

An Application of Z-transform in Pharmacokinetics

Mostafa Ghandehari^{1*}, Fred Kashefi²

¹Civil Engineering Dept University of Texas at Arlington Box 19305, Arlington, Texas 76019

²Computer Science and Engineering Dept., Box 19015 University of Texas at Arlington Arlington, Texas 76019

Original Research Article

*Corresponding author

Mostafa Ghandehari

Article History

Received: 16.02.2018

Accepted: 24.02.2018

Published: 30.03.2018

DOI:

10.21276/sjeat.2018.3.3.6



Abstract: Discrete Z transform is used to solve difference equations in pharmacokinetics for constant dosage with fixed time intervals. Difference equation for half dosage and fractional dosage are analyzed. Clinical application is proposed.

Keywords: Discrete Z transform, pharmacokinetics, dosage.

INTRODUCTION

Pharmacokinetics deals with study and characterization of drug absorption, distribution and elimination as a function of time. For a study of basic definitions in pharmacokinetics we refer the reader to textbooks by Bauer [1], Gibaldi [3], Shargel [8], and winter [9]. We will review required definitions as they are needed.

Concentration of a drug $c(t)$ as a function of time is important in pharmacokinetics. Using first order kinetic for one-compartmental model the concentration is given by

$$c(t) = \frac{D}{V} e^{-kt} \quad (1)$$

Where D denotes the dosage, V is the apparent volume of distribution and k is called elimination rate. For initial concentration of c_0 we have the formula

$$c(t) = c_0 e^{-kt} \quad (2)$$

For constant dosage regiment we obtain the difference equation

$$c_{n+1} = c_n e^{-kT} + c_0 \quad (3)$$

Where T fixed time interval and constant dosage of c_0 is added at each interval. In the above c_n denotes concentration at time- nT .

Variable dosage regimens can be used in clinical circumstances. For example in a mental health circumstances through counselling, education and therapeutic techniques, the client may learn to deal with stressful life situation better and gradually need less medication.

If we denote β the rate of decrease of concentration at each time interval, we obtain the difference equation

$$c_{n+1} = c_n e^{-kT} + c_0 \beta^n \quad (4)$$

If $\beta > 1$ then the rate is increased. If $\beta < 1$ the dosage is decreased. We can also subtract a fixed concentration D at each time interval. In this case the corresponding difference equation is given by

$$c_{n+1} = c_n e^{-kT} + (c_0 - nD) \quad (5)$$

In section 2 we discuss z-transform which is a useful mathematical technique to analyze difference equations. In section 3 we use z-transform to derive formulas for pharmacokinetic difference equations (3), (4), and (5). Conclusions and clinical applications are given in section 4.

Z-Transform: The Z-transform for a sequence $s(n)$ is given by

$$X(s(n)) = \sum_{n=-\infty}^{\infty} s(n) z^{-n} \tag{6}$$

A discussion of Z-transform and its properties can be found in any signal processing textbook, such as, Richard A. Haddad and Thomas W. Parsons [5], or John G. Proakis and Dimitris G. Manolakis [7], or Alan V. Oppenheim and Ronald W. Schafer [6].

The shifting property of Z-transform for delay signal $s(n - k)$ is given by

$$X(s(n - k)) = z^{-k} \times (s(n)) \tag{7}$$

The convolution of the two signals and $s_1(n)$ and $s_2(n)$ is given by

$$s_1(n) * s_2(n) = \sum_{k=-\infty}^{\infty} s_1(n - k) s_2(k) \tag{8}$$

An important property of the Z-transform is the convolution property i.e., the Z-transform of the convolution is equal to the product of individual transforms, namely,

$$X(s_1(n) * s_2(n)) = X(s_1(n)) * X(s_2(n)) \tag{9}$$

The discrete unit step-function is given by

$$u(n) = \begin{cases} 1 & \text{if } n \geq 0 \\ 0 & \text{if } n < 0 \end{cases}$$

If a signal $s(n)$ is defined for $n \geq 0$, we can extend the definition for all integers by multiplying $s(n)$ by $u(n)$.

The inverse Z-transform can be obtained by complex contour integration.

$$s(n) = \frac{1}{2\pi i} \oint X(s(n)) \cdot z^{n-1} dz$$

For a review of complex variables and contour integration see Brown and Churchill [2].

Analysis of difference equations

We use shifting property (7) to take the Z-transform of both sides of (3). Lets $\alpha = e^{-kT}$

$$X(c_{n+1}) = \alpha X(c_n) + c_0 X(1)$$

We obtain

$$z X(z) - z c_0 = \alpha X(z) + c_0 \frac{1}{1 - z^{-1}}$$

Then

$$(z - \alpha) X(z) = c_0 z + c_0 \frac{z}{z - 1}$$

Then

$$X(z) = c_0 \frac{z}{(z - \alpha)} + c_0 \frac{z}{(z - \alpha)(z - 1)}$$

Use partial fractions to obtain

$$X(z) = c_0 \left(\frac{1}{1 - \frac{\alpha}{z}} \right) - c_0 \frac{1}{1 - \alpha} \cdot \frac{1}{1 - \frac{\alpha}{z}} + c_0 \frac{1}{1 - \alpha} \cdot \frac{1}{1 - \frac{1}{z}}$$

Now use table of Z-transform and Cauchy integral formula,

$$\begin{aligned} c_n &= c_0 \alpha^n - c_0 \frac{1}{1 - \alpha} \cdot \alpha^n + c_0 \frac{1}{1 - \alpha} \\ &= c_0 \left[\frac{\alpha^n - \alpha^{n+1} - \alpha^n + 1}{1 - \alpha} \right] = c_0 \left[\frac{1 - \alpha^{n+1}}{1 - \alpha} \right] \end{aligned}$$

The solution of difference equation (3) is given by

$$c_n = c_0 \left[\frac{1 - e^{-k(n+1)T}}{1 - e^{-kT}} \right] \tag{10}$$

In section 4 we give pharmacokinetic use of equation (10).

Next, we discuss solution of difference equation (4). Take Z-transform of both sides of the equation

$$X(c_{n+1}) = \alpha X(c_n) + c_0 \frac{1}{1 - \frac{\beta}{z}}$$

Use shifting theorem to obtain

$$z X(z) - z c_0 = \alpha X(z) + c_0 \frac{1}{1 - \frac{\beta}{z}}$$

$$(z - \alpha) X(z) = c_0 z + c_0 \frac{1}{1 - \frac{\beta}{z}}$$

$$X(z) = c_0 \frac{z}{(z - \alpha)} + c_0 \frac{z}{(z - \alpha)(z - \beta)}$$

Use partial fraction to obtain

$$X(z) = c_0 \frac{1}{1 - \frac{\alpha}{z}} + c_0 \frac{1}{\alpha - \beta} \cdot \frac{1}{1 - \frac{\alpha}{z}} + c_0 \frac{1}{\beta - \alpha} \cdot \frac{1}{1 - \frac{\beta}{z}}$$

Then use Cauchy integral formula and table of z-transform to derive

$$c_n = c_0 \alpha^n - c_0 \frac{\alpha}{\alpha - \beta} \cdot \alpha^{n-1} + c_0 \frac{\beta}{\beta - \alpha} \cdot \beta^{n-1}$$

Simplify the algebra to obtain c_n . Also use $\alpha = e^{-kT}$

$$c_n = \frac{c_0 [(\beta - 1) e^{-k n T} - e^{-(n+1)k T} + \beta^n]}{\beta - \alpha} \tag{11}$$

Note that if $\beta = 1$ we can obtain equation (10). In section 4 we use (11) to discuss half and fractional dosing regimen.

Now, we take Z-transform to analyze equation (5).

$$z X(z) - z c_0 = \alpha X(z) + c_0 \frac{1}{1 - z^{-1}} + Dz \frac{dX}{dz} \tag{12}$$

Where we have used the fact that

$$X(na_n) = -z \frac{dX}{dz}$$

Simplifying algebra in equation (12) to obtain the first order linear differential equation

$$\frac{dX}{dz} + \frac{\alpha - z}{Dz} X(z) = \frac{c_0 z}{D(1 - z)} \tag{13}$$

It is possible to use difference equation (5) to directly show

$$c_n = c_0 \left(\frac{1 - \alpha^{n+1}}{1 - \alpha} \right) - D \alpha^{-(n+1)} \frac{1 - (n+1)\alpha^n + n\alpha^{n+1}}{(1 - \alpha)^2}$$

Let $\alpha = e^{-kT}$, then

$$c_n = c_0 \left(\frac{1 - e^{-(n+1)kT}}{1 - e^{-kT}} \right) - D \alpha^{-(n+1)kT} \frac{1 - (n+1)e^{-nkT} + ne^{-(n+1)kT}}{(1 - e^{-kT})^2} \tag{14}$$

For derivation of (14) use Ghandehari and Holyk [4]. Also by solving the differential equation (13) and taking inverse Z-transform a derivation of (14) can be obtained. In the next section we discuss implications of (10), (11) and (14) in a pharmacokinetics clinical setting.

Applications in pharmacokinetics

Equation (10) for constant dosage regimen can be used in two ways. First, direct calculation can be used to find concentration of medication at each time. If the certain amount of dosage is desired, then the value of c_0 can be adjusted so that minimum concentration is attained at each time interval. Also using algebra the value of n can be calculated so that the number of times the dosage is given is determined. If we use (10) and replace $(n + 1)$ by n , the algebra gives

$$1 - e^{-nkT} = \left(1 - e^{-kT}\right) \frac{c_n}{c_0}$$

Then
$$nkT = -\ln \left[1 - \left(1 - e^{-kT}\right) \frac{c_n}{c_0} \right]$$

Then,
$$n = \frac{-\ln \left[1 - \left(1 - e^{-kT}\right) \frac{c_n}{c_0} \right]}{kT} \tag{15}$$

If T is fixed and c_n is specified, equation (14) gives the number of time the dosage will be given.

If n and c_n are given, it is also possible for T to determine each time interval.

For narcotic patients it is desired to gradually decrease the dosage. Equation (11) can be used to reach the half dosage regimen, which is when the $\beta = \frac{1}{2}$. This can also be achieved when equation (11) is used to decrease concentration C_n by fractional dosage. For example if we use $\beta = 0.9$, the drug decrease adjustment will be moderate for the patient. Similarly analysis of equation (14), will help to decide the pharmacokinetics parameter (time interval, initial dosage, amount of decrease each time).

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