Variational models for pattern formation in biomembranes - a Γ-convergence result

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Abstract. Biological membranes are thin structures that are composed of various components. The different components often form microdomains, called lipid rafts, that are arranged in complex patterns. To explain this pattern formation, variational models based on Cahn-Hilliard type energies have been introduced that couple the local composition of the membrane to its local curvature, which renders the resulting functionals nonlocal. In this note we review and extend recent qualitative results on related variational models. This includes a technique to deal with Neumann-boundary conditions in the construction of a recovery sequence.

Keywords. Γ-convergence · biomembranes · nonlocal energy · sharp interface limit · Neumann boundary conditions.

1. Introduction

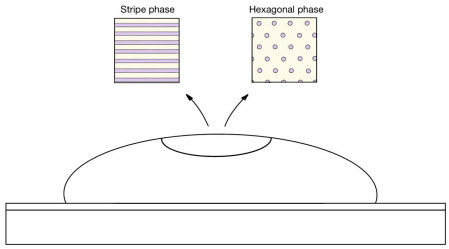
1.1. Motivation: formation of lipid rafts

Biological membranes are in essence lipid bi-layers surrounding the interior cells. In most eukaryotic organisms they consist of two types of lipids (saturated and unsaturated), various proteins, and cholesterol. These are hypothesized to form nanoscale microdomains within the membrane, commonly referred to as *lipid rafts*. The latter are believed to be responsible for many essential cellular processes, e.g. intracellular signaling, membrane trafficking and assembly of specialized structures [27]. Other biological processes that are suspected to be linked to membrane rafts are e.g. virus budding, endocytosis, and immune responses, [29, 25]. However, a nanoscale visualization of lipid rafts in unperturbed living cells is still incomplete, leading to increased skepticism about their existence, [22, 14]. The mechanisms behind their formation and (in)stability have been an active topic of research. Various types of lipid patterning have been observed in artificial membranes (see Figure 1 and [30]). In [19] it was suggested that morphological transitions on the membrane (i.e. formation of the rafts) can be related to the increase in surface tension. A nonlocal energy functional that includes the bending energy of the membrane and couples it to the local composition of the membrane has been proposed in [19].
Recent advances in the analysis of related variational problems are the main topic of this note. For a detailed discussion of the model see Section 2.

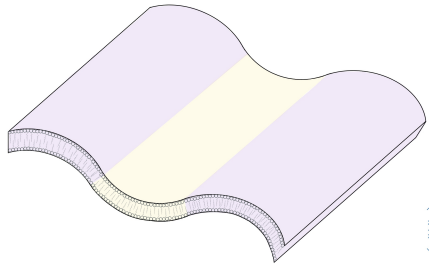
1.2. Membrane models: an overview

Here, we present a brief overview over the mathematical literature on related variational problems. We start with the classical Modica–Mortola functional that arises in the van der Waals–Cahn–Hilliard theory of phase transitions, i.e.

$$\mathcal{F}_\varepsilon^0[u] := \int_\Omega \frac{1}{\varepsilon} W(u) + \varepsilon |\nabla u|^2 dx.$$



(A) Hand-drawn picture of the patterns observed in model membranes, [30]



(B) Sketch of the relation between chemical composition and curvature, as suggested in [19]

Here, $W : \mathbb{R} \to [0, \infty)$ is a continuous double-well potential. It has been proven by Modica and Mortola [20, 21] and Sternberg [28] (as well as Carr, Gurtin, and Slemrod in the one-dimensional case [6]) that this sequence of functionals Γ-converges to a perimeter functional, as $\varepsilon \to 0$. In particular, the limiting functional is given by the length of the jumpset scaled by the factor $\int \sqrt{W(s)}ds$ (see, e.g. [1]). This is the energy of the so-called optimal profile, which approximates the optimal transition between the potential wells. In other words, such an energy tends to minimize the area of the interfaces. A similar result has been shown by Fonseca and Mantegazza in [12], where instead of the first, one considers a second-order singular perturbation, i.e. the functional

$$\mathcal{F}^1_\varepsilon[u] := \int_\Omega \frac{1}{\varepsilon} W(u) + \varepsilon^3 |\nabla^2 u|^2 dx.$$

In the proof of the $\Gamma-$convergence of such a family towards a perimeter functional, they use a slicing argument in order to show the lim inf-inequality and a one-dimensional optimal profile for the construction of the recovery sequence. Note that in this case, as pointed out in [12], the compactness would follow the same way as for the Modica-Mortola functional, if one could estimate $\varepsilon \|\nabla u\|^2_{L^2}$ in terms of $\mathcal{F}^1_\varepsilon$. In the author's Master's thesis [24] an energy functional involving the bending energy of the membrane, instead of the surface tension has been analyzed, namely

$$\mathcal{F}^2_\varepsilon[u] := \int_\Omega \frac{1}{\varepsilon} W(u) + \varepsilon^3 |\Delta u|^2 dx.$$

Similarly to before, a perimeter functional appears in the $\Gamma-$limit. However, in this case, the slicing argument for the proof of the lower bound fails. One thus needs to use the 'blow-up' argument of Fonseca and Müller [13] instead. This can be done following [18, 4]. Despite this, we show that the optimal profile is still one-dimensional. Additionally, we show in [15] that both the $\Gamma-$limit, as well as the corresponding compactness result, hold in the strong $L^2(\Omega)$-topology. In order to show compactness, we use an interior estimate for the Laplace operator and Vitali's convergence theorem. Hilhorst, Peletier and Schätzle [18] considered a family with an additional surface energy term, that is

$$\mathcal{F}^3_\varepsilon[u] := \int_\Omega \frac{1}{\varepsilon} W(u) + \varepsilon k |\nabla u|^2 + \varepsilon^3 |\Delta u|^2 dx.$$

A similar limiting functional appears as the $\Gamma-$limit of such a family. Additionally, we note that one may use the same argument as in [15] to show the corresponding compactness statement for this functional. A more significant change occurs when one assumes that the surface energy term comes with a negative coefficient i.e., for $q > 0$

$$\mathcal{F}^4_\varepsilon[u] := \int_\Omega \frac{1}{\varepsilon} W(u) - \varepsilon q |\nabla u|^2 + \varepsilon^3 |\nabla^2 u|^2 dx.$$

It was shown independently in [7, 8] that the $\Gamma-$limit can be computed for small parameter $q < q^*$, where $q^* > 0$ represents a critical value. Furthermore, in the case $\Omega \subseteq \mathbb{R}^d$ a $d-$dimensional optimal profile is used. It is not clear whether the optimal profile is actually one-dimensional.
Returning to modelling biological membranes, it was shown in [11] that the mentioned model for the

energy of a biomembrane that couples the local composition to the local curvature can be rewritten in the form

$$\mathcal{F}_\varepsilon^5[v] := \int_\Omega \frac{1}{\varepsilon} W(-\varepsilon^2 \Delta v + v) - \varepsilon q |\nabla v|^2 + (1-2q)\varepsilon^3 (\Delta v)^2 + (1-q)\varepsilon^5 |\nabla \Delta v|^2 dx \tag{1.1}$$

with an additional assumption that v satisfies Neumann boundary conditions. In [11], it was shown that the $\Gamma-$limit of such a family in the case $0 \leq q < q^*$ is again of perimeter type. Once again, a $d-$dimensional optimal profile is used. Here and in [15] we consider the case $q < 0$ and show the convergence towards a perimeter functional. The main novelty in [15] is the inclusion of Neumann boundary conditions in the construction of the recovery sequence. In what follows we explain the model in detail (Section 2), state the main result, and sketch the proof (Section 2). Detailed proofs can be found in [15].

2. Model and the main result

We start with the model of the energy of a membrane with two components proposed in [19] that couples the chemical composition of the membrane to the local curvature. The underlying intuition is that the geometry of the lipids determines their preferred place in the membrane, but also that the geometry of the membrane changes depending on the local composition of the molecules constituting that part of the membrane. More precisely, we consider the following energy functional

$$\mathcal{E}[\phi, h] = \int_\Omega \left(f(\phi) + \frac{1}{2} b |\nabla \phi|^2 + \frac{1}{2} \sigma |\nabla h|^2 + \frac{1}{2} \kappa |\Delta h|^2 + \Lambda \phi \Delta h \right) dx,$$

where $\Omega \subseteq \mathbb{R}^d$ is a flat reference domain, $\phi \in W^{1,2}(\Omega)$ is an order parameter related to the chemical composition of the membrane and $h \in W^{2,2}(\Omega)$ describes the height profile of the membrane. Moreover, $f : \mathbb{R} \mapsto [0, \infty)$ is a continuous double-well potential whose two potential wells correspond to pure chemical states. The parameters b, κ, and σ are non-negative and represent, respectively, line tension between regions with different components, surface tension, and bending rigidity of the membrane. These first four terms are relatively standard and appear frequently in the continuous mechanical theory of membranes. In particular, consider the Canham-Helfrich free energy, [5, 17], defined as

$$\mathcal{E}(\Gamma) := \int_\Gamma \frac{1}{2} \kappa H^2 + \sigma + \kappa_G K d\Gamma, \tag{2.1}$$

where Γ is a surface in $\mathbb{R}^3$ representing the membrane, H and K are the mean and Gaussian curvature. As before, the parameters $\sigma > 0$ and $\kappa, \kappa_G > 0$ represent the surface tension and bending rigidity, respectively. If there is a parameterization of Γ over a flat reference domain $\Omega \subseteq \mathbb{R}^2$ i.e., if there exists a function $h : \Omega \mapsto \mathbb{R}$ such that

$$\Gamma = \{(x, h(x)) : x \in \Omega\}$$

then the two curvatures may be rewritten as

$$H = -\nabla \cdot \frac{\nabla h}{(1 + |\nabla h|^2)^{1/2}} \qquad K = \frac{\det(\nabla^2 h)}{(1 + |\nabla h|^2)^{1/2}}.$$

We assume that $|\nabla h| \ll 1$ and that the Gaussian curvature term in the energy is constant. Then the functional, up to a constant, takes the following form

$$\mathcal{E}(h) = \int_\Omega \frac{1}{2} \kappa (\Delta h)^2 + \frac{1}{2} \sigma |\nabla h|^2 dx.$$

For a more detailed discussion see [9, Section 3.1]. The term involving $\Lambda > 0$, on the other hand, introduces the coupling between the local chemical composition of the membrane and the approximated local curvature (here we assume that the membrane is almost flat and thus Δh is a good approximation of the curvature). Our general goal is to analyze the minimizers of such an energy functional in various parameter regimes. Note that, since the coupling term in the energy can take negative values, the energy itself is possibly non-positive. Thus, in order to minimize the functional,

one would aim to have the last term with a negative sign and large in terms of the absolute value. As a starting point, we consider the case $\Omega \subseteq \mathbb{R}$. One possibility is to consider a height profile h_n with n oscillations and order parameter u_n that transitions frequently between $+1$ and -1 in a way that the sign of u_n is related to the sign of Δh_n, resulting in a negative coupling term (see also the discussion in the introduction of [11]). Then the energy roughly scales as

$$E(u_n, h_n) \sim \delta + b\frac{n^2}{\delta} + \sigma n^2 + \kappa n^4 - \Lambda n^2$$

where n is the number of oscillations and δ is the total length of the transition regions of u_n. The minimal energy thus depends greatly on the values of the problem parameters. In particular, one can optimize in n which leads to

$$n^2 \sim \max\left\{1, \frac{\Lambda - \sigma - b/\delta}{2\kappa}\right\}.$$

Note that for different parameter regimes the optimal value of n changes. This shows that there are parameter regimes in which uniform structures are not optimal, and pattern formation is expected. In particular, if $\Lambda \gg \sigma, \kappa, b$, then one would expect the optimal n to be large, i.e. formation of patterns would be energetically favourable. On the other hand, if $\Lambda \ll \sigma$ or $\Lambda \ll b$ or κ is large, one obtains $n = 1$ as the optimal number of transitions. We will below explain rigorous results from [11, 15] that show that there are parameter regimes in which uniform structures are preferred. A more detailed analysis of the minimal energy depending on the parameters is currently in preparation (see [16]). In this paper, we wish to focus on the case of a large surface tension or a small coupling constant. Following the steps of [11, Appendix] we may optimize in h and set

$$\varepsilon := \sqrt{\frac{\kappa}{\sigma}} \qquad q := 1 - \frac{b\sigma}{\Lambda^2} \qquad W(u) := \frac{2\kappa}{\Lambda^2} f(u) \qquad \mathcal{F}_\varepsilon := \frac{1}{\varepsilon}\frac{2\kappa}{\Lambda^2}\mathcal{E}.$$

This yields a family of functionals $\mathcal{F}_\varepsilon : L^2(\Omega) \to \mathbb{R} \cup \{+\infty\}$, given by

$$\mathcal{F}_\varepsilon[u] := \begin{cases} \frac{1}{\varepsilon}\int_\Omega \left(W(u) - u^2 + (1-q)\varepsilon^2|\nabla u|^2 + u\left(\mathbf{1} - \varepsilon^2\Delta\right)^{-1} u\right) dx, & \text{if } u \in W^{1,2}(\Omega); \\ +\infty, & \text{if } u \in L^2(\Omega) \setminus W^{1,2}(\Omega), \end{cases} \tag{2.2}$$

where $\left(\mathbf{1} - \varepsilon^2\Delta\right)^{-1}$ is a solution operator subject to Neumann-boundary conditions which appears as a consequence of solving the Euler-Lagrange equation for h.
Physically relevant values for b, σ, κ and Λ have been presented in [19]. Using those values, we can conclude that the relevant regime for new the parameters is $\varepsilon > 0$ close to 0 and $q \in (-1.1, 1)$. We are interested in analyzing the minimizers of the previously derived functionals as $\varepsilon \to 0$, but focus on the case $q < 0$. The following theorem is a slight generalization of [15, Theorem 1.3].

Theorem 2.1. *Let $\Omega \subseteq \mathbb{R}^d$ be an open, bounded domain with a C^4-boundary. Suppose that $W \in C(\mathbb{R}; [0, \infty))$ satisfies $W(s) = 0$ if and only if $s \in \{\pm 1\}$, and the growth condition*

$$c_1 \min\left\{(s-1)^2,\ (s+1)^2\right\} \le W(s) \le c_2 s^2 \qquad \text{for all } s \in \mathbb{R}. \tag{2.3}$$

Consider the family $\{\mathcal{F}_\varepsilon\}_{\varepsilon>0}$ defined in (2.2). Then it holds for the Γ-limit with respect to strong L^2-convergence

$$\Gamma - \lim_{\varepsilon\to 0} \mathcal{F}_\varepsilon[u] = \begin{cases} m_d Per_\Omega(\{u = -1\}), & \text{if } u \in BV(\Omega; \{\pm 1\}) \\ +\infty, & \text{if } u \in L^2(\Omega) \setminus BV(\Omega; \{\pm 1\}). \end{cases} \tag{2.4}$$

The constant m_d is defined via the optimal profile problem

$$m_d := \inf\left\{\int_{Q_\nu}\left(\frac{1}{\varepsilon}W(u) - \varepsilon q|\nabla u|^2 + \varepsilon^3(\Delta v)^2 + \varepsilon^5|\nabla\Delta v|^2\right) dx : 0 < \varepsilon \le 1, -\varepsilon^2\Delta v + v = u, v \in \mathcal{A}_\nu\right\} \tag{2.5}$$

where $(\nu_1, \dots, \nu_{d-1}, \nu)$ *is an orthonormal basis of* $\mathbb{R}^d$,

$$Q_\nu := Q_\nu(0,1) := \{x \in \mathbb{R}^d : |x \cdot \nu| < 1/2, |x \cdot \nu_i| < 1/2, \quad i = 1, \dots, d-1\} \tag{2.6}$$

represents the unit cube in direction $\nu \in S^{d-1}$ *and the set of admissible functions is given by*

$$\mathcal{A}_\nu = \big\{v \in W^{2,2}_{loc}(\mathbb{R}^d) : v = -1 \text{ in a neighborhood of } x \cdot \nu = -1/2,\ v = 1 \text{ in a neighborhood of } x \cdot \nu = 1/2, \\ v(x) = v(x + \nu_i) \text{ for all } x \in \mathbb{R}^d, i = 1, \dots, d-1\big\}. \tag{2.7}$$

Furthermore, the sequence $\{\mathcal{F}_\varepsilon\}_{\varepsilon>0}$ *is strongly equicoercive in* $L^2(\Omega)$.

Remark 2.2. *A major difficulty arises from the non-local term. To overcome this (especially for the construction in the proof of the* lim sup*-inequality), it turned out be convenient to rewrite the functional* $\mathcal{F}_\varepsilon$ *in a different way (see* [11, 15]*). We would like to simplify* $\mathcal{F}_\varepsilon$ *by getting rid of the solution operator. Therefore, given* $u \in W^{1,2}(\Omega)$*, we define* $v \in W^{2,2}(\Omega)$ *as the weak solution to*

$$\begin{cases} -\varepsilon^2 \Delta v + v = u\ , & \text{in } \Omega, \\ \dfrac{\partial v}{\partial \hat{n}} = 0\ , & \text{on } \partial\Omega, \end{cases} \tag{2.8}$$

where $\hat{n}$ *denotes the unit normal to* $\partial\Omega$*. Then one can check that we can equivalently work with a functional defined on* $W^{2,2}(\Omega)$ *functions with Neumann boundary conditions (c.f.* (1.1)*, for details see* [11, 15]*). As a consequence of this approach, one needs to include boundary conditions in the construction of the recovery sequence. This is described in Step 1 of the proof below.*

Remark 2.3. *The requirement that* Ω *is a* C^4*-domain arises from the specific construction of the recovery sequence. Notice that from the definition of the functional (c.f. in particular* (1.1)*), it is convenient for the recovery sequence to be of* C^3*-regularity. Close to the boundary we construct the sequence by extending mollified trace values constantly in the normal direction into the domain* [15, Proof of Theorem 1.3 part 2, Step 1]*. As the normal to a* C^k*-domain can only be guaranteed to be of class* C^{k-1}*, in order to end up with a* C^3 *function, a boundary of regularity* C^{3+1} *is needed. However, this assumption is only needed in the proof of the limsup-inequality. For compactness and the liminf-inequality, a piecewise* C^2*-boundary is sufficient.*

Proof. Here we only point to the main ideas of the proof. Details are presented in [15].

1. Compactness
   In [15], the double-well potential W is assumed to be twice continuously differentiable and to satisfy $\{W = 0\} = \{\pm 1\}$ as well as the growth condition

   $$\lambda_1 s^2 \le W(s) \le \lambda_2 s^2 \qquad \text{for all } s \ge \mathbb{R}. \tag{2.9}$$

   Clearly (2.3) implies (2.9) for appropriately chosen $\lambda_1, \lambda_2, R > 0$. On the other hand, as outlined in [15], the conditions assumed there imply (2.3) by Taylor's theorem.
   Carefully checking the proof, we find that the higher regularity of W is only used in the proof of compactness [15, Section 3.1]. Here, one introduces a potential $\tilde{W} \in C^2(\mathbb{R}; [0, \infty))$ satisfying (2.3) and $\tilde{W} \le CW$ for a constant C such that additionally $\tilde{W}$ has a uniformly bounded second derivative. Hence, if one replaces the construction given there by a function of the form

   $$\tilde{W}(x) := \begin{cases} p_1(x) & \text{if } \ 0 \le |x| \le 1/2, \\ c_1 \min\big\{(s-1)^2,\ (s+1)^2\big\} & \text{if } \ 1/2 \le |x| \le R, \\ p_2(x), & \text{if } \ R \le |x| \le R+1, \\ \lambda_1 x^2, & \text{if } \ |x| \ge R+1, \end{cases}$$

   with appropriately chosen polynomials p_1, p_2 such that additionally $\tilde{W} \in C^2(\mathbb{R}; [0, \infty))$, the argument can be carried over to our setting.

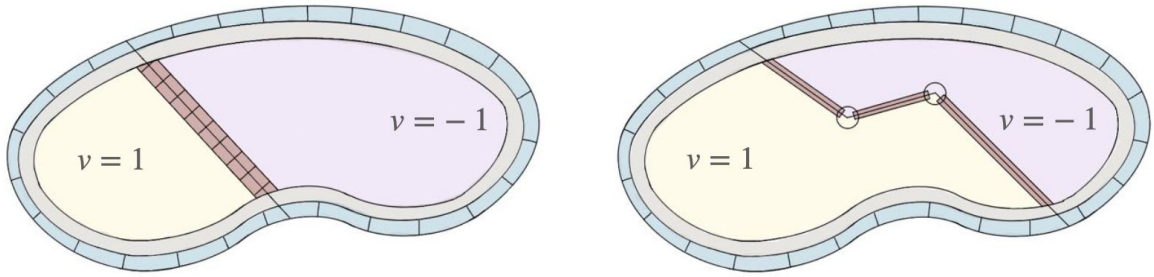


FIGURE 2. Sketch of the construction of the recovery sequence for flat and polygonal jumpsets, respectively.

2. lim inf-inequality
   The proof of this part closely follows the lines of [18, 4]. The main idea is the use of the 'blow-up' technique introduced in [13]. For the full proof we refer to [15].
3. lim sup-inequality
   The proof follows the steps of [15], which in turn is based on [11, Section 6], the main difference being in the first step of the construction. As explained in Remark 2.2, it will be beneficial here to consider the modified functional defined on functions $v \in W^{2,2}(\Omega)$ satisfying Neumann boundary conditions. Hence, for the proof of the lim sup-inequality, a recovery sequence satisfying Neumann boundary conditions is necessary. We first assume that $v \in BV(\Omega;\{\pm 1\})$ has a flat jumpset. The sequence is then constructed separately in different areas of the domain. We first mollify the trace of the function v locally on the boundary. In a neighborhood of the boundary of the domain (Figure 3, blue region), the regularized boundary values are extended constantly in the normal direction into the domain. In this way, Neumann boundary conditions are achieved. However, we would still like to have the almost optimal energy of this sequence. Thus, inside the domain, away from the boundary we cover the jump set by cubes (red squares in Figure 3) in which the (almost) optimal profile is used (as defined in (2.5)). In the remaining grey region, we interpolate between the two constructions. Finally, we can use a diagonal argument to decrease the thickness of the two tubular neighborhoods and obtain a recovery sequence. The rest follows by standard approximation arguments (see [15, 11, 2]).

□

Note here that the construction of the recovery sequence does not depend on the fact that $q < 0$. In particular, one may use the same construction in the setting of the proof of the lim sup-inequality from [11]. Let us briefly comment on the specific choice of construction in [11]. There, the constructed recovery sequence equals 0 in a small neighborhood of the boundary of the domain. However, in this case, the energy is larger than optimal, having an additional term of order $\mathrm{Per}(\Omega)$. One also has to be careful at which point to interpolate. As an example, if the trace of the BV-function is extended into the neighborhood first and then mollified, the Neumann boundary conditions are lost, independent of the size of the region. Another possibility for the construction could be to extend the values from the domain outwards, i.e., in the opposite direction compared to our construction. In particular, consider a tubular neighborhood of the boundary of the domain. Next, construct an almost optimal sequence in the interior of the domain, and identify the trace of this sequence on the boundary of the tubular neighborhood. Finally, inside the neighborhood, trace values are extended constantly outward in the normal direction. However, one would have to be careful about how to fit the regularity of the functions with the regularity of the boundary.

3. Conclusion and outline for future

We believe that the construction introduced in [15] can be used for other problems that require the construction of recovery sequences that satisfy Neumann boundary conditions.
In terms of biomembranes, since the $\Gamma-$convergence and compactness results from Theorem 2.1 hold in the same space, we may conclude convergence of almost minimizers. This in particular means that the formation of patterns is not expected in the regime $-\infty < q < q^*$. We currently build on the heuristics presented in Section 2 and precisely identify the regimes in which the raft formation is expected in order to analyze the properties of minimizers in those cases (see [16]).

Acknowledgement

I would like to thank Barbara Zwicknagl and Janusz Ginster for many helpful discussions, and for their continuous support. I would also like to thank Gurgen Hayrapetyan for various knowledgeable discussions. Furthermore, I am thankful to Jean-Dominique Deuschel, in particular for discussions about the local approximation of the energy and the stochastic view on it. This research is supported by *Deutsche Forschungsgemeinschaft* (DFG) project number 384950143 (RTG DAEDALUS). Support of the *Deutsche Forschungsgemeinschaft* under Germany's Excellence Strategy The Berlin Mathematics Research Center MATH+ and the Berlin Mathematical School (BMS) (EXC-2046/1, project 390685689) is also gratefully acknowledged.

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