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Discrete Fractional Calculus and Its Applications to Tumor Growth

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DISCRETE FRACTIONAL CALCULUS AND ITS APPLICATIONS TO TUMOR GROWTH

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ABSTRACT

Almost every theory of mathematics has its discrete counterpart that makes it conceptually easier to understand and practically easier to use in the modeling process of real world problems. For instance, one can take the "difference" of any function, from 1st order up to the n-th order with discrete calculus. However, it is also possible to extend this theory by means of discrete fractional calculus and make n any real number such that the ½-th order difference is well defined. This thesis is comprised of five chapters that demonstrate some basic definitions and properties of discrete fractional calculus while developing the simplest discrete fractional variational theory. Some applications of the theory to tumor growth are also studied.

The first chapter is a brief introduction to discrete fractional calculus that presents some important mathematical functions widely used in the theory. The second chapter shows the main fractional difference and sum operators as well as their important properties. In the third chapter, a new proof for Leibniz formula is given and summation by parts for discrete fractional calculus is stated and proved. The simplest variational problem in discrete calculus and the related Euler-Lagrange equation are developed in the fourth

chapter. In the fifth chapter, the fractional Gompertz difference equation is introduced. First, the existence and uniqueness of the solution is shown and then the equation is solved by the method of successive approximation. Finally, applications of the theory to tumor and bacterial growth are presented.

CHAPTER 1

A Brief Introduction to Discrete Fractional Calculus

Derivative and integral operators are two fundamental concepts of ordinary calculus (calculus on R (the set of real numbers)). Analogously, difference and sum operators are two fundamental concepts of discrete calculus (calculus on Z (the set of integers)) [**19**]. In general, derivative or difference operators can be applied to a function up to the n-th order where n is an integer, and they are denoted by $d^n f(x)/dx^n$, $\Delta^n f(x)$ respectively. The reasoning behind setting the order to an exact integer number, however, usually goes unnoticed in ordinary calculus. In fact, fractional calculus asserts that orders of derivative or integral operators can be arbitrary numbers, for instance, one could calculate the 1/2-th order derivative or $\sqrt{3}$-th order integral of a function.

Fractional calculus is a field of applied mathematics that deals with derivatives and integrals of arbitrary orders, and their applications appear in science, engineering, applied mathematics, economics and other fields [**10, 11, 14, 18, 20, 21, 24, 26**]. It is well known that there is a similarity between properties of differential calculus involving the operator $D = \frac{d}{dx}$ and properties of discrete calculus involving the operator $\Delta f(x) = f(x+1) - f(x)$ which is known as the forward difference operator. Expectedly, a similar correspondence exists between the operators of fractional and discrete fractional calculus.

1.1. Historical Background of Fractional Calculus

The seeds of fractional calculus were planted over 300 years ago in a letter from L'H$\widehat{o}$spital to Leibniz where L'H$\widehat{o}$spital raised a question about the meaning of $d^n y/dx^n$ if $n = 1/2$. In his reply, dated 30 September 1695, Leibniz wrote: 'This is an apparent paradox from which, one day, useful consequences will be drawn.'

Later, corresponding with Johann Bernoulli, Leibniz mentioned derivatives of 'general order'. He used the notation $d^{1/2}y$ to denote the derivative of order 1/2. After that fractional derivatives were mentioned in several different contexts: by Euler in 1730, by Lagrange in 1772 defining a fractional derivative by means of an integral, by Laplace in 1812, by Lacroix in 1819 devoting less than two pages of his 700-page text to the topic, by Fourier in 1822, by Liouville in 1832, by Riemann in 1847, by Greer in 1859, by Holmgren in 1865, by Griinwald in 1867, by Letnikov in 1868, by Sonin in 1869, by Laurent in 1884, by Nekrassov in 1888, by Krug in 1890 and by Weyl in 1917.

Although later on the derivative of fractional order $D^\alpha f$ has been considered extensively in the literature [**25, 27**], difference of fractional order has attracted less attention over the years. Differences of fractional order were first mentioned by Kuttner in 1956 [**1**].

For a_n is any sequence of complex numbers and s is any real constant, Kuttner defined the s-th order difference as

$$\Delta^s a_n = \sum_{m=0}^{\infty} \binom{-s-1+m}{m} a_{n+m}. \tag{1.1}$$

In 1974, Diaz and Osler [**2**] defined the fractional difference by the rather natural approach of allowing the index of differencing, in the standard expression for the n-th difference as

$$\Delta^\alpha f(x) = \sum_{k=0}^{\infty}(-1)^k \binom{\alpha}{k} f(x+\alpha-k), \tag{1.2}$$

$$\binom{\alpha}{k} = \frac{\Gamma(\alpha+1)}{\Gamma(\alpha-k+1)k!}, \tag{1.3}$$

where α is any real or complex number.

In 1989 Miller and Ross [**22**] defined the fractional order sum and difference operators as shown below respectively,

$$\Delta^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=a}^{t-\alpha}(t-\sigma(s))^{(\alpha-1)} f(s), \tag{1.4}$$

$$\Delta^\alpha f(t) = \Delta\Delta^{-(1-\alpha)} f(t) = \Delta \frac{1}{\Gamma(1-\alpha)} \sum_{s=a}^{t-1+\alpha}(t-\sigma(s))^{(-\alpha)} f(s), \tag{1.5}$$

where $t \equiv \alpha$ (mod1) and $0 < \alpha < 1$.

In 2009 Anastassiou [**3**] defined the Caputo like discrete fractional difference as

$$\Delta^\alpha f(t) = \Delta^{-(m-\alpha)}\Delta^m f(t) = \frac{1}{\Gamma(m-\alpha)} \sum_{s=a}^{t-m+\alpha}(t-\sigma(s))^{(m-\alpha-1)}\Delta^m f(s). \tag{1.6}$$

In this thesis we use definitions (1.3), (1.4). Following the work of Miller and Ross, Atici and Eloe [**6, 7, 8, 9**] defined and proved several properties of these operators and solved the initial value problems of fractional difference equations.

1.2. Gamma Function and Falling Factorial

In this section, we focus on the Gamma function and Falling factorial since the definition of the discrete fractional difference and sum operators involve them. We also list some well known properties of the Gamma function and Factorial polynomial.

1.2.1. Gamma Function. Gamma function is a special transcendental function denoted by $\Gamma(x)$, and was first introduced by Euler to generalize the factorial to noninteger values. For $x > 0$, it is defined as:

$$\Gamma(x) = \int_0^\infty t^{x-1} e^{-t} dt. \tag{2.1}$$

It follows that the Gamma function $\Gamma(x)$ (or the Eulerian integral of the second kind) is well defined and is analytic for $x > 0$.

We have,

$$\Gamma(1) = \int_0^\infty e^{-t} dt = 1 \tag{2.2}$$

and for $x > 0$, integration by parts yields

$$\Gamma(x+1) = \int_0^\infty t^x e^{-t} dt = [-t^x e^{-t}]_0^\infty + x \int_0^\infty t^{x-1} e^{-t} dt = x\Gamma(x), \tag{2.3}$$

and the relation $\Gamma(x+1) = x\Gamma(x)$ is an important functional equation.

For integer values functional equation becomes

$$\Gamma(n+1) = n! \tag{2.4}$$

and this is why the Gamma function can be interpreted as an extension of the factorial function to nonzero positive real numbers.

1.2.2. Falling Factorial. The falling factorial (factorial polynomial) $t^{(n)}$ is defined as

$$t^{(n)} = t(t-1)(t-2)(t-(n-1)) = \prod_{k=0}^{n-1}(t-k) = \frac{\Gamma(t+1)}{\Gamma(t+1-n)}, \tag{2.5}$$

for any integer $n \geq 0$ and Γ denotes the Gamma function.

These are some properties of the factorial polynomial that will be used in this thesis.

THEOREM 1.2.1. *(i)* $\Delta t^{(\alpha)} = \alpha t^{(\alpha-1)}$*, where* Δ *is the forward difference operator.*

(ii) $(t-\mu)t^{(\mu)} = t^{(\mu+1)}$*, where* $\mu \in R$*.*

(iii) $\mu^{(\mu)} = \Gamma(\mu+1)$*.*

(iv) $t^{(\alpha+\beta)} = (t-\beta)^{(\alpha)}t^{(\beta)}$*.*

Proof.

According to the definition of the falling factorial and its properties proofs can be shown directly as below.

(i)
$$\begin{aligned}
\Delta t^{(\alpha)} &= \Delta \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)} \\
&= \frac{\Gamma((t+1)+1)}{\Gamma((t+1)-\alpha+1)} - \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)} \\
&= \frac{\Gamma(t+2)}{\Gamma(t-\alpha+2)} - \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)} \\
&= \frac{(t+1)\Gamma(t+1)}{(t-\alpha+1)\Gamma(t-\alpha+1)} - \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)}
\end{aligned}$$

$$= \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)}(\frac{t+1}{t+1-\alpha} - 1) = \frac{\Gamma(t+1)}{\Gamma(t-\alpha+1)}\frac{\alpha}{(t-\alpha+1)}$$

$$= \alpha\frac{\Gamma(t+1)}{\Gamma(t-\alpha+2)} = \alpha t^{(\alpha-1)}.$$

(ii) $(t-\mu)t^{(\mu)} = (t-\mu)\frac{\Gamma(t+1)}{\Gamma(t+1-\mu)} = (t-\mu)\frac{\Gamma(t+1)}{(t-\mu)\Gamma(t-\mu)} = t^{(\mu+1)}.$

(iii) $\mu^{(\mu)} = \Gamma(\mu+1)$ directly from the definition of falling factorial.

(iv) $t^{(\alpha+\beta)} = \frac{\Gamma(t+1)}{\Gamma(t+1-\alpha-\beta)}$. Multiplying and dividing by $\Gamma(t-\beta+1)$ we get

$$= \frac{\Gamma(t-\beta+1)}{\Gamma(t+1-\alpha-\beta)}\frac{\Gamma(t+1)}{\Gamma(t-\beta+1)} = (t-\beta)^{(\alpha)}t^{(\beta)}.$$

Remark 1.2.1. In calculus, for any given real number $\alpha > 0$, we have $\frac{d}{dt}t^{\alpha} = \alpha t^{\alpha-1}$ and in discrete calculus we have $\Delta t^{(\alpha)} = \alpha t^{(\alpha-1)}$. Therefore, the powers x^n in ordinary calculus and $x^{(n)}$ in discrete calculus behave similarly.

Since some proofs in this thesis depend on the product rule for discrete calculus, let us define and prove this rule.

Example 1.2.1. Let f and g be real valued functions, then

$$\Delta(f(t)g(t)) = g(t)\Delta f(t) + f(\sigma(t))\Delta g(t) = g(\sigma(t))\Delta f(t) + f(t)\Delta g(t), \qquad (2.6)$$

where $\sigma(t) = t+1$. For the first equality, we have

$\Delta(f(t)g(t)) = f(t+1)g(t+1) - f(t)g(t).$

$$= f(t+1)g(t+1) - f(t+1)g(t) + f(t+1)g(t) - f(t)g(t).$$

$$= f(t+1)(g(t+1) - g(t)) + g(t)(f(t+1) - f(t)).$$

$$= f(\sigma(t))\Delta g(t) + g(t)\Delta f(t).$$

For the second equality, we have

$$\Delta(f(t)g(t)) = f(t+1)g(t+1) - f(t)g(t).$$

$$= f(t+1)g(t+1) - g(t+1)f(t) + g(t+1)f(t) - f(t)g(t).$$

$$= g(t+1)(f(t+1) - f(t)) + f(t)(g(t+1) - g(t)).$$

$$= g(\sigma(t))\Delta f(t) + f(t)\Delta g(t).$$

Remark 1.2.2. From the equation (2.6), we have

$$g(t)\Delta f(t) = \Delta(f(t)g(t)) - f(\sigma(t))\Delta g(t).$$

Applying the $\sum_{t=1}^{b-1}$ operator to both sides gives

$$\sum_{t=1}^{b-1}(g(t)\Delta f(t)) = \sum_{t=1}^{b-1}\Delta(f(t)g(t)) - \sum_{t=1}^{b-1}(f(\sigma(t))\Delta g(t)).$$

$$\sum_{t=1}^{b-1} g(t)\Delta f(t) = f(t)g(t)|_1^b - \sum_{t=1}^{b-1} f(\sigma(t))\Delta g(t), \tag{2.7}$$

where $b > 1$ is an integer. This is known as the summation by parts formula in discrete calculus [**19**].

CHAPTER 2

Fractional Sum Operator and Fractional Difference Operator

In this chapter some basic definitions and results are given about discrete fractional calculus. $\Delta_a^{-\alpha} f(x)$ will denote the fractional sum of a function $f(x)$ to an arbitrary order $\alpha > 0$, starting from a. $\Delta^{\alpha} f(x)$ will denote the fractional difference of a function $f(x)$ to an arbitrary order α where α is a positive real number.

2.1. Definition of α-order Fractional Sum and α-order Fractional Difference

Let a be any real number, α be any positive real number. The α-th fractional sum (α-sum) of f is defined by

$$\Delta_a^{-\alpha} f(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=a}^{t-\alpha} (t-\sigma(s))^{(\alpha-1)} f(s). \tag{1.1}$$

Here f is defined for $s = a \pmod 1$ and $\Delta_a^{-\alpha} f$ is defined for $t = a + \alpha \pmod 1$; in particular, $\Delta_a^{-\alpha}$ maps functions defined on $\mathbb{N}_a$ to functions defined on $\mathbb{N}_{a+\alpha}$, where $\mathbb{N}_t = \{t, t+1, t+2, \ldots\}$.

Remark 2.1.1. We note that for $\alpha = 1$ definition (1.1) reduces to discrete sum operator $\Delta_a^{-1} f(t) = \sum_{s=a}^{t-1} f(s)$.

Let a be any real number, α be any positive real number such that $m-1<\alpha<m$ where m is an integer. The α-order fractional difference (α-difference) of f is defined by

$$\Delta^{\alpha} f(t)=\Delta^{m}\Delta^{-(m-\alpha)} f(t)=\Delta^{m}\frac{1}{\Gamma(m-\alpha)}\sum_{s=a}^{t-m+\alpha}(t-\sigma(s))^{(m-\alpha-1)} f(s). \tag{1.2}$$

The fractional difference of a function can be defined by the fractional sum of the same function. This property can be interpreted as the fractional difference depending on its whole time history. It does not depend on just the instantaneous behavior of the function. Therefore, α-order difference and sum operators are perfectly suited for modeling of materials with memory, such as tumors.

2.2. Properties of the Fractional Difference and Fractional Sum Operators

2.2.1. Law of Exponent for Fractional Sums. The law of exponent for fractional sums is proved by Atıcı and Eloe [**6**] as below and it is very useful to calculate certain types of sums and to simplify the expressions that include them.

THEOREM 2.2.1. *Let f be a real valued function, and let $\mu, \alpha > 0$. Then for all t such that $t = \mu+\alpha, \quad (mod 1)$,*

$$\Delta^{-\alpha}[\Delta^{-\mu} f(t)] = \Delta^{-(\mu+\alpha)} f(t) = \Delta^{-\mu}[\Delta^{-\alpha} f(t)].$$

Proof. By definition of fractional sum, we have

$$\Delta^{-\mu}(\Delta^{-\alpha} f(t)) = \frac{1}{\Gamma(\alpha)}\Delta^{-\mu}\sum_{r=0}^{t-\alpha}(t-\sigma(r))^{(\alpha-1)} f(r)$$

$$= \frac{1}{\Gamma(\alpha)\Gamma(\mu)} \sum_{s=\alpha}^{t-\mu} (t-\sigma(s))^{(\mu-1)} \sum_{r=0}^{s-\alpha} (s-\sigma(r))^{(\alpha-1)} f(r)$$

$$= \frac{1}{\Gamma(\alpha)\Gamma(\mu)} \sum_{s=\alpha}^{t-\mu} \sum_{r=0}^{s-\alpha} (t-\sigma(s))^{(\mu-1)} (s-\sigma(r))^{(\alpha-1)} f(r).$$

Next we interchange the order of summation in the double sum to get

$$= \frac{1}{\Gamma(\alpha)\Gamma(\mu)} \sum_{r=0}^{t-(\mu+\alpha)} \sum_{s=r+\alpha}^{t-\mu} (t-\sigma(s))^{(\mu-1)} (s-\sigma(r))^{(\alpha-1)} f(r).$$

Let us call $x = s-(r+1)$. Then the above expression becomes

$$= \frac{1}{\Gamma(\alpha)\Gamma(\mu)} \sum_{r=0}^{t-(\mu+\alpha)} \Big(\sum_{x=\alpha-1}^{t-\sigma(r)-\mu} (t-\sigma(r)-\sigma(x))^{(\mu-1)} x^{(\alpha-1)} \Big) f(r).$$

By definition of the fractional sum operator, we have

$$= \frac{1}{\Gamma(\alpha)} \sum_{r=0}^{t-(\mu+\alpha)} (\Delta^{-\mu} (t-\sigma(r))^{(\alpha-1)}) f(r),$$

$$= \frac{1}{\Gamma(\alpha)} \sum_{r=0}^{t-(\mu+\alpha)} \frac{\Gamma(\alpha)}{\Gamma(\alpha+\mu)} (t-\sigma(r))^{(\alpha+\mu-1)} f(r),$$

$$= \Delta^{-(\mu+\alpha)} f(t). \qquad \square$$

Remark 2.2.1. Let f be a real valued function defined on the set of integers. In discrete calculus, we have $\Delta\Delta^{-1} f = f$. For any positive real number α, this equality is valid for discrete fractional calculus as well. In fact, by definition of the discrete fractional difference,

$$\Delta^{\alpha}\Delta^{-\alpha} f(x) = \Delta\Delta^{-(1-\alpha)}\Delta^{-\alpha} f(x),$$

where $0 < \alpha < 1$.

Thus using the exponent law (Theorem 2.2.1),

$$= \Delta\Delta^{-\alpha}\Delta^{-(1-\alpha)}f(x) = \Delta\Delta^{-1}f(x) = f(x).$$

2.2.2. Power Rule for Discrete Fractional Calculus. The power rule states the α order fractional sum of a factorial function. Miller and Ross [**22**] obtained the following lemma in the case that μ is a positive integer by induction and $\mu = 0$ with a straightforward calculation. For any positive real number μ, the power rule was proved by Atıcı and Eloe [**6**].

Lemma 2.2.1.

$$\Delta^{-\alpha}t^{(\mu)} = \frac{\Gamma(\mu+1)}{\Gamma(\mu+\alpha+1)}t^{(\mu+\alpha)}.$$

Remark 2.2.2. It is interesting to note that for any constant c, $\Delta^{\alpha}c$ is not zero. To see this, we use the power rule and the linearity property of sum operator, the fractional difference of a constant c is

$$\Delta\Delta^{-(1-\alpha)}c = \Delta\frac{c}{\Gamma(2-\alpha)}t^{(1-\alpha)} = \frac{c}{\Gamma(1-\alpha)}t^{(-\alpha)},$$

where $0 < \alpha < 1$.

For the definition of Caputo difference $\Delta^{\alpha}c$ is not zero with respect to definition 1.6.

Example 2.2.1. Let f and g be defined on the set of integers. For $\alpha = 1/2$ by means of the power rule, we can compute and generalize α-th sum of factorial polynomials as below.

$$\Delta^{-1/2}t^{(0)} = \frac{\Gamma(1)}{\Gamma(3/2)}t^{(1/2)} = \frac{\Gamma(1)}{\Gamma(3/2)}\frac{\Gamma(t+1)}{\Gamma(t+1/2)}.$$

$$\Delta^{-1/2}t^{(1)} = \frac{\Gamma(2)}{\Gamma(5/2)}t^{(3/2)} = \frac{\Gamma(2)}{\Gamma(5/2)}\frac{\Gamma(t+1)}{\Gamma(t-1/2)}.$$

$$\Delta^{-1/2}t^{(2)} = \frac{\Gamma(3)}{\Gamma(7/2)}t^{(5/2)} = \frac{\Gamma(3)}{\Gamma(7/2)}\frac{\Gamma(t+1)}{\Gamma(t-3/2)}.$$

So 1/2-th order sum for $t^{(n)}$ is

$$\Delta^{-1/2}t^{(n)} = \frac{\Gamma(n+1)}{\Gamma(n+3/2)}t^{(n+1/2)} = \frac{\Gamma(n+1)}{\Gamma(n+3/2)}\frac{\Gamma(t+1)}{\Gamma(t-n+1/2)}.$$

2.2.3. Commutative Property of the Fractional Sum and Difference Operators. The commutative property states that we can interchange the order of sum and difference operators and this effects the result as a constant. Since many mathematical proofs depend on this property, it is worthwhile to mention it here.

THEOREM 2.2.2. [**6**] *For any $\alpha > 0$, the following equality holds:*

$$\Delta^{-\alpha}\Delta f(t) = \Delta\Delta^{-\alpha} f(t) - \frac{(t-a)^{(\alpha-1)}}{\Gamma(\alpha)} f(a), \tag{2.1}$$

where f is defined on $\mathbb{N}_a$.

Proof. First recall the summation by parts formula [**19**]:

$$\Delta_s((t-s)^{(\alpha-1)}f(s)) = (t-\sigma(s))^{(\alpha-1)}\Delta_s f(s) - (\alpha-1)(t-\sigma(s))^{(\alpha-2)}f(s)).$$

Using summmation by parts to obtain

$$\frac{1}{\Gamma(\alpha)}\sum_{s=a}^{t-\alpha}(t-\sigma(s))^{(\alpha-1)}\Delta_s f(s) = \frac{\alpha-1}{\Gamma(\alpha)}\sum_{s=a}^{t-\alpha}(t-\sigma(s))^{(\alpha-2)}f(s) + \frac{(t-s)^{(\alpha-1)}f(s)}{\Gamma(\alpha)}\Big|_a^{t+1-\alpha}$$

$$= \frac{\alpha-1}{\Gamma(\alpha)}\sum_{s=a}^{t-\alpha}(t-\sigma(s))^{(\alpha-2)}f(s)+\frac{(\alpha-1)^{(\alpha-1)}f(t+1-\alpha)}{\Gamma(\alpha)}-\frac{(t-a)^{(\alpha-1)}}{\Gamma(\alpha)}f(a)$$

$$= \frac{1}{\Gamma(\alpha-1)}\sum_{s=a}^{t-(\alpha-1)}(t-\sigma(s))^{(\alpha-2)}f(s)-\frac{(t-a)^{(\alpha-1)}}{\Gamma(\alpha)}f(a).$$

Since $\Delta\Delta^{-\alpha}f(t) = \frac{1}{\Gamma(\alpha-1)}\sum_{s=a}^{t-(\alpha-1)}(t-\sigma(s))^{(\alpha-2)}f(s)$, the desired equality follows. □

Remark 2.2.3. Replace α by $\alpha+1$ in equation (2.1) and employ Theorem 2.2.2 to obtain

$$\Delta^{-\alpha-1}\Delta f(t) = \Delta^{-\alpha}f(t) - \frac{(t-a)^{(\alpha)}}{\Gamma(\alpha+1)}f(a).$$

This implies

$$\Delta^{-\alpha}f(t) = \Delta^{-\alpha-1}\Delta f(t) + \frac{(t-a)^{(\alpha)}}{\Gamma(\alpha+1)}f(a). \tag{2.2}$$

Remark 2.2.4. Let $p-1<\alpha<p$, where p is a positive integer. Theorem 2.2.2 implies that

$$\begin{aligned}
&\Delta\Delta^{\alpha}f(t) = \Delta\Delta^{p}(\Delta^{-(p-\alpha)}f(t)) = \Delta^{p+1}(\Delta^{-(p-\alpha)}f(t))\\
&\quad = \Delta^{p}(\Delta\Delta^{-(p-\alpha)}f(t)) = \Delta^{p}[\Delta^{-(p-\alpha)}\Delta f(t) + \frac{(t-a)^{(p-\alpha-1)}}{\Gamma(p-\alpha)}f(a)]\\
&\quad = \Delta^{p}\Delta^{-(p-\alpha)}\Delta f(t) + \Delta^{p}\frac{(t-a)^{(p-\alpha-1)}}{\Gamma(p-\alpha)}f(a)\\
&\quad = \Delta^{\alpha}\Delta f(t) + \frac{(t-a)^{(-\alpha-1)}}{\Gamma(-\alpha)}f(a).
\end{aligned}$$

So we conclude that (2.1) is valid for any real number α.

CHAPTER 3

Leibniz Formula and Summation by Parts Formula

3.1. Leibniz Formula

The Leibniz rule is a generalization of the product rule in calculus. If f and g are n times differentiable functions, then the n-th derivative of the product fg is given by

$$(f.g)^{(n)} = \sum_{k=0}^{n} \binom{n}{k} f^{(k)} g^{(n-k)}$$

In difference calculus, corresponding Leibniz rule is

$$\Delta^n(f.g) = \sum_{k=0}^{n+1} \binom{n}{k} \Delta^k f \Delta^{n-k} E^k g. \tag{1.1}$$

where $E^k g(t) = g(t+k)$ is the shift operator.

In discrete fractional calculus, a relevant question to ask is whether the product rules for fractional difference operators exist in the same way as they do in fractional calculus. The affirmative answer to this question can be found in an early paper by Miller and Ross [**22**]. Here we give an alternate proof to Leibniz formula for α-sum while carefully defining the domains of each function f and g.

LEMMA 3.1.1. *Let f be a real valued function defined on $\mathbb{N}_0$ and let g be a real valued function defined on $\mathbb{N}_\alpha \cup \mathbb{N}_0$, where α is a real number between 0 and 1. Then the following equality holds*

$$\Delta_0^{-\alpha}(fg)(t) = \sum_{k=0}^{\infty} \binom{-\alpha}{k} [\Delta^k g(t)][\Delta_0^{-(\alpha+k)} f(t+k)],$$

where $t \equiv \alpha$ (mod 1) and

$$\binom{-\alpha}{k} = \frac{\Gamma(-\alpha+1)}{\Gamma(k+1)\Gamma(-\alpha-k+1)}.$$

Proof. By definition of discrete fractional sum, we have

$$\Delta_0^{-\alpha}(fg)(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=0}^{t-\alpha} (t-\sigma(s))^{(\alpha-1)} f(s)g(s),$$

where $t \equiv \alpha$ (mod 1).

By Taylor expansion of $g(s)$ (page 40, [**13**]), we have

$$g(s) = \sum_{k=0}^{\infty} \frac{(s-t)^{(k)}}{k!} \Delta^k g(t) = \sum_{k=0}^{\infty} (-1)^k \frac{\Delta^k g(t)}{k!} (t-\sigma(s)+k)^{(k)}.$$

Thus by substituting the Taylor series expansion of $g(s)$ in the sum, we have,

$$\Delta_0^{-\alpha}(fg)(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=0}^{t-\alpha} (t-\sigma(s))^{(\alpha-1)} f(s) \sum_{k=0}^{\infty} (-1)^k \frac{\Delta^k g(t)}{k!} (t-\sigma(s)+k)^{(k)}.$$

Since $(t-\sigma(s))^{(\alpha-1)}(t-\sigma(s)+k)^{(k)} = (t+k-\sigma(s))^{(\alpha+k-1)}$, we have

$$\Delta_0^{-\alpha}(fg)(t) = \frac{1}{\Gamma(\alpha)} \sum_{k=0}^{\infty} (-1)^k \frac{\Delta^k g(t)}{k!} \sum_{s=0}^{(t+k)-(\alpha+k)} (t+k-\sigma(s))^{(\alpha+k-1)} f(s).$$

Since $(-1)^k = \dfrac{\Gamma(-\alpha+1)\Gamma(\alpha)}{\Gamma(-\alpha-k+1)\Gamma(k+\alpha)}$ for any nonnegative integer k, the above expression on the right becomes

$$\sum_{k=0}^{\infty} \binom{-\alpha}{k} [\Delta^k g(t)][\Delta_0^{-(\alpha+k)} f(t+k)].$$

This completes the proof of the lemma. □

Next we state and prove another version of the Leibniz formula which involves the nabla (∇) operator, $\nabla f(t) = f(t) - f(t-1)$.

LEMMA 3.1.2. *Let f and g be real valued functions defined on $\mathbb{N}_0$ and α be any real number between 0 and 1. Then the following equality holds*

$$\Delta_0^{-\alpha}(fg)(t) = \sum_{k=0}^{\infty} \binom{-\alpha}{k} [\nabla^k g(t-\alpha)][\Delta_0^{-(\alpha+k)} f(t)],$$

where $t \equiv \alpha$ (mod 1) and

$$\binom{-\alpha}{k} = \frac{\Gamma(-\alpha+1)}{\Gamma(k+1)\Gamma(-\alpha-k+1)}.$$

Proof. By definition of discrete fractional sum, we have

$$\Delta_0^{-\alpha}(fg)(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=0}^{t-\alpha} (t-\sigma(s))^{(\alpha-1)} f(s) g(s).$$

By Taylor expansion of $g(s)$ (see [**5**]), we have

$$g(s) = \sum_{k=0}^{\infty} \frac{(s-t)^{\bar{k}}}{k!} \nabla^k g(t) = \sum_{k=0}^{\infty} (-1)^k (t-s)^{(k)} \frac{\nabla^k g(t)}{k!},$$

where $(s-t)^{\bar{k}} = \dfrac{\Gamma(s-t+k)}{\Gamma(s-t)}$ is the rising factorial power.

Thus by substituting Taylor series of $g(s)$ at $t-\alpha$ in the sum, we have,

$$\Delta_0^{-\alpha}(fg)(t) = \frac{1}{\Gamma(\alpha)} \sum_{s=0}^{t-\alpha} (t-\sigma(s))^{(\alpha-1)} f(s) \sum_{k=0}^{\infty} (-1)^k \frac{\nabla^k g(t-\alpha)}{k!} (t-s-\alpha)^{(k)}.$$

Since $\displaystyle\sum_{s=t-\alpha-k+1}^{t-\alpha} (t-\alpha-s)^{(k)} = 0$ and $(t-\sigma(s))^{(\alpha-1)}(t-\alpha-s)^{(k)} = (t-\sigma(s))^{(\alpha+k-1)}$, we have

$$\Delta_0^{-\alpha}(fg)(t) = g(t-\alpha)\Delta^{-\alpha} f(t) + \frac{1}{\Gamma(\alpha)} \sum_{k=1}^{\infty} \Gamma(\alpha+k) \frac{\nabla^k g(t-\alpha)}{k!} (-1)^k \Delta_0^{-(\alpha+k)} f(t).$$

Since $(-1)^k = \dfrac{\Gamma(-\alpha+1)\Gamma(\alpha)}{\Gamma(-\alpha-k+1)\Gamma(k+\alpha)}$ for any nonnegative integer k, the above expression on the right becomes

$$\sum_{k=0}^{\infty} \binom{-\alpha}{k} [\nabla^k g(t-\alpha)][\Delta_0^{-(\alpha+k)} f(t)].$$

This completes the proof. □

Example 3.1.1. Let us derive the $\alpha-th$ order difference of the product $tf(t)$, where f and t are defined on $\mathbb{N}_0$ and on $\mathbb{N}_\alpha \cup \mathbb{N}_0$ respectively, and $0 < \alpha < 1$.

It follows from Lemma 3.1.1 that

$$\Delta^{\alpha}(tf(t)) = \Delta\Delta^{-(1-\alpha)}(tf(t))$$

$$= \Delta \sum_{k=0}^{\infty} \binom{-1+\alpha}{k} \Delta^k t \Delta^{-(1-\alpha+k)} f(t+k),$$

for $t \equiv \alpha \pmod 1$.

Since $\Delta^k t = 0$ for $k \geq 2$, we have

$$\Delta^\alpha(tf(t)) = \Delta[t\Delta^{-(1-\alpha)}f(t) + (\alpha-1)\Delta^{-(2-\alpha)}f(t+1)].$$

$$\Delta^\alpha(tf(t)) = \Delta^{-(1-\alpha)}f(t+1) + t\Delta^\alpha f(t) + (\alpha-1)\Delta^{-(1-\alpha)}f(t+1).$$

$$\Delta^\alpha(tf(t)) = \alpha\Delta^{-(1-\alpha)}f(t+1) + t\Delta^\alpha f(t), \tag{1.2}$$

for $t \equiv \alpha \pmod 1$.

If we consider the domain of the function $g(t) = t$ as the set of whole numbers, then it follows from Lemma 3.1.2 that

$$\begin{aligned}\Delta^\alpha(tf(t)) &= \Delta\Delta^{-(1-\alpha)}(tf(t)) \\ &= \Delta\sum_{k=0}^{\infty}\binom{-1+\alpha}{k}\nabla^k(t-1+\alpha)\Delta^{-(1-\alpha+k)}f(t),\end{aligned}$$

for $t \equiv \alpha \pmod 1$.

Since $\Delta^k t = 0$ for $k \geq 2$, we have

$$\Delta^\alpha(tf(t)) = \Delta[(t-1+\alpha)\Delta^{-(1-\alpha)}f(t) + (\alpha-1)\Delta^{-(2-\alpha)}f(t)].$$

$$\Delta^\alpha(tf(t)) = \Delta^{-(1-\alpha)}f(t) + (t+\alpha)\Delta^\alpha f(t) + (\alpha-1)\Delta^{-(1-\alpha)}f(t).$$

$$\Delta^\alpha(tf(t)) = \alpha\Delta^{-(1-\alpha)}f(t) + (t+\alpha)\Delta^\alpha f(t). \tag{1.3}$$

One immediate observation can now be made. Since $\lim_{\alpha\to1}\Delta^\alpha = \Delta$ (see[**22**]), we apply this limit to both sides of the equations in (1.2) and (1.3) to obtain the forward difference of the product $tf(t)$ in discrete calculus, namely,

$$\Delta(tf(t)) = f(t+1) + t\Delta f(t) = f(t) + (t+1)\Delta f(t).$$

3.2. Summation by Parts Formula in Discrete Fractional Calculus

One of the basic methods of integration in calculus is 'integration by parts' , the counterpart of which is 'summation by parts' in discrete calculus. In this section, we argue that a summation by parts formula can also be defined and proved for discrete fractional calculus. By doing this we see the generalization of the discrete summation by parts formula.

In order to obtain the summation by parts formula in discrete fractional calculus, we shall start by defining left and right discrete fractional difference operators.

3.2.1. The Left and the Right Discrete Fractional Difference Operators.

Definition 3.2.1. Let f be any real-valued function and α be a positive real number between 0 and 1. Then the left discrete fractional difference and the right discrete fractional difference operators are defined as follows, respectively,

$$ {}_t\Delta_a^{\alpha} f(t) = \Delta_t \Delta_a^{-(1-\alpha)} f(t) = \frac{1}{\Gamma(1-\alpha)}\, \Delta \sum_{s=a}^{t-1+\alpha} (t-\sigma(s))^{(-\alpha)} f(s), $$

$t \equiv a + 1 - \alpha \pmod 1$,

$$ {}_b\Delta_t^{\alpha} f(t) = -\Delta_b \Delta_t^{-(1-\alpha)} f(t) = \frac{1}{\Gamma(1-\alpha)}\, (-\Delta) \sum_{s=t+1-\alpha}^{b} (s-\sigma(t))^{(-\alpha)} f(s), $$

where $t \equiv b + \alpha - 1 \pmod 1$. We will use the symbol Δ^{α} for ${}_t\Delta_a^{\alpha}$ except otherwise stated.

Remark 3.2.1. Note that for $\alpha = 1$

${}_t\Delta_a^1 f(t) = \Delta f(t)$ and ${}_b\Delta_t^1 f(t) = -\Delta f(t)$.

3.2.2. Proof of the Summation by Parts Formula.

Theorem 3.2.2. *Let F and G be real valued functions and $0 < \alpha < 1$. If $F(b+\alpha-2) = 0$ and $F(a+\alpha-2) = 0$ or $G(a+\alpha-1) = 0$ and $G(b+\alpha-1) = 0$, then the following equality holds*

$$\sum_{s=a}^{b-1} F(s+\alpha-1)\,{}_s\Delta_{a+\alpha-1}^{\alpha} G(s) = \sum_{s=a}^{b-1} G(s+\alpha-1)\,{}_{b+\alpha-1}\Delta_s^{\alpha} F^{\rho}(s+2(\alpha-1)), \quad (2.1)$$

where $F^{\rho} = F \circ \rho$ with $\rho(t) = t-1$.

Proof. Using the definition of fractional difference on the left side of the equality, we have

$$\sum_{s=a}^{b-1} F(s+\alpha-1)\,{}_s\Delta_{a+\alpha-1}^{\alpha} G(s) = \sum_{s=a}^{b-1} F(s+\alpha-1)\Delta\Delta^{-(1-\alpha)} G(s).$$

Using summation by parts formula for Δ-operator, we have

$$\sum_{s=a}^{b-1} F(s+\alpha-1)\Delta_s\Delta_{a+\alpha-1}^{-(1-\alpha)} G(s) = F(s+\alpha-2)\,{}_s\Delta_{a+\alpha-1}^{-(1-\alpha)} G(s)\Big|_a^b - \sum_{s=a}^{b-1} {}_s\Delta_{a+\alpha-1}^{-(1-\alpha)} G(s)\Delta_s F(s+\alpha-2) \quad (2.2)$$

$$= \frac{-1}{\Gamma(1-\alpha)} \sum_{s=a}^{b-1} \sum_{\tau=a+\alpha-1}^{s-(1-\alpha)} (s-\sigma(\tau))^{(-\alpha)} G(\tau)\Delta_s F(s+\alpha-2).$$

Next we interchange the order of summation in the double sum to obtain

$$\frac{-1}{\Gamma(1-\alpha)} \sum_{\tau=a+\alpha-1}^{b-2+\alpha} \sum_{s=\tau+1-\alpha}^{b-1} (s-\sigma(\tau))^{(-\alpha)} G(\tau)\Delta_s F(s+\alpha-2).$$

Let us call $u = \tau + 1 - \alpha$. Then the above expression becomes

$$\frac{-1}{\Gamma(1-\alpha)} \sum_{u=a}^{b-1} \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} G(u+\alpha-1) \Delta_s F(s+\alpha-2). \tag{2.3}$$

Now let us look at the following expression closely,

$$\frac{-1}{\Gamma(1-\alpha)} \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} \Delta_s F(s+\alpha-2). \tag{2.4}$$

Using summation by parts, we have

$$\begin{aligned} &\sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} \Delta_s F(s+\alpha-2) \\ &\quad = [(s-\alpha-u-1)^{(-\alpha)} F(s+\alpha-2)]|_u^b - \sum_{s=u}^{b-1} \Delta_s (s-\alpha-u-1)^{(-\alpha)} F(s+\alpha-2). \end{aligned}$$

Since $[(s-\alpha-u-1)^{(-\alpha)} F(s+\alpha-2)]|_u^b = 0$, then

$$\begin{aligned} \frac{-1}{\Gamma(1-\alpha)} \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} \Delta_s F(s+\alpha-2) &= \frac{1}{\Gamma(1-\alpha)} \sum_{s=u}^{b-1} \Delta_s (s-\alpha-u-1)^{(-\alpha)} F(s+\alpha-2) \\ &= \frac{1}{\Gamma(1-\alpha)} (-\alpha) \sum_{s=u}^{b-1} (s-\alpha-u-1)^{(-1-\alpha)} F(s+\alpha-2). \end{aligned}$$

It follows from (Theorem 8.50, [**13**])

$$\Delta_u \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} F(s+\alpha-2) = \alpha \sum_{s=u}^{b-1} (s-\alpha-\sigma(u))^{(-1-\alpha)} F(s+\alpha-2).$$

Hence the expression in (2.3) becomes

$$\begin{aligned} \frac{-1}{\Gamma(1-\alpha)} \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} \Delta_s F(s+\alpha-2) &= \frac{-1}{\Gamma(1-\alpha)} \Delta_u \sum_{s=u}^{b-1} (s-\alpha-u)^{(-\alpha)} F(s+\alpha-2) \\ &= \frac{-1}{\Gamma(1-\alpha)} \Delta_u \sum_{s=u}^{b-1} (s-\sigma(u+\alpha-1))^{(-\alpha)} F^{\rho}(s+\alpha-1) \\ &= \frac{1}{\Gamma(1-\alpha)} (-\Delta_u) \sum_{s=u-1+\alpha}^{b+\alpha-1} (s-\sigma(u+2\alpha-2))^{(-\alpha)} F^{\rho}(s), \end{aligned}$$

$$={}_{b+\alpha-1}\Delta_s^{\alpha}F^{\rho}(u+2(\alpha-1)).$$

Replacing this back in (2.2) we have the desired result.

If we prove the equality (2.1), starting from its right side, we need to use the conditions $G(a+\alpha-1)=0$ and $G(b+\alpha-1)=0$.

Using the definition of fractional difference on the right side of the equality, we have

$$\sum_{s=a}^{b-1} G(s+\alpha-1)_{b+\alpha-1}\Delta_s^{\alpha}F^{\rho}(s+2(\alpha-1)) = \sum_{s=a}^{b-1} G(s+\alpha-1)\Delta_{b+\alpha-1}\Delta_s^{-(1-\alpha)}F^{\rho}(s+2(\alpha-1)). \tag{2.5}$$

Using summation by parts formula for Δ-operator, we have

$$\sum_{s=a}^{b-1} G(s+\alpha-1)\Delta_{b+\alpha-1}\Delta_s^{-(1-\alpha)}F^{\rho}(s+2(\alpha-1))$$

$$= G(s+\alpha-1)_{b+\alpha-1}\Delta_s^{-(1-\alpha)}F^{\rho}(s+2\alpha-1)\Big|_a^b$$

$$-\sum_{s=a}^{b-1} {}_{b+\alpha-1}\Delta_s^{-(1-\alpha)}F^{\rho}(s+2\alpha-1)\Delta_s G(s+\alpha-1)$$

$$= \frac{1}{\Gamma(1-\alpha)}\sum_{s=a}^{b-1}\sum_{\tau=s+\alpha}^{b+\alpha-1}(\tau-\sigma(s+2\alpha-1))^{(-\alpha)}F(\rho(\tau))\Delta_s G(s+\alpha-1).$$

Next we interchange the order of summation in the double sum to obtain

$$\frac{1}{\Gamma(1-\alpha)}\sum_{\tau=a+\alpha}^{b-1+\alpha}\sum_{s=a}^{\tau-\alpha}(\tau-\sigma(s+2\alpha-1))^{(-\alpha)}F(\rho(\tau))\Delta_s G(s+\alpha-1).$$

Let us call $u=\tau-\alpha$. Then the above expression becomes

$$\frac{-1}{\Gamma(1-\alpha)}\sum_{u=a}^{b-1}\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}F(u+\alpha-1)\Delta_s G(s+\alpha-1). \tag{2.6}$$

Now let us look at the following expression closely,

$$\frac{1}{\Gamma(1-\alpha)}\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}\Delta_s G(s+\alpha-1). \tag{2.7}$$

Using summation by parts, we have

$$\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}\Delta_s G(s+\alpha-1) = [(u-\alpha-s)^{(-\alpha)}G(s+\alpha-1)]|_a^{u+1} - \sum_{s=a}^{u}\Delta_s(u-\alpha-s)^{(-\alpha)}G(s+\alpha).$$

Since $[(u-\alpha-s)^{(-\alpha)}G(s+\alpha-1)]|_a^{u+1} = 0$, then

$$\frac{1}{\Gamma(1-\alpha)}\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}\Delta_s G(s+\alpha-1) = \frac{-1}{\Gamma(1-\alpha)}\sum_{s=a}^{u}\Delta_s(u-\alpha-s)^{(-\alpha)}G(s+\alpha)$$

$$= \frac{-1}{\Gamma(1-\alpha)}(-\alpha)\sum_{s=a}^{u}(u-\alpha-\sigma(s))^{(-1-\alpha)}G(s+\alpha).$$

It follows from (Theorem 8.50 [**13**])

$$\Delta_u\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}G(s+\alpha) = \alpha\sum_{s=a}^{u}(u-\alpha-\sigma(s))^{(-1-\alpha)}G(s+\alpha).$$

Hence the expression in (2.6) becomes

$$\frac{1}{\Gamma(1-\alpha)}\sum_{s=a}^{u}(u-\alpha-s)^{(-\alpha)}\Delta_s G(s+\alpha-1) = \frac{1}{\Gamma(1-\alpha)}\Delta_u\sum_{s=a}^{u}(u-\alpha-\sigma(s))^{(-\alpha)}G(s+\alpha)$$

$$= \frac{1}{\Gamma(1-\alpha)}\Delta_u\sum_{s=a}^{u}(u-\sigma(s+\alpha-1))^{(-\alpha)}G(s+\alpha-1)$$

With $v = s+\alpha-1$ transformation

$$= \frac{1}{\Gamma(1-\alpha)}\Delta_u\sum_{v=a+\alpha-1}^{u+\alpha-1}(u-\sigma(v))^{(-\alpha)}G(v)$$

$$=_u \Delta_{a+\alpha-1}^{\alpha}G(v) \qquad \square$$

REMARK 3.2.2. Here we note that for $\alpha = 1$, equation (2.1) reduces to the standard summation by parts formula for difference calculus as we proved in Section 1, the equation (2.7).

$$\sum_{t=1}^{b-1} g(t)\Delta f(t) = f(t)g(t)|_1^b - \sum_{t=1}^{b-1} f(t+1)\Delta g(t).$$

CHAPTER 4

Simplest Variational Problem in Discrete Fractional Calculus

The calculus of variations is one of the oldest and most developed branches of mathematics. The history of variational calculus dates back to the ancient Greeks, but no substantial progress was made until the seventeenth century in Europe. A classic problem of historical interest is the 'brachistochrone problem', *given two points A and B in a vertical plane, what is the curve traced out by a particle acted on only by gravity, which starts at A and reaches B in the shortest time?*, proposed by Johann Bernoulli in 1696. In fact, Newton was challenged to solve the problem by Johann Bernoulli. Later, the solution to the brachistochrone problem, which is a segment of a cycloid, was independently given by Johann and Jacob Bernoulli, Newton and L'Hospital.

Another important variational problem is the data modeling problem. A conventional approach is the method of least squares, first proposed by Legendre and Gauss in the early nineteenth century as a way of inferring planetary trajectories from noisy data [6]. More generally, the aim of a variational problem is to find a function which is the minimal or the maximal value of a specified functional. A functional is a correspondence that assigns a number to each function belonging to some class and can be formed by means of integrals involving an unknown function and its derivatives. The calculus of variations gives methods for finding extrema of such functionals. Problems that consist of finding minimal and maximal values of functionals are called variational problems.

In addition to its significance in mathematical theory, calculus of variations has been widely used in the solution of many problems of economics, engineering, biology and physics. The theory of calculus of variations in fractional calculus has been first introduced by Agrawal [**4**] in 2002, and later developed by other scientists [**15, 16**].

Here we will demonstrate one application of the summation by parts formula (Theorem 3.2.2), which we derived in Chapter 3, and introduce the calculus of variations in discrete fractional calculus.

4.1. Calculus of Variations and the Euler-Lagrange Equation

Let $F(t, u, v)$ be a real valued function with continuous partial derivatives and let $\mathfrak{D}$ be the set of all real valued functions y defined on $[a+\alpha-1, b+\alpha-1] \subset \mathbb{N}_{a+\alpha-1}$ with $y(a+\alpha-1) = y_a$ and $y(b+\alpha-1) = y_b$.

We consider the following functional

$$J[y] = \sum_{t=a}^{b-1} F(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1} y(t)).$$

Here our aim is to optimize this functional assuming that J has an extremum. This is called the 'simplest variational problem' in discrete fractional calculus. To develop the necessary conditions for the extremum, let us assume that $y^*(t)$ is the desired function such that

$$y(t) = y^*(t) + \epsilon\eta(t), \quad \epsilon \in \mathbb{R}$$

where $\eta \in \mathfrak{A} = \{w | w(t)$ is a real valued function defined on $[a+\alpha-1, b+\alpha-1]$ with $\eta(a+\alpha-1) = \eta(b+\alpha-1) = 0\}$.

Since ${}_t\Delta^{\alpha}_{a+\alpha-1}$ is a linear operator we have ${}_t\Delta^{\alpha}_{a+\alpha-1}y(t) = {}_t\Delta^{\alpha}_{a+\alpha-1}y^*(t) + \epsilon_t\Delta^{\alpha}_{a+\alpha-1}\eta(t)$.

If we substitute this expression into the functional, we have

$$J(y^*+\epsilon\eta) = \sum_{t=a}^{b-1} F(t+\alpha-1, y^*(t+\alpha-1)+\epsilon\eta(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y^*(t)+\epsilon_t\Delta^{\alpha}_{a+\alpha-1}\eta(t)).$$

Then differentiating $J(y^* + \epsilon\eta)$ with respect to ϵ, we have

$$\begin{aligned}\frac{\partial J(y^* + \epsilon\eta)}{\partial \epsilon} = \sum_{t=a}^{b-1} &[F_u(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y(t))\eta(t+\alpha-1) + \\ &F_v(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y(t))_t\Delta^{\alpha}_{a+\alpha-1}\eta(t)],\end{aligned}$$

where F_u and F_v are partial derivatives of $F(\cdot, u, v)$ with respect to u and v respectively.

Therefore for the functional $J[y]$ to have an extremum at $y = y^*(t)$, the following must hold

$$\frac{\partial J(y^* + \epsilon\eta)}{\partial \epsilon}\Big|_{\epsilon=0} = \sum_{t=a}^{b-1} F_u\eta(t+\alpha-1) + F_{vt}\Delta^{\alpha}_{a+\alpha-1}\eta(t) = 0. \tag{1.1}$$

Using summation by parts formula in discrete fractional calculus (Theorem 3.2.2), we have

$$\sum_{t=a}^{b-1} F_v(t+\alpha-1)_t\Delta^{\alpha}_{a+\alpha-1}\eta(t) = \sum_{t=a}^{b-1} \eta(t+\alpha-1)_{b+\alpha-1}\Delta^{\alpha}_{t}F^{\rho}_{v}(t+2(\alpha-1)),$$

where $F_v(\tau) = F_v(\tau, y(\tau), {}_t\Delta^{\alpha}_{a+\alpha-1}y(\tau-\alpha+1))$.

Hence (1.1) becomes

$$\sum_{t=a}^{b-1}[F_u(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y(t)) +_{b+\alpha-1}\Delta^{\alpha}_{t}F^{\rho}_{v}(t+2(\alpha-1))]\eta(t+\alpha-1) = 0.$$

Since $\eta(t+\alpha-1)$ is arbitrary, we have

$$F_u(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y(t))) +_{b+\alpha-1}\Delta^{\alpha}_{t}F^{\rho}_{v}(t+2(\alpha-1)) = 0,$$

on $[a+1, b-1]$.

We just proved the following theorem.

THEOREM 4.1.1. *If the simplest variational problem has a local extremum at $y^*(t)$, then $y^*(t)$ satisfies the Euler-Lagrange equation*

$$F_u(t+\alpha-1, y(t+\alpha-1), {}_t\Delta^{\alpha}_{a+\alpha-1}y(t)) +_{b+\alpha-1}\Delta^{\alpha}_{t}F^{\rho}_{v}(t+2(\alpha-1)) = 0, \tag{1.2}$$

for $t \in [a+1, b-1]$.

4.2. Modeling with Discrete Fractional Calculus

We developed the simplest variational problem for discrete fractional calculus. According to this theory, we now are concerned with the following optimization problem

$$J[y] = \min \sum_{t=0}^{T-1} U(y(t+\alpha-1))$$

with the constraint

$$\Delta^{\alpha} y(t-\alpha+1) = (b-1)y(t) + a \quad , \quad y(0) = c$$

or with a transformation $t = t + \alpha - 1$

$$\Delta^{\alpha} y(t) = (b-1)y(t+\alpha-1) + a, \tag{2.1}$$

where $y(t)$ is the size of a tumor and U is a function with continuous partial derivatives.

We have

$$J[y] = \sum_{t=0}^{T-1} \{U(y(t+\alpha-1)) + \lambda(t+\alpha-1)(\Delta^{\alpha} y(t) - (b-1)y(t+\alpha-1) - a)\}.$$

It follows from Theorem 4.1.1, Euler-Lagrange equations with respect to λ and y are

$$U_y(y(t+\alpha-1)) - \lambda(t+\alpha-1)(b-1) + {}_{T+\alpha-1}\Delta_t^{\alpha} \lambda^{\rho}(t+2(\alpha-1)) = 0, \tag{2.2}$$

or

$$U_y(y(t+\alpha-1)) - \lambda(t+\alpha-1)(b-1)$$
$$+\frac{1}{\Gamma(1-\alpha)}(-\Delta) \sum_{s=t+\alpha-1}^{T+\alpha-1} (s-\sigma(t+(2\alpha-1)))^{(-\alpha)} \lambda(\rho(s)),$$

and

$$\Delta^{\alpha} y(t) - (b-1)y(t+\alpha-1) - a = 0, \tag{2.3}$$

where $t \in [1, T-1]$.

At this point, to the best of our knowledge, there is no known numerical method for solving the above system of equations (2.2)-(2.3). In the next chapter, we will call equation (2.1) Gompertz fractional difference equation. We will focus on proving the existence and uniqueness result for this equation with an initial condition $y(0) = c$.

CHAPTER 5

Modeling for Tumor Growth

David Hilbert famously stated that ‘Physics is becoming too diffcult for physicists’ implying the increasing mathematical complexity of ideas necessary for modern physics. The same argument is becoming more and more applicable for today’s Mathematical Biology. As mathematical models describing biological phenomena are getting more sophisticated and realistic, the attention needed from specialists is growing at a fast pace. There are several recent areas of specialized research in mathematical biology: Enzyme kinetics, biological tissue analysis, cancer modeling, heart and arterial disease modeling being among the popular ones. In this thesis, we specifically focus on tumor growth modeling with newly developing discrete fractional calculus.

Cancer is a disease in which abnormal cells divide uncontrollably and have the potential to invade other tissues. These abnormal cells might form masses of tissues known as tumors. All tumors are not cancerous, tumors can be benign or malignant. Benign tumors are not cancerous and can often be surgically removed, in most cases they do not come back. Malignant tumors, on the other hand, aggressively expand and spread to other parts of the organism. The spread of cancer cells from one part of the body to another is called metastasis. A highly metastasised cancer is usually unstoppable and results in the death of the organism. The rapid growth of these tumors and the absence of a cure for cancer make the timing of diagnosis and treatment very crucial. Understanding the kinetics of tumor growth enables physicians to determine the best treatment available. There is a plethora of experimental data available pending for systematic analysis and therefore it is clear that mathematics could significantly contribute to many areas of experimental cancer investigation.

Although the kinetics of cancer is usually very complex depending on many details such as the type, location and stage of the cancer, over the years mathematical models for tumor growth have helped to quantitatively analyze the behavior of the disease at different stages. Mathematical modeling of tumors began in the early 1950s after scientists discovered that the initiation of cancerous growth could only occur after multiple successive mutations in a single cell's DNA. The first models were used statistics to examine the correlation between age and incidence of cancer, but the field continued to develop as more information about the disease became available. Today, many different types of models exist, including probabilistic and deterministic, continuous and discrete models.

Mathematically, tumor growth is a special relationship between tumor size and time. Three mathematical equations are typically used to model growth behavior in biology: Exponential, logistic and sigmoidal.

Exponential growth is given by $\dfrac{dG(t)}{dt} = \lambda G.$

Logistic growth is given by $\dfrac{dG(t)}{dt} = \lambda G(1 - \dfrac{G}{\theta}).$

Sigmoidal growth is given by $\dfrac{dG(t)}{dt} = -\lambda G \ \ln(\dfrac{G}{\theta}).$

In these equations, λ defines the growth rate and θ defines the carrying capacity.

In the literature, tumor growth, however, is best described by sigmoidal functions.

5.1. Gompertz Fractional Difference Equation

In 1825, Benjamin Gompertz introduced the Gompertz function, a sigmoid function, which is found to be applicable to various growth phenomena, in particular tumor and embryonic growth (see [**17**]).

The Gompertz difference equation describes the growth models and these models can be studied on the basis of the parameters a and b in the recursive formulation of the Gompertz law of growth [**11**]. a is the growth rate and b is the exponential rate of growth deceleration in the equation.

The Gompertz difference equation in [**11**] is given by

$$\ln G(t+1) = a + b \ln G(t).$$

Here we introduce Gompertz fractional difference equation

$$\Delta^\alpha \ln G(t-\alpha+1) = (b-1)\ln G(t) + a. \tag{1.1}$$

For simplicity if we replace $\ln G(t) = y(t)$, we obtain

$$\Delta^\alpha y(t-\alpha+1) = (b-1)y(t) + a. \tag{1.2}$$

5.2. Existence and Uniqueness for the Gompertz Fractional Difference Equation

Consider the following fractional difference equation with an initial condition

$$\Delta^\alpha y(t-\alpha+1) = f(t, y(t)), \quad t = 0, 1, 2, \cdots \tag{2.1}$$

$$y(0) = c \tag{2.2}$$

where $\alpha \in (0, 1]$, f is a real-valued function, and c is a real number.

Applying the $\Delta^{-\alpha}$ operator to both sides of the equation (2.1) and with $t + \alpha - 1$ shift at the same time, we obtain

$$\Delta^{-\alpha}\Delta^{\alpha}y(t) = \Delta^{-\alpha}f(t + \alpha - 1, y(t + \alpha - 1)), \tag{2.3}$$

where $t = 1, 2, \cdots$.

Applying Theorem 2.2.2 to the left-hand side of the equation (2.3), we get

$$\Delta^{-\alpha}\Delta^{\alpha}y(t) = \Delta^{-\alpha}\Delta\Delta^{-(1-\alpha)}y(t) = \Delta\Delta^{-\alpha}\Delta^{-(1-\alpha)}y(t) - \frac{(t + \alpha - 1)^{(\alpha-1)}y(0)}{\Gamma(\alpha)}. \tag{2.4}$$

Hence we have

$$y(t) = \frac{(t + \alpha - 1)^{(\alpha-1)}}{\Gamma(\alpha)}c + \frac{1}{\Gamma(\alpha)}\sum_{s=0}^{t-1}(t + \alpha - 1 - \sigma(s))^{(\alpha-1)}f(s, y(s)), \tag{2.5}$$

for $t = 0, 1, 2, \cdots$.

The recursive iteration to the sum equation implies that (2.5) represents the unique solution of the IVP.

5.3. Solution with the Method of Successive Approximation

We obtain a solution for the equation (2.1) with an initial value condition $y(0) = c$.

Replacing $f(s, y(s)) = (b - 1)y(s) + a$ in (2.5), the solution of the IVP (2.1)-(2.2) is

$$y(t) = \frac{(t + \alpha - 1)^{(\alpha-1)}}{\Gamma(\alpha)}c + \frac{1}{\Gamma(\alpha)}\sum_{s=0}^{t-1}(t + \alpha - 1 - \sigma(s))^{(\alpha-1)}[(b - 1)y(s) + a].$$

Next, we employ the method of successive approximations that is also known as the Picard iteration. Set

$$y_0(t) = \frac{(t+\alpha-1)^{(\alpha-1)}}{\Gamma(\alpha)}c + \Delta^{-\alpha}a(t+\alpha-1)^{(0)},$$

$$y_m(t) = (b-1)\Delta^{-\alpha}y_{m-1}(t+\alpha-1), \quad m = 1, 2, \cdots.$$

Apply the power rule (Lemma 2.2.1) to see that

$$\begin{aligned} y_1(t) &= (b-1)\Delta^{-\alpha}y_0(t+\alpha-1), \\ &= c(b-1)\frac{(t+2\alpha-2)^{(2\alpha-1)}}{\Gamma(2\alpha)} + (b-1)\Delta^{-2\alpha}a(t+2\alpha-2)^{(0)} \end{aligned}$$

and

$$y_2(t) = (b-1)\Delta^{-\alpha}y_1(t+\alpha-1),$$

$$= c(b-1)^2\frac{(t+3\alpha-3)^{(3\alpha-1)}}{\Gamma(3\alpha)} + (b-1)^2\Delta^{-3\alpha}a(t+3\alpha-3)^{(0)}.$$

With repeated applications of the power rule, it follows inductively that

$$y_m(t) = c(b-1)^m\frac{(t+(m+1)(\alpha-1))^{((m+1)\alpha-1)}}{\Gamma((m+1)\alpha)} + (b-1)^m a\frac{(t+(m+1)(\alpha-1))^{((m+1)\alpha)}}{\Gamma((m+1)\alpha+1)}.$$

$\sum_{m=0}^{\infty} y_m$ converges to the unique solution of the initial value problem

$$\Delta^{\alpha}y(t-\alpha+1) - (b-1)y(t) = a, \qquad y(0) = c.$$

Hence we have

$$y(t) = c\sum_{m=0}^{\infty}(b-1)^m \frac{(t+(m+1)(\alpha-1))^{((m+1)\alpha-1)}}{\Gamma((m+1)\alpha)} + a\sum_{m=0}^{\infty}(b-1)^m \frac{(t+(m+1)(\alpha-1))^{((m+1)\alpha)}}{\Gamma((m+1)\alpha+1)}.$$

One immediate observation can be made. Set $\alpha = 1$. Then

$$y(t) = c\sum_{m=0}^{\infty}(b-1)^m \frac{t^{(m)}}{\Gamma(m+1)} + a\sum_{m=0}^{\infty}(b-1)^m \frac{t^{(m+1)}}{\Gamma(m+2)}.$$

Since the IVP with $\alpha = 1$ has the unique solution

$$y(t) = cb^t + \frac{a}{b-1}b^t - \frac{a}{b-1}, \tag{3.1}$$

we obtain the equality $b^t = \sum_{i=0}^{\infty}\frac{(b-1)^i}{i!}t^{(i)}$ which appears as a special case of [**12**, Lemma 4.4] for a time scale $\mathbb{T} = \mathbb{Z}$, the set of integers.

The solution of the equation (1.1) is $G(t) = e^{y(t)}$.

5.4. Graphical Results

Growth comparisons, especially in tumor growth, are usually very important. These comparisons are typically made according to growth stimulation or growth inhibition.

There are two ways to measure growth alterations that are used in practice: Assays with time as the independent variable and the changing tumor size as the dependent variable or assays with tumor size as the independent variable and the time to reach a given size as the dependent variable. Since experiments are limited in time these assays generally measure alterations of growth rates. Therefore growth stimulation or growth inhibition usually refer to an increase or a decrease of the growth rate (see Figure 5.1, 5.2 and 5.3 for $\alpha = 1$, $\alpha = .94$ and $\alpha = .83$).

The gompertzian analysis of alterations of tumor growth patterns are shown in Figure 5.1, Figure 5.2 and Figure 5.3. We apply fractional gompertz model results to human renal cell carcinoma, which is a malignant tumor of the cells that cover and line the kidney, in nude mice data. (Nude mice are labaratuary mice without hair. They have inhibited immune system due to a greatly reduced number of T cells.) Parameters for control growth are taken from ([**10**]).

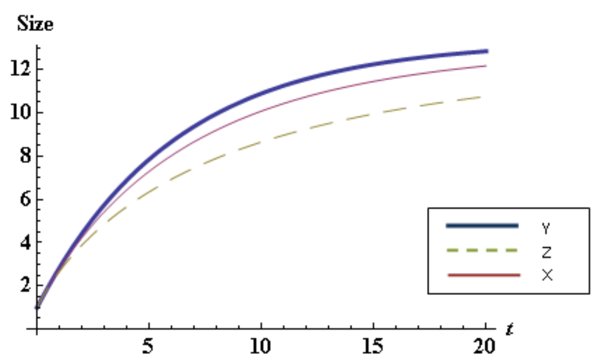

FIGURE 5.1. Alterations of Growth : Control Growth (a=2, b=.85, c=1, $Y : \alpha = 1$, $X : \alpha = .94$, $Z : \alpha = .85$)

Figure 5.1 shows the control growth with parameters $a = 2$, $b = .85$ and $c = 1$. We draw the control growth with different α values. First observation in here is when $\alpha \to 1$, fractional model converges to the continous model as expected. This convergence is clear for low values of t in Figure 5.1. So, α values other than 1, behave like the growth deceleration. Since the parameter b represents the exponential growth deceleration, next we change b to observe the growth behaviour.

In Figure 5.2, if we take $b = .9$, we observe stimulation for each α value. It can be seen that in this graph, curves Y and Z' behave similarly. Y is the curve with

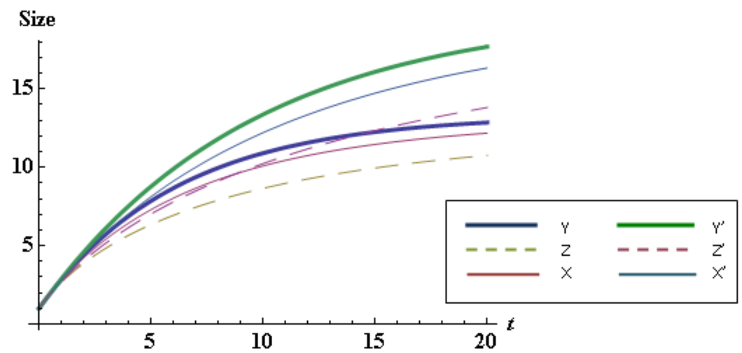

FIGURE 5.2. Alterations of Growth : Stimulation (a=2, b=.9, c=1, Y' : $\alpha = 1$, X' : $\alpha = .94$, Z' : $\alpha = .83$)

$b = .85$ and $\alpha = 1$ and Z' is the curve with $b = .9$ and $\alpha = .83$. This shows that we can observe different behaviors by changing the parameter α in discrete fractional calculus.

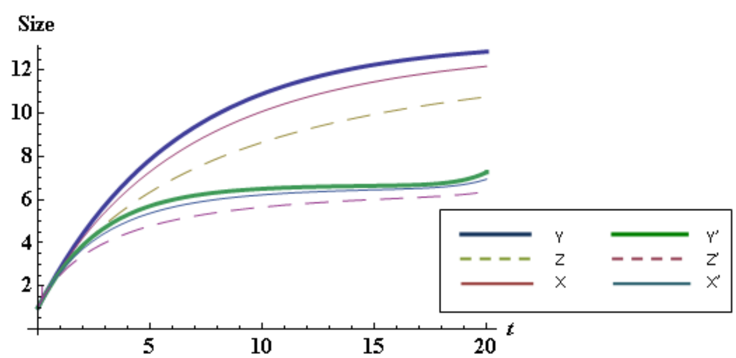

FIGURE 5.3. Alterations of Growth : Inhibition (a=2, b=.7, c=1, Y' : $\alpha = 1$, X' : $\alpha = .94$, Z' : $\alpha = .83$)

Moreover if we set $b = .7$, which is less than the control growth, we observe inhibition for each α value.

Based on the results above, we also observe that growth behaviour shows significant variation with respect to α. Using fractional calculus for curve fitting, we could get more accurate results for data analysis since we have one more fitting parameter, α, in addition to the model parameters. To support this insight, we compare our model for different α values with the continuous model by using real data.

5.4.1. Bacterial Growth Application. In this section, we evaluate the Gompertz fractional difference model and the Gompertz differential model for the growth curve of Pseudomonas putida which is a kind of soil bacterium. Then we compare two models searching for a better fit for the actual growth by varying α. Square of residuals (SQR) between the expected values and the experimental values is calculated for each of these models to determine the best fit clearly.

The bacterial growth curve([**28**]) is generally given by

$$U_t = A + BC^t \tag{4.1}$$

where U_t represents the time series value at the time t and A,B,C are constant parameters.

In the method of partial sums, the given time-series data are split up into three parts each containing n consecutive values of U_t corresponding to $t = 1, 2, \ldots, n$; $t = n+1, n+2, \ldots, 2n$; and $t = 2n+1, 2n+2, \ldots, 3n$.

Let S_1,S_2 and S_3 represent the partial sums of the three parts respectively so that:

$$S_1 = \sum_{t=1}^{n} U_t, \quad S_2 = \sum_{t=n+1}^{2n} U_t, \quad S_3 = \sum_{t=2n+1}^{3n} U_t.$$

Substituting equation (4.1) into S_1,S_2 and S_3, we get

$$S_1 = \sum_{t=1}^{n} (A + BC^t) = nA + B(C + C^2 + \cdots + C^n)$$

$$= nA + BC(\frac{C^n - 1}{C - 1}).$$

Similarly

$$S_2 = nA + BC^{n+1}(\frac{C^n - 1}{C - 1}),$$
$$S_3 = nA + BC^{2n+1}(\frac{C^n - 1}{C - 1}).$$

Subtracting S_1 from S_2 and S_1 from S_3, we get respectively:

$$S_2 - S_1 = BC\frac{(C^n - 1)^2}{(C - 1)}, \tag{4.2}$$
$$S_3 - S_2 = BC^{n+1}\frac{(C^n - 1)^2}{(C - 1)}. \tag{4.3}$$

Dividing equation (4.3) by (4.2), we have

$$\frac{S_3 - S_2}{S_2 - S_1} = C^n.$$

Therefore,

$$C = (\frac{S_3 - S_2}{S_2 - S_1})^{1/n}. \tag{4.4}$$

Substituting C in equation (4.2), we get

$$S_2 - S_1 = \frac{BC}{C - 1}\left[\frac{S_3 - S_2}{S_2 - S_1} - 1\right]^2.$$

Hence

$$B = \frac{(C - 1)(S_2 - S_1)^3}{C(S_3 - 2S_2 + S_1)^2}. \tag{4.5}$$

Finally substituting the values of B and C in the expression of S_1, we have

$$A = \frac{1}{n}\left[S_1 - \frac{BC}{C - 1}(C^n - 1)\right],$$
$$= \frac{1}{n}\left[S_1 - \frac{(S_2 - S_1)^3}{(S_3 - 2S_2 + S_1)^2}(C^n - 1)\right],$$
$$= \frac{1}{n}\left[S_1 - \frac{(S_2 - S_1)^3}{(S_3 - 2S_2 + S_1)^2}\left\{\frac{S_3 - S_2}{S_2 - S_1} - 1\right\}\right],$$
$$= \frac{1}{n}\left[S_1 - \frac{(S_2 - S_1)^3}{(S_3 - 2S_2 + S_1)^2}\left\{\frac{S_3 - 2S_2 + S_1}{S_2 - S_1}\right\}\right],$$

$$= \frac{1}{n}\left[S_1 - \frac{(S_2 - S_1)^2}{(S_3 - 2S_2 + S_1)}\right],$$

$$A = \frac{1}{n}\left[\frac{S_1 S_3 - S_2^2}{S_3 - 2S_2 + S_1}\right]. \tag{4.6}$$

Thus, by the method of partial sums, the three parameters A,B and C are determined and the modified exponential growth curve is fitted. Gompertz and discrete fractional Gompertz models are fitted by the same approach, modifying their basic equation into a form of an exponential growth curve.

Time(h)	Exp.Value		
1	0.216	14	0.482
2	0.22	15	0.492
3	0.24	16	0.592
4	0.25	17	0.544
5	0.26	18	0.584
6	0.27	19	0.594
7	0.28	20	0.62
8	0.29	21	0.644
9	0.33	22	0.648
10	0.36	23	0.648
11	0.38	24	0.648
12	0.4	25	0.648
13	0.46	26	0.648
		27	0.648

FIGURE 5.4. Growth rate of *P*seudomonas putida at various time intervals [27].

The equation of Gompertz curve is

$$y = ae^{-e^{(b-cx)}}$$

where a,b and c are parameters.

It is converted into a modified exponential form as

$$\ln y = \ln a - e^{b}(e^{-c})^{x}, \tag{4.7}$$

which can also be written as

$$U_t = A + BC^t, \tag{4.8}$$

where $U_t = \ln y$, $A = \ln a$, $B = -e^b$, $C = e^{-c}$ and $t = x$.

The ln values of the growth data in Figure 5.4 are calculated and a set of nine such values are summed up

$$S_1 = \sum_{n=1}^{9} \ln y_n, \quad S_2 = \sum_{n=10}^{18} \ln y_n, \quad S_3 = \sum_{n=19}^{27} \ln y_n.$$

Hence we get

$S_1 = -12.135$, $S_2 = -6.921$, $S_3 = -4.049$.

Using the formula (4.6), we obtain

$$A = \frac{1}{n}\left[\frac{S_1S_3 - S_2^2}{S_3 - 2S_2 + S_1}\right] = -0.0585. \tag{4.9}$$

Since $\ln a = -0.0585$ which gives $a = .943$.

Using the formula (4.4), we obtain

$$C = (\frac{S_3 - S_2}{S_2 - S_1})^{1/n} = 0.9358. \tag{4.10}$$

Since $e^{-c} = 0.93581$ which gives $c = .066$.

Using the formula (4.5), we obtain

$$B = \frac{(C-1)(S_2 - S_1)^3}{C(S_3 - 2S_2 + S_1)^2} = -1.773. \tag{4.11}$$

Since $-e^b = -1.773$ which gives $b = -.573$.

Therefore, the Gompertz curve for the growth of Pseudomonas putida is given by the parameters calculated above:

$$y = .943e^{-e^{(.573-.066x)}}. \tag{4.12}$$

We fit our model with these parameters. Our solution for $\alpha = 1$ is given by the equation (3.1) as

$$y(t) = (c + \frac{a}{b-1})b^t - \frac{a}{b-1}. \tag{4.13}$$

When we fit this equation by $y(t) = A + BC^t$, our parameters become

$A = -\dfrac{a}{b-1}$, $C = b$ and $B = c + \dfrac{a}{b-1}$.

After substituting the values $A = -0.0585$, $B = -1.773$ and $C = 0.9358$ and solving for a, b and c we obtain the paramaters for our model as $a = -.0037557$, $b = .9358$ and $c = -1.8315$.

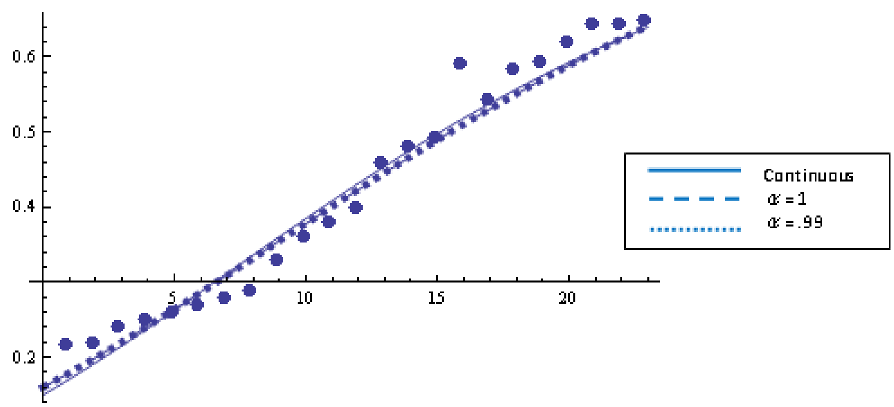

FIGURE 5.5. Data fitting

In Figure (5.5), it is shown that each curve visually gives reasonably good fits to the given data. To determine the curve that gives the best result, the table in Figure (5.6) presents the data points and the square of the residuals between the experimental and expected values. The best model is the one showing the least sum of the square of residuals.

It is clear from the table in Figure (5.5) that Gompertz fractional difference model with $\alpha = 1$ gives the least value of SQR(=.023986). It yields very close results

Time(h)	Exp.Value	Expected	SQR	α=1	SQR	α =.99	SQR	α-.995	SQR
1	0.216	0.179247	0.001351	0.179483	0.001333	0.182801	0.001102	0.181134	0.001216
2	0.22	0.199299	0.000429	0.199657	0.000414	0.204725	0.000233	0.20218	0.000318
3	0.24	0.220098	0.000396	0.220585	0.000377	0.226815	0.000174	0.223687	0.000266
4	0.25	0.241532	7.17E-05	0.242151	6.16E-05	0.249198	6.43E-07	0.245662	1.88E-05
5	0.26	0.263485	1.21E-05	0.264239	1.8E-05	0.271853	0.00014	0.268033	6.45E-05
6	0.27	0.285841	0.000251	0.28673	0.00028	0.294711	0.000611	0.290709	0.000429
7	0.28	0.308484	0.000811	0.309509	0.000871	0.31769	0.001421	0.313589	0.001128
8	0.29	0.331305	0.001706	0.332461	0.001803	0.340699	0.00257	0.33657	0.002169
9	0.33	0.354195	0.000585	0.355479	0.000649	0.363648	0.001132	0.359554	0.000873
10	0.36	0.377054	0.000291	0.37846	0.000341	0.386452	0.0007	0.382447	0.000504
11	0.38	0.399789	0.000392	0.40131	0.000454	0.409031	0.000843	0.405162	0.000633
12	0.4	0.422312	0.000498	0.423942	0.000573	0.431312	0.00098	0.427617	0.000763
13	0.46	0.444545	0.000239	0.446274	0.000188	0.453228	4.59E-05	0.44974	0.000105
14	0.482	0.466418	0.000243	0.468238	0.000189	0.47472	5.3E-05	0.471466	0.000111
15	0.492	0.487868	1.71E-05	0.489769	4.98E-06	0.495736	1.4E-05	0.492738	5.45E-07
16	0.592	0.508841	0.006915	0.510814	0.006591	0.516234	0.00574	0.513507	0.006161
17	0.544	0.529291	0.000216	0.531326	0.000161	0.536176	6.12E-05	0.533731	0.000105
18	0.584	0.54918	0.001212	0.551267	0.001071	0.555531	0.00081	0.553377	0.000938
19	0.594	0.568474	0.000652	0.570605	0.000547	0.574277	0.000389	0.572416	0.000466
20	0.62	0.58715	0.001079	0.589315	0.000942	0.592396	0.000762	0.590827	0.000851
21	0.644	0.605189	0.001506	0.60738	0.001341	0.609875	0.001165	0.608596	0.001253
22	0.648	0.622578	0.000646	0.624786	0.000539	0.626707	0.000453	0.625712	0.000497
23	0.648	0.639308	7.56E-05	0.641525	4.19E-05	0.642888	2.61E-05	0.64217	3.4E-05
24	0.648	0.655377	5.44E-05	0.657597	9.21E-05	0.65842	0.000109	0.657969	9.94E-05
25	0.648	0.670786	0.000519	0.673001	0.000625	0.673307	0.00064	0.673112	0.000631
26	0.648	0.685539	0.001409	0.687742	0.001579	0.687556	0.001565	0.687605	0.001569
27	0.648	0.699643	0.002667	0.701829	0.002898	0.701177	0.002828	0.701457	0.002858
			0.024245		0.023986		0.024569		0.02406

FIGURE 5.6. Data analysis for bacteria

to the continuous Gompertz curve as expected. It can also be seen that the fractional difference model with $\alpha = .995$ gives more accurate results than the continuous model.

To make sure our model works better than its continuous counterpart, we also found fitting parameters by using Mathematica's 'FindFit' function which computed a least-squares fit for the given 23 data points. As a result, we obtained the parameters $a = .0119493$, $b = .9488$ and $c = -1.9$ for our model. First, we draw the curves for $\alpha = 1$, $\alpha = .98$ and the continuous case. As is shown in Figure (5.7), each model visually gives a reasonably good fit to the given data.

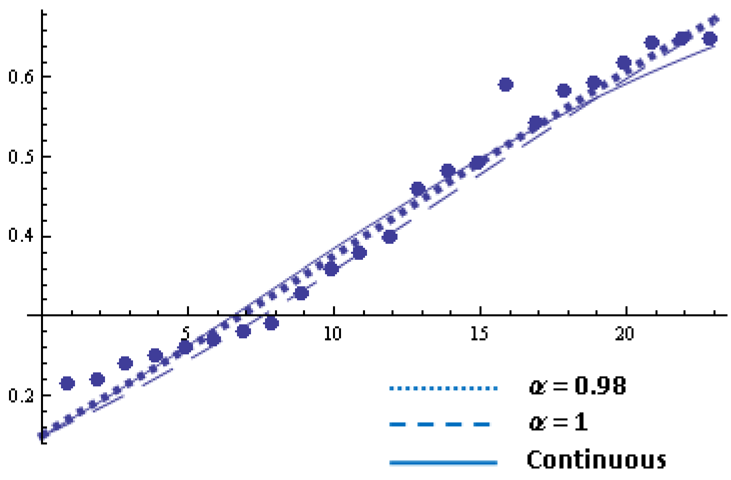

FIGURE 5.7. Data fitting

Data values and square of the residuals are also calculated for these paramaters. When we inspect the tables in Figure (5.8) and Figure (5.9), it is suprising that the best result is given by the fractional Gompertz model with $\alpha = .98$ and followed by $\alpha = .97$ closely. Our model with $\alpha = 1$ once again gives very close results to the continuous model as expected. With decreasing α values, square of the residual results are increasing, for instance see $\alpha = .96$. In conclusion, since the least sum of square of residuals between the experimental and expected values belongs to the discrete fractional model with $\alpha = .98$, we conclude that our model is stronger than the continuous model in this particular example.

5.4.2. Application on Mammary Tumors of the Rat. We also apply our model to mammary tumor data of rats Figure (5.10). Mammary tumors of rats are very important in the study of tumor induction and in the elucidation of the relationship between breast tumors, steroids and pituitary hormones. The growth data used in this thesis were obtained from the work of Durbin, Jeung, Williams

Time(h)	Exp.Value	Expected	SQR	α=1	SQR
1	0.216	0.179247	0.001350783	0.166832	0.002417492
2	0.22	0.199299	0.000428531	0.185049	0.001221572
3	0.24	0.220098	0.00039609	0.20417	0.001283789
4	0.25	0.241532	7.1707E-05	0.224135	0.000668998
5	0.26	0.263485	1.21452E-05	0.24488	0.000228614
6	0.27	0.285841	0.000250937	0.266335	1.34322E-05
7	0.28	0.308484	0.000811338	0.288427	7.10143E-05
8	0.29	0.331305	0.001706103	0.311079	0.000444324
9	0.33	0.354195	0.000585398	0.334215	1.77662E-05
10	0.36	0.377054	0.000290839	0.357755	5.04002E-06
11	0.38	0.399789	0.000391605	0.38162	2.6244E-06
12	0.4	0.422312	0.000497825	0.405734	3.28788E-05
13	0.46	0.444545	0.000238857	0.43002	0.0008988
14	0.482	0.466418	0.000242799	0.454406	0.000761429
15	0.492	0.487868	1.70734E-05	0.47882	0.000173712
16	0.592	0.508841	0.006915419	0.503195	0.007886328
17	0.544	0.529291	0.000216355	0.527469	0.000273274
18	0.584	0.54918	0.001212432	0.551582	0.001050927
19	0.594	0.568474	0.000651577	0.575479	0.000343027
20	0.62	0.58715	0.001079123	0.599108	0.000436476
21	0.644	0.605189	0.001506294	0.622424	0.000465524
22	0.648	0.622578	0.000646278	0.645385	6.83823E-06
23	0.648	0.639308	7.55509E-05	0.667953	0.000398122
			0.019595059		0.019102004

FIGURE 5.8. Data analysis for bacteria

and Arnold [**29**]. Tumor age was defined as the number of days a tumor had been growing starting from a 'reference size'. The size at which the mammary tumors are just detectable was determined to be a diameter of 1 cm and this was selected to be the 'reference size'. Growth of fibroadenoma from .5 to 5.0 gm was observed to be nearly exponential. Growth rate gradually decrased and eventually the limiting size was approached.

Such a growth pattern can be represented by a Gompertz function

$$G = ce^{\alpha/\beta(1-e^{-\beta t})} \tag{4.14}$$

α =.99	SQR	α =.98	SQR	α =.97	SQR	α =.96	SQR
0.170032	0.002113057	0.173293	0.00182389	0.176617	0.001551	0.180005	0.00129564
0.189988	0.00090072	0.195022	0.0006239	0.200151	0.000394	0.205376	0.000213861
0.210317	0.00088108	0.216575	0.00054873	0.222946	0.0002908	0.229426	0.000111809
0.231185	0.000354004	0.238353	0.00013565	0.245638	1.903E-05	0.253038	9.22944E-06
0.252616	5.45235E-05	0.260469	2.1996E-07	0.268437	7.118E-05	0.276517	0.000272811
0.274583	2.10039E-05	0.282942	0.0001675	0.291409	0.0004583	0.299982	0.00089892
0.297036	0.000290225	0.305749	0.00066301	0.314561	0.0011945	0.323469	0.001889554
0.319916	0.000894967	0.328848	0.00150917	0.337869	0.0022914	0.346976	0.003246265
0.343158	0.000173133	0.352186	0.00049222	0.361296	0.0009794	0.370484	0.001638954
0.366692	4.47829E-05	0.375707	0.00024671	0.384798	0.0006149	0.393958	0.001153146
0.390449	0.000109182	0.399352	0.0003745	0.408325	0.0008023	0.417363	0.001395994
0.41436	0.00020621	0.42306	0.00053176	0.431827	0.001013	0.440658	0.001653073
0.438359	0.000468333	0.446773	0.00017495	0.455256	2.251E-05	0.463804	1.44704E-05
0.46238	0.000384944	0.470435	0.00013375	0.478563	1.181E-05	0.486762	2.26766E-05
0.486361	3.17983E-05	0.493991	3.9641E-06	0.501704	9.417E-05	0.509494	0.00030604
0.510243	0.006684207	0.517391	0.0055665	0.524634	0.0045382	0.531966	0.003604081
0.53397	0.000100601	0.540587	1.1649E-05	0.547315	1.099E-05	0.554145	0.000102921
0.557491	0.000702727	0.563536	0.00041878	0.569709	0.0002042	0.576002	6.3968E-05
0.580759	0.000175324	0.586197	6.0887E-05	0.591783	4.915E-06	0.597508	1.23061E-05
0.60373	0.000264713	0.608532	0.00013152	0.613506	4.217E-05	0.618642	1.84416E-06
0.626364	0.000311028	0.63051	0.00018198	0.634853	8.367E-05	0.63938	2.13444E-05
0.648626	3.91876E-07	0.652101	1.6818E-05	0.655799	6.082E-05	0.659705	0.000137007
0.670484	0.00050553	0.673279	0.00063903	0.676323	0.0008022	0.679602	0.000998686
	0.015672487		0.01445708		0.0155556		0.019064603

FIGURE 5.9. Data analysis for bacteria

Time(days)	Model
13	1.19
16	1.4
30.1	5.28
34.3	9.03
51	12.3
51.2	11.34
68.8	31.3
72.5	23.1
92.8	21.2
96	29.8
116.5	65.7
119.6	48.1

FIGURE 5.10. Growth rate of the mammary tumors of the rat at various time intervals.

where c is the initial tumor weight and fixed at $c = .5$ gm. Parameters $\alpha = .085$ and $\beta = .0174$ are the initial growth rate and growth deceleration respectively. These parameters are calculated from the original data by a least-squares method.

To fit our model with these parameters, let us take the natural logarithm of the equation (4.14) as

$$\ln G(t) = \ln c + \frac{\alpha}{\beta}(1 - e^{-\beta t}).$$

Let $\ln G(t) = u(t)$. Then

$$u(t) = \ln c + \frac{\alpha}{\beta}(1 - e^{-\beta t}).$$

After taking the derivative of both side with respect to t, we have

$$u'(t) = \alpha e^{-\beta t}.$$

When we fix the equation $u'(t) + \beta u(t) = \beta \ln c + \alpha$ with our model equation (3.1), we get the parameters for our model as $a = \beta \ln c + \alpha = .0676425131$ and $b = 1 - \beta = 0.9865$.

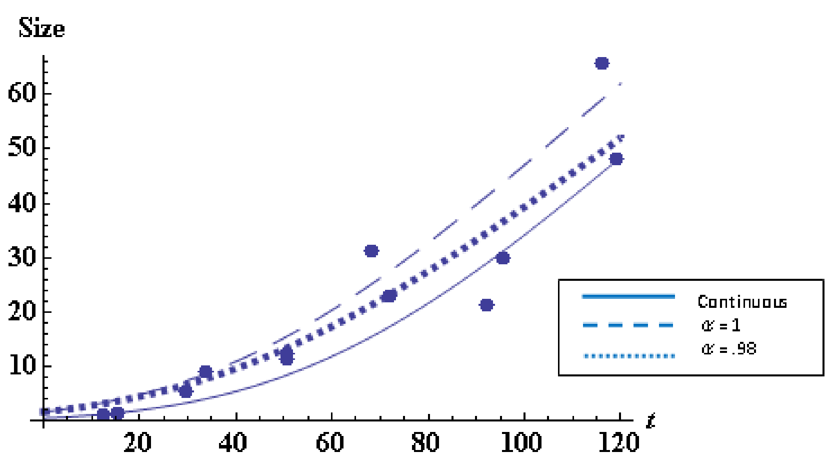

FIGURE 5.11. Data fitting

Figure (5.11) shows the data points, curves of the continuous model and our model for $\alpha = 1$ and $\alpha = .98$. Each model visually gives reasonably good fits for the given data. To determine which one gives the best fit, we once more perform a square of the residuals analysis. The values of growth for different values of time and α are calculated. Results are given in the tables in Figures (5.12) and (5.13).

Time(days)	Model	Continuous	SQR	α=1	SQR
13	1.19	0.542143	0.419719	3.42312	4.986825
16	1.4	1.63878	0.057016	3.98121	6.662645
30.1	5.28	4.49243	0.620267	7.49685	4.914424
34.3	9.03	4.10072	24.2978	8.85274	0.031421
51	12.3	8.85171	11.8907	15.7269	11.74364
51.2	11.34	8.91378	5.886543	15.8235	20.10177
68.8	31.3	15.1245	261.6468	25.5337	33.25022
72.5	23.1	16.5821	42.48302	27.8502	22.5644
92.8	21.2	25.0293	14.66354	41.797	424.2364
96	29.8	26.382	11.68272	44.1329	205.432
116.5	65.7	34.7599	957.2898	59.4244	39.38316
119.6	48.1	35.9545	147.5132	61.7384	186.006
			1478.451		959.3129

FIGURE 5.12. Data analysis table for mammary tumors of the Rats

α=.99	SQR	α=.98	SQR	α=.97	SQR	α=.96	SQR
3.32517	4.558951	3.23191	4.169396	3.14309	3.814561	3.05844	3.491068
3.8484	5.994663	3.72268	5.394842	3.60359	4.855809	3.49071	4.371068
7.10386	3.326465	6.7392	2.129265	6.40052	1.255565	6.08567	0.649104
8.3473	0.466079	7.88035	1.321695	7.44855	2.500984	7.04889	3.924797
14.6023	5.300585	13.5755	1.6269	12.6373	0.113771	11.7794	0.271024
14.6898	11.22116	13.6548	5.358299	12.7093	1.874982	11.8448	0.254823
23.4747	61.23532	21.6033	94.02599	19.9021	129.9121	18.3552	167.5678
25.5701	6.101394	23.4979	0.158324	21.6146	2.206413	19.9028	10.22209
38.2264	289.8983	34.9694	189.5964	32.0016	116.6746	29.2999	65.60838
40.3565	111.4397	36.9078	50.52082	33.7625	15.70141	30.897	1.203409
54.4046	127.5861	49.7747	253.6152	45.5158	407.4019	41.6076	580.4437
56.5487	71.38053	51.7533	13.3466	47.3351	0.585072	43.2749	23.28159
	698.5092		621.2637		686.8972		861.2889

FIGURE 5.13. Data analysis table for mammary tumors of the Rats

It is clear from the tables in Figures (5.12) and (5.13), the best fit is given by the discrete fractional model with $\alpha = .98$ determined by the residual sum of squares(SQR) analysis. For $\alpha = .99$ and $\alpha = .98$, results are very close but with decreasing α, residual sum of square values are increasing. Continuous case gives the least accurate result in this example and although $\alpha = 1$ is worse than the other α values, it is still better than the continuous case.

CONCLUSION AND FUTURE WORK

Discrete fractional calculus is a relatively new theory compared to ordinary calculus. There are still many open questions in this newly developing theory and although the theory shows great potential for analyzing real world applications, ordinary calculus is still much more commonly used in such problems. In this thesis, we closed some of the gaps in the theory of discrete fractional calculus and we showed that discrete fractional calculus could perform better in the modeling of particular applications. We gave a new proof of the Leibniz rule for two different function domains. We also developed the summation by parts formula, which is a very powerful formula, for discrete fractional calculus. To prove the summation by parts formula, we defined the left and right discrete fractional difference operators by carefully analyzing the domains. Later, we introduced the simplest variational problem for discrete fractional calculus. The summation by parts formula was instrumental in the development of the Euler-Lagrange equation for discrete fractional calculus. After mathematically justifying the use of the discrete fractional variational problem, we proposed applications for tumor modeling in order to demonstrate the power of discrete fractional calculus. Since tumor growth is best described by the Gompertz equation, we first wrote the corresponding discrete fractional Gompertz equation and we applied the variational theory to optimize tumor growth. Then, we compared our theory to ordinary calculus by using real data. According to our results, our model gave the best fit for different α values where α is defined as the order of the difference operator.

For future work, we would like to extend the ideas that were presented for the discrete Gompertz fractional difference equation. Although the current model with a saturating feedback mechanism is quite good, improvements can still be made in tumor growth modeling, for instance, by using different growth models, such as Richards growth equations.

$$Y'(t) = aY(1 - (\frac{Y}{K})^{\nu}). \tag{4.15}$$

Moreover, because discrete fractional theory is relatively new and undeveloped, there is no well-established numerical method to solve some of fractional difference equations, therefore another future direction could be to seek optimized numerical methods to solve various fractional difference equations.

APPENDIX

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

Figure(5.1)

Y	a = 2;	b = .85;	c = 1;	nu = 1;
X	a = 2;	b = .85;	c = 1;	nu = .94;
Z	a = 2;	b = .85;	c = 1;	nu = .85;

```
Y=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k]*Gamma[(k+1)*nu+1]))),{k,0,10}];

Plot[{Y,X,Z},{t,0,20},PlotStyle-
>{AbsoluteThickness[3],AbsoluteThickness[1],Dashing[{.05,.03}]},AxesLabel-
>{t,Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]
```

Figure(5.2)

Y’	a = 2;	b = .85;	c = 1;	nu = 1;
X’	a = 2;	b = .85;	c = 1;	nu = .94;
Z’	a = 2;	b = .85;	c = 1;	nu = .85;

```
Y=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k]*Gamma[(k+1)*nu+1]))),{k,0,10}];

Plot[{Y,X,Z,Y’,X’,Z’},{t,0,20},PlotStyle-
>{AbsoluteThickness[3],AbsoluteThickness[1],Dashing[{.05,.03}]},AxesLabel-
>{t,Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]
```

Figure(5.3)

Y’	a = 2;	b = .7;	c = 1;	nu = 1;
X’	a = 2;	b = .7;	c = 1;	nu = .94;
Z’	a = 2;	b = .7;	c = 1;	nu = .85;

```
Y=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k]*Gamma[(k+1)*nu+1]))),{k,0,10}];
```

```
Plot[{Y,X,Z,Y',X',Z'},{t,0,20},PlotStyle->{AbsoluteThickness[3],AbsoluteThickness[1],Dashing[{.05,.03}]},AxesLabel->{t,Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]
```

Figure(5.5)

```
f={{1,.216},{2,.220},{3,.240},{4,.250},{5,.260},{6,.270},{7,.280},{8,.290},{9,.330},{10,.360},{11,.380},{12,.400},{13,.460},{14,.482},{15,.492},{16,.592},{17,.544},{18,.584},{19,.594},{20,.620},{21,.644},{22,.644},{23,.648}}

fp=ListPlot[f,PlotMarkers->{Automatic,Medium}]

Y       a=-.0037557;  b=0.9358;  c=-1.8315;   nu=.99;
X       a=-.0037557;  b=0.9358;  c=-1.8315;   nu=1;

Y,X=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-k]*Gamma[(k+1)*nu+1]))),{k,0,10}];

PY,PX=Plot[{X,Y},{t,0,23},PlotStyle->{AbsoluteThickness[4],AbsoluteThickness[4],Dashing[{.01,.01}]},AxesLabel->{t,Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]

m = Plot[−.0037557* Exp[-Exp[(.9358 −1.8315*x)]],{x,0,23}]

Show[fp,PX,PY,m,PlotRange->All]
```

Figure(5.7)

```
f={{1,.216},{2,.220},{3,.240},{4,.250},{5,.260},{6,.270},{7,.280},{8,.290},{9,.330},{10,.360},{11,.380},{12,.400},{13,.460},{14,.482},{15,.492},{16,.592},{17,.544},{18,.584},{19,.594},{20,.620},{21,.644},{22,.644},{23,.648}}

fp=ListPlot[f,PlotMarkers->{Automatic,Medium}]

Y       a= .0119493;  b= .9488;  c −1.9;   nu=.98;
X       a= .0119493;  b= .9488;  c −1.9;   nu=1;

Y,X=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-k]*Gamma[(k+1)*nu+1]))),{k,0,10}];

PY,PX=Plot[{X,Y},{t,0,23},PlotStyle->{AbsoluteThickness[4],AbsoluteThickness[4],Dashing[{.01,.01}]},AxesLabel->{t,Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]
```

```
Model=q*Exp[-Exp[r-u*x]];

fit=FindFit[f,Model,{q,r,u},x]

{q->1.34651,r->0.734078,u->0.0487025}

m = Plot[1.34651* Exp[-Exp[(0.734078 −0.0487025*x)]],{x,0,23}]

Show[fp,PX,PY,m,PlotRange->All]
```

Figure(5.11)

```
f13={{16,1.4},{34.3,9.03},{51,12.3},{68.8,31.3},{96,29.8},{119.6,48.1},{13,1.19},{30.

1,5.28},{51.2,11.34},{72.5,23.1},{92.8,21.2},{116.5,65.7}}

fp=ListPlot[f13,PlotMarkers->{Automatic,Medium}]

X     a=.0676425131;     b=0.9865;     c=.5;   nu=1;
Y     a=.0676425131;     b=0.9865;     c=.5;   nu=.98;

Y,X=Exp[Sum[((c*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k+1]*Gamma[(k+1)*nu]))+(a*(b-1)^k*Gamma[t+(k+1)*(nu-1)+1]/(Gamma[t-
k]*Gamma[(k+1)*nu+1]))),{k,0,40}]];

PX,PY=Plot[{Y},{t,0,120} ,PlotStyle-
>{AbsoluteThickness[3],AbsoluteThickness[1],Dashing[{.05,.03}]},AxesLabel->{t,
Size},BaseStyle->{FontWeight->"Bold",FontSize->16}]

R=Plot[.5*Exp[.077/.0135*(1-Exp[-.0135*t])],{t,0,120}]

Show[P,fp,R,PX,PlotRange->All]
```

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