



Application of ACP Nonlinear Math in Analyzing Toxicokinetic and Pharmacokinetic Data (Application 5 and 6)

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Abstract

Analyses of toxicokinetic and pharmacokinetic are demonstrated using the ACP (asymptotic curve based and proportionality oriented) Alpha Beta ($\alpha\beta$) Nonlinear Math. In the new nonlinear concepts, various skewed-bell elementary “y” data are collected, followed by analyzing the asymptotic cumulative Y curves. In using the concise data, the asymptotic cumulative-numbers are emphasized and shun the use of unrelated elementary-numbers. The kinetic results are expressed as equations and straight lines in the proportionality graphs, where the change of the response β (Y, Yu, Yb) is proportional to the change of the time or dose α (X, Xu, Xb) and assuming the mathematical form $d\alpha = Kd\beta$. The K is the proportionality constant or the kinetic constant. The baseline asymptote Yb is mostly a nonlinear zero thus no need of calculation, but the upper asymptote Yu can be resolved through guided estimation using the coefficient of determination (COD) and graphical resolution.

Keywords: Asymptotic Concave and Convex Curve; Upper and Baseline Asymptote; Demulative Numbers (Opposite to Cumulative Numbers); Coefficient of Determination (COD); Proportionality and Position Constant; Skewed Bell; Sigmoid Curve; Symbols: $q = \text{Log}$ (Nonlinear Logarithmic); $\alpha\beta$ (Extension of XY); $\phi = (0)$ (Nonlinear Zero); $x =$ Elementary Independent Variable; y or $(y) =$ Elementary Dependent Variable or $y =$ Equation y (inside the graph); $X =$ Cumulative of x , $Y =$ Cumulative of y or (y)

Abbreviations: COD: Coefficient of Determination; $\alpha\beta$: Alpha Beta.

Introduction

In this Article we Introduce a Nonlinear Approach to Kinetics Analysis

In the last five decades, toxicokinetic and pharmacokinetic analyses have predominantly relied on curve fittings and approximations. However, these methods often lack a foundation in physical laws and true nonlinear mathematics. In this article, we propose a novel nonlinear concept for expressing kinetic outcomes. Our approach combines concrete statements with graphical representations and equations.

Specifically, we represent these graphs using straight lines governed by two parameters within a proportionality equation. The sole proportionality constant, denoted as **K**, dictates both the slope and direction of these lines. Remarkably, **K** serves as the only parameter necessary for presentation and comparison. We introduce five fundamental equations within the framework of Alpha Beta ($\alpha\beta$) Asymptotic Nonlinear Math. For illustrative purposes, we select two of these equations to apply in toxicokinetic and pharmacokinetic analyses. Additionally, the original pharmacokinetics graph by Bashar, et al. is provided in Appendix A for comparative analysis [1]. The key features of the Alpha Beta ($\alpha\beta$) math are outlined in Appendix B. This nonlinear approach promises to enhance our understanding of kinetics and streamline parameter estimation, ultimately leading to more robust results.



We Need the Nonlinear Math where the Asymptote is the Key

Many physical phenomena are associated with nonlinear variables where the variables have continuity and are associated with asymptotes such that the two variables can be expressed with an asymptotic concave or convex curve. These concave and convex curves can be expressed with ordinary or second order nonlinear equations having inclusion of asymptotes. Based on the asymptotic curves and their inherited proportionality nature, we can derive various differential and integral equations to express the nonlinear nature of the physical phenomena [2,3].

Four Basic form of Graphs and their Equations

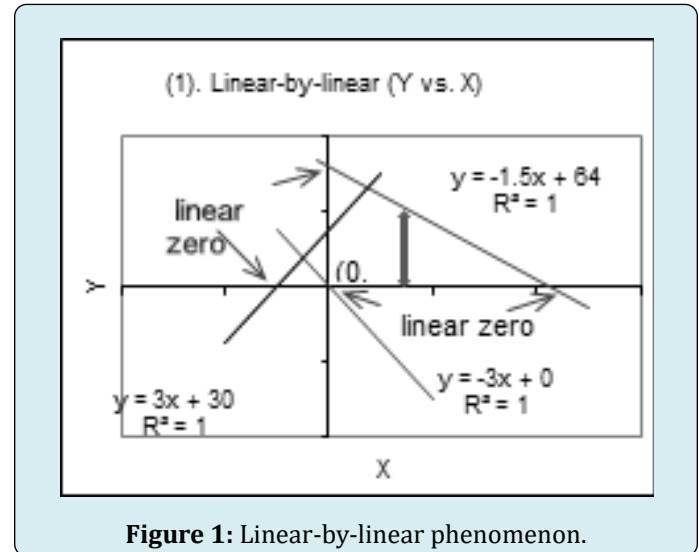


Figure 1: Linear-by-linear phenomenon.

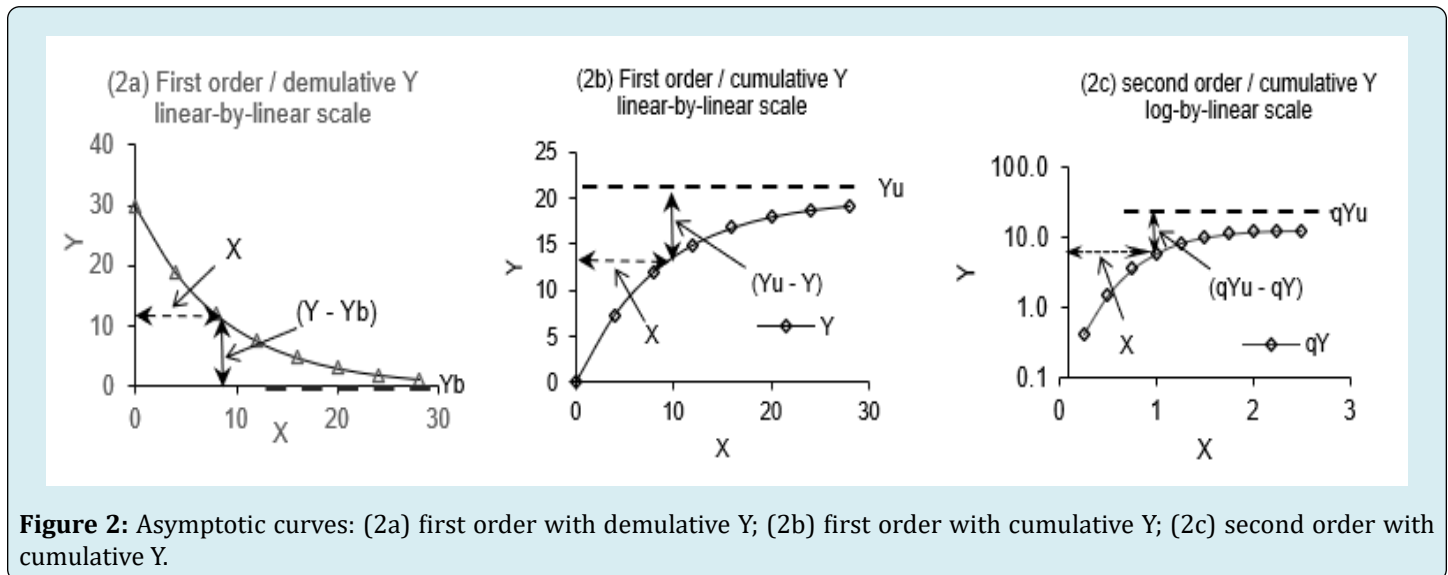


Figure 2: Asymptotic curves: (2a) first order with demulative Y; (2b) first order with cumulative Y; (2c) second order with cumulative Y.

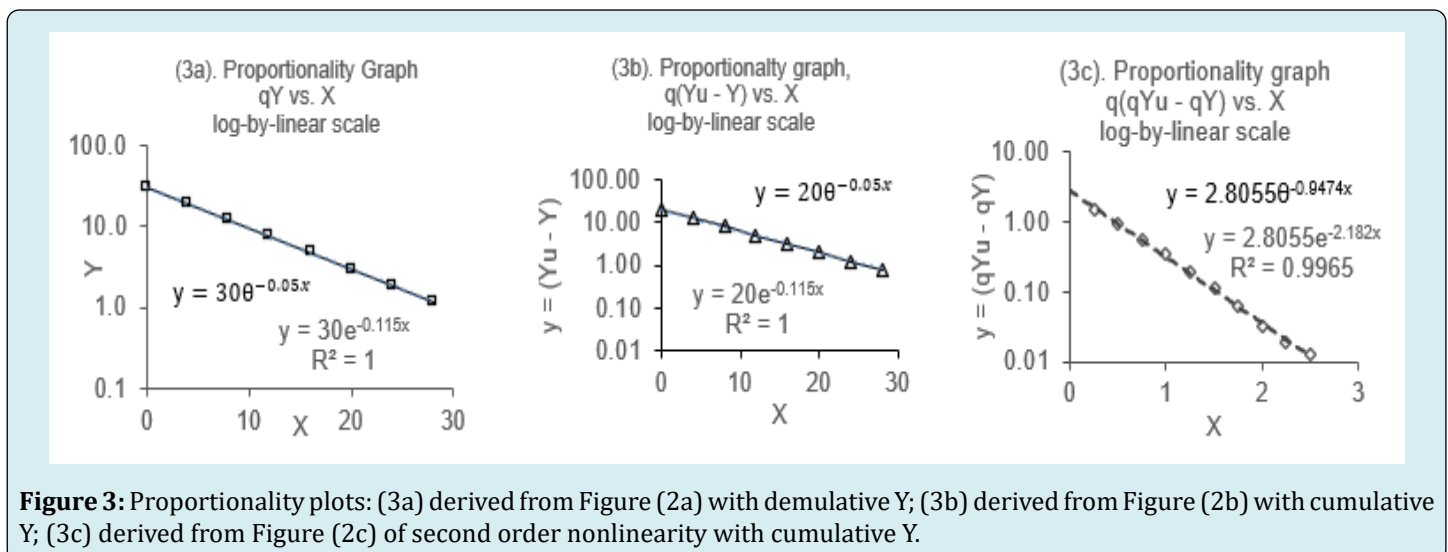


Figure 3: Proportionality plots: (3a) derived from Figure (2a) with demulative Y; (3b) derived from Figure (2b) with cumulative Y; (3c) derived from Figure (2c) of second order nonlinearity with cumulative Y.

Four basic forms of lines in the Alpha Beta ($\alpha\beta$) math are given in Figure 1 & Figure 3. Their differential and integral equations are given in Table 1. The importance of straight-lines is demonstrated in Figure 1 for the linear-by-linear phenomena and in Figure 3 for the nonlinear-by-linear phenomena. The straight lines in Figure 3 are derived (associated) from the nonlinear concave and convex lines in Figure 2.

For the two variables Y and X, we may have the following three basic situations for comparison: (Group A) the change of linear Y is proportional to the change of linear X, Equation

1; (Group B) the change of nonlinear Y is proportional to the change of linear X, Equations 2,3 & 4; (Group C) the change of nonlinear Y is proportional to the change of nonlinear X, Equations 5,6 & 7. In terms of the Y variable, Equations 2,3 & 5,6 are the first order nonlinear equations bearing a single "q"; Equations 4 & 7 are the second order nonlinear equations bearing two "q" in the equation. In Equation 4, the change of nonlinear Y of a second order of nonlinearity is proportional to the change of linear X; In Equation 7, the change of nonlinear Y of a second order of nonlinearity is proportional to the change of nonlinear X. In this article, we will discuss Equations 3 & 7.

Group	Eq. ()	Differential Equation	Eq. ()	Integral Equation	Asymptote in Y
A	1	$dY = -KdX$	1a	$Y = -KX + C$	0
B1(/Yb)	2	$d(q(Y - Yb)) = -KdX$	2a	$q(Y - Yb) = -KX + qC$	1 (single Yb)
B2(/Yu)	3	$d(q(Yu - Y)) = -KdX$	3a	$q(Yu - Y) = -KX + qC$	2 (one Yb hiding)
	4	$d(q(qYu - qY)) = -KdX$	4a	$q(qYu - qY) = -KX + qC$	2 (one Yb hiding)
C	5	$d(q(Y - Yb)) = -Kd(q(X - Xb))$	5a	$q(Y - Yb) = -K(q(X - Xb)) + qC$	1 (single Yb)
	6	$d(q(Yu - Y)) = -Kd(q(X - Xb))$	6a	$q(Yu - Y) = -Kq(X - Xb) + qC$	2 (one Yb hiding)
	7	$d(q(qYu - qY)) = -Kd(q(X - Xb))$	7a	$q(qYu - qY) = -K(q(X - Xb)) + qC$	2 (one Yb hiding)

Table 1: Basic differential and integral equations.

Note: the above equations have two parameters K and C; when $C = 1$, $qC = q1 = 0$; Independent variable be either dX or $d(q(X - Xb))$.

The above differential equations have a characteristic proportionality constant K, while the integral equations have an additional integral constant C for dictating the position of the straight-line in the graph, thus, we also call the C as a position constant, as will be shown in the next.

Graphs and Equations in Linear-by-Linear Cases (Equation 1)

Equations 1 & 1a describe the general linear-by-linear phenomena, where the change of linear Y is proportional to the change of linear X, as shown in Figure 1. The three straight lines indicate the change of Y is proportional to the change of X i.e., Equation 1 and have two parameters K and C in its integral equation Equation 1a. The three K (-1.5, -3, and 3) give the directions and slopes of the straight lines, and the three C (64, 0, and 30) give the position of the straight lines. All three lines can extend continuously forever in two directions and all pass through linear zero.

Graphs and Equations in Nonlinear-by-Linear Cases (Equations 2,3 & 4).

Figure 3 gives three proportionality plots and Figure 2 gives their corresponding asymptotic curves for Equations 2,3 & 4. For Equations 2 & 2a, the asymptotic curve and its corresponding proportionality plot are shown as Figures

2a & 3a. For Equations 3 & 3a, the asymptotic curve and its corresponding proportionality plot are shown as Figures 2b & 3b. For Equations 4 & 4a, the asymptotic curve and its corresponding proportionality plot are shown as Figures 2c & 3c.

In Figure 2, the solid double arrows are a measurement of face values relative to the upper and baseline asymptotes Yu or Yb. The dashed double arrows are measurement of face values $(X - Xb)$ or linear X. The relationship between the solid and dashed arrows is that as the solid arrow increases the dashed arrow decreases, or vice versa. In differential equation forms, it is the nonlinear change of $(Y - Yb)$ is negatively proportional to the linear change of X, i.e., Equation 2; the nonlinear change of $(Yu - Y)$ is negatively proportional to the linear change of X, i.e., Equation 3; and the nonlinear change of $(qYu - qY)$ is negatively proportional to the linear change of X, i.e., Equation 4.

Graphs and Equations in Nonlinear-by-Nonlinear Cases (Equations 5,6 & 7).

Graphs and equations for Equations 5,6 & 7 are like those of Equations 3,4 thus, for simplicity, we will not repeat their descriptions, but we will discuss Equation 7 in detail in Section 6.

Principle for Identification of Upper Asymptotes Yu in (Equations 3,4 & 6,7).

A convex asymptotic curve is always associated with a unique upper asymptote. In analyses we may not necessarily get that unique asymptote but can use guided estimation to identify an optimal asymptote based on the last value of Y data. In practice, we use the last Y (the largest acquired number) value as base to generate 7 - 8 estimated Yu, as shown in

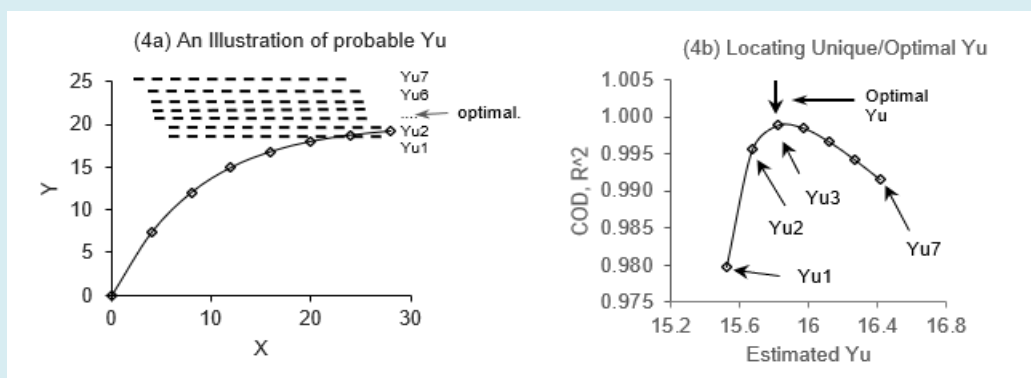


Figure 4: (4a) An illustration for assigning estimated Yu, and (4b) Locating unique Yu with estimated Yu vs. COD (R²).

Example in Arsenic Toxicokinetic

A 2-year-old child was given arsenic-containing water (from arsenical weedkiller) at a cookout party by accident. Subsequently he was sent to a hospital for emergency chelating treatment to remove arsenic as organic complex. The first day and 6th day urine samples were collected for 8 and 18 hours only; the rest are collected for 24 hours each day; after 13 days spot samples were collected at 17, 24, and 38 days. We will demonstrate data analysis using 8 days' data.

Table 2A gives the basic excretion data where cumulative time X in hours, sample weight "y" in mgs, and cumulative weight Y in mgs are given in Column B, E, and F. Column G (G3:G10) is for the calculation of nonlinear face value (Yu - Y) using the Active Estimated Yu in Cell G12, e.g., 15.82, the formula for Cell G3 is " $=\$G\$12-F3$ ", i.e., $15.82 - 0.9 = 14.92$, we can copy Cell G3 to G4 through G 10 to complete the column. Column H (H3:H10) is for the calculation of logarithmic transformation of the face value, i.e., $q(Yu - Y) = \log(Yu - Y)$. In the lower part of the table, Column B(B15:B21) and Column C(C15:D21) are for the generation of Estimated Yu from Yu1 to Yu7. In the guided estimation of Yu, we first select the last Y data in Column F (i.e., Cell F10) as the base, i.e., Yu0 = 15.37 and input into Cell B14. We also select an incremental Yu (ΔYu) at about 1% of Yu0, i.e., 0.15 ; $15.37 \times 0.01 = 0.15$. Then, we generate Yu1 to Yu7 for $\Delta Yu = 0.15$. Formula for Yu1 in Cell B15 is " $=B14 + \$B\12 ", as shown in the Formula bar on top of the Table 2B, it is 15.52. We can copy Cell B15 into Cell B16 through B21 to complete the

Column for the estimated Yu. Column C (C15:C21) is for recording COD (Coefficient of determination) for the given estimated Yu in Column B (B15:B21). Referring to Table 2B, to obtain COD, we input an Active Yu into Active cell G12 and generate COD in Active cell G13. Formula for Cell G13 is " $=CORREL(B3:B10, H3:H10)^2$ ", as shown in the formula bar on the top of Table 2B. We then copy the obtained COD in Cell G13 into corresponding Estimated Yu in Column C (C15:C21). After completing Column C, we locate the maximum COD as 0.998923 (marked in green color).

B15		fx		=B14+\$B\$12			
A	B	C	D	E	F	G	H
Sample collected	Cum. time hrs.	Volume mL	Conc. mg/L	Sample wt. mgs	Cum. wt. mgs	Yu - Y	q(Yu - Y)
x hrs.	X	z	y	Y			
8	8	~300 ^a	3.00	0.9	0.9	14.92	1.17
24	32	1200	4.92	5.9	6.8		
24	56	1700	1.80	3.06	9.86		
24	80	850	3.30	2.64	12.5		
24	104	1575	0.90	1.42	13.92		
18	122	950	0.65	0.62	14.54		
24	146	1450	0.34	0.49	15.03		
24	170	850	0.40	0.34	15.37		
	Δy_u	0.15				Active Yu =	15.82
			R ² for 0.15			R ² =	#DIV/0!
	Yu0 =	15.37					
	Yu1 =	15.52					
	Yu2 =						
	Yu3 =	15.82					
	Yu4 =						
	Yu5 =						
	Yu6 =						
	Yu7 =						

Table 2A: Arsenic data (basic data).

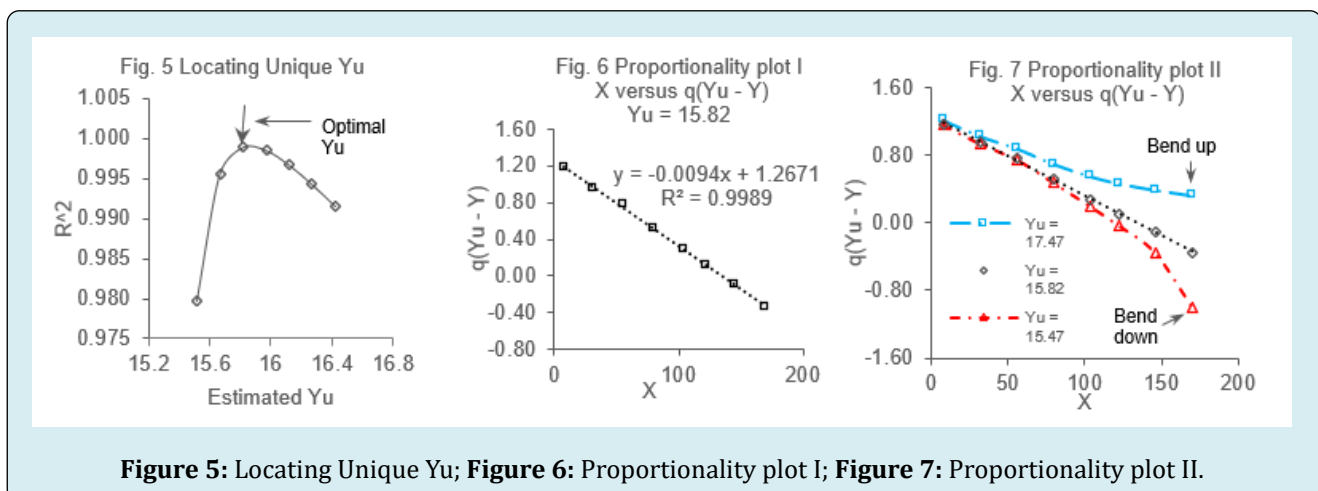
G13 $=CORREL(B3:B10,H3:H10)^2$								
	A	B	C	D	E	F	G	H
1	Sample collected	Cum. time hrs.	Volume	Conc. mg/L	Sample wt. mgs	Cum. wt. mgs	Yu - Y	q(Yu - Y)
2	x, hrs.	X	mL	z	y	Y		
3	8	8	~300*	3.00	0.9	0.9	14.92	1.17
4	24	32	1200	4.92	5.9	6.8	9.02	0.96
5	24	56	1700	1.80	3.06	9.86	5.96	0.78
6	24	80	850	3.30	2.64	12.5	3.32	0.52
7	24	104	1575	0.90	1.42	13.92	1.90	0.28
8	18	122	950	0.65	0.62	14.54	1.28	0.11
9	24	146	1450	0.34	0.49	15.03	0.79	-0.10
10	24	170	850	0.40	0.34	15.37	0.45	-0.35
11								
12	Δy_u	0.15			Active Yu =		15.82	
13			R^2 for 0.15		$R^2 =$		0.998923	
14	Yu0 =	15.37						
15	Yu1 =	15.52	0.979776					
16	Yu2 =	15.67	0.995617					
17	Yu3 =	15.82	0.998923					
18	Yu4 =	15.97	0.998537					
19	Yu5 =	16.12	0.996711					
20	Yu6 =	16.27	0.994265					
21	Yu7 =	16.42	0.991556					

Table 2B: Arsenic data (with active Yu = 15.82).

By plotting Column B (B15:B21) vs. Column C (C15:C21) for Estimated Yu vs. R^2 , we obtain Figure 5, where an arrow is pointing at the optimal Yu. By plotting Column B (B3:B10) vs. Column H (H3:H10) for X vs. $q(Yu - Y)$, we obtain Figure 6 with a straight-line equation $y = -0.0094X + 1.2671$, meaning the proportionality constant K is 0.0094, and the trendline gives $R^2 = 0.9989$.

Now, we have three prong evidence to prove the existence of unique (optimal) upper asymptote. First, in digital data form, referring to Table 2B, we identify the maximum R^2 is at 0.998923 in Column C for the Yu3 at 15.82 in Column B (colored green cells) for $\Delta Yu = 0.15$ case. Yu3 is at the maximum, while Yu1 to Yu2 and Yu4 to Yu7 are smaller. Second, in graphical form, by plotting Column B (B15:B21)

vs. Column C (C15:C21) for Estimated Yu vs. R^2 case, we obtain Figure 5 where an arrow is pointing to the optimal Yu at maximum R^2 . Third, in straight-line expression form, by plotting Column B (B3:B10) vs. Column H (H3:H10) for X vs. $q(Yu - Y)$, we obtain Figure 6 with a straight-line and the trendline gives $R^2 = 0.9989$; meanwhile, let us copy the worksheet of Figure 6 into two new worksheets and in one worksheet input 15.47 ($15.47 < 15.82$) into active cell G12 and in other worksheet input 17.47 ($17.47 > 15.82$) into active Cell G12, we will get a concave upward line for 15.47 case and a convex downward line for 17.47 case. Then, we copy Figures 6 & 7 and insert these two curved lines into Figure 7. As shown in Figure 7, we will get a straight line at optimal Yu, other values of estimated Yu will give strayed curves [4-6].



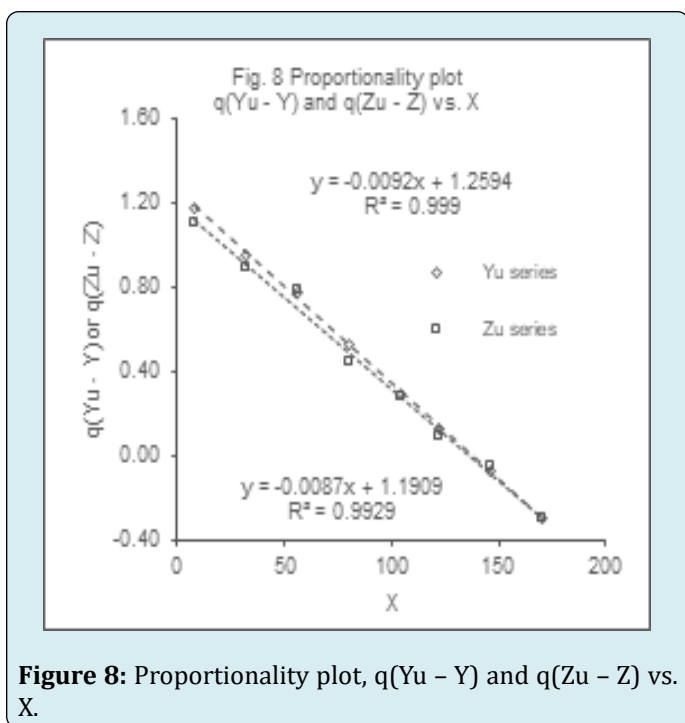


Figure 8: Proportionality plot, $q(Yu - Y)$ and $q(Zu - Z)$ vs. X .

A	B	C	D	E	F	G	H	I	J	K
Sample collected	Cum. time hrs	Volume	Conc. mg/L	Cum. conc. mg/L	Sample wt mgs	Cum. wt mgs	Yu - Y	q(Yu - Y)	Zu - Z	q(Zu - Z)
8	8	~300*	3.00	3	0.9	0.9	14.97	1.18	12.01	1.11
24	32	1200	4.92	7.92	5.3	6.8	9.07	0.96	7.89	0.90
24	56	1700	1.89	9.72	3.06	9.86	6.51	0.78	6.09	0.78
24	80	850	3.30	13.02	2.54	12.5	3.37	0.53	2.79	0.45
24	104	1575	0.99	13.92	1.42	13.92	1.95	0.29	1.89	0.28
18	122	960	0.65	14.57	0.52	14.54	1.33	0.12	1.24	0.09
24	146	1450	0.34	14.91	0.49	15.03	0.34	-0.08	0.90	-0.05
24	170	850	0.49	15.37	0.34	15.37	0.50	-0.30	0.50	-0.30
Totals			15.37	15.37	Zu = 15.31		R ² for 0.1		R ² for 0.1	
Yu0 =	15.47	0.98516	15.57	0.98785	Zu1 =		15.41	0.957409		
Yu1 =	15.67	0.98785	15.77	0.99043	Zu2 =		15.51	0.981759		
Yu2 =	15.87	0.99043	15.87	0.99304	Zu3 =		15.61	0.996835		
Yu3 =	15.97	0.99304	16.17	0.99594	Zu4 =		15.71	0.999544		
Yu4 =	15.87	0.99904	16.37	0.99875	Zu5 =		15.81	0.999924		
Yu5 =	15.97	0.99854	16.57	0.99875	Zu6 =		15.91	0.992155		
Yu6 =	16.07	0.99742	16.77	0.99503	Zu7 =		16.01	0.990781		
Totals			15.37	15.37	Zu =		15.81	0.992924		
R ² =			0.99904	R ² =		0.992924				

Table 2C: Arsenic data (with conc.-based active $Zu = 15.81$).

In ACP nonlinear analyses or any other analysis, it is important to compare one cumulative variable versus another cumulative variable without a need of attachment with physical unit in calculation. This is because we are working on the abstracted numbers in the calculation. As an example, we use weight-based Y to calculate Yu in Tables 2A & 2B, we can also use concentration-based Z to calculate Zu , as shown in Table 2C. Both approaches give similar results, as shown in the proportionality plot Figure 8, where the trendlines equations and R^2 are similar for Yu series and Z series [7].

For overall presentation of the results, we need to present only one table (Table 2B), one graph Figure 6, and one equation parameter ($K = 0.0094$) to represent the entire toxicokinetic system.

Example in Analysis of Prednisolone Pharmacokinetic

In this section, we demonstrate the use of Equations 7 & 7a to analyze the pharmacokinetics data. In a recent publication, Bashar, et al. studied the pharmacokinetics of a prednisolone tablet as a single oral dose in Bangladeshi volunteers [1]. Figure A1 in Appendix A shows the concentration versus time curves for the test formulation and reference prednisolone. Bashar's analysis uses linear trapezoidal method to calculate the area under the curve up to the last sampling point t , AUC_{0-t} and make up the last area with C_{last}/K_{el} , where K_{el} was the terminal elimination rate constant. The total ACU is $AUC_{0-\infty} = AUC_{0-t} + C_{last}/K_{el}$. The traditional analysis requires collection of many samples for generating smooth data to calculate trapezoids for approximating the curve; and with help from statisticians or rely on commercial software for data analysis. Besides, the calculation of the last area is awkward and out of consistency.

In the Alpha Beta ($\alpha\beta$) Math approach, we analyze the cumulative asymptotic curve of concentration for succession of time. For this approach, any high school student can do it by using the Microsoft Excel spreadsheet. No need for commercial software, nor need help from any statistician.

In the analysis, we need to use four types of graphs: primitive elementary graphs; primary graphs, leading graph (pre-proportionality graphs), and the proportionality graphs. The emphasis is to build a straight-line proportionality relationship for the time-response or dose-response data. In it, we demonstrate a methodology for solving the key upper asymptotes (Yu) like the last section on toxicokinetic for the proportionality equation using Microsoft Excel via determining the COD.

To start with, we simply take six (or seven) samplings and calculate their cumulative concentrations followed by analyzing the cumulative curve. The cumulative curve corresponds to their area under the curve; however, when applying the Alpha Beta ($\alpha\beta$) Math analysis, it is rather complete and more precise because the cumulative numbers are monotonic increasing and have a continuous smoothing momentum built in the system due to its connectivity. The advantage of cumulative numbers is the guarantee of monotonic increasing in numbers to give an asymptotic curve with smooth momentum of line transition. This in turn will provide reliable proportionality equations. In the following, we analyze the relationship between prednisolone concentrations versus time, using data from Figure 1 given by Bashar, et al. [1].

A	B	C	D	E	F
X, hr.	qX	y1, conc. (test form)	cum. Y	qYu - qY	q(qYu - qY)
0		0	0		
0.5	-0.3010	170	170	1.029622	
1	0.0000	360	530		
2	0.3010	690	1220		
4	0.6021	340	1560		
8	0.9031	150	1710		
12	1.0792	50	1760		
ΔYu	20		10		
		R ² (20)		R ² (10)	
Yu0 =	1760		1760		
Yu1 =	1780				
Yu2 =					
Yu3 =					
Yu4 =					
Yu5 =					
Yu6 =					
Yu7 =					
Yu8 =					
		Active Yu		1820.0	
		R ²			

Table 4A: Initial Data for test formulation (y1).

A	B	C	D	E	F	G
X, hr.	qX	y1, conc. (test form)	cum. Y	qYu - qY	q(qYu - qY)	
0		0	0			
0.5	-0.3010	170	170	1.029622	0.012678	
1	0.0000	360	530	0.535796	-0.271001	
2	0.3010	690	1220	0.173712	-0.760171	
4	0.6021	340	1560	0.066947	-1.174270	
8	0.9031	150	1710	0.027075	-1.567427	
12	1.0792	50	1760	0.014559	-1.836877	
ΔYu	20		10			
		R ² (20)		R ² (10)		
Yu0 =	1760		1760			
Yu1 =	1780	0.9803	1770	0.9582		
Yu2 =	1800	0.9936	1780	0.9803		
Yu3 =	1820	0.996651	1790	0.9893		
Yu4 =	1840	0.996614	1800	0.9936		
Yu5 =	1860	0.995300	1810	0.9957		
Yu6 =	1880	0.9935	1820	0.9966		
Yu7 =	1900	0.9916	1830	0.9969		
Yu8 =	1920	0.9892	1840	0.9966		
		Active Yu		1820.0		
		R ²		0.996651		

Table 4B: Calculated Data for test formulation (y1).

A	B	C	D	E	F
X, hr.	qX	y5, concentration (reference tablet)	cum. Y	qYu - qY	q(qYu - qY)
0		0	0		
0.5	-0.3010	190	190	0.991925	-0.003521
1	0.0000	365	555	0.526386	-0.278696
2	0.3010	640	1195	0.193311	-0.713744
4	0.6021	390	1585	0.070650	-1.150890
8	0.9031	150	1735	0.031379	-1.503356
12	1.0792	50	1785	0.019041	-1.720319
ΔYu	20		Active Yu		1865.0
		R ² (20)		R ²	0.996615
Yu0 =	1785				
Yu1 =	1805	0.9777			
Yu2 =	1825	0.9920			
Yu3 =	1845	0.9959			
Yu4 =	1865	0.9966			
Yu5 =	1885	0.9960			
Yu6 =	1905	0.9948			
Yu7 =	1925	0.9933			
Yu8 =	1945	0.9916			

Table 5A: Calculated Data for Reference formulation (y5).

From reading the graph in Appendix A, we select six data points each, and list them in Table 4A for the test formulation tablet. In Table 4A, Column A lists the time X in hours (cells A4:A10). As we can see, X is a nonlinear number with non-equal spacing; therefore, we need a column to give log of X (i. e., qX) for use in later calculation, as indicated in Column B (cells B5:B10). Column C lists the concentration of prednisolone for test formulation, y1. Column D gives the Cumulative Y, it is the cumulative of y1 for succession of X, e.g., D5 = D4 + C5, D6 = D5 + C6, D7 = D6 + C7 etc. Column E is for the calculation of the nonlinear face value (qYu - qY); and Column F gives the log of Column E, i.e., q(qYu - qY), it is for the calculation of the nonlinear transformation of the face value (qYu - qY), i.e., q(qYu - qY). Raw 12 is for listing the incremental upper asymptote ΔYu for calculating Yu1 to Yu8 in Rows 15 to Raw 22. We select two cases of ΔYu , one at 20 and the other at 10. Raw14 lists the initial value of estimated Yu, it is the last cumulative Y in Cell D10, i.e., Yu0 = 1760. Table 4B gives the calculated data using the Active Upper Asymptote Yu = 1820 in Cell E24. The procedures of filing the table are like those described in the last section. For the $\Delta Yu = 20$ series (marked in green color), the optimal Yu is 1820 at R² = 0.996651. For the $\Delta Yu = 10$ series (also marked in green color), the optimal Yu is 1830 at R² = 0.9969. The smaller ΔYu can give more precising toward the optimal Yu.

For comparison between test formula and reference formula, we calculate data for reference formulation in Table 5A. The optimal Yu is identified as Yu = 1865, as shown in green Cell in the table and in Figure 9. The direct comparison of two formulations is shown in Figure 10 where the face values (qYu - qY) versus X are plotted in a log-by-log scale, showing similar equation K and C; as well as in Figure 11 where the true values q(qYu - qY) versus qX are plotted in a liner-by-linear scale, showing similar K and C.

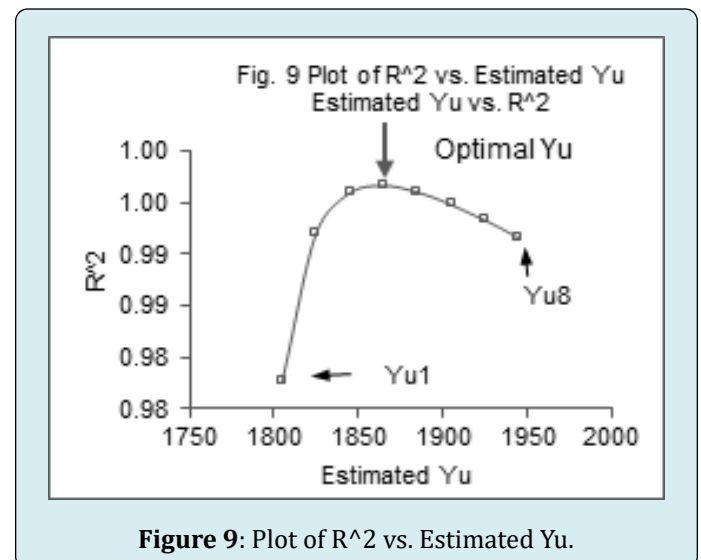


Figure 9: Plot of R² vs. Estimated Yu.

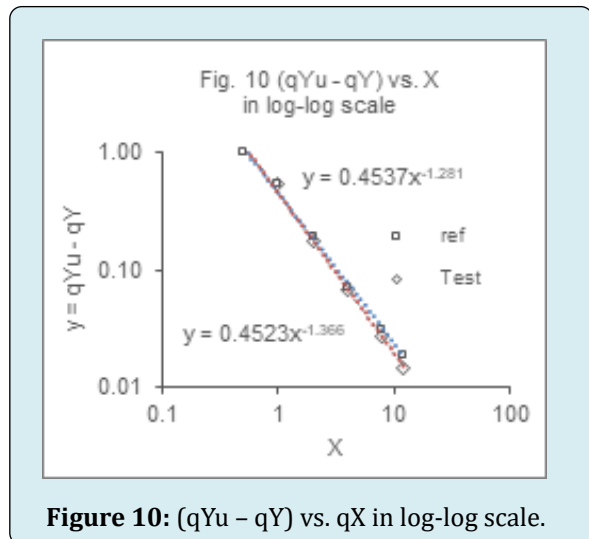


Figure 10: (qYu - qY) vs. qX in log-log scale.

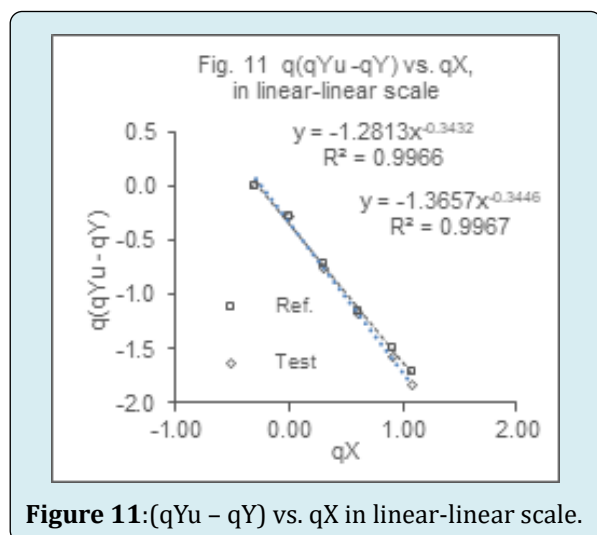
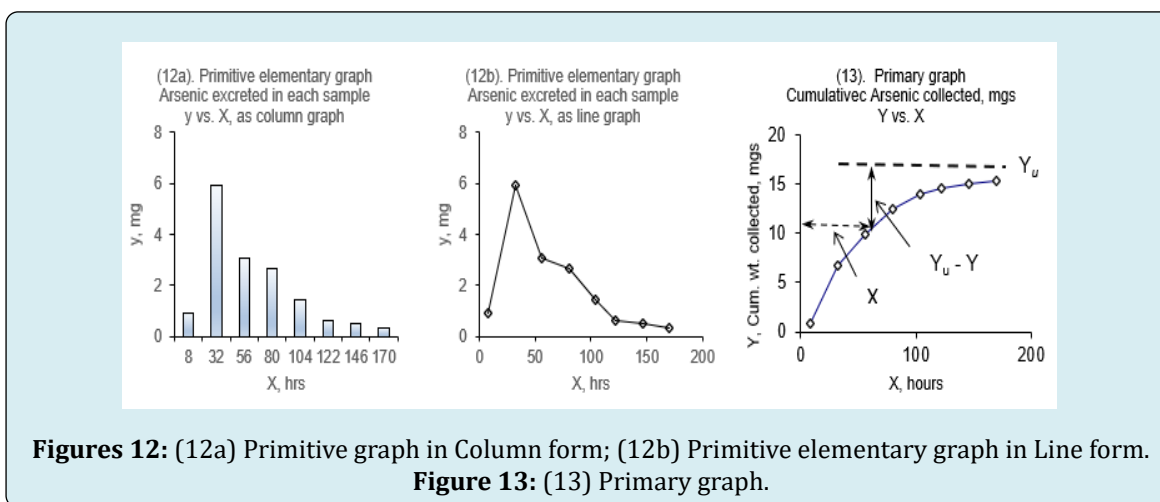


Figure 11: (qYu - qY) vs. qX in linear-linear scale.



Figures 12: (12a) Primitive graph in Column form; (12b) Primitive elementary graph in Line form.
Figure 13: (13) Primary graph.

In summary, the approach outlined above demonstrates an efficient method for data handling, analysis, and results presentation. Key highlights include:

1. Minimal data points: Utilizing only 6 data points instead of an excessive 12 allows us to conserve valuable resources.
2. Single Comprehensive Table: By consolidating all calculations and results into a single table, we achieve clarity and simplicity.
3. Unified Graph: The creation of a proportionality graph not only provides visual representation but also yields essential information, including the regression equation, the proportionality constant (rate constant) K and COD (Coefficient of Determination).

This streamlined approach underscores the elegance of efficient data management and analysis.

Discussions

The Vast difference between Primitive Elementary Graph and Primary Graph:

Referring to Table 2A containing arsenic data, we observe the following:

- **Primitive Elementary Graph** (Figures 12a & 12b):
 - ❖ We plot Column E against Column B for y versus X.
 - ❖ The resulting graph is the primitive elementary representation.
 - ❖ Interestingly, this graph differs from the primary graph.
 - ❖ Describing the primitive graph using mathematics would be challenging unless we employ a highly complex equation with numerous parameters.

- **Primary Graph** (Figure 13):

- ❖ By plotting Column F against Column B for Y versus X,

we obtain the primary graph.

- ❖ Unlike the primitive elementary graph, the primary

graph exhibits simplicity.

- ❖ The primary graph, however, lends itself more readily to equation attachment.
- **Asymptote and Nonlinear Line Relationship:**
- ❖ Understanding the existence of an asymptote and leveraging the relationship between the nonlinear line and the asymptote can simplify the process of developing equations and associated graphs.
- ❖ In summary, while the primitive graph poses mathematical complexities, the primary graph's simplicity allows for easier equation formulation when considering the asymptotic behavior. The characteristics of the asymptotic curve are that the data are cumulative and forever monotonically increasing toward an upper unique asymptote.

The Ordinary Order Versus Higher Order Nonlinearity

In an ordinary order nonlinear phenomenon, their characteristic equation is $d(q(Y_u - Y)) = -KdX$, Equation 2a their primitive elementary graph is a plot of vertical y versus X as a skewed-bell; their primary graph is a plot of Y versus X as an asymptotic convex curve, it is also a (the same as) primary graph. The first leg of the line between 0 (or origin) and the first data point is always the largest and the steepest (has the largest slope).

In a second order nonlinear phenomenon, their characteristic equations are $d(q(qY_u - qY)) = -KdX$ Equation 4 or $d(q(qY_u - qY)) = -Kd(X - X_b)$, Equation 7; their primitive elementary graph is a plot of vertical y versus X as a skewed-bell. For the phenomena follow the Equation 4, their primary graph is a plot of Y versus X as a sigmoid curve in a linear-by-linear scale; and an asymptotic convex curve is a leading graph in log-by-linear scale. For the phenomena follow the Equation 7, their primary graph is a plot of Y versus X as a sigmoid curve; and an asymptotic convex curve in a log-by-linear scale as a leading graph.

In Part 1 of this article, we reviewed the basic concepts and operations of $\alpha\beta$ math. They are: (I) continuous numbers are monotonic, non-terminating numbers; (II) these continuous numbers are classified into linear and nonlinear numbers; (III) the linear numbers are not associated with any asymptotes, but the nonlinear numbers are always associated with asymptotes; (IV) the change of nonlinear numbers need to measure relative to their asymptotes, and we call this measurement the nonlinear face value; (V) the change of continuous numbers is that the change of α is proportional to the change of β , i.e., $d\alpha = Kd\beta$, K is the proportionality constant or the rate constant. Their variations are the change of linear-by-linear is $d\alpha(Y) = Kd\beta(X)$; the change of nonlinear-by-nonlinear is $d\alpha(Y, Y_u, Y_b)$

$= Kd\beta(X, X_u, X_b)$; and the change of mixed numbers is $d\alpha(Y, Y_u, Y_b) = Kd\beta(X)$.

Use the Primary Graph as Base Rather than the Primitive Elementary Graph in Data Analysis

The primitive elementary graph can provide the peak information but not the essential rate and proportional relationship between two variables. To obtain essential rate and proportional relationship, we need to compare one cumulative number with another cumulative number (We need to compare apple with apple and orange with orange) [8,9]. We will use simulated data to demonstrate that four experiments may generate four different primitive curves for the same physical phenomenon, but they can be expressed with a single asymptotic curve and with simple straight line having an equation to representing the rate and proportionality relationship of two variables. In essence, we will use a case of skewed bell-curve having a sigmoidal line in primary graph, an asymptotic curve of second order of nonlinearity in leading graph and having the equation Equation 7a & 7b for illustration [10].

The physical meaning of the Equation 7a is that "the nonlinear change of nonlinear numbers Y , in second order of nonlinearity, is negatively proportional to the nonlinear change of nonlinear number X ". The left-hand side of the equation is the nonlinear change of nonlinear face value, $qY_u - qY$. The right-hand side of the equation is the nonlinear change of nonlinear face value, $X - X_b$, with $X_b = \phi = (0)$. Let us use equation Equation 7b and the round off parameters $Y_u = 1.50$, $K = 0.9$, and $C = 0.5$ for generating the simulated data.

In Table 7A, there are four sections for four series of X with various increments. Column A gives X values (in hours) for series t1; Column E gives X values for series t2; Column I gives X values for series t3; and Column M gives X values for series t4. Row 3 is blank; we reserve it for origin and nonlinear zero that cannot put out as 0. Now, let us generate 4 series of X data for comparing two large data versus two small data and two regulars versus two irregular data. i.e., Column A and Column E have 14 data points versus Column I and Column M have 9 data points; Column E and Column I give regular increment of X , while Column A and Column M give irregular data relative to Column E and Column I. For example in Column E, the X increases in the increment of $1.5X$, e.g., Cell E5 is " $= E4*1.5$ "; Cell E6 is " $= E5*1.5$ ", etc. Column E gives numbers for smooth increasing of X . In contrast, we generate Column A with numbers showing off-set relative to Column E. For example, Cell A4 = Cell E4 = 0.25; however, Cell A5 > Cell E5, Cell A5 = 0.50 is ahead of Cell E5 = 0.38; Cell A14 < E14, Cell A14 = 12 is behind Cell E14 = 14.42, etc. Likewise, Column I is for smooth increasing of X , with increasing of X at $2.0X$, e.g., Cell I5 is " $= I4*2.0$ "; Cell I6 is " $= I5*2.0$ ", etc. In

D4		=LOG(\$L\$14)-LOG(C4)	
X, hr	Theo. y	Theo. Y	qYu - qY
0.25	0.027	0.027	1.741
0.50	0.148	0.175	0.933
0.75	0.163	0.338	0.648
1	0.137	0.474	0.500
1.5	0.200	0.674	0.347
2	0.135	0.809	0.268
3	0.168	0.977	0.186
4	0.100	1.078	0.144
6	0.115	1.192	0.100
8	0.064	1.256	0.077
12	0.070	1.326	0.053
24	0.078	1.404	0.029
30	0.017	1.421	0.023
48	0.027	1.448	0.015

Table 7D: Calc. of (qYu - qY) in Columns D, H, L, and P.

of four series of X. Formula bar gives formula for Cell C4, “=($\$L\14) *10^{^-}($\$L\16) *(A4) Δ-($\$L\15)”. We can copy Cell C4 to Cell C5 through Cell C17 to complete Column C. We can use the same formula to calculate Columns G, K, and O, except we simply change the X from A4 to E4, then to I4, and M4 etc. In the next, we calculate elementary y in Columns B, F, J, and N. In Column B, y is the difference of two succession of Y, i.e., Cell B4 is “=C4-C3”, we can copy Cell B4 to Cell B5 through Cell B17 to complete the column. Likewise, we can complete the Columns F, J, and N, as shown in Table 7C.

Next, we calculate (qYu - qY) in Columns D, H, L, and P, as shown in Table 7D. Formula bar shows the formula for Cell D4 as “=LOG (\$L\$14)-LOG (C4)”. We copy Cell C4 to CellC5 through Cell C17 to complete the column. Likewise, we can calculate Columns H, L, and P. Formula for Cell H4 is “=LOG (\$L\$14)-LOG (G4)”. Formula for Cell L4 is “=LOG (\$L\$14)-LOG (K4)”, and Formula for Cell P4 is “=LOG (\$L\$14)-LOG (O4)”.

Next, we calculate four series of theoretical Y for each series of X. Table 7B gives calculated theoretical Y for each

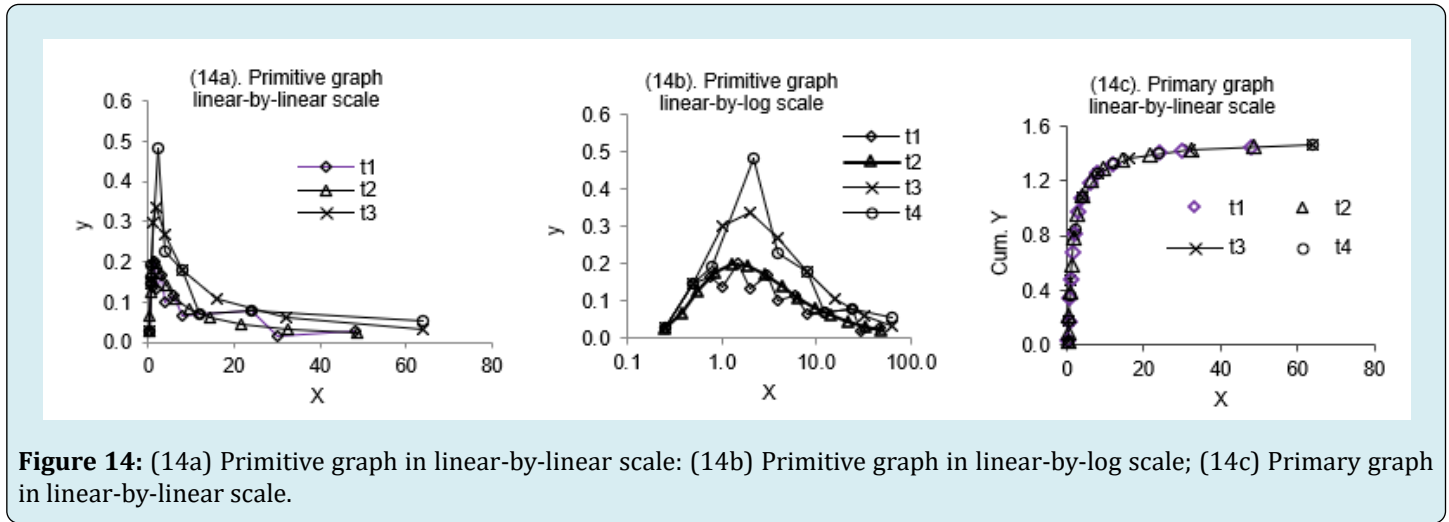


Figure 14: (14a) Primitive graph in linear-by-linear scale; (14b) Primitive graph in linear-by-log scale; (14c) Primary graph in linear-by-linear scale.

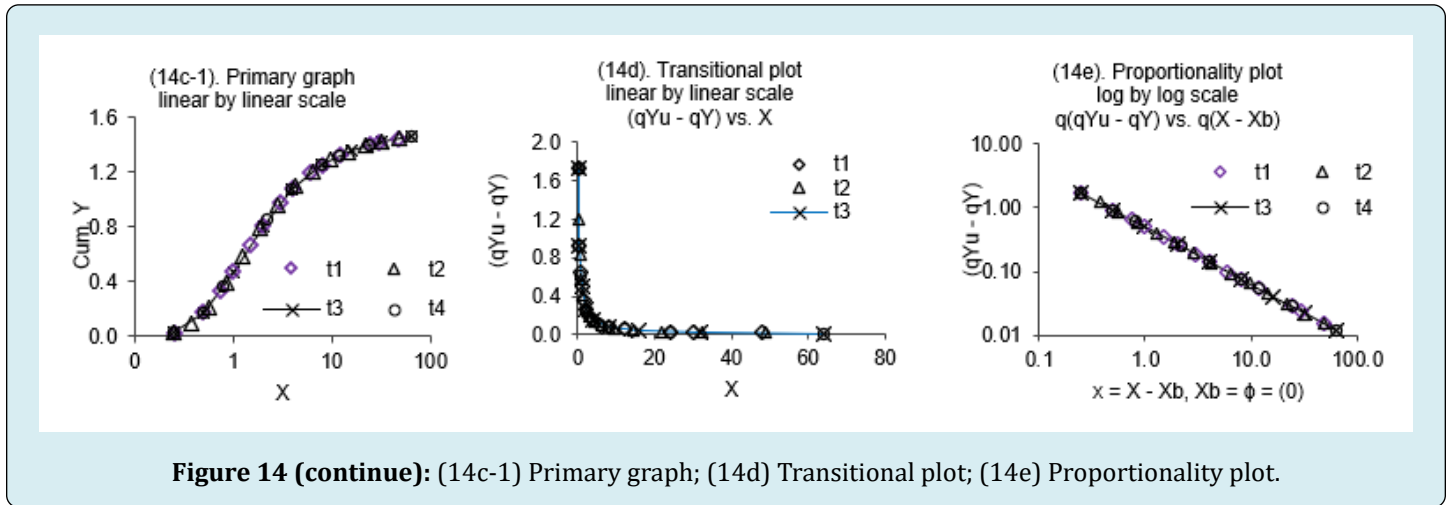


Figure 14 (continue): (14c-1) Primary graph; (14d) Transitional plot; (14e) Proportionality plot.

Based on Table 7D, we can generate four graphs as follows. We obtain primitive graph Figure 15a by plotting y_1 vs. X for t_1 series (Column B vs. Column A); by plotting y_2 vs. X for t_2 series (Column F vs. Column E); by plotting y_3 vs. X for t_3 series (Column J vs. Column I); and by plotting y_4 vs. X for t_4 series (Column N vs. Column M). We obtain Figure 15b by copying Figure 15a and then converting its X scales from linear into nonlinear logarithmic scale. Next, we obtain primary graph Figure 15c by plotting Y_1 vs. X for t_1 series (Column C vs. Column A); by plotting Y_2 vs. X for t_2 series (Column G vs. Column E); by plotting Y_3 vs. X for t_3 series (Column K vs. Column I); and by plotting Y_4 vs. X for t_4 series (Column O vs. Column M). By copying Figure 15c and converting the X -axis from linear into logarithmic scale, we obtain Figure 15c-1. Please note that all data fall into the same parabolic line in Figure 15c and fall into the same sigmoid line in Figure 15c-1. Comparing Figures 15a & 15b with Figure 15c, we can easily understand why we need to use the primary graph for data analysis rather than using primitive graph.

In the next, by plotting nonlinear face value ($qY_u - qY$) vs. linear face value X in linear-by-linear scale, we first obtain a transitional graph Figure 15d; then by converting both the axes from linear into nonlinear logarithmic scale, we obtain the last proportionality graph Figure 15e. We obtain Figure 15d by plotting ($qY_u - qY$) vs. X for t_1 series (Column D vs. Column A), by plotting ($qY_u - qY$) vs. X for t_2 series (Column H vs. Column E), by plotting ($qY_u - qY$) vs. X for t_3 series (Column L vs. Column I), and by plotting ($qY_u - qY$) vs. X for t_4 series (Column O vs. Column N). By plotting ($qY_u - qY$) vs. ($X - X_b$) in log-log scale, with $X_b = \phi = (0)$, we obtain Figure 15e. (Note: plotting ($qY_u - qY$) in logarithmic scale gives $q(qY_u - qY)$ as its true value; plotting ($X - X_b$) in logarithmic scale gives $q(X - X_b)$ as its true value.

As shown in transitional graph Figure 15d and proportionality graph Figure 15e, when we plot ($qY_u - qY$) vs. X , we get all the data points on the same line. Likewise, when we plot primary graph Figure 15c for cumulative Y vs. cumulative X , we get all the data points on the same line. However, when we plot elementary y vs. X in linear or nonlinear scale, we get a wide range of curves, with different peak high, or showing smooth or zigzag curves. These irregularities are due to improper selection of X (time). No matter how the primitive graphs look like, if we follow the analysis with cumulative X , we can end up with a reasonable, sensible analysis that follows the law of nature. The law of nature said the above phenomena are that the nonlinear change of nonlinear numbers Y is proportional to the change of linear or nonlinear numbers X .

In our analysis, we compare the monotonic nonlinear numbers Y with the other monotonic nonlinear numbers

X . Specifically; we compare their nonlinear face value with each other. The analysis is simple and easy such that every high school student can do it. In contrast, the traditional pharmacokinetics analysis involves tedious calculations of trapezoids and needs help with commercial software or help from statistician. Moreover, we need minimal numbers of sampling; we cut the sampling size in half from the original 12 to 6 in our analysis.

Traditional XY math is insufficient to describe the nonlinear phenomena; we need to extend the XY math into the $\alpha\beta$ Math to account for the existence of asymptotes, i.e., we need to extend $XY = \{(X), (Y)\}$ into $\alpha\beta = \{\alpha(Y, Y_u, Y_b), \beta(X, X_u, X_b)\}$. The $\alpha\beta$ Math classifies continuous monotonic numbers into linear and nonlinear numbers. Nonlinear numbers are associated with asymptotes, and their measurement of difference is the face value of the nonlinear numbers. The nonlinear face value can be a difference, a ratio of difference, or with logarithmic transformation (a logarithmic transformation is also called the nonlinear transformation), such as $(Y_u - Y)$, $(Y - Y_b)$, and $(qY_u - qY)$.

The Alpha Beta ($\alpha\beta$) Math is a science for connecting a straight line to asymptotic, sigmoid, and various bell curves in biomedical and physical sciences [5-10]. We provide illustration for building Excel Templates to solve for upper asymptotes and building a straight-line proportionality equation.

Conclusion

- Toxicokinetic can be described by an ordinary ACP nonlinear equation, whereas Pharmacokinetic can be described by a second order ACP nonlinear equation.
- The Alpha Beta ($\alpha\beta$) nonlinear math posits that “the change of the response (Y) is proportional to the change of the time or dose (X),” expressed mathematically as $d\alpha = Kd\beta$. Specifically, this physical law dictates that the nonlinear response change is negatively proportional to the linear change or nonlinear dose change. The mathematical forms are $d\alpha\{Y, Y_u, Y_b\} = -Kd\beta(X)$ or $d\alpha\{Y, Y_u, Y_b\} = -Kd\beta(X, X_u, X_b)$.
- Nonlinear phenomena can be effectively described using a simple proportionality equation and four types of graphs: primitive, primary, leading, and proportionality graphs. However, relying solely on a primitive elementary graph is insufficient for constructing a dose-response mathematical relationship. Each elementary “ y ” lacks mathematical connectivity, preventing direct mathematical relationships between individual cumulative numbers. Instead, we must establish connections between cumulative numbers and utilize the primary graph for rigorous mathematical analysis. Cumulative numbers signify the existence of connectivity.

- In life and biomedical fields, data must adhere to the law of nature. The experimental law stipulates that the response is either proportional to or negatively proportional to the dose. For dose-response data, we can establish straight-line proportionality relationship using log-linear and log-log graphs. This article, we present a guided estimation methodology for determining the key upper asymptotes for the proportionality equation using Microsoft Excel, leveraging the “coefficient of determination.” Our example includes a systematic demonstration of Excel data manipulation and extensive graphing.
- From the perspective of physical law, the response is either proportional to or negatively proportional to the dose, characterized by a proportionality constant **K**. This viewpoint underscores the fundamental principles governing nonlinear behavior.

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