Thermal motion of small particles

Diffusion

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Yes Yes !!!.

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Contents

Introduction

- Why is diffusion interesting...

- what are the key global principles?

The physical processes of the world around us act very strangely in the regime of the nano-world. Some notable differences are the scale of electrostatic forces, drag forces of different media, and thermal effects. Of the three mentioned, thermal effects are a driving force of motion. From an energetic perspective, the equipartion theorem states that for each degree of freedom the kinetic energy applied is given by:

$$E_{\mathbf{kin}} = \frac{3}{2} k_B T \tag{1}$$

In a world where there are no frictional losses and all energy is transformed into kinetic energy, the average speed of a particle is then scaled according to:

$$|v_i|^2 = \frac{k_B T}{m} \tag{2}$$

where i denotes the basis of the vector direction, k_b is the Boltzmann constant, and T is temperature. This intermediate result shows that as $k_B T \propto m$ the mean square velocity is clearly non-zero. This in turn results in a net displacement, or a **Diffusive Process**.

This energetic reality motivates the need to study processes that describe the microscopic movement of particles in more realistic systems including the aforementioned contributions. In addition, a general framework of such processes should be of interest, that of which includes not only fluid contributions, electromagnetic, but also to an extent quantum effects.

The relevant systems which this applies to can be found in various fields such as biological physics, chemical engineering, heat processes and many others.

Chapter 1

1.1. Diffusion from mass conservation

To begin discussion about diffusion, it is necessary to derive it from basic physical origins.

The particles in a solution can be defined in terms of a commonly measurable quantity: concentration. The concentration of a fluid can be measured by terms of mass per volume, or $\frac{g}{ml}$ for instance.

Thus, the flow of concentration can be modeled via the physical law of mass conservation. Specifically, since the flux at the boundaries of a tube is equation to the change in the concentration in the volume, the law takes on the following form:

$$V\frac{\partial c(x,t)}{\partial t} = A_{\text{in}}Q(x+\Delta x,t) - A_{\text{out}}Q(x,t) \tag{1.1}$$

Where V is the volume, A is the cross-sectional area of the flow. As we can note, the units that both sides of the equation hold are units of mass. Thus, by expanding the volume in terms of cross-sectional area times an infinitely small displacement Δx, $V = A\Delta x$. Note that this forces both areas to be identical in the limit of $\Delta x \to 0$.

$$\frac{\partial c(x,t)}{\partial t} = \frac{Q(x+\Delta x,t) - Q(x,t)}{\Delta x} \tag{1.2}$$

Then, by taking the limit:

$$\frac{\partial c(x,t)}{\partial t} = \frac{\partial Q(x,t)}{\partial x} \tag{1.3}$$

Then, noting that the unitary relationship between the concentration and the flux is a spatial term in the denominator. However, this is ad hoc. Rigourous treatment of this is difficult as it relies on the principle of a relationship between concentration of particles and flux thorugh a surface. This is simply stated as $Q = -D\frac{\partial c}{\partial x}$. Thus, we arrive at the one-dimensional diffusion equation.

$$\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{1.4}$$

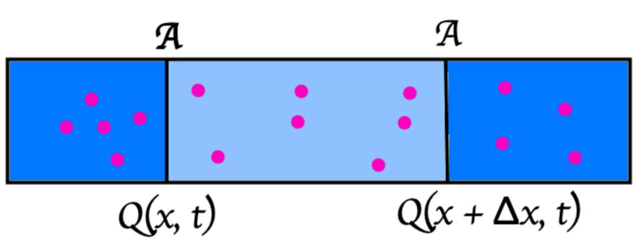
This result is expected from the treatment of particles as fluids. Curious readers may recall this is the form of the heat equation, which holds the same principle of conserved mass. As in the heat equation, the three dimensional case of this equation naturally extends via the Laplace operator. This will later be formulated in anisotropic diffusion, however, for now, the big picture of diffusion is then given by the following equation:

$$\frac{\partial c(\vec{r},t)}{\partial t} = D\nabla^2 c(\vec{r},t) \tag{1.5}$$

1.2. Solutions of the differential model

Given the powerful model of diffusion derived, there are important physical quantities which should be uncovered, right? First, lets solve the diffusion equation and interpret the results. For simplicity, we will return to the 1-dimensional case, which should describe the physical principles in a digestible way.

To solve the linear 2nd order PDE, the solutions can be easily derived as found in appendix A.



1.3. Conclusions

The differential formulation of diffusion provides insight to the bulk behavior of molecules on the macro scale. In the context of large-scale systems, such as particle dispersion, heat diffusion, or other similar processes, this describes the time-dependent equations on which the process evolves. In the large-scale, ergodic limit, all possible states are highly likely to be filled given the assumption all particles are equal. Further discussions in this regime fall under details of materials and diffusion tensors, which are applicable in the context of medical imaging, engineering, and other applied sciences. The discussion of the diffusion tensor is left to the appendix as it is pretty cool, but not relevant to my studies.

Chapter 2

The single molecule approach to diffusion is a very intuitive picture of how microscopic things move. This formulation emphasizes itself on how the motion of a single particle causes the macroscopic properties of diffusion, as deduced by the macroscopic picture, to naturally arises, proving themselves.

The discussion of non-equilibrium diffusion is a discussion about Brownian motion, or the random movement of particle in a thermal bath. Recalling some basic properties from equilibrium statistical mechanics, the possible states of a particle can be described by the Hamiltonian. This formulation assumes no losses and other annoying effects, however, it paints a picture for how to treat Brownian motion. In a potential, a simple, ideal particle will have the partition function given by the following sum:

$$Z = \sum_{\{i\}} \mathbf{exp}[-\beta(\mathscr{H})] \tag{2.1}$$

Where $\mathscr{H} = \frac{1}{2} m_i \dot{x}^2 + V(x, \dot{x})$. The sum $\{i\}$ denotes the sum over all possible states. What this fundamental equation describes is that the number of combination scales with the total energy in the system. Given a unique, or complicated potential, the total set of particles and some influx, or Canonical exchange of energy, such as a heat bath, there will be a set of possible energy states which the particle will take on.

So, a Brownian particle is placed into a heat bath, what now? Given that the particle will undergo thermodynamic heat transfer, the particle will gain energy. Due to the consequences of the equipartition theorem, we can deduce that the thermal energy will couple with the kinetic properties of the particle.

$$\begin{aligned} T = \frac{1}{2} m\dot{x}^2 &= \frac{1}{2} k_b T \\ \rightarrow \dot{x} &= \sqrt{m k_b T} \end{aligned} \tag{2.2}$$

This energetic result causes the particles to move in a violent, stochastic manner. This property is the sole cause of Brownian motion.

2.1. Langevin Equations

To start the journey into this beautiful realm of mathematics, Newton's law (of course!) is enacted. To be accurate, we must account for a simple particle in empty space. There is no resistances, that is, there is no friction. In the case of a thermal bath, such as that of a non-reactive, ideal gas the contributions to the forces of the particle will be stochastic in direction. This stochastic force is a stochastic process[1] which describes the vector addition of forces to the particle.

The properties of this stochastic force have great significance. As a start, lets assume a simple process where there is a large heat reservoir which places a uniformly random direction and constant intensity impulse each time step. Denote this random variable $\vec{\eta}(t)$. Newton's law then reads:

$$m\ddot{\vec{x}} = \vec{\eta}(t) \tag{2.3}$$

To obtain the equation of motion from this equation, we can simply take integrals over time.

$$\vec{x}(t) = x_0 + tx_1 + \frac{1}{m} \int_0^{t'} \int_0^t \vec{\eta}(t) dt dt' \tag{2.4}$$

Sadly, unless we know the exact trace of $\vec{\eta}$, this is incalculable. Instead, we can take a more natural quantity, the average and variance. In addition, working with position is difficult due to the coordinate system in place. in 3

[1] See Appendix for more details on this topic.

dimensions, the free movement of such a particle is non-holonomic in the sense that unless each step is kept track of, the overall position of the particle cannot be determined. Thus, in this formulation, it is easier to discuss the velocity of the particle.[2].

The velcotity of the particle is then described as:

$$\begin{aligned} \dot{\vec{v}} &= \frac{1}{m}\vec{\eta}(t) \\ \rightarrow \vec{v} &= \frac{1}{m}\int_0^t \vec{\eta}(t')dt' \end{aligned} \tag{2.5}$$

The average can be computed by averaging over all possible realizations (states) of η.

$$\langle \vec{v} \rangle = v_0 + \frac{1}{m}\int_0^t \langle \vec{\eta}(t') \rangle dt' \tag{2.6}$$

Since the average is uniform in all directions, the total average is 0, which stats that in the long-term, the particles net velocity is constant, equal to v_0.

This is perfectly valid, as the velocity is a stationary random process, which saids that the average velocity of the particle does not depend on time. However, this poses a problem. The average position can be calculated.

$$\langle \vec{x} \rangle = \vec{v}_0 t + \vec{x}_0 \tag{2.7}$$

This however, is deeply unphysical. I dont see particle moving infinitely due to a small initial velocity. The key detail in this formulation is a velocity dependent damping force[3]. The Langevin equation factors in a linear velocity term, which produces the fundamental equation for Langevin Brownian motion.

$$m\dot{\vec{v}} = -\lambda\vec{v} + \vec{\eta}(t) \tag{2.8}$$

The solution to this equation can be solved analytically. The solution is split into the homogenous and particle solution, which are both analytically solvable. The homogenous solution entails solving:

$$\begin{aligned} m\dot{\vec{v}} + \lambda\vec{v} &= 0 \\ \rightarrow v &= v_0\mathbf{exp}[-\frac{\lambda}{m}(t-t_0)] \end{aligned} \tag{2.9}$$

The particular solution can be solved by applying an integration factor of $e^{\frac{\lambda}{m}(t-t_0)}$. The langevin equation becomes:

$$\frac{d}{dt}\left(v\mathbf{exp}\left[\frac{\lambda}{m}(t-t_0)\right]\right) = \eta(t)\mathbf{exp}\left[\frac{\lambda}{m}(t-t_0)\right] \tag{2.10}$$

[2]A quick aside, the positional average and variance can be calculated simple given some constraints. For instance, if the particle was confined to a lattice, then the problem becomes a combinatorical problem which can be solved. For more information, see **[McCrea_Whipple_1940]**

[3]This isnt really well explained even in the literature. Intuitively, such this is okay, but im not sure how to physically 'prove' this is nessecary

Chapter 3

3.1. Motivation for measuring Diffusion

The diffusion coefficient is a measure of the positional uncertainty of small objects present in a thermal bath. From studies in the theory of thermal motion, we are aware that the diffusion of a body is independent from the mass. The Stokes-Einstein equation describes the diffusion to be inverse of the hydrodynamic radius:

$$D = \frac{k_b T}{6\pi\nu r} \tag{3.1}$$

In reference to applications, the diffusion coefficient is useful in several applications. In the field of atomic physics, the diffusion coefficient is related to the heat transfer of the mass constituented by the atoms. In biology, diffusive processes are often a dominant factor in several different biological functions. These include how vesicles transport, or how cells can move. Lastly, the applications of using the diffusion coefficient allow for devices and machines that utilize the random motion of diffusion to perform many tasks.

This chapter covers methods on measuring the diffusion coefficient in the lab. The applications will range from single-molecule measurements of diffusion to the bulk measurements, such as that of an ensemble of atoms. The benefits and downsides to many approaches are discussed in detail.

3.2. Single Molecule Studies of Diffusion

To study diffusion as we have discussed it, one obvious way to measure the diffusion is to simply *look* at the molecule moving around. From a collection of many movements, we can arrange a vector of the displacements over time.

Suppose that for some time-step interval, we have a set of consecutive photos of a molecule moving around. We can denote these photos as coordinates on a Cartesian grid and store them in a N-dimensional vector $\vec{x}$. The Smoluchowski equation, we know that the probability of a positional time step is proportional to the difference in time, Δt, and the difference in position, $\vec{\Delta x}$.

$$p(\vec{x}, t) = \frac{1}{\sqrt{2^{d+1}\pi D\Delta t}} \mathbf{exp}\left[\frac{(\vec{x} - \vec{x'})^2}{2^{d+1}D\Delta t}\right] \tag{3.2}$$

The resulting probability distribution is then realized based on the statistics of the trajectory, $\vec{x}$ as one would in a normal statistical analysis. Firstly, we note that this distribution will have a mean localized around 0 in the presence of free diffusion. Thus, unless there is a specific field of flow, assuming that the mean is 0 is a physically justified assumption. Secondly, the variance of this distribution is dependent on the number of dimensions that the diffusion is occuring in.

$$\langle x^2 \rangle = 2^d D\Delta t \tag{3.3}$$

Thus, by measuring the variance over a given time step interval, the trace of the variance, or mean, squared displacement (MSD) can be fitted against to obtain a diffusion coefficient. This method of obtaining the diffusion coefficient is known as MSD fitting.

3.2.1. MSD Methods

The class of MSD methods are simple yet powerful methods of obtaining the

Solutions to the Diffusion Equation

A.1. 1D free diffusion equation via Fourier Transform

The boundaries of the problem are stated that at very large x, the concentration is equation to 0. The easiest way to solve this equation is to use the Fourier transform. This is mainly due to the boundary conditions of this problem.

The diffusion problem starts with the equation of diffusion:

$$\partial_t c(x,t) = D\partial_{xx} c(x,t) \tag{A.1}$$

Take the Fourier transform of both sides. We can denote the Fourier transform as a hat $\widehat{c(x,t)}$.

$$\int_{-\infty}^{\infty} \partial_t c(x,t)\mathbf{exp}[-ikx]dx = \int_{-\infty}^{\infty} D\partial_{xx} c(x,t)\mathbf{exp}[-ikx]dx \tag{A.2}$$

The LHS of this equation is trivial due to Fubini's theorem.

$$\int_{-\infty}^{\infty} \partial_t c(x,t)\mathbf{exp}[-ikx]dx = \partial_t \widehat{c(x,t)} \tag{A.3}$$

The RHS can be simplified using an integration by parts.

$$\begin{aligned}\int_{-\infty}^{\infty} \partial_{xx} c(x,t)\mathbf{exp}[-ikx]dx &= \int_{-\infty}^{\infty} \partial_x c(x,t)\mathbf{exp}[-ikx](-ik)dx \\ &= \int_{-\infty}^{\infty} c(x,t)\mathbf{exp}[-ikx](ik)^2dx \\ &\rightarrow (ik)^2\widehat{c(x,t)}\end{aligned} \tag{A.4}$$

The full equation then reads:

$$\begin{aligned}\partial_t \hat{c}(k,t) = D(ik)^2\hat{c}(k,t) \\ \partial_t \hat{c}(k,t) + Dk^2\hat{c}(k,t) = 0\end{aligned} \tag{A.5}$$

Using an integration factor $\mathbf{exp}\left[\int Dk^2dt\right]$:

$$\partial_t\left[\hat{c}(x,t)\mathbf{exp}\left[Dk^2t\right]\right] = 0 \tag{A.6}$$

This can then be solved using a simple integration with respect to t. This gives the arbitrary constant some random dependence on k.

$$\hat{c}(x,t) = f(k)\mathbf{exp}\left[-Dk^2t\right] \tag{A.7}$$

The full solution is then given using the inverse Fourier transform.

$$c(x,t) = \int_{-\infty}^{\infty} f(k)\mathbf{exp}\left[-Dk^2t\right]\mathbf{exp}\left[ikx\right]dk \tag{A.8}$$

This is the solution in disguise. Since the initial condition implies that $c(x,0) = f(x)$, then, $\hat{c}(x,0) = f(k)$

This is demonstrated with the delta function. Given that a particle is fixed at the origin, the initial condition, or $f(k)$, is equal to 1 as the delta function and 1 is a Fourier pair.

$$c(x,t) = \int_{-\infty}^{\infty} \mathbf{exp}\left[-Dk^2t\right]\mathbf{exp}\left[ikx\right]dk \tag{A.9}$$

This is the inverse Fourier transform of the Gaussian function. Let $y = \sqrt{Dt}k$ and $\zeta = \frac{x}{\sqrt{Dt}}$

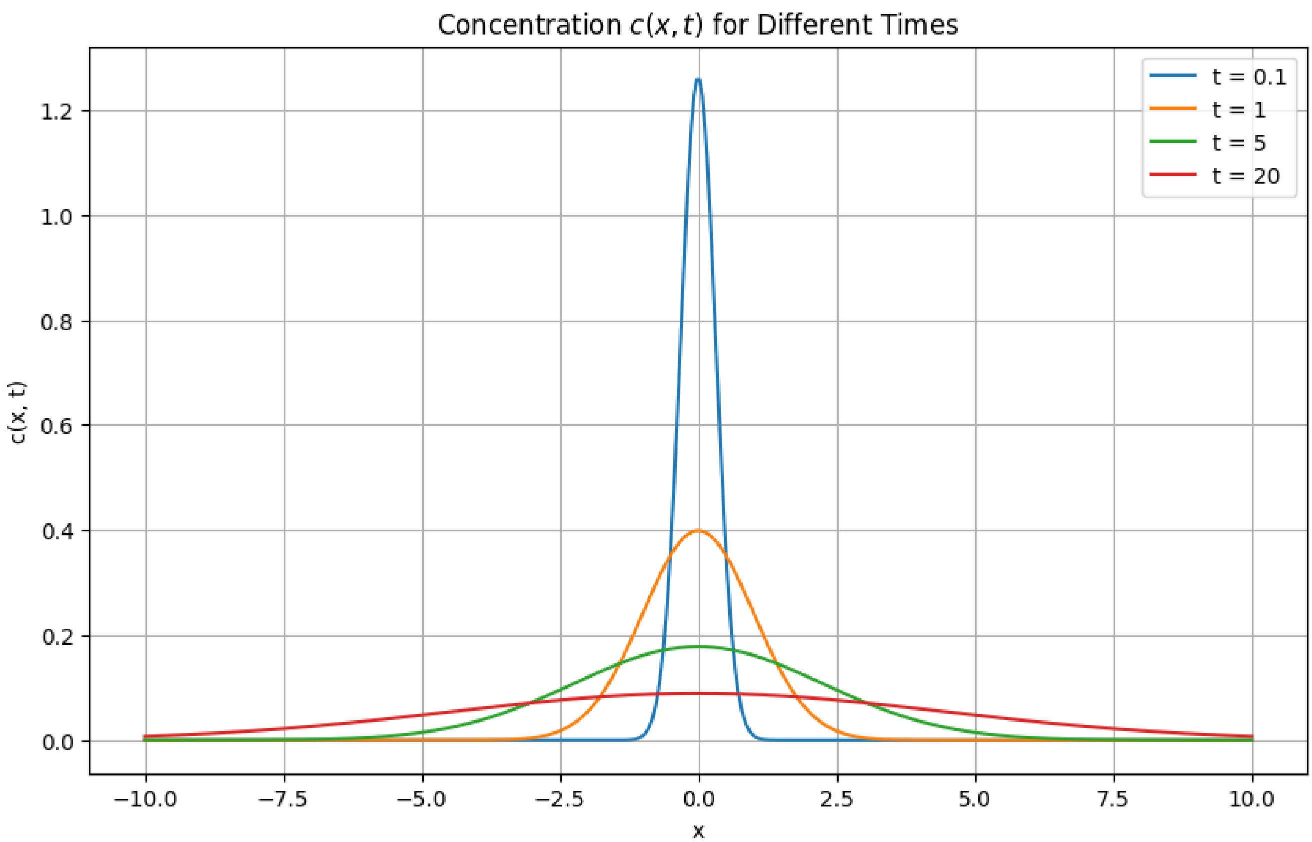
$$c(x,t) = \frac{1}{2\pi\sqrt{Dt}}\int_{-\infty}^{\infty} \mathbf{exp}\left[-y^2\right]\mathbf{exp}\left[ik\zeta\right]dy \\ \rightarrow \frac{1}{\sqrt{4\pi Dt}}\mathbf{exp}[-\zeta^2/4] \tag{A.10}$$

Thus, in its full glory:

$$c(x,t) = \frac{1}{\sqrt{4\pi Dt}}\mathbf{exp}\left[\frac{(x-x')^2}{4Dt}\right] \tag{A.11}$$

Where x' denotes the initial position of the particle. This is generalized for any starting position, as the delta function is shift invariant in terms of the resultant Fourier transform other than a phase factor which is easily recognizable.

This can be simply plotted to visualize the distribution.



A.2. 1D confined diffusion equation via Separation of Variables

The boundaries of the problem are stated that at $0, L$, the boundaries are reflective: $\partial_x C(0,t) = \partial_x C(L,t) = 0$Then, the diffusion equation can be read as:

$$\partial_t c(x,t) = D\partial_{xx}c(x,t) \tag{A.12}$$

Using the method of separation of variables, the solution is proposed as $c(x,t) = X(x)T(t)$, which then gives the form as:

$$\frac{T'}{T} = D\frac{X''}{X} \tag{A.13}$$

Since these equations are not of the same variables, but equal to themselves, they must be constants. The constant will have three forms, however, the time dependent form will be the same for each.

$$T(t) = \mathbf{exp}[-\lambda t] \tag{A.14}$$

The x equation can be solved in terms of exponential. Let the solution be guessed as $\mathbf{exp}[rx]$. Denote $\gamma = \sqrt{\frac{\lambda}{D}}$

$$r^2 + \frac{\lambda}{D} = 0 \tag{A.15}$$

If $\lambda = 0$, the solution is trivial and the solution is given as:

$$X_T(x) = Ax + B \tag{A.16}$$

If $\lambda > 0$, the solution is given in terms of hyperbolic sines.

$$X_H(x) = A\mathbf{sinh}(\gamma x) + B\mathbf{cosh}(\gamma x) \tag{A.17}$$

If $\lambda > 0$, the solution is given in terms of trigonometric sines.

$$X_S(x) = A\mathbf{sin}(\gamma x) + B\mathbf{cos}(\gamma x) \tag{A.18}$$

Applying the boundary conditions, the hyperbolic term cancels as there can only be a zero at 0. The trivial solution takes the form: $X = A$, which simply implies that $A = 0$. This provides the first solution being a constant.

To manage the sines, can simply take derivatives.

$$\begin{aligned} X_S' &= -\gamma A \sin(\gamma x) + \gamma B \cos(\gamma x) \\ 0 &= B\cos(\gamma x), \quad B = 0 \\ 0 &= -\gamma A \sin(\gamma L), \quad \gamma = \frac{n\pi}{L} \end{aligned} \tag{A.19}$$

So, the solution for x takes the simplified form of a cosine series:

$$X = \sum_{i=0}^{N} A_n \mathbf{cos}(\frac{n\pi}{L}x) \tag{A.20}$$

The full solution is then given as:

$$C(x,t) = \sum_{i=0}^{N} A_n \mathbf{exp}\left[-D\left(\frac{n\pi}{L}\right)^2 t\right] \mathbf{cos}(\frac{n\pi}{L}x) \tag{A.21}$$

Now, we can apply an initial condition to obtain a full solution. This will allow for a time-evolution of the diffusion concentration, or on a single-molecule level, the positional probability functions. This is due to the Fokker-Plank equations holding the same form for the diffusion equation.

Let the particle be found in the middle of the well:

$$C(x,0) = \delta\left(x - \frac{L}{2}\right) \tag{A.22}$$

The Fourier coefficient A_n can be found by applying an orthogonal integral.

$$\begin{aligned} C(x,0) = \delta\left(x - \frac{L}{2}\right) &= \sum_{i=0}^{N} A_n \mathbf{cos}(\frac{n\pi}{L}x) \\ \int_0^L \delta\left(x - \frac{L}{2}\right)\mathbf{cos}(\frac{m\pi}{L}x)dx &= \int_0^L \sum_{i=0}^{N} A_n \mathbf{cos}(\frac{n\pi}{L}x)\mathbf{cos}(\frac{m\pi}{L}x)dx \end{aligned} \tag{A.23}$$

The LHS of this equation is trivial. The RHS of this equation can be calculated using the fact that the product of cosines will be equal to 0 if $m \neq n$. If $m = n$, the integral can be evaluated by the following identity.

$$\int_{-\pi}^{\pi} \mathbf{cos}\left(\frac{m\pi}{L}x\right)\mathbf{cos}\left(\frac{n\pi}{L}x\right)dx = \pi\delta_{mn} \tag{A.24}$$

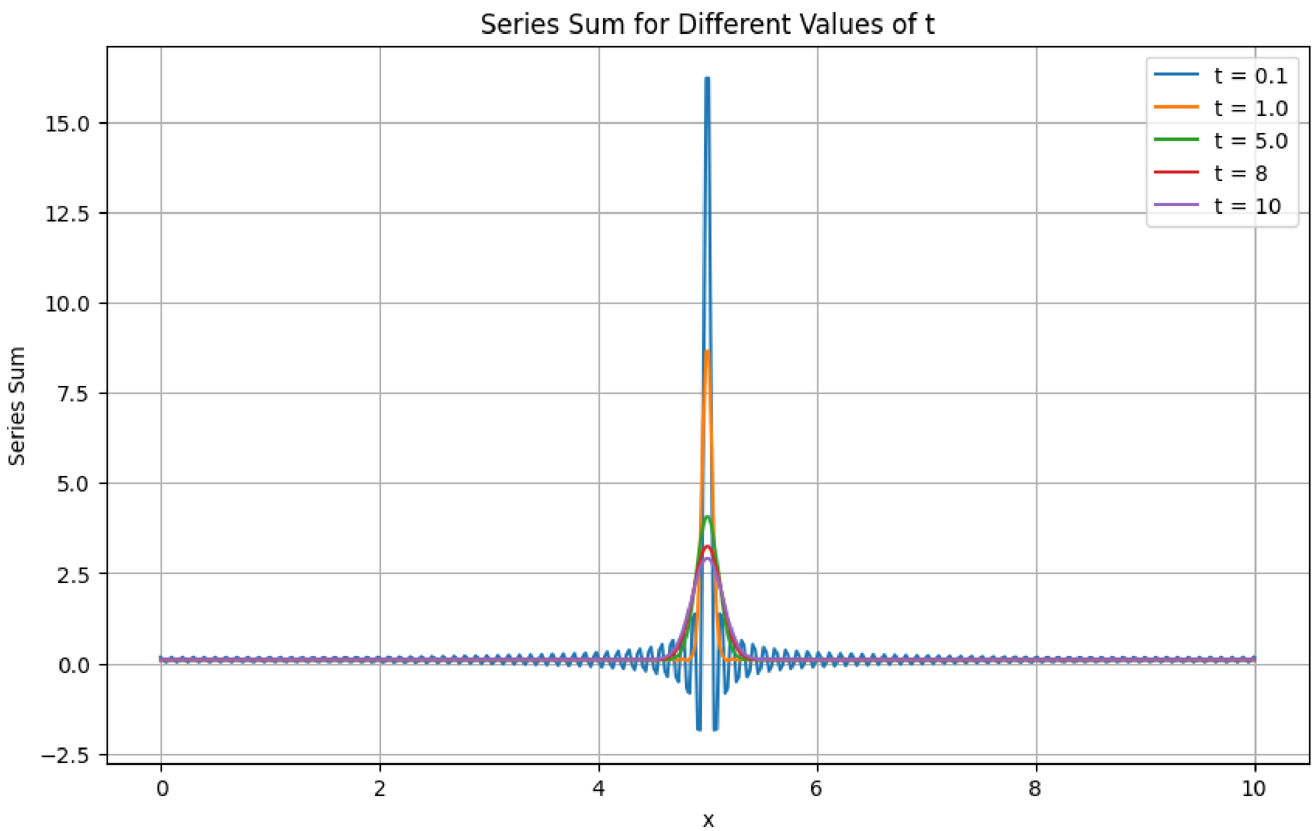
Thus, the Fourier coefficient is evaluated.

$$\begin{aligned} A_n\frac{L}{\pi}\int_0^{\pi}\mathbf{cos}(ny)\mathbf{cos}(my)dy = A_n\frac{L}{2} \\ A_n = \frac{2}{L}\mathbf{cos}(\frac{n\pi}{L}x') \end{aligned} \tag{A.25}$$

Where x' is a generalized initial location of the particle. The series solution is then written as:

$$C(x,t) = \frac{2}{L}\sum_{n=0}^{N}\mathbf{exp}\left[-D\left(\frac{n\pi}{L}\right)^2 t\right]\mathbf{cos}\left(\frac{n\pi}{L}x\right)\mathbf{cos}\left(\frac{n\pi}{L}x'\right) \tag{A.26}$$

To visualize this, the series solution is expanded upon and plotted at various timepoints:



A.3. 2D confined diffusion in polar coordinates

The diffusion equation in polar coordinates is especially important due to applications in measuring **confined diffusion**. Solve the Diffusion equation with the following boundary equations:

$$\begin{gathered}\frac{\partial p(r,\phi,t)}{\partial r}|_{r=a} = 0 \\ p(r,0,t) = p(a,2\pi,t)\end{gathered} \tag{A.27}$$

First, the wave equation in polar coordinates is stated. Due to the polar geometry, the Laplacian undergoes the following transformations[**cristofaro2017laplacian**].

$$\nabla^2 = \partial_{rr} + \frac{1}{r}\partial_r + \frac{1}{r^2}\partial_{\phi\phi} \tag{A.28}$$

The diffusion equation can then be stated:

$$\partial_t p(r,\phi,t) = D\left[\partial_{rr}p(r,\phi,t) + \frac{1}{r}\partial_r p(r,\phi,t) + \frac{1}{r^2}\partial_{\phi\phi}p(r,\phi,t)\right] \tag{A.29}$$

To solve this, the method of separation of variables can be attempted. First, start by defining that:

$$p(r,\phi,t) = R(r)\Phi(\phi)T(t) \tag{A.30}$$

Then, simply apply the Laplacian:

$$R\Phi T' = D\left[R''\Phi T + \frac{1}{r}R'\Phi T + \frac{1}{r^2}R\Phi'' T\right] \tag{A.31}$$

We can factor this equation into $\psi(r,\phi)$ and the time dependent $T(t)$:

$$\frac{T'}{T} = D\left[\frac{R''}{R} + \frac{1}{r}\frac{R'}{R} + \frac{1}{r^2}\frac{\Phi''}{\Phi}\right] \tag{A.32}$$

Since each side doesn't depend on each other, they must be both equal to a constant; $-\lambda$.

$$\begin{gathered}\frac{T'}{T} = -\lambda \\ D\left[\frac{R''}{R} + \frac{1}{r}\frac{R'}{R} + \frac{1}{r^2}\frac{\Phi''}{\Phi}\right] = -\lambda\end{gathered} \tag{A.33}$$

Before solving the equations, we can split this equation up one more time into Angular and Radial parts. By simply multiplying the second equation by r^2, the equation can be seperated into a second constant:

$$\begin{gathered}D\left[r^2\frac{R''}{R} + r\frac{R'}{R} + \frac{\Phi''}{\Phi}\right] = -\lambda r^2 \\ r^2\frac{R''}{R} + r\frac{R'}{R} + \frac{1}{D}\lambda r^2 = \frac{\Phi''}{\Phi}\end{gathered} \tag{A.34}$$

So, the three equations to solve are:

$$\begin{gathered}\frac{\partial T}{\partial t} = -\lambda T \\ r^2\frac{\partial^2 R}{\partial r^2} + r\frac{\partial R}{\partial r} + R(\frac{1}{D}\lambda r^2 - \gamma^2) = 0 \\ \frac{\partial^2 \Phi}{\partial \phi^2} = \gamma^2\Phi\end{gathered} \tag{A.35}$$

A.3.1. Time-Dependent Equation

The time dependent equation is the simplest to solve. This can be solved by solving the ODE. The general solution is listed below:

$$T(t) = T_0 \mathbf{exp}[-\lambda t] \tag{A.36}$$

This is consistent with all other workings of the diffusion equation.

A.3.2. Angular Equation

This equation is a simple linear 2nd order ODE. This can be solved by using the solution $\Phi = \mathbf{exp}[r\phi]$.

$$r^2 \mathbf{exp}[r\phi] - \gamma^2 \mathbf{exp}[r\phi] = 0 \tag{A.37}$$

Thus, there will only be solutions depending on the sign of γ^2. There are three cases. Each case must abide by the continuous and differentiable continuous BC of the angular components. Specifically, the equations must be 2π periodic. For $\gamma^2 = 0$, the solution is the linear:

$$\Phi = A\phi + b \tag{A.38}$$

This cannot be periodic, so $A, B = 0$. For $\gamma^2 > 0$, the system will be a sum of exponents with real coefficients. This is equal to a sum of hyperbolics:

$$\Phi = A\mathbf{sinh}(\gamma\phi) + B\mathbf{cosh}(\gamma\phi) \tag{A.39}$$

Same as in the first case, this cannot be periodic, hence, $A, B = 0$. For $\gamma^2 < 0$, the solution is the sum of imaginary exponentials, or a sum of sinusoids:

$$\Phi = A\mathbf{exp}[-i\gamma\phi] + B\mathbf{exp}[i\gamma\phi] \tag{A.40}$$

A.3.3. Radial Equation

Let $\frac{\lambda}{D} = \psi^2$. Then, let $x = \psi r$. The equation will then become:

$$\frac{1}{x}\frac{\partial}{\partial x}\left(x\frac{\partial}{\partial x}R\right) + R\left(1 - \frac{\gamma^2}{x^2}\right) = 0 \tag{A.41}$$

Expanding the LHS, the equation can be rewritten as a linear ODE:

$$\frac{\partial^2}{\partial x^2}R + \frac{1}{x}\frac{\partial}{\partial x}R + R\left(1 - \frac{\gamma^2}{x^2}\right) = 0 \tag{A.42}$$

Since $x = 0$ is a singular point, which can be see due to the divergence terms, the ODE can be solved using Frobenius methods. Thus, proposing a solution for $R(x)$:

$$R(x) = \sum_{n=0}^{\infty} a_n x^{n+s} \tag{A.43}$$

This leads to the recursion relation that:

$$a_n = -\frac{a_{n-2}}{(n+s)^2 - \gamma^2} \tag{A.44}$$

The fixed constants are a_0 and a_1. We find that $a_1 = 0$, which stems from the requirement that $s = \pm\gamma$. Thus, the recursion relation solidifies itself as:

$$a_n = -\frac{a_{n-2}}{n(n+2\gamma)} \tag{A.45}$$

This recursive relation can be solved via iteration with $n \to 2n$. Then, the solution that is forced upon all $n > 0$:

$$a_n = \left(-\frac{1}{4}\right)^n \frac{1}{n!(n+\gamma)!} a_0 \tag{A.46}$$

By a careful choice of a_0, this equation will form the general solution, which is known as the Bessel function of order γ.

$$J_\gamma(x) = \sum_{k=0}^{\infty} \frac{(-1)^k}{k!(k+\gamma)!} \left(\frac{X}{2}\right)^{2k+\gamma} \tag{A.47}$$

Thus, plugging in the value of x:

$$J_\gamma(r) = \sum_{k=0}^{\infty} \frac{(-1)^k}{k!(k+\gamma)!} \left(\frac{\psi r}{2}\right)^{2k+\gamma} \tag{A.48}$$

A.3.4. Boundary Conditions

The boundary conditions can now be applied. The boundary conditions for this problem are that there are vanishing derivatives at the edge of the boundary, as well as an angular symmetry:

$$\frac{\partial}{\partial r} p(r,\phi,t)|_{r=a} = 0 \tag{A.49}$$

$$p(r,0,t) = p(r,2\pi,t) \tag{A.50}$$

To apply the vanishing derivatives, we note that only the bessel functions will be dependent on r. Thus, the equation for the bessel function derivatives will vanish at 0.

$$J'_\gamma(a) = 0 \tag{A.51}$$

This imposes that $x = \psi a$ must be the roots of the derivative of the Bessel function, which I will denote $z_{\gamma m}$.

$$\psi_{\gamma m} = \frac{z_{\gamma m}}{a} \tag{A.52}$$

This imposes a condition on the previous constant λ. Recalling how λ is related to ψ we find that:

$$\lambda_{\gamma m} = D\psi^2 = D\frac{z_{\gamma m}^2}{a^2} \tag{A.53}$$

Applying the condition that $p(r,0,t) = p(r,2\pi,t)$, we find that the angular portion may only contain values of γ in the integers.

$$\Phi(\phi) = A\mathbf{cos}(\gamma\phi) + B\mathbf{sin}(\gamma\phi) \tag{A.54}$$

This gives the general form of the solution:

$$p(r,\phi,t) = \sum_{\gamma,m} \left[\mathbf{exp}(-\frac{z_{\gamma,m}^2}{a^2}Dt)\right] [A\mathbf{cos}(\gamma\phi) + B\mathbf{sin}(\gamma\phi)] \left[J_\gamma(\frac{z_{\gamma,m}r}{a})\right] \tag{A.55}$$

The initial conditions can be set by applying a Fourier-series to each coefficient. We applying the following identity **[borji_bessel]**:

$$\int_0^a J_{\gamma,m}(\frac{z_{\gamma,m}r}{a}) J_{\gamma,n}(\frac{z_{\gamma,n}r}{a}) = \begin{cases} 0 & m \neq n \\ \frac{a^2}{2}\left(1 - \frac{\gamma^2}{z_{\gamma,m}^2}\right) J_\gamma(z_{\gamma,m}) & \end{cases}$$

Thus, given some initial conditions $f(r,\phi)$, the resultant initial parameters are equal to the following explicit integrals:

$$A_{nm} = \frac{1}{\pi}\int_{-\pi}^{\pi}\int_0^a f(r,\phi)\sin(m\phi)\,J_\gamma\left(\frac{z_{\gamma m}r}{a}\right) r\,dr\,d\phi \Bigg/ \frac{a^2}{2}\left(1-\frac{\gamma^2}{z_{\gamma m}^2}\right)\left[J_\gamma(z_{\gamma m})\right]^2 \tag{A.56}$$

$$B_{nm} = \frac{1}{\pi}\int_{-\pi}^{\pi}\int_0^a f(r,\phi)\cos(m\phi)\,J_\gamma\left(\frac{z_{\gamma m}r}{a}\right) r\,dr\,d\phi \Bigg/ \frac{a^2}{2}\left(1-\frac{\gamma^2}{z_{\gamma m}^2}\right)\left[J_\gamma(z_{\gamma m})\right]^2 \tag{A.57}$$

$$B_{0m} = \frac{1}{\pi}\int_{-\pi}^{\pi}\int_0^a f(r,\phi)\,J_0\left(\frac{z_{0m}r}{a}\right) r\,dr\,d\phi \Bigg/ \frac{a^2}{2}\left[J_0(z_{0m})\right]^2 \tag{A.58}$$

$$\tag{A.59}$$

Thus, using these terms for values in Eqn A.3.4, the solution presents itself.

The MSD of this equation can be derived from the integral over all values of r in the radius of the confinement. The MSD of this solution is referenced in the following form [**bickel2007confined**]. This equation is important in the experimental context as it is often the form used in 2D microscope data.

$$\langle r^2\rangle = a^2\left(1 - 8\sum_{m=1}^{\infty}\mathbf{exp}\left[-\alpha_{1m}^2\frac{Dt}{a^2}\right]\frac{1}{\alpha_{1m}^2(\alpha_{1m}^2-1)}\right) \tag{A.60}$$

Where α_{1m} are the roots of the derivative of the 1st order Bessel function, a is the well radius, D is the diffusion, and t is a time step, or the exposure time. When fitting experimentally, fitting a, D and an offset is required.

A.4. 3D Confined Diffusion in Cylindrical Coordinates

The confined diffusion equation is given for the cylindrical coordinate system:

$$\frac{\partial p}{\partial t} = D\nabla^2 p \tag{A.61}$$

We first expand this equation in terms of the cylindrical laplacian.

$$\frac{\partial p}{\partial t} = D\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial p}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2 p}{\partial \phi^2} + \frac{\partial^2 p}{\partial z^2}\right) \tag{A.62}$$

Let the solution have the separable solution $p = T(t)\Phi(\phi)Z(z)R(r)$. This is expanded algebraically as previously seen before. The 4 separated equations are left to solve:

$$\frac{dT}{dt} + \lambda_1 T = 0 \tag{A.63}$$

$$\frac{d^2\Phi}{d\phi^2} + \lambda_2^2\Phi = 0 \tag{A.64}$$

$$\frac{d^2 Z}{dz} - \lambda_3^2 Z = 0 \tag{A.65}$$

$$\frac{d^2 R}{dr^2} + r^{-1}\frac{dR}{dr} - \left(\frac{\lambda_1}{D} - \lambda_3^2 - \frac{\lambda_2^2}{r^2}\right)R = 0 \tag{A.66}$$

A.4.1. Boundary Conditions:

The boundary conditions are defined as reflective, Neumann boundary conditions.

$$p(r, \phi, z) - p(r, \phi + 2\pi, z) = 0 \tag{A.67}$$

$$\frac{\partial p}{\partial z}|_{z=0,b} = 0 \tag{A.68}$$

$$\frac{\partial p}{\partial r}|_{r=a} = 0 \tag{A.69}$$

IMAGE ANALYSIS

B.1. LOCALIZATION REFINEMENT

B.1.1. 2D GAUSSIAN FITTING

One standard method of localizing particles is using a 2D Gaussian or airy pattern and minimizing a loss function to find the center of the particle. Presented below is a method that performs gaussian fitting in a fast-way with a low localization error [**anthony2009image**].

The Gaussian function is defined as an exponential raised to the second power. Then, it is normalized by an amplitude factor and a shift. For the N-dimensional case, the equation has the form of a sum of exponential coefficients,

$$f(x_1, x_2, \ldots x_n) = A\mathbf{exp}\left[\sum_i^n \frac{(x_i - x_{0,i})^2}{2\sigma_i}\right] \tag{B.1}$$

For the 2D case, this has the form:

$$f(x, y) = A\mathbf{exp}\left[\frac{(x - x_0)^2}{2\sigma_x} + \frac{(y - y_0)^2}{2\sigma_y}\right] \tag{B.2}$$

We can assume that the variances of each axis are equal so that the gaussian is symmetric. We then set $f(x, y)$ to an image and take the log of both sides. This will allow a matrix formulation of the system:

$$\mathbf{log}\left[f(x, y)\right] = a_4 + a_1 x + a_2 y - a_3(x^2 + y^2) \tag{B.3}$$

Where $a_1 = x_0/\sigma^2$, $a_2 = y_0/\sigma^2$, $a_3 = 1/\sigma^2$, and $a_4 = \mathbf{log}[A]$. Thus, this forms the following matrix system:

$$\begin{bmatrix} x_1 & y_1 & x_1^2 + y_1^2 & 1 \\ x_2 & y_2 & x_2^2 + y_2^2 & 1 \\ \vdots & \vdots & \vdots & \vdots \\ x_n & y_n & x_n^2 + y_n^2 & 1 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \\ a_3 \\ a_4 \end{bmatrix} = \begin{bmatrix} -\mathbf{log}[I + \varepsilon] \\ -\mathbf{log}[I + \varepsilon] \\ \vdots \\ -\mathbf{log}[I + \varepsilon] \end{bmatrix} \tag{B.4}$$

This is an implicit solution to the least-squares equation defined by the modulus squared error function [**anthony2009image**]. The solution to this problem will give the positions x_c, y_c of the Gaussian, as well as the fitted variance

B.1.2. RADIAL SYMMETRY SEARCH

Localization via a radial symmetry search algorithm is a technique developed by the Raghuveer Parthasarathy in 2012 [**Parthasarathy2012**]. This technique uses a fast search of discrete gradients to localize a weighted centroid using a least sqaures transformation based on a group symmetry assumption.

Suppose that a region around a particle is denoted by $f(x, y)$. This group of number is localized by a 2D mesh such that $f(x, y) \equiv f_{i,j}$. Suppose that the center of this image is given by x_c, y_c. The rotational symmetry property states that this centroid will be invariant under a rotation.

$$R(x_c, y_c) = x_c, y_c \tag{B.5}$$

One way to think about this is the top of a symmetric hill. Around the hill, the gradients of the hill will always be pointing towards the symmetric top. Thus, an algorithmn to find the top of the hill would be presented as follows:

Suppose that the gradient matrix of $f_{i,j}$ is given by $G_{x,y} = \tilde{R}_{x,y} \star f$, where $\star$ is the matrix convolution, and $\tilde{R}_{x,y}$ are the Robert Cross Matrices. Given the slope of all lines, as well as coordinate matricies x_m, y_m, the following equation is solved:

$$b_m = y_m - \left[\frac{-(G_y + G_x)}{G_y - G_x} \right] x_m \tag{B.6}$$

Then, a weighting is applied based on the centroids of the maximum intensity:

$$S = \sum_{i,j} G_x^2 + G_y^2 \tag{B.7}$$

$$x_c = \frac{\sum[(G_x^2 + G_y^2)x_m]}{S} \tag{B.8}$$

$$y_c = \frac{\sum[(G_x^2 + G_y^2)y_m]}{S} \tag{B.9}$$

The weighting matrix is calculated as follows:

$$w = \frac{(G_x^2 + G_y^2)}{\sqrt{(x_m - x_c)^2 + (y_m - y_c)^2}} \tag{B.10}$$

We aim to find a point (x_c, y_c) that best fits a set of lines in a least squares sense. Specifically, we want to minimize the weighted sum of squared perpendicular distances from this point to each line defined by $(y = m_i x + b_i)$, where:

- m_i and b_i are the slopes and intercepts of the lines, respectively.
- w_i are the weights associated with each line.

The perpendicular distance D_i from the point (x_c, y_c) to the line $y = m_i x + b_i$ is given by:

$$D_i = \frac{|-m_i x_c + y_c - b_i|}{\sqrt{1 + m_i^2}} \tag{B.11}$$

The loss function is chosen as the the weighted sum of squared distances due to the rotational invariance it posses.

$$S = \sum_{i=1}^{N} w_i D_i^2 = \sum_{i=1}^{N} w_i \left(\frac{-m_i x_c + y_c - b_i}{\sqrt{1 + m_i^2}} \right)^2 \tag{B.12}$$

$$S = \sum_{i=1}^{N} \frac{w_i}{1 + m_i^2} \left(-m_i x_c + y_c - b_i \right)^2 \tag{B.13}$$

Define $w_i' = \frac{w_i}{1+m_i^2}$ as a transformed weight matrix

So the objective function becomes:

$$S = \sum_{i=1}^{N} w_i' \left(-m_i x_c + y_c - b_i \right)^2 \tag{B.14}$$

To find the minimum of S, we take the partial derivatives of S with respect to x_c and y_c, set them to zero, and solve for x_c and y_c.

$$\frac{\partial S}{\partial x_c} = \sum_{i=1}^{N} 2w_i' \left(-m_i x_c + y_c - b_i \right) \left(-m_i \right) \tag{B.15}$$

$$= 0 \tag{B.16}$$

We simplify this and divide both sides away and provide solutions for both terms

$$-\sum_{i=1}^{N} w_i' m_i^2 x_c + \sum_{i=1}^{N} w_i' m_i y_c - \sum_{i=1}^{N} w_i' m_i b_i = 0 \tag{B.17}$$

$$-\sum_{i=1}^{N} w_i' m_i x_c + \sum_{i=1}^{N} w_i' y_c - \sum_{i=1}^{N} w_i' b_i = 0 \tag{B.18}$$

Let's define the following sums for simplicity:

$$S_{w'} = \sum_{i=1}^{N} w_i'$$

$$S_{mw'} = \sum_{i=1}^{N} m_i w_i'$$

$$S_{m^2w'} = \sum_{i=1}^{N} m_i^2 w_i'$$

$$S_{bw'} = \sum_{i=1}^{N} b_i w_i'$$

$$S_{mbw'} = \sum_{i=1}^{N} m_i b_i w_i'$$

Now, the partial derivatives become:

$$-S_{m^2w'} x_c + S_{mw'} y_c - S_{mbw'} = 0 \tag{B.19}$$

$$-S_{mw'} x_c + S_{w'} y_c - S_{bw'} = 0 \tag{B.20}$$

We can represent the system as a matrix

$$\begin{bmatrix} -S_{m^2w'} & S_{mw'} \\ -S_{mw'} & S_{w'} \end{bmatrix} \begin{bmatrix} x_c \\ y_c \end{bmatrix} = \begin{bmatrix} S_{mbw'} \\ S_{bw'} \end{bmatrix} \tag{B.21}$$

Let's denote:

$$A = \begin{bmatrix} -S_{m^2w'} & S_{mw'} \\ -S_{mw'} & S_{w'} \end{bmatrix}, \quad \mathbf{x} = \begin{bmatrix} x_c \\ y_c \end{bmatrix}, \quad \mathbf{b} = \begin{bmatrix} S_{mbw'} \\ S_{bw'} \end{bmatrix}$$

So, the system is $A\mathbf{x} = \mathbf{b}$. This can be simply solved using matrix rules. we first find the determinant and use Cramer's rule to find the solutions to x_c, y_c

$$D = \det(A) = (-S_{m^2w'})(S_{w'}) - (-S_{mw'})(S_{mw'}) = S_{mw'}^2 - S_{m^2w'} S_{w'} \tag{B.22}$$

Replace the first column of A with $\mathbf{b}$:

$$A_x = \begin{bmatrix} S_{mbw'} & S_{mw'} \\ S_{bw'} & S_{w'} \end{bmatrix} \tag{B.23}$$

$$\det(A_x) = S_{mbw'} \cdot S_{w'} - S_{mw'} \cdot S_{bw'} \tag{B.24}$$

So,

$$x_c = \frac{\det(A_x)}{D} = \frac{S_{mbw'} S_{w'} - S_{mw'} S_{bw'}}{D} \tag{B.25}$$

Similarly,

$$y_c = \frac{\det(A_y)}{D} = \frac{S_{mw'} S_{mbw'} - S_{m^2w'} S_{bw'}}{D} \tag{B.26}$$

references

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