Thermal Fluctuations of Anisotropic Semiflexible Polymers

by

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Preface

This thesis is written as part of the Master Biomedical Engineering at the Delft University of Technology (DUT) and concerns fluctuations of microtubules, one of the smallest structural units in animal cells. At first sight, the macro-structural themes that are commonly dealt with within the DUT department of Biomedical Engineering (e.g. the shoulder model, implants re-fixation, design of medical instruments) may seem to lie very distant from the topic that is covered in this thesis. In this preface, I will set out my personal reasons for choosing this specific topic and throughout this thesis I will argue why research on the sub-cellular scale is indispensable for achieving breakthroughs in various biomedical research areas.

During my Bachelor Applied Physics at the DUT, I got acquainted with the use of the universal language of mathematics to describe everyday physical phenomena. Although I very much liked the creation of a (mathematical) model to capture real world phenomena, I more than once lost the connection to the actual application of the studied phenomena. This was exactly the reason why I chose to continue with the Master Biomedical Engineering after completion of my Bachelor Applied Physics. During the master program, I experienced the complete opposite: the education was very application oriented, but I often felt as if there lacked a thorough fundamental understanding. Although that may not be surprising, given the immense complexity of the human body and its biomechanics, it often left me with feelings of great dissatisfaction. I especially noticed this dilemma while I was writing my literature study on patient-specific finite element modelling of bones. From that survey, I learned that the huge amount of parameters and external factors often hinders the creation and validation of accurate models.

The day that my tutor Amir Zadpoor and I discussed possible thesis topics and I was presented the work that was done on thermal fluctuations of biopolymers by others, I immediately recognized what I had been missing: the combination of a systematic mathematical basis and a relevant and (eventually) applicable topic. With much enthusiasm I agreed to start working on this subject, which soon turned out to be a highly interesting blend of biology, mathematics, physics and engineering concepts. Combining numerical modelling methods that are designed for engineering purposes, such as finite element modelling, with structural biology is exotic and has only been proposed recently [1]. Pioneering within this new field resulted in quite a challenge. Very quickly, it became evident that to make sense of the modelling work, a thorough knowledge of analytical and experimental work on polymers is an absolute requirement. As my literature survey had covered a completely different topic, I decided to
get myself acquainted with a good share of the available literature and wrote another literature overview covering some of the most fundamental concepts of Brownian dynamics modelling. This literature overview is presented in Chapter 1 of this thesis. The results of my modelling efforts are presented in the form of a scientific article, which is included in Chapter 2 of this thesis. Both articles are written as independent articles. Therefore, some formulas and concepts introduced in Chapter 1 may be revisited in Chapter 2.

Hopefully, this thesis is not only informative, but also persuades the reader to consider using the finite element method to unravel mechanics at the smallest scales and convinces the reader that an in-depth knowledge of cell mechanics on such a small scale may be, literally, of vital importance.
Chapter 1

Capturing thermal fluctuations of semiflexible polymers: a literature survey

Abstract

Semiflexible polymers that are submerged in a viscous fluid of finite temperature display incessant fluctuations. An accurate description of such thermal fluctuations of single semiflexible polymers forms the cornerstone of research on both synthetic and biological polymers in a wide variety of research fields, such as material science, mechanobiology, biophysics and bioengineering. The current study presents an overview of both analytical and numerical coarse-grained models that capture the Brownian dynamics of single semiflexible polymers. These models include the worm-like chain model, bead-rod, bead-spring and finite element models. The limitations of the discussed methods are addressed and suggestions are made for further research.

Keywords: semiflexible polymer, Brownian dynamics, thermal fluctuations, finite element method, bead-spring, bead-rod, worm-like chain, coarse-graining.

1.1 Introduction

The description of the playful spectacle of dancing pollen granules in water, recorded by the botanist Robert Brown in 1828 [2], marks the birth of the vision that our macroscopic world resides in a sea of fluctuations [3]. Ever since the discovery of this Brownian motion, it has become more evident that many biological, physical and chemical (and even economic) occurrences are fully governed by underlying thermal (random) processes. With the introduction of new types of experimental methods, such as dynamic light scattering [4] or video fluorescence microscopy [5], the interaction between microscopic randomness and macroscopic physical laws has been further explored. An excellent example of such interplay is the nontrivial problem of the statistical mechanics of a semiflexible polymer submerged in a fluid of finite temperature [6, 7, 8]: the interaction between the polymer and surrounding solvent
molecules causes characteristic fluctuations of the polymer, while the polymer retains its mean orientation due to internal stiffness [9].

Generally speaking, two types of semiflexible polymers can be distinguished: synthetic polymers (e.g. polyacrylamides, Kevlar, and polyesters) and biological polymers (e.g. DNA, rod-like viruses and actin filaments) [10]. Analytical and numerical models of the Brownian dynamics of semiflexible polymers can be applied to both synthetic and biological polymers. However, many researchers stress the relevance and applicability of their study by referring to biological applications [6, 11, 12, 13, 14]. The reason for this is twofold: first of all, biopolymers are easily observable and readily available. The three main types of cellular biopolymer, actin-filaments (also known as F-actin and microfilaments), intermediate filaments and microtubules, are found in large concentrations in every eukaryotic cell. These polymers are interconnected by accessory proteins into complex networks, which are together called the cytoskeleton. Thus, in vivo, biopolymers occur entangled with many other filaments forming network structures. However, by purifying single biopolymers, they form excellent in vitro experimental objects that - submerged in a viscous fluid - display observables, e.g. the time-dependent projected length, that can be used for validating (or falsifying) polymeric models [6, 7, 15].

Second of all, the ”holy grail” of capturing the intricate cellular dynamics through bottom-up modelling [16] stimulates the imagination. In this sense bottom-up means: describing the intricate rheological response of the cytoskeleton by considering the dynamics of the smallest building blocks (the cytoskeletal biopolymers). For such a modelling approach, a detailed description of single biopolymer mechanics and dynamics is key to gain insight on how the properties of the smallest structural elements underlie the intangible mechanical properties of the cytoskeleton and is essential in probing phenomena such as cell division and cell motility on various scales. In addition, perturbation in the architecture of the cytoskeleton may lead to marked pathologies [13]. Therefore, gaining a better understanding of the smallest structural level of the cytoskeleton may eventually accelerate therapeutic drug discovery.

For over 60 years, attempts have been undertaken to accurately capture the Brownian dynamics of semiflexible polymers through the use of analytical [9, 17, 18, 19, 20, 21] and numerical models [22, 23]. Significant progress has been made, but recent advancements in measurement techniques [7, 8] exposed the limitations of the conventional analytical and numerical approaches to describe newly discovered physics [24] of polymers with complex molecular structures (e.g. microtubules). To address these limitations, a new numerical approach, based on the finite element method, was recently developed.
The current work presents a concise overview of both analytical and numerical models that have been used to capture the stochastic dynamics of single semiflexible polymers. It may serve both as a quick reference guide to common parameters and observables, as well as a clarifying overview on how different methods are based on similar principles and to what extent they differ. The current work limits itself to the thermal dynamics of single polymers or an ensemble of single polymers. Networks of interconnected polymers are out of the scope of the current overview. Similarly, deterministic force application is left out of the discussion.

The current paper is organized as follows: first, the coarse-graining aspect of polymeric modelling is explained. Second, a common analytical derivation based on the worm-like chain model is presented and the limitations of this approach are highlighted. Third, we discuss conventional computational models and, finally, a newly proposed finite element based model. The current work aims at comparing these various modelling approaches, which, to the authors’ knowledge, has not been done before.

1.2 Coarse-grained description of semiflexible polymers

Polymers that are submerged in a viscous fluid show incessant thermal fluctuations. This behaviour is also known as Brownian motion or thermal dynamics. The underlying mechanism of these fluctuations is the constant interaction between thermally excited solvent molecules and the submerged polymer, causing simultaneously movement and damping of the polymer. One might consider modelling these interactions at the atomistic scale (Ångström, sub-picosecond). This would surely result in a very accurate model. However, many biopolymers (F-actin, microtubules, DNA, collagen) and synthetic polymers (glass fibres, carbon nanotubes, Kevlar) have a typical contour length of at least $1\mu m$ [10]. Furthermore, common observables typically span times of the order $1 \times 10^{-4}$ s up to 10 s [6, 7, 8, 25]. Therefore, such an explicit atomistic modelling attempt would lead to a formidably high computational cost. Additionally, superfluous details (e.g. vibrations of atomic bonds) would either obscure more important phenomena or would be negligible compared to the physics of interest (e.g. fluctuations of the polymer).

As an answer to these difficulties, the polymer system can be described on a coarser level [26]. This is done by accumulating microscopic building blocks and modelling their individual properties implicitly [27]. As an example, instead of explicitly modelling the electronic wave-functions of all solvent atoms, one can gather these atoms and substitute their collective properties by larger scale solvent molecules, described by Newtonian and statistical mechanics. Even one step further up in the hierarchy of
detail, one can neglect the explicit individual solvent molecules and solely model the actual collisions between solvent molecules and the polymer as independent draws from a Gaussian distribution. Thus, coarse-graining allows us to improve simulation efficiency and get rid of unnecessary details.

What can be considered ‘unnecessary detail’ depends on the observed phenomena. For Brownian dynamics, the length scale of observables is in general much larger than the length scale of the atomic microstructure of the polymer. Therefore, we can resort to the so-called mesoscopic scale. On such a mesoscopic scale, individual atoms are neglected and the polymer is accurately represented by a slender continuum. Fortunately, such a slender continuum shares many properties with structural beams and therefore can be well described by the beam theory [28, 29]. The beam theory, that was originally developed decades ago within the context of structural engineering and which is generally applied to much larger structures, can surprisingly well be applied to biopolymers. All of the models discussed in this review are based on the above described coarse-grained mesoscopic approach. Two of these models, the analytical worm-like chain model and numerical FE model, share also many assumptions with the classic beam theory.

1.3 Analytical models

1.3.1 Theory

A common analytical solution that describes much of the physics of semiflexible polymers is based on the worm-like (WLC) chain model. This model, which has been introduced over 60 years ago [17], is built on four fundamental properties that are seen in many (bio)polymers:

1. a practically inextensible backbone
2. slenderness ($d << L_c$), where $d$ is the filaments diameter and $L_c$ is its contour length
3. a contour length that is much smaller than its persistence length $\epsilon \equiv \frac{L_c}{\ell_p} << 1$, assuring that local curvatures are small
4. isotropic and homogeneous distributed material

In the WLC model, the polymer is modelled as a space curve $r(s)$, which is parameterized by the arc length $s \in [0; L_c]$ (Figure 1.1). Upon a bending moment that acts on a segment of the polymer, bending occurs. The level of bending depends on the bending rigidity (or flexural rigidity) of the polymer $\kappa$ and is given by the relation

$$\frac{d\theta}{ds}(s) = \frac{1}{\kappa} M(s).$$

(1.1)

For homogeneous isotropic beams the flexural rigidity can be expressed as $\kappa = EI$, where $E$ is the Young’s modulus and $I$ is the second moment of area. However,
for anisotropic beams the bending rigidity cannot be expressed in terms of material properties [15] and must in such cases be handled as an independent property of the polymer.

The thermal dynamics of a polymer is often discussed in terms of its persistence length, $\ell_p$, which is defined as the characteristic arc length over which the two tangent angles $\theta(0)$ and $\theta(s)$ become uncorrelated (Figure 1.1) [29]. This can be mathematically expressed as

$$\langle \cos(\theta(s) - \theta(0)) \rangle = \exp(-s/2\ell_p).$$

By means of the equipartition theorem, it can also be shown that [29]

$$\ell_p = \frac{\kappa}{k_B T},$$

where we used the bending rigidity of the polymer, $\kappa$, and introduced the thermal energy of the solvent, $k_B T$. Intuitively, the concept of persistence length can be interpreted as follows: the conformation of a polymer for which the contour length is much smaller than the persistence length, $L_c << \ell_p$, is determined by the bending rigidity and will appear very stiff, whereas the conformation of a polymer for which $L_c >> \ell_p$, is determined by the external thermal energy and will appear to be very flexible. Polymers for which the persistence length and contour length are of the same order, $L_c \approx \ell_p$, are called semiflexible.

### 1.3.2 The equation of motion

For elaborate derivations of the WLC model, the reader is referred to [9, 15, 26, 27]. Below follows a shorter version of the derivation, that specifically focuses on the limitations of the commonly used linear approximation. First, the equation of motion is derived for a free floating semiflexible polymer using appropriate boundary conditions and normal mode analysis. Next, solutions are presented for hinged boundary conditions. Finally, limitations of the derived solutions are highlighted.

*Here and throughout the rest of the work angular brackets indicate mean values*
As touched upon before, the conformation of the space curve (or polymer) is governed by the interplay between energy needed to bend the filament and the external energy (or thermal energy) of the surrounding fluid. First, to find the elastic energy density, \( g_{el} \), exerted by a polymer of conformation \( \mathbf{r}(s) \) we consider an external force field, \(-g_{el}\), that stabilizes the conformation \( \mathbf{r}(s) \). By means of minimization of the total free energy function [11]

\[
H(\mathbf{r}(s)) = H_{WLC}(\mathbf{r}(s)) + H_{ext}(\mathbf{r}(s)),
\]

(1.4)

in which we consider the effective free energy of the polymer conformation \( \mathbf{r}(s) \)

\[
H_{WLC}(\mathbf{r}(s)) = \frac{\kappa}{2} \int_{0}^{L} (\partial_{s}^{2} \mathbf{r})^{2} ds
\]

(1.5)

and the free energy of the external force field

\[
H_{ext}(\mathbf{r}(s)) = \int_{0}^{L} \partial_{s} g_{el} ds.
\]

(1.6)

we find the elastic force density \( g_{el}(s) \) that a polymer exerts at arc length \( s \), which is a function of the conformation \( \mathbf{r}(s) \) and is expressed by [11]

\[
g_{el} = -\kappa \partial_{s}^{4} \mathbf{r} + \partial_{s} (f \partial_{s} \mathbf{r}),
\]

(1.7)

where \( f \) can be interpreted as the line tension that ties the polymer together. This force arises due to the inextensibility constraint (see property 1 above)

\[
(\partial_{s} \mathbf{r})^{2} = 1.
\]

(1.8)

The interaction of the polymer with the surrounding fluid of finite temperature can be microscopically interpreted as local impacts or 'thermal kicks' from excited fluid molecules on the polymer. The noise correlations that result from this interaction are fixed through the fluctuation-dissipation theorem and are given by Eq. (1.9) and Eq. (1.10) respectively [9],

\[
\langle \xi_{i}(s, t) \rangle = 0
\]

(1.9)

\[
\langle \xi_{i}(s, t) \xi_{j}(s', t') \rangle = 2k_{B}T \zeta_{ij} \delta(s - s') \delta(t - t'),
\]

(1.10)

where the drag coefficient, \( \zeta_{ij} \), accounts for a local friction approximation. The Kronecker’s deltas, that appear in Eq. (1.10), assure that two thermal forces evaluated at different arc lengths or at different moments in time (\( s \neq s' \) or \( t \neq t' \)) are completely uncorrelated (also known as space-time white noise). This assumption only holds if the length scale of the polymer or the time scale of the studied phenomena are much

\[In \text{Eq.}(1.5) \text{and throughout the rest of this work the following notation is used}: \quad \frac{\partial^{n} \mathbf{r}}{\partial s^{n}} \equiv \partial_{s}^{n} \mathbf{r}.\]
1.3. ANALYTICAL MODELS

larger than those characteristic for the solvent molecules [11], which generally is the case for experimental observations on fluctuating polymers, as discussed in Section 1.2.

The movement of the polymer is damped by hydrodynamic drag caused by interaction of the polymer with the surrounding fluid. Two types of models are available for capturing this hydrodynamic interaction: non-local and local friction models. Non-local friction models take into account that the fluid $u(r)$ is locally disturbed by movement of more distant segments [9]. For polymers for which $d << L_c$ and $L_c << \ell_p$ (Section 1.3.1, property 2 and 3) the inter-segmental interaction will be small and can be accounted for by simple logarithmic corrections. For simplicity, we will only consider this so-called free-draining limit, as this approximation is sufficient to capture most single polymer problems [11].

The drag force experienced by the space curve per unit length is proportional to its velocity, $g_{fr} \propto \partial_t r(s,t)$. We account for different levels of friction parallel and perpendicular to the slender polymer through the drag coefficient tensor $\zeta = [\zeta_\perp (1 - \mathbf{r}' \otimes \mathbf{r}') + \zeta_\parallel \mathbf{r}' \otimes \mathbf{r}']$ (as a practical example, think of the low force needed to put a knife in a jar of syrup, and the high force needed to stir it). This allows us to write the drag force density as

\[ g_{fr}(s,t) = -\zeta(s,t) \partial_t r(s,t). \quad (1.11) \]

For slender bodies in a viscous fluid, $\zeta_\parallel$ and $\zeta_\perp$ can be approximated by [19, 30]

\[ \zeta_\parallel = \frac{1}{2} \zeta_\perp = \frac{2\pi \eta}{\ln(L_c/d)} \quad (1.12) \]

Now that we have found expressions for the elastic forces, drag forces and stochastic forces, we can write a force equilibrium per unit length as

\[ g_{el}(s,t) + g_{fr}(s,t) = \xi(s,t). \quad (1.13) \]

Eq. (1.13) and the expressions Eq. (1.7), (1.10) and (1.11) yield the equation of motion of the semiflexible polymer,

\[ \zeta \partial_t \mathbf{r} = -\kappa \partial_s^4 \mathbf{r} + \partial_s (f \partial_s \mathbf{r}) + \xi. \quad (1.14) \]

In Eq. (1.14) inertial forces are neglected, because for most semiflexible polymers they are negligibly small compared to friction forces [1]. The resulting highly nonlinear PDE Eq. (1.14) gives us the equation of motion of a semiflexible polymer submerged in a viscous fluid of finite temperature. The nonlinearity arises from the $f(s)$, which has to be determined from Eq. (1.8).
1.3.3 Decomposition and linearization of the equation of motion

In order to solve the equation of motion, we will linearize Eq.(1.14). For that purpose, we assume a stiff polymer ($\varepsilon = L/\ell_p << 1$ (Section 1.3.1, property 3)). Since the polymer is stiff, undulations of the polymer can be described as perturbations about a straight line (the weakly-bending limit) [11]. This allows us to parameterize the space curve by means of the transverse displacement $r_\perp$ and longitudinal displacement, $s - r_\parallel$, which are measures for the deviation of the space curve from a straight contour [14],

$$r(s) = (r_\perp, s - r_\parallel)^T, \quad \partial_4 r_\perp^2 = O(\varepsilon) << 1.$$  \hspace{1cm} (1.15)

Please note that for a straight polymer, both $r_\perp = 0$ and $r_\parallel = 0$. This parameterization lets us expand the inextensibility constraint Eq.(1.8) to the leading order [14]

$$\partial_4 s r_\perp^2 = \frac{1}{2} \partial_4 s r_\perp^2 + O(\varepsilon^2).$$  \hspace{1cm} (1.16)

By substitution of Eq.(1.15) and Eq.(1.16) into Eq.(1.14) we find decomposed expressions for the force equilibrium longitudinal and perpendicular to the polymer

$$\left\{ \begin{array}{l} \zeta_\perp \partial_4 s r_\perp = -\kappa \partial_4 s r_\perp + \partial_4 (f \partial_4 r_\perp) + \xi_\perp \\ \zeta_\parallel \partial_4 s r_\perp + (1 - \zeta_\parallel) \partial_4 s \partial_4 r_\perp = -\kappa \partial_4 s r_\perp + \partial_4 (f \partial_4 r_\parallel) + \xi_\parallel \end{array} \right.$$  \hspace{1cm} (1.17)

Scaling arguments [11] reveal that the mean square transverse displacements, MSD$_\perp$, are much smaller than the mean square longitudinal displacements, MSD$_\parallel$. More specifically, MSD$_\parallel$/MSD$_\perp \sim \varepsilon$, thus in the weakly-bending limit ($\varepsilon \to 0$), longitudinal fluctuations will be negligible compared to transverse fluctuations. The second relation in Eq.(1.17) reduces therefore to the leading order $O(\varepsilon^{1/2})$ to

$$\partial_4 s f = 0.$$  \hspace{1cm} (1.18)

We consider a force-free case $f = 0$, which allows us to linearize Eq.(1.17) into the single differential

$$\kappa \partial_4^4 r_\perp(s,t) + \zeta_\perp \partial_4 r_\perp(s,t) = \xi_\perp(s,t).$$  \hspace{1cm} (1.19)

1.3.4 Solving the linearized equation of motion

We look for a solution for the differential Eq.(1.19) by separation of variables, $r_\perp = \chi(t) \psi(s)$. As an arbitrary example, we consider the case of a polymer with hinged boundary conditions (Figure 1.2).

The boundary conditions for hinged ends are [31] $r_\perp|_{s=0,L} = \partial_4^2 r_\perp|_{s=0,L} = 0$. By performing separation of variables in Eq.(1.19) and applying boundary conditions we find the eigenvalue problem [31]

$$\left\{ \begin{array}{l} \partial_4^4 \psi_n(s) = \lambda \psi_n(s) \\ \psi_n(0) = \psi_n(L_c) = 0 \\ \partial_4^2 \psi_n(0) = \partial_4^2 \psi_n(L_c) = 0 \end{array} \right.$$  \hspace{1cm} (1.20)
The solution to this eigenvalue problem is given by a set of eigenvalues and simple sine functions \[\lambda = q_n^4 = \left(\frac{n\pi}{L}\right)^4, \quad \psi_n(s) = \sqrt{\frac{2}{LC}} \sin q_n s. \quad (1.21)\]

More specifically, we set the transverse displacements as a superposition of an infinite number of waves \[\chi_n(t)\] and eigenfunctions \[\psi_n(s)\]

\[r_\perp(s,t) = \sum_{n=1}^{\infty} \chi_n(t)\psi_n(s). \quad (1.22)\]

Substituting Eq. (1.21) in Eq. (1.22) and subsequently in Eq. (1.19), leads to the following family of ordinary differential equations:

\[\partial_t \chi_n(t) + \frac{\kappa}{\zeta_\perp} q_n^4 \chi_n(t) = \xi_n(t). \quad (1.23)\]

Solving for \(\chi_n(t)\) in Eq. (1.23), we find

\[\chi_n(t) = \int_0^t e^{-(t-t')/\tau_n} \xi_{\perp,n}(t') dt', \quad (1.24)\]

where we have defined the relaxation time \(\tau_n \equiv \frac{\zeta_\perp}{\kappa} q_n^{-4}\). For the hinged case, the eigenvalues are given by Eq. (1.21) and thus the relaxation times can be rewritten as

\[\tau_n^{\text{hinged}} = \frac{\zeta_\perp}{\kappa} \left(\frac{L}{n\pi}\right)^4. \quad (1.25)\]

In this particular case, we have considered a polymer with hinged ends. For a complete overview of all possible variations of boundary conditions, associated eigenfunctions and eigenvalues the reader is referred to the appendix of [31].

Now that we found the solution for the mode amplitudes for the differential equation Eq. (1.19), we consider the mean square displacement (MSD) of the transverse coordinate [32] by substitution of Eq. (1.21) and Eq. (1.24) in Eq. (1.22), and using the relationship for the noise correlation Eq. (1.10):

\[\text{MSD}_\perp(t) \equiv \frac{1}{LC} \int_0^L ds \left\langle (r_\perp(s,t) - r_\perp(s,0))^2 \right\rangle = 4\frac{1}{\ell_p LC} \sum_{n=1}^{\infty} q_n^{-4} \left(1 - \exp\left(-\frac{t}{\tau_n}\right)\right). \quad (1.26)\]
Since \((q_1/q_2)^{-4} = 16\), inspection of Eq. (1.26) shows that the amplitude of the first mode largely dominates the sum over all modes. Experimentally, measuring the MSD of the polymer can be difficult. However, the projected-length of a polymer (or end-to-end distance), which is easier to measure experimentally, can be related exactly \([18]\) to the MSD through

\[
\langle \delta R^2(t) \rangle \equiv \left( (R(t) - R(0))^2 \right) = \frac{L_c}{2\ell_p} \text{MSD}_\perp. \tag{1.27}
\]

Thus, substitution of Eq. (1.26) in Eq. (1.27) yields

\[
\langle \delta R^2(t) \rangle = 2 \frac{1}{\ell_p^2} \sum_{n=1}^{\infty} q_n^{-4} \left( 1 - \exp \left( -\frac{t}{\tau_n} \right) \right). \tag{1.28}
\]

This expression simplifies for the limit \(t >> \tau_1\), in which case the term in brackets reduces to approximately 1 and the series converges to \(\pi^4/90\). We find, after substitution of the eigenvalues for hinged ends, the universal equilibrium value for hinged ends:

\[
\langle \delta R^2(t) \rangle = 2 \frac{L_c^4}{90 \ell_p^2}, \text{ for } t >> \tau_1. \tag{1.29}
\]

For short times, \(t << \tau_1\), the series can be converted into an integral \([11]\), which evaluates to \([18]\]

\[
\langle \delta R^2(t) \rangle \approx \text{const} \frac{L_c^4}{\ell_p^2} \left( \frac{\kappa}{\zeta_\perp} \right)^{3/4} \frac{1}{t^{3/4}}, \text{ for } t << \tau_1. \tag{1.30}
\]

Until now, the WLC derivation disregarded internal friction of the polymer \([31]\). Internal friction is associated with conformational changes and fluid flowing through the pores of the filament. Accounting for internal friction, Eq. (1.19) becomes \([7, 33]\)

\[
\kappa \partial_s^4 r_\perp + \zeta_\perp \partial_t r_\perp + \zeta_{\text{int}} \partial_t \partial_s^4 r_\perp = \xi_\perp(s, t) \tag{1.31}
\]

and the adjusted relaxation time becomes \([33]\)

\[
\tau_n = \frac{\zeta_\perp + \zeta_{\text{int}} q_n^4}{\kappa q_n^4}. \tag{1.32}
\]

### 1.3.5 Validation

Experimental measurements of the projected length of actin filaments, performed by Le Goff and co-workers, showed the validity of the above described theoretical derivations \([6]\). In that research, the end-to-end distance power law (Eq. (1.30)) and the saturation value (Eq. (1.29)) were fitted to the experimentally obtained mean square displacement of the end-to-end distance, \(\langle \delta R^2(t) \rangle\), of various actin filaments. By doing so, plausible values were found for the persistence length and friction coefficient (Figure 1.3). Although such a ’parameter-fitting’ validation procedure may not be
very accurate in terms of amplitude of the end-to-end distance, the dominant scaling behaviour of the WLC model was indeed shown to be correct. Studies of shape fluctuations of microtubules by means of high-resolution particle tracking showed good correspondence with the analytical model for long contour lengths $L_c > 10 \mu m$ [7, 24]. For lower contour lengths divergence from the WLC model was reported (Figure 1.4). For these short contour lengths, relaxation times follow a $L^2$ dependence instead of a $L^4$ dependence. This deviation is assumed to be due to a hidden length dependence of the bending stiffness that results from the complex molecular structure of microtubules. For very short microtubules of $L_c < 5 \mu m$, internal friction contributes significantly to the total friction and needs to be taken into account.

1.3.6 Limitations and failure

In the above linear approximation, we assumed transverse displacements to be dominant over longitudinal displacements. However, by omission of the longitudinal friction term $\dot{\zeta} \partial_t r_{||}$, effects of tension propagation along the element are neglected, which results in a violation of the force balance between friction and driving force for short times ($t < \dot{\zeta}^4 L^8/\ell_p^4$ [21]). This assumption leads to an overestimation of longitudinal fluctuations by a factor of $[\tau_c/t]^{1/8}$ [6]. For such short times, the MSD of longitudinal fluctuations scales with $t^{7/8}$ instead of $t^{3/4}$ [21]. These effects are too small to be observed in experiments on free floating single polymers [6]. However, they may greatly influence the high frequency viscoelastic response of polymer networks, in which tension propagation at short times plays a significant role [34].
CHAPTER 1. LITERATURE SURVEY

Figure 1.4: Adapted from [24]. For short microtubules, experimental measurements diverge from the theoretical estimates of the WLC model. Left: relaxation time shows a deviating length dependence. Right: for short microtubules internal friction becomes significant.

WLC model is also inherently limited by some of its other main assumptions. The allowed conformations according to the effective free-energy potential are determined by the bending rigidity of the polymer. As discussed in Section 1.3.1, the bending rigidity can only be directly linked to the material properties if the polymer is homogeneous and isotropic [15]. Indeed, recent experimental research [24] has pointed out that biopolymers with complex microstructure architecture, e.g. microtubules, can only be described by the WLC to some extent. The failure of the WLC model to accurately describe the fluctuations of short microtubules can be attributed to oversimplification of the microscopic architecture of the filament and the neglect of internal friction contributions. A new theoretical model, in which a WLC bundle is considered instead of a single WLC [35, 36], largely overcomes these limitations and predicts a lower limit of the persistence length for short microtubules. This limit has indeed been observed in recent experimental investigations [24, 37]. Another limitation of the WLC model is that self-avoidance (excluded volume) is not taken into account. Self-avoidance becomes of particular importance when modelling semiflexible polymers in the flexible regime, such as DNA. Indeed, strong deviations from the WLC model have been observed in experiments on stretching and release of single stranded DNA [38, 39].

1.4 Numerical simulation - Bead models

1.4.1 Introduction

Section 1.3 showed the ability of the analytical WLC approach to accurately capture the Brownian dynamics of a single fluctuating polymer. Several limitations of the WLC model, e.g. capturing the Brownian dynamics of a polymer with complex material properties (anisotropy, internal friction) and describing thermal fluctuations
for very small time scales, were also discussed. In complementing theory and experiments, numerical techniques play an indispensable role. Which type of numerical technique is most suitable, depends on the spatial- and time-scale of interest. Two common types of coarse-grained numerical approaches (bead-rod, bead-spring) and one less common (finite element) are discussed in this section. The limitations of each approach are discussed below and their differences are highlighted.

The fluctuations of polymers subjected to intricate solvent flows (e.g. shear flow [40]), large displacements and interaction with entangled polymers are too complex to be solved analytically. To address many of these limitations, numerical bead models have been developed decades ago [41, 42]. Numerical bead models can predict rheological behaviour of polymers under challenging conditions [22]. Although such bead models are generally used to simulate polymeric solutions and polymer networks, they can also be used to describe the fluctuations of a single semiflexible polymer [40]. Specifically, bead models are often used for modelling slender and flexible polymers, e.g. DNA, under equilibrium and far-from equilibrium conditions, such as force-release.

1.4.2 Equation of motion

A common way of coarse-graining a flexible polymer is by neglecting the atomic vibrations and approximating the polymer by a freely jointed chain, in which \( n \) segments of length \( a \) (the Kuhn length) ought to behave like a very flexible slender rod [29]. A suitable Kuhn length depends on the parameters of the system, in general \( 2\ell_p = a \). Such a chain is usually implemented in the form of a bead-rod model. A bead-rod model of a polymer is schematically depicted in Figure 1.5 and consists of \( N \) beads separated by rigid constraints (rods) that keep every bead a distance \( a \) away from adjacent beads. The forces that act on each bead individually are given by the force

\[
\begin{align*}
\mathbf{u}_j = & u_{ij}\mathbf{e}_i + u_{ij+1}\mathbf{e}_{j+1} + \sum_{k=1}^{N-1} \theta_{j,k} \mathbf{r}_{k+1} - \mathbf{r}_k \\
\end{align*}
\]

Figure 1.5: This is a schematic drawing of a bead-rod model
results in the set of equations

\[ \mathbf{F}_i^H + \mathbf{F}_i^C + \mathbf{F}_i^B = 0, \; i = 0, 1, \ldots, N - 1, N \]  

(1.33)

where \( i \) refers to the number of the beads (Figure 1.5). Assuming an isotropic drag tensor and no solvent velocity and hydrodynamic interaction between distant beads, the hydrodynamic force is given by

\[ \mathbf{F}_i^H = -\zeta \partial_t \mathbf{r}_i \]  

(1.34)

The constraint force, which results from internal stresses \( T_i \) that arise in order to keep adjacent beads a distance \( a \) separated, is given by

\[ \mathbf{F}_i^C = T_i \mathbf{u}_i - T_{i-1} \mathbf{u}_{i-1}, \]  

(1.35)

where \( \mathbf{u}_i = (\mathbf{r}_{i+1} - \mathbf{r}_i)/a \) is the vector tangent to the rod between two beads (Figure 1.5). Similar to the fluctuation-dissipation theory as discussed in Section 1.3.1, we set

\[ \langle \mathbf{F}_i^B(t) \rangle = 0 \]  

(1.36)

\[ \langle \mathbf{F}_i^B(t) \mathbf{F}_i^B(t + \Delta t) \rangle = 2k_BT \zeta \delta_{ij} (\Delta t) \approx 2k_BT \zeta \delta_{ij} \Delta t \]  

(1.37)

By substitution and rearrangement of Eq. (1.34), (1.35), (1.36), (1.37) in Eq. (1.33) we find the differential equation and set of constraints

\[ \frac{\partial}{\partial t} \mathbf{r}_i = \frac{1}{\zeta} \mathbf{F}_i^C + \sqrt{\frac{2kT}{\zeta}} \partial_t \mathbf{W}_i, \; i = 0, 1, \ldots, N \]  

(1.38)

\[ \mathbf{u}_i \cdot \mathbf{u}_i = 1 \]  

(1.39)

where we used the Wiener process \( \mathbf{W}_i \) to represent the Gaussian distribution of Eq. (1.36) and Eq. (1.37). Equation (1.38) can be solved using several numerical methods, such as Newton’s method or using Lagrange multipliers. Often, the set of constraint Eq. (1.39) is rewritten as

\[ (\mathbf{r}_{i+1} - \mathbf{r}_i) \cdot (\mathbf{r}_{i+1} - \mathbf{r}_i) - a^2 = \phi^2, \]  

(1.40)

where \( \phi^2 \) is a user-specified tolerance.

### 1.4.3 Bead-spring models

At a higher level in the hierarchy of coarse-graining we find bead-spring models. The microstates of all the beads and rods in a bead-rod model result in a restoring force. This restoring force arises due to decrease in disorder (and thus entropy) under extension, which costs free energy. Therefore, a chain of beads and rods acts like an entropic spring. To coarse-grain a bead-rod model, we can substitute a set of
1.4. NUMERICAL SIMULATION - BEAD MODELS

adjacent beads and rods by a spring of several Kuhn lengths, that accounts for this restoring force. This results in a so called bead-spring model [29, 43]. Thus, the bead-spring model comprises \( M \) beads and \( M - 1 \) springs, where \( M \) is smaller as compared to the number of beads \( N \) in the bead-rod model of Section 1.4.2.

To that purpose, we replace the constraint force \( F_C^i \) in Eq. (1.38) by the effective spring force \( F_E^i \)

\[
F_E^i = \begin{cases} 
F_1^S & i = 1 \\
F_S^i - F_{i-1}^S & 1 < i < M \\
F_{M-1}^S & i = M
\end{cases} \tag{1.41}
\]

There are various spring laws available, of which here we present a commonly used spring law based on the WLC [22, 44]:

\[
F_{W^{LC}}^i = \frac{k_B T}{2 \ell_p} \left[ \frac{1}{2} \left( 1 - \frac{|Q_i|}{Q_0} \right)^2 - \frac{1}{2} + \frac{2 |Q_i|}{Q_0} \right] \frac{Q_i}{Q_0}, \tag{1.42}
\]

where \( Q_i = r_{i+1} - r_i \) the connector vector between two beads and \( Q_0 \) the maximum extensibility of the spring. Using Eq. (1.41), we rewrite Eq. (1.38) as [22]

\[
\partial_t r_i = \frac{1}{\zeta} F_S^i + \sqrt{\frac{2kT}{\zeta}} \partial_t W_i, \quad i = 0, 1, \ldots, M \tag{1.43}
\]

1.4.4 Discretization in time

Both explicit and fully implicit time schemes can be used for solving the equations of motion of the bead-rod and bead-spring models, Eq. (1.43) and Eq. (1.38), respectively. In general, implicit integration schemes, e.g. the fully implicit Newton’s method, perform better than explicit integration in terms of CPU efficiency [22]. However, the implementation of an implicit integration scheme for bead models is not as straight-forward as the implementation of explicit integration schemes. For an overview of different numerical discretization techniques see [22].

1.4.5 Validation

Researchers have compared predictions of bead-rod and bead-spring models with experimental results. Only a few studies concern the dynamics of a single macromolecule, such as the study by Hur and Shaqfeh [40], who studied the dynamics of a single DNA molecule under shear flow. In that study an excellent agreement between simulations based on a bead-rod chain and their experimental results was observed. A parametric study based on a bead-rod model of a semiflexible chain with configuration dependent anisotropic bead frictions coefficients was presented by Montesi and co-workers [45]. In that study, several ratios of the longitudinal and perpendicular frictions coefficients were considered. Their algorithm yielded a distribution of the cosine of angles between two distant rods that agreed well with the analytically
predicted distribution. However, by far the most validation studies concerned the rheological properties of entangled networks. Everaers and co-workers [46] studied the viscoelastic properties of high molecular weight polymeric liquids. Inter-polymer contact was simulated by means of bead-spring coarse-grained polymers entangled with other chains with identical properties. A good agreement with experimental results was found. Hur and Shaqfeh [47] investigated the dynamics of dilute and semi-dilute DNA solutions in start-up and shear flow. They compared experiments with Brownian dynamics simulations based on the Kramers’ bead-rod chain model and the worm-like bead-spring model. Simulation of WLC chains gave nearly identical results to the Kramer’s chain model. Simulation results were consistently 5% above experimental results. For an extensive review on the progress towards capturing the rheology of dilute solutions with Brownian dynamics bead-model simulations, see [48].

1.4.6 Limitations and failure

Bead models are notorious for the need for artificial constraints to ensure numerical stability. For example, in many cases, the longitudinal stiffness will be much larger than the bending stiffness. This will lead to very high frequency longitudinal vibration modes compared to the lower frequency transverse bending modes. These high frequencies are often irrelevant and may even obscure more important phenomena [20]. In terms of time integration, this means that very small time steps may be needed during Brownian dynamics simulations of a bead-spring model. Several solutions for this issue have been proposed, such as artificial softening of the springs [49], but these measures undermine the physical accuracy of the model [43].

In general, bead-rod models provide acceptable results, but at high computational costs. Good qualitative agreement with experiment is only seen after including essential physics such as finite extensibility of the molecules, hydrodynamic interaction and excluded volume (self-avoidance) [23, 50]. Furthermore, the (faster) implicit integration schemes are difficult to implement and result in many pitfalls. Therefore, much in-house coding is required, which limits the generality of bead models, of which the mathematical validity might be questionable [1]. Apart from the above, implementation of advanced material models in bead models will be very difficult or downright impossible. In addition, in order to accurately model pre-stressed networks or capture the transition from the entropy dominated regime (when thermal forces are predominant) to the elasticity dominated regime (e.g. stretching of polymers) axial strains need to be taken into account. Bead-rod models are less suitable to capture axial strains, due to the need for additional terms that compensate for enthalpic axial stretch contribution [51].
1.5 Numerical simulation - Finite element method

1.5.1 Introduction

Much of the limitations that have been pointed out in the bead-rod section can be addressed with a numerical approach called the finite element method [52], which is a common approach for solving partial differential equations on complex spatial domains. It was only recently [1, 53] that this method was suggested as a promising alternative for conventional bead-rod and bead-spring models for modelling thermal fluctuations of semiflexible polymers. Thus far, the FE method has been widely used in other research fields, e.g. structural engineering. This has resulted in a variety of user-friendly software packages, which facilitates the implementation of advanced material models. The additional advantages of the finite element modelling approach include its well-founded mathematical basis and implicit integration scheme. Furthermore, implicit integration allows for larger time steps (up to ten thousand times larger [53]) than those that are associated with the explicit integration schemes commonly used in bead models. The following derivation is based on the work by Cyron and Wall, who presented a mathematically consistent finite element approach to the simulation of Brownian polymer dynamics [1, 53].

1.5.2 The equation of motion

In analogue to the analytical derivation, we start off with the force equilibrium per unit length. However, in contrast to the analytical derivation, we will now also take backbone extensibility and shear deformation into account. The force density vector, \( \mathbf{g} \), will therefore include three components: an x-force, a y-force and a bending moment. Let us reintroduce the equilibrium between all forces on the polymer that must hold for all instances in time (see Eq. (1.13) for comparison),

\[
\mathbf{g}_{\text{el}}(\mathbf{u}, x) + \mathbf{g}_{\text{fr}}(\mathbf{u}, \partial_t \mathbf{u}, x) = \mathbf{\xi}(x),
\]

where we used a different type of parameterization: we again model the polymer as a curve in space, parameterized by the arc length \( s \in [0; L_c] \), which coincides with the neutral axis of the beam. Now, however, we also consider the position of the neutral axis in the global x-y plane described by \( [x(s)y(s)]^T \) and the angle between the neutral axis and cross-section\(^1\), given by \( [\theta(s)] \) (Figure 1.6).

\(^1\)The type of beam description in which the cross-sectional angle is explicitly parameterized is known as the Timoshenko beam theory. In the classical beam theory (Euler-Bernoulli) the cross-section is presumed orthogonal to the neutral axis. The arbitrary angle \( \theta \) between the beam’s cross-section and neutral axis in Timoshenko beam theory allows for accurate representation of shear deformation. Additionally, the numerical properties of Timoshenko beams are favourable over classic beams, reducing the number of iterations.
Thus, the configuration of the beam is completely described by the current state vector $x(s) = [x(s), y(s), \theta(s)]^T$ for all points on the neutral axis [53]

$$\Omega = \{ [x(s), y(s)]^T : 0 \leq s \leq L_c \} . \quad (1.45)$$

Let $X(s) = [X(s), Y(s), \Theta(s)]^T$ be a known stress-free reference configuration (in general that would be the straight contour), then we define the deformation vector as the difference between the current state and reference state vector

$$u(s) = x(s) - X(s) = [\Delta x, \Delta y, \Delta \theta]^T . \quad (1.46)$$

The (static) elastic force density, $g_{el}(u, x)$, can now be expressed as [1]

$$g_{el} = T(x) \left( \partial_s N_{int} \quad \partial_s Q_{int} \quad \partial_s M_{int} - Q_{int} \right)^T , \quad (1.47)$$

where the internal elastic forces $N_{int}$ are orthogonal to the cross-section, the internal forces are parallel to the cross-section $Q_{int}$ and internal bending moment $M_{int}$ are given by the relation [53]

$$\begin{pmatrix} N_{int} \\ Q_{int} \\ M_{int} \end{pmatrix} = \begin{pmatrix} EA & 0 & 0 \\ 0 & GA & 0 \\ 0 & 0 & EI \end{pmatrix} \left( T(x)^T \partial_s x - T(x)^T \partial_s X \right) . \quad (1.48)$$

In Eq.(1.47) and (1.48), $T$ is a transformation matrix that transforms the local coordinate system fixed to the beam to the global x-y coordinate system.

$$T = \begin{pmatrix} \cos(\theta) & -\sin(\theta) & 0 \\ \sin(\theta) & \cos(\theta) & 0 \\ 0 & 0 & 1 \end{pmatrix} . \quad (1.49)$$

The drag force density is, as discussed above (Eq.(1.12)), in the local friction approximation governed by two different friction coefficients (parallel and orthogonal to
1.5. NUMERICAL SIMULATION - FINITE ELEMENT METHOD

the backbone of the polymer). Such an anisotropic friction model has been success-
fully implemented in a finite element framework in [53]. However, in the following
derivation we limit ourselves to the isotropic friction assumption, which may be less
accurate but suffices as a first approximation [1]. In the simplified isotropic case, the
drag force density is therefore given by

$$
g_f(u, \partial_t u, x) = c \partial_t u,
$$

(1.50)

Additionally, we obtain the stochastic force vector by referring to Eq. (1.10) and by
using the damping matrix as introduced in Eq. (1.50)

$$
\langle \xi(x, t) \rangle = 0
$$

(1.51)

$$
\langle \xi(x, t) \otimes \xi(x, t) \rangle = 2k_B T c \delta(s - s') \delta(t - t').
$$

(1.52)

According to Eq. (1.51) and (1.52), we express the stochastic force vector as

$$
\xi(x, t) = \sqrt{2k_B T v} \partial_{x,t} W(x, t),
$$

(1.53)

where we used $vv^T = c$ and we introduced a two-dimensional Wiener process $W(x, t)$.

1.5.3 Discretization in time and space

To solve the differential that follows from Eq. (1.44), (1.47), (1.50) and (1.53),

$$
g_{el}(u, x) + c \partial_t u = \sqrt{2k_B T v} \partial_{x,t} W(x, t),
$$

(1.54)

we resort to discretization in both time and space domain. For more details on this
procedure the reader may be referred to [1] or a standard textbook on the finite
element method. In short, the spatial domain $\Omega$ is discretized (Figure 1.7) in $N - 1$
non-overlapping one-dimensional beam elements and $N$ nodes (two on each boundary
of the elements). The nodes in this procedure may be compared to the beads in
the bead-rod method. However, the finite element method allows for higher-order
interpolation between the nodes, e.g. quadratic interpolation, by the use of so-called
shape functions.

For discretization in time, we subdivide the total simulation time $T_S$ in $n$ small time
steps $\Delta t = T_S/n$. The conformation $u$ that satisfies the differential equation (1.54) is
determined at these time steps or, if needed for FE convergence, at smaller increments
$\delta t < \Delta t$. Let us express the conformation of the polymer as the discretized vector $U_i$
containing all the nodal displacement values, times a shape function tensor $N(x)$ that
interpolates the nodal values along the adjacent elements at time $i$ (Figure 1.8)\(^5\),

$$
u_i(x) = N(x) U_i.
$$

\(^5\)From now on, we will consistently use upper case bold font to express discrete entities.
CHAPTER 1. LITERATURE SURVEY

FE discretization

current configuration

reference configuration

continuum model

finite-element model

Figure 1.7: Left: reference and current configuration of a continuum model of a polymer. Right: one dimensional finite element idealization of both configurations

Figure 1.8: Linear shape functions $N_j$ interpolate the value of the $j$th node over the adjacent elements. The shape functions are stored in the shape function tensor $N$.

First, we express the velocity of an element $\partial_t \mathbf{u}$ in terms of the nodal displacements $\mathbf{U}$ and time steps $\Delta t$,

$$\partial_t \mathbf{u}^i = \mathbf{N} \frac{\mathbf{U}^i - \mathbf{U}^{i-1}}{\Delta t}. \quad (1.56)$$

This allows us to discretize the viscous force density $\mathbf{g}_{fr} = \mathbf{c} \partial_t \mathbf{u}$. Then, we map the continuous viscous force density on the discretized domain [53],

$$\mathbf{G}_{fr}^i = \int_{\Omega} \mathbf{N}^T \mathbf{g}_{fr}^i d\Omega = \int_{\Omega} \mathbf{N}^T \mathbf{c} \partial_t \mathbf{u}^i d\Omega. \quad (1.57)$$

By substitution of Eq.(1.56) in Eq.(1.57) we find the discrete counterpart of the viscous force density [53],

$$\mathbf{G}_{fr}^i = \int_{\Omega} \mathbf{N}^T \mathbf{cN} \frac{\mathbf{U}^i - \mathbf{U}^{i-1}}{\Delta t} d\Omega. \quad (1.58)$$

Eq.(1.58) can be simplified by using the element damping matrix $\mathbf{C}$ [53],

$$\mathbf{C} = \int_{\Omega} \mathbf{N}^T \mathbf{cNd}\Omega, \quad (1.59)$$
1.5. NUMERICAL SIMULATION - FINITE ELEMENT METHOD

giving us [53],

\[ G_i^{fr} = C \frac{U^i - U^{i-1}}{\Delta t}. \]  

(1.60)

Using the same line of reasoning as for the viscous force vector, we express the discrete stochastic force vector on the element level as

\[ G_i^{stoch} = \int_{\Omega} N^T g_{i}^{stoch} d\Omega = \int_{\Omega} N^T \sqrt{2k_BT} v \partial_{x,i} W(x,t^i) d\Omega \approx \sum_{GP} \sqrt{2k_BT w_{GP}} \frac{N^T v R_{GP}(0,1)}{\Delta t}, \]  

(1.61)

where we used Eq. (1.50) and (1.53) and replaced the Wiener process with \( R_{GP}(0,1) \), a vector of random numbers with mean and unit variance, and \( w_{GP} \), the integration weights for numerical quadrature of the damping matrix. We can then express the differential Eq. (1.54) in discrete form, which can be implemented in an implicit backward Euler integration scheme,

\[ G_i^{el}(U^i) + C \frac{U^i - U^{i-1}}{\Delta t} = G_i^{stoch}, \]  

(1.62)

where we used

\[ G_i^{el} = \int_{\Omega} N^T g_{i}^{el} [N(x)U] d\Omega. \]  

(1.63)

Equation (1.62) can be implemented and evaluated using a commercial FE-solver, such as Abaqus or ANSYS.

\[ \text{Figure 1.9: Adapted from [1]. Comparison of analytical solution (dashed line) and finite element simulation (solid line) of the normalized MSD. a.) The simulation based on an FE model with a discretization of 20 elements, step size } \Delta t = 0.01 \text{ s and 400 realizations. b.) Convergence to the analytical WLC solution for finer discretization in space (40 elements) and time ( } \Delta t = 0.001 \text{s), based on 4000 realizations.} \]
1.5.4 Validation, limitations and failure

Since FE modelling of semiflexible polymers is a relatively new approach, not much validation work has yet been published. However, the few studies that are available show excellent convergence of simulation results to analytical predictions for small elements ($N_e = 40$) and small time steps of $\Delta t = 0.001$ s [1], based on an FE framework that uses a simplified isotropic drag coefficient matrix and considers a semiflexible polymer with hinged ends (Figure 1.9). Improved results have been found by adjusting the FE framework to include anisotropic friction [53] for simulating rotational diffusion of stiff rods and thermal fluctuations of semiflexible polymers (Figure 1.10). This adjusted framework also accounts for short-range hydrodynamic interactions [53]. However, more validation studies that include long-range hydrodynamic interaction, excluded volume and long semiflexible polymers, are needed before FE modelling can be considered a full substitute for bead models.

1.6 Discussion and outlook

In the current literature review, we considered various coarse-grained approaches for modelling the thermal fluctuations of semiflexible polymers in equilibrium with a viscous solvent. We addressed the limitations of the analytical WLC model in capturing polymer dynamics at short times and pointed out the difficulties in introducing complex material models, such as anisotropic elasticity and viscoelasticity, some of which are observed in various biopolymers (e.g. microtubules [54]). Since the analytical derivation of the WLC model is based on the weakly-bending limit assumption ($\ell_p \ll << 1$), application of the WLC model is only appropriate on polymers that are short compared to their persistence length or on short subsections of arbitrary long

Figure 1.10: Adapted from [53]. Tangent correlation function as a function of contour length of an actin filament between plates. a.) Comparison between FE simulation with anisotropic friction model included, analytical solutions and experimental data. b.) Comparison of FE simulation based on different friction models.
polymers [11]. To overcome many of these limitations, researchers commonly resort to numerical methods. Two of the most commonly used numerical models, namely bead-rod and bead-spring models, have been discussed in this survey. Bead models are suitable and commonly used for modelling the dynamics of long semiflexible polymers (e.g. DNA [22, 43, 49, 55, 56]). However, for stiffer polymers bead models become computationally very expensive, due to resulting high frequency phonons. Solutions to these problems have been proposed (e.g. artificial softening of the springs of a bead-spring model [49]), but they miss essential physics and can result in an overestimation of the deformation of the polymer [43]. As an answer to many of these issues, we also presented a new approach to polymer modelling, suggested by Cyron and Wall [1], that is based on the FE method. Although similar to bead models, e.g. the nodes of an FE-model can be compared to the beads of a bead model, the FE method allows, unlike the bead models, for higher order interpolation between the nodes and thus for a more accurate description of the conformation of the polymer. The mathematical foundations of the FE method are well defined and commercially available FE solvers allow for easy implementation of complex material models and implicit time integration (e.g. implicit backward Euler integration). Therefore, FE modelling of polymers seems to be a promising new technique to simulate thermal fluctuations of semiflexible polymers. However, more validation studies are needed, e.g. on long-range hydrodynamic interaction, before one may regard FE modelling as a full substitute for bead models.
Chapter 2

Thermal fluctuations of anisotropic semiflexible polymers

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Abstract

Thermal fluctuations of microtubules (MTs) and other cytoskeletal filaments govern to a great extent the complex rheological properties of the cytoskeleton in eukaryotic cells. In recent years, much effort has been put into capturing the dynamics of these fluctuations by means of analytical and numerical models. These attempts have been very successful for, but also remain limited to, isotropic polymers. To correctly interpret experimental work on (strongly) anisotropic semiflexible polymers, there is a need for a numerical modelling tool that accurately captures the dynamics of polymers with anisotropic material properties. In the current study, we present a finite element framework for simulating the thermal dynamics of a single anisotropic semiflexible polymer. First, we demonstrate the accuracy of our framework by comparison of the simulated mean square displacement (MSD) of the end-to-end distance with analytical predictions based on the worm-like chain model. Then, we implement a transversely isotropic material model, characteristic for biopolymers such as MTs, and study the persistence length for various ratios between the longitudinal shear modulus, \( G_{12} \), and corresponding Young’s modulus, \( E_1 \). Finally, we put our findings in context by addressing a recent experimental work on grafted transversely isotropic MTs. In that research, a simplified static mechanical model was used to deduce a very high level of MT anisotropy to explain the observation that the persistence length of grafted MTs increases as contour length increases. We show, by means of our FE framework, that the anisotropic properties cannot account for the reported length-dependent persistence length.

Keywords: semiflexible polymer, anisotropy, finite element method, FEM, biopolymer, microtubule, cytoskeleton, nanomechanics, thermal fluctuation analysis.

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CHAPTER 2. THERMAL FLUCTUATIONS OF ANISOTROPIC SEMIFLEXIBLE POLYMERS

2.1 Introduction

The characteristic thermal fluctuations of biopolymers that are submerged in a viscous solvent have been extensively studied for over a decade [7, 8, 15, 21], mainly due to their important role in many biological processes [29, 57]. In eukaryotic cells for example, the thermal undulations of biopolymers are essential for the functioning of the dynamic network that these biopolymers constitute [58, 59]. This network is known as the cytoskeleton and consists of the biopolymers F-actin, intermediate filaments and microtubules, which are linked together by accessory proteins. The cytoskeleton gives the eukaryotic cell its mechanical properties, allows the cell to resist external stresses and plays a leading role in active force generation, cell mitosis and intracellular transport of vesicles and organelles [13, 59]. A good understanding of the mechanisms underlying these divergent roles of the cytoskeleton, requires a complete description of the mechanics and thermal dynamics of all of its structural components [16, 60].

The thermal dynamics of a submerged filament is often discussed in terms of its persistence length, \( \ell_p \). If the contour length, \( L_c \), of the polymer is much greater than its persistence length the dynamics of the polymer is dominated by thermal bending (flexible limit). Conversely, if the contour length is much smaller than the persistence length, the polymer dynamics will be dominated by elastic bending (stiff limit). Many biopolymers have a contour length close to their persistence length and are therefore called semiflexible. Formally, the persistence length is the characteristic length scale of the arc length for which two tangent angles along the polymer’s backbone \( \theta(0) \) and \( \theta(s) \) start to become uncorrelated [29]. In two-dimensions this translates to [15]:

\[
\langle \cos(\theta(s) - \theta(0)) \rangle = \exp(-s/2\ell_p). 
\]

By means of the equipartition theorem, the persistence length can be related to the bending rigidity of the polymer, \( \kappa \), and the external thermal energy, \( k_B T \), as [29]

\[
\ell_p = \kappa / k_B T. 
\]

For homogeneous isotropic filaments, \( \kappa \) equals the product of the Young’s modulus, \( E \), and second moment of area, \( I \). However, the effective bending stiffness of anisotropic polymers is nontrivial and cannot be expressed in terms of individual material properties [60].

Microtubules (MTs), which are among the cytoskeletal biopolymers that have attracted particular interest in recent years, mainly due to their key role in cell division [61], exhibit an intrinsic anisotropic material behaviour [8, 15, 54]. Underlying this anisotropic material behaviour is their complex molecular structure: MTs are hollow tubes with an outer diameter of 25 nm that consist of parallel aligned protofilaments.
of α- and β-tubulin heterodimers (Figure 2.1). The longitudinal Young’s modulus is determined by the strength of the head-tail αβ-αβ tubulin bonds, whereas the shear modulus is determined by the much weaker inter-protofilament bonds [62, 63, 64]. All-atom computer simulations [65] and in vitro mechanical testing of MTs [54] report anisotropic properties with one order difference between the longitudinal Young’s modulus and corresponding shear modulus.

![Schematic image of the microscopic architecture of microtubules. Microtubules are straight, hollow filaments and consist out of, on average, 13 parallel aligned protofilaments.](image)

**Figure 2.1:** Schematic image of the microscopic architecture of microtubules. Microtubules are straight, hollow filaments and consist out of, on average, 13 parallel aligned protofilaments.

Mainly due to the unfathomable relationship between anisotropic material properties of a polymer and its persistence length, it has been difficult to interpret recent experiments on grafted MTs submerged in a viscous fluid. In those experiments a hidden dependency of the persistence length of grafted MTs on their contour length was observed [8, 24]. Based on a simple Timoshenko beam model, that describes macroscopic elastic beams with shear contributions [28], and by assuming a static tip load and small displacements, anomalous MT material properties of a six orders lower longitudinal shear modulus than corresponding Young’s modulus were found. Various numerical modelling studies indeed confirmed contour length-dependency of the persistence length, but these studies are likewise limited to static loads and small displacements [66, 67, 68]. In this respect, the current research is limited by the lack of an intuitive computational modelling tool that allows for the study of the thermal dynamics of anisotropic polymers under distributed thermal force application and finite displacements.
Conventionally, polymers have been modelled numerically as a series of interconnected beads and rods or springs. This approach has its limitations, such as the lack of careful mathematical analysis, unavoidable artificial constraints and the need for (expensive) explicit time integration schemes [1]. Furthermore, bead models are limited to very slender and isotropic filaments, which makes these models less suitable for modelling the dynamics of relatively thick and anisotropic polymers, such as MTs. Driven by these limitations, a new method based on the finite element (FE) method was recently proposed [1]. In such an FE model, the microstructural complexity of a polymer is approximated by a continuum mechanical model, which is discretized into finite elements. The time-dependent partial differential equations (PDE’s), resulting from the interaction between the polymer and its fluid environment, are solved over each element using implicit time integration. It can be proven mathematically that the solution of the FE method converges to the solution of the analytical PDE for infinitely small elements and time steps [1]. Additionally, FE modelling has already been used for many decades in other research fields, such as computational engineering. This has resulted in versatile user-friendly software packages, allowing straightforward implementation of advanced material models. Furthermore, the FE method has been shown to be up to thousand times faster than traditional bead-rod models based on explicit time integration schemes [1]. The sound mathematical formulation, easy implementation of complex material models and favourable computational costs makes the FE method an accurate and intuitive modelling tool for capturing the thermal dynamics of single semiflexible polymers.

In the current study, we develop a finite element framework, based on a commercial solver (Abaqus/standard, Simulia), to model semiflexible polymers in thermal equilibrium with their viscous fluid environment. We first demonstrate the accuracy of this technique by comparing the simulated time evolution of the thermal fluctuations of freely floating and hinged isotropic filaments with analytical predictions based on the worm-like chain (WLC) model. We then change the boundary conditions to simulate a grafted MT and the mean square of the transverse displacement of its tip as a measure for its persistence length. Again, we show good correspondence with the theoretical predictions based on the worm-like chain (WLC) model. Finally, we implement highly anisotropic material properties and study the persistence length of MT of various lengths. We relate our findings to recent experimental research [8].

2.2 Methodology

Introduction

In this section, we describe the numerical framework for capturing the thermal dynamics of single anisotropic semiflexible polymers. This numerical framework is built around a commercial FE solver (Abaqus/Standard, Simulia) and is largely based
on the framework proposed by Cyron and Wall [1]. The finite element approach is, as argued by Cyron and Wall in [1, 53], an accurate, efficient and intuitive way of modelling the thermal dynamics of semiflexible polymers. In the current section, we first explain the workflow of the framework centred around its three main stages (pre-processing, solving and post-processing). Then, to confirm our approach, we pay particular attention to the validation of the framework. Based on the time evolution of the mean square displacement (MSD) of the end-to-end distance of simulated isotropic MTs, we show good correspondence between simulation output and the analytical solution based on the WLC-model. We do this for various parameters and boundary conditions. Finally, we introduce an anisotropic material model and adapt the validated framework to address a recent experimental study on grafted anisotropic MTs [8].

2.2.1 The finite element framework

From here on, we coarse-grain the exact atomic architecture of an MT by approximating it as a hollow slender continuum structure, as is common practice in Brownian dynamics modelling [8, 29]. Let us formulate a force equilibrium per unit length of internal and external forces to which the slender continuum is subjected [1],

\[ f_{\text{int}}(u, \dot{u}, x) = f_{\text{ext}}(x). \] (2.3)

In Eq. (2.3), the internal forces include bending (elastic) forces, \( f_{\text{el}}(u, x) \), and damping forces, \( f_{\text{visc}}(u, \dot{u}, x) \). Furthermore, since we do not consider any deterministic external forces, the right hand side of Eq. (2.3) only includes stochastic forces, \( f_{\text{stoch}}(x) \). We thus rewrite Eq. (2.3) as [1]

\[ f_{\text{el}}(u, x) + f_{\text{visc}}(u, \dot{u}, x) = f_{\text{stoch}}(x). \] (2.4)

Eq. (2.4) is a nonlinear partial differential equation, which cannot be solved analytically. Therefore, to find a solution for the displacement vector \( u \), we resort to FE modelling. In order to efficiently perform the simulations, a modelling framework was built around a commercial FE solver (Abaqus/Standard, SIMULIA), based on a Fortran user-subroutine, MATLAB and Python-scripting (Table 2.1). The three main stages in the workflow of the FE framework are illustrated in Figure 2.2 and will be described in detail below.

Table 2.1: Overview of the software that was used in the finite element framework

<table>
<thead>
<tr>
<th>Software</th>
<th>Version</th>
<th>Manufacturer</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Python</td>
<td>2.6.2</td>
<td>Beopen.com</td>
<td>pre/post-processor</td>
</tr>
<tr>
<td>Abaqus/Standard</td>
<td>6.10-1</td>
<td>SIMULIA</td>
<td>solver</td>
</tr>
<tr>
<td>Fortran</td>
<td>11</td>
<td>Intel</td>
<td>solver</td>
</tr>
<tr>
<td>MATLAB</td>
<td>R2011a</td>
<td>Mathworks</td>
<td>post-processor</td>
</tr>
</tbody>
</table>
**Pre-processing**

Let us consider a polymer confined to movement in the x-y plane (2-D). At \( t_{sim} = 0 \), the backbone of the polymer is aligned with the x-axis, which can be considered the stress-free or reference configuration \([69]\). The contour length of the polymer, \( L_c \), is a variable parameter and is specified by the user for each ensemble. The polymer is then discretised into 20 elements of length \( l_e = L_c/20 \) (Figure 2.3).
Cyron and Wall (2009) showed already excellent results for discretization into 20 elements to capture the thermal dynamics of semiflexible polymer of similar properties as in the current study, and only minor improvements were reported a for more accurate discretization [1]. For discretization we used one-dimensional Timoshenko beam elements. This specific type of elements was chosen due to their ability to accurately describe shearing, even for relatively thick beams and low shear modulus [70] and their favourable computational efficiency [69]. Additionally, several studies have shown that one-dimensional Timoshenko beam elements can accurately capture microtubule mechanics and are preferable over orthotropic shell models [71, 72]. The cross section of the filament is dependent on the type of polymer that is simulated and is presumed fixed throughout different ensembles\(^5\). Since we simulated MTs, which are tubular shaped, we assumed a hollow circular shaped cross-section, of which the dimensions are given in Table 2.2. We used one-dimensional continuum elements, thus the MT cross-section is only implicitly reflected by the second moment of area, \(I\) [69]:

\[
I = \pi \frac{r_o^4 - r_i^4}{4}
\]  

(2.5)

First, for validation of the FE framework, we implemented an isotropic material model by setting the shear modulus to \(G_{12}^{iso} = E_1/2(1 + \nu)\). See Table 2.2 for a listed overview of all the geometric and material properties that are used in this study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer radius</td>
<td>(r_o) (1.25 \times 10^{-2}) (\mu m)</td>
<td>[29]</td>
</tr>
<tr>
<td>Inner radius</td>
<td>(r_i) (7.5 \times 10^{-3}) (\mu m)</td>
<td>[29]</td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td>(\nu) 0.3</td>
<td>[73]</td>
</tr>
<tr>
<td>Density</td>
<td>(\rho) (1.0 \times 10^{9}) (mg \mu m^3)</td>
<td>[73]</td>
</tr>
<tr>
<td>Young’s modulus</td>
<td>(E) (1.3 \times 10^9) (pN \mu m^{-2})</td>
<td>[74]</td>
</tr>
<tr>
<td>Fluid viscosity</td>
<td>(\eta) (1 \times 10^{-3}) (pN \mu s \mu m^{-2})</td>
<td>[29]</td>
</tr>
<tr>
<td>Thermal energy</td>
<td>(k_B T) (4.045 \times 10^{-3}) (pN \mu m)</td>
<td>[53]</td>
</tr>
</tbody>
</table>

Stochastic forces are applied on each individual node of the discretized polymer by means of a user-defined distributed load subroutine (DLOAD). At the beginning of each simulation time step \(\Delta t_{FE}\) the DLOAD subroutine is called, upon which it outputs an array of random forces. These discrete forces are the equivalent of the noise correlations, fixed through the fluctuation-dissipation theorem [1, 9], that determine the continuous stochastic force density \(f_{stoch}\). These random nodal forces

\(^5\)In many cases, we will be interested in an ensemble of simulations with equal parameters. From now on, we will call the run of a single simulation a realization and the set of realizations with identical parameters an ensemble.
are sampled from a Gaussian distribution, which is defined by its first and second moment,
\[ \mu = 0 \]
\[ \sigma^2 = \frac{2k_B T \zeta}{\Delta t_{\text{stoch}} L_e} \]
respectively, where we introduced the thermal energy of the solvent, \( k_B T \), the drag-coefficient, \( \zeta \), and the variable \( \Delta t_{\text{stoch}} \), which represents the ‘refresh rate’ of the stochastic forces. The FE simulation step size, \( \Delta t_{\text{FE}} \), has to be smaller than \( \Delta t_{\text{stoch}} \) in order to obtain proper FE convergence. In the current framework, we have consistently used a FE step size \( \Delta t_{\text{FE}} \leq (0.1 \Delta t_{\text{stoch}}) \).

Similar to earlier work [1], we estimated the homogeneous isotropic drag coefficient, \( \zeta \), according to the formula for a rigid cylinder in a homogeneous flow [9] as,
\[ \zeta = \frac{4\pi \eta}{\ln(L_c/d)} \]
where \( \eta \) is the fluid viscosity and \( d \) is the diameter of the filament [69]. The logarithmic term is a correction factor that compensates for the neglect of hydrodynamic interactions between distant segments of the polymer [9, 75]. Although it has been demonstrated that contributions from internal friction cause a sharp increase in \( \zeta \) for very short MTs, \( \zeta \) may be presumed to obey Eq. (2.7) in the range of \( L_c \) considered in the current study [24]. We modelled damping according to the Rayleigh damping model:
\[ C(e) = \alpha M(e) + \beta K(e), \]
where \( C(e) \) is the elements damping matrix, \( M(e) \) is the elements mass matrix and \( K(e) \) is the elements stiffness matrix. In our particular case of linear Timoshenko beam elements, we set \( \alpha = \zeta / \rho A \), where \( \rho \) is the density of the membrane of the MT and \( A \) is the cross-sectional area, and \( \beta = 0 \).

**Solving**

Each realization was solved by the Abaqus/Standard FE solver on a Dell Precision T7500 workstation (Xeon X5680, two CPUs @ 3.33 GHz). The Abaqus/Standard FE solver is based on an efficient implicit time integration scheme, which makes it suitable for low-speed dynamic events, such as thermal undulations of polymers. The handling of the realizations (automatically starting the solver and collecting the data afterwards) is performed by a Python script.

For solving the model, we introduced two different timeframes: the simulation time frame, \( t_{\text{sim}} \), and the data collection time frame \( t_{\text{coll}} \). At \( t_{\text{sim}} = 0 \), the simulation is initiated and the initially straight contour of the filament starts to show bending fluctuations. To ensure that data collection is started after the polymer has reached equilibrium with its environment, we began data collection after the largest relaxation
time of the polymer, $\tau_c$, has elapsed, at which instant we set $t_{coll} = 0$ (Figure 2.5). This largest relaxation time of the polymer is determined by [15, 29]

$$\tau_c = \frac{\zeta}{\kappa_{iso}} q_{1}^{s-4} = \frac{\zeta}{EI} q_{1}^{s-4},$$  \hspace{1cm} (2.9)

where the wave vector of the first bending mode $q_{1}^{s}$ in Eq.(2.9) depends on the imposed boundary conditions. For example, for hinged boundary conditions $q_{1}^{s} = 1.5\pi/L_c$ [11] and for free boundary conditions $q_{1}^{s} = \pi/L_c$ [29] (Figure 2.4).

For various purposes, the dynamics need to be well described at very small timescales ($t \ll \tau_c$) as well as very large timescales ($t \gg \tau_c$) (e.g. for plotting the MSD of the end-to-end distance). In order to optimize the resolution for all timescales, variable time stepping is implemented: the time step that is used, depends on $\tau_c$ and the advancement of the realization. The procedure is as follows: first, the relaxation time is calculated based on the input parameters, Eq. (2.9). A coarse time stepping resolution is used to let the polymer equilibrate with its fluid environment ($0 < t < \tau_c$). Once the equilibrium has been obtained, the FE solver switches to the highest resolution and accurately captures the dynamics at the smallest timescale. The time resolution is gradually decreased, every decade of timescale, up to the largest time step that still allows for proper convergence of the realization (Figure 2.5).
CHAPTER 2. THERMAL FLUCTUATIONS OF ANISOTROPIC SEMIFLEXIBLE POLYMERS

In the current FE framework, the computational cost of the simulation is, due to the variable time stepping, to a great extent independent of the relaxation time. Therefore, the computational effort is largely independent of the contour length of the polymer, the boundary conditions, the drag coefficient and the bending rigidity. However, for very large relaxation times or very low polymer rigidity the gain of variable time stepping is limited, due to a limit to the maximum step size that still allows for proper FE convergence. As an indication, a typical realization ($30\tau_c$ of simulated time) of an isotropic polymer lasted $\pm 45$ minutes on the specified computer system. For high levels of anisotropy or very long relaxation times, the duration of a realization could take up to 4 hours.

The realizations within each ensemble are independent of each other (due to the ergodic nature of the studied phenomena). Therefore, simulations can be parallelized, reducing the overall simulation time.

**Post-processing**

The post-processing stage of the framework is done in MATLAB. The solver outputs data files that contain a global time stamp of each step $\Delta t_{FE}$ and the corresponding positions of the first and last nodes of the polymer. These files (one per realization, thus multiple per ensemble) are imported into MATLAB for further processing.

In order to quantify the time evolution of the polymer fluctuations, we define the mean square displacement (MSD) of the end-to-end distance as

$$\langle \delta R^2(t_{coll}) \rangle_{ensemble} \equiv \left\langle (|R(t_{coll}) - R(t_{coll} = 0)|)^2 \right\rangle_{ensemble}, \quad (2.10)$$

where $R(t_{coll})$ is the end-to-end distance or projected length of the filament (Figure 2.6). Due to collisions between the polymer and the thermally excited molecules, implicitly modelled through the Gaussian external forces, the MSD of the end-to-end distance will constantly change and is therefore time-dependent. As can be seen from Eq. (2.10), the MSD of the end-to-end distance is zero if $t_{coll} = 0$ and gradually increases with time. The end-to-end distance is determined by subtracting the position vector of the last node and the position vector of the first node of the polymer. This procedure is performed for all time steps $\Delta t_{FE}$. The end-to-end distance at the start of the collection $R(t_{coll} = 0)$ is subtracted from the total end-to-end distance and the resulting values are squared to obtain the displacement of the end-to-end distance $\delta R^2(t_{coll})$. We then average over all $N_R$ realizations in the ensemble to obtain the MSD of the end-to-end distance $\langle \delta R^2(t_{coll}) \rangle_{ensemble}$.

**2.2.2 Validation results**

For validation purposes, two sets of boundary conditions have been considered: a freely floating polymer and a polymer with hinged ends (Figure 2.4). In case of
hinged-hinged boundary conditions, the end-nodes of the polymer are allowed to move along the x-axis, but are constrained to move along the y-direction.

According to the theory of Brownian dynamics of polymers [6, 11, 18] two regimes can be identified in the time evolution of the mean square end-to-end distance: for very small times $t \ll \tau_c$, $\langle \delta R^2(t) \rangle$ increases, obeying a power law that scales with $t^{3/4}$, whereas for $t \gg \tau_c$, $\langle \delta R^2(t) \rangle$ reaches a universal equilibrium value of $\langle \delta R^2(t) \rangle_{eq} = L_c^4/90\ell_p$. We rescaled the simulated $\langle \delta R^2(t) \rangle$ and analytical solution by defining $F(t) = \langle \delta R^2(t) \rangle \left(90\ell_p/L_c^4\right)$ and we rescaled time by defining $\tilde{t} = t/\tau_c$. For both boundary conditions (free and hinged) and contour lengths (10 $\mu$m and 20 $\mu$m) a good agreement with the theoretical predictions of the WLC model [11, 18] is observed for over 5 decades of timescale. For MTs of a contour length of 20 $\mu$m and free boundary conditions (Figure 2.7), in the short time regime, a scaling behaviour of $t^{7/8}$ instead of $t^{3/4}$ is observed. This is in agreement with the WLC theory [4] which predicts that for times smaller than $t < \xi^4 L_C^8/\ell_P^4$, $\langle \delta R^2(t) \rangle$ scales with $t^{7/8}$. In all other cases $t^{3/4}$ scaling behaviour was observed in the short time regime, since the simulated times in this regime were larger than $\xi^4 L_C^8/\ell_P^4$. The jagged shape of the simulated curves is due to the random nature of the observed phenomenon and is expected to die out completely for a higher number of realizations, as shown in a similar research [1]. It is not the goal of this particular study to show convergence of the finite element towards the analytical solution for a large number of realizations (this has been done before in [1] for $N_R = 4000$). For the purpose of the current investigation, namely validation of the framework, $N_R = \pm 50$ realizations per ensemble was considered sufficient to show a good correspondence with the WLC theory.

2.2.3 Anisotropic polymers

For the validation of the framework we presumed isotropic material properties. However, due to their cylindrical atomic architecture (Figure 2.1), MTs are known to be anisotropic: the longitudinal Young’s modulus is determined by the strength of the head-tail $\alpha\beta - \alpha\beta$ tubulin bonds, whereas the shear modulus is determined by the much weaker inter-protofilament bonds [62, 63, 64]. Furthermore, in the plane of the transverse cross-section, MTs give an isotropic response to stress. From here on, we
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Figure 2.7: Rescaled MSD of the end-to-end distance, \( F(t) = \langle \delta R^2(t_{col}) \rangle \left( 90 \ell_p / L_c \right) \), as a function of rescaled time \( t/\tau_c \). The plots show the \( F(t) \) of various combinations of boundary conditions and contour lengths [(a) BC: free, \( L_c = 10 \mu m \), (b) BC: free, \( L_c = 20 \mu m \), (c) BC: hinged, \( L_c = 10 \mu m \), (d) BC: hinged, \( L_c = 20 \mu m \)]. Graph (b) shows \( t^{7/8} \) scaling behavior, as indeed predicted in [21], see text.

introduce a transversely isotropic material model, which accounts for the anisotropic material behaviour along the backbone of the MTs and isotropic properties along their cross-section. This approach is similar to other studies on MTs [8, 71]. According to linear elasticity theory, the elastic compliance matrix of a transversely isotropic material is defined by the Young’s moduli in the plane of isotropy, \( E_2 = E_3 = E_p \), the transverse Young’s modulus \( E_1 = E_t \), the Poisson ratio’s \( \nu_p \), \( \nu_{pt} \), \( \nu_{tp} \), and the in-plane and transverse shear moduli, \( G_{13} = G_{23} = G_p \) and \( G_{12} = G_t \), respectively.
Therefore, the 3-D stress-strain law reduces to:

\[
\begin{pmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\varepsilon_{33} \\
\gamma_{12} \\
\gamma_{13} \\
\gamma_{23}
\end{pmatrix} =
\begin{pmatrix}
1/E_t & -\nu_{tp}/E_t & -\nu_{tp}/E_t & 0 & 0 & 0 \\
-\nu_{pt}/E_p & 1/E_p & -\nu_{pt}/E_p & 0 & 0 & 0 \\
-\nu_{pt}/E_p & \nu_{pt}/E_p & 1/E_p & 0 & 0 & 0 \\
0 & 0 & 0 & 1/G_t & 0 & 0 \\
0 & 0 & 0 & 0 & 1/G_t & 0 \\
0 & 0 & 0 & 0 & 0 & 1/G_p
\end{pmatrix}
\begin{pmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\sigma_{12} \\
\sigma_{13} \\
\sigma_{23}
\end{pmatrix}
\] (2.11)

Because of the 2-D confinement of the simulation, deflection of the filament is only determined by the longitudinal elastic modulus, \(E_1\), and longitudinal shear modulus, \(G_{12}\). Therefore, we introduced the transverse isotropy through the parameter, \(\chi\), which sets the order of the ratio between the longitudinal shear modulus and corresponding Young’s modulus,

\[
\frac{E_1}{G_{12}} = 10^\chi. \tag{2.12}
\]

To conform our research as much as possible to the experimental work that has been done on grafted microtubules [2], we clamped the left-end of the MT by applying constraints in all three degrees of freedom (2 lateral, 1 rotational), whereas we left the right-end unconstrained (Figure 2.8). This new set of boundary conditions changes the longest wave vector, which is now given by \(q_1^* = \frac{1}{L_c}[31]\). Substitution of this wave vector in Eq. (2.9) gives us for an isotropic grafted polymer a relaxation time of

\[
\tau_{iso}^c = \frac{\zeta E}{4L_c^4}. \tag{2.13}
\]

For anisotropic polymers with a low shear modulus, it is expected that the effective bending rigidity decreases and thus the relaxation time increases. To estimate the effective relaxation time of an anisotropic polymer, \(\tau_{eff}^c\), we studied the MSD of the end-to-end distance, \(\langle \delta R^2(t_{coll}) \rangle\), for each unique set of parameters. Based on the onset of the \(\langle \delta R^2(t_{coll}) \rangle\) plateau we estimated \(\tau_{eff}^c\). For subsequent simulations, data was only collected after this effective relaxation time plus an additional safety margin elapsed. We then considered for each ensemble the position of the grafted MT tip in the x-y plane which we sampled at an interval of \(\tau_{eff}^c/10^3\). This allowed for accurate measurement of the distribution function \(P(x,y)\) and transverse displacement \(y_{\perp}\) of the tip position (Figure 2.8). Then, by integrating the probability distribution function over the y-axis, we found the asymmetric probability density function along the x-axis \(P(x)\).

For semiflexible polymers in the stiff limit (\(L_c < \ell_p\)), this asymmetric distribution is peaked toward full stretching and has a typical width of [76]:

\[
L_{\parallel} = \frac{L^2}{\ell_p}, \tag{2.14}
\]
Similarly, by integration along the x-axis, we obtained the distribution function $P(y)$, which is a Gaussian distribution centred at $y = 0$, the variance of which is given by the mean square transverse displacement $\langle y_\perp^2 \rangle$ [76]. This mean square transverse displacement $\langle y_\perp^2 \rangle$ can be directly related to the persistence length of the polymer, according to [29, 76, 77]:

$$\ell_p = \frac{L_c^3}{3 \langle y_\perp^2 \rangle}.$$  \hspace{1cm} (2.15)

For each realization that is added to the ensemble, the mean square transverse displacement, and thus the persistence length, changes. The ensemble was considered to contain enough realizations for a reliable estimate of the persistence length, if for each consecutive addition of the last five realizations to the ensemble the mean square transverse displacement did not change by more than 3%.

### 2.3 Results

First, to affirm our approach, we sampled the tip of grafted isotropic MTs of various lengths and calculated the simulated persistence length using Eq.(2.15). We found a good agreement with the theoretical persistence length ($\ell_p = EI/k_B T = 6.3 \text{ mm}$). As an illustration, Figure 2.9 shows the tip position of an isotropic MT of contour length $L_c = 10 \mu\text{m}$ in the x-y plane, based on $1.8 \times 10^6$ samples. By integration along the y-axis, we find the characteristic non-Gaussian and asymmetric distribution function $P(x)$ with a width of $L_\parallel = 0.015 \mu\text{m}$, as predicted by Eq.(2.14) according to the WLC theory [31]. Similarly, integration along the x-axis results in the Gaussian distribution $P(y)$, for which a good agreement is observed with the WLC theory (Figure 2.9). Indeed, we find a mean square transverse displacement of $\langle y_\perp^2 \rangle = 0.0550 \mu\text{m}$, which is within 4% accuracy of the theoretical value of $\langle y_\perp^2 \rangle = 0.0529$.

We calculated the effective persistence length for MTs of various contour lengths and orders of anisotropy by means of Eq.(2.15). These results are presented in Figure 2.10. We find that with increasing orders of transverse isotropy ($\chi = 1, 2, 3$) the persistence length decreases for all contour lengths. In this range of anisotropy, short MTs seem to be less affected by a lower longitudinal shear modulus than long MTs.
2.3. RESULTS

For highly anisotropic MTs ($\chi = 6$), we see a drop in persistence length of two orders compared to their isotropic counterpart. Although changes in persistence length with contour length are seen for all values of $\chi$, this dependency is only consistent for $\chi = 6$. For this value, a gentle, but noticeable, increase of the persistence length with increasing contour length is observed. In Figure 2.11, the contour length-dependency of the persistence length of MTs with the highest level of anisotropy ($\chi = 6$) of the FE simulations is compared to the simplified cantilever beam model, based on the Timoshenko beam formalism and single static tip load, as used in other studies [8, 24].

Figure 2.9: a) Point cloud of sampled tip position, based on $1.8 \times 10^6$ samples. b and c) After integration along the y and x-axis we find the two characteristic distributions $P(x)$ and $P(y)$, respectively. c) The solid line shows the analytical prediction according to the worm-like chain model.
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Figure 2.10: Persistence length versus contour length for various levels of anisotropy. The parameter $\chi$ refers to the order of difference between longitudinal shear modulus and Young’s modulus, see Eq.(2.12).

Figure 2.11: Persistence length versus contour length for MTs with a six-order lower longitudinal shear modulus than corresponding Young’s modulus according to the static Timoshenko beam model [8, 24] with single tip force (dashed) and dynamic FE simulations with distributed random forces (solid).
2.4 Discussion

Certain biopolymers, such as MTs, display an anisotropic material response, which is inherent to their molecular structure [15, 29]. Unfortunately, the effective persistence length of such anisotropic filaments cannot be explicitly expressed in terms of their material properties. Additionally, the anisotropic material properties and relative thickness of MTs cannot be accurately implemented in conventional numerical and analytical models, since such models are inherently built on slenderness and isotropy approximations. Therefore, researchers have been compelled to simple static models to interpret their experimental observations. For example, based on such a static model, unexplained length-dependency of the persistence length has been related to anomalously high levels of anisotropy [8]. However, the validity of such static models, which are based on small angle approximations and a single deterministic tip force, may be questionable when describing the finite displacements that are typically observed for highly anisotropic filaments under distributed random forces.

To overcome these limitations we developed and validated a framework, based on the FE method set out by Cyron and Wall in [1]. This FE framework accounts for the interaction between semiflexible polymers and solvent molecules by random force generation and application. The FE model also allows for the implementation of advanced material models and nonlinear elasticity. Additionally, the developed framework is computationally efficient compared to conventionally used bead models. By applying the FE framework to isotropic MTs of various contour lengths, we found that the time evolution of thermal fluctuations is in good agreement with the predictions of the WLC model [11, 18]. Furthermore, the FE framework allowed us to implement various levels of material anisotropy. By studying the distribution function of the tip of grafted isotropic and anisotropic MTs, we calculated the persistence length for four different contour lengths, \((L_c = 5, 10, 15, 20 \, \mu m)\). For isotropic MTs with a contour length of \(L_c = 10 \, \mu m\), we found a good correspondence with theoretical predictions and other Monte Carlo studies [76]. For isotropic MTs with contour lengths of \(L_c = 5, 15, 20 \, \mu m\) the simulations yielded a higher persistence length (up to 13%) than the theoretical persistence length of \(\ell_p = 6.3 \, \mu m\). This is in line with a similar FE study by Cyron and Wall that compares the effects of two different friction models on thermal fluctuations of polymers [53]. In that study, the isotropic friction model, which is the equivalent of the friction model that is used in the current study, resulted in a deviation from the theoretical persistence length for very short and long semiflexible polymers, similar to our findings. Thus, although in terms of absolute values our simulations may overestimate the persistence length up to 13%, mainly due to the assumptions of an isotropic friction model, the framework still allows for qualitative comparison between different orders of transverse isotropy and the identification of three trends: first, the implementation of a transversely isotropic material
model with a lower longitudinal shear modulus than corresponding Young’s modulus, results in a decrease of the persistence length for all contour lengths. Second, for the first three orders of transverse isotropy ($\chi = 1, 2, 3$), this reduction in persistence length is greater for long MTs than for short MTs. Third, implementing the highest order of transverse isotropy ($\chi = 6$) yields a two order decrease in persistence length, as compared to the isotropic case. Additionally, for $\chi = 6$, a slight increase of the persistence length with increasing contour length is observed.

The two orders lower persistence length of highly anisotropic MTs ($\chi = 6$) is of the same order as the persistence length reported in experimental studies for short and very short MTs [8, 37]. These experimental results have been explained by considering MTs as weakly-coupled (at intermediate length scales [24]) or decoupled (at short length scales [37]) assemblies of protofilaments. We can thus confirm that accounting for inter-protofilament decoupling by lowering the longitudinal shear modulus indeed results in such short persistence lengths. However, the above-mentioned experiments also confirmed a significantly longer persistence length of $4 – 8 \text{ mm}$ for long MTs of $L_c = 20 – 40 \text{ mm}$, as also established in earlier studies, e.g. [15]. Such a striking increase in persistence length has been attributed to the presumption that, in this length regime, MTs behave as fully coupled homogenous structures with negligible inter-protofilament sliding. From our simulation results, we conclude that a six order difference in longitudinal shear modulus and corresponding Young’s modulus alone cannot account for this reported length-dependence of the persistence length. Our findings agree well with previous research on MT rigidity, based on experimentally measurement of buckling force [33, 34] and mode decomposition of free-floating MTs [15], in which no significant length-dependency of flexural rigidity was reported. Furthermore, the outcomes of the current study reveal the limitations of the simplified mechanical cantilever model that was used in other studies [8, 24] to interpret the observed length-dependency. Such a static Timoshenko beam model is based on small angel approximations and a single tip load. Therefore, it is unsuitable for accurately capturing the intricate dynamics and large displacements of a highly anisotropic MTs in equilibrium with their fluid environment. The current research sheds new light on the unexplained discrepancy between the indirectly deduced longitudinal shear modulus (six order difference with corresponding Young’s modulus), based on such a simplified mechanical model, and direct experimental and computational measurements of the longitudinal shear modulus [54, 65] (up to three orders difference with corresponding Young’s modulus). The outcomes of the current study should be interpreted as an encouragement to consider other causes for the experimentally observed length-dependence than high anisotropy alone.

The current study is subject to several limitations. A first limitation is that internal friction due to liquid flowing through narrow pores of the MT, as pointed out in [24],
was neglected. Including internal friction would have caused a sharp peak in the drag coefficient for very short MTs. However, in the range of contour lengths considered in the current study, the drag coefficient may be presumed constant [24]. A second limitation of the current study is that we approximated friction by an isotropic friction model. Although an isotropic friction model serves as a good first approximation, [1] an anisotropic friction model, that takes into account different friction coefficients perpendicular and longitudinal to the filament, enhances the accuracy of the absolute values of the model, see [53]. Additionally, we only implicitly accounted for the hydrodynamic interactions between distant polymer sections through scaling of the drag coefficient by a logarithmic length-dependent correction factor. Indeed, we noticed small differences in the amplitude of the saturation plateau of the MSD of the end-to-end distance upon changing the drag coefficient correction factor. Such an approximation is common practice for stiff polymers, because for such stiff polymers remote interactions, such as one segment shielding another segment, will be negligible [78, 19]. However, for long and flexible polymers, hydrodynamic interaction between segments as well as self-avoidance may become appreciable and should be taken into account. In the current research the most flexible polymer ($L_c = 20 \mu m$, $\chi = 6$), was still in the stiff regime, $\frac{L_c}{\ell_p} < 0.1$. Therefore, it is expected that neglecting hydrodynamic interaction and self-avoidance will only have had a minor effect on the simulated values and a negligible effect on the observed trends [76]. Furthermore, we modelled the MTs to be confined to a two-dimensional plane, whereas the cited experimental work considered the two-dimensional projection of filaments in three-dimensional space. In three dimensions, there are two independent angular degrees of freedom [29] and this will increase the mean energy of a short MT segment from $\frac{1}{2} k_B T$ to $k_B T$. Therefore, the mean cosine of two tangent angles along the backbone $\theta(s)$ and $\theta(s + \Delta s)$ will decay twice as quickly. However, this additional factor 2 is compensated for by the three-dimensional counterpart of Eq. (2.15) and will not alter the calculated persistence length. Therefore, it is not expected that adding an extra dimension to the problem will alter the observed trends in any way.

Finally, due to high computational costs, the number of realizations that were performed per ensemble was limited. A higher number of realizations would have further improved the accuracy. Despite the above mentioned limitations, the accuracy of the model exceeds largely the required accuracy to support our main finding: a high anisotropy cannot account for the large length-dependence of the persistence length.

### 2.5 Future work

In future FE simulation work on the thermal fluctuations of semiflexible polymers, the above-mentioned limitations should be addressed. First, by the implementation
of an anisotropic drag coefficient tensor, the quantitative accuracy of the model may improve. Second, according to the authors’ opinion, upgrading the model from two-dimensions to three-dimensions is straightforward and would more accurately represent the experiment of Pampaloni and co-workers [8], but the gain may be minor compared to the additional computational costs. Finally, in several studies [7, 24], internal friction has been identified as a possible cause for the experimentally observed length-dependency of the persistent length. By including internal friction explicitly into the FE model, prediction of the associated effects may be enhanced.

The current study showed the accuracy of the current FE model to capture thermal fluctuations of stiff polymers under equilibrium conditions. It would be interesting to also explore the dynamics of polymers in the more flexible regime, e.g. F-actin and DNA. For polymers for which \( L_c = \ell_p \), different physics is expected that should be reproducible with the current FE framework, e.g. the double-peaked Gaussian distribution for grafted F-actin predicted in [76]. Furthermore, still unresolved issues exist regarding the modelling of semiflexible polymers under strong confinement [43, 79]. Understanding of DNA under strong confinements is relevant for understanding biological systems (e.g. bacteriophages), studying hybrid bio-nanostructures, (e.g. DNA confined inside a carbon nanotube) or for pioneering research on biotechnological innovations, such as drug delivery systems [43]. However, for such flexible and long polymers, hydrodynamic interaction and excluded volume start to play a significant role. Therefore, before the framework can be applied to slender flexible polymers, effort should be put into the implementation of these effects.

Semiflexible polymers under sudden stretch or release (far-from equilibrium conditions) have recently attracted much interest [80, 81, 82]. Similarly, the transition from the entropy-dominated to the elasticity-dominated regime and reverse is relevant for various biotechnological applications and experiment interpretation. The FE-method developed here can, to the authors’ opinion, relatively easily be used for the study of these far-from equilibrium conditions.

### 2.6 Acknowledgement

We are grateful to Christian Cyron for a fruitful discussion and his kind help.
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I would like to dedicate the last words of this thesis to the people who made it possible in the first place. Thank you, Amir, for your dedication as supervisor and your genuine interest in the progress of my work. You have initiated me in the sometimes wonderful, sometimes disappointing world of academic research. Teaming up with you in this research project has been a very positive experience that has changed my view on academic research. You continued to amaze me with your knowledge and patience. I am sure that you have a great career ahead of you and it is a matter of time before you will match up with Khademhosseini and consortium. Good luck to you!

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Gabi, thank you for your unconditional patience, especially during the last couple of weeks leading up to my graduation, in which I may not have been the best boyfriend. Graduating simultaneously has been quite a challenge, but we made it! I am looking forward to the adventure that awaits us in Asia and other, still unknown, destinations.

Last but not least, I am grateful to my MSc-exam committee members, Harrie Weinans, Amir Zadpoor and Paolo Tiso for the time they put into reading and correcting my thesis and attending my presentation and defence.
Bibliography


# Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Meaning</th>
<th>Units</th>
</tr>
</thead>
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<tr>
<td>$R(t)$</td>
<td>End-to-end distance</td>
<td>[m]</td>
</tr>
<tr>
<td>$\langle \delta R^2(t) \rangle$</td>
<td>Mean square end-to-end distance (MSD)</td>
<td>[m$^2$]</td>
</tr>
<tr>
<td>$E$</td>
<td>Young’s modulus</td>
<td>[Pa]</td>
</tr>
<tr>
<td>$I$</td>
<td>Second moment of area</td>
<td>[m$^4$]</td>
</tr>
<tr>
<td>$\zeta$</td>
<td>Drag coefficient</td>
<td>[Pa·s]</td>
</tr>
<tr>
<td>$k_B T$</td>
<td>Thermal Energy</td>
<td>[J]</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Fluid viscosity</td>
<td>[Pa·s]</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Density</td>
<td>[kg·m$^{-3}$]</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Bending rigidity</td>
<td>[N·m$^2$]</td>
</tr>
<tr>
<td>$M$</td>
<td>Bending moment</td>
<td>[N·m]</td>
</tr>
<tr>
<td>$L_c$</td>
<td>Bending moment</td>
<td>[m]</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Stochastic force</td>
<td>[N]</td>
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<td></td>
</tr>
<tr>
<td>$t$</td>
<td>Time</td>
<td>[s]</td>
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<tr>
<td>$q_n p$</td>
<td>Wave vector</td>
<td>[m$^{-1}$]</td>
</tr>
<tr>
<td>$W_n$</td>
<td>Wave function</td>
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</tr>
<tr>
<td>$\tau_n$</td>
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</tr>
<tr>
<td>$\langle \rangle$</td>
<td>Mean value</td>
<td></td>
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<tr>
<td>$\delta(i - j)$</td>
<td>Kronecker delta</td>
<td></td>
</tr>
<tr>
<td>$d$</td>
<td>Diameter</td>
<td>[m]</td>
</tr>
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<td>Outer radius</td>
<td>[m]</td>
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<td>$r_i$</td>
<td>Inner radius</td>
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<tr>
<td>$\nu$</td>
<td>Poisson’s ratio</td>
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</tbody>
</table>
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