

# DIPLOMARBEIT

## Microtubule Length Distribution: A Modeling Approach

zur Erlangung des Akademischen Grades  
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# Abstract

Microtubules are highly dynamic elements of the cytoskeleton of eukaryotic cells. In this thesis a model for the length distribution of microtubules in consideration of GTP caps is introduced. The presence of a GTP cap prevents a microtubule from depolymerization. Therefore, the dynamic of GTP caps plays a crucial role for the length distribution of microtubules. Under the biological motivated assumption that a microtubule that loses its GTP cap immediately starts to depolymerize, the length distribution of microtubules is investigated. It will be shown that the numerical approximation of the model developed in this thesis corresponds with molecular biological observations and with a different modeling approach which considers protein-induced severing of microtubules instead of GTP caps.



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# Chapter 1

## Introduction

### 1.1 Microtubule Structure, Function and Organization

Microtubules are stiff, hollow cylindrical tubules which form together with actin filaments and intermediate filaments the cytoskeleton (see figure 1.1) of all dividing eukaryotic cells and most differentiated cell types. In nondividing cells (interphase) microtubules position the nucleus, direct the intracellular transport of organelles, vesicles et cetera and build as bundled structures the flagellum and cilia (locomotion/sensory organelles). During cell division (mitosis) microtubules form the mitotic spindle and physically segregate the duplicated chromosomes.[1, 2, 3]

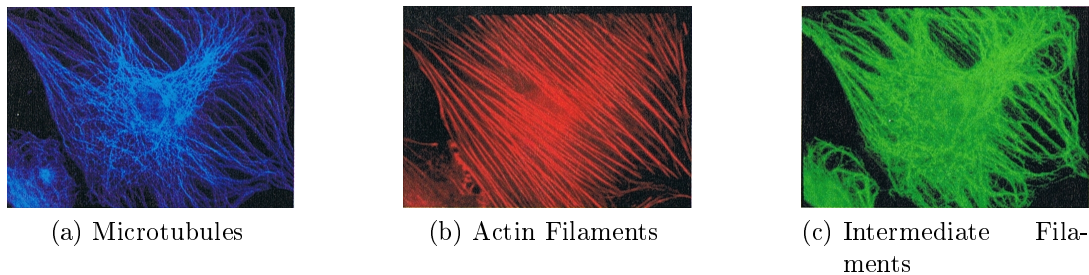


Figure 1.1: Cytoskeleton [1]

Microtubules are built up by the protein complex  $\alpha\beta$ -tubulin, a heterodimer of 8nm length consisting of the globular proteins  $\alpha$ -tubulin and  $\beta$ -tubulin.  $\alpha\beta$ -tubulin dimers are arranged in linear chains thus forming protofilaments with subunits ( $\alpha$ -tubulin,  $\beta$ -tubulin) alternating down. This provides a polar structure of microtubules with  $\alpha$ -tubulin exposed at the (-)end and  $\beta$ -tubulin at the (+)end. 13 parallel arranged protofilaments form the wall of a microtubule whose external diameter is about 25 nm.[1, 2]

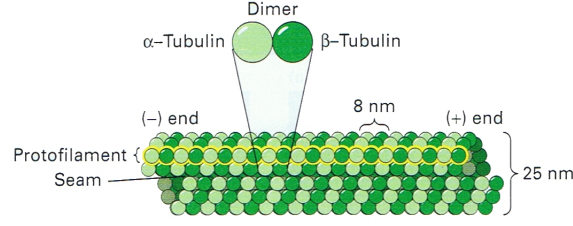


Figure 1.2: Build-up of a microtubule [1] (modified)

In contrast to intermediate and actin filaments, microtubules are not randomly distributed throughout the cell. Microtubules radiate from a microtubule organizing center, MTOC (see Figure 1.3). Whereas the (-)end of a microtubule is anchored at the MTOC. In animal cells the centrosome plays the role of a MTOC where the microtubules are nucleated in a radial array. A centrosome consists of a pair of orthogonally arranged centrioles and pericentriolar material in which hundreds of nucleation centers are embedded. A nucleation center is formed by a  $\gamma$ -tubulin ring complex where  $\alpha\beta$ -tubulin can assemble.[1, 2]

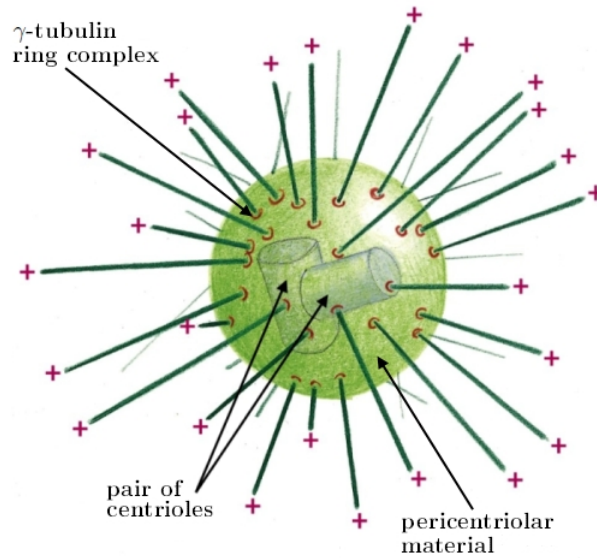


Figure 1.3: Microtubules growing from  $\gamma$ -tubulin ring complexes of the centrosome (MTOC) [1] (modified)

Like actin filaments, microtubules are highly dynamic structures. They change their length by assembling and disassembling of  $\alpha\beta$ -tubulin subunits, i.e. polymerization and depolymerization respectively. In principal polymerization and depolymerization occur at both ends of a microtubule but the kinetic rate constant for assembling and disassembling is much greater at the (+)end of a microtubule [1]. Thus in this thesis the (-)end of microtubules will be assumed as stable while the (+)end can undergo

phases of growth and shrinking. The frequent alternating between prolonged phases of polymerization and depolymerization is referred to as *dynamic instability*. A detailed description of *dynamic instability* and its consequences is given in the next section.

A more detailed description of microtubule structure, organization and functions can be found in various educational books on molecular cell biology like [2, 1] and an elaborate view on microtubule polymerization is presented in [3].

## 1.2 Dynamic Instability

While in cells nascent microtubules nucleated at the centrosome show persistent growth toward the cell margin, they display frequent fluctuations between phases of growth and shrinking when they have reached the cell margin.[4] These fluctuations are known as *dynamic instability*.

Since the (-)end of a microtubule remains anchored at the centrosome and thereby gets stabilized, the (+)end undergoes these phases of polymerization and depolymerization. Thereby the transition from growing to shrinking and vice versa is referred to as *catastrophy* and *rescue*, respectively.

The *dynamic instability* of microtubules is governed by the presence of a GTP cap.

GTP (guanosine triphosphate) is a nucleotide bound at each  $\alpha$  and  $\beta$  monomer. The GTP molecule bound to the  $\alpha$ -tubulin monomer is physically trapped and never hydrolyzed. The nucleotide at the  $\beta$ -tubulin monomer may be in either the GTP or the GDP (guanosine diphosphate) form.  $\alpha\beta$ -tubulin dimers which assemble to a microtubule are in a pure GTP state, i.e. the  $\alpha$ - as well as the  $\beta$ -tubulin monomer have bound a GTP molecule. A certain time after the assembly of an  $\alpha\beta$ -tubulin dimer to a microtubule the GTP bound to the  $\beta$ -tubulin will hydrolyze to GDP. If the assembly of  $\alpha\beta$ -tubulin dimers is faster than the hydrolysis of GTP to GDP, a GTP cap is generated at the (+)end of a microtubule.[2]

Studies have shown that single protofilaments containing GDP are curved while protofilaments with GTP are straight. This leads to the conclusion that GTP of newly added dimers forming a cap prevents the single protofilaments from curling. If this GTP cap is lost due to hydrolysis a *catastrophy* occurs. The protofilaments building up a microtubule will peel away and the microtubule starts to depolymerize (see Figure 1.4).[1]

Still  $\alpha\beta$ -tubulin dimers can assemble to depolymerizing microtubules. And if the assembly is fast enough a GTP cap may be regenerated. However, this *rescue* is a rare event compared with the polymerization rate of a microtubule containing a GTP cap.

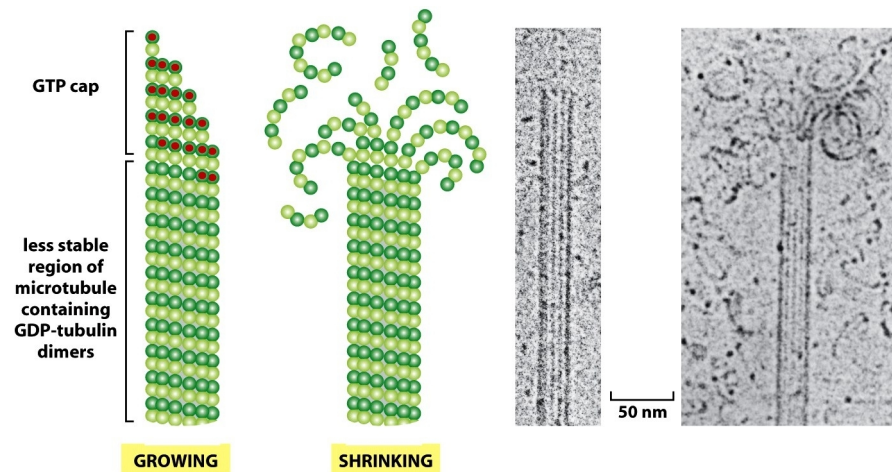


Figure 1.4: Scheme of growing and shrinking microtubule [1]

The basic properties of microtubules as part of the cytoskeleton, nucleating from the centrosome in a radial array and undergoing dynamic instability, results into a searching of the cytoplasmatic space. If a microtubule encounters a structure or organelle, it will be captured by a capping protein. Thereby the (+)end of the microtubule will be stabilized, i.e. its length stays constant. Whereas unattached microtubules will remain in a state of dynamic instability searching the space. This intrinsic property of *Search-and-Capture* is part of the mechanism to determine the overall distribution of the microtubule network in a cell.[1]

# Chapter 2

## Model

The aim of this chapter is to derive a system of partial differential equations and corresponding boundary conditions which will describe the length distribution of microtubules in an unconfined domain.

As described in Section 1.2 microtubules are either favoring polymerization or depolymerization depending on the presence of a GTP cap. Hence the length distributions will be modeled separately for microtubules containing a GTP cap and those lacking one. For this approach two different lengths will be taken into account: on the one hand the microtubules' length itself and on the other hand the length of GTP caps.

As for every modeling approach several assumptions and simplifications have to be introduced.

The tubule geometry of microtubules built up by protofilaments is reduced to an one-dimensional rod formed by subunits. Those subunits can be in two different states (GTP and GDP) corresponding to the different states of  $\beta$ -tubulin monomers described in the previous chapter, cf. Figure 1.2 and Figure 2.1.

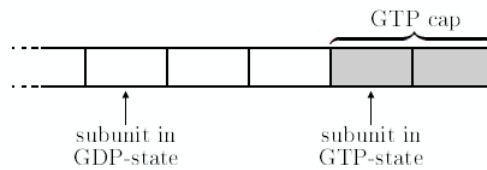


Figure 2.1: Schematic representation of a microtubule

Further assumptions are that

- sufficient, equally distributed tubulin is available, i.e. the probabilities of polymerization and depolymerization are constant throughout the whole domain,

- the nucleation center of a completely depolymerized microtubule will immediately be used to form a new one,
- spontaneous hydrolysis can occur in the interior of a GTP cap [5].

## 2.1 Derivation of model equations

In this section the model equations for the length distribution of microtubules are derived by first formulating the fundamental biological behavior of microtubules, i.e. polymerization and depolymerization of tubulin as well as hydrolysis of the GTP cap, via difference equations and second using Taylor series and a limit transition to get the corresponding differential equations.

As described in the previous chapter a microtubule shows distinct behavior depending on the presence of a GTP cap. A microtubule containing a GTP cap is highly favored to polymerize and protected from depolymerization. In contrast, an uncapped microtubule is rapidly depolymerizing, cf. Figure 1.4.

This fact suggests a separate description of capped and uncapped microtubules. Whereas the transition from one state to the other, i.e. capped microtubules lose their cap (*catastrophy*) and uncapped microtubules restart polymerizing (*rescue*), will be taken into account via boundary conditions.

### 2.1.1 Capped microtubules

A microtubule containing a GTP cap is characterized via two different lengths. On the one hand the microtubule's length itself denoted by the variable  $x$ , on the other hand the cap's length  $y$ , whereas  $y \leq x$ . Both variables are discretized into parts of equal length denoted by  $\Delta x$  and  $\Delta y$ , respectively.

As the cap length describes the state of connected subunits at the (+)end of a microtubule it is reasonable to use the same discretization increment for microtubule and GTP cap length, i.e.  $\Delta y = \Delta x$ .

At last a discretization of time  $t$  via  $\Delta t$  is introduced.

Summarized, the number of microtubules with length  $x_j = j\Delta x$  containing a GTP cap at its (+)end with length  $y_j = k\Delta y$  at time  $t_j = n\Delta t$  is denoted by  $C_{j,k}^n$ .

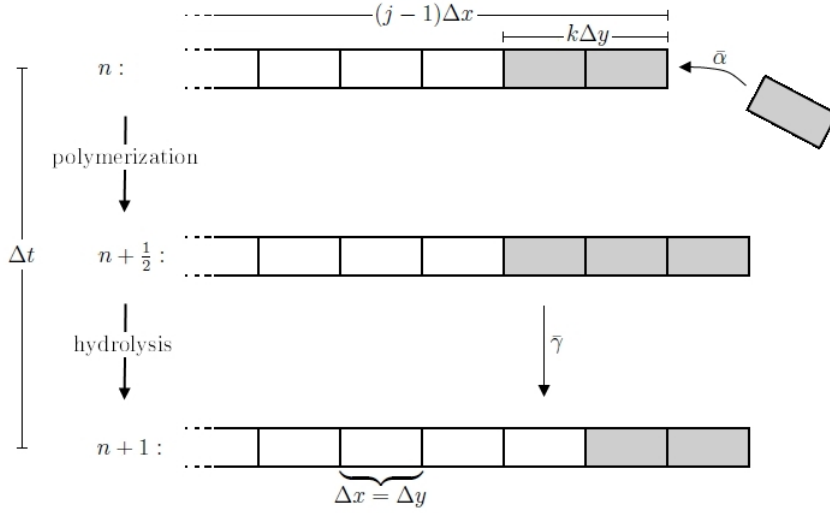


Figure 2.2: Polymerization of a microtubule and hydrolysis of the GTP-cap

To deduce the equation for capped microtubules from polymerization of subunits and hydrolysis of the cap an auxiliary timestep is introduced, where polymerization occurs. A capped microtubule grows by addition of one subunit with a constant rate  $\bar{\alpha}$  represented via

$$C_{j,k}^{n+\frac{1}{2}} = C_{j,k}^n + \bar{\alpha}C_{j-1,k-1}^n - \bar{\alpha}C_{j,k}^n. \quad (2.1)$$

After this auxiliary timestep the GTP cap hydrolyzes with a constant rate  $\bar{\gamma}$  at its left end represented via

$$C_{j,k}^{n+1} = C_{j,k}^{n+\frac{1}{2}} + \bar{\gamma}C_{j,k+1}^{n+\frac{1}{2}} - \bar{\gamma}C_{j,k}^{n+\frac{1}{2}} \quad (2.2)$$

Substituting 2.1 into 2.2 leads to

$$\begin{aligned} C_{j,k}^{n+1} = & C_{j,k}^n + \bar{\alpha} (C_{j-1,k-1}^n - C_{j,k}^n) + \bar{\gamma} (C_{j,k+1}^n - C_{j,k}^n) \\ & + \bar{\alpha}\bar{\gamma} (C_{j-1,k}^n - C_{j-1,k-1}^n + C_{j,k}^n - C_{j,k+1}^n) \end{aligned} \quad (2.3)$$

for every  $j - 1 \geq k \geq 1$ .

To derive a corresponding differential equation for (2.3) additional calculations have to be done. First  $C_{j,k}^n$  is subtracted from both sides. Further the right side of (2.3) is

extended to split the term related to  $\bar{\alpha}$  into parts for microtubule length and cap length, respectively.

$$C_{j,k}^{m+1} - C_{j,k}^m = \bar{\alpha} (C_{j-1,k-1}^m - C_{j,k-1}^m + C_{j,k-1}^m - C_{j,k}^m) + \bar{\gamma} (C_{j,k+1}^m - C_{j,k}^m) + \bar{\alpha}\bar{\gamma} (C_{j-1,k}^m - C_{j-1,k-1}^m + C_{j,k}^m - C_{j,k+1}^m) \quad (2.4)$$

Now, (2.4) is divided by  $\Delta t$  and the differences on the terms on the right side are extended by the corresponding length increment. Finally, the difference equation for length distribution of capped microtubules becomes

$$\begin{aligned} \frac{C_{j,k}^{m+1} - C_{j,k}^m}{\Delta t} = & \bar{\alpha} \frac{\Delta x}{\Delta t} \frac{C_{j-1,k-1}^m - C_{j,k-1}^m}{\Delta x} + \bar{\alpha} \frac{\Delta y}{\Delta t} \frac{C_{j,k-1}^m - C_{j,k}^m}{\Delta y} + \bar{\gamma} \frac{\Delta y}{\Delta t} \frac{(C_{j,k+1}^m - C_{j,k}^m)}{\Delta y} \\ & + \bar{\alpha}\bar{\gamma} \frac{\Delta y}{\Delta t} \frac{C_{j-1,k}^m - C_{j-1,k-1}^m}{\Delta y} + \bar{\alpha}\bar{\gamma} \frac{\Delta y}{\Delta t} \frac{C_{j,k}^m - C_{j,k+1}^m}{\Delta y}. \end{aligned} \quad (2.5)$$

Using the following notation

$$C_{j,k}^m = C(n\Delta t, j\Delta x, k\Delta y) = C(t, x, y)$$

the terms of (2.5) can be expressed via Taylor series as follows:

$$C_{j,k}^{m+1} = C(t, x, y) + \Delta t \frac{\partial C(t, x, y)}{\partial t} + \mathcal{O}(\Delta t^2) \quad (2.6)$$

$$C_{j-1,k-1}^m = C(t, x, y) - \Delta x \frac{\partial C(t, x, y)}{\partial x} - \Delta y \frac{\partial C(t, x, y)}{\partial y} + \mathcal{O}(\Delta x^2) + \mathcal{O}(\Delta y^2) \quad (2.7)$$

$$C_{j,k-1}^m = C(t, x, y) - \Delta y \frac{\partial C(t, x, y)}{\partial y} + \mathcal{O}(\Delta y^2) \quad (2.8)$$

$$C_{j,k+1}^m = C(t, x, y) + \Delta y \frac{\partial C(t, x, y)}{\partial y} + \mathcal{O}(\Delta y^2) \quad (2.9)$$

$$C_{j-1,k}^m = C(t, x, y) - \Delta x \frac{\partial C(t, x, y)}{\partial x} + \mathcal{O}(\Delta x^2) \quad (2.10)$$

Substituting (2.6)-(2.10) into (2.5) and summarizing the residuals of the Taylor series (2.5) can be rewritten as

$$\begin{aligned}
\frac{\partial C}{\partial t} = & -\bar{\alpha} \frac{\Delta x}{\Delta t} \frac{\partial C}{\partial x} - \bar{\alpha} \frac{\Delta y}{\Delta t} \frac{\partial C}{\partial y} + \bar{\gamma} \frac{\Delta y}{\Delta t} \frac{\partial C}{\partial y} \\
& + \underbrace{\bar{\alpha} \bar{\gamma} \frac{\partial C}{\partial y} - \bar{\alpha} \bar{\gamma} \frac{\partial C}{\partial y}}_{=0} + \frac{\mathcal{O}(\Delta t^2)}{\Delta t} + \frac{\mathcal{O}(\Delta x^2)}{\Delta x} + \frac{\mathcal{O}(\Delta y^2)}{\Delta y}
\end{aligned} \tag{2.11}$$

whereas for a shorter notation  $C = C(t, x, y)$  has been used.

Now,  $\Delta t$ ,  $\Delta x$  and  $\Delta y$  tend to zero in a homogeneous way such that  $\lim_{\Delta t, \Delta x \rightarrow 0} \frac{\Delta x}{\Delta t}$  and  $\lim_{\Delta t, \Delta y \rightarrow 0} \frac{\Delta y}{\Delta t}$  remain constant. Thus (2.11) becomes

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\partial C}{\partial y} = 0 \tag{2.12}$$

with  $\alpha = \bar{\alpha} \frac{\Delta x}{\Delta t} = \bar{\alpha} \frac{\Delta y}{\Delta t}$ , since  $\Delta x = \Delta y$ , and  $\gamma = \bar{\gamma} \frac{\Delta y}{\Delta t}$ .

In a final step two additional assumptions are introduced motivated by the work of Flyvbjerg. In [5] Flyvbjerg focuses on two experiments with contrary outcome by Drechsler et al. [6] and Walker et al. [7] and provides a description of the GTP cap's dynamics which copes with both experimental data.

Drechsler et al. dealt with the correlation between growth velocity of microtubules and their catastrophe rate. As described in previous sections the GTP cap of a microtubule grows by microtubule's polymerization and shrinks due to hydrolysis of GTP to GDP from its opposite end. If the latter accidentally catches up with the former a catastrophe happens, i.e. the cap vanishes and the microtubule starts to depolymerize. Due to this dynamic it is obvious that the probability of a catastrophe is dependent on the growth velocity of microtubules. Drechsler et al. show in [6] that the catastrophe frequency exponentially decays the faster a microtubule grows.

Analogously, one would expect that the GTP cap of a faster growing microtubule must take more time to disappear by hydrolysis than the cap of a slowly growing one if the growth is halted by flushing out the tubulin solution. Surprisingly, Walker et al. [7] found out that there was no correlation between the tubulin concentrations and consequently different growth velocities and the delay time between flushing out the tubulin and the incidence of depolymerization.

In [5] Flyvbjerg describes the dynamics of the GTP cap by assuming that the cap increases by addition of tubulin with an average growth rate  $v_g$  and decreases by the hydrolysis of GTP to GDP at the trailing edge of the GTP cap with an average rate

$v_h$ . This together leads to a constant growth/shrinking of the cap's length with the average velocity  $v = v_g - v_h$ . In addition Flyvbjerg assumes that GTP molecules located inside the GTP cap can hydrolyze too. Consequently, the length of a GTP cap can abruptly reduce to any fraction. This kind of cutting mechanism proportional to the cap's length guarantee that the cap remains limited in its length. Furthermore the cap's length is assumed to be influenced by an unbiased random walk parametrized by a diffusion constant. Finally, a GTP cap vanishes by combination of the cutting mechanism, reducing the cap's length to an accidentally small value, and the random walk, decreasing the length to zero. Based on the described dynamics of the GTP cap Flyvbjerg is able to provide a model for the catastrophe rate that fits with the experimental data of [6] and a model for the waiting time fitting [7].

Those two effects, the cutting mechanism and the diffusion process, are integrated into equation (2.12) for a more precise description of microtubules' length distribution.

Under the assumption that the hydrolysis of GTP to GDP is a random event, a diffusion term is added to equation (2.12)

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} \quad (2.13)$$

with diffusion constant  $D$ .

The spontaneous hydrolysis of GTP in the interior of the cap will be modeled with the same approach as the severing of actin filaments described in [8]. In [8] the authors develop a kinetic model that describes key details of actin filament dynamics, i.e. the severing of actin filaments.

The basic consequence of actin filament severing, i.e. reduction of filament length to any fraction, is similar to the assumed cutting of microtubules' GTP caps. Thus the formulation of the actin filament severing is used to model the cutting mechanism.

In [8] the length distribution of actin filaments ( $F(L, t)$ ) is given by the solution of the following integrodifferential equation.

$$\frac{\partial F(L, t)}{\partial t} = \underbrace{\nu (F(L - \delta, t) - F(L, t))}_{(1)} + \underbrace{r_5 P(L) \int_L^\infty F(s, t) ds}_{(2)} - \underbrace{r_5 F(L, t) \int_0^L P(s) ds}_{(3)} \quad (2.14)$$

The first term (1) represents the elongation or shortening (depending on the sign of  $\nu$ ,

a global (de)polymerization rate) of filaments by actin monomer addition or loss. The terms (2) and (3) represent the severing of actin filaments. Term (2) gives the gain of filaments of length  $L$  by fragmentation of longer filaments, and term (3) the loss of filaments of length  $L$  by fragmentation into shorter filaments. Here  $r_5$  is the severing rate of a specific protein involved in the fragmentation of actin filaments and  $P(L)$  is the filament-severing probability at length  $L$ . A detailed derivation of (2.14) can be found in [9] and [10].

This formulation for actin filament fragmentation (terms (2) and (3)) can be adapted to the needs of modeling the cutting of microtubules GTP caps. Using the notation for capped microtubules the cutting of GTP caps can be represented via

$$\bar{\kappa}\bar{P}(y) \int_y^x C(t, x, y') dy' - C(t, x, y) \int_0^y \bar{\kappa}\bar{P}(y') dy', \quad (2.15)$$

with a cutting parameter  $\bar{\kappa}$  and a cutting-probability to length  $y$  given by  $\bar{P}(y)$ .

Under the assumption that the hydrolysis of GTP to GDP in the interior of a GTP cap is uniformly distributed along all GTP cap lengths the cutting rate  $\bar{\kappa}\bar{P}(y)$  can be set to the constant  $\kappa$  for all  $y$ .

This assumption corresponds to [5] where Flyvbjerg suggests that the cutting of a GTP cap is proportional to its length.

Thus, the cutting mechanism is given by

$$\kappa \left( \int_y^x C(t, x, y') dy' - C(t, x, y) \int_0^y dy' \right). \quad (2.16)$$

Now, adding the cutting mechanism to (2.13) by using the formulation of (2.16), the final equation to model the length distribution of microtubules containing a GTP cap becomes

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} + \kappa \left( \int_y^x C(t, x, y') dy' - yC \right) \quad (2.17)$$

where  $\kappa$  represents the cutting rate.

### 2.1.2 Uncapped microtubules

The number of microtubules without a GTP cap can be described similarly to microtubules containing a GTP cap. Using the same discretization for time and space as in the previous subsection  $U_j^n$  denotes the number of uncapped microtubules at time  $t$  with length  $x$  whereas  $t = n\Delta t$  and  $x = j\Delta x$ .

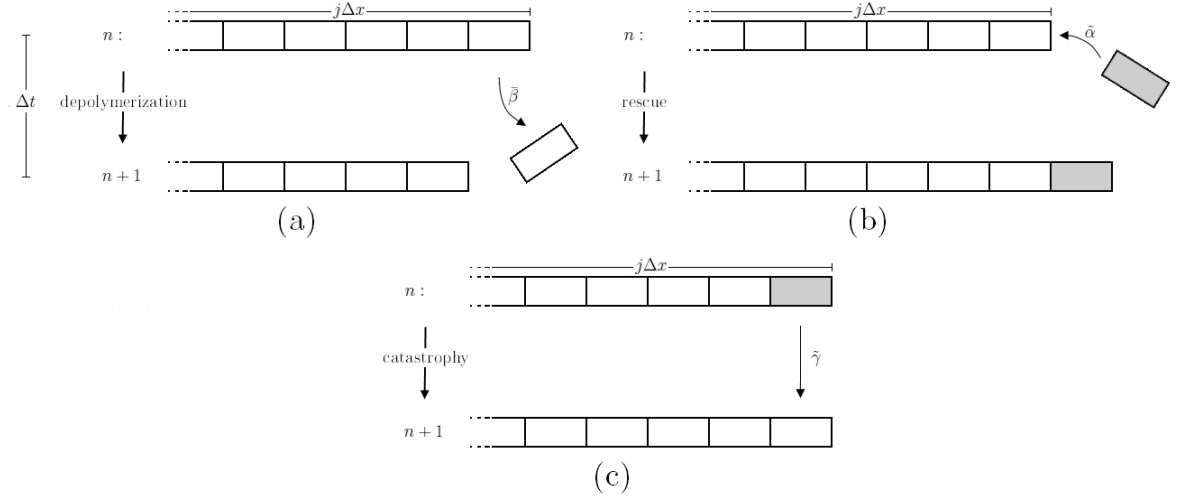


Figure 2.3: Depolymerization (a) and rescue (b) of an uncapped microtubule; catastrophe (c) of a capped

The dynamics of uncapped microtubules is mainly affected by depolymerization of tubulin subunits as consequence of a missing GTP cap. Although uncapped microtubules favor depolymerization the rare event of polymerization (and establishing a GTP cap) (*rescue*) has to be taken into account as well as the opposite event of capped microtubules losing their GTP cap (*catastrophe*).

Summing up, the dynamics of uncapped microtubules can be represented via

$$U_j^{n+1} = U_j^n + \bar{\beta}U_{j+1}^n - \bar{\beta}U_j^n + \tilde{\gamma}C_{j,1}^n - \tilde{\alpha}U_j^n. \quad (2.18)$$

The terms related to  $\bar{\beta}$  represent the depolymerization of uncapped microtubules,  $\tilde{\gamma}C_{j,1}^n$  describes *catastrophe* and uncapped microtubules starting polymerizing (*rescue*) are given by  $\tilde{\alpha}U_j^n$  with  $\tilde{\alpha} < \bar{\alpha}$  in (2.3).

In the same way as for capped microtubules a continuous version of (2.18) is derived.

First (2.18) is divided by  $\Delta t$  and the  $\bar{\beta}$  term is extended. This leads to

$$\frac{U_j^{n+1} - U_j^n}{\Delta t} - \bar{\beta} \frac{\Delta y}{\Delta t} \frac{U_{j+1}^n - U_j^n}{\Delta y} = \frac{\tilde{\gamma}}{\Delta t} C_{j,1}^n - \frac{\tilde{\alpha}}{\Delta t} U_j^n. \quad (2.19)$$

In a second step using the notation

$$U_j^n = U(n\Delta t, j\Delta x) = U(t, x)$$

the terms of (2.19) are expressed via Taylor series

$$U_j^{n+1} = U(t, x) + \Delta t \frac{\partial U(t, x)}{\partial t} + \mathcal{O}(\Delta t^2) \quad (2.20)$$

$$U_{j+1}^n = U(t, x) + \Delta x \frac{\partial U(t, x)}{\partial x} + \mathcal{O}(\Delta x^2) \quad (2.21)$$

Using (2.20) and (2.21) and the fact that  $C_{j,1}^n = C(t, x, \Delta y)$  (2.19) can be rewritten as

$$\frac{\partial U(t, x)}{\partial t} + \mathcal{O}(\Delta t^2) - \bar{\beta} \frac{\Delta x}{\Delta t} \frac{\partial U(t, x)}{\partial x} - \mathcal{O}(\Delta x^2) = \frac{\tilde{\gamma}}{\Delta t} C(t, x, \Delta y) - \frac{\tilde{\alpha}}{\Delta t} U(t, x). \quad (2.22)$$

Finally, the discretization increments  $\Delta t$ ,  $\Delta x$  and  $\Delta y$  tend homogeneously to zero which leads to the continuous formulation of (2.18)

$$\frac{\partial U}{\partial t} - \beta \frac{\partial U}{\partial x} = \gamma C|_{x=0} - \hat{\alpha} U \quad (2.23)$$

with  $\beta = \bar{\beta} \frac{\Delta x}{\Delta t}$ ,  $\gamma = \frac{\tilde{\gamma}}{\Delta t}$  (setting  $\tilde{\gamma} = \bar{\gamma} \Delta y$ ), and  $\hat{\alpha} = \frac{\tilde{\alpha}}{\Delta t}$  kept constant in the limit.

## 2.2 Initial and Boundary Conditions

The model equations derived in the previous sections represent a system of partial differential equations. A first-order partial differential equation (2.23) and a second-order partial differential equation (2.17) describing the distribution of uncapped and capped microtubules. To get a well-posed problem for this system of partial differential equations initial and boundary conditions are necessary.

### 2.2.1 Initial Conditions

For  $t = 0$  the initial condition for equation (2.17)

$$C(0, x, y) = C_0(x, y) \quad (2.24)$$

is introduced whereas  $C_0$  is a given function.

Analogously,

$$U(0, x) = U_0(x) \quad (2.25)$$

is the initial condition for equation (2.23) at  $t = 0$  with the given function  $U_0$ .

### 2.2.2 Boundary Conditions

To derive boundary conditions for the model of capped microtubules the quantity  $\bar{C}(t, x)$  is introduced. It represents the density of all capped microtubules with length  $x$  at time  $t$ . Thus  $\bar{C}(t, x)$  is given by

$$\bar{C}(t, x) = \int_0^x C(t, x, y) dy. \quad (2.26)$$

Now, equation (2.17) is integrated along  $y$  from 0 to  $x$ .

$$\begin{aligned} \int_0^x \frac{\partial C}{\partial t} dy + \alpha \int_0^x \frac{\partial C}{\partial x} dy + (\alpha - \gamma) \int_0^x \frac{\partial C}{\partial y} dy = \\ D \int_0^x \frac{\partial^2 C}{\partial y^2} dy + \kappa \left( \underbrace{\int_0^x \int_y^x C(t, x, y') dy' dy}_{(*)} - \int_0^x y C dy \right) \end{aligned} \quad (2.27)$$

To calculate (\*) integration by parts is used and Leibnitz theorem for differentiation of integral [11] is applied to interchange derivation and integration.

$$\begin{aligned}
\int_0^x 1 \cdot \int_y^x C(t, x, y') dy' dy &= \underbrace{\left( y \int_y^x C(t, x, y') dy' \right) \Big|_0^x}_{=0} - \int_0^x y \cdot \frac{\partial}{\partial y} \int_y^x C(t, x, y') dy' dy \\
&= - \int_0^x y \left( \int_y^x \underbrace{\frac{\partial C(t, x, y')}{\partial y}}_{=0} dy' - C(t, x, y) \right) dy \\
&= \int_0^x y C(t, x, y) dy
\end{aligned} \tag{2.28}$$

Now, substituting (2.28) into (2.27) leads to

$$\begin{aligned}
\int_0^x \frac{\partial C}{\partial t} dy + \alpha \int_0^x \frac{\partial C}{\partial x} dy + (\alpha - \gamma) \int_0^x \frac{\partial C}{\partial y} dy &= \\
D \int_0^x \frac{\partial^2 C}{\partial y^2} dy + \underbrace{\kappa \left( \int_0^x y C dy - \int_0^x y C dy \right)}_{=0} &
\end{aligned} \tag{2.29}$$

Using again Leibniz theorem [11] and (2.26), equation (2.29) becomes

$$\frac{\partial \bar{C}}{\partial t} + \alpha \frac{\partial \bar{C}}{\partial x} - \alpha C|_{y=x} + (\alpha - \gamma) C|_{y=0}^{y=x} = D \frac{\partial C}{\partial y} \Big|_{y=0}^{y=x} \tag{2.30}$$

From a modeling point of view, it is reasonable to ensure that microtubules at opposite ends of a domain do not interact. Under consideration of equation (2.30) this assumption can be fulfilled by setting the boundary condition at  $y = x$  to

$$\left( \gamma C + D \frac{\partial C}{\partial y} \right) \Big|_{y=x} = 0. \tag{2.31}$$

To derive a boundary condition at  $y = 0$  a new quantity  $M(t, x) = \bar{C}(t, x) + U(t, x)$ , the density of all microtubules (capped and uncapped), is introduced.

Granted that a microtubule completely depolymerizes the free nucleation center (see Section 1.1) will immediately be used to form a new microtubule. This behavior is approximated by the assumption that microtubules do not completely depolymerize. Hence, the dynamics governing the change of  $M(t, x)$  with respect to time will occur at the interior of the domain.

Now, differentiating  $M(t, x)$  with respect to  $t$  ( $\frac{\partial M}{\partial t} = \frac{\partial \bar{C}}{\partial t} + \frac{\partial U}{\partial t}$ ) and using (2.23), (2.30), (2.31) leads to

$$\frac{\partial M}{\partial t} + \alpha \frac{\partial \bar{C}}{\partial x} + \beta \frac{\partial U}{\partial x} = \left[ (\alpha - \gamma)C - D \frac{\partial C}{\partial y} \right] \Big|_{y=0} + \gamma C|_{y=0} - \hat{\alpha}U. \quad (2.32)$$

By setting the right site of (2.32) to 0 the assumption of just having a flux in the interior is met. Thus the boundary condition at  $y = 0$  is given by

$$\left( \alpha C - D \frac{\partial C}{\partial y} \right) \Big|_{y=0} = \hat{\alpha}U. \quad (2.33)$$

Finally, summing up the results of this chapter, the distribution of microtubules is described by the following system of partial differential equations and the associated boundary and initial conditions.

The dynamics of capped microtubules  $C(t, x, y)$  is given by

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} + \kappa \left( \int_y^x C(t, x, y') dy' - yC \right), \quad 0 < y < x \quad (2.34)$$

$$\gamma C(t, x, x) + D \frac{\partial C(t, x, x)}{\partial y} = 0 \quad \forall x, t > 0 \quad (2.35)$$

$$\alpha C(t, x, 0) - D \frac{\partial C(t, x, 0)}{\partial y} = \hat{\alpha}U(t, x) \quad \forall x, t > 0 \quad (2.36)$$

$$C(0, x, y) = C_0(x, y) \quad 0 < y < x \quad (2.37)$$

and for microtubules  $U(t, x)$  lacking a GTP cap by

$$\frac{\partial U}{\partial t} - \beta \frac{\partial U}{\partial x} = \gamma C|_{x=0} - \hat{\alpha} U \quad t, x > 0 \quad (2.38)$$

$$U(0, x) = U_0(x) \quad x > 0. \quad (2.39)$$

Here,  $C_0(x, y)$  and  $U_0(x)$  are given functions representing the initial distribution of capped and uncapped microtubules. Note,  $C(t, x, y)$  and  $U(t, x)$  are functions with compact support to ensure that microtubules have a finite length.

## 2.3 Dimensional analysis

In this section dimensional analysis is carried out for (2.34)-(2.37) and (2.38)-(2.39) to derive a dimensionless problem and therefore reduce the numbers of parameters.

First, dimensional analysis is used to derive a dimensionless equivalent of equation (2.34)

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} + \kappa \left( \int_y^x C(t, x, y') dy' - yC \right)$$

and equation (2.38)

$$\frac{\partial U}{\partial t} - \beta \frac{\partial U}{\partial x} = \gamma C|_{x=0} - \hat{\alpha} U$$

with a reduced number of parameters.

In a first step the dependent variables  $C(t, x, y)$  and  $U(t, x)$  and the independent variables  $t$ ,  $x$  and  $y$  are scaled by reference values  $\tilde{C}$ ,  $\tilde{U}$ ,  $\tilde{t}$ ,  $\tilde{x}$  and  $\tilde{y}$ , respectively. The variables are nondimensionalized as follows

$$C \rightarrow \tilde{C}C, \quad U \rightarrow \tilde{U}U, \quad t \rightarrow \tilde{t}t, \quad x \rightarrow \tilde{x}x, \quad y \rightarrow \tilde{y}y. \quad (2.40)$$

This will leave dimensionless variables whereas the same notation as in (2.34) and (2.38) has been used. From this point on  $C$ ,  $U$ ,  $t$ ,  $x$  and  $y$  are the dimensionless variables unless otherwise noted.

Now, to derive a dimensionless problem (2.40) is substituted into (2.34)

$$\frac{\tilde{C}}{\tilde{t}} \frac{\partial C}{\partial t} + \alpha \frac{\tilde{C}}{\tilde{x}} \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\tilde{C}}{\tilde{y}} \frac{\partial C}{\partial y} = D \frac{\tilde{C}}{\tilde{y}^2} \frac{\partial^2 C}{\partial y^2} + \kappa \left( \int_{\tilde{y}}^{\tilde{x}} \tilde{C} C(t, x, y') dy' - \tilde{y} y \tilde{C} C \right). \quad (2.41)$$

Dividing by the coefficient of the time derivative, the equation becomes

$$\frac{\partial C}{\partial t} + \alpha \frac{\tilde{t}}{\tilde{x}} \frac{\partial C}{\partial x} + (\alpha - \gamma) \frac{\tilde{t}}{\tilde{y}} \frac{\partial C}{\partial y} = D \frac{\tilde{t}}{\tilde{y}^2} \frac{\partial^2 C}{\partial y^2} + \kappa \tilde{y} \left( \int_y^{\frac{\tilde{x}}{\tilde{y}} x} C(t, x, y') dy' - y C \right). \quad (2.42)$$

In a same procedure one derives the dimensionless problem for (2.34)

$$\frac{\partial U}{\partial t} - \beta \frac{\tilde{t}}{\tilde{x}} \frac{\partial U}{\partial x} = \gamma \tilde{t} \frac{\tilde{C}}{\tilde{U}} C|_{x=0} - \hat{\alpha} \tilde{t} U. \quad (2.43)$$

Finally, the reference values  $\tilde{C}$ ,  $\tilde{U}$ ,  $\tilde{t}$ ,  $\tilde{x}$  and  $\tilde{y}$  are determined in a way such that some coefficients of (2.42) and (2.43) equal unity and reduce therefore the number of parameters for the model equations.

Setting

$$\tilde{t} = \frac{1}{\kappa \sqrt{\frac{\gamma}{\kappa}}}, \quad \tilde{x} = \sqrt{\frac{\gamma}{\kappa}}, \quad \tilde{y} = \sqrt{\frac{\gamma}{\kappa}}, \quad \frac{\tilde{C}}{\tilde{U}} = \frac{1}{\kappa \gamma \frac{\gamma}{\kappa}}$$

equals  $\gamma$  and  $\kappa$  to unity and leads to the dimensionless problems for equations (2.42) and (2.43).

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - 1) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} + \int_y^x C(t, x, y') dy' - yC \quad (2.44)$$

$$\frac{\partial U}{\partial t} - \beta \frac{\partial U}{\partial x} = C|_{x=0} - \hat{\alpha}U \quad (2.45)$$

Here, new parameters for polymerization, depolymerization et cetera are introduced as follows

$$\alpha = \frac{\tilde{t}}{\tilde{x}}\alpha = \frac{\tilde{t}}{\tilde{x}}\alpha, \quad D = \frac{\tilde{t}}{\tilde{y}^2}D, \quad \beta = \frac{\tilde{t}}{\tilde{x}}\beta, \quad \hat{\alpha} = \tilde{t}\hat{\alpha}.$$

Even though the parameters of (2.46) and (2.50) are denoted in the same way as in (2.34) and (2.38), they represent dimensionless quantities. This has been done to avoid an excessive number of symbols for parameters representing same the biological rates.

Summing up, by using dimensional analysis it is possible to reduce the number of parameters by two. With the same procedure as in 2.2 the initial and boundary conditions for the dimensionless problem are derived. The only difference to (2.34)-(2.37) and (2.38)-(2.39) is that the variables and parameters are meant in the sense of this section.

So the full dimensionless problem for capped microtubules is given by

$$\frac{\partial C}{\partial t} + \alpha \frac{\partial C}{\partial x} + (\alpha - 1) \frac{\partial C}{\partial y} = D \frac{\partial^2 C}{\partial y^2} + \left( \int_y^x C(t, x, y') dy' - yC \right), \quad 0 < y < x \quad (2.46)$$

$$C(t, x, x) + D \frac{\partial C(t, x, x)}{\partial y} = 0 \quad \forall x, t > 0 \quad (2.47)$$

$$\alpha C(t, x, 0) - D \frac{\partial C(t, x, 0)}{\partial y} = \hat{\alpha}U(t, x) \quad \forall x, t > 0 \quad (2.48)$$

$$C(0, x, y) = C_0(x, y) \quad 0 < y < x \quad (2.49)$$

and for uncapped microtubules by

$$\frac{\partial U}{\partial t} - \beta \frac{\partial U}{\partial x} = C|_{x=0} - \hat{\alpha} U \quad t, x > 0 \quad (2.50)$$

$$U(0, x) = U_0(x) \quad x > 0. \quad (2.51)$$

# Chapter 3

## Numerical Approximation

The aim of this chapter is to derive a numerical approximation of the system of partial differential equations (2.46)-(2.51).

The first section provides the discretization of the dimensionless problem. Approximations for the derivatives are given by appropriate difference quotients and the integral is approximated by a simplification of the trapezoidal rule.

The second section concentrates on the derivation of boundary conditions for the discretized dimensionless problem. In contrast to the continuous case the length of microtubules is restricted to a minimum length  $x_{min}$ . Consequently, an additional boundary condition is necessary. This has to be done to avoid difficulties with the boundary conditions (2.47) and (2.48) at the limit  $x \rightarrow 0$ . Additionally, a maximal microtubule length  $x_{max}$  is introduced.

The resulting system of linear equations given by a tridiagonal matrix will be solved in the last section by using a simplification of Gaussian elimination [12].

### 3.1 Discretization

For both capped and uncapped microtubules the same discretization of time  $t$ , microtubule length  $x$  and GTP cap length  $y$  is used. The discretization is done by using the following equidistant increments

$$\begin{aligned}\tau &= t_{n+1} - t_n \\ h &= x_{i+1} - x_i = y_{j+1} - y_j\end{aligned}$$

whereas

$$\begin{aligned}
t_n &\in [0, t_{max}] && \text{for } n = 0, \dots, N \\
x_i &\in [0, x_{max}] && \text{for } i = 1, \dots, I \\
y_j &\in [0, x_i] && \text{for } j = 0, \dots, i.
\end{aligned}$$

In addition, the discrete representatives for the number of capped microtubules  $C$  and uncapped microtubules  $U$  are given by

$$\begin{aligned}
C_{i,j}^m &\approx C(t_n, x_i, y_j), \\
U_i^n &\approx U(t_n, x_i).
\end{aligned}$$

### 3.1.1 Capped microtubules

A discrete formulation of (2.46) is derived by first using a combination of explicit and implicit Euler method to approximate the time derivative. The second-order derivative is evaluated at the time step  $t_{n+1}$  and all others at  $t_n$ .

$$\frac{C^{n+1} - C^n}{\tau} + \alpha \frac{\partial C^n}{\partial x} + (\alpha - 1) \frac{\partial C^n}{\partial y} = D \frac{\partial^2 C^{n+1}}{\partial y^2} + \int_y^x C^n(x, y') dy' - C^n \int_0^y dy' \quad (3.1)$$

with  $yC^n = C^n \int_0^y dy'$  and  $C^n$  representing  $C(t_n, x, y)$ .

Now, the first-order derivatives in  $x$  and  $y$  are approximated by using upwind difference quotients and the second-order derivative by a symmetric second-order difference quotient.

$$\begin{aligned}
\frac{C_{i,j}^{n+1} - C_{i,j}^n}{\tau} + \alpha \frac{C_{i,j}^n - C_{i-1,j}^n}{h} + (\alpha - \gamma) \frac{C_{i,j}^n - C_{i,j-1}^n}{h} = \\
D \frac{C_{i,j+1}^{n+1} - 2C_{i,j}^{n+1} + C_{i,j-1}^{n+1}}{h^2} + \int_0^{x_i} (\mathbb{1}_{y' > y_j} C_i^n(y') - \mathbb{1}_{y' < y_j} C_i^n(y_j)) dy'. \quad (3.2)
\end{aligned}$$

The integrals are approximated by the following operator  $I_i$ , a simplification of the trapezoidal rule.

Let  $x \mapsto f(x)$  be a function and  $x_k \in [0, x_n]$  an equidistant discretization with step size  $h$ . Then the operator  $I_i$  defined by

$$I_i(f) := h \sum_{k=1}^{i-1} f_k \quad (3.3)$$

where  $f_k = f(x_k)$  and  $0 \leq j \leq i \leq n$  represents an approximation for the integral  $\int_{x_i}^0 f(x)dx$ .

To apply the operators  $I'_i$  and  $I'_j$ , which represent summations along  $y'$ , on the integrals in (3.2) the limits of integration have to be adapted. To ensure that the value of the integrals do not change the integrands are rewritten by using the characteristic functions  $\mathbb{1}_{y'>y}$  and  $\mathbb{1}_{y'<y}$ , respectively. This leads to

$$\begin{aligned} \int_{y_j}^{x_i} C_i^n(y') dy' - \int_0^{y_j} C_{i,j}^n dy' &\approx I'_i(\mathbb{1}_{y'>j} C_{i,j'}^n) - I'_j(\mathbb{1}_{y'<j} C_{i,j}^n) = \\ &= h \sum_{j'=j+1}^{i-1} C_{i,j'}^n - \sum_{j'=1}^{j-1} C_{i,j}^n = h \left( \sum_{j'=j+1}^{i-1} C_{i,j'}^n - (j-1)C_{i,j}^n \right). \end{aligned} \quad (3.4)$$

Whereas a discretization of  $y'$  was used such that  $y' = y_{j'}$ . Thus  $y' = y_{j'} > y_j$  if and only if  $j' > j$ .

Finally, a discretization for (2.46) is given by

$$\begin{aligned} \frac{C_{i,j}^{n+1} - C_{i,j}^n}{\tau} + \alpha \frac{C_{i,j}^n - C_{i-1,j}^n}{h} + (\alpha - 1) \frac{C_{i,j}^n - C_{i,j-1}^n}{h} = \\ D \frac{C_{i,j+1}^{n+1} - 2C_{i,j}^{n+1} + C_{i,j-1}^{n+1}}{h^2} + h \left( \sum_{j'=j+1}^{i-1} C_{i,j'}^n - (j-1)C_{i,j}^n \right) \end{aligned} \quad (3.5)$$

### 3.1.2 Uncapped microtubules

The dynamics of uncapped microtubules given by (2.50) will be discretized in a similar way as (2.46). The approximation of the time derivative is derived by the explicit Euler method and the derivative with respect to  $y$  is again approximated by upwinding.

This leads to the following discrete formulation of (2.50)

$$\frac{U_i^{n+1} - U_i^n}{\tau} - \beta \frac{U_{i+1}^n - U_i^n}{h} = C_{i,0}^n - \hat{\alpha} U_i^n. \quad (3.6)$$

In the next section boundary conditions will be elaborated to complete the task of numerically approximating the dimensionless equivalent for the equations (2.34)-(2.37) and (2.38)-(2.39) which describe the dynamics of capped and uncapped microtubule.

## 3.2 Initial and boundary conditions

The initial and boundary conditions for the equations (3.5) and (3.6) are derived in a similar way as in Section 2.2 with the additional task of formulating boundary conditions at the minimal and maximal microtubule length.

### 3.2.1 Initial conditions

The initial conditions for the discretized model equations are given by the functions  $C_0(x, y)$  and  $U_0(x)$  from Subsection 2.2.1 evaluated at the discrete microtubule and GTP cap lengths,  $x_i$  and  $y_j$ .

### 3.2.2 Boundary conditions

In Subsection 2.2.2 the quantity  $\bar{C}(t, x)$ , the density of microtubules with length  $x$ , was introduced to derive the boundary conditions for the continuous model equations. Here, the discrete analogon  $\bar{C}_i^n$ , the number of microtubules with length  $x_i$ , is used to derive discrete boundary conditions. Thus  $\bar{C}_i^n$  is given by

$$\bar{C}_i^n = I_i(C_i^n) = h \sum_{j=1}^{i-1} C_{i,j}^n. \quad (3.7)$$

To ensure the existence of  $\bar{C}_i^n$  the restriction  $i \geq 2$  is introduced. Thus the minimal length of microtubules is set to  $x_{min} = x_2$ .

In a first step the operator  $I_i$  is applied to equation (3.5). This leads to

$$\begin{aligned} & \frac{\bar{C}_i^{n+1} - \bar{C}_i^n}{\tau} + \alpha \frac{\bar{C}_i^n - \bar{C}_{i-1}^n}{h} - \alpha C_{i-1,i-1}^n + (\alpha - 1) \underbrace{\frac{h \sum_{j=1}^{i-1} (C_{i,j}^n - C_{i,j-1}^n)}{h}}_{(1)} = \\ & D \underbrace{\frac{h \sum_{j=1}^{i-1} (C_{i,j+1}^{n+1} - 2C_{i,j}^{n+1} + C_{i,j-1}^{n+1})}{h^2}}_{(2)} + h^2 \left( \sum_{j=1}^{i-1} \sum_{j'=j+1}^{i-1} C_{i,j'}^n - \sum_{j=1}^{i-1} (j-1) C_{i,j}^n \right) \end{aligned} \quad (3.8)$$

where  $h \sum_{j=1}^{i-1} C_{i-1,j}^n = h \sum_{j=1}^{i-2} C_{i-1,j}^n + h C_{i-1,i-1}^n = \bar{C}_{i-1}^n + h C_{i-1,i-1}^n$  has been used.

Using the fact that the sums in (1) and (2) are telescoping sums, (3.8) simplifies to

$$\begin{aligned} & \frac{\bar{C}_i^{n+1} - \bar{C}_i^n}{\tau} + \alpha \frac{\bar{C}_i^n - \bar{C}_{i-1}^n}{h} - \alpha C_{i-1,i-1}^n + (\alpha - 1)(C_{i,i-1}^n - C_{i,0}^n) = \\ & D \left( \frac{C_{i,i}^{n+1} - C_{i,i-1}^{n+1}}{h} - \frac{C_{i,1}^{n+1} - C_{i,0}^{n+1}}{h} \right) + h^2 \left( \underbrace{\sum_{j=1}^{i-1} \sum_{j'=j+1}^{i-1} C_{i,j'}^n}_{(*)} - \sum_{j=1}^{i-1} (j-1) C_{i,j}^n \right). \end{aligned} \quad (3.9)$$

Similarly to (2.27) it can be shown that the second term on the right-hand side of (3.9) vanishes. Extracting (\*) leads to

$$\begin{aligned}
& \sum_{j=1}^{i-1} \sum_{j'=j+1}^{i-1} C_{i,j'}^n = \\
& \begin{array}{rcl}
& j = 1 : & C_{i,2}^n + C_{i,3}^n + C_{i,4}^n + \cdots + C_{i,i-2}^n + C_{i,i-1}^n \\
+ & j = 2 : & C_{i,3}^n + C_{i,4}^n + \cdots + C_{i,i-2}^n + C_{i,i-1}^n \\
+ & j = 3 : & C_{i,4}^n + \cdots + C_{i,i-2}^n + C_{i,i-1}^n \\
& \vdots & \vdots \\
+ & j = i-2 : & C_{i,i-2}^n + C_{i,i-1}^n \\
+ & j = i-1 : & C_{i,i-1}^n
\end{array} \\
& \hline
& = \sum_{j'=1}^{i-1} (j'-1) C_{i,j'}^n.
\end{aligned} \tag{3.10}$$

The discrete analogon to (2.30) is derived by substituting (3.10) into (3.9).

$$\begin{aligned}
& \frac{\bar{C}_i^{n+1} - \bar{C}_i^n}{\tau} + \alpha \frac{\bar{C}_i^n - \bar{C}_{i-1}^n}{h} - \alpha C_{i-1,i-1}^n + (\alpha - 1)(C_{i,i-1}^n - C_{i,0}^n) = \\
& D \left( \frac{C_{i,i}^{n+1} - C_{i,i-1}^{n+1}}{h} - \frac{C_{i,1}^{n+1} - C_{i,0}^{n+1}}{h} \right)
\end{aligned} \tag{3.11}$$

Now, the same argument as in the continuous case, i.e. microtubules at opposite ends of the domain will not interact, leads to the boundary condition for  $j = i$ .

$$\alpha(C_{i,i-1}^n - C_{i,-1,i-1}^n) - C_{i,i-1}^n - D \frac{C_{i,i}^{n+1} - C_{i,i-1}^{n+1}}{h} = 0 \tag{3.12}$$

To compute the boundary condition for  $j = 0$  the number of all microtubules at time step  $t_n$  with length  $x_i$  is introduced, cf. 2.2.2. It is given by  $M_i^n = \bar{C}_i^n + U_i^n$ . As in 2.2.2 the assumption that the dynamic governing the change of  $M_i^n$  with respect to time occurs in the interior of the domain will be used.

The differentiation of  $M(t, x)$  in 2.2.2 can be approximated by using the difference quotient  $(\frac{M_i^{n+1} - M_i^n}{\tau} = \frac{\bar{C}_i^{n+1} - \bar{C}_i^n}{\tau} + \frac{U_i^{n+1} - U_i^n}{\tau})$ . Hence,

$$\begin{aligned}
& \frac{M_i^{n+1} - M_i^n}{\tau} + \frac{(\alpha \bar{C}_i^n - \beta U_{i+1}^n) - (\alpha \bar{C}_{i-1}^n - \beta U_i^n)}{h} = \\
& (\alpha - \gamma) C_{i,0}^n - D \frac{C_{i,1}^{n+1} - C_{i,0}^{n+1}}{h} + \gamma C_{i,0}^n - \hat{\alpha} U_i^n
\end{aligned} \tag{3.13}$$

whereas (3.6) and (3.11) have been used.

Now, to ensure that the assumption of just having a flux in the interior of the domain holds, the right-hand side of (3.13) is set to zero. This leads to the boundary condition for  $j = 0$ .

$$\alpha C_{i,0}^n - D \frac{C_{i,1}^{n+1} - C_{i,0}^{n+1}}{h} = \hat{\alpha} U_i^n \quad (3.14)$$

In a final step the boundary condition for  $x_{min}$  and  $x_{max}$ , i.e. for  $i = 2$  and  $i = I$ , will be derived. For this purpose the quantity  $N(t)$  representing the total number of microtubules at time  $t$  is introduced. Thus  $N(t)$  is given by

$$N(t) = \int_{x_{min}}^{x_{max}} M(t, x) dx. \quad (3.15)$$

Now, it is assumed that the total number of microtubules is preserved, i.e.

$$\frac{d}{dt} N(t) = \int_{x_{min}}^{x_{max}} \frac{d}{dt} M(t, x) dx = 0. \quad (3.16)$$

The numerical approximation of (3.16) is done by using the operator  $I_I (= h \sum_{k=0}^{x_{I-1}} f_k)$  and a difference quotient. Before applying  $I_I$  on (3.16) the lower limit of integration has to be set to zero and thus the integrand has to be modified by the characteristic function to preserve the value of the integral, cf. (3.4).

$$\int_{x_{min}}^{x_{max}} \frac{d}{dt} M(t, x) dx = \int_0^{x_{max}} \frac{d}{dt} \mathbb{1}_{x > x_{min}} M(t, x) dx \approx h \sum_{i=3}^{I-1} \frac{M_i^{n+1} - M_i^n}{\tau} = 0 \quad (3.17)$$

The boundary conditions for  $x_{min}$  and  $x_{max}$  are now derived by summing (3.13) from  $i = 3$  to  $i = I - 1$  and using (3.14) and (3.17).

$$\begin{aligned}
h \sum_{i=3}^{I-1} \frac{M_i^{n+1} - M_i^n}{\tau} &= h \sum_{i=3}^{I-1} \frac{(\alpha \bar{C}_{i-1}^n - \alpha \bar{C}_i^n) - (\beta U_i^n - \beta U_{i+1}^n)}{h} \\
&= \underbrace{\alpha \bar{C}_2^n - \beta U_3^n}_{(1)} - \underbrace{(\alpha \bar{C}_{I-1}^n - \beta U_I^n)}_{(2)} = 0
\end{aligned} \tag{3.18}$$

Finally, (1) and (2) are set to zero to get the boundary conditions at  $x_{min}$  and  $x_{max}$ , respectively.

$$\alpha \bar{C}_2^n = \beta U_3^n \quad \text{with } \bar{C}_2^n = h C_{2,1}^n \tag{3.19}$$

$$\beta U_I^n = \alpha \bar{C}_{I-1}^n \tag{3.20}$$

Here, the same argument which gives the boundary condition (3.14), microtubules at opposite ends of the domain do not interact, has been used.

Still a boundary condition for one point,  $C_{2,2}^n$ , is missing. It is set to

$$C_{2,2}^n = C_{3,2}^n. \tag{3.21}$$

### 3.3 Solution

In this section a rough overview of the techniques used to solve the discrete model equations derived in the previous sections is presented. The full algorithm implemented in MATLAB can be found in the appendix.

Starting with the uncapped microtubules, (3.6) can be rewritten in the form of an explicit expression for the discrete solution at each point at time  $n + 1$  in terms of the solution at time  $n$ .

$$U_i^{n+1} = U_i^n + \tau \left( \beta \frac{U_{i+1}^n - U_i^n}{h} + C_{i,0}^n - \hat{\alpha} U_i^n \right) \tag{3.22}$$

The initial condition (2.51),  $U_i^0 = U_0(x_i)$ , is used as the starting point.

By rearranging (3.5), (3.12) and (3.14)  $C_{i,j}^{n+1}$  can be expressed for every  $i \geq 3$  in terms of solutions for capped and uncapped microtubules at the previous time step  $n$  by the following system of linear equations

$$\begin{pmatrix} a_{0,0} & a_{0,1} & 0 & 0 & \cdots & 0 & 0 & 0 \\ a_{1,0} & a_{1,1} & a_{1,2} & 0 & \cdots & 0 & 0 & 0 \\ 0 & a_{2,1} & a_{2,2} & a_{2,3} & \cdots & 0 & 0 & 0 \\ \vdots & & \cdots & & \ddots & \cdots & & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_{i-1,i-2} & a_{i-1,i-1} & a_{i-1,i} \\ 0 & 0 & 0 & 0 & \cdots & 0 & a_{i,i-1} & a_{i,i} \end{pmatrix} \begin{pmatrix} C_{i,0}^{n+1} \\ C_{i,1}^{n+1} \\ C_{i,2}^{n+1} \\ \vdots \\ C_{i,i-1}^{n+1} \\ C_{i,i}^{n+1} \end{pmatrix} = \begin{pmatrix} b_0 \\ b_1 \\ b_2 \\ \vdots \\ b_i - 1 \\ b_i \end{pmatrix}, \quad (3.23)$$

where the entries of the tridiagonal matrix  $\mathbf{A}$  are defined by

$$a_{l,l-1} = \begin{cases} -\frac{D}{h^2} & \text{for } 0 \leq l \leq i-1, \\ \frac{D}{h} & \text{for } l = i, \end{cases}$$

$$a_{l,l} = \begin{cases} \frac{D}{h} & \text{for } l = 0, \\ \frac{1}{\tau} + \frac{2D}{h^2} & \text{for } 1 \leq l \leq i-1, \\ \frac{D}{h} & \text{for } l = i, \end{cases}$$

$$a_{l,l+1} = \begin{cases} -\frac{D}{h} & \text{for } l = 0, \\ -\frac{D}{h} & \text{for } 1 \leq l \leq i-1, \end{cases}$$

and the vector  $\mathbf{b}$  is given by

$$b_l = \begin{cases} \hat{\alpha} U_i^n - \alpha C_{i,0}^n & \text{for } l = 0, \\ \frac{C_{i,l}^n}{\tau} - \alpha \frac{C_{i,l}^n - C_{i-1,l}^n}{h} + (\alpha - 1) \frac{C_{i,l}^n - C_{i,l-1}^n}{h} & \text{for } 1 \leq l \leq i-1, \\ +h \left( \sum_{l'=l+1}^{i-1} C_{i,l'}^n - (l-1) C_{i,l}^n \right) & \\ \alpha (C_{i,i}^n - C_{i-1,i}^n) - C_{i,i}^n & \text{for } l = i. \end{cases}$$

Due to the tridiagonal structure of the matrix  $\mathbf{A}$ , (3.23) can be solved easily and fast by using a simplification of Gauss elimination. The algorithm is expressed as MATLAB code in the appendix.

Again an initial condition (2.49) will be used as the starting point to derive the solution for (3.23).

In a final step the boundary conditions (3.19), (3.20) for capped and uncapped microtubules are used to complete the approximate solution for (2.46)-(2.51).

# Chapter 4

## Results

This chapter focuses on the qualitative behavior of the microtubule length distribution which results from the full model given by (2.34)-(2.39).

The first section presents the evaluation for the numerical approximation of (2.46)-(2.51) done in the previous chapter. The results are illustrated by a series of figures displaying the time evolution of the microtubule length distribution.

In the second section the results of this thesis will be compared to the biological observations in [13] and to the results of a different modeling approach for the microtubule length distribution given in [14].

### 4.1 Numerical evaluation

In this section the numerical approximation of (2.46)-(2.51) for one specific choice of parameters will be illustrated. The values of the parameters are given in Table 4.1.

The choice of parameters for the dimensionless problem (2.46)-(2.51) is arbitrary in the sense that the values do not reflect measurements of biological experiments. Nonetheless the chosen parameters meet two assumptions:

- the polymerization rate of capped microtubules is greater than the hydrolysis rate, i.e.  $\alpha > \gamma$
- the polymerization rate of capped microtubules is greater than polymerization rate of uncapped microtubules, i.e.  $\alpha > \hat{\alpha}$

Now, the results of the numerical approximation are given in Figure 4.1. The figure displays the resultant microtubule length distribution at the four time steps  $t_n = 100$ ,

| dimensionless parameters  |                |     |
|---------------------------|----------------|-----|
| polymerization rate       | $\alpha$       | 1.5 |
| depolymerization rate     | $\beta$        | 1.5 |
| rescue rate               | $\hat{\alpha}$ | 1.1 |
| diffusion constant        | $D$            | 1   |
| discretization increments |                |     |
| time                      | $\tau$         | 0.1 |
| microtubule length        | $h$            | 0.5 |
| GTP cap length            | $h$            | 0.5 |

Table 4.1: Overview of the values for the dimensionless parameters and the equidistant increments used for the discretization

$t_n = 150$ ,  $t_n = 200$ , and  $t_n = 275$ , where the dashed line represents the uncapped microtubules, the point-dashed line the capped microtubules, and the solid line the total number of microtubules.

Both types of microtubules, uncapped and capped, show a similar behavior in their length distribution apart from the boundary at length  $x = 0$ . Here, the number of capped microtubules is strictly increasing until a preferred microtubule length. In contrast, the number of uncapped microtubules show a decreasing behavior for very small lengths until a local minimum is reached. After reaching this local minimum the uncapped microtubules show the same behavior as the capped microtubules.

For lengths greater than the preferred length the number of capped and uncapped microtubules is declining to zero until the boundary at  $x = x_{max}$  is reached.

In Figure 4.1(d) the number of microtubules starts to increase again near the right boundary. This effect only arises due to the boundary condition (3.20). This boundary condition is necessary for the numerical approximation and thus does not reflect the overall behavior of the length distribution given by the continuous model equations (2.46)-(2.51).

Comparing Figure 4.1(a) to 4.1(d) a slight increase of the preferred microtubule length as well as widening of the length distribution can be observed.

Furthermore, the four plots in Figure 4.1 show a decrease of the scaling factor. The scaling factor for the "number of microtubules" - axis drops from  $10^{-15}$  at time step  $t_n = 100$  to  $10^{-38}$  at time step  $t_n = 275$ . Since this effect arises from the numerical approximation it does not conflict with the assumption that the total number of microtubules is preserved.

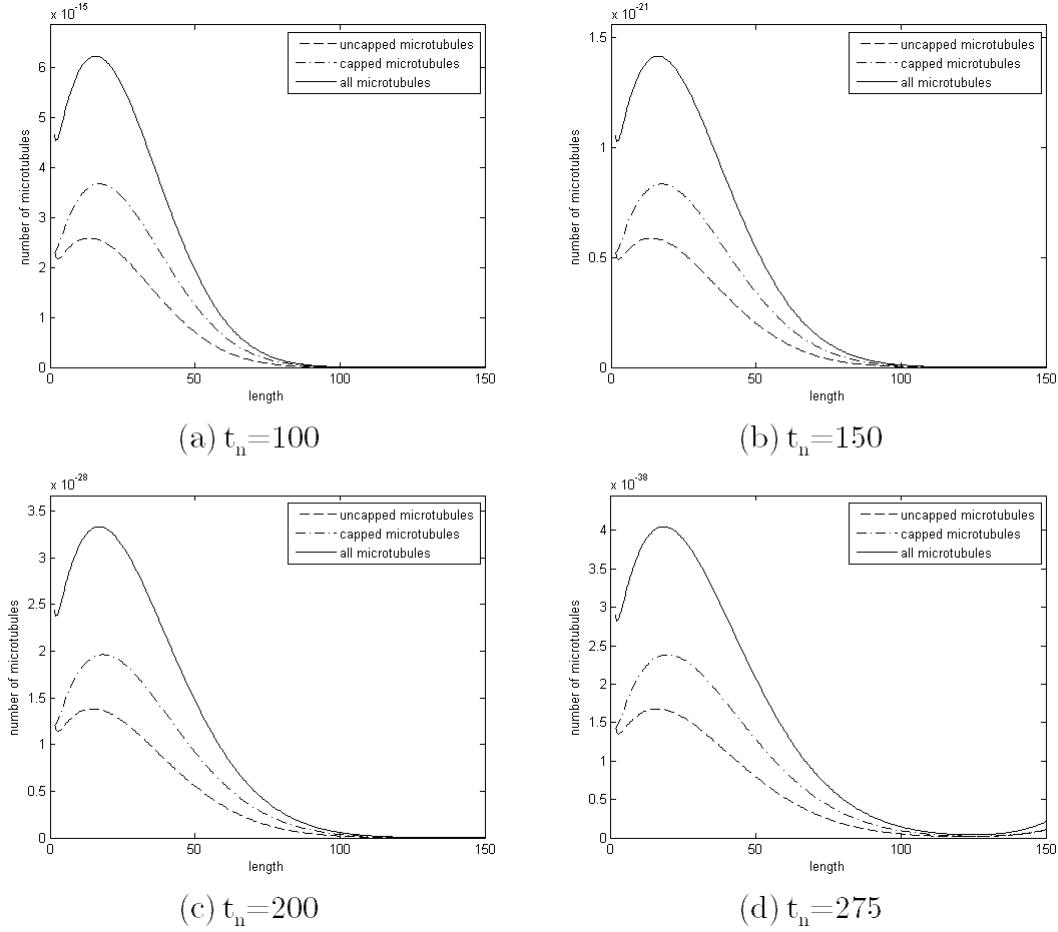


Figure 4.1: Results of the numerical approximation at several time steps

## 4.2 Comparison

First, the results of this thesis presented in the previous section are compared to the biological observations in [13].

In [13] Jeune-Smith and Hess measured the length distribution of microtubules polymerized *in vitro*. *In vitro* microtubules polymerize at both ends. This is contrary to the *in vivo*-like assumption of this thesis that the microtubule (-)end is anchored to a centrosome and therefore stable. Another contrast between this thesis and [13] is the fact that in [13] the tubulin monomers are depleted and so a steady state of the length distribution is reached, after which the disassembly of microtubules is inhibited by the drug paclitaxel (taxol).

Despite these differences the measured length distribution in [13] shows a similar behavior as the length distribution computed in this thesis.

The number of microtubules increases with increasing length until the maximum is reached at intermediate lengths followed by a slow decline in the frequency count towards higher lengths.

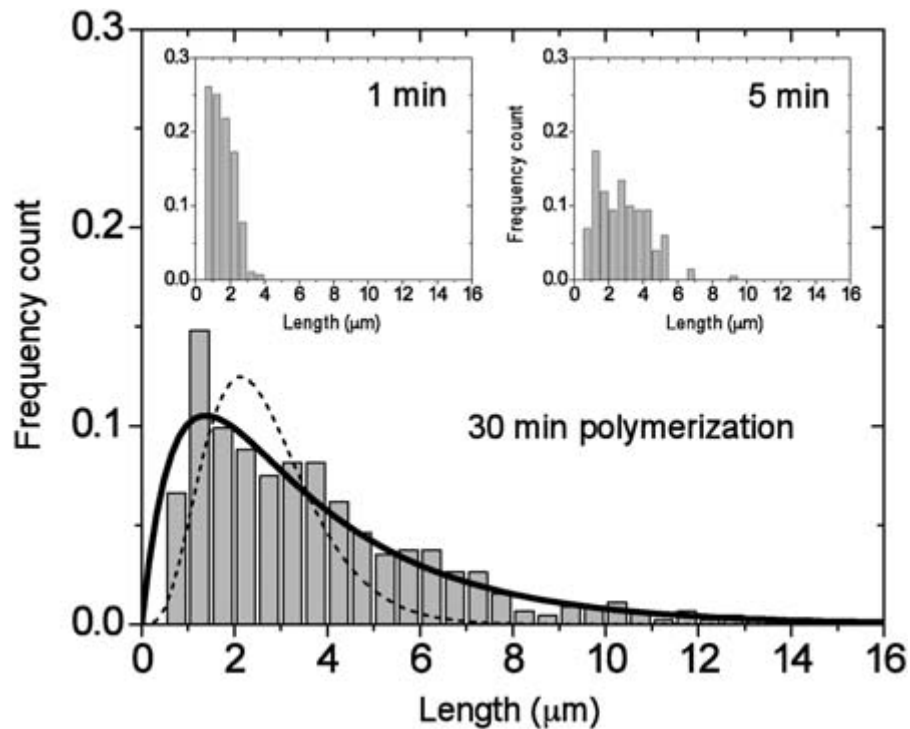


Figure 4.2: Length histogram of microtubules [13]

Figure 4.2 displays length histograms of the microtubules at 1 min, 5 min, and 30 min. The curve fit represented by the solid line has been made to an asymmetric growth model which is given in [13]. This model is based on molecular weight distributions in chain polymerization processes described by Schulz in [15]. The dashed curve fit represents a different length distribution proposed in [16].

Last, the results of a different modeling approach for microtubule length distribution given in [14] are compared to the results of this thesis.

In [14] Tindemans and Mulder investigate how the occurrence of microtubule severing at random positions influences the microtubule length distribution.

The severing of stable microtubules was noted by Vale [17] and traced back to a protein able to use ATP hydrolysis to sever microtubules. This protein was identified and named katanin [18]. Another microtubule severing protein named spastin has also been identified which shows a severing mechanism similar to that of katanin [19].

Tindemans and Mulder based their model on the dynamic instability model introduced by Dogterom and Leibler [20]. In [20], similar to this thesis, microtubules exist in either

a growing or shrinking state in which the microtubules extend with a speed  $v^+$  and retreat with a speed  $v^-$ , respectively. The transition between these states is modeled by a catastrophe rate  $r_c$  and a rescue rate  $r_r$ .

Now, Tindemans and Mulder modeled the microtubule severing by adding a severing term. The formulation of this severing term corresponds to the formulation of the cutting mechanism of GTP caps in Subsection 2.1.1.

The resulting model equations are given by

$$\begin{aligned} \frac{\partial}{\partial t} m^+(l, t) = & -r_c m^+(l, t) + r_r m^-(l, t) - v^+ \frac{\partial}{\partial l} m^+(l, t) \\ & - r_s l m^+(l, t) + r_s \int_l^\infty m^+(l', t) dl' \end{aligned} \quad (4.1)$$

$$\begin{aligned} \frac{\partial}{\partial t} m^-(l, t) = & +r_c m^+(l, t) - r_r m^-(l, t) + v^+ \frac{\partial}{\partial l} m^+(l, t) \\ & - r_s l m^-(l, t) + r_s \int_l^\infty [m^+(l', t) + 2m^-(l', t)] dl' \end{aligned} \quad (4.2)$$

and the boundary condition by

$$m^+(0, t) = \frac{r_n}{v^+}. \quad (4.3)$$

Here,  $m^+(l, t)$  and  $m^-(l, t)$  denote the length distribution of growing and shrinking microtubules, respectively. The severing rate of microtubules is given by  $r_s$  and the nucleation rate of new microtubules by  $r_n$ .

In the following Tindemans and Mulder investigated the corresponding steady state equations given in dimensionless form

$$\begin{aligned} \frac{d}{dx}f^+(x) = & -f^+(x) + rf^-(x) - sxf^+(x) \\ & + s \int_x^\infty f^+(x')dx' \end{aligned} \quad (4.4)$$

$$\begin{aligned} \frac{1}{v} \frac{d}{dx}f^-(x) = & -f^-(x) + rf^-(x) + sxf^-(x) \\ & - s \int_x^\infty [f^+(x') + 2f^-(x')]dx' \end{aligned} \quad (4.5)$$

whereas

$$\begin{aligned} f^+(x) &\equiv \frac{v^+}{r_n} m^+(l(x), t) \\ f^-(x) &\equiv \frac{v^+}{r_n} m^-(l(x), t) \\ v &\equiv \frac{v^+}{v^-} \\ r &\equiv \frac{r_r}{r_c} \\ s &\equiv \frac{r_s v^+}{r_c^2}. \end{aligned}$$

The dimensionless steady state equations were evaluated numerically for various values of  $s$  whereas  $v = 1/2$  and  $r = 1$ . The results are displayed in Figure 4.3.

For  $s = 0$ , i.e. no severing of microtubules, the microtubule length distribution is monotonically decreasing.

For  $s > 0$  the microtubule length distribution modeled by (4.1)-(4.3) shows a similar behavior as the length distribution derived in this thesis and the observed length distribution in [13]. The number of microtubules is increasing until a preferred microtubule length. This increase is followed by a monotonically decrease for greater lengths.

As it can be seen in Figure 4.4 this behavior is solely due to the contribution of growing microtubules. This is in contrast with the findings of this thesis where shrinking (uncapped) and growing (capped) microtubules have the same qualitative length distribution.

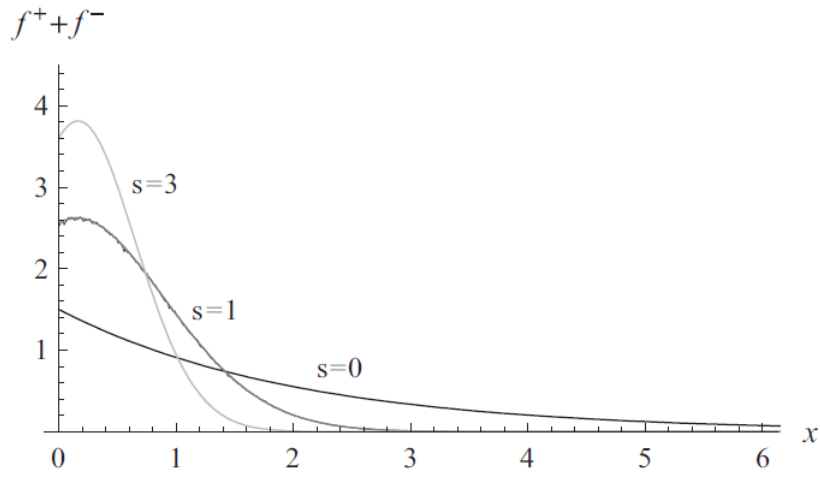


Figure 4.3: Numerically computed length distributions [14] (modified)

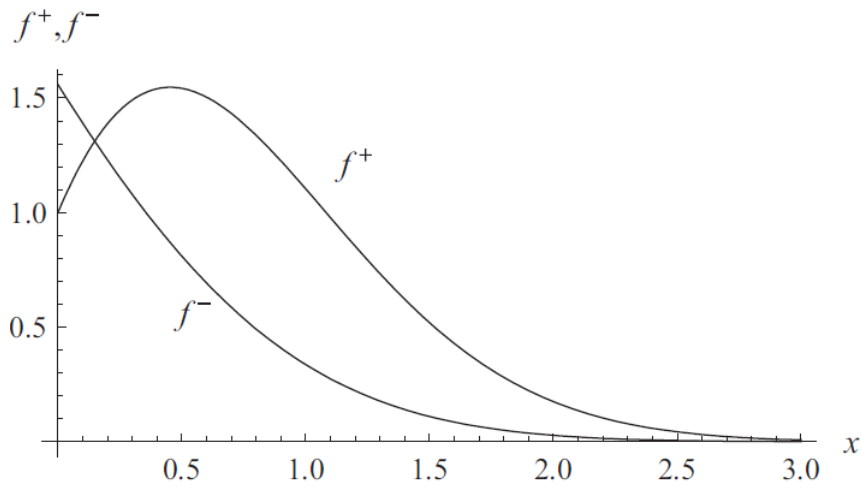


Figure 4.4: Length distribution for growing and shrinking microtubules ( $v = 1/2$ ,  $r=1$ ,  $s=1$ ) [14]



# Chapter 5

## Discussion

The model developed for this thesis is a rough approach to compute the length distribution of microtubules in interphase cells.

It has been shown that the numerical approximation of this model matches in a qualitative sense the experimental data provided by [13] and that similar modeling methods [14] are currently used in this field of research.

This indicates that the basic model approach of this thesis, i.e. distinguish between growing and shrinking microtubules as well as include the dynamics of the GTP cap as described in [5], may lead in the right direction to provide a full model for the microtubule length distribution in interphase cells.

The model given in this thesis is a first attempt to describe the dynamics of microtubules. Thus avoidable restrictions, e.g. artificial minimum length, are contained and some analysis, e.g. steady state analysis, should be done in further work.



# Appendix

```
1 %This script computes the length distributions of microtububles,
2 %based on a model given by PDEs.
3 %
4 %The numerical approximation/calculation is done by the function
5 %'calc_mts'. 'calc_mts' produces a system of linear equations
6 %represented by a tridiagonal matrix which is solved by the function
7 %'solvetridiag'.
8
9 clear
10 global alpha alpha_hat beta gamma kappa D C_init h x_max t_max x_min ...
11     tau n I T
12
13 %model parameters
14 alpha = 1.5;           %polymerization
15 alpha_hat = 1.1;       %rescue rate
16 beta = 1.5;            %depolymerization
17 gamma = 1;             %hydrolysis
18 kappa = 1;
19 D = 1;
20
21 %discretization parameters
22 h = 0.5;
23 tau = 1/5*h;
24 x_min = h;
25 x_max = 150;
26 t_max = 400;
27 I = x_max/h;
28 T = t_max/tau;
29
30 %preallocation
31 C_bar = zeros(I,T);
32 U = zeros(I,T);
33 N = zeros(T,1);
34 cap_length = zeros(I+1,T);
35 maxU = zeros(T,1);
36 maxC_bar = zeros(T,1);
37 data_U = zeros(T,1);
38 data_C_bar = zeros(T,1);
39
40
41 %initial condition
```

```

42 C_init = zeros(I,I+1);
43 u = 1;
44 if u == 2
45     C_init(10:21,10) = 1/(10*h^2);
46 else
47     C_init(50,50) = 1/(1*h^2);
48 end
49 C_old = C_init;
50 U_old = U;
51
52 for i = 3 : I
53     C_bar(i,1) = h*sum(C_init(i,2:i));
54 end
55 N(1) = h*sum(U(3:I-1,1)+C_bar(3:I-1,1));
56 maxC_bar(1) = max(C_bar(:,1));
57 data_C_bar(1) = find(C_bar(:,1) == maxC_bar(1)*ones(I,1),1)*h;
58 maxU(1) = max(U(:,1));
59 data_U(1) = find(U(:,1) == maxU(1)*ones(I,1),1)*h;
60
61 for j=1:I+1
62     cap_length(j,1) = h*sum(C_init(1:I,j));
63 end
64 tic;
65 for n = 1:T-1
66
67     %compute MTs
68
69     [U(:,n+1),C_new] = calc_mts(U(:,n),C_old);
70
71     for i=3:I
72         C_bar(i,n+1) = h*sum(C_new(i,2:i));
73     end
74
75     %cap length
76     for j = 1:I+1
77         cap_length(j,n+1) = h*sum(C_new(1:I,j));
78     end
79
80     %identify preferred length
81     maxU(n+1) = max(U(:,n+1));
82     maxC_bar(n+1) = max(C_bar(:,n+1));
83     data_U(n+1) = find(U(:,n+1) == maxU(n+1)*ones(I,1),1)*h;
84     data_C_bar(n+1) = find(C_bar(:,n+1) == maxC_bar(n+1)*ones(I,1),1)*h;
85
86     C_old = C_new;
87
88     %total number of microtubules
89     N(n+1) = h*sum(U(3:I-1,n+1)+C_bar(3:I-1,n+1));
90 end
91 toc;

```

```

1 %This function is called by 'compute_mts'. It produces a linear system
2 %of equations represented by a tridiagonal matrix. This system of
3 %equations is solved by 'solvetridiag'.
4
5 function [U_new,C_new]=calc_mts(U_old,C_old)
6
7 global alpha alpha_hat beta gamma kappa D h tau I
8
9 %preallocation
10 U_new=zeros(I,1);
11 C_new=zeros(I,I+1);
12
13 %depolymeriation
14 for i=3:I-1
15     U_new(i) = tau*(beta/h*(U_old(i+1)-U_old(i))+ ...
16               gamma*C_old(i,1)-alpha_hat*U_old(i))+U_old(i);
17 end
18
19 %nucleation
20 C_new(2,2) = beta/(alpha*h)*U_new(3);
21
22 %polymerization
23 A = zeros(I+1);
24 A(1,1:2) = [D/h -D/h];
25 A(2,1:3) = [-D/h^2 1/tau+2*D/h^2 -D/h^2];
26
27 for i=3:I
28
29     A(i,i-1:i+1) = [-D/h^2 1/tau+2*D/h^2 -D/h^2];
30     A(i+1,i:i+1) = [-D/h D/h];
31
32     b=zeros(i+1,1);
33     b(1) = alpha_hat*U_old(i)-alpha*C_old(i,1);
34     b(i+1) = alpha*(C_old(i,i)-C_old(i-1,i))-gamma*C_old(i,i);
35     k1 = ((1/tau - alpha/h - (alpha-gamma)/h)*ones(i-1,1) - ...
36           [1:i-1]'*kappa*h).*C_old(i,2:i)';
37     k2 = alpha/h*C_old(i-1,2:i)';
38     k3 = (alpha-gamma)/h*C_old(i,1:i-1)';
39     k4 = kappa*h*cumsum([0; C_old(i,i:-1:3)']');
40     b(2:i) = k1 + k2 + k3 +k4(end:-1:1);
41     C_new(i,1:i+1)=solvetridiag(A(1:i+1,1:i+1),b(1:i+1));
42
43 end
44
45 C_new(2,3)=C_new(3,3);
46 U_new(I)=alpha/beta*h*sum(C_new(I-1,2:I-1));
47 C_new = (sign(C_new.*ones(size(C_new)))+1)/2 .* C_new;

```

```

1  %solves A*x=b where A is tridiagonal square matrix
2
3  function x = solvetridiag(A,b)
4
5  n = numel(b);
6  c = zeros(n,1);
7  d = c;
8  x = c;
9  c(1) = A(1,2)/A(1,1);
10 d(1) = b(1)/A(1,1);
11
12 for i = 2:n-1
13     c(i) = A(i,i+1)/(A(i,i)-A(i,i-1)*c(i-1));
14     d(i) = (b(i)-d(i-1)*A(i,i-1))/(A(i,i)-A(i,i-1)*c(i-1));
15 end
16
17 d(n) = (b(n)-d(n-1)*A(n,n-1))/(A(n,n)-A(n,n-1)*c(n-1));
18 x(n) = d(n);
19
20 for i = n-1:-1:1
21
22     x(i) = d(i)-c(i)*x(i+1);
23
24 end

```

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# Zusammenfassung

Mikrotubuli sind hochdynamische Elemente des Zytoskeletts von eukaryotischen Zellen. In dieser Diplomarbeit wird ein Modell für die Längenverteilung von Mikrotubuli entwickelt, wobei der Einfluss von "GTP-Kappen" berücksichtigt wird. Die Dynamik der "GTP-Kappen" spielen eine entscheidende Rolle für die Längenverteilung der Mikrotubuli. Es wird angenommen, dass Mikrotubuli, die ihre "GTP-Kappe" verlieren, sofort depolymerisieren. Diese Annahme ist durch biologische Untersuchungen bestätigt. Desweiteren wird ein anderer Modellansatz, der ein Auseinanderbrechen von Mikrotubuli ausgelöst durch Proteine berücksichtigt, beschrieben. Es wird gezeigt, dass die numerische Auswertung des hier entwickelten Modells sowohl mit diesem Modellansatz als auch mit molekularbiologischen Untersuchungen übereinstimmt.



# Lebenslauf

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