

# Mathematical modelling of cell membranes

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**Abstract**—This article aims to show the latest methods of mathematical modelling of biological cell membranes. We first presented a literature review on recent research about incorporating multi-physics processes into mathematical models. We then presented a mathematical and numerical shape optimization framework using a gradient flow method and a finite element method to solve cell membrane dynamics specifically for the elastic bending energy on evolving surfaces.

## I. INTRODUCTION

Cell membranes are the foundation of the origin of life, but are also linked to the dynamics of virus infections and genetic mutations since it controls what substances can exit or enter the cell [1, 2]. In fact, a good understanding of the cell membrane is important for engineering proteins to manipulate various intracellular processes in living systems [3].

One of the primary components of the cell membranes is lipids which serve many different functions. The lipids form a bilayer with remarkable properties such as selective flexibility, fluidity, shape optimization and its ability to fuse or divide without creating any form of leakage [1]. Thus, physical processes like elastic bending forces, fluid dynamics, temperature and diffusion are essential to how a cell membrane will evolve [4, 5].

Generally, based on the principle of least action, will the dynamical system seek the minimal membrane energy configuration. For instance, let the membrane have an elastic bending energy functional, then will the cell membrane evolve towards an optimal shape for minimum mechanical energy. Another example is if there is a diffusion of a two-phase system on the membrane such that the concentrations of the two phases seek their minimal potential chemical energy. We will now describe how we could approach some of these problems mathematically.

### A. Elastic bending energy on evolving surfaces

Assuming that the system is a single-phase system, i.e., the lipids are uniformly distributed, can the elastic bending energy be modelled using the Canham-Helrich energy functional [6, 7, 4]. Let us denote  $b_b, b_k$  and  $H_0$  as parameters based on physical

models, then can the energy functional be denoted as,

$$\mathcal{E}_{CH}(\Gamma(t)) = \int_{\Gamma} b_b (H - H_0)^2 + b_k K. \quad (1)$$

Here is  $H = \kappa_1 + \kappa_2$  denoted as the mean curvature and  $K = \kappa_1 \kappa_2$  as the gaussian curvature with respectively and  $\kappa_1$  and  $\kappa_2$  as principal curvatures.  $\Gamma(t) = \Gamma$  is here an evolving 2-dimensional and closed surface in  $\mathbb{R}^3$ , for more info see section II. Using the Gauss-Bonnet theorem, can it be shown that the problem above is equivalent to the so-called Willmore energy functional [8, 9],

$$\mathcal{E}_W(\Gamma(t)) = \int_{\Gamma} \frac{1}{2} H^2. \quad (2)$$

This is a well-known problem in the mathematical community [10, 11, 12, 13]. In fact, it is a mathematical tool used to study the geometry of surfaces because it can be used to study the diffeomorphism from an initial surface to a minimal energy configuration, which are surfaces with the least possible area for a given boundary. This is important in many areas of mathematics, including differential geometry, topology, and mathematical physics [14, 15, 16].

It has been established many numerical methods for shape optimization problems [17, 18], evolving surface partial differential equations (PDE) [19, 20, 21, 22, 23, 24, 25] and specific algorithms for the Willmore energy problem (2) [26, 27, 28, 29, 30]. However, the field is still in active research since many methods is not rigorously shown to be consistent.

### B. Two-phase separation modelling on predefined evolving surfaces

It also turns out that the lipids often accumulate into so-called lipid rafts, which serve as a rigid platform for proteins with special properties such as intracellular trafficking of lipids and lipid-anchored proteins [31]. Modelling of lipid rafts formation can be modelled as a two-phase separation problem based on minimization of the Ginzburg-Landau energy functional [32],

$$\mathcal{E}_{GL}(c) = \int_{\Gamma(t)} \Psi(c) + \frac{\gamma}{2} |\nabla c|^2, \quad (3)$$

which describes the chemical energy for a concentration  $c : \Gamma(t) \times [0, T] \mapsto [0, 1]$ . Here is  $\Psi(c) : \mathbb{R} \mapsto \mathbb{R}$  denoted as a nonlinear scalar chemical potential function. Keep in mind that unlike the Willmore

energy functional (2), where the  $\Gamma(t)$  is determined by the elastic properties, should the energy functional (3) be interpreted as a chemical diffusion problem a predefined evolving domain  $\Gamma(t)$ . Usually is this problem solved by deriving equivalent variants of partial differential equations (PDE), such as the Allen-Cahn equation (or the Cahn-Hilliard equation if the total concentration is globally conserved) on evolving domains. For further details, see [32, 33, 34, 35, 36].

### C. Multiphysics problems on evolving surfaces

Ultimately, the cell membrane will consist of interactions of several physics (temperature, elasticity, chemical diffusion, internal fluid pressure etc.)[4]. Hence, being able to model several processes may give unforeseen results.

An interesting example is to couple the energy functionals (3) and (1) since the lipid-rafts formation is said to change the elasticity properties of the membrane, maybe a good model for how cell membranes evolve to specific shapes or execute cell division. One way to couple the energy functionals is to let the parameters  $b_b, b_k$  and  $H_0$  be some function of the time dependent concentration  $c$ , i.e.,

$$\begin{aligned} \mathcal{E}_{CHGL}(\Gamma(t), c(t)) = & \int_{\Gamma} b_b(c) (H - H_0(c))^2 \\ & + \int_{\Gamma} b_k(c) K \\ & + \int_{\Gamma} \Psi(c) + \frac{\gamma}{2} |\nabla c|^2, \end{aligned}$$

For more information, see [37].

Recently some authors also coupled diffusion processes and the so-called mean curvature energy, see [38, 39]. It is well known that lipids travel along the cell membrane in a fluidic manner, hence, it is also of interest to couple the Ginzburg-Landau energy functional (3) (or more specifically, the Cahn-Hilliard equation) with the Navier-Stokes equation. Some methods have been proposed methods for solving the problem on surfaces and evolving surfaces, but it remains a field of active research [40]. As far as an author knows, coupling the Canham-Helrich energy functional (1), Ginzburg-Landau energy functional (3), and Navier-Stokes equation remains an open problem.

Some physical processes may require constant area and volume. This can be added by introducing respective area and volume functionals, see [41, Definition 2.5].

Until now have all the models assumed that the membrane has no difference in internal and external pressure. As a matter of fact, osmotic pressure can be introduced by adding an energy functional using the van't Hoff formula. Let  $V_p$  be the volume of a

closed evolving surface  $\Gamma(t)$ , we can then model the difference of internal and external pressure as,

$$\Delta P(V_p) = P_{in} - P_{out} = iRT \left( \frac{n}{V_p} - \bar{c} \right),$$

where  $i, R, T, \bar{c}$  and  $n$  are the van't Hoff index, ideal gas constant, temperature, ambient molar concentration and molar amount of the enclosed solute. Then the energy functional has the form,

$$\mathcal{E}_p(\Gamma(t)) = \int_{\Gamma} \Delta P(V_p),$$

For more information, see [42].

### D. Outline of this report

The long-term goal would be to solve the multiphysics problems above. However, many of the problems presented are fairly complicated to solve numerically and require sophisticated techniques. Hence, in this report, we focus on the latest research within the numerical optimizations methods of finding the minima of the energy functional (2).

First of all, we will establish notation by including a section for definitions and important results from differential geometry and shape derivatives. We will then derive the underlying dynamical system of evolutionary system dynamics using the gradient flow technique inspired by shape optimization methods based on the work done in [43]. Lastly, we will establish the numerical methods of the system dynamics by applying recent methods using an evolutionary surface finite element method (FEM) [29, 30].

## II. BACKGROUND THEORY

### A. Calculus on surfaces

This subsection is inspired by the notation used in [29, 43]. Let  $\Gamma^0 \subset \mathbb{R}^3$  be an initial 2-dimensional, smooth, compact, and oriented surface with no boundary at  $t = 0$  s.t. we can assign any unique points  $p \in \Gamma^0$ . We define the time evolutionary surface to be on the form [29, Section 2.1],

$$\begin{aligned} \Gamma = \Gamma(t) &= \Gamma(X(\cdot, t)) \\ &= \{X(p, t) : p \in \Gamma^0\} \end{aligned}$$

transformed via the smooth mapping,

$$X : \Gamma^0 \times [0, T] \mapsto \mathbb{R}^3.$$

An important regularity result is that if  $\Gamma^0$  is of class  $C^\infty$ , then  $\Gamma$  is also of class  $C^\infty$  for  $\forall t \in [0, T]$  [17, 43].

We will define a unique evolutionary point  $x \in \Gamma(t)$  based on the smooth mapping  $X(p, t) = x$ . A way to imagine this is to have an initial point in  $\Gamma^0$  and the mapping  $X$  describes how this point will deform over time. The outer unit normal vector field of  $\Gamma(t)$  is defined as the mapping  $\nu : \Gamma \mapsto \mathbb{R}^3$ .

Using the notation presented in [43] and [29] can we define the basic surface differential operators.

Consider a scalar function,  $u : \Gamma \mapsto \mathbb{R}$ , and a vector-valued function,  $\hat{u} : \Gamma \mapsto \mathbb{R}^3$ . We can then denote  $\nabla_\Gamma u : \Gamma \mapsto \mathbb{R}^3$  as the projection gradient operator,

$$\nabla_\Gamma u = \nabla \tilde{u}|_\Gamma - \langle \nu, \nabla \tilde{u}|_\Gamma \rangle \nu.$$

Here  $\tilde{u}$  is a smooth extension of  $u : \Gamma \rightarrow \mathbb{R}$  to an 3-dim neighbourhood  $U \in \mathbb{R}^3$  of the surface  $\Gamma$  so that  $\tilde{u}|_\Gamma = u$ . For more information see [19, Definition 2.3].

Similarly, for the vector-valued function is the operator defined s.t.

$$\nabla_\Gamma \hat{u} = (\nabla_\Gamma u_1, \nabla_\Gamma u_2, \nabla_\Gamma u_3)^T.$$

The surface divergence for a vector-valued function is defined as

$$\nabla_\Gamma \cdot \hat{u} = \nabla \cdot \hat{u} - \nu^T D\hat{u} \cdot \nu$$

Here  $D\hat{u}$  denotes the Jacobian of  $\hat{u}$ . Similarly, the Laplace-Beltrami operator  $\Delta_\Gamma u : \Gamma \mapsto \mathbb{R}$  is proven to have the form [44, Lemma 1],

$$\begin{aligned} \Delta_\Gamma u &= \nabla_\Gamma \cdot \nabla_\Gamma u \\ &= \Delta u - \nu^T D^2 u \cdot \nu - H \partial_\nu u \end{aligned}$$

Here  $D^2 u$  denotes the Hessian of the scalar function  $u$ . In the case of a vector-valued function is the operator defined as

$$\Delta_\Gamma \hat{u} = (\Delta_\Gamma u_1, \Delta_\Gamma u_2, \Delta_\Gamma u_3)^T$$

A method to compute the mean curvature and the so-called Frobenius norm of the matrix  $A$  involves applying the extended Weingarten map,  $A(x) = \nabla_\Gamma \nu(x)$ , s.t. these identities holds ,

$$\begin{aligned} H &= \text{tr}(A) = k_1 + k_2, \\ |A|^2 &= k_1^2 + k_2^2, \end{aligned}$$

see [29]. We may also want to use these definitions to introduce the following identities,

$$\begin{aligned} \partial_\nu H &= -|A|^2, \\ \nabla_\Gamma H &= \Delta_\Gamma \nu + |A|^2 \nu. \end{aligned}$$

Again, see Lemma 3.3 and Lemma 3.2 in [43].

### B. Evolutionary Surface Dynamics

In this section will we develop a framework for evolutionary surface dynamics.

First of all, we can denote the velocity  $v : \Gamma \mapsto \mathbb{R}^3$  to be

$$\frac{dx}{dt} = v(x) \quad \forall x \in \Gamma(t). \quad (4)$$

Given a model of the velocity  $v$  makes it possible to solve the ordinary differential equation (ODE) (4) and determine the evolution of a point on the surface  $\Gamma(t)$ . In this article will we assume that the velocity only has a normal component to the surface, i.e., it exists a scalar function  $V : \Gamma \mapsto \mathbb{R}$  s.t.  $v = V\nu$ .

Recall that the point  $x = X(p, t)$  is arising from the smooth mapping from the point  $p$  in  $\Gamma^0$  to  $\Gamma(t)$ .

Now, let some arbitrary energy functional have the form,

$$\mathcal{J}(\Gamma(t)) = \int_{\Gamma(t)} \varphi(x).$$

For instance, in the case presented in (2) we define  $\varphi = H^2$ .

Based on [43], the shape derivative of this energy functional at some time  $t$  in the direction of the velocity  $v(x)$  from (4) is defined as

$$d\mathcal{J}(\Gamma(t); v) = \lim_{\varepsilon \rightarrow 0} \frac{\mathcal{J}(\Gamma(t + \varepsilon)) - \mathcal{J}(\Gamma(t))}{\varepsilon}.$$

For a more detailed description of the shape derivative, see [17, Definition 2.19].

Assume we have a scalar function  $f : \Gamma(t) \mapsto \mathbb{R}$ . Similarly, as for the shape derivative, we can now denote the material derivative at time  $t$  in the direction of the velocity  $v(x)$  as

$$\begin{aligned} \frac{D}{Dt} f(x, t; v) &= \frac{d}{dt} f(X(p, t), t) \\ &= \lim_{\varepsilon \rightarrow 0} \frac{f(X(p, t + \varepsilon), t + \varepsilon) - f(X(p, t), t)}{\varepsilon} \\ &= \frac{\partial f}{\partial t} + v \cdot \nabla f. \end{aligned}$$

See [17, Definition 2.74] or more specifically [19, Equation 5.1] for more information.

We denote the  $L^2(\Gamma)$  as the space of all functions that are square-integrable with respect to the surface measure, i.e.,

$$L^2(\Gamma) = \left\{ u : \Gamma \mapsto \mathbb{R} \mid \int_\Gamma |u|^2 < \infty \right\}$$

Let  $u, v \in L^2(\Gamma)$ , then can we define the norm and the inner-product

$$\begin{aligned} \|u\|_{L^2(\Gamma)}^2 &= \int_\Gamma |u|^2 \\ (u, v)_{L^2(\Gamma)} &= \int_\Gamma uv \end{aligned}$$

In this paper will we also the shorthand notation  $\|u\|_{L^2(\Gamma)} = \|u\|_\Gamma$  and  $(u, v)_{L^2(\Gamma)} = (u, v)_\Gamma$ . The Sobolev space  $H^1(\Gamma)$  is defined as the space of all functions and its first weak derivative with a finite  $L^2$ -norm, i.e.,

$$H^1(\Gamma) = \left\{ f : \Gamma \mapsto \mathbb{R} \mid \int_\Gamma |f|^2 + |\nabla_\Gamma f|^2 < \infty \right\},$$

with the following norm and inner product  $u, v \in H^1(\Gamma)$ ,

$$\begin{aligned} \|u\|_{H^1(\Gamma)} &= \|u\|_\Gamma + \|\nabla_\Gamma u\|_\Gamma, \\ (u, v)_{H^1(\Gamma)} &= (u, v)_\Gamma + (\nabla_\Gamma u, \nabla_\Gamma v)_\Gamma. \end{aligned}$$

If we have a vector-valued function that  $u : \Gamma \mapsto \mathbb{R}^3$  where each element is in  $H^1(\Gamma)$  or  $L^2(\Gamma)$ , then do we denote is as a member of respectively  $[H^1(\Gamma)]^3$  or  $[L^2(\Gamma)]^3$ .

The method we will use in this paper to minimize the energy functional (2) is to compute the so-called gradient flow. The fundamental idea of the

gradient flow is to give rise to evolutionary dynamics to decrease the overall energy functional both in space and time, i.e.,  $\mathcal{J}(\Gamma(t_2)) < \mathcal{J}(\Gamma(t_1))$  for all  $t_2 > t_1$ . For more information about gradient flows, see [45, 46]. Now assume we have the velocity defined in (4) to be  $v \in [L^2(\Gamma)]^3$ , then we define the  $L^2$  gradient flow s.t.

$$(v, \varphi)_\Gamma = -d\mathcal{J}(\Gamma; \varphi) \quad \forall \varphi \in [L^2(\Gamma)]^3.$$

It turns out that if  $v \neq 0$ , then is this equivalent to

$$d\mathcal{J}(\Gamma; v) = -\|v\|_{L^2(\Gamma)}^2 < 0, \quad (5)$$

see [18]. Hence, we finally have a toolbox which can be used to model evolutionary dynamics for moving surfaces.

### III. EVOLUTIONARY DYNAMICS OF THE WILLMORE FLOW

The goal is to derive the evolutionary dynamics of the Willmore energy (2).

Recall that we define the velocity (4) to only have a normal component, i.e.,  $v(x) = V\nu$ . The shape derivative for (2) in the direction of some velocity  $v \in [H^1(\Gamma)]^3$  has the form

$$d\mathcal{E}_W(\Gamma; v) = \int_\Gamma \left( -\Delta_\Gamma H + \frac{1}{2}H^3 - H|A|^2 \right) V$$

A complete derivation of the shape derivative can be found in [43, Corollary 4.7]. Consequently, by applying the gradient flow in (5) and using that  $\|v\|_\Gamma = \|V\|_\Gamma^2$ , will we end up with

$$\|V\|_\Gamma^2 = \int_\Gamma V^2 = -d\mathcal{E}_W(\Gamma; v).$$

Hence, the gradient flow is equivalent to

$$V = \Delta_\Gamma H + Q, \quad (6)$$

where we denote the nonlinear cubic term as  $Q = -\frac{1}{2}H^3 + H|A|^2$ .

From [29, Lemma 2.1] it derived that (6) must satisfy the following material derivatives,

$$\begin{aligned} \frac{D}{Dt} H &= -(\Delta_\Gamma + |A|^2) V, \\ \frac{D}{Dt} \nu &= (-\Delta_\Gamma + (HA - A^2)) z \\ &\quad + |\nabla_\Gamma H|^2 \nu - 2(\nabla_\Gamma \cdot (A\nabla_\Gamma H)) \nu \\ &\quad - A^2 \nabla_\Gamma H - \nabla_\Gamma Q. \end{aligned}$$

Here is the substitution variable introduced s.t.  $z = \Delta_\Gamma \nu + |A|^2 \nu$ .

It exists methods which do not exploit the material derivatives [28, 47]. However, it turns out that including these material derivatives brings additional computational costs, but provides so-called full-order approximation to the mean curvature,  $H$ , and the normal vector,  $\nu$ , and, thus, allows us to construct

rigorous convergence proofs for evolving surface FEM, see [29, 21].

Recent work has proposed that the current method may not conserve the mesh quality while the surface is restricted to evolving along the normal velocity. Thus, a new variation of the standard methods has been considered by introducing a tangential velocity component via the equation  $H = -v \cdot \nu$ . Hence, also allows the mesh to be less deformed, see more at [30]. However, in this article will we not consider it.

Finally, we end up with the following strong form of the second-order evolutionary system of PDE.

$$\frac{d}{dt} H = -\Delta_\Gamma V - |A|^2 V, \quad (7a)$$

$$V = \Delta_\Gamma H + Q, \quad (7b)$$

$$\begin{aligned} \frac{d}{dt} \nu &= (-\Delta_\Gamma + (HA - A^2)) z \\ &\quad + |\nabla_\Gamma H|^2 \nu \\ &\quad - 2(\nabla_\Gamma \cdot (A\nabla_\Gamma H)) \nu \\ &\quad - A^2 \nabla_\Gamma H - \nabla_\Gamma Q, \end{aligned} \quad (7c)$$

$$z = \Delta_\Gamma \nu + |A|^2 \nu, \quad (7d)$$

$$\frac{d}{dt} x = v. \quad (7e)$$

where the terms are,

$$v = V\nu,$$

$$Q = -\frac{1}{2}H^3 + H|A|^2,$$

$$A = \nabla_\Gamma \nu$$

Recall that the material derivative operator  $\frac{D}{Dt}$  is simply equivalent to the time derivative  $\frac{d}{dt}$ , thus, it is now possible to apply normal techniques for time discretization.

It turns out from basic numerical theory that rewriting an equivalent weak formulation (integral form) of the system dynamics (7) makes the problem suitable for numerical approximations since it involves complex shape dynamics. Hence, we will now introduce the weak formulation of the system dynamics.

Let us denote the following trial functions,

$$\begin{aligned} (H \times V \times \nu \times z) \in \\ (H^1(\Gamma), H^1(\Gamma), [H^1(\Gamma)]^3, [H^1(\Gamma)]^3), \end{aligned} \quad (8)$$

and similarly the test functions,

$$\begin{aligned} (\chi^H \times \chi^V \times \chi^\nu \times \chi^z) \in \\ (H^1(\Gamma), H^1(\Gamma), [H^1(\Gamma)]^3, [H^1(\Gamma)]^3). \end{aligned} \quad (9)$$

It has been proven that if you can find any trial functions (8) that does satisfy the following weak formulation (10) for all test functions (9), then the solution is equivalent to solving the dynamics presented in (7). See [29] for more information.

$$\left(\frac{d}{dt}H, \chi^H\right)_\Gamma = (\nabla_\Gamma V, \nabla_\Gamma \chi^H)_\Gamma - \left(|A|^2 V, \chi^H\right)_\Gamma, \quad (10a)$$

$$(V, \chi^V)_\Gamma = -(\nabla_\Gamma H, \nabla_\Gamma \chi^V)_\Gamma + (Q, \chi^V)_\Gamma, \quad (10b)$$

$$\begin{aligned} \left(\frac{d}{dt}\nu, \chi^\nu\right)_\Gamma &= (\nabla_\Gamma z, \nabla_\Gamma \chi^\nu)_\Gamma \\ &+ ((HA - A^2)z, \chi^\nu)_\Gamma \\ &+ \left(|\nabla_\Gamma H|^2 \nu, \chi^\nu\right)_\Gamma \\ &+ (A^2 \nabla_\Gamma H, \chi^\nu)_\Gamma \\ &+ 2(A \nabla_\Gamma H, \nabla_\Gamma \chi^\nu \nu)_\Gamma \\ &+ (Q, \nabla_\Gamma \cdot \chi^\nu)_\Gamma \\ &- (QH\nu, \chi^\nu)_\Gamma, \end{aligned} \quad (10c)$$

$$(z, \chi^z)_\Gamma = -(\nabla_\Gamma \nu, \nabla_\Gamma \chi^z)_\Gamma + \left(|A|^2 \nu, \chi^z\right)_\Gamma \quad (10d)$$

$$\frac{d}{dt}x = v. \quad (10e)$$

Note that the time-dependent variables  $\nu, H$  and  $x$  are initialized at  $t = 0$  based on  $\Gamma^0$ . It is also essential to take into account that this is a highly nonlinear PDE, hence, proving uniqueness is a difficult task. However, it has been proved that the Willmore flow has a unique solution if the initial surface  $\Gamma^0$  is close to a sphere [48]. It has also been discussed that under some shapes, does the Willmore functional, in fact, develop singularities [49]. Furthermore, no literature has shown the uniqueness of the Willmore flow coupled with the material derivatives, i.e., dynamics presented in (7).

#### IV. NUMERICAL METHODS

To be able to find a numerical approximation of the weak formulation (10) will we formulate an evolving surface element method (FEM) for the evolutionary equation PDEs coupled with the evolving surface velocity. We will mostly use the notation and methods described in [29, 30].

##### A. Triangular mesh for $\Gamma^0$

Let initial surface  $\Gamma^0 \in \mathbb{R}^3$  have the triangular mesh  $\mathcal{T}_h$  consisting of triangles  $T$ . We will assume that the mesh is conform, i.e., for any  $T_1, T_2 \in \mathcal{T}_h$ ,  $T_1 \neq T_2$  and  $T_1 \cap T_2 \neq \emptyset$ , then must  $T_1$  and  $T_2$  share either a vertex or a facet. Let diameter of each triangle  $h_T$  be denoted as,

$$\begin{aligned} h_T &= \max_{x_1, x_2 \in T} \text{dist}(x_1, x_2), \\ h_{\min} &= \min_{T \in \mathcal{T}_h} h_T, \\ h_{\max} &= \max_{T \in \mathcal{T}_h} h_T, \end{aligned}$$

where  $h_{\min}$  and  $h_{\max}$  is the maximum and minimum diameter of an individual triangle  $T$  in  $\mathcal{T}_h$ .

We define the chunkiness parameter  $c_T = h_T/r_T$ , where  $r_T$  is the largest ball inside inscribed in  $T$ . We will then assume that the mesh is shape regular and quasi-uniform, i.e.,  $c_T \leq c$  and  $h_{\max} \leq ch_{\min}$  for a constant  $c$  independent of  $h_T$  and  $T$ . See [19, Section 4.1] for more information.

##### B. Finite surface element

In this section is, the goal to develop discrete analogues of the definitions we introduced in subsections II-A and II-B.

Let  $\mathcal{T}_h$  be the triangulation of  $\Gamma^0$ . Now denote the vector  $\mathbf{x} = \mathbf{x}(t) \in \mathbb{R}^{3N}$  as a collection of all evolving nodes,  $x_j(t) \in \mathbb{R}^3$ ,  $j \in \mathcal{I}$ , by a piecewise polynomial interpolation with degree  $k$ . Here is the index of all the nodes defined as  $\mathcal{I} = \{1, \dots, N\}$ , where  $N$  is the total number of nodes.

We denote the discretized surface,  $\Gamma_h[\mathbf{x}(t)]$ , to be the numerical approximation of the surface  $\Gamma(t)$ . As an initial condition do we construct the initial nodes,  $x_j(0) = p_j \forall j \in \mathcal{I}$ , s.t.  $\Gamma_h^0 = \Gamma_h[\mathbf{x}(0)]$  interpolates the initial surface,  $\Gamma^0$  in the nodal points  $p_j \in \Gamma^0$ ,  $j \in \mathcal{I}$ .

An essential piece of the puzzle is the finite element basis on  $\Gamma_h[\mathbf{x}]$ , which is denoted to have the form,

$$\phi_j[\mathbf{x}] : \Gamma_h[\mathbf{x}] \mapsto \mathbb{R}, \quad j \in \mathcal{I}.$$

In fact, the basis satisfies the identity,

$$\phi_j[\mathbf{x}](x_i) = \delta_{ij} \quad \forall i, j \in \mathcal{I}.$$

Finally, we can now define the so-called evolving finite element space of  $\Gamma_h[\mathbf{x}(t)]$  as,

$$\begin{aligned} S_h[\mathbf{x}] &= S_h(\Gamma_h[\mathbf{x}]) \\ &= \text{span} \left\{ \sum_{j \in \mathcal{I}} c_j \phi_j[\mathbf{x}] \mid c_j \in \mathbb{R} \right\}. \end{aligned}$$

More precisely, can we denote a  $C^0$  finite element space of  $k$ -th order as,

$$\begin{aligned} S_{h,k}[\mathbf{x}] &= \{\chi_h \in C^0(\Gamma_h[\mathbf{x}]), \\ &\chi_h \in \mathcal{P}^k(T) \forall T \in \mathcal{T}_h\}, \end{aligned}$$

where  $\mathcal{P}^k$  is the set of all polynomials in three dimensions with order less or equal to  $k$ . We will use the notation  $S_h[\mathbf{x}] = S_{h,k}[\mathbf{x}]$  unless the order of the element is specified. In the three dimensions defined as,

$$S_h[\mathbf{x}]^3 = (S_h[\mathbf{x}], S_h[\mathbf{x}], S_h[\mathbf{x}])^T.$$

The discretized surface mapping,  $X_h : \Gamma_h^0 \mapsto \Gamma_h[\mathbf{x}(t)]$ , is denoted as

$$X_h(p_h, t) = \sum_{j \in \mathcal{I}} x_j(t) \phi[x(0)](p_h), \quad p_h \in \Gamma_h^0,$$



and the problem obviously does satisfy the identities;  
 $X_h(p_h, 0) = p_h \forall p_h \in \Gamma_h$ , the evolutionary property  
 $X_h(p_j, t) = x_j(t) \forall j \in \mathcal{I}$ , and

$$\begin{aligned}\Gamma_h &= \Gamma_h(t) = \Gamma_h[\mathbf{x}(t)] \\ &= \Gamma_h[X_h(\cdot, t)] \\ &= \{X_h(p_h, t) : p_h \in \Gamma_h^0\}.\end{aligned}$$

For shorthand notation, is the discretized point defined as  $x_h = X_h(p_h, t) \in \Gamma_h$ . Thus discretized velocity  $v_h(x_h, t) : \Gamma_h \mapsto \mathbb{R}^3$  is defined as

$$v_h(x_h, t) = \sum_{j \in \mathcal{I}} v_j(t) \phi_j[\mathbf{x}(t)](x_h).$$

Hence, by introducing  $\mathbf{v} = \mathbf{v}(t)$  as a collection of the velocity nodes,  $v_j \in \mathbb{R}^3$ , can we define the evolutionary dynamics of the nodal points  $\mathbf{x}$  s.t. this holds,

$$\frac{d}{dt} \mathbf{x}(t) = \mathbf{v}(t).$$

Ultimately, the discrete material derivative of a function  $f_h : \Gamma_h \mapsto \mathbb{R}$  is simply defined in the direction in the velocity  $v_h$  as

$$\begin{aligned}\frac{D}{Dt} f_h(x_h, t; v_h) &= \frac{d}{dt} f_h(x_h, t; v_h) \\ &= \sum_{j \in \mathcal{I}} \frac{df_j(t)}{dt} \phi_j[\mathbf{x}](x_h)\end{aligned}$$

where  $f_j$  is the nodal variables.

### C. Evolving surface finite element method

The goal is to construct a evolving finite element scheme using the evolving finite element space. Let us denote the following trial functions,

$$\begin{aligned}(H_h \times V_h \times \nu_h \times z_h) \in \\ (S_h[\mathbf{x}], S_h[\mathbf{x}], S_h[\mathbf{x}]^3, S_h[\mathbf{x}]^3),\end{aligned}\quad (11)$$

and similarly the test functions,

$$\begin{aligned}(\chi_h^H \times \chi_h^V \times \chi_h^\nu \times \chi_h^z) \in \\ (S_h[\mathbf{x}], S_h[\mathbf{x}], S_h[\mathbf{x}]^3, S_h[\mathbf{x}]^3),\end{aligned}\quad (12)$$

We will define the discrete helping functions as,

$$\begin{aligned}v_h &= V_h \nu_h, \\ Q_h &= -\frac{1}{2} H_h^3 + H_h |A_h|^2, \\ A_h &= \frac{1}{2} (\nabla_{\Gamma_h} \nu_h + (\nabla_{\Gamma_h} \nu_h)^T)\end{aligned}$$

The evolving surface FEM for (7) is to find trial functions (11) and  $x_h$  s.t. it satisfies the following discrete weak formulation (10) for all test functions (9). Again, see [29] for more information.

$$\begin{aligned}\left(\frac{d}{dt} H_h, \chi_h^H\right)_{\Gamma_h} &= (\nabla_{\Gamma_h} V_h, \nabla_{\Gamma_h} \chi_h^H)_{\Gamma_h} \\ &\quad - (|A_h|^2 V_h, \chi_h^H)_{\Gamma_h},\end{aligned}\quad (13a)$$

$$\begin{aligned}(V_h, \chi_h^V)_{\Gamma} &= -(\nabla_{\Gamma_h} H_h, \nabla_{\Gamma_h} \chi_h^V) \\ &\quad + (Q_h, \chi_h^V)_{\Gamma_h},\end{aligned}\quad (13b)$$

$$\begin{aligned}\left(\frac{d}{dt} \nu_h, \chi_h^\nu\right)_{\Gamma_h} &= (\nabla_{\Gamma_h} z_h, \nabla_{\Gamma_h} \chi_h^\nu)_{\Gamma_h} \\ &\quad + ((H_h A_h - A_h^2) z_h, \chi_h^\nu)_{\Gamma_h} \\ &\quad + (|\nabla_{\Gamma_h} H_h|^2 \nu_h, \chi_h^\nu)_{\Gamma_h} \\ &\quad + (A_h^2 \nabla_{\Gamma_h} H_h, \chi_h^\nu)_{\Gamma_h} \\ &\quad + 2(A_h \nabla_{\Gamma_h} H_h, \nabla_{\Gamma_h} \chi_h^\nu \nu_h)_{\Gamma_h} \\ &\quad + (Q_h, \nabla_{\Gamma_h} \cdot \chi_h^\nu)_{\Gamma_h} \\ &\quad - (Q_h H_h \nu_h, \chi_h^\nu)_{\Gamma_h},\end{aligned}\quad (13c)$$

$$\begin{aligned}(z_h, \chi_h^z)_{\Gamma_h} &= -(\nabla_{\Gamma_h} \nu_h, \nabla_{\Gamma_h} \chi_h^z)_{\Gamma_h} \\ &\quad + (|A_h|^2 \nu_h, \chi_h^z)_{\Gamma_h}\end{aligned}\quad (13d)$$

$$\frac{d}{dt} x_h = v_h. \quad (13e)$$

Note that the time-dependent variables  $\nu_h, H_h$  and  $x_h$  is initialized at  $t = 0$  based on  $\Gamma^0$ .

### D. The matrix-vector formulation

To simplify the system presented in (13) is it possible to solve a equivalent i a matrix-vector formulation.

First of all, let us represent the nodal values as vectors. Let the velocity have the form  $\mathbf{v} = (v_j) \in \mathbb{R}^{3N}$  with the corresponding speed  $\mathbf{V} = (V_j) \in \mathbb{R}^N$  and normal vector  $\mathbf{n} = (\nu_j) \in \mathbb{R}^{3N}$  s.t. it fulfills the Hadamard product  $\mathbf{v} = \mathbf{V} \circ \mathbf{n}$ .

Similarly, we define the mean curvature  $\mathbf{H} = (H_j) \in \mathbb{R}^N$  and the substitution variable  $\mathbf{z} = (z_j) \in \mathbb{R}^{3N}$ . To simplify notation will we introduce the block structured vectors,

$$\mathbf{u} = \begin{pmatrix} \mathbf{H} \\ \mathbf{n} \end{pmatrix} \in \mathbb{R}^{4N} \quad \text{and} \quad \mathbf{w} = \begin{pmatrix} \mathbf{V} \\ \mathbf{z} \end{pmatrix} \in \mathbb{R}^{4N}.$$

Recall the basis functions,  $\phi_i[\mathbf{x}] \in S_h[\mathbf{x}]$ ,  $i \in \mathcal{I}$ . We can then define the matrices

$$\mathbf{M}(\mathbf{x})_{i,j} = (\phi_i[\mathbf{x}], \phi_j[\mathbf{x}])_{\Gamma_h}, \quad i, j \in \mathcal{I}.$$

and

$$\mathbf{A}(\mathbf{x})_{i,j} = (\nabla_{\Gamma_h} \phi_i[\mathbf{x}], \nabla_{\Gamma_h} \phi_j[\mathbf{x}])_{\Gamma_h}, \quad i, j \in \mathcal{I}.$$

We may also define the corresponding diagonal block matrices using the Kronecker product s.t.

$$\begin{aligned}\mathbf{M}^4(\mathbf{x}) &= I \otimes \mathbf{M}(\mathbf{x}) \in \mathbb{R}^{4N \times 4N} \\ \mathbf{A}^4(\mathbf{x}) &= I \otimes \mathbf{A}(\mathbf{x}) \in \mathbb{R}^{4N \times 4N}\end{aligned}$$

using the identity  $I \in \mathbb{R}^{4 \times 4}$ . Moreover, we can also define the matrices  $\mathbf{F}_1(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^{N \times N}$ ,  $\mathbf{F}_2(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^{3N \times 3N}$  s.t.

$$\mathbf{F}_1(\mathbf{x}, \mathbf{u})_{i,j} = -(|A_h|^2 \phi_j[\mathbf{x}], \phi_i[\mathbf{x}])_{\Gamma_h},$$

where  $i, j \in \mathcal{I}$ . Likewise we define,

$$\mathbf{F}_2(\mathbf{x}, \mathbf{u})_{i,j} = ((H_h A_h - A_h^2) \phi_j[\mathbf{x}], \phi_i[\mathbf{x}])_{\Gamma_h},$$

where the indices are  $i, j = 1, \dots, 3N$ . Again, the corresponding block matrix is on the form,

$$\mathbf{F}(\mathbf{x}, \mathbf{u}) = \begin{pmatrix} \mathbf{F}_1(\mathbf{u}, \mathbf{x}) & 0 \\ 0 & \mathbf{F}_2(\mathbf{u}, \mathbf{x}) \end{pmatrix}.$$

Our goal now is to simplify the notation for the nonlinear functions. Let  $\mathbf{f}_2(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^{3N}$ ,  $\mathbf{g}_1(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^N$  and  $\mathbf{g}_2(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^{3N}$ . We can first define the function

$$\begin{aligned} \mathbf{f}_2(\mathbf{x}, \mathbf{u})_{j+(l-1)N} = & ( (|\nabla_{\Gamma_h} H_h|^2 \nu_h)_l, \phi_j[\mathbf{x}] )_{\Gamma_h} \\ & + ((A_h^2 \nabla_{\Gamma_h} H_h)_l, \phi_j[\mathbf{x}])_{\Gamma_h} \\ & + 2((A_h \nabla_{\Gamma_h} H_h) \cdot \nabla_{\Gamma_h} \phi_j[\mathbf{x}], (v_h)_l)_{\Gamma_h} \\ & + ((Q_h)_l, (\nabla_{\Gamma_h})_l \phi_j[\mathbf{x}])_{\Gamma_h} \\ & - (Q_h H_h (v_h)_l, \phi_j[\mathbf{x}])_{\Gamma_h}, \end{aligned}$$

for  $j \in \mathcal{I}$  and  $l = 1, 2, 3$ . Similarly, we let

$$\mathbf{g}_1(\mathbf{x}, \mathbf{u})_j = (Q_h, \phi_j[\mathbf{x}])_{\Gamma_h},$$

$$\mathbf{g}_2(\mathbf{x}, \mathbf{u})_{j+(l-1)N} = (|A_h|^2 (v_h)_l, \phi_j[\mathbf{x}])_{\Gamma_h},$$

for  $j \in \mathcal{I}$  and  $l = 1, 2, 3$ . This can now be collected into the vectors  $\mathbf{f}(\mathbf{x}, \mathbf{u}), \mathbf{g}(\mathbf{x}, \mathbf{u}) \in \mathbb{R}^{4N}$  s.t.

$$\mathbf{f}(\mathbf{x}, \mathbf{u}) = \begin{pmatrix} 0 \\ \mathbf{f}_2(\mathbf{x}, \mathbf{u}) \end{pmatrix}, \quad \mathbf{g}(\mathbf{x}, \mathbf{u}) = \begin{pmatrix} \mathbf{g}_1(\mathbf{x}, \mathbf{u}) \\ \mathbf{g}_2(\mathbf{x}, \mathbf{u}) \end{pmatrix}$$

Finally, we can write the fully matrix-vector formulation of (13).

$$\mathbf{M}^4(\mathbf{x}) \frac{d\mathbf{u}}{dt} = \mathbf{A}(\mathbf{x})^4 \mathbf{w} + \mathbf{F}(\mathbf{x}, \mathbf{u}) \mathbf{w} + \mathbf{f}(\mathbf{x}, \mathbf{u}), \quad (14a)$$

$$\mathbf{M}^4(\mathbf{x}) \mathbf{w} = -\mathbf{A}(\mathbf{x})^4 \mathbf{u} + \mathbf{g}(\mathbf{x}, \mathbf{u}), \quad (14b)$$

$$\frac{d\mathbf{x}}{dt} = \mathbf{v}. \quad (14c)$$

Another observation is that the initial condition of  $\mathbf{u}$  and  $\mathbf{x}$  is easy to compute using the initial closed surface  $\Gamma_0$ . On the other hand, initial conditions for  $\mathbf{w}$  has to be evaluated using (7b) and (7d).

## V. FURTHER WORK

The final scheme described in (14) is not yet completely numerical solvable and still need some work, thus, implying that it is necessary to implement an nonlinear PDE-solver method, such as the Newton's method, to obtain a solution.

Secondly, it also remains to find a proper method for time discretization. However, this should be reasonably straightforward by applying the implicit Euler scheme or more sophisticated standard methods such as the backward differential formulas or Runge-Kutta methods.

If the numerical schemes above are provided, then the formulation should be reasonably possible to implement the problem using the modern finite

element software framework NGSolve [50]. In fact, recently it was shown that a modified formulation of (13) could be solved using the same software library [30].

## VI. CONCLUSION

We have presented several interesting multiphysics processes to consider when modelling cell membrane dynamics. First, we introduced an elastic bending energy on evolving surfaces using the Canham-Helrich energy functional (1) and the equivalent Willmore energy functional. Secondly, we established that the diffusion of a two-phase system can be modelled using the Ginzburg-Landau energy functional (3) and discussed how we could combine the energy functional models to do multiphysics problems.

To demonstrate the techniques used to solve physical problems on evolving domains, we chose the Willmore energy functional (2). The background theory of calculus on surfaces and evolutionary dynamics was briefly discussed and then applied to define the strong and weak (or integral) formulation of the system dynamics. We then established a basic numerical framework and introduced the evolution surface finite element method.

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