Summary

Recent, increasingly accurate measurements of the properties of bio-relevant molecules challenge our understanding of macromolecules as having well-defined, fixed shapes that determine their function. The equilibrium distribution of their conformations is described by the Boltzmann distribution, which combines two terms: the influence of the temperature of the solvent and the potential energy of a given configuration, which in turn captures the elastic properties of the molecules. The behavior of elastic macromolecules is thus shaped by the competition of these two physical phenomena—whenever the valleys of the potential energy landscape are shallow in comparison to a typical thermal fluctuation, a wide variety of conformations are present; conversely, when they are deep, only small deviations from the energy-minimizing configurations can be observed.

The doctoral thesis presents a theoretical description of the conformational variability of elastic macromolecules and its effect on diffusion. The first part of the thesis provides an overview of theoretical fundamentals required for building coarse-grained models, which form the core of this work. It also delves into the theoretical underpinnings of the experimental methods used to validate simplifying assumptions made in the former. The second part of the thesis comprises a series of thematically linked publications and preprints in which we demonstrate methods for dealing with and taking advantage of both extremes of the elasticity spectrum.

Starting from molecules with very large persistence length compared to their size, we demonstrate how to model the approach of a very short DNA segment towards a nanopore and provide an analysis of the influence of wall interaction and hydrodynamic anisotropy in the nanopore capture process. By considering a rod-like molecule with uniformly distributed charge, we establish theoretical criteria for determining when and where the inclusion of wall corrections is necessary. Secondly, we investigate the impact of negative supercoiling and curvature on the hydrodynamic properties of 336 bp and 672 bp DNA minicircles. Utilizing linear elasticity theory and hydrodynamic calculations, we predict DNA shapes and diffusion coefficients. Our results show a favorable comparison with experimental data on diffusion and sedimentation coefficients obtained using analytical ultracentrifugation. For intermediate values of persistence length, we determine the range of lengths and g-forces under which sedimentation of a flexible, looped filament remains stable to buckling. Our analysis, based on linear elasticity theory combined with resistive force theory, yields a stability criterion reliant on a single dimensionless parameter.

In a more general case where both thermal fluctuations and elastic forces are significant, we propose a numerical approach. This approach is based on a stochastic differential equations integrator we developed, combined with hydrodynamic interactions based on the Rotne-Prager approximation. Additionally, we present a suite of Python packages designed to make small Brownian Dynamics simulations both fast to develop and fast to simulate, thanks to hardware acceleration.

We demonstrate that for intrinsically disordered proteins (IDPs), which represent the opposite extreme of the elasticity spectrum as compared to very stiff DNA, excluded volume interactions are the key factor determining the equilibrium conformational ensemble. We introduce the Globule-Linker model for generating conformations and combine it with the Minimum Dissipation Approximation to predict their hydrodynamic size. Using the comparison of the coarse-grained approach with the largest set of experimental values collected to date, we show that our first-principles approach outperforms phenomenological fits available in the literature.

Finally, we deal with the theoretical problem of equilibrium distributions of molecules with both very stiff degrees of freedom and comparatively free ones (such as the bond length and inter-bond angles, respectively, in molecular models). We identify the important details of the constraining potentials overlooked in earlier works and demonstrate a method of their computation, both in general and through specific examples.

Our results, which span a spectrum of possible elastohydrodynamic regimes, demonstrate the rich diversity of phenomena that arise from the competition of structural rigidity, viscous stresses and thermal fluctuations. In order to facilitate the analysis of such systems, we have created a number of open-source numerical tools, which have been published with documentation. The applicability of these tools was tested directly in relatively stiff biopolymers—the circular DNA—and soft structures of IDPs. Additionally, they provide an insight into the intermediate stiffness regimes, where thermal fluctuations compete with intramolecular interactions, and can be used for a better understanding of microscale elastohydrodynamic phenomena.