SUBDIFFUSIVE TRANSPORT IN NON-HOMOGENEOUS MEDIA AND NONLINEAR FRACTIONAL EQUATIONS

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\[ \rho_{\text{st}}(x) \sim x^{2/\mu} \]
This work studies subdiffusive transport in non-homogeneous media, involving nonlinear fractional equations. The subdiffusive dynamics are modelled by means of non-Markovian continuous time random walk models with space dependent microscopic escape rates, \( \gamma(x, \tau) \sim \mu(x)/\tau \), inversely proportional to residence time \( \tau \). This is equivalent to having the power-law mesoscopic waiting time probability density function (PDF) with space dependent power-law waiting time PDFs \( \psi(x, \tau) \sim 1/\tau^{1+\mu(x)} \) lacking the first moment for anomalous exponent \( 0 < \mu(x) < 1 \).

The work is presented as an alternative format thesis in which new results are contained in three published articles from the journal Physical Review E, and one article pre-print.

In the first article we study non-homogeneous subdiffusive fractional equations, with space dependent anomalous exponent \( \mu(x) \). We analyse the asymptotic behaviour of the lattice model both analytically and by Monte Carlo simulation. For the first time, we find that the fractional equations in a bounded domain are not structurally stable with respect to non-homogeneous perturbations of the anomalous exponent.

The second article rectifies the problem of structural instability by introducing the random death process to the random walk scheme. We derive the modified fractional master equation and analyse its asymptotic behaviour analytically and by Monte Carlo simulation. We find that this equation is structurally stable with respect to non-homogeneous spatial variations to the anomalous exponent. In the long-time, continuous limit we arrive at an advection diffusion equation in which advection and diffusion depend upon the anomalous exponent and death rate.

Morphogen gradient formation under nonlinear degradation and subdiffusive transport is the subject of the third article. We extend the linear reaction-subdiffusion equations and in the long-time limit obtain the nonlinear effect of degradation enhanced diffusion. We find a stationary profile of power-law type in which tail shape is determined by the anomalous exponent and independent of particle production at the source.

In the final article we investigate the interaction between subdiffusive transport, nonlinear particle interactions, and chemotaxis. We systematically derive nonlinear fractional equations from a random walk model with an additional particle escape rate dependent upon local mean field density. In the continuous limit we derive stationary equations and analyse the behaviour.
Declaration

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Chapter 1

Introduction

1.1 Aims

This thesis is a collection of the work I have produced and worked on over the past 3 years during my PhD studies, and to a lesser extent during the work on my Master’s thesis. It is presented here in an alternative format, where the main work is presented in the form of articles either published or under review.

The aims of the thesis are:

1. To study subdiffusion in an inhomogeneous environment, where the anomalous exponent of the subdiffusion is non-constant in space.

2. To remedy the ill effects arising from the problem of subdiffusion in an inhomogeneous environment, and apply the framework to the study of morphogenesis.

3. To study the effects of nonlinear reactions which act as a tempering to the random waiting time in the continuous time random walk formulation of subdiffusion.

4. To formulate a systematic way of deriving nonlinear subdiffusion-reaction equations involving external chemotactic signalling.

The first chapter will be an introduction to subdiffusion, and will motivate the work done in latter chapters. This first chapter will include several enlightening examples of subdiffusion occurring in nature, along with a concise introduction to the study of morphogenesis.
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The second chapter will introduce the mathematics of the non-Markovian random walk model. The master equation describing the process will be derived here from two different standpoints. It can be derived from a pair of integral equations for the evolution of the probability density and the flux of probability density. The alternative derivation involves the addition of a parameter creating a Markovian structured probability density function. This alternative derivation is useful for the introduction of reactions and non-linearity to the random walk process, and will be used extensively in the following articles.

In the third chapter subdiffusion is modelled as the limit of a continuous time random walk process which is recalled in this chapter. Fractional derivatives will be introduced, and the fractional Fokker-Planck equation (FFPE) will be derived from two standpoints. The FFPE is the archetypal equation used in the rest of the thesis, being the fractional analogue of the Fokker-Planck equation for normal forced diffusion.

Breaking from the page numbering, next will come four original works by myself and my supervisor, Prof. Fedotov, and a fellow PhD student. Three of these published works appear in the physical journal Physical Review E. The final is currently under review, and is presented here as a pre-print. The regulations for presentation of theses state that articles within a thesis must be presented exactly as they appear in print, including separate abstracts and bibliographies. Therefore, there will be a reasonable amount of repetition between the first two introductory chapters, and the published works. The regulations also require that these articles do not use the same page numbering, equation numbering, and section numbering as the main body of the thesis.

In the first article we address the first aim of the thesis. We study the problem of subdiffusion in an inhomogeneous environment. The anomalous exponent of a subdiffusive process is the most important parameter, describing the rate of diffusion, or rate of relaxation of the system. The anomalous exponent is directly related to the random anomalous trapping events which cause the diffusion to be subdiffusive. Starting from the framework of the continuous-time random-walk, it is clear that it should not be realistic to assume a spatially independent anomalous exponent can adequately describe the subdiffusion in an inhomogeneous environment. We find that the fractional equations are not structurally stable with respect to any small-space perturbations to the anomalous exponent. This causes the complete breakdown of the stationary behaviour, and leads to the
phenomenon of anomalous aggregation where all diffusing particles accumulate in the region corresponding to the global minimum of the anomalous exponent. Since any real environment is not homogeneous, and any small space perturbation destroys the long term behaviour of the system, the equations are not adequate to describe real events.

The purpose of the second article is to address the second aim of the thesis and remedy the structural instability of the fractional equations with the introduction of a death process. We introduce the death process as a stochastic process independent of that of the diffusion. It acts to remove particles from the system if they are immobile for too long. This is a physically motivated modification which acts as a tempering of the associated anomalous waiting time and counteracts the anomalous aggregation. Further, we find that rather unusually the diffusion coefficient is directly dependent on the anomalous exponent. This is the first time that a diffusion coefficient has been found to be dependent explicitly on the parameter of the subdiffusion.

The third aim of the thesis is addressed in the third article. We investigate the effect on the stationary behaviour of subdiffusive process which includes a nonlinear reaction. This is motivated by the study of morphogenesis, where nonlinear reactions have been shown to occur. Where the local concentration of particles grows too high, particles are randomly removed from the system. Here we found that a nonlinear particle reactions actually accelerate the slow subdiffusive process. This has a profound effect on the stationary behaviour and leads to a profile of power-law type. Now the diffusion coefficient is an increasing function of the nonlinear reaction rate.

In the final article we will tackle the final aim of the thesis. We are able to derive fractional Fokker-Planck type equations where the microscopic escape rate of particles is modified to include independent non-linear escape rates dependent on the local density of the mean field. This non-linear escape rate has the effect of a tempering to the anomalous trapping subdiffusive behaviour. In this article we study the interaction between the attractive forces of chemotaxis and subdiffusion, with the repulsive forces of non-linear tempering.

Finally in the fourth chapter we conclude the thesis and discuss ideas for further work.
1.2 What is anomalous diffusion?

Anomalous subdiffusion is an observed natural phenomenon relevant to many areas of scientific study including biology [1–8], physics [9–15], economics [16–20] however it is not one that is widely studied. It has been known since Richardson’s work on turbulent diffusion [21]. Thus before presenting the articles forming the main body of work, it is necessary to provide a sufficient introduction to both subdiffusion and morphogenesis for the thesis to be self contained.

An anomalous diffusion is one where the diffusion is non-normal, with scaling different to that of normal diffusion, and one where the ensemble averaged mean squared displacement (MSD) of diffusing particles grows in time as [15]:

$$\langle x^2(t) \rangle \sim t^\mu.$$  \hspace{1cm} (1.1)

The parameter $\mu$ is known as the anomalous exponent. Differences in anomalous exponent are summarised below, and in Figure 1.1:

- $0 < \mu < 1$ the diffusion is subdiffusive
- $1 < \mu < 2$ the diffusion is superdiffusive (sub-ballistic)
- $\mu = 1$ correspond to normal, Fickian, diffusion
- $\mu = 2$ correspond to ballistic motion.

Figure 1.1: Growth of the mean squared displacement for values of the anomalous exponent $\mu$: $\mu = 1/2$, $\mu = 1$, $\mu = 3/2$. 

![Graph showing the growth of mean squared displacement](image-url)
Subdiffusion is a diffusion so slow that it cannot be described by the same mathematical models as normal diffusion. It is so slow due to microscopic trapping events in which the mean trapping time is infinite. Subdiffusive systems are characterised by having a complex geometry \cite{22}, or chemical feedback mechanism, or other mechanism which causes particles to become trapped in space for an anomalously long time. Particles are trapped for random times distributed with an inverse power-law trapping time probability density function (PDF) $\psi(\tau) \sim \tau_0/\tau^{1+\mu}$, with power-law exponent $\mu$. This temporal disorder means these systems have no characteristic time scale \cite{9,23,24}.

It could be that there is a time dependence of another kind than described above in the relation (1.1), but we will be restricting to this power-law dependence. The anomalous behaviour of the MSD is directly related to the failure of the system behaviour to be described by the central limit theorem due to the divergence of the mean trapping time.

Subdiffusive transport is an observed natural phenomena, studied in many areas of science as diverse as dispersive charge transport \cite{9}, ion movement in dendritic spines \cite{8,25}, protein transport in cell membranes \cite{26}, and RNA molecules within cells \cite{27}. Further, it is theoretically studied in the fields of econophysics \cite{17,20} when looking at tick-by-tick dynamics in some high frequency trading markets there is sometimes an anomalously long wait between consecutive trades and the price of the asset is stuck for a time period not characteristic to the rest of the movement; in Migrating Neolithic populations were found to settle for long periods of time before moving on again \cite{28}. Diffusing particles can become trapped for anomalously long times within the complex geometries of the porous media \cite{29}.

Superdiffusive processes can arise from the same mathematics as subdiffusive processes. Subdiffusion arises from a trapping of a diffusing particle in space. Superdiffusion arises from trapping of a diffusing particle in velocity space \cite{30}. In the velocity space it is assumed that a particle undergoes collisions, velocity changes, such that the time between successive collisions is random and described by a PDF with a divergent second moment. Transport of a diffusing particle can be described in phase space by the Klein-Kramers equation. A fractional generalisation describing the sub-ballistic superdiffusion of a particle was introduced by Metzler and Sokolov in \cite{30} based on the fractional Klein-Kramers equation derived by Metzler and Klafter \cite{31}, and the fractional Kramers equation by Barkai...
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and Silbey [32].

The unifying idea of these two seeming polar opposites is the idea of an inherent feedback mechanism, or memory [33]. Normal diffusion could be described as ‘purely random’, in the sense that there is no tendency of microscopic particles to behave in any particular way. Whereas anomalous diffusion requires a tendency for the particles to behave in a certain way, without losing the random element which defines a diffusion.

1.3 Examples

The purpose of this section is to give a brief overview of three examples of observed subdiffusion. Although subdiffusion is a phenomenon which is not often studied, it is not only one which occurs naturally but is also one which is observed in several situations within our own body. Without knowing it, it is encountered every day.

1.3.1 Subdiffusion in dendritic spines

Dendrites are biological structures present in the brain, neurons, responsible for transporting chemical signals. Dendrites are, for all intents and purposes, tubes along which ions are free to diffuse in the presence of some potential field which influences the overall direction of flow. The transport of ions is responsible for the transmission of electrical signals within the brain, and are therefore extremely important. The study of dendritic spines has grown in recent years and led to the development of several cable models to explain the macroscopic effects. References within [34] describe how phenomenological models have been made to describe the effects of differing shapes [35], spine distributions [36 37], and relationship between spine and stem [38]. The tubes are not uniform in any way, and may vary wildly in diameter, or have local geometric features which affect the rate of diffusion. It is not fully understood how geometrical changes across types of neurons affects diffusion within the neurons.

However, it was found that transport of some particles within spiny dendrites is anomalous subdiffusive along the shaft or stem [7, 8, 39]. It was found that the diffusion become more anomalous, slower, as the density of spines increased. The authors in the aforementioned articles used numerical simulations to back-up their results. The dendritic spines act as traps for particles, which upon entering
the narrow neck of the spine are unable to freely escape. This significantly lowers the effective rate of diffusion such that the mean squared displacement of diffusing particles is subdiffusive $\langle x^2(t) \rangle \sim t^\mu$, $0 < \mu < 1$. On a microscopic level, this can be modelled as particles escaping from a spine at a rate $\gamma(\tau)$, 

$$\gamma(\tau) \sim \mu/\tau, \quad 0 < \mu < 1,$$  

(1.2)

where $\tau$ is the residence time: the amount of time spent in the trap already. This escape rate is related to the survival probability $\Psi(\tau)$, the probability for the particle to remain trapped for a time greater than $\tau$ by $\Psi(\tau) = e^{-\int_0^\tau \gamma(s)ds}$. This generates the power-law survival probability $\Psi(\tau) \sim 1/\tau^\mu$. The full details are given in Section 2.1 Here $\gamma(\tau)$ is the defined in the standard way for a transition probability, 

$$\gamma(\tau) = \lim_{h \to 0} \frac{\text{Pr}(\tau < T < \tau + h | T > \tau)}{h},$$  

(1.3)

where $T$ is the random time of transition, or in this case escape. This exactly describes the kind of long range memory, which particles must possess in order to be subdiffusive. The equation (1.2) simply states that the transition, or escape, rate is lowered as $\tau$ increases. The longer a particle remains trapped, the less likely it is to instantaneously escape. This rate of escape leads directly to the mean trapping time of particles in a spine being infinite. So the macroscopic effect of subdiffusion here should be attributed to the microscopic effect of individual particle trapping. The trapping is so strong that a particle which enters a trap is not expected to ever escape, on any timescale characteristic to the diffusion.
In many cases of subdiffusion the trapping is, likely, caused by the complicated geometry of the environment in which the diffusion is taking place. However, this is but one example and it could as well be the case that there is some external chemical reaction causing the trapping of particles, or an internal nonlinear effect, which in turn leads to macroscopic subdiffusive behaviour. Exploiting geometrical similarities between the dendrites and a comb, a comb model was proposed by Méndez and Iomin [40,41]. In these models the presence of chemical reactions within spines as well as an active membrane lead to the anomalous trapping of ions within the spines.

Fractional cable equations were derived and proposed as models for the sub-diffusion present in dendritic spines by Langlands, Henry, and Wearne [42–44]. These equations were derived from Nernst-Planck equations for the electro-diffusion of ions in nerves. The model takes into account the drift of ions due to different ionic concentrations outside and inside the cell membrane causing changes in the electric field.

1.3.2 Subdiffusion in protein transport on cell membranes

The diffusion of proteins within the membrane of cells can be thought of as taking place in an essentially two-dimensional environment. Proteins and other large molecules can be transported within cell membranes, and also between cells. However, the membranes of cells are not empty of other particles and structures which might interfere with the movement of particles as large as proteins [26,45]. They are crowded with solutes, skeletal proteins, lipids organised into raft structures, and immobile proteins. The crowded environment can provide opportunity for many interesting models of transport within and between cells [46].

Anomalous transport in cell membranes could be caused by at least two mechanisms: obstacles causing strong correlations in the diffusive motion, and transient binding to, immobile, traps [46,48]. Some cells possess a sub-cellular structure which provides a barrier to the free diffusion of some larger particles. This skeleton divides the cell membrane, making it difficult for particles to move from one compartment to another. In this situation the particle becomes trapped within a compartment and it unable to diffuse across the barrier. If the trapping is such that the transition rate between compartments can be described by an inverse power-law then the overall motion will be subdiffusive.

Anomalous diffusion has been found to commonly be a present feature in
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Figure 1.3: Picket fence model of sub-cellular skeletal structure of the cell membrane compartmentalises the field and provides a barrier to free diffusion within the membrane. Diffusing particles become trapped within compartments causing the diffusion to become anomalous.

the plasma membrane of cells [49–51]. The implication is that the membrane is a structure with a complex geometry, and a crowded environment for diffusing particles [52]. The exact reason for the subdiffusion is not yet fully established. Possible sources of the observed anomalous diffusion are: physical obstruction by the membrane or a subcellular skeleton and its bound proteins [53]; inclusion or exclusion from lipid domains [54]; binding to immobile traps [48,55]; and, of course, any combination of the preceding [56,57].

Experimental evidence shows large varying ranges of measurements in living cells and some experimental estimates are below the universal value predicted for subdiffusion due to obstacles. Some experimental evidence suggests that subdiffusion within cells is a transient phenomenon, with subdiffusion converging back to normal diffusion. Slowed-down Brownian motion could be considered as the macroscopic limit of transient subdiffusion. This could be due to obstacle hindrance or ligand binding [58]. Recently models were used by Berry and Chaté [53] in which obstacles were not fixed in space. Rather, they are free to move and this movement leads to transient subdiffusion for very mobile obstacles whilst preserving subdiffusion for relatively confined movement of obstacles. Such models could be key to understanding the chaotic nature of subdiffusion protein movement within cell membranes.
1.3.3 Subdiffusion in morphogenesis

Due to the importance of morphogenesis to two of our articles presented later, this subsection will give a more in-depth example than the previous two. In this subsection we will give a brief introduction to the science of morphogens, a specific example of morphogenesis, and a link to subdiffusion within the field.

Morphogens are the answer to the question of how a cell knows if its fate will be to become a finger, wing, or a liver cell; how a tiger gets its stripes, a cow its spots, or a peacock its patterns. In developing cells, when a cell knows its position, it causes different genes to be expressed which affect the further development of the cell. Alan Turing wrote an article in 1952 titled *The chemical basis of morphogenesis* [59] in which he described how non-uniformity and patterning, such as tiger stripes, could arise naturally from a homogeneous state. The theory became the reaction-diffusion theory of morphogenesis. What started as a theoretical model, was championed by fruit fly biologists, which lead to further advances in the field. Experimentalists later identified actual morphogens in the fruit fly which play a role in embryogenesis, and the work of Christiane Nusslein-Volhard was rewarded with the 1995 Nobel Prize in Physiology and Medicine.

The development of the limbs of the fruit fly is widely studied in the field of morphogenesis. Most of the patterning takes place in the syncytial environment called the pre-blastoderm embryo. A syncytial environment is one where...
a multinucleated mass of cytoplasm is not separated into individual cells. The pre-blastoderm embryo is the stage of development immediately following fertilisation of the egg. This is something specific to eukaryotes, organisms whose cells contain a distinct membrane bound nucleus.

The limbs of the fly develop from structures called imaginal discs. The discs which give rise to the thoracic imaginal disc are specified in response to two different morphogens [60, 61]: Wingless (Wg), which is expressed as a stripe just to the anterior of the boundary of this multisegment [62, 63]; and Decapentaplegic (Dpp), which is expressed as a lateral stripe running perpendicular to the cells expressing Wg. The anterior/posterior decision is controlled by the expression the gene called engrailed, which results in cells being posterior in orientation. Dpp is secreted when cells expressing engrailed interact with those not expressing, thus occurring at the boundary between the two. This is the dorsal/ventral axis. The dorsal/ventral decision is controlled by the apterous gene, which results in cells becoming dorsal. Wg is secreted at the boundary between those expressing and not expressing apterous. From their sources, Wg and Dpp diffuse across the field of cells in the imaginal disc, and form a concentration gradient in the two axes. Cell fates are determined by: whether they express engrailed or apterous; the concentration of Wg and Dpp to which they are exposed.

What is known now is the following. The morphogens are secreted from a source, and diffuse across the tissue to form a gradient of concentration. Cells respond to the local concentration at discrete thresholds [64]. This causes the expression of certain genes by the developmental cell, or causes a developed cell to react in another way such as secreting a molecule of its own. The expression of different genes by the cell determines the fate of the cell. The presence of a signalling morphogen at a certain threshold may even signal to the cell that it must die.

The most important aspect of the problem is the generation of the concentration gradient [60, 65, 67, 67, 80]. If there is some discrepancy in the shape of the morphogen gradient, it could lead to undesired consequences in the development of the tissue, including mutations [61, 63, 65, 81]. For example, in developing tissue, if the morphogen gradient profile were to have a longer tail it could cause more cells than required to be a certain type.

Many models for morphogenesis are based on Markovian, Normal diffusion models with linear reaction terms due to their ease of use. However, there is
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evidence suggesting models for diffusion with nonlinear reactions may be appropriate \cite{63,67,69,82,83}. The morphogen problem involving nonlinear reactions in a Markovian setting has been tackled in \cite{66} who found that nonlinear particle interactions leads to a robust stationary morphogen profile with heavy tails.

Models for subdiffusive transport of morphogens should also be considered as memory effects are likely to influence the motion of morphogens in the crowded and complex embryonic environment. The first to study subdiffusion with the morphogen problem was Hornung, Berkowitz, and Barkai \cite{75}. They argued that the complex extracellular surrounding may interact with the morphogens and lead to subdiffusion. However they did not obtain a stationary profile, only a nonstationary exponential profile.

One advantage of the subdiffusive transport with nonlinear degradations is that the stationary morphogen profiles are found to be particularly robust with respect to any physical inhomogeneities including fluctuations in production rate. The combination of subdiffusion with nonlinear particle interactions can lead to extra robustness, and shapes of morphogen profile which otherwise would not be seen. The morphogen problem involving subdiffusive transport with nonlinear reactions has been studied by Abad, Lindenberg, and Yuste \cite{70,84,85}. They began with the nonlinear reaction-subdiffusion equation \cite{70}:

\[
\frac{\partial c(x,t)}{\partial t} = K_\mu \frac{\partial^2}{\partial x^2} \left\{ e^{-k(x)t} D_1^{1-\mu} [e^{k(x)t} c(x,t)] \right\} - k(x)c(x,t), \tag{1.4}
\]

involving effective fractional diffusion coefficient $K_\mu$, reaction rate $k(x)$, and Riemann-Liouville fractional derivative of order $1 - \mu$ (which is defined in Section \ref{sec:3.1.1}). In the case of constant reactivity they found an exponential stationary profile with decay length dependent on the production rate $g$, reaction rate $k$, and anomalous exponent $\mu$:

\[
\begin{align*}
c_{\text{st}}(x) = \frac{g k^{\mu/2-1}}{2 \sqrt{K_\mu}} \exp \left\{ -|x| \sqrt{\frac{k^{\mu}}{K_\mu}} \right\}
\end{align*}
\tag{1.5}
\]

and analysed the interaction of subdiffusion with space dependent reaction, and its effect on the robustness of the profile. This nonlinear reaction-subdiffusion equation is also studied here in our third article, \textit{Nonlinear degradation-enhanced transport of morphogens performing subdiffusion}. 
1.4 Fractional equations for anomalous transport

Fractional equations arise naturally in the diffusion limit of certain random walk schemes. There they are a tool to describe the long range memory effects present in the non-Markovian processes. The main use of fractional calculus in physics is in describing non-local systems, with non-locality either in space or time. For subdiffusive transport, the non-locality is in the time domain. In recent years, the interest of physicists in non-local field theories has grown. An example of non-locality in space would be quantum non-locality, famously dubbed ‘spooky action at a distance’.

Moving from local to non-local descriptions in time brings with it the introduction of memory effects. With memory effects the actual behaviour of an object is not only affected by the actual state of the system, but also by events which happened in the past. The idea of memory in a physical system traces back as far as Aristotle, with the idea being that an object could in some way collect information and memorise past events. However, memory occurs in a much more natural way and objects do not store knowledge.

An excellent analogy can be found in [86], as follows. Consider the motion of a classical particle in a diluted gas, with no boundaries. With a given collision rate $\lambda(t)$, the system can be described by a local theory. Now introduce boundaries which gas molecules are reflected off. At a time $(t-\tau)$ a fixed rate of gas molecules are scattered, and at $(t-\tau/2)$ they collide with the boundaries and are reflected. So at time $t$ the dynamics of the system is described by an additional source term as compared with the boundaryless case. Besides $\lambda(t)$, the source terms contain a non-local term proportional to $\lambda(t-\tau)$. Neither the particles nor the system memorise past events with any intelligence, as perhaps was thought in Aristotle’s days. Rather, the boundaries generate a delayed reaction of the medium, resulting in a memory effect. Taken a step further, assign every point in space a complex reflection coefficient. This leads to Huygen’s principle from quantum mechanics, which states that every part of an advancing wave is the source of a new set of waves.

Fractional equations are best approached from a probabilistic point of view [87] and for anomalous diffusion in the presence of an external potential, the most common to approach the subject is continuous time random walk (CTRW) models. Other approaches have been used to study anomalous diffusion in potential
fields including fractional Brownian motion \cite{88, 89}, generalised diffusion equations \cite{90}, Langevin equations \cite{91, 92}, generalised Langevin equations \cite{93, 95}, generalised master equations \cite{96}, and generalised thermostatistics \cite{97}. However, only CTRW and generalised Langevin equations are consistent in the way which the system’s memory and shape of PDF is presented \cite{1}.

The fractional Fokker-Planck equation can be easily derived from a CTRW model. The fractional Fokker-Planck equation,
\[
\frac{\partial p}{\partial t} = D^{1-\mu}_t K_\mu \left[ \frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x} \frac{F(x)}{k_B T} \right] p(x,t),
\]

involves the fractional Riemann-Liouville derivative of order $D^{1-\mu}_t$. This is the archetypal equation for describing subdiffusive transport, being a direct analogue of the classical Fokker-Planck equation for normal diffusive transport. This equation is derived in detail in Section 3.2.1 and Section 3.2.2.

Within the main body of this thesis only the random walk theory will be addressed. This is the prevailing idea within the physical science side of the research into anomalous diffusion, most likely due to the ease of including external fields and formulating boundary value problems. Their mathematical structure also allows for methods of solution to standard problems being applicable to the fractional problems.

### 1.5 Continuous time random walks

Certain random walk schemes have limiting processes governed by fractional equations. In this thesis, as already mentioned, this is the only origin from where we will see fractional equations arise. Since the continuous time random walk is of such importance to the rest of the work, it is worth a short digression to talk about its origins.

The random walk theory can be traced back to the study of the irregular motion of pollen particles by the botanist Robert Brown in 1828. However it was not until the beginning of the twentieth century that random walks proper appeared in the literature. In 1900, Louis Bachelier \cite{98} proposed a random walk type object as being a model for stock price ticks. This was many decades before this became, by many arguments, the standard model for financial mathematics. He also saw the link between discrete random walks, and continuous diffusion.
equations. In fact, it was he who initiated the study of diffusion processes 5 years before the works of Einstein \cite{99} and Smoluchowski \cite{100}. He observed that the movement of stock prices could be analogous to the movement of small particles suspended in liquid, as described by Brown. With this assumption, he derived the underlying equations of motion and found pricing formulas for call and put options on underlying stocks following these dynamics.

However, the term random walk was first used by Karl Pearson in 1905 \cite{101}. His interest was in giving a simple model to describe a mosquito infestation in a forest, and he made the following analogy in a letter to \textit{Nature}. His letter was quickly answered by Lord Rayleigh, who had already solved a similar problem to Pearson in 1880, to do with sound waves in a non-homogeneous material. In the same year as the discussion between Rayleigh and Pearson, Einstein published his work on Brownian motion. He modelled the path of a dust particle performing a random walk driven by collisions with air particles. Seemingly, Einstein was unaware of Lord Rayleigh’s answer to Pearson’s letter. Since then, many authors have worked on the CTRW in various areas of science \cite{96,102,103,104,105,106}.

In his thesis, and following works, Bachelier made a number of breakthroughs which are considered standard in stochastic calculus and mathematical finance now: limits of random walks, Brownian motion, the martingale measure, the probability a Brownian motion does not exceed a given level and the distribution of the supremum, and the distribution of the Ornstein-Uhlenbeck process. However, his work went undiscovered for over 50 years until it was rediscovered by Samuelson \cite{107} and used to develop the geometric Brownian motion as a model for stock price dynamics. The culmination of the research of geometric Brownian motion in mathematical finance came with the work of Black, Scholes, and Merton \cite{108,109} who found fair prices for European call and put options, and were rewarded with the Nobel Prize for Economics in 1997.

In physics, Brownian motion is largely accredited to the work of Einstein and is often thought of as the a limit of a process of independent random jumps taken at asymptotically small intervals of fixed deterministic length \cite{110}. In fixed time intervals, a test particle is assumed to jump to one of its nearest neighbour sites. This can be modelled by the discrete time master equation,

\begin{equation}
    p(x, t + \Delta t) = \frac{1}{2}p(x - \Delta x, t) + \frac{1}{2}p(x + \Delta x, t),
\end{equation}

where $p(x, t)$ is the PDF to be at position $x$ at time $t + \Delta t$. In the limit $\Delta t \to 0$,
\[ \Delta x \to 0 \] Taylor expansions,

\[ p(x, t + \Delta t) = p(x, t) + \frac{\partial p}{\partial t} \Delta t + O((\Delta t)^2), \]

\[ p(x \pm \Delta x, t) = p(x, t) \pm \frac{\partial p}{\partial x} \Delta x + \frac{1}{2} \frac{\partial^2 p}{\partial x^2} (\Delta x)^2 + O((\Delta x)^3), \]

lead to the diffusion equation

\[ \frac{\partial p}{\partial t} = K \frac{\partial^2 p}{\partial x^2}, \quad K = \lim_{\Delta t \to 0, \Delta x \to 0} \frac{(\Delta x)^2}{2 \Delta t}, \]

with an appropriate truncation. This could be extended so that fixed inter-jump intervals are replaced by ticks of a Poisson process. This process is a Markovian continuous time random walk, with exponential inter-jump times.

Extended further, the inter-jump time can be drawn from the PDF \( \psi(t) \) of a distribution other than that of the exponential. So that the probability for a jump in the time interval \((t, t + \Delta t)\) is given by the probability \( \psi(t) \Delta t \). This is the basic idea of a general continuous time random walk, a series of independent random jumping and waiting events. However, when the inter-jump waiting time is not exponential the limiting process will no longer be the Brownian motion. Different types of CTRW processes can be characterised by the characteristic waiting time,

\[ \bar{T} = \int_0^\infty t \psi(t) dt, \]

being finite or diverging. In this general non-Markovian setting, the master equation has the form of an integro-differential equation involving the memory kernel \( K(t) \):

\[ \frac{\partial p}{\partial t} = \int_0^t K(t - \tau) \left( \int_{-\infty}^{\infty} p(x - z, \tau) w(z) dz - p(x, \tau) \right) d\tau. \]

If the waiting times between jumps \( \psi(t) \) are distributed exponentially, the memory kernel \( K(t) = \delta(t) \) and the Markovian master equation is recovered. Full discussion and derivation of this non-Markovian master equation is found in Section 2.2.

Random walks are now absolutely ubiquitous in science, engineering, and economics, and seem to show no signs of going out of fashion and is now ubiquitously studied in many areas of economics [16][20], physics [110][117], and is widely used
in Monte Carlo simulations for approximating a diffusion process \[118-120\].

In the next Chapter we describe the non-Markovian generalisation of the continuous time random walk in detail and derive the master equation from two different approaches. One method, described in Section 2.2.2 involves the introduction of an additional variable to create a Markovian random walk process from the general non-Markovian random walk.
In this chapter, we introduce the mathematical background behind the non-Markovian random walks and derive the non-Markovian master equation. It is possible to derive the fractional Fokker-Planck equation from a number of standpoints including generalised Langevin equations, and fractional Brownian motion. However we only consider stochastic models resulting in a master equation.

The non-Markovian random walk process can be described by a master equation, and derived in several ways. Here we present two methods to derive the non-Markovian master equation. The classical derivation is based on the integral equations for probability density and probability flux. These equations are based on the Chapman-Kolmogorov equations and describe the space-jump continuous time random walk model with arbitrary pausing distribution. With these equations it is easy to derive linear fractional diffusion equations, but incorporating nonlinearity and reactions can in some cases be problematic. We also present a derivation based upon the residence time structured probability density. This approach adds a parameter denoting the elapsed waiting time in the random walk model, thus making the evolution of the structured probability density Markovian. This approach is favoured by some authors for its ease of incorporating both nonlinearities and reactions.
CHAPTER 2. NON-MARKOVIAN RANDOM WALKS

2.1 CTRW

The purpose is to find an expression for the PDF $p(x,t)$ of a walker’s position $X(t)$ at time $t$. Assume the jumps $Z_1, Z_2, \ldots$ a walker makes are IID random variables occurring at random jump times $T_1, T_2, \ldots$, so that the intervals between jumps $Y_n = T_n - T_{n-1}$ are IID random variables. Without loss of generality it can be assumed $X(0) = 0$, then

$$X(t) = \sum_{i=1}^{N(t)} Z_i,$$  \hspace{1cm} (2.1)

where $N(t)$ is the number of jumps up to time $t$, $N(t) = \max\{n \geq 0|T_n \leq t\}$, known as a counting process.

The microscopic SDE for $X(t)$ can be written as

$$\frac{dX}{dt} = \sum_i Z_i \delta(t-T_i), \hspace{1cm} (2.2)$$

where $\delta(x)$ is the standard Kronecker delta and the RHS of the equation represents the particle making jumps of length $Z_i$ at random times $T_i$. The PDF for $X(t)$ having started at $X(0) = 0$ is denoted $p(x,t)$.

We begin in the CTRW framework, where the length of a given jump, and the waiting time between successive jumps are random variables characterised by the joint jump PDF $\Phi(x,t)$. The spatial jump PDF is given by

$$w(x) = \int_0^\infty \Phi(x,t)dt,$$ \hspace{1cm} (2.3)

and the waiting time PDF is given by

$$\psi(t) = \int_{-\infty}^\infty \Phi(x,t)dx = \lim_{\Delta t \to 0} \frac{\Pr\{\tau < T < \tau + \Delta t\}}{\Delta t}.$$ \hspace{1cm} (2.4)

In the case of the jump lengths and waiting times being independent, the joint PDF can be written as the product

$$\Phi(x,t) = w(x)\psi(t),$$ \hspace{1cm} (2.5)

and will be referred to as the decoupled PDF. Although the following equations
can be derived without independence of the two PDFs\footnote{123}, this is the case which will be considered mainly through the rest of the thesis. If both the PDFs are coupled, so that $\Phi(x,t) = p(x|t)\psi(t)$ or $\Phi(x,t) = p(t|x)w(x)$, there is an implied time cost of action. The implication being that in a given time a particle can only move a certain distance. This is not necessary for the models we are considering, and outside of this chapter we will only refer to the decoupled case where jumps are instantaneous.

CTRWs can be characterised by the mean waiting time

$$\bar{T} = \int_0^\infty \tau \psi(\tau) d\tau,$$

and the second moment of the jump PDF

$$\sigma^2 = \int_{-\infty}^{\infty} x^2 w(x) dx.$$  

(2.7)

Let us introduce some key quantities of the random walk model. We will denote the time of the next jump of a walker as $T$. First we introduce the survival probability of a walker, $\Psi(\tau)$. This is the probability that a walker remains without making a jump for a time $\tau$,

$$\Psi(\tau) = \Pr\{T > \tau\}.$$  

(2.8)

It is related to the waiting time PDF by,

$$\Psi(\tau) = \int_\tau^\infty \psi(s) ds = 1 - \int_0^\tau \psi(s) ds.$$  

(2.9)

Another important quantity will be the microscopic escape rate of a walker. This is defined as an instantaneous transition probability, and is known as the hazard function in reliability theory\footnote{124},

$$\gamma(\tau) = \lim_{\Delta t \to 0} \frac{\Pr\{T < \tau + \Delta t | T > \tau\}}{\Delta t},$$

(2.10)

the probability for a transition to take place after a wait in the interval $(\tau + \Delta t)$ given the wait has already been $\tau$. Using Bayes’ theorem, it is related to the
waiting time PDF (2.4) and survival probability (2.8) by [125].

\[ \gamma(\tau) = \frac{\psi(\tau)}{\Psi(\tau)}. \]  

(2.11)

Equivalently the three can also be related in the following ways:

\[ \psi(\tau) = \gamma(\tau)\Psi(\tau), \]

\[ \frac{\partial \Psi}{\partial \tau} = -\gamma(\tau)\Psi(\tau), \]  

(2.12)

and therefore we can write:

\[ \Psi(\tau) = e^{-\int_0^\tau \gamma(s)ds}. \]  

(2.13)

In the literature, authors deriving master equations from particular form of waiting time PDF \( \psi(\tau) \) or survival function \( \Psi(\tau) \) often do not link the two to the escape rate \( \gamma(\tau) \). In the standard integral equation method for deriving the master equation, in Section 2.2.1, the escape rate \( \gamma(\tau) \) is not needed in the formulation. However in the method involving the structured residence time, in Section 2.2.2 the escape rate is the key quantity.

These are the main mathematical quantities used in the non-Markovian random walk scheme. With the definition of them, the next sections will provide derivations of the master equation describing the evolution of the probability density \( p(x,t) \).

### 2.2 Master equation

To find an expression for the PDF \( p(x,t) \) we look to derive a master equation for the time evolution of the initial condition. The master equation is general in that it is valid for any waiting time distribution \( \psi(t) \), and therefore and survival function and escape rate also. Particular choices of waiting time PDF lead to different forms of the master equations. In particular the existence or divergence of the first moment of \( \psi(t) \) lead to greatly different master equations, both mathematically and qualitatively.

In deriving the master equation for the CTRW, there are two commonly used methods in the literature. One begins phenomenologically by writing a pair of balance equations for \( p(x,t) \) and for the flux of particles arrive at \( x \) at \( t \) [122].
Any anomalous behaviour is introduced phenomenologically through the choice of waiting time PDF $\psi(t)$.

The other approach is a microscopic Markovian method where by adding an addition parameter to the PDF, for the time residing in a location $\tau$, the structured PDF $\xi(x, t, \tau)$ is introduced. From this, the anomalous behaviour is introduced microscopically through the microscopic escape rate of particles leaving a point $x$, dependent on residence time parameter $\tau$.

At the end, both approaches lead to the same generalised master equation being derived,

$$\frac{\partial p}{\partial t} = \int_0^t K(t - \tau) \left( \int_{-\infty}^{\infty} p(x - z, \tau)w(z)dz - p(x, \tau) \right) d\tau. \quad (2.14)$$

This equation can then be specialised to the fractional master equation.

The master equation involves the memory kernel $K(t)$. This kernel is responsible for the introduction of memory to the process.

There is a function from reliability theory known as the renewal measure density \[121\] defined in Laplace space ($\mathcal{L}\{f(t)\} \rightarrow \hat{f}(s)$) as $\hat{m}(s) = \frac{\hat{\psi}(s)}{1 - \hat{\psi}(s)}$ associated with the PDF $\psi(t)$. The interpretation is that $\int_{\tau}^{t} m(u)du$ is the expected number of renewals in the time interval $(\tau, t]$. The memory kernel is the derivative of this function \[126\].

Its particular form is dependent upon the waiting time PDF $\psi(t)$, and in many cases it is not possible to write it explicitly. It is defined in Laplace space as,

$$\hat{K}(s) = \frac{s\hat{\psi}(s)}{1 - \hat{\psi}(s)}. \quad (2.15)$$

In master equation (2.14), the memory kernel is essentially an integral transform applied to the density $p(x, t)$. It is not always possible to invert the Laplace transform of the memory kernel, and as a result it is difficult to find an intuitive interpretation of it. In some sense, it is an integral transform which acts on the density $p(x, t)$ with the mesoscopic effect of adding memory effects to the evolution of $p(x, t)$.

If the waiting distribution is exponential with some rate $\lambda$, $\psi(t) = \lambda e^{-\lambda t}$, then $K(t)$ can be expressed in real time in terms of the Dirac delta function as $K(t) = \lambda \delta(t)$. In this case, the time convolution integral disappears, and along with it the memory effects.
When the $\hat{K}(s)$ is described by a power-law: $\hat{K}(s) \sim s^{1-\mu}$, $0 < \mu < 1$, in real time it becomes a fractional operator. This is the case for subdiffusion, and will be covered in Chapter 3.

### 2.2.1 Integral equation

The PDF for $X(t)$ having started at $X(0) = 0$ is denoted $p(x, t)$ and is found from the pair of balance equations [105],

$$p(x, t) = p_0(x)\Psi(t) + \int_0^t j(x, t - \tau)\Psi(\tau)d\tau, \quad (2.16)$$

$$j(x, t) = \int_{-\infty}^{\infty} p_0(x - z)\Phi(z, t)dz + \int_0^t \int_{-\infty}^{\infty} j(x - z, t - \tau)\Phi(z, \tau)dzd\tau, \quad (2.17)$$

where

$$\Psi(t) = \int_t^{\infty} \int_{-\infty}^{\infty} \Phi(z, \tau)dzd\tau = \int_t^{\infty} \psi(t)d\tau, \quad (2.18)$$

is the survival probability of a particle to remain without jumping for a time $t$. The first term of equation (2.16) represents the probability density of no transition having taken place: $p_0(x)$ is the initial density, and $\Psi(t)$ is the survival probability for the total time $t$. The second term represents the probability of arriving at $x$ at an earlier time $(t - \tau)$, $j(x, t - \tau)$, and not transitioning for the remaining time $\tau$. The arrival rate $j(x, t)$ is the flux of probability arriving at $x$ exactly at time $t$. Note that there is no spatial dependence on the waiting time PDF, or survival probability. This is the form of the model commonly used in the literature, however it is not what we use in the later chapters. The next subsection will include a derivation with this spatial dependence present. It is possible to include reaction terms in equation (2.16), and any such terms will appear also as exponential terms in a fractional reaction subdiffusion equation. Due to the highly non-Markovian nature of subdiffusion, it is not possible to separate reactions from transport [127] and reaction terms are not simply additive to transport terms in the diffusion approximation of the process. Reaction-subdiffusion equations have been studied by authors, with notable works including [117,128–133]. We study reaction-subdiffusion equations in our article Random death process for the regularization of subdiffusive fractional equations, and nonlinear reactions in Nonlinear degradation-enhanced transport of morphogens performing subdiffusion and Nonlinear tempering of subdiffusion with chemotaxis. However, we introduce
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the reaction terms using the method mentioned in the following chapter.

The analytical solution to the pair of balance equations (2.16), (2.17) can be found by passing to Fourier-Laplace space. However, in general it is not always possible to invert the transformation for a general joint jump PDF $\Phi(x, t)$ or waiting time PDF $\psi(t)$. In the case where it is not possible to invert the transformation, it is useful to derive a master equation, which could be solved directly or approximated by a partial differential equation and solved.

The Fourier-Laplace transform, $L\{F\{f(x, t)\}\} = \int_{-\infty}^{\infty} \int_{0}^{\infty} e^{ikx-st} f(x, t) dx dt = \tilde{f}(k, s)$, of equations (2.16), (2.17) is

$$\tilde{p}(k, s) = \tilde{p}_0(k) \hat{\Psi}(s) + \tilde{j}(k, s) \hat{\Phi}(s) \tag{2.19}$$

Rearranging equation (2.20) as

$$\tilde{j}(k, s) = \tilde{p}_0(k) \tilde{\Phi}(k, s) + \tilde{j}(k, s) \tilde{\Phi}(k, s). \tag{2.20}$$

Writing the survival function as $\hat{\Psi}(s) = \frac{1 - \hat{\psi}(s)}{s}$, and the joint jump PDF in the decomposed form $\tilde{\Phi}(k, s) = \tilde{\psi}(k) \hat{\psi}(s)$, the solution (2.21) can be written in the form known as the Montroll-Weiss equation

$$\tilde{p}(k, s) = \tilde{p}_0(k) \frac{1 - \hat{\psi}(s)}{s} \frac{1}{1 - \tilde{\psi}(k, s)} \hat{\psi}(s). \tag{2.22}$$

Note that balance equations (2.16), (2.17) can also be combined as

$$\tilde{p}(k, s) = \tilde{p}_0(k) \hat{\Psi}(s) + \tilde{j}(k, s) \tilde{\Phi}(k, s), \tag{2.23}$$

and the Fourier-Laplace transforms inverted to read in real space

$$p(x, t) = p_0(x) \Psi(t) + \int_0^t \int_{-\infty}^{\infty} p(x - z, t - \tau) \Phi(z, \tau) dz d\tau. \tag{2.24}$$
The interpretation is that the particles at \( x \) at \( t \) are the sum of particles which began there and remained till time \( t \), and the particles which were at locations \( x - z \) at time \( t - \tau \) and transitioned to \( x \) in the remaining time \( \tau \). An implication is that all particles must have begun the walk at time \( t = 0 \). It is possible to take into account other initial conditions, however these will introduce ageing effects which have been studied by other authors [134] but which we will not study here.

The equation (2.24) is formally equivalent to that of the generalised master equation, and can be shown either by direct differentiation, or passing to Fourier-Laplace space as we choose to do. From equation (2.22) we isolate the initial density term

\[
\tilde{p}_0(k) = \frac{s\hat{\psi}(s)}{1 - \hat{\psi}(s)},
\]

and manipulate the equation (2.22) to the form of the master equation in Fourier-Laplace space:

\[
s\tilde{p}(k, s) - \tilde{p}_0(k) = s\tilde{p}(k, s)\tilde{w}(k)\hat{\psi}(s) - \tilde{p}(k, s)\hat{\psi}(s)(1 - \tilde{w}(k))\frac{s\hat{\psi}(s)}{1 - \hat{\psi}(s)},
\]

\[
= \tilde{p}(k, s)\frac{s\hat{\psi}(s)}{1 - \hat{\psi}(s)}(\tilde{w}(s) - 1).
\]

Inverting equation (2.26) we obtain the integro-differential master equation,

\[
\frac{\partial p}{\partial t} = \int_0^t K(t - \tau) \left( \int_{-\infty}^{\infty} p(x - z, \tau) w(z) dz - p(x, \tau) \right) d\tau,
\]

where \( K(t) \) is the memory kernel, defined in terms of it’s Laplace transform

\[
\hat{K}(s) = \frac{s\hat{\psi}(s)}{1 - \hat{\psi}(s)}.
\]

This is the form of the generalised master equation which can be solved to find \( p(x, t) \). In general it is not possible to invert this transform for an arbitrary choice of waiting time distribution \( \psi \).
2.2.2 Residence time structured density

Some derivations of the FFPE begin from a phenomenological standpoint, and the introduction of the anomalous exponent is not seen as significant. In some derivations, it is possible to miss the significance of the anomalous exponent. In this subsection we will derive the generalised master equation equivalent to (2.27) where we begin from a CTRW model involving a residence time dependent escape rate $\gamma(x, \tau)$ and a structural density of particles $\xi(x, t, \tau)$. This approach has been used by many authors [127,129,135–138] for the study of non-Markovian random walks, and has recently been found to be one of the most suitable for further nonlinear generalisations [126,139–141].

Strictly speaking, this is not a traditional random walk model. There is no jump kernel to redistribute walkers at the end of waiting events. This approach is more likely akin to a non-Markovian generalisation of the classical Markov chain, or compound Poisson process, from probability theory [122].

In this derivation of the master equation we will, instead of talking about the position PDF $p(x, t)$, talk about the mean field density of particles $\rho(x, t)$. The two descriptions are equivalent, but the language required for this is somewhat easier for what we are describing. To begin with the master equation description it is necessary to first introduce the notion of a the escape rate of a particle from a point. The time of escape from a point is random and denoted by $T_x$. The escape rate $\gamma(x, \tau)$ is defined as in (1.3),

$$
\gamma(x, \tau) = \lim_{\Delta t \to 0} \frac{\text{Pr}(T_x < \tau + \Delta t | T_x > \tau)}{\Delta t},
$$

(2.29)

which takes the form of an instantaneous transition probability. The key fact of these escape rates is that they are dependent on the residence time variable $\tau$. This makes the process non-Markovian. This is where the parting of ways from the Markov chain theory occurs, for in a Markov chain this escape rate is a constant function with respect to the residence time variable $\tau$.

Note that a difference between this subsection and the previous subsection is that here we will allow a spatial dependence of the escape rate, and therefore waiting time PDF. In turn, this is exactly what will lead in the subdiffusive case to a spatially dependent anomalous exponent. It is clear how this arises naturally from the microscopic model, and describes the diffusion in a non-homogeneous environment. This is exactly what is considered in the later chapters, but it
not commonly used in the literature hence the reason for its exclusion from the previous subsection.

Note also that at this stage it is possible to consider various additional forms for the escape rate $\gamma(x, \tau)$. By the addition of extra terms to the escape rate which are independent of $\tau$ many different nonlinear effects can be introduced such as volume filling, quorum sensing, adhesion:

$$\gamma_\alpha(x, \tau) = \gamma(x, \tau) + \alpha(\rho).$$  \hfill (2.30)

Models including these nonlinear interactions of particles with the mean field have been covered in the excellent articles [142][143]. This is discussed in detail in the final article: Nonlinear tempering of subdiffusion with chemotaxis.

Recalling the definitions of the waiting time PDF, and survival probability respectively as,

$$\psi(x, \tau) = \text{Pr}\{\tau < T_x < \tau + \Delta t\}, \quad \Psi(x, \tau) = \text{Pr}\{T_x > \tau\},$$  \hfill (2.31)

Bayes’ Theorem allows us to relate the escape rates to both the waiting time PDFs and survival functions $\gamma(\tau) = \frac{\psi(x, \tau)}{\Psi(x, \tau)}$. Further, recalling from (2.9) that

$$\psi(x, \tau) = -\frac{\partial \Psi}{\partial \tau},$$  \hfill (2.32)

we can write the waiting PDF $\psi$ in terms of the escape rate $\gamma$,

$$\psi(x, \tau) = -\frac{\partial \Psi(x, \tau)}{\partial \tau} = \gamma(x, \tau)e^{-\int_0^\tau \gamma(x,s)ds},$$  \hfill (2.33)

and similarly the survival function

$$\Psi(x, \tau) = e^{-\int_0^\tau \gamma(x,s)ds}.  \hfill (2.34)$$
we write the microscopic evolution equation for a change in time $\Delta t$ and $\Delta \tau$.

\[ \xi(x, t + \Delta t, \tau + \Delta \tau) = \xi(x, t, \tau)(1 - \gamma(x, \tau))\Delta \tau + o(\Delta t) \]  

(2.35)

Since the residence time $\tau$ increases linearly with time $t$, $\Delta \tau = \Delta t$. In the limit as $\Delta t \to 0$ we obtain the equation [139]:

\[ \frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\gamma(x, \tau)\xi(x, t, \tau). \]  

(2.36)

In this formulation, we will impose a spatial dependence on the microscopic escape rate $\gamma$. This will lead in the end to a subdiffusion with a space dependent anomalous exponent. Since this is one of the main themes of the work within the thesis, it is important to be clear about where this arises from. When considering the microscopic random walk of a particle, it is natural inclusion. There have been attempts made to study a fractional diffusion equation with a space dependent anomalous exponent [144–150]. However, these approaches viewed the anomalous exponent as having a random and statistically distributed order. Further discussion about this can be found in the article: Subdiffusive master equation with space-dependent anomalous exponent and structural instability. An example of a work which includes a spatially dependent anomalous exponent in a similar manner to our own can be found in [151].

At this stage it is also possible to include additional external escape rates in the equation (2.36), becoming

\[ \frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -(\gamma(x, \tau) + \alpha)\xi(x, t, \tau), \]  

(2.37)

where $\alpha$ can be a function of space, particle density, or density of an external substance. This is also where reaction terms must be taken into account for subdiffusive processes, due to the non-trivial interactions between subdiffusion and reaction it is not possible to introduce reactions to the mesoscopic diffusion approximation [34,127,128,130,132,135,152]. Additional escape or evanescence terms included here will in the subdiffusive case appear as exponential tempering parameters which kill anomalous trapping. Exponential tempering of subdiffusion in heterogeneous media has been studied in [153,154].

We need to consider the initial state of the system of particles, and it’s convenient to choose a delta initial condition. This is convenient in the case of
Markovian diffusion too,
\[ \xi(x, 0, \tau) = \rho_0(x)\delta(\tau). \]  
(2.38)

All this says is that at the initial time \( t = 0 \) the initial density of particles, with residence times \( \tau = 0 \), are located at \( x \). The particles make jumps on a lattice with spacing \( a \) and with jump probability \( w(x|x-a,t) \), the probability of being at \( x-a \) at \( t \) and instantaneously jumping to \( x \). The residence time of a particle is renewed when it arrives at a new location, so we have the boundary condition for particles with zero residence time,
\[ \xi(x,t,0) = \sum_a \int_0^{t} \gamma(x,\tau)\xi(x-a,t,\tau)w(x|x-a,t)\,d\tau, \]  
(2.39)

The change in notation for \( w(x) \), defined originally in equation [2.3] as the marginal jump distribution of the joint jump PDF \( \Phi x,t \), is for two reasons: firstly, to demonstrate that this can be generalised to make a time dependent jump probability; secondly, for clarity to show the start and end point of a jump transition.

We need the master equation for the unstructured probability density \( \rho(x,t) \) though, so we must integrate over all residence times,
\[ \rho(x,t) = \int_0^{t} \xi(x,t,\tau)d\tau. \]  
(2.40)

The most important part of the CTRW model is the escape rate from a point. Here, it is convenient to introduce the integral escape rate \( i(k,t) \) as,
\[ i(x,t) = \int_0^{t} \gamma(x,\tau)\xi(x,t,\tau)d\tau, \]  
(2.41)

and the integral arrival rate \( j(x,t) \) as,
\[ j(x,t) = \xi(x,t,0). \]  
(2.42)

The integral arrival rate \( j(x,t) \) counts the number of particles, or the total probability of, arriving at \( x \) exactly at time \( t \). The integral arrival rate (2.42) is exactly the same as that from the balance equations in the previous subsection, equation (2.17). However, we can write the arrival rate in terms of the escape rate
from all other points,

\[
j(x, t) = \sum_a i(x - a, t)w(x|a, t).
\] (2.43)

Here \(w(x|a, t)\) is the redistribution kernel, which is the probability for a particle to jump from \((x - a)\) \(\to x\) at time \(t\). To find the master equation we must find the change in \(\rho(k,t)\) over time, by differentiating (2.40),

\[
\frac{\partial \rho}{\partial t} = \int_0^t \frac{\partial \xi}{\partial t} d\tau + \xi(x, t, \tau).
\] (2.44)

To eliminate the structured density \(\xi\) from the equations we substitute (2.36) into (2.40),

\[
\frac{\partial \rho}{\partial t} = -\int_0^t \frac{\partial \xi}{\partial t} d\tau - \int_0^t \gamma(x, \tau) \xi(x, t, \tau) d\tau + \xi(x, t, \tau),
\]

\[
\xi(x, t, \tau) = \sum_a i(x - a, t)w(x|a, t) - i(x, t).
\] (2.45)

At the same time, we need to solve (2.36) by the method of characteristics to get an expression for \(\xi(x, t, \tau)\) in terms of \(j(x, t)\). The characteristic system of ODEs is:

\[
\frac{\partial t(p, s)}{\partial p} = 1, \quad \frac{\partial \tau(p, s)}{\partial p} = 1, \quad \frac{\partial \xi(p, s)}{\partial p} = -\gamma(p)\xi(p, s),
\] (2.46)

along with

\[
t(0, s) = s, \quad \tau(0, s) = 0, \quad \xi(0, s) = \xi(s, 0).
\] (2.47)

Integrating the system (2.46) and using initial conditions (2.47) gives parametric solutions,

\[
t(p, s) = p + s, \quad \tau(p, s) = p, \quad \xi(p, s) = \xi(s, 0)e^{-\int_0^p \gamma(q) dq}
\] (2.48)

Then the reparameterised solution is,

\[
\xi(x, t, \tau) = \xi(x, t - \tau, 0)e^{-\int_0^\tau \gamma(x, s) ds}.
\] (2.49)

We should recognise this exponential term as the survival probability (2.34). So
now we can write the structured density in terms of the integral arrival rate and the survival function,

$$\xi(x, t, \tau) = j(x, t - \tau) \Psi(x, \tau).$$

(2.50)

This equation has a clear interpretation: all particles at \((x, t)\) with residence time \(\tau\) arrived to \(x\) at a time \((t - \tau)\) and survived for the remaining time \(\tau\). Inserting equation (2.50) into (2.40) gives

$$\rho(x, t) = \int_0^t j(x, t - \tau) \Psi(x, \tau) d\tau + \rho_0(x) \Psi(x, t).$$

(2.51)

Note that the integration with respect to residence time \(\tau\) in this equation is performed over the interval \(0 \leq \tau < t\), whilst in equation (2.40) it is performed over the full interval \(0 \leq \tau \leq t\), where we have a singularity at \(\tau = t\) due to the initial condition (2.38). The second term of this equation accounts for the special condition that all particles begin their random walk at time \(t = 0\). This equation has a clear interpretation, the first term represents the number density of particles at \((x, t)\) consisting of the ones which arrived there at an earlier time \((t - \tau)\) and survived [127]. The second term represents the particles at \((x, t)\) which began there and remained till time \(t\). An implication is that all particles must have begun the walk at time \(t = 0\). It is possible to take into account other initial conditions, however these will introduce ageing effects which other authors have studied [129] but which we shall not.

From the equation for the integral escape rate (2.41), using the characteristic solution of the structured balance equation (2.49), we have

$$i(x, t) = \int_0^t \gamma(x, \tau) \xi(x, t - \tau, 0) e^{-\int_0^\tau \gamma(x,s) ds} d\tau + \rho_0(x) \Psi(x, t).$$

(2.52)

Here, it’s easier to write this in terms of the residence time PDF, using the relation \(\psi(x, \tau) = \gamma(x, \tau) e^{-\int_0^\tau \gamma(x,s) ds}\), so that this equation for \(i\) becomes:

$$i(x, t) = \int_0^t j(x, \tau) \psi(x, t - \tau) d\tau + \rho_0(x) \Psi(x, t).$$

(2.53)

Some more algebra is required to close the equation and arrive at the generalised master equation. Taking the Laplace transform of equations (2.51) and (2.53) to eliminate the integral arrival rate term, \(j\), and using the convolution theorem for
Laplace transforms. The renewal type equation for $\rho(x,t)$, (2.51), becomes

\[
\hat{\rho}(x,s) = \hat{j}(x,s)\hat{\Psi}(x,s) + \rho_0(x)\hat{\Psi}(x,s), \tag{2.54}
\]

\[
\hat{j}(x,s) = \frac{\hat{\rho}(x,s)}{\hat{\Psi}(x,s)} - \rho_0(x). \tag{2.55}
\]

Inserting this into the Laplace transformed equation for the integral escape rate (2.53) gives,

\[
i(x,s) = \hat{\rho}(x,s)\frac{\hat{\psi}(x,s)}{\hat{\Psi}(x,s)}, \tag{2.56}
\]

with the inverse Laplace transform reading,

\[
i(x,t) = \int_0^t K(x,t-\tau)\rho(x,\tau)d\tau, \tag{2.57}
\]

where $\hat{K}(x,s) = \frac{\hat{\psi}(x,s)}{\hat{\Psi}(x,s)}$ is defined as the memory kernel. The memory kernel is defined in Laplace space, and for some choices of residence time probability, it may not even be possible to invert the transform. In this case, it is not possible to write the generalised master equation and the equation must be left in Laplace space.

Substitution of the final expression for the integral escape rate (2.57) into (2.45) gives the generalised master equation,

\[
\frac{\partial \rho}{\partial t} = \sum_a \int_0^t K(x-a,t-\tau)\rho(x-a,\tau)w(x|x-a,t)d\tau - \int_0^t K(x,t-\tau)\rho(x,\tau)d\tau. \tag{2.58}
\]

We have now derived the master equation from two different standpoints.

Note that we have not here derived neither the a nonlinear master equation, nor one containing any reaction terms. We will not cover nonlinearity except in the case of nonlinear reactions. Nonlinearity purely linked to the transport terms, derived from dependence of the jump kernel $w(z|\rho(x,t))$ upon $\rho(x,t)$ has been covered by several authors on the topic of subdiffusion [127,139,155,156]. Nonlinear reactions will be covered in the articles: Nonlinear degradation-enhanced transport of morphogens performing subdiffusion and Nonlinear tempering of subdiffusion with chemotaxis. However, we limit ourselves to only one diffusing species, reactions involving interactions between species. Such reactions are studied in detail in [157,161].
Chapter 3

Subdiffusive fractional equations

In this Chapter we will derive the fractional master equation, and its fractional Fokker-Planck approximation. The master equation (2.58) derived in the previous Chapter is specialised through the choice of the waiting time PDF $\psi(x, t)$ or escape rate function $\gamma(x, t)$. The choice of these quantities determines the form of the memory kernel (2.15) in equation (2.58). If in Laplace space the memory kernel has the form of a power-law $\hat{K}(s) \sim s^{1-\mu}$ then when inverted back to real space the result is a fractional operator. If the waiting time PDF and the escape rate are independent of the spatial variable then, in Laplace space, manipulations are possible resulting in a Riemann-Liouville fractional derivative on the RHS of the fractional master equation, or a Caputo derivative on the LHS.

The appearance of fractional operators for anomalous diffusion is quite natural. They arise naturally in the limit of random walk schemes involving long range memory effects, with inverse power-law waiting time PDFs. All that really must be known is that a convolution involving a power-law kernel in Laplace space results in a fractional operator in real space.

We will begin with an introduction to the basic material and history of fractional calculus. Then we will show how the fractional Riemann-Liouville derivative and Caputo derivative arise from the non-Markovian random walk model and master equation in Chapter 2.

3.1 Fractional Integration & Differentiation

In order to understand this thesis, it is important to know what a fractional order integral and derivative actually are. In this subsection, we shall briefly show how
CHAPTER 3. SUBDIFFUSIVE FRACTIONAL EQUATIONS

integer order calculus is commonly extended to that of fractional order calculus. Excellent introductions to fractional calculus, including the history of, can be found in the books [86, 162–165]. A geometrical interpretation is proposed by Igor Podlubny [166].

From a historical standpoint, fractional calculus can be described as the extension of derivative operations from integer \( n \) to arbitrary, real or complex, order \( \mu \) or even \( \mu(x, t) \). The approach for extending the integer order calculus to fractional order is extending the rule for repeated integration. Here there are two choices:

1. Extend the integer order repeated integral to allow non-integer and negative order. The fractional derivative is then simply a non-integer and negative order extended repeated integral.

2. Extend the integer order repeated integral to allow non-integer order integration. The fractional derivative is then simply the derivative of this non-integer and positive order repeated integral.

In actual fact, both approaches are used, however one is used much more widely.

The first recorded instance of the notion of generalising the derivative to non-integer orders was made by Leibniz in 1695. He remarked that the derivative to the order \( 1/2 \) should be expressed as \( x \sqrt{dx/x} \). In Liebniz’s calculus, with \( h = fg, \; dh = hdx \Rightarrow dh/dx = h \) and in general \( d^n = hdx^n \). However he found that \( \frac{d^\mu h}{dx^\mu} = \frac{d^\mu h}{(dh/h)^\mu} \neq h \), where \( dx = dh/h \).

Euler managed to partly solve Liebiz’s problem while he was trying to generalise factorials to non-integers. He introduced the Gamma function, and was able to write \( \frac{d^\beta x^\mu}{dx^\mu} = \frac{\Gamma(\beta+1)}{\Gamma(\beta-\mu+1)} x^{\beta-\mu} \) which is valid for non-integer \( \mu, \beta \).

Abel’s 1823 work on the tautochrone problem, in which he initiates the study of integral equations, would be for a long time the sole example of an applied use of fractional calculus [86].

In the mean time, Liouville tried to solve Liebniz’s problem for functions which were sums of exponentials, and tried \( \frac{d^\mu f}{dx^\mu} = \sum_k c_k \lambda_k^\mu e^{\lambda_k x} \) for \( f(x) \sim \sum_k c_k e^{\lambda_k x} \). From this he derived several other relations, and in particular found the fractional
integral and differential of order $\mu > 0$.

$$D^{-\mu} f(x) = \frac{1}{\Gamma(\mu)} \int_0^\infty f(x+y)y^{\mu-1}dy$$  \hspace{1cm} (3.1)

$$D^\mu f(x) = \frac{1}{\Gamma(n-\mu)} \int_0^\infty \frac{d^n}{dx^n} f(x+y)y^{n-\mu-1}dy \quad n-1 < \mu < n$$  \hspace{1cm} (3.2)

He had restricted his discussion to functions represented by exponential series with $\lambda_k > 0$ such that $f(-\infty) = 0$, and expanded the coefficients $\lambda_k$ such that he could introduce the idea of integer order derivatives as limits of difference quotients.

This idea was taken up by Grünwald whose calculus was based on the limits of difference quotients. Finally, Riemann then tidied up Liouville’s idea. Many forms of fractional derivatives are defined, due to work by Grünwald, Letnikov, Holmgren, Caputo, Riesz, and Weyl, amongst others. We will focus mainly on the Riemann-Liouville fractional derivative which is used extensively throughout the thesis. We will talk briefly about the Caputo fractional derivative, which is closely related, and is related to the work in the first publication.

Mandelbrot’s work on fractional geometries in the 1980s brought physicists to the field for the first time. They began working on fractional Brownian motion, leading to the creation of anomalous diffusion processes. However, they were not widely applied [167].

### 3.1.1 Riemann-Liouville Fractional Integral & Derivative

As very briefly discussed above, there are a number of ways to introduce the idea of fractional calculus. One such approach is that of extending the rule for repeated integration to fractional integrals [164]. Then fractional differentials can either be the continuation of this to negative orders, or integer derivatives of fractional integrals. The latter is the approach chosen by Riemann.

Given a locally integrable and real valued function $f$, integrating $n$ times gives:

$$D^{-n} f(t) = \int_a^t \int_{t_1}^t \cdots \int_{t_{n-1}}^t f(t_n)dt_n \cdots dt_2 dt_1$$

$$= \frac{1}{(n-1)!} \int_a^t (t-\tau)^{n-1} f(\tau)d\tau.$$  \hspace{1cm} (3.3)

This reduces iterated integration to a single convolution integral, known as the
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Cauchy formula for iterated integration,

\[ D^{-\mu} f(t) = \frac{1}{\Gamma(\mu)} \int_a^t (t - \tau)^{\mu-1} f(\tau) d\tau. \] (3.4)

Then fix \( n \geq 1 \) and choose an integer \( k > 0 \) and write,

\[ D^{(-k-n)} f(t) = \frac{1}{\Gamma(n)} D^{-k} \int_a^t (t - \tau)^{n-1} f(\tau) d\tau, \] (3.5)

where \( D^{-k} \) is \( k \) times iterated integration. Now, on the other hand, consider \( n \geq 1 \) and \( k \geq n \) then the \( (k-n) \)th derivative of \( f(t) \) can be written as:

\[ D^{(k-n)} f(t) = \frac{1}{\Gamma(n)} D^k \int_a^t (t - \tau)^{n-1} f(\tau) d\tau, \] (3.6)

where now \( D^k \) is \( k \) times iterated differentiation. The Riemann-Liouville fractional derivative we will denote as \[164\]

\[ D^\mu f(t) = \frac{d^{m+1}}{dt^{m+1}} \int_a^t (t - \tau)^{m-\mu} f(\tau) d\tau, \] (3.7)

where \( m \) is an integer such that \( m \leq \mu < m + 1 \). The superscript \( \mu \) is the order of fractional differentiation.

Since we mentioned the Grünwald-Letnikov derivative, it is a good time to note that if \( f(t) \in C^{m+1} \) (which is a requirement for \( f(t) \) in the Grünwald-Letnikov definition) then the Grünwald-Letnikov definition is equivalent to the Riemann-Liouville. Also, though this seems like a prohibitively strict requirement, actually a lot of problems in applied maths require that processes be smooth and free of discontinuities anyway. The requirement for a function \( f(t) \) in the Riemann-Liouville definition is that is integrable in \((a, t)\) and can be differentiated \( m + 1 \) times.

An important property of the Riemann-Liouville derivative is that it is the left inverse of the Riemann-Liouville integral. In general, fractional integration and differentiation do not commute.

The left Riemann-Liouville derivative is the most popular, and will be the only one to be used here, with a fixed lower terminal indicating the time of preparation of the system. When we talk about the left fractional derivative, we mean fractional derivative with a fixed lower terminal \( a \) (in all cases within this thesis
fixed to $a = 0$) and a moving upper terminal $t$, $a < t$. It is possible to consider the right fractional derivative with moving lower terminal $t$ and fixed upper terminal $b$. A simple interpretation of the difference between the two is elucidated in [164]. If you suppose $f(t)$ represents a dynamical function developing in time $t$. Take $\tau < t$, where $t$ is the present time, then the state $f(\tau)$ of the process $f$ belongs to the past. Conversely, take $\tau > t$, then the state $f(\tau)$ of process $f$ now belongs to the future. The left fractional derivative is an operation on the past states of the process, whilst the right fractional derivative is an operation on the future states. Due to causality, only left fractional derivatives are considered in this thesis as they have an interpretation in terms of physical dynamical processes.

$D_{1-t}^{1-\mu}$ is the Riemann-Liouville fractional derivative of order $1 - \mu$, defined as

$$D_{1-t}^{1-\mu} p(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t p(x,\tau)d\tau(t-\tau)^{1-\mu}, \quad 0 < \mu < 1.$$  \hspace{1cm} (3.8)

The Laplace transform of the fractional Riemann-Liouville fractional integral is:

$$\mathcal{L}\{D_{1-t}^{-\mu} f(t)\} = s^{-\mu} \hat{f}(s),$$  \hspace{1cm} (3.9)

and the Laplace transform of the fractional Riemann-Liouville fractional derivative is [162,163]:

$$\mathcal{L}\{D_{1-t}^{\mu} f(t)\} = s^\mu \hat{f}(s) - \sum_{k=0}^{n-1} s^k \left[D_{1-t}^{\mu-k-1} f(t)\right]_{t=0}, \quad n - 1 < \mu < n.$$  \hspace{1cm} (3.10)

Note that the initial condition involves the Riemann-Louville fractional derivative itself.

### 3.1.2 Caputo Fractional Derivative

Applied problems require definitions of fractional derivatives which allow for initial conditions with physical meaning. Unfortunately, Riemann-Liouville derivatives require initial conditions containing limits of more Riemann-Liouville values, eg. $\lim_{t \to 0} D_t^{\mu-n} f(t) = b_n$. There is no known physical interpretation for such conditions. The advantage of the Caputo derivative is that it leads to the initial conditions of the same form as the integer order problems. Another property of the Caputo derivative, that the Riemann-Liouville derivative does not share, is that the Caputo derivative of a constant is 0. The Riemann-Liouville derivative
of a constant $c$ is: $\mathcal{D}_t^\mu c = t^{-\mu}/\Gamma(1 - \mu)$, $0 < \mu < 1$.

The Caputo derivative is defined as,

$$\mathcal{C}_0^\mu D_t^\mu f(t) = \frac{1}{\Gamma(\mu - n)} \int_0^t f^{(n)}(\tau) \frac{d\tau}{(t - \tau)^{\mu + 1 - n}},$$

where $n - 1 < \mu < n$, and as $\mu \to n$ this becomes the conventional derivative.

To highlight the difference, compare the Laplace transform of the Riemann-Liouville (3.10) derivative to the Laplace transform of the Caputo derivative,

$$\mathcal{L}\{\mathcal{C}_0^\mu D_t^\mu f(t)\} = s^\mu \hat{f}(s) - \sum_{k=0}^{n-1} s^{\mu-k-1} f^{(k)}(0).$$

Note that the initial condition does not require a Caputo derivative, in contrast with the Riemann-Liouville derivative which requires a Riemann-Liouville derivative as the initial.

### 3.1.3 Mittag-Leffler Function

The Mittag-Leffler function is another extremely important function in fractional calculus. However, it is a function which is not well known to the majority of scientists, and wasn’t included in many books on special functions until the early 2000s. The exponential function is a special case of the Mittag-Leffler function and, in turn, the Mittag-Leffler function is a special case of the Fox function. The one parameter Mittag-Leffler function is defined as the infinite series \[164\]:

$$E_\mu(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\mu k + 1)}$$

The relationship with the exponential function is clear here. When $\alpha = 1$, the RHS becomes $\sum_{k=0}^{\infty} \frac{z^k}{k!}$ when $k$ is an integer.

The Mittag-Leffler function is of great importance to the CTRW formulation of fractional diffusion. When the survival probability function \[2.8\] $\Psi(\tau) = \text{Pr}\{T > \tau\}$ is defined to be given by the Mittag-Leffler function, then a fractional master equation can be derived, with a limit as the FFPE.

The function was related to the Laplace integral by Mittag-Leffler through
Figure 3.1: Solid line: Mittag-Leffler function $E_{1/2}(-(t/\tau_0)^{1/2})$; dashed line: $\exp\{- (t/\tau_0)^{1/2}/\Gamma(1 + 1/2)\}$; dot-dashed line: $-(t/\tau_0)^{-1/2}/\Gamma(1 + 1/2)$. For $t$ close to zero, the function behaves like a stretched exponential. $\tau_0 = 1/2$ for all three. For large $t$, the function behaves like an inverse power-law. Note the double logarithmic scales.

We will always see the function with the argument $E_\mu(-(t/\tau_0)^\mu)$, for in the case of a diffusion governed by the FFPE the mean displacement $\langle x(t) \rangle$ obeys

$$\frac{d\langle x(t) \rangle}{dt} = -\tau_0^{-\mu}D_1^{-1-\mu}\langle x(t) \rangle,$$

and the solution can be expressed by the Mittag-Leffler function:

$$\langle x(t) \rangle = \langle x(0) \rangle E_\mu(-(t/\tau_0)^\mu).$$

The function is characterised by its interpolation between short-time stretched exponential, and long-time inverse power-law asymptotics:

$$E_\mu(-(t/\tau_0)^\mu) \simeq \begin{cases} \exp\left\{-\frac{1}{\Gamma(1+\mu)}\left(\frac{t}{\tau_0}\right)^\mu\right\} & t \ll \Gamma(1+\mu)^{-\mu}\tau_0, \\ -\frac{1}{\Gamma(1+\mu)}\left(\frac{t}{\tau_0}\right)^{-\mu} & t \to \infty, \end{cases}$$

(3.17)
illustrated in Figure 3.1. The Laplace transform is given by

\[
\mathcal{L}\{E_\mu(-(t/\tau_0)\mu)\} = \frac{s^{\mu-1}}{s^{\mu} + \tau_0^{-\mu}}. \tag{3.18}
\]

The simple form of its Laplace transform is a great advantage to the CTRW study.

### 3.2 Fractional Fokker-Planck equation

The Fokker-Planck equation is the classic equation to describe diffusion in an external potential or velocity field. In one dimension it is also known as the Smoluchowski equation. In the classical paper Metzler, Barkai, and Klafter introduced the fractional Fokker-Planck equation (FFPE). The FFPE describes anomalous diffusion in a time independent external potential field \(F(x)\). This was the first time a fractional analogue of the Fokker-Planck equation had been derived which adequately described the observed properties of subdiffusion. This section will introduce the motivation behind the development of the fractional Fokker-Planck equation and some preliminary work before it is derived from the non-Markovian master equation by two methods in Section 3.2.1 and Section 3.2.2.

In their paper Metzler, Barkai, and Klafter sought an equation to describe anomalous transport in the same way which normal diffusive transport is described by the Fokker-Planck equation,

\[
\frac{\partial p}{\partial t} = L_{FP} p(x,t). \tag{3.19}
\]

Here, \(L_{FP}\) is the Fokker-Planck operator,

\[
L_{FP} = K_\gamma \left[ \frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x} \frac{F(x)}{k_B T} \right], \tag{3.20}
\]

They had four goals:

1. In the absence of an external field, the relation \(\langle x^2(t) \rangle \sim t^\gamma\) must be satisfied.

2. In the presence of an external, nonlinear, and time independent field, the stationary solution must be of Boltzmann type \(p_{st}(x) \propto e^{-\frac{E}{k_B T}}\).
3. The generalised Einstein relations \( D = \mu kT \) must be satisfied.

4. In the limit \( \gamma \to 1 \) the Fokker-Planck equation (3.19) must be recovered.

They made the link between continuous time random walk theory and anomalous diffusion through the use of the generalised master equation,

\[
\frac{\partial p(x, t)}{\partial t} = \int_{-\infty}^{\infty} \int_{0}^{t} K(x - z, t - \tau) p(z, \tau) d\tau dz. \tag{3.21}
\]

This equation includes a coupled jump PDF and memory kernel, and is equivalent to the form of derived master equation \((2.58)\) and \((2.27)\). The CTRW and master equation approach to deriving the FFPE is now widely used \([1,31,115,123,137,156,172–179]\).

The FFPE is an equation for the time evolution of a probability density function \( p(x, t) \) of finding a particle in a spatial interval \((x, x + \delta x)\) at a time \( t \). Theoretically, the FFPE can be written in terms of either the Riemann-Liouville fractional derivative or the Caputo fractional derivative:

\[
\frac{\partial p}{\partial t} = D_1^{1-\mu} L_{FP} p(x, t), \tag{3.22}
\]

or

\[
C_0 D_\mu p = L_{FP} p(x, t), \tag{3.23}
\]

respectively. \( D_1^{1-\mu} \) is the Riemann-Liouville fractional derivative of order \( 1 - \mu \) \((3.8)\). Here, \( L_{FP} \) is the Fokker-Planck operator,

\[
L_{FP} = K_\mu \left[ \frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x} \frac{F(x)}{k_B T} \right], \tag{3.24}
\]

and \( K_\mu \) is the anomalous diffusion coefficient with dimension \([K_\mu] = m^2 s^{-\mu}\).

However, it is the main result of the first two articles to show that in practice only the equation involving the Riemann-Liouville derivative can be used. The reason is that the equation involving the Caputo derivative is only valid when the anomalous exponent is constant, and independent, of the spatial variable.

At this stage we have derived the generalised master equation from two different standpoints, in Sections \(2.2.1\) & \(2.2.2\) We will begin with the master
equation (2.58),
\[
\frac{\partial \rho}{\partial t} = \sum_a \int_0^t K(x - a, t - \tau) \rho(x - a, \tau) w(x| x - a, t) d\tau - \int_0^t K(x, t - \tau) \rho(x, \tau) d\tau,
\]
which we will write in the compact form
\[
\frac{\partial \rho}{\partial t} = \sum a i(x, t) w(x| x - a, t) - i(x, t),
\]
in terms of the integral escape rate (2.57) \( i(x, t) \),
\[
i(x, t) = \int_0^t K(x, t - \tau) \rho(x, \tau) d\tau.
\]

The memory kernel \( K(x, t) \), defined in Laplace space as \( \hat{K}(x, s) = \frac{\hat{\psi}(x, s)}{\hat{\Psi}(x, s)} \), takes different forms depending on the waiting time distribution \( \psi(x, t) \) and equivalently survival probability \( \Psi(x, t) \). When the survival function takes the form of an asymptotic inverse power-law, the memory kernel becomes a time-fractional operator and the master equation can be approximated by the FFPE.

Note that this master equation will lead to a FFPE with space-dependent anomalous exponent. This is rarely studied in the literature \[146,147,180–182\], possibly due to the view that the anomalous exponent should be a global parameter. However, it should be clear from the derivation in Section 2.2.2 why this is a natural inclusion. Also, however, it is shown in the first article in this thesis why it is problematic for the model of subdiffusion.

In the following two subsections, we will show how the FFPE can be derived from particular forms of either the survival function \( \Psi(x, t) \), or the microscopic escape rate \( \gamma(x, t) \). Once the master equation has been derived, it is possible to use either method equivalently. Both are included here to provide a full theory for the residence time structured non-Markovian random walk model. For that model the microscopic escape rate is the most important quantity. All subdiffusive behaviour of the process emanates from this escape rate being inversely proportional to the residence time variable \( \tau \), as will be shown.

The choice of survival function as a Mittag-Leffler function also leads to a fractional master equation, and FFPE in the diffusion limit. This is the standard way to derive a subdiffusive limit of the non-Markovian random walk scheme \[1\].
However, the advantage of the other method as already mentioned is the ease of inclusion of reactions and non-linearity as modified escape rates.

### 3.2.1 FFPE from power-law survival function

The standard way of deriving a subdiffusive process in the limit of the non-Markovian random walk is through a power-law dependence of the survival function $\Psi(x, t)$. We can make use of the Mittag-Leffler function defined in equation (3.13) from Section 3.1.3:

$$E_\mu(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\mu k + 1)}. \quad (3.28)$$

If the survival function takes the form of the Mittag-Leffler function,

$$\Psi(x, t) = E_{\mu(x)} \left( -\left( \frac{t}{\tau_0(x)} \right)^{\mu(x)} \right), \quad (3.29)$$

then the Laplace transform of the survival function and waiting time PDF are given, respectively, as:

$$\hat{\Psi}(x, s) = \frac{\tau_0(x)(s\tau_0(x))^{\mu(x)-1}}{1 + (s\tau_0(x))^{\mu(x)}}, \quad \hat{\psi}(x, s) = \frac{1}{1 + (s\tau_0(x))^{\mu(x)}}. \quad (3.30)$$

From this the memory kernel can be written in Laplace space as,

$$\hat{K}(x, s) = \frac{s^{1-\mu(x)}}{\tau_0(x)^{\mu(x)}}. \quad (3.31)$$

The advantage of using the Mittag-Leffler survival function is that we can find the fractional transport equation without passing to the long time limit. The only difference in the resulting equation is the omission of the Gamma function of the correction term $g_\mu(x) = \Gamma(1 - \mu(x))\tau_0(x)^{\mu(x)}$.

Now consider a random walk such that the jump density only involves two outcomes, either a jump to the neighbour on the right or the left.

$$w(z|x, t) = r(x, t)\delta(z - a) + l(x, t)\delta(z - a), \quad (3.32)$$

where $r(x, t)$ is the jump probability from $x \to (x + a)$ and $l(x, t)$ is the jump
probability from $x \rightarrow (x - a)$, with the conservation condition,

$$r(x, t) + l(x, t) = 1.$$  

(3.33)

The FFPE is simply:

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x} \left( v_\mu(x, t) D_t^{1-\mu(x)} \rho(x, t) \right) + \frac{\partial^2}{\partial x^2} \left( D_\mu(x) D_t^{1-\mu(x)} \rho(x, t) \right),$$  

(3.34)

with fractional diffusion and drift coefficients, respectively:

$$D_\mu(x) = \frac{a^2}{2\tau_0(x)}; \quad v_\mu(x, t) = \frac{2(r(x, t) - l(x, t)) D_\mu(x)}{a}.$$  

(3.35)

Obviously, different choices of jump distribution $w(z|x, t)$ lead to different forms of the FFPE. The important requirement is that $r(x, t) - l(x, t) = O(a)$ to keep $v_\mu(x, t)$ finite as $a \rightarrow 0$.

### 3.2.2 FFPE from microscopic escape rate

The form of the waiting time distribution can either be introduced phenomenologically or introduced by specifying the form of the microscopic escape rate (2.10) $\gamma(x, \tau)$. When the microscopic escape rate of a particle is inversely proportional to its residence time $\tau$, the memory kernel also becomes a fractional operator. This is absolutely equivalent to the requirement for a survival function PDF of power-law type, since they are related as shown in equations (2.12), (2.13).

The assumption that $\gamma \sim 1/\tau$ is a natural one to make in many situations, with the interpretation being that the escape probability decreases as the residence time increases. A particle therefore has a tendency to remain. The likelihood of an particle, human, or animal to remain in one state given increasing as the time spent in that state increases is a could easily be seen in many situations.

Suppose the escape rate $\gamma(x, \tau)$ has the form,

$$\gamma(x, \tau) = \frac{\mu(x)}{\tau_0(x) + \tau}; \quad 0 < \mu(x) < 1$$  

(3.36)

where $\tau_0(x)$ is a parameter with unit of time. Then the survival probability can
be written as, using the relation (2.34):

$$\Psi(x, \tau) = e^{-\int_0^\tau \gamma(x, s) \, ds} = e^{-[\mu(x) \ln(\tau_0(x) + s)]_0^\tau},$$

$$= \frac{\tau_0(x)^{\mu(x)}}{(\tau_0(x) + \tau)^{\mu(x)}}, \quad (3.37)$$

From this equation (3.37), and relation (2.33) the waiting time PDF can be written as:

$$\psi(x, t) = \frac{\mu(x) \tau_0(x)^{\mu(x)}}{(\tau_0(x) + t)^{1+\mu(x)}}, \quad (3.38)$$

with the form of the final equality being motivated by the want to non-dimensionalise the time variable.

Equation (3.38) has the asymptotic Laplace transform approximation given by the Tauberian theorem [121] for \( s \to 0 \):

$$\hat{\psi}(x, s) \simeq 1 - g_\mu(x)s^{\mu(x)}, \quad g_\mu(x) = \Gamma(1 - \mu(x))\tau_0(x)^{\mu(x)}.$$  

With the definition of the memory kernel (2.15) \( \hat{K}(x, s) = \frac{s^{\mu(x)}}{1-\psi(x, s)} \) and the Laplace transform of the waiting time PDF (3.39):

$$\hat{K}(x, s) \simeq \frac{s^{1-\mu(x)}}{g_\mu(x)}.$$  

This is the Laplace transform of the Riemann-Liouville fractional differential operator of order \( 1 - \mu(x) \), defined in equation (3.10):

$$\mathcal{L}\{\mathcal{D}_t^n f(t)\} = s^n \hat{f}(s) - \sum_{i=0}^{n-1} s^i [\mathcal{D}_t^{n-1-i} f(t)]_{t=0}, \quad n - 1 < \mu < n.$$  

with the initial condition disappearing due to it being a delta function.

The expression for the integral escape rate (3.27) becomes,

$$i(x, t) = \mathcal{D}^{1-\mu(x)}_t \rho(x, t), \quad (3.42)$$
and the master equation (3.26) takes the fractional form,

$$\frac{\partial \rho}{\partial t} = \sum_a D_t^{1-\mu(x)} \rho(x, t) w(x|\rho - a, t) - D_t^{1-\mu(x)} \rho(x, t). \quad (3.43)$$

Now consider a random walk such that the jump density only involves two outcomes, either a jump to the neighbour on the right or the left,

$$w(z|x, t) = r(x, t)\delta(z - a) + l(x, t)\delta(z - a), \quad (3.44)$$

where \(r(x, t)\) is the jump probability from \(x \rightarrow (x + a)\) and \(l(x, t)\) is the jump probability from \(x \rightarrow (x - a)\), with the conservation condition,

$$r(x, t) + l(x, t) = 1. \quad (3.45)$$

The master equation (3.26) can then be written in the compact form,

$$\frac{\partial \rho}{\partial t} = r(x - a, t)i(x - a, t) + l(x + a, t)i(x + a, t) - i(x, t). \quad (3.46)$$

In the limit of lattice spacing \(a \rightarrow 0\), Taylor expansions give:

$$\frac{\partial \rho}{\partial t} = -a \frac{\partial}{\partial x} \left((r(x, t) - l(x, t))i(x, t)\right) + \frac{a^2}{2} \frac{\partial^2}{\partial x^2}i(x, t) + (o(a^2)). \quad (3.47)$$

Standard procedure for the Kramers-Moyall expansion neglects terms \((o(a^2))\), and yields diffusion approximation of the fractional master equation as:

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial x} \left(v_{\mu}(x, t) D_t^{1-\mu(x)} \rho(x, t)\right) + \frac{\partial^2}{\partial x^2} \left(D_{\mu}(x) D_t^{1-\mu(x)} \rho(x, t)\right), \quad (3.48)$$

with fractional diffusion and drift coefficients, respectively:

$$D_{\mu}(x) = \frac{a^2}{2g_{\mu}(x)}, \quad v_{\mu}(x, t) = \frac{2(r(x, t) - l(x, t))D_{\mu}(x)}{a}. \quad (3.49)$$

The jump kernel can also take a dependence upon the mean field density \(w(\rho|x, t)\), or upon the concentration of an external chemotactic substance \(w(C|x, t)\). Models considering a dependence on an external chemotactic to induce a transport bias will be used in the article: \textit{Nonlinear}
tempering of subdiffusion with chemotaxis. Chemotaxis is discussed in some detail in these later chapters, but far more discussion and example models can be found in [185].

This concludes the introductory section of the thesis. The main purpose was to motivate the study of subdiffusion, and to derive the governing fractional Fokker-Planck equation. It should have provided a sufficient introduction to the ideas of subdiffusion required to read the articles in the following chapters.
Subdiffusive master equation with space-dependent anomalous exponent and structural instability
Subdiffusive master equation with space-dependent anomalous exponent and structural instability

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We derive the fractional master equation with space-dependent anomalous exponent. We analyze the asymptotic behavior of the corresponding lattice model both analytically and by Monte Carlo simulation. We show that the subdiffusive fractional equations with constant anomalous exponent μ in a bounded domain [0, L] are not structurally stable with respect to the nonhomogeneous variations of parameter μ. In particular, the Gibbs-Boltzmann distribution is no longer the stationary solution of the fractional Fokker-Planck equation whatever the space variation of the exponent might be. We analyze the random distribution of μ in space and find that in the long-time limit, the probability distribution is highly intermediate in space and the behavior is completely dominated by very unlikely events. We show that subdiffusive fractional equations with the nonuniform random distribution of anomalous exponent is an illustration of a “Black Swan,” the low probability event of the small value of the anomalous exponent that completely dominates the long-time behavior of subdiffusive systems.

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I. INTRODUCTION

The last decade has seen increasingly detailed development of the fractional equations describing the anomalous transport in physics, biology, and chemistry [1–4]. Special attention has been paid to slow subdiffusive transport for which mean-squared displacement is sublinear (c^2(t)) ∼ t^μ, where μ is the anomalous exponent μ < 1. Subdiffusion is experimentally observed for proteins and lipids on cell membranes [3], RNA molecules in the cells [6], transport in spiny dendrites [7], anomalous exponent μ<1 is assumed to be constant.

I. INTRODUCTION

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The central result of this paper is that the subdiffusive fractional equations with constant anomalous exponent μ in a bounded domain [0, L] are not structurally stable with respect to the nonhomogeneous variations of parameter μ. It turns out that the space variations of the anomalous exponent lead to a drastic change in asymptotic behavior of p(x,t) for large t. To show this high sensitivity to nonhomogeneous perturbations, one can consider the following exponent:

μ(x) = μ + δν(x),

with constant μ and perturbation δν(x) (see Fig. 1). The asymptotic long-time behavior of the density p(x,t) with (4) is quite different from that of the solution to Eq. (1) with the constant value of μ. It means that the standard subdiffusive equation with constant μ is not a robust model for subdiffusive transport in heterogeneous complex media.

Now let us explain our main result. The standard way to deal with the fractional equation like (1) in the bounded domain [0, L] is a method of separation of variables [1]. Let us consider the case of the reflecting boundaries at x = 0 and x = L when (1) has a stationary solution p^r(x) satisfying

v_μ(x)p^r = 0 = (D_μ(x)p^r)_{x=0,L}.

We can write a partial solution of Eq. (1) in the form,

p(x,t) = p^r(x)Q(t).

The time evolution Q(t) is described by the fractional relaxation equation,

\frac{dQ}{dt} = -\lambda D_\mu Q,

where λ is the separation constant. The function Q(x) satisfies

\int_0^L Q^2(x)dx = C,

and the anomalous exponent μ < 1 is assumed to be constant.

The central result of this paper is that the subdiffusive fractional equations with constant μ in a bounded domain [0, L] are not structurally stable with respect to the nonhomogeneous variations of parameter μ. It turns out that the space variations of the anomalous exponent lead to a drastic change in asymptotic behavior of p(x,t) for large t. To show this high sensitivity to nonhomogeneous perturbations, one can consider the following exponent:

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The time evolution Q(t) is described by the fractional relaxation equation,

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where λ is the separation constant. The function Q(x) satisfies

\int_0^L Q^2(x)dx = C,
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FIG. 1. Nonuniform distribution of anomalous exponent \( \mu(x) \) on the interval \([0, L]\).

\( E_\mu(-\lambda t^\mu) \) with the power-law decay \( t^{-\mu} \) as \( t \to \infty \) [1–3] (see also [10]). The exponential decay \( \exp(-\lambda t) \) is recovered for \( \mu = 1 \).

In this paper we show that if we consider nonuniform perturbations of the anomalous exponent as (4), this relaxation picture is completely changed. The method of separation of variables does not work for space-dependent \( \mu(x) \). The asymptotic behavior of \( p(x,t) \) as \( t \to \infty \) is essentially different from that given by Eq. (9). It turns out that in the limit \( t \to \infty \) the probability density \( p(x,t) \) concentrates around the point \( x \), where the perturbation \( \delta \nu(x) \) is located, while the stationary distribution \( p(x) \) is completely irrelevant (see Figs. 2 and 3).

II. FRACTIONAL MASTER EQUATION WITH SPACE-DEPENDENT ANOMALOUS EXPONENT

The question is how to take into account the nonuniform distribution of the anomalous exponent \( \mu \). We cannot simply substitute the expression like (4) into (1). So we need a fractional master equation with space-dependent \( \mu(x) \). Chechkin, Gorenflo, and Sokolov were the first to derive the fractional diffusion equation with a varying fractional exponent [11]. They studied a composite system with only two separate regions with different anomalous exponents and found interesting effects involving a nontrivial average drift. A similar problem has been analyzed in terms of two equations with a different exponent by Korabel and Barkai [12]. Anomalous diffusion in composite media with space-dependent exponent \( \mu \) has been also considered in Ref. [13].

![Figure 2](image-url)  
**FIG. 2.** Long-time limit of the solution to the system (41) with \( \mu_i = 0.5 \) for all \( i \). Gibbs-Boltzmann distribution is represented by the line.

The next step is the introduction of the structured probability density function \( \xi(x,t,\tau) \) that the particle position \( X(t) \) at time \( t \) is in the interval \((x,dx)\) and its residence time \( T_x \) at point \( x \) is in the interval \((\tau,\tau + d\tau)\). The advantage of the structured density \( \xi \) is that a random walk can be considered as Markovian. This is a standard way to deal with non-Markovian processes [14] (see also [15–17]). This density \( \xi(x,t,\tau) \) obeys the balance equation,

\[
\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\gamma(x,\tau)\xi.
\]

Here we consider only the case when the residence time of random walker at \( t = 0 \) is equal to zero, so the initial condition is

\[
\xi(x,0,\tau) = p_0(x)\delta(\tau),
\]

where \( p_0(x) \) is the density for the initial position \( X(0) \). The boundary condition at \( \tau = 0 \) can be written as [14]

\[
\xi(x,t,0) = \int_0^t \gamma(x,\tau)\xi(x,z,t,\tau)w(z|x-z,t)d\tau dz,
\]

where \( w(z|x,t) \) is the probability density for jumps \( z \) from the point \( x \) at time \( t \) (jumps are independent from the residence time).

Our purpose now is to derive the fractional master equation for the probability density,

\[
p(x,t) = \int_0^t \xi(x,t,\tau)d\tau.
\]
It is convenient to introduce the integral escape rate,
\[ i(x,t) = \int_0^t \gamma(t,x)\xi(t,x,\tau)d\tau, \] (15)
and integral arrival rate,
\[ j(x,t) = \xi(x,t,0), \] (16)
as the density of particles with zero residence time. The boundary condition (13) can be rewritten as
\[ j(x,t) = \int_\mathbb{R} i(x-z,t)w(z|x-z,t)dz. \] (17)

Differentiation of Eq. (14) with respect to time and substitution of \( \partial \xi / \partial t \) from Eq. (11) together with Eq. (17) gives
\[ \frac{\partial p}{\partial t} = \int_\mathbb{R} i(x-z,t)w(z|x-z,t)dz - i(x,t). \] (18)

To close this equation we need to express the escape rate \( i(x,t) \) in terms of \( p(x,t) \). We solve (11) by the method of characteristics,
\[ \xi(x,t,\tau) = \xi(x,t,0)e^{-\int_0^\tau \gamma(x,s) ds}, \quad \tau < t. \] (19)

Here we recognize the survival function [14],
\[ \Psi(x,\tau) = \Pr[T_x > \tau] = e^{-\int_0^\tau \gamma(x,s) ds}, \] (20)
so the structural density \( \xi \) can be rewritten as
\[ \xi(x,t,\tau) = j(x,t-\tau)\Psi(x,\tau), \quad \tau < t. \] (21)

The residence time probability density function (PDF) \( \phi(x,\tau) \) is related to \( \gamma(x,\tau) \) as
\[ \phi(x,\tau) = -\partial \Psi / \partial \tau = \gamma(x,\tau) \exp \left( -\int_0^\tau \gamma(x,s) ds \right). \] (22)

The balance equation for \( p(x,t) \) can be found by substitution of Eq. (19) and the initial condition \( \xi(0,0) = p(0)\delta(t) \) into (14)
\[ p(x,t) = \int_0^t j(x,u)\Psi(x,t-u)du + p_0(0)\Psi(x,t). \] (23)

To obtain the equation for \( i(x,t) \) we substitute (19) and the initial condition into (15):
\[ i(x,t) = \int_0^t j(x,u)\phi(x,t-u)du + p_0(0)\phi(x,t). \] (24)

Using the Laplace transform in Eqs. (23) and (24) we eliminate \( j(x,t) \) and obtain [11]
\[ i(x,t) = \int_0^t K(x,t-\tau)p(x,\tau)d\tau, \] (25)
where \( K(x,t) \) is the memory kernel defined by its Laplace transform,
\[ \hat{K}(s) = \frac{\phi(x,s)}{\Psi(x,s)}. \] (26)

B. Anomalous subdiffusion in heterogeneous media

Let us consider the anomalous subdiffusive case with the survival probability [18]:
\[ \Psi(x,\tau) = E_{\mu(x)}^{-\tau} \left[ -\frac{t}{\tau(x)} \right]^{\mu(x)}, \quad 0 < \mu(x) < 1, \] (27)
where \( E_{\mu[z]} \) is the Mittag-Leffler function. The Laplace transforms of \( \Psi(x,\tau) \) and \( \phi(x,\tau) \) are
\[ \hat{\Psi}(s) = \frac{\tau(x)x(\tau(x))^{\mu(x)-1}}{1 + (\tau(x))^{\mu(x)}}, \quad \hat{\phi}(s) = \frac{1}{1 + (\tau(x))^{\mu(x)}}. \] (28)

The Laplace transform of the memory kernel \( K(x,t) \) is
\[ \hat{K}(s) = \frac{s^{1-\mu(x)}}{\tau(x)\Psi(x)}, \] (29)
and the integral escape rate \( i(x,t) \) can be written as
\[ i(x,t) = \frac{1}{\tau(x)\Psi(x)} D_t^{1-\mu(x)} p(x,t). \] (30)

Substitution of this expression into Eq. (18) gives the fractional master equation,
\[ \frac{\partial p}{\partial t} = \int_\mathbb{R} \frac{D_t^{1-\mu(x)} p(x-z,t)}{\tau(x-z)^{\mu(x)}} w(z|x-z,t)dz - \frac{1}{\tau(x)\Psi(x)} D_t^{1-\mu(x)} p(x,t), \] (31)
where \( D_t^{1-\mu(x)} \) is the Riemann-Liouville fractional derivative with varying order. This equation can be used to derive the general Fokker-Planck equation [19]. If we assume that the anomalous exponent \( \mu \) and time parameter \( \tau \) are independent from coordinate \( x \), this equation can be rewritten in terms of the Caputo derivative,
\[ \tau^\mu \frac{\partial p}{\partial \tau} = \int_\mathbb{R} p(x-z,t)w(z|x-z,t)dz - p(x,t). \] (32)

It should be noted that the fractional equation with the Caputo derivative cannot be served as a model for subdiffusion in heterogeneous media with varying in the space anomalous exponent \( \mu(x) \).

Master equation (31) can be a starting point for deriving nonlinear fractional equations. If instead of \( p \) we consider the mean density of particles \( \rho \) and assume that jump PDF \( w(z) \) depends on \( \rho \), then one can write
\[ \frac{\partial \rho}{\partial t} = \int_\mathbb{R} \frac{D_t^{1-\mu(x)} \rho(x-z,t)}{\tau(x-z)^{\mu(x)}} w(z|\rho(x-z,t))dz - \frac{1}{\tau(x)\Psi(x)} D_t^{1-\mu(x)} \rho(x,t). \] (33)

Expansion of this equation in \( z \) can give a variety of fractional nonlinear partial differential equations. As an example, let us consider the case of the symmetrical kernel \( w(z|\rho(x,t))dz = 0 \). Then (33) can be approximated by a nonlinear fractional equation,
\[ \frac{\partial \rho}{\partial t} = \frac{\partial^2}{\partial x^2} (D_\mu(\rho)D_t^{1-\mu(x)} \rho), \] (34)
with varying anomalous exponent $\mu(x)$ and nonlinear fractional diffusion coefficient $D_\mu(x)$:

$$D_\mu(x) = \frac{m_2(\rho)}{2\tau(x)^{\mu(x)}}; \quad m_2(\rho) = \int_{-\infty}^\infty z^2 w(z|\rho) dz.$$ 

(35)

First, let us consider random walk on a lattice with the space size $s$. We denote the probability of a particle moving right and left from the point $x$ as $r(x)$ and $l(x)$ correspondingly ($r(x) + l(x) = 1$). Then the jump PDF can be written as

$$w(z|x) = r(x)\delta(z-a) + l(x)\delta(z+a).$$ 

(36)

The fractional master Eq. (31) takes the form,

$$\frac{\partial p}{\partial t} = \frac{r(x-a)}{\tau(x-a)^{\mu(x)-a}D_\mu(x-a)}p(x-a,t) + \frac{l(x+a)}{(x+a)^{\mu(x)+a}D_\mu(x+a)}p(x+a,t) - \frac{D_\mu}{\tau(x)^{\mu(x)}}p(x,t).$$ 

(37)

In the limit of small $s$ and $\tau(x)$ [20] one can obtain from Eq. (37) the FFP equation with varying the anomalous exponent,

$$\frac{\partial p}{\partial t} = \frac{\partial (v_\mu(x)D_\mu(x)\partial_x - v^2(x))}{\partial x^2} + \frac{D_\mu}{\tau(x)^{\mu(x)}}p(x,t).$$ 

(38)

with the finite values of the fractional diffusion coefficient $D_\mu(x)$ and fractional drift $v_\mu(x)$:

$$D_\mu(x) = \frac{a^2}{2\tau(x)^{\mu(x)}}, \quad v_\mu(x) = \frac{2(r(x) - l(x))D_\mu(x)}{a}.$$ 

(39)

Note that in order to keep the fractional drift $v_\mu(x)$ finite as $a \to 0$, we need to assume that $r(x) - l(x) = O(a)$.

If we put the reflecting barriers at $x = 0$ and $x = L$ and consider constant exponent $\mu$ and diffusion $D_\mu$, then the FFP Eq. (38) admits the stationary solution in the form of the Gibbs-Boltzmann distribution:

$$p_i(x) = C \exp[-U(x)], \quad U(x) = -\int_{-\infty}^x v_\mu(z)dz.$$ 

(40)

with $C^{-1} = \int_{-\infty}^\infty \exp[-U(x)]dx$.

If $\mu$ is constant, the fractional time derivative does not affect the Gibbs-Boltzmann distribution [1,23]. But this result is structurally unstable with respect to any nonuniform variations of $\mu$. Let us show now that the Gibbs-Boltzmann distribution (40) is absolutely irrelevant for the long-time behavior of the solution to the FFP equation (38) with nonuniform distribution of $\mu(x)$ (4).

C. Discrete model

We divide the interval $[0, L]$ into $n$ discrete states. At each state $i$, the probability of jumping in the neighborhood to the left or right is given, respectively, by $l_i$ and $r_i$ ($l_i + r_i = 1$). The fractional Eq. (37) for $p_i(t)$ is $Pr[X(t) = i]$ can be rewritten as

$$p_i'(t) = \frac{r_{i-1}D_\mu(x)^{\mu(x)-1}p_{i+1}(t)}{\tau_{i-1}^{\mu(x)-1}} + \frac{l_{i+1}D_\mu(x)^{\mu(x)}p_{i+1}(t)}{\tau_{i+1}^{\mu(x)}}.$$ 

subject to the conditions $l_1 = r_1 = 0, r_i = 1$ and $l_n = 0$. Note that the FFP Eq. (38) is just a continuous approximation of Eq. (41). Taking the Laplace transform of (41) and using $\sum i \hat{p_i}(s) = \frac{1}{s}$, we obtain

$$\hat{p_i}(s) = \frac{r_{i-1}}{(s\tau_{i-1})^{\mu(x)-1}} + \frac{l_{i+1}}{(s\tau_{i+1})^{\mu(x)}} + \frac{1}{(s\tau_i)^{\mu(x)}}$$ 

(42)

If one $\mu_M$ is smaller than the others ($\mu_M < \mu_i, \forall i$), one can find that $\hat{p_i}(s) \to 0$ and $\hat{p_M}(s) \to 1$ as $s \to 0$. It means that in the limit $t \to \infty$, we obtain

$$p_i(t) \to 0, \quad p_M(t) \to 1.$$ 

(43)

This result in a continuous case can be rewritten as $p(x,t) \to \delta(x - x_{\text{final}})$ as $t \to \infty$, where $x_{\text{final}}$ is the point on the interval $[0,L]$ at which $\mu(x)$ takes its minimum value. A similar result was obtained for a symmetrical random walk in Ref. [17] in the context of chemotaxis (anomalous aggregation). Note that Shushin [21] considered a two-state anomalous system with a different anomalous exponent $\mu$ and found that in the long-time limit the probability is located in the slower state (see also [12,22]).

III. MONTE CARLO SIMULATIONS

To validate our results, we run Monte Carlo simulations with the following procedure. Random numbers with uniform distribution, $u$ and $v$, are generated and then transformed into Mittag-Leffler distributed random numbers using the following inversion formula $t_\mu = -\tau \log(u)\frac{\Gamma(1/\mu)}{\Gamma(1/\mu - 1)} - \cos(\mu\pi/2)$ [24] (see for details [25]). We take $L = 1$ and divide the interval $[0, 1]$ into 100 subintervals. We use $r_i = 1/2 + 5a(1 - 2ai)/21, 1 \leq i \leq 100$ and $a = 1/100$. This corresponds to

$$r(x) = \frac{1}{2} + 5a(\frac{1}{2} - x),$$ 

(44)

so the drift $v_\mu(x) = (10(1 - 2x)D_\mu$ and the potential,

$$U(x) = \frac{5}{2}(1 - 2x)^2.$$ 

(45)

All the random walkers start in the same state $i = 40$, their number $N = 10^4$, $\tau_i = 10^{-4}$ for all $i$, and the long-time limit is set at $T = 10^5$.

First step is to compute the exact stationary PDF given by Eq. (40) and see how well our Monte Carlo simulations work. Figure 2 shows that the Monte Carlo simulations agree with the Gibbs-Boltzmann distribution.

The next step is to show that the Gibbs-Boltzmann distribution (40) is absolutely irrelevant as far as the long-time behavior of the nonuniform system is concerned. The anomalous exponent $\mu_i$ is assumed to be $0.5$ for all states except one, $i = 42$, for which $\mu_{42} = 0.3$. One can see from Fig. 3 that in the long-time limit the probability is concentrated...
at state $i = 42$. One can conclude that there is a complete breakdown in the predictions based on the FFP equation with the uniform anomalous exponent. If the system were structurally stable we would expect to see something more like Fig. 2 again. However, the outcome is completely dominated by the perturbation $\mu_{42} = 0.3$. This result has a huge implication for modeling the anomalous subdiffusive transport of proteins, porous media, etc. In reality the environment in which anomalous transport takes place is never homogeneous.

Several attempts have been made to take into account the random distribution of the anomalous exponent (see, e.g., [26,27]). One can introduce PDF $f(\mu)$ for a random $\mu$ and write down the distributed-order fractional FPE as

$$\int_0^1 x^{\alpha-1} \left[ \frac{\partial}{\partial \mu} p(x,t) \right] \, d\mu = L_{FP} p.$$  

(46)

Let us show that if we generate the random field $\mu(x)$ along the space interval $[0,1]$, the asymptotic behavior of $p(x,t)$ will be quite different from that of the average fractional Eq. (46).

Figure 4 shows the PDF $f(\mu)$ which will be used to generate the discrete uncorrelated random field $\mu_i$. The probability is concentrated around the point $0.6$ such that $Pr[0.5 < \mu < 0.7] = 0.98$. This distribution is chosen so that extreme values are highly unlikely to occur, with a purpose to show that the extreme low values dominate the long-time behavior. Figure 5 shows one sample of random field $\mu(x)$ on the interval $[0,1]$ which is subdivided into 100 subintervals ($1 \leq i \leq 100$). Figure 5 shows clearly that the values of $\mu_i$ fluctuate around the mean. The value at $\mu_{82} = 0.01245$ has a very small probability, since $Pr[\mu < 0.02] = 2.5 \times 10^{-4}$. It is a very unlikely event, yet one can see from Fig. 6 the state $i = 82$ completely dominates the long-time outcome of Eq. (41). This phenomenon can be interpreted as a “Black Swan.” We use the term “Black Swan,” to capture the idea proposed by Taleb [28] of the disproportionate role of rare events with extreme impact. Here the “Black Swan” is an outlier (small value of anomalous exponent) that completely dominates the long-time behavior of subdiffusive systems. This event has a very low probability of happening. However, when it does occur it has a high impact on the future evolution of the process.

The distribution of $p(x,t)$ is highly intermediate for large $t$, so the average behavior described by Eq. (46) can be very misleading. It has been found [26] that the distribution of the anomalous exponent in Eq. (46) leads to ultraslow kinetics, but the stationary distribution is still given by the Gibbs-Boltzmann distribution [23]. Our results show that random space variation of the anomalous exponent leads to completely different behavior in the long-time limit (see Fig. 6). It should be noted that anomalous diffusion is just an intermediate asymptotic. When time tends to infinity we expect a crossover from anomalous diffusion to normal diffusion, and then we will recover the Gibbs-Boltzmann distribution. The standard tool for studying a subdiffusion is a subordination technique [29] with a constant anomalous exponent. It would be interesting to apply a similar technique if possible to the nonhomogeneous case. It would be also interesting to take into account chemical reactions together with the nonuniform anomalous exponent [30].

IV. CONCLUSIONS

We have demonstrated that when the anomalous exponent $\mu$ depends on the space variable $x$, the Gibbs-Boltzmann distribution is not a long-time limit of the fractional Fokker-Planck equation. Even very small variations of the exponent lead to a drastic change of $p(x,t)$ in the limit $t \to \infty$. We have derived the fractional master equation with the space-dependent anomalous exponent. We analyzed asymptotic behavior of the corresponding lattice model in a finite domain with $n$ states with different exponents. We have found that in this situation the probabilities $p_i(t)$ do not converge to the stationary distribution. To illustrate our ideas, we ran Monte Carlo simulations which show a complete breakdown.
in the predictions based on the FFP equation with the uniform anomalous exponent. Furthermore, we have shown that the idea of taking into account the randomness of the anomalous exponent $\mu$ by averaging the fractional equation with respect to the distribution $f(\mu)$ is not applicable to a nonhomogeneous finite domain. Monte Carlo simulations show that for every random realization of $\mu(x)$ the PDF $p(x,t)$ is highly intermediate, so the average behavior can be misleading. Although it is possible in theory to have a completely homogeneous environment, in which $\mu$ is uniform, it is not useful in any real application like chemotaxis [17] or morphogen gradient formation [31] because any nonhomogeneous variation destroys the predictions based on this model in the long-time limit. We have demonstrated that subdiffusive equations with the nonuniform random distribution of the anomalous exponent illustrate the “Black Swan” phenomenon [28], when an outlier (small value of anomalous exponent) completely dominates the long-time behavior of subdiffusive systems.

Random death process for the regularization of subdiffusive fractional equations
Random death process for the regularization of subdiffusive fractional equations

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The description of subdiffusive transport in complex media by fractional equations with a constant anomalous exponent is not robust where the stationary distribution is concerned. The Gibbs-Boltzmann distribution is radically changed by even small spatial perturbations to the anomalous exponent [S. Fedotov and S. Falconer, Phys. Rev. E 85, 031132 (2012)]. To rectify this problem we propose the inclusion of the random death process in the random walk scheme, which is quite natural for biological applications including morphogen gradient formation. From this, we arrive at the modified fractional master equation and analyze its asymptotic behavior, both analytically and by Monte Carlo simulation. We show that this equation is structurally stable against spatial variations of the anomalous exponent. We find that the stationary flux of the particles has a Markovian form with rate functions depending on the anomalous rate functions, the death rate, and the anomalous exponent. Additionally, in the continuous limit we arrive at an advection-diffusion equation where advection and diffusion coefficients depend on both the death rate and anomalous exponent.

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I. INTRODUCTION

Anomalous subdiffusion, where the mean squared displacement grows sublinearly with time \( \langle x^2(t) \rangle \sim t^{\mu} \), where the anomalous exponent \( \mu < 1 \), is an observed natural phenomena [1]. It is seen in areas as varied as dispersive charge transport in semiconductors [2], ion movement in spiny dendrites [3], and protein transport on cell membranes [4]. In the classical paper [5], Metzler, Barkai, and Klafter introduced the fractional Fokker-Planck equation (FFPE) that describes anomalous subdiffusion of particles in an external field \( F(x) \). This equation for the probability density \( p(x,t) \) is written as

\[
\frac{\partial p}{\partial t} = D_1^{1-\mu} L_{FP} p(x,t),
\]

where

\[
L_{FP} = K_\mu \left[ \frac{\partial^2}{\partial x^2} - \frac{\partial}{\partial x} F(x) \right] ^{\mu - 1},
\]

is the Fokker-Planck operator, \( K_\mu \) is the anomalous diffusion coefficient, and \( D_1^{1-\mu} \) is the Riemann-Liouville fractional derivative of order \( 1 - \mu \), defined as

\[
D_1^{1-\mu} p(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial \tau} \int_0^\tau p(x,\tau')d\tau',
\]

where \( \mu < 1 \). It was shown that the external field \( F(x) \) leads to a stationary solution to the FFPE in the form of the Gibbs-Boltzmann distribution [6]. However, in a recent paper [7], we have demonstrated that this fundamental result is not structurally stable with respect to spatial variations of the anomalous exponent \( \mu(x) \approx \mu + \delta \mu(x) \). This small perturbation, \( \delta \mu(x) \), destroys the Gibbs-Boltzmann distribution as the stationary solution to the FFPE.

The physical explanation for the occurrence of subdiffusion is the distribution of trapping sites throughout the complex media. It is hardly realistic to assume that the distribution, and structure, of the traps is uniform throughout. The main reason for the widespread use of constant \( \mu \) is the implicit assumption that this is a good approximation. However, we have shown previously that this is not the case. This question is of great importance for the problem of a morphological patterning of embryonic cells, which is controlled by the distribution of signaling molecules known as morphogens [8–10]. To ensure robust pattern formation, the morphogen gradients must be structurally stable with respect to the spatial variations of environmental parameters, including the anomalous exponent.

In fact, even the simple one-dimensional fractional subdiffusion equation with constant anomalous exponent and \( F(x) = 0 \), in the finite domain \( [0,L] \) with reflective boundary conditions, is structurally unstable. This equation should yield a uniform stationary distribution over the interval \( [0,L] \) in the long-time limit. However, if we use a slightly nonuniform anomalous exponent \( \mu(x) \), the probability density \( p(x,t) \) will be completely different from the uniform distribution: as \( t \rightarrow \infty \), it concentrates at the point where \( \mu(x) \) has a global minimum on \( [0,L] \). We called this phenomenon anomalous aggregation [11]. We should note that there is nothing physically wrong with the fractional equations with space-dependent anomalous exponents and accumulation of particles in a spatial domain with the smallest \( \mu(x) \). Note that unusual behavior of subdiffusive transport has been observed in an infinite system with two different values of anomalous exponents [12].

To rectify the structural instability involving unlimited growth of \( p(x,t) \), at the point of the minimum of the anomalous exponent \( \mu(x) \), we need a regularization of subdiffusive transport. The standard approach to regularize the fractional subdiffusive equations is to temper the power law waiting time distribution in such a way that the normal diffusion behavior in the long-time limit is recovered (see, for example, [13]). In a recent paper [14] the transient anomalous transport has been considered such that this subdiffusive transport becomes normal in the long-time limit. In this paper we suggest a completely different approach, where we do not introduce an exponential cutoff parameter, which is difficult to find experimentally. Instead, we introduce an experimentally measurable death rate. The main idea is to employ a random death process, which is quite natural for many biological applications, for example, the problem of morphogen gradient formation involving morphogen degradation. Although we
refer to this as the death process, in fact any reversible or irreversible reaction or conversion to another species ($A \rightarrow B$, $A \rightleftharpoons B$) or spontaneous evanescence ($A \rightarrow 0$) is valid. For discussion of this, see [15]. We show that as long as a death process is introduced, together with a particle production at the boundary, the stationary solution of the modified fractional master equation is structurally stable whatever the spatial variations of the anomalous exponent might be.

II. SUBDIFFUSIVE MASTER EQUATION

Let us consider a random walk of particles on a semi-infinite lattice with unit length. The particle performs a random walk as follows: it waits for a random time $T_k$ at each point $k$ before making a jump to the right with probability $r(k)$ and left with probability $l(k)$. We consider the anomalous subdiffusive case with the survival probability [16]

$$\Psi(k,t) = \Pr\{T_k > t\} = E_{\mu(k)}\left[-\left(\frac{t}{\tau_0}\right)^{\mu(k)}\right].$$

where $E_{\mu}[z]$ is the Mittag-Leffler function, $\tau_0$ is a constant with the unit of time, and $\mu(k)$ is the spatially dependent anomalous exponent: $0 < \mu(k) \leq 1$. For large $t$, the survival probability $\Psi(k,t)$ behaves as

$$\Psi(k,t) \sim \left(\frac{t}{\tau_0}\right)^{-\mu(k)}.$$

We assume that during the time interval $(t, t + \Delta t)$ at point $k$ the particle has a chance of dying, where $\theta(k)$ is the death rate ($\theta(k) > 0$).

We denote by $p(k,t)$ the average number of particles at point $k$ at time $t$. The anomalous subdiffusive master equation with the death process can be written as

$$\frac{\partial p(k,t)}{\partial t} = v(k-1)e^{-\theta(k-1)t}D_{1-\mu(k-1)}^1[p(k-1,t)e^{\theta(k-1)t}] + \eta(k+1)e^{-\theta(k+1)t}D_{1-\mu(k+1)}^1[p(k+1,t)e^{\theta(k+1)t}] - [v(k) + \eta(k)]e^{-\theta(k)t}D_{1-\mu(k)}^1[p(k,t)e^{\theta(k)t}] - \theta(k)p(k,t), \quad k \geq 2,$$

where $v(k) = \frac{r(k)}{\tau_0^{\mu(k)}}$, $\eta(k) = \frac{l(k)}{\tau_0^{\mu(k)}}$

are the anomalous rate functions. This fractional equation can be derived from a number of standpoints (see, for example, [17]). In this equation the anomalous exponent depends on the state, which is crucial for what follows. For the case of constant anomalous exponent $\mu$, this reaction-transport equation and its continuous approximations were considered in [15,18–20].

To ensure the existence of stationary structure in the long-time limit, we introduce the constant source term $g$ at the boundary of the semi-infinite lattice ($k = 1$). This is crucial for the problem of morphogen gradient formation, where $g$ models a localized source of morphogens [10]. We assume that the boundary is reflective, so we have the following equation for $p(1,t)$:

$$\frac{\partial p(1,t)}{\partial t} = \eta(2)e^{-\theta(2)t}D_{1-\mu(2)}^1[p(2,t)e^{\theta(2)t}] - v(1)e^{-\theta(1)t}D_{1-\mu(1)}^1[p(1,t)e^{\theta(1)t}] - \theta(1)p(1,t) + g.$$  

(5)

Note that any nonlinear proliferation term $g(p)$ can be included in the master equation (4).

A. Structural instability of a subdiffusive equation with a constant anomalous exponent

Without the reaction ($\theta = 0$) the fractional master equation (4) with a constant anomalous exponent $\mu$ can be written as

$$\frac{\partial p(k,t)}{\partial t} = v(k-1)D_{1-\mu}^1[p(k-1,t)] + \eta(k+1)D_{1-\mu}^1[p(k+1,t)] - [v(k) + \eta(k)]D_{1-\mu}^1[p(k,t)] - \theta(k)p(k,t), \quad k \geq 2.$$

The equation for $p(1,t)$ without proliferation term $g$ takes the form

$$\frac{\partial p(1,t)}{\partial t} = \eta(2)D_{1-\mu}^1[p(2,t)] - v(1)D_{1-\mu}^1[p(1,t)].$$

It follows from here that in the stationary case

$$p_{\mu}(k) = p_{\mu}(k-1)\frac{v(k-1)}{\eta(k)}, \quad k \geq 2.$$  

(6)

The stationary solution $p_{\mu}(k) = \lim_{t \to \infty} p(k,t)$ can be found as

$$p_{\mu}(k) = p_{\mu}(1)\prod_{j=1}^{k-1} \frac{v(j)}{\eta(j+1)}, \quad k \geq 2,$$

(7)

where

$$p_{\mu}(1) = \left(1 + \sum_{k=2}^{\infty} \prod_{j=1}^{k-1} \frac{v(j)}{\eta(j+1)} \right)^{-1},$$

(8)

provided the sum is convergent. This solution is structurally unstable with respect to partial variations of the anomalous exponent. When the anomalous exponent is not constant, the asymptotic behavior is completely different. Consider point $M$, at which the anomalous exponent is at a minimum $\mu(M) < \mu(k), \forall k \neq M$. Then, one can show [7] that

$$p(M,t) \to 1, \quad p(k,t) \to 0, \quad t \to \infty.$$  

(9)

See [21] for full details.

B. Stationary solution of master equations (4) and (5)

It is convenient to rewrite the fractional master equation (4) as

$$\frac{\partial p(k,t)}{\partial t} = -I(k,t) + I(k-1,t) - \theta(k)p(k,t), \quad k \geq 2,$$

(10)
where \( I(k,t) \) is the total flux of particles from \( k \) to \( k+1 \),
\[
I(k,t) = \nu(k)e^{-\theta(k+1)\tau}D_\theta^{1-\mu(k)}[p(k,t)e^{\theta(k+1)\tau}]
- \eta(k+1)e^{-\theta(k+1)\tau}D_\theta^{1-\mu(k+1)}[p(k+1,t)e^{\theta(k+1)\tau}].
\]
(11)

The equation for \( p(1,t) \) has the form
\[
\frac{\partial p(1,t)}{\partial t} = -I(1,t) - \theta(1)p(1,t) + g.
\]
(12)

The Laplace transform of the total flux \( I(k,t) \),
\[
\hat{I}(k,s) = \int_0^\infty I(k,t)e^{-st}dt,
\]
takes the form
\[
\hat{I}(k,s) = \nu(k)[s + \theta(k)]^{-\mu(k)}\hat{p}(k,s)
- \eta(k+1)[s + \theta(k)+1]^{-\mu(k+1)}\hat{p}(k+1,s).
\]

From here we can find the stationary flux \( I_{st}(k) = \lim_{s \to 0} s\hat{I}(k,s) \) as follows:
\[
I_{st}(k) = v_{st}(k)p_{st}(k) - \eta_{st}(k+1)p_{st}(k+1),
\]
(14)

where
\[
v_{st}(k) = \nu(k)[\theta(k)]^{-\mu(k)}, \quad \eta_{st}(k) = \eta(k)[\theta(k)]^{-\mu(k)},
\]
and \( p_{st}(k) = \lim_{s \to 0} s\hat{p}(k,s) \). The main feature of this stationary flux is that it has Markovian form, but the rate functions \( v_{st}(k) \) and \( \eta_{st}(k) \) depend on the anomalous rate \( \nu(k) \), the random death rate \( \theta(k) \), and the anomalous exponent \( \mu(k) \). This unusual form of the stationary flux is because of the non-Markovian character of subdiffusion.

Let us find the stationary distribution \( p_{st}(k) \) for the simple case where \( \theta \) is constant. In the long-time limit, at the boundary \( k = 1 \), we then have the following condition:
\[
I_{st}(1) = g - \theta p_{st}(1).
\]

We are able to obtain a general expression for the stationary flux at location \( k \),
\[
I_{st}(k) = g - \theta \sum_{j=1}^{k} p_{st}(j).
\]
(15)

This has a very simple physical meaning: as \( t \to \infty \), \( I_{st}(k) \) tends to the difference between the proliferation rate \( g \) and the sum of death rates at all states from the boundary up to \( k \). It is clear that as \( k \to \infty \), the stationary flux \( I_{st}(k) \to 0 \) since in the stationary state \( g \) should be equal to total death rate,
\[
g = \theta \sum_{j=1}^{\infty} p_{st}(j).
\]
(16)

We obtain
\[
\eta(k+1)\theta^{-\mu(k+1)}p_{st}(k+1) = v(k)\theta^{-\mu(k)}p_{st}(k) - \left( \frac{g}{\theta} - \sum_{j=1}^{k} p_{st}(j) \right).
\]
(17)

This equation allows us to find \( p_{st}(k) \) for all \( k \). For the symmetrical random walk for which \( v(k) = \eta(k) = \nu \) and \( \mu = \text{const} \), we have
\[
p_{st}(k+1) = p_{st}(k) - \frac{\theta\mu}{\nu} \left( \frac{g}{\theta} - \sum_{j=1}^{k} p_{st}(j) \right).
\]
(18)

\[ \]
\( \mu(x) = 1 \), we have classical drift and a diffusion coefficient independent from \( \theta(x) \). It has been found in [19] that the non-Markovian behavior of subdiffusion leads to an effective nonlinear diffusion.

D. Morphogen gradient formation

Let us illustrate our theory in terms of the problem of morphogen gradient formation involving morphogen degradation [8–10]. We consider a random walk with a constant drift \( v_\mu^\theta = -v \), diffusion \( D_\mu^\theta \), and degradation rate \( \theta \). We obtain the stationary morphogen profile from the equation

\[
\frac{d}{dx} \frac{\partial p_\mu(x)}{\partial x} + D_\mu^\theta \frac{\partial^2 p_\mu(x)}{\partial x^2} - \theta p_\mu(x) = 0. \tag{22}
\]

The solution of (22) is the exponential distribution

\[
p_{st}(x) = A \exp \left[ -\frac{v + \sqrt{v^2 + 4D_\mu^\theta \theta}}{2D_\mu^\theta} x \right], \tag{23}
\]

where \( A \) can be found from the condition \( g = \theta \int_0^\infty p_{st}(x)dx \):

\[
A = \frac{g(v + \sqrt{v^2 + 4D_\mu^\theta \theta})}{2\theta D_\mu^\theta}. \tag{24}
\]

When \( v_\mu^\theta = 0 \), we have the morphogen profile obtained in [10]:

\[
p_{st}(x) = \frac{g}{\theta D_\mu^\theta} \exp \left[ -\frac{\theta}{D_\mu^\theta} x \right]. \tag{25}
\]

We now simulate the fractional master equation with a random death process using Monte Carlo techniques. Throughout this we let \( t_0 = 1 \), so that this is the unit of time for the simulation; we take \( g = 1 \), so that we have a constant birth rate of one particle per unit time. The first particle begins a random walk at \( k = 1 \), such that at each point \( k \) waiting times are power law distributed, and jumps probabilities to the left and right of each point \( k \) are \( r(k) \) and \( l(k) \), respectively. A particle completes a random walk from when it is produced until the terminal time \( t = T \) or until its random time of death, exponentially distributed as \( \varphi(t) = \theta e^{-\theta t} \). Also note that unlike the waiting time, the death time is not renewed when the particle makes a jump.

\[ \text{FIG. 1. Stationary profile for the symmetric fractional master equation where } r(k) = l(k) = \frac{1}{2}, \mu(k) = \text{const} = 0.5, \tau_0 = 1, \text{ and } \theta = 10^{-3}. \]

First, let us consider the symmetrical random walk, where \( r(k) = l(k) = \frac{1}{2}, \mu(k) = 0.5, \) and \( \theta = 10^{-3}. \) Figure 1 shows the corresponding stationary density made up of \( 10^5 \) realizations of the random walk at time \( T = 10^6 \). We can see that our simulation is in agreement with the analytical values calculated from the recurrence relation (18).

Next, we show that the model is robust to nonhomogenous spatial perturbations in the anomalous exponent. Analogously to the simulation we presented in the previous work [7], we introduce a small perturbation to the anomalous exponent at one point in the space: all states have \( \mu = 0.5 \) except for \( k = 8 \), which has \( \mu = 0.4 \). From Fig. 2 we can see that although we observe a change to the stationary profile around the point \( k = 8 \), the stationary profile is structurally stable and exponential in character. We stress the importance of the death process in regulating the behavior of the process to ensure stability, whereas in our previous work, we showed that even a small perturbation in the anomalous exponent like this would lead to a breakdown in the Gibbs-Boltzmann stationary density. Additionally, we considered a nonsymmetrical random walk, which leads to a drift, and found that the profile is stable.

III. CONCLUSIONS

In summary, it was previously thought that as far as the fractional Fokker-Planck equation is concerned, the effect of subdiffusive trapping was just to cause a power law decay to the stationary state, such as the Gibbs-Boltzmann distribution. However, we showed that a nonuniform distribution of traps drastically changes the stationary structure itself and develops singularities like anomalous aggregation. This is a critical problem, especially for morphogen gradient formation, and we introduced the random death process as a natural remedy. Our approach is fundamentally different from tempering [13], which is just the truncation of the power law waiting time distribution by an exponential factor involving a tempering parameter. This parameter is extremely difficult to measure experimentally, but in our case it is quite the opposite. We introduce the death process, and the death rate can be easily measured independently of the transport process. Another advantage of our approach is that it can be easily extended to the case when the death rate depends on the density of particles. So we are not just employing a mathematical trick to overcome the problem of an infinite mean waiting time. We also find the
stationary flux of the particles has a Markovian form, with an unusual rate function depending on the anomalous rate functions, the death rate, and the anomalous exponent. We have shown that the long-time and continuous limit of this regularized fractional equation is the standard advection-diffusion equation that, importantly, is structurally stable with respect to spatial variations of the anomalous exponent $\mu$. Thus we have addressed the problem of applicability to modeling complex biological systems. We have found that the effective advection and diffusion coefficients, $v_\mu^\theta$ and $D_\mu^\theta$, are increasing functions of the death rate $\theta$: $v_\mu^\theta \sim D_\mu^\theta \sim \theta^{1-\mu}$.

We have applied a regularized fractional master equation and modified fractional Fokker-Planck equation to the problem of the morphogen gradient formation. We have shown the robustness of the stationary morphogen distribution against spatial fluctuations of anomalous exponent.

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Nonlinear degradation-enhanced transport of morphogens performing subdiffusion
Nonlinear degradation-enhanced transport of morphogens performing subdiffusion

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We study a morphogen gradient formation under nonlinear degradation and subdiffusive transport. In the long-time limit, we obtain the nonlinear effect of degradation-enhanced diffusion, resulting from the interaction of non-Markovian subdiffusive transport with a nonlinear reaction. We find the stationary profile of power-law type, which has implications for robustness, with the shape of the profile being controlled by the anomalous exponent. Far away from the source of morphogens, any changes in the rate of production are not felt.

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I. INTRODUCTION

During the development of an organism, a key stage is the differentiation of cell types [1]. It is known that the differentiation of these identical cells into different and distinct cell types is controlled by a signaling molecule called a morphogen [2]. One of the most widely studied organisms in the field of morphogenesis is the *Drosophila*, the common fruit fly, and particularly the development of its wings. The wings begin as a multinucleated mass of identical cells within a membrane, in the early embryo, called an imaginal disk. A morphogen from the TGF-β superfamily called decapentaplegic (Dpp) is secreted by a narrow strip of cells, from which it diffuses in essentially one dimension and degrades, causing a concentration gradient to form. The production, diffusion, and degradation of morphogens are controlled by a complex set of positive and negative feedback loops [3]. The cells in the imaginal disk react to the concentration gradient at discrete levels [4], enabling them to determine their position within the disk. From knowing their position, the cells are able to differentiate themselves to carry out different functions within the developing wing. Thus, to prevent mutations it is essential that the concentration gradient built up is robust to fluctuations in the secretion rate due to genetic alterations, temperature changes, or any other environmental effects [5].

There are differing thoughts on the mechanism behind the diffusion of the morphogen, such as whether the transport is primarily extracellular or intracellular [6], whether it is able to diffuse freely through the essentially two-dimensional (2D) plane of the imaginal disk, or whether the molecules are passed over between neighboring cells, a process called transcytosis [7]. It is thought that some morphogens require intracellular trafficking, while others may diffuse freely [8]. However, regardless of the specific mechanism, it is known that morphogens do form long-range concentration gradients, and that the robustness of the concentration gradient is of the utmost importance [1,3,7].

The standard model for morphogen transport is the diffusion equation with the degradation term,

$$\frac{\partial \rho}{\partial t} = D \frac{\partial^2 \rho}{\partial x^2} - \vartheta \rho,$$

(1)

where $\rho(x,t)$ is the density of the morphogen, $D$ is the diffusion coefficient, and $\vartheta$ is the degradation rate. This equation, together with the boundary condition with the constant source term at $x = 0$, gives a stationary concentration distribution which decays exponentially. It has been argued that an exponential profile cannot be robust to fluctuations in environmental conditions and production rate [9]. Therefore, the aforementioned authors argued that a power-law profile is preferable. Experiments have shown that in some circumstances, a power-law decay is observed for the morphogen profile [10]. One way to obtain this profile is to assume that the morphogens must decay rapidly close to their source while decaying at a much slower rate over the rest of the area. In other words, the degradation rate is an increasing function of the local concentration of diffusing morphogens. In this case, the only modification to (1) is the nonlinear rate $\vartheta(\rho)$. The topic has been tackled in [5,9], where the authors dubbed this the “self-enhanced degradation” of morphogens.

The robust stationary profile can be found from

$$D \frac{d^2 \rho_{st}(x)}{dx^2} = k \rho_{st}(x)^2,$$

with the boundary condition at $x = 0$: $-D \frac{d \rho_{st}}{dx} = g$. This leads to algebraic decay in the tails of the spatial distribution,

$$\rho_{st}(x) \sim \frac{A}{x^\alpha}, \quad x \to \infty,$$

(3)

where the amplitude $A$ is independent of the production term $g$. In [9], the authors take the independence of the production rate from the amplitude of the profile to be a key indicator of the robustness of the profile. A nonlinear degradation rate can arise from the situation in which the morphogen increases the production of a molecule, which in turn increases the rate of morphogen degradation. In the example of the *Drosophila* fly, the morphogen Shh is responsible for the expression of a receptor that both transduces the Shh signal and mediates the degradation of the morphogen [11,12].

Hornung, Berkowitz, and Barkai [13] published the first paper in which the subdiffusion of morphogens was considered. Subdiffusion is an observed natural phenomenon, seen in the diffusion of proteins in the cytoplasm and the nucleus of eukaryotic cells [14,15], along the surface of a cell membrane [16,17], and it has been suggested to explain morphogen movement in a heterogeneous environment of HSPG proteins. For the anomalous subdiffusion, the mean-squared displacement grows sublinearly with time $\langle x^2(t) \rangle \sim t^{\mu}$, where $\mu < 1$ is the anomalous exponent. Following Hornung et al. [13], several attempts have been made to take into account subdiffusion for the analysis of morphogen gradient formation [18–21]. Kruse and Iomin [18] developed...
a microscopic model of the receptor-mediated transport in a subdiffusive medium. They found subdiffusive and superdiffusive spreading of morphogens. Yuste et al. [19] analyzed the gradient formation of subdiffusive morphogens by using the reaction-subdiffusion equation obtained from a classical continuous time random walk (CTRW),

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2}{\partial x^2} \left[ \rho \left( \theta(\rho) dh(x,t) \right) - \theta(\rho) \rho, \right]$$

where $D_{\mu}$ is the fractional diffusion coefficient, and $D_1^{1-\mu}$ represents the Riemann-Liouville fractional derivative of order $1 - \mu$,

$$D_1^{1-\mu} f(x,t) = \frac{1}{\Gamma(\mu)} \frac{\partial}{\partial t} \int_0^t f(x,t') \left( t - t' \right)^{1-\mu} dt'.$$

The main difference of this work from that of [13] is that here the particles are not protected during trapping events. A stationary profile does not exist in the model of [13]; the authors obtained only a nonstationary exponential profile in space, with a power-law decay of amplitude in time. Yuste, Abad, and Lindenberg [19] found the stationary exponential profile and analyzed the interaction of subdiffusion and space-dependent degradation. A diffusion equation with a power-law density-dependent diffusion coefficient and nonlinear degradation has been analyzed in the recent paper [20]. The modified fractional Fokker-Planck equation was used for the analysis of morphogen gradient formation in [21], where the authors employed the random death process in such a way that the degradation term acts like a tempering of the waiting time distribution. This leads to the unusual effect of the dependence of the diffusion coefficient on the degradation rate. The authors considered only a linear death process and did not consider feedback effects in the degradation rate, and indeed many current models do not either.

The main purpose of this work is to analyze the interaction of the nonlinear degradation with non-Markovian subdiffusion, and its implications on the stationary structure. The result of this interaction is degradation-enhanced diffusion in the long-time limit. The gradient profile can be found from the nonlinear stationary equation for which the diffusion coefficient is a nonlinear function of the nonlinear reaction rate $\theta(\rho(x))$,

$$\frac{d^2}{dx^2} \left[ D_{\theta}(\rho(x)) \rho(x) \right] = \theta(\rho(x)) \rho(x).$$

Here the diffusion coefficient $D_{\theta}(\rho(x))$ is

$$D_{\theta}(\rho(x)) = \frac{\alpha^2}{2 \tau_0^\mu} \theta(\rho(x))^{1-\mu(x)}.$$

$\tau_0$ is the time parameter, and $\mu(x)$ the space-dependent anomalous exponent. This unusual form of the nonlinear diffusion coefficient is a result of the interaction between non-Markovian transport and nonlinearity. The interaction leads directly to a degradaion-enhanced diffusion. This effect does not exist for the Markovian random-walk model presented in [20].

II. SUBDIFFUSIVE TRANSPORT AND NONLINEAR DEGRADATION

We describe a random morphogen molecule’s movement in an extracellular surrounding as follows. We assume that molecules are produced at the boundary $x = 0$ of the semi-infinite domain $[0, \infty)$ at the given constant rate $g$, and we perform the classical continuous-time random walk involving symmetrical random jumps of length $a$ with random waiting time $T_x$ between jumps. If we assume that this random time is exponentially distributed with the rate parameter $\lambda$, then on the macroscopic level we obtain the classical diffusion term in (1) with diffusion coefficient $D = \lambda a^2/2$. In this paper, we consider the subdiffusive behavior for morphogen molecules when the residence time $T_x$ has the survival probability $\Psi(x,t) = Pr[T_x > t]$ given by the Mittag-Leffler function [23]

$$\Psi(x,t) = E_{\mu(\tau)} \left[ -\left( \frac{t}{\tau_0} \right)^{\mu(\tau)} \right], \quad 0 < \mu(\tau) < 1.$$ (8)

The Mittag-Leffler distribution is characterized by its interpolation between short-time stretched exponential and long-time power-law asymptotics,

$$\Psi(x,t) \simeq \begin{cases} \frac{1}{1 + \mu(\tau)} e^{-\frac{t}{\tau_0}}, & t \ll 1, \\ \frac{1}{1 - \mu(\tau)} \left( \frac{t}{\tau_0} \right)^{-\mu(\tau)}, & t \rightarrow \infty. \end{cases}$$ (9)

This distribution leads to the divergence of the mean waiting time,

$$\bar{T}_x = \int_0^\infty \frac{\partial \Psi(x,t)}{\partial t} dt, \quad 0 < \mu(\tau) < 1,$$ (10)

which explains the slow subdiffusive behavior. This emerges from the CTRW scheme when a molecule becomes immobilized in a region of space and the mean escape time diverges. The reasons for trapping are many, and vary depending on the circumstance. The particles could be trapped in intracellular space while cell surface receptors are occupied [3,18]. It could be that a particle enters a region with a very complicated geometry, such as a dendritic spine, and struggles to escape [24]. It could be immobilized by some chemical reactions.

We describe the morphogen degradation by the mass action law involving the nonlinear reaction term $\theta(\rho) \rho$,

$$\frac{\partial \rho}{\partial t} = \theta(\rho) \rho,$$ (11)

where the reaction rate $\theta(\rho)$ depends on the mean density $\rho$. The importance of a nonlinear reaction rate lies in the effect of self-enhanced ligand degradation, which underlies the robustness of morphogen gradients [5,9] (see also [12]). It should be noted that the authors of [13] consider a very different model in which morphogen molecules are protected during the trapping time $T_x$ and degradation occurs instantaneously at the end of a waiting time with a given probability.

Our assumptions lead to the following nonlinear reaction-subdiffusion equation for the mean density of morphogen molecules [25]:

$$\frac{\partial \rho}{\partial t} = \frac{\partial^2}{\partial x^2} \left[ D_{\theta}(\rho(x)) e^{-\int_0^t \theta(\rho(x')) dx'} D_1^{1-\mu(x)} e^{\int_0^t \theta(\rho(x')) dx'} \rho(x,t) \right] - \theta(\rho) \rho,$$ (12)
where
\[
D_\mu(x) = \frac{a^2}{2\tau_0^{\mu(x)}},
\]
(13)
a is the jump length, and \(\tau_0\) is the time parameter. See also [26, pp. 48–52]. The main characteristic of this reaction-transport equation is that the reaction and transport are not additive. Due to the non-Markovian nature of subdiffusion, it is not possible to separate reaction as an extra term on the right-hand side (RHS), as is the case for a regular diffusion such as (1). Instead, reaction terms also appear mixed in the derivative term as an exponential factor, as seen above. The presence of the Riemann-Liouville derivative indicates a long memory in the process, presenting itself in the integral over time, making it strongly non-Markovian.

It turns out that in the long-time limit this equation leads to a nonlinear diffusion with a diffusion coefficient depending on the nonlinear degradation. Note that nonlinear diffusion has been analyzed in [20], where the authors introduced a nonlinear dependence of the diffusion coefficient of the density independent from the reaction. Moreover, this nonlinear diffusion is independent from degradation. In this paper, we show how nonlinear diffusion emerges naturally from the microscopic random walk for which the nonlinear diffusion and degradation are not independent. We also take into account a spatially nonuniform distribution of anomalous exponent \(\mu(x)\). We have shown previously that any spatial variation in the anomalous exponent \(\mu\) leads to a drastic change in the stationary behavior of the fractional subdiffusive equations [27], a phenomenon called anomalous aggregation [28]. Note that the robustness of the stationary profile of diffusing morphogens is the most important feature [5].

The fractional reaction-transport equation (12) can be rewritten in the compact form
\[
\frac{\partial \rho}{\partial t} = \frac{a^2}{2} \frac{\partial^2 i(x,t)}{\partial x^2} - \theta(\rho)\rho(x,t),
\]
(14)
where \(i(x,t)\) is the total escape rate from the point \(x\). It follows from Eq. (12) that it can be written as
\[
i(x,t) = e^{-\int_0^t \theta(\rho) ds} \tau_0^{1-\mu(x)} D_\mu^{1-\mu(x)} \left[ e^{\int_0^t \theta(\rho) dt} \rho(x,t) \right].
\]
(15)
Different choices for the form of the escape rate can lead to many interesting equations in the diffusion limit [29].

### III. STATIONARY MORPHOGEN PROFILE

#### A. Linear degradation

In a previous publication [21], we gave full details on how the linear version of reaction-subdiffusion equation (12) approaches a stationary diffusion. In this section, we will recap this and extend to the current nonlinear consideration. The linear reaction-subdiffusion equation considered in [21] differs from (14), with the total escape rate \(i\) being given by
\[
i(x,t) = e^{-\theta(\rho) t} \tau_0^{\mu(x)} D_\mu^{1-\mu(x)} \left[ e^{\theta(\rho) t} \rho(x,t) \right].
\]
(16)
To obtain a stationary solution for the system, it is necessary to introduce a flux of new particles, \(g\). We choose to implement this on the boundary \(x = 0\). This directly corresponds to the morphogen problem, where particles are produced from a point source. For conservation reasons, the logical choice for production rate is \(g = \int_0^\infty \theta(x) \rho_0(x) ds\) [19].

The Laplace transform of the integral escape rate (16) is found by the shift theorem:
\[
\hat{i}(x,s) = \int_0^\infty i(x,t)e^{-st} dt = \left[ x + \theta(\rho) \right]^{1-\mu(x)} \tau_0^{\mu(x)} \hat{\rho}(x,s).
\]
(17)
The limit \(t \to \infty\) corresponds to the limit \(s \to 0\) of the Laplace variable. We write for the stationary total escape rate \(i_\mu(x)\),
\[
i_\mu(x) = \lim_{s \to 0} s \hat{i}(x,s) = \theta(\rho)^{1-\mu(x)} \tau_0^{\mu(x)} \rho_\mu(x),
\]
(18)
where \(\rho_\mu(x) = \lim_{t \to \infty} \rho(x,t)\). This follows from the standard final value theorem stating that when \(\lim_{t \to \infty} f(t)\) exists, then \(\lim_{t \to \infty} f(t) = \lim_{s \to 0} s \hat{f}(s)\). Note that Eq. (18) is a Markovian form, since the escape rate can be written in the form \(i_\mu(x) = \lambda \rho_\mu(x)\), where \(\lambda = \theta(\rho)^{1-\mu(x)} \tau_0^{\mu(x)}\) now depends upon the degradation rate. This shows the transition from subdiffusive dynamics to asymptotically normal diffusion.

Consider for contrast that if the death rate is constant in time and space, and independent of \(\rho\), and the drift is zero, then we find an analytic result for the stationary gradient distribution as an exponential function [19]. The stationary profile is given by
\[
\rho_\mu(x) = \frac{g}{\sqrt{D_\mu}} \exp \left[ -\sqrt{\frac{\theta(x)}{D_\mu}} x \right],
\]
(19)
and, as mentioned, the full details can be found in [21].

#### B. Nonlinear degradation

It has been argued that even for subdiffusion, a stationary exponential morphogen profile cannot be robust to fluctuations in both environmental effects and production rate [5,9]. The purpose of this subsection is to show that a robust stationary morphogen profile can be found as a result of the interaction of non-Markovian subdiffusion and nonlinear degradation. The question now is how to take into account a nonlinear reaction term. Actually, it turns out that the same techniques can be used as were used for the previous linear case. From the total escape rate (15) we seek to use the Laplace transform shift theorem to carry over the results to the nonlinear case. The limit \(t \to \infty\) corresponds to the limit \(s \to 0\) of the Laplace variable. We write for the stationary total escape rate \(i_\mu(x)\),
\[
i_\mu(x) = \lim_{s \to 0} s \hat{i}(x,s) = \theta(\rho)^{1-\mu(x)} \tau_0^{\mu(x)} \rho_\mu(x),
\]
(21)
Note that similar arguments have been made in [30]. For this escape rate, Eq. (14) can be rewritten in a stationary form as
\[
\frac{a^2}{2} \frac{d^2 i_\mu(x)}{dx^2} = \theta(\rho_\mu(x)) \rho_\mu(x).
\]
(22)
Finally, the stationary nonlinear reaction-subdiffusion equation takes the form of a nonlinear second-order ordinary differential equation (ODE),
\[
d^2\left(\alpha^2\theta(\rho_n(x))\right)^{1-\mu(x)} - \frac{2\gamma_0^\mu(x)}{\rho_n(x)} - \epsilon \theta(\rho_n(x))\rho_n(x) = 0. \tag{23}
\]
This equation has the form of Eq. (6), where the diffusion coefficient \(D_0\) is an increasing function of the nonlinear reaction rate (7).

Let us consider the commonly studied case of an \(n\)-fold superlinear reaction term in the stationary nonlinear reaction-subdiffusion equation (23), corresponding to a reaction term
\[
\theta(\rho) = k\rho^n - 1, \tag{24}
\]
where \(k\) is the reaction constant. In what follows, we consider only \(\mu(x) = \mu = \text{const}\). Here, the total escape rate is given by
\[
i(x,t) = \frac{e^{-k t} \int_0^{\tau} \rho^{-1} d\tau}{\tau^{\mu^2}} D^{1-\mu}\left[e^{k t} \rho^{-1} d\rho(x,t)\right]. \tag{25}
\]
We can write the nonlinear equation (23) as
\[
D_\mu k^{1-\mu} \frac{d^2}{dx^2} \left[\rho_n(x) \right]^{\alpha(1-1\mu)+1} = k\rho_n(x), \tag{26}
\]
where
\[
D_\mu = \frac{a^2}{2\tau_0^\mu}. \tag{27}
\]
The boundary conditions are given by
\[
-D_\mu k^{1-\mu} \frac{d}{dx} \left[\rho_n(x) \right]^{\alpha(1-1\mu)+1}] \bigg|_{x=0} = g \tag{28}
\]
at \(x = 0\) and \(\lim_{x \to -\infty} \rho_n(x) = 0\).

Equation (23) is written in the form of a balance equation between reaction and transport, however for a reaction-subdiffusion equation the two cannot be separated. The RHS of Eq. (23) is a pure reaction, balanced with the mixed reaction transport on the other side. We can make the interesting observation that if we multiply both sides of the equation by \(k^{1-1\mu}\), then we obtain exactly the same form for the equation as from the nonlinear theory [20]. In their model, the nonlinear diffusion is completely separate from the reaction. The authors introduced two nonlinear functions \(F\) and \(G\) into their Markovian random-walk model. However, in our non-Markovian model the nonlinear diffusion and the reaction are not independent and cannot be separated. We showed that the assumption of a nonlinear reaction leads directly to a “degradation enhanced diffusion.” This comes about from the nontrivial interaction between subdiffusion and reaction, which is a result of the long-range memory of the underlying random-walk model. In regular diffusion, such as in the model [20], a stationary profile can be obtained by simply equating the time derivative to zero; in subdiffusion, that is not the case [see Eq. (12)]. Note that here the nonlinear diffusion dependence on the reaction rate is not postulated, but it emerges naturally from the interaction of subdiffusion and nonlinear reactions. Despite the essential differences between the non-Markovian equation (12) and that which was presented in [20], the stationary equations (26) are similar and can be solved in the same way,
\[
\rho_\alpha(x) = \rho_\alpha(0) \left(1 + \frac{x}{x_0}\right)^{-\frac{1}{\alpha-1}}, \tag{29}
\]
where
\[
\rho_\alpha(0) = \frac{g^*}{\sqrt{\alpha + n}} \frac{1}{\sqrt{\alpha}} \frac{g}{\sqrt{D_\mu k^{2-\mu}}}, \tag{30}
\]
\[
x_0 = \frac{2\alpha}{n-\alpha} (g^*)^\frac{1}{\alpha} \left(\frac{\alpha + n}{2\alpha}\right)^\frac{1}{\alpha-n} \frac{D_\mu}{k^{2-\mu}}, \tag{31}
\]
\[
\alpha = (n-1)(1-\mu) + 1. \tag{32}
\]
When \(x/x_0 \gg 1\), we obtain the power-law profile,
\[
\rho_\alpha(x) \sim \frac{A}{x^{\frac{1}{\alpha(n-1)}}}, \quad x \to \infty, \tag{33}
\]
where the amplitude
\[
A = \rho_\alpha(0)x_0^{-\frac{1}{\alpha(n-1)}} \tag{34}
\]
is independent of the morphogen production rate \(g\). In the tails, this profile has an inverse dependence on the constant degradation rate \(k\), as illustrated in Fig. 1. The effect of decreasing \(\mu\) is a decrease in the amplitude of the tails. This should be expected since the interpretation of \(\mu\) is as a parameter controlling the strength of the spatial trapping of particles, with decreasing \(\mu\) increasing trapping strength, as seen in the behavior of the survival function (9). To counteract the trapping, the rate of diffusion is increased by the degradation rate, which we term degradation-enhanced diffusion. Comparing the tail behavior in the standard diffusion (3) with that of subdiffusion (31), the impact of \(\mu\) is clear.

C. Robustness

Let us now discuss the robustness of the profile (29) with respect to the morphogen production rate \(g\). It is convenient to write (29) in the following way:
\[
\rho_\alpha(x) = \frac{A}{(x_0 + x)^{\frac{1}{\alpha(n-1)}}}, \tag{35}
\]
where
\[
A = \rho_\alpha(0)(x_0)^{-\frac{1}{\alpha(n-1)}} \tag{36}
\]
where $A$ is defined in (32). The only parameter in (33) which is dependent on $g$ is $x_0$, 
\[ x_0 = \frac{B}{g^{\frac{n}{n-a}}} \]  
(34)
where the parameter $B$ is independent of $g$, and $\frac{n}{n-a} > 0$. From (33) and (34), it is clear that a change in $g$ produces a uniform shift in the stationary profile along the $x$ axis.

The robustness of the profile (29) to changes in the morphogen production rate $g$ can be assessed with a standard sensitivity analysis involving the relation
\[ \delta \rho_n(x) = \frac{\partial \rho_n(x)}{\partial g} \delta g, \]  
(35)
where $\delta g$ is a small change in the production rate. The nondimensional robustness parameter $R$ can be introduced in several ways (see, for example, [7,9,19]). We choose to define this measure from the following relation:
\[ \frac{\delta \rho_n(x)}{\rho_n(x)} = \frac{1}{R} \frac{\delta g}{g}, \]  
(36)
where
\[ \frac{1}{R} = \frac{g}{\rho_n(x)} \frac{\partial \rho_n(x)}{\partial x} \frac{\partial x_0}{\partial g}. \]  
(37)
This relates the relative change in the density at a given point $x$ with respect to the relative change in $g$. For large values of $R$, the system is robust. For the profile given by (33), we find the expression for $R$ to be
\[ R = \frac{n + \alpha}{n - \alpha} \lambda, \]  
(38)
where $\lambda$ is the local spatial decay length defined as
\[ \lambda = -\frac{\rho_n(x)}{\partial \rho_n(x)} = \frac{\partial x_0}{\partial x} \]  
(39)
Notice that this expression for the decay length (39) depends explicitly on the anomalous exponent $\mu$. The exponential profile (19) has a corresponding value of $R = 1$ and it is not robust to changes in $g$. From (34), (38), and (39), it is clear that $R \to \infty$ as either of the parameters $g \to \infty$, $x \to \infty$. This indicates that power-law profile (29) is robust to changes in the production rate $g$. This can also be seen in Fig. 2, where increasing values of the production rate cause convergence to the robust power-law profile even for smaller values of $x$. Additionally, for the values of $\log_{10}(x) > 10$, we have almost complete convergence. As mentioned by previous authors [9], this is an important quality for the morphogen gradient.

IV. DISCUSSION AND CONCLUSION

We studied the formation of a stationary morphogen gradient resulting from the non-trivial interaction of subdiffusion with a non-linear degradation. In particular, this interaction leads to the phenomenon of a degradation-enhanced diffusion in the long-time limit. We see that an increase in the rate of degradation actually leads to an increase in diffusion. Additionally, we have shown that the stationary profile is no longer of exponential type, rather it is of power-law type. The shape of the tails (31) is determined by the anomalous exponent $\mu$. The stationary solution as $x \to \infty$ is actually independent of the effects of the production rate entirely. It is well known that the importance of the power-law profile is due to its robustness to fluctuations in the production rate of morphogens, and also to other environmental effects.

We made a connection between the non-Markovian sub-diffusive model with nonlinear reaction and the Markovian nonlinear reaction-diffusion equations [20]. When, in the fractional formulation, we assume a constant value of anomalous exponent $\mu$ and a power-law ansatz for the reactive term, the steady-state reaction-subdiffusion equation takes the same form as that obtained from the nonlinear reaction-diffusion equation. The essential point of our paper is that that we have not just studied nonlinear diffusion, but we also derived the nonlinear dependence of diffusion on the nonlinear reaction in the long-time limit. In fact, we should note that this result can be extended to the general non-Markovian transport process. This is a subject for future work.

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Nonlinear tempering of subdiffusion with chemotaxis
Nonlinear tempering of subdiffusion with chemotaxis

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Abstract. The purpose of this paper is to implement nonlinear particle interactions into subdiffusive transport, involving chemotaxis and nonlinear effects such as volume filling and adhesion. We systematically derive nonlinear subdiffusive fractional equations with chemoattractant dependent forcing. We consider the diffusion limit of the master equation and analyse the role of nonlinear tempering in the stationary case. We study the interaction between attractive forces of anomalous aggregation and chemotaxis, with repulsive forces induced by nonlinear reactions. We show that this nonlinear interaction can prevent the phenomenon of anomalous aggregation when the local particle concentration grows too high. We also show that the effect of nonlinear tempering is to suppress the intermediate subdiffusive behaviour which results in an advection diffusion equation involving a nonlinear advection and diffusion coefficients.

1. Introduction

Anomalous subdiffusive behaviour is characterised by a sublinear growth of the mean squared displacement in time \( \langle x^2(t) \rangle \sim t^\nu, \) \( 0 < \nu < 1 \). The parameter \( \nu \) is known as the anomalous exponent. Subdiffusion in an observed natural phenomenon seen in areas as varied as transport of lipids on cell membranes [1], transport on fractal geometries [2], financial futures prices [3], signalling molecules in spiny dendrites [4, 5], and dispersive transport on amorphous semiconductors [6]. The standard model for subdiffusive transport is the continuous time random walk (CTRW) [7–9].

CTRWs which include waiting time distributions with infinite mean lead to fractional equations in the diffusive limit, including the fractional Fokker-Planck equation (FFPE),

\[
\frac{\partial \rho(x, t)}{\partial t} = -\frac{\partial (v(x) D_1^{1-\nu}(x) \rho)}{\partial x} + \frac{\partial^2 (D(v(x) D_1^{1-\nu}(x) \rho))}{\partial x^2},
\]

see equation (38) in [10]. Equation (1.1) involves fractional diffusion coefficient \( D(v(x) \) and fractional advection coefficient \( v(x) \), as well as the Riemann Liouville fractional derivative order

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\[ D_{t}^{1-\nu(x)} \rho(x,t) = \frac{1}{\Gamma(\nu(x))} \frac{\partial}{\partial \tau} \int_{0}^{t} \frac{\rho(x,\tau)d\tau}{(t-\tau)^{1-\nu(x)}}. \]  

It has been shown that the fractional equations are not structurally stable with respect to spatial fluctuations in the anomalous exponent [10]. Fluctuations lead to the breakdown of the stationary behaviour, and the phenomenon of anomalous aggregation [11], where particles accumulate in a small region of space where the anomalous exponent is small compared to the surrounding region. To counteract this, models have been proposed which temper the anomalous waiting time of the CTRW in a physically justifiable way [12, 13]. One such way is through nonlinear reactions which redistribute particles when the local concentration grows too high [14]. This normalises the subdiffusion, and allows for stationary behaviour to be realised once more.

However, transport equations for CTRWs with nonlinear particle interactions have only recently been studied [15–17]. Chemotaxis involves the reaction of biological cells to the concentration of an external signalling molecule which induces a bias in the random movement of the cells. If the bias is towards a region of greater concentration, the substance is known as a chemoattractant, and for the opposite case a chemorepellent.

The main aim of this paper is to implement nonlinear particle interactions into subdiffusive transport involving chemotaxis and nonlinear effects such as volume filling and adhesion. We introduce the additional nonlinear escape rate of particles which acts as a tempering to the anomalous trapping, characteristic of subdiffusion, and redistributes particles depending on the local mean field density. In this paper we use a rate based nonlinear random walk model involving residence time dependent escape rates and structural density of particles [15,18,19]. For the first time we derive generalised master equations, and diffusion approximations thereof, from the nonlinear random walk model involving separate modified nonlinear escape rates to the right and left. We introduce an additional instantaneous escape rate of particles dependent on the local mean field density. Here though the local mean field density is able to influence particles at any time, rather than just at the end of trapping events. Our flexible model allows for ease of extension to CTRW models which include more general transport operations than nearest neighbour jumps.

2. Nonlinear interaction of non-Markovian random walkers

In this paper we use a rate based nonlinear random walk model. A particle performs a random walk on a 1-D lattice, making instantaneous jumps from its location \( x \) of length \( l \) after random waiting times \( T_{x} \). Here we consider the waiting times preceding jumps to the right and left as being separate and independent random variables, denoting the waiting time preceding a jump to the right \( T_{x}^{\lambda} \) and a jump to the left \( T_{x}^{\mu} \). If \( T_{x}^{\mu} < T_{x}^{\lambda} \) the particle jumps to the left \( x \rightarrow (x - l) \), and if \( T_{x}^{\lambda} < T_{x}^{\mu} \) the particle jumps to the right \( x \rightarrow (x + l) \). The actual time a particle rests for is then

\[ T_{x} = \min\{T_{x}^{\mu}, T_{x}^{\lambda}\}. \]  

\( T_{x}^{\lambda} \) and \( T_{x}^{\mu} \) are drawn from the random waiting time PDFs \( \psi_{\lambda}(x, \tau) \) and \( \psi_{\mu}(x, \tau) \). The parameter \( \tau \) is the residence time parameter, representing the length of time a particle has remained at the
location \( x \).

One can generalise this to allow transitions to other sites. Denote the waiting time of a transition from \( x \to (x + il) \) as \( T^\lambda_{x,i} \) and from \( x \to (x - il) \) as \( T^\mu_{x,i} \). Then the actual transition time happens at \( T_x \) and is the minimum amongst the possible transitions to the left and right \( T_x = \min\{\ldots, T^\mu_{x,n}, \ldots, T^\lambda_{x,n}, \ldots\} \). Some details are presented in Section 4. In general, this random walk process is non-Markovian and known as a semi-Markov process, or generalised renewal process [20]. If \( T_x \) is drawn from the exponential distribution, only then will the process be Markovian.

The transition from one state to another can also be represented in the form of rates of escape, defined as instantaneous transition probabilities. The key fact of these escape rates is that they are dependent on the residence time variable \( \tau \), making the process non-Markovian. The rate of transition from \( x \to (x + l) \) is denoted by \( \lambda(x, \tau) \), and from \( x \to (x - l) \) is denoted by \( \mu(x, \tau) \):

\[
\lambda(x, \tau) = \lim_{\Delta t \to 0} \frac{\Pr\{T^\lambda_{x} < \tau + \Delta t \mid T^\lambda_{x} > \tau\}}{\Delta t}, \quad \mu(x, \tau) = \lim_{\Delta t \to 0} \frac{\Pr\{T^\mu_{x} < \tau + \Delta t \mid T^\mu_{x} > \tau\}}{\Delta t}. \tag{2.2}
\]

In survival analysis theory, this is known as the hazard rate function [21]. This way of thinking differs from standard random walk formulations involving the waiting time distribution. For escape rates which are constant with respect to residence time \( \tau \), you have the classical Markov process which in the diffusive limit is approximated by the standard advection diffusion equation. If the escape rate is inversely proportional to the residence time, \( [10] \): \( \mu, \lambda \sim \nu/\tau, 0 < \nu < 1 \), then the diffusive limit of such a process is the subdiffusive FFPE (1.1). Escape rates of this form mean walkers have a lower probability of escape for increasing residence time. This implies walkers experience long trapping events, with mean length \( T_x = \infty \). During these long trapping events it is an, implicit, assumption in other non-Markovian random walk models that walkers are protected from the influence of any external factors which would otherwise affect their transport. In the following subsection we describe a particle random walk model where the mean field density \( \rho \) may influence the rate of escape of particles.

### 2.1. Nonlinear interaction

In this Subsection we will modify the escape rates of particles to the right and left. This is quite a flexible generalisation which allows for several macroscopic nonlinear effects to be described. We introduce another stochastic process acting independently of the non-Markovian trapping. This process allows the mean field density to influence the transport of particles even during long trapping events. This acts to counter the anomalous aggregation of particles present in subdiffusive random walk models [10, 11]. We modify the escape rates \( \lambda(x, \tau) \) and \( \mu(x, \tau) \) as follows:

\[
\lambda_\alpha = \lambda(x, \tau) + \alpha_\lambda(\rho), \quad \mu_\alpha = \mu(x, \tau) + \alpha_\mu(\rho), \tag{2.1}
\]

where \( \alpha_\lambda(\rho) \) and \( \alpha_\mu(\rho) \) are the additional nonlinear escape rates to the right and left, with unspecified dependence upon \( x \) and \( l \). The probability of escape due to the nonlinear term is independent from the anomalous trapping, and in a time interval \( \Delta t \) the probability is \( \alpha(\rho)\Delta t \), where

\[
\alpha(\rho) = \alpha_\lambda(\rho) + \alpha_\mu(\rho).
\]
The exact dependence of these nonlinear escape rates upon the mean field density leads to different qualitative macroscopic effects. Volume filling effects can be introduced with the following choices for $\lambda_\alpha$ and $\mu_\alpha$:

$$\lambda_\alpha = \lambda(x, \tau) + \alpha_\lambda(\rho(x + l, t)), \quad \mu_\alpha = \mu(x, \tau) + \alpha_\mu(\rho(x - l, t)).$$

Volume filling effects describe the model where diffusing particles have a non-zero volume, and that by occupying an area they may prevent other particles from doing the same [22, 23]. This is modelled by imposing a dependence of the escape rate on the mean field density at the location the particle would escape to. For example $\alpha(\rho) = 1 - \frac{\rho}{N}$, where $N$ represents the maximum density.

Adhesion effects can be introduced with the following choices for $\lambda_\alpha$ and $\mu_\alpha$:

$$\lambda_\alpha = \lambda(x, \tau) + \alpha_\lambda(\rho(x - l, t)), \quad \mu_\alpha = \mu(x, \tau) + \alpha_\mu(\rho(x + l, t)).$$

Adhesion effects describe the sticking together of particles [24]. The escape rate of a particle from $x \to (x + l)$ is dependent on the density of particles at $(x - l)$, with an increasing density lowering the escape rate.

A dependence upon the local gradient of density [23] could be modelled also:

$$\lambda_\alpha = \lambda(x, \tau) + \kappa(\alpha_\lambda(\rho(x + l, t)) - \alpha_\lambda(\rho(x, t))), \quad \mu_\alpha = \mu(x, \tau) + \kappa(\alpha_\mu(\rho(x + l, t)) - \alpha_\mu(\rho(x, t))),$$

In the subdiffusive case, where $\lambda, \mu \sim 1/\tau$ the nonlinear terms $\alpha_\mu$ and $\alpha_\lambda$ have the effect of tempering factors preventing particles from being trapped for infinite times.

### 2.2. Structured density of particles

In order to derive a master equation for the evolution of the non-Markovian process let us introduce the structured number density of particles [15, 18, 19] $\xi(x, t, \tau)$ at location $x$, at time $t$, with residence time $\tau$. The described random walk model above leads to the balance equation for $\xi$,

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -(\lambda(x, \tau) + \alpha_\lambda(\rho(\cdot)))\xi(x, t, \tau) - (\mu(x, \tau) + \alpha_\mu(\rho(\cdot)))\xi(x, t, \tau),$$

and the objective is to derive a master equation for the unstructured density $\rho(x, t)$

$$\rho(x, t) = \int_0^t \xi(x, t, \tau) d\tau. \quad (2.1)$$

This approach has been used by many authors [10, 11, 15, 18, 19, 25] for the study of non-Markovian random walks, and has recently been found to be one of the most suitable for further nonlinear generalisations [13, 14, 17, 26].

Firstly, we define some key quantities from the random walk model. The survival functions PDFs for jumps to the right and left are denoted,

$$\Psi_\lambda(x, \tau) = \Pr\{T_x^\lambda > \tau\}, \quad \Psi_\mu(x, \tau) = \Pr\{T_x^\mu > \tau\}.$$
and define the probability a particle remains at $x$ for a time $\tau$. These are related to the waiting time PDFs through,

$$\Psi_{\lambda}(x, \tau) = \int_{\tau}^{\infty} \psi_{\lambda}(x, s) ds, \quad \Psi_{\mu}(x, \tau) = \int_{\tau}^{\infty} \psi_{\mu}(x, s) ds. \quad (2.3)$$

where,

$$\psi_{\lambda}(x, \tau) = \lim_{\Delta t \to 0} \frac{\Pr\{\tau < T_{x}^{\lambda} < \tau + \Delta t\}}{\Delta t}, \quad \psi_{\mu}(x, \tau) = \lim_{\Delta t \to 0} \frac{\Pr\{\tau < T_{x}^{\mu} < \tau + \Delta t\}}{\Delta t}, \quad (2.4)$$

are the PDFs for the waiting times for jumps to the right and left, respectively. Bayes’ Theorem allows us to relate the escape rates to both the waiting time PDFs,

$$\lambda(x, \tau) = \frac{\psi_{\lambda}(x, \tau)}{\Psi(x, \tau)}, \quad \mu(x, \tau) = \frac{\psi_{\mu}(x, \tau)}{\Psi(x, \tau)}, \quad (2.5)$$

where from the definition of $T_x = \min\{T_x^{\lambda}, T_x^{\mu}\}$, we can write the total survival PDF as

$$\Psi(x, \tau) = \Pr\{\min\{T_x^{\lambda}, T_x^{\mu}\} > \tau\} = \Psi_{\lambda}(x, \tau)\Psi_{\mu}(x, \tau),$$

$$= e^{-\int_{0}^{\tau} (\lambda(x,s) + \mu(x,s)) ds},$$

with the final equality following from (2.3) and (2.5). Differentiation of this equation with respect to $\tau$ gives the total waiting time PDF,

$$\psi(x, \tau) = \psi_{\lambda}(x, \tau) + \psi_{\mu}(x, \tau), \quad (2.6)$$

where waiting time densities $\psi_{\lambda}(x, \tau)$ and $\psi_{\mu}(x, \tau)$ are related by,

$$\psi_{\lambda}(x, \tau) = -\frac{\partial \Psi_{\mu}(x, \tau)}{\partial \tau} \Psi_{\lambda}(x, \tau), \quad \psi_{\mu}(x, \tau) = -\frac{\partial \Psi_{\lambda}(x, \tau)}{\partial \tau} \Psi_{\mu}(x, \tau).$$

In the next Section we will derive the non-Markovian master equation for the random walk model.

### 3. Nonlinear master equation

The balance equation (2.1) is written in terms of a sum of the two types of escape rates, the anomalous escape rates $\lambda(x, \tau) + \mu(x, \tau)$ and the additional escape rate $\alpha_{\lambda}(\rho) + \alpha_{\mu}(\rho)$. The initial condition at $t = 0$ is given by:

$$\xi(x, 0, \tau) = \rho_{0}(x)\delta(\tau)$$

where $\rho_{0}(x)$ is the initial density. The boundary condition for $\xi(x, t, \tau)$ at zero residence time $\tau = 0$ is:

$$\xi(x, t, 0) = \int_{0}^{t} [\lambda(x - l, \tau) + \alpha_{\lambda}(\rho)] \xi(x - l, t, \tau) d\tau + \int_{0}^{t} [\mu(x + l, \tau) + \alpha_{\mu}(\rho)] \xi(x + l, t, \tau) d\tau.$$
The number density of particles with residence time \( \tau \) escaping from \( x \to (x + l) \) to per unit time is \([\lambda(x, \tau) + \alpha_\lambda(\rho)]\xi(x, t, \tau)\), from \( x \to (x - l) \) is \([\mu(x, \tau) + \alpha_\mu(\rho)]\xi(x, t, \tau)\). The total escape rate to the right and left, respectively, is found by integrating over all \( \tau \),

\[
i_\lambda(x, t) = \int_0^t [\lambda(x, \tau)\xi(x, t, \tau)d\tau + \alpha_\lambda(\rho)]\rho(x, t),
\]

\[
i_\mu(x, t) = \int_0^t [\mu(x, \tau)\xi(x, t, \tau)d\tau + \alpha_\mu(\rho)]\rho(x, t),
\]

with the second terms in both equations due to equation (2.2). Solving equation (2.1) by method of characteristics yields, for \( \tau < t \),

\[
\xi(x, t, \tau) = \xi(x, t - \tau, 0)e^{-\int_0^t(\lambda(x,s)+\rho(x,s))ds}\frac{e^{\Phi(x,t-\tau)}}{e^{\Phi(x,t)}}
\]

(3.3)

where,

\[
\Phi(t) = \int_0^t [\alpha_\lambda(\rho) + \alpha_\mu(\rho)]ds
\]

Let us denote the integral arrival rate of particles arriving at \( x \) exactly at \( t \) as \( j(x, t) \) and,

\[
j(x, t) = \xi(x, t, 0),
\]

(3.4)

which, with equations (3.1), can be written as,

\[
j(x, t) = i_\lambda(x - l, t) + i_\mu(x + l, t).
\]

(3.5)

With characteristic solution (3.3) this becomes,

\[
j(x, t) = e^{-\Phi(t)} \int_0^t \psi_\lambda(x - l, \tau)j(x - l, t - \tau)e^{\Phi(t - \tau)}d\tau + \rho_0(x - l)\psi_\lambda(x - l, t)e^{-\Phi(t)}
\]

\[
+ \alpha_\lambda(\rho)\rho(x - l, t)
\]

\[
+ e^{-\Phi(t)} \int_0^t \psi_\mu(x + l, \tau)j(x + l, t - \tau)e^{\Phi(t - \tau)}d\tau + \rho_0(x + l)\psi_\mu(x + l, t)e^{-\Phi(t)}
\]

\[
+ \alpha_\mu(\rho)\rho(x + l, t),
\]

with second terms \( \rho_0(x) \) coming from the contribution of \( \xi(x, t, \tau)\big|_{\tau=t} \) due to the singularity of the initial condition. Inserting the expression (3.3) for \( \xi(x, t, \tau) \) into the expression for the unstructured density (2.2) \( \rho \):

\[
\rho(x, t) = e^{-\Phi(t)} \int_0^t \Psi(x, \tau)j(x, t - \tau)e^{\Phi(t - \tau)}d\tau + \rho_0(x)\Psi(x, t)e^{-\Phi(t)},
\]

(3.6)

Using equation (3.3) one can write the integral escape rates to the right and left respectively as

\[
i_\lambda(x, t) = e^{-\Phi(t)} \int_0^t \psi_\lambda(x, \tau)j(x, t - \tau)e^{\Phi(t - \tau)}d\tau + \rho_0(x)\psi_\lambda(x, t)e^{-\Phi(t)} + \alpha_\lambda(\rho)\rho(x, t),
\]

\[
i_\mu(x, t) = e^{-\Phi(t)} \int_0^t \psi_\mu(x, \tau)j(x, t - \tau)e^{\Phi(t - \tau)}d\tau + \rho_0(x)\psi_\mu(x, t)e^{\Phi(t)} + \alpha_\mu(\rho)\rho(x, t).
\]

(3.7)
To eliminate \( j(x, t) \), Laplace transforms of these equations (3.7) together with equation (3.6) yield expressions for integral escape rates:

\[
i_\lambda(x, t) = e^{-\Phi(t)} \int_0^t K_\lambda(x, t - \tau) \rho(x, \tau) e^{\Phi(\tau)} d\tau + \alpha_\lambda(\rho(x, t)) \rho(x, t), \\
i_\mu(x, t) = e^{-\Phi(t)} \int_0^t K_\mu(x, t - \tau) \rho(x, \tau) e^{\Phi(\tau)} d\tau + \alpha_\mu(\rho(x, t)) \rho(x, t),
\]

(3.8)

Here \( K_\mu(x, t) \) and \( K_\lambda(x, t) \) are the space dependent memory kernels, defined in terms of their Laplace transforms as,

\[
\hat{K}_\lambda(x, s) = \frac{\hat{\psi}_\lambda(x, s)}{\hat{\Psi}(x, s)}, \quad \hat{K}_\mu(x, s) = \frac{\hat{\psi}_\mu(x, s)}{\hat{\Psi}(x, s)}.
\]

(3.9)

By differentiating equation (2.2) and using the balance equation for \( \xi(x, t, \tau) \) (2.1), we find that the master equation for the unstructured density can be written as a balance of escape and arrival rates:

\[
\frac{\partial \rho}{\partial t} = j(x, t) - i_\lambda(x, t) - i_\mu(x, t).
\]

Due to conservation, the arrival rate of particles to \( x \) is the sum of escapes from \( (x \pm l) \), equation (3.5) for \( j(x, t) \)

\[
\frac{\partial \rho}{\partial t} = i_\lambda(x - l, t) + i_\mu(x + l, t) - i_\lambda(x, t) - i_\mu(x, t).
\]

This is simply the balance of particles arriving at and leaving the point \( x \). So that by inserting expressions (3.8) for \( i_\lambda \) and \( i_\mu \) we can write the full form of the generalised master equation for our random walk scheme,

\[
\frac{\partial \rho(x, t)}{\partial t} = e^{-\Phi(t)} \int_0^t K_\lambda(x - l, t - \tau) \rho(x - l, \tau) e^{\Phi(\tau)} d\tau + \alpha_\lambda(\rho(x - l, t)) \rho(x - l, t) \\
+ e^{-\Phi(t)} \int_0^t K_\mu(x + l, t - \tau) \rho(x + l, \tau) e^{\Phi(\tau)} d\tau + \alpha_\mu(\rho(x + l, t)) \rho(x + l, t) \\
- e^{-\Phi(t)} \int_0^t K(x, t - \tau) \rho(x, \tau) e^{\Phi(\tau)} d\tau - \alpha(\rho(x, t)) \rho(x, t)
\]

(3.10)

4. Multiple escape rates

In this section we show how we can generalise the model easily to allow transitions to occur not only between neighbouring lattice sites. Assuming the same procedure, that is the particle jumps a length \( il \) to one of the \( n \) sites to the left or \( n \) sites to the right after a time \( T_{\lambda x,i} \) or \( T_{\mu x,i} \). The total waiting time in this case would be, analogously to (2.1),

\[
T_x = \min\{T_{\mu x,n}, T_{\mu x,(n-1)}, \ldots, T_{\lambda x,(n-1)}, T_{\lambda x,n}\}.
\]
The random waiting times $T_{\lambda,i}^x$ and $T_{\mu,i}^x$ are distributed as $\psi_{\lambda,i}^x(x,\tau)$ and $\psi_{\mu,i}^x(x,\tau)$ respectively. The transition rate, in addition, is defined to be $\mu_i(x,\tau)$ for jumping from $x \rightarrow (x-il)$ and $\lambda_i(x,\tau)$ for jumping from $x \rightarrow (x+il)$, $i = 1, \ldots, n$. These are again modified:

$$\lambda_{\alpha,i} = \lambda_i(x,\tau) + \alpha_{\lambda,i}(\rho(x,t)),$$

$$\mu_{\alpha,i} = \mu_i(x,\tau) + \alpha_{\mu,i}(\rho(x,t)).$$

Then the balance equation for the structured density $\xi(x,t,\tau)$ now reads,

$$\frac{\partial \xi}{\partial t} + \frac{\partial \xi}{\partial \tau} = -\sum_{i=1}^n [\lambda_i(x,\tau) + \alpha_{\lambda,i}(\rho(x,t))]\xi(x,t,\tau) - \sum_{i=1}^n [\mu_i(x,\tau) + \alpha_{\mu,i}(\rho(x,t))]\xi(x,t,\tau).$$

All other relevant quantities can be defined in an analogous way as previously.

There are now $2n$ memory kernels, for $1 \leq i \leq n$:

$$\hat{K}_i^\lambda(x,s) = \frac{\hat{\psi}_{\lambda,i}^x(x,s)}{\Psi(x,s)}, \quad \hat{K}_i^\mu(x,s) = \frac{\hat{\psi}_{\mu,i}^x(x,s)}{\Psi(x,s)},$$

where the total survival PDF $\Psi(x,\tau)$ defined by:

$$\Psi(x,\tau) = \prod_{i=1}^n \Psi_i^\lambda(x,\tau) \times \prod_{j=1}^n \Psi_j^\mu(x,\tau),$$

$$= e^{-\int_0^\tau [\sum_{i=1}^n \lambda_i(x,s) + \sum_{j=1}^n \mu_j(x,s)] ds}.$$

The integral escape rates to the right and left $i_{\lambda}(x,t)$ and $i_{\mu}(x,t)$ are sums of the escape rates to each site to the right and left of $x$:

$$i_{\lambda}(x,t) = \sum_{i=1}^n \left( e^{-\Phi(x,t)} \int_0^t K_i^\lambda(x,t-\tau)\rho(x,\tau)e^{\Phi(x,\tau)}d\tau + \alpha_{\lambda,i}(\rho(x,t))\rho(x,t) \right),$$

$$i_{\mu}(x,t) = \sum_{i=1}^n \left( e^{-\Phi(x,t)} \int_0^t K_i^\mu(x,t-\tau)\rho(x,\tau)e^{\Phi(x,\tau)}d\tau + \alpha_{\mu,i}(\rho(x,t))\rho(x,t) \right).$$

So the master equation is written in terms of a sum over the escape related quantities of the memory kernel and additional escape tempering term:

$$\frac{\partial \rho}{\partial t} = \sum_{i=1}^n \left( e^{-\Phi(x-il,t)} \int_0^t K_i^\lambda(x-il,t-\tau)\rho(x-il,\tau)e^{\Phi(x-il,t-\tau)}d\tau \right.$$

$$+ \alpha_{\lambda,i}(\rho(x-il,t))\rho(x-il,t) \bigg)$$

$$+ \sum_{i=1}^n \left( e^{-\Phi(x+il,t)} \int_0^t K_i^\mu(x+il,t-\tau)\rho(x+il,\tau)e^{\Phi(x+il,t-\tau)}d\tau \right.$$

$$+ \alpha_{\mu,i}(\rho(x+il,t))\rho(x+il,t) \bigg)$$

$$- e^{-\Phi(x,t)} \int_0^t K(x,t-\tau)\rho(x,\tau)e^{\Phi(x,t-\tau)}d\tau + \alpha(\rho(x,t))\rho(x,t),$$

where $\alpha(\rho(x,t)) = \sum_{i=1}^n (\alpha_{\lambda,i}(\rho(x,t)) + \alpha_{\mu,i}(\rho(x,t)))$. 

8
5. Tempered Anomalous Subdiffusion

In this section we derive the fractional master equation as a special case of equation (3.10). When escape rates are inversely proportional to residence time \( \tau \) the memory kernel becomes a time fractional operator and the master equation can be approximated by the FFPE. We assume that the jumping rates are defined as:

\[
\lambda(x, \tau) = \frac{\nu_\lambda(x)}{\tau_0(x) + \tau}, \quad \mu(x, \tau) = \frac{\nu_\mu(x)}{\tau_0(x) + \tau}.
\]

Using the definition of the survival function (2.5), we find the survival functions have a power-law dependence,

\[
\Psi_\lambda(x, \tau) = \left[ \frac{\tau_0(x)}{\tau_0(x) + \tau} \right]^{\nu(x)}, \quad \Psi_\mu(x, \tau) = \left[ \frac{\tau_0(x)}{\tau_0(x) + \tau} \right]^{\nu(x)},
\]

and thus the total survival probability can be written as:

\[
\Psi(x, \tau) = \left( \frac{\tau_0(x)}{\tau_0(x) + \tau} \right)^{\nu(x)}, \quad (5.1)
\]

where \( \nu(x) = \nu_\lambda(x) + \nu_\mu(x) \) depends on the spatial variable \( x \). The total waiting time pdf defined in equation (2.6) has the Pareto form:

\[
\psi(x, \tau) = \frac{\nu(x)\tau_0(x)^{\nu(x)}}{(\tau_0(x) + \tau)^{1+\nu(x)}}, \quad (5.2)
\]

Let us introduce the probabilities of jumping to the right and left, as the ratio of \( \lambda(x, \tau) \) and \( \mu(x, \tau) \) to \( \lambda(x, \tau) + \mu(x, \tau) \), that are independent of the residence time \( \tau \), as:

\[
p_\lambda(x) = \frac{\nu_\lambda(x)}{\nu(x)}, \quad p_\mu(x) = \frac{\nu_\mu(x)}{\nu(x)}.
\]

The transition PDFs \( \psi_\lambda(x, \tau) = \lambda(x, \tau)\Psi(x, \tau) \) and \( \psi_\mu(x, \tau) = \mu(x, \tau)\Psi(x, \tau) \) can be rewritten in terms of the jumping probability as:

\[
\psi_\lambda(x, \tau) = p_\lambda(x)\psi(x, \tau), \quad \psi_\mu(x, \tau) = p_\mu(x)\psi(x, \tau)
\]

In the limit of \( t \to \infty \), by the Tauberian theorem, the memory kernels (3.9) have asymptotic approximations in Laplace space as \( s \to 0 \):

\[
\hat{K}_\lambda(x, s) \simeq \frac{p_\lambda(x)s^{1-\nu(x)}}{g(x)}, \quad \hat{K}_\mu(x, s) \simeq \frac{p_\mu(x)s^{1-\nu(x)}}{g(x)}, \quad (5.3)
\]

where,

\[
g(x) = \Gamma(1 - \nu(x))\tau_0(x)^{\nu(x)}.
\]
A combined memory kernel can be defined from (5.1) and (5.2),
\[ \hat{K}(x,s) = \hat{K}_\lambda(x,s) + \hat{K}_\mu(x,s), \]
\[ = \frac{s^{1-\nu(x)}[p_\lambda(x) + p_\mu(x)]}{g(x)} = \frac{s^{1-\nu(x)}}{g(x)}. \]

Using the expressions for the memory kernels (5.3), the integral escape rates to the right and left are:
\[ i_\lambda(x,t) = a(x)e^{-\Phi(x,t)}D_t^{1-\nu(x)}[\rho(x,t)e^{\Phi(x,t)}] + \alpha_\lambda(\rho(x,t))\rho(x,t), \]
\[ i_\mu(x,t) = b(x)e^{-\Phi(x,t)}D_t^{1-\nu(x)}[\rho(x,t)e^{\Phi(x,t)}] + \alpha_\mu(\rho(x,t))\rho(x,t), \]
where \( D_t^{1-\nu(x)} \) is the space dependent Riemann-Liouville fractional derivative (1.2) of order \( (1 - n(x)) \) and \( a(x) \) and \( b(x) \) are the anomalous rate coefficients,
\[ a(x) = \frac{p_\lambda(x)}{g(x)} = \frac{\nu_\lambda(x)}{\nu(x)\Gamma(1 - \nu(x))\tau_0(x)^{\nu(x)}}, \quad b(x) = \frac{p_\mu(x)}{g(x)} = \frac{\nu_\mu(x)}{\nu(x)\Gamma(1 - \nu(x))\tau_0(x)^{\nu(x)}}. \]
The fractional master equation then can be found:
\[ \frac{\partial \rho(x,t)}{\partial t} = a(x - l)e^{-\Phi(x-l,t)}D_t^{1-\nu(x-l)}[\rho(x - l,t)e^{\Phi(x-l,t)}] + \alpha_\lambda(\rho(x - l,t))\rho(x - l,t) \]
\[ + b(x + l)e^{-\Phi(x+l,t)}D_t^{1-\nu(x+l)}[\rho(x + l,t)e^{\Phi(x+l,t)}] + \alpha_\mu(\rho(x + l,t))\rho(x + l,t) \]
\[ - (a(x) + b(x))e^{-\Phi(x,t)}D_t^{1-\nu(x)}[\rho(x,t)e^{\Phi(x,t)}] - \alpha(\rho(x,t))\rho(x,t) \]
\[ (5.5) \]

6. Diffusion limit

In the limit as \( l \to 0 \) we can find, by Taylor series expansion, the nonlinear fractional Fokker-Planck equation
\[ \frac{\partial \rho(x,t)}{\partial t} = -i_\lambda(x,t) + i_\mu(x,t) + \frac{l^2}{2} \frac{\partial^2}{\partial x^2} [i_\lambda(x,t) + i_\mu(x,t)], \]
for \( i_\lambda(x,t) \) and \( i_\mu(x,t) \) defined in (5.4).

In what follows, let us consider the model for which the jump probabilities \( p_\lambda(x) \) and \( p_\mu(x) \) depend on the chemotactic substance \( S(x) \) as follows:
\[ p_\lambda(x) = Ae^{-\beta(S(x+t) - S(x))}, \quad p_\mu(x) = Ae^{-\beta(S(x-t) - S(x))}, \]
where the parameter \( A \) satisfies the probability conservation \( p_\lambda(x) + p_\mu(x) = 1 \). These jump probabilities describe the bias of cells’ movements with respect to the difference of local concentration of chemotactic substance. The difference satisfies:
\[ p_\lambda(x) - p_\mu(x) = \frac{e^{-\beta S(x+t)} - e^{-\beta S(x-l)}}{e^{-\beta S(x+t)} + e^{-\beta S(x-l)}}, \]
\[ 10 \]
and in the limit \( l \to 0 \) we have the standard chemotaxis model,
\[
a(x) - b(x) = p\lambda(x) - b(x) = -\frac{l\beta}{g(x)} dS + o(l).
\]
We now choose particular escape rates simply based on the local mean field density. The effect is particles will be more likely to escape from an area of high concentration, and this will counteract any crowding effects:
\[
\lambda_\alpha(x, \tau) = \lambda(x, \tau) + \alpha_\lambda(\rho(x, t)), \quad \mu_\alpha(x, \tau) = \mu(x, \tau) + \alpha_\mu(\rho(x, t)).
\]
We can organise the difference between \( \alpha_\lambda \) and \( \alpha_\mu \) in an analogous manner. If we write,
\[
p_{\alpha,\lambda}(x, t) = \frac{\alpha_\lambda(\rho(x, t))}{\alpha(\rho(x, t))}, \quad p_{\alpha,\mu}(x, t) = \frac{\alpha_\mu(\rho(x, t))}{\alpha(\rho(x, t))},
\]
and choose \( \alpha_\lambda \) and \( \alpha_\mu \) such that,
\[
p_{\alpha,\lambda}(x, t) = Be^{-\kappa(\rho(x+l,t)-\rho(x,t))}, \quad p_{\alpha,\mu}(x, t) = Be^{-\kappa(\rho(x-l,t)-\rho(x,t))},
\]
where \( B \) satisfies \( p_{\alpha,\lambda}(x, t) + p_{\alpha,\mu}(x, t) = 1 \). We can approximate the difference:
\[
p_{\alpha,\lambda}(x, t) - p_{\alpha,\mu}(x, t) = l\kappa \frac{\partial \rho}{\partial t} + o(l).
\]
We then obtain the nonlinear fractional equation written in full:
\[
\frac{\partial \rho(x, t)}{\partial t} = -\frac{\partial}{\partial x} \left[ \frac{l^2\beta}{g(x)} dS \Phi(x,t) D_t^{1-\nu}(\rho(x, t)) e^{\Phi(x,t)} + l^2\kappa \frac{\partial \rho}{\partial x} \alpha(\rho(x, t)) \right] + \frac{\partial^2}{\partial x^2} \left[ \frac{l^2}{2g(x)} e^{-\Phi(x,t)} D_t^{1-\nu}(\rho(x, t)) e^{\Phi(x,t)} + \left( \alpha(\rho(x, t)) \right) \rho(x, t) \right].
\]
Notice here that it is not possible to separate the additional escape from the subdiffusive transport terms, with the former appearing as a convolution under the fractional derivative operator. The transport and diffusion are controlled both by the chemotaxis and the local gradient of the mean field.

### 6.1. Linear tempering

In this subsection, we wish to find the stationary version of equation (6.1) when the additional nonlinear escape rates \( \alpha_\lambda(\rho(x, t)) \) and \( \alpha_\mu(\rho(x, t)) \) are independent of \( \rho \). Now \( \Phi(x, t) = \int_0^t \alpha(\rho(x, s)) ds = \alpha(x) t \) and the fractional escape rates (5.4) become:
\[
\begin{align*}
i_\lambda(x, t) &= a(x) e^{-\alpha(x)t} D_t^{1-\nu}(\rho(x, t)) e^{\alpha(x)t} + \alpha_\lambda(\rho(x, t)) \rho(x, t), \\
i_\mu(x, t) &= b(x) e^{-\alpha(x)t} D_t^{1-\nu}(\rho(x, t)) e^{\alpha(x)t} + \alpha_\mu(\rho(x, t)) \rho(x, t).
\end{align*}
\]
(6.2)
The stationary density is defined in limit $s \to 0$ as,
\[
\rho_{st}(x) = \lim_{s \to 0} s \hat{\rho}(x, s),
\]
and the stationary escape rates as,
\[
i_{\lambda, st}(x) = \lim_{s \to 0} s \hat{i}_\lambda(x, s), \quad i_{\mu, st}(x) = \lim_{s \to 0} s \hat{i}_\mu(x, s).
\]

By the shift theorem, the Laplace transforms of equations (6.2) are:
\[
\hat{i}_\lambda(x, s) = a(x)[s + \alpha(x)]^{1-\nu(x)} \hat{\rho}(x, s) + \alpha(x) \hat{\rho}(x, s),
\]
\[
\hat{i}_\mu(x, s) = b(x)[s + \alpha(x)]^{1-\nu(x)} \hat{\rho}(x, s) + \alpha(x) \hat{\rho}(x, s).
\]

Then the stationary escape rates can be written in the Markovian form,
\[
i_{\lambda, st}(x) = \lambda(x) \nu(x) \rho_{st}(x), \quad i_{\mu, st}(x) = \mu(x) \nu(x) \rho_{st}(x),
\]
where
\[
\lambda(x) = a(x) \alpha(x)^{1-\nu(x)} + \alpha(x) \lambda(x),
\]
\[
\mu(x) = b(x) \alpha(x)^{1-\nu(x)} + \alpha(x) \mu(x).
\]

The stationary limit of nonlinear fractional equation (6.1) reduces to the 2nd order ODE
\[
-\frac{\partial}{\partial x} (v_\nu(x) \rho_{st}(x)) = \frac{\partial^2}{\partial x^2} (D_\nu(x) \rho_{st}(x)),
\]
where,
\[
D_\nu(x) = \frac{l^2}{2} \left( \frac{\tau_0(x) \alpha(x)^{1-\nu(x)}}{\Gamma(1-\nu(x)) \tau_0(x)} + \alpha(x) \right), \quad v_\nu(x) = -D_\nu(x) \frac{dU(x)}{dx}
\]
with,
\[
\frac{dU(x)}{dx} = \frac{2 \lambda(x) - \mu(x)}{l \mu(x) + \lambda(x)}.
\]

Note that the velocity depends on the difference $\lambda(x) - \mu(x) = l \kappa \frac{\partial \rho}{\partial x} \alpha(x)$. So the shape of the mean field density can influence the transport.

The solution can be found on the interval $[0, L]$ with reflective boundary conditions if we introduce a new function $p(x) = D_\nu(x) \rho_{st}(x)$, which then satisfies the equation:
\[
-\frac{d}{dx} \left[ \frac{dU(x)}{dx} p(x) \right] = \frac{d^2 p(x)}{x^2},
\]
with solution of Boltzmann type,
\[
p(x) = N^{-1} e^{-U(x)}, \quad N = \int_0^L e^{-U(x)} dx.
\]

where $N$ is the normalisation constant,
6.2. Nonlinear tempering

If a stationary distribution exists, then the tempering parameter $e^{-\int_0^t \alpha(\rho(x,s))ds}$ can be written $e^{-\alpha(\rho(x,t))}$ as $t \to \infty$. Following the same procedure as for the linear case in the previous subsection, we arrive at the stationary nonlinear fractional equation:

$$-\frac{\partial}{\partial x} (v_\nu(\rho_{st}, x) \rho_{st}(x)) = \frac{\partial^2}{\partial x^2} (D_\nu(\rho_{st}, x) \rho_{st}(x)),$$

where,

$$v_\nu(\rho_{st}, x) = -l(\lambda_\nu(x) - \mu_\nu(x)),$$

$$= -\frac{l\beta}{g(x)} \alpha(\rho_{st})^{1-\nu(x)} + lK \frac{d\rho_{st}}{dx} \alpha(\rho_{st}),$$

and,

$$D_\nu(\rho_{st}, x) = \frac{l^2}{2} (\lambda_\nu(x) + \mu_\nu(x)),$$

$$= \frac{l^2}{2} \left( \frac{\tau_0(x) \alpha(\rho_{st})^{1-\nu(x)}}{\Gamma(1-\nu(x)) \tau_0(x)} + \alpha(\rho_{st}) \right).$$

This equation can be solved by direct Monte Carlo simulation of fractional master equation (3.10), or by simulation of Markovian evolution equation from which balance equation (2.1) is derived:

$$\xi(x, t + \Delta t, \tau + \Delta \tau) = \xi(x, t, \tau)(1 - \lambda(x, \tau)\Delta \tau - \mu(x, \tau)\Delta \tau)(1 - \alpha(\rho)\Delta t - \alpha(\rho)\Delta t).$$

7. Conclusion

In this paper we studied a non-Markovian random walk model which included nonlinear particle interactions and chemotactic forcing. The nonlinear particle interactions were introduced to the model through the modified escape rates (2.1). We derived the general non-Markovian master equation which included the exponential factors involving the nonlinear escape rates. In the subdiffusive case, the master equation includes the Riemann-Liouville fractional derivative with the nonlinear factors acting as a tempering to the anomalous trapping mechanism of subdiffusion.

We found in the diffusive limit we have a nonlinear fractional Fokker-Planck equation. In the long time stationary limit, the rate of diffusion includes both the rate of additional escape $\alpha$, subdiffusive anomalous exponent $\nu(x)$. We find that if the rate $\alpha$ is independent of the mean field density, the stationary solution can be found to be of Boltzmann type, and anomalous aggregation is not observed. In the case of nonlinear dependence of $\alpha$ upon $\rho$ we have also derived a stationary nonlinear Fokker-Planck equation. This nonlinear fractional equation could be solved by direct Monte Carlo simulation of the master equation (5.5), but we have not attempted that here.
References


Chapter 4

Conclusion

In this thesis we set out with a number of aims, listed in the introduction, which by and large we achieved. In doing so we also found other unexpected and interesting effects.

We set out with the first aim to study subdiffusion in an inhomogeneous environment. We systematically derive a model which includes a spatially dependent anomalous exponent and study interesting effects arising from this. In the first article we demonstrated that when the anomalous exponent $\mu$ depends on the space variable $x$, the Gibbs-Boltzmann distribution is not a long-time limit of the fractional Fokker-Planck equation. This structural instability means that even very small variations of the exponent lead to a drastic change of the stationary distribution as $t \to \infty$. Although it is possible in theory to have a completely homogeneous environment in which $\mu$ is uniform, it is not useful in any real application because any nonhomogeneous variation destroys the predictions based on this model in the long-time limit. We described this as a “Black Swan” phenomenon, when an outlier (small value of anomalous exponent) completely dominates the long-time behavior of subdiffusive systems. In this article we used Monte Carlo simulations to demonstrate the result of the stationary equation breakdown. We have shown that the idea of taking into account the randomness of the anomalous exponent by averaging the fractional equation with respect to some probability distribution $f(\mu)$ is not applicable to a nonhomogeneous finite domain.

Our next goal was to find a solution to the problem of anomalous aggregation with the fractional equations involving the anomalous exponent. In the second article we introduced the random death process as a natural remedy to
the problem of structural instability found in the first article. We introduced this in a fundamentally different way to that of the exponential tempering of power-law waiting time, which results in similar equations. Exponential tempering has already been studied in depth by Meerscaert et al. Our approach adds a physically measurable quantity (the death rate) and one which is present in several system including those presenting subdiffusion themselves. We also find the stationary flux of the particles has a Markovian form with an unusual rate function depending on the anomalous rate functions, the death rate, and the anomalous exponent. We have shown that the long-time and continuous limit of this regularized fractional equation is the standard advection-diffusion equation that, importantly, is structurally stable with respect to spatial variations of the anomalous exponent. Additionally we found that the effective rate and diffusion coefficients are increasing functions of the death rate.

We aimed to investigate the interaction between nonlinear reactions and sub-diffusive transport, and apply the study to the problem of morphogenesis, particularly focusing on the shape of the stationary profile. In the third article we considered the formation of a stationary morphogen gradient resulting from the non-trivial interaction of subdiffusion with a non-linear degradation. We discovered the phenomenon of degradation enhanced diffusion in which an increase in the rate of degradation actually leads to an increase in the effective rate of diffusion. We found that in this model the stationary distribution is no longer of exponential form, but has a power-law form with long tails determined by the anomalous exponent \( \mu \). We found that the stationary profile is independent of fluctuations in particle production rate. This is an important property for the application to morphogen gradient production in which robustness is the key goal.

We, finally, wanted to formulate a systematic way to derive nonlinear subdiffusion-reaction equations in the presence of an external chemotactic signalling substance. In the fourth article we systematically derived nonlinear fractional Fokker-Planck equations from a non-Markovian random walk model which included nonlinear particle interactions and chemotactic forcing. The nonlinearity was introduced through the modification of the microscopic escape rate. This approach with separate escape rates to different lattice sites including nonlinear escape rates is derived for the first time. In the diffusive limit we found a nonlinear FFPE in which the effective rate of diffusion is dependent upon the local mean field density. The effect of an increasing mean field density is to increase
the rate of diffusion and prevent anomalous aggregation. We found that this is a simple systematic way to take into account various nonlinear effects such as volume filling, quorum sensing, and adhesion. We studied this nonlinear subdiffusion in the presence of chemotactic forcing, in which the transport of particles is influenced by the gradient of concentration of an external signalling molecule.

For future work we suggest finding stationary solutions to the nonlinear subdiffusion-reaction equations by Monte Carlo simulation. With this framework of the random walk involving Markovian structured density it should be easier to construct algorithms for simulation of nonlinear subdiffusion. The problem with simulating the nonlinear random walk process is that when the random walk trajectory depends upon the state of the other walkers, it is necessary to simulate a large number of trajectories. Further, it may not be preferable to use the standard algorithm of generating waiting times for walkers, since any change in the state of the other walkers should affect this random waiting time. For this reason, it could be preferable to step through time in small increments whilst updating the states of all walkers. With the Markovian structured density it is only necessary to store information about the current state in order to generate the next state of the system. To our knowledge, this approach has not yet been used in the literature for the solution of nonlinear reaction-subdiffusion equations.

With the methods described in the final article, it should be possible to investigate many nonlinear effects within the non-Markovian random walk scheme, and study many limiting diffusive processes as a result. The adaptability of these models could be of use to scientists working in the field of biology looking to model observed nonlinear phenomena in a simple manner.
Bibliography


