

Chapter 9

Fractional Pharmacokinetics

It leads to a paradox, from which one day useful consequences will be drawn.

Gottfried Wilhelm von Leibnitz (1646–1716)
when asked (1695) by Guillaume de L'Hospital
“what would be the result of half-differentiating?”

by Dr. A. DOKOUMETZIDIS
Faculty of Pharmacy National and Kapodistrian
University of Athens

Diffusion is one of the main mechanisms of various processes in living species and as such, plays an important role in the course of a drug in the body. Processes like membrane permeation, dissolution of solids, and dispersion in cellular matrices are considered to take place by diffusion. As mentioned in Chapter 2, diffusion is classically described by Fick's law and is based on the fact that a molecule makes a random walk, where its mean squared displacement is proportional to time. However, in the last few decades, strong experimental evidence has suggested that this is not always true and diffusional processes that deviate from this law have been observed. These are either faster (super-diffusion) or slower (sub-diffusion) than the classic case and the mean square displacement is a power of time, with exponent greater or less than 1, respectively, [371]. This type of diffusion gives rise to kinetics that are referred to as anomalous, to indicate the fact that deviate from the classic description [371]. Moreover, anomalous kinetics can also result from *reaction-limited processes* and *long-time trapping*. It is thought that anomalous kinetics introduces memory effects in the process that need to be accounted for to correctly describe it. As mentioned in Chapter 7, a theory that describes such anomalous kinetics is the so-called *fractal kinetics* where explicit power functions of time, in the form of time-dependent coefficients, are used to account for the memory effects. In pharmacokinetics several data sets have been characterized by power laws [269, 372] which has been justified by the presence of anomalous

The original version of this chapter was revised. An erratum to this chapter can be found at (DOI: [10.1007/978-3-319-27598-7_15](https://doi.org/10.1007/978-3-319-27598-7_15))

diffusion. These include mainly pharmacokinetics of drugs that distributed in deeper tissues [369] and bone seeking elements [281, 373].

An alternative theory to describe anomalous kinetics uses *fractional calculus* [30, 374], which introduces derivatives and integrals of fractional order, such as half or 3 quarters. Although fractional calculus was introduced by Leibniz more than 300 years ago, it is only within the last couple of decades that real-life applications have been explored [375–377]. It has been shown that differential equations with *fractional derivatives* describe experimental data of anomalous diffusion more accurately. In this chapter the recent applications of fractional calculus in pharmacokinetics are presented, which have formed a new area of research referred to as *fractional pharmacokinetics*.

9.1 Fractional Calculus

9.1.1 The Fractional Derivative

Derivatives of integer order n , $d^n f(t)/dt^n$ of a function $f(t)$ are well defined. For a fractional order of differentiation α , where for simplicity we assume that $0 < \alpha < 1$, the α -th derivative is defined through *fractional integration* and successive ordinary differentiation. Fractional integration of order α is defined, according to the *Riemann–Liouville* integral [378]

$${}_0D_t^{-\alpha} f(t) \triangleq \frac{1}{\Gamma(\alpha)} \int_0^t (t-t')^{\alpha-1} f(t') dt'$$

where $\Gamma(\cdot)$ is the gamma function. Consequently, fractional differentiation is defined as

$${}_0D_t^\alpha f(t) \triangleq \frac{d}{dt} \left[\frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f(t')}{(t-t')^\alpha} dt' \right].$$

This is the Riemann–Liouville definition of the fractional derivative. One can notice that the fractional integration is basically a convolution integral between the function and a power law of time, i.e., ${}_0D_t^{-\alpha} f(t) = t^{\alpha-1} * f(t)$, where the star “*” denotes convolution, accounting for the memory effects of the studied process. The fractional derivatives have properties that are not intuitive, for example, the half derivative of a constant λ with respect to x does not vanish and instead is $\lambda/\sqrt{\pi x}$. The left-side index “0” of the D operator denotes the lower end of the integration which in this case has been assumed to be zero. However alternative lower bounds can be considered leading to different definitions of the fractional derivative with slightly different properties. An alternative lower bound which has been considered is “ $-\infty$ ” and is referred to as the Wyl definition [375], which accounts for the entire “history” of the studied function, and is considered preferable in some applications. In fact one of the disadvantages of the Riemann–Liouville definition with the “0” lower bound is that when used in differential equations it

gives rise to initial conditions that involve the fractional integral of the function and are difficult to interpret physically. This is one of the reasons the Wyl definition has been introduced, but this definition may not be very practical for most applications either, as it involves an initial condition at time $-\infty$.

An alternative definition of the fractional derivative which is referred to as the Caputo definition is preferable for most physical processes as it involves explicitly the initial condition at time zero [374]. The definition is

$${}_0^C D_t^\alpha f(t) = \frac{1}{\Gamma(1-\alpha)} \int_0^t \dot{f}(t') (t-t')^{\alpha-1} dt'$$

where the upper-left index “C” stands for Caputo and the “dot” in $\dot{f}(t)$ denotes classic differentiation. This definition for the fractional derivative, apart from the more familiar initial conditions, gives rise to more familiar properties, one of them being that the *Caputo derivative* of a constant is in fact zero as usual. The different definitions of the fractional derivative give different results but these are not contradicting, since they apply for different conditions and it is a matter of choosing the appropriate one for each specific application. All the definitions collapse to the usual derivative for integer values of the order of differentiation.

9.1.2 Fractional Differential Equations

The most common type of kinetics encountered in pharmaceutical literature are zero- and first-order kinetics. The fractional versions of these types of kinetics are presented below and take the form of fractional order ordinary differential equations (FDE). Throughout this presentation the Caputo version of the fractional derivative is considered for the reasons already explained.

9.1.2.1 Zero-Order Kinetics

The classical zero-order kinetics equation, where the rate of change of quantity $q(t)$, expressed in mass units, is considered to be constant and equal to k_0 , expressed in (mass) / (time) units, is given by $\dot{q}(t) = k_0$. Its solution is a linear function of time and when the initial condition is zero, it has the form $q(t) = k_0 t$. The fractional expression for the zero-order kinetics equation can be obtained by replacing the derivative of order 1 by a derivative of fractional order α

$${}_0^C D_t^\alpha q(t) = k_{0f}$$

where k_{0f} is a constant with dimension (mass) / (time) $^\alpha$. The solution of this equation for initial condition $q(t) = 0$ is a power law [374]

$$q(t) = \frac{k_{0f}}{\Gamma(\alpha + 1)} t^\alpha.$$

9.1.2.2 First-Order Kinetics

The first-order differential equation, where the rate of change of quantity $q(t)$ is proportional to its current value, is given by $\dot{q}(t) = k_1 q(t)$. Its solution by considering an initial condition of $q(t) = q_0$ is given by the classical equation of exponential decay $q(t) = q_0 \exp(-k_1 t)$. In fractional terms however, the first-order equation can be written by replacing the derivative of order 1 by a fractional one

$${}^C D_t^\alpha q(t) = -k_{1f} q(t) \quad (9.1)$$

where k_{1f} is a constant with (time) $^{-\alpha}$ dimension. The solution of this equation can be found in most books or papers of the fast growing literature on fractional calculus [374] and for initial condition $q(t) = q_0$ it has the form

$$q(t) = q_0 E_\alpha(-k_{1f} t^\alpha)$$

where $E_\alpha(\cdot)$ is a *Mittag-Leffler function* [374] which is defined as

$$E_\alpha(x) \triangleq \sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k + 1)}.$$

The function $E_\alpha(x)$ is a generalization of the exponential function and it collapses to the exponential when $\alpha = 1$, i.e., $E_1(x) = \exp(x)$. The general form of the Mittag-Leffler function with two parameters α and β is also defined as

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

The solution of equation 9.1 basically means that the fractional derivative of order α of the function $E_\alpha(t^\alpha)$ is itself a function of the same form, exactly like the classic derivative of an exponential is also an exponential. It also makes sense to restrict α to values $0 < \alpha < 1$, since for values of α larger than 1 the solution of equation 9.1 is non-monotonous and negative values for $q(t)$ appear.

From these elementary equations the basic relations for the time evolution in drug disposition can be formulated, with the assumption of diffusion of drug molecules taking place in heterogeneous space.

9.1.3 Solving FDE by the Laplace Transform

FDE can easily be written in the Laplace domain since each of the fractional derivatives can be transformed similarly to the ordinary derivatives, as follows, for order $\alpha \leq 1$

$$L \{ {}_0^C D_t^\alpha f(t) \} = s^\alpha \tilde{f}(s) - s^{\alpha-1} f(0) \tag{9.2}$$

where $\tilde{f}(s)$ is the Laplace transform of $f(t)$ [374]. For $\alpha = 1$, the Laplace transform 9.2 collapses to the classic expression for ordinary derivatives, i.e., $L \{ f'(t) \} = s\tilde{f}(s) - f(0)$.

For example, the following simple FDE

$${}_0^C D_t^{1/2} q(t) = -q(t)$$

with initial value $q(0) = 1$ can be written in the Laplace domain, by applying the transform 9.2, as follows

$$s^{1/2} \tilde{q}(s) - s^{-1/2} q(0) = -\tilde{q}(s).$$

By substituting the initial value, the above can be rearranged as

$$\tilde{q}(s) = \frac{1}{s + \sqrt{s}}$$

By applying the inverse Laplace transform to the previous expression, the analytical solution of the FDE can be obtained; it is a Mittag–Leffler function of order one-half, and

$$q(t) = E_{1/2}(-t^{1/2}) = \exp(t) [1 + \operatorname{erf}(-\sqrt{t})].$$

Although it is always easy to transform an FDE in the Laplace domain and in most cases feasible to rearrange it, solving it explicitly for the system variables, it is more difficult to apply the inverse Laplace transform, such that an analytical solution in the time domain is obtained. However, it is possible to perform that step numerically using a Numerical Inverse Laplace Transform (NILT) algorithm [379].

9.2 Fractional Calculus in Pharmacokinetics

9.2.1 A Basic Fractional Model

In the simplest pharmacokinetic relationship, the intravenous bolus injection with first-order elimination in a one-compartment model, the drug concentration $c(t)$ follows the common expression

$$\dot{c}(t) = -k_{10}c(t)$$

where k_{10} is the elimination rate constant. The fractional version of this equation [380] can be written as

$${}_0^C D_t^\alpha c(t) = -k_{10f} c(t)$$

where k_{10f} is a constant with dimensions $(\text{time})^{-\alpha}$. As already mentioned, the solution of this equation can be written as

$$c(t) = c_0 E_\alpha(-k_{10f} t^\alpha) \quad \text{for} \quad \alpha < 1 \quad (9.3)$$

where c_0 is the ratio (dose) / (volume of distribution). By introducing $t_0 = k_{10f}^{-\frac{1}{\alpha}}$, the above equation becomes

$$c(t) / c_0 = E_\alpha[-(t/t_0)^\alpha]. \quad (9.4)$$

This equation for small times behaves as a *stretched exponential*, i.e.,

$$\exp\left[-\frac{(t/t_0)^\alpha}{\Gamma(1+\alpha)}\right],$$

while for large values of time as a power law, i.e.,

$$\frac{(t/t_0)^{-\alpha}}{\Gamma(1-\alpha)}$$

(Figure 9.1). It is therefore a good candidate to describe various data sets exhibiting power-law-like kinetics due to the slow diffusion of the drug in deeper tissues.

The relationship 9.3 applies for the simplest case of fractional pharmacokinetics. It accounts for the anomalous diffusion process, which may be considered to be the limiting step of the entire kinetics. Classic clearance may be considered not to be the limiting process here and is absent from the equation.

9.2.2 Fractionalizing Linear Multicompartment Models

A single ordinary differential equation is easily fractionalized by changing the derivative on the left-hand side to a fractional order as in the previous paragraph. However, in pharmacokinetics and other fields where compartmental models are used, two or more ordinary differential equations are often necessary and it is not as straightforward to *fractionalize systems of differential equations*, especially when certain properties such as mass balance need to be preserved.

When a compartmental model with two or more compartments is being built, typically an outgoing mass flux becomes an incoming flux to the next compartment.

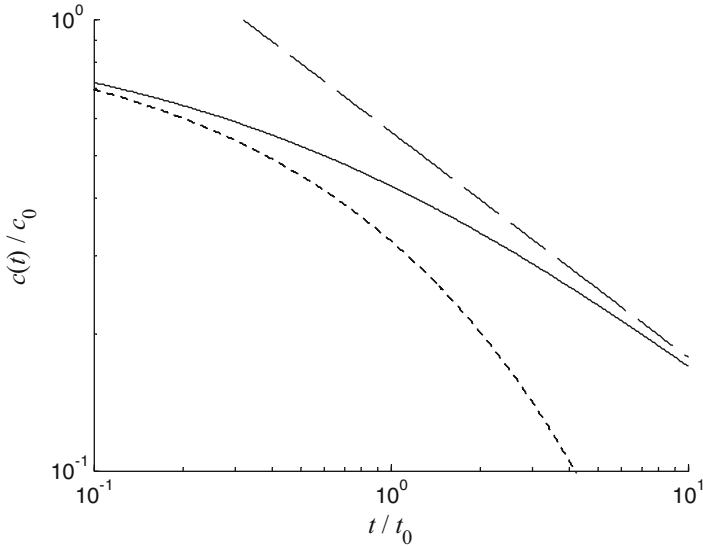


Fig. 9.1 Log–log plot of relationship 9.4 (solid line), the stretched exponential function (dotted line), and the power-law function (dashed line) for $\alpha = 0.5$. The relationship 9.4 starts close to the stretched exponential and finishes close to the power function

Thus, an outgoing mass flux that is defined as a rate of fractional order cannot appear as an incoming flux into another compartment, as a rate of a different fractional order, without violating mass balance [381]. It is therefore, in general, impossible to fractionalize multicompartment systems simply by changing the order of the derivatives on the left-hand side of the ordinary differential equations. The latter is possible only in the special case where a common fractional order is considered for all ordinary differential equations, what is referred of commensurate order. In the general case, of the non-commensurate orders, a different approach for fractionalizing systems of ordinary differential equations needs to be applied.

In the following part, a general form of a fractional two-compartment system is considered and then generalized to a system of an arbitrary number of compartments, which first appeared in [382]. A general ordinary linear two-compartment model is defined by the following system of linear ordinary differential equations

$$\begin{aligned} \dot{q}_1(t) &= -k_{12}q_1(t) + k_{21}q_2(t) - k_{10}q_1(t) + u_1(t) \\ \dot{q}_2(t) &= k_{12}q_1(t) - k_{21}q_2(t) - k_{20}q_2(t) + u_2(t) \end{aligned} \tag{9.5}$$

where $q_1(t)$ and $q_2(t)$ are the mass or molar amounts of material in the respective compartments and the k_{ij} constants control the mass transfer between the two compartments and elimination from each of them. The notation convention used for the indices of the rate constants is that the first corresponds to the source

compartment and the second to the target one, e.g., k_{12} corresponds to the transfer from compartment 1 to 2, k_{10} corresponds to the elimination from compartment 1, etc. The dimensions of all the k_{ij} rate constants are $(\text{time})^{-1}$. Input rates $u_i(t)$ in each compartment may be zero, constant, or time dependent. Initial values for $q_1(t)$ and $q_2(t)$ have to be considered also, $q_1(0)$ and $q_2(0)$, respectively.

In order to fractionalize this system, first the ordinary system is integrated, obtaining a system of integral equations and then the integrals are fractionalized as shown in [382]. Finally, the fractional integral equations are differentiated in an ordinary way. The resulting fractional system contains ordinary derivatives on the left-hand side and with Riemann–Liouville derivatives on the right-hand side

$$\begin{aligned} \dot{q}_1(t) &= -k_{12f} {}_0D_t^{1-\alpha_{12}} q_1(t) + k_{21f} {}_0D_t^{1-\alpha_{21}} q_2(t) - k_{10f} {}_0D_t^{1-\alpha_{10}} q_1(t) + u_1(t) \\ \dot{q}_2(t) &= k_{12f} {}_0D_t^{1-\alpha_{12}} q_1(t) - k_{21f} {}_0D_t^{1-\alpha_{21}} q_2(t) - k_{20f} {}_0D_t^{1-\alpha_{20}} q_2(t) + u_2(t) \end{aligned}$$

where $0 < \alpha_{ij} < 1$ is a constant representing the order of the specific process. Different values for the orders of different processes may be considered, but the order of the corresponding terms of a specific process is kept the same when these appear in different equations, e.g., there can be an order α_{12} for the transfer from compartment 1 to 2 and a different order α_{21} for the transfer from compartment 2 to 1, but the order for the corresponding terms of the transfer, from compartment 1 to 2, α_{12} , is the same in both equations. Also the index “ f ” in the rate constant was added to emphasize the fact that these are different to the ones of 9.5 and carry dimensions $(\text{time})^{-\alpha}$.

Now, it is convenient to rewrite the above FDE system with Caputo derivatives. An FDE with Caputo derivatives accepts the usual type of initial conditions involving the variable itself, as opposed to Riemann–Liouville derivatives which involve an initial condition on the derivative of the variable, which is not practical. When the initial values are zero then the respective Riemann–Liouville and Caputo derivatives are the same. This is convenient since a zero initial value is very common in compartmental analysis. When the initial value is not zero, converting to a Caputo derivative is possible, for the particular term with a non-zero initial value. The conversion from a Riemann–Liouville to a Caputo derivative is done with the following expression

$${}_0D_t^{1-\alpha_{ij}} q_i(t) = {}_0^C D_t^{1-\alpha_{ij}} q_i(t) + \frac{q_i(0) t^{\alpha_{ij}-1}}{\Gamma(\alpha_{ij})}. \quad (9.6)$$

Summarizing about initial conditions, we can identify three cases (1°) the initial condition is zero and then the derivative becomes a Caputo by definition, (2°) the initial condition is non-zero but it is involved in a term with an ordinary derivative so it is treated as usual, (3°) the initial condition is non-zero and is involved in a fractional derivative which means that in order to present a Caputo derivative, an additional term, involving the initial value appears, by substituting the

relationship 9.6. Alternatively, a zero initial value for that variable can be assumed, with a Dirac delta input to account for the initial quantity for that variable.

So, the previous system of FDE with two compartments can be reformulated, by using as fractional derivatives the Caputo derivatives. Also, it is easy to generalize the above approach to a system with an arbitrary number of n compartments as follows

$$\dot{q}_i(t) = -k_{i0} {}^C D_t^{1-\alpha_{i0}} q_i(t) - \sum_{j \neq i}^n k_{ij} {}^C D_t^{1-\alpha_{ij}} q_i(t) + \sum_{j \neq i}^n k_{ji} {}^C D_t^{1-\alpha_{ji}} q_j(t) + u_i(t) \tag{9.7}$$

for $i = 1 : n$. Here Caputo derivatives have been considered throughout since, as explained above, this is feasible. The system of equations 9.7 is too general for most purposes as it allows every compartment to be connected with every other. Typically the connection matrix would be much sparser than that, with most compartments being connected to just one neighboring compartment while only a few “hub” compartments would have more than one connection.

The advantage of the described approach of fractionalization is that each transport process is fractionalized separately, rather than fractionalizing each compartment or each equation. Thus, processes of different fractional orders can coexist since they have consistent orders when the corresponding terms appear in different equations. Also, it is important to note that equation 9.7 does not have problems, such as violation of mass balance or inconsistencies with the units of the rate constants.

As mentioned, FDE can easily be written in the Laplace domain. In the case of FDE of the form of equation 9.7 where the fractional orders are $1 - \alpha_{ij}$, the relationship 9.2 becomes

$$L \left\{ {}^C D_t^{1-\alpha_{ij}} q_i(t) \right\} = s^{1-\alpha_{ij}} \tilde{q}_i(s) - s^{-\alpha_{ij}} q_i(0).$$

9.3 Examples of Fractional Models

9.3.1 One-compartment Model with Constant Rate Input

A one-compartment model with a fractional elimination and a constant rate input is considered [382]. Even in this simple one-compartment model, it is necessary to employ the approach of fractionalizing each process separately, described above, since the constant rate of infusion is not in fractional order. That would have been difficult if one followed the approach of changing the order of the derivative of the left-hand side of the ordinary differential equation, however here it is straightforward.

The system can be described by the following equation

$$\dot{q}(t) = k_{01} - k_{10f} {}^C D_t^{1-\alpha} q(t) \quad (9.8)$$

with $q(0) = 0$ and where k_{01} is a zero-order input rate constant, with dimensions (mass)/(time), k_{10f} is a rate constant with units (time) $^{-\alpha}$, and α is a fractional order less than 1. The previous equation can be written in the Laplace domain as

$$s\tilde{q}(s) - q(0) = \frac{k_{01}}{s} - k_{10f} [s^{1-\alpha}\tilde{q}(s) - s^{-\alpha}q(0)].$$

Since $q(0) = 0$, the above equation can be solved to obtain

$$\tilde{q}(s) = \frac{k_{01}s^{\alpha-2}}{s^\alpha + k_{10f}}.$$

By applying the following inverse Laplace transform formula (equation 1.80 in ref. [374], page 21)

$$L^{-1} \left\{ \frac{s^{\alpha-\beta}}{s^\alpha + k} \right\} = t^{\beta-1} E_{\alpha,\beta}(-kt^\alpha)$$

where $E_{\alpha,\beta}$ is the Mittag–Leffler function with two parameters. For $\beta = 2$ the following is obtained

$$q(t) = k_{01}tE_{\alpha,2}(-k_{10f}t^\alpha). \quad (9.9)$$

In theorem 1.4 of ref. [374], the following expansion for the Mittag–Leffler function is proven to hold for $|z| \rightarrow \infty$

$$E_{\alpha,\beta}(z) = -\sum_{i=1}^p \frac{z^{-i}}{\Gamma(\beta - \alpha)} + O(|z|^{-1-p}).$$

Applying this formula for relationship 9.9 and keeping only the first term of the sum since the rest are of higher order, the limit of 9.9 for t going to infinity can be calculated [382]

$$\lim_{t \rightarrow \infty} \{q(t)\} = \lim_{t \rightarrow \infty} \{k_{01}tE_{\alpha,2}(-k_{10f}t^\alpha)\} \approx \lim_{t \rightarrow \infty} \left\{ \frac{k_{01}}{k_{10f}} \frac{t^{1-\alpha}}{\Gamma(2-\alpha)} \right\} = \infty,$$

for $\alpha < 1$. The fact that the limit of the relationship 9.9 diverges when t goes to infinity, for $\alpha < 1$, means that unlike the classic case, for $\alpha = 1$, where the relationship 9.9 approaches exponentially the steady state k_{01}/k_{10f} , for $\alpha < 1$, there is infinite accumulation. In Figure 9.2 left panel, a plot of relationship 9.9

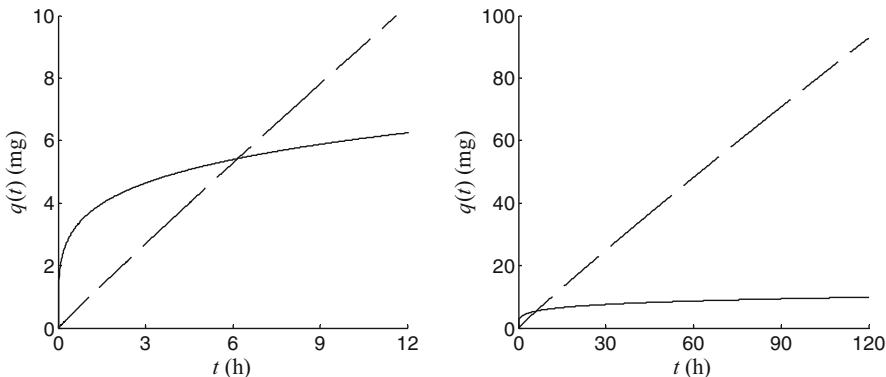


Fig. 9.2 For $\alpha = 0.25, k_{10f} = 0.1 \text{ h}^{-\alpha}$, and $k_{01} = 1 \text{ mg/l}$: Plot of relationship 9.9 with constant infusion (*dashed line*) which exhibits infinite accumulation and of relationship 9.10 with power-law infusion (*solid line*) which approaches a steady state. In the right panel, the profiles of left panel are for 10-times longer time span

is shown for $\alpha < 1$ showing that unlike the classic case where a steady state is approached, in the fractional case the amount keeps rising. In Figure 9.2 right panel, the same profiles are shown for 10-times larger time span, demonstrating the effect of continuous accumulation.

The lack of a steady state under constant rate administration which results to infinite accumulation is one of the most important clinical implications of the presence of fractional pharmacokinetics. It is clear that this implication extends to repeated doses as well as constant infusion, which is the most common dosing regimen, and can be important in chronic treatments. In order to avoid accumulation the constant rate administration must be adjusted to replaced by a decreasing with time rate. Indeed, in equation 9.8, if the constant rate of infusion k_{01} is replaced by the term $f(t) = k_{01}t^{-(1-\alpha)}$ [378], then the solution of the resulting FDE is, instead of relationship 9.9, the following

$$q(t) = k_{01} \Gamma(\alpha) t^\alpha E_{\alpha, \alpha+1}(-k_{10f} t^\alpha). \tag{9.10}$$

The previous solution converges to the steady state $\Gamma(\alpha) k_{01}/k_{10f}$ as time goes to infinity, while for the special case of $\alpha = 1$, the steady state is the usual k_{01}/k_{10f} . Similarly, for the case of repeated doses, if a steady state is intended to be achieved, in the presence of fractional elimination of order α , then the usual constant rate of administration, e.g., a constant daily dose, needs to be replaced by an appropriately decreasing rate of administration. As shown in [378], the decreasing rate of administration can be achieved by the following two approaches. The first approach uses the same dose given at increasing inter-dose intervals, i.e.,

$$T_i = (T_{i-1}^\alpha + \alpha \Delta \tau^\alpha)^{1/\alpha},$$

where T_i is the time of the i -th dose and $\Delta\tau$ is the inter-dose interval of the corresponding kinetics of order $\alpha = 1$. The second approach is based on a decreasing dose $q_{0,i}$ described by the following equation

$$q_{0,i} = \frac{q_0}{\alpha} [(i+1)^\alpha - i^\alpha].$$

given at constant time intervals. In this way an ever decreasing administration rate is implemented which compensates the decreasing elimination rate due to the fractional kinetics.

9.3.2 Two-Compartment Intravenous Model

Based on the generalized approach for the fractionalization of compartmental models, which allows mixing different fractional orders, developed in the previous section, a two-compartment fractional pharmacokinetic model is considered, shown schematically in Figure 9.3. Compartment 1 (central) represents general circulation and well-perfused tissues while compartment 2 (peripheral) represents deeper tissues. Three transfer processes (fluxes) are considered: elimination from the central compartment and a mass flux from the central to the peripheral compartment, which are both assumed to follow classic kinetics (order 1), while a flux from the peripheral to the central compartment is assumed to follow slower fractional kinetics accounting for tissue trapping.

The system is formulated mathematically as follows

$$\begin{aligned} \dot{q}_1(t) &= -(k_{10} + k_{12})q_1(t) + k_{21f} {}^C D_t^{1-\alpha} q_2(t) \\ \dot{q}_2(t) &= k_{12}q_1(t) - k_{21f} {}^C D_t^{1-\alpha} q_2(t) \end{aligned} \quad (9.11)$$

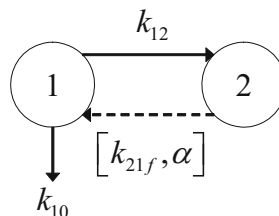


Fig. 9.3 A fractional 2-compartment pharmacokinetic model with an intravenous bolus. Elimination from the central compartment and a mass flux from the central to the peripheral compartment, which are both assumed to follow classic kinetics (order 1), while a flux from the peripheral to the central compartment is assumed to follow slower fractional kinetics, accounting for tissue trapping (*dashed arrow*)

with $\alpha < 1$ and initial conditions are $q_1(0) = q_0$, $q_2(0) = 0$ which account for a bolus dose injection and no initial amount in the peripheral compartment. Note that it is allowed to use Caputo derivatives here since the fractional derivatives involve only terms with $q_2(t)$ for which there is no initial amount, which means that Caputo and Riemann–Liouville derivatives are identical (relationship 9.6).

Applying the Laplace transform to the above system, the following algebraic equations are obtained

$$\begin{aligned} s\tilde{q}_1(s) - q_1(0) &= -(k_{10} + k_{12})\tilde{q}_1(s) + k_{21f}[s^{1-\alpha}\tilde{q}_2(s) - s^{-\alpha}q_2(0)] \\ s\tilde{q}_2(s) - q_2(0) &= k_{12}\tilde{q}_1(s) - k_{21f}[s^{1-\alpha}\tilde{q}_2(s) - s^{-\alpha}q_2(0)] \end{aligned}$$

Solving for $\tilde{q}_1(s)$ and $\tilde{q}_2(s)$ and substituting the initial conditions

$$\tilde{q}_1(s) = \frac{q_0(s^\alpha + k_{21f})}{(s + k_{12} + k_{10})(s^\alpha + k_{21f}) - k_{12}k_{21f}} \quad (9.12)$$

for the central compartment and

$$\tilde{q}_2(s) = \frac{q_0s^{\alpha-1}k_{12}}{(s + k_{12} + k_{10})(s^\alpha + k_{21f}) - k_{12}k_{21f}} \quad (9.13)$$

for the peripheral compartment. The above expressions can be used by a NILT algorithm [379] to simulate values of $q_1(t)$ and $q_2(t)$ in the time domain.

Kilbas et al. [383] pointed out that the inverse Laplace transform of such relationships could lead to closed-form solutions. These solutions were derived in [384] to be

$$\begin{aligned} q_1(t) &= q_0 \sum_{n=0}^{\infty} (-1)^n k_{21f}^n \sum_{\lambda=0}^n \Omega E_{1,\lambda+\alpha n+1}^{n+1} [-(k_{10} + k_{12})t] + \\ & q_0 \sum_{n=0}^{\infty} (-1)^n k_{21f}^{n+1} \sum_{\lambda=0}^n \Omega t^\alpha E_{1,\lambda+\alpha(n+1)+1}^{n+1} [-(k_{10} + k_{12})t] \quad (9.14) \end{aligned}$$

for relationship 9.12 and

$$q_2(t) = q_0 k_{12} \sum_{n=0}^{\infty} (-1)^n k_{21f}^n \sum_{\lambda=0}^n \Omega t E_{1,\lambda+\alpha n+2}^{n+1} [-(k_{10} + k_{12})t].$$

for relationship 9.13, with the common term

$$\Omega = \frac{k_{10}^\lambda n!}{(n-\lambda)! \lambda!} t^{\lambda+\alpha n}.$$

Nevertheless, these closed-form solutions involve terms with an infinite series of Mittag–Leffler functions and they are hard to implement and apply in practice.

Note, that primarily, $q_1(t)$ is of interest, since in practice, we only have data from this compartment. The time–amount profile $q_1(t)$ may be used to obtain the drug concentration in the blood $c(t)$ according to the elementary definition $c(t) \triangleq q_1(t)/V_1$ involving the distribution volume of the central compartment V_1 . The so obtained model $c(t)$ can be fitted to the pharmacokinetic data in order to estimate parameters $V_1, k_{10}, k_{12}, k_{21f}$, and α .

9.4 Applications of Fractional Models

9.4.1 Amiodarone Pharmacokinetics

An application of the fractional two-compartment model, the system of 9.11 to amiodarone, was presented in [382]. Amiodarone is an antiarrhythmic drug known for its anomalous, nonexponential pharmacokinetics, which have important clinical implications due to the accumulation pattern of the drug in long-term administration. The fractional two-compartment model of the previous section was used to analyze an amiodarone intravenous data set which first appeared in [385] and estimates of the model parameters were obtained. The values for $q_1(t)$ were obtained from the expression of $\tilde{q}_1(s)$ in the Laplace domain (relationship 9.12) using a NILT algorithm [379]. In Figure 9.4 the model predicted values are plotted together with the data demonstrating good agreement for the 60 day period of this study. The estimated fractional order was $\alpha = 0.587$ and nonexponential character of the curve is evident, while the model follows well the data both for long and for short times, unlike empirical power laws which explode at $t = 0$.

9.4.2 Other Pharmacokinetic Applications

Apart from the amiodarone example, other applications of fractional pharmacokinetics have appeared in literature. From the authors Popovic et al. various applications of fractional pharmacokinetics to model drugs have appeared, namely for diclofenac [386], valproic acid [387], bumetanide [388], and methotrexate [389]. Also, Copot et al. have used a fractional pharmacokinetics model for propofol [390]. In most of these cases the fractional model has been compared with an equivalent ordinary pharmacokinetic model and has been found superior.

FDE have been proposed to describe drug response too, apart from their kinetics. Verotta has proposed several alternative fractional pharmacokinetic–dynamic models that are capable to describe pharmacodynamic times series with favorable properties [391]. Although these models are empirical, i.e., they have no mechanistic

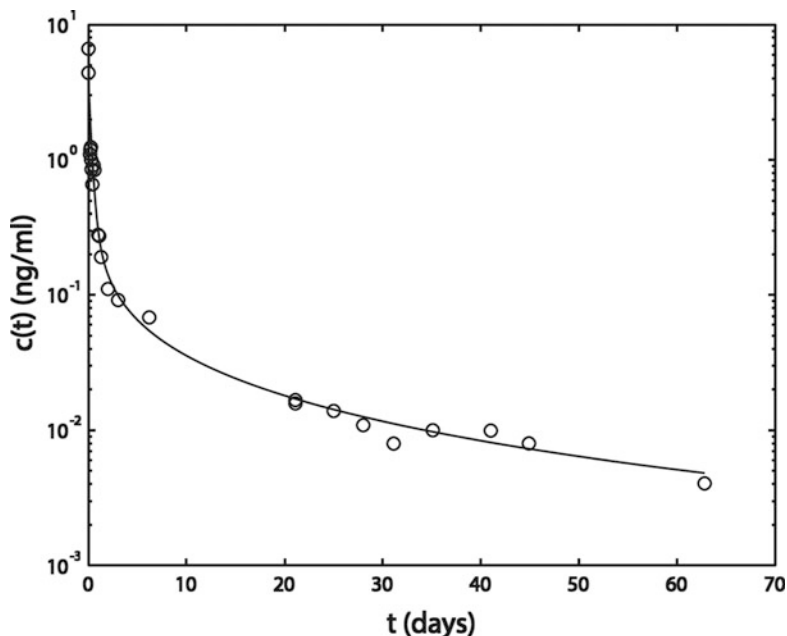


Fig. 9.4 The fractional two-compartment model of relationships 9.11. The fitted concentrations (line) to the amiodarone data (circles) were obtained from the expression $\tilde{q}_1(s)$ in the Laplace domain (relationship 9.12) using a NILT algorithm. Parameter estimates were: $k_{10} = 1.49 \text{ d}^{-1}$, $k_{12} = 2.95 \text{ d}^{-1}$, $k_{21f} = 0.48 \text{ d}^{-\alpha}$, $\alpha = 0.58$, $q_0/V_1 = 4.72 \text{ ng ml}^{-1}$

basis, they are attractive since the memory effects of the FDE can link smoothly the concentration to the response with a variable degree of influence, while the shape of the responses generated by fractional pharmacokinetic-dynamic models can be very flexible, with very few parameters.

Overall, fractional kinetics offers an elegant description of anomalous kinetics, i.e. nonexponential terminal phases, the presence of which has been acknowledged in pharmaceutical literature extensively. The approach offers simplicity and a valid scientific basis, since it has been applied in problems of diffusion in physics and biology. It introduces the Mittag–Leffler function which describes power-law behaved data well, in all time scales, unlike the empirical power laws which describe the data only for large times. Despite the mathematical difficulties, fractional pharmacokinetics is an interesting approach for the toolbox of the pharmaceutical scientist.