Quasi-two-dimensional diffusion of interacting protein monomers and dimers: a MPC simulation study

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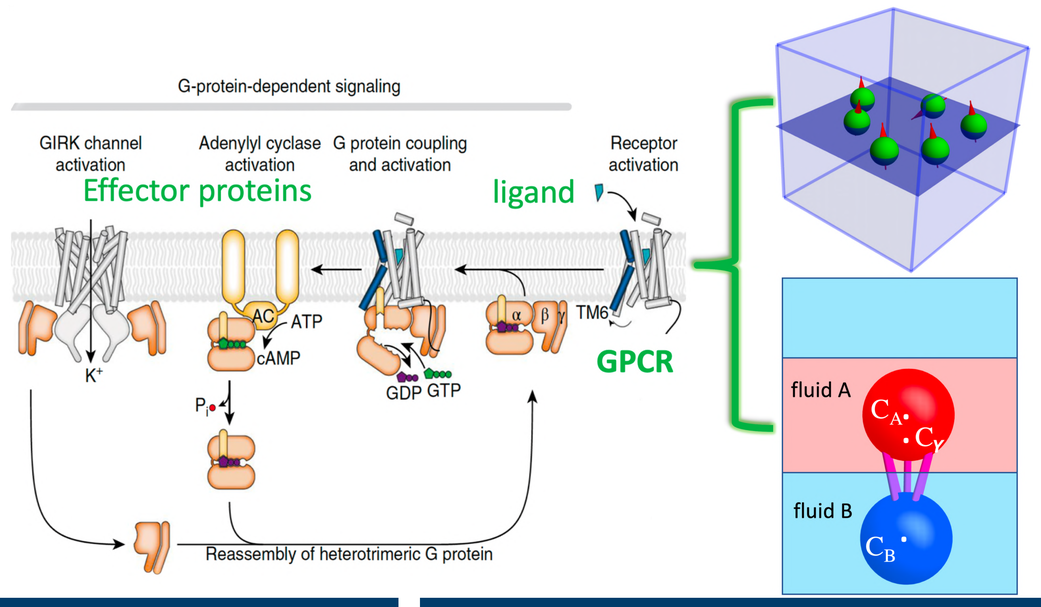
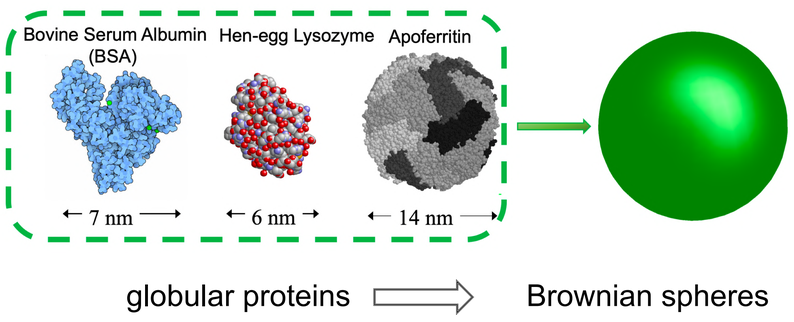
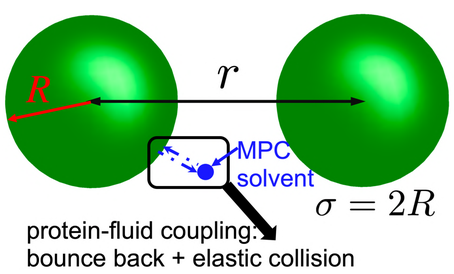
Abstract: Modeling lateral diffusion of proteins at a membrane

- **Diffusion of proteins along a membrane:** e.g., in neuronal signaling where proteins diffuse along a postsynaptic membrane, triggering a cascade of biochemical processes.
- **Minimalistic model:** Interacting Brownian particles embedded in a three-dimensional (3D) Newtonian fluid, but confined to a planar monolayer
- Anomalous enhancement of time-dependent, large-scale protein collective diffusion under quasi-two-dimensional (Q2D) confinement
- Hydrodynamic retardation effects in concentrated Q2D protein solutions
- **Methods:** Multiparticle collision dynamics (MPC) & Langevin dynamics (LD) simulations
- **More detailed model:** Non-spherical proteins diffusing along a fluid-fluid interface
- Explore effects of crowding and membrane-cytosol viscosity difference on protein diffusion



1. Globular protein model





o Proteins confined in-plane, interacting via short-range attraction (SA) & long-range electrostatic repulsion (LR)

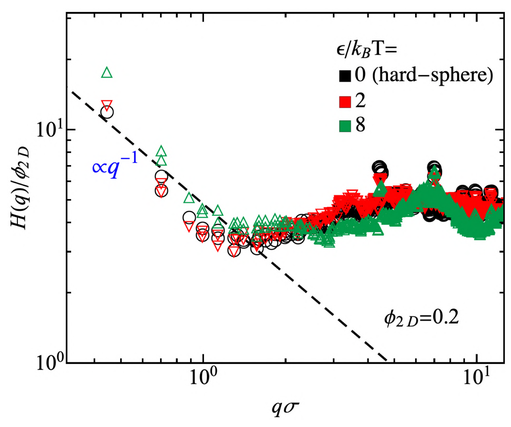
$$\beta U(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{100} - \left(\frac{\sigma}{r}\right)^{50}\right] + \ell_B Z_{eff}^2 \frac{e^{-r/\lambda}}{r}$$

hardcore + short-range attraction — long-range electrostatic repulsion

o Fluid motion described by MPC simulations

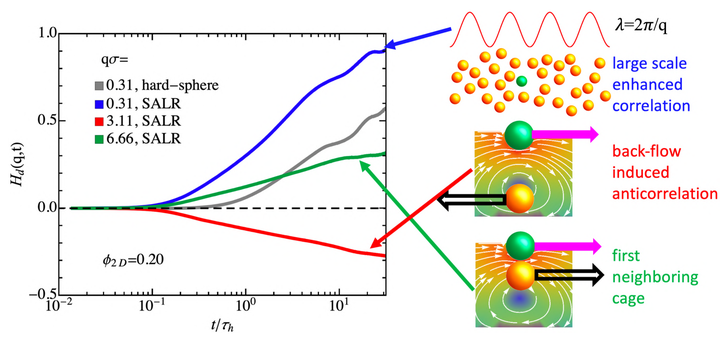
2. Anomalous enhancement of collective diffusion

Hydrodynamic function $H(q)$:
=> characterizes strength of hydrodynamic interactions (HIs)



- o $H(q) \propto q^{-1}$ for $qR \lesssim 1$
- o Stronger attraction increases HIs
- o ϕ_{2D} area fraction

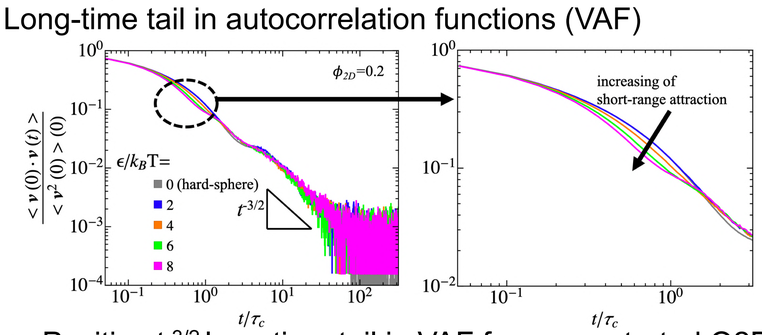
Time-dependent distinct hydrodynamic function $H_d(q,t)$:
=> cross-correlations due to time-dependent HIs



- o Onset of HIs at $t \sim \tau_h = R^2/\nu$: single-protein vorticity diffusion time, ν the kinematic viscosity
- o Three hydrodyn. length scales identified in Q2D $H_d(q,t)$[1]

3. Hydrodynamic retardation

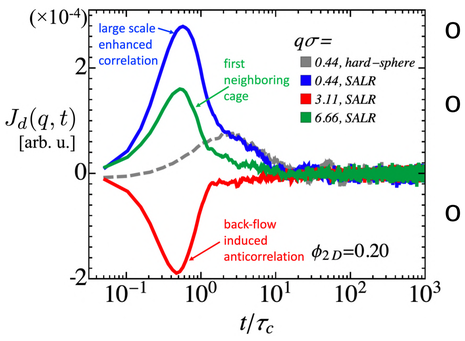
Vorticity diffusion:
Long-time tail in autocorrelation functions (VAF)



- o Positive $t^{-3/2}$ long-time tail in VAF for concentrated Q2D SALR protein systems at long times
- o Short-range attraction slows translational correlations at times earlier than single-protein sonic time $\tau_c = R/c_s$

Role of sound propagation:
Distinct longitudinal current-current correlation function

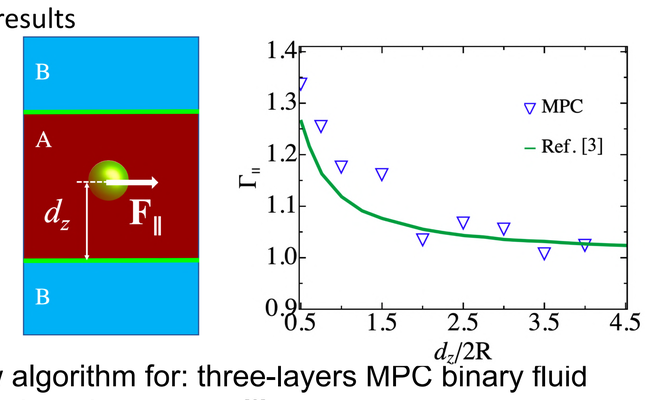
$$J_d(q,t) = \frac{1}{Nq^2}\left\langle \sum_{i=1}^{N}\sum_{j\neq i}^{N} \boldsymbol{q}\cdot\boldsymbol{v}_i(t)\boldsymbol{v}_j(0)\cdot\boldsymbol{q}\exp\left[i\boldsymbol{q}\cdot(\boldsymbol{R}_i-\boldsymbol{R}_j)\right]\right\rangle$$



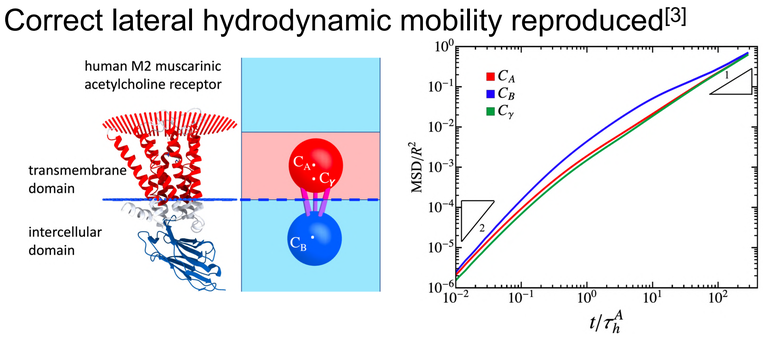
- o Amplified peaks at $t < \tau_c$
- o Long-time oscillations are suppressed
- o Three hydrodyn. length scales are identified at sonic times

4. Lateral diffusion of proteins near fluid-fluid interface

Effects of interfacial hydrodynamics and viscosity contrast:
MPC results



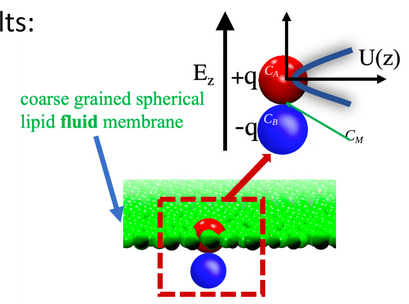
- o New algorithm for: three-layers MPC binary fluid with viscosity contrast [2]
- o Correct lateral hydrodynamic mobility reproduced[3]

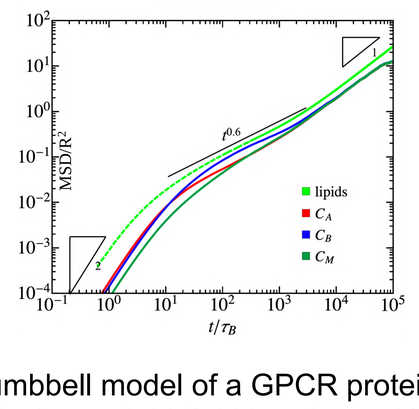


- o Hard-core (green) beads mimicking crowding effects of lipids
- o Sub-diffusive regimes recovered, spanning three decades
- o Center of mass / mobility of protein shows slowest diffusion

5. Effects of crowding

LD results:



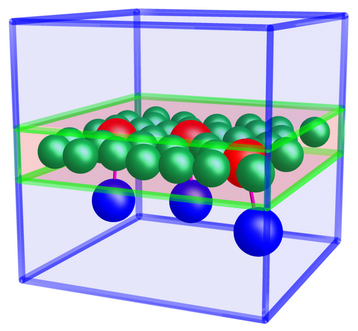


- o Dumbbell model of a GPCR protein diffusing at fluid-fluid interface with viscosity contrast
- o MSDs of different centers are tracked

6. Conclusions & Outlook

- Anomalous enhancement of collective diffusion of proteins already at inertial timescales
- Three different hydrodynamic length scales at inertial timescales are identified
- Multiple sound-scattering is suppressed by short-range attraction in crowded Q2D-SALR protein systems

➢ Outlook



- o Refined modeling: introduce lipid degrees of freedom and full HIs
- o GPU-based performance acceleration

7. References & Acknowledgement

[1] Z. Tan, J. K. G. Dhont, V. Calandrini, and G. Nägele, *in preparation* (2021).

[2] Z. Tan, V. Calandrini, J. K. G. Dhont, G. Nägele and R. G. Winkler, *submitted* (2021).

[3] J. Bławzdziewicz, M.L. Ekiel-Jeżewska, and E. Wajnryb, J. Chem. Phys., **133**, 114702 (2010).

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