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Abstract

A numerical approach for the computation of cell membrane deformations under the action of tethered point obstacles is presented. The motivation comes from cell biological phenomena, which are based on the interaction between membrane deformation and cytoskeleton dynamics. The point obstacles represent the ends of polymer filaments constituting parts of the cytoskeleton. These might be tethered to the membrane by breakable elastic protein linkages. The standard modeling approach to cell membrane deformation is via minimization of the Wilmore functional describing the bending energy. The breakable tethers add a strongly non-convex contribution to the potential energy, and the obstacles as well as volume and area restrictions are responsible for a number of constraints.

Penalization of the constraints leads to an approximation by an unconstrained model. This is discretized by a finite element method based on C^2 box splines. The gradient flow for the unconstrained discrete energy functional is used as nonlinear iteration, which can also be seen as part of the modeling in dynamic situations, where tethers break as a consequence of obstacle movement, and a nearby minimum of the modified energy functional is needed.

Simulations of a model problem exhibiting hysteresis effects due to the non-convexity of the energy functional are presented, together with recent results explaining the shape of cytoskeletal structures whose growth is influenced by the membrane geometry.

Keywords: cell membrane, finite element, obstacle problem, tether

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1 Introduction

The lamellipodium is a cell organelle with an important role in cell motility [**?**]. It takes the form of a flat protrusion [**?**], wrapped by cell membrane [**?**]. As a model for a piece of cell membrane close to the leading edge of the lamellipodium, we consider a smooth two-dimensional surface in $\mathbb{R}^3$ with boundary. Typically, it will resemble a bulged rectangle (see Fig. 1A). On the inner side, the surface is constrained by a set of dynamic point obstacles, which might also pull the surface inwards via elastic tethers (Fig. 1B). These tethers break when a threshold force is exceeded. Tangential forces applied to the backward segments of the boundary (which are assumed straight) create membrane tension (Fig. 1C). The width of the membrane piece is fixed, and the two boundary segments on the side (blue in Fig. 1A) are identified by a periodicity assumption to avoid additional boundary conditions. The effect of a volume constraint on a cell, which tries to expand, is described by a force on the membrane acting inwards in the normal direction (Fig. 1D). Finally, the area of the simulated membrane piece is fixed.

A standard model for the bending energy of cell membranes is the Helfrich energy [**?**], which reduces to the Willmore energy [**?**] (the surface integral of the squared mean curvature) in the absence of topological changes and spontaneous curvature. Additional contributions to the potential energy arise from the tethers, the forces on the boundary, and the inward force along the membrane. Constraints for the membrane deformation are caused by the obstacles and by fixing the membrane area and the straightness of the backward boundary segments.

The nonconvexity of the energy functional leads to nonuniqueness of local minimizers. In the presence of moving obstacles the membrane deformation is assumed to be quasistatic in the sense that a continuous curve of local minimizers is followed. In situations where this is impossible, e.g. when a tether breaks, the continuation is defined by the steady state of the gradient flow starting at the old minimizer.

Various aspects of our problem are related to well studied mathematical questions. The Willmore energy is closely connected to minimal surface theory [**?**]. The existence of minimizers has been studied in various settings [**?** **?**]. Solvability of the Helfrich problem (prescribed area and volume) has been shown for topological spheres [**?** **?**] and for surfaces with higher genus [**?**]. Obstacle problems have been studied extensively (e.g. in connection with the Dirichlet functional [**?** **?**]), but minimization of the Willmore functional subject to obstacle constraints has not received much attention yet. Finally, our model of tethered obstacles is related to various models for adhesive contacts, such as solid bodies with various rheological properties subject to viscoelastic adhesion [**?** **?**] to a foundation, or cylinder symmetric membrane geometries adhering to each other or to obstacles [**?** **?**]. The tethering model of this work is different from all those, and to consider

tethered point obstacles instead of smooth foundations seems to be entirely new.

Various numerical approaches have been used for deformable surfaces governed by the Willmore energy. We only mention phase field methods [**?** **?**] and surface finite elements [**?**]. Here we follow the approach of [**?**], where membranes are approximated by a C^2 Loop subdivision surfaces [**?**]. In our setting, where a rectangular parameter domain can be used, this reduces to C^2 box splines [**?**] on triangles in the parameter space. Two opposing edges of the parameter rectangle are identified as a consequence of the above mentioned periodicity assumption. Along the other two edges lines of exterior ghost nodes are added to ensure the same type of finite element representation on each interior triangle.

The constraints are replaced by penalty terms, facilitating the use of a gradient flow for the unconstrained total energy as a nonlinear iteration method. Since rather coarse meshes are used for the representation of the membrane, strong deformations arise in individual elements. Therefore the computation of surface integrals is based on a finer subtriangulation, which is also used for the computation of the distance of point obstacles from the surface.

The motivation for this work is the question for an explanation of the flat shape of the lamellipodium. In parallel work [**?**] by the same authors, a model for lamellipodial protrusion is derived, which is based on a stochastic growth and branching model for a network of actin filaments, where the filament dynamics is influenced by the shape of the cell membrane stretched around the filament ends. We therefore have to deal with moving point obstacles. This may lead to the breaking of the tether between an obstacle and the membrane. Because of the nonuniqueness of minima of the total energy, a decision has to be made as to which minimum is chosen for the continuation in time. The use of the gradient flow as a nonlinear iteration starting from the eequilibrium state at the previous time step then obtains also relevance as part of the continuous model.

The rest of this paper is organized as follows: After the problem formulation in Section 2, the numerical approach is presented in Section 3. Section 4 contains computational results on a model problem, while in Section 5 we present simulation results for the full lamellipodium model of [**?**].

2 The mathematical membrane model

Considering the periodicity assumption formulated above, the simulated membrane piece, Fig. **??**, lies in the domain $\mathbb{T}^1 \times \mathbb{R}^2$, with the one-dimensional torus $\mathbb{T}^1$ represented by the interval $[0, L_1]$. Since $L_1 = x_{max}$ is the approximate length of the leading edge and the membrane area A_0 is fixed (see below), the parameter space $S = \mathbb{T}^1 \times [0, L_2]$ with $L_2 = A_0/x_{max}$ is used for

the parametrization

$$\mathscr{M}(t) = \{\mathbf{r}(\mathbf{s},t) : \mathbf{s} \in S\} \subset \mathbb{T}^1 \times \mathbb{R}^2$$

of the membrane piece at time $t \geq 0$. The periodic nature of the membrane model is ensured by

$$\mathbf{r}(s_1 + L_1, s_2, t) = (r_1(\mathbf{s},t) + x_{max}, r_2(\mathbf{s},t), r_3(\mathbf{s},t)) .$$

The rear boundary $\Gamma_r(t) := \mathbf{r}(\mathbb{T}^1 \times \{0, L_2\}, t)$ is built up by a bottom and a top part with $s_2 = 0$ and, respectively, $s_2 = L_2$.

The energy functional

At each time $t \geq 0$ the membrane shape is a local minimizer of a potential energy functional, whose main contribution is the Willmore functional

$$E_{bend}[\mathscr{M}] := 2\mu_{bend} \int_{\mathscr{M}} H^2 d\sigma \,, \tag{1}$$

with the bending modulus μ_{bend} to account for the bending of the membrane. The mean curvature $H = \frac{k_1+k_2}{2}$ is derived from the principal curvatures $k_1 \leq k_2$ (see Fig. **??**.A), and $d\sigma = \sqrt{a}\, d\mathbf{s}$ denotes the surface element along $\mathscr{M}$. The constant value of μ_{bend} represents a homogeneity assumption on the membrane material. Local irregularities arising in the full lamellipodium model will be formulated as constraints (see Section 5).

The obstacle is a set of points $\mathbf{F}_i(t)$, $i \in I$, representing barbed ends of actin filaments that are tethered to the membrane for $i_t \in I_t \subseteq I$. The tethers are modeled as springs:

$$E_{tether}(t)[\mathscr{M}] := \mu_{tether} \sum_{i \in I_t(t)} \left(\min \left\{ d(\mathbf{F}_i(t), \mathscr{M}), \frac{\mathcal{F}_{max}}{\mu_{tether}} \right\} \right)^2 , \tag{2}$$

with the tether spring constant μ_{tether} and the signed distance $d(\mathbf{x}, \mathscr{M})$ of a point $\mathbf{x} \in \mathbb{R}^3$ to the membrane with the sign convention $d(\mathbf{x}, \mathscr{M}) > 0$ for $\mathbf{x}$ inside the cell, see Fig. **??**.B. The cut-off at the maximal force $\mathcal{F}_{max}$ models the breaking of tethers and makes the energy nonconvex.

Since only an open part of a full cell with fixed total membrane area is described here, membrane tension has to be created artificially by tangential pulling at the rear boundary. To incorporate such a nonconservative force into a variational framework needs a trick. We use the energy contribution

$$E_{pull}(\mathscr{M}^*)[\mathscr{M}] := \mu_{pull} \int_{\Gamma_r^*} \mathbf{r} \cdot \mathbf{a}_n^* \, ds^* \,, \tag{3}$$

where ds is the length element along $\partial\mathscr{M}$ and $\mathbf{a}_n$ is the unit tangent vector of $\mathscr{M}$ normal to $\partial\mathscr{M}$ and oriented inwards, Fig. **??**C. Quantities with the

superscript $*$ will not be considered as part of the argument $\mathscr{M}$ of E_{pull} in the energy minimization process.

Similarly, the effect of a fixed total volume of a cell trying to expand, is an inward force on the membrane (again nonconservative), which we incorporate by the energy contribution

$$E_{vol}(\mathscr{M}^*)[\mathscr{M}] := \mu_{vol} \int_{\mathscr{M}^*} \mathbf{r} \cdot \mathbf{n}^* \, d\sigma^* \,, \tag{4}$$

with the unit outward (with respect to the cell) normal $\mathbf{n}$, see Fig. **??**.D.

Constraints

All point obstacles have to lie inside the cell:

$$d(\mathbf{F}_i(t), \mathscr{M}(t)) \geq 0 \,, \qquad i \in I(t) \,, \quad t \geq 0 \,, \tag{5}$$

and the surface area of the simulated membrane piece is fixed:

$$\int_{\mathscr{M}(t)} d\sigma = \int_{\mathscr{M}(0)} d\sigma = A_0 \,. \tag{6}$$

Since the membrane material can be seen as a two-dimensional incompressible liquid, the shape of the rear boundary has to be prescribed. Its pieces are assumed to be line segments lying in a plane normal to the protrusion direction: For all $t \geq 0$ there exists $c(t)$ such that

$$\mathbf{r}_2(\mathbf{s}, t) = c(t), \qquad \mathbf{s} \in [0, L_1] \times \{0, L_2\} \,. \tag{7}$$

The full membrane model: With $\mathrm{M}(t)$, the set of all admissible membrane shapes $\mathscr{M}(t) = \mathbf{r}(S, t)$ meeting the constraints (5)–(7), the membrane's shape is a fixed point of the map $\mathscr{M}^* \mapsto \mathscr{M}$, defined by

$$\begin{aligned} \mathscr{M} &= \operatorname{argmin}_{\hat{\mathscr{M}} \in \mathrm{M}(t)} E(\mathscr{M}^*, t)[\hat{\mathscr{M}}] \,, \\ E(\mathscr{M}^*, t) &:= E_{bend} + E_{tether}(t) + E_{pull}(\mathscr{M}^*) + E_{vol}(\mathscr{M}^*) \,. \end{aligned}$$

Since there is the possibility of more than one fixed point, it is also required that $\mathscr{M}(t)$ depends continuously on time as long as possible. In other words, the membrane's shape follows a curve of local minimizers as long as the energy landscape does not change qualitatively. Jumps in the membrane deformation can be caused by two kinds of events. First, the local minimum might turn itno a saddle point as eigenvalues of the linearization of the energy change sign. We assume only non-degenerate cases with just one eigenvalue becoming zero at a time. In such a case the membrane's shape is slightly disturbed in the according eigendirection projected to the manifold of admissible membrane shapes. The nearest local minimum is found by a gradient flow, until another local minimum is reached. Second, the breaking of tethers changes the energy landscape, whence again a new local minimum is found as steady state of the gradient flow, starting at the old membrane position.

3 Numerical method

3.1 Penalization

The constraints (5)–(7) are replaced by quadratic penalty terms [**?**]:

Point obstacles:

$$P_{obst}(t)[\mathscr{M}] := \mu_{obst} \sum_{i \in I(t)} \left(d(\mathbf{F}_i(t), \mathscr{M})_-\right)^2$$

Surface area:

$$\begin{aligned} P_{area}[\mathscr{M}] \;&:=\; \mu_{area} \left(\int_{\mathscr{M}} d\sigma - A_0 \right)^2 \\ &\quad + \mu_{area,l} \int_{\mathscr{M}} \left(\left(\left(\sqrt{a} - \alpha\sqrt{a_0}\right)_- \right)^2 + \left(\left(\sqrt{a} - \beta\sqrt{a_0}\right)_+ \right)^2 \right) d\sigma \,, \end{aligned} \tag{8}$$

with $0 < \alpha < 1 < \beta$. The second line acts solely on the parametrization and does not influence the geometry of the membrane. It regulates the area distribution between the parameter space and the membrane. With $\sqrt{a_0} = 1$ it keeps the area distribution not too far (depending on α, β) from uniform, but position-dependent choices can be used for local grid refinement strategies, when a uniform grid on the parameter space is used, see Section 5.

FRAGE: Eigentlich $P_{area}(\mathscr{M}^*)[\mathscr{M}]$?

Rear boundary shape: Deviations from the mean

$$c_{\mathscr{M}} := \frac{\int_{\Gamma_r} \mathbf{r}_2 \, d\mathbf{s}}{\int_{\Gamma_r} d\mathbf{s}}$$

of $\mathbf{r}_2$-values along the rear boundary are penalized quadratically:

$$P_{rear}[\mathscr{M}] := \mu_{rear} \int_{\Gamma_r} \left(\mathbf{r}_2 - c_{\mathscr{M}}\right)^2 d\mathbf{s}$$

The penalized membrane model: The membrane model now becomes an unconstrained minimization problem with the set $\mathrm{M}(t)$ of admissible membrane deformations replaced by M_0 defined only by the smoothness requirement $\mathbf{r} \in (H^2(S))^3$. So $\mathscr{M}(t)$ is defined as fixed point of the map $\mathscr{M}^* \mapsto \mathscr{M}$, defined by

$$\begin{aligned} \mathscr{M} \;&=\; \mathrm{argmin}_{\hat{\mathscr{M}} \in \mathrm{M}_0} \mathscr{E}(\mathscr{M}^*, t)[\hat{\mathscr{M}}] \,, \\ \mathscr{E}(\mathscr{M}^*, t) \;&:=\; E_{bend} + E_{tether}(t) + E_{pull}(\mathscr{M}^*) + E_{vol}(\mathscr{M}^*) \\ &\quad + P_{obst}(t) + P_{area} + P_{rear}. \end{aligned}$$

Convergence of solutions to those of the original constrained problem as $\mu_{obst}, \mu_{area}, \mu_{rear} \to \infty$ can be expected (and has been proven for various applications of the penalty method, see e.g. [**? ? ?**]).

3.2 Discretization

Finite Elements: For approximating the membrane deformation $\mathscr{M}(t)$ box splines (see the appendix) are used. The parameter space $S = [0, L_1] \times [0, L_2]$ is discretized by a rectangular grid with constant step sizes, $h_i := L_i/n_i$ with $n_i \in \mathbb{N}$, $i = 1, 2$. The box spline M_Ξ is based on the matrix

$$\Xi = \begin{bmatrix} h_1 & h_1 & 0 & 0 & h_1 & h_1 \\ 0 & 0 & h_2 & h_2 & h_2 & h_2 \end{bmatrix}$$

This results in $M_\Xi \in C^2(\mathbb{R}^2)$, see Fig. **??**E. It can be written as

$$M_\Xi(\mathbf{s}) = \frac{1}{h_1 h_2} \int_{-1}^{1} (1 - |\tau|) \left(1 - \left|\frac{s_1}{h_1} - \tau\right|\right)_+ \left(1 - \left|\frac{s_2}{h_2} - \tau\right|\right)_+ d\tau \,,$$

with $\mathbf{s} \in \mathrm{supp}(M_\Xi)$ iff

$$\exists\, \tau \in [-1, 1] : \quad \max\left\{ \left|\frac{s_1}{h_1} - \tau\right|, \left|\frac{s_2}{h_2} - \tau\right| \right\} \le 1 \,.$$

The support is the union of 24 triangles, on each of which M_Ξ reduces to a polynomial of order at most 4 (see, e.g., [**?**] for a list of these polynomials).

For shifting the box spline, the finite lattice

$$J := \{\mathbf{j} \in \mathbb{R}^2 : \mathbf{j}_i = j_i h_i \,,\, j_1 \in \{0, \ldots, n_1 - 1\} \,,\, j_2 \in \{-1, \ldots, n_2 + 1\}\} \subseteq G\mathbb{Z}^2 \,,$$

based on the matrix

$$G := \begin{bmatrix} h_1 & 0 \\ 0 & h_2 \end{bmatrix} \,,$$

is used (see Fig. **??**). Note that the grid does not contain the line $s_1 = L_1$ ($j_1 = n_1$) which, by periodicity, is identified with $s_1 = 0$ ($j_1 = 0$). On the other hand, two exterior lines of gridpoints are added at $s_2 = -h_2$ and $s_2 = L_2 + h_2$ ($j_2 = -1, n_2 + 1$, respectively).

The approximate membrane is then parametrized by $3n_1(n_2 + 3)$ parameters, collected in $\mathbf{X}(t) = (\mathbf{x}(\mathbf{j}, t))_{\mathbf{j} \in J}$ with $\mathbf{x}(\mathbf{j}, t) \in \mathbb{R}^3$, $\mathbf{j} \in J$:

$$\mathscr{M}_h(\mathbf{X}(t)) = \{\mathbf{r}_h(\mathbf{s}, t) : \mathbf{s} \in S\} = \left\{ \sum_{\mathbf{j} \in J} \mathbf{x}(\mathbf{j}, t) M_\Xi(\mathbf{s} - \mathbf{j}) : \mathbf{s} \in S \right\}$$

For $j_1 = 0, 1, n_1 - 1$, the box splines $M_\Xi(\cdot - \mathbf{j})$ are extended by periodicity, see Fig. **??**. The extra grid lines ensure that the structure of the finite elements is the same in each triangle of the discretization grid.

The representation by box spline M_Ξ is a special case of Loop subdivision surfaces [**?**]. The shifts of M_Ξ generate a tessallation $\mathscr{T}$ of the parameter space S into the triangles $\mathbf{e}$, where the shifted box splines are polynomial (see Fig. **??** & **??**). While in our representation all tessallation nodes have valence six, subdivision surfaces can be based on general triangulations. This makes the method useful for shapes that cannot be approximated by rectangles, like spheres. The Loop subdivision scheme yields surfaces that are C^2 except at irregular node points, where it is C^1. The representation with Loop subdivision surfaces was introduced to thin shells [**?**] and used in [**?**] to simulate closed biological cells.

Quadrature: The evaluation of the various surface integrals in the energy functional require numerical quadrature. Since the complexity of the minimization is kept low by a rather course triangulation of the parameter space, the deformation of the membrane within one triangle can be significant (see Fig. **??**), and the integrands in the surface integrals might vary strongly over one grid triangle. Therefore the quadrature is based on a subtriangulation, where each triangle is split into q^2 subtriangles ($q \in \mathbb{N}$) with edge lengths h_1/q and h_2/q, see Fig. **??**. The quadrature is then based on a piecewise constant approximation of the integrands by evaluation at $\mathbf{r}_j = \mathbf{r}_h(\mathbf{s}_j)$, $j = 1, \ldots, 2n_1n_2q^2$ with the centers of mass $\mathbf{s}_j$ of all subtriangles.

Distance from the membrane: The signed distance of a point obstacle $\mathbf{F}_i$ to the membrane $\mathscr{M}$ can be written as

$$d(\mathbf{F}_i, \mathscr{M}) := \zeta_i \min_{\mathbf{s}\in S} |\mathbf{F}_i - \mathbf{r}(\mathbf{s})| \,,$$

with $\zeta_i \in \{-1, 1\}$ indicating whether $\mathbf{F}_i$ lies inside or outside the cell. An approximation is computed by replacing the membrane by a polyhedron consisting of tangent planes at the points $\mathbf{r}_1, \ldots, \mathbf{r}_{2n_1n_2q^2}$ introduced above. This results in the formula

$$d_h(\mathbf{F}_i, \mathscr{M}_h) := \zeta_i \min_{1\le j\le 2n_1n_2q^2} |(\mathbf{r}_j - \mathbf{F}_i) \cdot \mathbf{n}_j| \,,$$

where $\mathbf{n}_j$ is the unit outward normal to $\mathscr{M}_h$ at $\mathbf{r}_j$, and $\zeta_i = \mathrm{sign}((\mathbf{r}_{j_0} - \mathbf{F}_i) \cdot \mathbf{n}_{j_0})$ with the minimizer j_0 in the above minimization.
FRAGE: Wie wird das nach $\mathbf{X}$ differenziert?

Time discretization: The discrete unconstrained energy functional $\mathscr{E}_h(\mathbf{X}^*, t)[\mathbf{X}]$ is the approximation of $\mathscr{E}(\mathscr{M}_h(\mathbf{X}^*), t)[\mathscr{M}_h(\mathbf{X})]$ resulting from the use of the quadrature described above and of the discretized distance d_h. The parameter vector $\mathbf{X}(t)$ at time t is the fixed point of the map $\mathbf{X}^* \mapsto \mathbf{X}$, defined by

$$\mathbf{X} = \mathrm{argmin}_{\hat{\mathbf{X}}\in\mathbb{R}^{3n_1(n_2+3)}} \mathscr{E}_h(\mathbf{X}^*, t)[\hat{\mathbf{X}}] \,.$$

The evolution is computed by time stepping with a constant step size Δt. The parameter vector $\mathbf{X}(t)$ is computed as steady state of the gradient flow for the energy functional $\mathscr{E}_h$ starting at $\mathbf{X}(t-\Delta t)$, i.e., as limit (with an appropriate stopping criterion) of the recursive procedure

$$\mathbf{X}_{k+1} = \mathbf{X}_k - \tau_k \nabla \mathscr{E}_h(\mathbf{X}_k, t)[\mathbf{X}_k]\,, \quad \mathbf{X}_0 = \mathbf{X}(t-\Delta t)\,.$$

The pseudo time steps τ_k are determined by a line search algorithm [**?**].

4 Simulation of a model problem

In this section we describe simulations of model problem, demonstrating the ability of the numerical approach to deal with various difficulties. The model is used with biologically relevant parameter values, which can be found in [**?**].

The starting point of the time evolution is a membrane wrapped around five tethered obstacles, Fig. **??**A. Four of them are surrounding the fifth at $[x_{max}/2, 0, 0]$. The initial membrane shape already resembles the geometry of lamellipodial leading edges, as will be further discussed in the next section. The numerical parameters are collected in Table 4.
Es fehlen n_1, n_2, q.

Symbol	Value
Δt	0.1s
μ_{push}	10^3 pN/nm
$\mu_{area,g}$	10^{-3} pN/nm^{-3}
$\mu_{area,l}$	10^{-3} pN/nm^{-3}
μ_{rear}	10^2pN/nm^2

Table 1: Numerical parameters for the model problem.

As time progresses, the central obstacle moves forwards and then backwards according to the velocity

$$v = \begin{cases} [0, 100, 0] & \text{for } 0 \le t \le 1 \\ [0, -100, 0] & \text{for } t \ge 1, \end{cases}$$

Was bedeutet das?
where length is measured in nm and time in seconds. The other barbed ends remain at their initial positions.

During the first second the protruding barbed end pushes the membrane forward in the middle and forms a bulge, Fig. **??**B. Its creation is finished at time $t = 1$s with a shape that closely resembles a filopodium [**?**]. Notwithstanding the low number n_1 of discretization points in s_1-direction, see Fig.

??, the dent is resolved in a smooth and symmetric way. Along with the middle barbed end the membrane retracts during the second simulation second to its original position, Fig. **??**D. Further pull-back leads to the formation of an invagination in the membrane's center that enlarges until the tether's breaking force is reached, Fig. **??**E. The loss of the connection between the middle obstacle and the membrane leads to an immediate drastic change of the surface shape. A geometry similar to the initial condition is regained and this shows that the model is fully capable to capture hysteresis effects.

5 Full lamellipodium simulations

In this section we reproduce some of the results of [**?**] for a full lamellipodium model. The membrane model is adapted by introducing a region with modified mechanical properties, called the leading edge. There the geometric shape is influenced by special proteins that deform the membrane and simultaneously interact with the actin filament network, whose branching and growth dynamics, represented by the evolution of the point obstacles, is described by stochastic processes. The membrane deformation and actin dynamics problems are fully coupled, since the local geometric properties of the membrane influence the branching and growth of actin filaments. In the following we give a short overview of these additional model ingredients (see [**?**] for details).

5.1 The leading edge

The leading edge is a region where a protein cluster is attached to the membrane and influences its shape (see Fig. **??**). The positioning of the leading edge within the membrane is part of the solution, but it is fixed in the parameter space by $S_{\mathscr{L}} := \mathbb{T}^1 \times [L_2/2 - L/2, L_2/2 + L/2]$, and therefore given by

$$\mathscr{L}(t) := \{\mathbf{r}(\mathbf{s}, t) : \mathbf{s} \in S_{\mathscr{L}}\} \subset \mathscr{M}(t)\,, \qquad t \geq 0\,.$$

The molecules of the aggregated membrane protein IRSp53 at the leading edge are in parameter space aligned with the s_2-direction. In this direction they induce a prescribed curvature on the membrane (assumed to be the larger principal curvature). The width of the leading edge region in physical space is controlled by the assumption that s_2 is an arclength parameter within the leading edge:

$$\frac{\partial_{s_2 s_2}\mathbf{r} \cdot \mathbf{n}}{|\partial_{s_2}\mathbf{r}|^2} = k_2 = \overline{\kappa}\,, \quad |\partial_{s_2}\mathbf{r}| = 1\,, \qquad \text{in } S_{\mathscr{L}}\,. \tag{9}$$

The expectation that IRSp53 molecules line up side-by-side is expressed by the constraint

$$\partial_{s_1}^2\mathbf{r} \parallel \mathbf{n}\,, \qquad \text{for } s_2 = L_2/2\,. \tag{10}$$

As the other constraints, (9) and (10) are replaced by penalty contributions to the energy:

$$\begin{aligned}
P_{le,bend}[\mathscr{M}] &:= \mu_{le,bend} \int_{\mathscr{L}} \left(\frac{\partial_{s_2 s_2} \mathbf{r} \cdot \mathbf{n}}{|\partial_{s_2} \mathbf{r}|^2} - \overline{\kappa} \right)^2 d\sigma \,, \\
P_{curv}[\mathscr{M}] &:= \mu_{curv} \int_{\mathscr{L}} (k_2 - \overline{\kappa})^2 \, d\sigma \,, \\
P_{inex}[\mathscr{M}] &:= \mu_{inex} \int_{\mathscr{L}} \left(|\partial_{s_2} \mathbf{r}|^2 - 1 \right)^2 d\sigma \,, \\
P_{sym}[\mathscr{M}] &:= \mu_{sym} \int_0^{x_{max}} \left((\partial_{s_1 s_1} \mathbf{r} \cdot \mathbf{n})^2 - |\partial_{s_1 s_1} \mathbf{r}|^2 \right)_{s_2 = L_2/2} ds_1 \,.
\end{aligned}$$

Otherwise the lamellipodium model is as described in Sections 2 and 3 with the small exception that in the constraint (7), concerning the shape of the rear ends of the membrane, the $\mathbf{r}_2$-direction is replaced by the main protrusion direction computed from the actin filament directions described below.

We also mention that a local grid refinement in the strongly curved front region around the leading edge is achieved by a nonconstant choice of $\sqrt{a_0}$ in (8) with smaller values in the front part. The parameter values used in the penalization terms are listed in Table 5.1.

Symbol	Value
μ_{push}	1 pN/nm
$\mu_{area,g}$	10^{-3} pN/nm^{-3}
$\mu_{area,l}$	10^{-7} pN/nm^{-3}
μ_{inex}	$3.5^{-4}\cdot 20$kbT/nm^{-6}
$\mu_{le,bend}$	10^5pN nm
μ_{curv}	10^3pN nm
μ_{sym}	10^0pN/nm^2
μ_{rear}	10^2pN/nm^2

Table 2: Weights of the penalizations for the numerical treatment of a lamellipodial frontal piece. Warum die komische Einheit in μ_{inex}?

5.2 Actin filaments

Actin filaments are modeled as oriented rods that are immobile and rigid. They are characterized by their barbed end positions $\mathbf{F}_i(t)$ and their directions $\mathbf{f}_i \in S^2$, $i \in I(t) = \{1, \ldots, N(t)\}$. Morveover there are three distinct sets of actin filaments, namely those that are tethered to the membrane, $i \in I_t(t)$, untethered, $i \in I_u(t)$, or capped, $i \in I_c(t) = I(t) \setminus I_t(t) \setminus I_u(t)$. Tethering of a filament end is only possible, when the closest point on the membrane, i.e. the anchor for the tether, is in the leading edge region $\mathscr{L}$.

The filament dynamics includes growth by polymerization, nucleation of new filaments by branching, untethering, and capping. A short description is given below; for details see [**?**].

The polymerization speed of uncapped filaments $i \in I_t(t) \cup I_u(t)$ is

$$k_{p,i} = \frac{k_{p,max}}{1 + \exp(\gamma(\mathcal{F}_i - \mathcal{F}_{stall}/2)\delta_i/k_BT)} ,$$

with the force $\mathcal{F}_i$ acting between the filament end $\mathbf{F}_i$ and the membrane, the displacement $\delta_i = l(\mathbf{n} \cdot \mathbf{f}_i)$ of the membrane in the normal direction $\mathbf{n}$ by insertion of one monomer of length l, and the thermal energy k_BT. The two parameters $\mathcal{F}_{stall}$ and γ are chosen such that the maximal polymerization rate $k_{p,max}$ is reached up to a few percent for $\mathcal{F}_i = 0$, and that it is reduced to a few percent when $\mathcal{F}_i = \mathcal{F}_{stall}$. For the precise definition of $\mathcal{F}_i$ see [**?**].

Nucleation of a new filament by branching off from the end of the tethered filament $i \in I_t(t)$ occurs at the rate

$$k_{br,i} = \frac{k_{br,max}}{1 + \rho_i L/n_{ref}} ,$$

with the maximal branching rate $k_{br,max}$, the local density ρ_i of tethered barbed ends, and a reference barbed end number n_{ref}. The denominator describes the limiting effect of the branching agent Arp2/3 and regulates the distribution of tethered filament ends. For the computation of ρ_i, see again [**?**]. The rather intricate determination of the direction of the new filament is one of the central parts of the model. It involves several dependencies on the local geometry of the membrane and has the effect that filament directions tend to remain in a plane. The interested reader is again referred to the modeling paper [**?**]. The number $N(t)$ filaments is, of course, increased by one at each branching event.

Tethers between the filament barbed ends and the membrane are broken either by a pulling force stronger than the critical value,

$$\mathcal{F}_i = \mu_{tether} d(\mathbf{F}_i, \mathscr{M}) > \mathcal{F}_{max} ,$$

or by a filament end moving out of the leading edge region. Untethered filaments cannot form branches but keep polymerizing.

Additionally, untethered filaments are susceptible to capping by a rate p_{cap}, a process that completely inactivates the filament, whose end may, however, still act as an obstascle for the membrane.

The periodicity assumption on the membrane shape is transferred to the filament network. As an initial condition for the actin filaments, the barbed ends $\mathbf{F}_i(0)$, $i \in I_0 = \{1, \ldots, N_0\}$, are placed on a surface resembling a typical lamellipodium shape with randomly distributed directions $\mathbf{f}_i$.

The filament dynamics has been implemented numerically in a straightforward way. The growth by polymerization is discretized by a forward

Euler scheme, while branching and capping are computed via the Monte Carlo method [**?**]. The coupling between the membrane and the filament system is handled by an operator splitting approach.

5.3 Results for lamellipodia

The simulation results depicted in Fig. **??** show that the model reproduces membrane deformations typically found in the evolution of lamellipodia. The surface reacts to the pushing and pulling forces by the actin filament barbed ends in a sensitive way and keeps the typical leading edge shape by preserving the IRSp53 band at the front. Most notably, we were able to reproduce a sustained lamellipodium flatness along with the determination of key characteristics of the actin filament network [**?**].

Appendix: Box splines

We give a short sketch of basic properties of box splines [**?** **?**], following [**?**]. A box spline $M_\Xi : \mathbb{R}^n \to \mathbb{R}_+$ is a piecewise polynomial function with bounded support. It is uniquely determined by an associated $n \times m$ matrix $\Xi = (\xi_1, \ldots, \xi_m)$ with $0 \neq \xi_j \in \mathbb{R}^n$, $j = 1, \ldots, m$, and $\operatorname{rank}(\Xi) = n$. With the formal definition of the distribution

$$M_\xi(x) := \int_{-1/2}^{1/2} \delta(x - t\xi) dt \,,$$

the box spline is given by convolution:

$$M_\Xi := M_{\xi_1} * \cdots * M_{\xi_m} \,.$$

It is piecewise polynomial of degree at most $m - n$, and its support is the Minkowski sum of the line segments $[-1/2, 1/2]\xi_j$, $j = 1, \ldots, m$. Its regularity $M_\Xi \in C^{m(\Xi)-2}(\mathbb{R}^n)$ is determined by the minimal number $m(\Xi)$ of columns of Ξ that have to be removed such that the remaining ones do not span $\mathbb{R}^n$.

Given a lattice $G\mathbb{Z}^n$, a space S_M of $C^{m(\Xi)-2}$-splines can be constructed as the span of shifted versions of the box spline M_Ξ:

$$S_M := \operatorname{span} \{ M_\Xi(\cdot - \mathbf{j}) : \mathbf{j} \in G\mathbb{Z}^n \} \,.$$

Under the condition

$$\det(Z) \in \{0, -\det(G), \det(G)\} \,,$$

for all $(n \times n)$-submatrices Z of Ξ, the shifts $M_\Xi(\cdot - \mathbf{j})$ are linearly independent and form a Riesz basis of S_M.

References