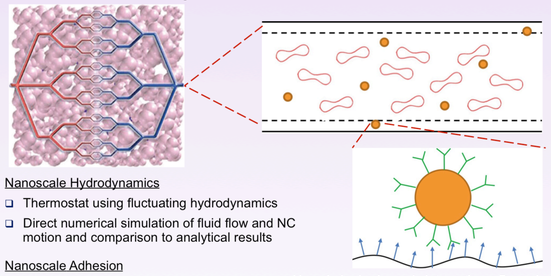
Generalized Langevin Dynamics for Functionalized Nanocarrier Adhesion to Cell Surfaces in the Presence of Hydrodynamic Interactions

Hsiu-Yu Yu, David Eckmann, Portonovo Ayyaswamy, Ravi Radhakrishnan

Mass Transport of Functionalized Nanocarriers



Nanoscale Hydrodynamics

- Thermostat using fluctuating hydrodynamics
- Direct numerical simulation of fluid flow and NC motion and comparison to analytical results

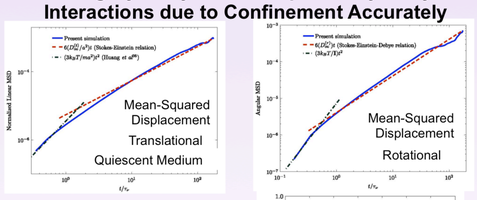
Nanoscale Adhesion

- Generalized Langevin equations for NC binding and tethering relaxation
- Comparison to analytical results

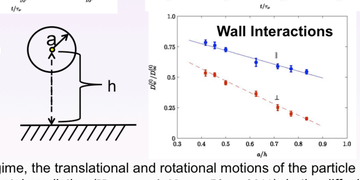
How do hydrodynamic interactions, Brownian forces, and ligand-receptor relaxations affect the Nanocarrier adhesion

Objective: To develop easily computable yet physiologically ***predictive next-generation pharmacodynamic models*** for targeted drug delivery to treat scales ranging from vasculature hydrodynamics to ligand-receptor mediated NC adhesion

Fluctuating Hydrodynamics Captures Hydrodynamic Interactions due to Confinement Accurately



Parallel and perpendicular diffusion coefficients are in good agreement with analytical predictions (Happel and Brenner, *Low Reynolds Number Hydrodynamics*, 1983).



In the ballistic regime, the translational and rotational motions of the particle agree with the experimental prediction (Huang et al, *Nature Phys.*, 2011). In the diffusive regime, the translational and rotational MSDs increase linearly in time to follow Stokes-Einstein and Stokes-Einstein-Debye relation, respectively.

NC Translational Velocity Autocorrelation Function and NC/ Receptor Position Fluctuation Autocorrelation Function

a=250 nm
k=1 N/m [1]
λ_p= λ_r=0.5
k_s=1.882 N/m [2]
$\zeta_{r,0}/k_s$=0.7 $s^{0.5}$ [2]
$\zeta_{r,0}/\zeta_{p,0}$=2.2x10^4

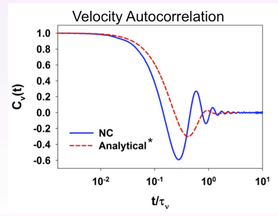
[1] Hanley et al, *J. Biol. Chem.*, 2003
[2] Min et al, *Phys. Rev. Lett.*, 2005

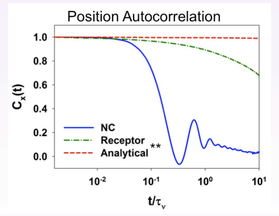
Analytical* result for VACF of free NC in unbounded space:

$$C_v(t)=\frac{\langle U(t)U(0)\rangle}{\langle U(0)^2\rangle}=E_{2-\lambda_p}\left[-\frac{\zeta_{p,0}(\lambda_p)}{m_p}\frac{\Gamma(1-\lambda_p)}{t^{2-\lambda_p}}\right]\qquad \zeta_{p,0}(\lambda_p)=\frac{6\pi m_p}{\Gamma(1-\lambda_p)}\left(\frac{\mu a}{m_p}\right)^{2-\lambda_p}$$

Analytical** result for fluctuation within a single free protein:

$$C_x(t)=\frac{\langle \delta x(t)\delta x(0)\rangle}{\langle \delta x(0)^2\rangle}=E_{\lambda_r}\left[-\frac{k_s}{\zeta_{r,0}(\lambda_r)\Gamma(1-\lambda_r)}t^{\lambda_r}\right]$$

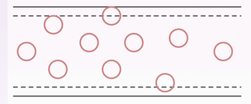




Multiscale Bridging that Integrates Vasculature Hydrodynamic Interactions and Nanoscale Adhesion

(1) Fast and Computable Approach: Dynamical Density Functional Theory (DDFT) Brader and Krüger, *Mol. Phys.*, 2011

Hard Sphere-like blood cells in a cylindrical vessel under a unidirectional flow field



Grand potential

$$\Omega[\rho(\mathbf{r})]=F[\rho(\mathbf{r})]-\int\mu\rho(\mathbf{r})d\mathbf{r}$$

$$F[\rho(\mathbf{r})]=F_{id}[\rho(\mathbf{r})]+F_{ex}[\rho(\mathbf{r})]+\int V_{ext}(\mathbf{r})\rho(\mathbf{r})d\mathbf{r}$$

DDFT yields a combined thermodynamic and hydrodynamic potential exerted by the blood cells on the NC

$$\frac{\delta\Omega[\rho(\mathbf{r})]}{\delta\rho(\mathbf{r})}=0 \qquad \mu(\rho)=\mu(\rho_b)$$

Steady-state blood cells distribution

$$\rho_{RBC}(\mathbf{r})=\rho_b\exp\left\{c^{(1)}(\mathbf{r})-c_b^{(1)}-\frac{V_{ext}(\mathbf{r})}{k_BT}+\int_0^r\frac{\langle u'\rangle_1}{D_0^w}dr'\right\}$$

DDFT Prediction — Wall potential

- $\nabla\Phi_{RBC}$ — Marginating potential from ρ_{RBC} (DDFT output)
- $u'(\mathbf{r})$ — Migration velocity (DDFT input)
- $\rho_{NC}(\mathbf{r})$ — NC distribution (DDFT output)

Nanoscale Fluctuating Hydrodynamics: Direct Numerical Simulation (DNS) to Treat Hydrodynamic Interactions and Stochastic Fluctuations

Governing equations for the fluid motion and rigid particles

$$\nabla\cdot\mathbf{u}=0$$

$$\rho_f\frac{D\mathbf{u}}{Dt}=\rho_f\mathbf{f}+\nabla\cdot\sigma=0$$

$$\sigma=-p\mathbf{I}+\mu\left[\nabla\mathbf{u}+(\nabla\mathbf{u})^T\right]+\underline{S}$$ (Random Stress)

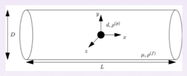
(Landau and Lifshitz, *Fluid Mechanics*, 1959)

$$m_i\frac{d\mathbf{U}_i}{dt}=-\int_{\partial\Omega_i(t)}\sigma\cdot\mathbf{n}\,ds$$

$$\frac{d(\mathbf{I}_i\omega_i)}{dt}=-\int_{\partial\Omega_i(t)}(\mathbf{x}-\mathbf{X}_i)\times(\sigma\cdot\mathbf{n})\,ds$$

Boundary conditions

$$\mathbf{u}=0 \text{ on } (\partial\Omega)_u \qquad \sigma\cdot\mathbf{n}=0 \text{ on } (\partial\Omega)_\sigma$$



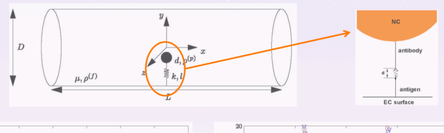
$$\mathbf{u}=\mathbf{V}_i+\omega_i\times(\mathbf{x}_i-\mathbf{X}_i) \text{ for } \mathbf{x}\in\partial\Omega_i(t)$$

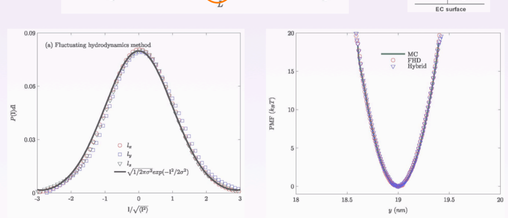
Initial conditions

$$\mathbf{u}=\mathbf{u}_0 \text{ on } \Omega_0(0)$$

$$\langle S_{ij}\rangle=0;\ \langle S_{ik}(\mathbf{x}_1,t_1)S_{lm}(\mathbf{x}_2,t_2)\rangle=2k_BT\mu(\delta_{il}\delta_{km}+\delta_{im}\delta_{kl})\delta(\mathbf{x}_1-\mathbf{x}_2)\delta(t_1-t_2)$$

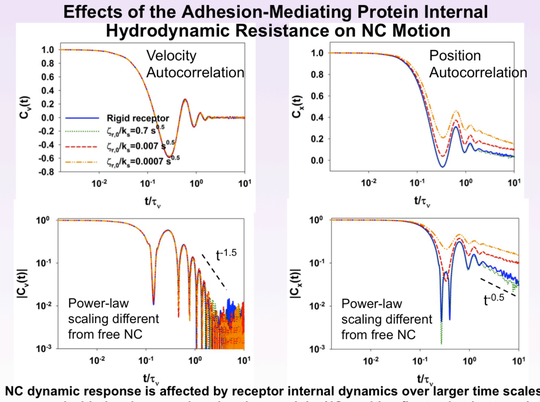
Hydrodynamic Interactions and Adhesive Interactions can be Simultaneously Modelled using Fluctuating Hydrodynamics





The Potential Mean Force (PMF) between NC and adhesive cell surfaces based on Metropolis Monte Carlo and the weighted histogram analysis method is compared with free energy obtained using fluctuating hydrodynamics and hybrid methods. The agreement is excellent.

Effects of the Adhesion-Mediating Protein Internal Hydrodynamic Resistance on NC Motion



NC dynamic response is affected by receptor internal dynamics over larger time scales compared with the viscous relaxation time, and the NC position fluctuation is strongly dependent on receptor relaxation

(2) Computationally Demanding but Rigorous Approach: Full Hydrodynamic Consideration using Equation-Free Brownian Dynamics (BD) and Direct Numerical Simulations (DNS)

Inner layer: DNS for full hydrodynamic equations

$$\rho^{(f)}\left[\frac{\partial\mathbf{u}}{\partial t}+(\mathbf{u}\cdot\nabla)\mathbf{u}\right]=-\nabla p+\nabla\cdot\boldsymbol{\tau}\qquad \nabla\cdot\mathbf{u}=0$$

The mobility tensor is computed ab initio using DNS and the dynamics of particles are evolved using BD

Outer wrapper for type-1 particles: coarse integration of equations of motion for blood cells

$$\Delta\mathbf{x}_i^{(1)}=\left\{\mathbf{U}_i^{(1)}+\sum_{j=1}^{N_1}\left[\frac{\mathbf{D}_{ij}^{(11)}}{k_BT}\cdot\mathbf{F}_j^{T1}+\nabla_j\cdot\mathbf{D}_{ji}^{(11)}\right]\right\}\Delta T_1 \quad\blacktriangleright\quad \rho_{RBC}(\mathbf{r},t)$$

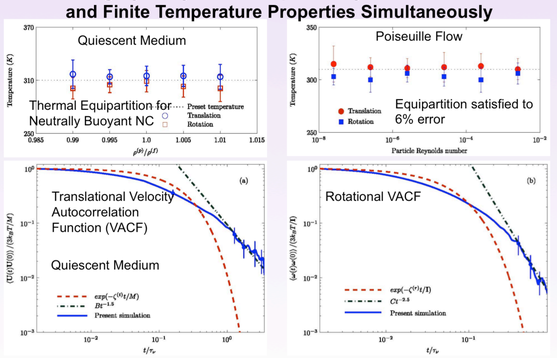
Outer wrapper for type-2 particles: coarse integration of equations of motion for NC

$$\left\langle\Delta\mathbf{x}_i^{(2)}\right\rangle_{N_1}=\left\{\left\langle\mathbf{U}_i^{(2)}\right\rangle_{N_1}+\sum_{j=1}^{N_1}\left[\left\langle\frac{\mathbf{D}_{ij}^{(22)}}{k_BT}\cdot\mathbf{F}_j^{T2}\right\rangle_{N_1}+\left\langle\nabla_j\cdot\mathbf{D}_{ji}^{(22)}\right\rangle_{N_1}\right]+\nabla_i\boldsymbol{\Phi}_{RBC}\left(y_i,\mathbf{r}^{N_2}\middle|\mathbf{r}^{N_1}\right)\right\}\Delta t+\left\langle\mathbf{x}_{Bi}^{(2)}(t)\right\rangle_{N_1}$$

$$\left\langle\mathbf{x}_{Bi}^{(2)}(t)\mathbf{x}_{Bj}^{(2)}(t)\right\rangle=2\mathbf{D}_{ij}^{(22)}k_BT\Delta t\qquad\left\langle\mathbf{x}_{Bi}^{(2)}(t)\right\rangle_{N_1}=0\quad\blacktriangleright\quad\rho_{NC}(\mathbf{r},t)$$

Kevrekidis et al, *AIChE J.*, 2004
Brady and Bossis, *Ann. Rev. Fluid Mech.*, 1988; Banchio and Brady, *J. Chem. Phys.*, 2003

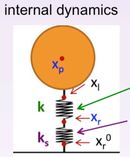
Fluctuating Hydrodynamics Captures Dynamical Correlations and Finite Temperature Properties Simultaneously



The translational and rotational VACF both follow exponential and power-law decay at short and long times, respectively. Our numerical findings agree with the experimental VACF of a Brownian particle in water (Huang et al, *Nature Phys.*, 2011).

Minimal Model for Adhesive Dynamics with Receptor Protein Relaxation using 1D Generalized Langevin Dynamics

Objective: To develop a fast and computable dynamic/thermodynamic model of NC hydrodynamics and adhesion consistent with fluctuating hydrodynamics and protein internal dynamics



Hookean springs model potential forces

receptor-antibody interaction

receptor protein dynamics

$$\bar{x}_p=x_p-a-l-x_r^0$$

$$x=x_r-x_r^0$$

$$-\frac{dV_i}{dx_i}=F_i=-k_ix_i$$

NC translation

$$m_p\frac{d^2\bar{x}_p(t)}{dt^2}=-\int_{-\infty}^{t}\zeta_p^{(trans)}(t-t')\frac{d\bar{x}_p}{dt'}dt'+k\left[x(t)-\bar{x}_p(t)\right]+R_p(t)$$

$$\zeta_p^{(trans)}(t-t')=\zeta_{p,0}(\lambda_p)|t-t'|^{-\lambda_p}\qquad\langle R_p(t)R_p(t')\rangle=k_BT\zeta_p^{(trans)}(t-t')$$

Receptor relaxation

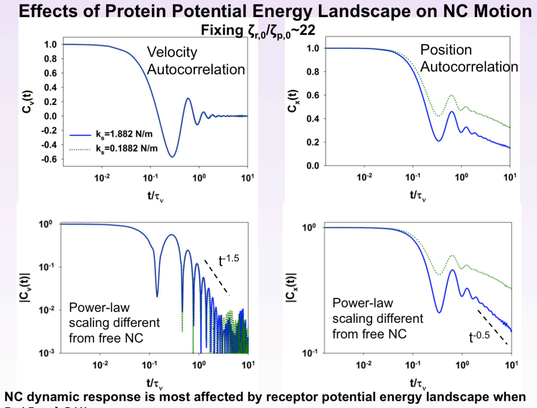
$$0=-\int_{-\infty}^{t}\zeta_r^{(trans)}(t-t')\frac{dx}{dt'}dt'-(k+k_s)x(t)+k\bar{x}_p(t)+R_r(t)$$

$$\zeta_r^{(trans)}(t-t')=\zeta_{r,0}(\lambda_r)|t-t'|^{-\lambda_r}\qquad\langle R_r(t)R_r(t')\rangle=k_BT\zeta_r^{(trans)}(t-t')$$

Power-law memory kernel satisfying fluctuation-dissipation theorem

Effects of Protein Potential Energy Landscape on NC Motion

Fixing $\zeta_{r,0}/\zeta_{p,0}$~22



NC dynamic response is most affected by receptor potential energy landscape when $\zeta_{r,0}/\zeta_{p,0}\rightarrow O(1)$

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