Fall 2014

Theory for diffusional encounters in heterogeneous environments and multivalent electrolyte screening of charged interface

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By Ran Li

Entitled
Theory for Diffusional Encounters in Heterogeneous Environments and Multivalent Electrolyte Screening of Charged Interface

For the degree of Doctor of Philosophy

Is approved by the final examining committee:

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Approved by Major Professor(s): BRIAN A. TODD

Approved by: M. R. Melloch 10-15-2014
Head of the Graduate Program Date
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ABSTRACT

Li, Ran Ph.D., Purdue University, December 2014. Theory for Diffusional Encounters in Heterogeneous Environments and Multivalent Electrolyte Screening of Charged Interface. Major Professors: Brian A. Todd and Thomas M. Talavage.

We develop a theory for encounter rates in a three-dimensional system of connected compartments. The model of connected compartments exhibits the length-scale dependent diffusion that is observed in many heterogeneous environments, such as porous catalysts and biological environments. We discovered a dimensionless number that is the dominant scaling variable and obtained, for the first time, an analytical expression for the encounter rate. The new theory generalizes the classic Smoluchowski diffusion limit to the case of heterogeneous environments. The new theory is tested using Brownian dynamics simulations.

We also experimentally investigated the behavior of multivalent electrolyte near a charged solid-liquid interface. We used the streaming potential technique to measure electrical potentials near negatively charged glass surface as a function of trivalent ion (Co(NH$_3$)$_6$Cl$_3$) concentration, monovalent ion (KCl) concentration, and pH. Charge inversion was observed. Measured electrical potentials were compared with predictions from a recent theory that models multivalent ions near the charged surface as two-dimensional strong coupled liquid (SCL). We found that SCL predictions agree quantitatively with our experimental data, which suggests that multivalent ions near charged surfaces form a two-dimensional highly correlated structure.
1. INTRODUCTION TO DIFFUSION-LIMITED REACTION RATE

1.1 Motivations and Applications

1.1.1 in vivo Biochemistry

Measurements of biological processes have historically been carried out in test tubes where molecules are isolated from their native environments (Fig. 1.1(A)). Many biological macromolecules lose their essential features when removed from their native environments, including their three-dimensional structures and biological functions. [1–5] A major effort is underway to enable biochemical processes to be measured in living organisms where the biochemical parameters and kinetics reflect their complex native environments (Fig. 1.1(B)). [6–20] The analytical theory that I will describe in this dissertation is part of this effort and can be used to interpret measurements of diffusion and reactions in complex heterogeneous environments. This theory is expected to provide a more appropriate upper bound on reaction rates in the heterogeneous environments than the classic theories developed for homogeneous environments. [21]

1.1.2 System Biology

Systems biology is a scientific discipline that endeavors to integrate molecular components of a biological system into quantitative and predictive description of cells, tissues, and whole organism. [23] Reaction networks play a central role in systems biology, describing the interactions between biological components. The essential parameter that characterizes the interactions between biological components in the reaction network is the rate constant. However, the values for rate constants are
Fig. 1.1. (A) Homogeneous diffusion in test tubes. Reaction kinetics and diffusions have historically been carried out in test tubes where reacting molecules are isolated from their native environments. Many biological macromolecules lose their essential features when removed from their native environments. (B) Diffusion in the intracellular environment. Cells usually contain high concentrations of macromolecules that impedes diffusion as obstacles. Biochemical parameters and kinetics measured in cells reflect the native complex heterogeneous environment. The cartoon of the cell interior is taken from Ref. [22]. (C) The simulation of reaction kinetics in the semipermeable connected compartments. The semipermeable walls represents the confinement imposed by high concentrations of obstacles. Simulations will be described in the later chapters of this dissertation.
almost completely unknown. Systems biologists working on reaction network models thus “invariably face a particularly acute problem, which is the lack of quantitative information about unitary reactions.” [24] Our analytical theory addresses this acute problem by providing predictions of the unitary rate constants from the rich data of biological diffusion. [6–20]

With the predicted reaction rate constant, reaction networks are expected to play a central role in describing the physiological state of individuals and to enable personalized health care. [23] Thus, while our focus is on the fundamental connection between diffusion and reaction rates in biological systems, our work will benefit society by addressing a technical barrier to personalized health care.

1.2 The Diffusion Limit of Reactions

Most biological reactions start with reactants separated in space. In order for the reaction to take place, reactants must first be transported to a common location through certain transport mechanism. In some cases, active transport plays particularly important role, for instance, in moving molecules across large cells [25], in transport of vesicles [26], and in enriching regions of the cell in particular molecules. [27] In other cases, reactants are attached to an organized framework (such as actin and myosin in muscle contraction) and thus are brought together by the movement of the framework. However, for most biological reactions, at least one of the reacting species starts off in the free intra- or extracellular environment, thus needs to be transported to their fellow reactants through one or more diffusional processes. Diffusion provides the final search mechanism by which molecules explore their local space to find fellow reactants, even with other transport mechanisms present.

A biological reaction may involve many steps. For instance, the reactants in a macromolecular reaction must first be brought in proximity through diffusion or other transport mechanism, and then attain certain orientation so that the reactive groups are properly aligned. A reaction intermediate may form at this point that permits the
subsequent chemical process to produce the final product. The overall reaction rate may be affected by interactions between the reactants during these steps, including the direct short-range interactions (electrostatic, hydrophobic, non-specific) [28, 29] and the dynamic forces (hydrodynamic effects) [30, 31]. Reacting mechanisms can be complicated and vary from reaction to reaction, but in general reactions can be divided into two categories according to the rate-limiting step: diffusion limited and reaction limited. As the name suggests, if the overall reaction rate is limited by diffusion, then the reaction is diffusion-limited or diffusion-controlled. If the overall reaction rate is limited by the chemical process, then the reaction is reaction-limited or reaction-controlled (or chemically controlled).

The simplest mechanism indicating the association of two different reactants is given by,

$$A + B \xrightarrow{k} C. \tag{1.1}$$

Here, two different reactants $A$ and $B$ collide and produce product $C$. The rate of this second order reaction is given by

$$Rate = k[A][B], \tag{1.2}$$

where $k$ is the reaction rate constant that characterizes the speed of the reaction, $[A]$ and $[B]$ are concentrations of reactants $A$ and $B$. For a diffusion-limited reaction, the time required to produce $C$ is negligible compare to the diffusion time of $A$ and $B$. In this case, the rate constant $k$ is the diffusion-limited reaction rate constant, and is mainly affected by the diffusion time.

Estimating the diffusion limit of reactions is particularly important in the biological systems. On one hand, many biological reactions are diffusion-limited, meaning that the overall reaction kinetics closely approaches the diffusion limit. [32] For such systems, precise prediction of the diffusion limit gives a close estimation on the overall reaction rate. On the other hand, diffusion limit sets an upper bound - a speed limit on the reaction rates of all reactions that involve diffusional processes, since the
reactions can not react any faster than the diffusion time. In this case, the reaction rate is upper bounded by the diffusion limit:

\[ k \leq k_{\text{encounter}}. \]  \hspace{1cm} (1.3)

1.3 Diffusion-Reaction in Homogeneous Solution

1.3.1 Random Walk in Liquid

In the microscopic view, diffusion is the random migration of small particles arising from the motion due to thermal energy. Diffusion in liquid is different from diffusion of ideal gas. In ideal gas, molecules carry momentum over distances much larger than the size of the molecule. In liquids, the mean free path is much shorter than the radius of even water molecules. Consequently, diffusion in liquids closely resembles the mathematical Wiener process where the velocity is random down to infinitesimal times.

Mean square displacement of the random walk

For an isotropic random walk in three dimensional space, the average position of the diffusing particles does not change as a function of time. Therefore, the average displacement of the particles is always 0. To estimate how much the particles spread, an easy measure is the mean-square displacement \( \langle x^2 \rangle \). In each dimension, the mean-square displacement is given by

\[ \langle x^2 \rangle = 2D_0t, \] \hspace{1cm} (1.4)

where \( D_0 \) is the translational diffusion coefficient of the given molecule in the given solvent at a given temperature. Eq. 1.4 shows that the root-mean-square displacement \( \sqrt{\langle x^2 \rangle} \) is proportional to the square root of time instead of time. The positions of the particles have a Gaussian distribution, with the mean position equal to the starting point and the variance \( \sigma_x^2 \) equal to the mean square displacement, \( \langle x^2 \rangle \). The Gaussian
distribution indicates that, after time $t$, there is about 68% chance that the particle did not wander as far as $\sqrt{2D_0t}$.

In two or three dimensions, the mean-square displacement can be trivially derived from the fact that the square of the displacement from the origin $r^2$ equals to $x^2 + y^2$ in 2D, and $x^2 + y^2 + z^2$ in 3D. Therefore, the mean square displacement $\langle r^2 \rangle$ is given by

$$\langle r^2 \rangle = 4D_0t$$ (1.5)

in 2D, and

$$\langle r^2 \rangle = 6D_0t$$ (1.6)

in 3D.

1.3.2 Fick’s Law and Fickian Diffusion

Fick’s Law is a classical theory that describes the spatial and temporal variation of nonuniform distributions of diffusing particles. Fick’s first law states that the net flux of the particles at a given time and position is proportional to the spatial concentration gradient, with proportionality constant $-D_0$.

$$J_x = -D_0 \frac{\partial C}{\partial x}$$ (1.7)

Fick’s second law states that the time rate of change in concentration is proportional to the spatial curvature of the concentration, with proportionality constant $D_0$.

$$\frac{\partial C}{\partial t} = D_0 \frac{\partial^2 C}{\partial x^2}$$ (1.8)

The solution to Fick’s law describes how the diffusing particles redistribute themselves in time and space in a sufficiently large and homogeneous environment. For instance, the solution to Fick’s second law for the initial condition of a delta function is Gaussian. Hence, the spread in concentration is just the probability density for the random walk.

Fick’s law lies in the core of understanding diffusions in solids, liquids and gases. Diffusion that obeys Fick’s law is refers to as “Fickian diffusion”.
1.3.3 Diffusion Coefficient, Translational and Rotational

For free Fickian diffusion, both translational diffusion coefficient $D_0$ and rotational diffusion coefficient $D_r$ can be obtained from the Einstein-Smoluchowski relation,

$$D_0 = \frac{k_B T}{f_0}$$  \hspace{1cm} (1.9)

and

$$D_r = \frac{k_B T}{f_r},$$  \hspace{1cm} (1.10)

where $k_B$ is the Boltzmann constant, $T$ is the absolute temperature, $f_0$ is the frictional drag coefficient for translational diffusion and $f_r$ is the frictional drag coefficient for rotational diffusion. According to Stoke’s law, for a uniform sphere in an incompressible, viscous liquid, the frictional drag coefficient for translational diffusion $f_{t,\text{sphere}}$ is given by,

$$f_{t,\text{sphere}} = 6\pi\eta a$$  \hspace{1cm} (1.11)

where $\eta$ is the viscosity of the medium and $a$ is the radius of the sphere. The frictional drag coefficient for rotational diffusion $f_{r,\text{sphere}}$ is

$$f_{r,\text{sphere}} = 8\pi\eta a^3$$  \hspace{1cm} (1.12)

In both cases, the frictional drag coefficient is linearly related to the viscosity of the medium. Changes in the viscosity produce proportional changes in both translational and rotational diffusion coefficient.

1.3.4 Smoluchowski Equation for Diffusion limit in homogeneous solution

The Smoluchowski limit gives an upper bound on the rate constant, $k_0$, for a second-order reaction brought about by diffusion. The Smoluchowski limit was obtained by Smoluchowski in 1917 [21], by solving Fick’s Laws for the diffusive flux of reactants with diffusion coefficient, $D_0$ into an absorbing sphere of radius, $R$. The Smoluchowski limit considers the diffusion-limited association of two different types of reacting molecules $A$ and $B$ as shown in Eq. 1.1. The reacting species are assumed
to be spheres with radii $R_A$ and $R_B$. In three dimensions, according to Fick’s law, the steady state radial flux is given by

$$J(r) = -(D_A + D_B) \frac{\partial P}{\partial r}, \quad (1.13)$$

with

$$\frac{1}{r^2} \frac{\partial}{\partial r} r^2 J(r) = 0. \quad (1.14)$$

For simplicity, define effective diffusion coefficient $D_0$ as $D_0 = D_A + D_B$ and effective reaction radius $R$ as $R = R_A + R_B$. The equations are then solved subject to the boundary conditions that reactants vanish at $r = R$, indicating that $P(R) = 0$, and the concentrations of $A$ and $B$ remain constant at infinitely far, indicating that $P(\infty) = [A][B]$. The solution is then given by

$$J(r) = -D_0[A][B] \frac{R}{r^2}. \quad (1.15)$$

The flux at the absorbing sphere is then

$$J(R) = -D_0[A][B] \frac{1}{R}. \quad (1.16)$$

The rate that reactants are absorbed by the sphere at $r = R$ equals the steady flux times the surface area of the sphere,

$$rate = -4\pi R^2 J(R) \quad (1.17)$$

The rate constant is then

$$k = \frac{rate}{[A][B]} = 4\pi D_0 R. \quad (1.18)$$

This is the classical Smoluchowski result of the diffusion-limited reaction rate constant. Any transition-state barrier will cause the reaction rate to be slower than the Smoluchowski diffusion limit. Hence, with reference to any real rate constant, $k_0$, Smoluchowski’s Eq. is expressed as the inequality,

$$k_0 \leq 4\pi D_0 R \quad (1.20)$$
The Smoluchowski limit suggests a linear proportionality between the diffusion coefficient $D_0$ and the reaction rate constant $k_0$.

The Smoluchowski equation has different variations/extensions to account for different geometries of reactants or non-negligible transition-state barrier during the reaction process, by replacing the capture radius $R$ with an effective reaction radius $R^*$. [32] For example, when the intermolecular forces between the reactants are included, the effective reaction radius $R^*$ is given by

$$R^* = 1/ \int_R^\infty r^{-2} e^{U(r)/k_B T} dr$$

(1.21)

where $U(r)$ is the intermolecular potential between the reactants. [28] With changes adapted in the Smoluchowski equation, reaction rate $k_0$ is still linearly proportional to the diffusion coefficient $D_0$, with adjusted proportionality constants.

1.4 Diffusion-Reaction in Biological Systems

1.4.1 Diffusion Measurements in Biological Systems

Diffusion in the biological environment has been extensively measured. Experimental data throughout the years has shown that translational diffusion coefficients measured in vivo over distances $>100$ nm are reduced 3-100 fold compared to those measured in vitro. [6–20] The substantial decrease in the diffusion coefficient was once characterized by large effective bulk viscosities of the biological medium. [20]. The “viscous” interpretation of the cell interior was later precluded by contrasting the translational and rotational diffusion coefficient. According to Eq. 1.11 and Eq. 1.12, the viscosity of the medium affects rotational and translational diffusion uniformly. However, rotational diffusion coefficients measured inside cells are maintained at 70 – 90% of their values in buffer, [33–35] whereas, translational diffusion coefficients drop to 0.1 – 20% of their values in buffer. [6–20]

The contrast between the diffusional and rotational diffusion coefficient is interpreted as meaning that, on average, the solution seen by a molecule in its immediate
vicinity has essentially the same viscosity as water. For rotation, this “watery” environment is all that matters. As the molecule translates, however, it encounters “obstacles” that impede translation, reducing diffusion coefficients. The “obstacles” in the biological systems are usually high concentrations of soluble macromolecules and networks of extended structures that are irrelevant to the reactions, such as cytoskeletons, intermediate filaments, microtubes, F-actin and membranous boundaries. These obstacles occupy a substantial fraction of the total volume (Fig. 1.2). This view is further supported by measurements in shrunken or swollen cells where the density of obstacles systematically changes rates of diffusion. [36]

The size dependence for biological diffusion also provides evidence that translational diffusion in biological environments is impeded by obstacles. Like a scooter weaving through a traffic jam, small molecules are more weakly affected by macromolecular obstacles in the biological environment than large diffusing molecules. This size dependence, with strong attenuation in diffusion for molecules with sizes of 20–40 nm [6–10] also provides a measure of the effective “pore” sizes in the intracellular environment.

Therefore, “the view of the cell interior has evolved from that of a viscous gel to that of a watery but crowded compartment.” [37] In this view, a rapid “watery”) diffusion predominates at short length scales and diffusion only becomes slow at larger length scales as obstacles are encountered. The biological diffusion is thus governed by two different diffusion coefficients: $D_0$ which is similar to that of water at short length scales and $D$ at larger length scales where obstacles impede diffusion.

### 1.4.2 Diffusion-Reaction Coupling in Biological Systems

In the homogeneous system, the classical Smoluchowski Equation (Eq. 1.20) indicates a direct proportionality between the diffusion coefficient and the reaction rate. At issue, is how to determine a limit on $k$, the corresponding rate constant *in vivo*, given a translational diffusion coefficient, $D$, observed over large length scales *in vivo*. 
Fig. 1.2. Interior of a typical *E. coli* cell with proper scales and concentrations of molecules, taken from Ref. [22]. (a) shows a size of 100nm window in the cytoplasm of the *E. coli* cell. (b) is a ten-times enlargement of the corner of (a). Water molecules are shown as circles. Small molecules including pre-curors and cofactors are shown as dark outlines. This figure illustrates that cell interior is very “crowded”. Small molecules diffusing in cells see a heterogeneous environment.
If we apply Smoluchowski’s approach, then we would simply replace $D_0$ with $D$. This predicts \textit{in vivo} diffusion-limit,

$$k \leq 4\pi DR.$$  \hspace{1cm} (1.22)

Eq. 1.22 has been used to predict the reaction rate in classic [3,4,38] and recent [39,40] theories in the biological systems. The Smoluchowski equation predicts that the 3 – 100 fold decrease in the diffusion coefficient in the biological environments will cause the diffusion limit of the reaction rate decrease by the same fold. However, Brownian dynamics simulations of the intracellular environment find that the Smoluchowski equation does not hold; [41] that is, the reaction rate constant exceeds the limit predicted by the Smoluchowski equation. Moreover, recent experiments observed that rates of protein dimerization in HeLa cells and in vitro were similar [42] and that crowding did not affect rates of DNA hybridization. [43] This was interpreted, [42] using the framework of macromolecular crowding, [3, 4, 38] as indicating that a decrease in diffusion-limited reaction rates was compensated by a crowding-induced lowering of activation barriers.

Recent experimental data has shown that the Smoluchowski equation does not apply in the biological systems. This is due to the fact that the Smoluchowski relation was derived under the assumption that diffusion is homogeneous at all length scales larger than the size of the diffusing molecule. However, the long term diffusion coefficient $D$ in the biological systems does not apply at the scale of the reaction radius. The diffusion-limited reaction rate is NOT linearly related to the diffusion coefficient in the heterogeneous environment. However, with notable exceptions [44, 45], little theory has been developed to predict reaction rates reaction rates for heterogeneous environments. Yet, fewer experiments have been done to correlate diffusion and reaction rates in living cells and tissues. [42] This misses the opportunity to use the relatively rich data available on biological diffusion to predict rates of biological reactions. We therefore see a need to establish a diffusion-limit appropriate for reactions occurring in biological environments.
1.5 Approaches to Diffusion-Reaction

1.5.1 Wiener Sausage Approach

Mathematical Wiener Process

Wiener Process is the mathematical description of Brownian motion. The Wiener Process \( \{W(t)\}_{t \geq 0} \) is a continuous-time stochastic process characterized by the following properties [46]:

1. \( W_0 = 0 \).
2. The function \( t \mapsto W_t \) is almost surely (with probability 1) everywhere continuous.
3. For any \( 0 \leq s \leq t \), the increment \( W_t - W_s \) has a Gaussian distribution with mean 0 and variance \( t - s \).
4. Increment for non-overlapping time intervals are independent and stationary.

The property of stationary increments means that for any \( 0 \leq s, t \leq \infty \), the distribution of the increment \( W_{t+s} - W_s \) has the same distribution as \( W_t - W_0 = W_t \). In general, a stochastic process with stationary and independent increments is referred to as the Lévy process. Wiener process is a special case of Lévy process.

Wiener Sausage

The term “Wiener Sausage” was first used in Ref. [47]. The “Wiener Sausage” can be mathematically defined as the following [48]: Let \( \beta(t), t \geq 0 \), be the standard Brownian motion (Wiener process) in \( \mathbb{R}^d \). The Wiener sausage with radius \( R > 0 \) is the process defined by

\[
V_R^R(t) = \bigcup_{0 \leq s \leq t} B_R(\beta(s)), t \geq 0,
\]

where \( B_R(x) \) is the open ball with radius \( R \) around \( x \in \mathbb{R}^d \).
Wiener sausage is the union of the neighborhood of a Wiener process. The neighborhood is defined as the volume of a sphere with a radius $R$. The wiener sausage can be visualized as the total volume visited by a sphere of radius $R$ doing Brownian motion.

**Wiener Sausage Approach to Diffusion-Reaction Coupling**

The process of the diffusing particle wandering around to find a target to react with can be thought of as a volume searching process. If the volume visited by the diffusing particle overlaps one or more targets, then the searching particle and its target have encountered and the diffusion-limited reaction rate can be determined. This can be seen from the units of a second order rate constant: volume per time. The volume of space contacted by a sphere undergoing diffusion is just the Wiener sausage volume. The connection between the Wiener sausage volume and the encounter rate is that each time the Wiener volume increases by the average volume containing one reactant, the diffusing particle encounters, on average, one reactant. The problem of describing the diffusion-limited reaction rate is thus the problem of determining the diffusive rate of volume exploration.

This way to determine the diffusion-limit is the Wiener sausage approach, pioneered by Berezhkovskii. [49,50] In this approach, one determines the volume of space, $V(t)$, that makes contact with a diffusing particle of radius, $R$ during a time period, $t$. The rate of increase of $V(t)$ is the diffusion-limited reaction rate, [50]

$$k = \lim_{t \to \infty} \frac{V(t)}{t}. \tag{1.24}$$

Indeed, for Fickian diffusion, $\lim_{t \to \infty} V(t)/t = 4\pi DR$, i.e., the rate of increase of the Wiener sausage volume is equivalent to Smoluchowski’s diffusion limit. [50] Therefore, finding the diffusion limit becomes equivalent to finding the rate of volume search by the diffusing particle.
1.5.2 Brownian Dynamics Simulation

Brownian Dynamics (BD) simulation is a way of calculating the random trajectory of Brownian particles. BD simulation discretizes the trajectory over sufficiently small time step $\Delta t$ and calculates the displacement that the diffusing particle has possibly achieved in that small time step. The calculation of the discrete displacement is based on Eq. 1.4. In each dimension, the step of the Brownian particle takes in time $\Delta t$ is given by

$$
\Delta x = \sqrt{2D_0 \Delta t \bar{\xi}},
$$

(1.25)

where $D_0$ is the diffusion coefficient in the medium of interest, and $\bar{\xi}$ is a Gaussian random variable that has property of $\langle \bar{\xi}(t) \rangle = 0$ and $\langle \bar{\xi}(t_1)\bar{\xi}(t_2) \rangle = \delta(t_1 - t_2)$. Eq. 3.14 specifies the discrete spatial step $\Delta x$ in a finite time step $\Delta t$, from the current physical position of the particle. The next physical position of the particle is given by,

$$
x_{i+1} = x_i + \Delta x.
$$

(1.26)

Propagating Eq. 1.26 gives the simulated trajectory in one dimension.

The random walk of the diffusing particle in each dimension is independent of other dimensions, thus can be calculated separately through similar procedure. In three dimensions, the next physical position of the particle is given by

$$
\bar{x}_{i+1} = \bar{x}_i + \Delta \bar{x}.
$$

(1.27)
2. ANALYTICAL SOLUTION FOR ENCOUNTER RATES IN HETEROGENEOUS ENVIRONMENTS

2.1 Abstract

We describe the diffusion limit for reaction rates in a three-dimensional system of connected compartments. This model exhibits the length-scale dependent diffusion that can be observed in many heterogeneous environments, such as porous catalysts and biological environments. We obtain a simple analytical expression for the diffusion limit applicable to any scale of the compartment confinement. This diffusion limit exceeds the classic Smoluchowski diffusion limit that was derived for homogeneous environments but is often applied to biological reactions in heterogeneous environments. We expect our new diffusion limit to provide a more appropriate upper bound on reaction rates in biological systems, porous structures, and other heterogeneous environments where obstacles create local confinement.

2.2 Model of Connected Compartments

We determine the diffusion-limit in a heterogeneous environment consisting of connected compartments of characteristic radius, $L$ (illustrated in Fig. 2.1(A)). Diffusion within compartments is free Fickian and characterized by diffusion coefficient, $D_0$. Here, the diffusive mean square displacement, $\langle r^2 \rangle$, would be the same as in the absence of confinement,

$$\lim_{r \ll L} \langle r^2 \rangle = 6D_0 t.$$  \hspace{1cm} (2.1)

Over larger distances, confinement imposed by the compartment retards transport, causing $\langle r^2 \rangle$ to increase more slowly with time. Over larger distances, confinement imposed by the compartment retards transport, causing $\langle r^2 \rangle$ to increase more slowly
with time. This transition occurs at length scales comparable to the compartment size, $L$. Over distances larger than $L$, the diffusing particle executes a random walk between compartments. Here, $\langle r^2 \rangle$ again increases linear with time but with a smaller diffusion coefficient, $D$,
\[
\lim_{r \gg L} \langle r^2 \rangle = 6Dt.
\] (2.2)

The ratio $\delta = D/D_0 < 1$ represents the scale of confinement. The Heterogeneity is incorporated in this model simply by having diffusion governed by two different coefficients, $D_0$ and $D$.

The particle moves into a different compartment at random times. Escape from compartments is similar to effusion from a Knudsen cell where the exit time or “residence time”, $\Delta t$ is a random variable governed by exponential probability density $se^{-s\Delta t}$, [51] where $s$ is the average rate of exiting compartments, or “switching rate” between compartments. The relation $s = 3D/L^2$ relates the exiting rate, $s$, to diffusion at length scales larger than $L$.

### 2.3 Analytical Expression for Encounter Rate

We adapt the Wiener sausage approach to determine the diffusion limit of reaction rates in a network of connected compartments of characteristic radius, $L$. In this approach, we determine the volume of space, $V(t)$, that makes contact with a diffusing particle of radius, $R$ during a time period, $t$. The rate of increase of $V(t)$ is the diffusion-limited reaction rate (Eq. 1.24). [50]

The complication that compartments introduce into the Wiener sausage problem is that the rate of increase of $V(t)$ changes discontinuously when the particle moves into a new compartment. This discontinuity is a consequence of the fact that $V(t)$ increases only when the particle encounters a region of space for the first time. The likelihood of encountering space for the first time changes abruptly when the particle moves from an old compartment into a new compartment. It is convenient to deal
Fig. 2.1. (A) Diffusion in the presence of compartments with typical size, \(L\). For small displacements the particle diffuses freely \textit{within} a compartment and diffusion is characterized by a diffusion coefficient, \(D_0\). (B) Over larger distances, diffusive transport is increasingly encumbered by the compartment and \(\langle r^2 \rangle\) increases more slowly with time. Over distances much larger than the compartment size, the particle executes a random walk \textit{between} compartments. At these length-scales, the mean square particle displacement, \(\langle r^2 \rangle\) increases linearly with time but with smaller diffusion coefficient, \(D\). For clarity, the cartoon is shown in two-dimensions but it is meant to depict three-dimensional diffusion.
with this discontinuity by writing $V(t)$ as the sum of incremental changes that occur within each compartment,

$$\lim_{t \to \infty} V(t) = \Delta V(0, \Delta t_1) + \Delta V(\Delta t_1, \Delta t_1 + \Delta t_2) + \ldots$$  \hspace{1cm} (2.3)$$

Because $\Delta t_i$ is a residence time, $\Delta V(t, t + \Delta t_i)$ is the increase in $V(t)$ that occurs during a single compartment occupancy. In addition to the random residence times, the expectation for a particular $\Delta V$ is also affected by the possibility that a particle returns to a compartment that it had previously entered. In order to calculate average quantities, we therefore group $\Delta V$’s according to 1st visits to a compartment, 2nd visits to a compartment, etc. Defining $N_i(t)$ as the number of times that the Brownian particle enters a compartment for the $i^{th}$ time, we can express Eq. 2.3 as,

$$\lim_{t \to \infty} V(t) = N_1(t)\langle \Delta V \rangle_1 + N_2(t)\langle \Delta V \rangle_2 + \ldots$$  \hspace{1cm} (2.4)$$

where $\langle \Delta V \rangle_i$ is the increase in Wiener sausage volume for an $i^{th}$ visit, averaged over residence times. Noting that the probability of an $i^{th}$ visit is $P_i = N_i(t)/N(t)$, where $N(t)$ is the total number of compartment entries in time $t$, we can write Eq. 2.4 as,

$$\lim_{t \to \infty} \frac{V(t)}{t} = \frac{N(t)}{t} (P_1\langle \Delta V \rangle_1 + P_2\langle \Delta V \rangle_2 + \ldots)$$  \hspace{1cm} (2.5)$$

$N(t)/t = s$ is just the rate of moving between compartments. The sum in parenthesis is the average increase in volume of the Wiener sausage per compartment occupancy. Denoting averaging over return possibilities with an overbar, we have,

$$\lim_{t \to \infty} \frac{V(t)}{t} = s\langle \Delta V \rangle_i.$$  \hspace{1cm} (2.6)$$

This equation expresses the rate of increase of the Wiener sausage volume as the rate of moving between compartments, $s$, times the average increase in Wiener sausage volume per compartment occupancy. The averaging involves two random variables: the exits times, $\Delta t$ and the return possibilities (i.e. the possibility of entering a compartment of the 1st time, 2nd time, \ldots).
The significance of Eq. 2.6 is that the diffusion-limited encounter rate for a heterogeneous environment containing compartments is reduced to the problem of calculating the appropriate expectation value for the Wiener sausage volume for a single visit to an isolated homogeneous compartment of finite size. Specifically,

\[
\langle \Delta V \rangle_i = \langle v(T_i) - v(T_{i-1}) \rangle_i
\]  

(2.7)

where \( v \) is the volume contacted by a particle of radius, \( R \) with diffusion constant, \( D_0 \), inside an isolated compartment of volume \( v_c = 4\pi L^3/3 \) after residing for a time, \( T_i \). The relationship between the cumulative residence time after \( i \) visits, \( T_i \) and the exit times for each single visit is \( T_i = \Delta t_1 + \cdots + \Delta t_i \). That the diffusion-limit for a heterogeneous environment can be deduced from a single isolated homogeneous compartment is a consequence of the fact that the compartment is the basic repeat unit of the environment. Hence, it represents the smallest level of coarse-graining over which an average property will reflect the environment as a whole.

We average \( v(T_i) \) over all residence times,

\[
\langle v(T_i) \rangle_i = \int_0^\infty \cdots \int_0^\infty v(T_i) s^{i-1} d\Delta t_1 \cdots d\Delta t_i
\]  

(2.8)

\( T_i \) is the sum of independent \( \Delta t_i \)'s and Eq. 2.8 can be rewritten in terms of the probability density for \( T_i \),

\[
\langle v(T_i) \rangle_i = \int_0^\infty v(T) s^i T^{i-1} e^{-sT} dT.
\]  

(2.9)

Equation 2.9 is the Laplace transform of \( v(T)s^i T^{i-1} \). Using well-known properties of Laplace transforms, this gives,

\[
\langle v(T_i) \rangle_i = \frac{(-1)^{i-1}}{(i-1)!} s^{i-1} d^{i-1} \mathcal{L}(v)
\]  

(2.10)

where \( \mathcal{L}(v) \) is the Laplace transform of \( v(T) \).

In order to obtain an explicit expression for the reaction rate requires only that we specify \( v(T) \). Unfortunately, there are no exact analytical solutions for the Wiener sausage in a finite domain. We approximate the rate of increase of \( v \) as proportional to the fraction of compartment volume that has not yet been touched by the particle,

\[
\frac{dv}{dT} \propto \frac{v_c - v(T)}{v_c}.
\]  

(2.11)
This assumes that the compartment is perfectly mixed so that the likelihood for the particle to touch a region of space for the first time is equal to the fraction of untouched volume remaining in the compartment. Because a particle is always near its own previous trajectory, correlations will cause the actual rate of increase of $v$ to be smaller than the rate given by Eq. 2.11. Hence, Eq. 2.11 though not exact, will establish a definite upper limit on the reaction rate. In contrast, Smoluchowski’s diffusion-limit is known to be violated by reaction rates in heterogeneous environments. [41] Equation 2.11 along with the initial condition $v(0) = 0$, specifies an easily solved initial value problem giving an explicit expression for $v(T)$,

$$v(T) = v_c \left(1 - e^{-T/\tau}\right), \quad (2.12)$$

with Laplace transform,

$$L(v) = \frac{v_c}{s(\tau s + 1)}. \quad (2.13)$$

Combining Eq. 2.13 with Eqs. 2.5, 2.7, and 2.10 we obtain an explicit expression for the average rate of increase for the Wiener sausage volume in a compartmentalized environment,

$$s\langle \Delta V \rangle_i = \frac{sv_c}{(\tau s + 1)} \sum_{i=1}^{\infty} P_i \left(\frac{\tau s}{\tau s + 1}\right)^{i-1}. \quad (2.14)$$

This sum converges rapidly because each successive term is the product of two terms ($P_i$ and $(\tau s/(\tau s + 1))^{(i-1)}$) both of which decrease exponentially with $i$. Hence, we can truncate the sum at $i = 2$ with little loss in accuracy. We approximate the probability that the particle returns to a compartment for the 2nd time with the return probability, $P_2 \sim P_r$. The probability that the particle enters a compartment for the first time, $P_1$ is simply the probability that it is not returning, $P_1 = 1 - P_r$. Return probabilities have been studied extensively in connections with diffusion in crystals.

[52] $P_r$ depends primarily on the coordination number of the crystal lattice. In the context of compartmentalized diffusion the coordination number would correspond to the number of different compartments that each compartment is connected to. For instance, in a lattice of cubic compartments the coordination number is 6 for the 6 faces of the cube through which a particle may enter or exit the compartment. The
return probability varies only weakly with coordination number, \(0.48 > P_r > 0.25\) for coordination numbers from 4 to 12. [52] Truncating the sum in Eq. 2.14 gives,

\[
\overline{s\langle \Delta V \rangle}_i = \frac{s_{vc}}{(\tau_s + 1)} \left(1 - P_R + P_R \frac{\tau_s}{\tau_s + 1}\right)
\]

(2.15)

Substituting Eq. 2.15 into Eqs. 1.24 and 2.6 and normalizing the reaction rate by Smoluchowski’s reaction rate, \(k_0 = 4\pi D_0 R\), we have,

\[
\frac{k}{k_0} = \frac{x}{x \zeta + 1} \left(1 - P_R + P_R \frac{x \zeta}{x \zeta + 1}\right)
\]

(2.16)

The reaction rate depends on only two dimensionless parameters: \(x = DL/D_0 R\), the dominant scaling variable and \(\zeta\), a factor that resolves the proportionality constant in Eq. 2.11 via the limit \(k/k_0 = 1\) when \(D/D_0 = 1\). \(\zeta\) is given by,

\[
\zeta = \frac{1}{2} - \rho + \sqrt{\frac{1}{4} - \rho P_R}
\]

(2.17)

with \(\rho = R/L\). From this equation it can be easily seen that \(\zeta \to 1\) as \(\rho \to 0\) whereby \(x\) becomes the sole parameter governing the diffusion-limited reaction rate. Equation 2.16 is our main result. It generalizes Smoluchowski’s diffusion-limit to heterogeneous environments where compartments produce local confinement. It is applicable to any level of compartment confinement.

### 2.4 Comparison with Brownian Dynamics Simulations

We tested Eq. 2.16 by comparing it with BD simulations of diffusion-limited reaction rate in a three-dimensional cubic lattice of compartments, as described by Powles et al. [53] In the simulations, a single diffusing particle searches a volume containing targets at a density of 1 target per 50 compartments. The simulated reaction rate constant is obtained as the average time required to find a target divided by the target density. We varied the compartment permeability to control the long-time diffusion coefficient, \(D\), and varied the compartment size, \(R/L\). For each set of parameters, the reaction rate was simulated with a range of different time steps. The set of encounter rates vs. time step was then extrapolated to zero time step to explicitly
obtain the encounter rate in the continuum limit. Detailed simulation algorithm and other simulation results are described in Chapter 3.

The simulated reaction rates are shown in Fig. 2.2 as symbols with error bars indicating 95% confidence intervals. In some cases, the error bars are smaller than the symbols. Also shown is the diffusion-limit predicted by the traditional Smoluchowski Eq. (Eq. 1.22, black dashed line). As previously reported, [41] simulated reaction rates exceed the diffusion-limit predicted by the Smoluchowski Eq., indicating that it is not an appropriate upper limit for reaction rates in compartmentalized diffusion. Equation 2.16, as expected, does define an upper limit; none of the simulated rates exceed the limit predicted by Eq. 2.16. The simulated error bars (typical scale ±5%) overlap the predictions of Eq. 2.16 in the two extreme limits, $D/D_0 \rightarrow 0$, and $D/D_0 \rightarrow 1$. In the cross-over regime between these limits, Eq. 2.16 overestimates the
simulated diffusion-limited reaction rates by as much as 18%. This accuracy compares favorably with the Smoluchowski Eq. and is sufficient to be usefully compared with many experimental measurements.

2.5 Discussions

Equation 2.16 is our main result. The parameter, $x$ appearing in Eq. 2.16 is the dominant scaling variable in compartmentalized diffusion-reaction. It can be understood as the ratio of the compartment volume, $v_c = 4\pi L^3/3$ to the volume searched by a freely diffusing particle during the compartment residence time, $k_0 t_{avg}$. If $x > 1$, this indicates that the diffusing particle will search only a small fraction of the compartment’s volume during its stay, i.e., as in three-dimensional Fickian diffusion (Fig. 2.3(a)), the search of volume remains sparse (Fig. 2.3(b)). [54] Hence, the compartmentalized diffusion-limit for sparse exploration remains similar to the diffusion-limit in the absence of compartments.

Importantly, sparse exploration is not synonymous with small changes to the diffusion coefficient; $x$ involves both the diffusion coefficient and the factor $R/L$, so, it is quite possible for $x$ to remain larger than 1 even when the diffusion coefficient is significantly reduced. Consequently, in compartmentalized environments, slow transport does not imply slow reaction rates. This can clearly be seen by Taylor expanding Eq. 2.16 with respect to $D/D_0$ about $D/D_0 = 1$,

$$k \sim 4\pi D_0 R \left(1 - \frac{R}{L} + \frac{R}{L} \frac{D}{D_0}\right); \quad (2.18)$$

the effect of reduced diffusion, $D/D_0$, is multiplied by the small factor, $R/L$. This weaker coupling between transport and reaction rates is qualitatively different from the traditional Smoluchowski diffusion-limit, Eq. 1.22, that predicts reaction rates directly proportional to the translational diffusion coefficient.

When $x < 1$, this indicates that the particle resides in the compartment for a sufficient time to search its entire volume many times over, i.e. the search of the compartment will be complete or compact (Fig. 2.3(c)). [54] In this case, the com-
Fig. 2.3. The searching of volume by a diffusing particle for (A) Free Fickian Diffusion, in (B) sparse exploration of compartments, and (C) compact exploration of compartments. (A) In free Fickian diffusion, the diffusional search is sparse; only a small fraction of the volume in the region traversed by the diffusing particle is searched (represented by the red line). (B) Confinement may cause a diffusing particle to traverse each compartment many times, substantially retarding transport. However, provided that the compartment volume remains sparsely searched, the reaction rate is only weakly affected. (C) If the particle resides in each compartment for sufficient time to compactly search the compartment, then the compartment size becomes an effective reaction radius. For clarity, the cartoons are drawn in two-dimensions but they are meant to depict three-dimensional diffusion.
partment size $L$ can be considered the effective reaction radius on the coarse-grained level where the particle exhibits a random walk between compartments. Taylor expansion of Eq. 2.16 with respect to $D/D_0$ about $D/D_0 = 0$ clearly brings this out,

$$k \sim 4\pi(1 - P_r) DL.$$  \hspace{1cm} (2.19)

The equation has a similar form to Smoluchowski’s Eq. 1.22, except that the reaction radius has been replaced by the compartment size. Since, $L$ may be much greater than $R$, the difference between Eq. 2.19 and Smoluchowski’s Eq. is significant.

### 2.6 Conclusion

Our results suggest that the coupling between diffusion and reaction rates in environments containing obstacles to diffusion is different than it is currently understood to be. Classic [3, 4, 38] and recent [39, 40] theories for the effects of “macromolecular crowding” on reaction rates in biological environments, for instance, assume Smoluchowski’s Eq. These theories therefore predict that the 3-100 fold reduction in translational diffusion coefficients observed in biological environments [10,36,37,40,55–57] implies a 3-100 fold reduction in reaction rates. Our results suggest that the changes in diffusion-limited reaction rates are more modest. Indeed, provided that the local compartments that reactants move in are sufficiently large, there may be very little change in the diffusion-limited reaction rate accompanying the decrease in translational diffusion coefficients (i.e. Eq. 2.18). This may explain why reaction rates recently measured inside biological cells do not follow the predictions of traditional theories for macromolecular crowding. [42] It is also possible that long-range depletion forces increase the reaction radius and compensate for retarded diffusion. [42,58,59]

Our theory does not include hydrodynamic interactions between the walls of the compartment and the diffusing particle. If hydrodynamic interactions were taken into account, diffusion would be attenuated near the compartment walls. This would reduce the average diffusion coefficient within the compartment and cause the search to be sparser along the compartment walls, relative to the compartment center. In
compartmentalized environments where hydrodynamic interactions are present we would still expect confinement to produce a transition from sparse to compact search of compartments, as described by our theory. However, if experiments or simulations involving hydrodynamic interactions were interpreted using our theory, the parameters $D_0$ and $L$ should be understood as phenomenological parameters that would be smaller than their microscopic counterparts.

We also mention that the effects described here are confined to three-dimensional reaction-diffusion and should not be extended to diffusion-limited reactions in two-dimensions (e.g. reactions in membranes [60]) or one-dimension (e.g. reactions occurring along DNA [61, 62]). The reason for this is that our theory hinges on the sparsity of the three-dimensional diffusional search. One- and two-dimensional diffusion limited reactions are not sparse, even in free Fickian diffusion. [54]
3. DIFFUSION-LIMITED ENCOUNTER RATE IN A THREE-DIMENSIONAL LATTICE OF CONNECTED COMPARTMENTS STUDIED BY BROWNIAN DYNAMICS SIMULATIONS

3.1 Abstract

We considered the rate at which a diffusing particle encounters a target in a three-dimensional lattice of compartments with semi-permeable walls. This chapter expands our previous theory (described in Chapter 2 and Ref. [63]) for the encounter rate in the dilute limit of targets to the general case of any density of targets. We also used Brownian dynamics (BD) simulations to evaluate the approximations in the analytical theory. We find that the largest errors in the analytical theory are on the order of 10%. This chapter demonstrates an analytical theory capable of describing the encounter rates in compartmentalized environments for any level of confinement and any target density.

3.2 Introduction

In many cases of practical interest, diffusion occurs through a liquid phase containing a field of less mobile obstacles. The most straightforward examples include porous catalysts [64] and rocks [65] but a similar physical picture also applies to diffusion in some biological environments. [3,4,38] Key features of all of these systems are a strong attenuation of the diffusion coefficient when the size of a diffusing particle approaches the pore size [6–8,10] and a variable diffusion coefficient at length-scales less than the pore size. [6–8,10–20] This latter property—the decrease in diffusion coefficient with increasing length—is often referred to as “anomalous sub-diffusion”. [66,67]
Theories for transport in porous materials are relatively well developed. One of the simplest models capable of describing the local confinement present in porous materials involves a periodic lattice of semipermeable barriers that retard, but do not forbid, the passage of a diffusing particle. [53] We favor this particular underlying model because it isolates the physical effect of local confinement from other factors such as the detailed physical interactions between the diffusing particle and the obstacles. For a lattice of semipermeable compartments, it is possible to obtain a simple analytical expression relating the microscopic properties of the compartments to diffusion at large length scales. [63]

While transport in compartmentalized environments is relatively well studied, the effects of confinement on diffusion-limited encounter rates are less well developed. Klann at el. found that the diffusion-limited reactions sense an intermediate diffusion coefficient between the unrestricted diffusion coefficient in a free environment and the attenuated diffusion coefficient at length scales larger than the pore size. [41] Guigas et al. showed by simulations that anomalous sub-diffusion increases the probability of of two nearby reactants encountering one another. [68] Haugh compared two different models of anomalous sub-diffusion and found that there are only subtle differences between the two models. [44]

In Chapter 2, we obtained an analytical expression for the diffusion-limited encounter rate in compartmentalized environments. [63] We used the “Wiener sausage” approach [49, 50] to find the volume of space contacted by a particle undergoing anomalous sub-diffusion in an environment containing compartments. The Wiener sausage volume refers to the volume of space contacted by a sphere whose time dependent position is a Wiener process, i.e. a continuous time random walk. Each time the Wiener sausage volume increases by the average volume containing one reactant, the diffusing particle encounters, on average, one reactant. Hence, the rate of increase of the Wiener sausage volume is the diffusion-limited encounter rate.

In this chapter, we describe the diffusion-limited encounter rate in a three-dimensional system of connect compartments. We generalize our previous theory on diffusion-
limited encounter rates in the dilute limit of targets (described in Chapter 2) to any density of targets. We also use Brownian dynamics (BD) simulation to check the approximations made in the analytical theory. We find that the deviations do not strongly affect the average rates predicted by our theory. This chapter shows that the analytical theory presented is applicable to any scale of confinement and any density of targets.

3.3 Problem Statement

We characterize the average time required for a single Brownian particle diffusing in an infinite cubic lattice of compartments to encounter a target (Fig 3.1). The walls of each compartment are semipermeable and impede movement of the particle between compartments. Targets are randomly distributed with number density $n$ per compartment. An encounter occurs when the separation between the Brownian particle and a target is less than a distance $R$, termed the “reaction radius” or “capture radius”.

Diffusion within a compartment is characterized by diffusion coefficient $D_0$. The compartment has size $a$ and permeability of the walls $\mathcal{P}$. $\mathcal{P}$ quantifies the difficulty with which the diffusing particle crosses a compartment wall. Infinite permeability is equivalent to no compartments and zero permeability means that the particle cannot pass a compartment wall. The diffusion coefficient observed at scales much larger than $a$ is given by, [53]

$$D = \left(1 + (\mathcal{P}a)^{-1}\right)^{-1}. \tag{3.1}$$

Hence, once the compartment size $a$ has been determined, either $D$ or $\mathcal{P}$ can be chosen to describe the level of confinement. We use $D$ because it is typically the more experimentally accessible parameter.

This problem contains one arbitrary length and one arbitrary time scale. We remove these two parameters by non-dimensionalizing all other quantities by a com-
Fig. 3.1. We characterize the average time required for a Brownian particle (red) diffusing in an infinite three-dimensional cubic lattice of semi-permeable compartments to encounter a target (blue). For clarity, the cartoon shows only four compartments but it is meant to depict an infinite three-dimensional lattice.
mon length and/or time scale. Throughout, we use the Latin alphabet for dimensional quantities and Greek letters to denote non-dimensionalized quantities.

All lengths are defined relative to the characteristic radius of compartment, \( L \). \( L \) is defined as the radius of a sphere with same volume as the compartment with size \( a \), \( L = \left( \frac{3}{4\pi} \right)^{\frac{1}{3}} a \). All times are relative to the transit time across a compartment \( t_0 = L^2/D_0 \). In this reduced form there are three parameters that completely specify the system: the relative reaction radius \( \rho = R/L \), the relative diffusion coefficient \( \delta = D/D_0 \), and the target density \( n \).

To obtain predictions for a particular reaction, our results need only be scaled by these quantities. For instance, \( \beta \)-enolase has a hydrodynamic radius of about 4 nm and diffusion coefficient in buffer \( D_0 = 56 \mu m^2 s^{-1} \). The diffusion coefficient in the cytosol of muscle cells is reduced to \( D = 13.5 \mu m^2 s^{-1} \). [69] Assume that the muscle cell has characteristic radius of \( L = 25 \text{ nm} \) (the typical values for the intracellular environment are \( L = 10 - 50 \text{ nm} \) [10, 36, 37, 40, 55–57]). In Fig. 3.5, the simulation result shows that for \( \delta = 0.2 \) (red curve), the relative reaction rate is \( \sim 1.2 \) at a target density \( n = 0.5 \) per compartment. This concentration of targets corresponds to \( C = n/N_A v_c = 0.025 \text{ M} \), where \( N_A \) is the Avogadro constant and \( v_c = 4/3\pi L^3 \) is the volume of the compartment. With \( t_0 = 6.7 \mu s \), the reaction rate constant needs to be scaled by \( n/(Ct_0) = 3 \times 10^6 \text{ s}^{-1} \text{ M}^{-1} \), resulting a predicted reaction rate constant of \( 3.6 \times 10^6 \text{ s}^{-1} \text{ M}^{-1} \).

### 3.4 Analytical Theory

#### 3.4.1 Dilute Limit of Targets

This section is a brief recapitulation of the analytical theory for the encounter rate in the dilute limit of targets from Ref. [63]. Only the key assumptions in the analytical theory are highlighted below as they will be tested in this chapter using BD simulations. For a complete derivation of the results in this Section, please refer to Ref. [63].
The encounter rate constant in the dilute limit is,
\[ k = \lim_{t \to \infty} \frac{V(t)}{t}, \tag{3.2} \]
where \( V(t) \) is the Wiener sausage volume. The average rate of increase of the Wiener sausage volume, \( \frac{V(t)}{t} \), can be obtained as the product of the rate of moving between compartments, \( s = 3D/L^2 \), and the average increase in Wiener sausage volume for an isolated compartment. We denote the Wiener sausage volume in an isolated compartment as \( v(t) \). In order to calculate an average value, we assume that the compartment residence times, \( \Delta t \), follow an exponential distribution,
\[ p(\Delta t) \sim se^{-s\Delta t}. \tag{3.3} \]
We also assume that the Wiener sausage volume in an isolated compartment follows an exponential rise to the full search of the compartment volume,
\[ v(\Delta t) \sim v_c \left(1 - e^{-\Delta t/\tau}\right), \tag{3.4} \]
where \( v_c \) is the compartment volume. The approximations in Eq. 3.3 and Eq. 3.4 are evaluated in Sections 3.6.1 and 3.6.1, respectively. Under these assumptions, an analytical solution to Eq. 3.2 is, \cite{63}
\[ \frac{k}{k_0} = \frac{x}{x\zeta + 1} \left(1 - P_R + P_R \frac{x\zeta}{x\zeta + 1}\right), \tag{3.5} \]
where \( k \) is the encounter rate in the dilute limit, and \( P_R \) is the probability of a particle returning to a compartment. \cite{52} Eq. 3.5 depends on two dimensionless parameters: \( x = DL/D_0R \), the dominant scaling variable and \( \zeta \) given by,
\[ \zeta = \frac{1}{2} - \rho + \sqrt{\frac{1}{4} - \rho P_R}. \tag{3.6} \]
\( \zeta \to 1 \) as \( \rho \to 0 \), whereby \( x \) becomes the sole parameter governing the diffusion-limited encounter rates.
3.4.2 Limit of Many Targets

In the dilute limit of targets, the diffusing particle needs to cross a compartment wall in order to encounter a target. As the density of targets increases, it becomes increasingly likely that the diffusing particle will start off in a compartment that contains at least one target. Since confinement tends to restrict the diffusing particle to the compartment, it is possible that the particle encounters one of these targets without ever crossing a compartment wall. This leads to different reaction kinetics than in the dilute limit.

In the extreme limit of many targets per compartment, the diffusing particle almost certainly encounters a target without ever crossing the compartment wall. In this case, a compartment behaves as an isolated reaction vessel. Diffusion occurs only within the compartment with diffusion coefficient $D_0$, the encounter rate is $k_0 = 4\pi D_0 R$, and the average time to the first encounter is $\tau_s = 1/ik_0$, where $i$ is the number of targets initially present in the compartment. To determine the average encounter time in this limit, we enumerate all of the different possible starting configurations and calculate the appropriate expectation value for $\tau_s$, the time for a purely intra-compartmental encounter. We use the subscript $s$ to denote the short time process without crossing a compartment barrier.

Let $P(i)$ be the probability that, in an environment with average density $n$ targets, there are $i$ targets initially present in a compartment. This probability is given by the Poisson distribution,

$$P(i) = \frac{n^i}{i!} e^{-n}. \quad (3.7)$$

$P(s \mid i)$ is the conditional probability that an encounter occurs inside a compartment given that there are initially $i$ targets present. We can again construct this probability from sampling statistics.

For a target that occupies volume $R^3$, the compartment contains $N = L^3/R^3$ volume elements that could contain a target. It takes a time $R^2/3D_0$ to move a distance $R$. So, within the average time the particle remains in the compartment,
\( \frac{L^2}{3D}, \) the particle will move between volume elements \( M = R^2 D / L^2 D_0 \) times. The probability of finding one of the \( i \) targets from \( N \) volume elements after \( M \) attempts is,

\[
P(s \mid i) = 1 - \left( \frac{N - i}{N} \right)^M
\]  
(3.8)

It is simple to show that \( M/N = x \) and in the limit of \( N \to \infty \),

\[
P(s \mid i) \sim 1 - e^{-i/x}.
\]  
(3.9)

The expectation value of the encounter time for the short processes is given by,

\[
\langle \tau_s \rangle = \sum_{i=0}^{\infty} P(s \mid i) P(i) \tau_s(i).
\]  
(3.10)

### 3.4.3 Intermediate Density of Targets

For an intermediate density of targets, an encounter may occur through a short process where the particle encounters a target present in its initial compartment. Or, an encounter may occur through a long process whereby the particle needs to cross a compartment wall. We assume that the average encounter time for the intermediate density of targets is the weighted sum of the long processes and the short processes averaged over all possible starting configurations.

\[
\langle \tau \rangle = \sum_{i=0}^{\infty} P(i) \left( P(s \mid i) \tau_s(i) + (1 - P(s \mid i)) \tau_l \right).
\]  
(3.11)

\( \tau_l = 1/nk \) is the time for the long process and \( \tau_s = 1/ik_0 \) is the time for the short process. Inserting and rearranging, we have

\[
\frac{\langle \tau \rangle}{\tau_l} = 1 + \sum_{i=0}^{\infty} P(i) P(s \mid i) \left( \frac{nk}{ik_0} - 1 \right).
\]  
(3.12)

For \( n \ll 1 \), the probability of having more than 1 target in a compartment is small. In this case, the summation can be truncated after \( i = 1 \). Additionally, \( P(1) \) can be approximated as \( n \), giving

\[
\frac{\langle \tau \rangle}{\tau_l} \sim 1 - n(1 - e^{-1/x}).
\]  
(3.13)
This equation expresses the fact that for a compartmentalized environment with $x < 1$, the average encounter rate acquires a dependence on target density that is not present in the absence of confinement.

3.5 Brownian Dynamics (BD) Simulation

3.5.1 BD for Free Diffusion

BD simulations numerically integrate a stochastic differential equation forward in time to create trajectories of Brownian particles. For free diffusion without inertia, the time-stepping equation for a Brownian particle between $\tau$ and $\tau + \Delta \tau$ in a three-dimensional space is given by

$$\vec{\chi}(\tau + \Delta \tau) = \vec{\chi}(\tau) + \sqrt{2\Delta \tau} \vec{\xi}.$$  

(3.14)

Each component of $\vec{\xi}$ is a Gaussian random variable with $\langle \xi(t) \rangle = 0$ and $\langle \xi(t_1)\xi(t_2) \rangle = \delta(t_1 - t_2)$. Both $\vec{\chi}$ and $\Delta \tau$ are dimensionless quantities as defined previously.

3.5.2 BD in Cubic Lattice of Compartments

In the compartment interior, the particle diffuses using BD identical to free diffusion. However, if the particle attempts to cross a compartment wall, the step is subject to reflection about the plane defined by the compartment wall with a probability $P_b$. The probability $P_b$ is the direct indication of the compartment permeability, and is calculated according to Eq. 8.4 in Ref. [53] as

$$P_b = \frac{1 + \mathcal{P}\lambda}{1 + 2\mathcal{P}\lambda},$$  

(3.15)

where $\lambda = \pi \sqrt{\Delta \tau}/4$ is the mean step size for the Gaussian random steps.

3.5.3 Encounter Rate

Each simulation is initiated by creating a field of randomly distributed targets and a single randomly placed particle. The particle diffuses with time step $\Delta \tau$ until
Fig. 3.2. Extrapolating discrete time Brownian Dynamics simulations to the continuum limit. Mean encounter times are obtained at 5 different values of the simulation time step (black squares). The values are then fitted to all possible over-determined non decreasing polynomials to obtain intercepts at $\Delta \tau = 0$. This process is repeated by iteratively removing the largest time step until only the two smallest time steps remained in the extrapolation. The mean encounter time at the continuum limit is then the mean of all extrapolations and the associated uncertainty are the union of the uncertainties of all extrapolations. This mean value and its uncertainty are plotted as the black dot with error bar slightly offset from 0 for clarity. The extrapolation polynomials are plotted as blues lines (order 0), red lines (order 1), cyan lines (order 2), magenta lines (order 3).

it encounters a target. The time required to encounter a target $\tau_i$ is one realization of the diffusion-limited encounter time. This procedure is repeated for at least 4000 times to obtain a mean encounter time, $\langle \tau \rangle$.

3.5.4 Extrapolations

The mean time required for a particle to encounter a target, $\langle \tau \rangle$, simulated by Brownian dynamics, has a prominent dependence on the simulation time step $\Delta \tau$. [70] To recover a continuum limit, we conducted simulations with five different time steps and then extrapolated the finite steps to $\Delta \tau = 0$ (shown in Fig. 3.2). The
extrapolation method is modified from the algorithm originally described by Ottinger. [71] We fitted $\langle \tau \rangle$ vs. $\sqrt{\Delta \tau}$ to all possible over-determined non decreasing polynomial and accepted all statistically reasonable fits. The encounter time at the continuum limit was then the mean of all accepted extrapolations and the associated uncertainty was the union of the uncertainties of all accepted extrapolations. Taking the union of all uncertainties results is a conservative estimate for the uncertainty in our simulated encounter times.

Mean diffusion-limited encounter times, $\langle \tau \rangle$ at different values of the simulation time step $\Delta \tau$ are plotted in Fig. 3.2 as black squares with error bars representing standard error of the mean. Each point is the mean of at least 4000 independent simulations. To obtain the continuum limit, we fitted $\langle \tau \rangle$ vs. $\sqrt{\Delta \tau}$ to all possible over-determined non decreasing polynomials (e.g. for 5 points, polynomials of order 3 and below), as described by Ottinger. [71] Any fit with a chi-squared probability value greater than 0.1 was accepted. [72] We then remove the simulation with largest $\Delta \tau$ from the series and repeat the fitting (with maximum polynomial order reduced by 1). This process is repeated until only the simulations with the two smallest $\Delta \tau$ remain. The accept fits are plotted for polynomials of order zero (dark blue lines), one (red lines), two (cyan lines), and three (magenta lines). The extrapolations to $\Delta \tau = 0$ are simply the zero-order terms in each fitted polynomial (symbols at $\Delta \tau = 0$). The uncertainties are the square roots of the zero order terms in each covariance matrix (error bars at $\Delta \tau = 0$).

The aggregate mean for all extrapolations (black dot, slightly offset from $\Delta \tau = 0$ for clarity) and the 95% confidence interval of the aggregate probability density (bold black error bar) define the continuum limit of the average encounter time and associated uncertainty. Because the 95% confidence interval is sensitive to the tails of the distribution, this procedure produces error bars that are essentially the union of the uncertainties of all extrapolations. These fits essentially represent all statistically reasonable description of the relationship between $\langle \tau \rangle$ and $\Delta \tau$. This procedure is used to extrapolate each encounter rate in all related calculations.
The example shown here is for a density of one target per 50 compartments, \( \rho = 0.16 \), and \( \delta = 1 \). Because \( \delta = 1 \) represents no confinement, we expect the continuum limit of these simulations to be equal to the Smoluchowski diffusion limit, \( 50/(4\pi \times 0.1) \sim 39.79 \).

### 3.5.5 Exit Time in an Isolated sphere

In developing the theory for dilute limit of targets, we assume that the distribution of the exit time in an isolated sphere is similar to the exponential distribution, as specified by Eq. 3.3. We examined the probability distribution of the exit time in an isolated sphere using BD simulations and compared the results with Eq. 3.3.

In order to calculate an exit time, the diffusing particle starts off at a random location and diffuses inside the sphere using BD. We define that the particle has exited the compartment when the distance between the center of the particle and the center of the sphere is larger than the characteristic radius \( L \). The distribution of the exit time was calculated from at least \( 10^4 \) samples.

### 3.5.6 Wiener Sausage Volume

The analytical theory for the dilute limit of targets was derived under the assumption that the Wiener sausage volume in an isolated compartment \( v(\Delta t) \) grows as specified by Eq. 3.4. To our knowledge, there is no analytical theory for the Wiener sausage volume in a finite domain. Thus we carried out a BD simulation to check this assumption.

A random trajectory of the diffusing particle was first generated up to time \( \tau \) using BD, \( \tilde{x}(\tau) \). The Wiener sausage volume is the volume of space that is within a distance \( \rho \) of any point in \( \tilde{x}(\tau) \),

\[
v(t) = \int I(\tilde{x}(t), \tilde{x}(t)) d\tilde{x}^3,
\]

(3.16)
where $I$ is the indicator function defined as

$$I(\chi(t), \tilde{\chi}(t)) = \begin{cases} 1, & \text{if } |\chi(t) - \tilde{\chi}(t)| \leq R \\ 0, & \text{otherwise.} \end{cases}$$

We evaluated this integral using Monte Carlo integration. Twenty independent trajectories were then generated and the Wiener sausage volume were averaged.

### 3.5.7 Computations

The BD simulations were run on 200 cores in parallel on BoilerGrid, a distributed computing system running HTCondor operated by Rosen Center for Advanced Computing at Purdue University over a period of several months.

### 3.6 Results

#### 3.6.1 Properties of Isolated Compartment

Two properties of a compartment that influence the rate of increase in the Wiener sausage volume in the dilute limit are (1) the average time that a diffusing particle spends in a compartment before exiting and (2) the average increase in Wiener sausage volume during its residence (see Eq. 3.2). In order to obtain an analytical solution, we approximated the distribution of exit times with Eq. 3.3, and we approximate the increase in Wiener sausage volume with Eq. 3.4. In the next two sections, we evaluated these two approximations with BD simulations.

#### Probability Density of the Exit Time

In developing the theory of encounter rates for the dilute limit of targets, one assumption made is that the distribution of exit times is similar to an exponential distribution (specified by Eq. 3.3). We numerically calculated exit times using BD
Fig. 3.3. The probability density distribution of the exit time in an isolated spherical compartment. The probability density calculated using Brownian Dynamics simulation (black circles) is plotted together with the probability density $se^{-\delta \Delta t}$ (red curves). Simulations were conducted with three relative diffusion coefficients, $\delta = 0.01$, $\delta = 0.2$ and $\delta = 1$, respectively.
simulations and compared the simulated distribution to the exponential distribution, Eq. 3.3.

The exit time is defined as the time required for a particle placed randomly within a compartment to pass through the compartment wall. Exit times were simulated with three different levels of confinement specified by three relative diffusion coefficients, \( \delta = 0.01, \delta = 0.2 \) and \( \delta = 1 \), respectively. Each of the probability densities were calculated from at least \( 10^4 \) samples. The simulated probability densities are plotted as black circles in Fig. 3.3. The exponential function specified by Eq. 3.3 is plotted as red curves alongside for comparison.

With very strong confinement \( (\delta = 0.01) \), the most probable exit time is small compared to the average exit time. For this case, the probability distribution resembles the exponential distribution specified by Eq. 3.3 where the most probable exit time is 0 (in Fig. 3.3(a), the black circles match the red curve). As the confinement weakens \( (\delta = 0.1 \) and \( \delta = 1 \)\), the average exit time becomes smaller and it can be seen that the most probable exit times in the BD simulations are non-zero. This simply reflects the fact that a randomly placed particle requires a finite time to diffuse to a compartment wall. For these highly permeable cases, the exit time distribution deviates from the exponential distribution. \( \delta = 1 \) is the limit of a completely permeable compartment so Fig. 3.3(c) represents the largest possible difference between the actual exit time distribution and the exponential distribution.

At \( \delta = 1 \), although the shape of the the simulated distribution deviates from the exponential distribution, the simulated distribution has a similar first moment to the exponential distribution (the mean of the exponential distribution is 0.33 and the mean of the simulated exit times is 0.28). In the analytical theory, we used the exit time probability density to calculate the expectation value of the Wiener sausage volume, \( v(\Delta t) = v_0(1 - e^{-\Delta t/\tau_c}) \) (Eq. 3.4). \( \Delta t \) has an average value of \( \langle \Delta t \rangle = 1/s = L^2/3D \), whereas \( \tau_c = L^3/3D_0R \). Because \( \Delta t \) is smaller than \( \tau_c \), \( \langle \Delta t \rangle / \tau_c \sim R/L \ll 1 \),
we can approximate $v(\Delta t)$ over the non-zero part of the probability density for $\Delta t$ by the first order term of its Taylor expansion about $\Delta t = 0$,

$$v(\Delta t) = v_0(1 - e^{-\Delta t/\tau_c}) \sim \frac{v_0}{\tau_c} \Delta t$$  \hspace{1cm} (3.17)$$

Because $v(\Delta t)$ is linear with respect to $\Delta t$, any probability density with the correct first moment will give the same expectation value for $v(\Delta t)$,

$$\langle v \rangle = \int \rho(\Delta t) v(\Delta t) d\Delta t$$  \hspace{1cm} (3.18)$$

$$\sim \frac{v_0}{\tau_c} \int \rho(\Delta t) d\Delta t$$  \hspace{1cm} (3.19)$$

$$\sim \frac{v_0}{\tau_c} \langle \Delta t \rangle$$  \hspace{1cm} (3.20)$$

Hence, even for $\delta = 1$, where the probability density function differs from the exponential, the expectation value calculated with respect to the exponential will be similar to its actual expectation value.

**Wiener Sausage Volume**

The analytical theory for the encounter rate in the dilute limit described in section 3.4.1 is based on the assumption that the Wiener sausage volume in an isolated
compartment \( v(\Delta t) \) evolves in time as described by Eq. 3.4. We used BD simulations to check this assumption. At time 0, a particle with size \( \rho \) was placed randomly inside a spherical compartment of unit radius. The Wiener sausage volume for the diffusing particle was calculated using Monte Carlo integration.

The numerical results are shown in Fig. 3.4 with Wiener sausage volume, \( v(t) \) normalized by the compartment volume, \( v_c \). The simulation time is normalized by the time constant, \( \tau_c \) in Eq. 3.4. Simulations were obtained with two different relative reaction radii, \( \rho = 0.16 \) (black squares) and \( \rho = 0.5 \) (red dots). The exponential increase assumed by Eq. 3.4 is plotted as the blue dashed line for comparison.

For \( \rho = 0.16 \), the initial increase in the Wiener sausage volume is indistinguishable from Eq. 3.4 (in Fig. 3.4, black squares overlap the blue line for \( \tau/\tau_c < 1 \)). As time increases, Eq. 3.4 approaches a limiting value of \( v/v_c = 1 \) exponentially. Around \( \tau/\tau_c \approx 1 \), the simulations begin to deviate below Eq. 3.4 and approaches the limiting value of \( v/v_c = 1 \) more slowly. The slower approach to the limiting value in the simulations is due to an excluded volume effect; the probability for a particle to touch a region of space is lower near the boundary of the compartment, as compared to the compartment interior. As \( \tau/\tau_c \) becomes large, nearly all of the space in the sphere that is not yet in the Wiener sausage volume is adjacent to the walls of the sphere. A particle can only touch a region of space adjacent to the boundary tangentially, whereas a point in the compartment interior can be contacted by any point within the particle. The improbability of precisely placing the particle in tangential contact with the boundary of the compartment causes the limiting approach to complete search of the compartments to be slower in the BD simulations than predicted by Eq. 3.4.

For \( \rho = 0.5 \), the simulated Wiener sausage volume initially increases more rapidly than predicted by Eq. 3.4 (in Fig. 3.4, the red dots are above blue line for \( \tau/\tau_c < 1 \)). The rapid increase in the Wiener sausage volume observed in the simulations is caused by the initial placement of a particle into a completely unexplored compartment. Thus, at \( \tau/\tau_c = 0 \) the Wiener sausage volume increased discontinuously by \( v/v_c = \rho^3 \). This discontinuity is not captured by Eq. 3.4. At longer times, the simulated Wiener
Fig. 3.5. The normalized average encounter time as a function of target density. The average encounter time \( \langle k \rangle \) combining both short and long processes is normalized by the encounter time in dilute limit. The blue, red and black dots are the Brownian Dynamic simulation data for \( \delta = 0.05 \), \( \delta = 0.2 \) and \( \delta = 1 \), respectively, while the reaction radii remain constant at \( \rho = 0.16 \). The dash lines are the predictions from Eq. 3.12 and the solid lines are predictions from Eq. 3.13.

The sausage volume makes a slower approach to the limiting value of \( v/v_c = 1 \) than predicted by Eq. 3.4 (red dots below blue line at \( \tau/\tau_c > 2 \)). This is caused by the same excluded volume effect as described above for \( \rho = 0.16 \).

A compartment must be larger than the particle it contains. Consequently, \( \rho = 0.5 \) represents an extreme case. Yet, even for \( \rho = 0.5 \), the time dependence for the Wiener sausage volume is approximately described by Eq. 3.4; namely, the time constant \( \tau_c \) captures the scale over which the Wiener sausage volume changes by a factor \( e^{-1} \). In Fig. 3.4, \( v/v_c = e^{-1} \) at \( \tau/\tau_c \sim 0.7 \) for red dots, i.e. similar to the predicted \( \tau/\tau_c = 1 \). For \( \rho < 0.5 \), the discontinuous increase in initial volume and the excluded volume at the boundary will be smaller and the increase in the Wiener sausage volume will more closely match the exponential, Eq. 3.4.
3.6.2 Effect of Finite Target Density

When many targets are present, it is possible that the particle encounters a target within its initial compartment without ever crossing a compartment wall. This leads to different encounter time than in the dilute limit. In section 3.4.3, we expanded the previous theory developed in the dilute limit of targets \[63\] to the case of finite density of targets. Here, we use BD simulations to check the analytical theory.

Simulated encounter rates as a function of number density of targets per compartment \(n\) are shown in Fig. 3.5 as symbols. The solid lines are predictions from Eq. 3.12, and the dashed lines are predictions from Eq. 3.13. The expected encounter times are normalized by the encounter time \(\tau\) at \(n = 1/50\), which approximates the infinitely dilute limit. Simulations were performed at \(\delta = 0.05\) (blue dots), \(\delta = 0.2\) (red dots) and \(\delta = 1\) (black dots), while keeping the relative reaction radius constant at \(\rho = 0.16\).

For all three different levels of confinement \((\delta = 1, \delta = 0.2\) and \(\delta = 0.05\)), there is no significant difference between the simulated encounter time and the predictions from Eq. 3.12 (in Fig. 3.5, all three solid curves can describe simulated data). The largest discrepancy, \(\sim 10\%\), occurs at \(n = 1, \delta = 0.2\). The simplified expression Eq. 3.13 is accurate for \(n < 0.2\) (dash lines). For \(n > 0.2\), Eq. 3.13 underestimates the encounter time. This deviation is caused by making the simplification that the time scale for the short process is sufficiently small to be considered 0.

3.7 Discussion

We considered the rate at which a diffusing particle encounters a target in a three-dimensional lattice of compartments with semi-permeable walls. Expanding on a previous theory that gave an analytical expression for the encounter rate in the dilute limit of targets, we have developed a theory that can now describe any density of targets (i.e. Eq. 3.12). The largest discrepancy between our theory and the BD simulations is \(\sim 10\%\). We have also used BD simulations to probe the most
difficult limits of parameter space for the approximations in the analytical theory and found that, where deviations exist (i.e. Fig. 3.3(c)), they do not strongly affect the average rates predicted by our theory. This chapter demonstrates an analytical theory capable of describing the diffusion-limit for encounter rates in compartmentalized environments for any value of the compartment confinement and any target density.

The compartmentalized environment that we consider is perhaps the simplest physical system that exhibits a length-scale dependent diffusion coefficient; within a compartment, a rapid, unencumbered diffusion predominates, whereas, diffusion between compartments is slower due to the impediments imposed by a compartment wall. This “anomalous sub-diffusion” is characteristic of diffusion in, for instance, biological environments where local diffusion is similar to diffusion in water [14,33–35,57] but translational diffusion over distances > 100 nm is 3-100 fold slower than diffusion in water. [6–8, 10–20] Because anomalous sub-diffusion is common to many real environments, we expect our analytical results to provide more appropriate predictions of diffusion-limited encounter rates than the classic Smoluchowski diffusion limit.

The theory that we described here makes a number of predictions that can be observed in experiments and that are qualitatively different from the traditional Smoluchowski diffusion-limit, \( k = 4\pi DR \). Namely, Smoluchowski’s Eq. predicts that the encounter rate is proportional to the diffusion-coefficient. In compartmentalized environments, the coupling between the encounter rate and the diffusion coefficient can be much weaker. Indeed, whenever \( x > 1 \), i.e. \( D/D_0 > R/L \) we expect that the encounter rate will be weakly affected by decreases in the diffusion coefficient. This may explain why reaction rates recently measured inside living cells were similar to those measured in vitro, despite an expected 5-fold decrease in the diffusion coefficient. [42]

A yet stronger signature of the effects described here would be the dependence of the relative encounter rate, \( k/k_0 \) on a single dominant scaling variable, \( x = DL/D_0R \). Thus, for any compartmentalized environment—with any values of the parameters \( D, D_0, L, \) and, \( R \)—we expect the relative encounter rate not to depend on the parameters individually but solely through their combination in the dimensionless number \( x \). It
may be possible to systematically test this prediction by engineering, for example, porous structures or gels with different pore sizes and checking whether $k/k_0$ vs. $x$ describes a single universal curve, as described by Eq. 3.5. Alternately, as more biological reactions are studied in vivo, we expect the reaction rate constants will fall on the single universal curve described by Eq. 3.5.

An additional signature of confinement is the change in the encounter rate “constant” as the target density approaches one target per compartment (section 3.4.3). In this regime, the average encounter time decreases relative to the encounter time for the dilute limit (see Eq. 3.12 and Fig. 3.5). This effect is caused by the high probability for an encounter to occur whenever a reaction is initiated with a diffusing particle and a target within the same compartment. This dependence of the encounter rate constant on target density is a clear indication of the role of confinement on the encounter rate. The change in the encounter time is again governed solely by the dimensionless variable $x$, according to Eq. 3.13. Hence, a measured change in reaction rate at $n \geq 1$ for $x < 1$ would be a clear signature of the role of the confinement.

Our theory has only focused on how local confinement affects diffusion-limited encounter rates. We have not included a number of other potentially important effects including hydrodynamic interactions between the diffusing particle and the compartment walls and variability in compartment properties. Consideration of the interplay of all these effects is a subject for future work.

3.8 Conclusion

In this chapter, we describe the rate at which a diffusing particle encounters a randomly placed target in a three-dimensional system of connected compartments with semi-permeable walls. This work expands our previous theory for the encounter rate in the dilute limit of targets to the general case of any density of targets. We also used BD simulations to numerically check approximations needed in order to obtain analytical solutions. For highly permeable compartments, the exponential distribution
of residence times assumed by our theory is violated. However, the average rate depends primarily on the first moment of the distribution which is accurately described by the exponential distribution. This chapter demonstrates an analytical theory that is capable of describing the encounter rates in compartmentalized environments for any level of confinement and any target density.
4. SUMMARY AND FUTURE WORK

In the first part (Chapter 1-4) of this dissertation, I described a theory for the diffusional encounters in the heterogeneous environment. In Chapter 2, we obtained a simple analytical expression for the encounter rates in the dilute limit of targets. The analytical predictions are compared with the Brownian Dynamics (BD) simulations in the network of connected compartments. The simulation results show that our theory provides a more appropriate upper bound in the heterogeneous environment than the classic Smoluchowski equation. In Chapter 3, we numerically checked the two key assumptions made in the theory for infinitely dilute targets. We also obtained a simple analytical expression that extends the reaction rates in the dilute limit to the case of finite target density. With the two analytical expressions combined, the reaction rates can be predicted for an arbitrary density of targets. Our analytical theory has been numerically tested.

The future work may involve the experimental measurements of the reaction rates in cells and tissues, to test our theory experimentally. The parameters in the theory are: the diffusion coefficient in homogeneous environment, $D_0$, the diffusion coefficient in the heterogeneous environment, $D$, the reaction radius, $R$ and the characteristic radius of the heterogeneous environment, $L$. $D_0$ and $R$ can be easily measured in the buffers. $D$ in the cells and tissues are experimentally accessible using techniques including fluorescence recovery after photobleach (FRAP) and fluorescence correlation spectroscopy (FCS). $L$ is not directly measurable in the cells, but can be inferred from the sieving observed in intracellular diffusion. In order to measure the reaction rates in biological environments, the reaction needs to be rapidly initiated and then the concentration of reactants and products are measured as a function of time. Optical methods prove convenient for accomplishing both of the tasks. For instance, the reaction can be initiated by “uncaging” a co-factor for a reaction using a brief
exposure to UV light. The concentration of products will then be monitored using Frester Resonant Energy Transfer (FRET) technique.

Another way to test our theory may involve measuring the reaction rates in a known porous structures, like porous glass. This has the advantage that $L$ is known and can be controlled by varying the pore size.
5. INTRODUCTION TO MULTIVALENT ION SCREENING

5.1 Motivations and Applications

Ions present in solution strongly modify the electrical properties of charged surfaces, reducing and sometimes even reversing the direction of the local electric field. While the monovalent ion screening can be well described by the classical theories, the multivalent ions can exhibit phenomena not seen with monovalent ions including: inversion of surface charge, [73–76] reentrant condensation of charged colloids and molecules, [77–79] and inducing attraction between like-charged molecules. [80–82]. Without the knowledge of how the multivalent ions screen charged surfaces, it would not be possible even to know the sign of the electrical potential on the charged surfaces.

The multivalent ion screening has important implications in many applications. For example, many important biological macromolecules such DNA are heavily charged, thus ion screening strongly affects the thermodynamic and transport properties of these macromolecules. [81,83] In colloid science, ions induce repulsions or attractions between the colloids thus determines the stability of the colloidal suspension. [73,74] In micro- and nano- fluidic devices, ion screening affects the electroosmotic flow, thus can be used as a way to manipulate fluids in these devices. For example, a well-patterned charge surface can induce a spiral electroosmotic flow thus can be used as a local mixing station for multiple Laminar flows. [84,85]
5.2 Monovalent Ion Screening of Charged Interface

5.2.1 The Electrical Double Layer Model: The Gouy-Chapman Theory

The electrical double layer model describes the structure of ion distribution at the liquid-solid interface. The first layer consists of ions that are relatively firmly bound to the solid phase, due to the ionization or adsorption process on the surface. Glass, for example, is negatively charged when in contact with water, due to the ionization of silanol group: \( \text{SiOH} \overset{\text{\textbullet}}{\rightarrow} \text{SiO}^- + \text{H}^+ \). At the equilibrium, this layer of charges has a fixed surface charge density. This first layer of charges attract ions with opposite sign (counter-ions) in the liquid phase to the region near the charged surface and repel ions with the same sign (co-ions) into the bulk. Therefore, there exists a second layer near the charged surface which contains higher concentration of counterions and lower concentration of co-ions compared to the bulk. The earliest theoretical study of the behavior of the second layer were made by Helmholtz and Perrin over a century ago. According to their theory, the second layer is a flat condenser, as it were, one plate of counter-ions in a liquid at a very small distance way from the first plate. [86]

This theory was later considered to be unrealistic, especially in the treatment of the electric charge in solution, since the co-ions are not completely excluded from the interface. [87]

Another theory was later proposed by Gouy (1910) and Chapman (1913) independently. In this theory, the counter-ions are not concentrated on the interface and form a flat condenser. Instead, the counter-ions are scattered in the liquid phase at a certain distance away from the interface. Thus, the second layer contains mobile counter-ions, referred to as the diffuse layer. The distribution of the ions in the diffuse layer are determined by the surface electrical potential and the thermal energy.

The surface charge layer together with the diffuse layer are referred to as the Gouy-Chapman Electrical Double Layer (EDL), as shown in Fig. 5.1. This “double layer” of charge drives electric potential increasingly closer to—but never quite reaches—the
electric potential of the bulk solution. This behavior is accurately described by the Poisson-Boltzmann equation (PBE). [88]

### 5.2.2 The Poisson-Boltzmann Equation

For monovalent ions in the ideal solution, the electrostatic interactions and spatial correlations between the ions can be neglected. Those ions can be approximated as point charges. In this case, the classic Poisson-Boltzmann Equation accurately describes the ion screening of a charged interface.

Statistical thermodynamics predicts that the likelihood that the system is at a particular state associated with energy $E$ has the form

$$p \propto \exp\left(\frac{-E}{k_B T}\right),$$  \hspace{1cm} (5.1)

where $k_B = 1.38 \times 10^{-23}$ J/K is the Boltzmann constant. Consider a system consisting of $n$ ionic species in the solution that contacts with a charged surface. The probability that ionic species $i$ have a electrical potential energy $w_i$ is $\exp\left(-\frac{w_i}{k_B T}\right)$. Therefore, the density of ion species $i$, $\rho_i$ can be written as

$$\rho_i = \rho_{i, \text{bulk}} e^{-w_i/k_B T}$$  \hspace{1cm} (5.2)

where $\rho_{i, \text{bulk}}$ denotes the density of ion species $i$ in the bulk solution, infinitely far from the charged surface.

In the ideal solution, we can the make the mean field approximation:

$$w_i = eZ_i \phi,$$  \hspace{1cm} (5.3)

where $\phi$ is the electrical potential, $e = 1.6 \times 10^{-19}$ C is the charge of an electron, and $Z_i$ is the valence of the $i$th ionic species. For monovalent ions, $Z_i = 1$.

The Poisson equation which links potential to the local charge density is

$$\nabla^2 \phi = -\frac{4\pi}{\epsilon} \rho$$  \hspace{1cm} (5.4)
We can then combine Eq. 5.2, Eq. 5.3 and Eq. 5.4 to get the Possion-Boltzmann equation,
\[ \nabla^2 \phi = -\frac{4\pi}{\epsilon} \sum_i \rho_i \text{bulk} Z_i e^{-eZ_i \phi/k_B T}. \] (5.5)

The Debye-Huckle Approximation

The Poisson-Boltzmann equation does not have a closed-form analytical solution due to the non-linear characteristic and the summation. However, we can make several approximations under certain conditions to linearize Poisson-Boltzmann equation and get a closed form solution.

First, if the curvature of the charged surface is negligible or the charged surface is planar, the Poisson-Boltzmann equation can be reduced to one dimensional. Here we assume \( z \) is the direction perpendicular to the charged surface. For solutions containing only monovalent ions, the concentrations of cation and anion are the same. Then we have \( \rho_{1,\text{bulk}} = \rho_{2,\text{bulk}} \) and \( |Z_1| = |Z_2| = 1 \). We can re-write the Poisson-Boltzmann equation as
\[ \frac{\partial^2 \phi'}{\partial z'^2} = \sinh \phi'. \] (5.6)

Here, electrical potential \( \phi' \) is \( \phi \) normalized by the thermal energy \( k_B T \), and position \( z' \) is normalized by the Debye length \( \lambda_D \). Debye Length \( \lambda_D \) is defined as
\[ \lambda_D = \sqrt{\frac{\epsilon \epsilon_0 k_B T}{2 N_A e^2 I}} \] (5.7)
where \( \epsilon \epsilon_0 \) is the permittivity for the solution and \( N_A = 6.02 \times 10^{23} \text{ mol}^{-1} \) is the Avogadro constant. \( I \) is the ionic strength defined as
\[ I = \frac{1}{2} \sum c_i Z_i^2 \] (5.8)
where \( c_i \) is the concentration of ith ionic species in the unit of molar.

When \( \phi' \) is small compare to 1, we can approximate the hyperbolic sine ”\( \sinh \)“ term by letting \( \sinh(x) \approx x \). Then the Poisson-Boltzmann equation becomes
\[ \frac{\partial^2 \phi'}{\partial z'^2} = \phi' \] (5.9)
This approximation is termed as the Debye-Huckle approximation, which is the linear variant of the Poisson-Boltzmann equation. The Debye-Huckle approximation is valid only when the electrical potential energy is small compared to the thermal energy $k_B T$.

With boundary conditions $\phi' = 0$ at $z' = \infty$ and $\phi' = \phi_0'$ at $z' = 0$, we can easily obtain the solution to this linearized equation,

$$\phi' = \phi_0' e^{-z'} \quad (5.10)$$

which is equivalent to

$$\phi = \phi_0 e^{-z/\lambda_D} \quad (5.11)$$

Thus the Debye-Huckle theory predicts the electrical potential near the charged surface has an exponential distribution and reaches the electrical potential of the bulk solution at infinitely far (Fig. 5.1). The Debye length $\lambda_D$ is the characteristic length which gives a rough measure of length over which the over-potential at the charged surface decays into the bulk solution. It is noteworthy that the Debye length is the property of the electrolyte solution and depends on the ionic strength of the solution.

Another two characteristic lengths worth mentioning here are the Bjerrum length $\lambda_B$ and Gouy-Chapman length $\lambda_{GC}$. The Bjerrum length is the separation at which the electrostatic interaction between two ions is comparable to the thermal energy, $k_B T$. The Bjerrum length is given by

$$\lambda_B = \frac{Z_1 Z_2 e^2}{4 \pi \varepsilon_0 \varepsilon_r k_B T}. \quad (5.12)$$

The Gouy-Chapman length is the separation at which the electrostatic interaction between an ion and a charged surface is comparable to the thermal energy. The Gouy-Chapman length is given by

$$\lambda_{GC} = \frac{\varepsilon_0 \varepsilon_r k_B T}{2 \pi Z e |\sigma|}, \quad (5.13)$$

where $\sigma$ is the surface charge density. Ions with high valence increase the Bjerrum length and decrease Gouy-Chapman length.
Fig. 5.1. The Gouy-Chapman electric double layer (EDL) model and the electric potential drop in the EDL predicted by Debye-Hückel theory.
5.3 Multivalent Ion Screening of Charged Interface

5.3.1 Previous Observations of Multivalent Ion Screening

The Poisson-Boltzmann description of the ion screening is valid when the ions can be approximated by point charges so that the mean-field approximation can be made. The Poisson-Boltzmann equation is no longer valid when the size of the ions or the spatial correlations between the ions are not negligible. For multivalent ions, electrostatic interactions between the ions are so strong that the ions do not distribute themselves randomly in the three-dimensional space, or rather the positions of the ions are highly correlated. Therefore, while the behavior of monovalent ions near charged surface can be accurately described by the Poisson-Boltzmann equation, multivalent ions (typically trivalent or higher) can exhibit phenomena not seen with monovalent ions.

With strong spatial corrections between the high valent ions, over-screening becomes possible, meaning that the high valent ion screening can pass the neutralization point and reverse the sign of surface charge. This phenomenon is referred to as the “charge inversion”. [73–76, 89] Another counter-intuitive phenomena due to the high valent ions is the attraction between the like-charged molecules. [80–82, 90] For instance, double stranded DNA molecules attract each other and form ordered condensates in dilute solution of multivalent ions. [91–93]. The attraction of like-charge molecules competes with the repulsion due to charge inversion and further induces reentrant condensation of charged colloids and molecules. [77–79] These phenomena cannot be described by the PBE, inspiring the development of many new theories for electrolytes containing multivalent ions. [94–118]

A theory that treats multivalent counterions as a strongly correlated liquid (SCL) can, in principle, describe all of the phenomena mentioned above. [94, 119] Indeed, counter-ion correlation theories have been shown to account for the experimentally observed charge inversion of several different charged surfaces by several different multivalent counterions. [75, 120, 121] Still La$^{3+}$ appears to invert the charge of surfaces
by a different mechanism related to van der Waals or chemical forces. [122] Similarly, the phenomena of reentrant condensation in electrolyte containing multivalent ions is surprisingly dependent on the monovalent co-ions present in solution [123] and can be described by Bjerrum pairing of the multivalent ions. [77] Hence, while several phenomena associated with multivalent ions are relatively established, the underlying mechanistic causes for these effects remain unclear.

5.3.2 Strong Coupled Liquid Theory

The strong coupled liquid theory was first proposed by Perel and Shklovskii. [104, 119] This theory models the multivalent ions near the charged surface as two-dimensional highly correlated liquid. The key idea of this theory is that for multivalent ions, the correlation between the ions are not negligible.

One parameter that characterizes the correlation strength between the counterions is the Coulomb coupling constant \( \Gamma \), which is defined as the ratio of the average Coulomb energy to the average kinetic energy. Thus, \( \Gamma \) is given by

\[
\Gamma = \frac{Z^2 e^2}{4 \pi \epsilon d k_B T},
\]

where \( d \) is the average separation between the ions. It is easy to see that coupling strength grows with the square of valence. Typically, the coupling is considered to be weak for \( \Gamma < 1 \).

Now we assume that a charged surface is completely neutralized by the counterions. For a typical high surface density at \( \tau = 1e/\text{nm}^2 \) screened by trivalent ions \( Z = 3 \), the coupling constant \( \Gamma = 6.4 \), the Guoy-Chapman length \( \lambda_{GC} \sim 0.1\text{nm} \), and \( d = 1\text{nm} \). [94] In this case, the multivalent ions are highly correlated (\( \Gamma \gg 1 \)) and the Guoy-Chapman length is so short (0.1nm) that the multivalent ions are condensed on the first molecular layer of the charge surface. At the same time, the repulsion between the multivalent ions is so strong, the typical separation between the ion is long so that the the ions form two-dimensional SCL, in which the short order of counter ions is similar to that of a Wigner crystal. [119]
The SCL theory treats such systems of multivalent ions as consisting of two subsystems: a SCL layer on the charged surface and the gaslike dilute phase into the bulk. The SCL system takes into account strong correlations using the energy of Wigner crystal as the approximation for the free energy of the SCL. The gaslike phase can be treated with classic Poisson Boltzmann equation. The boundary conditions are consistent with both subsystems. [119] Detailed calculations are described in Chapter 6.

5.4 Approaches to Probe Ion Screening

5.4.1 Electrokinetic Phenomena

Electrokinetics refer to the processes in which the boundary layer between the liquid phase and charged solid phase is forced to undergo some sort of shearing movement. The excess charges in one phase are moved more or less tangentially relative to the other phase. A group of phenomena can be observed from the relative movement, termed “electrokinetic phenomena”. [87, 88] Information about how the EDL reacts to the shearing motion can be obtained from analyzing the relative motion of the two phases. While it is not possible to measure the electric potential in the EDL directly, the electrokinetic phenomena provide rigorous ways of probing the ion distributions and electrical potentials at certain places.

The most commonly observed electrokinetic phenomena are: electrophoresis, electroosmosis, streaming potential and sedimentation potential. In this dissertation, we used the streaming potential method to measure the electrical potentials in the presence of multivalent ions.

Streaming Potential

Streaming potentials are electrical potentials generated when liquid containing electrolytes is forced through a narrow channel with electrically charged surfaces. [88]
The excess counter-ions near the charged surface are carried along with the fluid flow and give rise to a streaming current. The excess charges carried with fluid flow accumulate downstream and create an electrical potential difference in the opposite direction of the streaming current. The potential difference further leads to a return current that tends to balance the streaming current. A steady state is achieved after a very short period of time. The potential difference at the steady state is referred to as the “streaming potential”, and can be measured directly from an electrometer.

The streaming potential is proportional to the electrical potential difference between the bulk solution and the “shear plane” - the location of the no-slip hydrodynamic boundary near the charged wall. The experimentally accessible streaming potential thus gives a way to measure the electric potential very near a charged surface.

5.4.2 ζ Potential

ζ potential is the electrical potential at the shear plane relative to the electric potential in the bulk. The shear plane is the location of the no-slip hydrodynamic boundary, meaning that the fluid between the charge surface and the shear plane remains stationary in the fluid flow. The shear plane is the interface of the relative tangential motion of the two phases.

ζ potential can be obtained directly from the streaming potential measurement. Therefore, ζ potential links the electrokinetic phenomena with the electrical double layer. In the experiment that I will describe in this dissertation, we used streaming potential method to obtain ζ potentials as a function of trivalent ion (Co(NH$_3$)$_6$Cl$_3$) concentration, monovalent ion (KCl) concentration, and the pH. The location of the shear plane is determined independently.
Calculation of $\zeta$ Potential from Streaming Potential Measurements

$\zeta$ potential is electric potential at the shear plane relative to the electric potential in the bulk solution. $\zeta$ potential can be calculated from streaming potential $V_s$ as

$$\zeta = \frac{V_s \mu \lambda_0}{\Delta P \epsilon}, \quad (5.15)$$

where $\Delta P$ is the pressure difference applied across the ends of narrow channel, $\nu$ is the viscosity, $\lambda_0$ is the conductivity, and $\epsilon$ is the permittivity of the electrolyte at room temperature. Equation 5.15 neglects surface conduction.
6. MULTIVALENT ION SCREENING OF CHARGED GLASS SURFACE STUDIED BY STREAMING POTENTIAL MEASUREMENTS

6.1 Abstract

We used streaming potential technique to measure ζ potentials for glass as a function of Co(NH$_3$)$_6$Cl$_3$ concentration, KCl concentration and pH. Charge inversion was observed only at high surface charge densities and was inhibited by increased KCl concentration. Measured ζ potentials were compared with predictions from a recent theory by dos Santos et. al [A. P. dos Santos, A. Diehl, and Y. Levin, J. Chem. Phys. 132, 104105 (2010)] that models multivalent ions adsorbed to the charged surface as a strong coupled liquid (SCL). The location of shear plane was determined independent of the SCL theory, allowing a rigorous experimental test of the theory with no fitting parameters. We found that SCL predictions agree quantitatively with our experimental data.

6.2 Experimental Method

6.2.1 Schematic and Apparatus

Streaming potentials are electrical potentials generated when liquid containing electrolytes is forced through a narrow channel with electrically charged walls. [88] The counterions near the charged wall are carried along with the flowing liquid and accumulate down-stream. This accumulation of counterion charge creates an electrical potential difference between the up-stream and downstream direction that is referred to as the “streaming potential”. The streaming potential is proportional to the electrical potential difference between the bulk solution and the “shear plane” -
the location of the no-slip hydrodynamic boundary near the charged wall. The experimentally accessible streaming potential thus gives a way to measure the electric potential very near a charged surface. We measured streaming potentials induced as electrolyte containing multivalent counterions were forced through a glass capillary (Vitrocom CV3040, Mountain Lakes, NJ) using a syringe pump (Fig. 6.1).

6.2.2 Glass washing

The glass capillary was washed before and after each measurement. For each wash cycle, the capillary was first washed with 0.1 M NaOH solution, then rinsed with deionized water, followed by washing in the electrolyte of interest. In each step, the washing buffer was pushed through the capillary at 1 ml/min for 10 minutes. Using this washing procedure, we overcame the hysteresis described in previous streaming potential measurements on glass. [120]

6.2.3 Electrodes

Streaming potentials were measured via Ag/AgCl electrode produced by electrolyzing 0.125 mm diameter silver wire (World Precision Instruments, Sarasota, FL) at 0.5 V in 0.1 M HCl for 10 minutes. Electrodes produced were stable for the duration of all experiments. Electrodes were inserted through silicon tubing on either side of the glass capillary and sealed with epoxy.
6.2.4 Streaming potential, $V_s$

A syringe pump (Kent Scientific Corporation) drove a steady flow through the glass capillary. The pump was programmed to sequentially apply flow rates: $\pm 2$, $\pm 1$ and $\pm 0.5$ ml/min each for 3 minutes. Throughout the experiment, the potential difference across the capillary was measured by a Keithley 6517 high input impedance electrometer. Conductance was measured before and after each measurement with both polarities. This ensured that measurements were not contaminated by bubbles or changes in electrolyte concentrations.

6.2.5 Hydrodynamic Resistance of the device

In our experiments, we assert a known volumetric flow rate, $Q$, using a syringe pump. Positive $Q$ is defined as flow from the positive terminal of the electrometer toward the negative terminal. In order to calculate the pressure drop across the capillary, $\Delta P$, we need to determine the hydrodynamic resistance, $R_H$, defined by $\Delta P = QR_H$. The hydrodynamic resistances of two different devices were measured as $R_H = 4.41 \times 10^{11}$ Pa·s/m$^3$ and $R_H = 4.64 \times 10^{11}$ Pa·s/m$^3$ by raising the inlet 26 cm to create a known pressure difference and measuring the resulting flow rate. For our circular cross sectional capillaries, the expected hydrodynamic resistance is,

$$R_H = \frac{\mu L}{\pi R^4} \quad (6.1)$$

with viscosity $\mu = 0.91$ mPa·s for water at 25°C, total length $L = 10$ cm, and radius $R = 0.15$ mm. The expected $R_H = 4.53\times10^{11}$ Pa·s/m$^3$ was within 3% of the measured values.
6.2.6 Calculation of ζ Potential

ζ potential is electric potential at the shear plane relative to the electric potential in the bulk solution. ζ potential can be calculated from streaming potential as

\[ \zeta = \frac{V_s \mu \lambda_0}{\Delta P \epsilon} \]  

with conductivity of the electrolyte \( \lambda_0 \) and permittivity \( \epsilon = 78 \times 8.85 \times 10^{-12} \text{ F/m} \) for water at room temperature. Equation 6.2 neglects surface conduction. For each measurement, we measured conductivity of the solution and the conductance of the capillary. In every case, the conductance of the device was equal to the conductivity divided by the cell constant for the capillary. This verifies that surface conduction was indeed negligible. [88]

6.2.7 Location of the shear plane

Position of the shear plane can be estimated from the dependence of ζ potentials on the Debye length, according to the procedure described by Hunter. [88] The location of the shear plane \( t \), was obtained from the slope of \( \ln \tanh \frac{q\zeta}{4k_B T} \) versus \( \kappa \) according to (see Ref. 88, Eq. 5.4.1),

\[ \ln \tanh \frac{q\zeta}{4k_B T} = \ln \tanh \left( \frac{q\phi_0}{4k_B T} \right) - \kappa t. \]  

(6.3)

\( \phi_0 \) is electric potential at the surface. \( 1/\kappa \) is the Debye length. For determining the location of the shear plane, the Debye length was controlled using KCl concentration only, with no Co(NH₃)₆Cl₃ present.

6.2.8 Electrolyte Solutions

We controlled pH using three different solutions. pH 3 was 0.134 mM HCl. pH 4 buffer was 0.0125 mM NH₂CH₂COOH, 0.0095 mM NaCl and 0.0238 mM NaOH. pH 9 buffer was 0.126 mM Na₂B₄O₇ and 0.186 mM NaOH. Solution pH was verified
before each experiment. Co(NH$_3$)$_6$Cl$_3$ and KCl were added to these buffers to examine effects of multivalent and monovalent ions under different pHs.

### 6.2.9 Error bars

The most significant source of uncertainty in our measured ζ potentials arises from the variations in glass surface charge from measurement-to-measurement. Similar to previous measurements of acid cleaned glass, [124] we find that repeated measurements under identical conditions give an average variation in ζ potential of ±4 mV. This variation is displayed as nominal error bars of ±4 mV in all of the plotted ζ potentials.

### 6.3 Theory of Multivalent Ion Screening for Flat Plate Geometry

We compare our data with predictions of the PBE and with an SCL theory. The development of the SCL theory below is taken from dos Santos, Diehl, and Levin [125] who adapted Perel’s and Shklovskii’s approach. [119] dos Santos et. al also included the formation of counterion-coion clusters in the bulk solution (“Bjerrum pairing”). [126] The theory we describe in Section 6.3.2 is a straightforward adaptation of dos Santos et. al’s treatment of a dense suspension of spherical colloids to the simpler problem of an infinite charged plane in contact with an infinite reservoir of electrolyte solution.

#### 6.3.1 Poisson-Boltzmann Equation (PBE)

The electric potential, $\phi$, due to a charged surface with surface charge density $\sigma$ in electrolyte solution can be approximated at the mean-field level from the one-dimensional PBE,

$$\frac{d^2 \phi}{dx^2} = \frac{4\pi q}{\epsilon} \sum_i \rho_i Z_i e^{-\beta Z_i q \phi} \quad (6.4)$$
and the two boundary conditions,

\[ \frac{d\phi(0)}{dx} = -\frac{4\pi}{\varepsilon} \sigma \]  \hspace{1cm} (6.5)  \\
\phi(\infty) = 0. \hspace{1cm} (6.6)

\( \sigma \) is the charge density of the infinite plane and \( x \) is the distance from the plane to any point in the solution. \( Z_i \) and \( \rho_i \) are the valences and volume densities of ionic species \( i \) in the bulk. \( \beta \) is the inverse of the thermal energy and \( q \) is the proton charge.

In practice, it is convenient to convert this non-linear boundary value problem to an initial value problem by analytically integrating Eq. 6.4 once from \( x = \infty \) to \( x = 0 \) (see, for instance, Ref. 88, Eq. 2.3.22). This gives the analytical expression

\[ 0 = 4\pi \sigma^2 - \frac{2e}{\beta} \sum_i \rho_i \left( e^{-\beta q Z_i \phi(0)} - 1 \right), \]  \hspace{1cm} (6.7)

relating the electric potential at the surface, \( \phi(0) \), to \( \sigma \). \( \phi(0) \) can then be obtained by finding a value of \( \phi(0) \) that satisfies Eq. 6.7 and has same sign as \( \sigma \). Given \( \phi(0) \), along with Eq. 6.5, Eq. 6.4 can be numerically integrated from \( x = 0 \) to obtain the value of the electric potential at \( x \). To compare the PBE with our measurements of the \( \zeta \) potential, we integrate to the empirically determined location of the shear plane.

### 6.3.2 Strongly Coupled Liquid (SCL)

The basic idea in dos Santos et al.’s SCL theory is to treat the solution as consisting of two separate sub-systems (Fig. 6.2). Directly adjacent to the charged surface, counterion correlations dominate and the \( \alpha \)-valent counterions are described using the theory for a SCL. Further into the bulk, ions form a gaslike phase and are treated using the PBE. The number density of counterions in the SCL, \( \sigma_\alpha \), is obtained such that the effective charge and potential at the boundary between the two subsystems are consistent with both. The independent variables in the theory are identical to those in the conventional PBE.
Fig. 6.2. Theory for the electric potential near a surface with surface charge density, $\sigma$ in contact with an electrolyte containing counterions with valence $+\alpha$. The electrolyte is broken into two separate sub-systems: a strongly coupled liquid (SCL) adjacent the charged surface and a gaslike phase further into the bulk. The two sub-systems are coupled such that the effective charge, $\sigma_{\text{eff}}$ and effective electric potential, $\phi_{\text{eff}}$ at the boundary are consistent with both the SCL and the Poisson-Boltzmann Eq. (PBE). The electrolyte that we consider includes, $\alpha$-valent cations, mono-valent cations and anions, and Bjerrum pairs (BP) between the $\alpha$-valent ions and cations.
Following dos Santos et al. [125] the density of $\alpha$-valent counterions in the diffuse layer just adjacent the SCL is,

$$\rho_\alpha = \frac{\sigma_\alpha}{\lambda_{GC}} e^{-\beta(-\mu_c + \mu_e)}$$  \hspace{1cm} (6.8)

where the chemical potential of the SCL is,

$$\beta \mu_c = -(1.65\Gamma - 2.61\Gamma^{1/4} + 0.26 \ln \Gamma + 1.95)$$  \hspace{1cm} (6.9)

with plasma parameter,

$$\Gamma = \alpha^2 \lambda_B \sqrt{\pi \sigma_\alpha}.$$  \hspace{1cm} (6.10)

where $\lambda_B = q^2 \beta / \epsilon$ is the Bjerrum length associated with water. In implementation, it is convenient to think of the surface density of multivalent ions $\sigma_\alpha$ as specifying, via Eq. 6.8-6.10, an effective surface charge density and an effective potential at the boundary between the SCL and the PBE,

$$\phi_{\text{eff}} = -1/\alpha \ln (\rho_\alpha / \rho_{\alpha,\infty})$$  \hspace{1cm} (6.11)

$$\sigma_{\text{eff}} = \sigma + \alpha \sigma_\alpha.$$  \hspace{1cm} (6.12)

To implement, we guess a value of $\sigma_\alpha$ and this specifies $\phi_{\text{eff}}$ and $\sigma_{\text{eff}}$ for the SCL. We then check whether these values satisfy the PBE, Eq. 6.7, and have same sign. In practice, the guessing is handled by a root finding algorithm. Once, appropriate values of $\phi_{\text{eff}}$ and $\sigma_{\text{eff}}$ are identified, they are the initial conditions with which we can integrate Eq. 6.4 out to find the electric potential at any $x$. To compare the SCL theory with our measurements of the $\zeta$ potential, we integrate to the empirically determined location of the shear plane.

### 6.3.3 Bjerrum pairing

$\alpha$-valent cations can form complexes with anions to produce a new species with valence $\alpha - 1$ ("Bjerrum pair"). [125] Because of Bjerrum pairing, the density of an ionic species in the bulk, $\rho_i$, may differ from the density of the ion added to
Fig. 6.3. Flow rates, $\pm 2$, $\pm 1$ and $\pm 0.5$ ml/min are applied sequentially (a). Streaming potential response to flow rate is shown for pH 9, 0.4 mM (b) and for pH 9, 0.4 mM, $10^{-3}$ M Co(NH$_3$)$_6$Cl$_3$ (c). The reversal of polarity between (b) and (c) shows the charge inversion.
the solution, \( \rho_{i,0} \). The energy stabilizing the Bjerrum pair depends on the distance of closest approach, defined by the hard sphere radii of the ions. For simplicity, we follow dos Santos et al and assume that all ions are the same size with radius, \( r = 2 \text{ Å} \). According to Levin, \cite{126} the density of the Bjerrum pair is given by,

\[
\rho_{\alpha-1} = \xi_p \rho_\alpha \rho_- e^{-\beta (\mu_\alpha^{ex} - \mu_f^{ex} - \mu_-^{ex})},
\]

(6.13)

where,

\[
\xi_p = \frac{16 \pi r^3}{3} \left[ b^2 (\text{Ei}(b) - \text{Ei}(2) + e^2) - c^b (b^2 + b + 2) \right]
\]

(6.14)

with \( b = \alpha \lambda_B / 2 r \) and \( \text{Ei} \) is the exponential integral function, as defined by Abramowitz and Stegun \cite{127} Eq. 5.1.2. The chemical potentials of each ion species are,

\[
\beta \mu_\alpha^{ex} = -\frac{(\alpha - 1)^2 \lambda_B \kappa}{2 (1 + 2 \kappa r_{BP})},
\]

(6.15)

\[
\beta \mu_{\alpha-1}^{ex} = -\frac{\alpha^2 \lambda_B \kappa}{2 (1 + 2 \kappa r)},
\]

(6.16)

\[
\beta \mu_-^{ex} = -\frac{\lambda_B \kappa}{2 (1 + 2 \kappa r)}.
\]

(6.17)

The radius of the Bjerrum pair is \( r_{BP} = 1.191 r \). The Debye length is \( \kappa = \sqrt{8 \pi \lambda_B I} \) and the ionic strength is \( I = (\alpha^2 \rho_\alpha + (\alpha - 1)^2 \rho_{\alpha-1} + \rho_+ + \rho_-) / 2 \).

In implementation, the mole balances,

\[
\rho_\alpha = \rho_{\alpha,0} - \rho_{\alpha-1}
\]

(6.18)

\[
\rho_- = \rho_{-,0} - \rho_{\alpha-1}
\]

(6.19)

allow Eq. 6.13 to be written as a 2\textsuperscript{nd}—order polynomial in a single independent variable, \( \rho_{\alpha-1} \). Because the chemical potentials in Eq. 6.13 depend on the Debye length, however, the polynomial defined by Eq. 6.13 must be solved iteratively, each time updating the Debye length according to the densities of all ionic species.

### 6.4 Result

For each solution condition, we measured streaming potentials over a range of flow rates, each held steady for 3 mins (Fig. 6.3 (a)). At each flow rate, the streaming
Fig. 6.4. Streaming potential, $V_s$ vs. pressure drop across the capillary, $\Delta P$. Streaming potential is linearly related to the pressure drop. (a) and (b) illustrate the linear relationship for the data shown in Fig. 6.3 (b) and Fig. 6.3 (c), respectively. $\zeta$ potential can be calculated from the slope of this plot via Eq. 6.2.

Fig. 6.5. $\zeta$ potentials versus Co(NH$_3$)$_6$Cl$_3$ concentration at pH 3, 4 and 9. Black dots are measured with low KCl concentration (0.5 mM for pH 3, 0.4 mM for pH 4 and pH 9) and red squares are measured with high KCl concentration (30 mM). Dotted line is $\zeta$ potential predicted by PBE and solid line is $\zeta$ potential predicted by SCL theory.
potential acquired a constant value (Fig. 6.3 (b) & (c)). In electrolyte containing 0.4 mM KCl at pH 9, the streaming potentials have signs opposite the flow rates (Fig. 6.3 (b)). When $10^{-3}$ M $\text{Co(NH}_3\text{)}_6\text{Cl}_3$ is added to the solution, the streaming potentials have the same signs as the flow rates (Fig. 6.3 (c)).

For all measurements, the streaming potential was directly proportional to the pressure drop across the capillary (Fig. 6.4). Fig. 6.4 (a) and Fig. 6.4 (b) show streaming potential vs. pressure drop across the capillary for the data shown in Fig. 6.3 (b) and Fig. 6.3 (c) respectively. In KCl, the slope of the streaming potential versus pressure drop is negative, indicating a negative electric potential near the glass surface. With $10^{-3}$ M $\text{Co(NH}_3\text{)}_6\text{Cl}_3$ added (Fig. 6.4 (b)), the slope is positive, indicating a positive electric potential near the glass surface. For each solution condition, $\zeta$ potential is calculated from the slope of streaming potential versus pressure drop via Eq 6.2.

Figure 6.5 shows $\zeta$ potentials as a function of $\text{Co(NH}_3\text{)}_6\text{Cl}_3$ concentration at pH3, pH4 and pH9. Solution pH influences surface charge density, with larger pH producing larger negative surface charge density. [128] This is reflected in our data; as pH increases, $\zeta$ potentials increase. Charge inversion was only observed at pH 9 where charge densities are largest. Charge inversion was observed both at 0.4 mM KCl and 30 mM KCl. However, the $\text{Co(NH}_3\text{)}_6\text{Cl}_3$ concentration required for charge inversion is higher for 30 mM KCl than for 0.4 mM KCl.

The $\zeta$ potential is the electric potential at the shear plane located close to the glass surface. This data is therefore useful for testing theories that predict how multivalent ions affect electric potentials near charged surfaces. In order to make the comparison, we need to know the distance relative to the surface where the $\zeta$ potential is measured (shear plane). We determined the location of shear plane from the slope of Fig. 6.6, as described by Hunter [88] and in our Section 6.2.7. The average location of the shear plane determined by this method, $10.7 \text{ Å} \pm 1.3 \text{ Å}$, was not significantly different from previous measurements on glass (black dots, Fig. 6.6). [124]
Fig. 6.6. Position of the shear plane determined from the dependence of $\zeta$ on the Debye length. As shown by Eq. 6.3, $t$ is the slope of $\ln \tanh \frac{q_\kappa}{4 \kappa B T}$ vs. $\kappa$. Blue squares, green diamonds and red triangles are data at pH9, pH7 and pH4 respectively. The positions of the shear plane for pH 9, pH 7 and pH 4 are 8 Å, 12 Å and 12 Å respectively. Black dots are from Ref. 124. In all theoretical calculations, we use the average value of three pHs, $t = 10.7$ Å to evaluate the electric potential.
Figure 6.5 compares predictions of the PBE (dashed lines) and the SCL (solid lines) with our measured ζ potentials. In each of these theories, the surface charge density, σ, was the only unknown parameter. We choose this value such that the predicted ζ potential for each pH/KCl condition matched the measured ζ potential at 0 Co(NH₃)₆Cl₃. With σ fixed, the complete Co(NH₃)₆Cl₃-dependence of the ζ potential for each pH/KCl combination was predicted with no fitting parameters.

6.5 Discussion

ζ potentials for glass were measured as a function of Co(NH₃)₆Cl₃ concentration, KCl concentration, and pH. pH is seen as a means for modulating the surface charge density. Consistent with previous findings, we observe that charge inversion occurs at high surface charge densities [75,129] and that charge inversion is inhibited [120,122] rather than promoted [94] by increased monovalent ion concentrations.

By measuring the location of the shear plane, we were able to identify the measured ζ potential with the electric potential at a specific location from the charged glass surface. This characterization allowed us to compare our experimental data with the recent theory by dos Santos et. al that provides quantitative prediction of the electric potential in solutions containing both multivalent and monovalent ions.

The SCL theory predicted strong deviations from the PBE only at higher surface charge densities (pH 9, see black dots and solid black line in Fig. 6.5 (c)). This prediction was consistent with our experimental data. At the higher surface charge densities where ζ potentials differed from the PBE, the SCL made predictions consistent with the measured ζ potentials at high concentration of monovalent ions (30 mM KCl).

Differences were seen between the experimental data and the SCL theory at pH 9 and 0.4 mM KCl. However, these differences can be attributed to the assumption of constant surface charge density rather than to the SCL theory itself. Silica glass acquires charge primarily through the dissociation of terminal silanol groups. [130] This dissociation reaction is dependent on many factors, including the ionic strength of the
Fig. 6.7. Replot of Fig. 6.5 pH 9, ζ potential vs. Co(NH$_3$)$_6$Cl$_3$ concentration at pH 9 with 0.4 mM KCl. Solid line and dot-dash line are both predictions of SCL. For solid line, surface charge density is chosen, as in Fig. 6.5 pH 9, to match the measured ζ potential with no Co(NH$_3$)$_6$Cl$_3$ present. For dot-dash line, surface charge density is chosen to match the concentration at charge inversion.

solution (“charge regulation”). [128, 130] Hence, particularly at low KCl concentration where added Co(NH$_3$)$_6$Cl$_3$ significantly increases ionic strength, it is likely that the glass surface charge density changes as Co(NH$_3$)$_6$Cl$_3$ concentration changes. This interpretation is critically evaluated in Fig. 6.7 where we replot the data of Fig. 6.5, pH 9 with the SCL theory at two different surface charge densities. For the solid line, the surface charge density is chosen, as in Fig. 6.5 pH 9, to match the measured ζ potential at 0 Co(NH$_3$)$_6$Cl$_3$. For dot-dash line, surface charge density is chosen to match the concentration at charge inversion. Once this variation in surface charge density is allowed, the SCL theory is seen as consistent with the experimental data.

If we accept the agreement between experiment and theory in Fig. 6.7 as providing a reasonable indication of the surface charge density, then it would appear that the surface charge density of the glass increased by 27 fold in going from $10^{-8}$ to $10^{-7}$ M Co(NH$_3$)$_6$Cl$_3$ concentration. To affect a similar change in surface charge density via monovalent ions, a change in concentration of four orders of magnitude are required. [128] Since, this apparently dramatic change occurred at the same place
where strong deviations from the PBE are first observed (see black circles around \(\sim 10^{-8} \text{ M } \text{Co(NH}_3)_6\text{Cl}_3\) in Fig. 6.5 pH 9), this may indicate a cooperative effect between multivalent ion adsorption and surface deprotonation.

### 6.6 Conclusion

We measured \(\zeta\) potentials of glass as a function of Co(NH\(_3\))\(_6\)Cl\(_3\) concentration, KCl concentration, and pH using the streaming potential technique. Consistent with previous findings, we observed that charge inversion is promoted by high surface charge densities and low KCl concentration. [75, 129] We made quantitative comparisons between the experimental data and the SCL theory recently introduced by dos Santos et. al. [125] The SCL theory accurately predicted where deviations from the PBE would occur as a function of charge density and KCl concentration. Quantitative predictions for the \(\zeta\) potentials were consistent with data provided that we allow for charge regulation of the glass surface.
7. SUMMARY AND FUTURE WORK

In the second part (Chapter 5-7) of this dissertation, I described an experimental measurement of electrical potentials near the charged solid-liquid interface, in the presence of various concentrations of multi- and mono-valent ions. We used the streaming potential method to measure the electrical potentials of glass at the electrokinetic shear plane, the $\zeta$ potentials, as a function of trivalent ion $\text{Co(NH}_3\text{)_6Cl}_3$ concentration, monovalent ion (KCl) concentration and pH. The changes in pH of the solution induce the changes in the surface charge density. The charge inversion was observed at high trivalent ion concentrations and the monovalent ions appear to impede the formation of the charge inversion. We compared our experimental results with a recent theory by dos Santos [125], and found that the theory quantitatively agrees with our data.

In this experiment, we used dilute buffer solutions to maintain a relative stable pH of the solution, in order to maintain a relative stable surface charge density. The value of surface charge density in this experiment is not directly accessible. The surface charge density was calculated from the data measured in the absence of the multivalent ions and was assumed to be constant. In fact, when high concentrations of multivalent ions were added, the surface charge density appeared to be affected (see discussion section of Chapter 6). A future experiment that circumvents this problem may involve a neutral surface with covalently attached charged molecules. The surface charge density in this case would be a constant and known value, and can be controlled by varying the amount of molecules attached.

The strong coupled liquid (SCL) theory models the multivalent ions near the charged surface as highly correlated two-dimensional liquid. However, the direct information about the structure of the two-dimensional liquid was not available from the experiment described. A well patterned charge surface that has the same/opposite
distribution of charges may appear to substantially enhance/cancel the electrical potentials near the charged surface. The direct information about the distribution of the ions can be obtained from the pattern of the charges.
LIST OF REFERENCES
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