Dynamics of crowded macromolecules from atomistic simulations

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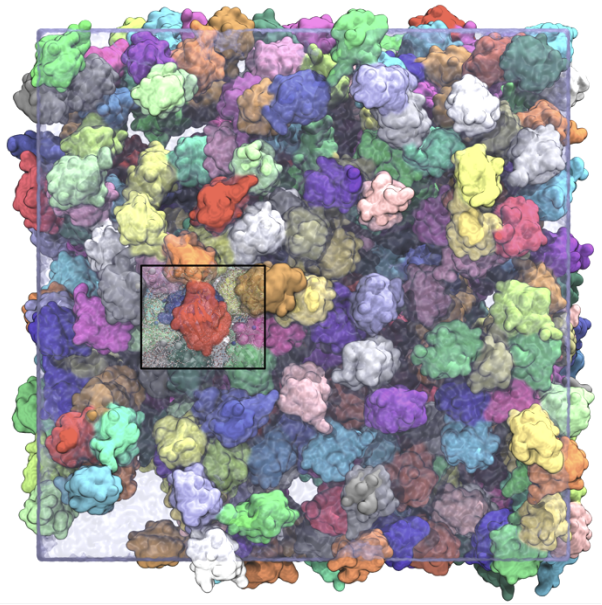
The interior of the cell is densely crowded, affecting thermodynamic and kinetic properties of the macromolecules within. It has only very recently become computationally feasible to simulate crowded macromolecular systems atomistically to address detailed questions on protein stability, interactions and transport properties like diffusion.

I present a large-scale molecular dynamics simulation study of atomistically-resolved crowded protein systems containing up to 540 fully flexible proteins with 3.6 million atoms in the microsecond range. [1] We find that using the Amber99SB*-ILDN-Q protein force-field in conjunction with the TIP4P-D water model gives a surprisingly accurate picture of the dynamics of concentrated protein solutions that agrees very well with experimental results.



Snapshot of an atomistic molecular dynamics simulation of 540 fully flexible ubiquitin proteins at 200 mg/ml concentration in explicit water.

The protein species studied here form dynamic clusters between which they constantly exchange. A theoretical model, based on the Stokes-Einstein equations, nearly quantitatively links the slow-down of translational and rotational diffusion, increase in viscosity and formation of protein clusters.

Using a colloidal model of sticky hard spheres, we relate the above properties to the dissociation constant of protein-protein interaction, allowing for an estimate of the concentration-dependent slow-down of protein diffusion given only the dissociation constant.

We build on the above framework to simulate mixed systems to address research questions like the postulated solubilizing properties of ATP (acting as a “hydrotrope”), phase-separation of intrinsically disordered proteins, or interactions between RNA and transcription factors.

Reference:

[1] Sören von Bülow, Marc Siggel, Max Linke, Gerhard Hummer (2019) Dynamic cluster formation determines viscosity and diffusion in dense protein solutions. *Proc Natl Acad Sci* 116:9843-9852.