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Development of Fractional Trigonometry and an Application of Fractional Calculus to Pharmacokinetic Model

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DEVELOPMENT OF FRACTIONAL TRIGONOMETRY AND AN APPLICATION OF FRACTIONAL CALCULUS TO PHARMACOKINETIC MODEL

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DEVELOPMENT OF FRACTIONAL TRIGONOMETRY AND AN APPLICATION OF FRACTIONAL CALCULUS TO PHARMACOKINETIC MODEL

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Our translation of real world problems to mathematical expressions relies on calculus, which in turn relies on the differentiation and integration operations. We differentiate or integrate a function once, twice, or any whole number of times. But one may ask what would be the 1/2-th or square root derivative of x. Fractional calculus generalize the operation of differentiation and integration to non-integer orders. Although it seems not to have significant applications, research on this subject could be valuable in understanding the nature.

The main purpose of this thesis is to develop fractional trigonometry and generalize Wronskian determinant that can be used to determine the linear independence of a set of solutions to a system of fractional differential equations. We also introduce a new set of fractional differential equations whose solutions are fractional trigonometric functions.

The first chapter gives a brief introduction to fractional calculus and the mathematical functions which are widely used to develop the theory of this subject. The second chapter introduces the reader to fractional derivative and fractional integral, and the most important properties of these two operators that are used to develop the following chapters. The third chapter focuses on the Laplace transform which is the means that will

be used to solve the fractional differential equations. In the fourth chapter, we develop fractional trigonometric functions, generalized Wronskian, also classes of fractional homogeneous differential equations and the characteristic equations, as well as the solution to these types of equations. Also, we present a new method to solve a system of fractional differential equations, and by using this method we solve a system that generates a solution of a linear combination of two fractional trigonometric functions. The fifth chapter is the conclusion of this thesis and is devoted to demonstrating an application of fractional calculus to pharmacokinetic model, which is used to study the drug concentration in the body.

CHAPTER 1

Introduction to Fractional Calculus

The fractional calculus is a natural extension of the traditional calculus. It is like many other mathematical branches and ideas; it has its origin in the pursuing for the extension of meaning. Well known examples are the extension of the integer numbers to the rational numbers, of the rational numbers to the real numbers, and of the real numbers to the complex numbers. The question of extension of meaning in differential and integral calculus: Can the derivative $\frac{d^n y}{dx^n}$ of integer order $n > 0$, be extended to n any order - fractional, irrational or complex? The answer of this question has led to the development of a new theory which is called fractional calculus.

Fractional calculus is a new subject; it may find its way into innumerable questions and applications. Some of the mathematical theory applicable to the study of the fractional calculus was developed prior to the turn of the 20th Century. In this thesis, we develop *"fractional trigonometric functions"* with investigation of the behavior of *"fractional cosine"* and *"fractional sine"* curves. Also, we generalize the Wronskian determinant theory to determine the linear independence of a set of solutions to higher order fractional differential equations. We will introduce a system of differential equations where *"fractional cosine"* and *"fractional sine"* appear as a solution for that system.

The purpose of studying theories is to apply them to real world problems. Over the last few years, mathematicians pulled the subject of fractional calculus to several applied fields of engineering, science and economics [1,2,7,22,23]. In this work, we present an application of fractional calculus to the pharmacology field. In particular to Pharmacokinetic science which studies the drug metabolite kinetics in the body.

1.1 Historical Development of Fractional Calculus

The concept of fractional calculus is believed to have emerged from a question raised in the year 1695 by Marquis de L'Hôpital. In a letter dated September 30th, 1695 L'Hôpital wrote to Leibniz asking him about a particular notation he had used in his publications for the $n-$th derivative $\frac{d^n f(x)}{dx^n}$ of the linear function $f(x) = x$. L'Hôpital posed the question to Leibniz, what would be the result be if $n = 1/2$. Leibniz responded to the question, that "$d^{1/2}x$ will be equal to $x\sqrt{dx : x}$". In these words, fractional calculus was born [8,9]. Following this question, many mathematicians contributed to the fractional calculus. In 1730, Euler mentioned interpolating between integral orders of a derivative. In 1812, Laplace defined a fractional derivative by means of an integral, and in 1819 there appeared the first discussion of fractional derivative in a calculus text written by S.F.Lacroix [24].

Starting with

$$y = x^m \tag{1.1}$$

where m is a positive integer, Lacroix found that the $n-$th derivative of x^m :

$$\frac{d^n x^m}{dx^n} = \frac{m!}{(m-n)!}x^{m-n}, \qquad m \geq n. \tag{1.2}$$

Then, he replaced n with $1/2$ and let $m = 1$, thus the derivative of order $1/2$ of the function x is

$$\frac{d^{1/2}}{dx^{1/2}}x = \frac{2\sqrt{x}}{\sqrt{\pi}}. \tag{1.3}$$

This result obtained by Lacroix is the same as that yielded by the present day Riemann-Liouville definition of a fractional derivative. But Lacroix considered the question of interpolating between integral orders of a derivative. He devoted only two of the 700 pages of his text to this topic.

Fourier, in 1822, was the next to mention a derivative of arbitrary order. But like Euler, Laplace, and Lacroix, he gave no application. The first use of fractional operation was by Niel Henrik Abel in 1823 [21]. Abel applied the fractional calculus to the solution of an integral equation, which arose in his formulation of the tautochrone problem: to find the shape of a frictionless wire lying in a vertical plane, such that the time required for a bead placed on the wire to slide to the lowest point of the wire is the same regardless of where the bead is first placed. We will present Abel's elegant solution later in Chapter 3, after developing appropriate notation and terminology for the fractional calculus.

Probably Joseph Liouville was fascinated by Laplace's and Fourier's brief comments or Abel's solution, so he made the first major study of fractional calculus. He published three large memoirs on this topic in 1832 (beginning with [15]) followed by more papers in rapid succession. Liouville's first definition of a derivative of arbitrary order ν involved an infinite series. This had the disadvantage that ν must be restricted to those values for which the series converges. Liouville seemed aware of the restrictive nature of his first definition, therefore, Liouville tried to put his effort to define fractional derivative again of x^{-a} whenever x and a are positive.

Starting with a definite integral we have:

$$I = \int_0^\infty u^{a-1} e^{-xu}\, du. \tag{1.4}$$

With the change of variable $xu = t$, we obtain

$$I = x^{-a} \int_0^\infty t^{a-1} e^{-t} \, dt.$$

This integral is closely related to the Gamma integral of Euler which is defined as

$$\Gamma(a) = \int_0^\infty t^{a-1} e^{-t} \, dt.$$

Therefore, equation (1.4) can be written in term of Legendre's symbol Γ for the generalized factorial

$$I = x^{-a} \Gamma(a) \tag{1.5}$$

which implies

$$x^{-a} = \frac{I}{\Gamma(a)}. \tag{1.6}$$

By "operating" on both sides of this equation with d^ν/dx^ν, and by assuming that $d^\nu(e^{ax})/dx^\nu = a^\nu e^{ax}$ for any $\nu > 0$, Liouville was able to obtain the result known as his second definition:

$$\frac{d^\nu}{dx^\nu} x^{-a} = \frac{(-1)^\nu \Gamma(a+\nu)}{\Gamma(a)} x^{-a-\nu}. \tag{1.7}$$

After these attempts, still the second definition of fractional derivative is restricted to some functions like $f(x) = x^{-a}$. The $(-1)^\nu$ term in this expression suggests the need to broaden the theory to include complex numbers. Indeed, Liouville was able to extend this definition to include complex values for a and ν. By piecing together the somewhat disjointed accomplishments of many notable mathematicians, especially Liouville and Riemann, modern analysts can now define the integral of arbitrary order. The fractional integral of order ν is defined as follows

$$D^{-\nu} f(x) = \frac{1}{\Gamma(\nu)} \int_c^x (x-t)^{\nu-1} \, f(t) \, dt. \tag{1.8}$$

1.2 Special Function of the Fractional Calculus

There are some basic mathematical functions which are important in the study of the theory of fractional calculus. In the next subsection, we will concentrate on the Gamma function, and we will list some well known properties of this function.

1.2.1 Gamma Function

One of the basic fractional functions is Euler's Gamma function. This function is tied to fractional calculus by the definition as we will see later on in the fractional-integral definition. The most basic interpretation of the Gamma function is simply an extension of the factorial function to noninteger values. The Gamma function is defined by the integral

$$\Gamma(x) = \int_0^\infty e^{-t} t^{x-1}\, dt, \qquad x \in \mathbb{R}^+. \tag{1.9}$$

Its relation to the factorials is that for any natural number n, we have

$$\Gamma(n) = (n-1)! \tag{1.10}$$

The Gamma function satisfies the following functional equation

$$\Gamma(x+1) = x\Gamma(x), \qquad x \in \mathbb{R}^+. \tag{1.11}$$

This can be shown through a simple integration by parts:

$$\Gamma(x+1) = \lim_{b\to\infty} \int_0^b e^{-t} t^x \, dt = \lim_{b\to\infty} \left[-e^{-t}x\right]_0^b + \lim_{b\to\infty} \left[x \int_0^b t^{x-1} e^{-t}\, dt\right] = x\Gamma(x).$$

In 1730, Euler generalized the formula

$$\frac{d^n}{dx^n} x^m = \frac{m!}{(m-n)!} x^{m-n}.$$

By using the following property

$$\Gamma(m+1) = (m)!$$

we obtain

$$\frac{d^n}{dx^n}x^m = \frac{\Gamma(m+1)}{\Gamma(m-n+1)}x^{m-n}. \tag{1.12}$$

The incomplete Gamma function is more generalized form of the Gamma function, it is given by

$$\Gamma^*(\nu,t) = \frac{1}{\Gamma(\nu)t^\nu}\int_0^t e^{-x}x^{\nu-1}\,dx, \qquad Re\ \nu > 0. \tag{1.13}$$

[For more details on the Gamma function, you may refer to any book on introductory fractional calculus, for example, "Fractional Differential Equation" by Igor Podlubny (1999).]

1.2.2 The Beta Function

One of the useful mathematical functions in fractional calculus is the Beta function. Its solution is defined through the use of multiple Gamma functions. Also, it shares a form that is characteristically similar to the fractional integral or derivative of many functions, particularly polynomials of the form t^a. The Beta function is defined by a definite integral. The following equation demonstrates the Beta integral and its solution in terms of the Gamma function

$$B(p,q) = \int_0^1 (1-u)^{p-1}u^{q-1}\,du = \frac{\Gamma(p)\Gamma(q)}{\Gamma(p+q)}, \qquad \text{where } p,q \in \mathbb{R}^+.$$

1.2.3 The Mittag-Leffler Function

Another important function of the fractional calculus is the Mittag-Leffler function which plays a significant role in the solution of non-integer order differential equations. The one-parameter representation of the Mittag-Leffler function is defined over the entire complex plane by

$$E_\alpha(x) = \sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k+1)}, \qquad \alpha > 0, x \in \mathbb{C}. \tag{1.14}$$

and is named after Mittag-Leffler who introduced it in 1903 [11], therefore, it is known as the Mittag-Lffler function. In particular, when $\alpha = 1/n, (n \in N\backslash\{1\})$, the function $E_{1/n}(x)$ has the following representation

$$E_{1/n}(x) = e^{x^n}\left\{1 + n\int_0^x e^{-z^n}\left[\sum_{k=1}^{n-1}\frac{z^{k-1}}{\Gamma(k/n)}\right]dz\right\}. \tag{1.15}$$

The two parameter generalized Mittag-Leffler function, which was introduced later, is also defined over the entire complex plane, and is given by

$$E_{\alpha,\beta}(x) = \sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k+\beta)}, \qquad \alpha > 0, \beta > 0, x \in \mathbb{C}. \tag{1.16}$$

It may be noted that when $\beta = 1$, $E_{\alpha,1}(x) = E_\alpha(x)$. Also notice that if we replace α, β by 1, we obtain

$$E_{1,1}(x) = \sum_{k=0}^{\infty} \frac{x^k}{\Gamma(k+1)} = \sum_{k=0}^{\infty} \frac{x^k}{k!} = e^x. \tag{1.17}$$

And this also, can be written in terms of one-parameter of Mittag-Leffler function

$$E_1(x) = E_{1,1}(x) = e^x. \tag{1.18}$$

If we let $x = 0$ in (1.16), we have

$$E_{\alpha,\beta}(0) = 1. \tag{1.19}$$

The Mittag-Leffler function is a natural extension of the exponential function. solutions of fractional order differential equations are often expressed in terms of Mittag-Leffler functions in much the same way that solutions of many integer order differential equations may be expressed in terms of exponential functions. The following lemma lists some properties of Mittag-Leffler function which are useful in the study of fractional calculus.

LEMMA 1.2.1

(i) $\dfrac{1}{\Gamma(\beta)} + xE_{\alpha,\alpha+\beta}(x) = E_{\alpha,\beta}(x)$, where $x \in \mathbb{C}$.

(ii) $e^x[1 + Erf\,(x)] - 1 = xE_{1/2,3/2}(x)$,

where $Erf\,(x)$ is the error function and is given by

$$Erf\,(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2}\, dt, \quad x \in \mathbb{R}.$$

(iii) $\dfrac{d}{dx}[E_{\alpha,\beta}(x)] = \dfrac{1}{\alpha x}[E_{\alpha,\beta-1}(x) - (\beta - 1)E_{\alpha,\beta}(x)]$.

Proof. Using the definition of the Mittag-Leffler function, the proofs can be shown directly as below.

(i) We will proceed the proof by using the definition of Mittag-Leffler function in (1.16) and the properties of the summation, thus

$$\begin{aligned} \frac{1}{\Gamma(\beta)} + xE_{\alpha,\alpha+\beta}(x) &= \frac{1}{\Gamma(\beta)} + x\sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k + \alpha + \beta)} \\ &= \frac{1}{\Gamma(\beta)} + \sum_{k=0}^{\infty} \frac{x^{k+1}}{\Gamma(\alpha(k+1) + \beta)} \end{aligned}$$

If we let $m = k + 1$ in the above sum notation, we obtain

$$\begin{aligned} \frac{1}{\Gamma(\beta)} + xE_{\alpha,\alpha+\beta}(x) &= \frac{1}{\Gamma(\beta)} + \sum_{m=1}^{\infty} \frac{x^m}{\Gamma(\alpha m + \beta)} \\ &= \frac{1}{\Gamma(\beta)} + \sum_{m=0}^{\infty} \frac{x^m}{\Gamma(\alpha m + \beta)} - \frac{1}{\Gamma(\beta)} \\ &= \sum_{m=0}^{\infty} \frac{x^m}{\Gamma(\alpha m + \beta)} \\ &= E_{\alpha,\beta}(x) \end{aligned}$$

(ii) By using the definition of the fractional Mittag-Leffler function in (1.15), we have

$$\begin{aligned} E_{1/2}(x) &= e^{x^2}[1 + \frac{2}{\sqrt{\pi}} \int_0^x e^{-z^2} dz] \\ &= e^{x^2}\left[1 + Erf(x)\right]. \end{aligned}$$

From the property in (i), it can be seen easily that

$xE_{1/2,3/2}(x) = E_{1/2,1}(x) - 1 = E_{1/2}(x) - 1$

By observing the above two equation, we may conclude that

$$e^x[1 + Erf\,(x)] - 1 = xE_{1/2,3/2}(x)$$

(iii) By looking at the left hand side of the equation in (iii), we have

$$\begin{aligned}
\frac{d}{dx}[E_{\alpha,\beta}(x)] &= \frac{d}{dx}\left[\sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k + \beta)}\right] \\
&= \sum_{k=0}^{\infty} \left[\frac{1}{\Gamma(\alpha k + \beta)}\right] \frac{d}{dx} x^k \\
&= \sum_{k=0}^{\infty} \frac{k x^{k-1}}{\Gamma(\alpha k + \beta)}
\end{aligned}$$

Then, the right hand side of the equation is

$$\begin{aligned}
\frac{1}{\alpha x}[E_{\alpha,\beta-1}(x) - (\beta - 1)E_{\alpha,\beta}(x)] &= \frac{1}{\alpha x}\left[\sum_{k=0}^{\infty} \frac{x^k}{\Gamma(\alpha k + \beta - 1)} - (\beta - 1)\sum_{k=o}^{\infty} \frac{x^k}{\Gamma(\alpha k + \beta)}\right] \\
&= \frac{1}{\alpha x}\left[\sum_{k=0}^{\infty} \frac{x^k(\alpha k + \beta - 1)}{(\alpha k + \beta - 1)\Gamma(\alpha k + \beta - 1)} - \sum_{k=o}^{\infty} \frac{x^k(\beta - 1)}{\Gamma(\alpha k + \beta)}\right] \\
&= \frac{1}{\alpha x}\left[\sum_{k=0}^{\infty} \frac{(\alpha k)x^k + \beta x^k - x^k}{\Gamma(\alpha k + \beta)} - \sum_{k=o}^{\infty} \frac{\beta x^k - x^k}{\Gamma(\alpha k + \beta)}\right] \\
&= \sum_{k=0}^{\infty} \frac{(\alpha k)x^k}{\Gamma(\alpha k + \beta)}\left(\frac{1}{\alpha x}\right) \\
&= \sum_{k=0}^{\infty} \frac{k x^{k-1}}{\Gamma(\alpha k + \beta)}.
\end{aligned}$$

Hence, we conclude that

$$\tfrac{d}{dx}[E_{\alpha,\beta}(x)] = \tfrac{1}{\alpha x}[E_{\alpha,\beta-1}(x) - (\beta - 1)E_{\alpha,\beta}(x)].$$

properties of the Mittag-Leffler function have been summarizes in several references [1,11,12,14].

CHAPTER 2

Fractional Integral and Derivative

There are more than one version of the fractional integral exist. For example, it was touched above in the introduction that the fractional integral can be defined as follows

$$ {}_cD_x^{-\nu}\ f(x) = \frac{1}{\Gamma(\nu)} \int_c^x (x-t)^{\nu-1}\ f(t)\ dt,\ \nu > 0. \tag{2.1}$$

It is called the Riemann version, where ${}_cD_x^{-\nu}\ f(x)$ denote the fractional integration of a function to an arbitrary order ν, and ν is any nonnegative real number. In this notation, c and x are the limits of integration operator.

The other version of the fractional integral is called the Liouville version. The case where negative infinity in place of c in (2.1), namely,

$$ {}_{-\infty}D_x^{-\nu}\ f(x) = \frac{1}{\Gamma(\nu)} \int_{-\infty}^x (x-t)^{\nu-1}\ f(t)\ dt. \tag{2.2}$$

In the case where $c = 0$ in (2.1), we obtain what is called the Riemann-Liouville fractional integral:

$$ {}_0D_x^{-\nu}\ f(x) = \frac{1}{\Gamma(\nu)} \int_0^x (x-t)^{\nu-1}\ f(t)\ dt. \tag{2.3}$$

However, our main focus in this thesis will be on what is called the Riemann-Liouville version. For convenience, we will omit the limits of integration from the operator. That is, instead of ${}_cD_x^{-\nu}$, we will simply write $D^{-\nu}$.

2.1 Definition of the Fractional Integral

As we have stated before, our development of the fractional calculus will be based on the Riemann-Liouville fractional integral. We begin this section with a formal definition of the Riemann-Liouville fractional integral as we see below.

Let ν be a real number. Let f be piecewise continuous on $\acute{J} = (0, \infty)$ and integrable on any finite subinterval of $J = [0, \infty)$. Then for $x > 0$ we call

$$D^{-\nu}\ f(x) = \frac{1}{\Gamma(\nu)} \int_0^x (x-t)^{\nu-1}\ f(t)\ dt, \qquad \nu > 0 \tag{2.4}$$

the Riemann-Liouville fractional integral of f of order ν. The definition of the Riemann-Liouville integral can be obtained in several ways. One approach uses the theory of linear differential equations (See Fractional Calculus: Definitions and Applications[7]).

EXAMPLE 2.1.1. Let evaluate $D^{-\nu}\ x^{\mu}$, where $\mu > -1$ and $\nu > 0$.

By definition of the Riemann-Liouville fractional integral, we have

$$\begin{aligned} D^{-\nu}\ x^{\mu} &= \frac{1}{\Gamma(\nu)} \int_0^x (x-t)^{\nu-1} t^{\mu}\ dt. \\ &= \frac{1}{\Gamma(\nu)} \int_0^x x^{\nu-1} (1 - \frac{t}{x})^{\nu-1} t^{\mu}\ dt. \end{aligned}$$

By changing the variable $t/x = u$, then $dt = xdu$, we obtain

$$\begin{aligned} D^{-\nu}\ x^{\mu} &= \frac{1}{\Gamma(\nu)} \int_0^1 x^{\nu} (1-u)^{\nu-1} (xu)^{\mu}\ du. \\ &= \frac{1}{\Gamma(\nu)} x^{\nu+\mu} \int_0^1 (1-u)^{\nu-1} u^{\mu}\ du. \\ &= \frac{1}{\Gamma(\nu)} x^{\nu+\mu} B(\nu, \mu+1) \\ &= \frac{1}{\Gamma(\nu)} x^{\nu+\mu} \frac{\Gamma(\mu+1)\Gamma(\nu)}{\Gamma(\mu+1+\nu)} \\ &= \frac{\Gamma(\mu+1)}{\Gamma(\mu+1+\nu)} x^{\nu+\mu}. \end{aligned}$$

Hence, we conclude that

$$D^{-\nu}\ x^{\mu} = \frac{\Gamma(\mu+1)}{\Gamma(\mu+1+\nu)} x^{\nu+\mu}. \tag{2.5}$$

If we let $\mu = 0$ above, then $x^{\mu} = x^0 = 1$. then by (2.5), the fractional integral of a constant k of order ν is

$$D^{-\nu}\ k = \frac{k}{\Gamma(1+\nu)} x^{\nu},\ \ \nu > 0. \tag{2.6}$$

In particular, if $\nu = \dfrac{1}{2}$

$$D^{-1/2}x^0 = \frac{1}{\Gamma(3/2)}x^{1/2} = 2\sqrt{\frac{x}{\pi}}. \tag{2.7}$$

EXAMPLE 2.1.2. Let $f(t) = e^{at}$, where a is a constant. Then by (2.4) we have

$$D^{-\nu}e^{at} = \frac{1}{\Gamma(\nu)}\int_0^t (t-x)^{\nu-1}\ e^{ax}\ dx, \qquad \nu > 0.$$

By changing the variable $y = t - x$, we obtain

$$D^{-\nu}e^{at} = \frac{e^{at}}{\Gamma(\nu)}\int_0^t y^{\nu-1}\ e^{-ay}\ dy, \qquad \nu > 0. \tag{2.8}$$

If we refer to (1.18), we observe that the above equation may be expressed in terms of the incomplete Gamma function

$$D^{-\nu}e^{at} = t^{\nu}e^{at}\Gamma^*(\nu, at). \tag{2.9}$$

2.2 Properties of the Fractional Integral

One of the most important properties in the development of fractional calculus is the law of exponents which is very useful to calculate fractional integral and fractional derivative for some functions, also to prove some relations that are related to fractional calculus theory. In this section we state the theorem of the law of exponents for fractional calculus without proof.

THEOREM 2.1.1. [16] Let f be continuous function on J and let $\mu, \nu > 0$. Then for all $t > 0$,

$$D^{-\mu}[D^{-\nu}f(t)] = D^{-(\mu+\nu)}f(t) = D^{-\nu}[D^{-\mu}f(t)]. \tag{2.10}$$

Another useful property in the study of fractional calculus is the commutative property. Many mathematical proofs rely on the commutative property where we can interchange the integer order of the derivative and the fractional order of the integral. So it is worthwhile to mention it here.

THEOREM 2.1.2. [16] Let f be continuous on J and let $\nu > 0$, If Df is continuous, then for all $t > 0$,

$$D[D^{-\nu} f(t)] = D^{-\nu}\left[Df(t)\right] + \frac{f(t)|_{t=0}}{\Gamma(\nu)} t^{\nu-1}. \tag{2.11}$$

2.3 Definition of the Fractional Derivative

The notation that is used to denote the fractional derivative is $D^{\alpha}\ f(x)$ for any arbitrary number of order α. Fractional derivative can be defined in terms of the fractional integral as follows

$$D^{\alpha} f(t) = D^{n}[D^{-u} f(t)], \tag{2.12}$$

where $0< u < 1$, and n is the smallest integer greater than α such that $u = n - \alpha$.

EXAMPLE 2.2.1. If $f(x) = x^{\mu}$, where $\mu \geq 0$. Then, for $n = 1$, the α derivative of x^{μ} is

$$\begin{aligned} D^{\alpha} x^{\mu} &= D^{1}[D^{-(1-\alpha)} x^{\mu}], \quad \text{where } u = 1 - \alpha. \\ &= D^{1}\left[\frac{\Gamma(\mu+1)}{\Gamma((\mu-\alpha+1)+1)} x^{\mu-\alpha+1}\right] \\ &= (\mu-\alpha+1)\frac{\Gamma(\mu+1)}{(\mu-\alpha+1)\Gamma(\mu-\alpha+1)} x^{\mu-\alpha} \\ &= \frac{\Gamma(\mu+1)}{\Gamma(\mu-\alpha+1)} x^{\mu-\alpha}. \end{aligned}$$

Hence, we conclude

$$D^{\alpha} x^{\mu} = \frac{\Gamma(\mu+1)}{\Gamma(\mu-\alpha+1)} x^{\mu-\alpha}. \tag{2.13}$$

Notice that if $f(x) = k$, where k is a constant, then α order derivative of a constant is

$$D^{\alpha} k = \frac{k}{\Gamma(-\alpha+1)} x^{-\alpha}.$$

It is interesting to observe that for any constant k, $D^{\alpha}k$ is not zero where $0 < \alpha < 1$. For example, the 1/2 order derivative of k is

$$D^{1/2}k = \frac{k}{\Gamma(1/2)}x^{-1/2} = \frac{k}{\sqrt{\pi x}}.$$

REMARK 2.2.1. Let f be a real valued function. In the traditional calculus, we have $DD^{-1}f = f$. For any positive real number α, this equality valid for fractional calculus as well. To see this, we use definition of the fractional derivative and the exponent law (Theorem 2.1.1) ,

$$\begin{aligned} D^{\alpha}D^{-\alpha}f(x) &= D^{n}[D^{-(n-\alpha)}(D^{-\alpha}f(t))]. \\ &= D^{n}[D^{-(n-\alpha+\alpha)}f(x)] = D^{n}D^{-n}f(x) = f(x), \end{aligned}$$

where n is the smallest integer greater than α.

REMARK 2.2.2. Let y be continuous on J. Then the following equality holds

$$D^{1/2}[D^{1/2}y(t)] = Dy(t).$$

We can prove this equality directly by using definition of fractional derivative and the commutative law (Theorem 2.1.2)

$$\begin{aligned} D^{1/2}[D^{1/2}y(t)] &= D^{1/2}[D(D^{-1/2}y(t))] \\ &= D^{1/2}\left\{[D^{-1/2}(Dy(t))] + \frac{y(t)|_{t=0}}{\Gamma(1/2)}t^{-1/2}\right\}. \end{aligned}$$

Let $y(0)|_{t=0} = 0$, this implies

$$D^{1/2}D^{1/2}y(t) = D^{1/2}[D^{-1/2}(Dy(t))].$$

Using (Remark 2.2.1), we obtain

$$D^{1/2}D^{1/2}y(t) = Dy(t).$$

LEMMA 2.2.1. Let f be continuous on J, then the fractional equation

$$D^{1/2}y(t) - y(t) = -1, \tag{2.14}$$

can be converted to the following differential equation

$$D\ y(t) - y(t) = -1 - \frac{1}{\sqrt{\pi t}}. \tag{2.15}$$

Proof. Using the distributive property of fractional derivative and (Remark 2.2.2), proof can be shown directly as below.

Taking the 1/2 order derivative on both sides of equation (2.14) yields :

$$D^{1/2}[D^{1/2}y(t)] - D^{1/2}y(t) = D^{1/2}(-1).$$

This implies

$$Dy(t) - D^{1/2}y(t) = \frac{-1}{\sqrt{\pi t}}.$$

If we refer to equation (2.14), we may write the above equation as:

$$D\ y(t) - (y(t) - 1) = \frac{-1}{\sqrt{\pi t}}.$$

This implies

$$D\ y(t) - y(t) = -1 - \frac{1}{\sqrt{\pi t}}.$$

REMARK 2.2.3. A useful tool for computation of the fractional derivative of a product of two functions $f(x)$ and $g(x)$ is the generalized Leibniz rule [26]:

$$D^{\alpha}f(x)g(x) = \sum_{n=0}^{\infty}\binom{\alpha}{n}D^{n}f(x)D^{\alpha-n}g(x), \tag{2.16}$$

where D^n is the ordinary differentiation operator $d^n/dx^n, D^{\alpha-n}$ is a fractional operator and $\binom{\alpha}{n}$ is the generalized binomial coefficient $\dfrac{\Gamma(\alpha+1)}{n!\Gamma(\alpha-n+1)}$. When taking the arbitrary derivative of a product, it is often convenient to choose the factor in such a way that the series above terminates after n ordinary differentiation. For example,

$$D^{1/2}(xg(x)) = xD^{1/2}g(x) + \tfrac{1}{2}D^{-1/2}g(x)$$

terminates for $n = 1$. The generalized Leibniz rule can be used in applications as we will see in the next section.

2.4 Applications of Fractional Integral and Derivative

The first to use a fractional operation was by Niel Henrik Abel in 1823. Abel applied the fractional calculus to the solution of an integral equation which arose in his formulation of the tautochrone problem : A bead on a frictionless wire starts from rest at some point (x_0,y_0) and falls under the influence of gravity. What shape wire has the property that the time it takes the bead to descend is independent of its srarting point? Since the kinetic energy gained equals the potential energy lost, $1/2m(d\lambda/dt)^2 = mg(y_0 - y)$,where λ is the distance of the bead along the wire, m is the mass, and g is the gravitational acceleration. Thus

$$-\frac{d\lambda}{\sqrt{y_0 - y}} = \sqrt{2g}dt$$

and integration from top to bottom (time $t = 0$ to time $t = T$), gives

$$\sqrt{2g}T = \int_{y=0}^{y=y_0} (y_0 - y)^{-1/2} d\lambda.$$

The tautochrone problem requires that the left side of this integral be a constant which we will denote by k. The path length λ may be expressed as a function of the height, say $\lambda = F(y)$, so that $d\lambda/dy = F'(y)$. If we change variable y_0 and y to x and t, and replace F' by f, the tautochrone integral equation becomes $k = \int_0^x (x-t)^{-1/2} f(t)dt$. Our problem is to determine the function f. this can be done by the convolution theorem of Laplace transform theory. Abel, however, multiplied the equation by $1/\Gamma(1/2)$ to obtain

$$\frac{k}{\Gamma(1/2)} = \frac{1}{\Gamma(1/2)} \int_0^x (x-t)^{-1/2} f(t) dt = D^{-1/2} f(x)$$

By operationg on the extreme terms of this equation with $D^{1/2}$, he obtained $D^{1/2}k = \sqrt{\pi} f(x)$. Then by computing the derivative of order 1/2 of the constant k (as in Example 2.2.1, for instance) Able obtained $f(x) = k/\pi\sqrt{x}$. He then went on to show that the solution to tautochrone problem is a cycloid.

As another application, consider the problem of determine $f(x)$ explicitly from the integral equation

$$x f(x) = \int_0^x (x-t)^{-1/2} f(t) dt.$$

The right side of this equation is $\Gamma(1/2) D^{-1/2} f(x)$, thus we can write this equation as follows

$$x f(x) = \Gamma(1/2) D^{-1/2} f(x). \tag{2.17}$$

Operating on both sides with $D^{1/2}$ yields

$$D^{1/2}\{x f(x)\} = \sqrt{\pi} f(x).$$

Using the generalized Leibniz rule (2.16) yields

$$x D^{1/2} f(x) + \tfrac{1}{2} D^{-1/2} f(x) = \sqrt{\pi} f(x).$$

Using the fractional derivative definition, we have

$$x D[D^{-1/2} f(x)] + \tfrac{1}{2} D^{-1/2} f(x) = \sqrt{\pi} f(x).$$

If we refer to equation (2.17), we may write the above equation as

$$xD\{xf(x)/\sqrt{\pi}\} + \tfrac{1}{2}\{xf(x)/\sqrt{\pi}\} = \sqrt{\pi}f(x).$$

By using the chain rule to compute the first derivative of $xf(x)$, we obtain

$$x\{[xf'(x) + f(x)]/\sqrt{\pi}\} + \tfrac{1}{2}\{xf(x)/\sqrt{\pi}\} = \sqrt{\pi}f(x).$$

Multiplying both side by $\sqrt{\pi}$ yields

$$x\{[xf'(x) + f(x)]\} + \tfrac{1}{2}\{xf(x)\} = \pi f(x),$$

which implies

$$x^2 f'(x) + (\tfrac{3x}{2} - \pi)f(x) = 0,$$

which has the solution

$$f(x){=}ke^{-\pi/x}x^{-3/2}.$$

The same result can be obtained from the original integral equation by the use of Laplace transform. However, fractional calculus might suggest a solution to a complicated functional equation without using other means, like Laplace transform.

CHAPTER 3

Laplace Transform

The main idea behind the Laplace transform is that we can solve an equation (or system of equations) containing differential and integral terms by transforming the equation in "t-space" to one in "s-space". Laplace transform makes the problem much easier to solve by converting the differential equation to an algebraic equation and is particularly suited for differential equations with initial conditions.

In this chapter, we present definition of the Laplace transform and its properties. Then we calculate the Laplace transform of the fractional integral and fractional derivative.

3.1 Definition of the Laplace Transform

The Laplace transform of a function $f(t)$ of a real variable $t \in R^{+} = (0, \infty)$ is defined by

$$\mathcal{L}\{f(t)\} = \int_0^\infty e^{-st}\ f(t)\ dt\ = F(s) \qquad (s \in \mathbb{C}). \tag{3.1}$$

The Laplace transform of the function $f(t)$ is said to exist if (3.1) is a convergent integral. The requirement for this is that $f(t)$ does not grow at a rate higher than the rate at which the exponential term e^{-st}decreases. We use the notation $\mathcal{L}^{-1}\{F(s)\}$to denote the inverse Laplace transform of $F(s)$. Using basic elementary calculus, we obtain a short table of Laplace transforms of some functions:

$$\mathcal{L}\{t^{\mu}\} = \frac{\Gamma(\mu+1)}{s^{\mu+1}}, \qquad \mu \geq -1.$$

$$\mathcal{L}\{e^{at}\} = \frac{1}{s-a}, \qquad a \in \mathbb{R},\ s \neq a.$$

$$\mathcal{L}\{\cos at\} = \frac{s}{s^2+a^2}, \qquad a \in \mathbb{R}.$$

$$\mathcal{L}\{\sin at\} = \frac{a}{s^2+a^2}, \qquad a \in \mathbb{R},$$

where they are well-defined.

3.2 Properties of the Laplace Transform

If the Laplace transformation of $f(t)$ and $g(t)$ exist, then

(i) $\mathcal{L}\{f(t)+g(t)\} = \mathcal{L}\{f(t)\} + \mathcal{L}\{g(t)\}$.

(ii) $\mathcal{L}\{cf(t)\} = c\mathcal{L}\{f(t)\}$, where c is a constant .

(iii) If $F(s)$ and $G(s)$ are the Laplace transform of $f(t)$ and $g(t)$, respectively, then

$$\mathcal{L}\{f(t) * g(t)\} = F(s)G(s),$$

where the operator $*$ is a convolution product and is defined by

$$f(t) * g(t) = \int_0^t f(t-z)\ g(z)\ dz.$$

(iv) The Laplace transform of the $n-th$ derivative of the function $f(t)$ is given by

$$\mathcal{L}\{f^{(n)}(t)\} = s^n F(s) - \sum_{k=0}^{n-1} s^{n-k-1} f^{(k)}(t)|_{t=0}.$$

where n is an integer order.

In the next two sections, we present the Laplace transform of the fractional integral and derivative.

3.3 Laplace Transform of the Fractional Integral

The fractional integral of $f(t)$ of order α is

$$D^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \int_0^t (t-z)^{\alpha-1} f(z)\ dz, \qquad 0 < \alpha \leq 1.$$

This equation is actually a convolution product. So, by taking the Laplace transform we have

$$
\begin{aligned}
\mathcal{L}\{D^{-\alpha}f(t)\} &= \frac{1}{\Gamma(\alpha)}\mathcal{L}\left\{\int_0^t (t-z)^{\alpha-1}f(z)\ dz\right\} \\
&= \frac{1}{\Gamma(\alpha)}\mathcal{L}\{t^{\alpha-1} * f(t)\} \\
&= \frac{1}{\Gamma(\alpha)}\mathcal{L}\{t^{\alpha-1}\}\mathcal{L}\{f(t)\} \\
&= \frac{1}{\Gamma(\alpha)}\frac{\Gamma(\alpha)}{s^{\alpha}}\mathcal{L}\{f(t)\} = s^{-\alpha}\mathcal{L}\{f(t)\}
\end{aligned}
$$

By using the Laplace transform of the fractional integral, one can simply calculate the Laplace transform of the following functions

$$
\begin{aligned}
\mathcal{L}\{D^{-\alpha}t^{\mu}\} &= \frac{\Gamma(\mu+1)}{s^{\mu+\alpha+1}}. \\
\mathcal{L}\{D^{-\alpha}e^{at}\} &= \frac{1}{s^{\alpha}(s-a)}. \\
\mathcal{L}\{D^{-\alpha}\cos at\} &= \frac{1}{s^{\alpha-1}(s^2+a^2)}. \\
\mathcal{L}\{D^{-\alpha}\sin at\} &= \frac{a}{s^{\alpha}(s^2+a^2)}.
\end{aligned}
$$

where they are well-defined.

3.4 Laplace Transform of the Fractional Derivative

We recall that the fractional derivative of $f(t)$ is

$$
D^{\alpha}f(t) = D^{n}[D^{-(n-\alpha)}f(t)],
$$

where n is the smallest integer greater than α. Now, let's calculate the Laplace transform of $D^{\alpha}\ f(t)$:

$$
\begin{aligned}
\mathcal{L}\{D^{\alpha}f(t)\} &= \mathcal{L}\{D^{n}[D^{-(n-\alpha)}f(t)]\} \\
&= s^{n}\mathcal{L}\{D^{-(n-\alpha)}f(t)\} - \sum_{k=0}^{n-1} s^{n-k-1}D^{k}[D^{-(n-\alpha)}f(t)|_{t=0}.] \\
&= s^{n}s^{-(n-\alpha)}\mathcal{L}\{f(t)\} - \sum_{k=0}^{n-1} s^{n-k-1}D^{k-n+\alpha}f(t)|_{t=0} \\
&= s^{\alpha}\mathcal{L}\{f(t)\} - \sum_{k=0}^{n-1} s^{n-k-1}D^{k-n+\alpha}f(t)|_{t=0}.
\end{aligned}
$$

In particular, if $0 < \alpha \leq 1$, then $n = 1$ and the Laplace transform of the fractional derivative of $f(t)$ becomes

$$\mathcal{L}\{D^{\alpha} f(t)\} = s^{\alpha}\mathcal{L}\{f(t)\} - D^{-(1-\alpha)} f(t)|_{t=0}.$$

EXAMPLE 3.4.1 Let's solve the following initial value problem

$$D^{\alpha} y(t) = 0.02 y(t),$$

$$D^{-(1-\alpha)} y(t)|_{t=0} = 1.$$

where $0 < \alpha \leq 1$.

By taking the Laplace transform of both sides of the equation above, we have

$$\mathcal{L}\{D^{\alpha} y(t)\} = 0.02\mathcal{L}\{y(t)\},$$

which implies that

$$s^{\alpha} Y(s) - D^{-(1-\alpha)} y(t)|_{t=0} = 0.02 Y(s), .$$

where $Y(s) = \mathcal{L}\{y(t)\}$. By replacing $D^{-(1-\alpha)} y(0)$ by 1, we obtain

$$s^{\alpha} Y(s) - 1 = 0.02 Y(s).$$

Solving for $Y(s)$, we obtain

$$Y(s) = \frac{1}{s^{\alpha} - 0.02}.$$

Finally, by using Table 3.1, we find the inverse Laplace transform of $Y(s)$

$$y(t) = t^{\alpha-1} E_{\alpha,\alpha}(0.02\ t^{\alpha}).$$

Remark 3.4.1. The above example show that, if $y(t) = t^{\alpha-1} E_{\alpha,\alpha}(a\ t^{\alpha})$, then

$$D^\alpha t^{\alpha-1}E_{\alpha,\alpha}(a\ t^\alpha) = at^{\alpha-1}E_{\alpha,\alpha}(a\ t^\alpha)$$

where $a \neq 0$ is a constant and $0 < \alpha \leq 1$. Also, we notice that $y(t)$ can not be equal to zero for all $t > 0$.

Table (3.1) gives a brief summary of some useful Laplace transform pairs. We will frequently refer to this table when we are solving fractional differential equations in the following chapters.

$F(s)$	$f(t)$
$\frac{1}{s}$	1
$\frac{1}{s^2}$	t
$\frac{1}{s^\alpha}$	$\frac{t^{\alpha-1}}{\Gamma(\alpha)}$
$\frac{1}{(s+a)^\alpha}$	$\frac{t^\alpha}{\Gamma(\alpha)}e^{-at}$
$\frac{1}{s^\alpha - a}$	$t^{\alpha-1}E_{\alpha,\alpha}(at^\alpha)$
$\frac{s^\alpha}{s(s^\alpha + a)}$	$E_\alpha(-at^\alpha)$
$\frac{a}{a(s^\alpha + a)}$	$1 - E_\alpha(-at^\alpha)$
$\frac{1}{s^\alpha(s-a)}$	$t^\alpha E_{1,\alpha+1}(at)$
$\frac{s^{\alpha-\beta}}{s^\alpha - a}$	$t^{\beta-1}E_{\alpha,\beta}(at^\alpha)$
$\frac{1}{s-a}$	e^{at}
$\frac{1}{(s-a)(s-b)}$	$\frac{1}{b-a}(e^{at} - e^{bt})$

Table 3.1. Laplace transform (a and b are real constants and $a \neq b$; $\alpha, \beta > 0$ are arbitrary)

LEMMA 3.4.1 For $0 < \alpha \leq 1$ the following equality holds :

$$D^\alpha[E_\alpha(at^\alpha) - 1] = aE_\alpha(at^\alpha).$$

where E_α is the Mittag-Leffler function in one parameter.

Proof. By taking the Laplace transform of the left hand side of the equation, we have

$$\begin{aligned}
\mathcal{L}\{D^\alpha[E_\alpha(at^\alpha)-1]\} &= s^\alpha \mathcal{L}\{E_\alpha(at^\alpha)-1)\} - D^{-(1-\alpha)}[E_\alpha(0)-1] \\
&= s^\alpha[\mathcal{L}\{E_\alpha(at^\alpha)\} - \mathcal{L}\{1\}] - D^{-(1-\alpha)}(t)|_{t=0} \\
&= s^\alpha\left(\frac{s^\alpha}{s(s^\alpha-a)} - \frac{1}{s}\right) - 0 \\
&= \frac{as^\alpha}{s(s^\alpha-a)}
\end{aligned}$$

Applying the inverse Laplace transform to each sides of the above equation, we have the desired result

$$D^\alpha[E_\alpha(at^\alpha)-1] = aE_\alpha(at^\alpha).$$

CHAPTER 4

Fractional Trigonometric Functions

In this chapter we develop fractional trigonometry based on the multi-valued fractional generalization of the exponential function, Mittag-Leffler function. Mittag-Leffler function plays an important role in the solution of fractional order differential equations. The development of fractional calculus has involved new functions that generalize the exponential function. These functions allow the opportunity to generalize the trigonometric functions to "fractional" or "generalized" versions. In this chapter, we discuss the relationships between Mittag-Leffler function and the new fractional trigonometric functions. Laplace transform are derived for the new functions and are used to generate the solution sets for various classes of fractional differential equations. Then we generalize the Wronskian for a system of fractional derivative equations as well. Also, a new method is presented for solving system of fractional differential equations.

4.1 Generalized Exponential Function

As we pointed out, Mittag-Leffler function can be written in terms of two parameters α and β as

$$E_{\alpha,\beta}[t] = \sum_{n=0}^{\infty} \frac{t^n}{\Gamma(n\alpha+\beta)}, \qquad \alpha, \beta > 0.$$

This function will often appear with the argument at^{α}, thus it can be written as

$$E_{\alpha,\beta}[at^{\alpha}]= \sum_{n=0}^{\infty} \frac{(at^{\alpha})^n}{\Gamma(n\alpha+\beta)}, \qquad \text{where } \alpha, \beta > 0 \text{ and } a \in \mathbb{C}.$$

The exponential function can be written in terms of Mittag-Leffler function as

$$E_{1,1}[at]= \sum_{n=0}^{\infty} \frac{(at)^n}{\Gamma(n+1)} = e^{at}.$$

Based on Mittag-Leffler function, the generalized form of the exponential function can be written as

$$e_{\alpha,\alpha}(a,t) = t^{\alpha-1}E_{\alpha,\alpha}[at^{\alpha}], \qquad t > 0. \tag{4.1}$$

4.2 Generalized Trigonometry

This section develops fractional trigonometry based on the generalization of the exponential function $e_{\alpha,\alpha}(a,t)$. Because of the fractional characteristics of α we will see trigonometric functions to have families of functions for fractional trigonometric functions instead of a single function. "Fractional" or "generalized" trigonometric functions can be derived from $e_{\alpha,\alpha}(a,t)$.

One way to define the (integer order) trigonometry is based on the close relation to the exponential function.

$$\cos t = \frac{e^{it} + e^{-it}}{2}, \tag{4.2}$$

and

$$\sin t = \frac{e^{it} - e^{-it}}{2i}. \tag{4.3}$$

To derive the multi-valued character of the new trigonometric functions we consider the generalization of the exponential function, Then fractional cosine can be defined as

$$\cos_{\alpha,\alpha}(a,t) = \frac{e_{\alpha,\alpha}(ai,t) + e_{\alpha,\alpha}(-ai,t)}{2}, \qquad t > 0, \tag{4.4}$$

and fractional sine can be defined as

$$\sin_{\alpha,\alpha}(a,t) = \frac{e_{\alpha,\alpha}(ai,t) - e_{\alpha,\alpha}(-ai,t)}{2i}, \qquad t > 0. \tag{4.5}$$

Also, we can define fractional tangent function as

$$\tan_{\alpha,\alpha}(a,t) = \frac{\sin_{\alpha,\alpha}(a,t)}{\cos_{\alpha,\alpha}(a,t)}, \qquad t > 0. \tag{4.6}$$

The development for the remaining functions (i.e. $\sec_{\alpha,\alpha}(a,t), \csc_{\alpha,\alpha}(a,t)$ and $\cot_{\alpha,\alpha}(a,t)$) would be based on the relationship between these functions and the two functions cosine and sine.

These functions, identities (4.4)-(4.6), generalize the circular functions of the normal or integer order trigonometry and are used as the basis of the relationships that follow.

4.3 Properties of Fractional Trigonometric Functions

It is directly observed from the definition of $\cos_{\alpha,\alpha}(a,t)$ and $\sin_{\alpha,\alpha}(a,t)$, equation (4.4) and (4.5), that

$$\cos_{\alpha,\alpha}(-a,t) = \cos_{\alpha,\alpha}(a,t), \tag{4.7}$$

and

$$\sin_{\alpha,\alpha}(-a,t) = -\sin_{\alpha,\alpha}(a,t). \tag{4.8}$$

Substituting equation (4.7) and (4.8) into (4.6) gives

$$\tan_{\alpha,\alpha}(-a,t) = \frac{-\sin_{\alpha,\alpha}(a,t)}{\cos_{\alpha,\alpha}(a,t)} = -\tan_{\alpha,\alpha}(a,t), \qquad t > 0. \tag{4.9}$$

Figure 4.1 and 4.2 show the fractional cosine and the fractional sine for various values of α. We notice that two curves of fractional cosine at $\alpha = .98$ and $\alpha = .95$ behave similarly.

Notice that the curves of both fractional cosine and sine are approaching the traditional cosine and sine, respectively as α approaches 1.

It is directly follows from (4.4) and (4.5) that

$$e_{\alpha,\alpha}(ai,t) = \cos_{\alpha,\alpha}(a,t) + i\sin_{\alpha,\alpha}(a,t), \qquad t > 0. \tag{4.10}$$

From the above equation and equations (4.7) and (4.8) , it follows that

$$e_{\alpha,\alpha}(-ai,t) = \cos_{\alpha,\alpha}(a,t) - i\sin_{\alpha,\alpha}(a,t), \qquad t > 0. \tag{4.11}$$

Squaring equation (4.4) yields

$$\cos^2_{\alpha,\alpha}(a,t) = \frac{1}{4}\{e^2_{\alpha,\alpha}(ai,t) + e^2_{\alpha,\alpha}(-ai,t) + 2e_{\alpha,\alpha}(ai,t)e_{\alpha,\alpha}(-ai,t)\}. \tag{4.12}$$

And squaring equation (4.5) yields

$$\sin^2_{\alpha,\alpha}(a,t) = \frac{-1}{4}\{e^2_{\alpha,\alpha}(ai,t) + e^2_{\alpha,\alpha}(-ai,t) - 2e_{\alpha,\alpha}(ai,t)e_{\alpha,\alpha}(-ai,t)\}. \tag{4.13}$$

Adding the above two equations (4.12) and (4.13) gives

$$\cos^2_{\alpha,\alpha}(a,t) + \sin^2_{\alpha,\alpha}(a,t) = \quad e_{\alpha,\alpha}(ai,t)e_{\alpha,\alpha}(-ai,t), \qquad t > 0. \tag{4.14}$$

Substituting α and a by 1 in equation (4.14) yields

$$\cos^2 t - \sin^2 t = 1$$

Subtracting (4.13) from (4.12) yields

$$\cos^2_{\alpha,\alpha}(a,t) - \sin^2_{\alpha,\alpha}(a,t) = \frac{1}{2}\{e^2_{\alpha,\alpha}(ai,t) + e^2_{\alpha,\alpha}(-ai,t)\ \}, \qquad t > 0. \tag{4.15}$$

Let α and a be equal to 1 in equation (4.15), we obtain

$$\cos^2 t - \sin^2 t = \frac{1}{2}\{e^{2it} + e^{-2it}\} = \cos(2t).$$

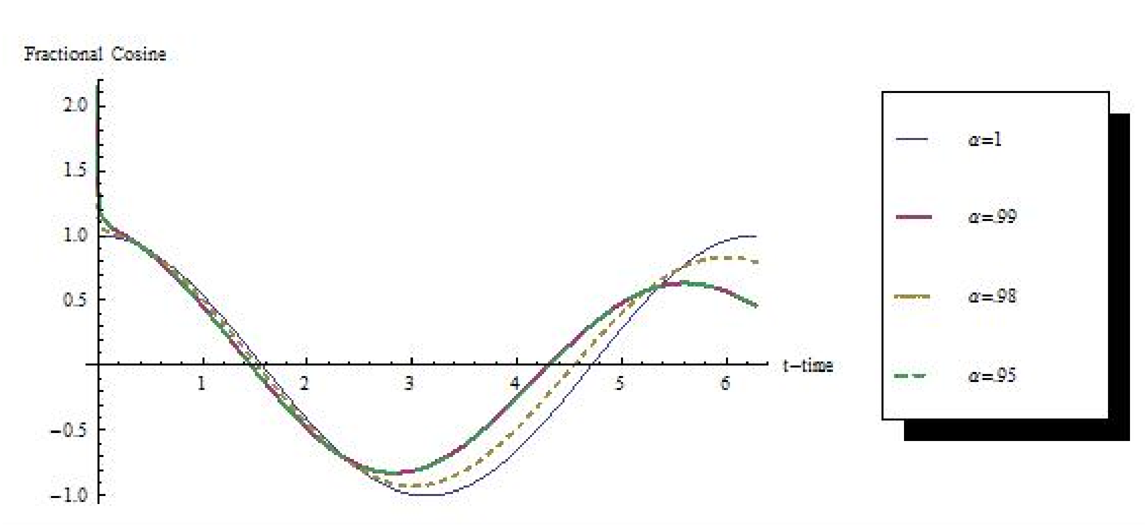

Figure 4.1. Fractional cosine ($\cos_{\alpha,\alpha}(a,t)$) vs. t-time

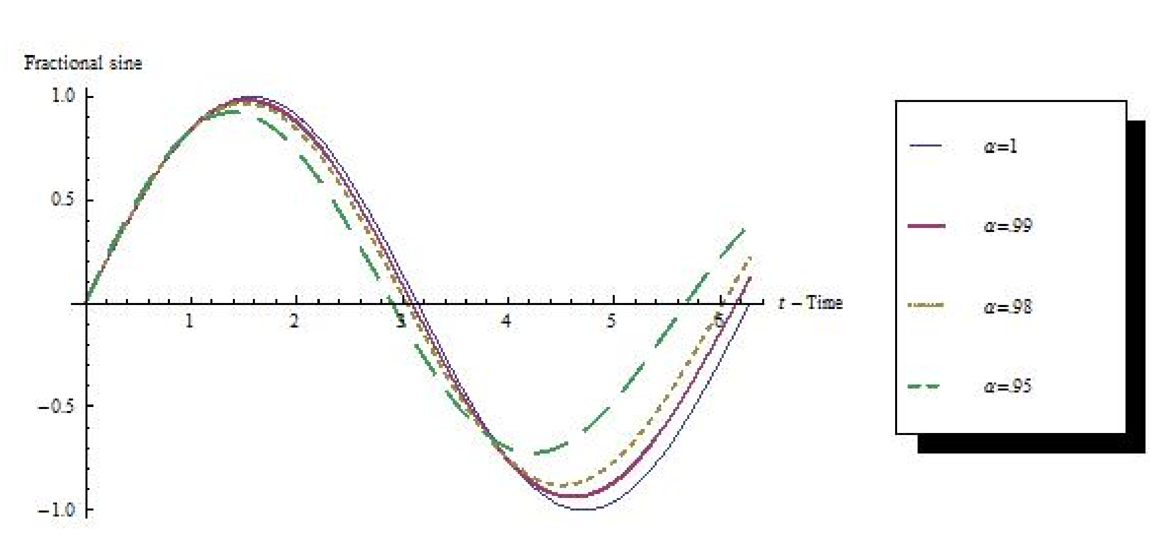

Figure 4.2. Fractional sine ($\sin_{\alpha,\alpha}(a,t)$) vs. t-time

The fractional trigonometric functions based on the Mittag-Leffler Function are generalizations of the standard circular functions and this is readily shown by the substitution $\alpha = 1$ in the definition of the fractional trigonometric functions, that is;

$\cos_{1,1}(a,t) = \cos(at)$, $\qquad t > 0,$

and

$\sin_{1,1}(a,t) = \sin(at),$ $\qquad t > 0.$

In the same manner we can define the fractional hyperbolic functions, these are

$$\cosh_{\alpha,\alpha}(a,t) = \frac{e_{\alpha,\alpha}(a,t) + e_{\alpha,\alpha}(-a,t)}{2}, \qquad t > 0, \tag{4.16}$$

and

$$\sinh_{\alpha,\alpha}(a,t) = \frac{e_{\alpha,\alpha}(a,t) - e_{\alpha,\alpha}(-a,t)}{2}, \qquad t > 0. \tag{4.17}$$

4.4 Laplace Transform of the Fractional Trigonometric Functions

Once we calculate the Laplace transform of the generalized exponential function, it would be easy to derive the Laplace transform of the fractional trigonometric functions and of the hyperbolic functions too.

So, let's calculate the Laplace transform of the generalized exponential function

$$\begin{aligned}
\mathcal{L}\{e_{\alpha,\alpha}(a,t)\} &= \mathcal{L}\{t^{\alpha-1}E_{\alpha,\alpha}(at^{\alpha})\} \\
&= \mathcal{L}\{t^{\alpha-1}\sum_{n=0}^{\infty}\frac{a^n t^{\alpha n}}{\Gamma(\alpha n+\alpha)}\} \\
&= \mathcal{L}\{\sum_{n=0}^{\infty}\frac{a^n}{\Gamma(\alpha n+\alpha)}t^{\alpha n+\alpha-1}\} \\
&= \sum_{n=0}^{\infty}\frac{a^n}{\Gamma(\alpha n+\alpha)}\mathcal{L}\{t^{\alpha n+\alpha-1}\} \\
&= \sum_{n=0}^{\infty}\frac{a^n}{\Gamma(\alpha n+\alpha)}\frac{\Gamma(n\alpha+\alpha)}{s^{n\alpha+\alpha}} \\
&= \frac{1}{s^{\alpha}}\sum_{n=0}^{\infty}(\frac{a}{s^{\alpha}})^n. \\
&= \frac{1}{s^{\alpha}-a}, \qquad t > 0.
\end{aligned}$$

where $\left|\frac{a}{s^\alpha}\right| < 1$.

The following table (Table 4.1) gives a summary of the Laplace transform of both integer and fractional exponential function, trigonometric functions and hyperbolic functions.

4.5 Generalized Wronskian and Linear Independence

Wronskian is a determinant formulated by Polish mathematician and philosopher Józef Maria Hoëne-Wroński. It is especially important in the study of differential equations,

Integer Function	Laplace Transform	Fractional Function	Laplace Transform
e^{at}	$\frac{1}{s-a}$	$e_{\alpha,\alpha}(a,t)$	$\frac{1}{s^\alpha - a}$
$\cos(at)$	$\frac{s}{s^2+a^2}$	$\cos_{\alpha,\alpha}(a,t)$	$\frac{s^\alpha}{s^{2\alpha}+a^2}$
$\sin(at)$	$\frac{a}{s^2+a^2}$	$\sin_{\alpha,\alpha}(a,t)$	$\frac{a}{s^{2\alpha}+a^2}$
$\cosh(at)$	$\frac{s}{s^2-a^2}$	$\cosh_{\alpha,\alpha}(a,t)$	$\frac{s^\alpha}{s^{2\alpha}-a^2}$
$\sinh(at)$	$\frac{a}{s^2-a^2}$	$\sinh_{\alpha,\alpha}(a,t)$	$\frac{a}{s^{2\alpha}-a^2}$

Table 4.1. Laplace transform of exponential,trigonometric, and hyperbolic functions.

where it can be used to determine whether a set of solutions is linearly independent. Two functions that are linearly dependent are multiples of each other, whereas linearly independent ones are not. If the Wronskian is zero at all points, which means it vanishes everywhere, then the functions are linearly dependent. In mathematical terms, for two functions f and g, this means $W(f,g) = 0$. In this section we generalize the Wronskian for a system of fractional differential equations, then we prove the linear independence for a set of solutions.

Consider a linear differential equation that has the form

$$a_n(D^\alpha)^n y(x) + a_{n-1}(D^\alpha)^{n-1} y(x) + ... + a_1 D^\alpha y(x) + a_0 y(x) = g(x), \tag{4.18}$$

where $(D^\alpha)^n = \underbrace{D^\alpha D^\alpha ... D^\alpha}_{n-\text{times}}$, $0 < \alpha \leq 1$,and $(D^\alpha)^n \neq D^{\alpha n}$, also, a_j are constants, where $j = 0, 1, 2, ..., n$, and $g(x)$ depends solely on the variable x. In other words, they do not depend on y or any derivative of y.

If $g(x) = 0$, then the equation (4.18) is called homogeneous; if not, (4.18) is called a non-homogeneous fractional equation.

4.5.1 Definition of the Generalized Wronskian of a Set of Functions

Let $\{y_1, y_2, ..., y_n\}$ be a set of functions which are defined on the interval I. The determinant

$$W[y_1, y_2, ..., y_n] = \begin{vmatrix} y_1 & y_2 & \cdots & y_n \\ D^\alpha y_1 & D^\alpha y_2 & \cdots & D^\alpha y_n \\ \vdots & \vdots & \ddots & \vdots \\ (D^\alpha)^{n-1} y_1 & (D^\alpha)^{n-1} y_2 & \cdots & (D^\alpha)^{n-1} y_n \end{vmatrix}$$

is called the generalized Wronskian of the given set of functions. It is the determinant constructed by placing the functions in the first row, the α derivative of each function in the second row, and so on where $0 < \alpha \leq 1$.

4.5.2 The Generalized Wronskian Test for the Linear Independence

Let $\{y_1, y_2, ..., y_n\}$ be a set of n solutions of a fractional linear homogeneous differential equation.

The set is linearly independent $\Longleftrightarrow$ generalized Wronskian is not identically equal to zero.

Theorem 4.5.1. Let $y_1(t)$ and $y_2(t)$ be solution of

$$D^\alpha D^\alpha y(t) + pD^\alpha y(t) + qy(t) = 0, \qquad \text{on an interval } I,$$

where p, q are constants.

And,

$$W[y_1, y_2] = \begin{vmatrix} y_1 & y_2 \\ D^\alpha y_1 & D^\alpha y_2 \end{vmatrix} = y_1 D^\alpha y_2 - y_2 D^\alpha y_1 \qquad \text{for all } t \text{ in } I.$$

Then, $y_1$and y_2 are linearly independent on I if and only if $W[y_1, y_2] \neq 0$ for some t in I.

Proof. ($\Leftarrow$) We prove by showing " $y_1$and y_2 are linearly dependent$\Longrightarrow W = 0$".

If $y_1$and y_2 are linearly dependent, then $y_2 = ky_1$ for some constant k (or $y_1 = ky_2$ for some constant k which leads to a similar argument to follow). Thus

$$\begin{aligned} W[y_1, y_2] &= y_1 D^\alpha y_2 - y_2 D^\alpha y_1 \\ &= ky_1 D^\alpha y_1 - ky_1 D^\alpha y_1 = 0. \end{aligned}$$

($\Rightarrow$) We prove by showing "$W = 0 \Rightarrow y_1$and y_2 are linearly dependent".

Assume $y_1 \neq 0$, and $y_2 \neq 0$. Consider the linear system of equations.

$$\begin{aligned} k_1 y_1(t_0) + k_2 y_2(t_0) &= 0 \\ k_1 D^\alpha y_1(t_0) + k_2 D^\alpha y_2(t_0) &= 0, \end{aligned}$$

where k_1 and k_2 are unknown. Now, we combine the two equations by using a matrix form

$$\begin{bmatrix} y_1(t_0) & y_2(t_0) \\ D^\alpha y_1(t_0) & D^\alpha y_2(t_0) \end{bmatrix} \begin{bmatrix} k_1 \\ k_2 \end{bmatrix} = 0$$

By Cramer's theorem, if $\begin{vmatrix} y_1(t_0) & y_2(t_0) \\ D^\alpha y_1(t_0) & D^\alpha y_2(t_0) \end{vmatrix} = 0 \qquad (i.e\ W = 0),$

the system has non-trivial solution; that is k_1 and k_2 are not both zero. using these k_1 and k_2 to construct a function

$$y(t) = k_1 y_1(t) + k_2 y_2(t).$$

Then $y(t) = k_1 y_1 + k_2 y_2$ is a solution of

$$D^\alpha D^\alpha y(t) + pD^\alpha y(t) + qy(t) = 0, \text{ and satisfies the initial conditions}$$
$$D^{-(1-\alpha)} y(t_0) = 0, \text{ and } D^\alpha y(t_0) = 0.$$

By Existence and Uniqueness theorem [16], we know that the solution of the IVP

$$D^\alpha D^\alpha y(t) + pD^\alpha y(t) + qy(t) = 0$$
$$D^{-(1-\alpha)} y(t_0) = 0, \text{ and } D^\alpha y(t_0) = 0.$$

is unique and $k_1 y_1 + k_2 y_2 = 0$ on I. Since k_1 and k_2 are not both zero, y_1 and y_2 are linearly dependent. □

The proof for a set of n solutions is almost identical to the proof in the special case $n = 2$.

4.5.3 The Characteristic Equation

Corresponding to the fractional differential equation

$$D^\alpha D^\alpha y(t) + pD^\alpha y(t) + qy(t) = 0, \qquad (4.19)$$

in which p and q are constants, is the algebraic equation

$$\lambda^2 + p\lambda + q = 0, \tag{4.20}$$

which is obtained from equation (4.19) by replacing $D^\alpha D^\alpha y(t)$, $D^\alpha y(t)$ and y by $\lambda^2,\ \lambda^1,$ and $\lambda^0 = 1$, respectively. Equation(4.20) is called *characteristic equation* of (4.19).

In general, the characteristic equation of fractional homogeneous equation (4.18) is given by

$$a_n\lambda^n + a_{n-1}\lambda^{n-1} + ... + a_1\lambda + a_0 = 0.$$

4.5.4 Solution of Homogeneous Equation

If λ_1 and λ_2 are two distinct roots of (4.20). Then the solution of (4.19) can be written as a linear combination of two functions y_1 and y_2 where

$$y_1 = t^{\alpha-1}E_{\alpha,\alpha}(\ \lambda_1 t^\alpha)$$

and

$$y_2 = t^{\alpha-1}E_{\alpha,\alpha}(\lambda_2 t^\alpha).$$

Then, the general solution of (4.19) is

$$\begin{aligned} y(t) &= c_1 t^{\alpha-1}E_{\alpha,\alpha}(\ \lambda_1 t^\alpha) + c_2 t^{\alpha-1}E_{\alpha,\alpha}(\lambda_2 t^\alpha) \\ &= c_1 e_{\alpha,\alpha}(\lambda_1, t) + c_2 e_{\alpha,\alpha}(\lambda_2, t), \end{aligned}$$

where c_1 and c_2 are constants.

EXAMPLE 4.5.1. We claim that the following equation

$$D^\alpha D^\alpha y + 5D^\alpha y + 6y = 0, \tag{4.21}$$

where $0 < \alpha \leq 1$ and $t > 0$ has the solution

$$y(t) = c_1 y_1 + c_2 y_2,$$

where $y_1 = e_{\alpha,\alpha}(-3,t)$ and $y_2 = e_{\alpha,\alpha}(-2,t)$.

y_1 and y_2 are two solutions of (4.21), then y_1 and y_2 must satisfy equation (4.21), so we have

$$\begin{aligned} & D^\alpha D^\alpha y_2 + 5D^\alpha y_2 + 6y_2 \\ = \; & D^\alpha D^\alpha e_{\alpha,\alpha}(-3,t) + 5D^\alpha e_{\alpha,\alpha}(-3,t) + 6e_{\alpha,\alpha}(-3,t). \end{aligned}$$

Using Remark 3.4.1, this implies

$$\begin{aligned} & D^\alpha D^\alpha y_2 + 5D^\alpha y_2 + 6y_2 \\ = \; & -3D^\alpha e_{\alpha,\alpha}(-3,t) - 15e_{\alpha,\alpha}(-3,t) + 6e_{\alpha,\alpha}(-3,t) \\ = \; & 9e_{\alpha,\alpha}(-3,t) - 15e_{\alpha,\alpha}(-3,t) + 6e_{\alpha,\alpha}(-3,t) \\ = \; & 0. \end{aligned}$$

This completes the proof of the claim.

We expect to obtain the same result by finding the roots of the characteristic equation of (4.21), so we have

$$\lambda^2 + 5\lambda + 6 = 0.$$

This implies

$$(\lambda + 3)(\lambda + 2) = 0.$$

Thus, the roots of the characteristic equation are

$$\lambda_1 = -3 \text{ and } \lambda_2 = -2.$$

Finally, the solution of equation (4.21) is

$$y(t) = c_1 e_{\alpha,\alpha}(-3,t) + c_2 e_{\alpha,\alpha}(-2,t).$$

Similarly, one can show that y_2 satisfies equation (4.21).

4.6. Fractional Derivative of Trigonometry

Derivative operator plays an important role in calculus. Therefore, in this section, we derive the derivative of fractional trigonometric functions, in particular, fractional cosine and fractional sine.

We calculate the derivative of fractional cosine directly by using the definition of $\cos_{\alpha,\alpha}(a,t)$ and the derivative of the fractional exponential function

$$\begin{aligned} D^\alpha \cos_{\alpha,\alpha}(a,t) &= D^\alpha\{\frac{e_{\alpha,\alpha}(ai,t) + e_{\alpha,\alpha}(-ai,t)}{2}\} \\ &= \frac{1}{2}\{D^\alpha e_{\alpha,\alpha}(ai,t) + D^\alpha e_{\alpha,\alpha}(-ai,t)\} \\ &= \frac{1}{2}\{aie_{\alpha,\alpha}(ai,t) - aie_{\alpha,\alpha}(-ai,t)\} \\ &= \frac{-a}{2i}\{e_{\alpha,\alpha}(ai,t) - e_{\alpha,\alpha}(-ai,t)\} \\ &= -a\sin_{\alpha,\alpha}(a,t). \end{aligned}$$

Then, we conclude that

$$D^\alpha \cos_{\alpha,\alpha}(a,t) = -a\sin_{\alpha,\alpha}(a,t), \text{ where } 0<\alpha \le 1$$

In similar manner, one can show that the α derivative of $\sin_{\alpha,\alpha}(a,t)$ is

$$D^\alpha \sin_{\alpha,\alpha}(a,t) = a\cos_{\alpha,\alpha}(a,t).$$

In Carl F.Lorenzo and Tom T.Hartley's paper in 2004, there was an open question about finding classes of special fractional differential equations that have solutions of the new fractional trigonometry functions or a linear combination of them. In this section we develop classes of fractional differential equation with the solution of a linear combination of $\cos_{\alpha,\alpha}(a,t)$ and $\sin_{\alpha,\alpha}(a,t)$.

4.7 System of Linear Fractional Differential Equations with Constant Matrix Coefficients.

This section deals with the study of the following system of linear fractional equations. We present a new proof for the solution for a system of fractional differential equations.

$$D^{\alpha}Y(t) = AY(t) + F(t) \tag{4.22}$$

$$D^{-(1-\alpha)}Y(t)|_{t=0} = C,$$

where $D^{\alpha}Y(t)$ is the fractional derivative of order $0 < \alpha \leq 1$, and C is $n \times 1$ vector, $Y(t)$ and $F(t)$ are $n \times 1$ vector valued functions, A is $n \times n$ constant matrix.

We will formulate the unique solution of the system by using the Laplace transform. Let's define $\mathcal{L}\{Y(t)\} = Y^*(s)$ and $\mathcal{L}\{F(t)\} = F^*(s)$, so taking the Laplace transform of both sides of the equation (4.22) yields

$$\mathcal{L}\{D^{\alpha}Y(t)\} = A\mathcal{L}\{Y(t)\} + \mathcal{L}\{F(t)\}$$

Using the role of Laplace transform of the fractional derivative, we obtain

$$s^{\alpha}Y^*(s) - D^{-(1-\alpha)}Y(t)|_{t=0} = AY(s) + F^*(s).$$

Since $D^{-(1-\alpha)}Y(t)|_{t=0} = C$, we have

$$(Is^{\alpha} - A)Y^*(s) - C = F^*(s),$$

which implies

$$(Is^{\alpha} - A)Y^*(s) = C + F^*(s).$$

Taking the inverse of $(Is^{\alpha} - A)$ yields

$$\begin{aligned}
Y^*(s) &= (Is^{\alpha} - A)^{-1}[C + F^*(s)] \\
&= (s^{\alpha}(I - s^{-\alpha}A))^{-1}[C + F^*(s)] \\
&= s^{-\alpha}(I - s^{-\alpha}A)^{-1}[C + F^*(s)] \\
&= s^{-\alpha}\sum_{k=0}^{\infty}(As^{-\alpha})^k[C + F^*(s)] \\
&= \sum_{k=0}^{\infty}(As^{-\alpha})^k s^{-\alpha}C + F^*(s)\sum_{k=0}^{\infty}(As^{-\alpha})^k s^{-\alpha} \\
&= \sum_{k=0}^{\infty}\frac{A^k}{s^{\alpha k+\alpha}}C + F^*(s)\sum_{k=0}^{\infty}\frac{A^k}{s^{\alpha k+\alpha}}.
\end{aligned}$$

Let $\sum_{k=0}^{\infty}\frac{A^k}{s^{\alpha k+\alpha}} = G^*(s)$, then

$$\begin{aligned}
G(t) &= \mathcal{L}^{-1}\{\sum_{k=0}^{\infty}\frac{A^k}{s^{\alpha k+\alpha}}\} \\
&= \sum_{k=0}^{\infty}A^k\mathcal{L}^{-1}\{\frac{1}{s^{\alpha k+\alpha}}\} \\
&= \sum_{k=0}^{\infty}A^k\frac{t^{\alpha k+\alpha-1}}{\Gamma(\alpha k+\alpha)} \\
&= t^{\alpha-1}E_{\alpha,\alpha}\{at^{\alpha}).
\end{aligned}$$

Thus,

$$Y(s) = \sum_{k=0}^{\infty}\frac{A^k}{s^{\alpha k+\alpha}}C + \mathcal{L}\{F(t) * G(t)\},$$

where $\mathcal{L}\{G(t)\} = G^*(s)$.

Then, taking the inverse Laplace Transform of the last equation and using Table 3.1, we obtain

$$\begin{aligned} Y(t) &= \sum_{k=0}^{\infty} A^k \frac{t^{\alpha k+\alpha-1}}{\Gamma(\alpha k+\alpha)} C + \int_0^t F(t-z)G(z)dz \\ &= t^{\alpha-1}E_{\alpha,\alpha}(At^\alpha)C + \int_0^t (t-z)^{\alpha-1}E_{\alpha,\alpha}(A(t-z)^\alpha)F(z)dz \end{aligned}$$

Replacing $\alpha = 1$, we obtain

$$\begin{aligned} Y(t) &= E_{1,1}(At)C + \int_0^t E_{1,1}(A(t-z))F(z)dz \\ &= e^{At}C \ + \int_0^t e^{A(t-z)}F(z)dz \end{aligned}$$

Since solving equation (4.22) involves the matrix Mittag-Leffler function, $t^{\alpha-1}E_{\alpha,\alpha}(At^\alpha)$, we will first look at this important function. We will state the next two theorems without proof.

THEOREM 4.7.1 [16]. (Extended Putzer Algorithm) If A is 2×2 constant matrix, then the solution to the IVP

$$D^\alpha Y(t) = AY(t), \qquad D^{-(1-\alpha)}Y(t)|_{t=0} = C, \tag{4.23}$$

where

$$A = \begin{bmatrix} a & b \\ c & d \end{bmatrix}, \qquad Y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix}, \qquad 0 < \alpha \leq 1.$$

is given by

$$Y(t) = k_{\alpha,\alpha}(At^{\alpha})C$$

where

$$k_{\alpha,\alpha}(At^{\alpha}) = t^{\alpha-1}E_{\alpha,\alpha}(At^{\alpha}),$$

and $k_{\alpha,\alpha}(At^{\alpha})$, is the matrix Mittag-Leffler function, and C is 2×1 vector.

THEOREM 4.7.2 [16]. If λ_1 and λ_2 are (not necessarily distinct) eigenvalues of the 2×2 matrix A, then

$$k_{\alpha,\alpha}(At^{\alpha}) = p_1(t)M_0 + p_2(t)M_1,$$

where

$$M_0 = I = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \qquad M_1 = A - \lambda_1 I = \begin{bmatrix} a-\lambda_1 & b \\ c & d-\lambda_1 \end{bmatrix},$$

and the vector function p defined by

$$p(t) = \begin{bmatrix} p_1(t) \\ p_2(t) \end{bmatrix}, \qquad t \in \mathbb{R},$$

is a solution to the IVP

$$D^{\alpha}p(t) = \begin{bmatrix} \lambda_1 & 0 \\ 1 & \lambda_2 \end{bmatrix} p(t), \qquad \begin{bmatrix} D^{-(1-\alpha)}p_1(t)|_{t=0} \\ D^{-(1-\alpha)}p_2(t)|_{t=0} \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \end{bmatrix}.$$

EXAMPLE 4.7.1. Let $0 < \alpha \leq 1$, then the following IVP

$$D^{\alpha}D^{\alpha}y(t) + a^2y(t) = 0 \tag{4.24}$$

$$D^{\alpha}y(t)|_{t=0} = c_1 \text{ and } D^{-(1-\alpha)}y(t)|_{t=0} = c_2$$

can be transformed into a system of fractional differential equations by the change of the variables, such that

$$y_1 = y \text{ and } y_2 = D^{\alpha} y$$

This implies

$$D^{\alpha} y_1 = D^{\alpha} y = y_2$$

and

$$D^{\alpha} D^{\alpha} y = -a^2 y = -a^2 y_1,$$

where $y_1(t)|_{t=0} = c_1$ and $y_2(t)|_{t=0} = c_2$. Then, we have the following linear system of fractional differential equations

$$D^{\alpha} Y(t) = AY(t), \qquad D^{-(1-\alpha)} Y(t)|_{t=0} = C,$$

where

$$A = \begin{bmatrix} 0 & 1 \\ -a^2 & 0 \end{bmatrix}, \qquad Y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix}, \text{ and } C = \begin{bmatrix} c_1 \\ c_1 \end{bmatrix}$$

which has the solution

$$Y(t) = k_{\alpha,\alpha}(At^{\alpha})C.$$

Let's compute $k_{\alpha,\alpha}(At^{\alpha})$ by using Theorem 4.6.2.

First, we calculate λ_1 and λ_2, where λ_1 and λ_2 are the eigenvalues of A

$$\lambda_1 = \frac{(a+d) - \sqrt{a^2 - 2ad + 4bc + d^2}}{2}.$$

Thus,

$$\lambda_1 = -ai.$$

And,

$$\lambda_2 = \frac{(a+d) + \sqrt{a^2 - 2ad + 4bc + d^2}}{2}.$$

Thus,

$$\lambda_1 = ai.$$

By the Extended Putzer algorithm,

$$k_{\alpha,\alpha}(At^\alpha) = \sum_{k=0}^{1} p_{k+1}(t) M_k = p_1(t) M_0 + p_2(t) M_1,$$

where,

$$M_0 = I = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \qquad M_1 = A - \lambda_1 I = \begin{bmatrix} ai & 1 \\ -a^2 & ai \end{bmatrix}.$$

The vector function is $p(t)$ given by

$$p(t) = \begin{bmatrix} p_1(t) \\ p_2(t) \end{bmatrix}, \qquad t \in \mathbb{R},$$

is a solution to the IVP

$$D^\alpha p(t) = \begin{bmatrix} \lambda_1 & 0 \\ 1 & \lambda_2 \end{bmatrix} p(t), \qquad D^{-(1-\alpha)} p(t)|_{t=0} = \begin{bmatrix} 1 \\ 0 \end{bmatrix}.$$

The first component $p_1(t)$ of $p(t)$ solve the IVP

$$D^\alpha p_1(t) = (-ai) p_1(t), \qquad D^{-(1-\alpha)} p_1(t)|_{t=0} = 1.$$

Taking the Laplace transform of both sides, we have

$$\mathcal{L}\{D^\alpha p_1(t)\} = (-ai)\mathcal{L}\{p_1(t)\}$$

Using the rule of the Laplace transform of the fractional derivative yields

$$s^{\alpha}P_1(s) - D^{-(1-\alpha)}p_1(t)|_{t=0} = (-ai)P_1(s),$$

where $\mathcal{L}\{p_1(t)\} = P_1(s)$.

Since $D^{-(1-\alpha)}p_1(t)|_{t=0} = 1$, then we have

$$s^{\alpha}P_1(s) - 1 = (-ai)P_1(s),$$

which implies

$$P_1(s) = \frac{1}{s^{\alpha} + ai}.$$

Using Table 3.1, we obtain the inverse Laplace transform of $P_1(s)$

$$\begin{aligned} p_1(t) &= t^{\alpha-1}E_{\alpha,\alpha}(-ait^{\alpha}) \\ &= e_{\alpha,\alpha}(-ai,t). \end{aligned}$$

The second component $p_2(t)$ of $p(t)$ solves the IVP

$$D^{\alpha}p_2(t) = t^{\alpha-1}E_{\alpha,\alpha}(-ait^{\alpha}) + (ai)p_2(t), \qquad D^{-(1-\alpha)}p_2(t)|_{t=0} = 0.$$

Using the Laplace transform, we have that

$$\mathcal{L}\{D^{\alpha}p_2(t)\} = \mathcal{L}\{t^{\alpha-1}E_{\alpha,\alpha}(-ait^{\alpha})\} + (ai)\mathcal{L}\{p_2(t)\},$$

Again, by using the rule of the Laplace transform of the fractional derivative, we obtain

$$s^{\alpha}P_2(s) - D^{-(1-\alpha)}p_2(t)|_{t=0} = \frac{1}{s^{\alpha} + ai} + (ai)P_2(s),$$

where $\mathcal{L}\{p_2(t)\} = P_2(s)$.

Since $D^{-(1-\alpha)}p_2(t)|_{t=0} = 0$, then we have

$$(s^\alpha - ai)P_2(s) = \frac{1}{s^\alpha + ai},$$

which implies

$$P_2(s) = \frac{1}{(s^\alpha + ai)(s^\alpha - ai)}.$$

Using partial fractions yields,

$$\frac{1}{(s^\alpha + ai)(s^\alpha - ai)} = \frac{1}{-2ai}\left[\frac{1}{s^\alpha + ai} - \frac{1}{s^\alpha - ai}\right]$$

By employing Table 3.1, we obtain the inverse Laplace transform of $P_2(s)$ as follows

$$\begin{aligned} p_2(t) &= \frac{t^{\alpha-1}}{-2ai}[E_{\alpha,\alpha}(-ait^\alpha) - E_{\alpha,\alpha}(ait^\alpha)] \\ &= \frac{1}{-2ai}[e_{\alpha,\alpha}(-ai,t) - e_{\alpha,\alpha}(ai,t)]. \end{aligned}$$

Finally, we have

$$\begin{aligned} k_{\alpha,\alpha}(At^\alpha) &= p_1(t)M_0 + p_2(t)M_1 \\ &= \begin{bmatrix} \frac{1}{2}[e_{\alpha,\alpha}(ai,t) + e_{\alpha,\alpha}(-ai,t)] & \frac{1}{2ai}[e_{\alpha,\alpha}(ai,t) - e_{\alpha,\alpha}(-ai,t)] \\ \frac{a}{-2i}[e_{\alpha,\alpha}(ai,t) - e_{\alpha,\alpha}(-ai,t)] & \frac{1}{2}[e_{\alpha,\alpha}(ai,t) + e_{\alpha,\alpha}(-ai,t)] \end{bmatrix} \\ &= \begin{bmatrix} \cos_{\alpha,\alpha}(a,t) & \frac{1}{a}\sin_{\alpha,\alpha}(a,t) \\ -a\sin_{\alpha,\alpha}(a,t) & \cos_{\alpha,\alpha}(a,t) \end{bmatrix} \\ &= \begin{bmatrix} \cos_{\alpha,\alpha}(a,t) & \frac{1}{a}\sin_{\alpha,\alpha}(a,t) \\ D^\alpha[\cos_{\alpha,\alpha}(a,t)] & D^\alpha[\frac{1}{a}\sin_{\alpha,\alpha}(a,t)] \end{bmatrix}. \end{aligned}$$

Thus, the solution of equation (4.27) is

$$Y(t) = k_{\alpha,\alpha}(At^{\alpha})C = \begin{bmatrix} \cos_{\alpha,\alpha}(a,t) & \frac{1}{a}\sin_{\alpha,\alpha}(a,t) \\ D^{\alpha}[\cos_{\alpha,\alpha}(a,t)] & D^{\alpha}[\frac{1}{a}\sin_{\alpha,\alpha}(a,t)] \end{bmatrix} C.$$

Therefore, the general solution to (4.28) is given by

$$y(t) = c_1 \cos_{\alpha,\alpha}(a,t) + \frac{c_2}{a}\sin_{\alpha,\alpha}(a,t),$$

where c_1 and c_2 are arbitrary real constants.

In this example, we showed that the general solution of equation (4.28) is a linear combination of two fractional trigonometric functions (fractional cosine and fractional sine).

THEOREM 4.7.3. Fractional cosine ($\cos_{\alpha,\alpha}(a,t)$) and fractional sine ($\sin_{\alpha,\alpha}(a,t)$) are two linearly independent functions for all $t > 0$.

Proof. In Example 4.7.1, the homogeneous fractional differential equation

$$D^{\alpha}D^{\alpha}y(t) + a^2 y(t) = 0$$

generates a solution of linear combination of fractional cosine and fractional sine.

To show that $\cos_{\alpha,\alpha}(a,t)$ and $\sin_{\alpha,\alpha}(a,t)$ are two linearly independent solutions, we use generalized Wronskian test (Theorem 4.5.1), that is

$$\begin{aligned} W[y_1, y_2] &= \begin{vmatrix} \cos_{\alpha,\alpha}(a,t) & \sin_{\alpha,\alpha}(a,t) \\ D^{\alpha}\cos_{\alpha,\alpha}(a,t) & D^{\alpha}\sin_{\alpha,\alpha}(a,t) \end{vmatrix} \\ &= \begin{vmatrix} \cos_{\alpha,\alpha}(a,t) & \sin_{\alpha,\alpha}(a,t) \\ -a\sin_{\alpha,\alpha}(a,t) & a\cos_{\alpha,\alpha}(a,t) \end{vmatrix} \\ &= a\cos^2_{\alpha,\alpha}(a,t) - a\sin^2_{\alpha,\alpha}(a,t) \\ &= \frac{a}{2}\{e^2_{\alpha,\alpha}(ai,t) + e^2_{\alpha,\alpha}(-ai,t)\ \} \end{aligned}$$

Since $e_{\alpha,\alpha}(a,t) \neq 0$ for all $t > 0$ and a any arbitrary number, then $e^2_{\alpha,\alpha}(a,t) \neq 0$.

Therefore

$$W[y_1, y_2] \neq 0$$

which implies $\cos_{\alpha,\alpha}(a,t)$ and $\sin_{\alpha,\alpha}(a,t)$ are two linearly independent functions.

CHAPTER 5

An Application of Fractional Calculus to Pharmacokinetic Model

Development of new drugs or recommending drugs for patients requires large numbers of statistics to assist the researcher in the study. Therefore, we need an efficient method to help us to compensate missing data. For example, in the study of changing drug concentration over time after intravenous bolus administration to the body, we need to collect large numbers of plasma samples to see how the change happens. However, taking large numbers of samples from a patient is difficult. As a consequence, mathematical models are used to predict missing data. Specifically, pharmacokinetic is the model that is used to study drugs.

Pharmacokinetic, abbreviated as PK, is a branch of pharmacology dedicated to studying the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug. The study of these processes plays a significant role for choosing an appropriate dose and dosing regimen for a particular patient.

Pharmacokinetic analysis is performed by noncompartment or compartment methods. Noncompartment methods estimate the exposure to a drug by estimating the area under the curve of a concentration-time graph. Compartment methods estimate the concentration-time graph.

The most commonly used models in pharmacokinetic analysis are compartment models. All drugs initially distribute into a central compartment before distributing into the peripheral compartment. If a drug rapidly distribute within the tissue compartment, the disposition kinetics of the drug can be described as one compartment model. It is called one compartment because all accessible sites have the same distribution kinetics. However, drugs which exhibit as low equilibration with the peripheral tissues, are described with a two compartment model.

In this thesis, we specifically consider one compartmental model with the newly developing fractional calculus. We compare our model with the ordinary calculus by utilizing real data. The core of comparison is based on statistical evidences. Also, we employ a new theory to give the best parameter estimation. Once we have the best model and suitable parameter values, one can use the model to make predictions.

5.1 One Compartment Model

One compartment model can be shown as this compartmental diagram

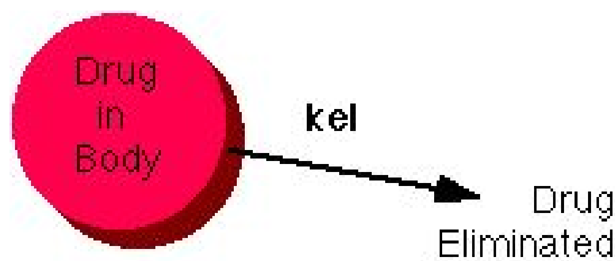

Figure 5.1. One compartment model

Following rapid intravenous injection of a drug that distributes in the body according to a one compartment model and is eliminated by apparent first-order kinetic, the rate of loss of drug from the body is given by

$$\frac{dc_p(t)}{dt} = -(kel)c_p(t), \tag{5.1}$$

where c_p is the concentration of the drug in the body at time t after injection, kel is apparent first-order elimination rate constant for the drug. The negative sign indicates the drug is being lost in the body.

The solution of this equation is given by the mono-exponential decline function:

$$c_p(t) = c_{p_0} e^{-(kel)t} \tag{5.2}$$

where c_{p_0} is the initial concentration at time zero.

Our goal now to approximate the solution of (5.1) using a fractional differential equation. To achieve this goal, we consider

$$D^{\alpha} c_p(t) = -(kel) c_p(t),$$

$$D^{-(1-\alpha)} c_p(t)|_{t=0} = c_{p_0},$$

where $0 < \alpha \leq 1$. For simplicity let $kel = k$, then we have

$$D^{\alpha} c_p(t) = k c_p(t). \tag{5.3}$$

We will solve (5.3) using the Laplace transform which is discussed in Chapter 4. Taking the Laplace transform on both sides of the equation we obtain

$$\mathcal{L}\{D^{\alpha} c_p(t)\} = -k\mathcal{L}\{c_p(t)\}$$

Using the Laplace transform of the fractional derivative, we have

$$s^{\alpha}\mathcal{L}\{c_p(t)\} - D^{-(1-\alpha)} c_p(t)|_{t=0} = -k\mathcal{L}\{c_p(t)\}$$

Let $\mathcal{L}\{c_p(t)\} = C_p(s)$, then we have

$$C_p(s)(s^{\alpha} + k) = c_{p_0},$$

which implies

$$C_p(s) = \frac{c_{p_0}}{s^\alpha + k}.$$

Finally, taking the inverse Laplace transform of both sides of the above equation yields:

$$c_p(t) = c_{p_0} t^{\alpha-1} E_{\alpha,\alpha}(-kt^\alpha). \tag{5.4}$$

Notice that if we replace α by 1, we obtain

$$c_p(t) = c_{p_0} e^{-kt}.$$

In the next section, we explore how a curve behavior change with fractional model with different values of α.

5.2 Graphical results

A comparison between several models play a significant role in data analysis. No surprise that different models give diverse results. What is important is no model produces results discordant from the other models. In this section we will see how the behavior of a curve changes with different models and different parameters as well.

In Figure 5.2 shows plasma concentration versus time with different α values and parameters $c_{p_0} = 1002.42$ and $k = 0.011$ [Parameters for drug concentration are taken from [21]. With various α values, we observe different behavior of concentration-time curves. We notice that curves X2, X3, X4 and X5 behave like the mono-exponential decline. Also, notice that fractional model approaches the first order differential model as $\alpha \to 1$. Additionaly, we observe that curves decrease faster for low values of α. Next we change the elimination rate constant k of drug in plasma.

In Figure 5.3, we take the rate constant $k = .019041$. It can be seen that in this graph, X2 and X3 behave similarly. X2 is the curve with $\alpha = .5$ and $k = .019041$ but $X3$ is the curve with $k = 0.011$ and $\alpha = .8$.

Following the above results, we observe that the curve behavior shows significant variation with respect to α. Since fractional model have one more fitting parameter, α, in addition to the model parameters.

Observed and fitted data are shown in Figure 5.4. Data are taken from [10]. The difference between the integer model (thin line) and fractional model (thick line) is clearly demonstrated, thin curve ($\alpha = 1$) does not go through our data but most of our data are closer to the thick curve ($\alpha = .91$). As a result, fractional calculus for curve fitting may give more accurate results for data analysis.

5.3 Initial Parameter Estimation

In this section, we evaluate fractional model with various values of α for prediction of plasma concentration. Then we compare the models searching for a better fit for the observed data points of drug concentration. Two approaches are employed to show that fractional calculus gives the best model for data analysis of drug concentration over time. One approach determines that fractional model gives the best fit to the given data. The second approach determines that fractional model is the best model for prediction. To start off, let's first estimate the initial parameters which are the theoretical concentration at time zero, c_{p_0}, and the elimination rate constant, k. Notice that the two models (5.1) and (5.3) have the same parameters. Therefore, we just need to determine the parameters for one of these models. Then we can use the result parameters for both models. The predicted plasma concentration is given by:

$$c_p = c_{p_0} e^{-kt}.$$

It is converted into a modified exponential form as

$$\ln c_p = \ln c_{p_0} - kt,$$

which can also be written as

$$Y(t) = A + Bt, \tag{5.5}$$

where $Y(t) = \ln c_p$, $A = \ln c_{p0}$ and $B = -k$.

In Table 5.1, plasma samples were obtained following bolus intravenous dosing and the data follow a mono-exponential decline. We estimate the two parameter A and B and fit the modified exponential decline curve to the given data and the fractional model as well. Notice that the time is not periodic in Table 5.1. There are missing data which would affect the result in parameter estimation. Therefore, a new theory is proposed to handle the parameter estimation in an effective way without losing information.

Time scale is a new developing theory which has a potential to deal with time, which is represented by isolated points (not continuous). It is defined as follows:

A time scale is an arbitrary nonempty closed subset of the real numbers. Thus

$$\mathbb{R},\ \mathbb{Z},\ \mathbb{N},\ \mathbb{N}_0,$$

i.e., the real numbers, the integers, the natural numbers, and the nonnegative integers are examples of time scales, as are

$$[0,1] \cup [2,3],\ [0,1] \cup \mathbb{N},\ \text{and the Cantor set,}$$

while

$$\mathbb{Q},\ \mathbb{R}\backslash\mathbb{Q},\ (0,1),$$

i.e., the rational numbers, the irrational numbers, and the open interval between 0 and 1, are not time scales. We denote a time scale by the symbol $\mathbb{T}$.

Forward and backward operators are two important operators in time scale calculus and their definitions are given as follows

Let $\mathbb{T}$ be a time scale. For $t \in \mathbb{T}$ we define the *forward jump* operator $\sigma : \mathbb{T} \longrightarrow \mathbb{T}$ by

$$\sigma(t) := \inf\{s \in \mathbb{T} : s > t\},$$

while the *backward jump* operator $\rho : \mathbb{T} \longrightarrow \mathbb{T}$ by

$$\rho(t) := \sup\{s \in \mathbb{T} : s < t\}.$$

In this definition we put $\inf(\phi) = \sup(\mathbb{T})$ (i.e., $\sigma(t) = t$ if $\mathbb{T}$ has a maximum t) and $\sup(\phi) = \inf(T)$ (i.e., $\rho(t) = t$ if $\mathbb{T}$ has a minimum t), where ϕ denotes the empty set. If $\sigma(t) > t$, we say that t is *right-scattered*, while if $\rho(t) < t$ we say that t is *left-scattered.* Points that are right-scattered and left-scattered at the same time are called isolated.

ThEOREM 5.3.1 [22]. Assume a and $b \in \mathbb{T}$ and $f : \mathbb{T} \longrightarrow \mathbb{R}$ is ld-continuous.

(i) If $\mathbb{T} = \mathbb{R}$, then

$$\int_a^b f(t)\nabla(t) = \int_a^b f(t)dt,$$

where the integral on the right is the Riemann integral from calculus.

(ii) If $\mathbb{T}$ consists of only *isolated points,* then

$$\int_a^b f(t)\nabla(t) = \int_{[a,b]\cap\mathbb{T}} f(t)\nabla(t) = \sum_{t\in(a,b]\cap\mathbb{T}} f(t)\nu(t), \qquad \text{if } a < b.$$

where $\nu(t)$ is called graininess function and defined as

$$\nu(t) = t - \rho(t).$$

As we point out the solution of (5.1) can be written in the form

$$Y(t) = A + Bt.$$

The given time-scale data in Table 5.1 are split up into two sets S_1 and S_2

$$S_1 = \int_{[0,50]\cap\mathbb{T}} Y(t)\nabla(t),$$

which implies

$$S_1 = \sum_{t\in(0,50]\cap\mathbb{T}} Y(t)\nu(t)$$

and

$$S_2 = \int_{[50,110]\cap\mathbb{T}} Y(t)\nabla(t),$$

which implies

$$S_2 = \sum_{t\in(50,110]\cap\mathbb{T}} Y(t)\nu(t).$$

where π is time scale and is given by

$$\mathbb{T} = \{10, 20, 30, 40, 50, 60, 70, 90, 110, 150\}.$$

Substituting equation (5.5) in S_1 and S_2, we get

$$\begin{aligned} S_1 &= \sum_{t\in(0,50]\cap\mathbb{T}} (A + Bt)\nu(t) \\ &= (10 + 10 + 10 + 10 + 10)A + B[(10)(10) + (20)(10) + (30)(10) + (40)(10) + (50)(10)] \\ &= 50A + 1500B \end{aligned}$$

Similarly,

$$\begin{aligned} S_2 &= \sum_{t\in(50,150]\cap\mathbb{T}} (A + Bt)\nu(t) \\ &= (10 + 10 + 20 + 20 + 40)A + B[(60)(10) + (70)(10) + (90)(20) + (110)(20) + (150)(40)] \\ &= 100A + 11300B. \end{aligned}$$

S_1 is the sum of the product of natural logarithm of the observed values times the backward graininess function, so that

$$\begin{aligned} S_1 &= \sum_{t\in(0,50]\cap\mathbb{T}} \ln c_p(t)\nu(t) \\ &= 10\ln(920) + 10\ln(800) + 10\ln(750) + 10\ln(630) + 10\ln(610) \\ &= 315.61606 \end{aligned}$$

Similarly,

$$\begin{aligned} S_2 &= \sum_{t\in(50,150]\cap\mathbb{T}} \ln c_p(t)\nu(t) \\ &= 10\ln(530) + 10\ln(520) + 20\ln(380) + 20\ln(350) + 40\ln(200) \\ &= 519.9368. \end{aligned}$$

To obtain A and B, we solve the following system of equations

$$\begin{aligned} 315.61606 &= 50A + 1500B. \\ 519.9368 &= 100A + 11300B \end{aligned}$$

Hence, we get

$A = 6.91067$ and $B = -0.010434$

Since $\ln c_{p_0} = 6.91067$, this implies $c_{p_0} = 1002.92$, and $B = -k$, this implies $k = 0.010434$.

We fit our model with the estimated elimination rate k, and by gussing method we consider the initial concentration as $c_{p_0} = 1070$. Based on these parameters, the exponential decline curve of the predicted drug concentration is given by:

$$c_p(t) = 1070e^{-0.010434t}.$$

We fit fractional model with the same parameters as well, so that

$$c_p(t) = 1070t^{\alpha-1}E_{\alpha,\alpha}(-0.010434t^v).$$

Visually, each curve gives reasonably good fit to the given data. However, if we look closely at the curves in Figure 5.5, we observe that data points are closer to the curves with $\alpha = 0.99$ and $\alpha = 0.98$ than the curve with $\alpha = 1$. To determine which curve gives the best "fitting", we perform the square of residuals (SQR) analysis between the observed values and the predicted values, which is given by

$$e_i = y_i - \hat{y}_i,$$

where y_i is the observed value and $\hat{y}_i$ is the predicted at time t_i and $i = 1, 2, ..., 10$. Then, we compute the mean squared error (MSE), which defined as

$$\text{MSE}=\frac{e_1^2 + e_2^2 + ... + e_n^2}{n},$$

where $n = 10$ in this example. The best model is the one showing the least mean squared error (MSE).

Table 5.2 and 5.3 present the data points and the square of residuals between the observed values and the predicted values with MSE as well for fractional model with $\alpha = 1, 0.99, 0.98,$ and 0.97.

Based on MSE analysis for each model, the best fit is given by fractional model with $\alpha = 0.98$, which gives the least mean squared error. It can also be seen that the fractional model with $\alpha = 0.99$ and $\alpha = 0.97$ give more accurate results than the model with $\alpha = 1$.

To make sure that our model works better, we compare between the results that we have for MSE with the results that is given in [10] for the same data set. In that book

[10], linear regression was used to determine the parameters. MSE was 432.738 using the first order differential model. However, our model with the method of time scale, MSE was (426.2016023) with $\alpha = 0.98$. These results support our insight that fractional model is stronger than the integer model in this particular example. In the next section, we show that fractional model gives the best prediction, not just the best fitting.

5.4 Model of Best Prediction

Statisticians believe that how well the model fits statistics is not a good guide to determine how well a model will predict. Evaluating such a model may demonstrate adequate prediction capability on the training set, but might fail to predict future unseen data. Cross-validation is primarily a way of measuring the predictive performance of a model. The idea of cross-validation was originated in 1930s [25]. A clear statement to cross-validation which is similar to current version of $k-$fold of cross-validation, first appeared in [19]. In 1970s, Stone [20] employed cross-validation as means for choosing proper model parameters, as opposed to using cross-validation purely for estimating model performance. The goal of cross-validation is to measure the predictive ability of a model by testing it on a set of data not used in estimation. This is called as a "test set," and the data used for estimation is the "training set". The predictive accuracy of a model can be measured by the mean squared error (MSE) on the test set.

In $k-$fold of cross-validation, the original data sample randomly partitioned into k subsamples are used as training set. The cross-validation process then is repeated k times and in each step, m observations are left out as validation data for testing the model. Each of the k subsamples are used once as the validation data. Then, the accuracy measures are obtained as follows.

Suppose there are n independent observations $y_{1,}y_{2,}..., y_n$. We let m observations of the original sample form the test set, and we fit the model for the remaining data (training set). Then, we compute the square of the residual error ($e_i = y_i - \hat{y}_i$). We repeat the same steps for each of the k supsamples. Finally, we compute the mean squared error (MSE).

In Table 5.1, we randomly split our data into five subsamples $G_1, G_{2,...}, G_5$ such that each subsample consists of eight observations as a training set, and for each a training set there is one test set T_i ($i = 1, 2, ..., 5$) consists of two observations (the remaining data) corresponding to that set. Table 5.4 shows the five training sets and the corresponding test sets where where y_i is the observed value at time t_i, for $i = 1, 2, ..., 10$.

We fit our model for each training set to estimate the parameters using time scale calculus as we did in the previous section, then we employ the result parameters to compute the predicted value for each corresponding test set.

For G_1, $\mathbb{T} = \{20, 30, 40, 50, 60, 70, 90, 150\}$

where $G_1 = \{800, 750, 630, 610, 530, 520, 380, 200\}$, then S_1 and S_2 can be written as

$$S_1 = \sum_{t \in (0,50] \cap \mathbb{T}} Y(t)\nu(t),$$

and

$$S_2 = \sum_{t \in (50,150] \cap \mathbb{T}} Y(t)\nu(t).$$

But $S_1 = \sum_{t \in (0,50] \cap \pi} (A+Bt)\nu(t)$ and $S_2 = \sum_{t \in (50,150] \cap \pi} (A+Bt)\nu(t)$, so to obtain the parameters A and B we solve the following system

$$S_1 = \sum_{t \in (0,50] \cap \pi} (A + Bt)\nu(t)$$
$$S_2 = \sum_{t \in (50,150] \cap \pi} (A + Bt)\nu(t).$$

After solving the above system of equations, we have

$c_{p_0} = 1003.52$, where $A = \ln c_{p_0}$, and

$k = 0.010674$, where -$k = B$

Finally, calculating $\hat{y}_1$ and $\hat{y}_9$ at $t = 10$ and 110 respectively, using the fractional model (5.4) with $\alpha = 1, 0.99$, and 0.98, then we obtain this short table

Fractional Model	$\hat{y}_1$	$\hat{y}_9$
$\alpha = 1$	970.659	333.806
$\alpha = 0.99$	952.68	330.07
$\alpha = 0.98$	917.804	325.785

Similarly, we fit our model to G_2, then we use the result parameters to calculate y_2, y_3 at time $t = 20$, and 30 respectively, so we have

$$S_1 = \sum_{t\in(0,60]\cap\pi} Y(t)\nu(t),$$

and

$$S_2 = \sum_{t\in(60,150]\cap\pi} Y(t)\nu(t).$$

Again, S_1 and S_2 can be written in terms of A and B, so we have

$$S_1 = \sum_{t\in(0,60]\cap\pi} (A + Bt)\nu(t)$$
$$S_2 = \sum_{t\in(60,150]\cap\pi} (A + Bt)\nu(t).$$

By solving the above system of equations, we obtain

$c_{p_0} = 974.46$, where $A = \ln c_{p_0}$, and

$k = 0.010181$, where -$k = B$

Using these parameters with fractional model (5.4), we obtain the following short table

Fractional Model	$\hat{y}_2$	$\hat{y}_3$
$\alpha = 1$	856.561	773.647
$\alpha = 0.99$	829.152	748.057
$\alpha = 0.98$	802.456	723.114

We continue on this manner until we calculate all predicted values corresponding to each of the test sets. Table 5.5 presents all the predicted values with fractional model for different values of α and $900 \leq c_{p_0} \leq 1080$, and MSE is calculated as well in this table.

It is clear from Table 5.5 the best prediction is given by the fractional model with $\alpha = 0.98$ determined by the means squared errors (MSE). The model with $\alpha = 1$ gives the least accurate result in comparison to $\alpha = 0.99$ and $\alpha = 0.98$.

We show that fractional calculus gives the best prediction performance and the best fitting as well in this particular application. This demonstrates how our model is strong as a means for prediction as a means for prediction and fitting.

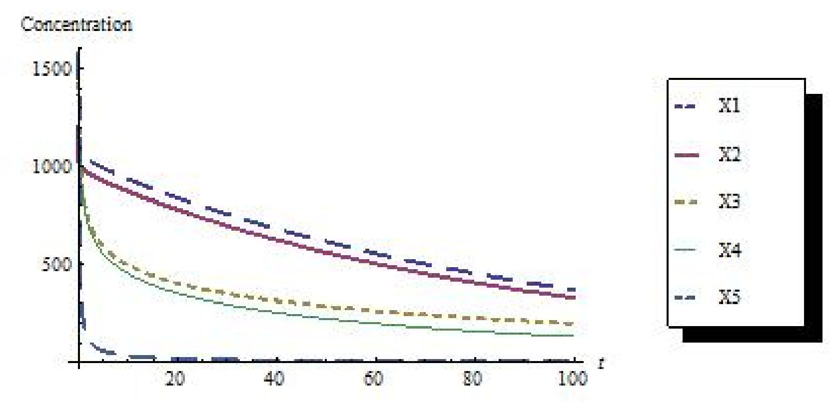

Figure 5.2. Plot of drug concentration following intravenous bolus dose versus time.

(X1: α=1, X2: α=.99, X3: α=.8, X4: α=.5, X5 :α=.2)

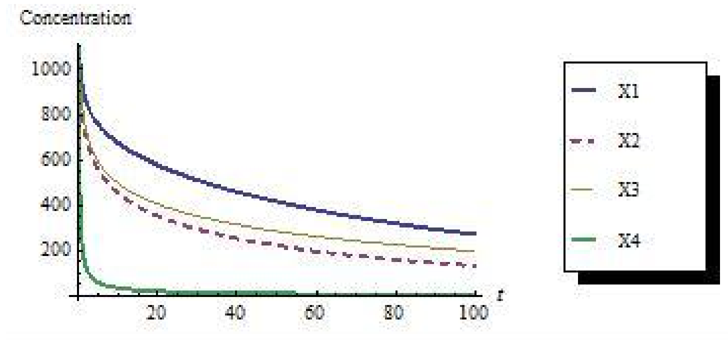

Figure 5.3.Plot of drug concentration following intravenous bolus dose versus time.

(c_{p_0}=1002.42 and k=0.011, X1: α=.9 ,X2: α=.5 ,X4: α=.2, X3: c_{p_0}=1002.42, k=.019041, α=.8)

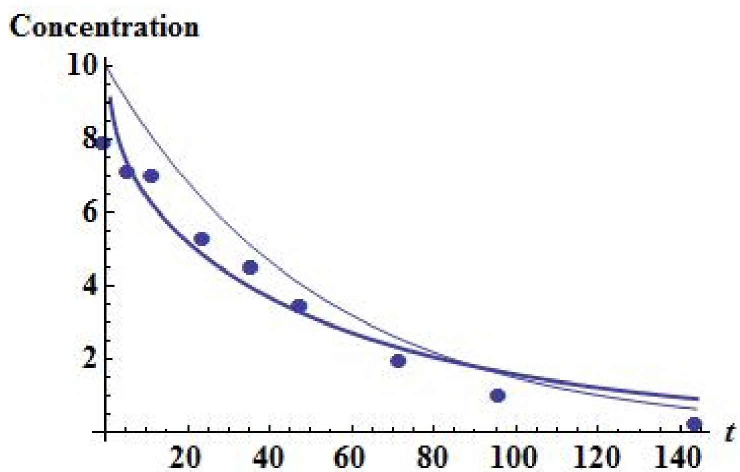

Figure 5.4.Obseved (symbols) and predicted (solid line) plasma concentration-time data following intravenous injection of dose

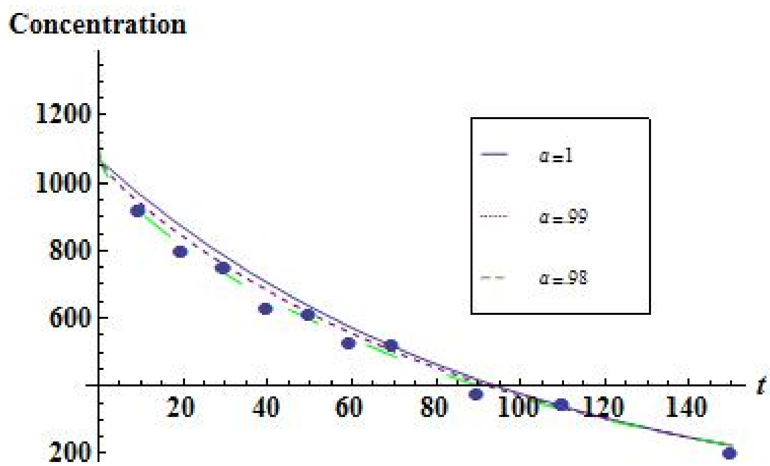

Figure 5.5. Data Fitting

Time (min)	Concentration (mg/L)
10	920
20	800
30	750
40	630
50	610
60	530
70	520
90	380
110	350
150	200

Table 5.1. Data of concentration at various time from a volunteer was given intravenous bolus dosing

Time(min)	Y	$Y1$	SQR	$Y0.99$	SQR
10	920	964.002	1937.936484	937.464	304.991296
20	800	868.54	4697.7316	840.818	1666.109124
30	750	782.516	1057.290256	756.752	45.589504
40	630	705.011	5626.650121	682.166	2721.291556
50	610	635.183	634.183489	615.521	30.481441
60	530	572.272	1786.921984	555.76	663.5776
70	520	515.591	19.439281	502.058	321.915364
90	380	418.516	1483.482256	410.202	912.160804
110	350	339.717	105.740089	335.564	208.398096
150	200	223.836	568.154896	225.2	6874.514785
MSE			1791.753		1374.903

Table 5.2. Data analysis for drug concentration

(Observed value:Y, predicted values : Y_1at α=1, and Y_2 at α=0.99 and SQR :square of residual error)

Time (min)	$Y0.98$	SQR	$Y0.97$	SQR
10	911.487	72.471169	886.08	1150.5664
20	813.813	190.798969	787.512	155.950144
30	731.632	337.383424	707.149	1836.208201
40	659.811	888.695721	637.948	63.170704
50	596.167	191.351889	577.133	1080.239689
60	539.371	87.815641	523.13	47.1969
70	488.475	993.825625	474.876	2036.175376
90	401.553	464.531809	392.616	159.163456
110	330.88	365.5744	325.715	589.761225
150	225.876	669.567376	225.901	670.861801
MSE		426.202		778.930

Table 5.3. Data analysis for drug concentration

(Predicted values : Y_1at $\alpha = 0.98$, $Y0.97$ at $\alpha = 0.97$, and SQR: Square of residual error)

Training Set	Selected Observations	Test Set	Selected Observations
G_1	$\{y_2, y_3, y_4, y_5, y_6, y_7, y_8, y_{10}\}$	T_1	$\{y_1, y_9\}$
G_2	$\{y_1, y_4, y_5, y_6, y_7, y_8, y_9, y_{10}\}$	T_2	$\{y_2, y_3\}$
G_3	$\{y_1, y_2, y_3, y_6, y_7, y_8, y_9, y_{10}\}$	T_3	$\{y_4, y_5\}$
G_4	$\{y_1, y_2, y_3, y_4, y_5, y_8, y_9, y_{10}\}$	T_4	$\{y_6, y_7\}$
G_5	$\{y_1, y_2, y_3, y_4, y_5, y_6, y_7, y_9\}$	T_5	$\{y_8, y_{10}\}$

Table 5.4. Five-fold cross-validation

Time (min)	Observed value	$\alpha = 1$	SQR	$\alpha = 0.99$	SQR	$\alpha = 0.98$	SQR
10	920	970.659	2566.334	952.68	1067.982	917.804	4.822416
20	800	856.561	3199.147	829.152	849.8391	802.456	6.031936
30	750	773.647	559.1806	748.057	3.775249	723.114	722.857
40	630	704.768	5590.254	681.905	2694.129	659.534	872.2575
50	610	635.206	635.3424	615.511	30.37112	596.127	192.4601
60	530	560.281	916.939	544.153	200.3074	528.141	3.455881
70	520	504.594	237.3448	491.392	818.4177	478.137	1752.511
90	380	390.064	101.2841	380.938	0.879844	371.619	70.24116
110	350	333.806	262.2456	330.07	397.2049	325.785	586.3662
150	200	223.391	547.1389	223.059	531.7175	222.146	490.4453
MSE			1461.521		659.4624		470.1448

Table 5.5. Model of best prediction

CONCLUSION AND FUTURE WORK

Fractional calculus is a generalized form of the ordinary calculus. The operations in classical calculus are restricted to integer order, however, fractional calculus extends the order to include all positive real numbers. There are still many open questions in this newly developing theory needed to be answered. In this thesis we closed some of the gaps in the theory of fractional calculus. We developed fractional trigonometry based on the multi-valued fractional generalization of the exponential function, Mittag-Leffler function. We introduced the characteristic polynomials of fractional homogenous differential equations and the solutions of these equations as well. Generalized Wronskian determinant which is worthwhile in the study of linearly independence of solutions to a system of fractional differential equations was developed. Also, we presented a new method of solving a system of fractional differential equations. A linear combination of two fractional trigonometric functions was generated by solving a system of fractional differential equations with the new method.

After investigation, we noticed that the fractional calculus has a great potential in analyzing real world problems. We demonstrated that fractional calculus performs better in the modeling in particular applications. For that, we proposed an application of fractional calculus to pharmacokinetic model. This model is important in clinical study to recommend a dose or regimen. In particular, we applied our theory to one compartment model which gives the relationship between drug concentration and time. We first approximate the solutions using fractional model. Then we compare between our theory to ordinary calculus by using real data. Our study showed that fractional models gave the best fitting to the given data, not just that, also the best prediction to the future data.

In the next step to broaden this research, we would like to investigate the inverse fractional trigonometry. What would be the identities, the Laplace transform and the derivative of the inverse fractional trigonometric functions? Are they similar to what we have in the integer order inverse trigonometry?

Also, we hope to extend fractional model applications to approximate the solution of two compartment models. Such models study the plasma concentration over time in two compartments instead of one compartment.

APPENDIX

The following Mathematica codes were used to comput and plot the graphs

Figure 4.1

```
X1      \[Alpha] := 1

X2      \[Alpha] := 0.99

X3      \[Alpha]:= 0.98

X4      \[Alpha]:= 0.95

X1 = (2)^-1* x^(\[Alpha] - 1) (Sum[(Sqrt[-1] x)^k/Gamma[\[Alpha]*k + \[Alpha]], {k, 0,
100}] + Sum[(-Sqrt[-1] x)^k/Gamma[\[Alpha]*k + \[Alpha]], {k,
    0, 100}])

PX1 = Plot[{X1}, {x, 0, 2 Pi}, PlotStyle ->
    {AbsoluteThickness[1]},
    BaseStyle -> {FontWeight -> "Bold", FontSize -> 16}]

Show[PX1, PX2, PX3, PX4, PlotRange -> Automatic]
```

Figure 4.2

```
X1      \[Alpha] := 1

X2      \[Alpha] := 0.99

X3      \[Alpha]:= 0.98

X4      \[Alpha]:= 0.95

X1 = (2*Sqrt[-1])^-1* x^(\[Alpha] - 1) (Sum[(Sqrt[-1] x)^k/Gamma[\[Alpha]*k + \[Alpha]],
{k, 0, 100}] - Sum[(-Sqrt[-1] x)^k/Gamma[\[Alpha]*k + \[Alpha]], {k,
    0, 100}])

PX1 = Plot[{X1}, {x, 0, 2 Pi}, PlotStyle ->
    {AbsoluteThickness[1]},
```

```
    BaseStyle -> {FontWeight -> "Bold", FontSize -> 16}]
Show[PX1, PX2, PX3, PX4, PlotRange -> Automatic]
```

Figure 5.2

```
a:=1002,42;    b:=0.011
X1    \[Alpha] := 1;
X2    \[Alpha] := 0.99;
X3    \[Alpha]:= 0.80;
X4    \[Alpha]:= 0.50;
X5    \[Alpha]:= 0.20;
X1 := a*x^(\[Alpha] - 1)*Sum[(-(b) x^\[Alpha])^k/Gamma[\[Alpha]*k +\[Alpha]], {k, 0,
100}]
    Plot[{X1}, {x, 0, 100}, PlotStyle ->
    {Thick}, AxesLabel -> {t, Concentration}]
Show[PX1, PX2, PX3, PX4,PX5, PlotRange -> Automatic]
```

Figure 5.3

```
a:=1002,42;    b:=0.011
X1    \[Alpha]:= 0.90;
X3    \[Alpha]:= 0.50;
X4    \[Alpha]:= 0.20;
X2    \[Alpha]:= 0.80;    a:=1002,42;    b:=0.019041
X1 := a*x^(\[Alpha] - 1)*Sum[(-(b) x^\[Alpha])^k/Gamma[\[Alpha]*k +\[Alpha]], {k, 0,
100}]
    Plot[{X1}, {x, 0, 100}, PlotStyle ->
    {Thick}, AxesLabel -> {t, Concentration}]
```

```
Show[PX1, PX2, PX3, PX4,PX5, PlotRange -> Automatic]
```

Figure 5.4

```
Lp := {{0, 7.88}, {6, 7.10}, {12, 6.97}, {24, 5.27}, {36, 4.52}, {48,
    3.43}, {72, 1.97}, {96, 1.01}, {144, .23}}
P = ListPlot[Lp, PlotMarkers -> {Automatic, Medium}]
a:=10;     b:=0.019
X1     \[Alpha]:= 1;
X2     \[Alpha]:= 0.91;
X1 := a*x^(\[Alpha] - 1)*Sum[(-(b) x^\[Alpha])^k/Gamma[\[Alpha]*k +\[Alpha]], {k, 0,
100}]
Needs["PlotLegends`"]
Plot[{X1, X2}, {x, 0, 144}, PlotStyle ->
    {Thin, Thick}, PlotLegend -> {"\[Alpha]=1", "\[Alpha]=.91"},
LegendPosition -> {1.1, -0.4}]
PX1 = Plot[{X1}, {x, 0, 144}, PlotStyle ->
    {Thick, Purple}, BaseStyle -> {FontWeight -> "Bold", FontSize -> 16}]
Show[PX1, PX2, P, AxesLabel -> {t, Concentration}, PlotRange -> All]
```

Figure 5.5

```
Lj = {{10, 920}, {20, 800}, {30, 750}, {40, 630}, {50, 610}, {60,
    530}, {70, 520}, {90, 380}, {110, 350}, {150, 200}}
J = ListPlot[Lj, PlotMarkers -> {Automatic, Medium}]
a:=1070;     b:=0.010434
X1     \[Alpha]:= 1;
X2     \[Alpha]:= 0.99;
```

```
X3      \[Alpha]:= 0.98;

X1 := a*x^(\[Alpha] - 1)*Sum[(-(b) x^\[Alpha])^k/Gamma[\[Alpha]*k +\[Alpha]], {k, 0,
100}]

PX1 = Plot[{X1}, {x, 0, 144}, PlotStyle ->
    {Thick, Purple}, BaseStyle -> {FontWeight -> "Bold", FontSize -> 16}]

Needs["PlotLegends`"]

Plot[{X1, X2}, {x, 0, 144}, PlotStyle ->
    {Thin, Thick}, PlotLegend -> {"\[Alpha]=1", "\[Alpha]=.91"},
    LegendPosition -> {1.1, -0.4}]

Show[PX1, PX2, P, AxesLabel -> {t, Concentration}, PlotRange -> All]
```

Table 5.2 and Table 5.3

```
a:=1070;     b:=0.010434

X1      \[Alpha]:= 1;

X2      \[Alpha]:= 0.99;

X3      \[Alpha]:= 0.98;

X1 := a*x^(\[Alpha] - 1)*Sum[(-(b) x^\[Alpha])^k/Gamma[\[Alpha]*k +\[Alpha]], {k, 0,
10000}]

Table[X1, {x, 10, 150, 10}].
```

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