa_b \sum_{e:(i,j)} N_e \sin (\theta_e - \theta_0) \frac{\partial \theta_e}{\partial \mathbf{x}_m}. \tag{B.1}
\]

Similarly, for the linearized version the force is

\[
\mathbf{F}^{1st}_m = -\frac{\partial E^{1st}}{\partial \mathbf{x}_m} = -\kappa_b \sum_{e:(i,j)} (\theta_e - \theta_0) \frac{\partial \theta_e}{\partial \mathbf{x}_m}. \tag{B.2}
\]

Therefore, the primitive element for calculation of force is the partial derivative of the dihedral angle’s supplementary angle with respect to position, that is, \( \partial \theta_e / \partial \mathbf{x}_m \) \([70]\).
Appendix C. Discrete force for scheme B

Force on vertex $x_m$ is the negative derivative of the discrete energy in Eq. (13)

$$\mathbf{F}_m = -\frac{\partial E}{\partial x_m} = -2\kappa_b \frac{\partial M_2}{\partial x_m} - \frac{4\alpha\kappa_b\pi}{\mathcal{A}} \frac{\partial \mathcal{M}_1}{\partial x_m} + \frac{2\alpha\kappa_b\pi}{\mathcal{A}^2} M_1^2 \frac{\partial A}{\partial x_m} + 4\kappa_b H_0 \frac{\partial \mathcal{M}_1}{\partial x_m}$$

$$+ \frac{2\alpha\kappa_b\pi}{\mathcal{A}} \frac{\Delta A_0}{D} \frac{\partial M_1}{\partial x_m} - \frac{2\alpha\kappa_b\pi}{\mathcal{A}^2} \frac{\Delta A_0}{D} M_1 \frac{\partial A}{\partial x_m} - 2\kappa_b H_0^2 \frac{\partial A}{\partial x_m} + \frac{\alpha\kappa_b\pi}{2\mathcal{A}^2} \left( \frac{\Delta A_0}{D} \right)^2 \frac{\partial A}{\partial x_m}. \quad (C.1)$$

Equivalently, $\mathbf{F}_m = \mathbf{F}^H_m + \mathbf{F}^{AD}_m$, due to force of Helfrich and ADE energy. We need to calculate the derivatives of the three moments as

$$\frac{\partial \mathcal{M}_0}{\partial x_m} = \frac{\partial A}{\partial x_m} = \sum_{i=1}^{N_e} \frac{\partial A_i}{\partial x_m},$$

$$\frac{\partial \mathcal{M}_1}{\partial x_m} = \sum_{i=1}^{N_e} \left( \frac{\partial H_i}{\partial x_m} A_i + H_i \frac{\partial A_i}{\partial x_m} \right),$$

$$\frac{\partial \mathcal{M}_2}{\partial x_m} = \sum_{i=1}^{N_e} \left( 2H_i \frac{\partial H_i}{\partial x_m} A_i + H_i \frac{\partial A_i}{\partial x_m} \right). \quad (C.2)$$

The constituting elements of derivatives are $\partial H_i/\partial x_m$, and $\partial A_i/\partial x_m$, which are given explicitly as follows.

Given $H_i$ in Eq. (21), its derivative with respective to $x_m$ reads

$$\frac{\partial H_i}{\partial x_m} = \frac{1}{4A_i} \sum_{e:(i,j)} N_e \left( \frac{\partial l_e}{\partial x_m} \theta_e + l_e \frac{\partial \theta_e}{\partial x_m} \right) - H_i \frac{\partial A_i}{A_i \partial x_m}, \quad (C.3)$$

where summation runs over $N_e$ neighboring edges around vertex $i$. Given $A_i$ in Eq. (22), its derivative with respective to $x_m$ reads

$$\frac{\partial A_i}{\partial x_m} = \frac{1}{3} \sum_{\ell:(i,j,k)} \frac{\partial A'_i}{\partial x_m}, \quad (C.4)$$

where summation runs over $N_e$ neighboring triangles around vertex $i$. It remains a few primitive derivatives

$$\frac{\partial l_e}{\partial x_m}, \quad \frac{\partial A'_i}{\partial x_m}, \quad \frac{\partial \theta_e}{\partial x_m}, \quad (C.5)$$

to be evaluated as follows. Consider an edge $\langle i, j \rangle$, triangle $\langle i, j, k \rangle$, and a dihedral angle between triangles $\langle i, j, k \rangle$ and $\langle i, l, j \rangle$.

$$\frac{\partial l_e}{\partial x_i} = \frac{x_j - x_i}{|x_j - x_i|}, \quad (C.6)$$

$$\frac{\partial A'_i}{\partial x_i} = n_1 \times (x_j - x_i), \quad (C.7)$$

$$\frac{\partial \theta_e}{\partial x_i} = -\frac{1}{l_{ij}} (\cot \phi_k n_1 + \cot \phi_l n_2), \quad (C.8)$$

using notations on Fig. 1.

Appendix D. Discrete force for scheme C

It is convenient to write an expression for the discrete total energy in the following form

$$E = \sum_{i}^{N_e} E_i = \sum_{i}^{N_e} E(A_i, h_i), \quad (D.1)$$
where \( h_i = A_i H_i \). To compute local area \( A_i \), we introduce several scalar and vector quantities for every triangle (omitting index \( i \)) as

\[
e_j = x'_i - x'_j, \quad e_k = x'_i - x'_k, \quad s'_j = |e'_j|, \quad s'_k = |e'_k|, \quad c'_j = \cot \phi'_j, \quad c'_k = \cot \phi'_k,
\]

so that the local area is simply

\[
A = \frac{1}{8} \sum_{t<i,j,k>} c'_j s'_k + c'_k s'_j,
\]

where summation runs over all neighboring triangles. To compute \( h_i \), triangle’s normal \( u' \) is further required (omitting index \( i \))

\[
h = 1 \cdot n, \quad 1 = \frac{1}{2} \sum_{t<i,j,k>} c'_j e'_k + c'_k e'_j, \quad n = \frac{m}{|m|}, \quad m = \sum_{t<i,j,k>} \phi'_i u'.
\]

Since discrete energy is a function of all vertex coordinates in neighboring triangles, a complete explicit expression for the force is extremely tedious. We give an implicit expression by considering the variation of \( E(A, h) \) for the perturbation of every triangle \( t \) as

\[
\delta_t E = \delta_t E(A, h) = E_A \delta_t A + E_h \delta_t h,
\]

where \( E_A \) and \( E_h \) are the corresponding partial derivatives. After some transformations and omitting index \( t \), we obtain

\[
\delta E = \frac{E_A}{2} \delta u + \frac{E_h}{8} \delta \phi_i + \frac{E_A}{4} c_j \delta c_j + \frac{E_h}{8} \delta c_k - \frac{E_A}{4} e_j \delta e_j + \frac{E_h}{8} c_k \delta c_k
\]

\[
- \frac{E_h}{4} e_j \delta c_k + \frac{E_A}{8} c_k \delta s_k - \frac{E_h}{4} c_k \delta e_j + \frac{E_A}{8} s_k \delta c_k,
\]

where \( L = 1 - \frac{d|n|}{dn} \). Primitive variation can be expressed as linear functions of \( \delta x_i, \delta x_j, \) and \( \delta x_k \), which lead to an explicit expression for the forces on all vertices in the triangle due to energy at vertex \( i \). It is required to specify expressions for \( E \) and its derivatives. In our case, constitute moments are the essential terms

\[
A = E(A, h) = A, \quad AH = E(A, h) = h, \quad AH^2 = E(A, h) = h^2/A.
\]

**Appendix E. Analytical solutions for a prescribed shape**

For verification of the energy and force on a triangulated mesh, we calculate these quantities analytically for a prescribed biconcave–oblate shape, which is described by an empirical function [61]. We employ the algebra software “Maxima” and parameterize the membrane surface as

\[
x_1 = \sin u_1 \sin u_2, \quad x_2 = \sin u_1 \cos u_2, \quad x_3 = F(\cos u_1),
\]

where \( (x_1, x_2, x_3) \) are the Cartesian coordinates and \( (u_1, u_2) \) are the parametric coordinates, \( F(q) = q \) for the sphere with radius \( R = 1 \), area \( A = 4\pi \) and \( F(q) = 0.5435 q^3 + 0.121435 q^5 \) for the biconcave–oblate with radius \( R = 1 \) (largest distance of a point away from the axis of symmetry) and area \( A \approx 8.77 \) [61].

Hence, normal unit vector \( n \) of the surface defined in Eq. (A.3) of Appendix A points inwards of a closed surface. Given the definitions of moments in Eq. (6) and force density in Eq. (8), we apply Eq. (E.1) to compute analytically the energies and forces in the minimal, SC and ADE models.

**Appendix F. Energy and force due to area constraint**

Due to the weak compressibility, we consider an extra energy to penalize its global area variation

\[
E_A^x = \kappa_{ag} \frac{(A - A_0)^2}{A_0},
\]

where \( h_i = A_i H_i \). To compute local area \( A_i \), we introduce several scalar and vector quantities for every triangle (omitting index \( i \)) as

\[
e_j = x'_i - x'_j, \quad e_k = x'_i - x'_k, \quad s'_j = |e'_j|, \quad s'_k = |e'_k|, \quad c'_j = \cot \phi'_j, \quad c'_k = \cot \phi'_k,
\]

so that the local area is simply

\[
A = \frac{1}{8} \sum_{t<i,j,k>} c'_j s'_k + c'_k s'_j,
\]

where summation runs over all neighboring triangles. To compute \( h_i \), triangle’s normal \( u' \) is further required (omitting index \( i \))

\[
h = 1 \cdot n, \quad 1 = \frac{1}{2} \sum_{t<i,j,k>} c'_j e'_k + c'_k e'_j, \quad n = \frac{m}{|m|}, \quad m = \sum_{t<i,j,k>} \phi'_i u'.
\]

Since discrete energy is a function of all vertex coordinates in neighboring triangles, a complete explicit expression for the force is extremely tedious. We give an implicit expression by considering the variation of \( E(A, h) \) for the perturbation of every triangle \( t \) as

\[
\delta_t E = \delta_t E(A, h) = E_A \delta_t A + E_h \delta_t h,
\]

where \( E_A \) and \( E_h \) are the corresponding partial derivatives. After some transformations and omitting index \( t \), we obtain

\[
\delta E = \frac{E_A}{2} \delta u + \frac{E_h}{8} \delta \phi_i + \frac{E_A}{4} c_j \delta c_j + \frac{E_h}{8} \delta c_k - \frac{E_A}{4} e_j \delta e_j + \frac{E_h}{8} c_k \delta c_k
\]

\[
- \frac{E_h}{4} e_j \delta c_k + \frac{E_A}{8} c_k \delta s_k - \frac{E_h}{4} c_k \delta e_j + \frac{E_A}{8} s_k \delta c_k,
\]

where \( L = 1 - \frac{d|n|}{dn} \). Primitive variation can be expressed as linear functions of \( \delta x_i, \delta x_j, \) and \( \delta x_k \), which lead to an explicit expression for the forces on all vertices in the triangle due to energy at vertex \( i \). It is required to specify expressions for \( E \) and its derivatives. In our case, constitute moments are the essential terms

\[
A = E(A, h) = A, \quad AH = E(A, h) = h, \quad AH^2 = E(A, h) = h^2/A.
\]

**Appendix E. Analytical solutions for a prescribed shape**

For verification of the energy and force on a triangulated mesh, we calculate these quantities analytically for a prescribed biconcave–oblate shape, which is described by an empirical function [61]. We employ the algebra software “Maxima” and parameterize the membrane surface as

\[
x_1 = \sin u_1 \sin u_2, \quad x_2 = \sin u_1 \cos u_2, \quad x_3 = F(\cos u_1),
\]

where \( (x_1, x_2, x_3) \) are the Cartesian coordinates and \( (u_1, u_2) \) are the parametric coordinates, \( F(q) = q \) for the sphere with radius \( R = 1 \), area \( A = 4\pi \) and \( F(q) = 0.5435 q^3 + 0.121435 q^5 \) for the biconcave–oblate with radius \( R = 1 \) (largest distance of a point away from the axis of symmetry) and area \( A \approx 8.77 \) [61].

Hence, normal unit vector \( n \) of the surface defined in Eq. (A.3) of Appendix A points inwards of a closed surface. Given the definitions of moments in Eq. (6) and force density in Eq. (8), we apply Eq. (E.1) to compute analytically the energies and forces in the minimal, SC and ADE models.

**Appendix F. Energy and force due to area constraint**

Due to the weak compressibility, we consider an extra energy to penalize its global area variation

\[
E_A^x = \kappa_{ag} \frac{(A - A_0)^2}{A_0},
\]
where $A = \sum_{t:(i,j,k)} A^t$ and $A_0$ are the current and original total area, respectively. To regularize each triangle area, we introduce another energy on penalizing the local area as

$$E^A_i = \kappa_{al} \sum_{t:(i,j,k)} \frac{(A^t - A_0^t)^2}{A_0^t}, \quad (F.2)$$

where $A^t$ and $A_0^t$ are the current and target area of the triangle with index $t$. The strength of the penalization is controlled by $\kappa_{ag}$ and $\kappa_{al}$, respectively. The force is

$$F^A = -\frac{\partial E^A}{\partial \mathbf{x}_m} = -\kappa_{ag} \frac{2 (A - A_0)}{A_0} \sum_{t:(i,j,k)} \frac{\partial A^t}{\partial \mathbf{x}_m} - \kappa_{al} \sum_{t:(i,j,k)} \frac{2 (A^t - A_0^t)}{A_0^t} \frac{\partial A^t}{\partial \mathbf{x}_m}, \quad (F.3)$$

where index $m$ for position $\mathbf{x}_m$ is any one of the three vertices $i$, $j$, and $k$.

**Appendix G. Energy and force due to volume constraint**

Due to osmotic pressure, a close membrane regulates its volume accordingly. Therefore, we consider an extra energy on penalizing the total volume variation as

$$E^V = \kappa_v \frac{(V - V_0)^2}{V_0}, \quad (G.1)$$

where $V$ and $V_0$ are the current and target volume enclosed by the membrane, respectively. Total volume $V = \sum_{t:(i,j,k)} V^t$, where $V^t$ is the volume of the tetrahedron formed by triangle $t$ and the origin, that is, $V^t = (\mathbf{a} \times \mathbf{b}) \cdot \mathbf{c}/6$, 

![Fig. H.15. Force density (absolute value) versus radial distance of vertices from axis for a biconcave–oblate with $\kappa_b = 1$, $h_0 = 0$ and $\alpha = 0$. For scheme A $\tilde{\kappa}_b = \sqrt{3/3}$.](image-url)
where $\mathbf{a}$, $\mathbf{b}$ and $\mathbf{c}$ are vectors of the three edges of triangle $t$. A coefficient $\kappa_v$ controls the strength of the penalization to achieve the target volume or its conjugate osmotic pressure. The force is

$$F^V = -\frac{\partial E^V}{\partial \mathbf{x}_m} = -\kappa_v \frac{2}{V_0} \sum_{t:\{i,j,k\}} \frac{N_t}{\partial V^t}{\partial \mathbf{x}_m},$$ (G.2)

where index $m$ for position $\mathbf{x}_m$ is one of $i$, $j$, and $k$.

$$\frac{\partial V^t}{\partial \mathbf{x}_i} = \frac{A^{0jk}}{3} \mathbf{n}_{0jk},$$ (G.3)

where index 0 corresponds to the point at the origin. $A$ and $\mathbf{n}$ are triangle area and normal.

**Appendix H. Numerical results on force for a prescribed shape**

We present the force in this section with a caveat; the computed energy is robust to a moderate change of the triangulated mesh, whereas the corresponding force is highly sensitive. We shall bear this in mind when interpreting the numerical results.
For each scheme, we present the force density with three resolutions in Fig. H.15, where analytical lines are computed with software Maxima. There is no convergence of force in the strict sense as reported previously. However, results from scheme B, C, D with $N_t \geq 1280$ follow the reference line reasonably close, with a few exceptions at turning points of the curvature. The results of scheme A are off the reference. We may draw similar conclusions from the results of Fig. H.16 that all three extended schemes are noisy, but follow the reference lines closely. For the force due to ADE energy, we observe that scheme C is less accurate in comparison with the other two schemes, as shown on Fig. H.17.

References

