Stochastic Mathematical and Computational Models in Microbiology

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Overview

- **Stochastic Immersed Boundary Method** for Microbiological Simulation

- **Homogenization Theory** for Effective Transport Properties of Brownian Motors

- **Stochastic Drift-Diffusion Parameterization of Water Dynamics near Solute**
Stochastic Immersed Boundary Method

Overview

- Extension of Immersed Boundary Method to incorporate thermal fluctuations relevant for microscale simulations
- Stochastic numerical error analysis
- Numerical simulations of polymers and simple molecular motor model
Stochastic Immersed Boundary Method

Charles Peskin developed Immersed Boundary Method as an efficient simulation of fluid systems with immersed structures.

- philosophy is to treat heterogeneous system as a single fluid
- material properties of immersed structures reflected in forces applied to Navier-Stokes equations

Originally developed for macrobiology (blood flow through heart), more recently extended (with Paul Atzberger (UCSB) and Peskin (NYU)) with a view toward microbiology applications with important thermal and fluid components

- molecular motors
- bacterial locomotion including osmotic gel swelling effects
- exocytosis of vesicles from cells
Exocytosis, pancreatic acinar cell
Stochastic Immersed Boundary Equations I

\[ \rho \left( \frac{\partial u(x, t)}{\partial t} + u(x, t) \cdot \nabla u(x, t) \right) \]

\[ = \mu \Delta u(x, t) - \nabla p(x, t) + f(x, t) + f_T(x, t), \]

\[ \nabla \cdot u(x, t) = 0, \]

**Navier-Stokes equations:**

- \( u(x, t) \) is fluid velocity,
- \( \rho \) is fluid density (often assumed constant),
- \( \mu \) is dynamic viscosity,
- \( f(x, t) \) is structural force density acting on fluid.
- \( f_T(x, t) \) is thermal force density.
Immersed particles induce force on fluid:

\[ f(x, t) = - \sum_{j=1}^{N} \nabla_j \Phi(\{X^{[j']} (t)\}) \delta_a (x - X^{[j]} (t)) \]
Stochastic Immersed Boundary Equations II

Immersed particles induce force on fluid:

\[
f(\mathbf{x}, t) = -\sum_{j=1}^{N} \nabla_j \Phi(\{X[j'](t)\}) \delta_a(\mathbf{x} - X[j](t))
\]

where:

- \( N \) is the number of particles,
- \( \Phi \) is the total potential on the particles due to interaction and/or external influences.
- \( X[j](t) \) is location of particle \( j \) at time \( t \).
- \( \delta_a(\cdot) \) is function which spreads force over region with linear dimension \( a \) (effective particle size).
Immersed particles induce force on fluid:

\[ f(x, t) = - \sum_{j=1}^{N} \nabla_j \Phi(\{X^{[j']} (t)\}) \delta_a(x - X^{[j]} (t)) \]

Immersed membranes and fibers handled similarly as collection of elementary particles.
Stochastic Immersed Boundary Equations III

Thermal force density from fluctuation-dissipation theorem:

\[
\begin{align*}
    \mathbf{f}_T(\mathbf{x}, t) &= \sum_k \mathbf{f}_{T,k}(t) e^{2\pi i \mathbf{k} \cdot \mathbf{x} / L}, \\
    \mathbf{f}_{T,k}(t) &= \sqrt{\frac{4\pi^2 k^2 \mu k_B T}{L^5}} \frac{d\tilde{W}_k(t)}{dt}.
\end{align*}
\]

- \( L \) is length scale of domain.
- \( T \) is absolute temperature; \( k_B \) is Boltzmann’s constant.
- independent complex Brownian processes \( \{\tilde{W}_k(t)\}_k \):

\[
\begin{align*}
    \langle d\tilde{W}_k(t) \otimes d\tilde{W}_k(t') \rangle &= 0, \\
    \langle d\tilde{W}_k(t) \otimes d\tilde{W}_k^*(t') \rangle &= 2\mathcal{I} \delta(t - t') dt \, dt'.
\end{align*}
\]
Stochastic Immersed Boundary Equations IV

The immersed particles move at a velocity obtained by interpolating the local fluid velocity over length scale $a$:

$$\frac{dX[j](t)}{dt} = u_a(X[j](t), t),$$

$$u_a(x, t) = \int_{\Omega} u(x', t) \delta_a(x - x') \, dx',$$

where $\Omega$ is the spatial domain and the interpolation function $\delta_a$ is the same function as was used to spread force. (Important for energy conservation properties).
Spatial discretization

Start with spatially discretized IB scheme, defined on periodic fluid lattice $h\mathbb{Z}_K^3$, with

- $\mathbb{Z}_K^3 \equiv [1, 2, \ldots, K]^3$,
- $K = L/h$. 

![Spatial discretization diagram](image-url)
Discretized Immersed Boundary Equations

Because Reynolds number small, start for simplicity with explicit update scheme:

- Have also implemented semi-implicit formulation following Peskin’s standard scheme.
Discretized Immersed Boundary Equations

Because Reynolds number small, start for simplicity with explicit update scheme:

- Have also implemented semi-implicit formulation following Peskin’s standard scheme.

Fluid evolution:

\[
\rho \left( \frac{u^{n+1} - u^n}{\Delta t} + (u^n \cdot \nabla^S_h u^n) \right) = -\nabla^0_h p^n + \mu \Delta^0_h u^n + f^n + f^n_T,
\]

\[
\nabla^0_h \cdot u^{n+1} = 0,
\]
Discretized Immersed Boundary Equations

Because Reynolds number small, start for simplicity with explicit update scheme:

- Have also implemented semi-implicit formulation following Peskin’s standard scheme.

Particle evolution:

\[ X^{n+1,[j]} = X^{n,[j]} + \Delta t \sum_{x \in hZ^3_K} u^n(x) \delta_a(x - X^{n,[j]}) h^3. \]
Discretized Immersed Boundary Equations

Because Reynolds number small, start for simplicity with explicit update scheme:

• Have also implemented semi-implicit formulation following Peskin’s standard scheme.

Update deterministic force density on fluid due to immersed structures:

\[ \mathbf{f}^{n+1}(\mathbf{x}) = - \sum_{j=1}^{N} \nabla_j \Phi(\{ \mathbf{X}^{n+1,[j]} \}) \delta_a(\mathbf{x} - \mathbf{X}^{n+1,[j]}) \]
Fourier-space decomposition

For periodic cubic domain with linear length $L$, express random force as Fourier series:

$$f^n_T(x) = \sum_{k \in \mathbb{Z}_K^3} e^{2\pi i k \cdot x / L} f_{T,k}^n,$$

with

$$f_{T,k} = \sqrt{\frac{\rho k_B T \alpha_k}{L^3 \Delta t}} \tilde{Z}_k^n$$

where
Fourier-space decomposition

For periodic cubic domain with linear length $L$, express random force as Fourier series:

$$f^n_T(x) = \sum_{k \in \mathbb{Z}_K^3} e^{2\pi i k \cdot x / L} f^n_{T,k},$$

with

$$f_{T,k} = \sqrt{\frac{\rho k_B T \alpha_k}{L^3 \Delta t}} \tilde{Z}_n$$

where

$$\alpha_k \equiv -\nu \mathcal{F}_k(\Delta_h^0) = \frac{4\nu}{h^2} \sum_{m=1}^{3} \sin^2 \frac{\pi k_j}{K},$$

$$\nu = \mu / \rho,$$
Fourier-space decomposition

For periodic cubic domain with linear length $L$, express random force as Fourier series:

$$f^n_T(x) = \sum_{k \in \mathbb{Z}_K^3} e^{2\pi i k \cdot x/L} f^n_{T,k},$$

with

$$f_{T,k} = \sqrt{\frac{\rho k_B T \alpha_k}{L^3 \Delta t}} \tilde{Z}_k^n$$

where the $\{\tilde{Z}_k^n\}_{k \in \mathbb{Z}_K^3, n \in \mathbb{N}}$ are standard complex Gaussian random variables which are independent (except $\tilde{Z}_{-k,n} = \tilde{Z}_{k,n}^*$) with $\langle \tilde{Z}_k^n \rangle = 0$, $\langle \tilde{Z}_k^n \otimes \tilde{Z}_k^n \rangle = 0$, and $\langle \tilde{Z}_k^n \otimes \tilde{Z}_k^* \rangle = 2l$. (Some exceptional handling for modes at fundamental zone boundary).
Stiffness Issues

The numerical method described requires time step $\Delta t$ to be small compared to all fluid and structural time scales. Fluid relaxation time scales:

- $\alpha_k^{-1} \sim 10-1000$ ns for typical microbiological simulation parameters
- structural time scales $\sim \mu s$–s

This can create stiff numerical simulation. One solution: fully underresolve fluid dynamics and approximate with quasi-steady theory (Brownian/Stokesian dynamics)

But time step resolving structural dynamics may be comparable to time scale of some fluid modes.
IB Method with Larger Time Step

Alternative scheme (with Atzberger and Peskin) remains valid at low Reynolds number for time steps which are restricted only to resolve time scales of immersed structures.

Idea: neglect advective nonlinearity in Navier-Stokes equation and decompose into Fourier modes:

$$u(x, t) = \sum_{k \in \mathbb{Z}^3_K} e^{2\pi i k \cdot x / L} u_k(t),$$
Time-Dependent Stokes Equations

\[ d\mathbf{u}_k(t) = -\alpha_k \mathbf{u}_k dt + \rho^{-1} \mathcal{P}_k \mathbf{f}_k dt + D_k \mathcal{P}_k d\tilde{W}_k(t) \]

where

\[ \mathcal{P}_k = 1 - \frac{\mathcal{F}_k(\nabla^0_h) \otimes \mathcal{F}_k(\nabla^0_h)}{|\mathcal{F}_k(\nabla^0_h)|^2}, \]

\[ \mathcal{F}_k(\nabla^0_h) = \frac{i}{h} \sum_{m=1}^3 \hat{e}_m \sin \frac{2\pi k_m}{K}, \]

\[ D_k = \frac{k_B T}{\rho L^3} \alpha_k, \]

and

\[ f(\mathbf{x}, t) = \sum_{\mathbf{k} \in \mathbb{Z}_K^3} e^{2\pi i \mathbf{k} \cdot \mathbf{x}/L} f_k(t). \]
Solution when Structure Time Scales Resolved

If time step $\Delta t$ small enough to resolve structural dynamics, then $f_k(t)$ can be approximated as constant over time step.

- Stokes equation can then be solved exactly over a time step
- No assumption necessary on relative size of $\Delta t$ and $\alpha_k$

Then, in temporal discretization, we define both instantaneous velocity values:

$$u^n(x) = u(x, n\Delta t)$$

and time-averaged velocities:

$$\bar{u}^n(x) = \frac{1}{\Delta t} \int_{n\Delta t}^{(n+1)\Delta t} u(x, t) \, dt.$$
Numerical Updating of Velocity Field

We update these (through their Fourier coefficients) as follows:

\[
\begin{align*}
    u_k^{n+1} &= e^{-\alpha_k \Delta t} u_k^n + \frac{1 - e^{-\alpha_k \Delta t}}{\rho \alpha_k} \mathcal{P}_k f_k \\
    &\quad + \mathcal{P}_k c_{1,k}(\Delta t) \tilde{Z}_k^n, \\
    \bar{u}_k^{n+1} &= \bar{u}_k'^{n+1} + c_{2,k}(\Delta t) \mathcal{P}_k \tilde{Z}_k^n + c_{3,k}(\Delta t) \mathcal{P}_k \tilde{Y}_k^n,
\end{align*}
\]
Numerical Updating of Velocity Field

We update these (through their Fourier coefficients) as follows:

\[ u_{k}^{n+1} = e^{-\alpha_k \Delta t} u_{k}^{n} + \frac{1 - e^{-\alpha_k \Delta t}}{\rho \alpha_k} \mathcal{P}_k f_k \]

\[ + \mathcal{P}_k c_{1,k}(\Delta t) \tilde{Z}_k^n, \]

\[ \bar{u}_{k}^{n+1} = \bar{u}_{k}^\sharp,n+1 + c_{2,k}(\Delta t) \mathcal{P}_k \tilde{Z}_k^n + c_{3,k}(\Delta t) \mathcal{P}_k \tilde{Y}_k^n, \]

where the \( \tilde{Z}_k^n \) and \( \tilde{Y}_k^n \) are each collections of mutually independent standard complex Gaussian random variables. \( \{c_{1,k}, c_{2,k}, c_{3,k}\}_{k \in \mathbb{Z}_K^3} \) are deterministic constants depending on the mode number \( k \) and time step \( \Delta t \).
Numerical Updating of Velocity Field

We update these (through their Fourier coefficients) as follows:

\[
    u_{k}^{n+1} = e^{-\alpha_k \Delta t} u_k^n + \frac{1 - e^{-\alpha_k \Delta t}}{\rho \alpha_k} \mathcal{P}_k f_k \\
    + \mathcal{P}_k c_{1,k}(\Delta t) \tilde{Z}_k^n, \\
    \bar{u}_{k}^{n+1} = \bar{u}_{k}^{\#;n+1} + c_{2,k}(\Delta t) \mathcal{P}_k \tilde{Z}_k^n + c_{3,k}(\Delta t) \mathcal{P}_k \tilde{Y}_k^n,
\]

The predictable component of the time-averaged fluid velocity is

\[
    \bar{u}_{k}^{\#;n+1} = \frac{1 - \exp(-\alpha_k \Delta t)}{\alpha_k \Delta t} u_k^n \\
    + \frac{\exp(-\alpha_k \Delta t) + \alpha_k \Delta t - 1}{\rho \alpha_k^2 \Delta t} \mathcal{P}_k f_k^n.
\]
Numerical Updating of Particle Positions and Forces

Once, the velocity field is updated, the positions of the elementary particles are updated using the time-averaged velocity:

\[ X^{n+1, [j]} = X^{n, [j]} + \Delta t \sum_{x \in h\mathbb{Z}_K^3} \bar{u}^n(x) \delta_a(x - X^{n, [j]}) h^3, \]

and the particle force density field is correspondingly updated:

\[ f^{n+1}(x) = - \sum_{j=1}^N \nabla_j \Phi(\{X^{n+1, [j]}\}) \delta_a(x - X^{n+1, [j]}), \]
Random Variable Coefficients

The coefficients of the random variables in the velocity update formulas are given by:

\[
\begin{align*}
    c_{1,k}(\Delta t) &= \sqrt{\frac{D_k(1 - \exp(-2\alpha_k \Delta t))}{\alpha_k}}, \\
    c_{2,k}(\Delta t) &= -\frac{2}{1 + \exp(-\alpha_k \Delta t)}, \\
    c_{3,k}(\Delta t) &= \sqrt{\frac{2D_k}{\alpha_k^3} (\alpha_k \Delta t - 2 \tanh(\alpha_k \Delta t/2))}
\end{align*}
\]
Accuracy of Numerical Method

In absence of particle forces \((\Phi = 0)\),
Accuracy of Numerical Method

In absence of particle forces ($\Phi = 0$),

- velocity field exactly simulated (in zero Reynolds number limit)
Accuracy of Numerical Method

In absence of particle forces ($\Phi = 0$),

- strong error for particle positions

$$e_{prt}(\Delta t) = \mathbb{E} \left[ |X(t + \Delta t) - X_{sim}(t + \Delta t)| \right]$$

where $X_{sim}(t) = X(t)$]

satisfies:

$$e_{prt}(\Delta t) \approx \begin{cases} C_1 (v_{thm} \Delta t)^2 & \text{for } \Delta t \ll \frac{a^2}{\nu}, \\ C_2 \frac{D}{a} \Delta t & \text{for } \frac{a^2}{\nu} \ll \Delta t. \end{cases}$$

where $v_{thm} = \sqrt{k_B T \rho a^3}$ is thermal particle velocity scale and $D$ is diffusivity of elementary particle. $C_1$ and $C_2$ are nondimensional order unity expressions w.r.t. $\alpha_k$ and $\delta_1(\alpha)$. 
Remarks on Error Estimates

Numerical method behaves as strong first order method in fully resolved regime $\Delta t \ll a^2/\nu$. But accuracy is also maintained when velocity field underresolved, provided: $\Delta t \ll \tau_{\text{mov}}(a)$, where $\tau_{\text{mov}}(a) = a^2/D$ is time scale for particle to move distance comparable to its size $a$.

- Relative size of error $C_2(D/a)\Delta t$ to magnitude of true change $\sqrt{6D\Delta t}$ over time step is $C_2\sqrt{D\Delta t}/a \ll 1$ provided $\Delta t \ll \tau_{\text{mov}}(a)$.

In presence of force, error estimates become more complicated, but theoretical accuracy maintained for all $\Delta t \ll \tau_{\text{mov}}(a)$. 
Numerical Verification of Theoretical Error Estimate for Fully Resolved Regime
Numerical Verification of Theoretical Error Estimate for Underresolved Regime
Physical Consistency of Thermal Forcing Scheme

- Agrees with correct nonlinear statistical mechanics of fluid and vibrational modes of particles, provided:
  - time scale of elementary particles resolved,
  - vibrations not strongly nonlinear
  - density and temperature fluctuations can be ignored (OK for physiological conditions with $h \gg 1$ nm).
Numerical simulations

Latest version of code due to Atzberger

- Pre-release version available on request from http://www.cims.nyu.edu/~paulatz/computational_projects/projects.html
- Polymer knot and kinesin model simulations
- developing simulations for osmotic pumps, membranes, Golgi apparatus

Undergraduate research (NSF CSUMS) by Sam Hughes on microswimmer models.
### Osmotic Pressure of Polymer Knots

<table>
<thead>
<tr>
<th>Knot Type</th>
<th>Osmotic Pressure (amu/nm · ns²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknotted</td>
<td>0.16</td>
</tr>
<tr>
<td>Trefoil Knot</td>
<td>0.0439</td>
</tr>
<tr>
<td>Figure Eight Knot</td>
<td>0.0392</td>
</tr>
</tbody>
</table>
Motor Velocity-Force Relation

![Graph showing the relationship between motor velocity (µm/s) and drag force (pN). The graph illustrates a decrease in motor velocity as the drag force increases.]
Molecular Motors

Biological engines capable of transforming thermal energy, through chemically activated processes, into mechanical work.

• Molecular pumps.
• Walking motors: Kinesin, Myosin.
• Flagellar motors.
• Polymer Growth.
Molecular Motors

Biological engines capable of transforming thermal energy, through chemically activated processes, into mechanical work.

- Molecular pumps.
- Walking motors: Kinesin, Myosin.
- Flagellar motors.
- Polymer Growth.

http://multimedia.mcb.harvard.edu
Brownian Motors as Mathematical Model

\[ dX = U \, dt, \]

\[ m \, dU = (-\gamma U - \nabla V(X(t), F(t)) + Y(t)) \, dt + \sqrt{2\gamma k_B T} \, dW(t), \]
Brownian Motors as Mathematical Model

\[ dX = U \, dt, \]
\[ m dU = (-\gamma U - \nabla V(X(t), F(t)) + Y(t)) \, dt + \sqrt{2 \gamma k_B T} \, dW(t), \]

• System represented by low-dimensional state variable \( X(t) \)
• Spatially periodic potential \( V \) modeling repetitive structure or cycle
• External driving (chemical activation) represented through stochastic processes \( Y(t) \) and \( F(t) \)
• Interaction with environment: friction coefficient \( \gamma \) and thermal fluctuations
Brownian Motors as Mathematical Model

\[ \text{d}X = U \text{d}t, \]

\[ \text{m} \text{d}U = (-\gamma U - \nabla V(X(t), F(t)) + Y(t)) \text{d}t + \sqrt{2\gamma k_B T} \text{d}W(t), \]

Potential with spatial period \( L \): \( V(x + L\hat{e}_i, \cdot) = V(x, \cdot) \), for coordinate vectors \( \hat{e}_i \).

d\(W(t)\) represents Gaussian white noise forcing with

\[ \langle \text{d}W(t) \rangle = 0, \]

\[ \langle \text{d}W_i(t)\text{d}W_j(s) \rangle = \delta_{ij}\delta(t - s)dtds. \]
Brownian Motors as Mathematical Model

\[ \begin{align*}
    \frac{dX}{dt} &= U dt, \\
    m \frac{dU}{dt} &= (-\gamma U - \nabla V(X(t), F(t)) + Y(t)) \, dt + \sqrt{2\gamma k_B T} \, dW(t),
\end{align*} \]

Often overdamped limit adequate:

\[ \begin{align*}
    \frac{dX(t)}{dt} &= \gamma^{-1} (-\nabla V(X(t), F(t)) + Y(t)) \, dt + \sqrt{2D} \, dW(t).
\end{align*} \]

with \( D = k_B T / \gamma \). Remove \( \gamma \) by appropriate rescaling of parameters.
Gaussian Long-Time Statistics from Central Limit Argument

Effective transport properties characterized entirely by drift vector and diffusion matrix:

\[ U_{\text{eff}} = \lim_{t \to \infty} \frac{\langle X(t) \rangle}{t}, \]

\[ D_{\text{eff}} = \lim_{t \to \infty} \frac{\langle (X(t) - \langle X(t) \rangle) \otimes (X(t) - \langle X(t) \rangle) \rangle}{2t}. \]
Homogenization Theory Provides Means for Calculating Drift and Diffusion Coefficients

Potential advantages over existing theoretical calculations

• Does not rely on one-dimensionality or special structure
• Provides means of calculating diffusion coefficient
• Sets up further calculations in various asymptotic parameter limits


• Originally one-dimensional with discrete states; two-dimensional generalization (2007)
Our Homogenization Studies So Far

With Juan Latorre and Grigorios Pavliotis (Imperial)

- Connection between Homogenization and WPE equations.
- Systematic application of homogenization theory on simple flashing ratchet example
  - Previous work with homogenization (Pavliotis 2005) and WPE (2003) considered steady potentials with constant mean force $F$
  - First passage time formulation (Reimann et al, 2002)
- Numerical methods to apply Homogenization Theory to more complex models
On-Off Flashing Ratchet

\[ dX(t) = -V'(X(t))F(t)dt + \sqrt{2D}dW(t), \]

with \( F(t) \in \{1, 0\} \).
On-Off Flashing Ratchet

\[ dX(t) = -V'(X(t))F(t)dt + \sqrt{2D}dW(t), \]

with \( F(t) \in \{1, 0\} \).

Sample trajectory
On-Off Flashing Ratchet

\[ dX(t) = -V'(X(t))F(t)dt + \sqrt{2D}dW(t), \]

with \( F(t) \in \{1, 0\} \).

Explore how design parameters influence:

- drift \( U_{\text{eff}} \)
- Peclét number: measure of coherence of transport

\[ Pe = \frac{LU_{\text{eff}}}{2D_{\text{eff}}}. \]
On-Off Flashing Ratchet

\[ dX(t) = -V'(X(t))F(t)dt + \sqrt{2D}dW(t), \]

with \( F(t) \in \{1, 0\} \).

Nondimensionalize/rescale: \( L = 1, A = 1 \).

Remaining parameters: \( D, k_{ij}, \alpha \).
Effective Drift As Function of Transition Rates

\[ D = 10^{-1.5}, \alpha = 0.75 \]
Peclét Number as Function of Transition Rates

$$D = 10^{-1.5}, \alpha = 0.75$$
Ongoing and Future Work

- Extension to *multiple degrees* of freedom
  - motor and cargo
  - particle sorters
- Applications to more realistic models
- “Quenched” random modulations of potential
- Numerical efficiency studies for computational schemes (*homogenization* vs. *WPE*)
Stochastic Parameterization of Water Dynamics near Solute

Simplified statistical description of water dynamics as possible basis for implicit solvent method to accelerate molecular dynamics simulations for proteins, etc. (with Adnan Khan and Shekhar Garde (Biochemical Engineering))

As a first step, we explore stochastic parameterization of water near $C_{60}$ buckyball molecule.

- isotropic, chemically simple
Molecular Dynamics Snapshot of Buckyball Surrounded by Water
Statistical dynamics encoded in biophysical literature in terms of a diffusion coefficient:

(Makarov et al, 1998; Lounnas et al, 1994,

\[ D_B(r) \equiv \left\langle \frac{|X(t + 2\tau) - X(t)|^2}{6\tau} \left| \begin{array}{c} X(t) = r \\ X(t + \tau) = r \end{array} \right\rangle - \left\langle \frac{|X(t + \tau) - X(t)|^2}{6\tau} \right\rangle \right\rangle 

But this seems to mix together inhomogeneities in mean and random motion.
Drift-Diffusion Framework

We explore capacity of models of the form

\[ dX = U(X(t)) \, dt + D(X(t)) \, dW(t), \]

for water molecule center-of-mass position \( X(t) \).

- **drift vector coefficient** \( U(r) \)
- **diffusion tensor coefficient** \( D(r) \)

For isometric solute (**buckyball**):

- \( U(r) = U_{||}(|r|)\hat{r}, \)
- \( D(r) = D_{||}(|r|)\hat{r} \otimes \hat{r} + D_{\perp}(|r|)(I - \hat{r} \otimes \hat{r}), \)

for position \( r = |r|\hat{r} \) relative to center of symmetry.
Physically Inspired (DD-I) Model

In analogy to Brownian dynamics simulations, take

\[ U(r) = -\gamma^{-1} \nabla \phi(r), \]
\[ D(r) = D_0 l. \]
Physically Inspired (DD-I) Model

In analogy to Brownian dynamics simulations, take

\[ U(\mathbf{r}) = -\gamma^{-1} \nabla \phi(\mathbf{r}), \]
\[ D(\mathbf{r}) = D_0 \text{l}. \]

- Potential of mean force obtained from measuring concentration \( c(\mathbf{r}) \) and Boltzmann distribution \( c(\mathbf{r}) \propto \exp(-\phi(\mathbf{r})/k_BT) \).
- Diffusivity unchanged from bulk value.
- Friction coefficient from Einstein relation \( \gamma = k_BT/D_0 \).
Physically Inspired (DD-I) Model

In analogy to Brownian dynamics simulations, take

\[ U(r) = -\gamma^{-1} \nabla \phi(r), \]
\[ D(r) = D_0 l. \]
Physically Inspired (DD-I) Model

In analogy to Brownian dynamics simulations, take

\[ U(r) = -\gamma^{-1} \nabla \phi(r), \]

\[ D(r) = D_0 l. \]
Systematic, Data-Driven Parameterization (DD-II) Model

Parametrize drift and diffusion functions from mathematical definitions:

\[
U_{\parallel}(|r|) = \lim_{\tau \downarrow 0} \left\langle \frac{X(t + \tau) - X(t)}{\tau} \cdot \hat{r} \middle| X(t) = r \right\rangle,
\]

\[
D_{\parallel}(|r|) = \lim_{\tau \downarrow 0} \left\langle \left| \frac{X(t + \tau) - X(t) - U_{\parallel}(r)\hat{r}\tau}{2\tau} \right|^2 \middle| X(t) = r \right\rangle.
\]
Systematic, Data-Driven Parameterization (DD-II) Model

Parametrize drift and diffusion functions from mathematical definitions:

\[
D_\perp(|r|) = \lim_{\tau \downarrow 0} \left\langle \frac{1}{4\tau} \left| X(t + \tau) - X(t) \right| \cdot (\mathbf{I} - \hat{r} \otimes \hat{r}) \right|^{2} \right| X(t) = r \right\rangle.
\]

Obtain statistical data from MD simulations.
Time Difference $\tau$ must be chosen carefully

Taking $\tau = \Delta t$ (time step of MD simulation) may not be appropriate

- Limit $\tau \downarrow 0$ implicitly refers to times large enough for drift-diffusion approximation to be valid.

Must choose $T_v \ll \tau \ll T_x$, where:

- $T_v$ is time scale of momentum.
- $T_x$ is time scale of position.

See also Pavliotis and Stuart (2007) about need to undersample.

How choose $\tau$ in practice?
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]

\[ m \, dV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_BT\gamma} \, dW(t) \]
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]

\[ mdV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_BT \gamma} \, dW(t) \]

Forces: friction, potential, and thermal.
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]
\[ m \, dV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_B T \gamma} \, dW(t) \]

Nondimensionalize:

\[ dX = V \, dt, \]
\[ dV = -aV \, dt - aX \, dt + a \, dW(t) \]
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]
\[ m \, dV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_BT} \gamma \, dW(t) \]

Nondimensionalize:

\[ dX = V \, dt, \]
\[ dV = -aV \, dt - aX \, dt + a \, dW(t) \]

where \( a = \frac{\gamma^2}{m\alpha} \) is ratio of position to momentum time scale.
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]
\[ mdV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_B T \gamma} \, dW(t) \]

Nondimensionalize:

\[ dX = V \, dt, \]
\[ dV = -a V \, dt - a X \, dt + a \, dW(t) \]

Exact drift-diffusion coarse-graining when \( a \gg 1 \):

\[ dX = -X \, dt + dW(t) \]
Explore simple Ornstein-Uhlenbeck (OU) model

\[ dX = V \, dt, \]

\[ mdV = -\gamma V \, dt - \alpha X \, dt + \sqrt{2k_B T \gamma} \, dW(t) \]

Nondimensionalize:

\[ dX = V \, dt, \]

\[ dV = -a V \, dt - a X \, dt + a \, dW(t) \]

What if we try to obtain this from analysis of trajectories with finite but large \( a \)?
Drift and diffusion coefficients of exact OU solution sampled with finite time difference $\tau$
Drift and diffusion coefficients of exact OU solution sampled with finite time difference $\tau$

Longitudinal Diffusivity for OU, $a=132$

Blue : Exact
Red : Asymptotic
Inferences from OU model

- Good choice of $\tau$ may be the one which maximizes drift magnitude and diffusivity.
- Beginning estimate obtained from OU model with same $\alpha$ value.
OU Model Insights → MD Data Parameterization in DD-II Model

To obtain time scales, approximate main well in potential of mean force by quadratic.

This gives $a = 132$. 
OU Model Insights → MD Data Parameterization in DD-II Model

Examine drift and diffusivity computed from various choices of $\tau$. 
OU Model Insights → MD Data Parameterization in DD-II Model

Examine drift and diffusivity computed from various choices of $\tau$.

![Longitudinal Drift](image)

- Blue: $\tau=20\text{ fs}$
- Green: $\tau=40\text{ fs}$
- Red: $\tau=60\text{ fs}$
- Magenta: $\tau=80\text{ fs}$
- Cyan: $\tau=100\text{ fs}$
OU Model Insights → MD Data Parameterization in DD-II Model

Examine drift and diffusivity computed from various choices of $\tau$.

![Graph showing longitudinal diffusivity for different values of $\tau$.]
OU Model Insights → MD Data Parameterization in DD-II Model

Examine drift and diffusivity computed from various choices of $\tau$. Both desiderata about drift and diffusivity behavior not simultaneously satisfiable.

- Correct bulk diffusivity behavior more important

We choose $\tau = 0.2 \text{ ps} = 200 \text{ fs}$. 
Parameterization Used in DD-II Model

Longitudinal Drift

Blue: DD-II output
Red: DD-II input from MD data

U_{\parallel} (\text{nm/ps}) vs. r (nm)
Parameterization Used in DD-II Model

Longitudinal Diffusivity

Blue : DD-II output
Red  : DD-II input from MD Data
Parameterization Used in DD-II Model

\[
D_\perp (\text{nm}^2/\text{ps})
\]

Lateral Diffusivity

Blue : DD–II output
Red : DD–II input from MD data

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Compare Predictions of Biophysical Diffusivity Formula

\[ D_B(r) \equiv \left\langle \frac{|X(t + 2\tau) - X(t)|^2}{6\tau} \bigg| X(t) = r \right\rangle \\
- \left\langle \frac{|X(t + \tau) - X(t)|^2}{6\tau} \bigg| X(t) = r \right\rangle \]
Compare Predictions of Biophysical Diffusivity Formula

$D_B (r)$ for DD–I Model

$D_B (r)$ for DD–II Model
Future Work

Next steps

- anisotropies
- chemical heterogeneity