

# Modeling the tumor growth with the theory of discrete fractional calculus

Modelando un tumor con la teoría de cálculo fraccionario discreto

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## ABSTRACT

In this paper we describe the basics of modeling the growth of cancerous tumors, based on the formalism of the calculation of fractional order differences. Version is used in the Gompertz equation of differences, a simulation with arbitrary values of the growth rates of decline and the initial value.

## RESUMEN

En este artículo se describen los fundamentos de modelado de crecimiento de tumores cancerosos, basado en el formalismo del cálculo en diferencias de orden fraccionario. Es empleada la versión de la ecuación de Gompertz en diferencias, una simulación con valores arbitrarios de tasas de crecimiento, decrecimiento y valor inicial.

## INTRODUCTION

Cancer is a leading cause of death worldwide, accounting for nearly eight million deaths per year. Experts predict that deaths will continue rising (globally), with an estimated nine million people dying from cancer in 2015 and 11.4 million succumbing in 2030. Thus, cancer poses major public health questions.

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. Not all tumors are cancerous, as tumors can be benign or malignant. Benign tumors usually have a controlled growth and do not present metastasis (spread to other parts of the organism), they can often be surgically removed and in most cases they do not come back. Malignant tumors, on the other hand, aggressively expand and present 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 crucial. Understanding the kinetics of tumor growth enables physicians to determine the best treatment available.

Although the kinetics of cancer are usually very complex depending on many details such as the type, location and stage of the cancer, over the

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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 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.

### Mathematical Models

An ideal mathematical model for a real world situation should satisfy several criteria:

- the model should have a basis in reality;
- the model should have a minimum number of parameters;
- variables represented in the model should be measurable so to make it possible to collect experimental data;
- the model's predictions should be reasonably accurate and be a good fit to experimental data, and
- the model should improve our understanding of the real world situation.

### Model of tumor growth

In the case of tumor growth, the model should have a physiological basis. In addition, it should improve general understanding at microscopic as well as macroscopic level of tumor growth, and it should have breadth, in the sense that it should be applicable to different patients or animals with the same type of tumor.

The size of a dynamically changing entity (be it a single cell, tumor, urban population or economy) depends on a rate of increase and a rate of loss. In Biology, terms such as proliferation and synthesis indicate growth. Words like death or degradation describe loss. Ludwig von Bertalanffy (Marušić, 1996) proposed a general form for such models

$$\frac{dy}{dt} = ay^\alpha + by^\beta,$$

where  $y$  is a measure of the size of the organism and  $a$ ,  $b$ ,  $\alpha$  and  $\beta$  are constants. This equation is called a generalized Bertalanffy model with parameters  $\alpha$  and  $\beta$ .

The solution to the equation is

$$\frac{dV}{dt} = aV^\alpha - bV^\beta.$$

The special case  $\alpha = 1$ ,  $\beta = 2$  gives the logistic equation

$$\frac{dV}{dt} = aV - bV^2, \quad V(0) = V_0.$$

The solution is

$$V(t) = \frac{aV_0}{bV_0 + e^{-at}(a - bV_0)} = \frac{a}{b} \left[ 1 - \left( 1 - \frac{a}{bV_0} \right) e^{-at} \right]^{-1},$$

$$\frac{dV}{dt} = aV^\alpha - bV^\alpha \ln V.$$

In the special case  $\alpha = 1$ , we have

$$\frac{dV}{dt} = aV - bV \ln V, \quad V(0) = V_0.$$

The solution we have is

$$V(t) = e^{\frac{a}{b} \left( \frac{a}{b} - \ln V_0 \right) e^{-bt}}.$$

### Brief introduction to discrete fractional calculus

Notice that there is some similarity between the properties (Diaz & Osler, 1974; Kelley & Peterson, 2001).

$$D = \frac{d}{dx} \leftrightarrow \Delta f(x) = f(x+1) - f(x),$$

$$D^\alpha = \frac{d^\alpha}{dx^\alpha} \leftrightarrow \Delta^\alpha f(x) = \sum_{k=0}^{\infty} (-1)^k c_k^\alpha f(x + \alpha - k),$$

$$c_k^\alpha = \frac{\Gamma(\alpha + 1)}{\Gamma(\alpha - k + 1)k!}$$

where  $\alpha$  is any real or complex number.

Miller and Ross (Atici & Sevgi, 2010) defined operators

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

where  $\sigma(s) = s + 1$

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

where  $t \equiv \alpha \pmod{1}$  and  $0 < \alpha < 1$ .

Anastassion (Sevgi, 2010) defined the Caputo like discrete fractional difference as

$$\begin{aligned} \Delta^\alpha f(t) &= \Delta^{-(m-n)} \Delta^m f(t) = \\ &= \frac{1}{\Gamma(m-\alpha)} \sum_{s=a}^{t-m+\alpha} (t-\sigma(s))^{(m-\alpha-1)} \Delta^m f(s). \end{aligned}$$

• Definition 1. The falling factorial  $t^{(n)}$  is defined as

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

for any  $n \geq 0$ .

### The summation by parts formula

Let  $f$  and  $g$  be real valued functions, then

$$\begin{aligned} \Delta(f(t)g(t)) &= g(t)\Delta f(t) + f(\sigma(t))\Delta g(t) \\ &= g(\sigma(t))\Delta f(t) + f(t)\Delta g(t), \end{aligned}$$

where  $\sigma(t) = t+1$ .

From this equation, 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

$$\begin{aligned} \sum_{t=1}^{b-1} (g(t)\Delta f(t)) &= \sum_{t=1}^{b-1} \Delta(f(t)g(t)) - \sum_{t=1}^{b-1} (f(\sigma(t))\Delta g(t)), \\ \sum_{t=1}^{b-1} g(t)\Delta f(t) &= f(t)g(t) \Big|_1^b - \sum_{t=1}^{b-1} f(\sigma(t))\Delta g(t), \end{aligned}$$

where  $b > 1$  is an iterger.

### Some results of discrete fractional calculus

• Theorem 1. Let  $f$  be a real valued function, and let  $\mu, \alpha > 0$ . Then for all  $t$  such that  $t = \mu + \alpha, \pmod{1}$ ,

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

• Lemma. Let  $\mu \neq -1$  and assume  $\mu + \alpha = 1$  is not a non-positive interger. Then

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

• Theorem 2. For any  $\alpha > 0$ , then

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

where  $f$  is defined on  $N_a$ .

### Gompertz fractional difference equation

The Gompertz difference equation is given by

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

where  $a$  is the growth rate and  $b$  is the exponential rate of growth deceleration in the equation.

The Gompertz fractional difference equation is

$$\Delta^\alpha G(t-\alpha+1) = (b-1) \ln G(t) + \alpha.$$

Where replce

$$\ln G(t) = y(t),$$

and thus

$$\Delta^\alpha y(t-\alpha+1) = (b-1)y(t) + \alpha.$$

### The solution of the Gompertz equation

Consider the Gompertz equation with initial condition

$$\Delta^\alpha y(t-\alpha+1) = (b-1)y(t) + \alpha, \quad t = 0, 1, \dots$$

$$y(0) = c$$

where  $\alpha \in [0, 1]$ .

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

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

where  $t = 1, 2, \dots$

Applying Theorema 2 to this equation, and the result is

$$\begin{aligned} \Delta^{-\alpha} \Delta^\alpha y(t) &= \Delta^{-\alpha} \Delta \Delta^{-(1-\alpha)} y(t) = \Delta \Delta^{-\alpha} \Delta^{-(1-\alpha)} y(t) \\ &= \frac{(t + \alpha - 1)^{(\alpha-1)} y(0)}{\Gamma(\alpha)}. \end{aligned}$$

Hence we have

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

We employ the method of successive approximations, and thus we have

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

If  $\alpha = 1$

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

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