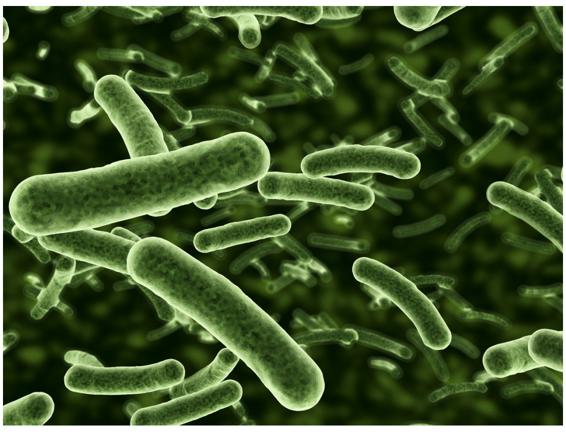
Research Project

Mathematical Modelling of Cell Membrane Dynamics

Isak Hammer



Department of Mathematical Sciences
Norwegian University of Science and Technology

1 Introduction

Cell membrane dynamics has recently had many important applications. For instance, it has been linked to detecting deceases such as Alzheimer's disease, cancer cells and is as well important for development new methods and vaccines [1].

Add more sources.

One of the primary components of the cell membranes are lipids which serve many different functions. A key function is that it is consisting of a bilayer of lipids which controls the structural rigidity and the fluidity of the membrane [2]. It also turns out that the lipids often accumulate into so-called lipid rafts which serves as a rigid platform for proteins with special properties such as intracellular trafficking of lipids and lipid-anchored proteins [3].

Modelling of lipid rafts formation can be modelled as a two-phase separation problem based on minimization of the Ginzburg-Landau energy functional [4]

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

which is describing the chemical energy for a concentration $c : \Gamma \times [0,T] \mapsto [0,1]$ over a surface membrane Γ. Several authors have solved this problem often results by deriving variants of Cahn Hilliard Equation or Allen Cahn Equation if the concentration is not conserved both standstill and evolving domains [4, 5, 6, 7, 8, 4]
.

Assuming that the system is a single-phase system can the elastic bending energy be modelled using the Canham Helrich energy functional [9, 5]

$$\mathcal{E}_e(\Gamma) = \int_\Gamma c_b H^2 + c_k K$$
.

Here is $H = \kappa_1 + \kappa_2$ denoted as the mean curvature and $K = \kappa_1\kappa_2$ as the gaussian curvature with respectively c_b and c_k as tuning parameters and κ_1 and κ_2 as principal curvatures. Using the Gauss-Bonnet theorem can it be shown that the problem above is equivalent to the so-called Willmore energy functional [10, 11]

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

This is a well known problem in the mathematical community [12, 13, 14]. In fact, it is a mathematical tool used to study the geometry of surfaces because it can be used to study the properties of minimal surfaces, 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 [15, 16, 17].

It has been established many numerical methods for for shape optimization problems [18, 19], evolving surface partial differential equations (PDE) [20, 21, 22] and specific algorithms for the Willmore energy problem (1) [23, 24, 25, 26, 24].

je

In this report will we establish a numerical scheme on minimization on this functional. However, we will first establish notation by including a section for definitions and important results from differential geometry. We will then derive the underlying PDE's for this equation. Lastly we will establish the model for the problem and discretize the problem using evolutionary parametric FEM methods.

2 Background Theory

2.1 Differential Calculus

This subsection is inspired by the notation used in [26, 27]. Let some initial surface $\Gamma^0 \subset \mathbb{R}^3$ smooth compact and oriented surface with no boundary where we can assign a unique point $p \in \Gamma^0$. We define define the time evolutionary surface to be on the form,

$$\begin{aligned}\Gamma = \Gamma(t) &= \Gamma(\chi(p,t)) \\ &= \left\{\chi(p,t) : \; p \in \Gamma^0\right\}\end{aligned}$$

transformed via the smooth mapping,

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

An important regularity result is that if Γ^0 is of class C^∞, then Γ is also of class C^∞ for $\forall t \in [0,T]$ [18, 27].

Formally in [18, p 48], it might be an idea to formulate normal unit-vector regularity as C^∞

We will define a unique evolutionary point $x \in \Gamma(t)$ based on the smooth mapping $\chi(p,t) = x$. A way to imagine this is to have a initial point in Γ^0 and the mapping χ 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 [27] and [26] 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 tangential operator,

$$\nabla_\Gamma u = \nabla u - \langle \nu, \nabla u \rangle \nu.$$

May be an idea to define a extension $\widetilde{u}\;|_\Gamma$ and look into regularity. See definitions in [20].

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 defined s.t.

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

Here is $D^2 u$ denotes as 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 matrix A involves applying the extended Weingarten map, $A(x) = \nabla_\Gamma \nu(x)$, s.t. these identities holds ,

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

see [26]. 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 [27].

2.2 Evolutionary Surface Dynamics

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

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

$$\frac{dx}{dt} = v(x) \quad \forall x \in \Gamma(t). \tag{2}$$

Given a model of the velocity v can we solve the ordinary differential equation (ODE) (2) 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 $x = \chi(p, t)$ is arising from the smooth mapping from the point p in Γ^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 (1) we define $\varphi = H^2$. Based on [27],the shape derivative of this energy functional at some time t in the direction of the velocity $v(x)$ from (2) is defined as

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

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 as

$$\begin{aligned}\frac{D}{Dt} f(x,t) &= \frac{d}{dt} f(\chi(p,t), t) \\ &= \lim_{\varepsilon \to 0} \frac{f(\chi(p, t+\varepsilon)) - f(\chi(p,t))}{\varepsilon}\end{aligned}$$

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

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

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 $\left[H^1(\Gamma)\right]^3$ or $\left[L^2(\Gamma)\right]^3$.

The method we will use in this paper to minimize the energy functional (1) is to compute the so-called gradient flow. The fundamental idea of the gradient flow is to give rise of 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 for information about gradient flows please check out [28, 29]. Now assume we have the velocity defined in (2) to be $v \in \left[L^2(\Gamma)\right]^3$, then we define the L^2 gradient flow s.t.

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

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

$$d\mathcal{J}(\Gamma; v) = -\|v\|^2_{L^2(\Gamma)} < 0.. \tag{3}$$

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

3 Evolutionary dynamics of the Willmore energy

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

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

A complete derivation of the shape derivative can be found in [27, Corally 4.7]. Consequently, by applying the gradient flow in (3) and using that $\|v\|_\Gamma = \|V\|_\Gamma^2$ can we easily see that,

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

Hence, the gradient flow is equivalent to

$$V = \Delta_\Gamma H + Q, \tag{4}$$

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

Need to define a way to compute $\Delta_\Gamma H$ in the background theory.

From [26, Lemma 2.1] it derived that (4) must satisfy the following material derivatives,

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

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 [25, 30].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, ν, and ,thus, allows us to construct rigorous convergence proofs for evolving surface FEM, see [26].

An interesting recent used introducing tangential velocity [24] Finally we end up with the following fourth-order time dependent system of equation

References

[1] Scott A Small and Sam Gandy. "Sorting through the cell biology of Alzheimer's disease: intracellular pathways to pathogenesis". In: (2006).

[2] Saul L. Neidleman. "Effects of Temperature on Lipid Unsaturation". In: (1987), pp. 245–268. DOI: 10.1080/02648725.1987.10647839.

[3] Michael Edidin. "The State of Lipid Rafts: From Model Membranes to Cells". In: *Annual Review of Biophysics and Biomolecular Structure* (2003), pp. 257–283.

[4] Vladimir Yushutin et al. "A computational study of lateral phase separation in biological membranes". In: (2019). DOI: https://doi.org/10.1002/cnm.3181.

[5] Udo Seifert. "Configurations of fluid membranes and vesicles". In: *Advances in Physics* (1997), pp. 13–137. DOI: 10.1080/00018739700101488.

[6] Andreas Rätz. "A benchmark for the surface Cahn–Hilliard equation". In: (2016), pp. 65–71. DOI: https://doi.org/10.1016/j.aml.2015.12.008.

[7] P. Gera and David Salac. "Cahn-Hilliard on surfaces: A numerical study". In: (2017), pp. 56–61.

[8] D. CAETANO and C. M. ELLIOTT. "Cahn–Hilliard equations on an evolving surface". In: (2021), 937–1000. DOI: 10.1017/S0956792521000176.

[9] Xiaoqiang Wang and Qiang Du. "Modelling and simulations of multi-component lipid membranes and open membranes via diffuse interface approaches". In: *Journal of mathematical biology* 56 (Apr. 2008), pp. 347–71. DOI: 10.1007/s00285-007-0118-2.

[10] S. Montiel, A. Ros, and D.G. Babbitt. *Curves and Surfaces*. 2009. Chap. 8.5.

[11] Thomas Willmore. *Riemannian geometry*. 1996. Chap. 7.2, p. 270.

[12] Peter Topping. "Towards the Willmore conjecture". In: (2000).

[13] Fernando C Marques and Andre Neves. "The willmore conjecture". In: (2014).

[14] Florian Link. "Gradient flow for the Willmore functional in Riemannian manifolds of bounded geometry". In: *arXiv preprint arXiv:1308.6055* (2013).

[15] Thomas Koerber. "The area preserving Willmore flow and local maximizers of the Hawking mass in asymptotically Schwarzschild manifolds". In: (2021).

[16] Ruben Jakob. “Singularities and full convergence of the Mobius-invariant Willmore flow in the 3-sphere”. In: (2022).

[17] Fabian Rupp. “The volume-preserving Willmore flow”. In: (2020). DOI: 10.48550/ARXIV.2012.03553.

[18] Jan Sokolowski and Jean-Paul Zolésio. *Introduction to shape optimization.* 1992, pp. 47–48.

[19] Kazufumi Ito, Karl Kunisch, and Gunther H Peichl. “Variational approach to shape derivatives”. In: *ESAIM: Control, Optimisation and Calculus of Variations* ().

[20] Gerhard Dziuk and Charles M Elliott. “Finite element methods for surface PDEs”. In: ().

[21] Gerhard Dziuk and Charles M Elliott. “Finite elements on evolving surfaces”. In: ().

[22] Tim Binz and Balázs Kovács. “A convergent finite element algorithm for generalized mean curvature flows of closed surfaces”. In: (2022).

[23] Francesco Palmurella and Tristan Rivière. “The parametric approach to the Willmore flow”. In: *Advances in Mathematics* 400 (2022), p. 108257.

[24] Jiashun Hu and Buyang Li. “Evolving finite element methods with an artificial tangential velocity for mean curvature flow and Willmore flow”. In: (2022).

[25] Andrea Bonito, Ricardo H Nochetto, and M Sebastian Pauletti. “Parametric FEM for geometric biomembranes”. In: (2010).

[26] Balázs Kovács, Buyang Li, and Christian Lubich. “A convergent evolving finite element algorithm for Willmore flow of closed surfaces”. In: (2021).

[27] Ricardo H Doğan Günay; Nochetto. “First variation of the general curvature-dependent surface energy”. In: (2012).

[28] Gunay Dogan et al. “Discrete gradient flows for shape optimization and applications”. In: (2007).

[29] G Dogan et al. “Finite element methods for shape optimization and applications”. In: *Preprint* (2005).

[30] Andrea Bartezzaghi, Luca Dedè, and Alfio Quarteroni. “Isogeometric analysis of geometric partial differential equations”. In: *Computer Methods in Applied Mechanics and Engineering* 311 (2016), pp. 625–647.