arXiv:1711.11192v2 [math.AP] 7 Dec 2017

ON DIFFERENTIABILITY OF THE MEMBRANE-MEDIATED MECHANICAL INTERACTION ENERGY OF DISCRETE–CONTINUUM MEMBRANE–PARTICLE MODELS

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Abstract. We consider a discrete–continuum model of a biomembrane with embedded particles. While the membrane is represented by a continuous surface, embedded particles are described by rigid discrete objects which are free to move and rotate in lateral direction. For the membrane we consider a linearized Canham–Helfrich energy functional and height and slope boundary conditions imposed on the particle boundaries resulting in a coupled minimization problem for the membrane shape and particle positions.

When considering the energetically optimal membrane shape for each particle position we obtain a reduced energy functional that models the implicitly given interaction potential for the membrane-mediated mechanical particle–particle interactions. We show that this interaction potential is differentiable with respect to the particle positions and orientations. Furthermore we derive a fully practical representation of the derivative only in terms of well defined derivatives of the membrane. This opens the door for the application of minimization algorithms for the computation of minimizers of the coupled system and for further investigation of the interaction potential of membrane-mediated mechanical particle–particle interaction.

The results are illustrated with numerical examples comparing the explicit derivative formula with difference quotient approximations. We furthermore demonstrate the application of the derived formula to implement a gradient flow for the approximation of optimal particle configurations.

Acknowledgement

1. Introduction

Membrane proteins are crucial for various processes that involve the shaping of biological membranes. In some of these cases the proteins act as inclusions in the membrane and induce local deformations in the vicinity of the interface between the membrane and the proteins . As the membrane itself consists of a lipid bilayer, which in lateral direction can be seen as a fluid , particles are able to move easily within the membrane. Since the local protein-induced membrane deformation implicitly defines a membrane mediated mechanical protein–protein interaction proteins can tend to assemble in energetically preferable patterns .

Various research has been done in order to gain more insight into the shaping of membranes as well as membrane-mediated particle-particle interactions. A

common description of biological membranes is based on a representation as continuous surface that minimizes an elastic energy [3, 13]. It was later shown that there are long-range interactions between particles that are predominantly membrane-mediated [9]. Since then further work has been done to investigate particle interactions within elasticity models. Typically a flatness assumption on the membrane is made and particles are modeled as circular disks or points and their coupling to the membrane is prescribed by radially symmetric boundary conditions for which the interaction energy can either be computed analytically or approximately by asymptotic expansion [17, 21, 6, 23, 8]. However, it turns out that the shape of particles has a significant impact on their interaction [16]. More recent work is also interested in numerical computations with pattern formation of many non-circular particles [12, 15], and attention was also given to situations where the flatness assumption is no longer fulfilled [19, 20]. Also more elaborate models for proteins in continuum elastic models have recently been considered in [2].

For efficient computations with moving particles it therefore is desirable to quantify the forces exerted on the particles by the membrane in a framework that is as widely applicable as possible. General results in this direction have been obtained based on arguments from differential geometry [5]. The methods derived therein give insight into the qualitative behavior of particle interactions, but—to the best of the authors' knowledge—they have not yet been made fully available for numerical computations.

In this paper we consider a discrete–continuum model where the membrane is modeled as a continuous graph minimizing a linearized Canham–Helfrich bending energy and where an arbitrary amount of particles are embedded into the membrane. These particles are modeled as discrete entities which are coupled to the membrane through certain boundary conditions. As particles are free to move in the membrane, those boundary conditions depend on each particle's position. Consequently, the overall system's energy given fixed boundary conditions and an optimal membrane shape can be written as a function of the particle positions, which we call the *interaction energy*.

In this setting we propose a method to prove differentiability of the interaction energy for arbitrary shapes and boundary conditions. Furthermore, we derive an expression for the derivative that can be evaluated numerically within a finite element scheme and where the evaluation error is bounded in terms of the discretization error of the finite element approximation. The proof is based on an application of the implicit function theorem and ideas from shape calculus [14, 4]. As such, the method is rather general and hence it naturally extends to a wider class of models that for example use nonlinear elastic energies or certain other membrane–particle couplings.

In the following we give an outline of this paper. In Section 2 we introduce the Canham–Helfrich energy in Monge-gauge as a model for the membrane and parametric boundary conditions for the coupling of the particles. Section 3 is then concerned with further mathematical notation that we use in order to define the interaction energy. There we also reformulate the parametric boundary conditions as linear constraints by using trace operators and appropriate projection operators. Afterwards, in Section 4, we prove differentiability of the interaction energy and derive a numerically feasible expression for the gradient. Finally, Section 5 shows

some example computations that illustrate that the derived formula can indeed be applied in a numerical scheme.

2. Membrane and particle model

To model the membrane itself we choose the well-established *linearized Canham–Helfrich model in Monge-gauge*. Given a 2-dimensional reference domain $\Omega \subseteq \mathbb{R}^2$ and a function $u \in H^2(\Omega)$, the membrane shape is described by the graph $u(\Omega)$ of u. The bending energy of this membrane is approximated by

$$J(\Omega, u) := \frac{1}{2} \int_\Omega \kappa (\Delta u(x))^2 + \sigma \left\| \nabla u(x) \right\|^2 \, \mathrm{d}x$$

where $\kappa > 0$ and $\sigma \geq 0$ denote the *bending rigidity* and the *surface tension*, respectively. It is noted that this is already a linearized formulation of the bending energy that makes the assumption that the membrane is "rather flat" with respect to the reference domain Ω.

In absence of particles that interact with the membrane, this model determines the stationary shape of the membrane solely by minimizing this energy. In the following we explain how the embedded particles are coupled to the membrane, before we state the model problem that is central to this paper.

For simplicity we first consider a single *transmembrane particle* that interacts with the membrane. Such a particle is not merely connected to the membrane but rather is included in it, comparable to a wedge in the membrane. We assume that the particle is rigid, which means that it stays constant in shape, and we approximate it by a rigid 3-dimensional shape $\mathcal{B} \subseteq \mathbb{R}^3$.

Suppose furthermore that this particle has a *hydrophobic belt*, i.e. a region to which the membrane connects preferentially, and that the particle's belt is approximated by a curve $\mathcal{G}$. We assume that $\mathcal{G}$ is a simple closed curve that can be parameterized over the 2-dimensional Euclidean plane. This means that there exists a simple closed curve $\Gamma \subseteq \mathbb{R}^2$ and a continuous function $g_0 \colon \Gamma \to \mathbb{R}$ such that $\mathcal{G} = \{(x, g_0(x) \mid x \in \Gamma\}$. This gives rise to the boundary condition $u|_\Gamma = g_0$, which models that the membrane is connected to the particle at the interface $\mathcal{G}$. It is common to impose the additional constraint that the membrane attaches to the interface with a fixed slope. This is modeled via a function $g_1 \colon \Gamma \to \mathbb{R}$ describing the slope and via the boundary condition $\partial_\nu u|_\Gamma = g_1$. Here ν is an oriented unit normal on Γ and $\partial_\nu u|_\Gamma$ denotes the normal derivative of u on Γ.

Those constraints do not yet account for the fact that the particle is in principle free to move in space. To this end we parameterize the current position of the particle using translations x_j along the x_j-axes and rotations α_j around the x_j-axes. More precisely, let $\mathcal{B}^0$ be a reference state of the particle that is centered in the origin, and let $R_j(\alpha_j) \in \mathbb{R}^{3 \times 3}$ be the α_j-rotation matrix around the x_j-axis. Then we define the parameterized particle as

$$\mathcal{B}(x_1, x_2, x_3, \alpha_1, \alpha_2, \alpha_3) := \left\{ R_1(\alpha_1) R_2(\alpha_2) R_3(\alpha_3) y + (x_1, x_2, x_3)^T \mid y \in \mathcal{B}^0 \right\}.$$

The curves $\mathcal{G}^0$ and Γ^0 that are associated to $\mathcal{B}^0$ could be parameterized like this, too. However, we decide to only approximate this parameterization instead. We make the simplifying assumption that the reference set $\mathcal{B}^0$ is oriented in such a way that the belt $\mathcal{G}^0$ is flat, by which we mean that $\max_{x \in \Gamma^0} \left| g_0^0(x) \right| / \left\| x \right\|$ is small. And, in the spirit of the Monge-gauge linearization, we also assume that α_1 and α_2 are

small so that we can apply a small angle approximation in the rotation matrices. We define

$$R(\alpha) := \begin{pmatrix} \cos(\alpha) & -\sin(\alpha) \\ \sin(\alpha) & \cos(\alpha) \end{pmatrix}. \tag{2.1}$$

Under these geometric assumptions and upon linearization it is justified to approximate the actual reparameterized curve Γ by

$$\Gamma(x_1, x_2, \alpha_3) := \left\{ R(\alpha_3)y + (x_1, x_2)^T \mid y \in \Gamma^0 \right\}.$$

The zeroth and first order boundary condition then essentially stem from a linear perturbation of the reference conditions. We use the shortcut $p = (x_1, x_2, \alpha_3)$ and define the helper

$$\varphi(p; y) := R(\alpha_3)y + \begin{pmatrix} x_1 \\ x_2 \end{pmatrix}, \qquad \varphi^{-1}(p; y) := R(-\alpha_3) \left(y - \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} \right). \tag{2.2}$$

Using these functions we get

$$\Gamma(p) = \varphi(p; \Gamma^0), \qquad\qquad \Gamma^0 = \varphi^{-1}(p; \Gamma(p)).$$

Together with $g_k(p; y) := g_k^0(\varphi^{-1}(p; y))$ the boundary conditions then read

$$u(y) = g_0(p; y) + \alpha_2(y_1 - x_1) + \alpha_1(y_2 - x_2) + x_3 \qquad \text{on } \Gamma(x_1, x_2, \alpha_3),$$
$$\partial_\nu u(y) = g_1(p; y) + \alpha_2\nu_1 + \alpha_1\nu_2 \qquad\qquad \text{on } \Gamma(x_1, x_2, \alpha_3).$$

Since those boundary conditions are linear in x_3, α_1, and α_2 it is convenient to include the variability of these variables into the boundary conditions, which then become *parametric boundary conditions*:

$$\exists \gamma \in \mathbb{R}^3 \colon \begin{cases} u|_{\Gamma(p)}(y) & = g_0(p; y) + \gamma_1 y_1 + \gamma_2 y_2 + \gamma_3 \\ \partial_\nu u|_{\Gamma(p)}(y) & = g_1(p; y) + \gamma_1 \nu_1 + \gamma_2 \nu_2. \end{cases} \tag{2.3}$$

Therefore, x_3, α_1, and α_2 are no longer relevant for describing the particle's position and are now rather implicit to the boundary conditions. A particle in the model is then solely determined by its reference curve Γ^0, its reference boundary conditions g_0^0, g_1^0, and its position $p = (x_1, x_2, \alpha_3)$ in the Euclidean plane.

In the case where multiple particles are present we state the constraints analogously by imposing the above constraints for each particle separately.

3. INTERACTION ENERGY

Before we can formulate the final model problem, we need to introduce some notation. We also augment the parametric boundary conditions by zero boundary conditions on the outer boundary $\partial\Omega$ and we are going to reformulate these conditions as a simple linear constraint.

We consider N particles with reference curves Γ_i^0, height profiles g_{i0}^0 and slopes g_{i1}^0. Given a *particle configuration* $\mathbf{p} = (\mathbf{p}_i)_{i=1,\dots,N} \in \mathbb{R}^{N\times3}$ we define the curves

$$\Gamma_i(\mathbf{p}_i) := \{\varphi(\mathbf{p}_i; y) \mid y \in \Gamma_i^0\}$$

and $\Gamma_0 := \Gamma_0^0 := \partial\Omega$. Their union is $\Gamma(\mathbf{p}) := \bigcup_{i=0}^N \Gamma_i(\mathbf{p}_i)$ where we use $\mathbf{p}_0 := 0$ and $\Gamma_0(\mathbf{p}_0) := \Gamma_0$ for the sake of a consistent notation. For $i > 0$ we denote the set enclosed by $\Gamma_i(\mathbf{p}_i)$ by $B_i(\mathbf{p}_i)$ and the union of these is denoted by $B(\mathbf{p}) := \bigcup_{i=1}^N B_i(\mathbf{p}_i)$. We define the **p**-dependent reference domain as $\Omega(\mathbf{p}) := \Omega \setminus B(\mathbf{p})$.

Based on this we define the interior of the set of *feasible particle configurations* as

$$\Lambda^\circ := \left\{ \mathbf{p} \in \mathbb{R}^{N \times 3} \mid \forall i, j \in \{1, \dots, N\}, i \neq j : \ \Gamma_i(\mathbf{p}_i) \subseteq \Omega^\circ \ \wedge \ \overline{B_i(\mathbf{p}_i)} \cap \overline{B_j(\mathbf{p}_j)} = \emptyset \right\},$$

and consequently we have $\Lambda := \overline{\Lambda^\circ}$.

Now suppose $\mathbf{p} \in \Lambda$. Then we define the trace operators

$$T_i(\mathbf{p}) \colon H^2(\Omega(\mathbf{p})) \longrightarrow H^{3/2}(\Gamma_i^0) \times H^{1/2}(\Gamma_i^0)$$

(3.1)

$$u \longmapsto \begin{pmatrix} u|_{\Gamma_i(\mathbf{p}_i)} \circ \varphi(\mathbf{p}_i) \\ (\partial_\nu u|_{\Gamma_i(\mathbf{p}_i)}) \circ \varphi(\mathbf{p}_i) \end{pmatrix}.$$

Here ν is the unit outer normal on $\Gamma(\mathbf{p})$ with respect to the domain $\Omega(\mathbf{p})$. We define the joint trace operator by $T(\mathbf{p})u := (T_i(\mathbf{p})u)_{0=1,\dots,N}$. We also define $g_{0k}^0 := 0$, and $g := ((g_{i0}^0, g_{i1}^0))_{i=0,\dots,N}$.

In the next step we prove a useful reformulation of the parametric boundary conditions as linear constraints. To this end, define for $y \in \mathbb{R}^2$

$$\eta_{i1}(y) := y_1, \qquad \eta_{i2}(y) := y_2, \qquad \eta_{i3}(y) := 1,$$

and for $i \in \{1, \dots, N\}$ let

$$C_i \colon \mathbb{R}^3 \longrightarrow L^2(\Gamma_i^0) \qquad\qquad \widetilde{C}_i \colon \mathbb{R}^3 \longrightarrow L^2(\Gamma_i^0)$$

$$s \longmapsto \sum_{j=1}^{3} s_j \eta_j|_{\Gamma_i^0} \qquad\qquad s \longmapsto \sum_{j=1}^{3} s_j \partial_\nu \eta_j|_{\Gamma_i^0}.$$

and

$$P_i \colon L^2(\Gamma_i^0) \times L^2(\Gamma_i^0) \longrightarrow L^2(\Gamma_i^0) \times L^2(\Gamma_i^0)$$

$$(v_1, v_2) \longrightarrow \begin{pmatrix} v_1 - C_i(C_i^* C_i)^{-1} C_i^* v_1 \\ v_2 - \widetilde{C}_i(C_i^* C_i)^{-1} C_i^* v_1 \end{pmatrix}.$$

We furthermore define $P_0(v_1, v_2) := (v_1, v_2)$ for $(v_1, v_2) \in L^2(\partial\Omega) \times L^2(\partial\Omega)$.

Lemma 3.1 (parametric boundary conditions as linear constraint). *Let $i \in \{1, \dots, N\}$. Then P_i is well-defined and a projection operator such that for all $u \in H^2(\Omega(\boldsymbol{p}))$*

(3.2)
$$P_i T_i(\boldsymbol{p}) u = P_i g_i$$

holds if and only if there exists a $\gamma \in \mathbb{R}^3$ such that for all $y \in \Gamma_i(\boldsymbol{p}_i)$ and $\hat{y} := \varphi(\boldsymbol{p}_i)^{-1}(y)$

(3.3)
$$u|_{\Gamma_i}(y) = g_{i1}(\hat{y}) + \gamma_1 y_1 + \gamma_2 y_2 + \gamma_3$$
$$\partial_\nu u|_{\Gamma_i}(y) = g_{i2}(\hat{y}) + \gamma_1 \nu_1 + \gamma_2 \nu_2$$

is fulfilled.

For $i = 0$ equation (3.2) is equivalent to $u|_{\partial\Omega} = \partial_\nu u|_{\partial\Omega} = 0$.

Proof. The statement for $i = 0$ is trivial, hence let $i \in \{1, \dots, N\}$. First we show that P_i is indeed well-defined. To that end note that the adjoint C_i^* is given by

$$(C_i^*(v))_j = \langle \eta_j, v \rangle_{L^2(\Gamma_i^0)}.$$

Thus, $C_i^* C_i \in \mathbb{R}^{3 \times 3}$ where

$$(C_i^* C_i)_{kl} = \langle \eta_k, \eta_l \rangle_{L^2(\Gamma_i^0)}.$$

It is readily seen that the scalar product $\langle \cdot, \cdot \rangle_{L^2(\Gamma_i^0)}$ is positive definite on the space that is spanned by the $\eta_j|_{\Gamma_i^0}$. Moreover, the $\eta_j|_{\Gamma_i^0}$ are linearly independent on $L^2(\Gamma_i^0)$ and thus $C_i^* C_i$ is symmetric positive definite and in particular invertible. This makes P_i well-defined.

We define the shorthands $Q := C_i(C_i^* C_i)^{-1} C_i^*$ and $\widetilde{Q} := \widetilde{C}_i(C_i^* C_i)^{-1} C_i^*$ and note that $Q^2 = Q$ and $\widetilde{Q}Q = \widetilde{Q}$. Now, P_i is obviously linear and

$$P_i^2(v_1, v_2) = P_i\left(v_1 - Qv_1, v_2 - \widetilde{Q}v_1\right)$$
$$= \begin{pmatrix} v_1 - Qv_1 - Q\left(v_1 - Qv_1\right) \\ v_2 - \widetilde{Q}v_1 - \widetilde{Q}\left(v_1 - Qv_1\right) \end{pmatrix}$$
$$= \begin{pmatrix} v_1 - Qv_1 \\ v_2 - \widetilde{Q}v_1 \end{pmatrix}$$
$$= P_i(v_1, v_2).$$

Therefore P is a linear projection operator.

Let $\hat{u} := u|_{\Gamma_i(\mathbf{p}_i)} \circ \varphi(\mathbf{p}_i)$ and $\partial_\nu \hat{u} := \partial_\nu u|_{\Gamma_i(\mathbf{p}_i)} \circ \varphi(\mathbf{p}_i)$. Suppose that (3.2) holds. If we define $\widetilde{\gamma} := (C_i^* C_i)^{-1} C_i^*(\hat{u} - g_{i1})$, then we get

$$P_i T_i(\mathbf{p})u = P_i g_i \iff \begin{pmatrix} \hat{u} - Q\hat{u} \\ \partial_\nu \hat{u} - \widetilde{Q}\hat{u} \end{pmatrix} = \begin{pmatrix} g_{i1} - Q g_{i1} \\ g_{i2} - \widetilde{Q} g_{i1} \end{pmatrix}$$
$$\iff \begin{pmatrix} \hat{u} \\ \partial_\nu \hat{u} \end{pmatrix} = \begin{pmatrix} g_{i1} + Q(\hat{u} - g_{i1}) \\ g_{i2} + \widetilde{Q}(\hat{u} - g_{i1}) \end{pmatrix}$$
$$\iff \begin{cases} \hat{u} &= g_{i1} + \sum_{j=1}^3 \widetilde{\gamma}_j \eta_j|_{\Gamma_i^0} \\ \partial_\nu \hat{u} &= g_{i2} + \sum_{j=1}^3 \widetilde{\gamma}_j \partial_\nu \eta_j|_{\Gamma_i^0}. \end{cases}$$

This implies for almost-every $y \in \Gamma_i(\mathbf{p}_i)$ with $\hat{y} := \varphi(\mathbf{p}_i)^{-1}y$, $x = (\mathbf{p}_{i1}, \mathbf{p}_{i2})^T$, and $\alpha = \mathbf{p}_{i3}$

$$u(y) = g_{i1}(\hat{y}) + \sum_{j=1}^3 \widetilde{\gamma}_j \eta_j(\hat{y}) = g_{i1}(\hat{y}) + \begin{pmatrix} \widetilde{\gamma}_1 \\ \widetilde{\gamma}_2 \end{pmatrix} \cdot R(-\alpha)(y - x) + \widetilde{\gamma}_3$$

and

$$\partial_\nu u(y) = g_{i2}(\hat{y}) + \begin{pmatrix} \widetilde{\gamma}_1 \\ \widetilde{\gamma}_2 \end{pmatrix} \cdot R(-\alpha)\nu(y)$$

where we used the relation $R(-\alpha)\nu(y) = \nu(\hat{y})$. Therefore (3.3) holds with $(\gamma_1, \gamma_2)^T = R(\alpha)(\widetilde{\gamma}_1, \widetilde{\gamma}_2)^T$ and $\gamma_3 = \widetilde{\gamma}_3 - (\widetilde{\gamma}_1, \widetilde{\gamma}_2)^T R(-\alpha)x$.

Similarly it can be shown that (3.3) implies (3.2). Altogether this proves the statement. $\qquad\square$

For notational convenience we define $Pv := (P_i v_i)_{i=0,\dots,N}$. The set of *feasible membranes given the particle configuration* $\boldsymbol{p}$ is defined by

$$U(\mathbf{p}) := \left\{ u \in H^2(\Omega(\mathbf{p})) \mid P(T(\mathbf{p})u - g) = 0 \right\}.$$

We use the shorthand $J(\mathbf{p}, u) := J(\Omega(\mathbf{p}), u)$ to define the *interaction energy*

$$\mathcal{J}(\mathbf{p}) := \min_{u \in U(\mathbf{p})} J(\mathbf{p}, u)$$

where we use the convention $\min(\emptyset) := +\infty$.

We note that the interaction energy is well-defined for g smooth enough. This statement can be proven analogously to [7, Theorem 1].

Altogether, our model problem reads

$$\min_{\mathbf{p}\in\Lambda}\mathcal{J}(\mathbf{p}).$$

4. Differentiation of the reduced interaction energy

In this section we investigate the differentiability of $\mathcal{J}$ on Λ°. First we derive a technical result which shows that the admissible membrane sets $U(\mathbf{p})$ are isomorphic and which allows us to pose our problem locally over a fixed reference domain $\Omega(\mathbf{p})$. Afterwards we apply the implicit function theorem to prove differentiability of the reduced interaction potential and use matrix calculus to derive an explicit and numerically feasible expression for the first order derivatives.

4.1. Trace-preserving diffeomorphisms between the reference domains.
In this part we construct a local diffeomorphism between the domains $\Omega(\mathbf{p})$ that preserves the boundary conditions. The construction is based on ordinary differential equations (ODEs) and in particularly requires the following result from ODE theory.

Lemma 4.1. *Let $\mathcal{B} \subseteq \mathbb{R}^{N\times 3}$ be an open connected set, $m > 1$ and let $\mathcal{V} \in C^m([0,1] \times \mathcal{B} \times \mathbb{R}^2, \mathbb{R}^2)$ be Lipschitz-continuous. For $\boldsymbol{q} \in \mathcal{B}$ and $x \in \mathbb{R}^2$ let $\eta(\cdot,\boldsymbol{q},x)\colon [0,1] \to \mathbb{R}^2$ be the unique solution of the ordinary differential equation*

$$\frac{\partial\eta}{\partial t}(t,\boldsymbol{q},x) = \mathcal{V}(t,\boldsymbol{q},\eta(t,\boldsymbol{q},x)), \qquad \eta(0,\boldsymbol{q},x) = x.$$

Then the map $\mathcal{X}$ defined by $\mathcal{X}(\boldsymbol{q},x) := \eta(1,\boldsymbol{q},x)$ fulfills $\mathcal{X} \in C^m(\mathcal{B} \times \mathbb{R}^2, \mathbb{R}^2)$ and is an m-diffeomorphism onto its image for all $\boldsymbol{q} \in \mathcal{B}$.

For all $\hat{\boldsymbol{q}} \in \mathbb{R}^{N\times 3}$ with $\eta_{\hat{q}} \in C([0,1] \times \mathcal{B} \times \mathbb{R}^2, \mathbb{R}^2)$ as the unique solution of

(4.1)
$$\frac{\partial\eta_{\hat{q}}}{\partial t}(t,\boldsymbol{q},x) = \frac{\partial\mathcal{V}}{\partial\boldsymbol{q}}(t,\boldsymbol{q},\eta(t,\boldsymbol{q},x))\,\hat{\boldsymbol{q}} + \frac{\partial\mathcal{V}}{\partial x}(t,\boldsymbol{q},\eta(t,\boldsymbol{q},x))\eta_{\hat{q}}(t,\boldsymbol{q},x)$$

$$\eta_{\hat{q}}(0,\boldsymbol{q},x) = 0$$

holds $\partial_{\hat{q}}\mathcal{X}(\boldsymbol{q},x) = \eta_{\hat{q}}(1,\boldsymbol{q},x)$. Also, for all $y \in \mathbb{R}^2$ with $\eta_y \in C([0,1] \times \mathcal{B} \times \mathbb{R}^2, \mathbb{R}^2)$ as the unique solution of

(4.2)
$$\frac{\partial\eta_y}{\partial t}(t,\boldsymbol{q},x) = \frac{\partial\mathcal{V}}{\partial x}(t,\boldsymbol{q},\eta(t,\boldsymbol{q},x))\eta_y(t,\boldsymbol{q},x), \qquad \eta_y(0,\boldsymbol{q},x) = y$$

holds $\partial_y\mathcal{X}(\boldsymbol{q},x) = \eta_y(1,\boldsymbol{q},x)$.

Proof. The global existence and uniqueness of η is a consequence of the Lipschitz-continuity of $\mathcal{V}$ and the well-known Picard–Lindelöf theorem. In particular, $\mathcal{X}$ is well-defined.

The smoothness of $\mathcal{X}$ and the characterization of its derivatives is a consequence of [11, Theorem 3.1, Theorem 4.1]

Concerning the inverse of $\mathcal{X}(\mathbf{q})$, let μ be the unique solution of

$$\frac{\partial\mu}{\partial t}(t,\mathbf{q},x) = -\mathcal{V}(1-t,\mu(t,\mathbf{q},x)), \qquad \mu(0,\mathbf{q},x) = x.$$

Let $\widetilde{\eta}(t,\mathbf{q},x) := \eta(1-t,\mathbf{q},x)$. From

$$\frac{\partial\widetilde{\eta}}{\partial t}(t,\mathbf{q},x) = -\mathcal{V}(t,\mathbf{q},\eta(1-t,\mathbf{q},x)), \qquad \widetilde{\eta}(0,\mathbf{q},x) = \mathcal{X}(\mathbf{q},x)$$

and the uniqueness of μ we infer $\widetilde{\eta}(t, \mathbf{q}, x) = \mu(t, \mathbf{q}, \mathcal{X}(\mathbf{q}, x))$, and in particular also $\mu(1, \mathbf{q}, \mathcal{X}(\mathbf{q}, x)) = \widetilde{\eta}(1, \mathbf{q}, x) = x$. Therefore $\mathcal{X}(\mathbf{q})^{-1}$ exists and is given by $\mathcal{X}(\mathbf{q})^{-1} = \mu(1, \mathbf{q}, \cdot)$. Again, the smoothness of $\mathcal{V}$ implies m-smoothness of μ, and consequently $\mathcal{X}$ is an m-diffeomorphism. $\qquad\square$

In the following we restrict ourselves to a special class of vector fields that is described in the result below. We show afterwards that the diffeomorphisms induced by such vector fields have a certain trace preserving property that again can be used to construct an isomorphism between the admissible membrane sets.

Lemma 4.2. *Let $\boldsymbol{p} \in \Lambda^\circ$ and $m \geq 1$. Then there exists an open neighborhood $\mathcal{B} \subseteq \mathbb{R}^{N \times 3}$ of $0 \in \mathbb{R}^{N \times 3}$ and a Lipschitz-continuous map $\mathcal{V} \in C^m([0,1] \times \mathcal{B} \times \mathbb{R}^2, \mathbb{R}^2)$ such that for all $t \in [0,1]$, $\boldsymbol{q} \in \mathcal{B}$, and $i \in \{0, \dots, N\}$ holds*

(4.3)
$$\mathcal{V}(t, \boldsymbol{q}, \cdot)|_{\Gamma_i(\boldsymbol{p}_i + t\boldsymbol{q}_i)} = \begin{pmatrix} \boldsymbol{q}_{i1} \\ \boldsymbol{q}_{i2} \end{pmatrix} + \boldsymbol{q}_{i3} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} \left(\cdot - \begin{pmatrix} \boldsymbol{p}_{i1} + t\boldsymbol{q}_{i1} \\ \boldsymbol{p}_{i2} + t\boldsymbol{q}_{i2} \end{pmatrix} \right)$$
$$D\mathcal{V}(t, \boldsymbol{q}, \cdot)|_{\Gamma_i(\boldsymbol{p}_i + t\boldsymbol{q}_i)} = \boldsymbol{q}_{i3} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix}.$$

Proof. This is a consequence of the Whitney extension theorem, Theorem 8.1. It uses the fact that the Γ_i are pairwise disjoint and that the right hand sides in (4.3) smoothly extend to $\mathbb{R}^2$. $\qquad\square$

Lemma 4.3. *Let $\mathcal{V}$ be as in Lemma 4.2 for $m \geq 2$ and let $\mathcal{X}$ as in Lemma 4.1 be induced by $\mathcal{V}$. Then $\mathcal{X}(0, \cdot) = \mathrm{id}_{\mathbb{R}^2}$, $\mathcal{X}(\boldsymbol{q}, \Omega(\boldsymbol{p})) = \Omega(\boldsymbol{p} + \boldsymbol{q})$, and for all $u \in H^2(\Omega(\boldsymbol{p}))$ holds*

(4.4)
$$T(\boldsymbol{p})u = T(\boldsymbol{p} + \boldsymbol{q})(u \circ \mathcal{X}(\boldsymbol{q})^{-1}).$$

Proof. From $\mathcal{V}(t, 0, \cdot) = 0$ follows immediately that $\mathcal{X}(0, x) = \eta(1, 0, x) = x$, i.e. $\mathcal{X}(0) = \mathrm{id}_{\mathbb{R}^2}$.

We now prove (4.4). First we show that $\mathcal{X}$ preserves the boundaries. From the properties (4.3) it follows that for $i \in \{0, \dots, N\}$ and $x \in \Gamma_i(\mathbf{p}_i)$ the value of $\mathcal{X}(\mathbf{p}, x)$ can be computed explicitly. Recalling the definition of φ in (2.2) and the convention $\mathbf{q}_0 := \mathbf{p}_0 := 0$, this value is given by

(4.5)
$$\mathcal{X}(\mathbf{p}, x) = \varphi\left(\mathbf{p}_i + \mathbf{q}_i; \varphi^{-1}(\mathbf{p}_i; x)\right).$$

In particular holds $\mathcal{X}(\mathbf{p}, \Gamma_i(\mathbf{p}_i)) = \Gamma_i(\mathbf{p}_i + \mathbf{q}_i)$. Another immediate consequence of (4.5) is – now recalling the definition of the rotation matrix R in (2.1) – that

(4.6)
$$\nu|_{\Gamma_i(\mathbf{p}_i + \mathbf{q}_i)}(\mathcal{X}(\mathbf{q}, x)) = R(\mathbf{q}_{i3})\nu|_{\Gamma_i(\mathbf{p}_i)}(x)$$

for $x \in \Gamma_i(\mathbf{p}_i)$. And, similarly, using the properties (4.3) of $\mathcal{V}$ also allows us to compute $\frac{\partial X}{\partial x}(\mathbf{q}, x)$ on $\Gamma_i(\mathbf{p}_i)$ from solving the ODE (4.2). The result is

(4.7)
$$D\mathcal{X}(\mathbf{q}, x) = R(\mathbf{q}_{i3}).$$

Now, let $\widetilde{u} := u \circ \mathcal{X}(\mathbf{q})^{-1}$. From (4.5) we infer for $x \in \Gamma_i(\mathbf{p}_i + \mathbf{q}_i)$ that

(4.8)
$$\widetilde{u}(x) = u\left(\varphi(\mathbf{p}_i; \varphi^{-1}(\mathbf{p}_i + \mathbf{q}_i; x))\right).$$

Also, from (4.6) and (4.7) we infer for $x \in \Gamma_i(\mathbf{p}_i + \mathbf{q}_i)$ that

$$
\begin{aligned}
\partial_\nu \widetilde{u}(x) &= Du(\mathcal{X}^{-1}(\mathbf{q}; x)) \frac{\partial \mathcal{X}^{-1}(\mathbf{q}; x)}{\partial x} \nu|_{\Gamma_i(\mathbf{p}_i + \mathbf{q}_i)}(x) \\
&= Du(\mathcal{X}^{-1}(\mathbf{q}; x)) R(-\mathbf{q}_{i3}) R(\mathbf{q}_{i3}) \nu|_{\Gamma_i(\mathbf{p}_i)}(\mathcal{X}^{-1}(\mathbf{q}; x)) \\
&= \partial_\nu u(\mathcal{X}^{-1}(\mathbf{q}; x)) \\
&= \partial_\nu u \left(\varphi(\mathbf{p}_i; \varphi^{-1}(\mathbf{p}_i + \mathbf{q}_i; x)) \right).
\end{aligned}
$$
(4.9)

Recalling the definition of the trace operators, (3.1), we have for almost-every $x \in \Gamma_i^0$ by (4.8)

$$
T_{i1}(\mathbf{p} + \mathbf{q}) \widetilde{u}(x) = \widetilde{u}(\varphi(\mathbf{p}_i + \mathbf{q}_i; x)) = u \left(\varphi(\mathbf{p}_i; x) \right) = T_{i1}(\mathbf{p}) u(x)
$$

and by (4.9)

$$
T_{i2}(\mathbf{p} + \mathbf{q}) \widetilde{u}(x) = \partial_\nu \widetilde{u}(\varphi(\mathbf{p}_i + \mathbf{q}_i; x)) = \partial_\nu u \left(\varphi(\mathbf{p}_i; x) \right) = T_{i2}(\mathbf{p}) u(x).
$$

Altogether this proves equation (4.4).

In order to show the equality $\mathcal{X}(\mathbf{q}, \Omega(\mathbf{p})) = \Omega(\mathbf{p} + \mathbf{q})$ we define the set

$$
\mathcal{Z} = \{(t, \eta(t, \mathbf{q}, x)) \mid x \in \partial\Omega(\mathbf{p})\}.
$$

Now let $x_0 \in \Omega(\mathbf{p})^\circ$ and assume that $\mathcal{X}(\mathbf{q}, x_0) = \eta(1, \mathbf{q}, x_0) \notin \Omega(\mathbf{p} + \mathbf{q})$. By continuity of $\mathcal{X}$ this would imply that there exists a $\hat{t} \in [0, 1]$ such that $\eta(\hat{t}, \mathbf{q}, x_0) \in \mathcal{Z}$ and therefore, by definition of $\mathcal{Z}$, there would exist a $x_1 \in \partial\Omega(\mathbf{p})$ such that $\eta(\hat{t}, \mathbf{q}, x_0) = \eta(\hat{t}, \mathbf{q}, x_1)$. As of $x_0 \neq x_1$ this would be a contradiction to the uniqueness of η. □

Lemma 4.4. *Let $\mathcal{X}$ be as in Lemma 4.3. Then for all $\boldsymbol{q} \in \mathcal{B}$ the map*

$$
\Phi(\boldsymbol{q}) \colon U(\boldsymbol{p}) \longrightarrow U(\boldsymbol{p} + \boldsymbol{q}), \qquad u \longmapsto u \circ \mathcal{X}(\boldsymbol{q})^{-1}
$$

is well-defined and an isomorphism.

Proof. From Lemma 4.3 we know for every $\mathbf{q} \in \mathcal{B}$ that the restriction $\mathcal{X}(\mathbf{q}, \cdot)|_{\Omega(\mathbf{p})}$ is a 2-diffeomorphism onto $\Omega(\mathbf{p} + \mathbf{q})$. Because $\overline{\Omega(\mathbf{p})}$ is compact we can assume without loss of generality that $\det \frac{\partial}{\partial x} \mathcal{X}(\mathbf{q}, x)$ is uniformly bounded, i.e. that there exists a $c \in \mathbb{R}_{>0}$ such that for all $\mathbf{q} \in \mathcal{B}$ and $x \in \Omega(\mathbf{p})$ holds $c \leq \left| \det \frac{\partial}{\partial x} \mathcal{X}(\mathbf{q}, x) \right| \leq \frac{1}{c}$. Elsewise we may replace $\mathcal{B}$ by an appropriate sub-neighborhood. Hence, [1, Theorem 3.35] is applicable and the map

$$
\widetilde{\Phi}(\mathbf{q}) \colon H^2(\Omega(\mathbf{p})) \longrightarrow H^2(\Omega(\mathbf{p} + \mathbf{q})), \qquad u \longmapsto u \circ \mathcal{X}(\mathbf{q})^{-1}
$$

is well-defined and an isomorphism, and in particular also the restriction $\Phi(\mathbf{q}) = \widetilde{\Phi}(\mathbf{q})|_{U(\mathbf{p})}$ is well-defined and an isomorphism onto its image.

It remains to show that $\text{range}(\Phi(\mathbf{q})) = U(\mathbf{p} + \mathbf{q})$. Suppose $u \in U(\mathbf{p})$ and $\widetilde{u} \in U(\mathbf{p} + \mathbf{q})$. Because of the trace preserving property (4.4) and by definition of $U(\mathbf{p})$ and $U(\mathbf{p} + \mathbf{q})$ it follows that $\Phi(\mathbf{q})u = u \circ \mathcal{X}(\mathbf{q}) \in U(\mathbf{p} + \mathbf{q})$ and $\Phi(\mathbf{q})^{-1}\widetilde{u} = \widetilde{u} \circ \mathcal{X}(\mathbf{q}) \in U(\mathbf{p})$, and so $\text{range}(\Phi(\mathbf{q})) = U(\mathbf{p} + \mathbf{q})$. □

4.2. **Differentiability.** In this part we use the maps $\mathcal{X}$ from Lemma 4.3 and Φ from Lemma 4.4 to transform the domain of definition for the functions $J(\mathbf{p} + \mathbf{q})$ from $U(\mathbf{p} + \mathbf{q})$ to $U(\mathbf{p})$. Afterwards we apply the implicit function theorem to derive a differentiability result.

For $\mathbf{q} \in \mathcal{B}$ and $u \in U(\mathbf{p})$ the *transformed energy* is defined as

$$(4.10) \qquad \hat{J}(\mathbf{q}, u) := J(\mathbf{p} + \mathbf{q}, \Phi(\mathbf{q}, u)),$$

and the *transformed reduced interaction energy* is

$$\hat{\mathcal{J}}(\mathbf{q}) := \min_{v \in U(\mathbf{p})} \hat{J}(\mathbf{q}, v).$$

We write the affine linear subspace $U(\mathbf{p})$ as $U(\mathbf{p}) = U_0 + \hat{g}$ where $U_0 \subseteq H^2(\Omega(\mathbf{p}))$ is a linear subspace and $\hat{g} \in H^2(\Omega(\mathbf{p}))$ is a function such that $T(\mathbf{p})\hat{g} = g$.

For notational convenience we define $D^k := \frac{\partial^k}{\partial x^k}$ to be the differential with respect to the spatial coordinates.

Lemma 4.5. *Let $\boldsymbol{q} \in \mathcal{B}$ and define*

$$\mathcal{A}(\boldsymbol{q}, x) := |\det D\mathcal{X}(\boldsymbol{q}, x)| \, (D\mathcal{X}(\boldsymbol{q}, x))^{-1} (D\mathcal{X}(\boldsymbol{q}, x))^{-T}.$$

It holds

$$(4.11) \qquad \hat{J}(\boldsymbol{q}, u) = \frac{1}{2} \int_{\Omega(\boldsymbol{p})} \kappa \frac{\operatorname{div}(\mathcal{A}(\boldsymbol{q})\nabla u)^2}{|\det D\mathcal{X}(\boldsymbol{q})|} + \sigma \|\nabla u\|^2_{\mathcal{A}(\boldsymbol{q})} \, \mathrm{d}x$$

and $\hat{J}_u \in C^{m-2}(\mathcal{B} \times U(\boldsymbol{p}), U_0')$.

Proof. Equation (4.11) is a direct application of Lemma 8.3 applied to $X = \mathcal{X}(\mathbf{q})$.

Furthermore, for all $v \in H^2(\Omega)$ we have

$$\hat{J}_u(\mathbf{q}, u; v) = \int_{\Omega(\mathbf{p})} \kappa \frac{\operatorname{div}(\mathcal{A}(\mathbf{q})\nabla u) \, \operatorname{div}(\mathcal{A}(\mathbf{q})\nabla v)}{|\det D\mathcal{X}(\mathbf{q})|} + \sigma \mathcal{A}(\mathbf{q})\nabla u \cdot \nabla v \, \mathrm{d}x.$$

As of $\mathcal{X} \in C^m$ we know that $D\mathcal{X}(\mathbf{q})$ and $D^2\mathcal{X}(\mathbf{q})$ are both $(m-2)$ times continuously differentiable. Because the $\mathcal{X}(\mathbf{q})$ are diffeomorphisms with $\mathcal{X}(0)$ and because $\mathcal{X}$ is continuous we have $\det(D\mathcal{X}(\mathbf{q})) > 0$. Because $\overline{\Omega(\mathbf{p})}$ is compact, we can assume without loss of generality that there exists a $c \in \mathbb{R}_{>0}$ such that $\det(D\mathcal{X}(\mathbf{q})) > c$, else we replace $\mathcal{B}$ by a suitable sub-neighborhood. Consequently, the integrand of $\hat{J}_u$ is $(m-2)$ times differentiable with respect to $\mathbf{q}$. Moreover, the integrand is even smooth with respect to u and hence application of the dominated convergence theorem yields $\hat{J}_u \in C^{m-2}(\mathcal{B} \times U(\mathbf{p}), U_0')$. $\square$

Lemma 4.6. *There exists a neighborhood $\hat{\mathcal{B}}$ of $0 \in \mathbb{R}^{N \times 3}$ such that $\mathcal{J} \in C^{m-2}(\hat{\mathcal{B}} + \boldsymbol{p})$ and for all $\boldsymbol{q} \in \hat{\mathcal{B}}$ and multi-indices α with $|\alpha| \leq m - 2$ holds*

$$\frac{\partial^\alpha}{\partial \boldsymbol{p}^\alpha} \mathcal{J}(\boldsymbol{p} + \boldsymbol{q}) = \frac{\partial^\alpha}{\partial \boldsymbol{q}^\alpha} \hat{\mathcal{J}}(\boldsymbol{q}).$$

In particular, if $m \geq 3$ and $u = \arg\min_{v \in U(\boldsymbol{p})} J(\boldsymbol{p}, v)$ then

$$(4.12) \qquad \frac{\partial}{\partial \boldsymbol{p}} \mathcal{J}(\boldsymbol{p}) = \frac{\partial}{\partial \boldsymbol{q}} \hat{J}(0, u).$$

Proof. Let $\hat{J}_u := \frac{\partial}{\partial u} \hat{J}$ and $\hat{J}_{uu} := \frac{\partial^2}{\partial u^2} \hat{J}$. Define

$$F \colon \mathcal{B} \times U_0 \longrightarrow U_0', \qquad (\mathbf{q}, v) \longmapsto \hat{J}_u(\mathbf{q}, v + \hat{g}).$$

Suppose that $u \in U(\mathbf{p})$ is the unique solution of $\min_{v \in U(\mathbf{p})} J(\mathbf{p}, v)$, and define $\hat{u} := u - \hat{g}$. Then by (4.10) and because of $\Phi(0)u = u$ it also follows that u is the unique minimizer of $\hat{J}(0, \cdot)$ over $U(\mathbf{p})$ and therefore and therefore

$$F(0, \hat{u}) = \hat{J}_u(0, \hat{u} + \hat{g}) = \hat{J}_u(0, u) = 0 \in U_0'.$$

Moreover, for all $v, w \in U_0$ holds

$$F_u(0, \hat{u}; v, w) = \hat{J}_{uu}(0, u; v, w) = \int_{\Omega(\mathbf{p})} \kappa \Delta v \, \Delta w + \sigma \nabla v \cdot \nabla w \, \mathrm{d}x.$$

This defines an elliptic bilinear form over U_0 and hence $F_u(0, \hat{u})$ is invertible in U_0 by virtue of Lax–Milgram's theorem. Application of the implicit function theorem, Theorem 8.2, yields a neighborhood $\hat{\mathcal{B}} \subseteq \mathcal{B}$ of 0 and a function $\hat{\mathbf{u}} \in C^{m-2}(\hat{\mathcal{B}}, U_0)$ such that $\hat{\mathbf{u}}(0) = \hat{u}$ and $F(0, \hat{\mathbf{u}}(\mathbf{q})) = 0$ for all $\mathbf{q} \in \hat{\mathcal{B}}$. In particular, $\hat{\mathcal{J}}(\mathbf{q}) = \hat{J}(\mathbf{q}, \hat{\mathbf{u}}(\mathbf{q}) + \hat{g})$ for all $\mathbf{q} \in \mathcal{B}$. From $\mathcal{J}(\mathbf{p} + \mathbf{q}) = \hat{\mathcal{J}}(\mathbf{q})$ we infer

$$\frac{\partial^\alpha}{\partial \mathbf{p}^\alpha} \mathcal{J}(\mathbf{p}) = \frac{\partial^\alpha}{\partial \mathbf{q}^\alpha} \hat{\mathcal{J}}(\mathbf{q})$$

for all multi-indices α with $|\alpha| \leq m - 2$. For $m \geq 3$ this in particularly implies

$$\frac{\partial}{\partial \mathbf{p}} \mathcal{J}(\mathbf{p}) = \frac{\partial}{\partial \mathbf{q}} \hat{J}(0, \hat{\mathbf{u}}(0) + \hat{g}) + \hat{J}_u(0, \hat{\mathbf{u}}(0) + \hat{g}) \frac{\partial}{\partial \mathbf{q}} \hat{\mathbf{u}}(0) = \frac{\partial}{\partial \mathbf{q}} \hat{J}(0, u).$$

$\square$

4.3. A numerically feasible representation of the first derivative.

In the following paragraphs we discuss a way to derive a numerically feasible expression for the first order derivative $\partial_{\mathbf{e}} \mathcal{J}(\mathbf{p})$ of the reduced interaction energy $\mathcal{J}$ in $\mathbf{p} \in \Lambda^\circ$ in direction of an $\mathbf{e} \in \mathbb{R}^{N \times 3}$.

An important component of the integrand's derivative is $\partial_{\mathbf{e}} \mathcal{X}(0)$ and its spatial derivatives. From (4.1) we know that this derivative can be evaluated by solving an ODE. This is not practically feasible, however, because those computations would be too expensive. Besides, it also requires knowledge of the vector field $\mathcal{V}$, which may be hard to construct explicitly. Instead we restrict ourselves to a subclass of vector fields in the sense of Lemma 4.2 for which $\partial_{\mathbf{e}} \mathcal{X}(0)$ is can be computed easily from information that is available a-priori.

To this end, suppose a vector field $V \colon \Omega(\mathbf{p}) \to \mathbb{R}^2$ such that for $i \in \{0, \ldots, N\}$

(4.13)
$$V|_{\Gamma_i(\mathbf{p}_i)} = \begin{pmatrix} \mathbf{e}_{i1} \\ \mathbf{e}_{i2} \end{pmatrix} + \mathbf{e}_{i3} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} \left(\cdot - \begin{pmatrix} \mathbf{p}_{i1} \\ \mathbf{p}_{i2} \end{pmatrix} \right)$$

$$DV|_{\Gamma_i(\mathbf{p}_i)} = \mathbf{e}_{i3} \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix}$$

where we again use the convention $\mathbf{e}_0 := 0$. Usually it is easy to construct such a V in a way that it is also numerically accessible. Next we extend this to a vector field $\mathcal{V}$ such that (4.3) is fulfilled, where we can make the simplifying assumption that $\mathcal{B}$ is a ball of radius $r \in \mathbb{R}_{>0}$, and such that for all $t \in [0, 1]$ and $\lambda \in (0, r)$ the scaling properties

(4.14)
$$\mathcal{V}(t, \lambda \mathbf{e}, x) = \frac{\lambda}{r} \mathcal{V}\left(\frac{\lambda}{r} t, r\mathbf{e}, x \right)$$

$$\mathcal{V}(0, r\mathbf{e}, x) = rV(x)$$

hold.

In view of (4.1) and given $x \in \Omega(\mathbf{p})$, we have $\partial_{\mathbf{e}} \mathcal{X}(0, x) = \eta_{\mathbf{e}}(1, x)$ where $\eta_{\mathbf{e}}(\cdot, x)$ solves the ODE

$$\frac{\partial \eta_{\mathbf{e}}}{\partial t}(t, x) = \partial_{\mathbf{e}} \mathcal{V}(t, 0, \eta(t, 0, x)) + D\mathcal{V}(t, 0, \eta(t, 0, x))\eta_{\mathbf{e}}(t, x), \qquad \eta_{\mathbf{e}}(0, x) = 0.$$

As of $\mathcal{V}(t, 0, \cdot) \equiv 0$ we have $\eta(t, 0, x) = x$ and $D\mathcal{V}(t, 0, \eta(t, 0, x)) = 0$. Furthermore, from (4.14) we are able to conclude

$$\partial_{\mathbf{e}} \mathcal{V}(t, 0, x) = \lim_{\lambda \searrow 0} \frac{\mathcal{V}(t, \lambda\,\mathbf{e}, x) - \mathcal{V}(t, 0, x)}{\lambda} = \lim_{\lambda \searrow 0} \frac{\mathcal{V}\left(\frac{\lambda}{r} t, r\mathbf{e}, x\right)}{r} = V(x).$$

Therefore, $\eta_{\mathbf{e}}$ is the solution of the ODE

$$\frac{\partial \eta_{\mathbf{e}}}{\partial t}(t, x) = V(x), \qquad \eta_{\mathbf{e}}(0, x) = 0,$$

which implies $\eta_{\mathbf{e}}(t, x) = t\,V(x)$ and hence also $\partial_{\mathbf{e}} \mathcal{X}(0) = V$.

When computing the derivative, we will make use of the following identities from matrix calculus.

Lemma 4.7. *Suppose $M \in C^1(\mathbb{R}^d, \mathbb{R}^{n \times n})$ and that $M(x)$ is invertible for all $x \in \mathbb{R}^d$. Then*

$$(4.15) \qquad \frac{\partial}{\partial x_i} \det(M(x)) = \det(M) \operatorname{Tr}\left(M(x)^{-1} \frac{\partial}{\partial x_i} M(x)\right)$$

$$(4.16) \qquad \frac{\partial}{\partial x_i} M(x)^{-1} = -M(x)^{-1} \frac{\partial M(x)}{\partial x_i} M(x)^{-1}$$

$$(4.17) \qquad \frac{\partial}{\partial x_i} \operatorname{Tr}(M(x)) = \operatorname{Tr}\left(\frac{\partial}{\partial x_i} M(x)\right).$$

Proof. See literature on matrix calculus, e. g. [18, Chapter 9]. $\qquad \square$

Lemma 4.8. *Let $V := \partial_{\mathbf{e}} \mathcal{X}(0)$, $u := \arg\min_{v \in U(\mathbf{p})} J(\mathbf{p}, u)$, and*

$$\mathcal{A}'(0) := \operatorname{div}(V)I - DV - DV^T.$$

Then

$$(4.18) \qquad \begin{aligned} \partial_{\mathbf{e}} \mathcal{J}(\mathbf{p}) &= \int_{\Omega(\mathbf{p})} \kappa \Delta u \left(\mathcal{A}'(0) : D^2 u - \Delta V \cdot \nabla u - \frac{1}{2} \operatorname{div}(V)\Delta u\right) \, \mathrm{d}x \\ &\quad + \int_{\Omega(\mathbf{p})} \frac{\sigma}{2} \|\nabla u\|_{\mathcal{A}'(0)}^2 \, \mathrm{d}x. \end{aligned}$$

Proof. From (4.12) we know that $\partial_{\mathbf{e}} \mathcal{J}(\mathbf{p}) = \partial_{\mathbf{e}} \hat{J}(0, u)$ and hence it suffices to compute the latter. In the following we use without further emphasis the identities $D\mathcal{X}(0, \cdot) \equiv \operatorname{id}_{\mathbb{R}^2}$ and $\det D\mathcal{X}(0) \equiv 1$. Based on this and on the identities (4.15) and (4.16) we have

$$(4.19) \qquad \begin{aligned} \frac{\partial}{\partial \mathbf{e}} \det(D\mathcal{X}(\mathbf{q}))\bigg|_{\mathbf{q}=0} &= \det(D\mathcal{X}(\mathbf{q})) \operatorname{Tr}\left(D\mathcal{X}(\mathbf{q})^{-1} \frac{\partial}{\partial \mathbf{e}} D\mathcal{X}(\mathbf{q})\right)\bigg|_{\mathbf{q}=0} \\ &= \operatorname{Tr}\left(\frac{\partial}{\partial \mathbf{e}} D\mathcal{X}(\mathbf{q})\right) = \operatorname{div}(V) \end{aligned}$$

$$(4.20) \qquad \begin{aligned} \frac{\partial}{\partial \mathbf{e}} D\mathcal{X}^{-1}(\mathbf{q})\bigg|_{\mathbf{q}=0} &= -D\mathcal{X}(\mathbf{q})^{-1} \frac{\partial D\mathcal{X}(\mathbf{q})}{\partial \mathbf{e}} D\mathcal{X}(\mathbf{q})^{-1}\bigg|_{\mathbf{q}=0} \\ &= -\frac{\partial D\mathcal{X}(0)}{\partial \mathbf{e}} = -DV. \end{aligned}$$

By definition of $\mathcal{A}$ we have

$$\mathcal{A}(\mathbf{q}) = \det(D\mathcal{X}(\mathbf{q})) \, D\mathcal{X}(\mathbf{q})^{-1} D\mathcal{X}(\mathbf{q})^{-T},$$

where we again used $\det(\mathcal{X}(\mathbf{q})) > 0$. The product rule together with the identities (4.19) and (4.20) then leads us to

(4.21)
$$\begin{aligned}
\mathcal{A}'(0) := \left. \frac{\partial}{\partial \mathbf{e}} \mathcal{A}(\mathbf{p}) \right|_{\mathbf{q}=0} \\
= \left. \frac{\partial \det(D\mathcal{X}(\mathbf{q}))}{\partial \mathbf{e}} \right|_{\mathbf{q}=0} D\mathcal{X}(\mathbf{q})^{-1} D\mathcal{X}(\mathbf{q})^{-T} \\
+ \det(D\mathcal{X}(\mathbf{q})) \left. \frac{\partial D\mathcal{X}(\mathbf{q})^{-1}}{\partial \mathbf{e}} \right|_{\mathbf{q}=0} D\mathcal{X}(\mathbf{q})^{-T} \\
+ \det(D\mathcal{X}(\mathbf{q})) D\mathcal{X}(\mathbf{q})^{-1} \left. \frac{\partial D\mathcal{X}(\mathbf{q})^{-T}}{\partial \mathbf{e}} \right|_{\mathbf{q}=0} \\
= \operatorname{div}(V) I - DV - DV^T.
\end{aligned}$$

Equation (4.21) gives us, using $\partial_i := \frac{\partial}{\partial x_i}$,

$$\partial_i \mathcal{A}'(0) = \left(\sum_{k=1}^{2} \partial_{ik} V_k \right) I - \partial_i DV - \partial_i DV^T$$

and so

(4.22)
$$\begin{aligned}
\sum_{i=1}^{2} \partial_i \mathcal{A}'_{ij}(0) = \sum_{i,k=1}^{2} \partial_{ik} V_k \delta_{ij} - \sum_{i=1}^{2} (\partial_{ij} V_i + \partial_{ii} V_j) \\
= \sum_{k=1}^{2} \partial_{jk} V_k - \sum_{i=1}^{2} (\partial_{ij} V_i + \partial_{ii} V_j) \\
= \sum_{i=1}^{2} \left(\partial_{ji} V_i - \partial_{ij} V_i - \sum_{i=1}^{2} \partial_{ii} V_j \right) \\
= -\Delta V_j
\end{aligned}$$

for $j \in \{1,2\}$. Noting

$$\begin{aligned}
\operatorname{div}(\mathcal{A}(\mathbf{q}) \nabla u) = \sum_{i=1}^{2} \partial_i \left(\sum_{j=1}^{2} \mathcal{A}(\mathbf{q})_{ij} \partial_j u \right) \\
= \sum_{i,j=1}^{2} \left(\mathcal{A}(\mathbf{q})_{ij} \partial_{ij} u + \partial_i \mathcal{A}(\mathbf{q})_{ij} \partial_j u \right) \\
= \mathcal{A}(\mathbf{q}) : D^2 u + \sum_{j=1}^{2} \left(\sum_{i=1}^{2} \partial_i \mathcal{A}(\mathbf{q})_{i*} \right) \partial_j u
\end{aligned}$$

we therefore conclude

(4.23)
$$\left. \frac{\partial}{\partial \mathbf{e}} \operatorname{div}(\mathcal{A}(\mathbf{q}) \nabla u) \right|_{\mathbf{q}=0} = \mathcal{A}'(0) : D^2 u - \Delta V \cdot \nabla u$$

where $\Delta V := (\Delta V_i)_{i=1,\dots,n} \in \mathbb{R}^2$.

We recall

$$\hat{J}(\mathbf{q}, u) = \frac{1}{2} \int_{\Omega(\mathbf{p})} \kappa \frac{\operatorname{div}(\mathcal{A}(\mathbf{q})\nabla u)^2}{\det D\mathcal{X}(\mathbf{q})} + \sigma \mathcal{A}(\mathbf{q})\nabla u \cdot \nabla u \, \mathrm{d}x.$$

Combining (4.19), (4.21) and (4.23) yields

$$\begin{aligned}
\frac{\partial}{\partial \mathbf{e}} \hat{J}(\mathbf{q}, u) \Big|_{\mathbf{q}=0} &= \frac{1}{2} \int_{\Omega(\mathbf{p})} 2\kappa \operatorname{div}(\mathcal{A}(\mathbf{q})\nabla u) \, \frac{\partial}{\partial \mathbf{e}} \operatorname{div}(\mathcal{A}(\mathbf{q})\nabla u) \Big|_{\mathbf{q}=0} \, \mathrm{d}x \\
&\quad - \frac{1}{2} \int_{\Omega(\mathbf{p})} \kappa \frac{\operatorname{div}(\mathcal{A}(\mathbf{q})\nabla u)^2}{(\det D\mathcal{X}(\mathbf{q}))^2} \, \frac{\partial}{\partial \mathbf{e}} \det(D\mathcal{X}(\mathbf{q})) \Big|_{\mathbf{q}=0} \, \mathrm{d}x \\
&\quad + \frac{1}{2} \int_{\Omega(\mathbf{p})} \sigma \, \frac{\partial}{\partial \mathbf{e}} \mathcal{A}(\mathbf{q}) \Big|_{\mathbf{q}=0} \nabla u \cdot \nabla u \, \mathrm{d}x \\
&= \int_{\Omega(\mathbf{p})} \kappa \Delta u \left(\mathcal{A}'(0) : D^2 u - \Delta V \cdot \nabla u - \frac{1}{2} \operatorname{div}(V)\Delta u \right) \\
&\quad + \frac{\sigma}{2} \|\nabla u\|^2_{\mathcal{A}'(0)} \, \mathrm{d}x,
\end{aligned}$$

which proves the claim as stated. $\qquad\square$

In general, the exact minimizer for $\mathcal{J}(\mathbf{p})$ is unknown and can only be approximated. The following result gives an upper bound on the approximation error.

Lemma 4.9. *Let $u = \arg\min_{v \in U(\boldsymbol{p})} J(\boldsymbol{p}, v)$ and $\widetilde{u} \in H^2(\Omega(\boldsymbol{p}))$. Then there exists a constant $C > 0$ such that*

$$\left| \partial_e \hat{J}(0, u) - \partial_e \hat{J}(0, \widetilde{u}) \right| \leq C \, \|V\|_{C^2(\Omega(\boldsymbol{p}))} \, \|u + \widetilde{u}\|_{H^2(\Omega(\boldsymbol{p}))} \, \|u - \widetilde{u}\|_{H^2(\Omega(\boldsymbol{p}))}$$

Proof. Note from (4.18) that $\hat{J}_u$ is induced by a non-symmetric bilinear form, i. e. there exists a bilinear form $a \colon H^2(\Omega(\mathbf{p})) \times H^2(\Omega(\mathbf{p})) \to \mathbb{R}$ such that $\hat{J}_u(v) = a(v, v)$. Upon investigation of the coefficients of a it is readily seen that there exists a $C \in \mathbb{R}_{>0}$ such that for all $v, w \in H^2(\Omega(\mathbf{p}))$

$$|a(v, w)| \leq C \, \|V\|_{C^2(\Omega(\mathbf{p}))} \, \|v\|_{H^2(\Omega(\mathbf{p}))} \|w\|_{H^2(\Omega(\mathbf{p}))} \,.$$

Now, consider

$$\begin{aligned}
\left| \partial_\mathbf{e} \hat{J}(0, u) - \partial_\mathbf{e} \hat{J}(0, \widetilde{u}) \right| &= |a(u, u) - a(\widetilde{u}, \widetilde{u})| \\
&= \left| \frac{1}{2} a(u + \widetilde{u}, u - \widetilde{u}) + \frac{1}{2} a(u - \widetilde{u}, u + \widetilde{u}) \right| \\
&\leq C \, \|V\|_{C^2(\Omega(\mathbf{p}))} \, \|u + \widetilde{u}\|_{H^2(\Omega(\mathbf{p}))} \, \|u - \widetilde{u}\|_{H^2(\Omega(\mathbf{p}))} \,.
\end{aligned}$$

$\qquad\square$

It is important to note that while the derivative $\frac{\partial}{\partial \mathbf{e}} \mathcal{J}(\mathbf{p})$ itself is independent of V, the actual choice of V very well enters the approximation error. Therefore it is desirable to construct a V with a bounded C^2-norm.

5. NUMERICAL EXAMPLES

In this section we illustrate our formula for the derivative by numerical computations for various particle configurations. Here we always defiened the bending rigidity $\kappa = 1$ and specified no surface tension $\sigma = 0$. The optimal membrane shapes $u(\mathbf{p})$ for fixed particle configurations $\mathbf{p}$ were approximated by finite element
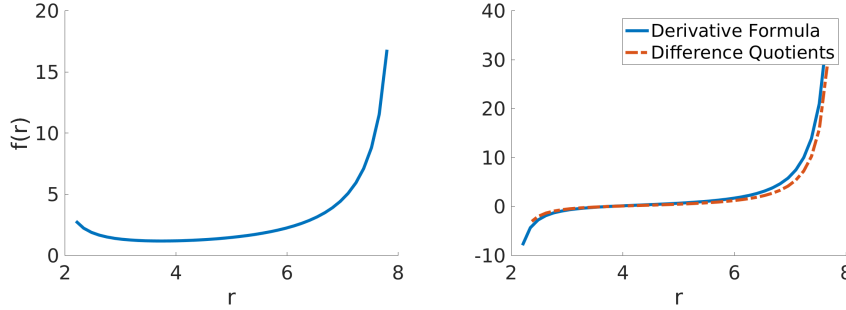
FIGURE 5.1. Left: Elastic energy for two circular inclusions as a function of their distance. Right: Comparison of difference quotients with the derivative formula (4.18) for this function.

discretizations $u_h(\mathbf{p}) \approx u(\mathbf{p})$. A possible discretization using a penalty approach is discussed in [10] where we also gave a proof of convergence. The vector fields V that occur in the derivative where explicitly constructed in such a way that they both fulfill (4.13) and can be represented as finite element functions within the used discretization. The expressions for the discretized derivatives were evaluated exactly by using standard quadrature methods.

5.1. **Two circular particles.** Let $\Omega = [-10, 10]^2$ and consider two circular particles of radius one B_1, B_2 that each induce on $\Gamma_i := \partial B_i$ the boundary conditions

$$u|_{\Gamma_i}(y) = 0 + \gamma_{i1}y_1 + \gamma_{i2}y_2 + \gamma_{i3}, \qquad \partial_\nu u|_{\Gamma_i}(y) = 1 + \gamma_{i1}\nu_1(y) + \gamma_{i2}\nu_2(y).$$

We are interested in the interaction energy as a function of the distance of these two particles and therefore we define

$$\hat{\mathbf{q}} := \begin{pmatrix} -1 & 0 & 0 \\ 1 & 0 & 0 \end{pmatrix}, \qquad \mathbf{q} := \frac{\hat{\mathbf{q}}}{\|\hat{\mathbf{q}}\|}, \qquad f(r) := \mathcal{J}(r\mathbf{q}).$$

In this formulation r is the distance between the particle centers and the particles touch for $r = 2$.

On the left picture of Fig. 5.1 we depict the approximate values of $f(r)$ for $2.06 \leq r \leq 7.94$ that we obtained from our discretization, and on right we show two approximations of $f'(r)$. One approximation was obtained by computing the difference quotients from the function values and the other one was obtained from the derivative formula (4.18).

5.2. **Two peanut shaped particles.** Let $\Omega = [-5, 5]^2$ and consider particles whose shape is defined by the zero level set of

$$\frac{1}{20} - x^4 + \frac{19}{20}x^2 - 2x^2y^2 - \frac{19}{20}y^2 - y^4.$$

We assume that each particle induces the following boundary conditions:

$$u|_{\Gamma_i}(y) = 0 + \gamma_{i1}y_1 + \gamma_{i2}y_2 + \gamma_{i3}, \qquad \partial_\nu u|_{\Gamma_i}(y) = \partial_\nu g(y) + \gamma_{i1}\nu_1(y) + \gamma_{i2}\nu_2(y)$$
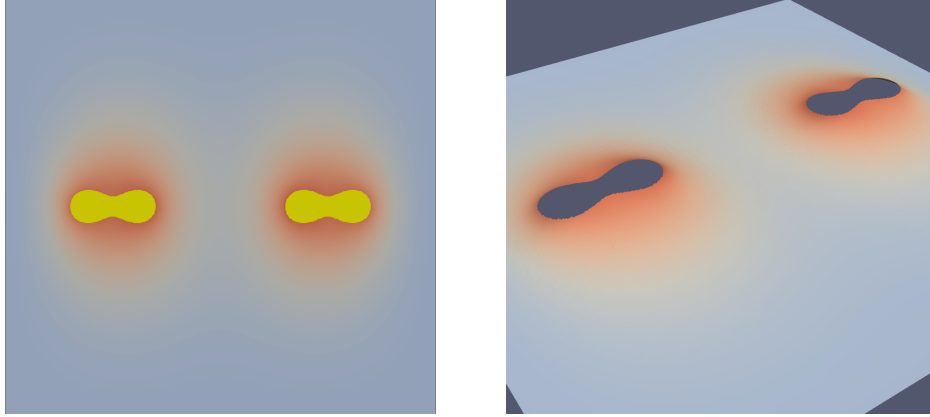
FIGURE 5.2. Left: Level set view of the optimal membrane shape for the particle configuration $\mathbf{p}$. Right: Rendered 3D view.
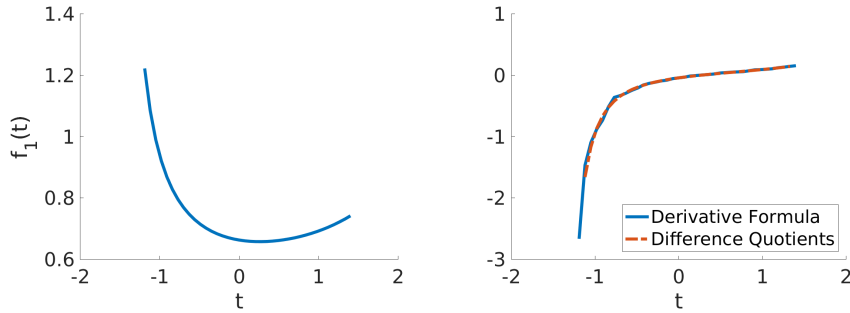

FIGURE 5.3. Left: Plot of $f_1(t)$. Right: Comparison of difference quotients with the derivative formula (4.18).

where $g(y) := \frac{1}{2}(y_1^2 + y_2^2)$. Let

$$\mathbf{p} = \begin{pmatrix} -2.5 & 0 & 0 \\ 2.5 & 0 & 0 \end{pmatrix}, \quad \mathbf{q}^1 = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{q}^2 = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{q}^3 = \begin{pmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \end{pmatrix}$$

and define $f_i(t) := \mathcal{J}(\mathbf{p} + t\mathbf{q}^i)$.

In Fig. 5.2 we show an example of an optimal membrane shape given the particle configuration $\mathbf{p}$ as obtained from our discretization. In Fig. 5.3, Fig. 5.4 and Fig. 5.5 we evaluate the functions $f_i(t)$ for $-1.4 \leq t \leq 1.4$ and compare the approximation of $f_i'(t)$ by difference quotients with the approximation obtained from evaluating the derivative formula (4.18).

Also in this setting we observe that our formula is generally in good agreement with the approximation by difference quotients.

5.3. **Gradient flow.** An immediate application of our findings is to employ a gradient flow

$$\mathbf{p}'(t) = -\nabla \mathcal{J}(\mathbf{p}(t)), \qquad \mathbf{p}(0) = \mathbf{p}_0$$
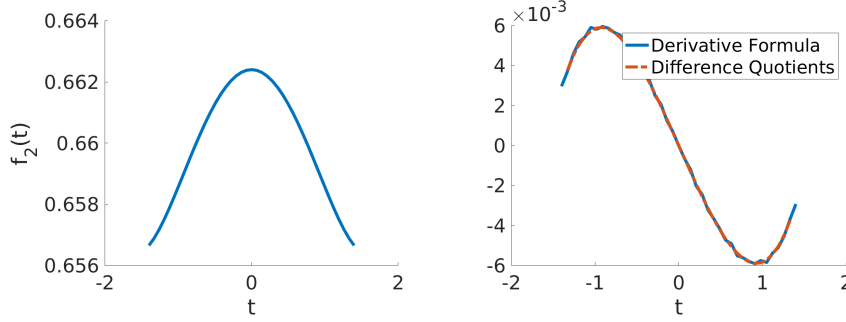
FIGURE 5.4. Left: Plot of $f_2(t)$. Right: Comparison of difference quotients with the derivative formula (4.18).
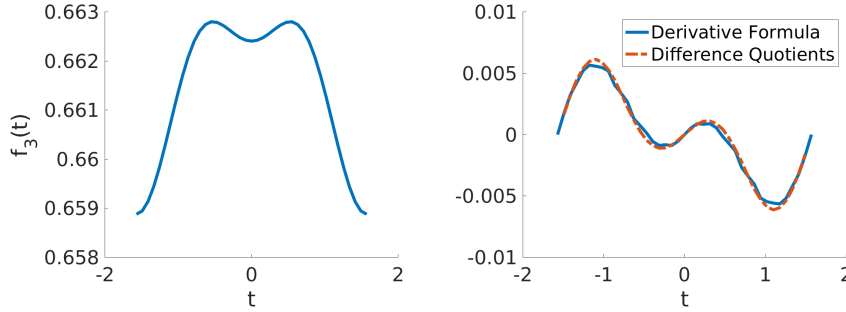

FIGURE 5.5. Left: Plot of $f_3(t)$. Right: Comparison of difference quotients with the derivative formula (4.18).

in order to investigate stable particle configurations.

In Fig. 5.6 we illustrate some time steps of the flow for two elliptic particles of different size on a square domain Ω. Here we assume the boundary conditions

$$u|_{\Gamma_i}(y) = \gamma_i, \qquad \partial_\nu u|_{\Gamma_i}(y) = 1$$

for each particle. The computations use a discretization of the gradient flow by an explicit Euler scheme

$$\mathbf{p}_{k+1} := \mathbf{p}_k - \tau \nabla \mathcal{J}(\mathbf{p}_k)$$

with a fixed time step size $\tau > 0$. The gradient $\nabla \mathcal{J}(\mathbf{p}_k)$ is approximated using the derivative formula (4.18) for a finite element approximation of u. In fact, the time discrete gradient flow can be viewed as gradient descent method with fixed step size for the computation of minimizers of $\mathcal{J}$. Notice, that the simple gradient flow approach was used to simplify the presentation and that more sophisticated iterative methods based on first order derivatives could be used.

For the given setting with initially unaligned particles, the gradient flow leads to a configuration where the long axes of the elliptic particles are aligned. Furthermore the distance of the particles is initially reduced and remains unchanged in a later stage indicating that the implicit particle–particle interaction is attractive and that this configuration is (close to) a local minimizer of $\mathcal{J}$.
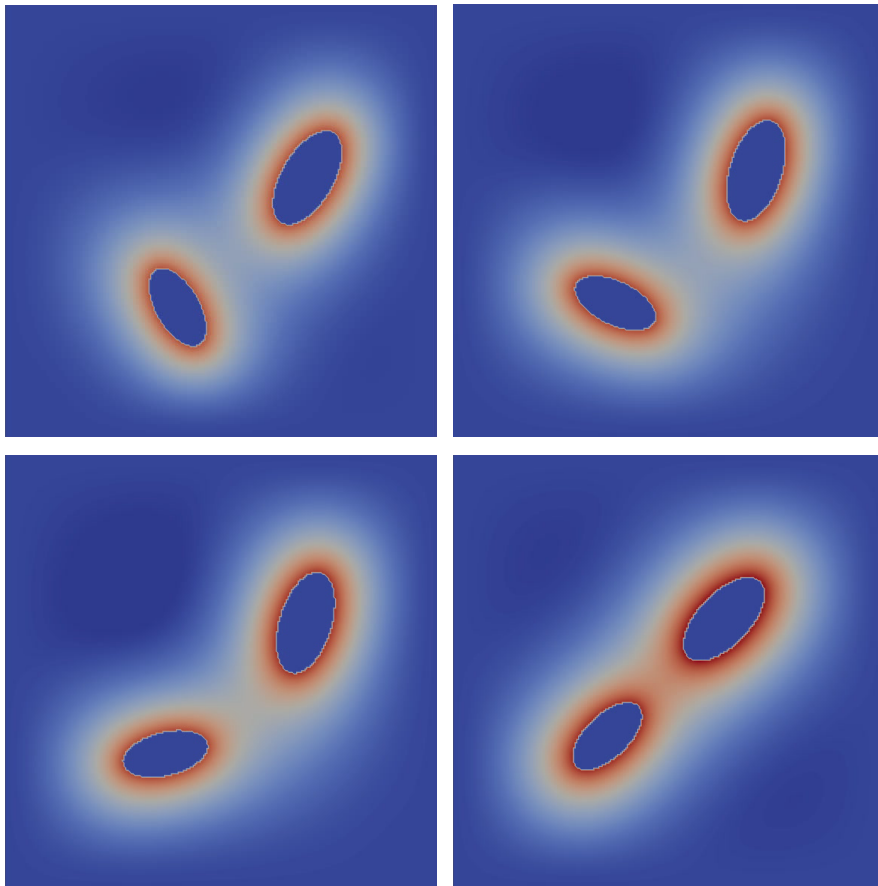
FIGURE 5.6. Time steps $\mathbf{p}_0, \mathbf{p}_5, \mathbf{p}_{10}$, and $\mathbf{p}_{75}$ of a discretized gradient flow for $\mathcal{J}$ with two elliptic particles (from left to right, top to bottom).

6. CONCLUSION

This paper considered a typical model for membrane-mediated particle interactions where the membrane is described as a continuous surface and where the particles are treated as discrete entities that couple to the membrane through certain constraints. Based on methods from shape calculus and the implicit function theorem we were able to give a proof for the differentiability of the interaction energy. Matrix calculus then allowed us to derive a formula for the first derivative that is numerically feasible in the sense that it can be evaluated from a finite element approximation of the optimal membrane shape for a fixed particle configuration and that it is possible to bound the approximation error of the derivative in terms of the discretization error of the finite element method. Numerical examples suggest the correctness of our results.

We emphasize that the approach chosen in this paper is rather general and we expect that it can be used to prove similar results for other model formulations, too. Furthermore, as the differentiability proof is based on the implicit function theorem

this readily gives constructive instructions on how to derive analogous formulas for higher order derivatives.

Our results allow the efficient differentiation of the interaction potential and may therefore be applied in order to develop new algorithms for investigating stable particle configurations.

7. Acknowledgements

8. Appendix

Theorem 8.1 (Whitney extension theorem). *Let $A \subseteq \mathbb{R}^n$ be closed, $m \in \mathbb{N} \cup \{\infty\}$, and $f_\alpha \colon A \to \mathbb{R}$ for all multi-indices $\alpha \in \mathbb{N}^n$ with $|\alpha| \leq m$. Suppose that for all multi-indices α with $|\alpha| \leq m$ and all $x, x' \in A$ holds*

$$f_\alpha(x') = \sum_{|\beta| \leq m - |\alpha|} \frac{f_{\alpha+\beta}(x)}{\beta!} (x' - x)^\beta + R_\alpha(x'; x)$$

where $R_\alpha \colon A \times A \to \mathbb{R}$ is such that for all $x_0 \in A$ and all $\varepsilon \in \mathbb{R}_{>0}$ there exists $\delta \in \mathbb{R}_{>0}$ such that

$$\forall x, x' \in A \colon \quad \|x - x_0\| < \delta \ \wedge \ \|x' - x_0\| < \delta \implies |R(x'; x)| \leq \|x - x'\|^{m - |\alpha|} \varepsilon.$$

Then there exists a function $F \in C^m(\mathbb{R}^n)$ such that $\partial^\alpha F(x) = f_\alpha(x)$ for all $x \in A$ and all multi-indices α with $|\alpha| \leq m$.

Proof. See [22, Theorem I]. $\square$

Theorem 8.2 (Implicit function theorem). *Let X, Y, Z real Banach spaces, $A \subseteq X \times Y$ open, $F \colon A \to Z$ and $(x_0, y_0) \in A$ such that $F(x_0, y_0) = 0$. Suppose that the partial Fréchet-derivative F_y exists on A, and F and F_y are continuous in (x_0, y_0).*

If $F_y(x_0, y_0)$ is invertible, then there exists an open neighborhood $\mathcal{B}(x_0)$ and a unique function $y \colon \mathcal{B}(x_0) \to Y$ such that $(x, y(x)) \in A$ and $F(x, y(x)) = 0$ for all $x \in \mathcal{B}(x_0)$. Furthermore, if $F \in C^m(A, Z)$ for some $m \in \mathbb{N}$, then also $y \in C^m(\mathcal{B}, Y)$.

Proof. See [14]. $\square$

Lemma 8.3 (Transformation of derivatives). *Suppose $X \colon \Omega_1 \to \Omega_2$ is a diffeomorphism and let $u \in H^2(\Omega_1)$. Then*

$$\int_{\Omega_2} \kappa(\Delta(u \circ X^{-1}))^2 + \sigma \left\| \nabla(u \circ X^{-1}) \right\|^2 \mathrm{d}x = \int_{\Omega_1} \kappa \frac{\operatorname{div}(A\nabla u)^2}{|\det DX|} + \sigma \|\nabla u\|_A^2 \ \mathrm{d}x$$

where

$$A(x) := |\det DX(x)| \ (DX(x))^{-1}(DX(x))^{-T}$$

and

$$\|\nabla u(x)\|_{A(x)}^2 := \nabla u(x)^T A(x) \nabla u(x).$$

Proof. First note that for $x \in \Omega_2$ and $v \in H^1(\Omega)$

(8.1)
$$\nabla(v \circ X^{-1})(x) = (D(X^{-1})(x))^T \nabla v(X^{-1}(x)) = (DX(X^{-1}(x)))^{-T} \nabla v(X^{-1}(x))$$

holds almost-everywhere. Equation (8.1) together with the transformation formula applied to the diffeomorphism X we obtain for all $v, w \in H^1(\Omega)$

(8.2)
$$\int_{\Omega_2} \left(\nabla(v \circ X^{-1})(x)\right)^T \nabla(w \circ X^{-1})(x) \, \mathrm{d}x$$
$$= \int_{\Omega_2} \nabla v(X^{-1}(x))^T (DX(X^{-1}(x)))^{-1} (DX(X^{-1}(x)))^{-T} \nabla w(X^{-1}(x)) \, \mathrm{d}x$$
$$= \int_{\Omega_1} \nabla v(x)^T DX(x)^{-1} DX(x)^{-T} \nabla w(x) \, |\det DX(x)| \, \mathrm{d}x$$
$$= \int_{\Omega_1} \langle \nabla v(x), \nabla w(x) \rangle_{A(x)} \, \mathrm{d}x.$$

By integration by parts and (8.2) we know that for all $\phi \in C_0^\infty(\Omega_1)$ holds

(8.3)
$$\int_{\Omega_2} \Delta(u \circ X^{-1})(x) \, (\phi \circ X^{-1})(x) \, \mathrm{d}x$$
$$= -\int_{\Omega_2} \nabla(u \circ X^{-1})(x) \cdot \nabla(\phi \circ X^{-1})(x) \, \mathrm{d}x + \int_{\partial\Omega_2} \partial_\nu(u \circ X^{-1})(x) \, (\phi \circ X^{-1})(x) \, \mathrm{d}x$$
$$= -\int_{\Omega_1} (A(x)\nabla u(x)) \cdot \nabla \phi(x) \, \mathrm{d}x$$
$$= \int_{\Omega_1} \mathrm{div}\, (A(x)\nabla u(x)) \, \phi(x) \, \mathrm{d}x - \int_{\partial\Omega_1} (A(x)\nabla u(x)) \, \partial_\nu \phi(x) \, \mathrm{d}x$$
$$= \int_{\Omega_1} \mathrm{div}\, (A(x)\nabla u(x)) \, \phi(x) \, \mathrm{d}x$$

where the boundary terms vanish as of $\phi \circ X^{-1} \in C_0^\infty(\Omega_2)$ and $\phi \in C_0^\infty(\Omega_1)$, respectively. On the other hand, application of the transformation formula also yields

(8.4)
$$\int_{\Omega_2} \Delta(u \circ X^{-1})(x) \, (\phi \circ X^{-1})(x) \, \mathrm{d}x = \int_{\Omega_1} \Delta(u \circ X^{-1})(X(x)) \, \phi(x) \, |\det DX(x)| \, \mathrm{d}x.$$

Combining (8.3) and (8.4) leads to

$$\int_{\Omega_1} |\det DX(x)| \, \Delta(u \circ X^{-1})(X(x)) \, \phi(x) \, \mathrm{d}x = \int_{\Omega_1} \mathrm{div}\, (A(x)\nabla u(x)) \, \phi(x) \, \mathrm{d}x$$

for all $\phi \in C_0^\infty(\Omega_1)$. The fundamental theorem of calculus of variations then readily implies that

(8.5)
$$\Delta(u \circ X^{-1})(X(x)) = \frac{\mathrm{div}\, (A(x)\nabla u(x))}{|\det DX(x)|}$$

holds for almost-every $x \in \Omega_1$. Because X is a diffeomorphism, this expression is well-defined as of $|\det DX(x)| \neq 0$ for all $x \in \Omega_1$. Hence, by virtue of the

transformation formula and (8.5) we obtain

$$
(8.6) \quad \int_{\Omega_2} (\Delta(u \circ X^{-1})(x))^2 \, \mathrm{d}x = \int_{\Omega_1} \left(\Delta(u \circ X^{-1})(X(x)) \right)^2 |\det DX(x)| \, \mathrm{d}x
$$
$$
= \int_{\Omega_1} \frac{\operatorname{div}(A(x)\nabla u(x))^2}{|\det DX(x)|} \, \mathrm{d}x.
$$

Finally, the desired assertion is a direct consequence of (8.2) and (8.6). □

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