TECHNISCHE UNIVERSITÄT WIEN

VIENNA UNIVERSITY OF TECHNOLOGY

Diplomarbeit

Models for the length distribution of actin filaments

Ausgeführt an der Fakultät für
Mathematik
der Universität Wien

unter der Anleitung von Univ.Prof. Dr. Christian Schmeiser

eingereicht an
der Technischen Universität Wien

durch

Christoph Flamm
Rauchenwarth 18
2320 Rauchenwarth

_____ _____

Datum Unterschrift

Imagination is more important than knowledge.

- Albert Einstein

This diploma thesis is my first extensive scientific work, which in itself thought me a great lesson for life.

My family supported me during my studies and this work and therefore I thank them. Of course I mention my adviser Prof. Christian Schmeiser, because I am grateful for his enduring help and sophisticated challenges. Special thanks go to Andreas Graef, a dear friend of mine, for his assistance and encouragement during this work. I also want to thank Christoph Winkler for his biting sarcasm, that promoted this work in ways he would never have imagined.

Preface

The aim of this diploma thesis is to give an introduction in the mathematical modeling of actin filament dynamics. At the beginning we want the reader to get a grasp at the ideas that inspired us for writing this work as it is.

This diploma thesis is written under the background of a large model for the movement of a fish keratocyte cell. The prime goal of this master model is the description of a steady cell movement. We imagine that during this steady movement the processes inside the cell also run at constant levels. The filament distribution and the protein concentrations are in a stable dynamic equilibrium during this steady movement.

This seems very natural from the biological point of view, but from the mathematical point of view it is not so clear. Which processes shall be included in the model and how are they modeled to get a steady state filament distribution? We assume that the main processes in actin networks are polymerization and depolymerization, therefore we will try to get stationary distributions using these two processes as the main components of our models.

An important question arises when modeling actin filament dynamics: Do the filaments know of each other, and if there is knowledge how does it affect the filament's evolution.
In our work we will present two models with complete different ideologies: Our first model includes information between filaments, but in our second model there is no communication between them.

In our second model we will add a fragmentation effect to the two aforementioned processes. This will lead to a linear model for the ending distribution with the underlying idea that the filaments do not communicate with each other. A filament polymerizes, breaks or is created out of a longer filament by fragmentation, but they have no information from other filaments.
Despite this fact there exists a steady state length distribution of the filaments, where all initial distributions converge to.

In contrary the first model will have a balancing effect between polymerization and depolymerization through information by depolymerizing proteins in the cell. These proteins regulate the depolymerization probability of a filament, and over this probability the filaments know how many other filaments are present.
This effect will be displayed in the non-linear flux function of our first model. The properties of the flux function and the control of the total filament number by a non-standard boundary condition will lead to a very simple steady state distribution of the filaments.

The viewpoints of these two models will also differ in another point. There will be no information over the starting points of the filaments in the second model, only in the first model this will be used to regulate the total filament number by the boundary condition.

Summing up, we try to highlight the most important topics in the modeling of actin filament dynamics. There is a lot of knowledge accumulated in this work and we hope to communicate our main ideas to the reader.

Contents

Chapter 1

Introduction

The movement of cells is crucial for live. A lot of important processes base on the transport of information and matter by cells. Three prominent examples are the flagellum based movement of sperm cells to fertilize an egg, the migration of white blood cells to an inflammation site and the travel of fibroblasts to a wound site for wound healing.
In cellular biology the ability of cells to move spontaneously and actively is called cell motility. During this process energy is consumed. This movement is often highly directed along some kind of gradient or towards other points. There exist a lot of different techniques that cells use for locomotion like flagella, cilia and lamellipodia. In all these types the protein actin plays a major role.

In this work we will focus on lamellipodia driven cells, which are renowned for their steady movement. The lamellipodium is a large flat prolongation of the cell at its mobile edge.
It has a thin sheetlike form, and its most important substructure is the cytoskeleton, which is a flat meshwork of actin filaments. The lamellipodium pulls the cell across a substrate and is its main source of locomotion (see [1]). Lamellipodia are found primarily in very mobile cells, in particular the keratocytes of fish and frogs, which are involved in the quick repair of wounds. Figure 1.1 shows a fish keratocyte and its lamellipodium. During movement the shape of this lamellopdium is very stable.

In lamellipodia driven cells the movement is caused by the growth of the actin cytoskeleton. Therefore, to analyze their locomotion means to investigate the behavior and the properties of the cytoskeleton. The basic building parts of this skeleton are the filaments themselves, and therefore we analyze actin filament dynamics in order to gain more insight in the cell's movement.

The dynamic behavior of actin filaments has been the subject of research

and mathematical modeling for three decades now (see [2] and [3]) and it is still not completely understood.

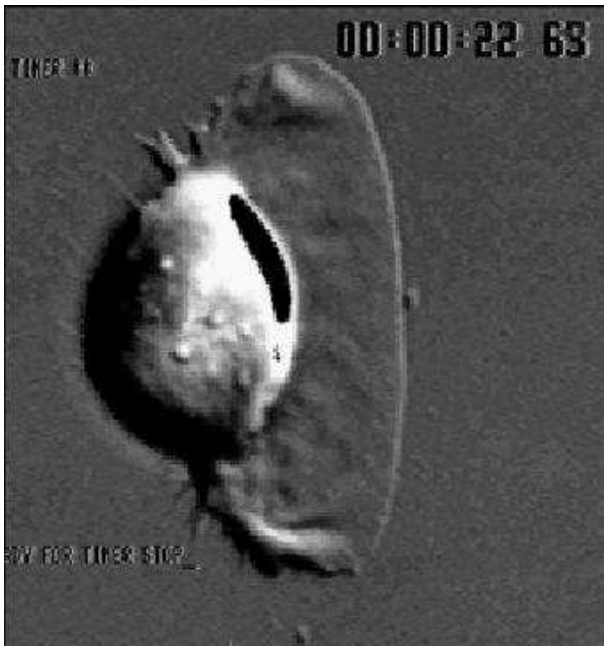


Figure 1.1: Picture of a fish keratocyte

1.1 Goals

In this master thesis we will give a short introduction to modeling actin filament dynamics. This includes a brief overview over the most important facts of actin and the effects that influence its temporal evolution.
The main part will be the derivation and discussion of a simple model for the time evolution of actin filaments in the lamellipodium of a fish keratocyte. A second model will be presented, which features other aspects, to show another approach to the topic and to broaden the understanding.
We conclude by giving a short overview over other approaches in the literature and the most important actin influencing proteins.

The original idea behind this master thesis is to extend the model of a moving fish keratocyte cell given in the thesis of Dr. Dietmar Ölz (see [4]) by a model for the length distribution of the actin filaments. Altough we aim to extend his model, our work is mainly complementary to his.

The main goal of this master thesis is the understanding of the presented models and their behavior in order to be able to use them in further works.

The main aspects in our analysis for this will be:

- the constitutive equation of the models,
- its mathematical properties,
- possible steady state solutions and convergence to them,
- essential boundary and initial conditions and
- the physical and biological interpretation.

This work comprises modeling a biological process and in biology lots of different factors influence the events. We want to present a simple model for actin dynamics, that is the starting point for further investigations. Of course we have to make many assumptions and skip dependencies, which we consider not important in order to keep it simple and straight.

This work is applied mathematics and our main interest lies in the modeling of the processes. In some places we will skip rigorous argumentation and sketch only our ideas.

1.2 A short introduction to actin

Actin is a structure protein which occurs in all eukaryotic cells. Its main function is the building of actin filaments. These filaments serve as building parts of the cytoskeleton, for the stability of the cell shape and for intracellular transport means.
A very good introduction to this topic is given in [5], where we have a lot of information from.
In vitro[1] actin filaments are flexible and buckle easily, but *in vivo*[2][3] cells create a dense network of short branched filaments by thightly coupling nucleation, branching, and cross-linking of filaments in the lamellipodium. The stiffness of the network enables new filaments to exert force on the membrane and and provides the structural basis for polymerization driven protrusion of the cell's leading edge.

There is a special mechanism for the creation of filaments: First the nucleotide Adenosine Triphosphate binds to an actin monomer. After that an ATP loaded actin monomer can bind to another actin monomer, the energy for this process comes from the hydrolysis of ATP to ADP where a phosphate molecule is dissociated. This binding of two monomers is also called

[1] *In vitro* means during experiments in the laboratory
[2] *In vivo* refers to observations in natural surroundings
[3] The term *in silico* refers to observations from computations alone

polymerization.
So actually chains of actin monomers can evolve by a huge number of monomers connecting with each other, they create actin filaments. Exactly spoken a filament consists of two chains of polymerized actin monomers, that are wrought together helix-like.
At the beginning of the filament creation the association of two or three actin proteins is very unstable, but after they have formed a so called nucleus, the polymerization is very rapid.

Polymerized actin forms filaments with two distinct ends. The barbed (or plus) end is the preferred polymerization site for monomers, whereas the pointed (or minus) end favors depolymerization. Of course there happen a lot more processes than just polymerization and depolymerization activity in an actin network like the cytoskeleton of the fish keratoctze's lamellipodium.

The processes and activities of actin filaments are heavily influended by other proteins. They can be grouped by the effect they have on the filaments:

- Severing proteins: These proteins normally bind between two adjacent ADP actin monomers of a filament and weaken their connection, so the actin filament breaks apart at this point.
- Capping proteins: They bind to an ending and magnify or inhibit polymerization and depolymerization there.
- Sequestering proteins: These proteins sequester actin monomers to prevent polymerization.
- Crosslinking proteins: They may link filaments together or to the substratum.

The turnover of actin filaments and the depolymerization of actin monomers at the filament's ends can be very rapid according to the cell's needs.

For further informations on proteins see appendix chapter B in this work.

1.2.1 The modeling of actin dynamics

Actin dynamics and especially actin filament polymerization has been extensively studied, see [6] for a short introduction. A pioneer work on this field is Oosawa and Asakura (1975) (see [7]), where they describe a nucleation-elongation model characterized by an unfavorable nucleation step followed by a more favorable elongation after a stable nucleus is formed. Elongation here simply means polymerization.
The model presented in this pioneer work is expanded in [3], where four main elements for modeling actin filament dynamics are proposed:

- nucleation,
- polymerization and depolymerization,
- fragmentation and
- annealing

Nucleation is the creation of a nucleus, which consists of roughly three actin monomers, and is the commencing point for the polymerization of a filament.
Polymerization and depolymerization are self explanatory and refer to the actins ability to add or remove actin monomers from the ends of existing actin filaments. The barbed (or plus) end prefers polymerization and the pointed (or minus) end promotes depolymerization.
The expression *fragmentation* refers to the breaking of an actin filament into two smaller filaments. This is caused by severing proteins and/or large mechanical forces on the filament.
Annealing is the merging of two small filaments into one large filament. It is still not clear if and how this really affects actin dynamics.

Of course there is a lot more activity going on in the actin network, but these four elements cover the most important processes. Recent approaches to actin dynamics modeling use some or all of these elements.
In our main model we will include nucleation, polymerization and depolymerization, and in the second model we will skip the nucleation and add fragmentation. Of course different effects will be observable in these models.

In all the approaches we have listed so far, actin is the focal point of all observations. This is one ideology of coping with actin filament dynamics. But there exists another concept of analysis characterized by seeing actin as a component of a more complex system. For further informations see chapter A in the appendix. However, we will follow the idea of actin beeing in the center of the analysis.

1.3 Assumptions and notations

This work is meant to give an introduction to actin filament dynamics in lamellipodia, so we will adress only the most important facts.
As we mentioned above, one of this work's main goals is the extension of a bigger model in the thesis of Dr. Ölz by a model for the density of actin filaments. Therefore, we will use the notation introduced in his thesis. We will also adopt his assumptions concerning our work, and introduce new

ones suiting our cause.

When we speak of the actin network and a filament we have the standard array as shown in figure 1.2. We use this figure to explain some of our structural assumptions.

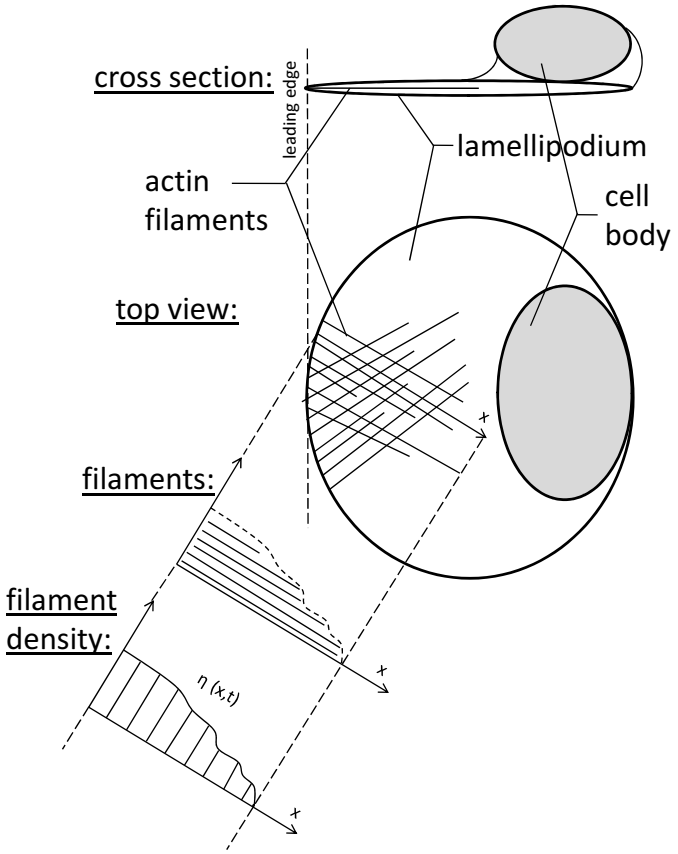


Figure 1.2: schematic picture of a keratocyte

Structural Assumption 1.1. *There is one main direction of filaments, where a huge number of almost parallel filaments exist. This main direction is preserved during the cell's movement.*

There is a lot of information gathered in this assumption. Recent research suggests there actually exist two main directions of filaments in the main area of the lamellipodium, as seen in figure 1.2, but they are symmetric in respect to the mirror axis of the cell. Hence this symmetry we assume there is only one main direction for our calculations.
We set our main axis along this main direction, and name it the x-axis. It

starts at $x = 0$ at the front edge of the cell and goes inward. When we say inside the cell, we mean the region $x > 0$.
The idea of the main direction also yields the parallelity assumption. The large number of filaments is a biological fact and justifies the continuum calculations we are going to do.
This axis is static relative to the cell. When the cell moves into an arbitrary direction, the main direction stays the same inside the cell.

Structural Assumption 1.2. *All filaments are parallel to the x-axis. They start with their barbed ends at the leading edge at $x = 0$ and go in the positive x direction.*

Actin filaments are oriented, and in the lamellipodium almost all the barbed ends point to the front edge. The assumption, that all filaments start at the edge, is very strong but it simplifies our calculations immensly.
From now on, we refer to the barbed end (at $x = 0$) also as the beginning of a filament, and to the pointed end as the end or ending of a filament. Furthermore, we will call the negative x direction left and the positive x direction to the right. This follows basic intuition looking at our setup.
In chapter 3 we will show another model and will modify this assumption slightly.

Structural Assumption 1.3. *Polymerization only occurs at the barbed end and depolymerization only happens on the pointed end of a filament.*

Although this is not exactly true, the rate constants in [8] justify this assumption. The polymerization rate at the barbed end is much larger than at the pointed end. On the other hand the depolymerization rate at the pointed end of a filament is much higher than at the barbed end.

Structural Assumption 1.4. *The concentration of actin monomers and other proteins have a constant influence on the actin filament dynamics.*

We consider all actin monomers and other proteins to be in a stable concentration. That means that there are no changes in the properties of these proteins and thus no changes in the influences of these proteins. In the case of actin monomers, at every time there are enough free monomers for all processes to happen in the cell. The number of free monomers is not a limiting factor in the processes, thus there are always enough actin monomers for the polymerization or nucleation to happen at $x = 0$.
In our model we only deal with actin, the influence from other proteins is included in rate constants and other factors.

After our assumptions we introduce the notations used in this work. To describe the actin dynamics we will use the density of the actin filaments

$\eta(t,x)$ (as seen in figure 1.2) and the density of the (pointed) ends of the actin filaments $\varrho(t,x)$. The density of endings can be seen as the continuous limit of the number of endings divided by the total number of filaments. This follows the derivation of this quantity as seen in the next chapter. In analogy the same ist true for the density of filaments.

$$\begin{aligned} \eta(t,x) &= \text{density of filaments at position } x \text{ at time } t \\ \varrho(t,x) &= \text{density of filament endings at position } x \text{ at time } t \end{aligned}$$

We go to the discrete level for showing the connection between them. The number of endings at a point is simply the difference in the number of filaments between the corresponding positions. In the continous case $\varrho(t,x)$ is the negative derivative of $\eta(t,x)$ with respect to x.
In the other direction the number of filaments is just the sum of endings right of the corresponding point. For this we have to assume that $\varrho(t,\infty) = 0$, which means there is no filament with infinite length. Then $\eta(t,x)$ is simply the integral of all endings right of the point x.

Since every filament starts at $x = 0$, the state of a filament can be described either by its length, or by the position of its ending, the information is the same. In conclusion we have:

$$\begin{aligned} \varrho(t,x) &= -\partial_x \eta(t,x) \\ \eta(t,x) &= \int_x^\infty \varrho(t,y)\,\mathrm{d}y \end{aligned}$$

This is a bijective connection, therefore we can do the calculations with either $\varrho(t,x)$ or $\eta(t,x)$. We will mostly use $\varrho(t,x)$, because our modeling approach is based on the endings. In figure 1.3 an example for η and ϱ are given.

Remark 1.5. In the main part of our work x describes a position variable, this is clear according to its introduction. A common approach in literature (see [9] and many others) is to analyze the actin filament length distribution, and in these models x is a length variable. But because we have assumption 1.2 our density of endings $\varrho(t,x)$ describes exactly the length distribution of our actin filaments. So it is not necessary to distinguish between x as a postion or a length variable in our main model.
In chapter 3 we will show an approach using x as a length variable but the notation will stay the same.

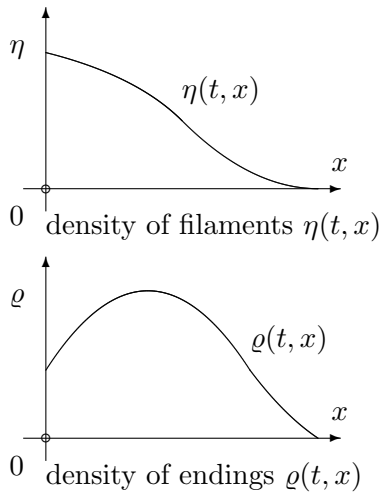


Figure 1.3: connection between η and ϱ

Chapter 2

Polymerization and nucleation model

Now we derive a simple model for actin filament dynamics. In this model we will include the effects of

- polymerization,
- depolymerization and
- nucleation.

We start by modeling the two first effects by our constitutive equation and will introduce the nucleation later in the boundary condition. We use a common approach in PDE modeling: First we will make a discrete model for the filament's ends. Then we will make a homogenization limit for getting a PDE describing the temporal evolution of the filament ending density.
This approach will get us a hyperbolic transport equation. For the completion of the model we also have to give an initial and a boundary condition. The latter one will be a challenge, because we will see, that the boundary condition will affect the system immmensly.
For the analysis of the system we will give an introduction to the topic of conservation laws, and we will also show the results of numerical simulations. Summarizing we will discuss the behavior of the system and the convergence to a proposed steady state distribution.

2.1 Derivation of the model

The actin filaments are one dimensional structures according to our structural assumptions. For our modeling approach we will treat actin filaments as simple chains of monomers. Altough this is not exactly true in reality, it is a very good approximation for our model.

We start by discretizing the x axis into parts of equal length Δx. We enumerate these intersection points from left to right with the index j starting with $j = 1, 2, 3, \ldots$. Here Δx corresponds to the typical length of one actin monomer. In our model we are looking at the endings of the filaments, and these ends are located on the intersection points. An ending at $j = 1$ gives a filament of length 1 monomer, an ending at $j = 2$ gives a filament of length 2 monomers, in general an ending at $j = \ell$ gives a filament of length ℓ monomers (see figure 2.1).
For the means of clarification: an end going to the right means a filament gets longer, one going to the left means a filament gets shorter. When an end goes from position $j = 1$ to the left the corresponding filament dissolves, its monomers go into the global monomer pool and the filament is not considered any more.

During this whole work we will describe time with the variable t. For the model we discretize time, meaning we look at our system in timesteps of equal length Δt and enumerate them with index n. Δt can be interpreted as a characteristic time for the polymerization of one monomer at the barbed ends. The timestep $n = 0$ corresponds to the initial time $t = 0$, timestep $n = 1$ corresponds to the time $t = \Delta t$, in general timestep $n = \ell$ corresponds to the time $t = \ell \Delta t$.

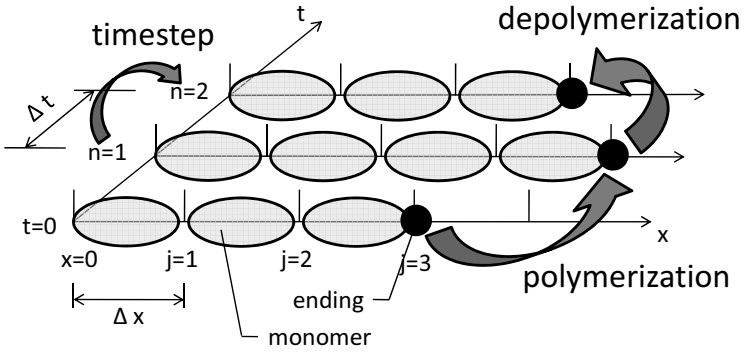


Figure 2.1: model scheme

After the discretization, we look at only one filament and note what can happen to the ending of this single filament. Through the polymerization of one actin monomer at the filament's beginning (at the barbed end; $x = 0$), the whole monomer chain is moved one postion to the right, and therefore the ending of the filament moves one position to the right.

At the filament's end depolymerization of one or two monomers can occur with a certain probability. When one monomer depolymerizes the ending travels one position to the left, the depolymerization of two monomers moves the ending two positions to the left.
Nucleation can only happen at the leading edge and means that one new ending, and therefore one new filament, comes into life. This effect will be covered by the boundary condition.

It is important to mention here: We have set Δt as the characteristic time for the polymerization of one monomer, and we assume that during one timestep either one or two depolymerization steps can occur. This is a very strong and confining assumption. But our efforts for a simple balancing model led us to this ratio of polymeriaztion and depolymerization.

These were the effects for the ending of one filament, now we look at a continuum of endings and its behavior. According to structural assumption 1.1 we have a huge number of filaments and therefore ends, so this is justifiable. We define r_j^n and discuss the change of this quantity in time.

$$r_j^n := \text{number of filament endings at position } j \text{ at timestep } n$$

At first we consider depolymerization in an auxiliary timestep. Depolymerization only happens on the pointed ends, which are at the right end of the filament. So the depolymerization of one monomer means that the end of this filament moves one postion to the left. We suppose that during one timestep only the depolymerization of one or two monomers at the pointed end can happen, as we mentioned above.

$$r_j^{n+\frac{1}{2}} = r_j^n + p_2(r_{j+2}^n)r_{j+2}^n + p_1(r_{j+1}^n)r_{j+1}^n - p_1(r_j^n)r_j^n - p_2(r_j^n)r_j^n$$

Depolymerization yields the new number of endings at position j is equal to the old number plus the number of endings that come from position $j+2$ plus the number from $j+1$ minus the number of endings that travel to position $j-1$ minus the number of endings travelling to $j-2$. Here we haved used the following:

$$\begin{aligned} p_1 : &= \text{probability that endings travel one position to the left} \\ &= \text{probability for the depolymerization of one monomer} \\ p_2 : &= \text{probability that endings travel two positions to the left} \\ &= \text{probability for the depolymerization of two monomers} \end{aligned}$$

These probabilities depend on the number of endings at that position. Our idea behind p_1 and p_2 is, that for an increasing number of endings they should decrease, so their derivatives should be negative.

This comes from a biological fact: there is only a limited number of depolymerizing proteins at each point. Therefore few endings at a point would have a higher probability of depolymerization, because there are more proteins present to depolymerize them, and a high number of endings would have a small probability of depolymerization. We imagine $p_1(\varrho)$ and $p_2(\varrho)$ having a form similar to a decaying function, see figure 2.2. For our model derivation $p_1(r_j^n)$ and $p_2(r_j^n)$ are just discrete values from these functions.

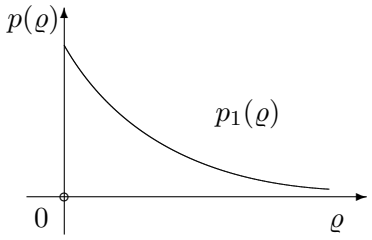


Figure 2.2: characteristic form of the depolymerization probability $p_1(\varrho)$

We will talk later about p_1 and p_2 in the section over the flux function, and in the numerics section we will give an explicit example for p_1 and p_2. Furthermore it is important to mention, that p_1 and p_2 only influence the local behavior, because they affect only two positions apart. This is important for the limit $n \to \infty$.

After the auxiliary step we incorporate polymerization. We assume that during one timestep one monomer is polymerized at the barbed ends of all filaments, so all other monomers and also the filament's end are shifted one position to the right.

$$r_j^{n+1} = r_{j-1}^{n+\frac{1}{2}}$$

These two processes together give:

$$\begin{aligned} r_j^{n+1} = r_{j-1}^n \quad &+ \quad p_2(r_{j+1}^n) r_{j+1}^n + p_1(r_j^n) r_j^n \\ &- \quad p_1(r_{j-1}^n) r_{j-1}^n - p_2(r_{j-1}^n) r_{j-1}^n \qquad j = 2, 3, \ldots \end{aligned} \tag{2.1}$$

If you change the order of polymerization and depolymerization the result r_j^{n+1} stays the same, so equation (2.1) is independent of the two processes' order.

In order to calculate r_j^{n+1} in equation (2.1) we have to know r_{j-1}^n, therefore it only holds for $j = 2, 3, \ldots$. This represents the absence of a boundary condition, or in other words a rule for r_1^n. We only know that, in each timestep each ending is moved one position to the right, but we have not defined yet what happens at $j = 1$. We will work on this matter later.

Now we will do some calculations with the expression (2.1). We subtract r_j^n at the left and right side and extend the right hand side. Then we divide both sides by Δt and extend the right hand side by Δx.

$$\begin{aligned} r_j^{n+1} - r_j^n = -(r_j^n - r_{j-1}^n) \quad &+ \quad p_2(r_{j+1}^n) r_{j+1}^n \overbrace{-p_2(r_j^n) r_j^n + p_2(r_j^n) r_j^n}^{=0} - p_2(r_{j-1}^n) r_{j-1}^n \\ &+ \quad p_1(r_j^n) r_j^n - p_1(r_{j-1}^n) r_{j-1}^n \end{aligned}$$

$$\begin{aligned} \frac{r_j^{n+1} - r_j^n}{\Delta t} = \quad &- \quad \frac{\Delta x}{\Delta t} \frac{(r_j^n - r_{j-1}^n)}{\Delta x} + \frac{\Delta x}{\Delta t} \frac{p_2(r_{j+1}^n) r_{j+1}^n - p_2(r_j^n) r_j^n}{\Delta x} \\ &+ \quad \frac{\Delta x}{\Delta t} \frac{p_2(r_j^n) r_j^n - p_2(r_{j-1}^n) r_{j-1}^n}{\Delta x} + \frac{\Delta x}{\Delta t} \frac{p_1(r_j^n) r_j^n - p_1(r_{j-1}^n) r_{j-1}^n}{\Delta t} \end{aligned}$$

We set $a := \frac{\Delta x}{\Delta t}$ the characteristical velocity of polymerization.

$$\begin{aligned} \frac{r_j^{n+1} - r_j^n}{\Delta t} = a \Big(\quad &- \quad \frac{(r_j^n - r_{j-1}^n)}{\Delta x} + \frac{p_2(r_{j+1}^n) r_{j+1}^n - p_2(r_j^n) r_j^n}{\Delta x} \\ &+ \quad \frac{p_2(r_j^n) r_j^n - p_2(r_{j-1}^n) r_{j-1}^n}{\Delta x} \\ &+ \quad \frac{p_1(r_j^n) r_j^n - p_1(r_{j-1}^n) r_{j-1}^n}{\Delta t} \Big) \end{aligned} \tag{2.2}$$

The idea now, is to make a so called homogenization limit: we let Δx and Δt tend to zero (the ratio between them is fixed $\frac{\Delta x}{\Delta t} = a$), but before this we introduce some other things.
For this technique we assume that r_j^n is the discretization of a sufficiently smooth (in x and t) function $\varrho(t, x)$, which is interpreted as the density of endings because r_j^n is the number of endings.

$$r_j^n = \varrho(n\Delta t, j\Delta x) = \varrho(t, x)$$

Then we can use the taylor expansion for rewriting r_j^{n+1}, r_{j-1}^n and r_{j+1}^n, also assuming that p_1 and p_2 are sufficiently smooth.

$$\begin{aligned} r_j^{n+1} &= \varrho(t + \Delta t, x) = \\ &= \varrho(t, x) + \Delta t \; \partial_t \varrho(t, x) + \mathcal{O}(\Delta t^2) \\ r_{j-1}^n &= \varrho(t, x - \Delta x) = \\ &= \varrho(t, x) - \Delta x \; \partial_x \varrho(t, x) \pm \mathcal{O}(\Delta x^2) \\ r_{j+1}^n &= \varrho(t, x + \Delta x) = \\ &= \varrho(t, x) + \Delta x \; \partial_x \varrho(t, x) + \mathcal{O}(\Delta x^2) \end{aligned}$$

We insert this in eqation (2.2), fix x and t, make the limit $\Delta t \to 0$ and $\Delta x \to 0$. During the limit we mind the following changes occur:

$$\begin{aligned}
r_j^n &\to \varrho(t,x) \\
\frac{r_j^{n+1} - r_j^n}{\Delta t} &\to \partial_t \varrho(t,x) \\
\frac{r_j^n - r_{j-1}^n}{\Delta x} &\to \partial_x \varrho(t,x) \\
\frac{p_2(r_{j+1}^n) r_{j+1}^n - p_2(r_j^n) r_j^n}{\Delta x} &\to \partial_x (p_2(\varrho(t,x))\varrho(t,x)) \\
\frac{p_2(r_j^n) r_j^n - p_2(r_{j-1}^n) r_{j-1}^n}{\Delta x} &\to \partial_x (p_2(\varrho(t,x))\varrho(t,x)) \\
\frac{p_1(r_j^n) r_j^n - p_1(r_{j-1}^n) r_{j-1}^n}{\Delta x} &\to \partial_x (p_1(\varrho(t,x))\varrho(t,x))
\end{aligned}$$

All in all we get the following equation for the density of the endings:

$$\begin{aligned}
\partial_t \varrho(t,x) = a\Big(&- \partial_x \varrho(t,x) + \partial_x (p_2(\varrho(t,x))\varrho(t,x)) + \\
&+ \partial_x (p_2(\varrho(t,x))\varrho(t,x)) + \partial_x (p_1(\varrho(t,x))\varrho(t,x))\Big)
\end{aligned}$$

So the number of endings r_j^n transforms into the density of endings $\varrho(t,x)$. We simplify the last expression and skip the dependencies of ϱ to get our final equation.

$$\partial_t \varrho = -\partial_x \Big(a\varrho\big(1 - 2p_2(\varrho) - p_1(\varrho)\big)\Big) \qquad \forall (t,x) \in (0,\infty) \times (0,\infty) \tag{2.3}$$

By definig the *flux function* $f(\varrho)$ we can rewrite (2.3) in a shorter way and in analogy to classic conservation laws.

$$f(\varrho) := \Big(a\varrho\big(1 - 2p_2(\varrho) - p_1(\varrho)\big)\Big) \tag{2.4}$$

$$\partial_t \varrho + \partial_x f(\varrho) = 0 \tag{2.5}$$

So this is the equation that governs the movement of our filament's endings.

2.2 The flux function

Now we take a look at the properties of the flux function $f(\varrho)$ from equation (2.4). The analysis of this funcion is essential for the understanding of the system's behavior.

Our original idea on p_1 and p_2 was, that they are decreasing as shown in figure 2.2. Their derivative should be negative and they should tend to zero for a high number of endings. With these properties for p_1 and p_2, simple considerations reveal that the flux function $f(\varrho)$ would have the shape shown in figure 2.3 with one inflection point at ϱ_i.

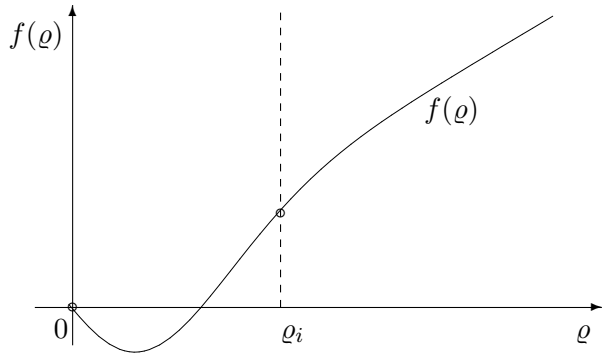


Figure 2.3: complete flux function

However, if we assume, that ϱ_i is very large compared to characteristic densities of the system, we would stay in the domain $0 \leq \varrho(t,x) < \varrho_i$ all the time. In this domain the flux function is convex, which helps us because the theory of convex flux functions is far better understood than non-convex ones.
So for the remainder of this work we assume that ϱ_i is large compared to characteristical ending densities, and therefore we only look at the domain, where the flux function is convex.

From this assumption together with considerations concerning p_1 and p_2 we derived postulations on f. A function $f(\varrho)$ that satisfies these postulations is an admissable flux function for our system. For the rest of this work we will only use f and skip using p_1 and p_2.
We postulate four properties for a function to be an admissable flux function,

and simply call these four properties $(* f)$:

$$(* f) \quad \begin{cases} f(\varrho) \text{ is smooth,} \\ f(\varrho = 0) = 0, \\ f(\varrho) \text{ has exactly one positive zero and} \\ \partial_\varrho^2 f(\varrho) > 0. \end{cases}$$

The second property is explained looking at the original derivation of the flux function in equation (2.4): the flux is zero, when the density is zero. The third is equal to $(1 - 2p_2(\varrho) - p_1(\varrho))$ having exactly one positve zero, and the last postulate yields the convexity. All together a flux function $f(\varrho)$ shall have the characteristic form seen in figure 2.4.

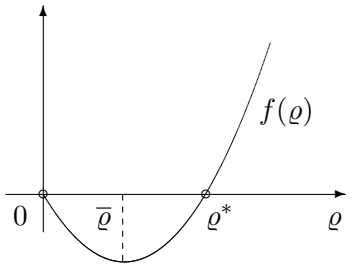


Figure 2.4: characteristic form of the flux function $f(\varrho)$

The crucial information that will be important for our system is included in this characteristic form of the flux function, therefore we only postulate the requirements on $f(\varrho)$ and skip p_1 and p_2. A flux function with the aforementioned properties will lead to the existence of a non-trivial steady state of our system.

From now on we call the positive zero ϱ^* and the density, where the minimum of the flux function occurs, $\overline{\varrho}$. It is clear that $\overline{\varrho} < \varrho^*$.

Our original considerations on this matter started with $p_1(\varrho)$ and $p_2(\varrho)$,and it turned out, that only the shape of $f(\varrho)$ is important. Our thoughts on this topic were, that for an increasing number of ϱ the probabilies $p_1(\varrho)$ and $p_2(\varrho)$ should decrease. This comes from the biological fact of a limited number of depolymerizing proteins at each point, like we have mentioned before. We will give an example for $p_1(\varrho)$, $p_2(\varrho)$ and $f(\varrho)$ later in this chapter.

So far we have only talked about the reasons for the characteristic shape of the flux function, but not its meaning. It is important to understand the mathematical properties for our further calculations.

The flux function (as seen in figure 2.4) shows that small densities ($0 < \varrho < \varrho^*$) have a negative flux, and big densities ($\varrho > \varrho^*$) have a positive flux. This tells us something about the transition of the endings.
The propagation speed of the densities is given by the derivative $f'(\varrho)$, so very small densities ($\varrho < \overline{\varrho}$) have a negative propagation velocity and middle to large densities ($\varrho > \overline{\varrho}$) have a positive speed.
For readers not used to these terms, this topic will be discussed thoroughly in the conservation law section of this chapter.

2.3 The initial and boundary condition

In the first chapter we have already made the assumption, that there is no filament of infinite length. This imposes some kind of boundary condition at $x = \infty$:

$$\varrho(t, \infty) = 0 \qquad \forall t \in [0, \infty)$$

2.3.1 The initial condition

Right now our model only consists of equation (2.5). It is incomplete, because it lacks side conditions.
At first we give an initial condition for our model, that represents the initial density of the endings.

$$\varrho(t = 0, x) = \varrho_0(x) \qquad \forall x \in [0, \infty) \tag{2.6}$$

The initial density ϱ_0 shall be piecewise smooth. An assumption we will also later impose on the solution.

2.3.2 The boundary condition

Next we will focus on the boundary $x = 0$, which represents the cell's leading edge where all the filaments begin. We have to explain what happens there in order to complete our model. We give this boundary condition so that our problem is well posed.

It turns out, that this boundary condition is highly non-trival and gathers a lot of knowledge. It was one of our main works on this model.
At first we present our idea behind the boundary condition, and then we will state it without further explanation.
At this point we are still missing knowledge about conservation laws to fully understand how the boundary condition exactly works. Its mechanism will be explained after the introduction to the conservation laws, because we will

use the information given there.

At this point we have a constitutive equation which describes the behavior of the actin filament endings in the interior of the cell. But how is this behavior regulated? Our main idea is the following:

- when the number of filaments is too small, new filaments should be nucleated at the boundary and
- when there are too many filaments, they system can evolve unconstrained.

So we want to control the system through the total number of filaments, which is reasonable according to the biological background.
But after stating this, immediately three questions arise:

- How does the boundary know about the interior of the cell? Mathematically and biologically?
- What is nucleation?
- What does unconstrained evolution mean in the first case and what happens in that case?

The first question is easily answered: We assume that all flaments start at $x = 0$. So at the cell's edge there is information present how many filaments exist in total, because each filament ending in the interior refers to a filament and has a corresponding beginning at the boundary. It is clear that the total number of endings is equal to the total number of filaments, therefore we do not have to distinguish between these two numbers.

With nucleation we mean an increase in the number of filaments. Our idea is, that new endings (=new filaments) are created at the boundary, and then travel inside the cell (=the filaments grow).
We actually assume there exist enough nuclei at the boundary $x = 0$ and they are only stimulated to grow into real filaments, because real nucleation has another time scale than polymerization.

The third question is a little bit more problematic. It will turn out, that in the case of too many filaments present, at first parts and then the whole density will start moving to the left. When travelling left an ending may cross the boundary $x = 0$, this means the corresponding filament is dissolved and the total number of filaments decreases.
The constitutive equation of $(*\varrho_{ponu})$ demands this behavior. The density with too many filaments will first move to the right a little, and then start moving to the left. Then the number of filaments decreases. We will explain

this behavior rigorously later.

So our approach seems very natural, because we have created some kind of regulating mechanism, which will work well:

- When the number of filaments is too high it decreases according to the constitutive equation and
- when it is too low we increase it by nucleation at the boundary.

For now we only state the boundary condition and explain its building parts according to our idea. After the conservation law introduction we will return to the boundary condition for a deeper analysis.

We start with the quantity we want to control: the total number of filaments, wich we will define as $m(t)$. As we recall this is equal to the total number of endings.

$$\begin{aligned} m(t) &:= \int_0^\infty \varrho(t,x)\mathrm{d}x \\ &= \text{total number of endings} \\ &= \text{total number of filaments} \end{aligned}$$

By definition $m(t)$ is equal to $\eta(t,0)$ which is indeed the number of total filaments.

What we do now is clear: we compare $m(t)$ to a refernce number of endings M. This gives the number of missing filaments, which has to be positive. Then we define the number of endings that shall be nucleated $\nu(t)$, in order reach the reference number, by scaling the aforementioned difference.

$$\begin{aligned} \nu(t) &:= \frac{\alpha}{a}\left(M - m(t)\right)_+ \\ &= \text{number of newly nucleated filaments} \\ M &:= \text{reference number of filaments} \\ \alpha &:= \text{growth factor} \quad ; \quad \alpha \in (0,1] \end{aligned}$$

Here a is the polymerization velocity from the derivation, and the growth factor α regulates the nucleation of new filaments, we assume α to be constant for simplification reasons, although other dependencies are conceivable. The small plus sign right under the brackets in the definition of $\nu(t)$ refers to the term's positive part.

So $\nu(t)$ gives the number of endings, that should be nucleated. But we encounter a problem here: When the present density of endings at the boundary is very low $\varrho(t,0) < \overline{\varrho}$ there is actually a negative flux that prevents

the new endings to enter the system. So new endings are only nucleated, when the nucleation dominates the outward flow. This seems natural but it is eventually very hard to describe mathematically, because the existing ending density at $x = 0$ may influence the nucleation of new endings.

We simply write down the possible cases and the reactions of the system at the boundary, respective the value of the ending density at the boundary. We refer to this boundary behavior as $\varrho(t,0) = \varrho_b(t)$, but this is just notation. The cases are true for every time $t \in [0, \infty)$.

$$\varrho_b := \begin{cases} 1. & \nu(t) \geq \varrho(t,0) > \overline{\varrho} & \Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0 \\ 2. & \nu(t) > \overline{\varrho} \geq \varrho(t,0) & \\ \quad a. & f(\nu(t)) > f(\varrho(t,0)) & \Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0 \\ \quad b. & f(\nu(t)) \leq f(\varrho(t,0)) & \Rightarrow \text{no boundary condition} \\ 3. & \overline{\varrho} \geq \nu(t) \geq \varrho(t,0) & \Rightarrow \text{no boundary condition} \\ 4. & \varrho(t,0) \geq \nu(t) > \overline{\varrho} & \Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0 \\ 5. & \varrho(t,0) > \overline{\varrho} \geq \nu(t) & \Rightarrow \varrho(t+\tau,0) = \overline{\varrho} \quad \tau > 0 \\ 6. & \overline{\varrho} \geq \varrho(t,0) > \nu(t) & \Rightarrow \text{no boundary condition} \end{cases}$$

(Note: For $t = 0$ you have to insert: $\varrho(t,0) = \varrho(0,0) = \varrho_0(0)$)
So we have not explicitly defined the boundary condition, rather implicitly. At every timestep we look at the present density at the edge $\varrho(t,0)$ and compare it with $\overline{\varrho}$ and $\nu(t)$, and decide how the system will react in the next instant.
The entry *no boundary condition* means, that the system can evolve unconstrained (we will use this term to refer to this state) according to the rules of conservation laws. We will see that in this case endings may only flow outwards and no lack of information occurs.

This exotic boundary condition yields, that new endings (=new filaments) are only really nucleated, when they dominate the outward flow.
This is a rather uncommon boundary condition, but it describes the desired mechanisms perfectly. After the conservation laws introduction we will return to the boundary condition to give further explanations and show that the problem is well posed.

2.4 The model

Now we hold on for a moment and recapitulate our findings. All in all we have equations (2.4), (2.6) and the boundary condition from the last section:

Complete polymerization and nucleation modell ($*\varrho_{ponu}$):

$$\begin{aligned} \partial_t \varrho + \partial_x f(\varrho) &= 0 && \forall (t,x) \in (0,\infty)^2 \\ \varrho(0,x) &= \varrho_0(x) && \forall x \in [0,\infty) \\ \varrho(t,0) &= \varrho_b(t) && \forall t \in (0,\infty) \end{aligned}$$

The flux function has properties according to section 2.2 and the boundary condition is defined in section 2.3.2. We will use ($*\varrho_{ponu}$.1) to refer to the constitutive equation of the model, ($*\varrho_{ponu}$.2) for the initial condition and respective ($*\varrho_{ponu}$.3) for the boundary condition.

For a better understanding we will use the expressions and definitions introduced in [10]. We look at the first equation of our system ($*\varrho_{ponu}$.1), and find, that it has the form of a *scalar conservation law*. By applying the derivative onto the flux function we get a slightly different notation. Since we postulated the smoothness of $f(\varrho)$ we are allowed to do this.

$$\partial_t \varrho + f'(\varrho)\partial_x \varrho = 0 \tag{2.7}$$

And this is the exact form of a *first order quasilinear partial differential equation*. For this type of equation, we will use the common method of characteristics for the analysis. In the next section this approach will be introduced thoroughly.
We mention here that the non-linearity of the problem comes from the flux function, and displays some kind of communication between the filaments.

Right now we want to explain why ($*\varrho_{ponu}$.1) is called a conservation law. This is because in interior of the domain, the mass (=sum of endings) is conserved, and new mass (=new endings) can only enter the system via its

boundaries. We see this by simply integrating the equation over the domain:

$$\begin{aligned}
\partial_t \varrho + \partial_x f(\varrho) &= 0 \qquad / \int_0^\infty . \, \mathrm{d}x \\
\int_0^\infty (\partial_t \varrho + \partial_x f(\varrho)) \, \mathrm{d}x &= 0 \\
\int_0^\infty \partial_t \varrho \, \mathrm{d}x + \int_0^\infty \partial_x f(\varrho) \, \mathrm{d}x &= 0 \\
\partial_t \int_0^\infty \varrho \, \mathrm{d}x &= -\int_0^\infty \partial_x f(\varrho) \mathrm{d}x \\
\partial_t \, m(t) &= -\underbrace{f(\varrho(t, x=\infty))}_{=0} + f(\varrho(t, x=0)) \\
\partial_t \, m(t) &= f(\varrho(t,0)) \qquad (2.8)
\end{aligned}$$

So the total number of endings changes according to the flux of the endings at the boundary $x = 0$. This is natural but we will draw a lot of conclusions from that later.

Before going furhter we want to mention, that ($*\varrho_{ponu}$.1) and (2.7) of course describe the same equation. We will use the form which suits our demands at best for the following analysis.

2.5 Introduction to conservation laws - Part 1

For the following analysis of our system and for a better understanding, we give an introduction to conservation laws. Hereby we follow the approach given in [10].

We start by applying the *method of characteristics* to our problem ($*\varrho_{ponu}$). The idea behind this method is simple: We want to convert our PDE into a system of ODEs. Suppose $\varrho(t, x)$ solves ($*\varrho_{ponu}$) and fix an admissable point (t, x). We would would like to calculate $\varrho(t, x)$ by finding some curve lying in the coordinate region, connecting (t, x) with a point $(0, x_0)$ and along wich we can compute $\varrho(t, x)$. Because we have an initial condition for time, we know $\varrho(0, x_0)$. We hope then to be able to calculate ϱ all along the curve, and so in particular at (t, x).

In this two dimensional case this procedure is equal to building the solution surface $\varrho(t, x)$ over the (t, x) plane out of space curves. The projections of these space curves to the (t, x) plane are the aforementioned connecting curves. This whole procedure is accomplished by trying to find a new parametrization (s, x_0) of the solution surface, where the space curves only depend on the parameter s and their starting point only depends on x_0.

Having this representation of the solution we could transform back to the original parameters, but this is not always possible in the general case. For further informations see [10].

Now we apply this method to our problem, but we exclude the boundary condition ($*\varrho_{ponu}.3$) at first and analyze its effect later. So our system consists of:

$$\begin{aligned} \partial_t \varrho + f'(\varrho)\partial_x \varrho &= 0 \\ \varrho(0,x) &= \varrho_0(x) \end{aligned} \tag{2.9}$$

We choose a new parametrization (s, x_0) for the solution surface $\varrho = \varrho(t,x)$ such that it is now described by the following equations: (We use $x = x(s,x_0)$, $t = t(s,x_0)$ and $\varrho(t,x) = \widehat{\varrho}(s,x_0)$)

$$\begin{aligned} \frac{\partial t}{\partial s} &= 1 \\ t(0,x_0) &= 0 \\ \frac{\partial x}{\partial s} &= f'(\widehat{\varrho}(s,x_0)) \\ x(0,x_0) &= x_0 \\ \frac{\partial \widehat{\varrho}(s,x_0)}{\partial s} &= 0 \\ \widehat{\varrho}(0,x_0) &= \varrho_0(x_0) \end{aligned} \tag{2.10}$$

Of course this system can be seen as a transformation of the original system via:

$$\frac{\partial \varrho(t,x)}{\partial s} = \frac{\partial \widehat{\varrho}(s,x_0)}{\partial s} = \frac{\partial \widehat{\varrho}}{\partial x}\frac{\partial x}{\partial s} + \frac{\partial \widehat{\varrho}}{\partial t}\frac{\partial t}{\partial s}$$

We start solving system (2.10) by solving the first equation using its initial condition.

$$\begin{aligned} \frac{\partial t}{\partial s} = 1 \Rightarrow t &= s + \text{const}(x_0) \overset{t(0,x_0)=0}{=} s \\ t &= s \end{aligned} \tag{2.11}$$

So s and t are equal. Next we switch to the last equation of the transformed system and its initial condition.

$$\begin{aligned} \frac{\partial \widehat{\varrho}(s,x_0)}{\partial s} = 0 \Rightarrow \widehat{\varrho}(s,x_0) &= \text{const}(x_0) = \widehat{\varrho}(0,x_0) = \varrho_0(x_0) \\ \widehat{\varrho}(s,x_0) &= \varrho_0(x_0) \end{aligned} \tag{2.12}$$

This is very interesting, since it shows that $\widehat{\varrho}$ and therefore ϱ is constant along the charcteristics, ϱ is independent of s and has the value of the initial

point $\varrho(0, x_0)$ along the characteristic.
Exactly spoken the space curves $(s, x(s), \varrho(x(s)))$ are called *characteristics* of the system, but we will also call their projections to the (t, x) plane characteristics.
At last we focus on the remaining equation

$$\begin{aligned} \frac{\partial x}{\partial s} &= f'(\widehat{\varrho}(s, x_0)) = f'(\varrho_0(x_0)) \Rightarrow \\ x &= f'(\varrho_0(x_0))s + \text{const}(x_0) \overset{x(0,x_0)=x_0}{=} f'(\varrho_0(x_0))s + x_0 \\ x &= f'(\varrho_0(x_0))s + x_0 \end{aligned} \tag{2.13}$$

We summarize or findings starting with the charcteristics. We simply insert (2.11) in (2.13) to get

$$x = f'(\varrho_0(x_0))\, t + x_0 \tag{2.14}$$

So the characteristics are straight lines in the (t, x) plane. They start at the value x_0 and have a slope of $f'(\varrho_0(x_0))$. So their slope depends on the density of the initial point $\varrho_0(x_0)$, and on the first derivative of the flux function. It is very important, that $f'(\varrho_0(x_0))$ can be interpreted as the velocity of the density, since the characteristics travel in x direction with this velocity.
Equation (2.12) yields that along characteristics ϱ is constant. So constant densities travel with the aforementioned velocity (see figure 2.5).

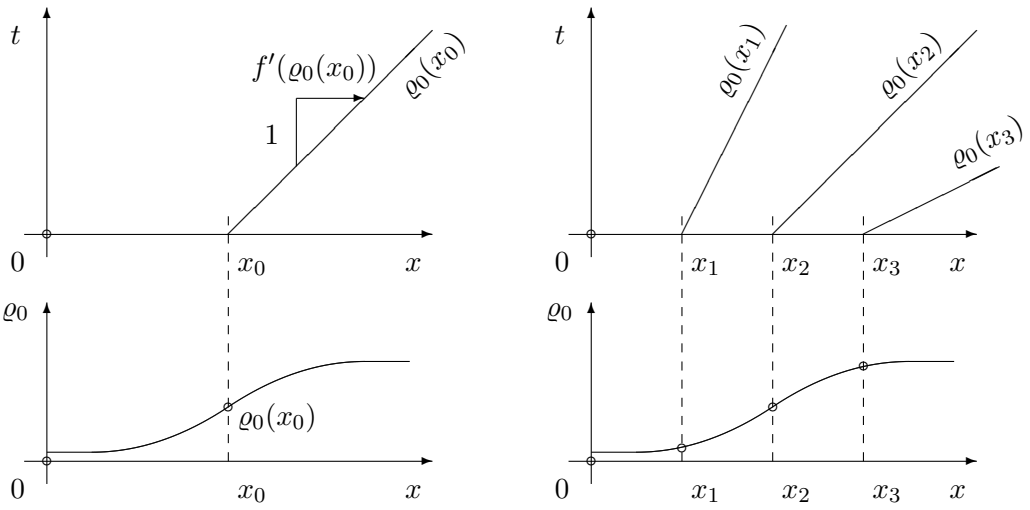


Figure 2.5: characteristics

These are some very important and useful informations, and we will keep them in mind.

We would like to transform $\widehat{\varrho}(s, x_0)$ back to have an explicit solution of the form $\varrho = \varrho(t, x)$, but this is not possible in the general case and also not possible for our setting. The only thing, we can achieve is an implicit representation of $\varrho(t, x)$ by rewriting (2.14) and using (2.12)

$$\begin{aligned} x_0 &= x - f'(\varrho_0(x_0))\, t \\ \varrho(t,x) &= \widehat{\varrho}(s, x_0) = \varrho_0(x_0) = \varrho_0(x - f'(\varrho_0(x_0))) = \varrho_0(x - f'(\varrho(t,x))) \\ \varrho(t,x) &= \varrho_0(x - f'(\varrho(t,x))) \end{aligned}$$

Altough this equation can not be solved in the general case, we have extracted a lot of information of system (2.10) so far, like the characteristics and that the densities are constant along them. We also know the propagation speed of the densities.

All our findings so far are only true as long as the characteristics with different densities do not intersect.
We recall the characteristic form of our flux function$f(\varrho)$ from figure 2.4. So the derivative of the flux function could have the form seen in figure 2.6 (left) and therefore intersections of characteristics are possible, see figure 2.6 (right).

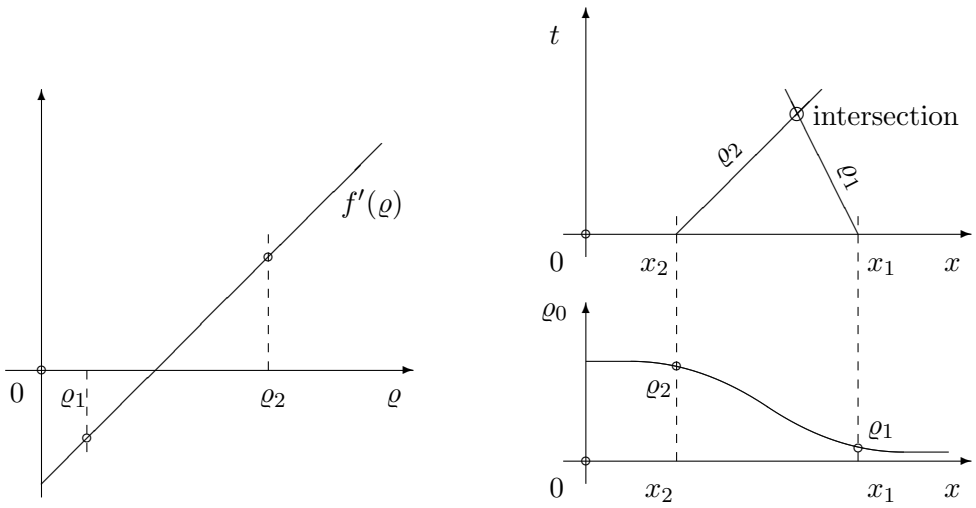


Figure 2.6: intersection of characteristics

Crossing characteristics: So it is possible for characteristics to intersect. Since (2.12) shows that ϱ is constant along the characteristics given in (2.14), an apparent contradiction arises. The resolution is that *our system* $(*\varrho_{ponu})$ *does not in general have a smooth solution, existing for all times* $t > 0$.

2.6 Introduction to conservation laws - Part 2

In this section we give a brief overview over chapter 3.4.1 in [10] and its most important facts in order to understand the most important properties of conservation laws. The facts we will give can be applied to general conservation laws and especially to our problem.

The result of the last chapter suggests, we must devise some way to interpret a less regular function ϱ "solving" our system. But the PDE (the constitutive equation from system 2.9)

$$\partial_t \varrho - f'(\varrho)\partial_x \varrho = 0$$

does not even makes sense, if ϱ is not differentiable. The idea is to multiply this equation by a smooth function v, integrate over the whole domain and use integration by parts, thereby transferring the derivatives onto v.
This kind of solution is called *integral solution*. We skip the details here and refer to [10] for further information.

From now on, we assume that ϱ has a simple structure: it is piecewise smooth. Then we can deduce another important fact for the integral solutions of conservation laws: *the velocity of a shock curve* σ, by the *Rankine - Hugoniot condition*:

$$\sigma = \frac{f(\varrho_l) - f(\varrho_r)}{\varrho_l - \varrho_r} \tag{2.15}$$

Here f denotes the flux function, ϱ_l means the limit of the density from the left and respectively ϱ_r from the right. Obviously the speed σ can vary according to the values of ϱ_l and ϱ_r (see figure 2.7).

We now try to solve a similar problem as shown in figure 2.7, now assuming ϱ_0 with $\varrho_l < \varrho_r$. At first this problem seems trivial. The Rankine Hugoniot condition applies and we get a shock curve. But we can construct another solution that satisfies the requirements for an integral solution too (see figure 2.8).

The right picture in figure 2.8 shows a *rarefaction wave*, where characteristics with all densities between ϱ_l and ϱ_r start. It is also an integral solution of our system.
Thus we see that integral solutions are not in general unique. Presumbly the class of integral solutions include various "nonphysical" solutions, which we want to exclude.

Entropy condition: To build a "physically correct" solution, we expect ϱ to be the limit of solutions ϱ^ε of an approximating solution. The idea is to

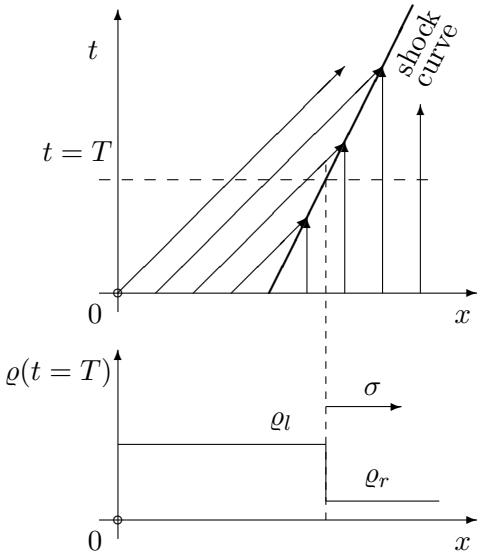


Figure 2.7: velocity of a shock curve

include a diffusion term in our system, let the diffusion tend to zero, and watch the behavior of the solution.

We say ϱ is an *entropy solution* of the system (2.9), if ϱ^ε solves

$$\begin{aligned} \partial_t \varrho + f'(\varrho)\partial_x \varrho &= \varepsilon \partial_x^2 \varrho \\ \varrho(0,x) &= \varrho_0(x) \end{aligned} \tag{2.16}$$

and ϱ^ϵ tends to ϱ in some sense.

$$\varrho^\varepsilon \overset{\varepsilon\to 0}{\longrightarrow} \varrho \qquad \text{a.e.}$$

For further details we refer to [10]. We also want to state that this kind of convergence is very hard to prove.
An entropy solution is sometimes also called viscosity solution, because the limit process is called viscosity limit.

This definition of a physical solution is somehow not useful. However it can be shown that this definition is equal to a definition reached from far simpler considerations:
We know that we typically encounter the crossings of characteristics and resultant discontinuities in the solution, if we move *forward* in time. But we can hope, that if we start at some point, some time $T > 0$ and go *backwards* in time along a characteristic, we will not cross any others. In other words, let us consider the class of, say, piecewise-smooth integral solutions of (2.9) with the property, that if we move backwards in t along any characteristic,

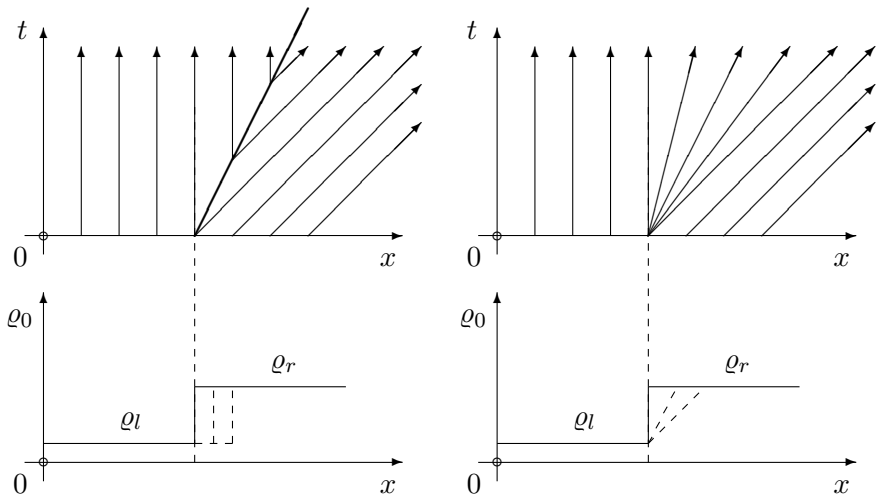


Figure 2.8: left: unnatural shock right: rarefaction wave

we will not encounter any discontinuities in ϱ.

This consideration together with the assumption that $f(\varrho)$ is uniformly convex (which is true since we postulated it) shows that *shocks* can only occur when the following is true:

$$\varrho_l > \varrho_r$$

When it is the other way round $\varrho_l < \varrho_r$, a rarefaction wave occurs. In the first case the propagation speed of a shock is limited by:

$$f(\varrho_l) > \sigma > f(\varrho_r)$$

This definition of a physically correct solution is much more usable than the first one, and because it is very important for us, we want to repeat it one more time:
When there is a discontinuity in ϱ with $\varrho_l > \varrho_r$ it propagates as a shock according to the Rankine-Hugoniot condition. From a discontinuity with $\varrho_l < \varrho_r$ a rarefaction wave emerges. This is a conclusion from the fact, that no new characteristics can spread from a shock.

2.7 The influence of the boundary condition

With the knowledge of the last two sections we are ready to cope with the boundary condition. We start by recalling the characteristic form of the flux function and the idea of the boundary condition:

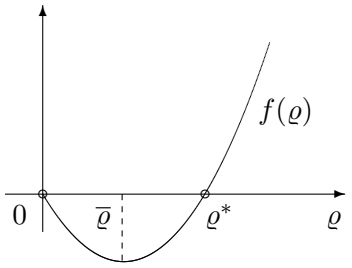


Figure 2.9: characteristic form of the flux function $f(\varrho)$

- When the number of filaments is too high, the system may evolve unconstrained,
- when it is too low we increase it by nucleation, but new filaments only enter when they dominate the outward flow.

What the first point means is clear now, we do not give any additional information and let the system evolve according to the theory of conservation laws. With the characteristic form of the flux function, characteristics with a negative slope ($f'(\varrho) < 0$), created from rarefaction waves or low densities, are possible. These will travel to the left over the boundary, and simply vanish there. During this process the total number of endings decreases.

We recall: When the characteristics do not cross, the speed of a density is $f'(\varrho)$. In the unconstrained case this is important, because the maximal possible value of the ending density at the boundary $\varrho(t, 0) \quad t > 0$ can only be $\overline{\varrho}$ (remember $f'(\overline{\varrho}) = 0$). This is clear, since lower densities ($\varrho < \overline{\varrho}$) have a negative speed and would travel to the left, and from the boundary no characteristics with higher density enter. So a characteristics with density $\overline{\varrho}$ exactly at the boundary would have no velocity, and therefore the boundary value would stay constant. (Note: In this case the flux is negative, and after some time, $\nu(t)$ would dominate the outward flow.)

The second point is also clear: Only when the newly generated endings $\nu(t)$ would enter the system, they are set as a boundary condition. This means, only if the new information from $\nu(t)$ has a positive speed, it is set

as boundary condition. So there are some points that have to be satisfied in order that $\nu(t)$ is set as a boundary condition:

- $\nu(t) > \overline{\varrho}$: The new endings shall have a positive speed.
- $\nu(t) > \varrho(t,0)$: The new endings shall have a higher density than the one present at the boundary in order for a shock to emerge. (The initial denisty is an exception here.)
- $\sigma = \frac{f(\nu(t)) - f(\varrho(t,0))}{\nu(t) - \varrho(t,0)} > 0$: The aforementioned shock shall have a positive velocity.

These are the requirements for new endings to really enter the system.

Now we recall the boundary condition from the section 2.3.2 and look at it under the viewpoint of the newly acquired knowledge:

1.	$\nu(t) \geq \varrho(t,0) > \overline{\varrho}$	$\Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0$
2.	$\nu(t) > \overline{\varrho} \geq \varrho(t,0)$	
a.	$f(\nu(t)) > f(\varrho(t,0))$	$\Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0$
b.	$f(\nu(t)) \leq f(\varrho(t,0))$	$\Rightarrow$ no boundary condition
3.	$\overline{\varrho} \geq \nu(t) \geq \varrho(t,0)$	$\Rightarrow$ no boundary condition
4.	$\varrho(t,0) \geq \nu(t) > \overline{\varrho}$	$\Rightarrow \varrho(t+\tau,0) = \nu(t+\tau) \quad \tau > 0$
5.	$\varrho(t,0) > \overline{\varrho} \geq \nu(t)$	$\Rightarrow \varrho(t+\tau,0) = \overline{\varrho} \quad \tau > 0$
6.	$\overline{\varrho} \geq \varrho(t,0) > \nu(t)$	$\Rightarrow$ no boundary condition

Case 1. is clear: the new endings dominate the outward flow and will have a positive velocity, the same is true for case 2.a., so $\nu(t)$ is set as boundary value. On the contrary in the cases 2.b., 3. and 6. the outward flow dominates or is equal to the new endings, so no action is taken, and the system can evolve unconstrained according to the theory of entropy solutions. Cases 4. and 5. cope with big initial densities at the boundary, but function exactly like the others.
So with the conservation law knowledge the boundary condition is just a triviality. Of course the cases of the boundary condition can change dynamically, but that reflects the nature of the system.

We want to highlight case 2a.: It shows that low ending densities are hindered from entrance, when there are nearly no other endings present. Thus, the presence of some endings promotes the growth of new ones. In biological terms, when the depolymerizing proteins deal with present endings, new

endings can be nucleated easier. All in all this can be seen as some entrance resistance.

We also want to give a graphic approach for the better understanding of the boundary condition through figure 2.10.

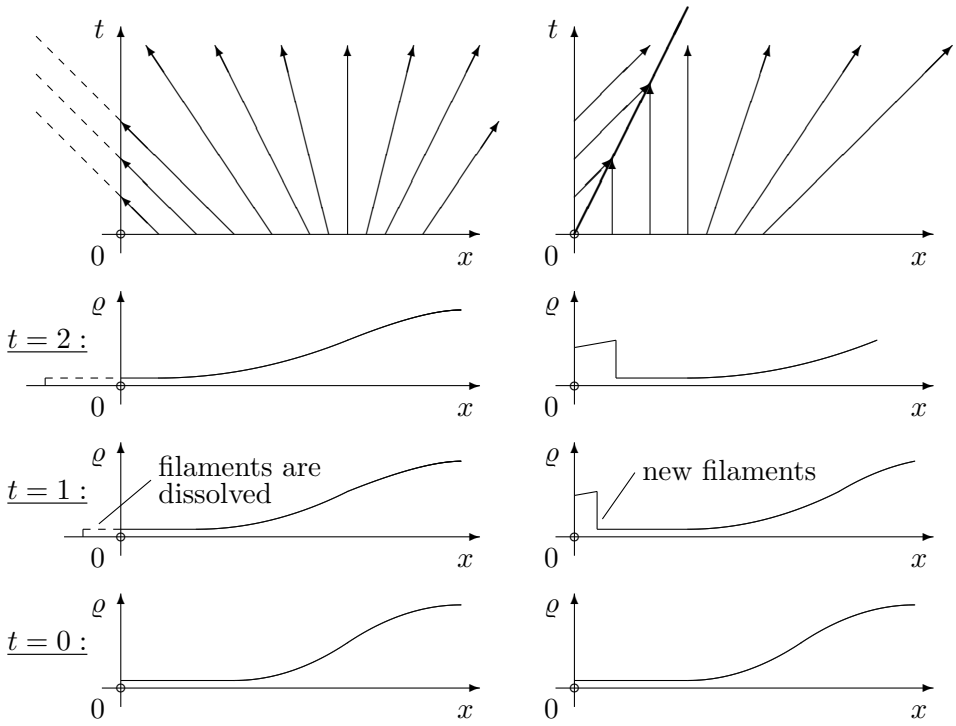


Figure 2.10: influence of the boundary condition

The left side of figure 2.10 shows the unconstrained state, the endings can travel to the left over the boundary and dissolve. The right side shows, when the total number of filaments is too low, new ones are nucleated and they really enter the system. Of course the distinction between the cases depends on the total number of filaments, not seen in these pictures.

2.8 Numerics

Now after having studied the basic properties of conservation laws we move further to the numerical simulations. We have seen that it is very unlikely to explicitly solve our system ($*\varrho_{ponu}$), so we aim at finding other means for the description of the system's behavior.

With the information of the last sections, we have a very good point to commence from. Through the characteristics we know how different densities move and we know about shocks and rarefaction waves. But even with this information it is hard to describe the evolution of the system. Therefore we will use numerical simulation to our aid. We will simulate different scenarios and look how the system evolves. We will compare this behavior with our previous findings and will draw important conclusions. The main goal of this section is to get information about the qualitative behavior of the system.

However, this task will not be easily accomplished, because the numerical simulation of partial differential equations is difficult. In our case we attempt to solve a non-linear (the flux function f is nonlinear) conservation law numerically. We will run into additional problems compared to linear equations, because the nonlinearity makes everything harder.
A very good introduction to the topic of numerical simulation of partial differential equations is [11]. For the simulation of conservation laws and especially their nonlinear versions we recommend [12]. We draw a lot of information from the second book.

For our simulations we take a very natural approach. We commence from our very first equation (2.1) and derive a numeric scheme according to our modeling approach.

$$\begin{aligned} r_j^{n+1} &= r_{j-1}^n + p_2(r_{j+1}^n)r_{j+1}^n + p_1(r_j^n)r_j^n - p_1(r_{j-1}^n)r_{j-1}^n - p_2(r_{j-1}^n)r_{j-1}^n \\ r_j^{n+1} &= r_j^n - r_j^n + p_2(r_{j+1}^n)r_{j+1}^n + p_1(r_j^n)r_j^n \\ &+ \underbrace{p_2(r_j^n)r_j^n - p_2(r_j^n)r_j^n}_{=0} + r_{j-1}^n - p_1(r_{j-1}^n)r_{j-1}^n - p_2(r_{j-1}^n)r_{j-1}^n \end{aligned}$$

$$\begin{aligned} r_j^{n+1} = r_j^n &- (r_j^n - p_2(r_{j+1}^n)r_{j+1}^n - p_2(r_j^n)r_j^n - p_1(r_j^n)r_j^n) \\ &+ r_{j-1}^n - p_2(r_j^n)r_j^n - p_2(r_{j-1}^n)r_{j-1}^n - p_1(r_{j-1}^n)r_{j-1}^n \end{aligned}$$

By defining the *numerical flux function* F

$$F(r_j^n, r_{j+1}^n) := r_j^n - p_2(r_{j+1}^n)r_{j+1}^n - p_2(r_j^n)r_j^n - p_1(r_j^n)r_j^n \tag{2.17}$$

we can rewrite the above equation into a much simpler form.

$$r_j^{n+1} = r_j^n - \Big(F(r_j^n, r_{j+1}^n) - F(r_{j-1}^n, r_j^n)\Big) \tag{2.18}$$

This is the exact from we need for applying a *conservative method* for numerical simulation of conservation laws (see [12]).
We define a time stepsize k and a space stepsize h, and are able to write down our numeric scheme according to the last equation.

$$r_j^{n+1} = r_j^n - \frac{k}{h}\Big(F(r_j^n, r_{j+1}^n) - F(r_{j-1}^n, r_j^n)\Big) \tag{2.19}$$

We will use this equation as our prime rule for our numerical simulations. In this context we see r_j^n as the density of endings at postion j at timestep n. $j = 1$ stands for the left boundary and the boundary condition is included in the definition of r_1^n. Furthermore, $n = 1$ represents time $t = 0$ and the initial condition is included via r_j^1.

A very important property of our numerical flux function is, that by setting the second argument of $F(r_j^n, r_{j+1}^n)$ to r_j^n we exactly get our original flux function. This is also a necessary condition for the applicability of this scheme.

$$F(r_j^n, r_j^n) = r_j^n - p_2(r_j^n)r_j^n - p_2(r_j^n)r_j^n - p_1(r_j^n)r_j^n = f(r_j^n)$$

We could have also used the normal flux function f instead of the numerical one in the simulations, meaning we could have simply rediscretized equation $(*\varrho_{ponu}.1)$.
Of course there exist a lot of other numerical schemes for conservation laws, including flow directions and so on, but our approach is very natural according to the derivation of the model and it yields qualitative good outputs.

In the simulations we do not use f directly, we take the original approach with p_1 and p_2 as the flux function's main building parts. We have used the following functions (see figure 2.11), according to the idea that they represent the probabilty for a one or two step depolymerization of a monomer.

$$\begin{aligned} p_1(\varrho) &:= e^{-0.0704\,\varrho}\,(1 - 0.6\,e^{-0.0704\,\varrho}) \\ p_2(\varrho) &:= 0.6\,e^{-0.1408\,\varrho} \end{aligned}$$

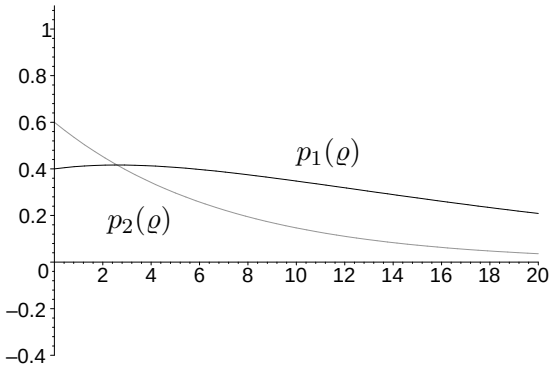


Figure 2.11: depolymerization probabilities $p_1(\varrho)$ and $p_2(\varrho)$

Thus the resulting flux function (see figure 2.12) is

$$\begin{aligned} f(\varrho) &= \varrho(1 - 2p_2(\varrho) - p_1(\varrho)) \\ f(\varrho) &= \varrho\Big(1 - 1.2\, e^{-0.1408\,\varrho} - e^{-0.0704\,\varrho}(1 - 0.6\, e^{-0.0704\,\varrho})\Big) \end{aligned}$$

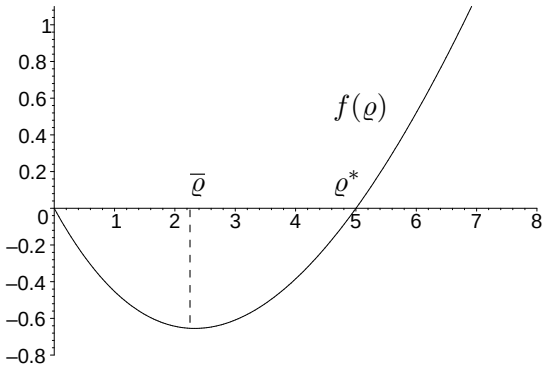


Figure 2.12: flux function $f(\varrho)$

Because we use the original derivation of the flux function, our densties have to stay under $\varrho_i = 25,62$ in the simulations. We have to check two conditions to ensure this: $\frac{\alpha}{a} M < \varrho_i$ and $\varrho_0(x) < \varrho_i \,\forall\, x$. And both conditions are satisfied.
The positive zero of this flux function is

$$\varrho^* = 5.00$$

The minimum of the flux function is at

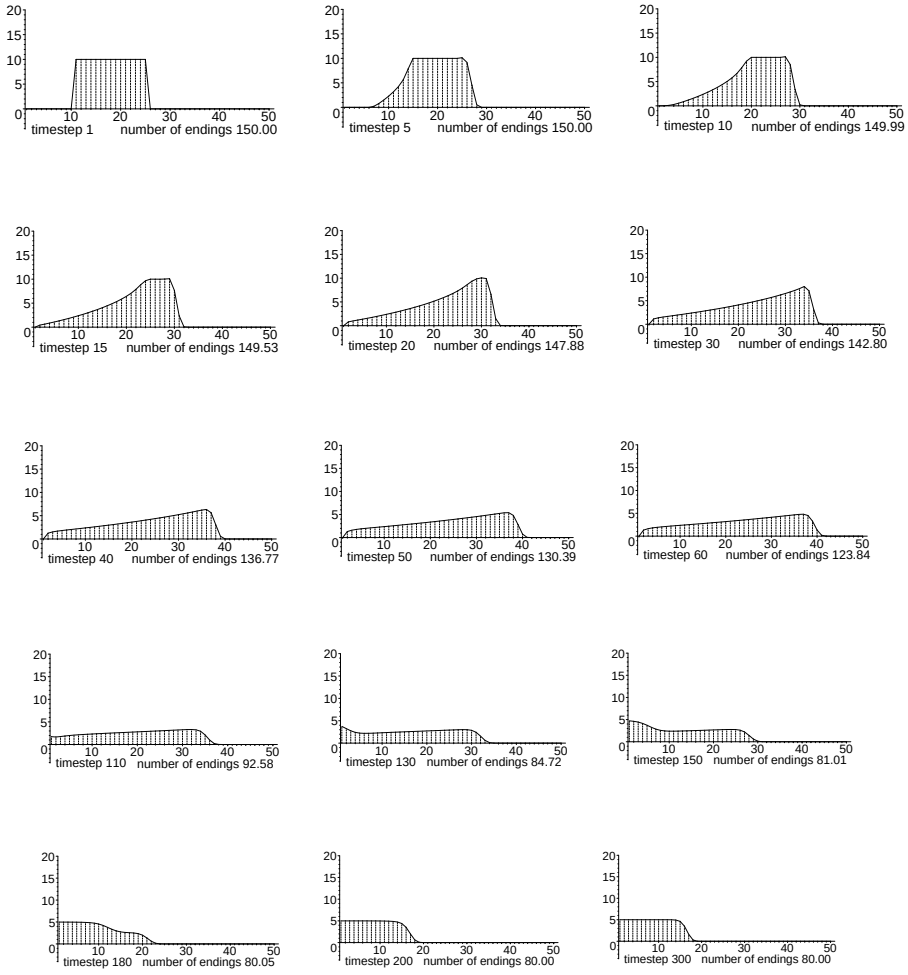
$$\overline{\varrho} = 2.23\,.$$

We could also prescribe a flux function, instead of starting with p_1 and p_2, but then we could have to adapt our numerics scheme, because it is derived from the original modeling approach.

2.8.1 Experiment 1

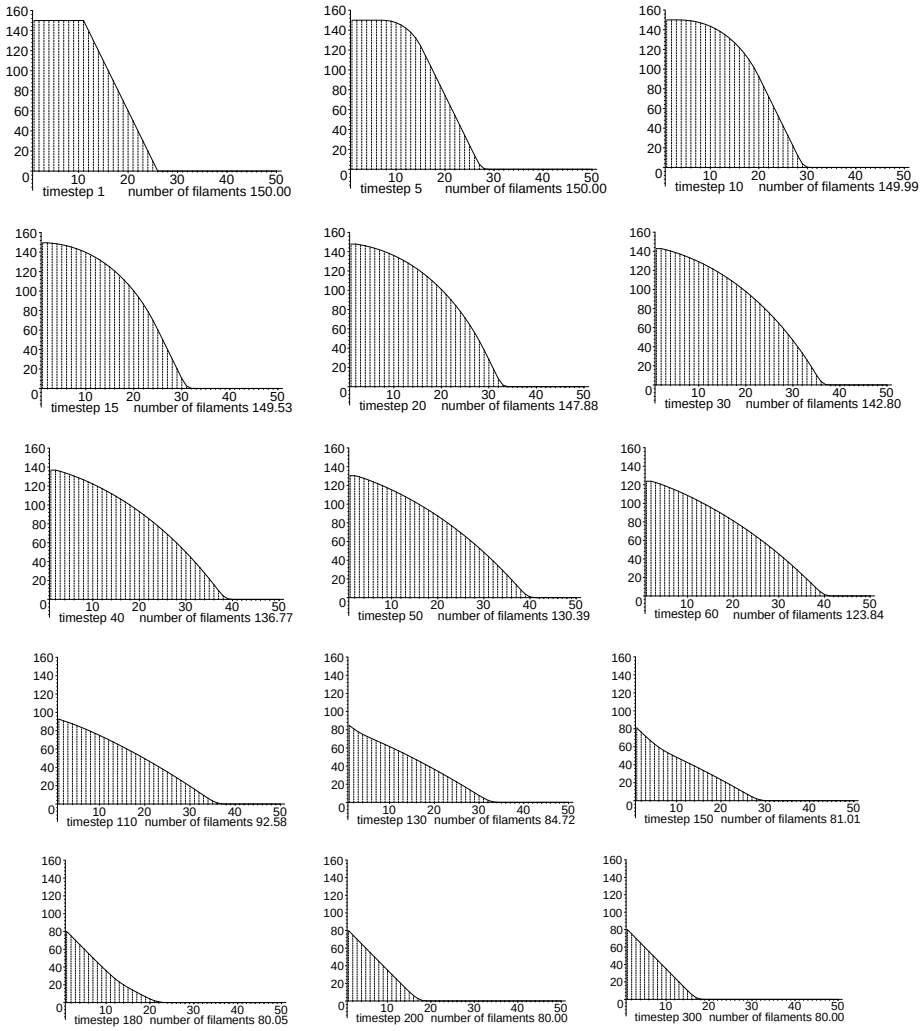
We have a simple initial condition: $\varrho = 0$ everywhere, except between $j = 10$ and $j = 25$, where the density is $\varrho = 10$. We want to know how this simple initial condition evolves.
The parameters used are: $h = 0.1$ (space stepsize), $k = 0.1$ (time stepsize), $a = 1$ (polymerization velocity), $\alpha = 0.25$ (growth factor) and $M = 100$ (reference number of endings/filaments).

Evolution of the endings



In the following we show the temporal evolution of the filament density. The pictures dircetly correspond to the ending densities on the left, the connection is explained on the next page.

Evolution of the filaments



At first we explain the given figures:
On the left page we have the temporal evolution of the ending density. Each picture represents the density of the endings at a given timestep. Exactly spoken the values of r_j^n are depicted, which are the discretization of $\varrho(t,x)$ according to our modeling.
The main goal of this work is a model for the filament density and therefore we also show the filament density (on the right page) corresponding to the ending density seen on the left. We depict the number of filaments k_j^n, which are seen as the discretization of $\eta(t,x)$, derived from the number of endings via

$$k_j^n := \text{number of filaments at point } j \text{ at timestep } n \ = \sum_{i=j}^{N} r_i^n$$

This connection is analog to the relation between ϱ and η:

$$\eta(t,x) = \int_x^\infty \varrho(t,y)\,\mathrm{d}y$$

The x-axis of each picture is the common x-axis of our modeling approach. The caption of the axis refers to the number j of the intersection points. We remember, we have discretized the x-axis into equal parts of length Δx and started numerating these points with $j = 1, 2, 3, \ldots$. The boundary $x = 0$ is represented by the point $j = 1$, the first point to the left.
The y-axis of the shown pictures gives the value for the ending (respective the filament) density.

For the evolution of the system we have arranged the pictures according to their temporal structure. We start with timestep $n = 1$ showing the initial condition and commence with increasing time step number, left to right, top to bottom. The number of the timestep is written left under the densities. Also the total number of endings, which is equal to the total number of filaments, is displayed right under each picture.

Observations from experiment 1

We focus on the ending density, because it is the main building part of our modeling approach. The filament density is a byproduct of our calculations and just shown for clarification.

First, we clearly notice the formation of a shock at the right of the ending density, and also a rarefaction wave at the left side. This is in very good accordance with our findings from the conservation laws. The form of the shock on the right side is blurred by the numerics.

We also observe there exist two distinct phases:
In the first phase the system evolves unconstrained. At the beginning the total number of filaments is greater than the reference number $m(t) > M$. The plateau travels to the right and decreases in width. Then it completely vanishes and the remaining peak keeps travelling to the right, loosing height in the process.
Meanwhile the rarefaction wave to the left hits the boundary and endings start flowing over the boundary. This means filaments are dissolved and so the total number of filaments decreases.

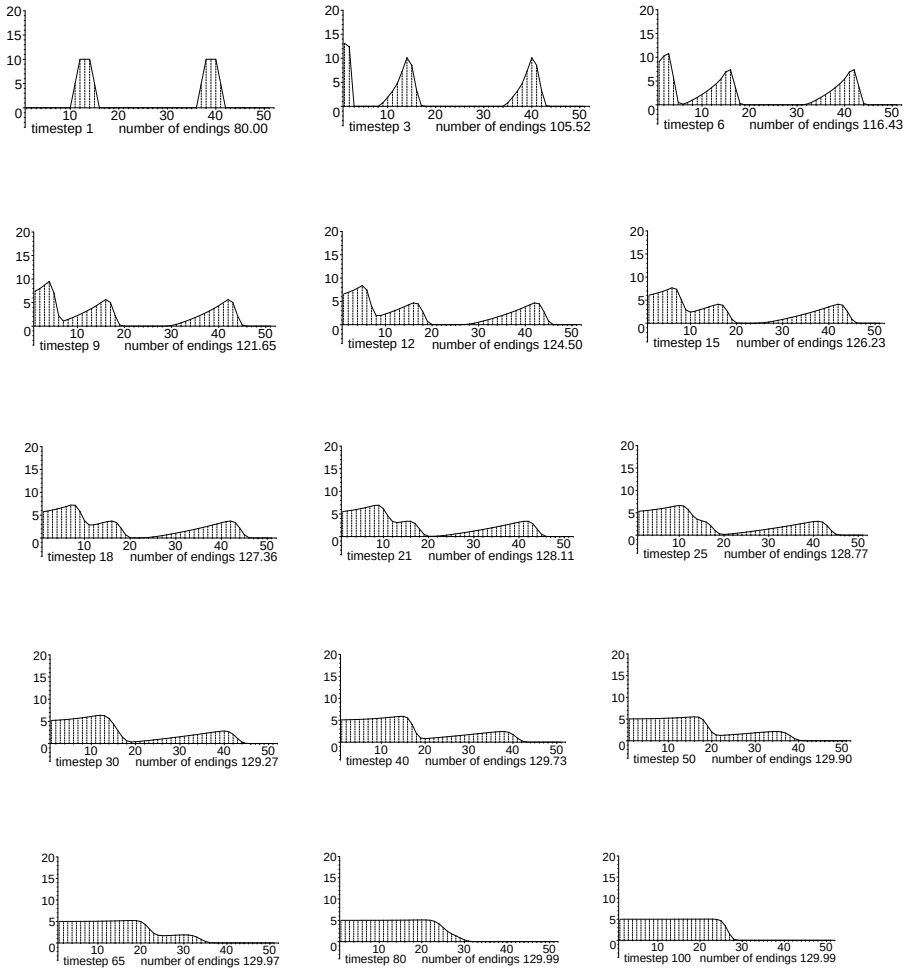
The number of filaments is strictly decreasing, reaching the point when $m(t) = M$ and the nucleation of new filaments begins. Because the outward flow of the system is still stronger, it dominates over the nuleation and the filament number is decreasing unperturbed.

On a certain point the nucleation starts dominating the outward flow, this is the beginning of the second phase:
A right travelling wave emerges, and this wave balances the whole density as it moves to the right. The number of filaments is decreasing very slowly now and the number of nucleated endings rises accordingly.
After some time a uniform distribution of the ending density settles, which is stationary.

It seems that the ending density converges to a stationary steady state with a formidable simple form. In this form the nucleation and the outward flow seem to chancel each other, also the shock to the right is stationary. Furthermore the balanced number of filaments is not the reference number, it is lower.

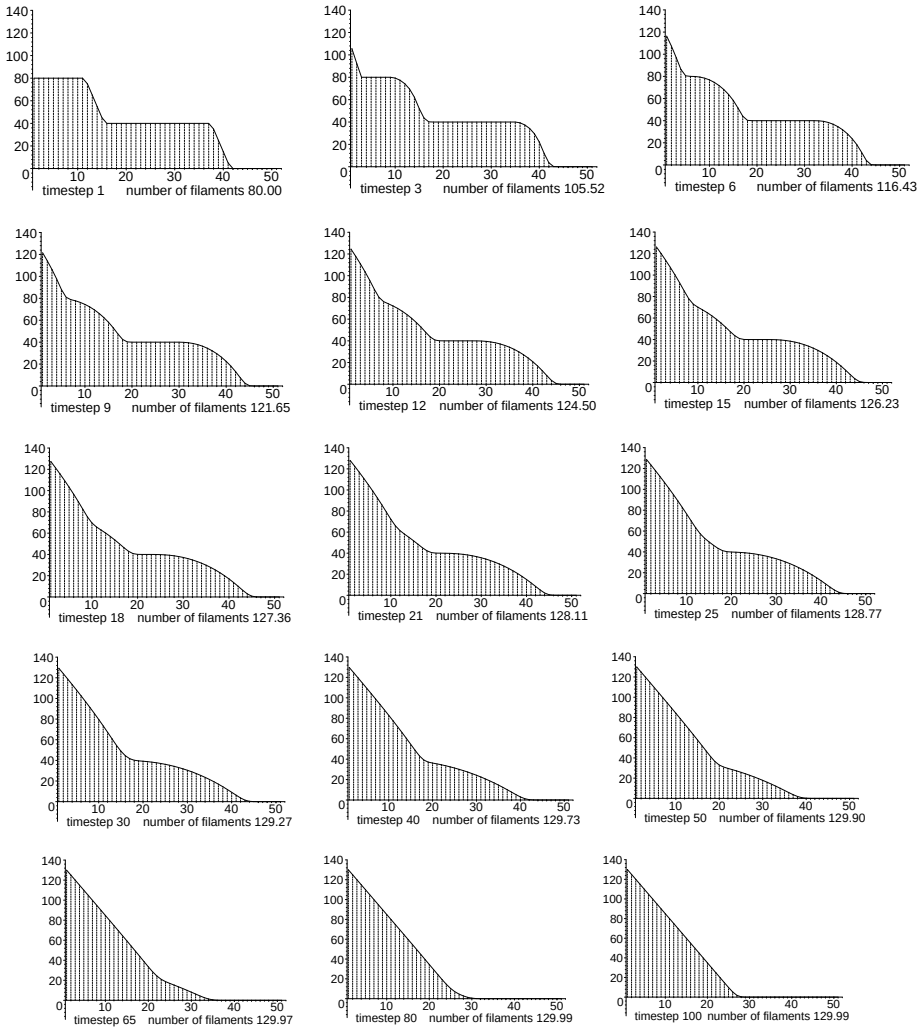
2.8.2 Experiment 2

Also in experiment 2 we have a rather simple initial condition. Two aggregations of endings, with a steep slope. At the top they have a density of $\varrho = 10$, otherwise no endings. Will we observe a similar behavior as in experiment 1?
The parameters used are: $h = 0.1$, $k = 0.1$, $a = 1$, $\alpha = 0.15$ and $M = 150$.
Evolution of the endings



Evolution of the filaments

Analog to experiment 1 we present here the filament densities corresponding to the ending densities to the left.



Observations from experiment 2

Here not enough filaments are present from the beginning, this is the most important difference to experiment 1. So new filaments are nucleated right from the start. Because a large number of filaments is missing, a large number of filaments is nucleated. These new endings emerge in a wave from the boundary.

Meanwhile the two endings aggregations move, a shock-like shifting to the right and a rarefaction wave to the left. They are behaving similarly to the mass in experiment 1. The two peaks move to the right losing height in the process.
The nucleation wave from the boundary also moves to the right, its front decreasing in height and starting to devour the first peak.
The mass is constantly increasing and so the number of newly nucleated filaments sinks at the boundary. But it is still large enough to transport the whole nucleation wave to the right.

As the time passes the nucleation wave flattens and its front is only slightly higher than the rest.
The first aggregation is incorporated into the wave from the left. The right one has flattened out and starts moving to the left, we have seen this behavior in another scale from the big mass in experiment 1.

Eventually the nucleation wave devours the remaining parts of the second aggregation and balances itself in a uniform stationary distribution. We have seen this shape in experiment 1, although its evolution was different.

So we guess there exists a unique stationary density, where our system converges to. Of course we did a lot of other simulations not shown here, all confirming this conjecture.
By comparing the results of experiment 1 and 2 we see, that this stationary distribution has a value near the zero of our flux function. But they differ in the length of the distribution. Furthermore, we have to investigate the stationary number of filaments.

2.9 Analysis of the system

In this section we want to analyze the behavior of our polymerization and nucleation model, using our gathered knowledge and findings.

Initially we want to state that there exists a steady state for the ending

density. Further we will use this to show that the system will converge to this steady state. All the proofs will be heuristic and not rigorous. However, we will state an idea how everything can be done exactly.

2.9.1 The steady state

The numerical experiments from the last section suggest that there exists a steady state for the ending density. Now we will show the derivation and the properties of this steady state.

We start by recalling the constitutive model equation ($*\varrho_{ponu}.1$):

$$\partial_t \varrho + \partial_x f(\varrho) = 0$$

A steady state solution means $\partial_t \varrho = 0$ and there are no changes in the density any more. For a conservation law equation and its theory the flux therefore has to be zero. According to the characteristic shape of our flux function (see figure 2.4) we have two values for ϱ where the flux is zero:

$$f(\varrho = 0) = 0 \quad \text{and} \quad f(\varrho = \varrho^*) = 0$$

We assumed that our solutions should be piecewise smooth functions, so we can actually build a density function with interchanging values of $\varrho = 0$ and $\varrho = \varrho^*$ with flux zero all over the distributionThe only. But due to the occurence of shocks and rarefaction waves, such functions would not be stationary. There actually exists only one stationary shape of a density in time, it has the following form:

$$\varrho(x) = \begin{cases} \varrho^* & \text{for } x \in [0, L] \\ 0 & \text{for } x \in (L, \infty) \end{cases}$$

The shock at the right end of this distribution is stationary since the Rankine - Hugoniot condition states

$$\sigma = \frac{f(\varrho^*) - f(0)}{\varrho^* - 0} = 0$$

The only remaining question is, what is the value of L? Of course, the first guess would be $L = M/\varrho^*$, so that the area under the density (=total number of fialments) would be M, the reference number of filaments. But then $\nu(t)$ would be zero, and in the next instant a rarefaction would emerge.

So we also have to guarantee the stability state at the boundary. The simplest solution to this is that the newly nucleated filaments are equal to the

prevailing density in the domain $\nu(t) = \varrho^*$. Simple calculations reveal that therefore the number of filaments has to be constant at a distinct value.

$$\begin{aligned} \nu(t) = \frac{\alpha}{a}\left(M - m(t)\right)_+ &= \varrho^* \\ m(t) &= M - \frac{a}{\alpha}\varrho^* \\ m_\infty &:= M - \frac{a}{\alpha}\varrho^* \end{aligned}$$

We call this the *equilibrium number of filaments*, and observe that it is always lower than M. So when this number of filaments m_∞ is present, our boundary value is equal to the desired value $\nu(t) = \varrho(t,0) = const. = \varrho^*$. So we can calculate L over the area under the density distribution to match m_∞

$$L = \frac{M}{\varrho^*} - \frac{a}{\alpha}$$

So all in all we get the following steady state distribution, which will stay constant at all times. All other conceivable distributions are not stationary, but this one is.

$$\varrho_\infty(x) := \begin{cases} \varrho^* & \text{for } x \in \left[0, \frac{M}{\varrho^*} - \frac{a}{\alpha}\right] \\ 0 & \text{for } x \in \left(\frac{M}{\varrho^*} - \frac{a}{\alpha}, \infty\right) \end{cases} \tag{2.20}$$

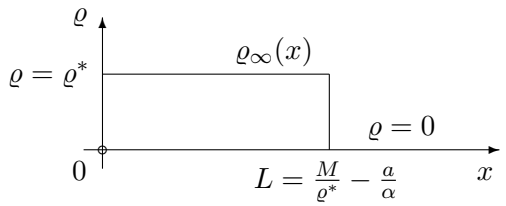


Figure 2.13: characteristic form of the steady state density ϱ_∞

Of course, inserting (2.20) in $(*\varrho_{ponu})$ shows that is indeed a solution.
It is very interesting that the number of filaments does not tend to the refernce number M, but to the equilibrium number m_∞. And we want to mention one more time, when this number is present it does not change any more. We recall equation (2.8):

$$\partial_t m(t) = f(\varrho(t,0)) = f(\varrho^*) = 0 \quad \Rightarrow \quad m(t) = \text{const.} = m_\infty$$

So everything fits perfectly, because the steady state observed in our numerical simulations matches the one from theoretical considerations.
We are quite clear that this is the only steady state and hope that the absence of a rigorous proof is made up by the arguments we have given.

2.9.2 Convergence to the steady state

In the last section we have shown the existence of a steady state $\varrho_\infty(x)$ for our system $(*\varrho_{ponu})$, and of course now we want to show the convergence to this steady state. Like in the previous section we give heutistic arguments for the convergence rather than a rigorous proof.
We divide our argumentation in two cases depending on the total mass, because the total mass influences the density at the boundary and therefore regulates the flux via equation (2.8).

1. $m(t=0) \leq m_\infty$
2. $m(t=0) > m_\infty$

The first case is when the starting number of filaments is smaller than the equilibrium number, in the second case it is greater. We will need this simple calculation later:

$$\begin{aligned} m(t=0) &\leq m_\infty \\ \big(M - m(t=0)\big) &\geq \big(M - m_\infty\big) \\ \underbrace{\frac{\alpha}{a}\big(M - m(t=0)\big)_+}_{=\nu(0)} &\geq \underbrace{\frac{\alpha}{a}\big(M - m_\infty\big)_+}_{=\varrho^*} \\ \nu(0) &\geq \varrho^* > \overline{\varrho} \end{aligned} \tag{2.21}$$

First case: $m(t=0) \leq m_\infty$
So the starting number of filaments is lower than the equilibrium number. The shown calculation (2.21) yields, that instantly new filaments are nucleated, and this keeps going on.

$$\begin{aligned} \nu(t) = \varrho(t,0) &\geq \varrho^* > \overline{\varrho} \\ \Rightarrow \partial_t m(t) &= f(\varrho(t,0)) \geq f(\varrho^*) = 0 \end{aligned}$$

The number of filaments $m(t)$ rises to the equilibrium number of filaments m_∞ and accordingly the newly generated filaments $\nu(t) = \varrho(t,0)$ decrease to ϱ^*. This behavior represents the solution of the following ODE, derived from equation (2.8) and the boundary condition:

$$\begin{aligned} \partial_t m(t) &= f(\varrho(t,0)) = f(\nu(t)) = f(\frac{\alpha}{a}\,(M - m(t))) \\ \partial_t m(t) &= f(\frac{\alpha}{a}\,(M - m(t))) \\ m(0) &= m_0 \end{aligned} \tag{2.22}$$

This behavior is exactly what we observed in numerical experiment 2: The filament number gradually rose to the equilibrium number, while the boundary value dropped to ϱ^*. When these points were reached, they stayed fixed and the remaining density evolved into the equilibrium density $\varrho_\infty(x)$.

This is exactly what happens in the analytical system, although the exact values won't be reached that quickly: as the filament number and the boundary value evolve, the characteristics from the newly nucleated endings produce a shock wave that propagates inwards. Commencing from the boundary, these characteristics gradually change the existing ending density into the equilibrium density $\varrho_\infty(x)$.

When the starting number of filaments is equal to the equilibrium number, the boundary value of ϱ^* will stay exactly fixed, and the same things as mentioned before will occur. So this is a special case of the aforementioned considerations.

All in all this is a very strong result, and it seems that the boundary condition alone regulated the whole density to the steady state. So in the first case the convergence to the steady state is clear.

Second case: $m(t=0) > m_\infty$
In this case our total number of filaments is larger than the equilibrium number, and in analogy to (2.21) we derive that for this case the number of filaments keeps decreasing.

$$\begin{aligned} m(t=0) &> m_\infty \\ \big(M - m(t=0)\big) &< \big(M - m_\infty\big) \\ \underbrace{\frac{\alpha}{a}\big(M - m(t=0)\big)_+}_{=\nu(0)} &< \underbrace{\frac{\alpha}{a}\big(M - m_\infty\big)_+}_{=\varrho^*} \\ \nu(0) &< \varrho^* \end{aligned}$$

So the density at the boundary after the starting time is either given by a small number of nucleation or the unconstrained evolution of the existing endings. And this does not change in a short time intervall. In the unconstrained case we recall from the section over the boundary condition's influence $\varrho(t,0) \leq \overline{\varrho} < \varrho^*$. So in either case the boundary value is lower than ϱ^*:

$$\begin{aligned} \varrho(t,0) &< \varrho^* \\ \Rightarrow \partial_t m(t) &= f(\varrho(t,0)) \begin{cases} < 0 & \text{for} \quad 0 < \varrho(t,0) < \varrho^* \\ = 0 & \text{for} \quad \varrho(t,0) = 0 \end{cases} \end{aligned}$$

Hence the number of endings is decreasing as long as the boundary value is greater than zero, and the filament number is larger than the eqilibrium number. In this case the filament number does not constantly decrease, e.g. when the boundary density is zero. The decline in the filament number depends on the evolution and the positions of the existing ends in the domain.

So far we have seen that $\partial_t m(t) = f(\varrho(t,0)) \leq 0$ is true for this case. The problem is when there is an equal sign in this equation and stays during the evolution, because then the filament number would not decrease. This would be the case when no mass would travel to the left and when no endings would flow over the boundary. But this is not possible, because the constitutive equation guarantees that after some time all endings will be dissolved.
In numerical experiment 1 we have seen that the starting mass is transported to the right at the beginning. But after some time the peaks decrease in height and all endings start travelling to the left, so eventually all endings would dissolve, if there would be no nucleation boundary condition.
This is in perfect accordance with conservation law theory. The characteristics from the initial condition have a velocity according to their density, so high densities have a positve velocity at first. But after crossing the zero characteristics from the right (remember density $\varrho = 0$ has a negative velocity according to our characteristic flux function shape $f'(0) < 0$) they vanish, and the velocity from the remaining characteristics gets less and less.
From the biological point of view it is also very reasonable. A high density of endings would mean a large number of filaments with equal length, and according to the idea of p_1 and p_2 their depolymerization probability would be very low. But as they grow longer in each step, their number decreases gradually. After their number has shrunken far enough, they depolymerize normally.

So the number of endings really decreases after some time. We again refer to numerical experiment 1 as a very good example: At first the endings move to the right, but eventually their number gets lower and lower. At some point the nucleation starts, but the net number of filaments is still decreasing. Commencing from the boundary a wave flattens out the whole distribution while the boundary value rises to ϱ^* and the number of filaments sink to the eqilibrium number.

Depending on the initial conditions, the decrease of the number of filaments can be rather unsteady, but it happens.
Altough this behavior is not as nice as in case 1, it is exactly what we wanted and is in perfect accordance with the idea of our boundary condition. The number of filaments is controlled, but the true equilibrium number is be-

low the reference number we gave at first. Summing up, in either case the

ending density converges to the equilibrium density. We did not prove ths rigorously, but we explained the underlying ideas extensively. Altough we have said nothing about the velocity and the type of the convergence this is very interesting.

We want to conclude this section by stating that the boundary condition has a very strong influence on the system. Our idea was that it regulates the number of filaments, and it really accomplishes this task. The system behaves according to our wishes.

2.10 Viscosity limit

So far we have described the behavior of the system with arguments, not rigorous proofs. As we have noted proving something in this setting of a non-linear conservation law with a non-standard boundary condition is somehow complicated. However, we have a good idea how this could be done.

Commencing from the idea of entropy solutions (see equation (2.16)), we imagine our system $(*\varrho_{ponu})$ to be the limit of a system disturbed by a diffusion term. We call the new disturbed system $(*\varrho_{diff})$:

$$\begin{aligned} \partial_t \varrho + \partial_x f(\varrho) &= \varepsilon\, \partial_x^2 \varrho \\ \varrho(0,x) &= \varrho_0(x) \\ \varrho(t,0) &= \underbrace{\frac{\alpha}{a}\left(M - \int_0^\infty \varrho(t,x)\mathrm{d}x\right)_+}_{=\nu(t)} \end{aligned}$$

The system is similar to $(*\varrho_{ponu})$ except the diffusion term and the boundary condition.
The idea now is to let ε tend to zero, this limit is called the *viscosity limit*.

The problem now is, that you have to do this limit for the whole system. You do not simply solve the system and make the limit $\varepsilon \to 0$ in the solution. So you have to check that the constitutive equation, the boundary condition, the initial condition and the solution itself tend to their counterparts in $(*\varrho_{ponu})$.

This is a highly non-trivial problem, because the convergence itself is not clear, nor its type of convergence. Even for our main problem $(*\varrho_{ponu})$ we have not rigorously given the corresponding function spaces, and for the

extended problem as mentioned here this problem gets worse, because you have to include this in the convergence proofs.

This whole technique is used, because the first equation in the system $(*\varrho_{diff})$ is a parabolic equation, and in general parabolic equations are far better understood than hyperbolic equations (where our main problem belongs to). The idea is to use this knowledge and then return to the original problem.

2.10.1 Boundary layer

The idea of the viscosity limit is very natural and at first sight the convergence should work in some way. The most apparent difference between the two systems is in the boundary condition of $(*\varrho_{diff})$, because it reads $\varrho(t,0) = \frac{\alpha}{a}\left(M - \int_0^\infty \varrho(t,x)\mathrm{d}x\right)_+$. So in this setting $\nu(t)$ is set as boundary value all the time. But how does that work, when in the original system also other boundary values are possible?

In the limit process $\varepsilon \to 0$ drastic changes in ϱ near the boundary are possible. This behavior is called a *boundary layer* process. With this we are able to cope with the different boundary values in our systems.

Such a difference occurs in two cases:

$$\begin{aligned} &1. \quad \nu(t) = \varrho(t,0)_{\text{diff}} \;<\; \varrho(t,0)_{\text{ponu}} \quad (\leq \overline{\varrho}) \\ &2. \quad \nu(t) = \varrho(t,0)_{\text{diff}} \;>\; \varrho(t,0)_{\text{ponu}} \end{aligned}$$

The first case represent the situation, when mass is flowing out, but there is no or not enough nucleation (because the filament number is still high enough). And the second case can be an example for point 2.b. from our $(*\varrho_{ponu})$ boundary condition when the number of newly nucleated filaments would be too low to actually enter the system.

We show how this works only for the first case, the second works similarly. Without loss of generality we asume, that $\nu(t) = 0$ and $\varrho(t,0)_{\text{ponu}} = \varrho_r \leq \overline{\varrho}$ $(\varrho_r > 0)$, so there is a difference in the boundary values of the two systems. We want to produce a situation as shown in figure 2.14 with our density ϱ in the limit $\varepsilon \to 0$. ϱ varies drastically in a short change of x, therfore we introduce a variable that describes this fast change.
We start with the constitutive equation of $(*\varrho_{diff})$

$$\partial_t \varrho + \partial_x f(\varrho) \;=\; \varepsilon\, \partial_x^2 \varrho$$

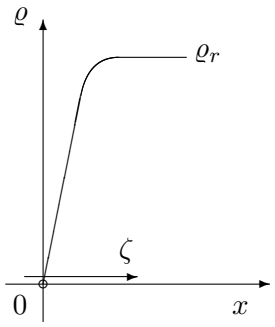


Figure 2.14: boundary layer

and by defining the *boundary layer variable* $\zeta := \frac{x}{\varepsilon}$ we can rewrite the last equation. This variable varies rapidly when ε changes and is used only near $x = 0$ to describe this fast processes. Furthermore we will use the notation $\widehat{\varrho}(t, \zeta) = \varrho(t, \underbrace{\zeta\,\varepsilon}_{=x})$.

$$\begin{aligned} \partial_t \widehat{\varrho} + \tfrac{1}{\varepsilon}\,\partial_\zeta f(\widehat{\varrho}) &= \tfrac{1}{\varepsilon}\,\partial_\zeta^2 \widehat{\varrho} && / * \varepsilon \\ \varepsilon\,\partial_t \widehat{\varrho} + \partial_\zeta f(\widehat{\varrho}) &= \partial_\zeta^2 \varrho && / \lim \varepsilon \to 0 \\ \partial_\zeta f(\widehat{\varrho}) &= \partial_\zeta^2 \widehat{\varrho} \end{aligned}$$

In the limit $\varepsilon \to 0$ a time independent second order ODE remains for $\widehat{\varrho}$, with the following boundary conditions:

$$\begin{aligned} \widehat{\varrho}(0) &= 0 \\ \partial_\zeta \widehat{\varrho} &= 0 \qquad \text{for large } \zeta \end{aligned}$$

We solve the ODE by simply integrating it one time and use the second boundary condition, getting

$$\begin{aligned} \partial_\zeta \widehat{\varrho} &= f(\widehat{\varrho}) + \text{const.} \\ \partial_\zeta \widehat{\varrho} &= f(\widehat{\varrho}) - f(\varrho_r) \end{aligned} \tag{2.23}$$

Together with the first boundary condition this yields the exact form we wished as shown in figure 2.14. A rapid jump from $\varrho(x = 0)$ to ϱ_r. The careful reader may note, this is only true for $\varrho_r \leq \overline{\varrho}$, but for the boundary value ϱ_r from unconstrained ending movement only values lesser or equal $\overline{\varrho}$ are possible, as we have noted before.

So in this case the occuring boundary layer solves the problem with the differences in the boundary values. The second case works similarly, and

therefore we have solved the first most apparent problem for the visosity limit.

2.11 Summary

In this chapter we derived a simple model for the evolution of actin filament endings based on the effects of polymerization, depolymerization and nucleation. Commencing from the behavior of one end, we looked at the behavior of an ending continuum and made a continous limit to get a partial differerential equation.

This PDE describes the evolution of the filament endings in our system and therefore we also know the evolution of the filaments, which was our original goal. The system itself consists of a non-linear conservation law constitutive equation, a non-standard boundary condition and an initial condition. The non-linearity in the equation comes from depolymerization probabilities which incorporate some kind of information between the filaments.

The two most remarkable features of our model are the non-linear flux function and the non-standard boundary condition. Commencing from the biological fact of a limited number of depolymerization proteins, the flux function promotes the polymerization of many filaments with equal length and encourages the depolymerization of a small number of equally long filaments. The boundary condition simply regulates the total filament number.

A short introduction to conservation laws provided the most important knowledge to understand the behavior of our system. Our theoretic considerations are in perfect accordance with the findings from numerical simulations. In both cases we find the same steady state distribution for the endings, where the system converges to.

There are two distinct phases in the evolution of the endings. When the total number of endings is larger than the equilibrium number, the endings may evolve and depolymerize freely, and when the filament number is smaller, new filaments are nucleated until the equilibrium number is reached. The number of filaments tends to the equilibrium number and during this process the equilibrium ending density evolves to its characteristic shape as seen in figure 2.15.

The equilbrium ending density has a very simple form: It has constantly the value of the positive zero of the flux function up to a point determined by the system's parameter, and after that it is equal to zero. Therefore the equilibrium filament density is simply linear decreasing (see figure 2.15). These two shapes are very simple, but this is not surprising since we derived our model from basic simple mechanisms.

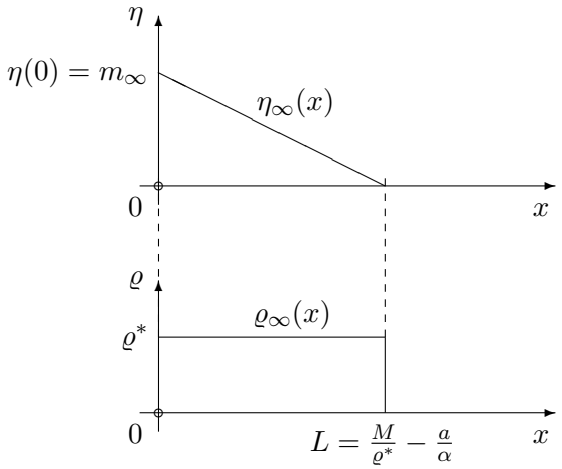


Figure 2.15: steady state of ending and filament density

Summing up, the system converges to the equilbrium ending distribution determined by the system's parameters but independent of the initial condition.

2.12 Outlook and discussion

Like we said before, we tried to keep our model as simple as possible on one hand but produce a stationary distribution based on biological facts on the other. There are a lot of points and assumptions that are disputable, but they serve also as a good starting point for further analysis and models.

We derived our flux function under the assumption, that locally one polymerization step and two depolymerization steps balance each other. Maybe the number or ratio of these steps should be changed. Furthermore the depolymerization probabilities only depend on the total number of endings at a point, but they could also depend on the region of the cell, e.g. the depolymerization of long filaments and polymerization of short ones could be encouraged.

Another idea is to loosen the assumption of the constant protein influences by introducing protein concentrations or protein distributions inside the cell. So some constants in our model could be protein concentration dependent.

So far we have only talked about extensions of the model, but also rigorous mathematical proofs for the model's behavior, as it stands, have to be done. This will be some work because of the non-standard boundary condition. We have given an idea how this could be done, but maybe other easier ways are possible.

Actually there are a lot of ideas how to extend and improve our model, but we should not forget our goal to reach a stationary actin distribution in the end. And with more factors this goal gets harder to achieve.
One has to keep in mind the complexity of the model on one hand and the correctness of the results on the other hand, because the first and foremost role of mathematical modeling is to reproduce observable biological facts.

Chapter 3

Polymerization and fragmentation model

The model we present in this chapter is the simplification of a model from a recent research work modeling actin filament dynamics (see [13]). The main focus in this paper was to analyze and model the influence of the severing protein ADF/cofilin on actin dynamics. A short introduction to this paper is given in chapter A of this diploma thesis.

The following effects will be included in the presented model:

- polymerization and
- fragmentation.

Our main reason for presenting this model is to broaden the reader's understanding of modeling actin dynamics by showing another approach. As we said before, the main work of this master thesis is the model in the previous chapter. The findings of the model in this chapter are mainly complementary. For this polymerization and fragmentation model we will only highlight and show the most important topics. Other effects than in the previous chapter will occur here.

At first we will state the model and explain its components, then we will find a steady state and prove the convergence to it. Concluding we will summarize and discuss the model's properties.

The main difference to the polymerization and nucleation model is that in this chapter x is a *length variable*, not a position variable. So x refers to the

length of filaments and therefore the meaning of ϱ and η changes:

$$\begin{aligned} \varrho(t,x) &= \text{distribution of filaments with length } x \text{ at time } t \\ \eta(t,x) &= \text{number of filaments with length greater than } x \text{ at time } t \end{aligned}$$

Of course the following relations stay true:

$$\begin{aligned} \varrho(t,x) &= -\partial_x \eta(t,x) \\ \eta(t,x) &= \int_x^\infty \varrho(t,y)\,\mathrm{d}y \end{aligned}$$

This looks all similar to chapter 2, but the meaning is different. We want to underline this fact strongly.

This change in the meaning of $\varrho(t,x)$ also affects our structural assumptions a little. Our main direction axis does not start at a given point, it only gives the direction. Stuctural assumptions number 1.1., 1.3. and 1.4. hold unchanged. We only have to change assumption 1.2. into:

Structural Assumption 1.2.* *All filaments are parallel to the x-axis. The barbed end of the filaments are nearer to the leading edge than the pointed end.*

We do not give information over the position of the filaments inside of the cell except from the orientation, we only want the orientation unchanged, so the barbed end of an filament is nearer to the cell's leading edge.
The original structural assumption is not reasonable here, because the location of the edge ($x = 0$ in the former chapter) has no influence on the model. All the processes are simply happening inside the cell.

We have not made any assumptions over the exact p of the filaments, but of course we could assume that all filaments start at the leading edge and then we would have the exact setup as in chapter 2.

3.1 The model

Now we state the model and explain its properties. For further informations see chapter A or [13].

Complete polymerization and fragmentation model ($*\varrho_{pofra}$):

$$\begin{aligned} \partial_t \varrho(t,x) + v\partial_x \varrho(t,x) &= \kappa\Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho(t,x)\Big) && \forall (t,x) \in (0,\infty)^2 \\ \varrho(0,x) &= \varrho_0(x) && \forall x \in [0,\infty) \\ \varrho(t,0) &= 0 && \forall t \in (0,\infty) \end{aligned}$$

We will refer to the constitutive equation as ($*\varrho_{pofra}$.1), use ($*\varrho_{pofra}$.2) for the initial condition and respective ($*\varrho_{pofra}$.3) for the boundary condition. Furthermore we will skip the dependencies of ϱ and will write them only for a better understanding.

Now we explain the meaning of the building parts of ($*\varrho_{pofra}$.1):

$$\underbrace{\partial_t \varrho(t,x) + v\partial_x \varrho(t,x)}_{(1)} = \kappa\Big(\underbrace{\int_x^\infty \varrho(t,y)\,\mathrm{d}y}_{(2)} \underbrace{-x\varrho(t,x)}_{(3)}\Big)$$

The left hand side (1) reminds us of a conservation law similar to the previous chapter.

$$\partial_t \varrho(t,x) + v\partial_x \varrho(t,x)$$

Here $f'(\varrho) = v$ and therefore the velocity of the densities would be v which is in this case the net *polymerization velocity* (the velocity of polymerization minus the velocity of depolymerization). We assume

$$v \;=\; \text{const.} > 0$$

So v is positive and we have polymerization included in our model.

The second term (2) represents fragmentation by severing a filament at position x. This expression can be interpreted as some kind of source term: A long filament gets cut at length x and so the number of filaments with length x increase.

$$\kappa \int_x^\infty \varrho(t,y)\,\mathrm{d}y$$

But this whole term without the κ is $\eta(t,x)$, the number of filaments longer than x. So the increase of filaments with length x is proportional to the number of filaments with length greater than x.

The positive constant κ here is a *severing rate* for the filaments.

When a filament is cut there actually remain two smaller filaments. But in this model we assume, that only the filament with the original barbed end remains, and the fragment with the original pointed end is dissociated.

The last term (3) gives the removal of a filament of length x by cutting anywhere between length 0 and x.

$$-\kappa\, x \varrho(t,x)$$

This is some kind of sink term: When a filament of length x is cut, the number of filaments with length x decrease. We observe that the decrease gets lower proportional to x, meaning very short filaments are very unlikely to break, and very long filaments are very likely to break.

So far we have talked about the composition of the system's constitutive equation, but we have not classified it. $(*\varrho_{pofra}.1)$ is a *linear integro partial differential equation*.
Furthermore it also has a very interesting property we encountered in conservation laws, because it conserves the total number of filaments. We define in analogy to the second chapter:

$$m(t) := \int_0^\infty \varrho(t,y)\,\mathrm{d}y = \text{total number of filaments} < \infty$$

The careful reader may note, that $\eta(t,x)$ is equal to the number of filaments by definition:

$$\eta(t,0) = \int_0^\infty \varrho(t,y)\,\mathrm{d}y = m(t)$$

To show this conservation property we simply integrate $(*\varrho_{pofra}.1)$ over the whole domain and do some calculations. We assume ϱ decays fast for $x \to \infty$

$$
\begin{aligned}
\partial_t \varrho + v\partial_x \varrho &= \kappa\Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho(t,x)\Big) && / \int_0^\infty .\,\mathrm{d}x \\
\int_0^\infty (\partial_t \varrho + v\partial_x \varrho)\,\mathrm{d}x &= \kappa\int_0^\infty \Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho(t,x)\Big)\mathrm{d}x \\
\int_0^\infty \partial_t \varrho\,\mathrm{d}x + v\int_0^\infty \partial_x \varrho\,\mathrm{d}x &= \kappa\Big(\int_0^\infty\int_x^\infty \varrho(t,y)\,\mathrm{d}y\mathrm{d}x - \int_0^\infty x\varrho(t,x)\mathrm{d}x\Big) \\
\Big(v\int_0^\infty \partial_x \varrho\,\mathrm{d}x &= v\Big(\underbrace{\varrho(x=\infty)}_{=0} - \underbrace{\varrho(x=0)}_{=0}\Big) = 0\Big) \\
\partial_t \int_0^\infty \varrho\,\mathrm{d}x &= \kappa\Big(\underbrace{\int_0^\infty 1\int_x^\infty \varrho(t,y)\,\mathrm{d}y\mathrm{d}x}_{\text{integration by parts}} - \int_0^\infty x\varrho(t,x)\mathrm{d}x\Big) \\
\Big(\int_0^\infty 1\int_x^\infty \varrho(t,y)\,\mathrm{d}y\mathrm{d}x &= \underbrace{x\int_x^\infty \varrho(t,y)\,\mathrm{d}y|_{x=0}^{x=\infty}}_{=0} - \int_0^\infty x(-\varrho(t,x))\mathrm{d}x\Big) \\
\partial_t\, m(t) &= \kappa\Big(\int_0^\infty x\varrho(t,x)\mathrm{d}x - \int_0^\infty x\varrho(t,x)\mathrm{d}x\Big) \\
\partial_t\, m(t) &= 0
\end{aligned}
$$

So the number of filaments is constant, it is equal to m_0, which is the number of filaments in the initial condition.

$$m(t) = \text{const.} = m(t=0) = \int_0^\infty \varrho_0(y)\,\mathrm{d}y =: m_0$$

As a consequence of this $\eta(t,0)$ does not change either. It is constantly equal to m_0.

$$\eta(t,0) = m(t) = m_0$$

3.2 Steady state

In this section we will calculate the steady state distribution for our system $*\varrho_{pofra}$. We simply assume a steady state exists, do the calculations, and then we will see this assumption is justified.

A steady state means, there are no changes in the distribution any more, the distribution does not change in time

$$\partial_t \varrho = 0$$

Because there are no changes in time we can skip the time dependencies in this calculation and write

$$\varrho(t,x) = \varrho(x)$$
$$\eta(t,x) = \eta(x)$$

Before doing the calculations, we recall the definition of η and its derivative, because we will use this later (Note: here we use η without time dependency).

$$\begin{aligned}\eta(x) &= \int_x^\infty \varrho(y)\mathrm{d}y \\ \eta(x)' &= \partial_x\eta(x) = -\varrho(x) \\ \eta(x)'' &= -\varrho(x)'\end{aligned}$$

We begin our work by recalling the constitutive equation.($*\varrho_{pofra}.1$)

$$\partial_t\varrho + v\partial_x\varrho = \kappa\Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho\Big)$$

Then we use the prliminary results earlier in this this section to rewrite this equation into

$$0 + v\big(-\eta(x)''\big) = \kappa\big(\eta(x) + x\eta(x)'\big) = \kappa\big(x\eta(x)\big)'$$

Summed up, we get the following ordinary differential equation, together with its initial conditions.

$$\begin{aligned}-v\,\eta(x)'' &= \kappa\big(x\,\eta(x)\big)' \\ \eta(0) &= m_0 \\ \eta(0)' &= -\varrho(0) = 0\end{aligned} \tag{3.1}$$

To solve (3.1) we simply integrate the whole equation one time getting

$$-v\,\eta(x)' = \kappa\,x\,\eta(x) + c_1$$

By inserting the second initial condition $\eta(0)' = 0$ we get, that the constant is zero $c_1 = 0$. Then we bring all η terms on one side and the rest to the other side

$$\frac{\eta(x)'}{\eta(x)} = -\frac{\kappa}{v}\,x$$

We integrate again and, that leads us to

$$\ln(|\eta(x)|) = -\frac{\kappa}{v}\,\frac{x^2}{2} + c_2$$

We apply the exponential function to the right and left side. The absolute value goes away, because η is always positive.

$$\eta(x) = \exp(-\frac{\kappa}{v}\,\frac{x^2}{2})\,\exp(c_2)$$

The second initial condition $\eta(0) = m_0$ yields the final solution.

$$\eta(x) = m_0 \exp(-\frac{\kappa}{v}\frac{x^2}{2})$$

So we have calculated the steady state number of filaments greater than length x. We will call this function η_∞, its negative first deravitive is the steady state distribution of filaments with length x, called ϱ_∞, we originally searched.

$$\eta_\infty(x) = m_0 \exp(-\frac{\kappa}{v}\frac{x^2}{2}) \tag{3.2}$$

$$\varrho_\infty(x) = m_0 \frac{\kappa}{v} x \exp(-\frac{\kappa}{v}\frac{x^2}{2}) \tag{3.3}$$

Of course the number of filaments in the steady state does not change and stays the number of filaments from the initial distribution $m_0 = \int_0^\infty \varrho_0(y)\,\mathrm{d}y$.

By inserting $\varrho_\infty(x)$ into $(*\varrho_{pofra})$, we see that it is indeed a solution of our system, and $\partial_t \varrho_\infty = 0$. Thus, all our calculations were justified.

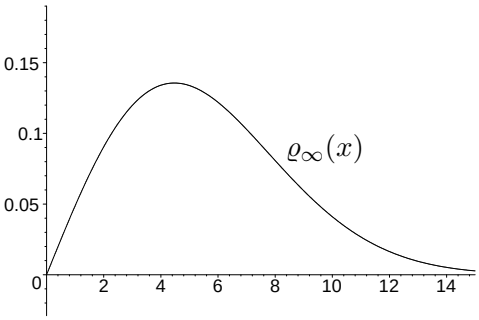


Figure 3.1: Characteristical form of the steady state length distriution ϱ_∞

Now we want to hold on for a moment and think about, what this steady state density tells us:
There are only very few long filaments, because the distribution decreases exponentially for large lengths. There is clearly a peak in the distribution which tells us, that most of the filaments have short to medium length.

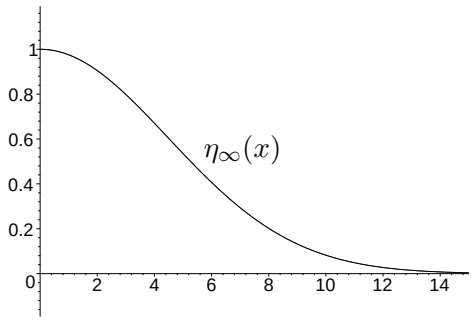


Figure 3.2: Characteristical form of the steady state η_∞

3.3 Convergence to the steady state

In the last section we derived a steady state for the length distribution of the filaments. Our hope is now that all distributions converge to this staedy state.

We have observed, that all distributions $\varrho(t,x)$ tend to the steady state form ϱ_∞ in some sense. To prove this will be some work, but before going to the calculations we have to specify the type of convergence. There exist strong and weak forms of convergence, and we want to show the following

$$\partial_t \int_0^\infty \frac{\big(\varrho(t,x)-\varrho_\infty(x)\big)^2}{2\varrho_\infty(x)}\,\mathrm{d}x \;<\; 0 \qquad \text{for } \varrho(t,x)\neq\varrho_\infty(x) \tag{3.4}$$

$$\partial_t \int_0^\infty \frac{\big(\varrho(t,x)-\varrho_\infty(x)\big)^2}{2\varrho_\infty(x)}\,\mathrm{d}x \;=\; 0 \qquad \text{for } \varrho(t,x)=\varrho_\infty(x) \tag{3.5}$$

This represents an L^2 weighted distance that decreases in time, and stops decreasing, when the steady state distribution is reached. Of course this is a very weak result of convergence.

To prove this convergence will take some time and we start by some preliminary steps. First we look at the left hand side quantity in (3.4) and (3.5)

and find out, that we can rewrite it in an easier way.

$$\begin{aligned}
\partial_t \int_0^\infty \frac{\big(\varrho(t,x)-\varrho_\infty(x)\big)^2}{2\varrho_\infty(x)}\,\mathrm{d}x &= \partial_t \int_0^\infty \frac{\varrho(t,x)^2 - 2\varrho(t,x)\varrho_\infty(x) + \varrho_\infty(x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x \\
&= \partial_t \int_0^\infty \frac{\varrho(t,x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x - \partial_t \int_0^\infty \frac{2\varrho(t,x)\varrho_\infty(x)}{2\varrho_\infty(x)}\,\mathrm{d}x \\
&\quad + \partial_t \int_0^\infty \frac{\varrho_\infty(x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x \\
&= \partial_t \int_0^\infty \frac{\varrho(t,x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x - \partial_t \underbrace{\int_0^\infty \varrho(t,x)\,\mathrm{d}x}_{=m_0} \\
&\quad + \partial_t \underbrace{\int_0^\infty \frac{\varrho_\infty(x)}{2}\,\mathrm{d}x}_{=\frac{m_0}{2}} \\
&= \partial_t \int_0^\infty \frac{\varrho(t,x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x - \underbrace{\partial_t m_0}_{=0} + \underbrace{\partial_t \frac{m_0}{2}}_{=0}
\end{aligned}$$

$$\begin{aligned}
\partial_t \int_0^\infty \frac{\big(\varrho(t,x)-\varrho_\infty(x)\big)^2}{2\varrho_\infty(x)}\,\mathrm{d}x &= \partial_t \int_0^\infty \frac{\varrho(t,x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x \\
D(\varrho(t,x)) &:= \partial_t \int_0^\infty \frac{\varrho(t,x)^2}{2\varrho_\infty(x)}\,\mathrm{d}x
\end{aligned}$$

So with this definition we only have to check (3.4) and (3.5) on $D(\varrho)$, which is a small but very helpful improvement.
For the sake of simplification we skip the dependencies of ϱ and ϱ_∞, we will only write them if they are not clear in the context. When we write $\varrho(x)$ we actually mean $\varrho(t,x)$, so we may skip only the temporal dependency when we see it fit.

In the next preliminary step, we rewrite the right hand side of the constitutive equation ($*\varrho_{pofra}.1$) and introduce a new notation for shortening.

$$\begin{aligned}
\kappa\Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho(t,x)\Big) &= \kappa\Big(\int_{y=0}^\infty \varrho(t,y)\mathbb{1}_{[x,\infty)}(y)\,\mathrm{d}y - \int_{y=0}^\infty \varrho(t,x)\mathbb{1}_{[0,x]}(y)\mathrm{d}y\Big) \\
&= \kappa \int_{y=0}^\infty \varrho(t,y)\mathbb{1}_{[x,\infty)}(y) - \varrho(t,x)\mathbb{1}_{[0,x]}(y)\,\mathrm{d}y \\
Q(t,x,\varrho(t,x)) &:= \kappa \int_{y=0}^\infty \varrho(t,y)\mathbb{1}_{[x,\infty)}(y) - \varrho(t,x)\mathbb{1}_{[0,x]}(y)\,\mathrm{d}y
\end{aligned}$$

We observe, that Q is by definition linear in ϱ. In this definition we have used the index function $\mathbb{1}$:

$$\mathbb{1}_A(x) := \begin{cases} 1 & x \in A \qquad \text{(A is a set)} \\ 0 & \text{else} \end{cases}$$

When the context is clear, we will also only write $Q(\varrho)$ for $Q(t, x, \varrho(t, x))$. With the definition of Q at hand we can write $(*\varrho_{pofra}.1)$ in a much shorter and compacter way.

$$\partial_t \varrho + v\, \partial_x \varrho = Q(\varrho) \tag{3.6}$$

We only need one last auxiliary result before going to the main part of the proof. We insert the steady state ϱ_∞ in the constitutive equation of our system $(*\varrho_{pofra}.1)$ and mind that its time derivative is zero $\partial_t \varrho_\infty = 0$. Then the remaining part, using the notation of Q, reads

$$v\, \partial_x \varrho_\infty = Q(\varrho_\infty) \tag{3.7}$$

These were all preliminary results we need. Now we switch to the main part: the proof of the convergence. We show now, that (3.4) and (3.5) hold. All calculations are presented but we will explain only important points in detail, the rest is self explanatory. Furthermore, we use all the things we have mentioned so far in this section.
We commence from $(*\varrho_{pofra}.1)$ in its short version (3.6).

$$\begin{aligned}
\partial_t \varrho + v\, \partial_x \varrho &= Q(\varrho) \\
\partial_t \varrho &= -v\, \partial_x \varrho + Q(\varrho) \qquad / * \frac{\varrho}{\varrho_\infty} \\
(\partial_t \varrho)\frac{\varrho}{\varrho_\infty} &= -v\, (\partial_x \varrho)\frac{\varrho}{\varrho_\infty} + Q(\varrho)\frac{\varrho}{\varrho_\infty} \qquad / \int_{x=0}^{\infty} .\, \mathrm{d}x \\
\int_{x=0}^{\infty} (\partial_t \varrho)\frac{\varrho}{\varrho_\infty} \mathrm{d}x &= -v \int_{x=0}^{\infty} (\partial_x \varrho)\frac{\varrho}{\varrho_\infty} \mathrm{d}x + \int_{x=0}^{\infty} Q(\varrho)\frac{\varrho}{\varrho_\infty} \mathrm{d}x \\
\int_{x=0}^{\infty} \partial_t \Big(\frac{\varrho^2}{2\,\varrho_\infty}\Big) \mathrm{d}x &= v \int_{x=0}^{\infty} -\partial_x \Big(\frac{\varrho^2}{2}\Big)\frac{1}{\varrho_\infty} \mathrm{d}x + \int_{x=0}^{\infty} Q(\varrho)\frac{\varrho}{\varrho_\infty} \mathrm{d}x
\end{aligned}$$

We have just used $(\partial_t \varrho)\varrho = \partial_t \Big(\frac{\varrho^2}{2}\Big)$ for the last step, which is also true for ∂_x. In the next step we use integration by parts to shift the derivation inside the first right integral. We assume the boundary terms are zero, this is a good guess since the nominator is quadratic and the denominator only linear. For the remaining part on the shifted derivative we use (3.7).
Additionally we assume that all conditions are met to change the order of the integral and the time derivative on the left side. After this change we

have exactly $D(\varrho)$ on the left side.

$$\begin{aligned}
\partial_t \underbrace{\int_{x=0}^{\infty} \frac{\varrho^2}{2\,\varrho_\infty} \mathrm{d}x}_{=D(\varrho)} &= \underbrace{-v\Big(\frac{\varrho^2}{2\,\varrho_\infty}\Big)|_{x=0}^{\infty}}_{=0} + v\int_{x=0}^{\infty} \frac{\varrho^2}{2} \partial_x\Big(\frac{1}{\varrho_\infty}\Big)\mathrm{d}x + \int_{x=0}^{\infty} Q(\varrho)\frac{\varrho}{\varrho_\infty}\mathrm{d}x \\
\partial_t D(\varrho) &= \int_{x=0}^{\infty} \frac{\varrho^2}{2}\,\frac{-1}{\varrho_\infty^2}\,\underbrace{v\partial_x\varrho_\infty}_{=Q(\varrho_\infty)}\,\mathrm{d}x + \int_{x=0}^{\infty}\frac{\varrho}{\varrho_\infty}Q(\varrho)\mathrm{d}x \\
\partial_t D(\varrho) &= \int_{x=0}^{\infty} \frac{\varrho}{\varrho_\infty}Q(\varrho) - \frac{\varrho^2}{2\,\varrho_\infty^2}\,Q(\varrho_\infty)\,\mathrm{d}x \\
\partial_t D(\varrho) &= \int_{x=0}^{\infty} \frac{\varrho}{\varrho_\infty}\Big(Q(\varrho) - \frac{\varrho}{2\,\varrho_\infty}\,Q(\varrho_\infty)\Big)\,\mathrm{d}x
\end{aligned}$$

To get rid of the $\frac{\varrho}{\varrho_\infty}$ term we introduce an auxiliary integration step. Moving on, we will use the linearity of Q in the ϱ argument.

$$\begin{aligned}
\partial_t D(\varrho) &= \int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}} \Big(Q(\varrho) - n\,Q(\varrho_\infty)\Big)\,\mathrm{d}n\,\mathrm{d}x \\
\partial_t D(\varrho) &= \int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}} \Big(Q(\varrho) - Q(n\,\varrho_\infty)\Big)\,\mathrm{d}n\,\mathrm{d}x \qquad /*(-1) \\
-\partial_t D(\varrho) &= \int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}} \Big(Q(n\,\varrho_\infty) - Q(\varrho)\Big)\,\mathrm{d}n\,\mathrm{d}x \qquad /\text{insert definition of } Q \\
-\partial_t D(\varrho) &= \kappa\int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(x)}\int_{y=0}^{\infty} n\,\varrho_\infty(y)\mathbb{1}_{[x,\infty)}(y) - n\,\varrho_\infty(x)\mathbb{1}_{[0,x]}(y) - \\
&\quad -\varrho(y)\mathbb{1}_{[x,\infty)}(y) + \varrho(x)\mathbb{1}_{[0,x]}(y)\,\mathrm{d}y\,\mathrm{d}n\,\mathrm{d}x \\
-\partial_t D(\varrho) &= \kappa\int_{x=0}^{\infty}\int_{y=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(x)} \Big(n\,\varrho_\infty(y) - \varrho(y)\Big)\,\underbrace{\mathbb{1}_{[x,\infty)}(y)}_{=\mathbb{1}_{[0,y]}(x)} - \\
&\quad -\Big(n\,\varrho_\infty(x) - \varrho(x)\Big)\mathbb{1}_{[0,x]}(y)\,\mathrm{d}y\,\mathrm{d}n\,\mathrm{d}x \\
-\partial_t D(\varrho) &= \kappa\int_{x=0}^{\infty}\int_{y=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(x)} \Big(n\,\varrho_\infty(y) - \varrho(y)\Big)\mathbb{1}_{[0,y]}(x)\mathrm{d}n\,\mathrm{d}y\,\mathrm{d}x - \\
&\quad -\kappa\int_{x=0}^{\infty}\int_{y=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(x)} \Big(n\,\varrho_\infty(x) - \varrho(x)\Big)\mathbb{1}_{[0,x]}(y)\,\mathrm{d}n\,\mathrm{d}y\,\mathrm{d}x
\end{aligned}$$

In the first integral we now interchange the order of integration, assuming the prequisites for Fubini's theorem are met. In the second integral we change the names of the variables: we interchange x and y. This is just a transformation of variables, so it is legal.

Then we combine the two integrals.

$$\begin{aligned}
-\partial_t D(\varrho) &= \kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(x)}\Big(n\,\varrho_\infty(y)-\varrho(y)\Big)\mathbb{1}_{[0,y]}(x)\mathrm{d}n\,\mathrm{d}x\,\mathrm{d}y - \\
&\quad -\kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\int_{n=0}^{\frac{\varrho}{\varrho_\infty}(y)}\Big(n\,\varrho_\infty(y)-\varrho(y)\Big)\mathbb{1}_{[0,y]}(x)\,\mathrm{d}n\,\mathrm{d}x\,\mathrm{d}y \\
-\partial_t D(\varrho) &= \kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\int_{n=\frac{\varrho}{\varrho_\infty}(y)}^{\frac{\varrho}{\varrho_\infty}(x)}\Big(n\,\varrho_\infty(y)-\varrho(y)\Big)\mathbb{1}_{[0,y]}(x)\mathrm{d}n\,\mathrm{d}x\,\mathrm{d}y
\end{aligned}$$

At this point we already see, that the left side is greater or equal zero: $-\partial_t D(\varrho)\geq 0$. To see this ,we distinguish two cases: if $\frac{\varrho}{\varrho_\infty}(x)\geq n\geq\frac{\varrho}{\varrho_\infty}(y)$ (so the integration over n goes in the positive direction) then the integrand is also positive $\Big(n\,\varrho_\infty(y)-\varrho(y)\Big)\geq 0$. And in the other case we have a negative direction and a negative integrand, so all in all we get $-\partial_t D(\varrho)\geq 0$.
In the next step we execute the integration over n by variable transformation.

$$\begin{aligned}
-\partial_t D(\varrho) &= \kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\int_{n=\frac{\varrho}{\varrho_\infty}(y)}^{\frac{\varrho}{\varrho_\infty}(x)}\Big(n\,\varrho_\infty(y)-\varrho(y)\Big)\mathbb{1}_{[0,y]}(x)\mathrm{d}n\,\mathrm{d}x\,\mathrm{d}y = \\
&= \left|\begin{array}{l} m = n\,\varrho_\infty(y)-\varrho(y) \\ \mathrm{d}m = \mathrm{d}n \end{array}\right| = \\
-\partial_t D(\varrho) &= \kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\mathbb{1}_{[0,y]}(x)\int_{n=\frac{\varrho}{\varrho_\infty}(y)}^{\frac{\varrho}{\varrho_\infty}(x)} m\,\mathrm{d}m \quad \mathrm{d}x\,\mathrm{d}y \\
-\partial_t D(\varrho) &= \kappa\int_{y=0}^{\infty}\int_{x=0}^{\infty}\mathbb{1}_{[0,y]}(x)\ \frac{m^2}{2}\Big|_{n=\frac{\varrho}{\varrho_\infty}(y)}^{\frac{\varrho}{\varrho_\infty}(x)}\mathrm{d}x\,\mathrm{d}y \\
-\partial_t D(\varrho) &= \frac{\kappa}{2}\int_{y=0}^{\infty}\int_{x=0}^{\infty}\mathbb{1}_{[0,y]}(x)\ \Big(n\,\varrho_\infty(y)-\varrho(y)\Big)^2\Big|_{n=\frac{\varrho}{\varrho_\infty}(y)}^{\frac{\varrho}{\varrho_\infty}(x)}\mathrm{d}x\,\mathrm{d}y \\
-\partial_t D(\varrho) &= \frac{\kappa}{2}\int_{y=0}^{\infty}\int_{x=0}^{\infty}\mathbb{1}_{[0,y]}(x)\ \Big(\big(\frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y)-\varrho(y)\big)^2 - \\
&\quad -\underbrace{\big(\frac{\varrho(y)}{\varrho_\infty(y)}\varrho_\infty(y)-\varrho(y)\big)^2}_{=0}\Big)\,\mathrm{d}x\,\mathrm{d}y \\
-\partial_t D(\varrho) &= \frac{\kappa}{2}\int_{y=0}^{\infty}\int_{x=0}^{\infty}\underbrace{\Big(\frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y)-\varrho(y)\Big)^2}_{=:R(\varrho)}\ \mathbb{1}_{[0,y]}(x)\mathrm{d}x\,\mathrm{d}y \qquad (3.8)
\end{aligned}$$

With the definition of $R(\varrho):=\Big(\frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y)-\varrho(y)\Big)^2$ we have only left to show two points:

$$R(\varrho)\geq 0$$

Which is clear since the definition of $R(\varrho)$ is quadratic. And the second point is to show, that $R(\varrho)$ is only zero iff $\varrho = \varrho_\infty$, which is also very obvious.

$$\begin{aligned} R(\varrho) = 0 \quad &\Leftrightarrow \quad \Big(\frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y) - \varrho(y)\Big)^2 = 0 \Leftrightarrow \frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y) - \varrho(y) = 0 \Leftrightarrow \\ &\Leftrightarrow \quad \frac{\varrho(x)}{\varrho_\infty(x)}\varrho_\infty(y) = \varrho(y) \Leftrightarrow \frac{\varrho(x)}{\varrho_\infty(x)} = \frac{\varrho(y)}{\varrho_\infty(y)} \overset{\text{separation}}{=} \lambda = \text{const.} \Leftrightarrow \\ &\Leftrightarrow \quad \varrho = \lambda\,\varrho_\infty \Leftrightarrow \left| \begin{array}{l} \int \varrho_\infty \mathrm{d}x = \int \varrho\,\mathrm{d}x = m_0 \\ \Rightarrow \lambda = 1 \end{array} \right| \Leftrightarrow \\ &\Leftrightarrow \quad \varrho = \varrho_\infty \end{aligned}$$

Together with (3.8) we have now shown that

$$\begin{aligned} \partial_t D(\varrho) &< 0 \qquad \text{for } \varrho \neq \varrho \\ \partial_t D(\varrho) &= 0 \qquad \text{for } \varrho = \varrho_\infty \end{aligned}$$

Which is the exact proof for (3.4) and (3.5).

3.4 Summary

In this chapter we have presented another model for actin filament dynamics. The most important change compared to our first model is using x as a length variable. Some very intetersting considerations come with that fact. The interpretation of ϱ and η in the two presented model is different. However, through the assumption that all filaments start at the cell's edge in the $(*\varrho_{pofra})$ setting, we are exactly in the setting of the polymerization and nucleation model.

The new effect described in this chapter is fragmentation, which refers to breaking of a long filament into two smaller parts. It is included by the terms on the right hand side of the constitutive equation.
The probabilty of a breach is equal in each point of the filament, and a natural extension would be a length dependent breaking probabilty.
This fragmentation effects each filament, but there is no communication between the filaments.

We have eplicitly derived a steady state distribution Furthermore, we proved that all distributions tend to the steady state in a weak way. These results are much stronger than in the last chapter, where our arguments were mainly heuristic.
The steady state distribution reflects the fragmentation effect in a good manner: the long filaments are cut apart, only the short ones remain.

One of the problems with this model is actually its length dimesion. In our nucleation model the density only propagated a finite way, and its steady state is also bounded in length. But in this fragmentation model the filaments in the steady state distribution can have any length due to the expontial function in its definition. This leads to problems with the finite length of the cells. Of course we can neglect long filaments due to their exponentially low number, but the problem stays.

3.5 Outlook

As we said at the beginning of this chapter ($*\varrho_{pofra}$) is actually the simplification of a model in [13], where its original form is more complex. From this source we have a lot of ideas how to extend our polymerization and fragmentation model e.g. with a length dependent breaking probability like we mentioned before, or with a non-constant density dependent velocity v perhaps even a non-linear transport term akin chapter 2. There exist a lot of conceivable extensions, but more complex systems are normally harder to solve.

From our point of view we are of course interested in a merge of our two presented models. But there are a lot of open questions to be solved concerning this problem.

Chapter 4

Conclusion

In this master thesis we have presented two models for the temporal evolution of actin filaments. Their main components were polymerization and depolymerization and they both converged to a steady state distribution, but their underlying ideologies were completely different.

In the first model information about the exact postion of the filaments was given and used for the interaction of the filaments. This resulted in a nonlinear conservation law equation. The total number of filaments was controlled by a non-standard boundary condition, that represented nucleation. The basics of conservation law theory helped us to determine the behavior of the system and also its steady state.

We used a different approach in the second model. We looked at the length distribution of the filaments and included a fragmentation effect in the description. There was no communication between the filaments, but despite this fact we directly showed the convergence to a steady state.

We see, that there are different biological processes that lead to a stable steady state. But apart from polymerization and depolymerization we only described one additional effect to reach this equilibrium. Of course, the next challenge will be to add these processes together and analyze the merged system. Furthermore, there are other processes, like the annealing of filaments, that have to be observed and maybe included in a complete model.

There exist lots of ideas for the extension of the models on their own let alone their merge. But the first point will be a thorough discussion with biologists, because the first and foremost role of mathematical modeling is to reproduce observable biological facts.

Modeling the dynamcis of actin filaments is a great challenge and will stay

a large research topic in the future, because a complete model for actin dynamics is far from being complete. We hope to have performed a small part of work in order to reach this goal, by providing a good introduction with this diploma thesis.

We hope to have helped Dr. Ölz by providing new ideas for his master model. Furthermore, we hope to have given the reader new insights and an enjoyable time reading this work.

Appendix A

Models in the literature

In this chapter we want to present three selected works and their different approach to modeling actin filament dynamics.

In the model we have derived and analyzed in chapter 2, we used x as a position variable, and we have assumed a lot of influences from the surrounding lamellipodium. But in the literature there exist a huge number of other approaches to cope with the problem of actin dynamics, each assuming other sideconditions.
The main goal of these works is to show particular effects, but even now with a lot of researchers working on this topic a complete model for actin filament dynamics is far from completion.

Actin filament dynamics have been studied both analytically and computationally in the last three decades and the studies fall into two broad categories (see [2]):
The first is characterized by a focus on individual actin filaments, or actin networks, as a component of a more complex system. The questions adressed include the mechanisms for force generation and the mechanism for symmetry breaking in filament networks. A recent review of this approach is given in [14].
The second approach focuses on spontaneous polymerization of highly purified actin monomers. Experimental conditions can be controlled more precisely than in vivo situations, and this leads to simpler mathematical models that can be analyzed in detail. The main interest here is the steady state length distribution and the statistical properties of the dynamics of an ensemble of actin filaments. Our model from chapter 2 falls into this category, but it also features aspects of the other category.

A theoretical approach to actin filament dynamics (see [2])

Jifeng Hu, Anastasios Matzavinos and Hans G. Othmer

We start with a paper that classicaly falls under the second category. Its main aim is to understand the temporal evolution of the length distribution in vitro in order to understand what the relevant timescales are for establishment of a time invariant distribution.

In this paper only polymerization and depolymerization is modeled, and a very simple kinetic scheme is used to describe the processes.
We will give a short sketch of the model: Let M_n denote a filament of length n, and let C_n be the corresponding concentration, then we have the following scheme:

$$M_1 + M_1 \underset{k_1^-}{\overset{k_1^+ M}{\rightleftharpoons}} M_2 \underset{k_2^-}{\overset{k_2^+ M}{\rightleftharpoons}} M_3 \underset{k_3^-}{\overset{k_3^+ M}{\rightleftharpoons}} M_4 \quad \cdots \quad M_n \underset{k_n^-}{\overset{k_n^+ M}{\rightleftharpoons}} M_{n+1}$$

where k_n^+ and k_n^- are kinetic constants reported from other papers. $k_1^\pm$ and $k_2^+\pm$ are very distinct to the rest and through this fact also nucleation is included in this work.
Assuming mass action kinetics for the monomer addition and release, the above kinetic scheme leads to a system of ordinardy differential equations

$$\begin{aligned}
\frac{d\,C_1}{dt} &= -2(k_1^+ C_1^2 - k_1^- C_2) - \sum_{n=3}^{N}(k_{n-1}^+ C_1 C_{n-1} - k_{n-1}^- C_n) \\
&\vdots \\
\frac{d\,C_n}{dt} &= (k_{n-1}^+ C_1 C_{n-1} - k_{n-1}^- C_n) - (k_n^+ C_1 C_n - k_n^- C_{n+1}) \\
&\vdots \\
\frac{d\,C_N}{dt} &= (k_{N-1}^+ C_1 C_{N-1} - k_{N-1}^- C_N)
\end{aligned}$$

In this model a closed system is considered, so there is a maxiaml length of filaments N. A thermodynamically open system would be $N \to \infty$.

Then numerical simulations are done, and the results are analytically discussed. Easy calculations show that there exists a steady state for this model, and the convergence to it is confirmed by free energy considerations.

In the main analysis the different stages in the evolution of the length distribution are discussed. There exist three distinct regimes: The initial stage characterized by formation of a maximum peak heigtht in the distribution, the subsequent polymerization driven advective phase in which the mean

length increases, and a slow final stage in which monomers are redistributed among filaments and the length distribution evolves to the steady state distribution.

For future works of this group there exist ideas to incorporate annealing and fragmentation in the model. Also the influence of other proteins in actin network formation in vivo are mentioned and how to include this in the model.

Stochastic severing of actin filaments by actin depolymerizing factor/cofilin controls the emergence of a steady state dynamical regime (see [13])

Jeremy Roland, Julien Berro, Alphee Michelot, Laurent Blanchion and Jean-Louis Martiel

Now we present a paper which goes a different way. The behavior of the actin monomers is simulated on a molecule basis using a stochastic simulation algorithm (see [15]). The different states of actin are distinguished and also the protein ADF/cofilin is introduced. We mention this paper, because the model presented in chapter 3 is derived as a minor result here.

The main goal of this work is to show that ADF/cofilin regulation maintains actin filaments in a highly dynamical state compatible with the cytoskeleton dynamics observed in vivo. Therefore this work falls into the second category mentioned at the beginnning of this chapter.

In this paper a minimal kinetic model is developed, which describes key details of actin filament dynamics in the presence of actin depolymerizing factor (ADF)/cofilin. The molecular mechanisms are limited to

- the spontaneous growth of filaments by actin polymerization,
- the ageing of actin subunits in filaments,
- the cooperative binding of ADF/cofilin to actin and
- filament severing by ADF/cofilin.

We give a sketch for the main model, where the aforementioned effects are included: First each polymerized ATP-actin subunit hydrolizes its ATP independently in a first order reaction that is not influenced by surrounding

subunits. Second, ADF/cofilin accelerates phosphate dissociation. Then ADF/cofilin binds cooperatively to subunits in the filament. It is assumed, that ADF/cofilin severs filaments only between two adjacent decorated subunits only. Finally the set of chemical reactions (in the presence of a large excess of actin monomers) is simulated.
The gillespie algorithm (see [15]) is used to determine the evolution of the filament and the chemical transformation of the subunits. This molecule based approach provides precise information on the dynamics of actin.

One of the main findings is, that the key issue of actin filament length control is the severing ability of ADF/cofilin.

A minor result of this work is presented in its appendix, but is very important to us: The corresponding model for the length distribution of the filaments is given, which is the basis for our model in chapter 3.
We will introduce this model and its notation:

$$\begin{aligned} L &= \text{filament length} \\ t &= \text{time} \\ F(L,t) &= \text{number of filaments with length } L \text{ at time } t \\ \nu &= \text{global (de)polymerization rate} \\ \delta &= \text{length of one actin monomer} \\ r_5 &= \text{severing rate of F-ADP - } (\text{ADF})_2 \\ P(L) &= \text{filament severing probability at} \\ &\quad \text{a distance } L \text{ from postion } x = 0 \end{aligned}$$

So in this context L is naturally a length variable.
To get the quantity $F(L,t)$ an integrodifferential equation has to be solved:

$$\begin{aligned} \frac{\partial F(L,t)}{\partial t} &= \underbrace{\nu\Big(F(L-\delta,t) - F(L,t)\Big)}_{(1)} \\ &+ \underbrace{r_5 P(L)\int_L^\infty F(s,t)\,\mathrm{d}s}_{(2)} - \underbrace{r_5 F(L,t)\int_0^L P(s)\,\mathrm{d}s}_{(3)} \end{aligned}$$

The first term (1) represents filament elongation (or shortening) by monomer addition at the filament barbed end ($x = 0$). The second term (2) represents the fragmentation by severing the filament at position L. The last term (3) gives the removal of a filament of length L by cutting anywhere between $x = 0$ and L.

Since a typical filament length L is much larger than δ, one uses the taylor expansion of the first term to obtain:

$$\frac{\partial F(L,t)}{\partial t} = -\underbrace{\nu\delta}_{=:v}\frac{\partial F(L,t)}{\partial L} + \underbrace{r_5}_{:=\kappa}\underbrace{P(L)}_{=1}\int_L^\infty F(s,t)\,\mathrm{d}s - r_5 F(L,t)\int_0^L \underbrace{P(s)}_{=1}\,\mathrm{d}s$$

This is the general form of the equation for the evolution of the filament length density.
For chapter 3 we do some moderate modifications: We assume ν is constant, $P(L) \equiv 1$ and introduce another notation . We also use ϱ instead of F and x instead of L (so x is also a length variable!) to state the equation we used.

$$\partial_t \varrho(t,x) + v\partial_x \varrho(t,x) = \kappa\Big(\int_x^\infty \varrho(t,y)\,\mathrm{d}y - x\varrho(t,x)\Big) \tag{A.1}$$

Returning to the paper we have presented here, we want to conclude by mentioning that all the calculations done in it refer to a general actin network. But there exist also ideas to extend the model to in vivo situations like the cytoskeleton in the lamellipodium of a fish keratocyte.

A minimal model of locomotion applied to the steady gliding movement of fish keratocyte cells (see [16])

A. Mogilner and E. Marland and D. Bottino

At last we present an article, which gives a different view. The focus of this work is in describing the steady movement of the fish keratocyte. Actin itself plays only a describing role, so this model is a representative for the first category mentioned at the beginning of this chapter.

The fish keratocyte is seen as a simple system because its movement can be intersected into just three substeps of motility. First, growth of the actin network leads to the extension of the leading edge of the cell. Secondly graded substratum-coupled anchoring is developed, so that at the front the lamellipodium adheres to the surface much more firmly than at the cell's rear. Finally, the lammellipodial cytoskeleton is contracted, causing forward translocation of the cell body.

We give only the basic ideas for the model underlying these three processes mentioned in this paper:

The protrusion is generated by polymerization of actin alone. The idea is that the free energy of the polymerization is used through the brownian ratchet mechanism. The effective polymerization rate of actin is derived via a thermodynamic equilibrium, when the growth of the filaments is stalled. Nothing more is stated over the polymerization of actin. The rate of protrusion is simply calulated over a force equilibrium.
The forward translocation is accomplished by myosin motor cells. They break the actin network apart by pulling the actin filaments together into bipolar bundles. In this process the whole cell is pulled forward. The concentrations of myosin, the actin network and the actin bundles are used along a cross section of the cell to describe this mechanism. These three quantities are the core components of this system.
The adhesion is accomplished by integrin proteins that connect the cytoskeleton with the substratum through the cell membrane. In the last point the system is closed by a model for the nucleation of actin, where the nucleation depends on the concentration of integrin at the edge.

All in all a self consistent 1-D model of a steady moving cell is derived and some simulations are made. The characteristic timescales for all processes are of the same order of magnitude, so they are made at the same time.

We presented this paper because it shows actin as a small building part of a greater model, and also introduces other proteins influencing cell motility.

Appendix B

Proteins

So far we have only talked about actin, but there exist a lot of other proteins that influence the behavior and the properties of the actin network in the lamellipodium. In this chapter we want to give a short introduction to the most important proteins of actin filament dynamics. Great parts of this summary are taken from [2].

The proteins controlling acin filament turnover can be grouped by their function as follows:

- Severing proteins: these sever actin filaments to generate more filament ends assembly or disassembly. They include the ADF (actin depolymerizing factor)/cofilin family of proteins and gelsolin.
- Capping proteins: Other proteins function to cap filament ends to regulate addition or loss of actin subunits (capping protein, gelsolin, the Arp 2/3 complex), to nucleate filament growth (the Arp 2/3 complex, formin), or to enhance subunit dissociation by cofilin.
- Sequestering proteins: These sequester actin monomers to prevent spontaneous nucleation of filaments (β-thymosins) or interact with actin monomers to enhance nucleotide exchange (profilin).
- Crosslinking proteins: these crosslink the actin filaments and can induce a sol to gel transition. An example is α-actinin. Others such as vinculin, talin and zyxin link the cortex (the network adjacent to the membrane) to the plasma membrane.

This classification is not exclusively because some proteins execute two or more functions, like twinfilin. The protein twinfilin is known for its regulating effects on actin dynamics. It sequesters actin monomers and caps the barbed ends of filaments, thus inhibiting polymerization there.

The Arp 2/3 complex, so called because it contains the actin related proteins Arp2 and Arp3, nucleates new actin filaments, probably in response to signals. In vitro the Arp 2/3 induces branching of actin filaments, caps the slow growing (pointed) ends of filaments, and nucleates actin assembly.

The mechanism by which ADF/cofilin proteins control the filament size distribution is not completely clear. Initially severing was thought to be a major factor but there exist forms of cofilin that increase actin polymerization without severing the filaments.
Gelsolin is also a strong actin fragmenter, but it also acts as a capper and as a nucleation site. Still the exact role of gelsolin is not understood.

The interplay of all these factors produces a dynamically actin network and a varying distribution of actin filament length. But the complete process of actin filament dynamics is far from being understood.

Bibliography

[1] Bruce Alberts et al. *Molecular Biology of the Cell.* Garland Science, Taylor and Francis Group, New York, 4th edition, 2002.

[2] Hans G. Othmer, Jifeng Hu, and Anastasios Matzavinos. A theoretical approach to actin filament dynamics. *Journal of Statistical Physics*, 128(1-2):111–138, 2007.

[3] David Sept, Jingyuan Xu, Thomas D. Pollard, and J. Andrew McCammon. Annealing accounts for the length of actin filaments formed by spontaneous polymerization. *Biophysical Journal*, 77:1911–2919, 1999.

[4] Ölz Dietmar. *Asymptotic nonlinear models in mathematical Physics and Biology.* University of Vienna, Vienna, 2007. PhD Thesis.

[5] Pollard T. D. and Earnshaw W. D. *Cell Biology.* Saunders, New York, st1 edition, 2004.

[6] M.F. Carlier. Actin: Protein structure and filament dynamics. *Journal of Biological Chemistry*, 266:1–4, 1991.

[7] F. Oosawa and S. Asakura. *Thermodynamics of the polymerization of protein.* Academic Press, London, New York, 1975.

[8] Hans G. Othmer and Anastasios Matzavinos. A stochastic analysis of actin polymerization in the presence of twinfilin and gelsolin. *Journal of Theoretical biology*, 249(1-2):723–736, 2007.

[9] Leah Edelstein-Keshet and G. Bard Ermentrout. A model for actin-filament length distribution in a lamellipod. *Journal of Mathematical Biology*, (43):325–355, 2001.

[10] Lawrence C. Evans. *Partial Differential Equations*, volume 19 of *Graduate Studies in Mathematics.* American Mathematical Society, Providence, Rhode Island, 1998.

[11] Winfried Auzinger. *Numerik partieller Differentialgleichungen - Eine Einführung.* Lecture Script. University of Technology Vienna, Vienna, 2003.

[12] Randall J. and LeVeque J. *Numerical Methods for Conservation Laws.* Lectures in Mathematics, ETH Zürich. Birkhäuser Verlag, 2nd edition, 1992.

[13] Jeremy Roland, Julien Berro, Alphee Michelot, Laurent Blanchion, and Jean-Louis Martiel. Stochastic severing of actin filaments by actin depolymerizing factor/cofilin controls the emergence of a steady dynamical regime. *Biophysical Journal*, 94:2082–2094, 2008.

[14] Alex Mogilner. On the edge:Modeling protrusion. *Current Opinion in Cell Biology*, 18:32–39, 2006.

[15] A. D. Gillespie. A generally method for numerically simulating the stochastic time evolution of coupled chemical reactions. *Journal of Computational Physics*, 22:403–434, 1976.

[16] A. Mogilner, E. Marland, and D. Bottino. *A minimal model of locomotion applied to the steady gliding movement of fish keratocyte cells*, pages 269–289. in: Philip K. Maini, Hans G. Othmer: Mathematical Models for Biological Pattern Formation. Springer, 2000.