# DERIVATION OF A MODEL FOR SYMMETRIC LAMELLIPODIA WITH INSTANTANEOUS CROSS-LINK TURNOVER

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Abstract. We start with a model for the actin-cytoskeleton in a symmetric lamellipodium (cp. [OSS08]) which includes the description of the life-cycle of chemical bonds based on age-structured models. Based on the assumption that their average lifetime is actually small as compared to the time scale of the dynamics in which we are interested we pass, after applying an appropriate scaling, to a limit where this average lifetime goes to zero. We obtain a gradient flow model and formulate a time step approximation scheme. We use it to construct solutions analytically, proving their local in time existence, and present a typical numerical solution based on this scheme.

## 1. Introduction

The starting point of this work is a model for the actin-cytoskeleton in the lamellipodium, which has been derived in [Oel09]. Here the special case of a rotationally symmetric lamellipodium (already introduced in [OSS08]) will be considered and some simplifying assumptions on the parameters will be made in order to facilitate the analysis. The model will be presented in a dimensionless form (see [Oel09] for details on the nondimensionalization).

The basic modeling assumptions are that the lamellipodium is a 2-dimensional structure and that the antic filaments can be described as a diagonal array of curves, i.e. the network consists of two families of locally parallel curves intersecting each other transversally.

In the rotationally symmetric situation, all filaments can be constructed from one reference filament, whose position at time $t$ is given by

$$z(t,s) \in \mathbb{R}^2 \,,$$

where $s \in [0,1]$ is an arc length parameter and 1 is the maximal length of filaments. In both families filaments are assumed to be continuously distributed and their positions are determined by

$$F^+(t,\alpha,s) = R(\alpha)z(t,s)\,, \qquad F^-(t,\alpha,s) = D(-\alpha)z(t,s)\,,$$

for $-\pi \le \alpha < \pi$, with

$$R(\alpha) := \begin{pmatrix} \cos\alpha & -\sin\alpha \\ \sin\alpha & \cos\alpha \end{pmatrix}\,, \qquad D(\alpha) := R(\alpha)\begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}\,.$$

The filaments $F^+$ of the family of the reference filament are constructed by rotation of the reference filament and the filaments $F^-$ of the other family by reflection with respect to the horizontal axis followed by rotation. In terms of polar coordinates $z = |z|(\cos\phi, \sin\phi)$, the following assumptions on the geometry of the reference filament will be made:

$$\partial_s |z| > 0\,, \qquad \partial_s \phi < 0\,.$$

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The first assumption means that the $s$-direction is pointing outward, the circle

$$\{F^+(t,\alpha,1):\ -\pi \le \alpha < \pi\} = \{F^-(t,\alpha,1):\ -\pi \le \alpha < \pi\}$$

represents the leading edge of the lamellipodium, and $|z(t,1)|$ its radius. As a consequence of the second assumption, the filaments in the family of the reference filament are called "clockwise" and the others "anti-clockwise", cp. Figure 1. The points $z(t,0)$ and $z(t,1)$ are called the "pointed end" and the "barbed end", respectively, of the reference filament.

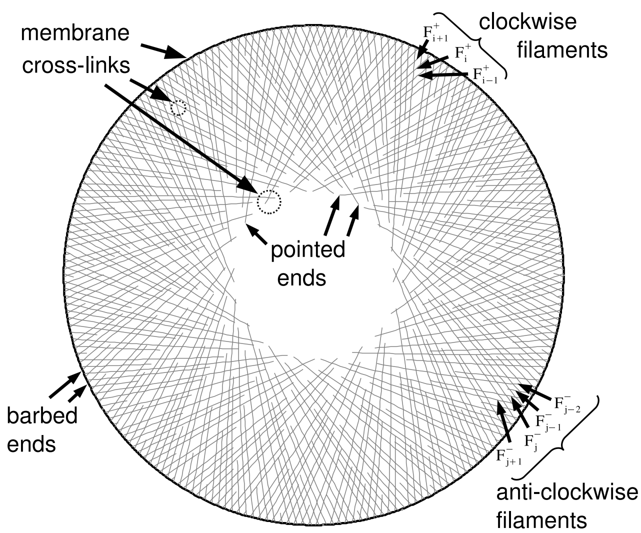


FIGURE 1. Constituent elements of the model.

Very simple models of polymerization and depolymerization are used. It is assumed that all barbed ends touch the leading edge and that filaments polymerize there with constant polymerization speed 1. The assumption that $\sigma = s + t$ is a Lagrange coordinate (identifying mass points) incorporates this assumption as well as inextensibility of the filaments (since $s$ represents arc length). As a consequence of a stochastic depolymerization process at the pointed ends it is assumed that there is a stationary length distribution of filaments, characterized by the (given) function $\eta(s)$. Its values represent the fraction of filaments having at least length $1-s$ as measured from the barbed end. The function $\eta$ is therefore assumed nonnegative and monotonically increasing with $\eta(1) = 1$.

The model is based on the description of chemical bonds, so called adhesions between filaments and the substrate and cross-linking proteins between crossing filaments. Figure 2 describes the "life" of one cross-link. It has been established at time $t-a$ between two binding sites, one on each of the two dotted filaments. Observe that in this situation the two binding sites overlap. At the present time $t$ the two filaments, now drawn by solid lines, have moved on and the two binding sites with them. This displacement has happened against the resistance of elastic forces caused by stretching and twisting the cross-linking protein. Eventually, the cross-link will break by unbinding of the protein from at least one of the two filaments. The model uses the time-dependent density $\rho(t,s,a)$ of cross-links in terms of binding site position $s$ and age $a \ge 0$. Analogously, $\rho_{\text{adh}}(t,s,a)$ is the density of adhesions in terms of position $s$ along the reference filament and of age $a$. The age structures of cross-link and adhesion distributions will be needed in the following for the identification of the binding sites.

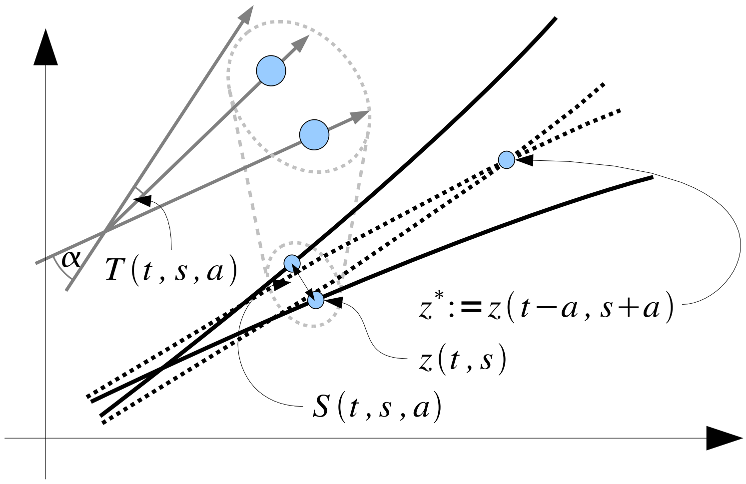


FIGURE 2. Shifting: A cross-link between two filaments at two different points in time.

The model consists of three coupled submodels: A quasistatic balance of elastic forces determining the position of the reference filament and two age-structured population models for the adhesion and cross-link densities. We start with the description of the former.

At each point in time, the position of the reference filament has to belong to the set of admissible functions

$$\mathcal{A} := \left\{ w \in H^2(0,1)^2 : \ |\partial_s w| = 1 \right\} . \tag{1}$$

The model requires that at any time $t \geq 0$ the filament position is a minimizer of a potential energy functional:

$$z(t,.) = \mathrm{argmin}_{w \in \mathcal{A}}\, U(t)[w] . \tag{2}$$

The potential energy of the network has the form

$$U(t)[w] := U_{\mathrm{membrane}}[w] + U_{\mathrm{bending}}[w] + U_{\mathrm{adh}}(t)[w] + U_{\mathrm{scl}}(t)[w] + U_{\mathrm{tcl}}(t)[w] , \tag{3}$$

arising from the combined effects of

(1) *Stretching of the membrane,* which is modelled as an elastic rubber band with elasticity $\kappa^M$:

$$U_{\mathrm{membrane}}[w] := \frac{\kappa^M}{2}(|w(1)| - R_0)_+^2 .$$

Here $R_0$ is the force-free equilibrium radius of the membrane.

(2) *Stiffness of the filaments:*

$$U_{\mathrm{bending}}[w] := \frac{1}{2}\int_0^1 |\partial_s^2 w|^2 \, \eta \, ds ,$$

where the bending stiffness is 1 in this scaling.

(3) *Stretching of adhesions:*

$$U_{\mathrm{adh}}(t)[w] := \frac{\kappa^A}{2\varepsilon}\int_0^1 \int_0^\infty |w - z^*|^2 \, \rho_{\mathrm{adh}} \eta \, da \, ds , \tag{4}$$

which involves the scaled elasticity $\kappa^A/\varepsilon$ and the effective density $\rho_{\rm adh}\eta$ of adhesions. The abbreviation $z^* := z(t-\varepsilon a, s+\varepsilon a)$ denotes the position of the binding site on the substrate of an adhesion of age $a$ connected to the filament at the position $z(t,s)$. The dimensionless parameter $\varepsilon$ is the ratio between the reference value for the age of adhesions and the maximal life time of a monomer as part of a filament. This parameter will be assumed small in the following, and the fact that the cross-link elasticity is $O(\varepsilon^{-1})$ is a scaling assumption required for a nonvanishing effect of adhesions in the limit $\varepsilon \to 0$. This is not obvious, however. Actually, when replacing $w(s)$ by the minimiser $z(t,s)$, then the energy $U_{\rm adh}(t)[z(t,\cdot)]$ is formally $O(\varepsilon)$. It will be shown below that, in the limit $\varepsilon \to 0$, it still contributes to the formulation of the limiting problem.

(4) *Stretching of cross-links:*

$$U_{\rm scl}(t)[w] := \frac{\kappa^S}{2\varepsilon}\int_0^1\int_0^\infty |S|^2\rho\eta^2|\partial_s\phi^*|\,da\,ds\,. \tag{5}$$

This expression involves the elasticity $\kappa^S/\varepsilon$ and the effective density $\rho\eta^2|\partial_s\phi^*|$ of cross-links, where the factor $\eta^2$ accounts for the graded lengths of both filaments involved in a cross-link, and the factor $|\partial_s\phi^*| = -\partial_s\phi(t-\varepsilon a, s+\varepsilon a)$ requires some explanation: A cross-link of age $a$, binding to the reference filament at position $s$ at time $t$ connects the reference filament to the anti-clockwise filament with label $\alpha$, where

$$z(t-\varepsilon a, s+\varepsilon a) = F^-(t-\varepsilon a, \alpha, s+\varepsilon a)$$

holds. A straightforward computation shows that this is equivalent to $\alpha = -2\phi(t-\varepsilon a, s+\varepsilon a)$ (recalling that $\phi$ is the argument of $z$). A more precise interpretation of $\rho$ is that of a probability distribution of the cross-link with respect to age $a$ and anti-clockwise filament label $\alpha$. Therefore, the integration in (5) should actually be carried out with respect to $\alpha$ instead of $s$. The relation above obviously implies $d\alpha = 2|\partial_s\phi^*|ds$, explaining the last factor in the effective density (the factor 2 has been absorbed in $\kappa^S$).

The main term in (5) is the distance between the binding sites computed from $S = z(t,s) - F^-(t,-2\phi^*,s)$:

$$|S| := 2|w|\,|\sin(\psi-\phi^*)|\,, \tag{6}$$

where the polar coordinates $w = |w|(\cos\psi, \sin\psi)$ have been used.

(5) *Twisting of cross-links:*

$$U_{\rm tcl}(t)[w] := \frac{\kappa^T}{2}\int_0^1\int_0^\infty T^2\rho\eta^2|\partial_s\phi^*|\,da\,ds\,. \tag{7}$$

This contribution originates from the assumption that the system of two cross-linked filaments has a stress free equilibrium conformation with an angle $\varphi_0$ between the filaments. The effective cross-link density is as above. The term

$$T = \arccos(\partial_s z(t,s)\cdot\partial_s F^-(t,-2\phi^*,s)) - \varphi_0$$

denotes the deviation of the angle between crossing filaments from $\varphi_0$ (see Figure 2). Again a convenient expression can be derived in terms of polar coordinates:

$$T = T_0 + 2(\phi^*-\psi)\,, \qquad \text{with} \quad T_0 := 2\arccos(\partial_s|w|) - \varphi_0\,. \tag{8}$$

The evolution of the cross-link density is determined by

$$\begin{aligned} &\varepsilon D_t\rho + \partial_a\rho = -\zeta(S,T)\rho\,,\\ &\rho(t,s,0) = \beta(T_0)\left(1-\textstyle\int_0^\infty \rho\,da\right)\,, \quad \rho(t,1,a) = 0\,. \end{aligned} \tag{9}$$

The first equation is the standard transport equation in age structured population models involving the material derivative $D_t := \partial_t - \partial_s$. The decay term on the right hand side models the breaking of cross-links whose rate might depend on their stretching and twisting, where $S$ and $T$ (defined above) are evaluated at $w = z(t,\cdot)$. The boundary condition at $a = 0$ describes the building of new cross-links with a rate $\beta$ depending on the deviation of the angle between the filaments from the equilibrium. The second factor guarantees that the total probability of having a cross-link does not exceed 1. In other words, there can be at most one cross-link between any 2 filaments. The boundary condition at the pointed end $s = 1$ is a consequence of the fact that no preexisting cross-links are present, when filaments start to cross by polymerization.

The density of adhesions $\rho_{\rm adh}$ satisfies

$$\begin{aligned} &\varepsilon D_t \rho_{\rm adh} + \partial_a \rho_{\rm adh} = -\zeta_{\rm adh}(S_{\rm adh})\rho_{\rm adh}\,, \\ &\rho_{\rm adh}(t,s,0) = \beta_{\rm adh}\left(1 - \textstyle\int_0^\infty \rho_{\rm adh}\,da\right)\,, \quad \rho_{\rm adh}(t,1,a) = 0\,. \end{aligned} \tag{10}$$

Here the upper bound 1 for the integral of the density with respect to age has to be interpreted as the scaled density of possible binding sites for integrins along the filament, and $S_{\rm adh} = z - z^*$ is the stretching of adhesions.

The problem (2)–(10) is a problem with distributed delays. For the computation of $z(t,\cdot)$ the filament positions at all previous times are required, where the values of the cross-link and adhesion densities do not vanish. Initially, a start-up procedure is necessary, where initial data for the cross-link and adhesion density distributions have to be given satisfying $\rho(0,s,a) = \rho_{\rm adh}(0,s,a) = 0$ for $a > \overline{a}$ and then the filament positions $z(t,s)$ have to be prescribed for $-\varepsilon\overline{a} < t < 0$.

## 2. The limit of instantaneous cross-link and adhesion turnover

The main inconvenience (in particular from a simulation point of view) of the problem (2)–(10) is the fact that it is a delay problem. In our scaling however, the average value for delays is $O(\varepsilon)$. In this section the limit $\varepsilon \to 0$ will be carried out formally. The limiting problem will be local in time.

We start with (10). The formal limiting equations

$$\partial_a \rho_{\rm adh} = -\zeta_{\rm adh}(0)\rho_{\rm adh}\,, \quad \rho_{\rm adh}(a=0) = \beta_{\rm adh}\left(1 - \int_0^\infty \rho_{\rm adh}\,da\right)\,,$$

have the solution

$$\rho_{\rm adh}(t,s,a) = \rho_{\rm adh}(a) = \frac{\beta_{\rm adh}\zeta_{\rm adh}(0)}{\beta_{\rm adh} + \zeta_{\rm adh}(0)} e^{-\zeta_{\rm adh}(0)a}\,.$$

This is a singular limit, since the small parameter $\varepsilon$ multiplies the time derivative. An eventual initial time layer will be ignored and the quasi-stationary approximation used in the following.

Analogously we deal with (9). The main difference is that the limiting equations

$$\partial_a \rho = -\zeta(0,T_0)\rho\,, \quad \rho(a=0) = \beta(T_0)\left(1 - \int_0^\infty \rho\,da\right)\,,$$

and therefore also the limiting solution

$$\rho = \frac{\beta(T_0)\zeta(0,T_0)}{\beta(T_0) + \zeta(0,T_0)} e^{-\zeta(0,T_0)a}$$

depend on the displacement of the filaments via $T_0$.

If the limit $\varepsilon \to 0$ is carried out formally in (4) and (5), these contributions from the adhesions and from stretching the cross links disappear. In order to reveal their influence, the solution of the variational problem needs to be discussed.

The displacement $z(t,\cdot)$ at time $t$ has to satisfy the variational equation $\delta U(t)[z]\delta z = 0$ for all admissible variations $\delta z$, where $\delta U(t)$ is the variation of the total energy (3). Considering the constraint $|\partial_s z| = 1$, admissible variations have to satisfy $\partial_s \delta z \cdot \partial_s z = 0$. In the following the variations of the energy contributions and their limits as $\varepsilon \to 0$ are computed individually.

(1) The variation of the stretching energy of the membrane reads

$$\delta U_{\text{membrane}}[z]\delta z = \kappa^M (|z(t,1)| - R_0)_+ \frac{z(t,1)}{|z(t,1)|} \cdot \delta z(1)\,.$$

(2) For the variation of the bending energy of the filaments we obtain

$$\delta U_{\text{bending}}[z]\delta z = \int_0^1 \partial_s^2 z \cdot \partial_s^2 \delta z \, \eta \, ds\,.$$

(3) The remaining contributions involve delay terms. The variation of the stretching energy of the adhesions is straightforward and reads

$$\delta U_{\text{adh}}(t)[z]\delta z = \frac{\kappa^A}{\varepsilon} \int_0^1 \int_0^\infty (z - z^*) \cdot \delta z \, \rho_{\text{adh}} \eta \, da \, ds\,.$$

In the limit $\varepsilon \to 0$, a material derivative occurs:

(11) $$\delta U_{\text{adh}}(t)[z]\delta z = \mu^A \int_0^1 D_t z \cdot \delta z \, \eta \, ds\,,$$

with

(12) $$\mu^A = \kappa^A \int_0^\infty a \rho_{\text{adh}} \, da = \frac{\kappa^A \beta_{\text{adh}}}{\zeta_{\text{adh}}(0)(\beta_{\text{adh}} + \zeta_{\text{adh}}(0))}\,.$$

(4) Using $\delta|z| = \frac{z\cdot\delta z}{|z|}$ and $\delta\phi = \frac{z^\perp \cdot \delta z}{|z|^2}$ with $z^\perp = (-z_2, z_1)$, we get for the variation of the stretching

$$\delta S = \frac{2}{|z|}\Big(\sin(\phi - \phi^*) z + \cos(\phi - \phi^*) z^\perp\Big) \cdot \delta z\,.$$

The variation of the energy contribution by stretching the cross-links can now be written as

(13) $$\delta U_{\text{scl}}(t)[z]\delta z = 4\kappa^S \int_0^1 \int_0^\infty \frac{\sin(\phi - \phi^*)}{\varepsilon a} \Big(\sin(\phi - \phi^*) z + \cos(\phi - \phi^*) z^\perp\Big) \cdot \delta z \, a \rho \eta^2 |\partial_s \phi^*| \, da \, ds\,.$$

The definition of $\phi^*$ implies $\sin(\phi - \phi^*) = \varepsilon a D_t \phi + O(\varepsilon^2)$, and therefore passing to the limit $\varepsilon \to 0$ gives

(14) $$\delta U_{\text{scl}}(t)[z]\delta z = \int_0^1 \mu^S D_t \phi (z^\perp \cdot \delta z) \, \eta^2 \, ds\,,$$

with

(15) $$\mu^S(\partial_s \phi, \partial_s |z|) = 4\kappa^S \int_0^\infty a\rho \, da = \frac{4\kappa^S \beta(T_0)|\partial_s \phi|}{\zeta(0,T_0)(\beta(T_0) + \zeta(0,T_0))}\,.$$

(5) We now consider the variation of the energy contribution by twisting the cross-links. First observe that

$$\begin{aligned}\delta(\partial_s|z|) &= \frac{1}{|z|}\left(\left(\partial_s z - \frac{z\cdot\partial_s z}{|z|^2}z\right)\cdot\delta z + z\cdot\partial_s(\delta z)\right)\\ &= \frac{1}{|z|}\left(\frac{z^\perp\cdot\partial_s z}{|z|^2}z^\perp\cdot\delta z + z\cdot\partial_s(\delta z)\right) = |z|\partial_s\phi\,\delta\phi + \frac{z\cdot\partial_s z^\perp}{|z|}\partial_s z^\perp\cdot\partial_s(\delta z)\ ,\end{aligned}$$

since the spatial derivative of an admissible variation can be written as $\partial_s(\delta z) = \partial_s z^\perp\,\partial_s z^\perp\cdot\partial_s(\delta z)$. Now the constraint $1 = |\partial_s z|^2 = (\partial_s|z|)^2 + |z|^2(\partial_s\phi)^2$ implies

$$\arccos'(\partial_s|z|) = \frac{-1}{\sqrt{1-(\partial_s|z|)^2}} = \frac{1}{|z|\partial_s\phi}\ .$$

We finally obtain for the twisting, as defined in (8),

$$\delta T = \delta\Big(2\arccos(\partial_s|z|) - 2\phi\Big) = \frac{2z\cdot\partial_s z^\perp}{|z|^2\partial_s\phi}\partial_s z^\perp\cdot\partial_s(\delta z) = -2\partial_s z^\perp\cdot\partial_s(\delta z)\ . \tag{16}$$

Passing to the limit $\varepsilon\to 0$ in the variation of the energy contribution from twisting the cross links gives

$$\delta U_{\mathrm{tcl}}(t)[z]\delta z = \int_0^1 \mu^T\left(2\arccos(\partial_s|z|) - \varphi_0\right)(-\partial_s z^\perp)\cdot\partial_s(\delta z)\,\eta^2\,ds\,, \tag{17}$$

with

$$\mu^T(\partial_s\phi, \partial_s|z|) = 2\kappa^T\int_0^\infty \rho\,da = \frac{2\kappa^T\beta(T_0)|\partial_s\phi|}{\beta(T_0)+\zeta(0,T_0)}\ . \tag{18}$$

Collecting our results leads to the variational equation

$$\begin{aligned}\kappa^M(|z|-R_0)_+\frac{z\cdot\delta z}{|z|}\bigg|_{s=1} + \int_0^1\bigg[&\partial_s^2 z\cdot\partial_s^2\delta z + \mu^A D_t z\cdot\delta z\\ &+\mu^S D_t\phi\,(z^\perp\cdot\delta z)\,\eta - \mu^T\left(2\arccos(\partial_s|z|)-\alpha\right)\partial_s z^\perp\cdot\partial_s(\delta z)\,\eta\bigg]\eta\,ds = 0\end{aligned} \tag{19}$$

for all admissible variations $\delta z$. One might interpret this equation also in the following way: If we look at the set of admissible functions as a submanifold of the function space, then the admissible variations can be seen as tangent vectors to that manifold. Hence the equation (19) describes an equality in the space of linear functionals on the tangent space, namely the equality of a linear functional which involves the time derivative of the solution, i.e. the left hand side, and another functional that involves the actual position $z(t,.)$. We therefore may see the solution $z(t,s)$ as a gradient flow on the manifold. However, the role of the term involving $D_t\phi$ does not quite fit into this interpretation.

In order to represent (19) in a less abstract way we enforce the side condition by a Lagrangian approach, introduce the Lagrange-multiplier function $\lambda(t,s)$, and add the contribution

$$U_L[z,\lambda] := \int_0^1 \frac{\lambda}{2}\left(|\partial_s z|^2 - 1\right)ds\ ,$$

to the energy functional. Its $z$-variation reads

$$\delta U_L[z,\lambda]\delta z = \int_0^1 \lambda\partial_s z\cdot\partial_s\delta z\,ds\,, \tag{20}$$

where now the variations $\delta z$ are unrestricted. Combining (19) and (20) and a formal integration by parts yields the (vector valued) Euler-Lagrange equation

$$\partial_s^2\left(\eta\partial_s^2 z\right) - \partial_s(\lambda\partial_s z) + \mu^A\eta\, D_t z + \mu^S\eta^2\, D_t\phi\, z^\perp + \partial_s\left(\mu^T\eta^2\left(2\arccos\left(\partial_s|z|\right)-\alpha\right)\partial_s z^\perp\right) = 0 \tag{21}$$

coupled with the (vector valued) boundary conditions

$$\begin{aligned} &-\partial_s\left(\eta\partial_s^2 z\right) + \lambda\partial_s z - \mu^T\eta^2\left(2\arccos\left(\partial_s|z|\right)-\alpha\right)\partial_s z^\perp = 0\,,\\ &\partial_s^2 z = 0\,, \end{aligned} \tag{22}$$

at $s = 0$ and

$$\begin{aligned} &-\partial_s\left(\eta\partial_s^2 z\right) + \lambda\partial_s z - \mu^T\eta^2\left(2\arccos\left(\partial_s|z|\right)-\alpha\right)\partial_s z^\perp + \kappa^M\left(|z|-R_0\right)_+\frac{z}{|z|} = 0\,,\\ &\partial_s^2 z = 0\,, \end{aligned} \tag{23}$$

at $s = 1$, and complemented by the constraint

$$|\partial_s z| = 1\,. \tag{24}$$

The Euler-Lagrange equation (21) together with (22)–(24), is a reformulation of the problem (19). We expect this problem subject to an initial condition

$$z(0,s) = z_I(s)\,, \tag{25}$$

with an appropriate initial datum to be well posed.

## 3. Analysis - construction of solutions

In this section, an approximation scheme in the spirit of the Jordan-Kinderlehrer-Otto time-step approximation for gradient flows (see [DGMT80, DG93, AGS05]) will be presented. On the one hand this provides a numerical scheme to approximate solutions to (21)–(25), on the other hand it will allow to prove their existence. The existence result is local in time since we are unable to prove that our basic assumptions on the geometry of the network persist. In the rotationally symmetric situation these are represented by the facts that the standard filament is clockwise and heading outwards, and that the meshwork stays away from the origin. It will be proved that these conditions are preserved at least locally in time if satisfied by the initial data. For that purpose we define for every $\delta > 0$:

$$\mathcal{A}_\delta := \{z \in \mathcal{A} :\ \delta \le \partial_s|z| \le 1-\delta,\ |z| \ge \delta\}\,.$$

It will be important in the following that $\mathcal{A}_\delta$ is a closed subset of $H^2(0,1^2$.

**Assumption 1.** There exists $\delta > 0$ such that $z_I \in \mathcal{A}_{2\delta}$.

In the next assumption the properties of the parameters are collected. In particular, the model will be simplified compared to the previous section by assuming that the macroscopic elasticity parameters are constant. Also the graded length distribution is assumed to be bounded away from zero, implying that a nonvanishing fraction of the filaments has the maximal length.

**Assumption 2.** The parameters $R_0$, $\kappa^M$, $\mu^A$, $\mu^S$, and $\mu^T$ are positive constants. The function $\eta :\ [0,1] \to [0,1]$ is nondecreasing and satisfies $\eta(0) > 0$.

A time stepping procedure will be introduced, which, in a sense, undoes the limit of the last section. However, instead of distributed delays, a delay of fixed length $\tau$ is introduced. This can be seen as a caricature of the original model, where all cross-links and adhesions are built and broken at discrete times in a synchronized way. In the discretized model, the polymerization at the barbed end is described by adding a straight piece of filament of length $\tau$ (since the scaled polymerization speed is 1) at each time step. This and the corresponding shift in the $s$-variable is contained in the definition

$$\hat{z}(s) = \begin{cases} z(s+\tau)\,, & \text{for } 0 \le s \le 1-\tau\,, \\ z(1) + (s+\tau-1)\partial_s z(1)\,, & \text{for } 1-\tau < s \le 1\,. \end{cases}$$

Now we are ready for defining modified versions of the energy contributions due to adhesions and stretching and twisting of cross-links:

$$\overline{U}_{\rm adh}(z)[w] := \mu^A \int_0^1 \frac{|w-\hat{z}|^2}{2\tau}\,\eta\,ds\,, \tag{26}$$

$$\overline{U}_{\rm scl}(z)[w] := \mu^S \int_0^1 |z|^2 \frac{(\psi-\hat{\phi})^2}{2\tau}\,\eta^2\,ds\,, \tag{27}$$

$$\overline{U}_{\rm tcl}(z)[w] := \frac{\mu^T}{4}\int_0^1 (2\arccos(\partial_s|w|) - \varphi_0 - 2\psi + 2\hat{\phi})^2\,\eta^2\,ds\,.$$

These functionals are chosen such that the limits as $\tau \to 0$ of their variations for $z = z(t-\tau)$ are the same as the limits for the original functionals as $\varepsilon \to 0$. We define a time stepping procedure by $Z^0 = z_I$ and by the recursion

$$Z^{n+1} = \mathrm{argmin}_{w\in\mathcal{A}_\delta}\,\overline{U}(Z^n)[w]\,,$$

with

$$\overline{U}(Z^n)[w] := U_{\rm membrane}[w] + U_{\rm bending}[w] + \overline{U}_{\rm adh}(Z^n)[w] + \overline{U}_{\rm scl}(Z^n)[w] + \overline{U}_{\rm tcl}(Z^n)[w]\,,$$

and $\delta$ as in Assumption 1. The norm defined by

$$\|z\|^2_{H^2(0,1)} := |z(1)|^2 + \|\partial_s^2 z\|^2_{L^2(0,1)}\,,$$

will be used, which is equivalent to the standard norm on $H^2(0,1)^2$. It simplifies the proof of the following coercivity result.

**Lemma 1.** *There exist positive constants $\kappa$ and $c$ such that*

$$U_{\rm membrane}[w] + U_{\rm bending}[w] \ge \kappa\|w\|^2_{H^2(0,1)} - c\,.$$

*Proof.* It is easily seen that

$$U_{\rm membrane}[w] + U_{\rm bending}[w] \ge \frac{\kappa^M}{4}|z(1)|^2 - \frac{\kappa^M}{2}R_0^2 + \frac{\eta(0)}{2}\|\partial_s^2 w\|^2_{L^2(0,1)}\,,$$

implying the result. □

**Lemma 2.** *Let $\delta,\tau > 0$ and $Z^n \in \mathcal{A}_\delta$. Then $U_{\rm bending}$ is weakly lower semicontinuous and $U_{\rm membrane}$, $\overline{U}_{\rm adh}(Z^n)$, $\overline{U}_{\rm scl}(Z^n)$, and $\overline{U}_{\rm tcl}(Z^n)$ are weakly continuous on $\mathcal{A}_\delta$ with respect to the $H^2(0,1)^2$-topology.*

*Proof.* Weak lower semicontinuity is a consequence of the convexity of $U_{\rm bending}$. The integrands of the other energy contributions only depend on the values of $w$ and of $\partial_s w$ in a Lipschitz continuous way. The result is therefore a consequence of the compact imbedding of $H^2(0,1)$ in $C^1([0,1])$. □

The preceding two results prove the existence of the sequence $\{Z^n : n \ge 0\}$. However, it is not defined uniquely do to a lack of convexity. In particular, the set $\mathcal{A}$ (and therefore also $\mathcal{A}_\delta$) is made nonconvex by the condition $|\partial_s w| = 1$. The time-stepping procedure is in the spirit of the JKO-scheme. It corresponds to a gradient flow of the functional obtained as formal limit as $\tau \to 0$ of $\overline{U}(Z^n)[Z^{n+1}]$:

$$E[w] := U_{\text{membrane}}[w] + U_{\text{bending}}[w] + \frac{\mu^T}{4}\int_0^1 (2\arccos(\partial_s |w|) - \varphi_0)^2 \eta^2\, ds\,.$$

However, our problem is not conservative. Energy is added to the system by polymerization and therefore stretching the membrane and/or cross-links and adhesions as well as by creating cross-links, where the angle between the involved filaments is different from the equilibrium angle. On the other hand, energy is removed by depolymerization. A bound on the energy growth can be proven.

**Lemma 3.** *There exists a constant $c$, independent from $n$ and $\tau$, such that*

$$E[Z^n] \le E[z_I] + cn\tau\,.$$

*Proof.* We start with the obvious inequality

$$\overline{U}(Z^n)[Z^{n+1}] \le \overline{U}(Z^n)[Z^n] \tag{28}$$

and estimate the contributions to the right hand side. Since

$$Z^n(s) - \hat{Z}^n(s) = \begin{cases} Z^n(s) - Z^n(s+\tau)\,, & 0 \le s \le 1-\tau\,, \\ Z^n(s) - Z^n(1) - (s-1+\tau)\partial_s Z^n(1)\,, & 1-\tau \le s \le 1\,, \end{cases}$$

the inequality

$$|Z^n - \hat{Z}^n| \le \tau \tag{29}$$

is a consequence of $|\partial_s Z^n| = 1$ by $Z^n \in \mathcal{A}_\delta$. Therefore also

$$\overline{U}_{\text{adh}}(Z^n)[Z^n] \le c\tau\,,$$

holds. Here and in the rest of the proof, $c$ denotes positive constants independent from $n$ and $\tau$, whose value might change from one formula to the next. For the angles we have by the mean value theorem

$$\phi^n - \hat{\phi}^n = \frac{\tilde{z}^\perp}{|\tilde{z}|^2}\cdot (Z^n - \hat{Z}^n) \qquad \Longrightarrow \qquad |\phi^n - \hat{\phi}^n| \le \frac{\tau}{|\tilde{z}|}\,,$$

where $\tilde{z}$ lies between $Z^n$ and $\hat{Z}^n$. Since $|\hat{Z}^n| > |Z^n|$ by $Z^n \in \mathcal{A}_\delta$, $|\tilde{z}| \ge |Z^n|$ holds. These observations imply

$$\overline{U}_{\text{scl}}(Z^n)[Z^n] \le c\tau\,.$$

By $Z^n \in \mathcal{A}_\delta$ also $|\phi^n - \hat{\phi}^n| \le \tau/\delta$ holds. This and the fact that the integrand in $\overline{U}_{\text{tcl}}(Z^n)[Z^n]$ depends Lipschitz continuously on $\phi^n - \hat{\phi}^n$ (with a $Z^n$-independent Lipschitz constant), imply

$$\overline{U}_{\text{tcl}}(Z^n)[Z^n] \le \frac{\mu^T}{4}\int_0^1 (2\arccos(\partial_s |Z^n|) - \varphi_0)^2 \eta^2\, ds + c\tau\,,$$

with the consequence

$$\overline{U}(Z^n)[Z^n] \le E[Z^n] + c\tau\,. \tag{30}$$

An analogous argument leads to

$$\overline{U}_{\rm tcl}(Z^n)[Z^{n+1}] \ge \frac{\mu^T}{4}\int_0^1 (2\arccos(\partial_s|Z^{n+1}|) - \varphi_0)^2\eta^2\,ds - c\|Z^{n+1}-\hat Z^n\|_{L^2(0,1)}\,.$$

Since, by Assumption 2,

$$\overline{U}_{\rm adh}(Z^n)[Z^{n+1}] \ge \frac{\kappa}{\tau}\|Z^{n+1}-\hat Z^n\|^2_{L^2(0,1)}\,,$$

holds, we have

$$\begin{aligned}\overline{U}(Z^n)[Z^{n+1}] \quad &\ge \quad E[Z^{n+1}] - c\|Z^{n+1}-\hat Z^n\|_{L^2(0,1)} + \frac{\kappa}{\tau}\|Z^{n+1}-\hat Z^n\|^2_{L^2(0,1)} \\ &\ge \quad E[Z^{n+1}] - \frac{c^2\tau}{4\kappa}\,.\end{aligned} \tag{31}$$

Using this and (30) in (28) gives $E[Z^{n+1}] \le E[Z^n] + c\tau$, concluding the proof. □

Approximations of the solution of the continuous problem are defined by linear interpolation and by piecewise constant extension:

$$\left.\begin{array}{l} Z_\tau(t,s) := Z^n(s) + \left(\frac{t}{\tau}-n\right)\left(Z^{n+1}(s)-Z^n(s)\right)\,, \\ Z_\tau^{\rm old}(t,s) := Z^n(s)\,, \\ Z_\tau^{\rm new}(t,s) := Z^{n+1}(s)\,, \end{array}\right\} \quad \text{for } n\tau < t \le (n+1)\tau\,.$$

**Lemma 4.** *For every fixed finite $T>0$, $Z_\tau \in H^1((0,T),L^2(0,1))$ uniformly in $\tau$.*

*Proof.* From (28), (30), and (31) we obtain

$$\frac{\kappa}{\tau}\left(\|Z^{n+1}-\hat Z^n\|_{L^2(0,1)} - c\tau\right)^2 \le E[Z^n] - E[Z^{n+1}] + c\tau\,. \tag{32}$$

Since the time derivative of $Z_\tau$ is piecewise constant, we have

$$\int_0^{m\tau}\|\partial_t Z_\tau\|^2_{L^2(0,1)}dt = \frac{1}{\tau}\sum_{n=0}^{m-1}\|Z^{n+1}-Z^n\|^2_{L^2(0,1)} \le \frac{1}{\tau}\sum_{n=0}^{m-1}\left(\|Z^{n+1}-\hat Z^n\|_{L^2(0,1)}+\tau\right)^2\,,$$

where the inequality is due to (29). With the constant $c$ from (32), this implies

$$\begin{aligned}\int_0^{m\tau}\|\partial_t Z_\tau\|^2_{L^2(0,1)}dt \quad &\le \quad \frac{2}{\tau}\sum_{n=0}^{m-1}\left(\|Z^{n+1}-\hat Z^n\|_{L^2(0,1)} - c\tau\right)^2 + 2(c+1)^2 m\tau\,, \\ &\le \quad \frac{2}{\kappa}\left(E[z_I] + cm\tau\right) + 2(c+1)^2 m\tau\,,\end{aligned}$$

completing the proof. □

This result sets the stage for passing to the limit in the approximate solutions.

**Lemma 5.** *For every fixed finite $T>0$,*

$$\lim_{\tau\to 0} Z_\tau = z \in L^\infty\left((0,T);H^2(0,1)\right) \cap C^{0,1/8}\left([0,T];C^1([0,1])\right) \cap H^1\left((0,T);L^2(0,1)\right)\,,$$

*(restricting to subsequences) where the convergence is strong in $C\left([0,T];C^1([0,1])\right)$, weak in $H^1\left((0,T);L^2(0,1)\right)$, and weak* in $L^\infty\left((0,T);H^2(0,1)\right)$. The piecewise constant approximations $Z_\tau^{\rm old}$ and $Z_\tau^{\rm new}$ converge to $z$ strongly in $L^\infty\left([0,T];C^1([0,1])\right)$ and weakly* in $L^\infty\left((0,T);H^2(0,1)\right)$.*

*Proof.* Lemma 1 and Lemma 3 imply $Z_\tau \in L^\infty\big((0,T);H^2(0,1)\big)$ uniformly in $\tau$, which already shows the weak* convergence. The weak convergence is a consequence of the previous lemma, which also implies that $Z_\tau$ is uniformly bounded in $C^{0,1/2}\big([0,T];L^2(0,1)\big)$. The interpolation inequality

$$\|u\|_{C^{1,\alpha}([0,1])} \le c\|u\|_{L^2(0,1)}^{(1-2\alpha)/4}\|u\|_{H^2(0,1)}^{(3+2\alpha)/4}$$

for $0\le\alpha\le 1/2$, can then be used together with the $H^2(0,1)$-bound to obtain

$$\|Z_\tau(t_2)-Z_\tau(t_1)\|_{C^{1,\alpha}([0,1])} \le c_T|t_2-t_1|^{(1-2\alpha)/8}\,,$$

completing the convergence proof for $Z_\tau$ by an application of the Arzela-Ascoli theorem. The convergence results for $Z_\tau^{\rm old}$ and $Z_\tau^{\rm new}$ are straightforward consequences. □

By the continuity in time and by $z_I\in\mathcal{A}_{2\delta}$, the solution initially stays away from the $\delta$-dependent bounds defining $\mathcal{A}_\delta$.

**Corollary 6.** *There exists $T^*>0$ such that, for all $t\in[0,T^*]$ and $s\in[0,1]$,*

$$\delta<\partial_s|z(t,s)|,\partial_s|Z_\tau(t,s)|<1-\delta\,,\quad |z(t,s)|,|Z_\tau(t,s)|>\delta\,.$$

This implies that these side conditions are not active and can be neglected in the time stepping procedure:

$$Z^{n+1}=\operatorname{argmin}_{w\in\mathcal{A}}\overline{U}(Z^n)[w]\,,\qquad \text{for } (n+1)\tau\le T^*\,. \tag{33}$$

It is our goal to show that the limit $z$ of $Z_\tau$ satisfies the weak formulation of (21)–(25). By construction, $Z^{n+1}$ satisfies $\delta\overline{U}(Z^n)[Z^{n+1}]\delta z=0$ for all admissible variations, i.e., $\delta z\in H^2(0,1)$, $\partial_s Z^{n+1}\cdot\partial_s(\delta z)=0$. A Lagrange multiplier $\lambda^{n+1}$ will be identified, such that

$$\delta\overline{U}(Z^n)[Z^{n+1}]\delta z+\delta U_L[Z^{n+1},\lambda^{n+1}]\delta z=0$$

for arbitrary variations $\delta z\in H^2(0,1)$. An arbitrary variation can be written in the form

$$\delta z=\delta z(1)-\int_s^1\Big(\theta^\perp(\partial_s Z^{n+1})^\perp+\theta\partial_s Z^{n+1}\Big)\,d\tilde s\,,$$

with arbitrary $\delta z(1)\in\mathbb{R}^2$ and $\theta,\theta^\perp\in H^1(0,1)$. It can be split into its admissible and unadmissible parts

$$u=\delta z(1)-\int_s^1\theta^\perp(\partial_s Z^{n+1})^\perp d\tilde s\,,\qquad v=-\int_s^1\theta\partial_s Z^{n+1}d\tilde s\,,$$

respectively. Since

$$\delta U_L[Z^{n+1},\lambda^{n+1}]\delta z=\int_0^1\lambda^{n+1}\partial_s Z^{n+1}\cdot\partial_s(\delta z)ds=\int_0^1\lambda^{n+1}\theta\,ds=\delta U_L[Z^{n+1},\lambda^{n+1}]v\,,$$

$\lambda^{n+1}$ has to satisfy

$$\delta\overline{U}(Z^n)[Z^{n+1}]v+\delta U_L[Z^{n+1},\lambda^{n+1}]v=0\,,$$

for every choice of $\theta$. The computation of the first term is a lengthy exercise where most of the work has been done in the previous section already. We only state the result that the above equation is the weak formulation of

$$\begin{aligned}\lambda^{n+1} &= -|\partial_s^2 Z^{n+1}|^2\eta + \mu^A \partial_s Z^{n+1}\cdot\int_0^s \frac{Z^{n+1}-\hat Z^n}{\tau}\eta\,d\tilde s \\ &\quad +\mu^S\partial_s Z^{n+1}\cdot\int_0^s |Z^{n+1}|^2\frac{\phi^{n+1}-\hat\phi^n}{\tau}(Z^{n+1})^\perp\eta^2\,d\tilde s \\ &\quad -\mu^T\Big(2\arccos(\partial_s|Z^{n+1}|)-\varphi_0-2\phi^{n+1}+2\hat\phi^n\Big)\frac{Z^{n+1}\cdot\partial_s Z^{n+1}}{(Z^{n+1})^\perp\cdot\partial_s Z^{n+1}}\eta^2\,.\end{aligned} \tag{34}$$

By the first term on the right hand side, no better information than $\lambda^{n+1}\in L^1(0,1)$ is available. By the second term, this is not uniform with respect to $\tau$. A continuous-time-version of the approximate Lagrange multiplier is defined as piecewise constant:

$$\lambda_\tau(t) := \lambda^{n+1} \qquad \text{for } n\tau < t \le (n+1)\tau\,. \tag{35}$$

**Lemma 7.** *The approximate Lagrange multiplier defined by* (34), (35) *satisfies* $\lambda_\tau\in L^2\big((0,T^*);L^1(0,1)\big)$, *uniformly in* $\tau$. *Therefore* $\lim_{\tau\to 0}\lambda_\tau=\lambda$ *(restricting to subsequences) in* $L^2((0,T^*);\mathcal{M}(0,1))$ *weak*, where* $\mathcal{M}(0,1)$ *is the set of bounded Radon measures on the interval* $(0,1)$.

*Proof.* On the right hand side of (34), the first term is uniformly bounded in $L^\infty\big((0,T^*);L^1(0,1)\big)$ by Lemma 3. In the second term,

$$\frac{Z^{n+1}-\hat Z^n}{\tau} = \partial_t Z_\tau + \frac{Z^n-\hat Z^n}{\tau}\,, \tag{36}$$

which is uniformly bounded in $L^2\big((0,T^*);L^2(0,1)\big)$ by Lemma 4 and (29). An analogous argument can be used for the third term, and the fourth term is uniformly bounded. □

**Theorem 8.** *There exist* $z\in L^\infty((0,T);H^2(0,1))\cap C^{0,1/8}([0,T];C^1([0,1]))\cap H^1((0,T);L^2(0,1))$ *and* $\lambda\in L^2((0,T^*);\mathcal{M}(0,1))$, *where* $T^*>0$ *is as in Corollary 6, satisfying* $|\partial_s z|=1$ *and*

$$\begin{aligned}\int_0^{T^*}\Bigg[\kappa^M(|z|-R_0)_+\frac{z\cdot w}{|z|}\Bigg|_{s=1} + \int_0^1\Big[\partial_s^2 z\cdot\partial_s^2 w\,\eta+\mu^A D_t z\cdot w\,\eta \\ +\mu^S D_t\phi(z^\perp\cdot w)\,\eta^2-\mu^T\left(2\arccos\left(\partial_s|z|\right)-\alpha\right)\partial_s z^\perp\cdot\partial_s w\,\eta^2+\lambda\partial_s z\cdot\partial_s w\Big]ds\Bigg]dt=0\,,\end{aligned}$$

*for every smooth* $w:[0,T^*]\times[0,1]\to\mathbb{R}^2$.

*Proof.* By construction,

$$\delta\overline{U}(Z^n)[Z^{n+1}]w(t,\cdot)+\delta U_L[Z^{n+1},\lambda^{n+1}]w(t,\cdot)=0\,,$$

for $n\tau<t\le(n+1)\tau$. With the definitions of $Z_\tau$, $Z_\tau^{\rm old}$, and $Z_\tau^{\rm new}$, this can be written as

$$\begin{aligned}&\delta\overline{U}_{\rm membrane}[Z_\tau^{\rm new}]w+\delta\overline{U}_{\rm bending}[Z_\tau^{\rm new}]w+\mu^A\int_0^1\left(\partial_t Z_\tau+\frac{Z_\tau^{\rm old}-\hat Z_\tau^{\rm old}}{\tau}\right)\cdot w\,\eta\,ds \\ &+\mu^S\int_0^1\frac{|Z_\tau^{\rm old}|^2}{|Z_\tau^{\rm new}|^2}\left(\partial_t\phi_\tau+\frac{\phi_\tau^{\rm old}-\hat\phi_\tau^{\rm old}}{\tau}\right)(Z_\tau^{\rm new})^\perp\cdot w\,\eta^2\,ds+\int_0^1\lambda_\tau\partial_s Z_\tau^{\rm new}\cdot\partial_s w\,ds \\ &-\mu^T\int_0^1\Big(2\arccos(\partial_s|Z_\tau^{\rm new}|)-\varphi_0-2\phi_\tau^{\rm new}+2\hat\phi_\tau^{\rm old}\Big)\partial_s(Z_\tau^{\rm new})^\perp\cdot\partial_s w\,\eta^2\,ds=0\,.\end{aligned}$$

After integration with respect to $t$, we pass to the limit. Note that the weakly convergent terms $\partial_s^2 Z_\tau^{\rm new}$ (appearing in $\delta\overline{U}_{\rm bending}[Z_\tau^{\rm new}]$), $\partial_t Z_\tau+(Z_\tau^{\rm old}-\hat Z_\tau^{\rm old})/\tau$, $\partial_t\phi_\tau+(\phi_\tau^{\rm old}-\hat\phi_\tau^{\rm old})/\tau$, and $\lambda_\tau$

(converging to, respectively, $\partial_s^2 z$, $D_t z$, $D_t \phi$, and $\lambda$) occur only linearly, and that all other terms converge strongly. $\square$

## 4. Numerical computations

We use the scheme (33) to compute a numerical approximation of a solution to the model (21). The scaled parameters of the model as well as the macroscopic parameters are determined on the basis of the parameter values used in [OSS08] to simulate the microscopic model. To maintain the comparability with those numerical results, we do not scale with respect to the polymerisation rate and to the maximal length of the filaments and keep their numerical values at $v_0 = 8$ and $L = 6$ respectively. Furthermore we use $\kappa^M = 6.7705$, $R_0 = 8$, $\alpha = 70°$ and $\eta(s) = 0.1 + 0.9s/L$. The macroscopic parameters which describe the effect of the cross-links according to (15) and (18) are given by $\mu^S = 1.1946 \times 10^6 \, |\partial_s \phi|$ and $\mu^T = 2150.4 \, |\partial_s \phi|$.

Unfortunately, with respect to integrin bonds, the scaling, which leads to (12) and which is based on the assumption that the average lifetime of chemical bonds is small, is not well justified by experimental findings (cp. [LREM03]). They suggest that integrin complexes typically do not detach spontaneously but when the mechanical load exceeds a certain threshold value. Hence a scaling limit which considers this threshold value as small compared to the typical mechanical load on an integrin would be the appropriate one. The necessary computations, however, turn out to be lengthy. Therefore, and since the present study focuses on justifying the use of the macroscopic model (21)–(24) in general, we follow another procedure to obtain an appropriate macroscopic friction coefficient $\mu^A$ for the numerical computations: Since the symmetric lamellipodium is stationary, i.e. it does not move, integrin bonds within one time interval typically will be stretched by a distance in the magnitude of $\tau v_0$. This value, by evaluating $0.012 \exp(\tau v_0/0.04)$ (cp. [OSS08] and [LREM03]), already gives a typical decay rate which we plug into (12) (replacing $\zeta_{\mathrm{adh}}(0)$) obtaining the macroscopic value $\mu^A = 1.9531$.

The following six frames are picked from a numerically computed sequence $(Z^n)_{n=1,2,\ldots}$ with the size of time steps given by $\tau = 0.02$. We use a uniform grid in $s$-direction with size $N = 41$. The discretised material derivatives in the expressions (26) and (27) are represented as the sum of the time derivative and the spatial derivative (cp. (36)).

The six frames at times $t = 0, 0.04, 0.18, 0.5, 0.98, 2.38$ illustrate the evolution of the network starting with the initial condition depicted in figure 3(a). The filaments perform a rotating movement, i.e. those showing in clockwise direction move clockwise and those pointing in anti-clockwise direction move anti-clockwise. This is indeed the movement which in the biological literature is referred to as lateral flow. In the figures 3(a)-3(f) we painted one specific filament (the standard filament $z$) with a thicker line to illustrate this movement. Additionally the dots along this filament represent fixed points (monomers) and you may follow them through the series of frames thus observing their backward movement. In the literature this movement is referred to as treadmilling. The rotating quasi-equilibrium state is reached quickly. Already at time $t = 0.5$ the shape of the filaments resembles the numerical result for a long-time quasi-equilibrium state of the microscopic model (cp. figure 3 in [OSS08]) which stresses the usefulness of the scaling limit we perform in this study.

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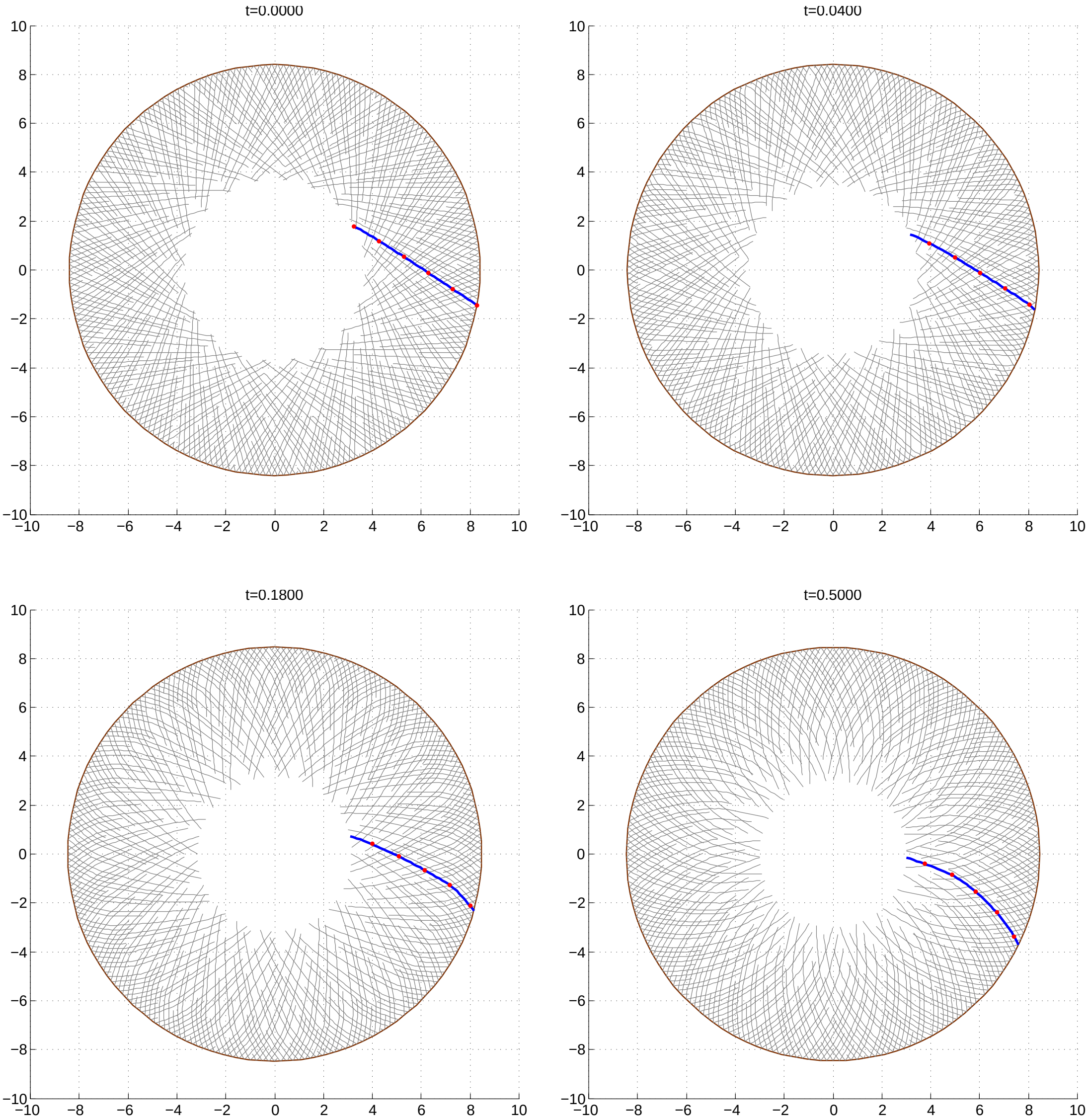


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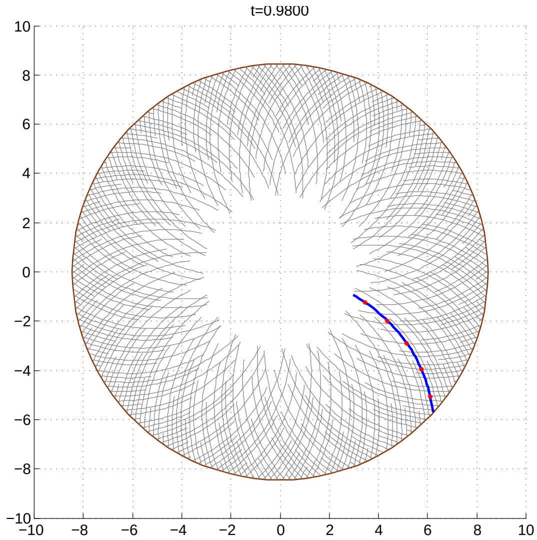


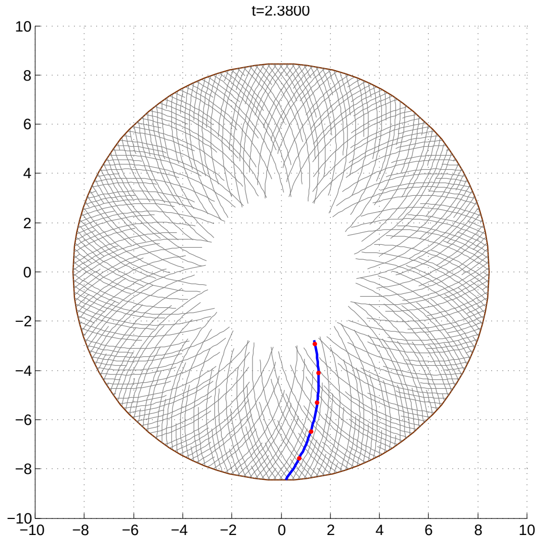


(f) Almost quasi-equilibrium situation.