

Short-time diffusive dynamics of proteins in a naturally crowded environment: Coarse-grained simulations

Hender Lopez

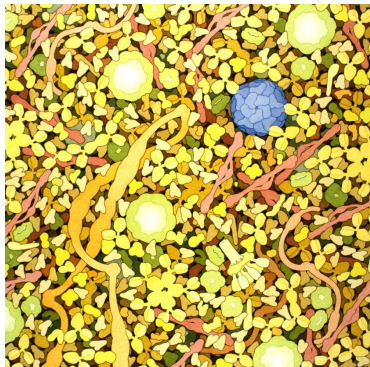
School of Physics, Technological University Dublin (TUDublin), City Campus

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Introduction

Crowding – Diffusion

- Cell environment is packed (volume fraction ~ 0.4)
- Diffusion is reduced compared to a dilute case
- Diffusion limited processes are affected



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Introduction

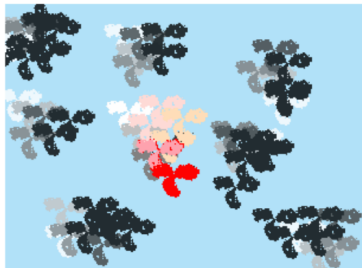
Time scales we are studying!!!

Short-time diffusion

Slow down due to hydrodynamic interactions (HI) mediated by the water:

$$t \ll R_H^2/D_0 \sim 500 \text{ ns}$$

For immunoglobulin (Ig)



Introduction

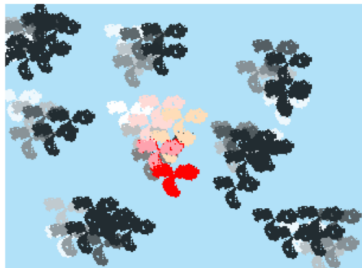
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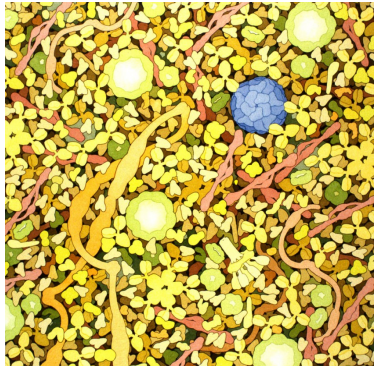
For immunoglobulin (Ig)



Introduction

Complexity (polydispersity) of the *E. coli* environment

- 70% water
- 15% proteins
- 7% RNA/DNA
- 2-3% polysaccharides
- 2-3% phospholipids
- inorganic ions and metabolites

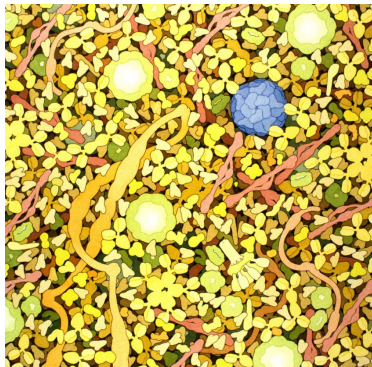


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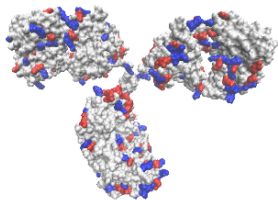


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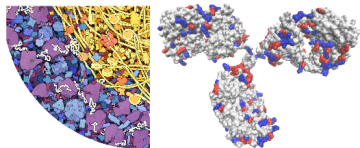
Introduction

Experiments – Ig in crowded environments

Ig (self crowded)



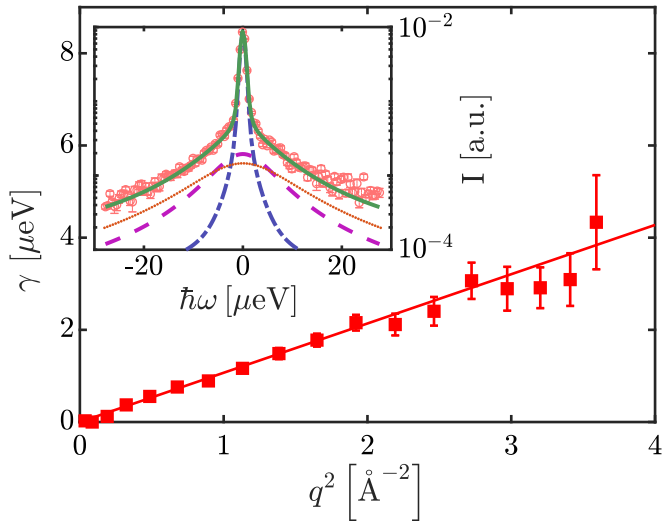
Ig + lysate (D_2O *E. coli*)



Quasi-Elastic Neutron Backscattering, Time scales: 10ps – 1ns

Introduction

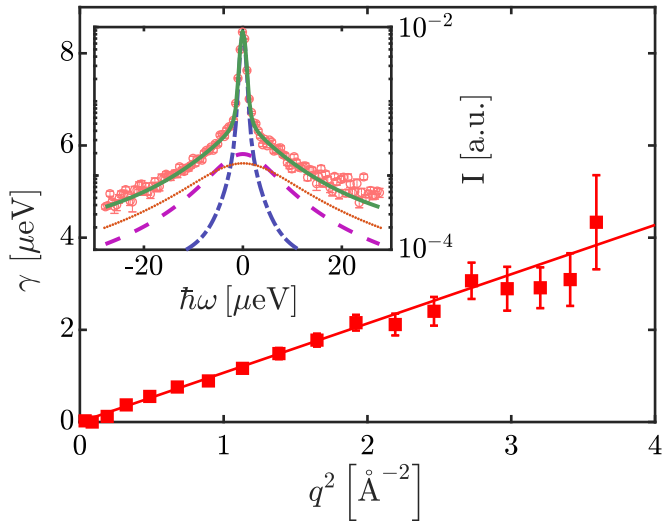
Typical experimental results – D is apparent diffusion



HWHM: $\gamma = Dq^2$, Fit to three Lorentzian

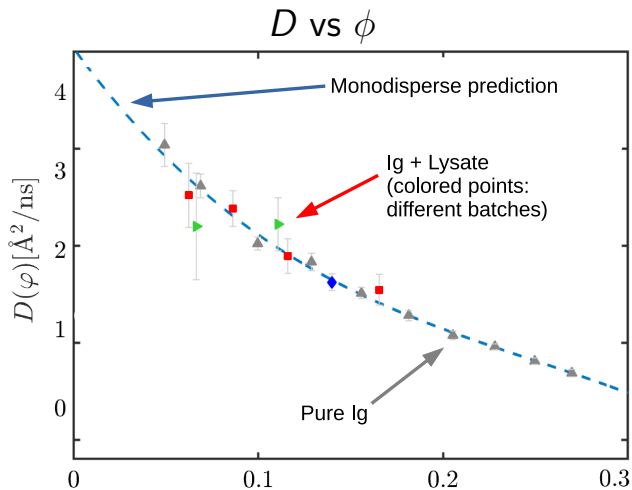
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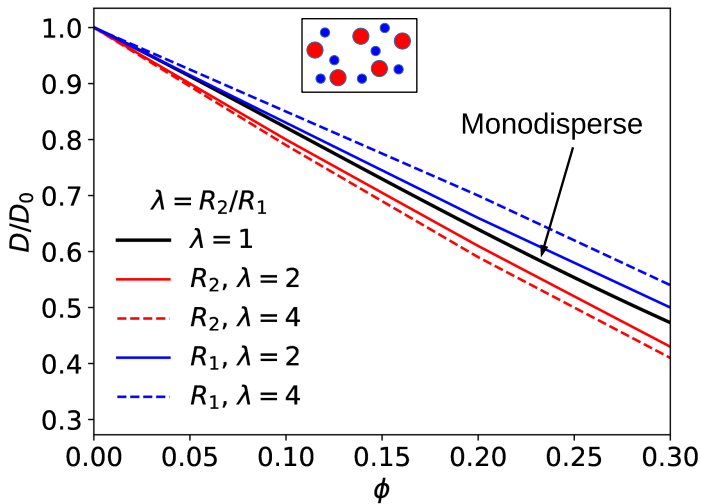
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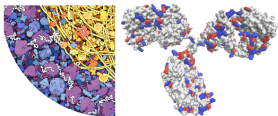
What about in Bidisperse suspensions?

1 = small particle, 2 = big particle, $y = \phi_2/\phi = 0.5$



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Ig + lysate

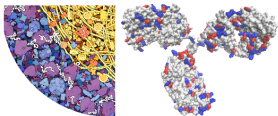


Modelling this system

- Hydrodynamic interactions (HIs) mediated by water must be considered.
- HIs are long-range and non-pairwise-additive.
- How much detail of the protein structure is needed? Ando & Skolnick (PNAS, 2010) showed that hard spheres can be used
- Some previous approaches: Ando & Skolnick (PNAS, 2010) Stokesian Dynamics, McGuffee & Elcock (PLoS Comput. Biol., 2010) Atomically detailed MD, Bucciarelli *et al.* (Sci. Adv., 2016) MPCD.
- Other options: DPD, MD with explicit water, LB, BD with HI, ...?

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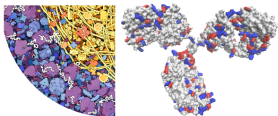


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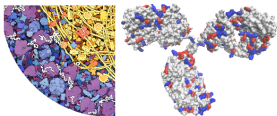


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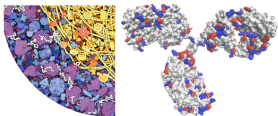


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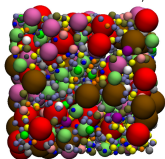
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Methods

We employed a technique based on **Stokesian dynamics** simulation (Brady's group).

- Random distributions of polydisperse systems are generated (MC, MD, ...).
- The resistance tensor is calculated from the coordinates and sizes.
- The short-time diffusion coefficient is obtained by inverting the resistance tensor.

Snapshot
(Generated with MC, MD,..)



$$\mathbf{R} = (\mathbf{M}^\infty)^{-1} + \mathbf{R}_{2B} - \mathbf{R}_{2B}^\infty$$

Calculate the resistance tensor from using the positions and sizes



Invert \mathbf{R} and calculate \mathbf{D}

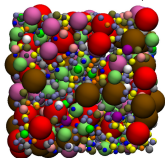
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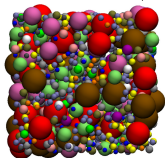
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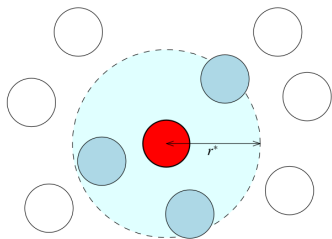
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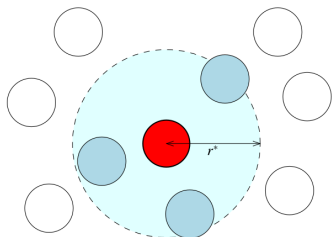
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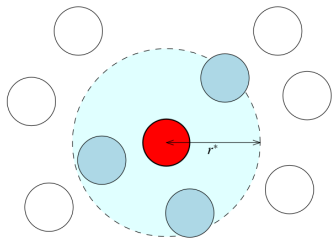


We calculate \mathbf{R} which includes far-field and near-field (lubrication) interactions as:

$$\mathbf{R} = (\mathbf{M}^\infty)^{-1} + \mathbf{R}_{2B} - \mathbf{R}_{2B}^\infty$$

- We use “F version” of Stokesian dynamics for \mathbf{M}^∞ : Ewald summation of the Rotne-Prager tensor with only Force-translational velocities coupling ($3N \times 3N$ matrix).
- Exact two body lubrication solutions (Jeffrey & Onishi, Typos corrected reported by A. Townsend)

Methods



After \mathbf{R} is calculated, the short-time diffusion coefficients are given by:

$$\mathbf{D} = k_b T \langle \text{tr}(\mathbf{R}^{-1}) \rangle$$

What should we use as crowder (lysate)?

Previous computational models for *E. coli*

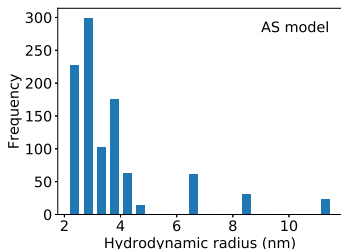
Ando & Skolnick (AS)

$\langle R \rangle = 3.53 \text{ nm}$, $\alpha = \sigma / \langle R \rangle = 1.05$
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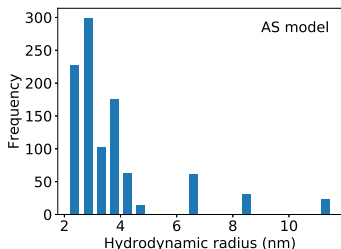
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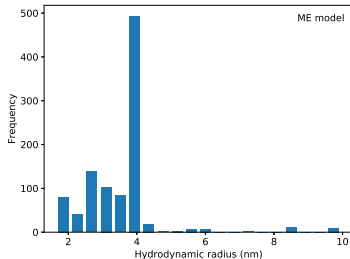
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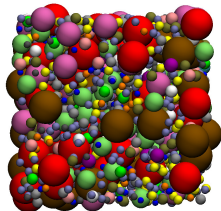
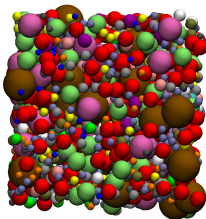
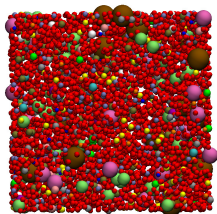
McGuffee & Elcock (ME)



$\langle R \rangle = 3.64$ nm, $\alpha = \sigma / \langle R \rangle = 0.51$
PLoS Comp. Biol. (2010),
6:e1000694.

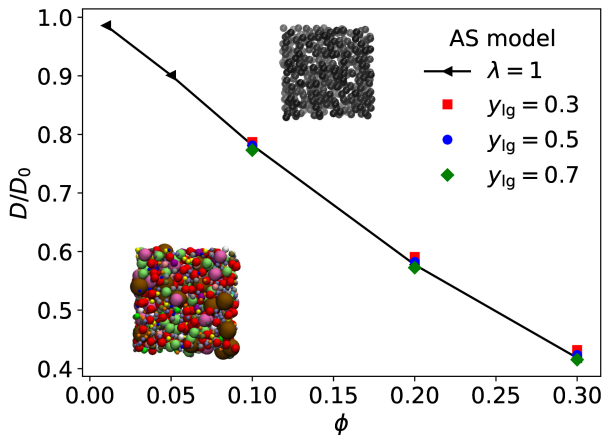
Other simulation parameters

- Systems are characterized by ϕ and $y_{tr} = \phi_{tr}/\phi$.
- We study different sizes of tracers.
- Typical snapshot is made of ~ 3000 spheres.
- At least 50 snapshots are used for each D calculation.



Results

D vs ϕ (Tracer of the size of Ig)

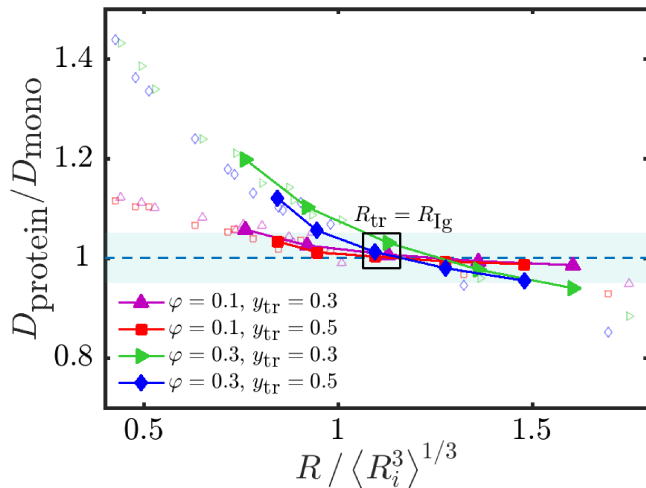


Similar results for the MS model.

J. Phys. Chem. Lett. (2019) 10:1709-1715

Results

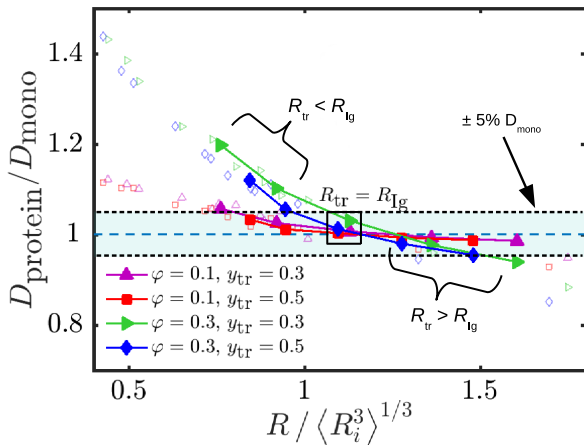
AS model



$R_{\text{eff}} = \sqrt[3]{\langle R_i^3 \rangle}$ – prediction using leading order term of \mathbf{M}^∞ . $R = R_{\text{eff}}$ behaves as in a monodisperse suspension.

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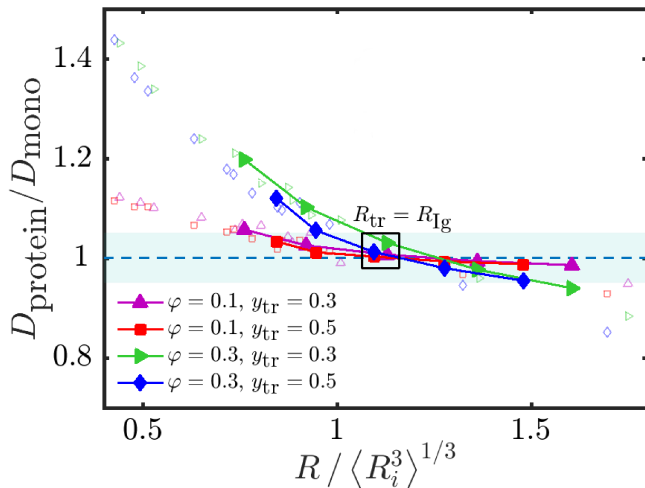
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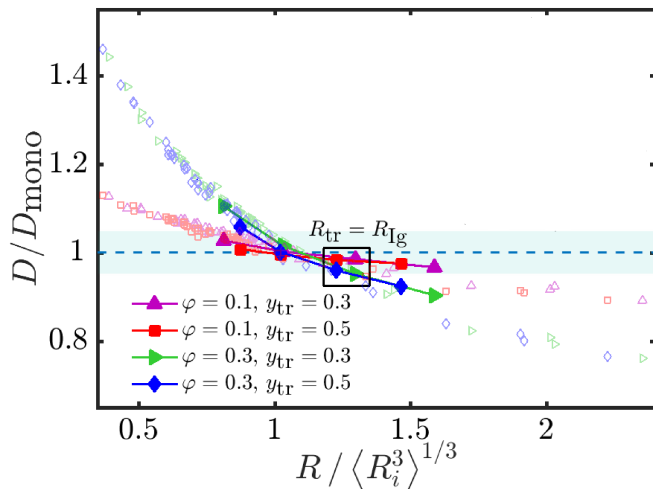
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MS model



Summary

- Simple colloid models (which proper treatment of the HIs) can capture “some” of the relevant physics in rather complex systems.
- Qualitative agreement model \longleftrightarrow experiment.
- Moderate deviations from monodisperse system are due to the Ig size, $R_{Ig} \approx \sqrt[3]{\langle R_i^3 \rangle}$.
- We are now testing our prediction with proteins of different sizes.
- Challenges: How to include HIs in a cheap way? When are they really necessary?
- Open questions: What happens when there is attraction between the proteins? When is the shape important?

Acknowledgments

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- Institut für Angewandte Physik, Universität Tübingen: Stefano Da Vela, Fajun Zhang, Martin Oettel, Frank Schreiber
- European Synchrotron Radiation Facility (ESRF): Alessandro Mariani
- LiPhy, Université Grenoble Alpes: Jean-Louis Barrat

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