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Transport equations for subdiffusion with nonlinear particle interaction

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HIGHLIGHTS

- A microscopic stochastic model for subdiffusion with nonlinear interaction (volume filling and adhesion) is developed.
- Macroscopic governing differential equations are derived which are consistent with the microscopic stochastic model.
- Examples of stationary particle densities are computed which are subject to anomalous aggregation and nonlinear interaction.

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ABSTRACT

We show how the nonlinear interaction effects 'volume filling' and 'adhesion' can be incorporated into the fractional subdiffusive transport of cells and individual organisms. To this end, we use microscopic random walk models with anomalous trapping and systematically derive generic *non-Markovian and nonlinear* governing equations for the mean concentrations of the subdiffusive cells or organisms. We uncover an interesting interaction between the nonlinearities and the non-Markovian nature of the transport. In the subdiffusive case, this interaction manifests itself in a nontrivial combination of nonlinear terms with fractional derivatives. In the long time limit, however, these equations simplify to a form without fractional operators. This provides an easy method for the study of aggregation phenomena. In particular, this enables us to show that volume filling can prevent "anomalous aggregation," which occurs in subdiffusive systems with a spatially varying anomalous exponent.

1. Introduction

Stochastic models for the diffusive motion of biological cells and organisms are well established in the mathematical biology community. Random walk models, stochastic differential equations and their governing nonlinear partial differential equations have been very successful from a mathematical modelling standpoint. They provide tractable means to incorporate various taxis effects such as the directed transport along the concentration gradient of external signals (Othmer and Hillen, 2002; Hillen and Painter, 2009; Stevens, 2000), particle generation and degradation rates which depend on particle concentrations (Murray, 2007; Oelschläger, 1989), density dependent dispersal rates (Méndez et al., 2012; Murray, 2007), volume exclusion effects (Painter and Hillen, 2002; Simpson and Baker, 2011; Fernando et al., 2010), and adhesion between particles (Anguige, 2011; Armstrong et al., 2006; Johnston et al., 2012). A defining feature of most such nonlinear reaction–diffusion-taxis equations is that the macroscopic transport processes involving diffusion and advection are derived from microscopic Markovian random walk models; see the excellent review by Stevens and Othmer (1997). However, this does not fit well with anomalous non-Markovian subdiffusive systems, for which the transport operators are non-local in time and the mean squared displacement of individual particles grows proportionally to t^{μ}, where $0<\mu<1$ (Metzler and Klafter, 2000). Anomalous transport occurs microscopically on the level of individual cells, e.g. for the transport of macromolecules within living cells (Golding and Cox, 2006; Tolić-Nørrelykke et al., 2004; Weiss et al., 2004; Banks and Fradin, 2005). Moreover, it has been found that the motion of individual cells is anomalously diffusive (Dieterich et al., 2008; Mierke et al., 2011; Fedotov et al., 2013).

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The main mathematical models for subdiffusive dynamics are the Continuous Time Random Walk (CTRW) and fractional Brownian motion (fBm). Both processes are non-Markovian, unlike Brownian motion. The CTRW appears to be the most popular model for anomalous dynamics (Metzler and Klafter, 2000), presumably because it admits a tractable PDE formalism (Barkai et al., 2000; Henry et al., 2010). However, it should be noted that most articles on anomalous transport deal with linear fractional PDEs without particle interactions. Unlike for Markovian dynamics, it is challenging to incorporate nonlinearities into the subdiffusive PDEs. For instance, even if the particle death rate is bounded below, by naively adding a degradation term to the PDE one can achieve negative particle concentrations (Henry et al., 2006). Transport equations for CTRWs with nonlinear reactions have only recently been derived (Mendez et al., 2010; Angstmann et al., 2013). Apart from an article by one of the authors (Fedotov, 2013), to our knowledge, particle interactions have not yet been incorporated into the CTRW framework. The challenge is to take into account non-linear effects: volume exclusion (Painter and Hillen, 2002) and adhesion (Anguige, 2011) together with subdiffusive transport.

The main purpose of this article is to systematically derive generic *non-Markovian and non-linear* integro-differential equations for the mean concentration of particles such as randomly moving cells or individual organisms. Our aims are: (i) to understand the interaction of non-Markovian transport and nonlinearities due to volume filling and adhesion effects and (ii) to find the stationary solutions of nonlinear non-Markovian transport equations that describe aggregation phenomena.

On our way towards goal (i), we give a formalism which connects nonlinearly interacting microscopic CTRWs with nonlinear and non-Markovian diffusion equations. As it turns out, our formalism also applies to the situation where the anomalous exponent μ, which governs the trapping behaviour of the CTRW, varies in space (Chechkin et al., 2005). This situation is very significant for biology because it may explain the widespread phenomenon of anomalous accumulation of bacteria in particular patches. One example is the aggregation of phagotrophic protists (Fenchel and Blackburn, 1999), where "cells become immobile in attractive patches, which will then eventually trap all cells." Another example is the formation of nodules on the roots of nitrogen-fixing plants that contain the colony of nitrogen-fixing bacteria (Wadhams and Armitage, 2004).

It is well known that the movement of bacteria in environments with varying favorability is in the most cases determined by chemokinesis rather than chemotaxis. The reason for this is that typically the bacteria/cells are too small to sense the macroscopic gradient of a chemotactic substance $S(x)$ (Erban and Othmer, 2005). Hence a model for the random motility of microorganisms should take into account the dependence of the transition probability γ on the nonuniformly distributed concentration $S(x)$, rather than the dependence of a cell's jump direction on the gradient $\partial S/\partial x$. With this in mind, CTRWs with space-varying anomalous exponent μ arise very naturally as models for chemokinesis: suppose that $\mu=\mu(S(x))$ is a decreasing function of a favourable substance with concentration $S(x)$. Then the transition probability γ (i.e. the probability of a jump away from x) equals

$$\gamma(\tau,S(x))=\frac{\mu(S(x))}{\tau_0+\tau},$$

where τ is the residence time and τ_0 is a constant (see Eq. (14)). Hence the rate at which a bacterium jumps away from a favourable environment at x is small, which leads to the phenomenon of anomalous aggregation (Fedotov and Falconer, 2012).

The setup is as follows: In Section 2 we quickly reiterate the derivation of nonlinear Markovian transport equations from microscopic stochastic models. Section 3 contains a quick overview over the anomalous sub-diffusion literature and fractional diffusion equations. In Section 4 we use the structured density approach and recover Markovian methods for CTRWs; this allows for the derivation of nonlinear differential equations involving subdiffusion. Finally, in Section 5 we give examples of stationary solutions to nonlinear fractional PDEs that describe the aggregation phenomenon.

2. Markovian transport with nonlinear particle interaction

In this section, we briefly review the standard derivation of nonlinear diffusion equations, starting from a microscopic random walk model. For simplicity, we consider a one dimensional lattice of sites x which are evenly spaced with spacing h. We study the dynamics of the concentration $\rho(x,t)$ of particles (e.g. cells and bacteria). We assume that particles perform instantaneous jumps to neighbouring lattice sites. We write $T^+(x,t)$ and $T^-(x,t)$ for the rates of jumps to the right resp. left. Rates are instantaneous and may vary in space x and in time t. The total jump rate is then $T(x,t):=T^+(x,t)+T^-(x,t)$. The master equation for $\rho(x,t)$ reads

$$\frac{\partial\rho(x,t)}{\partial t}=T^+(x-h,t)\rho(x-h,t)+T^-(x+h,t)\rho(x+h,t)-T(x,t)\rho(x,t). \tag{1}$$

Transport models for diffusion, chemotaxis, volume filling and adhesion have been studied by Anguige (2011), Anguige and Schmeiser (2009) and Painter and Hillen (2002). A general model which accommodates all the above effects is given by

$$T^{\pm}(x,t)=\lambda_0(1-[S(x\pm h,t)-S(x,t)])q(\rho(x\pm h,t))a(\rho(x\mp h,t)) \tag{2}$$

Here, λ_0 is the rate parameter, and $S(x,t)$ is a spatio-temporally varying external signal (e.g. a chemoattractant or chemorepellent concentration). The functions $q(\rho)$ and $a(\rho)$ model volume filling and adhesion phenomena; they are decreasing with respect to the concentration density $\rho(x,t)$ and map to values in $[0,1]$. The volume filling function $q(\rho(x,t))$ can be interpreted as the probability that a particle will be accommodated at x, should it attempt to jump there at time t. With the remaining probability $1-q(\rho(x,t))$, it will not find enough room at x and hence will not jump. Similarly, the adhesive effect is modelled with the function $a(\rho(x,t))$: Given that a particle attempts to jump from x to $x+h$ at time t, it succeeds in jumping there with probability $a(\rho(x-h,t))$. With probability $1-a(\rho(x-h,t))$, it will stay "glued" to the particles at position $x-h$ and thus not jump.

Eq. (1) governs the evolution of the concentration $\rho(x,t)$ on the discrete lattice. We perform a Taylor expansion in the lattice spacing h (see appendix) and consider the spatiotemporal scaling limit:

$$h\downarrow 0,\quad \lambda_0\uparrow\infty,\quad h^2\lambda_0\to D_0. \tag{3}$$

The particle concentration is then governed by the nonlinear advection–diffusion equation:

$$\frac{\partial\rho}{\partial t}=\frac{\partial}{\partial x}\left[D(\rho)\frac{\partial\rho}{\partial x}-\rho v(\rho)\right] \tag{4}$$

with diffusion coefficient $D(\rho)$ and drift coefficient $v(\rho)$ given by

$$D(\rho) = D_0[a(\rho)q(\rho) + 3a'(\rho)q(\rho)\rho - a(\rho)q'(\rho)\rho]$$

$$v(\rho) = -2D_0 a(\rho)q(\rho)\frac{\partial S}{\partial x},$$

(note that $a'(\cdot)$ and $q'(\cdot)$ are plain derivatives of the functions $a(\cdot)$ and $q(\cdot)$). Anguige (2011), for instance, studies volume filling and adhesion phenomena by setting

$$q(\rho) = 1-\rho, \quad a(\rho) = 1-\alpha\rho$$

with adhesion parameter $\alpha > 0$, resulting in

$$D(\rho) = D_0\left[3\alpha\left(\rho - \frac{2}{3}\right)^2 + 1 - \frac{4}{3}\alpha\right],$$

$$v(\rho) = -2D_0(1-\alpha\rho)(1-\rho)\frac{\partial S}{\partial x}.$$

3. Non-Markovian transport

This section is a short overview of fractional subdiffusion transport equations. These equations have been successfully applied to subdiffusive systems, whose main feature is a mean squared displacement of sublinear growth $\sim t^\mu$ where $\mu \in (0,1)$. This is in stark contrast to systems with Brownian noise, where mean squared displacement grows linearly. The "standard" fractional diffusion equation governing the particle density $\rho(x,t)$ is

$$\frac{\partial^\mu \rho}{\partial t^\mu} = D_\mu \frac{\partial^2 \rho}{\partial x^2}, \quad \rho(x,0) = \rho_0(x), \tag{5}$$

where D_μ is a fractional diffusion constant with units length^2 /time$^\mu$, and where the Caputo derivative of order μ is defined via

$$\frac{\partial^\mu}{\partial t^\mu} f(t) := \int_0^t f'(t-s)\frac{s^{-\mu}}{\Gamma(1-\mu)}\,ds \tag{6}$$

with $\Gamma(\cdot)$ denoting the Gamma function. We note that in the limit $\mu \uparrow 1$, the kernel $s^{-\mu}/\Gamma(1-\mu)$ converges to the a Dirac delta, and the Caputo derivative is then the plain derivative of order 1. Similarly to the manner in which the standard diffusion equation with $\mu = 1$ is derived from a random walk, (5) is derived from a Continuous Time Random Walk (CTRW) (Metzler and Klafter, 2000; Meerschaert and Scheffler, 2004; Meerschaert and Sikorskii, 2011). Suppose that a particle at the origin at time $t=0$ performs a random walk on a one-dimensional lattice, and suppose that the waiting time W between each jump is distributed according to a power law with tail parameter $\mu \in (0,1)$:

$$P(W > t) \sim \frac{(t/\tau_0)^{-\mu}}{\Gamma(1-\mu)}, \quad (t \to \infty). \tag{7}$$

Let $X(t)$ denote the random position of the particle at time t, and write $p(x,t)$ for its probability density in space x at time t. Introducing the scaling parameters h for space and τ_0 for time, we consider the rescaled position $hX(t/\tau_0)$. Its probability density is $p(x/h, t/\tau_0)/h$. Applying the scaling limit in which both τ_0 and h tend to 0 and the ratio $h^2/(2\tau_0^\mu)$ converges

$$h \downarrow 0, \quad \tau_0 \downarrow 0, \quad \frac{h^2}{2\tau_0^\mu} \to D_\mu, \tag{8}$$

this probability density also converges to a probability density $P(x,t)$ which solves the same equation as (5). If one considers a collection of a large number of particles with the above dynamics and assumes that the individual trajectories do not interact, then $P(x,t)$ may be replaced by $\rho(x,t) = CP(x,t)$, where C denotes the total mass of particles. As (5) is linear, $\rho(x,t)$ is also a solution. It is common to use this CTRW representation for Monte-Carlo simulations of solutions of (5) (Meerschaert and Sikorskii, 2011; Zhang et al., 2008).

The above correspondence between CTRWs and fractional PDEs extends to CTRWs with spatial variations, which can be applied to model chemotaxis problems (Langlands and Henry, 2010). Suppose a collection of particles perform independent CTRWs and respond to an external force $F(x)$ with a biased jump probability, i.e. a probability $1/2 + hF(x)$ to jump right and $1/2 - hF(x)$ to jump left. Then a scaling limit as in (8) yields a concentration $\rho(x,t)$ which is governed by the fractional Fokker–Planck equation:

$$\frac{\partial^\mu \rho(x,t)}{\partial t^\mu} = \frac{\partial^2}{\partial x^2}\left[D_\mu \rho(x,t)\right] - \frac{\partial}{\partial x}\left[D_\mu F(x)\rho(x,t)\right], \quad \rho(x,0) = \rho_0(x), \tag{9}$$

Chemotaxis is usually modelled via a bias in the particle jumps which depends on a chemotactic substance with concentration $S(x,t)$ according to $1/2 \pm h\chi(\rho,S)\partial S/\partial x$ (Hillen and Painter, 2009; Langlands and Henry, 2010). Here the chemotactic sensitivity $\chi(\rho,S)$ may be positive in the case of chemoattraction, or negative in the case of chemorepulsion. This dynamics may be interpreted within the fractional Fokker–Planck framework by letting the signal $F(\cdot)$ depend on both space and time:

$$F(x,t) = \chi(\rho(x,t), S(x,t))\frac{\partial S(x,t)}{\partial x}.$$

Importantly, however, Eq. (9) only holds for external signals which do *not* vary with time. The correct generalisation of the fractional Fokker–Planck equation for time-varying signals $F = F(x,t)$ is

$$\frac{\partial \rho(x,t)}{\partial t} = \frac{\partial^2}{\partial x^2}\left[D_\mu \mathcal{D}_t^{1-\mu}\rho(x,t)\right] - \frac{\partial}{\partial x}\left[D_\mu F(x,t)\mathcal{D}_t^{1-\mu}\rho(x,t)\right],$$
$$\rho(x,0) = \rho_0(x), \tag{10}$$

(Henry et al., 2010) with order $1-\mu$ Riemann–Liouville fractional derivative:

$$\mathcal{D}_t^{1-\mu} f(t) = \frac{d}{dt}\int_0^t f(t-s)\frac{s^{\mu-1}}{\Gamma(\mu)}\,ds = \frac{\partial^{1-\mu} f(t)}{\partial t^{1-\mu}} + f(0)\frac{t^{\mu-1}}{\Gamma(\mu)}.$$

A further avenue of introducing spatial variations into fractional transport is by letting the anomalous parameter vary in space, $\mu = \mu(x)$, see e.g. Chechkin et al. (2005). Eq. (7) then becomes

$$P(W > t) \sim \frac{(t/\tau_0(x))^{-\mu(x)}}{\Gamma(1-\mu(x))}, \quad (t \to \infty)$$

(Fedotov and Falconer, 2012). For small h and τ_0, the dynamics of the particle density $\rho(x,t)$ can be approximated by

$$\frac{\partial \rho(x,t)}{\partial t} = \frac{\partial^2}{\partial x^2}\left[D_\mu(x)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)\right] - \frac{\partial}{\partial x}\left[D_\mu(x)F(x,t)\mathcal{D}_t^{1-\mu(x)}\rho(x,t)\right],$$
$$\rho(x,0) = \rho_0(x) \tag{11}$$

where

$$D_\mu(x) = \frac{h^2}{2\tau_0^\mu(x)}.$$

Finally, we remark that many articles study "Caputo forms" of (10) and (11), which are obtained by simply substituting $F(x,t)$ for $F(x)$ and $\mu(x)$ for μ in (9). Such equations are not linked to (Continuous Time) Random Walk models, and hence do not have any physical interpretation. The authors deem it unlikely that a Caputo form of a transport equation like (9) can be derived from a chemotaxis model on the lattice and strongly advocate the use of the Riemann–Liouville type equations (10) and (11).

4. Non-Markovian transport with nonlinear interaction

This section contains the main results of our paper. We derive nonlinear fractional equations involving subdiffusion, volume filling and adhesion effects. CTRWs whose waiting times between jumps are not exponentially distributed do not satisfy the Markov property. However, they are *semi-Markov processes* (Meerschaert and Straka, 2014) (or generalised renewal processes), meaning that the Markov property applies at the random times at which a jump occurs. As a consequence, at any time t the law of the future trajectory of a particle depends only on its position x at time t and the residence time τ, i.e. the time which has elapsed since the last jump. In mathematical terms, the dynamics are Markovian on the state space $(x,\tau) \in \mathbb{R} \times [0,\infty)$.

As in Vlad and Ross (2002), Mendez et al. (2010), we introduce the *structured density* $\xi(x,\tau,t)$ of particles at position x at time t whose residence time equals τ. Then the cell density $\rho(x,t)$ is recovered from the structured density via simple integration:

$$\rho(x,t) = \int_0^\infty \xi(x,\tau,t)\,d\tau \tag{12}$$

As most other paper in the field, we assume the initial condition $\xi(x,\tau,0) = \rho_0(x)\delta(\tau)$ at time $t=0$. In this case, at time t no residence time can exceed the value t, and it suffices to integrate over the domain $[0,t]$.

The structured density dynamics of a single particle are as follows: the residence time τ increases linearly with time t at the rate 1, until the particle escapes the site x. Upon escape, τ is reset to 0. In this paper, we assume that the rate at which a particle escapes from a site x depends on two effects. Firstly, it depends on the (external) environment at x and neighbouring sites at time t, and secondly on its (internal) residence time τ at x, which reflects a memory effect typical for CTRWs. The external effect is comprised in the escape rate $\alpha(x,t)$, which may be a function e.g. of the particle density ρ at x and neighbouring sites, and thus may account for volume-exclusion and/or adhesion effects. Additionally, it may be a function of the density $S(x,t)$ of a nearby chemically signalling substance (see below). The internal effect, on the other hand, is comprised in the escape rate $\gamma(x,\tau)$. For CTRWs, one typically assumes a waiting time distribution with density $\psi(x,\tau)$ for the times between jumps, with tail function $\Psi(x,\tau) = \int_\tau^\infty \psi(x,\tau')\,d\tau'$. Then

$$\gamma(x,\tau) = \psi(x,\tau)/\Psi(x,\tau) \tag{13}$$

holds (Fedotov and Falconer, 2012). A subdiffusive trapping effect at x occurs when $\gamma(x,\tau)$ is a decreasing function in τ. For instance, a Pareto distribution $\Psi(x,\tau) = (1+\tau/\tau_0)^{-\beta}$ with characteristic time scale τ_0 and tail parameter $\mu \in (0,1)$ yields

$$\gamma(x,\tau) = \mu/(\tau_0+\tau); \tag{14}$$

For the exponential distribution $\Psi(x,\tau) = \exp(-t/\tau_0)$, one has $\gamma(x,\tau) = 1/\tau_0$, independent of τ, reflecting the typical lack of memory.

For tractability, we assume that the internal and external effects are independent. This means that the escape rates add up to a total escape rate $\alpha(x,t)+\gamma(x,\tau)$. The probability of an escape in the infinitesimal time interval $(t,t+dt)$ is then $\alpha(x,t)\,dt+\gamma(x,\tau)\,dt$. Now the dynamics of the structured density $\xi(x,\tau,t)$ can be seen to satisfy the equation:

$$\frac{\partial}{\partial t}\xi(x,\tau,t) = -\frac{\partial}{\partial \tau}\xi(x,\tau,t) - [\alpha(x,t)+\gamma(x,\tau)]\xi(x,\tau,t), \quad t>0, \quad \tau>0, \tag{15}$$

which describes the linear increase of the residence time and the decay in the structured particle density due to particle escapes.

Upon escape from x, the residence time τ is reset to 0, and the particle is placed back onto the lattice as follows: It jumps to the neighbouring left resp. right lattice site with probability L resp. R, or it does not jump with probability C. We assume $L+R+C=1$. Moreover, the probabilities L and R (and hence C) only depend on external cues at x at time t, and not on the internal residence time τ at the time of the jump: $L=L(x,t)$, $R=R(x,t)$. We incorporate volume filling, adhesion and chemotactic drift into $L(x,t)$ and $R(x,t)$ via

$$L(x,t)=q(\rho(x-h,t))a(\rho(x+h,t))\left[\frac{1}{2}-\frac{S(x+h)-S(x-h)}{4}\right]$$
$$R(x,t)=q(\rho(x+h,t))a(\rho(x-h,t))\left[\frac{1}{2}+\frac{S(x+h)-S(x-h)}{4}\right],$$
$$C(x,t)=1-L(x,t)-R(x,t).$$

Here the functions $q(\rho)$, $a(\rho)$ and $S(x)$ play the same roles (volume filling, adhesion and external signal) as described in (2). One can check that L, R and C are all probabilities, i.e. lie in the interval $[0,1]$. Other choices for the impact of $S(x)$ on $L(x,t)$ and $R(x,t)$ are conceivable, as in our derivation below we only assume that the bias equals $\left[1\pm hS'(x,t)+O(h^3)\right]/2$. However the choice of terms $[1+S(x\pm h)-S(x)]/2$ is not suitable, since we do not allow $L(x,t)+R(x,t)>1$.

The probabilities L, R and C thus define a dispersal kernel

$$w(x,t;z)=L(x,t)\delta(z+h)+R(x,t)\delta(z-h)+C(x,t)\delta(z),$$

which is the probability distribution of a jump $z\in\{-h,+h,0\}$ given that the jump occurs at time t with base point x. If all particles with density $\rho(x,t)$ are displaced according to $w(x,t;z)$, this results in the density

$$\begin{aligned}\mathcal{W}\rho(x,t)&:=\int_{z\in\mathbb{R}}\rho(x-z,t)w(x-z,t;z)\,dz\\&=R(x-h,t)\rho(x-h,t)+L(x+h,t)\rho(x+h,t)+C(x,t)\rho(x,t).\end{aligned}$$

The total escape flux from site x at time t is

$$\begin{aligned}i(x,t)&:=\int_0^\infty[\alpha(x,t)+\gamma(x,\tau)]\xi(x,t,\tau)\,d\tau\\&=\alpha(x,t)\rho(x,t)+\int_0^\infty\gamma(x,\tau)\xi(x,t,\tau)\,d\tau.\end{aligned}\tag{16}$$

Since all jumps are of nearest neighbor type, the quantity

$$J\left(x+\frac{h}{2},t\right):=R(x,t)i(x,t)h-L(x+h,t)i(x+h,t)h$$

is readily interpreted as the net flux of particles from lattice point x to lattice point $x+h$. Moreover, one confirms that

$$h^{-1}\left[J\left(x+\frac{h}{2},t\right)-J\left(x-\frac{h}{2},t\right)\right]=-\mathcal{W}i(x,t)+i(x,t).\tag{17}$$

By definition of $J(x,t)$ and conservation of mass, the above left-hand side equals $-\partial\rho(x,t)/\partial t$. Assuming that the right-hand side admits a valid Taylor expansion in the x-variable, we can write

$$\frac{\partial\rho(x,t)}{\partial t}=h^2\mathcal{A}i(x,t)+\mathcal{O}(h^3),\tag{18}$$

where $\mathcal{A}$ is the transport operator

$$\begin{aligned}\mathcal{A}i&=\frac{1}{2}\frac{\partial}{\partial x}\left[a(\rho)q(\rho)\left[\frac{\partial}{\partial x}i+i\left(\frac{3}{a(\rho)}\frac{\partial a(\rho)}{\partial x}-\frac{1}{q(\rho)}\frac{\partial q(\rho)}{\partial x}-2\frac{\partial S}{\partial x}\right)\right]\right]\\&=\frac{1}{2}\frac{\partial}{\partial x}\left[a(\rho)q(\rho)\left[\frac{\partial}{\partial x}i+i\frac{\partial}{\partial x}\left(\log\frac{a(\rho)^3}{q(\rho)}-2S\right)\right]\right]\end{aligned}\tag{19}$$

acting on the x-variable only (see Appendix). Recall the conservation of mass equation $\partial\rho/\partial t+\partial J/\partial x=0$; the above equation then allows for an interpretation of the flux $J(x,t)$ as the decomposition into four components: (i) the local gradient of the escape rate $i(x)$, (ii) adhesion effects due to $a(\rho)$, (iii) crowding effects due to $q(\rho)$ and (iv) the external signal $S(x,t)$. Eq. (19) will serve as the starting point for non-linear transport equations, of both Markovian and time-fractional type, as we show in the following two examples (it remains to express $i(x,t)$ in terms of $\rho(x,t)$).

4.1. Markovian nonlinear transport equations

If the residence time based escape rate $\gamma(x,\tau)$ vanishes and if $\alpha(x,t)=2\lambda_0$, (16) reads

$$i(x,t)=2\lambda_0\rho(x,t).\tag{20}$$

Now applying the diffusive scaling limit (3), we reproduce the standard Markovian transport equation (4). In particular, the flux equals

$$J(x,t)=-D_0a(\rho)q(\rho)\left[\frac{\partial\rho}{\partial x}+\rho\frac{\partial}{\partial x}\left(\log\frac{a(\rho)^3}{q(\rho)}-2S\right)\right],$$

where $D_0=h^2\lambda_0$.

Table 1
Waiting time distributions and their corresponding renewal measure densities. The Mittag–Leffler density assumes $0<\mu<1$ and decays as $t\to\infty$, according to a power-law $\propto t^{-1-\mu}$. The renewal measure density for the mixture of exponentials is $m_E(t)=b_1b_2/b_1a_2+b_2a_1+((b_1-b_2)^2a_1a_2)/b_1a_2+b_2a_1\times e^{-(b_1a_2+b_2a_1)t}$ (Asmussen, 2003, Problem III.5.2).

	$\psi(t)$	$\hat{\psi}(\lambda)$	$m(t)$
Exponential	$\tau_0^{-1}\exp(-t/\tau_0)$	$(1+\tau_0\lambda)^{-1}$	$1/\tau_0$
Mittag–Leffler	$-\frac{\partial}{\partial t}E_\mu\left[-\left(\frac{t}{\tau_0}\right)^\mu\right]$	$\frac{1}{1+(\tau_0\lambda)^\mu}$	$t^{\mu-1}\tau_0^{-\mu}/\Gamma(\mu)$
Gamma	$\frac{t\exp(-t/\tau_0)}{\tau_0^{-2}}$	$(1+\tau_0\lambda)^{-2}$	$\frac{1-\exp(-2t/\tau_0)}{2\tau_0}$
Mixed exp.	$a_1e^{-b_1t}+a_2e^{-b_2t}$	$\frac{a_1}{c_1+\lambda}+\frac{a_2}{c_2+\lambda}$	$m_E(t)$

4.2. Fractional nonlinear transport equations

Suppose now that $\alpha(x,t)$ vanishes and that the residence time based escape rate is given by (13), where

$$\Psi(x,\tau)=E_\mu\left[-(t/\tau_0)^\mu\right]$$

and E_μ denotes the Mittag–Leffler function (also see Table 1). Then one has

$$i(x,t)=\tau_0^{-\mu}\mathcal{D}_t^{1-\mu}\rho(x,t) \tag{21}$$

(Fedotov and Falconer, 2012, Eq. (30)). Applying the anomalous scaling limit (8), the anomalous transport equation then equals

$$\frac{\partial\rho(x,t)}{\partial t}=\frac{\partial}{\partial x}\left[D_\mu a(\rho)q(\rho)\left[\frac{\partial}{\partial x}\left(\mathcal{D}_t^{1-\mu}\rho\right)+\left(\mathcal{D}_t^{1-\mu}\rho\right)\frac{\partial}{\partial x}\left(\log\frac{a(\rho)^3}{q(\rho)}-2S\right)\right]\right],$$

$$\rho(x,0)=\rho_0(x),$$

with general adhesion and volume filling effects $a(\rho(x,t))$ and $q(\rho(x,t))$, external signal $S(x,t)$ and anomalous diffusion coefficient $D_\mu=h^2/2\tau_0^\mu$. For instance, setting $q(\rho)\equiv1$ (no volume filling effect) and $a(\rho)=1-m\rho$ with adhesion parameter m yields the fractional adhesion–diffusion equation:

$$\frac{\partial\rho}{\partial t}=\frac{\partial}{\partial x}\left[D_\mu(1-m\rho)\left[\frac{\partial}{\partial x}\left(\mathcal{D}_t^{1-\mu}\rho\right)+\left(\mathcal{D}_t^{1-\mu}\rho\right)\frac{\partial}{\partial x}(3\log(1-m\rho)-2S)\right]\right],$$

$$\rho(x,0)=\rho_0(x).$$

4.3. Nonlinear transport equations with general memory effects

In the remainder of this section, we derive transport equations as (20) and (21) in the case where internal and external effects $\gamma(x,\tau)$ and $\alpha(x,t)$ coexist. This will provide models in which intermediate-time asymptotics are subdiffusive, and long-time asymptotics are diffusive, see below. We begin by solving the PDE (15). For abbreviation, we introduce the dimensionless functions:

$$\Psi(x,t)=\exp\left(-\int_0^t\gamma(x,s)\,ds\right),\quad \Phi(x,t)=\exp\left(-\int_0^t\alpha(x,s)\,ds\right)$$

which take values in $(0,1]$. They may be interpreted as the probability that in the time interval $[0,t]$ a particle has not escaped from x due to an internal (resp. external) effect. (Note that the above is consistent with (13).) Assuming independence of the two effects, the probability that a particle does not jump in the time interval $[0,t]$ is then $\Psi(x,t)\Phi(x,t)$. We also note that

$$\psi(x,t):=-\frac{\partial}{\partial t}\Psi(x,t)=\gamma(x,t)\Psi(x,t),\quad t>0$$

is a probability density. We write

$$j(x,t):=\xi(x,0,t) \tag{22}$$

for the flux of particles arriving at x. A heuristic explanation for this interpretation is as follows: The collection of particles at x at time t whose residence time lies in the interval $(0,\varepsilon)$ have arrived there during the time interval $(t-\varepsilon,t)$ and they have not escaped during this interval. This balance equation reads

$$\int_0^\varepsilon\xi(x,\tau,t)\,d\tau=\int_{t-\varepsilon}^t j(x,s)\left[1-\int_s^t\alpha(x,r)\,dr-\int_s^t\gamma(x,r-s)\,dr+o(\varepsilon)\right]ds.$$

Now if we divide by ε and let $\varepsilon\downarrow0$ we arrive at (22).

For simplicity, we assume that the initial structured density equals $\xi(x,\tau,0)=\rho_0(x)\delta(\tau)$, i.e. at time 0 all particles have residence time 0 and their spatial distribution is $\rho_0(x)$. Then we find via the method of characteristics (see appendix)

$$\xi(x,\tau,t)=\Psi(x,\tau)\frac{\Phi(x,t)}{\Phi(x,t-\tau)}j(x,t-\tau)+\frac{\Psi(x,\tau)}{\Psi(x,\tau-t)}\Phi(x,t)\rho_0(x)\delta(\tau-t). \tag{23}$$

Substituting this into (12) and (16) gives the equation pair

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

$$i(x,t) = \alpha(x,t)\rho(x,t) + \int_0^t \psi(x,\tau)\frac{\Phi(x,t)}{\Phi(x,t-\tau)} j(x,t-\tau)\, d\tau + \psi(x,t)\Phi(x,t)\rho_0(x).$$

We rewrite this in convenient shorthand notation:

$$\frac{\rho}{\Phi} = \Psi *_t \frac{j}{\Phi} + \Psi\rho_0 \tag{24}$$

$$\frac{i}{\Phi} = \frac{\alpha\rho}{\Phi} + \psi *_t \frac{j}{\Phi} + \psi\rho_0 \tag{25}$$

The symbol $*_t$ denotes a convolution in the time-variable t (but not in the space variable x). In order to derive an analytic form for the escape rate $i(x,t)$, we introduce the function $m(x,t)$, defined via its Laplace transform in t as

$$\hat{m}(x,\lambda) = \int_0^\infty e^{-\lambda t} m(x,t)\, dt = \frac{\hat{\psi}(x,\lambda)}{1-\hat{\psi}(x,\lambda)} \tag{26}$$

for any fixed x. This function is well-known in renewal theory as the *renewal measure density*[1] associated with the probability density $t \mapsto \psi(x,t)$ (Feller, 1966). Its interpretation is that $\int_a^b m(x,t)\, dt$ equals the expected number of events (renewals) in the time interval $(a,b]$, where the inter-arrival time of events is i.i.d. distributed with density $t \mapsto \psi(x,t)$. Two generic cases appear: if $\psi(x,t)$ has finite first moment $\mu_1 := \int_0^\infty t\psi(x,t)\, dt$, then for large times the rate of jumps evens out and approaches the value $1/\mu_1$. In the case of a diverging first moment, i.e. $\mu_1 = \infty$, very long waiting times tend to occur, which means that for very late times the rate of jumps decays to 0. Four examples are collected in Table 1. Now we can use Laplace transforms and the convolution formula to show that (24) is equivalent to

$$\frac{\partial}{\partial t}\left(m *_t \frac{\rho}{\Phi}\right) = \psi *_t \frac{j}{\Phi} + \psi\rho_0. \tag{27}$$

Indeed, the Laplace transform of (24) is

$$\left(\frac{\rho}{\Phi}\right)^{\wedge} = \hat{\Psi}\left(\frac{j}{\Phi}\right)^{\wedge} + \hat{\Psi}\rho_0$$

whereas the Laplace transform of (27) is

$$\lambda\hat{m}\left(\frac{\rho}{\Phi}\right)_t = \hat{\psi}\left(\frac{j}{\Phi}\right)_t + \hat{\psi}\rho_0,$$

and the latter two equations are seen to be equivalent due to (26) and $1-\lambda\hat{\Psi} = \hat{\psi}$.

Using (25) then gives the result

$$i = \alpha\rho + \Phi\frac{\partial}{\partial t}\left(\frac{\rho}{\Phi} *_t m\right)$$

or, in detailed notation,

$$i(x,t) = \alpha(x,t)\rho(x,t) + \Phi(x,t)\frac{\partial}{\partial t}\int_0^t \frac{\rho(x,s)}{\Phi(x,s)} m(t-s)\, ds, \tag{28}$$

where $\Phi(x,t) = \exp\left(-\int_0^t \alpha(x,s)\, ds\right)$.

The generalised Master equation takes the form:

$$\frac{\partial\rho(x,t)}{\partial t} = \frac{h^2}{2}\frac{\partial}{\partial x}\left[a(\rho)q(\rho)\left[\frac{\partial i}{\partial x} + i\left(\frac{3}{a(\rho)}\frac{\partial a(\rho)}{\partial x} - \frac{1}{q(\rho)}\frac{\partial q(\rho)}{\partial x} - 2\frac{\partial S}{\partial x}\right)\right]\right] + \mathcal{O}(h^3),$$

where as above $a(\rho(x,t))$ describes the adhesion effect, $q(\rho(x,t))$ describes the volume filling effect and $S(x,t)$ is an external signal. Let us consider a few examples illustrating the above equation. If we set $q(\rho) \equiv 1$ (no volume filling effect), $S = 0$ and $a(\rho) = 1 - m\rho$ with adhesion parameter m, this yields the following master equation:

$$\frac{\partial\rho(x,t)}{\partial t} = \frac{h^2}{2}\frac{\partial}{\partial x}\left[(1-m\rho)\left[\frac{\partial i}{\partial x} - i\left(\frac{3m}{1-m\rho}\frac{\partial\rho}{\partial x}\right)\right]\right] + \mathcal{O}(h^3)$$

with

$$i(x,t) = \alpha(x,t)\rho(x,t) + e^{-\int_0^t \alpha(x,s)\, ds}\frac{\partial}{\partial t}\int_0^t e^{\int_0^s \alpha(x,u)\, du}\rho(x,s)m(t-s)\, ds.$$

In the anomalous case, when the renewal measure density is

$$m(t) = t^{\mu(x)-1}\tau_0^{-\mu(x)}/\Gamma(\mu(x)),$$

[1] Although the renewal measure has an atom (singularity) at 0, the renewal measure density $t \mapsto m(x,t)$ does not have a delta function term at 0.

we can rewrite the last expression for the total escape rate i in terms of the fractional derivative $\mathcal{D}_t^{1-\mu(x)}$:

$$i(x,t)=\alpha(x,t)\rho(x,t)+\tau_0^{-\mu(x)}e^{-\int_0^t \alpha(x,s)\,ds}\,\mathcal{D}_t^{1-\mu(x)}\left[e^{\int_0^t \alpha(x,u)\,du}\rho(x,t)\right]. \tag{29}$$

Eq. (29) is the sought generalisation of Eqs. (20) and (21). The Markovian situation (20) may be recovered by setting $\alpha=2\lambda_0$ and $\gamma=0$, or equivalently by setting $\alpha=0$ and $\gamma=2\lambda_0$. The fractional situation (21) results if $\alpha=0$ and if $\gamma(x,\tau)$ is as in (13), where $\psi(x,\tau)$ at scale τ_0 is Mittag–Leffler (see Table 1).

Assume now the fractional situation as above, with the modification that $\alpha(x,t)$ be non-zero, finite and independent of the time scale τ_0. Taking the subdiffusive scaling limit (8) in Eq. (18) together with $\alpha\tau_0\ll 1$ results in the subdiffusive fractional evolution equation:

$$\frac{\partial\rho(x,t)}{\partial t}=2\mathcal{A}\left[D_\mu(x)\Phi(x,t)\mathcal{D}_t^{1-\mu(x)}\frac{\rho(x,t)}{\Phi(x,t)}\right] \tag{30}$$

where the transport operator $\mathcal{A}$ is defined in (19). One can write this equation in the form:

$$\begin{aligned}\frac{\partial\rho(x,t)}{\partial t}=&\frac{\partial}{\partial x}\left\{D_\mu(x)a(\rho)q(\rho)\frac{\partial}{\partial x}\left[\Phi(x,t)\mathcal{D}_t^{1-\mu(x)}\frac{\rho(x,t)}{\Phi(x,t)}\right]\right\}\\&+\frac{\partial}{\partial x}\left\{D_\mu(x)a(\rho)q(\rho)\left[\Phi(x,t)\mathcal{D}_t^{1-\mu}\frac{\rho(x,t)}{\Phi(x,t)}\right]\left(\frac{3}{a(\rho)}\frac{\partial a(\rho)}{\partial x}-\frac{1}{q(\rho)}\frac{\partial q(\rho)}{\partial x}-2\frac{\partial S}{\partial x}\right)\right\}\end{aligned}$$

We note however that the PDE for the stationary solution has a much simpler form (32).

5. Aggregation phenomena in nonlinear subdiffusive systems

The purpose of this section is to analyse aggregation phenomena in subdiffusive systems, which appear to be particularly intricate. Fedotov and Falconer (2012) have shown that a simple spatial variation in the anomalous exponent μ (i.e. the power law exponent of the waiting times) can cause the stationary profile to collapse, with all particles very slowly aggregating at the one point where μ attains its minimum. In a physical system, the particle count at any location will of course remain bounded if particles have positive volumes, and such behaviour would be deemed unphysical. With the developed theory, this "volume exclusion effect" can be taken into account for subdiffusive aggregation.

5.1. Stationary structured density

We look for necessary conditions for the structured density to yield a stationary state. We assume that $t\mapsto\xi(x,\tau,t)$ is constant for every (x,τ); in this case the dependence on t can be dropped, and we write $\xi_{st}(x,\tau)$ for the stationary structured density. It follows that the density ρ and escape flux i from (12) and (16) are also stationary, and similarly we define $\rho_{st}(x)$ and $i_{st}(x)$. Further assuming that $\alpha(x,t)=\alpha(x)$ does not depend on t, Eq. (15) may now be reinterpreted as

$$\frac{\partial}{\partial\tau}\xi_{st}(x,\tau)=-[\alpha(x)+\gamma(x,\tau)]\xi_{st}(x,\tau),$$

with solution

$$\xi_{st}(x,\tau)=\xi_{st}(x,0)\exp(-\tau[\alpha(x)])\Psi(x,\tau). \tag{31}$$

At equilibrium, the net flux $J(x,t)$ vanishes identically. Eqs. (22) and (17) then imply $\xi_{st}(x,0)=j_{st}(x)=\mathcal{W}i_{st}(x)=i_{st}(x)$, and hence

$$\xi_{st}(x,\tau)=i_{st}(x)\exp(-\tau[\alpha(x)])\Psi(x,\tau).$$

and integration over $\tau\in(0,\infty)$ yields

$$\rho_{st}(x)=i_{st}(x)\hat{\Psi}(x,\alpha(x))$$

where $\lambda\mapsto\hat{\Psi}(x,\lambda)$ denotes the Laplace transform of $\tau\mapsto\Psi(x,\tau)$. We note that $\Psi(x,\alpha(x))$ equals the expected value of the random "waiting time" T whose tail function $\mathbb{P}(T>\tau)$ equals $\Psi(x,\tau)e^{-\tau\alpha(x)}$. This is a kind of *exponential tempering* with tempering parameter $\alpha(x)$, a modification which ensures that all moments of a random waiting time are finite. This is similar, but not identical to the tempering studied e.g. by Meerschaert et al. (2008) and Stanislavsky et al. (2008), where the factor $e^{-\tau\alpha(x)}$ is applied to $\psi(x,\tau)$ (and not $\Psi(x,\tau)$). Finally, according to (17), equilibrium holds if

$$\mathcal{W}\left[\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}\right]-\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}=0,$$

which in the continuum limit becomes the aggregation equation:

$$\mathcal{A}\left[\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}\right]=0, \tag{32}$$

where the nonlinear transport operator $\mathcal{A}$ is defined in (19). This equation is one of the main results of this paper. One can also write

$$\frac{\partial}{\partial x}\left[a(\rho_{st})q(\rho_{st})\left[\frac{\partial}{\partial x}\left[\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}\right]+\left[\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}\right]\frac{\partial}{\partial x}\left(\log\frac{a(\rho_{st})^3}{q(\rho_{st})}+2S\right)\right]\right]=0.$$

Apart from the transport operator $\mathcal{A}$ the stationary equation (32) involves a very important function $\hat{\Psi}(x,\alpha(x))$. Since

$$\hat{\Psi}(x,\lambda)=\frac{1-\hat{\psi}(x,\lambda)}{\lambda},$$

for the anomalous subdiffusive case with

$$\hat{\psi}(x,\lambda)=\frac{1}{1+(\tau_0\lambda)^{\mu(x)}},$$

we obtain

$$\frac{\rho_{st}(x)}{\hat{\Psi}(x,\alpha(x))}=\alpha(x)\rho_{st}(x)+\frac{\alpha(x)\rho_{st}(x)}{(\tau_0\alpha(x))^{\mu(x)}}. \tag{33}$$

When $\tau_0\alpha(x)$ is small, the second term becomes dominant and determines the stationary profile $\rho_{st}(x)$ as a solution of the equation:

$$\mathcal{A}\left[\frac{\alpha(x)\rho_{st}(x)}{(\tau_0\alpha(x))^{\mu(x)}}\right]=0. \tag{34}$$

We should note that Eq. (32) for the stationary distribution $\rho_{st}(x)$ cannot be obtained by simply equating the RHS of the non-stationary master equation:

$$\frac{\partial\rho(x,t)}{\partial t}=h^2\mathcal{A}\left[\alpha(x)\rho(x,t)+e^{-\alpha(x)t}\frac{\partial}{\partial t}\int_0^t e^{\alpha(x)s}\rho(x,s)m(t-s)\,ds\right]$$

to 0.

Let us illustrate our general results by considering how nonlinear volume filling effects interact with tempered anomalous aggregation. On the unit interval $x\in[0,1]$, we find the stationary solutions to Eq. (32) supposing that the anomalous exponent is distributed as $\mu(x)=0.7+0.2x$, that the external signal equals $S(x)=2x$ and that volume filling and adhesion effects are absent. In the fractional case ($\alpha=0$, see (21)), it is known that in the long time limit all particles accumulate at the minimum point of the anomalous exponent $\mu(x)$, independently of the initial configuration of the system (Fedotov and Falconer, 2012). That is, the stationary density is singular, and in our case equals the delta function $\delta(x)$ at 0. We illustrate this "anomalous aggregation phenomenon" again in Fig. 1, but in a different way: We first find the stationary solution $\rho_{st}(x)$ in the intermediate case (29) with $\alpha>0$, which interpolates between fractional and Markovian dynamics. We then let the parameter α tend to 0, which means that $\rho_{st}(x)$ will approximate the stationary solution in the fractional case. (It should be noted that although the stationary distributions seemingly converge as $\alpha\downarrow 0$, the case $\alpha=0$ is inherently different from the case $\alpha>0$, because the stationary structured density $\xi_{st}(x,\tau)$ (31) only exists in the latter case.)

We compute $\rho_{st}(x)$ in the intermediate case by solving (32) with a nonlinear differential equation solver using Mathematica (see Appendix C). We do this for shrinking values of the parameter α and indeed observe that $\rho_{st}(x)$ approaches, albeit slowly, the delta function; see Fig. 1. This occurs in spite of an external signal $S(x)=2x$ which pushes the particles towards the right. We hence claim that anomalous aggregation is stronger than any (bounded) external signal $S(x)$.

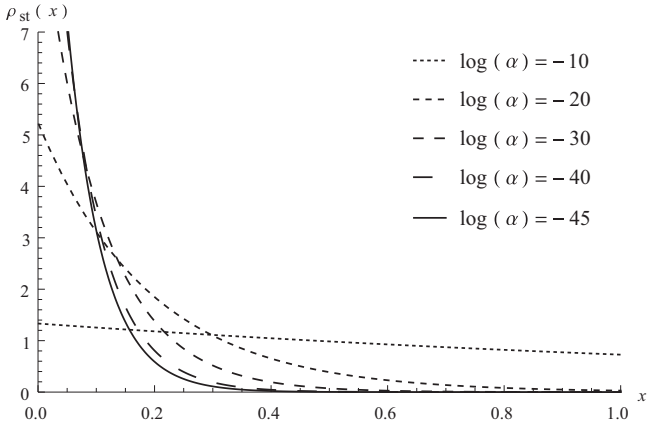

Fig. 1. Aggregation of subdiffusive cells, with $\mu(x)=0.7+0.2x$, $S(x)=2x$, $\alpha(\rho)=1$ and $q(\rho)=1$. As $\alpha\downarrow 0$, the dynamics approach fractional dynamics.

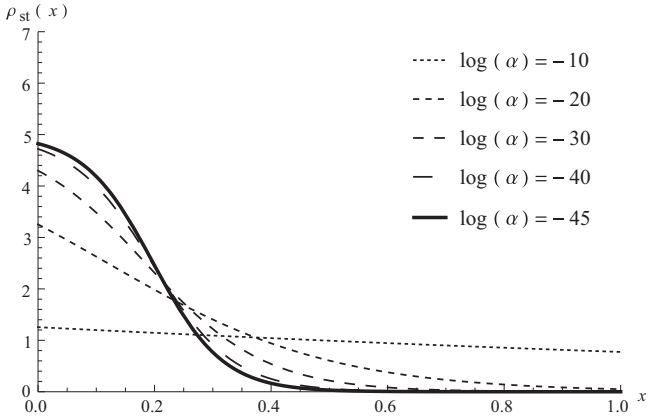

Fig. 2. A system identical to Fig. 1, except with a nonlinear volume filling effect $q(\rho)=1-0.2\rho$. Anomalous aggregation is now visibly limited.

In Fig. 2 we consider the same system, but with a volume filling effect $q(\rho)=1-0.2\rho$. Again, as $\alpha\downarrow 0$, the stationary solutions seem to converge. The limiting $\rho_{st}(x)$ however stays bounded below 5 as $q(5)=0$. We hence claim that nonlinear volume filling effects may effectively limit anomalous aggregation.

6. Conclusions

The main challenge of this paper has been to implement nonlinear effects such as volume filling and adhesion into fractional subdiffusive transport. Starting with microscopic random walk models, we have derived *non-Markovian and nonlinear* master equations for the mean concentration of random walkers (cells, bacteria, etc.). We have taken into account anomalous trapping, non-stationary tempering and nonlinear reactions together with nonlinear volume filling and adhesion effects. We have shown that in the subdiffusive case these equations involve a nontrivial combination of the nonlinear terms together with fractional derivatives. The main point is that these equations cannot be easily written phenomenologically. This is due to non-Markovian character of transport process involving anomalous trapping together with tempering. It turns out that in the long time limit these equations take a relatively simple form without fractional time derivatives which allows to find the stationary solutions and thereby to study aggregation phenomena. We have shown that nonlinear volume filling effects limit anomalous aggregation in subdiffusive transport systems with spatially nonuniform anomalous exponent.

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Appendix A. Taylor expansions

For the Taylor expansion of (1) we use the following mathematica input:

```
(T^+)[x_,h_]:=(1-(S[x+h]-S[x]))q[\[Rho][x+h]]a[\[Rho][x-h]]

(T^-)[x_,h_]:=(1-(S[x-h]-S[x]))q[\[Rho][x-h]]a[\[Rho][x+h]]

A[\[Rho]_,x_,h_]:=(T^+)[x-h,h]\[Rho][x-h]+(T^-)[x+h,h]\[Rho][x+h]
                  -((T^-)[x,h]+(T^+)[x,h])\[Rho][x]

Series[A[\[Rho],x,h],{h,0,2}];

Normal[%]/h^2

Integrate[%,x]

Collect[%,\[Rho]'[x]]
```

This yields the output

$$3\rho q(\rho)\rho' a'(\rho)-\rho a(\rho)\rho' q'(\rho)+2\rho a(\rho)q(\rho)S'+a(\rho)q(\rho)\rho' \tag{A.1}$$

from which we read off (4).

For the Taylor expansion of the right-hand side of (17), we use

```
L[x_,h_]:=q[\[Rho][x-h]]a[\[Rho][x+h]] (1/2-(S[x+h]-S[x-h])/4)

R[x_,h_]:=q[\[Rho][x+h]]a[\[Rho][x-h]] (1/2+(S[x+h]-S[x-h])/4)

c[x_,h_]:=1-L[x,h]-R[x,h]

W[i_,x_,h_]:=R[x-h,h]i[x-h]+L[x+h,h]i[x+h]+c[x,h]i[x]

Normal[Series[W[i,x,h]-i[x],{h,0,2}]];

Integrate[%,x];

Expand[%/(h^2/2 a[\[Rho][x]]q[\[Rho][x]])];

Collect[%,i[x]]
```

which yields the output

$$i(x)\left(\frac{3\rho'(x)a'(\rho(x))}{a(\rho(x))}-\frac{\rho'(x)q'(\rho(x))}{q(\rho(x))}-2S'(x)\right)+i'(x)$$

and we can read off (19).

Appendix B. The method of characteristics

We transform the PDE (15) on the domain $x \in \mathbb{R}$, $t > 0$, $\tau > 0$ into an ODE along the characteristics

$$u(s) = (x, \tau, t) - s(0, 1, 1), \quad s \in [0, \min\{\tau, t\}]$$

We write ξ_τ and ξ_t for the partial derivatives of $\xi(\tau, t)$ with respect to the first resp. second argument, and find

$$\frac{d}{ds}\xi(u(s)) = -\xi_\tau(u(s)) - \xi_t(u(s)) = [\alpha(u(s)) + \gamma(u(s))]\xi(u(s))$$

where by slight abuse of notation we let $\alpha(x, \tau, t) := \alpha(x, t)$ and $\gamma(x, \tau, t) := \gamma(x, \tau)$. This solves to

$$\xi(u(s)) = C \exp\left(\int_0^s [\alpha(u(y)) + \gamma(u(y))]\, dy\right)$$

and setting $s = 0$ yields the constant $C = \xi(x, \tau, t)$. If $\tau \le t$, then

$$\xi(x, 0, t-\tau) = \xi(u(\tau)) = \xi(x, \tau, t) \exp\left(\int_0^\tau [\alpha(x, t-y) + \gamma(x, \tau-y)]\, dy\right),$$

and if $\tau \ge t$, then

$$\xi(x, \tau-t, 0) = \xi(u(t)) = \xi(x, \tau, t) \exp\left(\int_0^t [\alpha(x, t-y) + \gamma(x, \tau-y)]\, dy\right).$$

A change of integration variable together with the definition variable together with the definition of $\Phi(x, t)$ and $\Psi(x, \tau)$ then yields (23).

Appendix C. Stationary distributions

The following Mathematica code generates Fig. 1:

```
\[Mu][x_]:=0.7+0.2x

S[x_]:=2x

\[Alpha][\[Rho]_]:={10^-10,10^-20,10^-30,10^-40,10^-45}

q[\[Rho]_]:=1

a[\[Rho]_]:=1

mass=1;

J[i_,x_]:=-a[\[Rho][x]] q[\[Rho][x]](
            D[i,x]+i D[Log[a[\[Rho][x]]^3/q[\[Rho][x]]]-2 S[x],x])

\[Tau][x_]=10^0;

MLtailL[\[Mu]_,s_,\[Tau]_,x_]:=s^(\[Mu][x]-1)
            /(\[Tau][x]^-\[Mu][x]+s^\[Mu][x])

i[x]=\[Rho][x]/MLtailL[\[Mu],\[Alpha][\[Rho][x]],\[Tau],x];

LHS = J[i[x],x];

DElist=Table[Extract[%,i]==0,{i,5}];

Table[NDSolve[{Extract[DElist,i], U'[x]==\[Rho][x],U[0]==0,
      U[1]==mass},{\[Rho],U},{x,0,1}],{i,5}];

nonmarkovsol=\[Rho][x]/.%;

Needs["PlotLegends`"]

Plot[nonmarkovsol,{x,0,1},PlotRange->{{0,1},{0,7}},
     AxesLabel->{x,Subscript[\[Rho], st][x]},
     PlotStyle->{{Black,Dashing[Tiny]},{Black,Dashing[Small]},
     {Black,Dashing[Medium]},{Black,Dashing[Large]},
{Black,Thick}},PlotLegends->Placed[{
"log(\[Alpha])=-10","log(\[Alpha])=-20","log(\[Alpha])=-30",
"log(\[Alpha])=-40","log(\[Alpha])=-45"},{0.8,0.7}]]
```

note that the Laplace transformed Mittag Leffler function `MLtailL` is chosen according to Eq. (28) in Fedotov and Falconer (2012):

$$\hat{\Psi}(x,s) = \frac{s^{\mu(x)-1}}{\tau(x)^{-\mu(x)} + s^{\mu(x)}}$$

If Line 4 of the code is replaced by

```
q[\[Rho]_]:=1-0.2 \[Rho]
```

then the volume filling effect is set to carrying capacity $5 = 1/0.2$, and Fig. 2 results.

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