Progress in Fractional Differentiation and Applications
An International Journal

http://dx.doi.org/10.18576/pfda/110307

An Exploration of Discrete Fractional Calculus with Applications to Intermittent Oncological Modeling

*Casey J. Mills and Raegan Higgins**

Department of Mathematics and Statistics, Texas Tech University, Lubbock, USA

Received: 15 May 2024, Revised: 2 Nov. 2024, Accepted: 7 Dec. 2024
Published online: 1 Jul. 2025

Abstract: In this work, we use and unify time scale calculus and discrete fractional calculus to develop a new approach to modeling intermittent androgen deprivation therapy, a standard prostate cancer treatment. The novel time scale model previously developed assumes a constant length of time for on- and off-treatment intervals. By creating a time scale that more accurately represents time data, we explore the use of fractional calculus to model treatment. Current fractional calculus theory only allows for strictly continuous or discrete domains. We create a strictly discrete time scale and construct a dynamic equation on this time scale. We then develop theory that allows us to calculate the fractional difference of this dynamic equation. Finally, we model intermittent androgen deprivation therapy using this fractional difference and find that an improved fit is achieved for most of the patients tested.

Keywords: discrete fractional calculus, difference calculus, time scales, intermittent androgen deprivation therapy.

1 Introduction

Prostate cancer is a common cancer among males in the United States [18]. The progression of prostate cancer is measured using prostate-specific antigen (PSA) levels, which are known to track relative changes in tumor volume well [12]. A PSA level over 4.0 μg/L may indicate cancerous cells in the prostate [13,17]. A frequent treatment for patients with metastatic prostate cancer is intermittent androgen deprivation (IAD) [14]. Androgen is any type of male sex hormone, like androstenedione or testosterone, which is required for prostate health. During IAD, a patient alternates between periods of off-treatment and on-treatment [7]. When a patient is on-treatment, surgical or chemical castration is performed. IAD is generally performed prior to radiation to shrink tumors to make treatment more effective, or when surgery or radiation are not an option.

The main goal of our original work [10] was to develop a new approach to modeling intermittent cancer treatment therapy using time scales. Motivated by the work of [5] and [15], we model the dynamics of prostate cancer treatment using the theory of time scales. A *time scale* is an arbitrary, nonempty, closed subset of the real numbers. Time scales combine continuous and discrete time and had not been used to model IAD therapy prior to our original work. Time scales allow us to make a distinction between when a patient is on and off treatment with respect to time, which is generally not done in IAD models. In our initial work, we chose a time scale that assumes constant length of time for on- and off-treatment intervals as it is an efficient way to illustrate the union of disjoint intervals. These disjoint intervals represent the collection of all off-treatment intervals. In this paper, we modify the assumption that the length of time a patient is on- and off-treatment remains constant. Additionally, we introduce new fractional difference theory and explore its application to IAD therapy.

This article is organized as follows. In Section 2, we give the necessary fundamentals of time scales. Section 3 follows with a comparison of the novel model [10] and a newly constructed refined model. Section 4, provides an introduction to existing fractional difference calculus. Using this theory as a basis, in Section 5, we introduce new fractional difference theory as a means to improve the refined model. With the new theory in hand, we construct and analyze a fractional difference model and provide a comparison to the refined model. We conclude with Section 6 summarizing our results and discussing future work.

* Corresponding author e-mail: raegan.higgins@ttu.edu

2 Elements of Time Scale Calculus

We provide some foundational concepts regarding time scales. The material presented here can be found in Bohner and Peterson [3].

A *time scale* $\mathbb{T}$ is an arbitrary nonempty closed subset (under the relative topology inherited from the usual Euclidean topology on $\mathbb{R}$) of the real numbers. While $\mathbb{N}$, the Cantor set, and $[0,1]\cup[2,3]$ are examples of time scales, the open interval (a,b), the complex numbers, and the irrational numbers are not.

Definition 1. *Let $\mathbb{T}$ be a time scale. For $t\in\mathbb{T}$ we define the forward jump operator $\sigma:\mathbb{T}\to\mathbb{T}$ by*

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

while we define the backward jump operator $\rho:\mathbb{T}\to\mathbb{T}$ as

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

Note that $\sigma(t)\geq t$ and $\rho(t)\leq t$ for all $t\in\mathbb{T}$. We think of $\sigma(t)$ as the successor and $\rho(t)$ as the predecessor. On $\mathbb{R}$, $\sigma(t)=\rho(t)=t$ for every t. For the discrete time scale $\mathbb{Z}$, $\sigma(t)=t+1$ and $\rho(t)=t-1$ for every t. On $\mathbb{T}=\left\{\frac{n}{2}:n\in\mathbb{N}_0\right\}$, $\sigma(t)=t+\frac{1}{2}$ for all $t\in\mathbb{T}$ and

$$\rho(t)=\begin{cases}t-\frac{1}{2} & \text{if} \quad t=\frac{n}{2},\ n\in\mathbb{N},\\ 0 & \text{if} \quad t=0.\end{cases}$$

Definition 2. *Let $\mathbb{T}$ be a time scale. Then for each $t\in\mathbb{T}$, the graininess function $\mu:\mathbb{T}\to[0,\infty]$ is defined by*

$$\mu(t):=\sigma(t)-t.$$

The nonnegative function $\mu(t)$ is thought of as the space between a point and its successor. On $\mathbb{R}$, $\mu(t)=0$ for every t, while on $\mathbb{Z}$, $\mu(t)=1$ for every t. When $\mathbb{T}=\left\{\frac{n}{2}:n\in\mathbb{N}_0\right\}$, $\mu(t)=\frac{1}{2}$.

The forward jump operator and graininess function are critical in differentiation.

Definition 3. *We say a function $f:\mathbb{T}\to\mathbb{R}$ is delta differentiable at $t\in\mathbb{T}^\kappa$ provided there exists an α such that for all $\varepsilon>0$ there is a neighborhood U of t such that*

$$\left|[f(\sigma(t))-f(s)]-\alpha(\sigma(t)-s)\right|\leq\varepsilon|\sigma(t)-s| \quad \textit{for all } s\in U,$$

where

$$\mathbb{T}^\kappa=\begin{cases}\mathbb{T}\setminus(\rho(\sup\mathbb{T}),\ \sup\mathbb{T}] & \textit{if} \quad \sup\mathbb{T}<\infty\\ \mathbb{T} & \textit{if} \quad \sup\mathbb{T}=\infty.\end{cases}$$

If α exists, we denote it by $f^\Delta(t)$ and call $f^\Delta(t)$ the delta derivative of f at $t\in\mathbb{T}^\kappa$.

Note that set $\mathbb{T}^\kappa$ is needed to ensure the derivative of a function f is only taken at points t that have a successor $\sigma(t)$. If $\mathbb{T}=\mathbb{R}$, then the delta derivative concurs with the classical derivative.

Theorem 1. *Assume $f:\mathbb{T}\to\mathbb{R}$ is a function and let $t\in\mathbb{T}^\kappa$. If f is delta differentiable at t, then $f(\sigma(t))=f(t)+\mu(t)f^\Delta(t)$.*

This result gives a relationship between σ and μ. Note, that when $\mathbb{T}=\mathbb{Z}$, $\mu(t)=1$, and so $f^\Delta(t)=f(t+1)-f(t)$ for all t.

To describe delta integrable functions, we first need regulation and right-dense continuity.

Definition 4. *A function $f:\mathbb{T}\to\mathbb{R}$ is called regulated provided its right-sided limits exist (are finite) at all right-dense points in $\mathbb{T}$ and its left-sided limits exist (are finite) at all left-dense points in $\mathbb{T}$.*

Definition 5. *We say that a function $f:\mathbb{T}\to\mathbb{R}$ is rd-continuous provided it is continuous at right-dense points in $\mathbb{T}$ and its left-sided limit exists at left-dense points in $\mathbb{T}$.*

Any continuous real-valued function defined on a time scale $\mathbb{T}$ is rd-continuous. Furthermore, a rd-continuous function is also regulated. So although the forward jump operator σ is not continuous, it is right dense-continuous (rd-continuous) and regulated. We can now integrate on $\mathbb{T}$.

Definition 6. *Assume $f:\mathbb{T}\to\mathbb{R}$ is regulated. Then a function $F:\mathbb{T}\to\mathbb{R}$ is called an antiderivative of f provided $F^{\Delta}(t)=f(t)$ for all $t\in\mathbb{T}^{\kappa}$. In this case, we define the (Cauchy) integral by*

$$\int_s^t f(\tau)\Delta\tau = F(t)-F(s) \quad for \quad s,t\in\mathbb{T}.$$

An antiderivative of 0 is 1 and an antiderivative of 1 is t. Furthermore, on a completely discrete time scale with $a<b$, we have

$$\int_a^b f(t)\Delta t = \sum_{t\in[a,\rho(b)]} \mu(t)f(t)$$

for any rd-continuous function f. We use the delta integral to define the generalized exponential function.

Definition 7. *Suppose $p:\mathbb{T}\to\mathbb{T}$ is rd-continuous and such that $1+\mu(t)p(t)\neq 0$ for all $t\in\mathbb{T}^{\kappa}$. Then the generalized exponential function is given by*

$$e_p(t,s) = exp\left(\int_s^t \xi_{\mu(\tau)}(p(\tau))\Delta\tau\right) \quad for \quad s,\, t\in\mathbb{T},$$

where the cylinder transform $\xi_h(z):\mathbb{C}_h\to\mathbb{Z}_h$ $(h\geq 0)$ is given by

$$\xi_h(z)=\begin{cases}\dfrac{1}{h}Log(1+zh) & if\ h>0\\ z & if\ h=0.\end{cases}$$

When $h>0$, we have $\mathbb{C}_h=\left\{z\in\mathbb{C}:z\neq\dfrac{1}{h}\right\}$ and $\mathbb{Z}_h=\left\{z\in\mathbb{C}:-\dfrac{\pi}{h}<Im(z)<\dfrac{\pi}{h}\right\}$. For $h=0$, $\mathbb{C}_h=\mathbb{C}=\mathbb{Z}_h$.

On $\mathbb{Z}$ with $p(t)=1$, $e_p(t,0)=2^t$ because $\xi_h(z)=\text{Log}(2)$ and $z=1$. It can be shown that $e_p(t,t_0)=(1+p)^{t-t_0}$ when $\mathbb{T}=\mathbb{Z}$ and $p(t)=p\in\mathbb{R}$. Unlike the exponential function on $\mathbb{R}$, the general exponential function can attain negative values. To learn more about the generalized exponential function, refer to Chapter 2 of [3].

3 Foundational Models

3.1 The Novel Model

The work presented in this section is an overview of our original work. For further details on the construction of the novel model, refer to [10]. Initially, we made three key assumptions. The first is that the length of both on-treatment and off-treatment intervals do not change over time (and are not necessarily equal to one another). To reflect this, we built our model on the time scale

$$\mathbb{P}_{a,b}=\bigcup_{k=0}^{\infty}[k(a+b),k(a+b)+a],$$

where $a,\ b>0$. Here $\mathbb{P}_{a,b}$ represents the union of a patients' off-treatment intervals, where a is the number of months a patient is off treatment and b is the number of months a patient is on treatment. Parameter k is the number of treatment cycles a patient undergoes. We chose this time scale because it is an efficient way to illustrate the union of disjoint intervals. The time scale can be drawn as

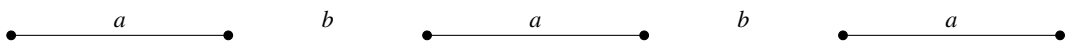


Fig. 1: Visual Representation of $\mathbb{P}_{a,b}$

The second key assumption is while a patient is off-treatment, prostate-specific antigen (PSA) levels grow exponentially. We estimate the PSA level of a patient at time t using the function $N(t)$. For $\gamma>1$, we have $N(t)=\gamma^t$ for $t\in\mathbb{P}_{a,b}$. The final key assumption (also known as the β assumption) is the PSA level depreciates by some proportion β

between 0 and 1 whenever a patient is on treatment. This accounts for the depletion of cancer cells due to treatment, as well as any cells that may die due to natural apoptosis (cell death). It is important to note that the value of $N(t)$ at the end of an on-treatment interval is equal to β times the value of $N(t)$ at the beginning of that on-treatment interval. Mathematically, this is expressed as

$$N((k+1)(a+b)) = \beta N(k(a+b)+a)$$

for $k \in \mathbb{N}_0$, when the patient is on treatment.

Using the three key assumptions, we solved a first order dynamic equation on $\mathbb{P}_{a,b}$ to obtain the following general form:

$$N(t) = \alpha(\beta\gamma^a)^k \gamma^{t-(a+b)k}$$

on the $(k+1)$th off-treatment interval $[k(a+b), k(a+b)+a]$ where $k \in \mathbb{N}_0$, $a, b > 0$, and α is a scaling factor. A description of all model parameters is summarized in Table 1.

We found that the length of both on-treatment and off-treatment intervals rarely remains constant over time in clinical data [4]. For all but one of the patients whose treatment interval lengths best matched our the assumptions of $\mathbb{P}_{a,b}$, the model fit the data quite well. For the final patient, the time scale and the actual off-treatment intervals aligned poorly. This lead to a poor fit because the scale α and base γ are found using the data fitting function *fmincon* in MATLAB R2018b. The difference for *fmincon* is only calculated when $t \in \mathbb{P}_{a,b}$ corresponds to actual off-treatment data points; the fewer such t, the worse the fit. The assumption that the length of on- and off-treatment intervals remain constant over time prevented us from considering the remaining patients from the clinical data [4]. This assumption was necessary for the construction and application of this new time scales approach to intermittent androgen deprivation therapy but may now be altered.

3.2 Construction and Analysis of Our Refined Model

In this section, we explore a time scale which allows us to modify the assumption that the length of treatment intervals remains consistent over time. We constructed a time scale with a varying length for off-treatment intervals and varying length for on-treatment intervals. This is written as

$$\mathbb{P}_{a_k,b_k} = \bigcup_{k=0}^{\infty} \left[\sum_{n=0}^{k-1} (a_n + b_n), \sum_{n=0}^{k-1} (a_n + b_n) + a_k \right],$$

where $a_k,\ b_k > 0$. An illustration of $\mathbb{P}_{a_k,b_k}$ is

Fig. 2: Visual Representation of $\mathbb{P}_{a_k,b_k}$

Adjusting the β assumption of the novel model to allow a unique scale for each on-treatment interval, we introduce the β_k assumption

$$N\left(\sum_{n=0}^{k} (a_n + b_n)\right) = \beta_k N\left(\sum_{n=0}^{k-1} (a_n + b_n) + a_k\right).$$

Using a similar construction to [10], on the $(k+1)$th off-treatment interval, the PSA level is given by

$$N(t) = \alpha \left[\prod_{n=0}^{k-1} (\beta_n \gamma^{a_n}) \right] \gamma^{t - \sum_{n=0}^{k-1} (a_n + b_n)}$$

for some scale $\alpha > 0$.

We now discuss our methods for data cleaning, parameterization, and model comparison. We then provide a brief comparison of the the novel model and the model constructed on $\mathbb{P}_{a_k,b_k}$ based on analysis performed across 12 patients from the clinical data [4].

Parameter value	Description
k	Number of treatment cycles
α	Scaling factor
γ	Base for exponential growth of PSA during off-treatment
a	Length of off-treatment interval (months)
b	Length of on-treatment interval (months)
β	Proportion reduction in PSA during treatment
a_k	Length of kth off-treatment interval (months)
b_k	Length of kth on-treatment interval (months)
β_k	Proportion reduction in PSA during kth treatment

Table 1: Model Parameters

3.2.1 Computational Analysis

The computational analysis in this paper varies from that of [10]. As our time scale only estimates PSA levels during off-treatment intervals, $t = 0$ must be the start of the first off-treatment interval. In light of this, we have disregarded any data prior to a patient's first recorded off-treatment interval. Biologically, it is expected that PSA levels will drop drastically when treatment begins. There were instances when a patient's PSA level increased during their first month on treatment. It is not unreasonable to assume that a PSA level would have been measured during the initial doctor's visit prior to the actual treatment taking place. Considering this, if a patient's PSA level increased during the first month on treatment, we relabeled this measurement as an off-treatment data point.

When a patient did not return for several months between visits, we assumed the patient was on- or off-treatment according to the last available data point and did not consider PSA levels for these months. If a patient had two visits within ten days, usually only one of these visits had an associated PSA level, we used the data from this particular visit. Lastly, in the rare instance that both visits had a recorded PSA level, we used the average of the two measurements as the PSA level for the associated month.

During our analysis, the variables k, a, b, β, a_k, b_k, and β_k are inserted from the data. Specifically, the variables a, b, and β are input from the patients' first off- and on-treatment intervals while the variables a_k, b_k, and β_k are input from the patients' kth off- and on-treatment intervals. Note that $a = a_0, b = b_0$, and $\beta = \beta_0$. The parameters α and γ and are found using the data fitting function *fmincon* in MATLAB R2018b. Our cost in *fmincon* is the sum of the least squares between our model and the data. We only calculate the difference when the value t in our time scale corresponds to actual off-treatment data points. The function *fmincon* finds the lowest cost for differing α and γ values, keeping the pair of values that produces the local minimum cost.

3.2.2 Tools for Mathematical Comparison of the Models

To assess model fit, we use two information-based criteria that are common in the statistical comparison of models: the corrected Akaike's Information Criteria (AICc) and the Bayesian Information Criteria (BIC). These criterion take into account both the accuracy and simplicity of a model. The more parameters a model has and the higher the sum of squared error (SSE) for the model is, the larger the AICc and BIC become. Thus, the smaller the AICc and BIC, the better.

We calculate the SSE using all values of t in the time scale that align with data points, regardless if they are on- or off-treatment data points. If the time scale overshoots the available data, we calculate the SSE for the remaining t values in our time scale using the terminating PSA level of the final off-treatment interval of the data. If the time scale undershoots the available data, we calculate the SSE for the remaining data points using the value of $N(t)$ given by the terminating value of t in our time scale.

According to John's Macintosh Project [16], AICc and BIC are defined as follows:

$$AICc = n\ln\left(\frac{SSE}{n}\right) + 2p + \frac{2p(p+1)}{(n-1-p)} + n\ln(2\pi) + n,$$
$$BIC = n\ln\left(\frac{SSE}{n}\right) + p\ln(n) + n\ln(2\pi) + n,$$

where p is the number of estimated parameters in the model and n is the number of observations used in the model. Lower values for p, n, and the SSE result in lower AICc and BIC values, which is desired. For each of the models, α and γ are parameterized; the remaining required parameters are read from the data, determining p. The value n, however, is highly patient specific and calculated based on the number of observations used for each patient.

3.2.3 A Comparison of $\mathbb{P}_{a,b}$ and $\mathbb{P}_{a_k,b_k}$

The 6 patients analyzed in [10] were chosen because their treatment intervals best reflect $\mathbb{P}_{a,b}$. While the novel time scale model accounts for continuous and discrete time simultaneously, it does not accurately represent all potential time-data. The goal of the model constructed on $\mathbb{P}_{a_k,b_k}$ is to improve the novel model by better representing the time-data. We again analyze the 6 patients selected for analysis in [10], as well as an additional 6 patients randomly selected from the subset of patients who have data for two or more treatment intervals. For each patients, the AICc and BIC values have been calculated for each of the models. We provide the average of these values over the 12 patients analyzed in Table 2.

Table 2: Average Value of AICc and BIC for $\mathbb{P}_{a,b}$ and $\mathbb{P}_{a_k,b_k}$ Models

Time Scale	Average AICc	Average BIC
$\mathbb{P}_{a,b}$	220.18	225.12
$\mathbb{P}_{a_k,b_k}$	180.41	179.76

The time scale $\mathbb{P}_{a_k,b_k}$ leads to a clear improvement of model fit. Motivated by the success of Atici et al. [1] modeling tumor volumes in mice by applying fractional calculus to Gompertz equations, in the next two sections, we introduce established fractional difference calculus, makes adjustments to $\mathbb{P}_{a_k,b_k}$ so the existing theory may be used, and introduce a new definition that unifies fractional difference calculus on two types of time scales. We use this new definition to construct a fractional difference model, then analyze and discuss this model.

4 Fractional Difference Calculus

In this section, we provide foundational definitions and theorems regarding discrete fractional sums and differences. The definitions and theorems presented in this section may be found in [8,11].

The functions typically considered are defined on sets of the form

$$\mathbb{N}_r = \mathbb{N}_0 + \{r\} = \{r, r+1, r+2, \ldots\}, \quad r \in \mathbb{R},$$

and

$$\mathbb{N}_r^h = h\mathbb{N}_0 + \{r\} = \{r, r+h, r+2h, \ldots\}, \quad r \in \mathbb{R}, h > 0 \text{ fixed.}$$

Note, these sets are equivalent when $h = 1$.

Definition 8. *The gamma function is defined by*

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

for any $z \in \mathbb{C}$ for which the real part of z is positive.

Definition 9. *The generalized falling function is defined by*

$$t^{\underline{\nu}} := \frac{\Gamma(t+1)}{\Gamma(t-\nu+1)}$$

for any $t, \nu \in \mathbb{R}$ for which the right-hand side is well-defined (that is, where $t+1$ and $t-\nu+1$ are not negative integers).

We now have the tools required to introduce the fractional sum and fractional difference.

Definition 10. *Let $f : \mathbb{N}_r \to \mathbb{R}$ and $\nu > 0$. Then the ν-th fractional sum of f is defined by*

$$\Delta_r^{-\nu} f(t) := \frac{1}{\Gamma(\nu)} \sum_{s=r}^{t-\nu} (t - \sigma(s))^{\underline{\nu-1}} f(s) \quad \text{for } t \in \mathbb{N}_{r+\nu}.$$

Definition 11. *Let $f : \mathbb{N}_r \to \mathbb{R}$ and $\nu > 0$ be given. Choose $n \in \mathbb{N}$ such that $n-1 < \nu \leq n$. Then the ν-th fractional difference of f is defined by*

$$\Delta_r^{\nu} f(t) := \Delta^n \left(\Delta_r^{-(n-\nu)} \right) f(t) \quad \text{for } t \in \mathbb{N}_{r+n-\nu}.$$

As shown in Higgins and Berger [9], for any real number r, the half-derivative of t on $\mathbb{Z}$ is

$$\Delta_r^{1/2} t = \frac{2}{\sqrt{\pi}} \left[\frac{1}{2} r(t-r)^{\underline{-1/2}} + (t-r)^{\underline{-1/2}} \right].$$

The following theorem provides a very useful formula for $\Delta_r^{\nu} f(t)$ and is called the alternate definition of the ν-th fractional difference. This theorem allows one to calculate the fractional difference of a function without first having to calculate the fractional sum.

Theorem 2. *Let $f : \mathbb{N}_r \to \mathbb{R}$, $\nu > 0$ be given. Choose $n \in \mathbb{N}$ such that $n-1 < \nu \leq n$. Then*

$$\Delta_r^{\nu} f(t) = \begin{cases} \dfrac{1}{\Gamma(-\nu)} \displaystyle\sum_{s=r}^{t+\nu} (t-\sigma(s))^{\underline{-\nu-1}} f(s) & \text{for } n-1 < \nu < n \\ \Delta^n f(t) & \text{for } \nu = n. \end{cases}$$

The next definitions for the ν-th fractional sum and difference, respectively, are equivalent to the prior two definitions when $h = 1$.

Definition 12. *Let $f : \mathbb{N}_r^h \to \mathbb{R}$ and $\nu > 0$. Then the ν-th fractional sum of f is defined by*

$${}_h\Delta_r^{-\nu} f(t) := \frac{h^{\nu}}{\Gamma(\nu)} \sum_{\substack{s=r \\ \text{by } h}}^{t-\nu h} \left(\frac{t-\sigma(s)}{h} \right)^{\underline{\nu-1}} f(s) \quad \text{for } t \in \mathbb{N}_{r+\nu h}^h,$$

where the "by h" condition under the summation indicates that the sum occurs in increments of h, that is, for $s = r, r+h, r+2h$, and so on.

Definition 13. *Let $f : \mathbb{N}_r^h \to \mathbb{R}$, $\nu > 0$, $n \in \mathbb{N}$ and $n-1 < \nu \leq n$. The ν-th fractional difference of f is defined by*

$${}_h\Delta_r^{\nu} f(t) := \Delta^n \left({}_h\Delta_r^{-(n-\nu)} \right) f(t) \quad \text{for } t \in \mathbb{N}_{r+(n-\nu)h}^h.$$

5 The Discrete Fractional Model

With the work of [1] as motivation, we construct a discrete fractional time scale and its associated model.

5.1 Discretizing the Model Associated with $\mathbb{P}_{a_k,b_k}$

Existing fractional difference theory requires the time scale to be strictly discrete. We transition from a combination of continuous and discrete time with $\mathbb{P}_{a_k,b_k}$ to the new discrete time scale $\mathbb{N}_{a_k,b_k,r_k}$.

Definition 14. *Let a_k, $b_k > 0$, $r_k \in \mathbb{R}$, and $k \in \mathbb{N}_0$. We define the time scale $\mathbb{N}_{a_k,b_k,r_k}$ corresponding to the discrete analog of $\mathbb{P}_{a_k,b_k}$ by*

$$\mathbb{N}_{a_k,b_k,r_k} := \bigcup_{k=0}^{\infty} \left\{ \sum_{n=0}^{k-1} (a_n + b_n) + r_k, \sum_{n=0}^{k-1} (a_n + b_n) + 1 + r_k, \ldots, \sum_{n=0}^{k-1} (a_n + b_n) + a_k + r_k \right\}.$$

We note that for each $k \in \mathbb{N}_0$ the value of r_k differs and that $\mathbb{N}_{a_k,b_k,r_k}$ is a subset of $\bigcup_{k=0}^{\infty} \mathbb{N}_{r_k}$. Visually, a portion of this time scale is represented in Figure 3, noting that a_0, a_1, a_2, b_0, and b_1 can be any positive integer and that the value of r_k determines a shift to the left or right for each collection of points.

Fig. 3: Visual Representation of $\mathbb{N}_{a_k,b_k,r_k}$

Each set of points in Figure 3 represents the collection of months during an off-treatment cycle. Let $k \in \mathbb{N}_0$ and $r_k \in \mathbb{R}$. We define

$$F_k := \left\{ \sum_{n=0}^{k-1}(a_n+b_n)+r_k, \sum_{n=0}^{k-1}(a_n+b_n)+1+r_k, \ldots, \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k-1 \right\}$$

and

$$f_k := \left\{ \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k \right\}.$$

F_k is the collection points in the $(k+1)$th off-treatment cycle such that $\sigma(t) = t+1$ and f_k is the "endpoint" of the $(k+1)$th off-treatment cycle, where $\sigma(t) = t+\mu_k$ and μ_k is the graininess of $t \in f_k$. Moving forward, we use the convention for $t \in F_k$, $t_0^k = \sum_{n=0}^{k-1}(a_n+b_n)+r_k$, and for $t \in f_k$, $t_0^k = \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k$, performing the appropriate shifts where necessary.

For the models discussed earlier, we made three key assumptions. Here, we maintain two of them. We assume that while a patient is off-treatment, PSA levels grow exponentially. This requires us to reconsider the exponential needed to build $N(t)$ on our new time scale $\mathbb{N}_{a_k,b_k,r_k}$. For $t \in F_k$, where $\sigma(t) = t+1$, by Definition 7, we have

$$\begin{aligned} e_{g(t)}(t,t_0^k) &= \exp\left(\int_{t_0^k}^{t} \xi_1\left(g(\tau)\right)\Delta\tau\right) \\ &= \exp\left(\int_{t_0^k}^{t} \mathrm{Log}(1+g(\tau))\Delta\tau\right) \\ &= \exp\left((t-t_0^k)\mathrm{Log}(1+g)\right) \quad \text{letting } g(t) = g \in \mathbb{R} \\ &= (1+g)^{(t-t_0^k)}. \end{aligned} \tag{1}$$

We also maintain the β_k assumption that PSA levels decrease by a scale β_k while a patient is on-treatment. With this assumption, we may establish the delata difference for $t \in f_k$.

Theorem 3. *For $t = \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r$ in $\mathbb{N}_{a_k,b_k,r}$, suppose the β_k assumption*

$$N\left(\sum_{n=0}^{k}(a_n+b_n)+r\right) = \beta_k N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right)$$

holds. Then

$$N^{\Delta}\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right) = \frac{(\beta_k-1)}{\mu_k} N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right).$$

Proof. Suppose $t = \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r$ in $\mathbb{N}_{a_k,b_k,r}$ and

$$N\left(\sum_{n=0}^{k}(a_n+b_n)+r\right) = \beta_k N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right).$$

It follows that

$$\begin{aligned} N\left(\sum_{n=0}^{k}(a_n+b_n)+r\right) - N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right) &= (\beta_k-1)N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right) \\ \frac{N\left(\sum_{n=0}^{k}(a_n+b_n)+r\right) - N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right)}{\mu_k} &= \frac{(\beta_k-1)N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right)}{\mu_k} \\ N^{\Delta}\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right) &= \frac{(\beta_k-1)}{\mu_k} N\left(\sum_{n=0}^{k-1}(a_n+b_n)+a_k+r\right). \end{aligned}$$

where we have used Theorem 1.

With this result, we can now describe the delta derivative of $N(t)$ for $t \in f_k$, that is,

$$N^{\Delta}(t) = \frac{(\beta_k - 1)}{\mu_k} N(t) \quad \text{for} \quad t \in f_k. \tag{2}$$

Combining (1) on F_k and the solution of (2) on f_k, we have

$$N(t) = \begin{cases} e_g(t, t_0^k) N_0^k & \text{for } t \in F_k \\ e_{\frac{\beta_k - 1}{\mu_k}}(t, t_0^k) N_0^k & \text{for } t \in f_k, \end{cases}$$

which is equivalent to

$$N(t) = \begin{cases} (1+g)^{(t-t_0^k)} N_0^k & \text{for } t \in F_k \\ \beta_k^{\frac{1}{\mu_k}(t-t_0^k)} N_0^k & \text{for } t \in f_k, \end{cases} \tag{3}$$

where $N_0^k = N(t_0^k)$.

Note that this model is similar to the model associated with $\mathbb{P}_{a_k, b_k}$. The primary differences are that the exponential base is now $1+g$ as opposed to γ and the time scale is now discrete and shifted by r.

5.2 The Fractional Sum and Difference

Applications of discrete fractional calculus have been made on time scales such as $\mathbb{N}_r$ and $\mathbb{N}_r^h$ [1,2,6]. However, to our knowledge, this application is the first to unify these sets. When modeling discrete sets, the results for any given value of t should inform the results for $\sigma(t)$. Hence, we introduce the following definition.

Definition 15. *Let $r \in \mathbb{R}$, $n \in \mathbb{N}$, and $\nu > 0$ be such that $n-1 < \nu < n$. Let f be a function whose domain is the time scale $\mathbb{H} \subseteq \mathbb{N}_r$ such that r is the smallest element of $\mathbb{H}$, $\mu(t) = 1$ for all $t \in \mathbb{H}$ except the largest two elements, and $\mu(t) = h$ for the second largest element of $\mathbb{H}$. For $t \in \mathbb{H}^{\kappa}$, the unified ν-th fractional difference of f is defined by*

$$\Delta_r^{\nu} f(t) = \begin{cases} \Delta^n \left(\Delta_r^{-(n-\nu)} \right) f(t) & \text{for } h = \mu(t) = 1 \\ \Delta_r^{\nu} f(\rho(t)) + \Delta^n \left({}_h\Delta_{r+t}^{-(n-\nu)} \right) f(t) & \text{for } h = \mu(t) \neq 1. \end{cases}$$

In our application, $\mathbb{H}^{\kappa}$ represents all months in a particular off-treatment interval. If we allow $\mathbb{H}^{\kappa}{}_k$ to represent the $(k+1)$th off-treatment interval, then $\mathbb{H}^{\kappa}{}_k = F_k \cup f_k$.

We now calculate the fractional sum and difference of $N(t)$ as defined in (3). For $t \in F_k$ we have that $N : \mathbb{N}_{t_0^k} \to \mathbb{R}$, $N(t) = (1+g)^{(t-t_0^k)} N_0^k$, and $\sigma(s) = s+1$. Let the $(k+1)$th domain $\mathbb{N}_{t_0^k}$ be bounded above by the number $t = \sum_{n=0}^{k-1} (a_n + b_n) + a_k - 1$.

Using Definition 10, for $\nu > 0$ the fractional sum is given by

$$\begin{aligned} \Delta_{r_k}^{-\nu} N(t) &= \frac{1}{\Gamma(\nu)} \sum_{s=r_k}^{t-\nu} (t - \sigma(s))^{\underline{\nu-1}} N(s) \\ &= \frac{1}{\Gamma(\nu)} \sum_{s=t_0^k}^{t-\nu} (t - (s+1))^{\underline{\nu-1}} \left[(1+g)^{(s-t_0^k)} N_0^k \right] \\ &= \frac{1}{\Gamma(\nu)} \sum_{s=t_0^k}^{t-\nu} \left[\frac{\Gamma(t-s)}{\Gamma(t-s-\nu+1)} \right] \left[(1+g)^{(s-t_0^k)} N_0^k \right] \end{aligned}$$

for $t \in \left\{ \sum_{n=0}^{k-1} (a_n + b_n) + r_k + \nu, \sum_{n=0}^{k-1} (a_n + b_n) + 1 + r_k + \nu, \ldots, \sum_{n=0}^{k-1} (a_n + b_n) + a_k + r_k + \nu - 1 \right\}$.

Now, choose $n \in \mathbb{N}$ such that $n-1 < \nu < n$. By Theorem 2, the fractional difference is given by

$$\begin{aligned}
\Delta_{r_k}^{\nu} N(t) &= \frac{1}{\Gamma(-\nu)} \sum_{s=r_k}^{t+\nu} (t-\sigma(s))^{\underline{-\nu-1}} N(s) \\
&= \frac{1}{\Gamma(-\nu)} \sum_{s=t_0^k}^{t+\nu} (t-(s+1))^{\underline{-\nu-1}} \left[(1+g)^{(s-t_0^k)} N_0^k \right] \\
&= \frac{1}{\Gamma(-\nu)} \sum_{s=t_0^k}^{t+\nu} \left[\frac{\Gamma(t-s)}{\Gamma(t-s+\nu+1)} \right] \left[(1+g)^{(s-t_0^k)} N_0^k \right]
\end{aligned}$$

for $t \in \left\{ \sum_{n=0}^{k-1}(a_n+b_n)+r_k+n-\nu, \sum_{n=0}^{k-1}(a_n+b_n)+1+r_k+n-\nu, \ldots, \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k-\nu-1 \right\}$.

We now consider the "endpoints." For $t \in f_k$, we have $N : \mathbb{N}_{t_0^k}^{\mu_k} \to \mathbb{R}$ given by $N(t) = \beta_k^{\frac{1}{\mu_k}(t-t_0^k)} N_0^k$ and $\sigma(s) = s+\mu_k$. Let the $(k+1)$th domain $\mathbb{N}_{t_0^k}^{\mu_k}$ be bounded above by the number $t = \sum_{n=0}^{k}(a_n+b_n)$.

Using Definition 12, for $\nu > 0$ the fractional sum is given by

$$\begin{aligned}
{}_{h_k}\Delta_{r_k}^{-\nu} N(t) &= \frac{h_k^{\nu}}{\Gamma(\nu)} \sum_{\substack{s=r_k \\ \text{by } h_k}}^{t-\nu h_k} \left(\frac{t-\sigma(s)}{h_k} \right)^{\underline{\nu-1}} N(s) \\
&= \frac{h_k^{\nu}}{\Gamma(\nu)} \sum_{\substack{s=r_k \\ \text{by } \mu_k}}^{t-\nu h_k} \left(\frac{t-(s+\mu_k)}{\mu_k} \right)^{\underline{\nu-1}} \left[\beta_k^{\frac{1}{\mu_k}(s-t_0^k)} N_0^k \right] \\
&= \frac{h_k^{\nu}}{\Gamma(\nu)} \sum_{\substack{s=r_k \\ \text{by } \mu_k}}^{t-\nu h_k} \left[\frac{\Gamma\left(\frac{t-s-\mu_k}{\mu_k}+1\right)}{\Gamma\left(\frac{t-s-\mu_k}{\mu_k}-\nu+2\right)} \right] \left[\beta_k^{\frac{1}{\mu_k}(s-t_0^k)} N_0^k \right]
\end{aligned}$$

for $t \in \left\{ \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k+\nu h_k \right\}$.

Finally, let $n \in \mathbb{N}$ and $n-1 < \nu < n$ and $\tilde{r}_k = \sum_{n=0}^{k-1}(a_n+b_n)+r_k$. Using Definition 12 and Definition 15, the fractional difference is given by

$$\begin{aligned}
{}_{h_k}\Delta_{r_k}^{\nu} N(t) &= \Delta_{\tilde{r}_k}^{\nu} f(\rho(t)) + \Delta^n \left[{}_{h_k}\Delta_{r_k}^{-(n-\nu)} N(t) \right] \\
&= \Delta_{\tilde{r}_k}^{\nu} f(\rho(t)) + \Delta^n \left[\frac{h_k^{(n-\nu)}}{\Gamma(n-\nu)} \sum_{\substack{s=r_k \\ \text{by } h_k}}^{t-(n-\nu)h_k} \left(\frac{t-\sigma(s)}{h_k} \right)^{\underline{n-\nu-1}} N(s) \right] \\
&= \Delta_{\tilde{r}_k}^{\nu} f(\rho(t)) + \Delta^n \left[\frac{\mu_k^{(n-\nu)}}{\Gamma(n-\nu)} \sum_{\substack{s=r_k \\ \text{by } \mu_k}}^{t-(n-\nu)h_k} \left(\frac{t-(s+\mu_k)}{\mu_k} \right)^{\underline{n-\nu-1}} \left[\beta_k^{\frac{1}{\mu_k}(s-t_0^k)} N_0^k \right] \right] \\
&= \Delta_{\tilde{r}_k}^{\nu} f(\rho(t)) + \Delta^n \left[\frac{\mu_k^{(n-\nu)}}{\Gamma(n-\nu)} \sum_{\substack{s=r_k \\ \text{by } \mu_k}}^{t-(n-\nu)h_k} \left[\frac{\Gamma\left(\frac{t-s-\mu_k}{\mu_k}+1\right)}{\Gamma\left(\frac{t-s-\mu_k}{\mu_k}-n+\nu+2\right)} \right] \left[\beta_k^{\frac{1}{\mu_k}(s-t_0^k)} N_0^k \right] \right]
\end{aligned}$$

for $t \in \left\{ \sum_{n=0}^{k-1}(a_n+b_n)+a_k+r_k+(n-\nu)h_k \right\}$.

We now prove two theorems that allow us to shift the limits of summation of our fractional differences. This is needed to perform the model analysis because the time-data consists of positive integer values, each representing one month of treatment. The proof of the following theorem was motivated by a portion of the proof of Theorem 2.45, the Fractional Binomial Formulas, of [8].

Theorem 4. *Let $f:\mathbb{N}_r\to\mathbb{R}$ and $0<\nu\le n$ be given. Choose $m\in\mathbb{N}_0$ such that $t=r+n-\nu+m$ for some $t\in\mathbb{N}_{r+n-\nu}$. Then*

$$\Delta_r^{\nu}f(t)=\frac{1}{\Gamma(-\nu)}\sum_{s=0}^{n+m}\frac{\Gamma(n-\nu+m-s)}{\Gamma(n+m-s+1)}f(s+r).$$

Proof. Let $N:\mathbb{N}_r\to\mathbb{R}$, $0<\nu\le n$, and fix $t\in\mathbb{N}_{r+n-\nu}$. Then $t=r+n-\nu+m$ for some $m\in\mathbb{N}_0$. It follows that

$$\begin{aligned}\Delta_r^{\nu}f(t)&=\frac{1}{\Gamma(-\nu)}\sum_{s=r}^{t+\nu}(t-\sigma(s))^{\underline{-\nu-1}}f(s)\\&=\frac{1}{\Gamma(-\nu)}\sum_{s=r}^{t+\nu}\frac{\Gamma(t-s)}{\Gamma(t-s+\nu+1)}f(s)\\&=\frac{1}{\Gamma(-\nu)}\sum_{s=r}^{r+n+m}\frac{\Gamma(r+n-\nu+m-s)}{\Gamma(r+n+m-s+1)}f(s)\\&=\frac{1}{\Gamma(-\nu)}\sum_{s=0}^{n+m}\frac{\Gamma(n-\nu+m-s)}{\Gamma(n+m-s+1)}f(s+r).\end{aligned}$$

The following theorem is equivalent to Theorem 4 when $h=1$.

Theorem 5. *Let $f:\mathbb{N}_r^h\to\mathbb{R}$ and $0<\nu\le n$ be given. Choose $m\in\mathbb{N}_0$ such that $t=r+(n-\nu)h+m$ for some $t\in\mathbb{N}_{r+(n-\nu)h}$. Then*

$${}_h\Delta_r^{\nu}f(t)=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=0\\ \text{by } h}}^{m}\left[\frac{\Gamma\left(\frac{(n-\nu)h+m-s-h}{h}+1\right)}{\Gamma\left(\frac{(n-\nu)h+m-s-h}{h}-n+\nu+2\right)}\right]f(s+r).$$

Proof. Let $N:\mathbb{N}_r^h\to\mathbb{R}$, $0<\nu\le n$, and fix $t\in\mathbb{N}_{r+(n-\nu)h}$. Then $t=r+(n-\nu)h+m$ for some $m\in\mathbb{N}_0$. It follows that

$$\begin{aligned}{}_h\Delta_r^{\nu}f(t)&=\Delta^n\left({}_h\Delta_r^{-(n-\nu)}\right)f(t)\\&=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=r\\ \text{by } h}}^{t-(n-\nu)h}\left(\frac{t-\sigma(s)}{h}\right)^{\underline{n-\nu-1}}f(s)\\&=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=r\\ \text{by } h}}^{t-(n-\nu)h}\left(\frac{t-(s+h)}{h}\right)^{\underline{n-\nu-1}}f(s)\\&=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=r\\ \text{by } h}}^{t-(n-\nu)h}\left[\frac{\Gamma\left(\frac{t-s-h}{h}+1\right)}{\Gamma\left(\frac{t-s-h}{h}-n+\nu+2\right)}\right]f(s)\qquad(4)\\&=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=r\\ \text{by } h}}^{\substack{r+(n-\nu)h+\\ m-(n-\nu)h}}\left[\frac{\Gamma\left(\frac{r+(n-\nu)h+m-s-h}{h}+1\right)}{\Gamma\left(\frac{r+(n-\nu)h+m-s-h}{h}-n+\nu+2\right)}\right]f(s)\\&=\Delta^n\frac{h^{(n-\nu)}}{\Gamma(n-\nu)}\sum_{\substack{s=0\\ \text{by } h}}^{m}\left[\frac{\Gamma\left(\frac{(n-\nu)h+m-s-h}{h}+1\right)}{\Gamma\left(\frac{(n-\nu)h+m-s-h}{h}-n+\nu+2\right)}\right]f(s+r).\end{aligned}$$

We are now ready to calculate and analyze the models of the fractional difference of $N(t)$ on $\mathbb{N}_{a_k,b_k,r_k}$ for values of $\nu\in[0,1)$.

5.3 Analysis of the Discrete Model and the Fractional Difference

In this section we compare the models of the fractional difference of $N(t)$ for values of $\nu \in [0,1)$. Table 3 shows the time scale $\mathbb{N}_{a_k,b_k,r_k}$. These time scales represent the collection of all off-treatment months for each patient. Recall that the data has been cleaned to ensure $t=0$ is the start of a patients first off-treatment interval; an explanation of all refinements made to the data can be found in Section 3.2.2.

Table 3: $\mathbb{N}_{a_k,b_k,r_k}$ for Each Patient

Patient	$\mathbb{N}_{a_k,b_k,r_k}$
Patient 100	$\{0,1,...7,18,19,...,26,37,38,...,51\}$
Patient 91	$\{0,1,...,10,21,22,...,28,39,40,...,45\}$
Patient 77	$\{0,1,...,6,16,17,...,23,35,36,...,39\}$
Patient 75	$\{0,1,...,7,23,24,...,29,44,45,...,48,59,60,...,63\}$
Patient 63	$\{0,1,...,9,19,20,...,28,40,41,...,55\}$
Patient 60	$\{0,1,...,8,22,21,...,30,43,44,...,52,63,64,...,72\}$
Patient 58	$\{0,1,...,14,25,26,...,33,45,46,...,55\}$
Patient 55	$\{0,1,...,10,21,22,...,27,39,40,...,45,59,60,...,66\}$
Patient 39	$\{0,1,...,6,18,18,...,24,35,36,...44,57,58,...,74\}$
Patient 37	$\{0,1,...,11,21,22,...,31,43,44,...,53,61,62,...,65\}$
Patient 28	$\{0,1,...,13,24,25,...,37,49,50,...,64\}$
Patient 1	$\{0,1,...,5,15,16,...,21,32,33,...,40,52,53,...,59,71,72,73\}$

5.3.1 Applications to the New Theory

We first consider $N(t)$ as defined on the time scale $\mathbb{N}_{a_k,b_k,r_k}$ $(\nu=0)$. Recall that

$$N(t)=\begin{cases}(1+g)^{(t-t_0^k)}N_0^k & \text{for} \quad t\in F_k\\ \beta_k^{\frac{1}{\mu_k}(t-t_0^k)}N_0^k & \text{for} \quad t\in f_k,\end{cases}$$

and for random a_k, b_k, and β_k on the $(k+1)$th off-treatment interval, we have the general form

$$N(t)=\alpha\left[\prod_{n=0}^{k-1}\beta_n(1+g)^{a_n}\right](1+g)^{t-\sum_{n=0}^{k-1}(a_n+b_n)}$$

where $\alpha>0$ is the initial condition.

When we wrote the code for the model on $\mathbb{P}_{a,b}$, we set the spacing between each point considered to be one. This convention was continued in the coding for the model on $\mathbb{P}_{a_k,b_k}$, making the model computationally discrete. Consequently, the results for $N(t)$ on the time scale $\mathbb{N}_{a_k,b_k,r_k}$ are identical to the results for $N(t)$ as defined on the time scale $\mathbb{P}_{a_k,b_k}$. In particular, $g=\gamma-1$.

Next we consider the fractional difference of $N(t)$ for $\nu\in(0,1)$. For $t\in F_k+\{1-\nu\}$ and $h_k=1$, by Theorem 4 we have

$$\begin{aligned}{}_{h_k}\Delta_{r_k}^{\nu}N(t)&=\frac{1}{\Gamma(-\nu)}\sum_{s=r_k}^{t+\nu}\left[\frac{\Gamma(t-s)}{\Gamma(t-s+\nu+1)}\right]N(s)\\&=\frac{1}{\Gamma(-\nu)}\sum_{s=0}^{m+1}\left[\frac{\Gamma(1-\nu+m-s)}{\Gamma(1+m-s+1)}\right]N(s+r_k).\end{aligned}$$

For $\nu \in (0,1)$, $t \in f_k + \{(1-\nu)h_k\}$, and $h_k = \mu_k$, by Theorem 5 we have

$$
\begin{aligned}
{}_{h_k}\Delta^{\nu}_{r_k} N(t) &= \Delta^{\nu}_{\tilde{r}_k} f(\rho(t)) + \Delta^{1}\left[\frac{h_k^{(1-\nu)}}{\Gamma(1-\nu)} \sum_{\substack{s=r_k \\ \text{by } h_k}}^{t-(1-\nu)h_k} \left[\frac{\Gamma\left(\frac{t-s-h_k}{h_k}+1\right)}{\Gamma\left(\frac{t-s-h_k}{h_k}-1+\nu+2\right)}\right] N(s)\right] \\
&= \Delta^{\nu}_{\tilde{r}_k} f(\rho(t)) + \Delta^{1}\left[\frac{h_k^{(1-\nu)}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } h_k}}^{m} \left[\frac{\Gamma\left(\frac{m-\nu h_k-s}{h_k}+1\right)}{\Gamma\left(\frac{m-\nu h_k-s}{h_k}+\nu+1\right)}\right] N(s+r_k)\right] \\
&= \Delta^{\nu}_{\tilde{r}_k} f(\rho(t)) + \Delta^{1}\left[\frac{\mu_k^{(1-\nu)}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } \mu_k}}^{m} \left[\frac{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+1\right)}{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+\nu+1\right)}\right] N(s+r_k)\right] \\
&= \Delta^{\nu}_{\tilde{r}_k} f(\rho(t)) + \frac{1}{\mu_k}\frac{\mu_k^{(1-\nu)}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } \mu_k}}^{m+\mu_k} \left[\frac{\Gamma\left(\frac{m+\mu_k-\nu\mu_k-s}{\mu_k}+1\right)}{\Gamma\left(\frac{m+\mu_k-\nu\mu_k-s}{\mu_k}+\nu+1\right)}\right] N(s+r_k) \qquad (5) \\
&\quad - \frac{1}{\mu_k}\frac{\mu_k^{(1-\nu)}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } \mu_k}}^{m} \left[\frac{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+1\right)}{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+\nu+1\right)}\right] N(s+r_k) \\
&= \Delta^{\nu}_{\tilde{r}_k} f(\rho(t)) + \frac{\mu_k^{-\nu}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } \mu_k}}^{m+\mu_k} \left[\frac{\Gamma\left(\frac{m+(1-\nu)\mu_k-s}{\mu_k}+1\right)}{\Gamma\left(\frac{m+(1-\nu)\mu_k-s}{\mu_k}+\nu+1\right)}\right] N(s+r_k) \\
&\quad - \frac{\mu_k^{-\nu}}{\Gamma(1-\nu)} \sum_{\substack{s=0 \\ \text{by } \mu_k}}^{m} \left[\frac{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+1\right)}{\Gamma\left(\frac{m-\nu\mu_k-s}{\mu_k}+\nu+1\right)}\right] N(s+r_k). \qquad (6)
\end{aligned}
$$

In (5) we have applied Theorem 1, where $\sigma(t) = t + \mu_k$, and we have repeated calculation (4), replacing t with $t + \mu_k$ and performing an identical shift. Since PSA levels can never be negative, we take the absolute value in each case. For this application $r_k = 0$ for all $k \in \mathbb{N}_0$. We are now ready to analyze the fractional difference of $N(t)$ for values of $\nu \in [0,1)$.

5.3.2 Results

We examine the fractional difference of $N(t)$ for $\nu = 0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5,\ 0.6,\ 0.7,\ 0.8,\ 0.9$ for each of the 12 patients. Table 4 shows the average AICc and BIC across the 12 patients for the various values of ν. In terms of the average AICc, the fractional difference of $N(t)$ for $\nu = 0.7,\ 0.8,\ 0.9$ provides an improved fit from $N(t)$ $(\nu = 0)$ on $\mathbb{N}_{a_k,b_k,r_k}$. Similarly, with respect to the average BIC, the fit is improved for $\nu = 0.6,\ 0.7,\ 0.8,\ 0.9$.

Table 4: Average Value of AICc and BIC for Various Values of ν

Value of ν	Average AICc	Average BIC
0	180.406	179.763
0.1	222.885	222.242
0.2	207.661	207.018
0.3	196.573	195.930
0.4	187.153	186.510
0.5	182.053	181.410
0.6	180.077	179.434
0.7	179.558	178.915
0.8	179.638	178.995
0.9	179.911	179.268

We see very little change in the PSA level between the final off-treatment month of the first off-treatment cycle and the month prior for the majority patients. This is less prevalent for smaller values of ν. In general, the smaller ν is, the larger the change in PSA levels between these two months. This is because $\frac{1}{\Gamma(1-\nu)}$ is much smaller for larger values of ν since $\lim_{\nu\to 1}\Gamma(1-\nu)=\infty$; so Definition 15 yields a small shift in ${}_{h_k}\Delta^{\nu}_{r_k}N(t)$ between the final off-treatment month of the first off-treatment cycle and the month prior. This is less prevalent as the treatment cycles progress because the summations in (6) increase faster than $\frac{1}{\Gamma(1-\nu)}$ decreases.

The following tables provide the SSE, AICc, and BIC for the four best choices of ν for three selected patients. We include the SSE, AICc, and BIC for $N(t)$, that is, the $\nu=0$ case, for comparison. For Patients 100 and 91, the ν-th fractional difference for $\nu=0.6,\ 0.7,\ 0.8,\ 0.9$ provides a better fit than $N(t)$, and $N(t)$ provides a better fit than the ν-th fractional difference for $\nu=0.1,\ 0.2,\ 0.3,\ 0.4,\ 0.5$. For both of these patients, the 0.9-th fractional difference provides the best fit. For Patient 58, the 0.3-th fractional difference provides the best fit. The fractional difference outperforms $N(t)$ for all values of ν tested excluding $\nu=0.1$.

Table 5: Patient 100

ν	SSE	AICc	BIC
0	89.169	144.816	148.427
0.6	86.812	144.013	147.624
0.7	80.917	141.903	145.514
0.8	79.069	141.210	144.821
0.9	78.718	141.076	144.687

Table 6: Patient 91

ν	SSE	AICc	BIC
0	73.984	125.985	123.731
0.6	52.202	117.616	115.361
0.7	43.735	113.369	111.114
0.8	40.637	111.605	109.351
0.9	39.491	110.919	108.664

Table 7: Patient 58

ν	SSE	AICc	BIC
0	201.733	175.913	180.922
0.2	169.010	170.249	175.259
0.3	158.090	168.112	173.122
0.4	171.399	170.698	175.708
0.5	182.273	172.666	177.676

Plots of the three best fitting solutions are provided following the conclusion section.

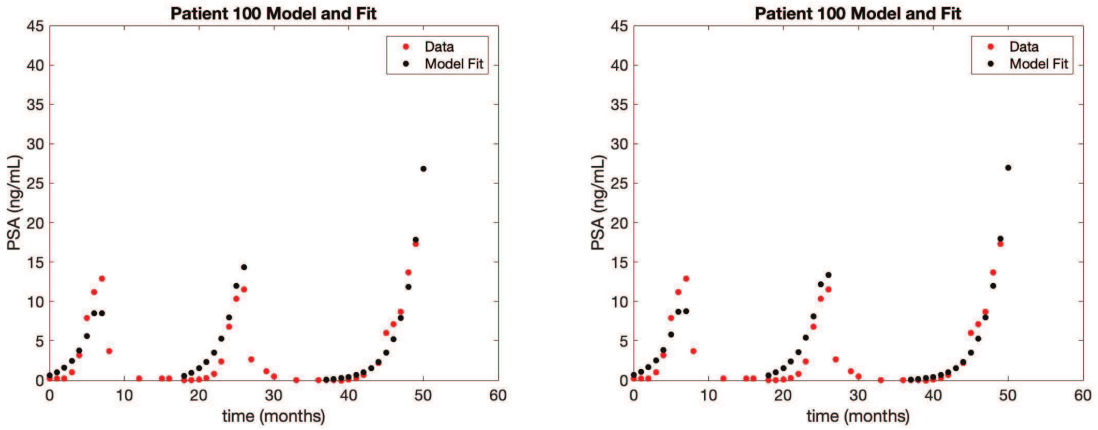
6 Conclusion

In this paper, we refine the novel time scale approach to modeling intermittent androgen deprivation (IAD) therapy introduced in [10] by developing further time scale and discrete fractional calculus theory. In section 3.2, we adjust the assumption made in the novel model construction that the length of both on-treatment and off-treatment intervals do not change over time by constructing a time scale, $\mathbb{P}_{a_k,b_k}$. This time scale allows the length of on-treatment and off-treatment intervals to vary and is thus able to accurately represent intermittent time-data. Additionally, we slightly adjust the β assumption of the novel model that PSA levels decrease by some scale while a patient is on-treatment. For the novel model, the value for β remained constant. For the refined model, the β_k assumption is introduced and allows a unique scale to be used for each k. With these altered assumptions, we construct a model on $\mathbb{P}_{a_k,b_k}$ and provide a brief comparison of the models using two information based criterion, the corrected Akaike's Information Criteria (AICc) and the Bayesian Information Criteria (BIC). The refined model provides a marked improvement in fit.

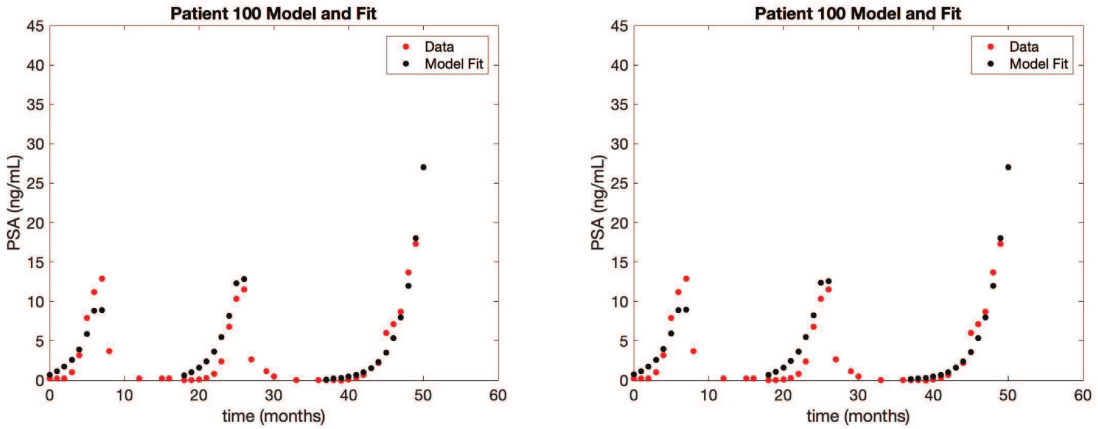
In section 5, we explore fractional difference calculus as a means of further improving the model. We discretize the time scale $\mathbb{P}_{a_k,b_k}$ and construct a model on the new discrete time scale $\mathbb{N}_{a_k,b_k,r_k}$. To the authors' knowledge, at the time of this work, fractional difference theory existed for two sets, $\mathbb{N}_r$ and $\mathbb{N}^h_r$ [11], however, unifying these sets had not been attempted. The goal of Definition 15 and the theorems proven thereafter is to establish this theory. Using this theory, we derive the ν-th fractional difference of $N(t)$. We again use AICc and BIC to compare the models. Overall, in terms of AICc, the fractional difference of $N(t)$ for some value of $\nu\in(0,1)$ provides an improved fit from $N(t)$ ($\nu=0$) on $\mathbb{N}_{a_k,b_k,r_k}$ for 10 of the 12 patients analyzed. With respect to BIC, the fractional difference provides an improved fit for 9 of the 12 patients analyzed. In particular, averaging the values for AICc and BIC across the 12 patients, the fractional difference of $N(t)$ outperforms $N(t)$ ($\nu=0$) on $\mathbb{N}_{a_k,b_k,r_k}$ for $\nu=0.7,\ 0.8,\ 0.9$ (in terms of the average AICc) and for $\nu=0.6,\ 0.7,\ 0.8,\ 0.9$ (in terms of average BIC).

The concepts discussed in this work have potential applications outside of intermittent oncological treatments; these ideas may be applied to any system that involves exponential growth with intermittent changes due to some variable. One example is a fish-harvest model that predicts maximum sustainable yield, which is used to determine when to harvest fish. Fish population grows exponentially and the β assumption could be replaced with some catch limit. Another example is an algae bio-fuel model, where algae is grown and then harvested to be used for fuel. The algae grows exponentially and

the harvest limit would replace the β assumption. In this work, we have used time scale calculus and discrete fractional calculus to develop a new approach to modeling intermittent androgen deprivation therapy. In this process, we unified time scales and discrete fractional calculus in a new and interesting way. We are excited to see not only how this model can potentially improve the modeling of IAD therapy, but also how it can potentially impact the fields of time scale calculus and discrete fractional calculus.

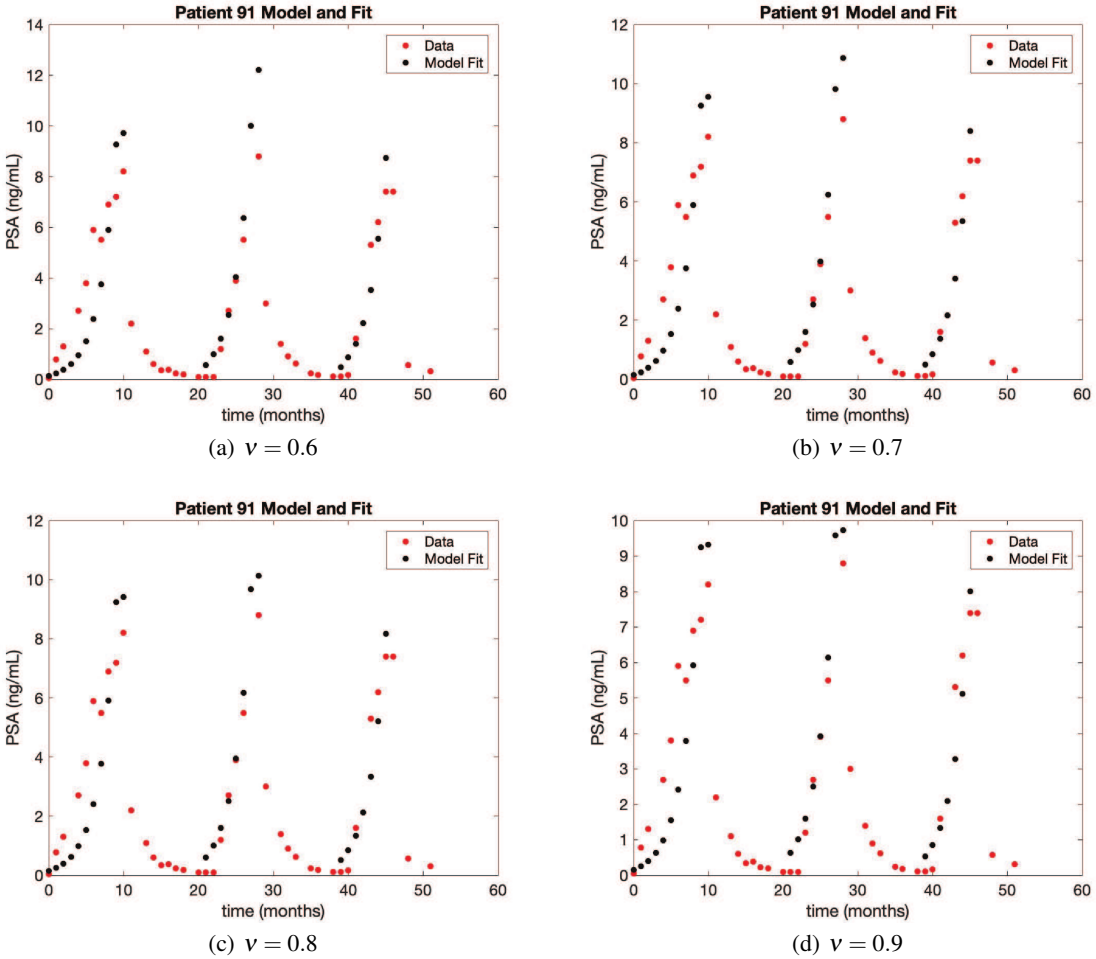


(a) $\nu = 0.6$ (b) $\nu = 0.7$



(c) $\nu = 0.8$ (d) $\nu = 0.9$

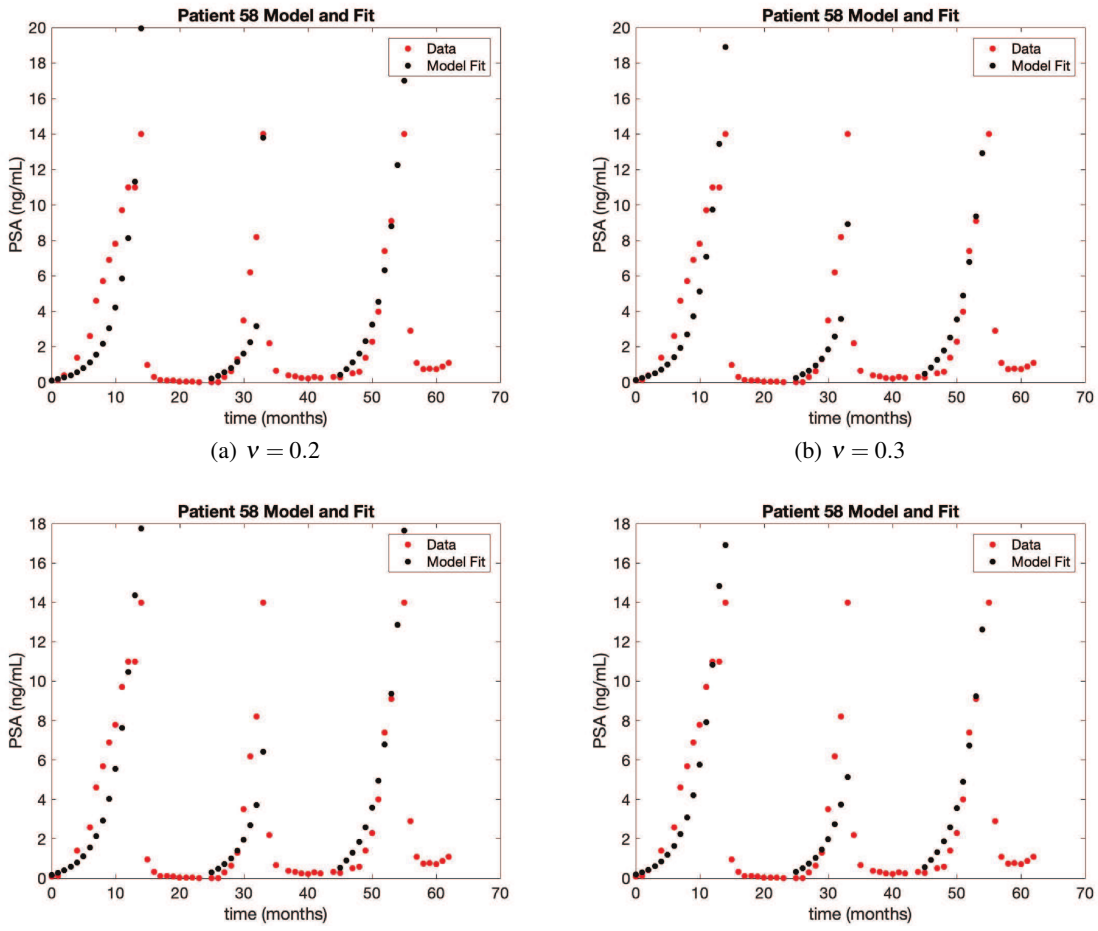
Fig. 4: Plots of the data and fractional differences for Patient 100



(a) $\nu = 0.6$ (b) $\nu = 0.7$

(c) $\nu = 0.8$ (d) $\nu = 0.9$

Fig. 5: Plots of the data and fractional differences for Patient 91



(a) $\nu = 0.2$ (b) $\nu = 0.3$

(c) $\nu = 0.4$ (d) $\nu = 0.5$

Fig. 6: Plots of the data and fractional differences for Patient 58

References

[1] ATICI, FM AND ATICI, M AND HRUSHESKY, WJM AND NGUYEN, N: *Modeling Tumor Volume with Basic Functions of Fractional Calculus.* Progress in Fractional Differentiation and Applications, **1** (2015), 229–241.

[2] ATICI FERHAN M. AND ELOE, PAUL W.: *Fractional q-calculus on a time scale.* Journal of Nonlinear Mathematical Physics, **14(3)** (2007, 333–344.

[3] BOHNER, MARTIN AND PETERSON, ALLAN C., *Dynamic equations on time scales:An introduction with applications*, Birkhäuser Boston, Inc., Boston, MA, 2001.

[4] BRUCHOVSKY N, KLOTZ L, CROOK J, MALONE S, LUDGATE C, MORRIS WJ, GLEAVE ME, GOLDENBERG SL: *Final results of the canadian prospective phase ii trial of intermittent androgen suppression for men212in biochemical recurrence after radiotherapy for locally advanced prostate cancer: clinical parameters.* Cancer, **107 (2)** (2006), 389—395.

[5] EVERETT R, PACKER A, KUANG Y: *Can mathematical models predict the outcomes of prostate cancer patients undergoing intermittent androgen deprivation therapy?* Biophysical Reviews and Letters, **9(02)** (2014), 173—191.

[6] FAILLA, GIUSEPPE AND ZINGALES, MASSIMILIANO.: *Advanced materials modelling via fractional calculus: challenges and perspectives.* Philosophical Transactions of The Royal Society A, **378** 2020.

[7] GLEAVE M, KLOTZ L, TANEJA SS: *The continued debate: intermittent vs. continuous hormonal ablation218for metastatic prostate cancer.* In: Evans CP (ed) Annual Meeting of the Society of Urologic Oncol-219ogy/Society for Basic Urologic Research, Elsevier, DOI doi.org/10.1016/j.urolonc.2008.07.025220, 81—86, 2007.

[8] GOODRICH, CHRISTOPHER AND PETERSON, ALLAN C. *Discrete Fractional Calculus*, Springer, Switzerland, 2015.

[9] HIGGINS, R AND BERGER, H: *The* $\mathbb{N}_0$ *Story: Discrete Fractional Calculus.* Notices of the American Mathematical Society, **69(2)** (2022), 180–189.

[10] HIGGINS R, MILLS CJ, PEACE A: *A time scales approach for modeling intermittent hormone therapy for prostate cancer.* Bulletin of Mathematical Biology, **82(11)** (2020), 1-–16.

[11] HOLM, MICHAEL *The theory of discrete fractional calculus: Development and application*, The University of Nebraska-Lincoln, 2011.

[12] KUANG Y, NAGY JD, EIKENBERRY SE: *Introduction to mathematical oncology, vol 59.* CRC Press, 2016.

[13] LABRIE F: *Blockade of testicular and adrenal androgens in prostate cancer treatment.* Nature Reviews Urology, **8(2):73** (2011).

[14] NELSON PS: *Molecular states underlying androgen receptor activation: a framework for therapeutics targeting androgen signaling in prostate cancer.* Journal of clinical oncology, **30(6)** (2012), 644—646.

[15] PORTZ T, KUANG Y, NAGY JD: *A clinical data validated mathematical model of prostate cancer228growth under intermittent androgen suppression therapy.* AIP Advances, **2(1)** (2012), 011,002.

[16] SAS INSTITUTE I: *Likelihood, AICc, and BIC.* https://www.jmp.com/support/help/en/16.0/index.shtml#page/jmp/likelihood-230aicc-and-bic.shtml, accessed: 2020-12-16.

[17] SHARIFI N, GULLEY JL, DAHUT WL: *Androgen deprivation therapy for prostate cancer.* Jama, **294(2)** (2005), 238—244.

[18] SIEGEL R, D NAISHADHAM D, A J: *Cancer statistics.* A cancer Journal of Clinicians, **63(1)** (2013), 11-–30, DOI 10.3322/caac.21166.