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FRACTIONAL ORDER COMPARTMENT MODELS*

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Abstract. Compartment models have been used to describe the time evolution of a system undergoing reactions between populations in different compartments. The governing equations are a set of coupled ordinary differential equations. In recent years fractional order derivatives have been introduced in compartment models in an ad hoc way, replacing ordinary derivatives with fractional derivatives. This has been motivated by the utility of fractional derivatives in incorporating history effects, but the ad hoc inclusion can be problematic for flux balance. To overcome these problems we have derived fractional order compartment models from an underlying physical stochastic process. In general, our fractional compartment models differ from ad hoc fractional models and our derivation ensures that the fractional derivatives have a physical basis in our models. Some illustrative examples, drawn from epidemiology, pharmacokinetics, and in-host virus dynamics, are provided.

Key words. compartment models, fractional calculus, epidemiology, pharmacokinetics, stochastic models

AMS subject classifications. 34A08, 60G22, 60K40, 92C45, 92D30

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1. Introduction.

Compartment models are typically used to model a wide variety of phenomena, including epidemics [21], in-host pathogen dynamics [28], and pharmacokinetics of active substances in the human body [7, 10]. These models identify states of the system as compartments, for example, the population of individuals in a particular state of health (e.g., susceptible, infected, or removed), or the concentration of a drug in different parts of the body (e.g., lungs, liver, or blood).

In a standard compartment model the populations or concentrations of species are evolved through a set of coupled ordinary differential equations (ODEs). The model assumes that each compartment is well mixed with a homogeneous population. The coupling terms in the ODEs model interactions between populations in different compartments. These terms may, for example, be simple constant rate removal processes, or they may represent reactions between multiple populations. In some compartment models it is important to know when an individual entered a compartment. This leads to age structured integrodifferential models with applications to both pharmacokinetic [19, 15, 13] and epidemiology [22, 33]. For particular choices of kernels, these models can be formulated as fractional order differential equations [2].

In recent years there has been a proliferation of compartment models incorporating fractional derivatives. These include fractional epidemiological, susceptible, infected, removed (SIR) models [4, 5, 11, 12, 17, 18, 36], as well as fractional pharmacokinetic models [13, 15]. Typically, the fractional derivatives are incorporated in an ad hoc way by replacing integer order time derivatives with noninteger Caputo fractional derivatives. Whilst this may be mathematically interesting, and there is some motivation in incorporating history effects into the dynamics of compartment models,

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there is no a priori reason ad hoc fractional compartment models provide models of a physical system. If the fractional derivatives are not incorporated without care there can be difficulties in interpreting the units of constants [2] and conservation of mass may be violated [14]. There have been various attempts to address some of these difficulties [13, 15].

In this paper we derive a general framework for formulating fractional order compartment models by considering the governing equations from underlying stochastic processes. In the stochastic process models, particles enter a compartment, waiting for a random time, and then leave the compartment. The governing equations we derive describe the time evolution of an ensemble of particles that are undergoing this process. If the particles that leave one compartment always enter another compartment, the stochastic process is equivalent to a generalized continuous time random walk (CTRW) [26] with waiting times moderating transitions between compartments. As such, this formalism for the compartment model dynamics further extends the theory of CTRWs with reactions [20, 16, 35, 1, 27] and it generalizes recent work on fractional order SIR models [3, 2]. Fractional order compartment models are obtained when the waiting time in a compartment is governed by a non-Markovian process, whereby the probability of leaving the compartment is dependent on the length of time spent in the compartment. The fractional models can be formulated as age structured integrodifferential models; however, the formulation using fractional derivatives enables ready comparison with the growing literature on fractional order compartment models. Moreover, the age structured integrodifferential models can be derived from the underlying stochastic processes considered here.

The remainder of this paper is organized as follows: In section 2, starting with a stochastic process, we derive the governing equation for an ensemble of particles in a single compartment. This is reduced to a fractional order differential equation by considering a power-law distribution for the time that a particle remains in the compartment. Fractional order multicompartment models can be constructed by linking multiple fractional order single compartment models. Details on this are provided in section 3, and in section 4, where examples of fractional order multicompartment models are developed.

2. Single compartment model. In order to develop a general compartment model we first consider the dynamics of a single compartment. We derive a generalized master equation that describes the population of the compartment through time, and show the assumptions that lead to fractional dynamics. We will then combine multiple single compartments together to form the general model.

In a single compartment we consider an ensemble of particles. We assume that each member of this ensemble is undergoing a stochastic process in which the following occurs: they are created, they last for a random amount of time, and then they are removed from the compartment. In general, new particles can be created in this ensemble by a number of distinct creation processes, and similarly particles can be removed from the ensemble by a number of distinct removal processes.

We assume that the creation of the particles in the ensemble is governed by N_{C} distinct creation processes. In the mean field, the arrival flux of particles due to the ith creation process is labeled $\beta_i(t)$. The expected number of particles created in the compartment by the creation process between times t and $t + \delta t$ is $\beta_i(t)\delta t + o(\delta t)$.

The total arrival flux, $q(t)$, is the sum of the fluxes due to the creation processes,

$$q(t) = \sum_{i=1}^{N_C} \beta_i(t)\,. \tag{1}$$

A particle remains in a compartment until removed by one of the removal processes. We allow for an arbitrary number N_R of *Markovian* removal processes where the probability of a particle being removed from the ensemble at time t only depends on the state of the system at time t. For each individual Markovian removal process, the probability of surviving, from time t_0 to t, is $\Lambda_i(t, t_0)$. The probability of surviving all Markovian removal processes from time t_0 to t is then given by $\Theta(t, t_0) = \prod_{i=1}^{N_R} \Lambda_i(t, t_0)$. As a particle cannot be created and removed in the same instance, we have $\Theta(t_0, t_0) = 1$.

In general, the probability that a particle will be removed by the ith Markovian removal process in the time interval t to $t + \delta t$ will be $\lambda_i(t)\delta t + o(\delta t)$. This allows us to write the survival function as

$$\Theta(t, t_0) = \exp\left(-\int_{t_0}^{t} \omega(s) ds\right), \tag{2}$$

where

$$\omega(t) = \sum_{i=1}^{N_R} \lambda_i(t). \tag{3}$$

From this we can see that the Markovian survival function must obey the semigroup property,

$$\Theta(t, t_0) = \Theta(t, u)\Theta(u, t_0) \tag{4}$$

for any $t_0 \le u \le t$. And, furthermore,

$$\frac{\mathrm{d}\Theta(t, t_0)}{\mathrm{d}t} = -\omega(t)\Theta(t, t_0)\,. \tag{5}$$

We also include a *non-Markovian* removal process, where the probability that a particle is removed from the ensemble is dependent on the length of time since the particle entered the compartment, i.e., if the particle entered the compartment at time t_0 the process at time t will be dependent on the variable $t - t_0$. The survival probability for the non-Markovian removal process is given by $\Phi(t)$, and we require that $\Phi(0) = 1$. It can be expressed in terms of a waiting time density, $\phi(t)$,

$$\Phi(t) = 1 - \int_0^t \phi(u)\,\mathrm{d}u\,. \tag{6}$$

The waiting time density $\phi(t)$ gives the likelihood of waiting in a compartment for a length of time t having arrived at time 0. From (6) the derivative of the survival function is

$$\frac{d\Phi(t)}{dt} = -\phi(t). \tag{7}$$

For a particle to be in the compartment at time t, it must have entered the compartment at some earlier time t_0 and survived until time t. We assume that the

various removal processes are independent and hence can say that the probability of surviving all of the removal processes, given an arrival time of t_0, is given by $\Phi(t-t_0)\Theta(t,t_0)$. Thus the number of particles in the compartment at time t, $\rho(t)$, can be written

$$\rho(t) = \int_0^t \Phi(t-t_0)\Theta(t,t_0)\, q(t_0)\, \mathrm{d}t_0\,. \tag{8}$$

We have assumed that there are no particles in the compartment before time zero, i.e., $\rho(t) = 0$ for $t < 0$.

To obtain a differential equation that governs the dynamics of the number of particles in the compartment, we take the derivative of ρ. This can be done by using the Leibniz rule for differentiating under the integral sign provided that the integrand is continuous [1]. Here, we wish to consider the case where there can be an injection of flux into the compartment at time $t = 0$, with the flux a continuous function for $t > 0$. Thus we write,

$$q(t) = i_0\delta(t-0^+) + q^+(t), \tag{9}$$

where i_0 is the initial injection and $q^+(t)$ is right continuous at $t = 0$ and continuous for all $t > 0$. Substituting (9) into (8) we can write

$$\rho(t) = i_0\Phi(t)\Theta(t,0) + \int_0^t \Phi(t-t_0)\Theta(t,t_0)\, q^+(t_0)\, \mathrm{d}t_0\,, \tag{10}$$

this ensures that the integrand is continuous for continuous survival functions. Taking the derivative of (10), applying the Leibniz rule and using (5) and (7), we find that

$$\frac{\mathrm{d}\rho}{\mathrm{d}t} = q^+(t) - \omega(t)\rho(t) - F_\phi(t), \tag{11}$$

where we have defined

$$F_\phi(t) = \int_0^t \phi(t-t_0)\Theta(t,t_0)q(t_0)\, \mathrm{d}t_0\,, \tag{12}$$

which denotes the outgoing flux due to the non-Markovian process. The outgoing flux $F_\phi(t)$ can be expressed in terms of ρ by using Laplace transform techniques. We divide (8) and (12) by $\Theta(t,0)$, and using the semigroup property (4), we find

$$\frac{\rho(t)}{\Theta(t,0)} = \int_0^t \Phi(t-t_0)\, \frac{q(t_0)}{\Theta(t_0,0)}\, \mathrm{d}t_0, \tag{13}$$

$$\frac{F_\phi(t)}{\Theta(t,0)} = \int_0^t \phi(t-t_0)\, \frac{q(t_0)}{\Theta(t_0,0)}\, \mathrm{d}t_0\,. \tag{14}$$

As both these equations are convolutions, taking the Laplace transform gives

$$\mathcal{L}_t\left\{\frac{\rho(t)}{\Theta(t,0)}\right\} = \mathcal{L}_t\{\Phi(t)\}\,\mathcal{L}_t\left\{\frac{q(t)}{\Theta(t,0)}\right\}, \tag{15}$$

$$\mathcal{L}_t\left\{\frac{F_\phi(t)}{\Theta(t,0)}\right\} = \mathcal{L}_t\{\phi(t)\}\,\mathcal{L}_t\left\{\frac{q(t)}{\Theta(t,0)}\right\}. \tag{16}$$

Rearranging (15) and substituting into (16), we simplify this to

$$\mathcal{L}_t\left\{\frac{F_\phi(t)}{\Theta(t,0)}\right\} = \mathcal{L}_t\{K(t)\}\,\mathcal{L}_t\left\{\frac{\rho(t)}{\Theta(t,0)}\right\}, \tag{17}$$

where we have defined the *memory kernel* $K(t)$ as

$$\mathcal{L}_t\{K(t)\} = \frac{\mathcal{L}_t\{\phi(t)\}}{\mathcal{L}_t\{\Phi(t)\}}. \tag{18}$$

Taking the inverse Laplace transform of (17) allows us to express $F_\phi(t)$ as

$$F_\phi(t) = \int_0^t K(t-t_0)\,\Theta(t,t_0)\,\rho(t_0)\,\mathrm{d}t_0\,. \tag{19}$$

Using (19) in (11) we write

$$\frac{\mathrm{d}\rho}{\mathrm{d}t} = q^+(t) - \omega(t)\rho(t) - \int_0^t K(t-t_0)\Theta(t,t_0)\rho(t_0)\,\mathrm{d}t_0. \tag{20}$$

This is the governing equation for an ensemble of particles in a single compartment, where the particles are created and removed by underlying stochastic processes. This equation is true for an arbitrary waiting time distribution for the non-Markovian removal process. The formulation of (11) relies on the history of $q(t)$ while (20) relies on the history of $\rho(t)$. We shall show that, with the appropriate choice of a waiting time distribution, the convolution over the memory kernel may be expressed as a fractional derivative.

2.1. Relationship to age-structure models. Age-structured compartment models [21, 25, 9] allow for the dynamics of the system to depend on "system" time, as well as the length of time particles have been in a particular compartment. The governing evolution equation for age-structured dynamics can be shown to be equivalent to the governing evolution equation for an ensemble of particles in a single compartment, where the particles are created and removed by underlying stochastic processes. Moreover, the governing evolution equation for age-structured dynamics can be derived from the underlying stochastic process. In the derivations below we consider the simplification in which the arrival density $q(t)$ is continuous for $t \geq 0$.

2.1.1. Derivation of age-structured dynamics from an underlying stochastic process. Considering the underlying stochastic process for single compartment dynamics introduced in section 2 we define $\widehat{\rho}(t,a)$ as the number density of particles in the compartment at time t with age a. Similar to (8) this is given by

$$\widehat{\rho}(t,a) = \int_0^t \Phi(t-t_0)\Theta(t,t_0)q(t_0)\delta(t-t_0,a)\;dt_0, \tag{21}$$

where the delta function has been introduced to select those particles that arrived in the compartment at time t_0 and have age a at time t. The integral over all times t_0 leads to

$$\widehat{\rho}(t,a) = \Phi(a)\Theta(t,t-a)q(t-a). \tag{22}$$

The evolution equation for the age-structured number density can now be found by differentiating (21) with respect to time. This results in

$$\begin{aligned}\frac{\partial \widehat{\rho}(t,a)}{\partial t}+\frac{\partial \widehat{\rho}(t,a)}{\partial a} &= \frac{d\Phi(a)}{da}\Theta(t,t-a)q(t-a)\\ &\quad +\Phi(a)q(t-a)\left(\frac{\partial}{\partial t}\Theta(t,t-a)+\frac{\partial}{\partial a}\Theta(t,t-a)\right),\end{aligned} \tag{23}$$

where we have used the results that

$$\frac{dt}{dt}=\frac{da}{dt}=1$$

and

$$\frac{\partial}{\partial t}q(t-a)=-\frac{\partial}{\partial a}q(t-a).$$

In general, we can write the survival function as

$$\Phi(a)=\exp\left(-\int_0^a \gamma(s)\,ds\right), \tag{24}$$

where

$$\gamma(a)=\frac{\psi(t)}{\Phi(t)} \tag{25}$$

is the associated hazard rate dependent on age [3]. Furthermore, recalling

$$\Theta(t,t-a)=\exp\left(-\int_{t-a}^{t}\omega(s)ds\right), \tag{26}$$

it is a simple exercise to show that

$$\frac{\partial}{\partial t}\Theta(t,t-a)+\frac{\partial}{\partial a}\Theta(t,t-a)=-\omega(t)\Theta(t,t-a), \tag{27}$$

and using (24),

$$\frac{d\Phi}{da}=-\gamma(a)\Phi(a). \tag{28}$$

We can now substitute (28) and (27) into (23) and simplify, using (22), to obtain

$$\frac{\partial \widehat{\rho}(t,a)}{\partial t}+\frac{\partial \widehat{\rho}(t,a)}{\partial a}=-\gamma(a)\widehat{\rho}(t,a)-\omega(t)\widehat{\rho}(t,a), \tag{29}$$

which is the governing evolution equation for the number density of particles in an age-structured model. The terms on the right-hand side of this equation identify a non-Markovian removal process dependent on the age of the particle, with a corresponding rate $\gamma(a)$ and a Markovian removal process with rate $\omega(t)$. It also follows from (22), (24), and (26) that

$$\widehat{\rho}(t,0)=q(t), \tag{30}$$

so that the flux from creation processes, $q(t)$, are incorporated into the model as a boundary condition. The governing equation, (29), encompasses models such as Kermack and McKendrick's structured SIR model [21].

2.2. From age-structured dynamics to stochastic compartment dynamics. We can obtain the evolution equation for the stochastic compartment dynamics from the governing evolution equation for the number density of particles in an age-structured model. First, we note that

$$\rho(t) = \int_0^t \widehat{\rho}(t,a)\,da. \tag{31}$$

As $q(t)$ is continuous, $\widehat{\rho}(t,a)$ is also continuous and we can differentiate with respect to time using Leibniz rule to arrive at

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} = \int_0^t \frac{\partial\widehat{\rho}(t,a)}{\partial t}\mathrm{d}a + \widehat{\rho}(t,t). \tag{32}$$

Taking the integral of the evolution equation for age-structured dynamics, (29), with respect to a, we obtain,

$$\int_0^t \frac{\partial\widehat{\rho}(t,a)}{\partial t}\mathrm{d}a + \widehat{\rho}(t,t) - \widehat{\rho}(t,0) = -\omega(t)\int_0^t \widehat{\rho}(t,a)\,\mathrm{d}a - \int_0^t \gamma(a)\widehat{\rho}(t,a)\,\mathrm{d}a. \tag{33}$$

The results in (31), (32), and (33) can be combined to arrive at

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} - \widehat{\rho}(t,0) = -\omega(t)\rho(t) - \int_0^t \gamma(a)\widehat{\rho}(t,a)\,\mathrm{d}a. \tag{34}$$

We now replace $\widehat{\rho}(t,a)$ and $\widehat{\rho}(t,0)$ using (22) and (30), respectively. This results in

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} = q(t) - \omega(t)\rho(t) - \int_0^t \gamma(a)\Phi(a)\Theta(t,t-a)q(t-a)\,da, \tag{35}$$

and after a change of variables $a = t - t_0$,

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} = q(t) - \omega(t)\rho(t) - \int_0^t \gamma(t-t_0)\Phi(t-t_0)\Theta(t,t_0)q(t_0)\,\mathrm{d}t_0. \tag{36}$$

It follows from (25) that

$$\gamma(t-t_0)\Phi(t-t_0) = \phi(t-t_0), \tag{37}$$

so that we can use the same sequence of steps as (15)–(19) to arrive at the governing evolution equation for stochastic compartment dynamics

$$\frac{\mathrm{d}\rho(t)}{\mathrm{d}t} = q(t) - \omega(t)\rho(t) - \int_0^t K(t-t_0)\Theta(t,t_0)\rho(t_0)\,\mathrm{d}t_0, \tag{38}$$

which is equivalent to (20) in the case on continuous $q(t)$.

2.3. Fractional order single compartment model. The inclusion of a fractional derivative in the governing equations requires a power-law tailed waiting time distribution for the non-Markovian removal process. The use of such a distribution implies that the longer particles have been in a compartment the slower their rate of removal by this process. If there are no other removal processes, this is akin to particles becoming trapped in the compartment as the expected time until removal diverges. To obtain the fractional derivatives at all times, rather then simply asymptotically,

we will take the non-Markovain waiting time to be Mittag–Leffler distributed. This distribution has a power-law asymptotic decay [6] as $t \to \infty$, i.e., $\phi(t) \sim t^{-1-\alpha}$. The survival function of a Mittag–Leffler distribution is easily expressed in terms of a Mittag–Leffler function,

$$\Phi(t) = E_{\alpha,1}\left(-\left(\frac{t}{\tau}\right)^{\alpha}\right), \tag{39}$$

for an exponent $0 < \alpha \leq 1$, and time scale parameter $\tau > 0$. When $\alpha = 1$ the survival function reduces to an exponential, and the distribution to an exponential distribution. The two parameter Mittag–Leffler function is defined as

$$E_{\alpha,\beta}(t) = \sum_{k=0}^{\infty} \frac{t^k}{\Gamma(k\alpha + \beta)}. \tag{40}$$

Taking the Laplace transform of the Mittag–Leffler survival function from t to s gives

$$\mathcal{L}_t\{\Phi(t)\} = \frac{1}{s(1 + (\tau s)^{-\alpha})}. \tag{41}$$

The Laplace transform of the corresponding memory kernel K, calculated from (18), is

$$\mathcal{L}_t\{K(t)\} = \tau^{-\alpha} s^{1-\alpha}, \tag{42}$$

where we have used (6) and the fact that $\mathcal{L}_t\{\phi\} = 1 - s\mathcal{L}_t\{\Phi\}$.

Again using Laplace transforms, we can rewrite the outgoing flux due to the non-Markovian removal process, $F_\phi(t)$, as

$$\begin{aligned} F_\phi(t) &= \int_0^t K(t - t_0)\Theta(t, t_0)\, \rho(t_0)\, \mathrm{d}t_0 \\ &= \Theta(t, 0) \int_0^t K(t - t_0)\, \frac{\rho(t_0)}{\Theta(t_0, 0)}\, \mathrm{d}t_0 \\ &= \Theta(t, 0)\mathcal{L}_s^{-1}\left\{\tau^{-\alpha} s^{1-\alpha} \mathcal{L}_t\left\{\frac{\rho(t)}{\Theta(t, 0)}\right\}\right\}. \end{aligned} \tag{43}$$

This Laplace space representation of the flux can be related to a Riemann–Liouville fractional derivative, allowing us to write the governing equation as a fractional order differential equation.

A Riemann–Liouville fractional integral of order α, with $\alpha > 0$, is defined by

$${}_0\mathcal{D}_t^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t \frac{f(t_0)}{(t - t_0)^{1-\alpha}}\, \mathrm{d}t_0.$$

A Riemann–Liouville fractional derivative of order $1 - \alpha$, with $0 < \alpha \leq 1$, is defined by [29],

$${}_0\mathcal{D}_t^{1-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \frac{\mathrm{d}}{\mathrm{d}t} \int_0^t \frac{f(t_0)}{(t - t_0)^{1-\alpha}}\, \mathrm{d}t_0.$$

As this definition is a convolution, we can express the Laplace transform of the Riemann–Liouville fractional derivative as [24]

$$\mathcal{L}_t\{\, {}_0\mathcal{D}_t^{1-\alpha} f(t)\} = s^{1-\alpha}\mathcal{L}_t\{f(t)\} - \, {}_0\mathcal{D}_t^{-\alpha} f(t)|_0. \tag{44}$$

We assume that $f(t) = \frac{\rho(t)}{\Theta(t,0)}$ is continuous for $t \geq 0$ in which case we have [24],

$$ {}_0\mathcal{D}_t^{-\alpha} \left(\frac{\rho(t)}{\Theta(t,0)} \right) \Big|_0 = 0. \tag{45} $$

Using (44) we can simplify (43) to

$$ F_\phi(t) = \tau^{-\alpha} \Theta(t,0)\, {}_0\mathcal{D}_t^{1-\alpha} \left(\frac{\rho(t)}{\Theta(t,0)} \right). \tag{46} $$

Finally, substituting this into (20), we have

$$ \frac{\mathrm{d}\rho}{\mathrm{d}t} = q^+(t) - \omega(t)\rho(t) - \tau^{-\alpha} \Theta(t,0)\, {}_0\mathcal{D}_t^{1-\alpha} \left(\frac{\rho(t)}{\Theta(t,0)} \right). \tag{47} $$

This is the fractional order governing equation for a single compartment model. We will use this to construct general compartment models. It should be noted that the regularity condition given in (45) can be relaxed by considering a Grünwald–Letnikov derivative in place of the Riemann–Liouville derivative; see, for example, [35].

2.4. Equilibrium state analysis. The inclusion of the fractional derivative leads to some complication with the calculation of equilibrium states. This is due to the fact that the Riemann–Liouville derivate of a constant is nonzero. A further complication is the explicit t dependence in the $\Theta(t,0)$ function. As such, to find the equilibrium behavior of the model we need to consider the behavior of solutions as $t \to \infty$. The system approaches an equilibrium solution if the limit

$$ \lim_{t\to\infty} \rho(t) = \rho^* \tag{48} $$

exists. It should be noted that this limit may be dependent on the initial condition of the system, and hence multiple equilibrium solutions are possible. The first requirement for the existence of an equilibrium is that the rates associated with the Markovian removal processes and the incoming flux all approach a constant as $t \to \infty$, i.e.,

$$ \lim_{t\to\infty} \omega(t) = \omega^*, \tag{49} $$

$$ \lim_{t\to\infty} q^+(t) = q^*. \tag{50} $$

For simplicity we will consider the case where $\omega(t) = \omega^*$ for all time so that

$$ \Theta(t,0) = \exp\left(-\omega^* t\right). \tag{51} $$

Consider the limit of (47),

$$ \lim_{t\to\infty} \frac{\mathrm{d}\rho}{\mathrm{d}t} = \lim_{t\to\infty} \left(q^+(t) - \omega(t)\rho(t) - \tau^{-\alpha} \Theta(t,0)\, {}_0\mathcal{D}_t^{1-\alpha} \left(\frac{\rho(t)}{\Theta(t,0)} \right) \right). \tag{52} $$

From (48) the left-hand side is zero, and the first two terms on the right-hand side simplify trivially leaving

$$ 0 = q^* - \omega^* \rho^* - \tau^{-\alpha} \lim_{t\to\infty} \exp\left(-\omega^* t\right)\, {}_0\mathcal{D}_t^{1-\alpha} \left(\exp\left(\omega^* t\right) \rho(t) \right). \tag{53} $$

To evaluate the last term on the right-hand side of (53), we take the Laplace transform, and apply the well-known shift identity, as well as the binomial expansion, to yield

$$\begin{aligned}(54)\qquad &\mathcal{L}_t\left\{\exp\left(-\omega^* t\right)\,{}_0\mathcal{D}_t^{1-\alpha}\left(\exp\left(\omega^* t\right)\rho(t)\right)\right\}\\ &\quad=\mathcal{L}_t\left\{\,{}_0\mathcal{D}_t^{1-\alpha}\left(\exp\left(\omega^* t\right)\rho(t)\right);s+\omega^*\right\}\\ &\quad=(s+\omega^*)^{1-\alpha}\mathcal{L}_t\left\{\exp\left(\omega^* t\right)\rho(t);s+\omega^*\right\}\\ &\quad=(s+\omega^*)^{1-\alpha}\mathcal{L}_t\left\{\rho(t);s\right\}\\ &\quad=\mathcal{L}_t\left\{\rho(t)\right\}\left((\omega^*)^{1-\alpha}+(1-\alpha)(\omega^*)^{-\alpha}s+\mathcal{O}(s^2)\right).\end{aligned}$$

This equation can be inverted term-by-term due to the linearity of the Laplace transform. Hence we find

$$(55)\qquad \exp\left(-\omega^* t\right)\,{}_0\mathcal{D}_t^{1-\alpha}\left(\exp\left(\omega^* t\right)\rho(t)\right)=(\omega^*)^{1-\alpha}\rho(t)+(1-\alpha)(\omega^*)^{-\alpha}\frac{\mathrm{d}\rho}{\mathrm{d}t}+\mathcal{L}_s^{-1}\left\{\mathcal{O}(s^2)\right\}.$$

Thus in the limit we find

$$(56)\qquad \lim_{t\to\infty}\exp\left(-\omega^* t\right)\,{}_0\mathcal{D}_t^{1-\alpha}\left(\exp\left(\omega^* t\right)\rho(t)\right)=(\omega^*)^{1-\alpha}\rho^*.$$

Note that this is the same result as simply substituting a constant ρ^* in to the original expression, the key point that we have demonstrated being that the nonlocality of the fractional derivative is not unduly affected by preasymptotic behavior. Substituting (56) into (53) and taking the limit gives

$$(57)\qquad \rho^*=\frac{q^*}{\omega^*+\tau^{-\alpha}\left(\omega^*\right)^{1-\alpha}}.$$

Analysis of the stability of the equilibrium points is possible; however, this is difficult in a general setting. The specific example of a fractional order SIR model has previously been considered [3].

3. Fractional order multiple compartment model. In general, any number of fractional order single compartment models can be composed together to form a fractional order multiple compartment model. The exact nature of how the compartments are joined is system dependent. Consider a set of N compartments, the dynamics of each compartment will be governed by a governing equation of the form

$$(58)\qquad \frac{\mathrm{d}\rho_k}{\mathrm{d}t}=q_k^+(t)-\omega_k(t)\rho_k(t)-\tau_k^{-\alpha_k}\Theta_k(t,0)\,{}_0\mathcal{D}_t^{1-\alpha_k}\left(\frac{\rho_k(t)}{\Theta_k(t,0)}\right),$$

where $k=1,\ldots,N$ indicates the compartment.

In a multiple compartment model the flux entering a compartment, $q_k(t)$, may be dependent on the flux leaving another compartment. This is achieved by matching removal processes from a compartment to creation processes in another. It is also possible to have creation processes that do not depend on removal processes from other compartments. The Markovian rates, $\omega_k(t)$, are general functions of time and hence may depend on the population in any compartment.

Using this approach we can build the governing equations for any given compartment model, with fractional dynamics. Further demonstration is best done by way of examples and reductions to existing models.

4. Examples of fractional order compartment models. The general framework which we have established in this paper can be used to create specific examples of fractional order compartment models. With the appropriate choice of fluxes, rates, and fractional parameters the general governing equation reduces to the fractional recovery SIR model [3]. We provide fractional models for epidemiological, pharmacokinetic, and in-host disease dynamics, with figures demonstrating the fluxes between compartments. In these figures we have defined Markovian transitions with a regular arrow and anomalous transitions with a dashed arrow.

4.1. Reduction to the fractional recovery SIR model. The fractional recovery SIR model [3] is an extension of the standard SIR epidemiological model where there is a fractional order recovery of individuals from the disease. This model reproduces the observed behavior of a disease with chronic infection, where a proportion of individuals fail to recover from the disease. This model comprises three compartments, susceptible S, infected I, and recovered R. An individual begins as a susceptible, with a mass action Markovian transition into the infected compartment, βSI. Infected individuals recover with a fractional order, α, and rate μ. The model includes vital dynamics that comprise a death rate, γ, from each compartment and a birth rate, λ, into the S compartment, as can be seen in Figure 1.

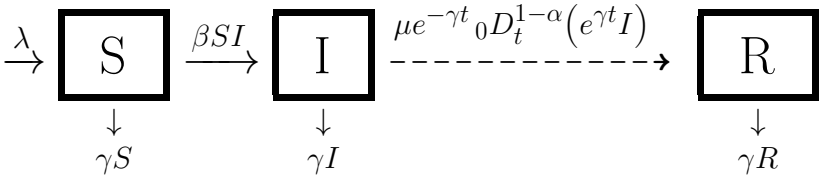

FIG. 1. *Flux flow of fractional SIR model.*

To obtain this model from the general fractional order multiple compartment model, (58), we consider three compartments, $\rho_1 = S$, $\rho_2 = I$, and $\rho_3 = R$. Taking $q_1(t) = s_0\delta(t - 0^+) + \lambda$ gives $q_1^+(t) = \lambda$, setting $\omega_1(t) = \gamma + \beta I$, and assuming no non-Markovian removal process (i.e., $\Phi_1(t) = 1$), gives the equation for the susceptible compartment,

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \lambda - \gamma S - \beta SI. \tag{59}$$

The flux into the I compartment originates in the S compartment, hence $q_2(t) = i_0\delta(t - 0^+) + q_2^+(t)$ with $q_2^+(t) = \beta SI$. The Markovian removals from the I compartment are due to the death of an individual, and we take $\omega_2(t) = \gamma$. $\Theta_2(t, 0)$ can be found from (2). The non-Markovian removals from the I compartment correspond to the recovery of an individual from the disease, and we take $\alpha_2 = \alpha$ and $\tau_2^{-\alpha_2} = \mu$. This gives the governing equation for the infectious compartment as

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - \gamma I - \mu \exp(-\gamma t)\ {}_0\mathcal{D}_t^{1-\alpha}\left(\exp(\gamma t)\, I\right). \tag{60}$$

Finally, for the R compartment we have the incoming flux from the infectious com-

partment,

$$q_3^+(t) = \mu \exp(-\gamma t)\ {}_0\mathcal{D}_t^{1-\alpha}\left(\exp(\gamma t)\, I\right). \tag{61}$$

The only removal process is again the Markovian death process, so $\omega_3(t) = \gamma$, and $\tau_3^{-\alpha_3} = 0$. The governing equation is then

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \mu \exp(-\gamma t)\ {}_0\mathcal{D}_t^{1-\alpha}\left(\exp(\gamma t)\, I\right) - \gamma R. \tag{62}$$

The equations (59), (60), and (62), subject to the initial conditions $S(0) = s_0$, $I(0) = i_0$, and $R(0) = 0$, correspond to the frSIR model.

4.2. An SIS model with fractional resusceptibility. Similar to the fractional recovery SIR model, a fractional, susceptible, infected, susceptible (SIS) model is a generalization of the standard SIS model. This model splits the population into a susceptible compartment, S, and an infected compartment, I. Individuals start in the susceptible compartment, then transition into the infected compartment through a mass action term, as in the SIR model. Subsequently, individuals undergo an anomalous transition back into the susceptible compartment, as represented in Figure 2.

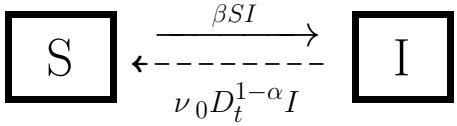

FIG. 2. *Flux flow of fractional SIS model.*

We obtain this model from (58). Here, we have two compartments, $\rho_1 = S$ and $\rho_2 = I$. We take the flux into the infected compartment to be $q_2^+(t) = \beta SI$. There is no Markovian removal process from the infected compartment, so that $\omega_2(t) = 0$, and, using (2), $\Theta(t, 0) = 1$. In the fractional SIS model we are considering an anomalous resusceptibility, we define $\alpha_2 = \alpha$ and $\tau_2^{-\alpha} = \nu$. This yields the governing evolution equation for the infected compartment,

$$\frac{dI}{dt} = \beta SI - \nu\, {}_0\mathcal{D}_t^{1-\alpha}(I). \tag{63}$$

Taking $q_1^+(t) = \nu\, {}_0\mathcal{D}_t^{1-\alpha}(I)$, $\omega_1 = \beta S$, and, as there is no non-Markovian removal process, i.e., $\Phi_1(t) = 1$, we can define the governing equation for the susceptible compartment,

$$\frac{dS}{dt} = -\beta SI + \nu\, {}_0\mathcal{D}_t^{1-\alpha}(I). \tag{64}$$

There are no vital dynamics in this model so that the total population is constant for all time, and $S(t) + I(t) = N$, where N is the total population. Equations (63) and (64), subject to the initial conditions $S(0) = s_0$ and $I(0) = i_0$, define the complete dynamics of the fractional SIS model. While we have constructed this model as an epidemic model, the standard SIS model has been used for general applications such as changing opinion dynamics [34] and it is feasible that the fractional SIS model could be used in a similar way where the time spent in a state affects the probability of switching states.

4.3. A compartment model for in vivo dynamics of HIV. Many mathematical models have been developed to study HIV infection and drug treatment in vivo, and the response of the immune system to the infection. These models are typically concerned with modeling the population of CD4+ T cells, the primary target of HIV, and the population of the virus itself [30].

Here we present a simplistic two-compartment model for the population dynamics of the virus and infected CD4+ T-cells. We consider the case of combined antiretroviral therapy with 100% efficacy, meaning there will be no replenishment of the infected T-cells from uninfected stock. We let I denote the number of infected CD4+ T cells and V the number of HIV virions. Virions from long-lived infected cells are typically observed after treatment has begun [31]. To model this we will have a fractional death of infected cells using (58) with $\rho_1(t) = I(t)$ and $\rho_2(t) = V(t)$; see Figure 3.

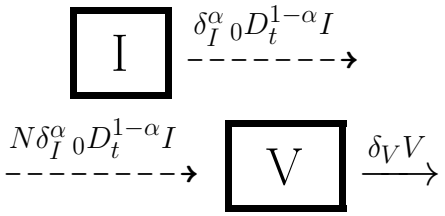

FIG. 3. *Flux flow of fractional HIV model.*

As no new infected cells are created, $q_1^+(t) = 0$ and the only flux into the infected compartment occurs as the initial conditions, we assume there is no Markovian removal process of infected cells hence, $\omega_1(t) = 0$. We take $\alpha_1 = \alpha$ and $\tau_1 = 1/\delta_I$. This gives us the governing equation for infected cells,

$$\frac{dI}{dt} = -\delta_I^\alpha\, {}_0\mathcal{D}_t^{1-\alpha} I, \tag{65}$$

subject to the initial conditions $I(0) = i_0$. Upon the death of an infected cell, virions are released. This occurs through a burst event and we will assume that on average N virions are created from each infected cell death. As such we take $q_2^+(t) = N\delta_I^\alpha\, {}_0\mathcal{D}_t^{1-\alpha} I$, and assuming no long lived virions, we will only consider a Markovian death rate of virions. Hence, $\omega_2(t) = \delta_V$, i.e., the governing evolution equation for the number of virions is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = N\delta_I^\alpha\, {}_0\mathcal{D}_t^{1-\alpha} I - \delta_V V\,, \tag{66}$$

subject to the initial conditions $V(0) = V_0$.

The well-known solution [32] of (65) is

$$I(t) = I_0 E_{\alpha,1}\left(-(\delta_I t)^\alpha\right). \tag{67}$$

Substituting (67) into (66) we can then use an integrating factor method to solve for

$V(t)$,

$$V(t) = e^{-\delta_V t} I_0 N \left(\left[1 - e^{\delta_V t} E_{\alpha,1} \left(-(\delta_I t)^\alpha \right) \right] + \delta_V \int_0^t e^{\delta_V s} E_{\alpha,1} \left(-(\delta_I s)^\alpha \right) \, \mathrm{d}s \right)$$

$$+ V_0 e^{-\delta_V t}. \tag{68}$$

4.4. A compartment model for chromium clearance in mice. A fractional order compartment model can be used to model the clearance of chromium in mice. When chromium enters the body a variety of processes may cause it to become trapped. This includes chemical reactions and the physical trapping of chromium within red blood cells [23]. We can use (47) to model the whole-body clearance of chromium in mice. In this model we consider a single compartment model which represents the concentration of chromium remaining in the cell; see Figure 4.

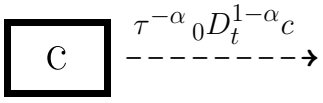

FIG. 4. *Flux flow of chromium clearance.*

In this example, $\rho = c$ and we consider the only flux into the compartment to occur as an initial dose, i.e., $i_0 = c_0$ and $q^+(t) = 0$. We assume that there are no Markovian removal processes, hence $\omega(t) = 0$ which yields the equation

$$\frac{dc}{dt} = -\tau^{-\alpha}\, {}_0\mathcal{D}_t^{1-\alpha} \left(c\left(t\right) \right), \tag{69}$$

where $c(0) = c_0$.

We can solve (69), as we did in (65), to give us the solution for the chromium content in the mouse body over time, hence

$$c(t) = c_0 E_{\alpha,1} \left(- \left(\frac{t}{\tau} \right)^\alpha \right). \tag{70}$$

We compare this model to the experiment by Bryson and Goodall [8], in which the whole-body chromium clearance of mice is observed over time. In this experiment, a high dose of Cr(VI), as potassium dichromate, is injected into a cohort of mice at time $t = 0$. Mice were sacrificed at three, seven, and twenty one days after the initial dose and the total whole body chromium concentration was measured. The experimental results reveal that whole-body clearance of chromium from mice is observed to be rapid during the first week, with 31% of the initial dose remaining after three days and 16% after seven days. Clearance then slows dramatically, at 21 days 7.5% of the initial dose remains [8]. Using a least squares fit, we found the best parameters for the Mittag–Leffler solution in (70) to be $\alpha = 0.71$ and $\tau = 1.60$. We compare this fit to the solution of a standard constant-decay ODE model for which the solution is an exponential function, $c(t) = c_0 \exp(-t/\tau)$, i.e., $\alpha = 1$. Plots of the solutions are shown in Figure 5. The Mittag–Leffler solution shows excellent agreement with the experimental data.

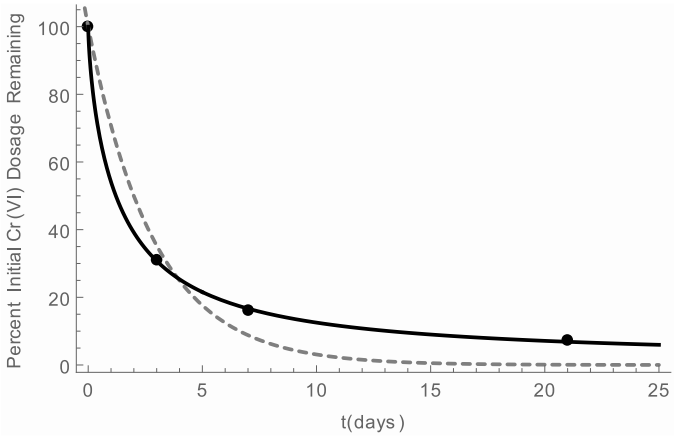

FIG. 5. *Percentage of initial chromium dose remaining in mice after a time (dots), the ODE single compartment prediction (dashed), and fractional order single compartment prediction (full).*

5. Conclusion. We have derived the governing evolution equations for compartment model dynamics from the stochastic process of particles undergoing a continuous time random walk. The resulting dynamics are represented by a coupled set of master equations, (58), derived through sections 2 and 3. Under a natural, power law, the choice of waiting time probabilities of these master equations become coupled ODEs with fractional dynamics, as demonstrated in section 2.3.

The use of fractional derivatives in compartment models has attracted increasing levels of interest in recent years. It is easy to construct fractional order compartment models by including fractional derivatives in an ad hoc manner, e.g., simply replacing integer order derivatives with fractional order derivatives. The approach for developing fractional order compartment models in this paper starts by considering an underlying stochastic process and fractional order evolution equations are obtained systematically by considering power law distributed waiting times in compartments. The ad hoc inclusion of fractional derivatives in compartment models can result in equations that are unphysical; they may violate conservation of mass. In (58) we observe an entanglement of the Markovian removal waiting times in the non-Markovian removal processes. This ensures a conservation of probability or mass between the local operators and the nonlocal fractional derivative operator. Furthermore, in a given physical system, it is to be expected that only some reactions will experience trapping or power-law waiting time. Our derivation accommodates this.

Finally, we have provided some simple examples of fractional order multicompartment models whose governing evolution equations have been obtained using the methods of this paper.

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