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Positioning of the centrosome by microtubules

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Contents

1   Abstract

The centrosome is an important part of a cell which is responsible for the spatial organisation inside the cell, cell division and other processes. Therefore its activity is highly necessary to keep the cell alive. It is known that it loses its function if it moves away too far from the center. The centralisation mechanism is mainly caused by microtubule dynamics. In this thesis a basic introduction on those dynamics is given. Furthermore some mathematical models shall represent some of those complex behaviours like buckling or dynamic instabilty.

2 Abstract (german)

Das Centrosom gilt als einer von vielen zentralen Bausteinen der Zelle und ist für einige wichtige Prozesse innerhalb der Zelle verantwortlich, wie zum Beispiel der Prozess der Zellteilung oder die räumliche Anordnung innerhalb der Zelle. Es ist daher essenziell, dass das Centrosom nicht seine Aktivität verliert. Dies geschieht laut derzeitigen Erkenntnissen, wenn das Centrosom sich zu weit von seiner ursprünglichen Position nahe dem Zentrum entfernt. Damit dies nicht passiert verfügt die Zelle über einen cleveren Mechanismus, ein Zusammenspiel von Microtubuli und deren komplexen Dynamiken, der das Centrosom in einem stetigen Prozess an zentraler Position hält. Diese Arbeit beschäftigt sich vor allem mit diesen Dynamiken. Nach einer kurzen Einführung werden einige mathematische Modelle dargelegt, die Eigenschaften wie dynamische Instabilität oder das Verbiegen der Microtubuli nachempfinden sollen.

3 Introduction

As this thesis is a combination of cell biology and mathematical modelling I want to start by giving a short cell biological introduction to the readers (especially to "pure" mathematicians. Afterwards we should be ready to dive right into the models. There are many different types of cells to distinguish, for example if they are prokaryotes or eukaryotes where the category of prokaryotes contains archea and bacteria and the category of eukaryotes contains plants, animals etcetera. As prokaryotes do not even have a nucleus we can ignore them and therefore from now on only talk about eukaryotic cells.

In this thesis I really want to focus on those parts of a cell which contribute in some way to the mechanisms we are going to discuss. Anyway getting into too much detail is not advisable at this point. I refer to a sketch of a cell in the figure below for the more curious people out there and just go directly to the parts of the cell which are of our interest.
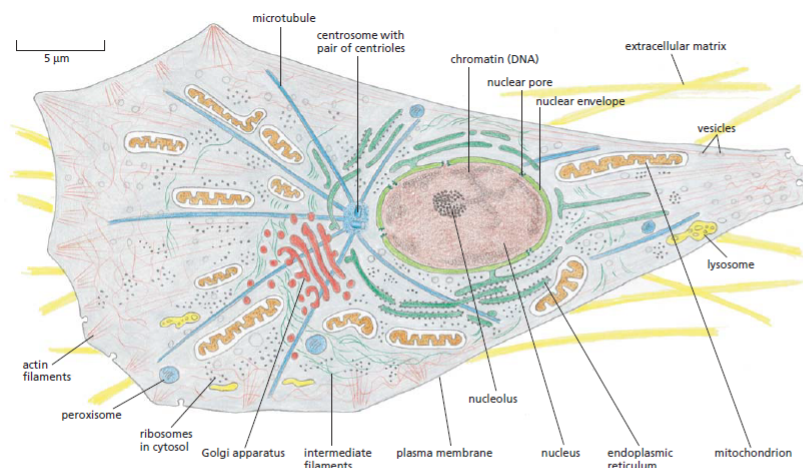

Figure: sketch of a cell [9]

3.1 Relevant parts of a cell

- The cytoplasm is a very large and complex structure in a cell. It is basically all the material within a living cell excluding the nucleus. Especially it contains organelles, the cytoskeleton and the main fluid-filled space inside cells where many chemical reactions happen. [9]

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- The whole cytoskeleton itself will not be hugely important for our purpose. It serves several functions such as cell shape changes (it can be seen as the skeleton of the cell, though it is much more flexible), cell movement and intracellular transportation. The cytoskeleton contains three different types of protein filaments. Those are the actin filaments, intermediate filaments and the microtubules. The latter will be observed in greater detail. [9]

- In most eukaryotic cells lacking a cell wall the cell membrane is modulated as well as it controlls the surface of the cell (id est the shape) by the cell cortex. Interestingely it is mechanically rigid and highly plastic at the same time.Later in our models it can be seen as some sort of boundary. [9]

- The nucleus which is embedded in the cytoplasm is a (most of the time) spherical-shaped organelle and contains chromosomes composed of DNA. [9]
  The position of the nucleus itself is crucial for the spatial organisation of the cell. It is linked to the centrosome. Therefore changes of the position of the centrosome also influence the position of the nucleus [5]. Thus the fate of the centrosome and nucleus are associated to each other.

- Close to the nucleus the so-called centrosome is located. The name suggests its position, that is the center of the cell. The centrosome itself is responsible for the spatial organisation inside the cell or for the cell division, both with the help of microtubules. This is the reason why the centrosome is called a MTOC (microtubule organisation center). It is known that the cell's organisation (direction of microtubule network, orientation of microtubules) and function is lost if the centrosome moves too far away from the center.[3],[5],[9] Here the microtubules come into play, as they keep the position of the centrosome intact. [1],[2],[3],[6], [9] The interactions between microtubules and the centrosome are quite complicated processes as microtubules themselves show pretty complicated behaviour.

- Microtubules are one of the three types of filaments sitting in the cytoskeleton. They consist of tubulin molecules. In contrast to the other types they are very stiff and long hollow tubes. They emanate from the centrosome.
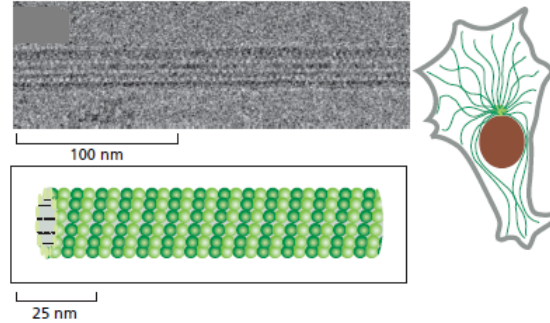
Figure: microtubule under a microscope; sketch of the structure of a microtubule; nucleus, centrosome and microtubules [9]

> They are polar with the minus end directed to the centrosome. They maintain via poly- and depolymerisation. Their main purpose though is the intracellular transport of organelles and vesicles (so they can quasi be seen as the motorways of cells). This is done by so called motor proteins. There are two types of motor proteins with respect to microtubules, kinesins and dyneins, both with a head region and a tail region. The head region binds to the surface of the microtubules and the tail region carries the load. Dyneins (which are later of our interest) "walk" from the plus to the minus end of a microtubule and kinesins vice versa. [9]

3.2   Microtubule dynamics

Now that we gained some basic knowledge it is time to take a closer look at the complicated behaviour of microtubules that we might use for our models.

As previously mentioned microtubules emanate from the centrosome with their minus end directed to the centrosome. This polarity leads to a radial structure. They grow towards the cell periphery by adding free tubulin molecules which are uniformly spread in the cytoplasma. This process is called polymerization [1],[2],[3],[9]. The farther the tip diverges from the centrosome the faster decreases the polymerization speed. This is caused by more and stronger force is acting on the tip of a microtubule when growing against a cellular object like the cortex. It has to be mentioned that a considerable component of the force is acting on the microtubule parallel to the elongation direction.[5],[7],[8]

One might think that they stop growing as they reach the cortex. In fact they continue with polymerization and grow perpendicular to the original

growth direction along the cortex. This process is called sliding. In the described case little force is acting on the tip of the microtuble. There exists also the possibility that the tip gets caught on some irregularity of the cortex (either after sliding or immediately when hitting the cortex). Then the tip of the microtubule is pivoting around this spot for a moment while the force acting on the tip enhances and at some point the microtubule buckles. There is much more force needed for this to happen if the microtubule is small, which means that in experiments where an MTOC is placed close to a boundary buckling of small microtubules could not be observerd. Therefore only longer ones show this phenomena and the longer they become the likelier it gets.[5],[7],[8]

The symmetry of the microtubule network plays a key role in the positioning process of the centrosome. Sliding and buckling may break the radial array and therefore the symmetry of the microtubule network.[3],[4],[6]. This would be bad news for the centralization of the centrosome if the cell would not know how to deal with that. Actually it shows quite a clever mechanism which will be explained in more detail.

Generally the centrosome is centered by pushing and pulling forces acting on the microtubules. Pushing forces arise when the microtubules get closer to the cortex or if they hit the cortex (or other objects in the cytoplasma). Then the force acts contrary to the growth direction and thus pushes the centrosome towards the center. If the centrosome is close to one edge of the cell, the smaller microtubules at this have much more impact on the pushing mechanism than the long ones on the other side as more microtubules reach the cortex.[2],[5],[6]

Pulling forces on the other hand are caused by the motorprotein dynein. Dyneins carry a load on their tailregion along the surface of a microtubule from the cell periphery to the center, so in direction to the minus end of the microtubule. This wandering causes a pulling force. It can be somehow compared to the process of a tug war.
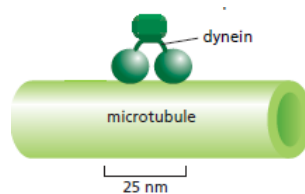

Figure: dynein on a microtubule [9]

One side wants to reach the marker by pulling the rope in their direction.

In this case the hands advancing towards the marker are the dyneins and the marker is the centrosome.

There are two different types of dyneins, the cytoplastic dynein and the cortical dynein. Cortical dynein is located at the cortex and attaches to the tips of microtubules(and when sliding possibly also to that part of the microtubule) whereas cytoplastic dynein sits at organelles in the cytoplasma and can attach along the whole microtubule. In contrast to pushing forces pulling forces boost with the length of microtubule as more dyneins can attach to a longer filament.[1],[2],[3],[6]

Both, pushing and pulling forces, scale with the number of microtubules. The interaction of those two components play the crucial role in the centering process. It is not entirely clear whether the pushing or the pulling force is dominant here. But centrosome decentering is considered to result from asymmetric (cortical) pulling force, whereas microtubule dynamics in form of pushing alone is not sufficient to position the centrosome. Therefore pulling by dynein might be dominant. Furthermore it is not obvious at all whether cortical dynein has a greater influence on the pulling mechanism than cytoplasmic dynein. Although there are models suggesting that cortical dynein is more important as the sliding of microtubules leads not only to microtubule tip - cortical dynein contact but also there is contact along the side of the filament. [1],[2],[6]

The balance of these forces and therefore the centering process is disturbed if microtubule start to buckle. Then the pushing force of buckled microtubules might be reduced significantly.[6] The cell deals with this problem with the so-called dynamic instability:

After growing for a long time at some moment microtubule performs a catastrophe. This means that the polymerization process immediately stops and depolymerization starts. Then this goes on until the microtubule comes to a stage where it flips and the polymerization starts once again. There is no clear length of a microtubule where polymerization begins. It might be that a microtubule shrinks back completely to the centrosome and a new one grows instead or it stops shrinking somewhere in the middle. The same holds for depolymerization, but a catastrophe is much more likely to happen in near future when the microtubule hitted the cortex some time ago (and/or already buckled). Opposing force might influence catastrophe rate and time in regions closer to the cortex. Depolymerization is the only way for a microtubule to lose contact with the cortex. Should for some reason the cell not be able to perform dynamic instability properly anymore, which means that a microtubule loses its ability to shrink, then this would not only break the symmetry of the network but also in a long run the network might get chaotic.[3],[4],[5],[7]

Factors that we do not take into account   There are other factors which also play a role or might play a role in the centralization process of the centrosome. Those are: the motor protein actomyosin or contact with the actin network; noncentrosomal microtubules which can affect the MT network; cell shape or cell type; the motorprotein kinesin which carries load from the minus end to the plus end of a microtubule; interactions with the nucleus[6]

4 Models

4.1 Introductory pushing-pulling model

Finally we are able to dive into our first model. In experiments a drug was added near the cortex which benefits depolymerization of microtubules by interfering polymerization. This led to microtubules losing contact with the cortex and therefore with cortical dynein. The result was that pulling force was reduced in that direction and the centrosome moved to the opposite one. (To see this they actually blocked a protein which causes the cytoskeleton to move rearward). In another experiment they went even a step further and used a dynein blocking antibody which resulted in a dramatic centrosome displacement form its normal position in the cell center to the nearest cell margin [1],[2].

   We are going to model this now in a very simple way. Assume the position of our centrosome, here denoted by C, is somewhere in the interval $[0, L]$. This interval represents two microtubules connected with each other of total length L. Furthermore let $Z_1 = \kappa C, Z_2 = \kappa(L - C)$ be length dependend pulling functions with dynein force component κ and $S_1 = S(C)$, $S_2 = S(L-C)$ (also depending on the length) our functions of pushing. The constant κ is positive and S is monotonically decreasing. $S_1, Z_1 \in [0, C]$ and $S_2, Z_2 \in [C, L]$

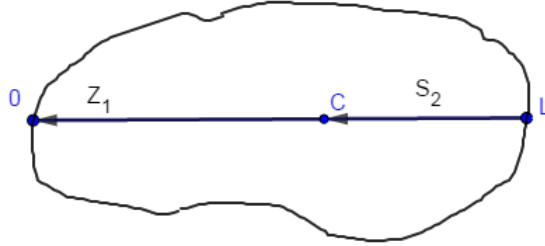**Figure:** sketch of a cell, together with the centrosome connecting two microtubules and a pulling force Z_1 and pushing force S_2

   A very naive model which describes the case where dynein is blocked completely would be just looking at the total change of force, namely :

$$0 = Z_2 - Z_1 + S_1 - S_2 - \mu\dot{C}$$
$$\Leftrightarrow \mu\dot{C} = \kappa(L - 2C) + S(C) - S(L - C), \qquad (1)$$

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where μ is a friction coefficient.

Unfortunately one can easily observe that this will never fulfill our conditions. Not only the right part of the equation is monotone decreasing everywhere, also the equilibrium $\bar{C} = \frac{L}{2}$ exists even if $\kappa = 0$.

A way to sidestep this problem would be to disturb the symmetry. The idea is to let one microtubule buckle and therefore change the pushing component of the equation. The new equation is of the form

$$\mu \dot{C} = \kappa(L - 2C) + S_b(C) - S(L - C)$$

Here $S(C) = s_0 - a_0 C$ and $S_b(C) = s_0 - a_b C$ for simplicity and of course $a_0 < a_b$ constants, as pushing force of an already buckled microtubule shall be lower than of a non buckled one. s_0 represents the initial pushing force. In this case, after a little calculation, we get two new equilibria. The first one is given by $\bar{C}_1 = \frac{\kappa + a_0}{2\kappa + a_0 + a_b} L < \frac{L}{2}$ and for $\kappa = 0$ (which means no dynein activity) we have $\bar{C}_2 = \frac{a_0}{a_0 + a_b} L$ such that $\bar{C}_2 < \bar{C}_1 < \frac{L}{2}$. If we take a look at the stability of the equilibria, we can see easily those are asymptotically stable whenever $a_0 < a_b$. This is what we expect as the buckling on one side and then turning off the pulling factor leads to stronger pushing force from the intact side.

Going back to our original equation we now try to look what happens if we lose dynein activity on just one side. We do so by setting $Z_1 = \kappa_1 C$, $Z_2 = \kappa_2(L - C)$ where first $\kappa_1 = \kappa_2$ when everything is fine and then take $\kappa_1 = \varepsilon$ if we shut down the dynein on one side.

This would lead to a second equilibrium $\tilde{C} = \frac{a + \kappa}{\varepsilon + \kappa} L > \frac{L}{2}$ in the simple case of $S(C) = s_0 - aC$ for the system

$$\varepsilon C - \kappa(L - C) + S(C) - S(L - C) < \kappa(L - 2C) + S(C) - S(L - C) = 0.$$

And so indeed our centrosome moves away from the center. It moves in the "right" direction (that is $\tilde{C} > \bar{C}$ if the magnitude of pushing and pulling are almost equal (id est if $\alpha \approx \kappa$)

4.2 Beam Models

In this section our goal is to describe the behaviour of a microtubule of some length when forces are acting on the tips and we want to investigate what minimal energy is needed for buckling or sliding. This will be done based on the models of Euler-Bernoulli Beams. First we are going to construct a general model and afterwards we are going to treat different cases by applying suitable boundary conditions on this model.

From now on a microtubule shall be represented via a parametrization of a curve $x(s)$ with endpoints x_0 and x_1, where s is a Lagrange coordinate. This little detail guarantees us that if time is changing we indeed get the orbit of a point. The behaviour of a microtuble is described by a potential Energy L which consists of several components: A resistance to curvature denoted by κ, the arc length σ of the curve $x(s)$, forces F_0 and F_1 acting on x_0 and x_1 respectively, and a condition on the total length of the microtubule which is introduced via a Lagrange multiplier λ. This just adds this extra condition via a minimum of L into the model. All together we then have:

- End points $x_i = (\xi_i, \eta_i)$, $i = 0, 1$, together with the norm $|x_i| = \parallel x \parallel_2$

- The microtubule represented by :

  $x(s) = x_0(1 - s) + x_1 s + u(s)v$, where $v = \frac{(x_1 - x_0)^\perp}{|x_1 - x_0|}$ is the normalized normalvector. $u(s)$ is a deflection of the curve and unknown. As we want to have $x(0) = x_0$ and $x(1) = x_1$ we always need the condition $u(0) = u(1) = 0$.

- The arc length of $x(s)$ denoted by $\sigma : d\sigma = |x'| ds$

- Some resistance to curvature:$\kappa = \frac{1}{|x'|}\left(\frac{x'}{|x'|}\right)'$

- Pushing forces F_0 and F_1

$$F_0 \qquad\qquad\qquad\qquad\qquad\qquad\qquad F_1$$
$$x_0 = (\xi_0, \eta_0) \qquad\qquad x(s) \qquad\qquad x_1 = (\xi_1, \eta_1)$$
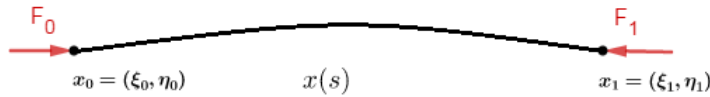
Figure: sketch of a microtubule $x(s)$ (where $\eta_0 = \eta_1$) with a small deflection

and

$$L = \frac{1}{2}\int_0^1 \left(\frac{1}{|x'|}\left(\frac{x'}{|x'|}\right)'\right)^2 d\sigma + \lambda\left(\int_0^1 d\sigma - 1\right) + <F_1, x_1> + <F_0, x_0> .$$

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The $< .,. >$ denotes the ordinary scalar product in $\mathbb{R}^n$. Now some work needs to be done to get it into a well looking shape. As the procedure of substituting and computing at this point is quite technical I explain it in more detail. Let us start by looking at the part depending on κ of the formula:

First we simply use the product rule and the chain rule. Then one needs to substitute correctly for the derivatives of $x^{(k)}$ (these are given in the appendix) and just calculate. Be aware of the orthogonal factor which leads to shorter results due to Pythagoras' Theorem. Collecting terms of order ε^2 and higher then leads to the final result. Here the steps are visualized:

$$
\begin{aligned}
\kappa &= \frac{1}{|x'|}\left(\frac{x'}{|x'|}\right)' \\
&= \frac{x''}{|x'|^2} - x'\frac{x'x''}{|x'|^4} \\
&= \frac{\varepsilon u''\frac{(x_1-x_0)^\perp}{|x_1-x_0|}}{|x_1-x_0|^2\left(1+\frac{\varepsilon^2 u'(s)^2}{|x_1-x_0|^2}\right)} - \frac{\varepsilon^2 u'(s)u''(s)\left(x_1-x_0+\varepsilon u'(s)\frac{(x_1-x_0)^\perp}{|x_1-x_0|}\right)}{|x_1-x_0|^4\left(1+\frac{\varepsilon^2 u'(s)^2}{|x_1-x_0|^2}\right)} \\
&\approx \frac{\varepsilon u''\frac{(x_1-x_0)^\perp}{|x_1-x_0|}}{|x_1-x_0|^2} - \mathcal{O}(\varepsilon^2)
\end{aligned}
$$

Now we can continue with our derivation of a better looking formula for L. We use this result for κ and calculate directly after substituting. Here we collect terms of order ε^3 and higher. In mathematical terms this means: (to keep it shorter I dropped the terms with the scalar product at this stage)

$$
\begin{aligned}
L &= \frac{1}{2}\int \kappa^2 d\sigma + \lambda\left(\int d\sigma - 1\right) \\
&= \frac{1}{2}\int \frac{\varepsilon^2 u''^2 v^2}{|x_1-x_0|^4}|x'|ds + \lambda\left(\int |x'|ds - 1\right) \\
&= \frac{1}{2}\int \frac{\varepsilon^2 u''^2 v^2}{|x_1-x_0|^2}\left(|x_1-x_0|\left(1+\frac{\varepsilon^2 u'^2}{2|x_1-x_0|}\right)\right) + \lambda\left(\int |x_1-x_0|\left(1+\frac{\varepsilon^2 u'^2}{2|x_1-x_0|}\right)\right) \\
&= \frac{1}{2}\int \frac{\varepsilon^2 u''^2 v^2}{|x_1-x_0|^3}ds + \mathcal{O}(\varepsilon^3) + \lambda\left(\int |x_1-x_0| + \frac{\varepsilon^2 u'^2}{2|x_1-x_0|}ds - 1\right) \\
&= \frac{1}{2}\int \frac{\varepsilon^2 u''^2 v^2}{|x_1-x_0|^3}ds + \mathcal{O}(\varepsilon^3) + \lambda\left(|x_1-x_0| + \frac{1}{2|x_1-x_0|}\int \varepsilon^2 u'^2 ds - 1\right)
\end{aligned}
$$

Finally we omit the ε^2 terms in order to say that the deflection u is small

and recognize that $v^2 = 1$. This leads to the compact form of L:

$$L = \frac{1}{2|x_1 - x_0|^3} \int_0^1 u''^2 ds + \lambda \left(|x_1 - x_0| + \frac{1}{2|x_1 - x_0|} \int_0^1 u'^2 ds - 1 \right)$$
$$+ <F_1, x_1> + <F_0, x_0> . \tag{2}$$

When this is the point where we start with our observations.

4.2.1 First boundary conditions

First we want to look at the case when we know the position of $x_0 = (0,0)$ and besides $u(0) = u(1) = 0$ we have no further conditions on u. Moreover there shall be a pushing force $F_1 = (f_1, 0)$ acting horizontally on x_1 and no force on x_0, which means $F_0 = (0,0)$. The amount of force f_1 acting on x_1 is known as some sort of critical buckling force. $x_1 = (\xi_1, 0)$ is unknown and needs to be determined.
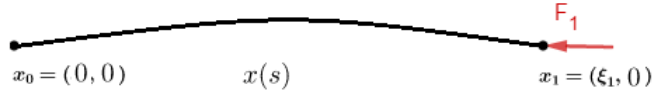

Figure: First boundary conditions applied on a microtubule with small deflection

Using this information our equation (2) for L is now of the form

$$L = \frac{1}{2\xi_1^3} \int_0^1 u''^2 ds + \frac{\lambda}{2} \left(\xi_1 + \frac{1}{2\xi_1} \int_0^1 u'^2 ds - 1 \right) + f_1 \xi_1.$$

We tackle this problem by computing diverse extrema. This leads to a system of equations for our unknown variables. Taking the derivative with respect to ξ_1 and λ therefore gives us

$$\frac{dL}{d\xi_1} = \frac{-3}{2\xi_1^4} I_2 + \lambda - \frac{\lambda}{2\xi_1^2} I_1 + f_1 = 0 \tag{3}$$

$$\frac{dL}{d\lambda} = \xi_1 + \frac{1}{2\xi_1} I_1 = 1, \tag{4}$$

where we want to denote $I_j = \int_0^1 u^{(j)^2} ds$ from now on to ensure lucidity.

Furthermore we need to compute the Fréchet derivative with respect to u, id est applying $\delta_u = u + v$ to L for small and arbitrary v and then only

letting the terms of order one survive. This arbitrary choice of v implies that also v has to fulfill the conditions $v(0) = v(1) = 0$. As this turns out to be a quite technical task (and is needed more often) I will show it in some more detail. In the following calculation I highlighted that v is small by assigning it with an ε term. In this way we substitute $u + \varepsilon v$ for u first and afterwards we take the derivative with respect to ε at $\varepsilon = 0$.

$$
\begin{aligned}
L &= \frac{1}{2\xi_1^3} \int u''^2 ds + \frac{\lambda}{2} \left(\xi_1 + \frac{1}{2\xi_1} \int u'^2 ds - 1 \right) + f_1 \xi_1 \\
L(u + \varepsilon v) &= \frac{1}{2\xi_1^3} \int (u'' + \varepsilon v'')^2 ds + \frac{\lambda}{2} \left(\xi_1 + \frac{1}{2\xi_1} \int (u' + \varepsilon v')^2 ds - 1 \right) + f_1 \xi_1 \\
&= \frac{1}{2\xi_1^3} \int u''^2 + 2\varepsilon u'' v'' + \varepsilon^2 v''^2 ds \\
&\quad + \frac{\lambda}{2} \left(\xi_1 + \frac{1}{2\xi_1} \int u'^2 + \varepsilon u' v' + \varepsilon^2 v' ds - 1 \right) + f_1 \xi_1 \\
\frac{dL(u + \varepsilon v)}{d\varepsilon} \Big|_{\varepsilon=0} &= \frac{1}{2\xi_1^3} \int 2 u'' v'' ds + \frac{\lambda}{4\xi_1} \int u' v' ds \stackrel{\wedge}{=} \delta_u L(v)
\end{aligned}
$$

It appears to be smart to take integration by parts twice at this stage. This leaves the following equation which will be observed in more detail:

$$
\delta_u L(v) = \frac{1}{\xi_1^3} \left(u'' v' - u^{(3)} v \right) \Big|_0^1 + \int_0^1 v \left(\frac{u^{(4)}}{\xi_1^3} - \frac{\lambda u''}{\xi_1} \right) ds = 0 \qquad (5)
$$

As again this has to hold for all functions v we obtain from the integral part a very nice ordinary differential equation for u. If we set $-\gamma^2 = \xi_1^2 \lambda$, it looks like

$$
u^{(4)} - \gamma^2 u'' = 0. \qquad (6)
$$

This basically means that our solutions will be of the shape of a series of sine and cosine if they exist at all. The other part of the equation gives us two more boundary conditions on u. Those are $u''(0) = u''(1) = 0$. This means that rotation is possible. Now we try the ansatz

$$
a + bs + c \sin(\gamma s) + d \cos(\gamma s) \qquad (7)
$$

for the solution. Here it is time to use the boundary conditions for u. It is easy to see that $u(0) = 0$ gives $a = 0$ and $u(1) = 0$ leads to $b + d = 0$. Actually the conditions on the second derivatives at 0 and 1 result in the solution only having the term with sine. Furthermore $-\gamma^2 = \pi^2$. All together we have

$$
u(s) = c \sin(\pi s).
$$

Due to the simple shape of the solution everything simplyfies quite a bit and it is easy to derive $I_1 = \frac{\pi^2 c^2}{2}$, $I_2 = \frac{\pi^4 c^2}{2}$ and $\lambda = \frac{-\pi}{\xi_1^2}$. From the derivative with respect to λ we can compute the value of the constant c, which is $c^2 = \frac{4(\xi_1 - \xi_1^2)}{\pi^2}$.

It remains to compute ξ_1. The straight forward way to continue would be to solve the equation

$$
\frac{-3\pi^4 c^2}{4\xi_1^4} + \lambda - \frac{\lambda \pi^2 c^2}{4\xi_1^2} + f_1 = 0
$$
$$
\Leftrightarrow \underbrace{2\pi^2 - \pi^2 \xi_1^2 - \xi_1^3 f_1}_{h(\xi_1)} = 0 \tag{8}
$$

with respect to ξ_1. But this solution $\xi_1 = \tilde{h}_f$, where $\tilde{h}_f$ is just the solution for (8) depending on f is of no use and it is much cleverer at this point to look at it the other way around. Solving the equation for f_1 leads to

$$
f_1 = \frac{2\pi^2 - \pi^2 \xi_1}{\xi_1^3} \tag{9}
$$

and we see that for $\xi_1 < 1$ the force f_1 will grow ($f_1 > \pi^2$ for $\xi_1 < 1$). As the relation between f_1 and ξ_1 is invertible a unieque solution for f_1 implies a unique solution for ξ_1.

To complete this first example we take a look at the potential Energy

$$
E_{pot} = E = \frac{1}{2\xi_1^3} I_2 + \xi_1 f_1.
$$

If we plug in what we know at this point, it actually has the form

$$
\begin{aligned}
E &= \frac{\pi^2 (\xi_1 - \xi_1^2)}{\xi_1^3} + \xi_1 f_1 \\
&= \frac{\pi^2 (3\xi_1 - 2\xi_1^2)}{\xi_1^3} \tag{10}
\end{aligned}
$$

We want to show that E is indeed a minimum for L. So that it is a steady state and it means that there can be no kinetic energy created by losing potential energy. Before we do that I just want to note the following things.

First of all $u = 0$ is always a solution and in this case we get $\xi_1 = 1$ and $E = f_1$. If we look at other potential solutions ξ_1 for different values of f_1, then after a few lines one can see that $E < f_1$ is always true for positive ξ_1 except in the case $\xi_1 = 1$. E is getting bigger the farther ξ_1 is getting away from the value 1. Something that might not be very relevant is that if $\xi_1 < 0$ (or $\xi_1 > 2$) then the pushing force f_1 is changing its sign and therefore acting in the opposite direction.

4.2.2 Formal proof for minimum

To show that we are indeed computing a Minimum (w.r.t. the Energy) we proceed in several steps. First of all we show that $E(u) = \frac{1}{2\xi^3} I_2 + f_1 \xi_1$ has a lower bound.

This can be seen by looking at the range of possible solutions for ξ_1. From our condition (4) ,which is $\xi_1^2 - \xi_1 + \frac{1}{2} I_1 = 0$ we get that

$$\xi_1 = \frac{1}{2} + \sqrt{\frac{1}{4} - \frac{1}{2} I_1}$$

The negative solution of this quadratic equation is not possible because our Integral I_1 has a positive value and therefore it would not fulfill the equation. In fact we can even say that $I_1 = \int_0^1 c^2 \pi^2 \cos^2(\pi s) ds = \int_0^1 4(\xi_1 - \xi_1^2) \cos^2(\pi s) ds$, where the constant factor $4(\xi_1 - \xi_1^2)$ is well known to be smaller or equal than 1 and therefore $I_1 \leq \frac{1}{2}$. This leads to $\xi_1 \in [\frac{1}{2}, 1]$. Now we can use this information to get a lower bound for $E(U)$ and for I_2.

$$2(E + |f_1|) \geq \underbrace{2\xi_1^3 (E - \xi_1 f_1)}_{=I_2} \geq 2\xi_1^3 (E - |f_1|)$$

$$E = \frac{1}{2\xi_1^3} I_2 + f_1 \xi_1 \geq f_1 \xi_1 \geq -|f_1|.$$

Now that we know that $E(u)$ is bounded from below, we can assume that there exists a infimum which satisfies

$$\inf_{\substack{u \in \mathcal{H}^2((0,1)) \\ \int_0^1 u'^2(s) ds \leq \frac{1}{2}}} E(U) = E_0.$$

Furthermore there exists a minimizing sequence u_n such that $\lim_{u \to \infty} E(u_n) = E_0$. Our goal is to show that there exists a u such that $E(u) = E_0$.

We continue by showing that u_n is bounded in $\mathcal{H}^2((0,1))$ due to coerzivity, where $u \in \mathcal{H}^k((0,1))$ if $||u||_{k,2} := \sum_{|\beta| \leq k} ||\partial^\beta u||_2^2 < \infty$ ($||.||_2$ of course L^2 norm). There exists a weakly convergent subsequence $u_{n_k} \rightharpoonup u \in \mathcal{H}^2((0,1))$ because bounded sequences in reflexive spaces possess one.

Then we can use that $\mathcal{H}^2((0,1))$ is compactly embedded in $C^1([0,1])$ which leads to (strong) convergence of the subsequence in the space $C^1([0,1])$. Thus by the final result follows that I_2 is weakly lower semicontinous, so that $\lim_{k \to \infty} E(u_{n_k}) = E_0 = E(u)$. And therefore our Energy is a minimum.

A Banach space X is compactly embedded in a larger Banach space Y (in mathematical terms $X \subset\subset Y$) if

a) the space X is relatively compact in Y

and   *b)* For all functions u in X the condition $||u||_Y \leq c||u||_X$ is fulfilled.

are satisfied. If only the *b)* holds, one says it is continuously embedded (denoted by $X \hookrightarrow\hookrightarrow Y$) . The spaces $C^k([a,b])$ are Banach spaces as well as $\mathcal{H}^k([a,b])$ is (even Hilbert for all k). The trick is that we use a result of lower degree for k. So that $\mathcal{H}^1((0,1))$ is compactely embedded in $C([0,1])$ If we know that, it is easy to show that $\mathcal{H}^2((0,1))$ is compactly embedded in $C^1([a,b])$ follows immediately. $\mathcal{H}^1((0,1)) \subset\subset C([a,b])$ holds due to the following argument:

Proof: Let u be in $\mathcal{H}^1((0,1))$, which means $\int_0^1 u'(s)^2 ds < \infty$. Then we can use the Cauchy-Schwartz inequality to show that u is even Hölder continuous with $\alpha = \frac{1}{2}$ via

$$|u(x) - u(y)| = |\int_y^x 1 * u'(z)dz| \leq \sqrt{|x-y|}\sqrt{\int_y^x u'(z)^2 dz}$$

So $\mathcal{H}^1((0,1))$ is continuously embedded in the space $C^{0,\frac{1}{2}}([0,1])$ and this is compactly embedded in $C([0,1])$ due to the following Theorem:

Theorem 1. *Let Ω be a bounded domain in $\mathbb{R}^n$ and let $k_1, k_2 \geq 0$ with $k_1 \leq k_2$ and $\alpha_1, \alpha_2 \in (0,1]$ such that $\alpha_1 < \alpha_2$. Then every bounded set in $C^{k_2, \alpha_2}(\bar{\Omega})$ is relatively compact in $C^{k_1, \alpha_1}(\bar{\Omega})$ and every bounded set in $C^{k_1, \alpha_1}(\bar{\Omega})$ is relatively compact in $C^{k_1}(\bar{\Omega})$. [10]*

It is clear that every Hölder continuous function is continuous, just take $\delta = (\frac{\varepsilon}{c})^{\frac{1}{\alpha}}$ for the classical $\varepsilon - \delta$ definition of continuity. $\square$

That I_2 is weakly lower semicontinuous can be seen from the following general theorem. For this it shall be noted that $I[\omega] = \int_U L(D(\omega(x)), \omega(x), x)dx$ is an energy functional, $L : \mathbb{M}^{m \times n} \times \mathbb{R}^n \times \bar{U} \longrightarrow \mathbb{R}$ is a smooth Lagrangan function, U a domain in $\mathbb{R}^n$ and $\mathbb{M}^{m \times n}$ the space of real $m \times n$ matrices.

Theorem 2. *Let L be bounded from below and $p \longmapsto L(p, z, x)$ is convex for all $z \in \mathbb{R}, x \in \Omega$. Then $I[.]$ is weakly lower semicontinuos. [10]*

Here one has to be a bit careful. Applying the theorem straight forward might get you into trouble because the integrand has a second derivative and furthermore our problem also contains some side conditions. Still the theorem holds because L depending on the second derivative is convex in the second derivative (which is clear because it is of quadratic shape). Moreover in this example ξ_1 can be derived from the condition (3) (or equivalently from (8))

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and thus the Energy does not depend on ξ_1 anymore. The resulting problem does not possess disturbing side conditions. Finally we have a minimizer by

Theorem 3. *Let L satisfy the coercivity inequality $\exists \alpha > 0, \beta \geq 0$ such that $L(p, z, x) \geq \alpha |p|^q - \beta \ \forall p \in \mathcal{R}^n, z \in \mathcal{R}, x \in \Omega$ and L be convex in p. Furthermore the admissible set A is non empty, then $\exists u_0$ such that $I[u_0] = \min_{u_k \in A} I[u_k]$. [10]*

If you read carefully, it remains still to show that $E(u, \xi_1)$ is convex. $E(u, \xi_1)$ is convex if the Hessian matrix is positive definite. The entries on the diagonal are clearly positive (since the integral is positive), so the crucial thing here is to show that for a function $g(\varepsilon) = E(u + \varepsilon v, \xi + \varepsilon \eta)$ the second derivative at zero $g''(0) \geq 0$. A straight forward calculation shows

$$g(\varepsilon) = \frac{1}{2(\xi_1 + \varepsilon \eta)^3} \int_0^1 (u'' + \varepsilon v'')^2$$

$$g'(\varepsilon) = \frac{-3\eta}{2(\xi_1 + \varepsilon \eta)^4} \int_0^1 (u'' + \varepsilon v'')^2 + \frac{1}{2(\xi_1 + \varepsilon \eta)^3} \int_0^1 2u''v'' + 2\varepsilon v''^2$$

$$g''(\varepsilon) = \frac{6\eta^2}{(\xi_1 + \varepsilon \eta)^5} \int_0^1 (u'' + \varepsilon v'')^2 - \frac{3\eta}{2(\xi_1 + \varepsilon \eta)^4} \int_0^1 2u''v'' + 2\varepsilon v''^2$$

$$+ \frac{1}{2(\xi_1 + \varepsilon \eta)^3} \int_0^1 2v''^2 - \frac{3\eta}{2\xi_1 + \varepsilon \eta)^4} \int_0^1 2u''v'' + 2\varepsilon v''^2$$

$$g''(0) = \int_0^1 \frac{1}{\xi_1} \left(\frac{3u''\eta}{\xi_1^2} - \frac{v''}{\xi_1} \right)^2 - \frac{3\eta^2}{\xi_1^5}$$

In general $g''(0) \geq 0$ does not hold. But in our case it is actually enough that the parts depending on u are greater equal than zero and this is obviously the case here as it is of quadratic form.

This concludes the proof.

4.2.3 Second boundary conditions

Another possibility which probably makes a lot of sense is to let one end
of the filament move along a horizontal wall, or along the $x-$axis so to say.
One end therefore is assumed to be clamped to the cortex. In this case again
$x_0 = 0$ is fixed but now $x_1 = (\xi_1, 0)$ is unknown. As a further restriction to
our boundary conditions $u(0) = u(1) = 0$ we now also have $u'(0) = 0$. The
pushing forces will be unchanged, so $F_0 = 0$ and $F_1 = (f_1, 0)$, so it just acts
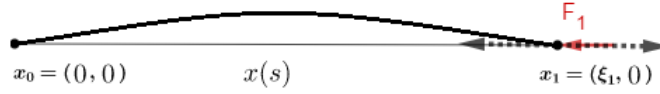on the "right" end. To visualize this I hint at the figure below.

Figure: Second boundary conditions applied on a microtubule with small
deflection. Here x_1 is able to move in the dotted directions along the hori-
zontal line

Starting with our equation (2) for L, the new conditions lead to the
absolute same shape of L after plugging in. So

$$L = \frac{1}{2\xi_1^3} \int_0^1 u''^2 ds + \frac{\lambda}{2}\left(\xi_1 + \frac{1}{2\xi_1}\int_0^1 u'^2 ds - 1\right) + f_1\xi_1.$$

Also there is nothing new if we take the derivatives with respect to λ and ξ_1

$$\frac{dL}{d\xi_1} = \frac{-3}{2\xi_1^4}I_2 + \lambda - \frac{\lambda}{2\xi_1^2}I_1 + f_1$$
$$\frac{dL}{d\lambda} = \xi_1 + \frac{1}{2\xi_1}I_1 = 1.$$

The main difference is now this extra boundary condition which also leads
to a different solution of u. So if we again take a brief look at

$$\delta_u L(v) = \frac{1}{\xi_1^3}\left(u''v' - u^{(3)}v\right)\Big|_0^1 + \int_0^1 v\left(\frac{u^{(4)}}{\xi_1^3} - \frac{\lambda u''}{\xi_1}\right) = 0,$$

it is easy to see that now $u''(0) = 0$ does not need to hold anymore but
$u''(1) = 0$ does. This already suffices to get a flavour of what u looks like
now. If we again use the ansatz (7) for $u(s)$ and the new boundary conditions,
it leads after trivial calculation to these relations for the constants

$$a = -d, \quad b = -\gamma c, \quad c = -\frac{d\cos(\gamma)}{\sin(\gamma)} \quad ,$$

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where as previously $\gamma^2 = \xi_1^2 \lambda$. So it remains to determine d. Let ω represent the solutions of the equation $\tan(\gamma) = \gamma$, then

$$u(s) = -d + \omega s d \frac{\cos(\omega)}{\sin(\omega)} - d \frac{\cos(\omega)}{\sin(\omega)} \sin(\omega s) + d \cos(\omega s)$$

satisfies equation (5).

This slightly more complicated solution already leads to more difficulties. For example I_1 and I_2 become quite ugly

$$I_1 = \frac{w(d^2 \sin(2w) + 2d^2 w + 4\lambda^2 w - 4d\lambda \sin(2w))}{4\sin(w)^2} - \lambda^2 w^2$$

$$I_2 = \frac{d^2 w^4 - \frac{d^2 w^3 \sin(2w)}{2}}{2\sin(w)^2},$$

and as a consequence mathematica struggles to solve the other equations and one needs optimization methods.

4.2.4 Third boundary conditions

Finally we think of a microtuble being able to march on a vertical wall. This scenario shall of course deal with the ability of microtubules to slide along the cortex. Our assumptions that $x_0 = 0$ and $u(0) = u(1) = 0$ stay the same but for x_1 we now have $x_1 = (\xi_1, \eta_1)$, where of course ξ_1 is known and fixed. Here we put the condition

$$\eta_1 + u'(0)v_\eta = 0$$

on the tangential vector of x_1 (which is more or less equivalent to $\eta'(0) = 0$) instead of requiring $u'(0) = 0$ like before. In fact we will use

$$0 = (\eta_1 + u'(0)v_\eta)^2 = \eta_1^2(\xi_1^2 + \eta_1^2) - u'(0)^2, \tag{11}$$

where v_η is the normal vector with respect to $\eta = \frac{\xi_1}{\sqrt{\xi_1^2 + \eta_1^2}}$. Here tit is not necessary to take pushing forces into account and so $F_i = 0$.
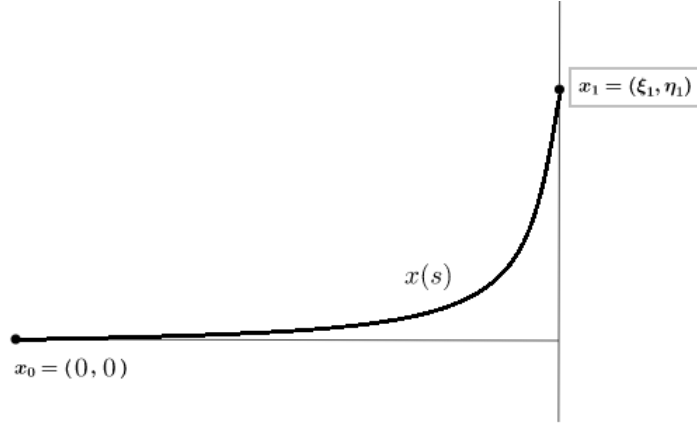

Figure: Third boundary conditions applied on a straight microtubule. The distal end is able to climb a vertical wall.

Unfortunately our new condition (11) might lead to a lot of problems if we look at it as a ordinary boundary condition because it depends on u as well and therefore some terms in the Fréchet derivative could be missing. To deal with that issue we introduce another Lagrange multiplier μ and add this condition directly to the equation. Hence instead of our

$$L = \frac{1}{2|x_1 - x_0|^3} \int_0^1 u''^2 ds + \lambda \left(|x_1 - x_0| + \frac{1}{2|x_1 - x_0|} \int_0^1 u'^2 ds - 1 \right) + <F_1, x_1> + <F_0, x_0>$$

we now consider

$$\tilde{L} = \frac{1}{2|x_1 - x_0|^3} \int_0^1 u''^2 ds + \lambda \Big(|x_1 - x_0| + \frac{1}{2|x_1 - x_0|} \int_0^1 u'^2 ds - 1 \Big)$$
$$+ \mu \Big(\eta_1^2(\xi_1^2 + \eta_1^2) - u'(0)^2 \Big). \tag{12}$$

If we want to continue with our routine and take derivatives with respect to diverse components, we need to pay attention. First of all we have now two components in x_1 and the system is not simplyfing as much as before. But more importantly η_1 will now change as well and thus in computing the Fréchet derivative we have to take care of that as well. (so not only mapping $u \longrightarrow u + v$ but also $\eta_1 \longrightarrow \eta_1 + \tilde{\eta}$). If we keep that in mind and hopefully avoid calculation errors, we now get

$$\frac{d\tilde{L}}{d\eta_1} = \frac{\eta_1}{|x_1|} \Big(\frac{-3}{2|x_1|^4} I_2 + \lambda - \frac{\lambda}{|x_1|^2} I_1 + 2\mu\eta_1^2 |x_1| \Big) + 2\mu\eta_1 |x_1|^2 = 0 \quad (13)$$

$$\frac{d\tilde{L}}{d\lambda} = |x_1| + \frac{1}{2|x_1|} I_1 = 1 \tag{14}$$

$$\delta_u \tilde{L}(v) = \frac{1}{|x_1|^3} u''(1)v'(1) - v'\Big(\frac{1}{|x_1|^3} u''(0) + 2\mu u'(0) \Big)$$
$$+ \int_0^1 v\Big(\frac{u^{(4)}}{|x_1|^3} - \frac{\lambda u''}{|x_1|} \Big) ds = 0. \tag{15}$$

Not surprisingly we obtain $u''(1) = 0$. We also have a completely fresh and unfortunately rather unappealing condition (11). Luckily our differential equation stays the same $u^{(4)} + \gamma^2 u'' = 0$ with γ as usual. Additionally we get a new equation

$$u''(0) + 2\mu|x_1|^3 u'(0) = 0$$

from where we can derive μ.

With the same ansatz (7) as always we get for u the following relations for the constants:

$$a = -d, \quad c = -\frac{d\cos(\gamma)}{\sin(\gamma)}, \quad b = \pm\eta_1\sqrt{\xi_1^2 + \eta_1^2} - c\gamma.$$

γ itself satisfies now $\gamma = \frac{d \mp \eta_1 \sqrt{\xi_1^2 + \eta_1^2}}{d \frac{\cos(\gamma)}{\sin(\gamma)}}$.

Alltogether u is now of the form

$$u(s) = -d\Big(\pm \eta_1\sqrt{\xi_1^2 + \eta_1^2} - c\gamma \Big) s - \frac{d\cos(\gamma)}{\sin(\gamma)}\sin(\gamma s) + d\cos(\gamma s).$$

Interestingely mathematica shows here complex solutions

$$u(s) = \pm \frac{i\eta_1 \sqrt{\eta_1^2 + \xi_1^2}((-1+s)\sin(\gamma) + sin(\gamma - \gamma s)}{\sqrt{-(-\gamma\cos(\gamma) + \sin(\gamma))^2}}.$$

But as in the previous case optimization methods at this stage are more useful.

4.2.5 Beam Model with Dynein

We can extend our beam models even further and include a pulling force caused by dynein. Especially it is clever to do this in the case of the third boundary conditions. I am not going to elaborate on which kind of dynein we are speaking here, but one might argue after looking at the model below that it has more of a flavour of a cytoplasmic dynein (with cortical dynein) model than a pure cortical dynein model. We introduce two new factors

- f_d...pure pulling force caused by dynein

- $\int \frac{y_1-y_0+\nu_y\nu'}{|y_1-y_0+\nu_y\nu'|}$... sacling factor depending on the length of the filament. De facto $y_i = x_i$, $\nu_y = v_y$ and $\nu' = u'$.

Using this and let it act on the microtubule $x(s)$ we have our dynein dependent component

$$\int \frac{y_1 - y_0 + \nu_y\nu'}{|y_1 - y_0 + \nu_y\nu'|} f_d x(s) ds. \tag{16}$$

Now we can put everything together to get the total model for a filament, where the direction of the filament determines the direction of the pulling force. Actually before showing the model I want to emphasise something. It is important here to be aware of some technical problems which would arise if the dynein component would be included without changing the names of variables. The main problem results from the Fréchet derivative and some error terms. Therefore we first calculate and then substitute y_i to x_i etcetera.

Furthermore if we just look at terms of maximal order ε (like in our very basic model if you look at the calculation above), our equation states

$$L = \frac{1}{2|x_1 - x_0|^3} \int_0^1 u''^2 ds + \lambda \Big(|x_1 - x_0| + \frac{1}{2|x_1 - x_0|} \int_0^1 u'^2 ds - 1 \Big)$$
$$+ <F_1, x_1> + <F_0, x_0> + \int_0^1 \frac{y_1 - y_0 + \nu_y\nu'}{|y_1 - y_0|} f_d x(s) ds.$$

Actually, as we only consider the special case of our model dealing with sliding we can ignore the scalar products ($<,>$) because $F_i = 0$ then, as there is no pushing force included in the model. This is a more or less small change of the original shape of L but quite a dramatic one in sense of investigation. If we compare the derivatives to the ones in our previous discussion, only the one in direction to λ remains unchanged. Again taking the Fréchet derivative

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with respect to u in L leads to

$$\delta_u L(v) = \frac{1}{|x_1|^3}u''(1)v'(1) - v'(0)\Big(\frac{1}{|x_1|^3}u''(0) + 2\mu u'(0)\Big) + \int_0^1 v\Big(\frac{u^{(4)}}{|x_1|^3} - \frac{\lambda u''}{|x_1|}\Big)ds$$
$$+ \int_0^1 v(s)f_d\nu \cdot \frac{(y_1 - y_0) + \nu'\nu_y}{|y_1 - y_0|}ds = 0,$$

where the dot shall highlight the scalar product (technically it is the same scalar product as $< .,. >$). Multiplying the additional factor out gives a simpler form

$$\delta_u L(v) = \frac{1}{|x_1|^3}u''(1)v'(1) - v'(0)\Big(\frac{1}{|x_1|^3}u''(0) + 2\mu u'(0)\Big) + \int_0^1 v\Big(\frac{u^{(4)}}{|x_1|^3} - \frac{\lambda u''}{|x_1|}\Big)ds$$
$$+ \int_0^1 v(s)\frac{\nu' f_d}{|y_1 - y_0|}ds = 0.$$

Moreover in this case the derivative with respect to η_1 now satisfies

$$\frac{dL}{d\eta_1} = \frac{\eta_1}{|x_1|}\Big(\frac{-3}{2|x_1|^4}I_2 + \lambda - \frac{\lambda}{|x_1|^2}I_1 + 2\mu\eta_1^2|x_1|\Big) + 2\mu\eta_1|x_1|^2$$
$$+ \int_0^1 f_d\frac{(y_1 - y_0) + \nu'\nu_y}{|(y_1 - y_0)|} \cdot \Big(\frac{\begin{pmatrix}-1\\0\end{pmatrix}|x_1| - x_1^\perp\eta_1\frac{1}{|x_1|}}{|x_1|^2}\Big)ds = 0.$$

After this technicalities it is time to substitute x_i for y_i and continue with the recipe of the first section. As $x_0 = 0$ the added parts of the equations are getting simplified and therefore we have

$$\frac{dL}{d\eta_1} = \frac{\eta_1}{|x_1|}\Big(\frac{-3}{2|x_1|^4}I_2 + \lambda - \frac{\lambda}{|x_1|^2}I_1 + 2\mu\eta_1^2|x_1|\Big) + 2\mu\eta_1|x_1|^2$$
$$+ \int_0^1 f_d\frac{x_1 + u'v_x}{|(x_1)|} \cdot \Big(\frac{\begin{pmatrix}-1\\0\end{pmatrix}|x_1| - x_1^\perp\eta_1\frac{1}{|x_1|}}{|x_1|^2}\Big)ds = 0, \qquad (17)$$

$$\delta_u L(v) = \frac{1}{|x_1|^3}u''(1)v'(1) - v'(0)\Big(\frac{1}{|x_1|^3}u''(0) + 2\mu u'(0)\Big)$$
$$+ \int_0^1 v\Big(\frac{u^{(4)}}{|x_1|^3} - \frac{\lambda u''}{|x_1|}\Big)ds + \int_0^1 v\frac{u' f_d}{|x_1|}ds = 0 \qquad (18)$$

when

$$v_x = \frac{(x_1)^\perp}{|x_1|}, x_1^\perp = \begin{pmatrix}-\eta_1\\\xi_1.\end{pmatrix}$$

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Let us look at the second part in (18) which helps us finding the solution of u. It is similar to the previous one plus a term with a first derivative. This seemingly small modification is in fact not small at all. Actually it causes some troubles as there is no classical solution available anymore for

$$u^{(4)} - \lambda u''|x_1|^2 + u' f_d |x_1|^2 = 0. \tag{19}$$

One possibility to still get something out of it is to think of $u' f_d |x_1|^2$ as a small perturbation of the original problem and therefore try to find an approximate solution via an asymptotic expansion. This approximate solution then would be of the form

$$\bar{u} = u_0 + \varepsilon u_1 + \mathcal{O}(\varepsilon^2),$$

where u_0 is the well known solution of the reduced ordinary differential equation $u^{(4)} - \lambda u^{(2)}|x_1|^2 = 0$. u_1 can be derived by comparing coefficients (with respect to the order of the ε^k terms). All in all u_0 and u_1 look like the following:

$$u_0(s) = \pm \frac{i\eta_1 \sqrt{\eta_1^2 + \xi_1^2}((-1+s)\sin(\gamma) + sin(\gamma - \gamma s)}{\sqrt{-(-\gamma\cos(\gamma) + \sin(\gamma))^2}}$$

$$\begin{aligned} u_1(s) = &\frac{1}{2\gamma^4 \sqrt{-(-\gamma\cos(\gamma) + \sin(\gamma))^2}} * \bigg(\mp ih\Big[-\gamma^4|x_1|\sin(\gamma - \gamma s) \\ &- f|x_1|^2(2 + (\gamma^2 s - 2)\cos(\gamma) + 2\gamma\sin(\gamma))\sin(\gamma s) \\ &- f|x_1|^2(-2(\gamma s + \sin(\gamma)) + \gamma(-1+s)(2\cos(\gamma) + \gamma s\sin(\gamma))) \\ &+ \gamma^4|x_1|\sin(\gamma) - \gamma^4 s|x_1| + f_1|x_1|^2\cos(\gamma s)(-2\gamma\cos(\gamma) + (\gamma^2 s - 2)\sin(\gamma))\Big]\bigg). \end{aligned}$$

I think the shape of this solutions already tells you everything. A lot of work needs to be done. Probably optimization methods are again the best chance to get somewhere. If the outcome is satisfying at all, is another question.

4.2.6   Other filament lenghts

The final step to finish this chapter will be taking different lengths of filaments into account. As the length of microtubules is permanently changing due to dynamic instability and more over not all microtubules are of same length at a time we should take this into account. Mercifully we do not have to change much in our models. Since our Lagrange multiplier λ takes care of the length we just need to change something there, in fact we replace -1 by $-l$ and so

our starting model would look like

$$L = \frac{1}{2|x_1 - x_0|^3} \int_0^1 (u'')^2 ds + \lambda \left(|x_1 - x_0| + \frac{1}{2|x_1 - x_0|} \int_0^1 u'^2 ds \text{red-l} \right)$$
$$+ <F_1, x_1> + <F_0, x_0> .$$

This modification has also an impact on the derivative with respect to λ, id est

$$\frac{dL}{d\lambda} = |x_1 - x_0| + \frac{1}{2|x_1 - x_0|} I_1 = \text{-l}.$$

After investing so much time in this models we will now continue with something else.

4.3   Model pushing-pulling in one dimension part 2

Let us come back to our one dimensional pushing-pulling model

$$\mu\dot{C} = \kappa(L - 2C) + S(C) - S(L - C).$$

and see it from a different angle to combine it with the information we gained from our previous models. Instead of our pushing function $S(C)$ and $S_b(C)$ we define a simliar function

$$\tilde{S}(\xi.) := s_0 - a\xi..$$

s_0 as before and $\xi.$ shall be the ratio of equilibrium lengths, id est there are $\xi_l := \frac{C}{L_l}$ and $\xi_r := \frac{L-C}{L_r}$ such that $L_r > L - C, L_l > C$. This is equal to $L - L_r < C - L_l$ or $L_r + L_l > L$ which is a necessary condition for buckling since the length of a filament should exceed the length of a cell to let something like this happen. L in this case is again the total length of the microtubule (or actually two connected mmicrotubules). L_l is the length of the interval $[0, C]$ (therefore the "left microtubule") and L_r of $[C, L + b]$.

First we take a look at the general case with $\kappa \neq 0$. Our equation is of this shape now:

$$\mu\dot{C} = \kappa(L - 2C) + s_0 - a\xi_l - (s_0 - a\xi_r) \tag{20}$$

This would lead to $\hat{C} = \frac{\kappa LL_lL_r + aLL_l}{2\kappa L_lL_r + aL_l + aL_r}$ as an equilibrium and in the case of $\kappa = 0$ we would get $\hat{C}_0 = \frac{LL_l}{L_l + L_r}$.

As in section (4.1) one can relate those two equilibria. We get $\hat{C}_0 < \hat{C} < \frac{L}{2}$ whenever $L_l < L_r$.

But actually this time we are interested in a more concrete model and we are going to use the critical value of force (9) that we have computed in our example above. Therefore let $f_1 = \tilde{S}(\xi_1) = \pi^2 * \frac{2 - \xi_1^2}{\xi_1^3}$. In fact ξ_1 depends on C and therefore we write $S(C) = \tilde{S}(\xi_1)$ to keep it in same style as in the first section. If we plug this in our system, when we get

$$\kappa(L - 2C) + \pi^2\left(\frac{2 - (\frac{C}{L_l})^2}{(\frac{C}{L_l})^3} - \frac{2 - (\frac{L-C}{L_r})^2}{(\frac{L-C}{L_r})^3}\right) = 0.$$

We are again interested in equilibria and in which direction the centrosome is moving after losing dynein activity. As in the linear case above one can see that for $\kappa = 0$ there is an equilibrium $\tilde{C}_0 = \hat{C}_0 = \frac{LL_l}{L_l + L_r}$. Since this model comes from the linear one by using a special pushing force $\tilde{S}(\xi_1)$ there exists also an equilibrium $\tilde{C}$ for $\kappa \neq 0$ and the analogue result $\tilde{C}_0 < \tilde{C} < \frac{L}{2}$ has to hold.

4.4   Length distribution of microtubules

In this final section we are going to deal with dynamic instability behaviour of microtubules. As switching from polymerization to depolymerization (catastrophes) is a process which takes place at random time it should not be a surprise that this will be a probabilistic approach.

The length of our filaments are described via the distribution function $\varrho(l, t)$. Polymerization happens with constant speed v. To make our life a bit easier we assume that catastrophes and recoveries are one instantaneous event only occuring above a certain length L_0. It is modelled as a Poisson process with catastrophe rate parameter r_c and it leads to a reduction of length by L_1 which is of course less than L_0.
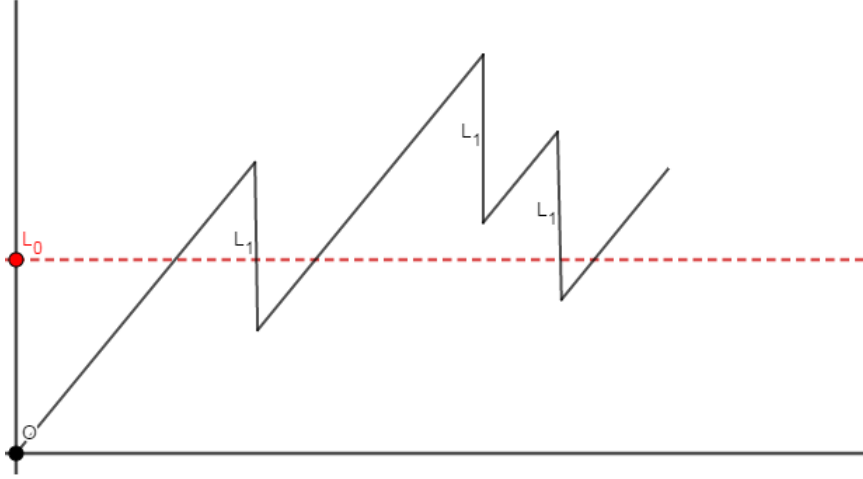

Figure: Growing process of a microtubule with cutting events of length L_1 above a certain level L_0 at random time.

We want to exclude the case that new filaments can be created and this results in the boundary condition at $l = 0$. Then the model which describes the evolution of length is given by

$$\partial_t \varrho(l, t) + v \partial_l \varrho(l, t) = r_c \left(\mathbb{1}_{l+L_1>L_0} \varrho(l + L_1, t) - \mathbb{1}_{l>L_0} \varrho(l, t) \right),$$
$$\varrho(0, t) = 0.$$

The first part is a transport equation and would describe pure growth if the left side would be zero. Therefore the right side takes care of the jumps of length L_1 we would like to have in our model. Integrating both sides from 0

to ∞ leads to

$$\frac{d}{dt}\int_0^\infty \varrho(l)dl = r_c\left(\int_{L_0-L_1}^\infty \varrho(l+L_1)dl - \int_{L_0}^\infty \varrho(l)dl\right) = 0.$$

The first part arises since interchanging of derivative and integral is legal by Fubini's theorem and $\varrho(0) = \varrho(\infty) = 0$. The second part holds simply by shifting the integral. Thus our model preserves $\int_0^\infty \varrho dl = 1$.

Our goal now is to look for an equilibrium distribution $\varrho_\infty(l)$. This is independent of time which means that the time derivative drops out. From now on $\varrho'_\infty = \partial_l\varrho_\infty$. We dinstinguish into three different cases.

First case is when $l < L_0 - L_1$ holds. It is easy to see that $\varrho_\infty(l) = 0$ then. $\varrho'_\infty = 0$ due to right side of the equation being outside of the support and our boundary condition $\varrho_\infty(0) = 0$ completes the statement.

In the second case we look at $l > L_0$. This gives us the delay differential equation

$$v\varrho'_\infty(l) = r_c\varrho_\infty(l+L_1) - r_c\varrho_\infty(l).$$

Luckily this is quite a mild one and we try to solve it by simply guessing the existence of a solution of the form $\varrho_\infty(l) = \varrho_0 e^{\lambda(l-L_0)}$, together with an equation

$$v\lambda = r_c(e^{\lambda L_1} - 1) \tag{21}$$

for λ. This equation might either have zero, one or two solutions (graph). In the following we assume that for $v < r_cL_1$ it has a unique negative solution.

Finally we consider $L_0 - L_1 < l < L_0$. This kicks the last term in the equation, so

$$v\varrho'_\infty(l) = r_c\varrho_\infty(l+L_1).$$

We use the solution of ϱ_∞ we have already determined such that

$$\varrho'_\infty(l) = \varrho_0\frac{r_c}{v}e^{\lambda(l+L_1-L_0)}.$$

Now we integrate this equation with respect to l and we want that $\varrho_0 = \varrho(L_0)$ holds. This leads to

$$\varrho_\infty(l) = \varrho_0\left(1 - \frac{r_ce^{\lambda L_1}}{v\lambda}\left(1 - e^{\lambda(l-L_0)}\right)\right) = \varrho_0\left(1 - \frac{e^{\lambda(l-L_0)} - 1}{e^{-\lambda L_1} - 1}\right),$$

where the second equation arises from using the equation (21) for λ The condition that the integral over ϱ is equal to one gives us the normalization factor $\varrho_0 = \frac{1}{L_1}$.

So our final result is of the form:

$$\varrho_\infty(l) = \begin{cases} 0 & l < L_0 - L_1 \\ \frac{1}{L_1}\left(1 - \frac{e^{\lambda(l-L_0)}-1}{e^{-\lambda L_1}-1}\right) & L_0 - L_1 < l < L_0 \\ \frac{1}{L_1}e^{\lambda(l-L_0)} & l > L_0 \end{cases}$$

5   Appendix

Terms with respect to derivatives of x

Here are some terms with respect to diverse derivatives of x which we need in several computations in the third chapter about beam models.

$$x' = x_1 - x_0 + \varepsilon u'(s)\frac{(x_1 - x_0)^\perp}{|x_1 - x_0|}$$

$$|x'|^2 = |x_1 - x_0|^2 + \varepsilon^2 u'(s)^2 = |x_1 - x_0|^2 \left(1 + \frac{\varepsilon^2 u'(s)^2}{|x_1 - x_0|^2}\right)$$

$$\text{now using } (a+b)^{\frac{1}{2}} = a + \frac{b}{2} + \frac{1}{2}\frac{-1}{2}b^2\frac{1}{2} + ...$$

$$\text{leads to } \sqrt{|x'|^2} = |x'| = |x_1 - x_0|(1 + \frac{\varepsilon^2 u'(s)^2}{2|x_1 - x_0|^2})$$

$$|x'|^4 = |x_1 - x_0|^4(1 + \frac{\varepsilon^2 u'(s)^2}{|x_1 - x_0|^2})^2$$

$$x'x'' = \varepsilon^2 u'(s)u''(s)$$

Additional computation for L in case with pulling force by dynein

Here we just use the geometrical series to get:

$$\frac{x_1 - x_0 + u'v}{|x_1 - x_0 + u'v|} \approx \frac{x_1 - x_0 + u'v}{|x_1 - x_0|}\left(1 - \frac{u'^2}{2|x_1 - x_0|^2}\right) \approx \frac{x_1 - x_0 + u'v}{|x_1 - x_0|}$$

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