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Kinetic Monte Carlo Methods for Computing First Capture Time Distributions in Models of Diffusive Absorption

Daniel Schmidt
Harvey Mudd College

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Daniel D. Schmidt

Andrew J. Bernoff, Advisor

Alan E. Lindsay, Reader

HARVEY MUDD COLLEGE

Department of Mathematics

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Abstract

In this paper, we consider the capture dynamics of a particle undergoing a random walk above a sheet of absorbing traps. In particular, we seek to characterize the distribution in time from when the particle is released to when it is absorbed. This problem is motivated by the study of lymphocytes in the human blood stream; for a particle near the surface of a lymphocyte, how long will it take for the particle to be captured? We model this problem as a diffusive process with a mixture of reflecting and absorbing boundary conditions. The model is analyzed from two approaches. The first is a numerical simulation using a Kinetic Monte Carlo (KMC) method that exploits exact solutions to accelerate a particle-based simulation of the capture time. A notable advantage of KMC is that run time is independent of how far from the traps one begins. We compare our results to the second approach, which is asymptotic approximations of the FPT distribution for particles that start far from the traps. Our goal is to validate the efficacy of homogenizing the surface boundary conditions, replacing the reflecting (Neumann) and absorbing (Dirichlet) boundary conditions with a mixed (Robin) boundary condition.

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Chapter 1

Introduction

Imagine a molecule floating in the bloodstream. This molecule diffuses around until it happens to bump into a cell; if this the particle bumps into a small receptor on the cell, it may bind to the receptor. An example of such a situation is an antigen floating in the blood stream that may bind to a T-lymphocyte (Robert et al. (2012)). At this microscopic scale, the motion of a particle in a fluid is best modeled by a random walk, also known as Brownian motion (Durrett (2010)). This is called a diffusive capture problem, diffusion being the mechanism of motion and capture being the particle colliding with the receptor. Diffusive capture problems model any situation where an agent randomly wanders until it collides with something of interest; other biological examples include an anteater wandering around the forest until she finds an anthill full of tasty snacks, or a grain of pollen floating on the breeze until it latches on to another flower. Why does diffusion work as a reliable and predictable means of transit for these cases? All three problems describe biological functions critical to the life processes that rely on them: cells need to sense concentration levels in the fluid around them, anteaters need to find food, and plants need to reproduce. So why rely on what is essentially a random process?

This question was first tackled in earnest by Howard Berg and Edward Purcell in a 1977 paper *Physics of Chemoreception* (Berg and Purcell (1977)). They used mathematical tools from physics to consider probability of particle capture, time to capture, the effective capture rate of many small traps, and other diffusion to capture related questions. Although Berg and Purcell's results were ground breaking at the time, they are rough approximations when the geometry of the problem becomes complicated. In particular, the case of multiple small pores on a reflecting surface has been an object of

research since (see Lindsay et al. (2016), Muratov and Shvartsman (2008), Berezhkovskii et al. (2014)).

The specific random-walk capture problem considered here is a planar pore problem, an approximation of the spherical cell model. To model this situation mathematically, one can use the fact that in a continuous medium, the probability distribution in time and space for the location of a particle undergoing a random walk can be found by solving the diffusion equation, a partial differential equation (PDE). In a few simplified cases, such as when a plane is completely absorbing, traditional PDE methods can be used to solve for the distribution exactly. In more complicated models, the interesting distributions come from heterogeneous geometries of receptors and reflecting surfaces. The model most often used for the chemoreception problem is a sphere in three dimension, with N small circular receptors on it's surface distributed around the surface of the sphere (Berg and Purcell (1977), Lindsay et al. (2016)). The small circular receptors are absorbing, and the surface of the sphere reflects oncoming particles. An image of this model is given in Figure 2.1. Here I consider a simplified model that describes a particle relatively close to a large sphere, as shown in Figure 3.1. This model is a circular receptor tiled on an infinite plane, where the spaces between the receptors are reflecting. The end goal of this analysis is approximating the time distribution to capture in the case of the infinite plane covered in periodic arrangements of receptors.

Chapter 2

Background

2.1 Random Walks and Capture Problems

2.1.1 An Overview of Random Walks

A random walk is most easily visualized on a lattice. In one dimension, you stand on a line and flip a coin to decide whether you will step forward or step backward. In two dimensions, you are on an infinite checker board, and you choose one of the four neighboring squares to step to by flipping two coins. In three dimensions, you choose between stepping up, down, forward, back, left, or right at random. An interesting note here is that dimension is important for general properties of random walks. By Polya's recurrence theorem, random walks in one dimension and two dimensions will always eventually reach every point in the domain (Durrett (2010)). However, in three dimensions recurrence only occurs with some probability less than one. Stated loosely, this means that if you are lost and want to find your way home, randomly walking around will eventually get you there. But if you are lost in space and decide to move around randomly, you may never find your way back to Earth.

In capture problems, this fact about random walks and dimension plays a fundamental role in investigating time to capture. For example, on a compact domain, a randomly walking particle will eventually traverse the entire domain. Capture problems on a bounded domain, such as an ion inside of a cell that bounces around until it finds a way out, are called narrow escape problems. See Schuss et al. (2007) for more details on these problems. While these problems share many similarities, the difficulties addressed with the methods in this paper arise from the unbounded domain we are

considering.

To model physical situations such as particles being randomly bumped by other particles in a liquid or a grain of pollen being bumped around by turbulence, we want to consider a continuous model rather than an arbitrary lattice. As the lattice size goes to zero and the particle is allowed to take more and more steps, the problem of stepping on a lattice turns into the heat equation. The heat equation is a partial differential equation that says the speed at which a particle moves is proportional to the Laplacian, i.e.

$$u_t = D\nabla^2 u$$

where u is the probability distribution of the particles location as a function of time, and D is the diffusion coefficient which has units of area per time. The free space solution to the heat equation for a particle that begins at location $\vec{x_0}$ in dimension d is a Gaussian distribution,

$$u(\vec{x}, t) = \frac{1}{(4\pi D t)^{d/2}} e^{\frac{-|x-x_0|^2}{4Dt}}$$

This solution will be useful in solving for the time distribution under various geometries. It also gives an intuition about random walks. We see that the most likely location for the particle grows as $\sqrt{Dt}$, the standard deviation. We also see that the difficulty in solving for time distributions from the heat equation all comes from the geometry of the boundary conditions. Symmetric boundary conditions are more likely to yield tractable solutions than heterogeneous geometries.

2.1.2   Time Dependence: Laplace's Equation or The Heat Equation

The heat equation captures the full joint distribution of the particle's position in both time and space. However, it is often useful to ignore the details of time dependence in order to simplify the problem. One situation is when a time-dependent solution reaches a steady-state equilibrium. In this case, $u_t = 0$, so the heat equation becomes Laplace's equation,

$$\nabla^2 u = 0 \tag{2.1}$$

$$u(x, y, 0, t)|_{\partial\Omega^a} = 0 \tag{2.2}$$

$$u(x, y, 0, t)_z|_{\partial\Omega^r} = 0 \tag{2.3}$$

where $\partial\Omega^a$ is the absorbing portion of the boundary and $\partial\Omega^r$ is the reflecting portion. In the case of a particle in a capture problem, the steady state
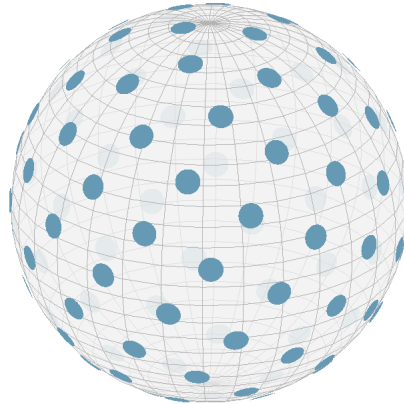
Figure 2.1   A model for a cell with small circular absorbing traps.

of $\lim_{t \to \infty} u_t$ gives the capture probability. Another case where Laplace's equation becomes useful is considering the source problem, where particles are continuously sourced from somewhere in space. Under appropriate circumstances, the flux of particles into absorbers can be considered steady, and so a steady-state solution in this instance can be transitioned back to say something about model parameters. We will see later how this approach can be used to find simplifying approximations under various geometries.

Another note on using steady-state methods for capture problems is that there is an analogy with physics, specifically electrostatics. Laplace's equation yields harmonic functions, and there is a large literature of methods for solving problems of this type due to their physical importance. It is perhaps this connection that motivated the original study of diffusion capture problems by biophysicists.

2.2   Biophysics: Berg and Purcell

Howard Berg's book *Random Walks In Biology* Berg (1993) treats the chemoreception problem by considering a hierarchy of simplified problems that build up to more complex models. These simplified models estimate the steady-state particle current into the absorbing areas. The idea is to first find current into a perfectly absorbing sphere, then into a single absorbing disk, then to estimate the current of multiple receptors by finding an expression for multiple receptors that matches both limits of a completely covered sphere and a sphere with a single receptor. These time-independent results

are useful as a starting point for thinking about the point of my research, which is investigating the time-dependent problem.

To solve the time independent problem we solve Laplace's Equation

$$\nabla^2 u = 0 \tag{2.4}$$

with various boundary conditions. For an absorbing sphere of radius R, the boundary conditions are spherical, with $u(\infty) = u_0$ and $u(R) = 0$. Laplace's equation in spherical coordinates with only radial dependence is

$$\frac{1}{r^2} \frac{d}{dr} \left(r^2 \frac{du}{dr} \right) = 0. \tag{2.5}$$

Berg gives the solution as

$$u(r) = u_0 \left(1 - \frac{R}{r} \right) \tag{2.6}$$

The flux into the sphere, which is really the quantity of interest for capture problems, is

$$J(r) = -Du_r(r) = -Du_0 \frac{R}{r^2} \tag{2.7}$$

where D is the diffusion constant of units length squared per time. If we multiply by the surface area of the sphere, $4\pi R^2$ and set $r = R$, we get the absorption rate

$$I = 4\pi D R u_0 \tag{2.8}$$

which is in units of particles per second. Note here that, perhaps contrary to intuition, the absorption rate increases linearly with the radius, not with the surface area.

It is worth thinking about the consequences of equation 2.8 depending on the radius of the traps instead of the surface area. What is the physical intuition for why this is the case? Well, suppose a particle diffuses until it collides with the reflecting surface. Once near the surface, it is likely to stay near the surface. It is possible that it randomly walks away, but it is highly likely that it continues to bounce along until it hits a receptor. Once a particle is on the surface then, the time to capture depends on the distance to the nearest receptor, which is a function of the perimeter, not the area.

Another non-intuitive consequence of this result is that for any given fraction of the surface covered by receptors, the flux can be made arbitrarily large by considering smaller and smaller individual receptors. Later we will derive problem parameters based on the fraction of surface covered by receptors: from these considerations, we see that those parameter results only make sense once the geometry has been fixed so that determining the fraction covered determines the perimeter of individual receptors.

Another interesting case to consider is a circular absorber of radius s, considered on a reflecting plane. If the concentration at infinity is u_0, then the diffusion current into the disk is

$$I = 4Dsu_0 \tag{2.9}$$

(a derivation can be found in Crank (1980)). This represents the case of a particle near the surface of a sphere that only has one receptor. This planar pore solution has been the basis for much of the recent work in approximating capture distributions, Lindsay et al. (2016). By summing up the contributions of individual pores and correcting for the pore-pore interactions, one can approximate the flux through a finite set of pores.

2.2.1   Matching the Asymptotics for the Spherical Cell

The expressions for the rate of absorption for a receptor on the plane and the sphere are somewhat similar, so Berg assumes that a non-absorbing sphere with small receptors on the surface would have a similar rate of absorption to that of the plane. The idea to estimate this rate is that for N small receptors on a sphere the rate should be something like $4DNsu_0$, the sum of the rate for an individual pore ignoring pore-pore interactions. As the sphere gets more and more covered, the rate should approach a perfectly sphere rate $4\pi DRu_0$. Berg appeals to an electrical analogue and matches these asymptotic limits to argue that the absorption rate would be

$$I = \frac{4\pi DRu_0}{1 + \frac{\pi R}{Ns}} \tag{2.10}$$

The insight from this equation is that N does not have to be very big for the absorption rate to be almost the same as the completely absorbing sphere. The biological perspective is that a cell can carry a few small receptors for many different antigens and still be nearly as efficient at capturing antigens as if the cell was dedicated to just one type of antigen.

2.3   Refining Berg and Purcell: Homogenization and Pore-Pore Interactions

The difficulty in studying the problem of small circular receptors is that the boundary conditions for the differential equation are heterogeneous, and are thus difficult to analyze analytically. One way to get around this is to imagine a particle far from the surface relative to the pore radius. Since the time to capture in this case mostly depends on getting to the surface, the exact geometry of how the receptors are arranged would seem to be negligible in determining the capture time distribution. This intuition leads one to consider homogenization, replacing the heterogeneous problem with a homogeneous problem. Berg and Purcell essentially had this approach, although recent work has been more explicitly focused on homogenization.
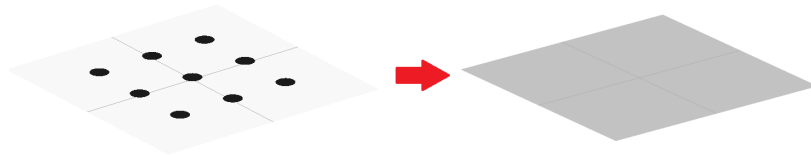
Figure 2.2   We seek to replace the heterogeneous boundary conditions with a homogeneous, semi-absorbing boundary condition.

Zwanzig (1990) applied a homogenization process to derive a modified form of Berg and Purcell's estimate for absorption rate with multiple small receptors on the surface of the sphere. Homogenization depends on making the plane semi-absorbing, with some "stickiness" parameter κ. Zwanzig's reasoning was that the effective κ would be a weighted average of the purely absorbing and purely reflecting case. This gives

$$\kappa(\sigma) = \frac{4D\sigma}{\pi a(1 - \sigma)}$$

Although this expression was for finitely many pores on a sphere instead of the planar problem, it is noteworthy in that the limiting behavior of κ is correct: as $\sigma \to 0$, $\kappa \to 0$, and as $\sigma \to 1$, $\kappa \to \infty$.

For the planar problem with finite pores, estimates for κ can be derived by summing the solution for a single pore, and then correcting for pore interactions to higher orders until the desired accuracy is achieved. Examples

of this approach are . However, with an infinite number of pores, the sum used with the finite pores does not work because the sum diverges. Perhaps for this reason, previous research on the infinitely tiled plane has relied on heuristically guessed formulations. In Berezhkovskii et al. (2006), a homogenization formula for κ is given as

$$\kappa(\sigma) = \frac{4D}{\pi a} \left(\frac{\sigma(1 + A\sqrt{\sigma} - B\sigma^2)}{(1 - \sigma)^2} \right)$$

where A and B are fit for different tiling geometries. This formula was guessed by numerically estimating κ and then guessing the scaling as $\sigma \to 0$ and $\sigma \to 1$.

Muratov and Shvartsman (2008) reconsider homogenization of a periodic array of receptors, the problem I first evaluate in this thesis. An interesting result from this paper is the exact solution by Moizhes for the homogenization parameter for the case of a plane tiled with infinite stripes. The exact solution came from a complex variables method, and is given by

$$\kappa(\sigma) = -\frac{\pi\sigma}{\ln \sin \frac{\pi\sigma}{2}}$$

This formula is useful for evaluating the accuracy of the numerical results against an exact solution. It also contains a logarithmic term in the denominator, which hints at a dependence on the Green's function because of the two dimensional nature of the stripes problem.

More recent questions consider various modifications of the problem. Berezhkovskii et al. (2014) continues a homogenization approach to treating the geometry of receptor layout, in the case of clusters of pores. The approach with small clusters is to replace a cluster of small pores with one equivalent pore. For well-localized traps, this strategy may be more effective than an overall surface homogenization.

2.4   Kinetic Monte Carlo

One way statistics can be computed for capture times is through a Monte Carlo simulation. Random walks are simulated by taking random steps on a lattice, and the geometry of the problem is coded in to terminate the walk when the particle has been captured. The number of steps is recorded, and the algorithm is repeated many times to capture the distribution. An example of such an approach is Northrup (1988). In Northrup's simulation,

this standard Monte Carlo technique is used to evaluate Berg and Purcell's estimation with regards to the number of receptor sites. The paper finds that the Berg and Purcell approximation matches the numerics in the limits of small numbers of receptors and nearly completely absorbing spheres, but deviates in the middle region. One trick the paper uses to evaluate different geometrics is saving the random walk trajectories away from the surface for the simulated particles. Then the computation of capture time is done separately, so that the computationally intensive step of generating the trajectory can be used multiple times over different geometries. This trick is an attempt to help reduce the inherent difficulty with lattice based methods on an unbounded domain, which is that some walks can take a very large number of steps before they are captured, especially if the particle starts far away or the pores are very small. We seek to solve this computational issue.

Simulating random walks step-by-step is one way to go about this problem, but a more powerful way that is employed here is called Kinetic Monte Carlo (KMC). In KMC, the diffusion process is broken into steps, where each step corresponds to a diffusion problem on a simpler geometry that can be solved analytically. For example, in the case of a reflecting plane with periodic absorbing receptors, the distribution of time and location to the plane can be solved exactly and then sampled to hop the particle down. This way, long trajectories where the particle may float around for many many time steps before eventually returning to the plane can be modeled precisely and efficiently. This method was laid out by Opplestrup et al. (2006) in the context of simulating large N-body problems. The application is different, but the underlying idea of sampling known distributions to speed up convergence time is very useful in simulating these capture problems. Another paper using this method for Brownian motion simulations is in Wu and Lu (2006). This paper uses statistics of passage time to the sphere to speed up simulation of diffusion in the context of sphere-receptor problems in chemical reactions.

Chapter 3

The Half-Plane Problem

Consider the capture problem of a particle that starts above an infinite plane periodically tiled with circular receptors. The geometry can be seen in Figure 3.1
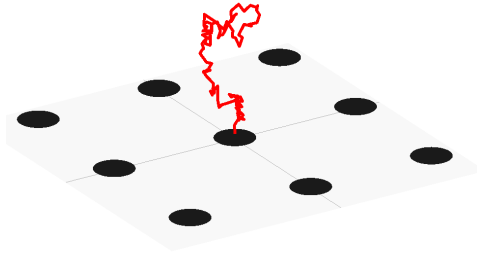
Figure 3.1   The half-plane capture problem geometry.

The partial differential equation that describes the probability density function for the position of the particle over time is

$$u_t = \nabla^2 u, \; z > 0 \tag{3.1}$$

$$u(x, y, z, 0) = \delta(x - x_0)\delta(y - y_0)\delta(z - z_0) \tag{3.2}$$

$$u(x, y, 0, t)|_{\partial\Omega^a} = 0 \tag{3.3}$$

$$\frac{\partial u(x, y, 0, t)}{\partial z}|_{\partial\Omega^r} = 0 \tag{3.4}$$

where $\partial\Omega^a$ is the (Dirichlet) absorbing receptors and $\partial\Omega^r$ is the (Neumann) reflecting boundary. Due to the heterogeneous boundary conditions, this problem is not easily solved by conventional methods. We seek to replace

this problem with a homogenized problem of

$$u_t = \nabla^2 u \tag{3.5}$$

$$u(x, y, z, 0) = \delta(x - x_0)\delta(y - y_0)\delta(z - z_0) \tag{3.6}$$

$$\frac{\partial u(x, y, 0, t)}{\partial z} = \kappa u(x, y, 0, t) \tag{3.7}$$

This PDE represents a semi-absorbing problem, where the flux through the plane is proportional to the concentration near the plane . The "stickiness" parameter κ determines how absorbing the plane is, and is the main parameter to estimate in homogenizing the problem. The goal is to derive κ in terms of the parameters of the problem, i.e. the proportion of the plane covered by receptors and the initial height above.

3.1   Semi-Absorbing Plane

The semi-absorbing plane problem can be written in one dimension with homogeneous boundary conditions as

$$u_t = u_{xx} \tag{3.8}$$

$$u(x, 0) = \delta(x - x_0) \tag{3.9}$$

$$\frac{\partial u(0, t)}{\partial x} = \kappa u(0, t) \tag{3.10}$$

To solve this, we will solve a transformed problem where the transformation is a trick from Carslaw and Jaeger (1959). Consider the linear operator $L[v] = \frac{\partial v}{\partial x} - \kappa v$. Let $\phi(x, t) = L[u]$. Then ϕ must satisfy

$$\phi_t = \phi_{xx} \tag{3.11}$$

$$\phi(x, 0) = \delta'(x - x_0) - \kappa\delta(x - x_0) \tag{3.12}$$

$$\phi(0, t) = 0 \tag{3.13}$$

We can solve for ϕ by the method of images using the Green's function for the heat equation. If we denote the Green's function $G(x, t)$, then

$$\phi(x, t) = G_x(x + x_0, t) + G_x(x - x_0, t) - \kappa[G(x - x_0, t) - G(x + x_0, t)]$$

To solve for $u(x, t)$, we solve the equation

$$u_x - \kappa u = \phi$$

Using an integrating factor,

$$(e^{-\kappa x}u)_x = e^{-\kappa x}\phi(x,t)$$

$$u = e^{\kappa x}\int_x^\infty e^{-\kappa x'}\phi(x',t)dx'$$

Now the function we are interested in is given by the flux at the origin, $u_x(0,t)$. We have by differentiating

$$-u_x(x,t) = \phi(x,t) + \kappa e^{\kappa x}\int_x^\infty e^{-\kappa x'}\phi(x',t)dx'$$

Because $\phi(0,t) = 0$,

$$u_x(0,t) = -\kappa\int_0^\infty e^{-\kappa x'}\phi(x',t)dx'$$

Plugging in the Green's function solution for $\phi(x,t)$ and integrating gives us the distribution of time to absorbtion as

$$F(t) = \frac{\kappa}{\sqrt{\pi t}}e^{-\frac{x_0^2}{4t}} - \kappa^2 e^{\kappa(\kappa t + x_0)}\text{erfc}\left(\frac{2\kappa t + x_0}{2\sqrt{t}}\right) \tag{3.14}$$
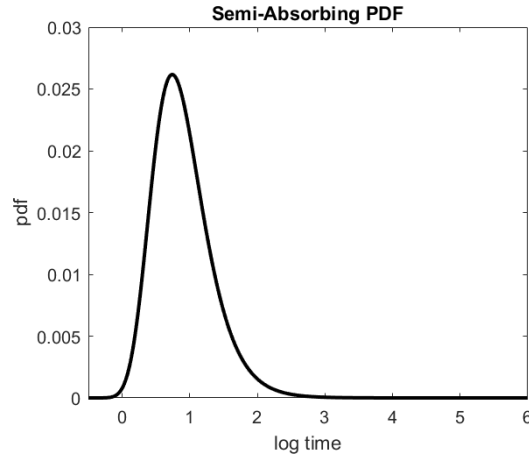

Figure 3.2   The semi-absorbing probability density function, shown on a log scale in time.

This function, shown in Figure 3.2 gives us the relationship between time, height above the plane, and the constant κ that will be used to estimate a function for κ given simulations.

Chapter 4

The Kinetic Monte Carlo Method

To estimate the time distribution to absorption, I wrote a diffusion simulator that uses the Kinetic Monte Carlo method. The historical method to simulate particle diffusion is by moving a particle in random spatial steps, a random walk on a lattice. This can be a powerful method, but it fails in our circumstance for a simple reason: for geometries where a small fraction of the surface is absorbing, the particle can take a very long time to be absorbed, and may spend a lot of time wandering aimlessly around. This slows down runtime, and limits the number of particles one can realistically simulate. Instead, we take advantage of the fact that the diffusion equation may be solved exactly for certain geometries, namely diffusion to the plane and diffusion to a surrounding sphere.

There are two repeated steps in the periodic plane algorithm. The first is to jump the particle from its starting location above the plane to the plane by sampling from an exact joint distribution. The complete joint distribution for this can be found by solving the three dimensional heat equation and computing the flux through the plane. Then time and location can be integrated out, and inverse sampling can be used to generate random samples of this distribution. Once on the plane, a check is performed to see if the particle has been captured. If it has, the algorithm terminates. If it has not, the next step is executed, which is to bounce off the plane. Bouncing off the plane is equivalent to diffusing to a hemisphere around the particle. In order to optimize runtime, the radius of this hemisphere is chosen to be the

distance from where the particle is on the plane to the nearest absorber. The jump to the plane step is then repeated, and the process continues until the particle is eventually absorbed. In order to implement this method, we must first solve the two PDE problems, the joint distribution to the plane and the joint distribution to the sphere.
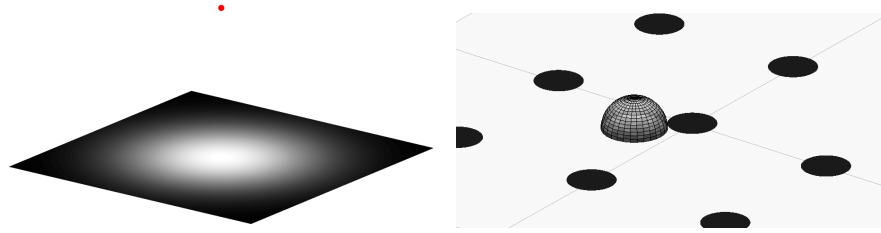
a. The particle is projected onto the plane by sampling an exact spatial probability distribution of where it will land.

b. The particle is jumped to a random location on a small hemisphere above the plane.

Figure 4.1   The two steps in hopping a particle with the Kinetic Monte Carlo method.

4.1   Joint Distribution to the Plane

Transit time to the plane is given by the solution to the one-dimensional PDE

$$u_t = u_{xx} \tag{4.1}$$

$$u(x, 0) = \delta(x - x_0) \tag{4.2}$$

$$u(0, t) = 0 \tag{4.3}$$

This can be solved with a Green's function as

$$u(x, t) = \frac{1}{2\sqrt{\pi t}} \left(e^{-\frac{(x-x_0)^2}{4t}} - e^{-\frac{(x+x_0)^2}{4t}} \right) \tag{4.4}$$

The flux through the boundary describes the transfer time, so differentiating at $x = 0$ we get

$$u_x(0, t) = \frac{x_0}{2\sqrt{\pi} t^{3/2}} e^{-\frac{x_0^2}{4t}} \tag{4.5}$$

This is the probability distribution of transit time to the plane. The cumulative distribution function is given by

$$F(t) = \int_0^t \frac{x_0}{2\sqrt{\pi}\tau^{3/2}} e^{-\frac{x_0^2}{4\tau}} d\tau = \text{erfc}\left(\frac{x_0}{2\sqrt{t}}\right) \tag{4.6}$$

Deriving this equation has two main uses for analyzing the problem of measuring time to absorption. The first is that it describes the case where the surface is completely absorbing, and so any expression for the mixed boundary condition case should tend to this distribution in the limit of larger absorbing area. The second is that we can use this distribution in the Kinetic Monte Carlo simulation to "jump" the particle forward to the plane.

4.2   Time Distribution to the Sphere

Choosing a random location on a sphere is a well-known problem, but the time dimension requires a bit more thought. A formula from Litwin (1980) gives the cumulative time distribution as

$$F(t) = 1 + 2\sum_{n=1}^{\infty}(-1)^n e^{-\left(\frac{n\pi}{r}\right)t} \tag{4.7}$$

This may be derived by solving the PDE problem

$$u_t = \nabla^2 u \tag{4.8}$$

$$u(\rho, \theta, \phi, 0) = \delta(\rho) \tag{4.9}$$

$$u(1, \theta, \phi, t) = 1 \tag{4.10}$$

This problem can be solved by separation of variables, and then a Fourier transform in the radial direction. Expression 4.7 is $u(1, t)$.

The sum in 4.7 converges quickly for large t, but for not for small t. However, a theta function identity can be used to invert the dependence on t. The Fourier identity

$$\sum_{n=-\infty}^{\infty} e^{-\pi t(n+a)^2} = \sum_{n=-\infty}^{\infty} t^{-1/2} e^{-\pi n^2/t} e^{2\pi i n a} \tag{4.11}$$

from Chapter 4 of Stein and Shakarchi (2003) can be applied to this function. Substituting $a = \frac{1}{2}$ and rewriting the sums as sums from 1 to ∞, we get

$$F(t) = 2\sqrt{\pi} t^{\frac{1}{2}} \sum_{n=1}^{\infty} e^{-(n+\frac{1}{2})^2\frac{\pi^2}{t}} \tag{4.12}$$
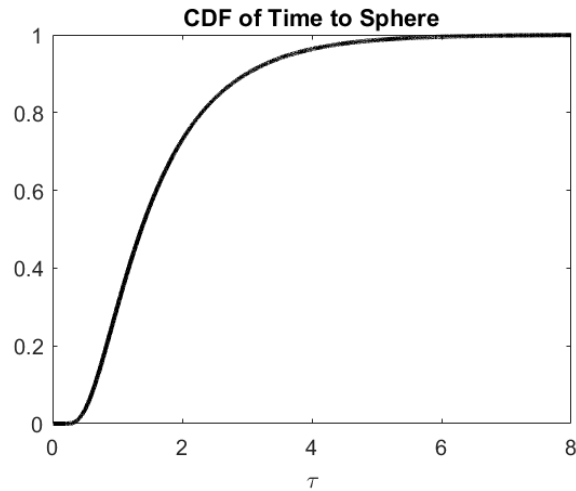
Figure 4.2   The transit time to the sphere. For large times, the expression 4.11 is used. For small times, 4.12 is computed instead.

This function is shown in Figure 4.2. These approximations are used for appropriate time scales, and the function is numerically inverted to sample the time distribution to the hemisphere.

4.3   Fitting κ

With these distributions in hand, we can simulate a large number of particles and have a model that should fit this distribution. That leaves us with the optimization problem of fitting κ. Here I consider two optimization objectives. The first is to compute both the theoretical cumulative distribution function and the empirical cumulative distribution function, and then minimize the average squared error difference between the two curves. If $CDF(\kappa, t)$ denotes the theoretical CDF, and $\overline{CDF}(\kappa, t)$ denotes the estimated CDF, then the error function is

$$\sum_{i=1}^{N}(CDF(\kappa, t_i) - \overline{CDF}(\kappa, t_i))^2$$

The second objective function is a maximum likelihood approach, where

the probability of observing a set of times **t** given a particular κ is given by

$$P(\mathbf{t}|\kappa) = \prod_{i=1}^{N} P(t_i|\kappa)$$

We can then maximize the expression

$$\sum_{i=1}^{N} \log P(t_i|\kappa)$$

Comparing the two objective functions gives a check on consistency in computing κ. To get an estimate of the error in fitting κ by either method, a bootstrap is performed where the set of times is resampled with replacement, and then κ is refit. A set of κ estimates is computed; the standard deviation of the κ estimates is an estimate of the uncertainty in κ. This bootstrap estimation of the uncertainty is repeated 20 times, where each sample is a resample of as many entries in the time to capture set, typically 10^5 or 10^6 data points.

4.3.1   Downside of the Method: Large σ

An underlying assumption of the κ estimation method as described so far is that the time distribution to the sphere is sensitive to κ. This assumption is accurate for a surface that has a small fraction of its surface covered, but for surfaces that are mostly absorbing, this assumption breaks down. The reason is that in the almost completely absorbing case, the time distribution to the plane is dominated by particles that never hit the reflecting surface. We get a sampling problem, where few of the particles give meaningful information that could distinguish between different κ parameters. This issue could be fixed by starting particles randomly on the reflecting regions, but the theory would have to be adapted to fit a modified time distribution.

Chapter 5

Asymptotics

We have seen that κ may be determined numerically for a particular geometry using the Kinetic Monte Carlo method. Here we investigate the problem of finding an asymptotic expression for κ derived by approximating the problem in limits of small receptors.

5.1 The Asymptotic Approach: Linear Steady State Approximation

The idea to finding an expression for κ asymptotically is to take advantage of the fact that the size of the absorbing traps is small in comparison to the diffusion length of the particle. This implies that if the length scale of the trap is ϵ, then we want to consider heights z above the plane where

$$\epsilon \ll z \ll 1$$

In this region, we expect that the concentration u is roughly linear, and thus follows the steady-state PDE

$$\nabla^2 C = 0$$

$$\lim_{z \to \infty} C \approx a + bz$$

$$C(x, y, 0) = 1 \text{ on } \partial\Omega^a$$

$$C_z(x, y, 0) = 0 \text{ on } \partial\Omega^r$$

Where C is linear, the far-field solution assuming homogeneous boundary conditions $C_z(x, y, 0) = \kappa C(x, y, 0)$ is approximately

$$C \approx z + \frac{1}{\kappa}.$$

Now we obtain a new problem,

$$C(x, y, z) = z + \frac{1}{\kappa} - \phi(x, y, z)$$

so that

$$\nabla^2 \phi = 0$$

$$\lim_{z \to \infty} \phi(x, y, z) = 0$$

$$\phi(x, y, 0) = \frac{1}{\kappa} \text{ on } \partial\Omega^a$$

$$\phi_z(x, y, 0) = 1 \text{ on } \partial\Omega^r$$

This new problem lends itself to various asymptotic approximation methods, such as complex variables methods and Green's function asymptotic methods.

5.2   The Stripes Problem: Complex Variables Methods

If the problem is two dimensional, complex variables methods may be used to solve Laplace's equation. If an analytic complex function can be written down that satisfies the boundary conditions properly, the real component will necessarily satisfy the PDE. In our case, if the geometry of the traps on the plane is a set of alternating absorbing and reflecting stripes, then the problem becomes a two dimensional problem. The complex variables solution to the stripes problem given by Muratov and Shvartsman (2008) is

$$u(x, y) = \text{Re}\{w(x + iy)\}$$

where

$$w(z) = iz + \frac{2i}{\pi\sigma} \arccos\left(\frac{\sin(\frac{\pi\sigma z}{2})}{\sin(\frac{\pi\sigma}{2})}\right).$$

If we want κ as a function of σ, we get the expression

$$\kappa(\sigma) = -\frac{\pi\sigma}{2 \ln \sin(\frac{\pi\sigma}{2})} \tag{5.1}$$

This exact formula is both useful for evaluating the kinetic Monte Carlo method, as well as for providing some insight into how absorption time changes with varying σ.

5.3   Green's Function Approach

A Green's function approach to this problem is given in Bernoff and Lindsay (2017). The method presented there solves for the flux in the case of finitely many pores on the plane. Their final expression for the flux for circular traps of radius a is

$$J = 4aDN \left[1 - \frac{2a}{N\pi} \sum_{j \neq k} \frac{1}{|x_j - x_k|} + \frac{4a^2}{N\pi^2} \sum_{j \neq k} \sum_{i \neq j} \frac{1}{|x_j - x_k||x_i - x_j|} + O(a^3) \right].$$

(5.2)

This formula is derived by asymptotically expanding the solution near each pore, solving near each pore by a superposition of Green's functions, and then matching the expressions in the far-field. The importance of equation 5.2 is to show the relationship between the spatial configuration of finitely many pores and the flux. For our purposes here, the Green's function approach is a way to approximate the heterogeneous steady-state problem proposed in Section 5.1. Variations on the method used to derive this result may be used for the case of infinite periodic pores. This approach will be shown in the forthcoming Bernoff et al. (2017), where the result for κ as a function of σ is the asymptotic expression

$$\kappa(\sigma) \approx 4 \sqrt{\frac{\sigma}{\pi}} \left[1 - \frac{4R_{00}\sqrt{\sigma}}{\sqrt{\pi}} \right]^{-1}$$

(5.3)

where $R_{00} \approx 0.5654$.

Chapter 6

Results

The research process shows early success in fitting the homogenization parameter κ after simulating a particle capture. Simulating $100,000$ particles with about 5% of surface absorbing takes under a minute on my Lenovo X1 laptop. The current code takes advantage of MATLAB's fast vectorized implementation of matrix computations using a batch resizing algorithm.

6.1 Quality of the κ Fit

The current method that has been most successful in fitting κ to the simulated data is to minimize the mean square error between the empirical cumulative distribution of times to capture and the homogenized cumulative distribution function. The fit qualitatively matches the observed data, with absolute error less than 10^{-3}.
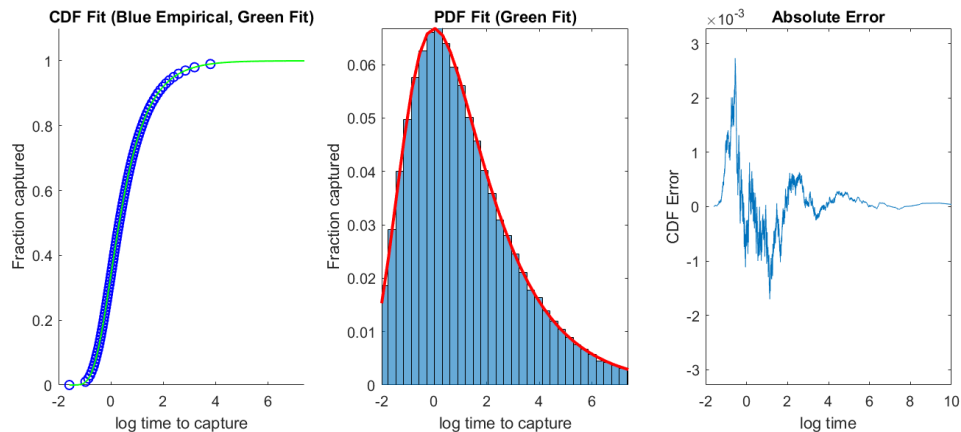
Figure 6.1   The fit distribution compared to the observed times. The CDF qualitatively fits, the histogram matches the distribution, and the absolute error is less than 10^{-3} for all times. This simulation was done with 10^5 particles, $\sigma = 0.2$.

Of note in looking at the distribution in Figure 6.1 is that the tail on the time distribution is long. This means that quantitative analysis of first capture time based on the mean of this distribution will significantly overestimate the typical time to capture, and experimental data on this quantity will be easily skewed by a few results. Rather, the mode of the data seems to capture more information about a typical time to capture, with the caveat that some particles may take a very long time to be captured.

Figure 6.1 also shows for what times homogenization is a good approximation. For large times, both cumulative density functions approach one. In the intermediate region, the error looks like a random walk, which should be due to the step function form of the empirical CDF. For very small times, the distribution seems to not fit quite as well, but this fits the assumptions of the problem. Particles that never bounce along the surface break the homogenization assumption, so we would expect that these small times are where the approximation is least accurate. But most importantly, the large mode of the distribution appears well-fit by the homogenization approximation.

6.2   Stripe Absorbers

Here we compare the exact formula for $\kappa(\sigma)$ given in equation 5.1 to κ estimated via Kinetic Monte Carlo.
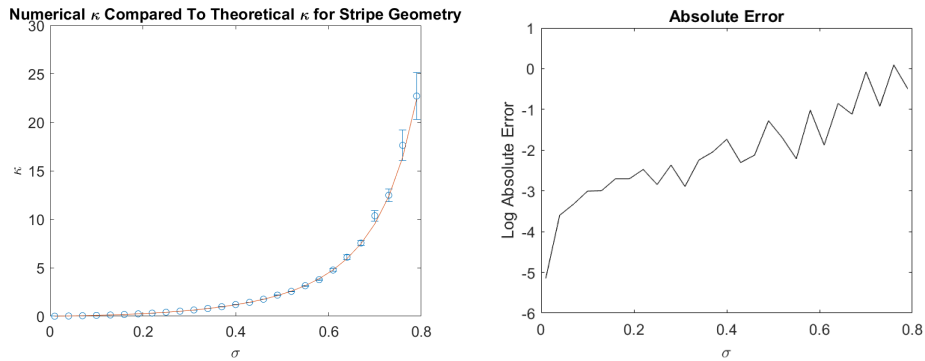
Figure 6.2 Comparison of derived dependence of κ on σ and estimated κ. The simulation method appears to be more accurate for smaller σ.
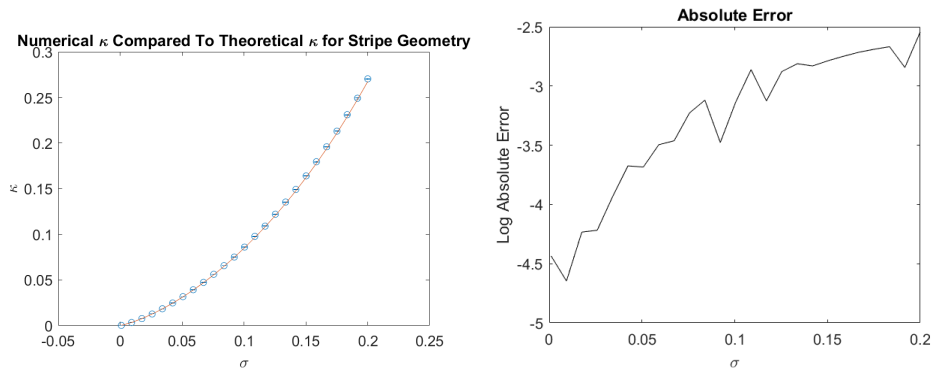

Figure 6.3 More simulated points showing the accuracy for small σ.

In the case of stripe absorbers, Figure 6.2 shows the agreement between the numerically estimated κ and the theoretically predicted formula for a plane covered periodically with stripes. Each estimation of κ is done for 10^6 particles, and the error bars are estimated with a bootstrap method.

6.3 Periodic Pores

We do not have an exact formula for $\kappa(\sigma)$ in the periodic pore geometry. Here the asymptotic result from equation 5.3 is compared to KMC estimates for $\kappa(\sigma)$.
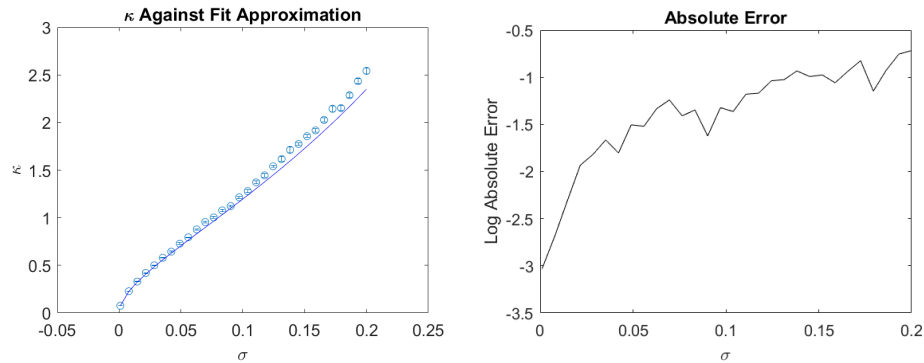
Figure 6.4   Estimated κ for small σ compared to the asymptotic approximation given in Bernoff et al. (2017). Each point is a simulation of 10^6 particles.

For pores periodically arranged on a square lattice, κ as a function of σ is shown in 6.4. Here we note a few important results. One is that the asymptotic approximation captures the limiting behavior as $\sigma \to 0$ of the decay as $\sqrt{\sigma}$. The second is that there is an intermediate near-linear region, and the asymptotic approximation seems to do well there as well. In Figure 6.5, we see the breakdown of the accuracy in estimating κ for $\sigma \to 1$. From the numerical approach, the difficulty is in getting enough samples that reflect off of the surface. We also see the divergence of the asymptotic estimate from the numerical estimate.
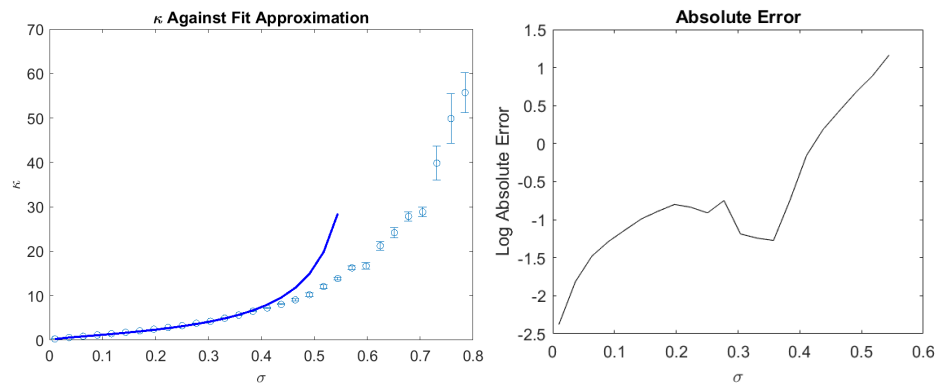

Figure 6.5 $\kappa(\sigma)$ for the entire range of possible σ under this geometry. The asymptotic approximation breaks down in estimating κ around $\sigma \approx 0.5$.

Chapter 7

Conclusions and Future Work

Kinetic Monte Carlo methods are an accurate and efficient way to simulate particle diffusion for problems where exact solutions to the diffusion equation can be computed. This simulation method has been used to compute κ in the striped and square lattice of pores absorbing geometries on the infinite reflecting plane. Comparison to approximations for κ shows the accuracy of the method and provides an evaluation of new asymptotic results.

Future work on this problem would be to extend the Kinetic Monte Carlo method to the sphere problem. The challenge with the sphere problem is in the second hop step that would hop off of the surface. Hopping to a hemisphere is not possible due to the sphere geometry: the exact diffusion problem of two intersecting spheres with reflection on the surface and absorbing on the outer sphere is not easy. There are a few possibilities. One is to use more traditional lattice-based random walk simulation for this step. Another could be to map the spherical geometry to planar, sample to the hemisphere, and then map back. In any case, the sphere problem can be simulated with the KMC method, it is just more challenging to solve the exact distributions.

Another direction for future work would be to investigate a variety of different pore geometries, whether on the plane or on the sphere. These issues have been investigated to some extent in Berezhkovskii et al. (2014), but with new results for the infinitely tiled plane and with the Kinetic Monte Carlo method, the results presented there could be refined and made more precise.

Finally, the Kinetic Monte Carlo method as described here applies to static problems, where the geometry is fixed. In real world applications, traps are often moving or changing in time: cells do not sit still and wait for

particles to float to them. It is potentially possible to generalize the Kinetic Monte Carlo method to time-dependent problems, it becomes a matter of solving potentially more complicated time dependent diffusion problems.

I have very much enjoyed working on this problem. Random walk problems are fascinating to me, both due to the breadth of their applications and to the mix of mathematics involved in studying them.

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