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A fast platform for simulating semi-flexible fiber suspensions applied to cell mechanics

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ABSTRACT

We present a novel platform for the large-scale simulation of three-dimensional fibrous structures immersed in a Stokesian fluid and evolving under confinement or in free-space in three dimensions. One of the main motivations for this work is to study the dynamics of fiber assemblies within biological cells. For this, we also incorporate the key biophysical elements that determine the dynamics of these assemblies, which include the polymerization and depolymerization kinetics of fibers, their interactions with molecular motors and other objects, their flexibility, and hydrodynamic coupling. This work, to our knowledge, is the first technique to include many-body hydrodynamic interactions (HIs), and the resulting fluid flows, in cellular assemblies of flexible fibers. We use non-local slender body theory to compute the fluid–structure interactions of the fibers and a second-kind boundary integral formulation for other rigid bodies and the confining boundary. A kernel-independent implementation of the fast multipole method is utilized for efficient evaluation of HIs. The deformation of the fibers is described by nonlinear Euler–Bernoulli beam theory and their polymerization is modeled by the reparametrization of the dynamic equations in the appropriate non-Lagrangian frame. We use a pseudo-spectral representation of fiber positions and implicit time-stepping to resolve large fiber deformations, and to allow time-steps not excessively constrained by temporal stiffness or fiber–fiber interactions. The entire computational scheme is parallelized, which enables simulating assemblies of thousands of fibers. We use our method to investigate two important questions in the mechanics of cell division: (i) the effect of confinement on the hydrodynamic mobility of microtubule asters; and (ii) the dynamics of the positioning of mitotic spindle in complex cell geometries. Finally to demonstrate the general applicability of the method, we simulate the sedimentation of a cloud of semi-flexible fibers.

1. Introduction

Semi-flexible biopolymers constitute a principal mechanical component of intracellular structures [11,66,6]. Together with molecular motors, fiber networks consisting of such polymers form the cytoskeleton that is the cell's mechanical machinery for executing several key tasks including cell motility, material transport, and cell division [41]. From these semi-flexible

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filaments (microtubules, actin filaments and intermediate filaments) and a variety of molecular motors the cytoskeleton is able to reorganize into supramolecular architectures that are distinctly designed to perform a particular task [24,41].

Due to their central role in intracellular structures the rheology and collective dynamics of semi-flexible fiber suspensions and networks has attracted increasing interest in engineering and biology [11,92].

The basic physical difference between semi-flexible fibers and their better-understood counterpart, polymer chains, is the significantly larger bending rigidity of fibers that then yields larger end-to-end distances. This results in many interesting differences between the rheology of semi-flexible polymers and that of the two extreme limits of flexibility, polymer melts and rigid fiber suspensions. For example, the stiffness of semi-flexible networks can increase or decrease under compression and their suspensions show negative normal stress differences [7,66,11].

With advancements in microscopy and data acquisition at small time- and length-scales, we now know a great deal about the interactions of the individual microscopic filaments and their associated motor proteins. On the other hand, we know very little about how they interact collectively and how these interactions determine the ensemble behavior of cellular matter and structures.

Microrheological measurements provide a strong basis for understanding the mechanical behavior of cytoskeletal structures and matter [110,66,98], but do not directly inform us of the relationship between microscopic interactions and macroscopic behaviors. Moreover, living systems typically operate far from equilibrium — due to internally generated forces being much larger than thermal forces — and a constitutive relationship is required to extract rheological behavior based on, for example, the trajectories of probe particles. Finding microscopic constitutive relations is difficult even for the simplest of out-of-equilibrium complex fluids, a hard-sphere colloidal suspension, due to the complex and nonlinear relationships between rheological properties and microstructural dynamics [68].

Dynamic simulation is a powerful tool to gain insight into the underlying physical principles that govern the formation and reorganization of cytoskeletal structures and to ultimately find relevant constitutive relationships. With the continuous advancements in *in vitro* reconstitution of cellular matter, comparing experiments with *in silico* reconstitution (i.e., detailed, large-scale, dynamic simulation of cellular structures) is within reach [6]. To this end, this paper presents a computational platform for dynamic simulation of semi-flexible fiber suspensions in three-dimensional Stokes flow. Our method explicitly accounts for fiber flexibility, their polymerization and depolymerization kinetics, their interactions with molecular motors, and hydrodynamic interactions (HIs). From a physical point of view, what distinguishes our method is the inclusion of HIs, which has been almost entirely ignored in the previous theoretical and numerical studies of cellular structures [11].

A common argument for ignoring HIs is that these potentially long-ranged interactions are screened, due to the presence of other filaments, beyond length-scales larger than the average separation inter-filament distance. However, whether effective screening is actually present depends on many technical details of the flow, such as whether the immersed bodies exert net forces or torques on the fluid, or are free to move [79,72]. Our computational studies, presented here and elsewhere [69], strongly argue that long-ranged HIs are essential components of cellular mechanics. For example, in a concurrent work [69], we computationally study so-called *pronuclear migration*, which occurs in the lead-up to the first cell division in C. elegans embryo. For proposed force-transduction mechanisms for migration, we show that ignoring HIs leads to mispredictions of the required active forces by an order of magnitude. We show further that each mechanism gives rise to unique features in the generated cytoplasmic flows, and we propose flow measurement as a tool to differentiate between active mechanisms. In Section 4.1 of this work, we show that while coarse-grained theories such as the Brinkman equation for porous medium flow can predict some features of the mechanics of cytoskeletal motion, other features, including the relaxation time of microtubule filaments of the cytoskeleton, cannot be predicted. One important use of detailed simulations, like those presented here, is to directly test the validity of simplifying assumptions such as screening or use of a Brinkman approximation, as well as to inform and modify theories for the collective behavior of complex assemblies such as the cytoskeleton.

We consider suspensions of hydrodynamically interacting rigid bodies and flexible fibers immersed in a Stokesian fluid, either under confinement or in free-space. Our approach is based upon boundary integral formulations of solutions to the Stokes equations. The flows associated with the motion of rigid bodies and confining surfaces are represented through a well-conditioned second-kind boundary integral formulation [80]. The fluid flows associated with the dynamics of fibers are accounted for using *non-local slender body theory* [48,44,31,102].

Related work. Modeling approaches to suspensions and networks of fibers can be roughly categorized into volume- and particle-based methods. In volume-based methods, the Stokes (or Navier–Stokes) equation is solved by discretizing the entire computational domain. Within this class, immersed boundary methods have been applied to study the dynamics of single [99,55] or several [109] flexible fibers. The fibers are typically represented by a discrete set of points (forming a one-dimensional curve [99,109], or a three-dimensional cylinder [55]) whose interactions capture stretching stiffness and internal elastic stresses. These points on the fibers are Lagrangian and so are moved with the background fluid flow. The consequent stretching or bending of the discretized fiber creates elastic forces represented at the Lagrangian points. These forces are distributed to the background grid, which then provides forcing terms solving anew the Stokes or Navier–Stokes equations for the updated background flow. This cycle is then repeated. A similar update strategy has been adopted using the Lattice Boltzmann method [112] to study the rheology of flexible fiber suspensions. Typically, to properly account for fluid–structure interactions in volume-based methods, the size of the volume grid is taken to be several times smaller than the smallest dimension of the immersed bodies. As a result, these methods become computationally expensive for simulating slender bodies such as fibers and thin disks. Moreover, these methods typically use explicit time-stepping to evolve fiber shapes, and elastic forces that substantially limits the region of time-step stability [56] due to temporal stiffness.