

Research paper

Handling of computational in vitro/in vivo correlation problems by
Microsoft Excel: I. principles and some general algorithms

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Received 1 June 2001; accepted in revised form 20 September 2001

Abstract

Most computations in the field of in vitro/in vivo correlations can be handled directly by Excel worksheets, without the need for specialized software. Following a summary of Excel features, applications are illustrated for numerical computation of AUC and Mean, Wagner–Nelson and Loo–Riegelman absorption plots, and polyexponential curve fitting. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Correlation in vitro/in vivo; In vitro/in vivo correlations; Excel; SAS; Kinetica; WinNonlin; Moments; AUC; Mean; Wagner–Nelson; Loo–Riegelman

1. Introduction

In vitro/in vivo correlations (IVIVC) for drug products, as defined by United States Pharmacopoeia [1] and Food and Drug Administration [2], establish quantitative mathematical relationships between drug release time profiles observed in vitro, and corresponding response profiles (plasma concentration, urinary excretion) in vivo. With the growing importance of IVIVC, also due to the regulatory status, there is a revived interest in relevant literature and computer software. The topic is covered in modern textbooks of pharmacokinetics or biopharmaceutics, [3–6]; but without comprehensive treatment. Workshop proceedings [7] focus more on new sophisticated techniques rather than to summarize fundamentals.

With regard to computer software, SAS [8] with its interactive matrix language (IML) is deemed the most professional tool for general computations. Packages such as WinNonlin [9] or Kinetika [10] are specifically designed to handle pharmacokinetic tasks. But also there, many standard IVIVC tasks are not covered and must be programmed by the user.

In this situation it is worth to note that IVIVC problems do not require specialized software, but may well be handled by MS Excel [11] as a general-purpose mathematical software. The main advantage of Excel is its ample distribution: Probably each scientific worker worldwide has access to

Excel without any additional costs. Another advantage is that Excel is compatible with programs such as WinNonlin or Kinetika; both are in fact based on Excel, and the programming language of Excel (VisualBasic, VBA) is the language in which a user of either may program his/her own additional program modules.

2. Excel features

In Excel, data belonging to related topics are best stored in a common workbook which contains several worksheets related to this topic. Each sheet represents an almost unlimited tabular arrangement of cells which one may fill with numerical data, formulas, text, or embedded charts. The structure of workbooks and sheets is mainly dictated by the convenience to display them on the screen and/or the printed page.

2.1. Formulas and references

Whenever the text in a cell starts with ‘=’, Excel automatically interprets this as a *formula* to compute and display a numerical result. The formula must be typed according to strict rules, otherwise it will be rejected or it returns an error message as result. This is especially important if the formula contains *references* to other cells or ranges of cells, and if the same formula is intended to be used in a range of cells rather than a single cell. If the formula is properly defined, it may be copied directly to a range of rows or columns.

For extensive calculations, it is beneficial to replace the standard A1 notation by its R1C1 equivalent, where columns are identified by their number rather than an alpha-

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betic character. The advantage is that *absolute* and *relative* references can be distinguished in a more transparent manner: **R4C5** as absolute reference to row 4 and column 5; **R[–1]C** as relative reference to the preceding row of the same column; **R[–1]C3** as mixed reference to the preceding row of column 3.

For ease of handling, references may be substituted by labels or names e.g. assigning a name *OBS* to the range **R1C1:R1C20** and *FIT* to the range **R1C5:R1C5**, a formula such as **=OBS–FIT** will be easier to understand than its equivalent **=R1C1:R1C20–R1C5:R1C5**. Within a worksheet, *labels* above data columns or left to data rows may be used directly in formula references to these columns or rows. A more general technique, also working for references between different sheets, is to assign unique *names* to cell ranges.

Array formula is a single formula entered into an entire array of cells. To insert such a formula, select the entire range of cells, type the formula, and enter it by pressing **CTRL + SHIFT + ENTER**. Of course, all references must conform with the general rules of Excel formulas. This feature is most convenient for large data arrays and comes most close to a true matrix language.

2.2. Functions

Excel provides more than 200 functions for all kinds of mathematical and statistical applications. To use a function, type its name in the formula or use the *Insert: Function* command. The general format of a function is **NAME(p;q;r...)**, where the function name is followed by a set of parameters, enclosed in parentheses and separated by semicolons. Functions may freely be combined with arithmetic operations, and may be nested within other functions. Four functions are especially designed for matrix operations, which is of interest for handling large arrays of numbers. With the exception of **MDETERM**, these formulas must be entered as array formulas into a range which conforms with the expected result.

2.2.1. Matrix transpose and determinant

{=TRANPOSE(A)} computes a matrix **A'** with rows and columns exchanged. This operation is used in many algorithms, particularly if matrix multiplication is involved (see the statistics example shown below).

=MDETERM(A) computes the determinant $\det(\mathbf{A})$ of a square matrix, which is a single numeric value (hence no array formula is required) used for solving a system of linear equations. It is computed as the sum of all possible elements of **A** parallel to the main diagonal, minus the sum corresponding to all elements parallel to the second diagonal. A well-known example is the determinant $D = a_{11}a_{22} - a_{12}a_{21}$ of a quadratic equation. Its value determines whether the equation has two real roots ($D > 0$), two roots falling together into one value ($D = 0$), or two complex roots ($D < 0$).

2.2.2. Matrix product

{=MMULT(A;B)} computes the matrix product **C = AB** of two matrixes. This operation is possible if **B** has the same number of rows as **A** has columns. The result **C** has rows according to **A**, and columns according to **B**

$$\begin{array}{c} \mathbf{A} \\ (3 \times 4) \end{array} \begin{array}{|c|c|c|c|} \hline a_{11} & a_{12} & a_{13} & a_{14} \\ \hline a_{21} & a_{22} & a_{23} & a_{23} \\ \hline a_{31} & a_{32} & a_{33} & a_{34} \\ \hline \end{array} \begin{array}{|c|c|} \hline b_{11} & b_{12} \\ \hline b_{21} & b_{22} \\ \hline b_{31} & b_{32} \\ \hline b_{41} & b_{42} \\ \hline \end{array} \begin{array}{c} \mathbf{B} \\ (4 \times 2) \end{array} \quad (1)$$

$$\begin{array}{|c|c|} \hline c_{11} & c_{12} \\ \hline c_{21} & c_{22} \\ \hline c_{31} & c_{32} \\ \hline \end{array} \begin{array}{c} \mathbf{C} \\ (3 \times 2) \end{array}$$

Eq. (1), often known as ‘Falk’ scheme [12], best visualizes the arrangement of the matrices involved. Each element of **C** is generated by selecting the corresponding row of **A** and column of **B**, forming all products of the elements of these vectors, and summing these products, e.g. $c_{32} = a_{31}b_{12} + a_{32}b_{22} + a_{33}b_{32} + a_{34}b_{42}$

A typical example is a system of linear equations, as found in spectrophotometric multi-component analysis. Assume three components with concentrations c_1, c_2, c_3 . At three wavelengths, each component has its specific absorptivity, e.g. ϵ_{ij} for component j at wavelength i . Then the total absorbance at the three wavelengths is given by the product **A = EC**, where **E** is the square matrix of all absorptivities

$$\begin{array}{c} \mathbf{E} \\ \begin{array}{|c|c|c|} \hline \epsilon_{11} & \epsilon_{12} & \epsilon_{13} \\ \hline \epsilon_{21} & \epsilon_{22} & \epsilon_{23} \\ \hline \epsilon_{31} & \epsilon_{32} & \epsilon_{33} \\ \hline \end{array} \end{array} \begin{array}{|c|} \hline c_1 \\ \hline c_2 \\ \hline c_3 \\ \hline \end{array} \begin{array}{c} \mathbf{C} \\ \mathbf{A=EC} \end{array} \quad (2)$$

Another typical example of matrix multiplication (and transpose) is found in statistics. The **Z** matrix in the following scheme records observations of an experiment. The first column contains only ‘ones’, additional columns contain values of independent x and dependent y variables (only one column is shown for both).

$$\begin{array}{c} \mathbf{Z}' \\ \begin{array}{|c|c|c|} \hline 1 & x_1 & y_1 \\ \hline 1 & x_2 & y_2 \\ \hline 1 & x_3 & y_3 \\ \hline \end{array} \end{array} \begin{array}{c} \mathbf{Z} \\ \mathbf{Z'Z} \end{array} \quad (3)$$

$$\begin{array}{|c|c|c|} \hline N & \sum x & \sum y \\ \hline \sum x & \sum x^2 & \sum xy \\ \hline \sum y & \sum xy & \sum y^2 \\ \hline \end{array}$$

The matrix product **Z'Z** computes the number N of the

observations, together with the sums of the x and y values and all relevant sums of squares and cross-products.

2.2.3. Matrix inverse

{=MINVERSE(**A**)} computes the inverse \mathbf{A}^{-1} of a given square and non-singular matrix **A**. As shown by the Falk scheme below, \mathbf{A}^{-1} is of the same size as **A**. It is computed from the relationship $\mathbf{A}\mathbf{A}^{-1} = \mathbf{I}$, where **I** denotes the identity matrix of the same size, which contains only '1' in the main diagonal and '0' otherwise

		-9	4
		7	-3
3	4	1	0
7	9	0	1

 \mathbf{A}^{-1}
(4)

		1	0
		0	1
3	4	1	0
7	9	0	1

 \mathbf{I}

Matrix inversion is used for solving a system of linear equations e.g. in the multi-component analysis of Eq. (2), the relationship $\mathbf{A} = \mathbf{E}\mathbf{C}$ can be changed to $\mathbf{C} = \mathbf{E}^{-1}\mathbf{A}$, which computes unknown concentrations once the vector **A** is measured at three wavelengths the absorptivity matrix **E** is known from a separate experiment.

2.3. The 'Analysis ToolPak'

This add-in package, run by *Tools: DataAnalysis...*, provides a manifold of standard statistical analyses, e.g. descriptive statistics, t -test (paired, equal or unequal variances), F -test, ANOVA (single-factor, two-factor), correlation, covariance, Fourier analysis, regression. The data to be analyzed are available as a worksheet table, conveniently arranged in columns headed by a descriptive column label.

A model-specific dialog box permits to specify all relevant details. *InputRange* defines the range of cells in the worksheet containing the raw data; for regression, one

single column contains the y values; a block of one or more columns contains the independent x variables. *OutputRange* specifies the range or its upper-left cell, where the output table is to be displayed. *GroupedBy* selects either columns or rows, depending on how the data are arranged. *Labels* specifies specific labels in the output tables. *ChartOutput* specifies graphical presentations as part of the output, and where to place them in the worksheet.

After the Analysis ToolPak has been started successfully, it places self-explanatory tables and graphics containing the results of the analysis into the specified ranges of the worksheet. From there, the results may be re-formatted or copied into other places of the sheet, another sheet or workbook, or a Word document.

2.4. The 'Solver' tool

The 'Solver' of Excel is a most powerful tool for mathematical problems that can only be handled by an iterative algorithm. The reason might be that an explicit formula does not exist, is too cumbersome to handle, or is simply not known when you need it. (Note: The Solver is an add-in utility which is not automatically installed; if not available, install it from the Office Setup program).

Its dialog box, shown in Fig. 1, lets you specify these items. *SetTargetCell* is a single cell containing the formula for which you want to find a certain value. *EqualTo* specifies the target as either maximum, minimum, or a specific value (typically '0'). *ByChangingCells* lists all cells or ranges the value of which may be changed iteratively to approach the target. *SubjectToTheConstraints* lists all constraints for the changing cells or the target cell. These are specified by using the operators '=', '<=', and '>='. Special buttons are available to Add/Change/Delete these constraints (Unfortunately, '<' and '>' are not allowed in this context). The *Options...* button permits to adjust further controlling options of the iterative process.

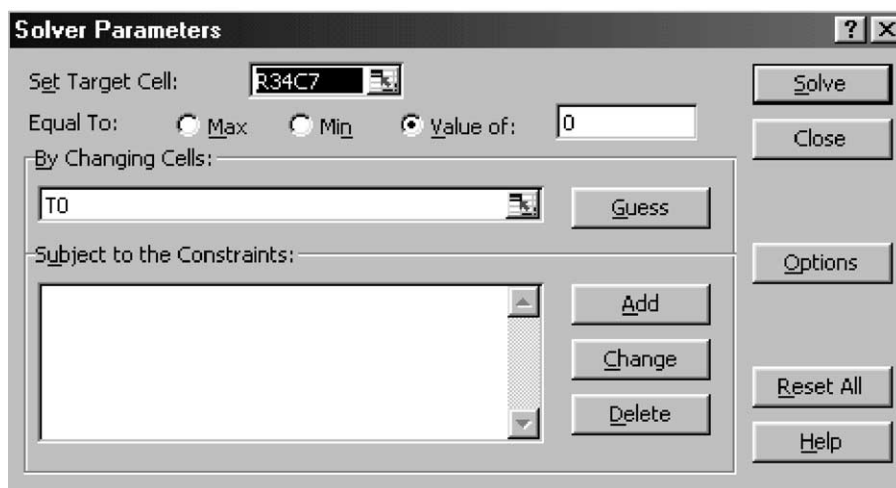


Fig. 1. Dialog box of the Solver tool of Excel.

2.4.1. Peak coordinates

A frequent application is to find the peak coordinates t_{\max} and C_{\max} of a plasma concentration profile described by a convenient function. Instead of solving complicated equations, the Solver provides an approach which is easier to handle by an inexperienced user. Just enter an arbitrary time value in cell R1C1, and the Bateman formula in R2C1, as shown below

$$\begin{aligned} \text{R1C1} &= 0 \\ \text{R2C1} &= 100 * (\exp(-0.1 * \text{R1C1}) - \exp(-0.5 * \text{R1C1})) \end{aligned}$$

R2C1 will display the function value for the arbitrary value in R1C1. After starting the Solver, specify R2C1 as target cell, maximum as goal, and R1C1 as cell to be varied, you obtain the values of t_{\max} and C_{\max} in both cells.

2.4.2. Roots of a polynomial function

Another application is finding the roots of a higher order polynomial, a task that occurs in the context of a generalized analysis of compartment models and will be discussed in a following paper. The root of the *linear* equation $y = a + bx$ is $x_0 = a/b$, and the roots of the *quadratic* equation $y = ax^2 + bx + c$ are given as

$$x_{1,2} = (-b \pm \sqrt{b^2 - 4ac})/2a \quad (5)$$

For polynomials of cubic or higher order, no explicit expression is available, but an iterative solution can be found with the Solver. The procedure is to write the polynomial function in a named cell

$$Y = A * X^3 + B * X^2 + C * X + D$$

where X is a named cell containing an arbitrary value of the independent variable, and A , B , C , D are cells containing the given coefficients. Specifying Y as target cell with '0' as goal, and X as the cell to be varied, the Solver finds a value of X where Y is zero. A strategy to find all roots will be presented in a following paper.

2.4.3. Minimizing a sum of squares

Most statistical estimations are based on minimizing a sum of squares of deviations between computed and observed data

$$SSQ = \sum (OBS - FIT)^2 \quad (6)$$

If the corresponding data are arranged in two columns named as *OBS* and *FIT*, a target cell *SSQ* may be defined with the formula $=\text{SUMXMY2}(OBS - FIT)$. With 'minimum' as specified goal, the Solver varies all function parameters used in calculating the *FIT* values, until a minimum of *SSQ* is reached. Polyexponential curve fitting as a typical example will be discussed in a following paper.

2.5. Charts

Excel permits to create graphical presentations (charts) immediately from the data stored in worksheet ranges,

either as separate sheets in a workbook or as objects embedded in the sheet containing the data and formulas. For scientific applications, the most frequent graphic is the 'x-y' plot with data series plotted according to a horizontal abscissa and a vertical ordinate. It is possible to attach two ordinate axes to a common abscissa. Scales of the two ordinates are displayed on the left and right margin. Data series may be freely assigned to either of the two axes. Each data series may be formatted with or without data point markers, and with or without connecting lines. The 'Smooth' facility permits to draw a smooth curve from a few fixed points.

A finished chart may be formatted freely later on. Opening the chart by double-clicking you have access to all existing elements, as shown in Table 1, either by clicking the mouse near the element, or by scrolling through the list with arrow keys. (In fact all x-y plots in this paper were originally created as embedded Excel charts and then copied into the Word document.)

3. Numerical integration applications

Numerical integration is frequently used, e.g. to compute the total area AUC, the mean time, or the time profile of a fraction absorbed. The raw data belonging either to a probability density function (pdf, e.g. plasma response in vivo) or a cumulative distribution function (cdf, e.g. drug release in vitro) are usually supplied in the first columns of a worksheet. Additional columns contain the results computed by a numerical integration formula such as the trapezoidal rule. All integration columns start with a value of '0' at $t = 0$, to be entered manually. Further rows contain this recursive formula

$$F_i = F_{i-1} + (t_i - t_{i-1})(f_i - f_{i-1})/2 \quad (7)$$

which may be copied by mouse dragging or entered as array formula. If the observations cover a sufficiently large time range, the last value is a satisfactory estimate of the final value F_{∞} .

Table 1
Typical elements of an x-y chart and their formatting

Element	Description	Formats
Chart	Entire chart area	Border, area, font
Plot	Plot area including axes	Border, area
Legend	Symbols and explanation	Position, font, size
Axis1	First axis (ordinate)	Pattern, font, text, scale
Axis2	Second axis (abscissa)	Pattern, font, text, scale
TextAxis1	Text attached to Axis1	Pattern, font, text
TextAxis2	Text attached to Axis2	Pattern, font, text
Text1	Unattached text (#1)	Position, font, size
Arrow1	Free-form straight line	Line, arrowhead
S1	First data series	Line connection, symbol
S2	Second data series	Line connection, symbol
S1P1	First point of first series	Special symbol

Table 2

Tabular arrangement of observations to compute AUC and MEAN for given PDF and CDF data

TIME	PDF	AUC	MEAN1	CDF	MEAN2
0	0	0	0	0	0
1	0.2387	0.1193	0.1193	0.1548	0.0774
2	0.2325	0.3549	0.4712	0.3996	0.4445
4	0.1170	0.7045	1.4044	0.7477	1.4888
6	0.0473	0.8688	2.1563	0.9029	2.2651
9	0.0110	0.9563	2.7304	0.9779	2.8276

3.1. Curve moments: AUC and Mean

Numerical computation of AUC and MEAN is illustrated in Table 2 and Fig. 2 for a data set generated from a biexponential with $a_1 = 1$, $b_1 = 0.5$, $a_2 = -1$, $b_2 = 1$. Columns *TIME*, *PDF*, and *CDF* contain the raw data. The other columns are computed by the trapezoidal rule, assuming linear interpolation between the data points.

3.1.1. Probability density functions (pdf)

Exact values of a pdf., e.g. plasma response in vivo, are listed in the column *PDF*, according to

$$f(t) = \sum a e^{-bt} = e^{-0.5t} - e^{-1t} \quad (8)$$

Values in column *AUC* are computed according to

$$AUC = \int_0^{\infty} f(t) dt = \sum \frac{a}{b} = \frac{1}{0.5} - \frac{1}{1} = 1 \quad (9)$$

with this recursive Excel formula

$$AUC = R[-1]C + (RC1 - R[-1]C1) * (R[-1]C2 + RC2) / 2$$

Column *MEAN1* illustrates the computation of the mean time according to

$$MEAN1 = \int_0^{\infty} t f(t) dt / \int_0^{\infty} f(t) dt = \sum \frac{a}{b^2} / \sum \frac{a}{b} = 3 \quad (10)$$

with this recursive formula

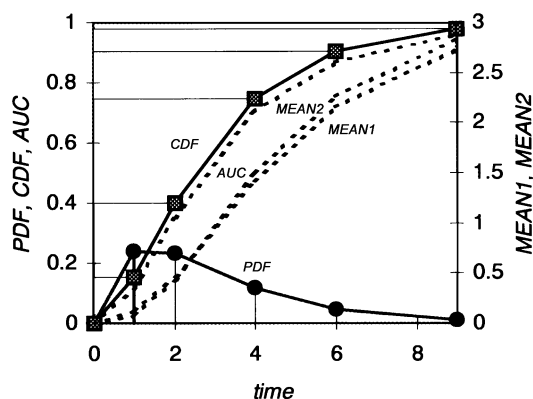


Fig. 2. Time profiles encountered for AUC and MEAN calculation for the data of Table 2. Exact profiles are shown with markers: (●) PDF; (■) CDF.

$$MEAN1 = R[-1]C + (RC1 - R[-1]C1) * (RC1 * RC2 + R[-1]C1 * R[-1]C2) / 2$$

In Eq. (10), the numerator is computed by integrating the function $t f(t)$ over t between 0 and ∞ . The denominator is the AUC according to Eq.(9); if the data are reported in normalized units, it equals to '1'. The recursive formula for *MEAN1* computes all values for the numerator. When compared with the AUC formula, the terms *RC2* and *R[-1]C2* are multiplied by *RC1* and *R[-1]C1*, respectively.

3.1.2. Cumulative distribution functions (cdf)

Considering a cumulative form, e.g. drug release in vitro, exact values are listed in column *CDF*, according to

$$F(t) = \sum \frac{a}{b} (1 - e^{-bt}) = 1 - (2e^{-0.5t} - e^{-1t}) \quad (11)$$

In this case, *AUC* is directly read from the last entry in this column, unless the final plateau was not reached and must be extrapolated by an exponential tail. The mean is computed according to

$$MEAN2 = \int_0^{\infty} t dF(t) \quad (12)$$

with this recursive formula

$$MEAN2 = R[-1]C + (RC3 - R[-1]C3) * (R[-1]C1 + RC1) / 2$$

This algorithm, described by Brockmeier et al. [13] in several papers, computes the mean by integrating t over $F(t)$. It is best understood by considering *CDF* as abscissa and *TIME* as ordinate, i.e. by interchanging both coordinates.

3.2. 'Fraction absorbed' algorithms

Table 3 and Fig. 3 illustrate a 'classical' IVIVC task, the numerical estimation of drug absorption from observed plasma response. The algorithm was proposed by Wagner and Nelson [14] for the open one-compartment model with plasma as only body compartment, and extended by Loo and Riegelman [15] to the open two-compartment model with plasma and tissue as body compartments. Details of the algorithms have been discussed in [16] and [17].

For any observed time point t , the amount absorbed is computed from a mass balance according to

$$C_A(t) = C_P(t) + k_e \int_0^t C_P dt + k_{12} e^{k_{21}t} \int_0^t C_P e^{k_{21}t} dt \quad (13)$$

Eq. (13), corresponding with Eq. (5) of [16], expresses the amount of drug absorbed, C_A , as the sum of three compartments. The first term represents the actual amount in plasma. The second term represents the amount excreted., computed from the area under the plasma curve between time 0 and t . The third term represents the actual amount in the tissue compartment.

All terms are based on plasma concentrations C_P , e.g. in

Table 3

Example of a Wagner–Nelson and Loo–Riegelman calculation of fraction of drug absorbed

TIME	PLAS	ELIM	ABS1	'5'	'6'	TISS	ABS2
0	0	0	0	0	0	0	0
0.05	17.23	0.22	17.45	17.67	0.44	0.65	18.09
0.10	29.72	0.80	30.52	31.24	1.66	2.37	32.90
0.20	44.46	2.66	47.12	49.14	5.68	7.71	54.83
0.30	50.25	5.02	55.27	58.38	11.06	14.28	69.55
0.40	50.90	7.55	58.45	62.17	17.09	20.98	79.44
0.50	47.78	10.02	57.80	61.35	23.26	27.18	84.98
0.60	45.33	12.35	57.68	61.19	29.39	32.66	90.34
0.75	39.45	15.53	54.98	57.40	38.28	39.47	94.45
1.00	30.67	19.91	50.58	50.57	51.78	47.11	97.69
1.50	20.28	26.28	46.56	42.93	75.15	53.25	99.81
2.00	16.03	30.82	46.85	43.57	96.78	53.41	100.25
3.00	13.12	38.10	51.22	58.80	147.97	49.52	100.75
4.00	11.69	44.31	56.00	86.38	220.56	44.77	100.77
6.00	9.48	54.89	64.37	190.41	497.35	37.14	101.51

ng/ml. Consequently, the result C_A is also a concentration in the same unit. After being multiplied by a virtual volume, all terms are understood as drug *amounts*, and after division by the final value, as *fractions* absorbed.

According to Eq. (13), the Wagner–Nelson method is a special case of the Loo–Riegelman approach, for $k_{12} = 0$. Therefore, both algorithms can be handled by a single Excel worksheet. Table 3 uses data originally reported in Table 1 of [16], and analyses them according to both methods. Obviously, all observed and computed columns are 0 in the first row. The plasma observations are listed in the first two columns, *TIME* and *PLAS*. Columns *ELIM* and *ABS1* perform a Wagner–Nelson computation, using $k_e = 0.5$, which may be estimated from the data themselves

$$ELIM = R[-1]C + KE * (RC1 - R[-1]C1) * (RC2 + R[-1]C2) / 2$$

$$ABS1 = RC2 + RC3$$

The profile of *ABS1* strongly indicates the need for a further compartment. The absorption model is improved by computing additional columns relating to a tissue

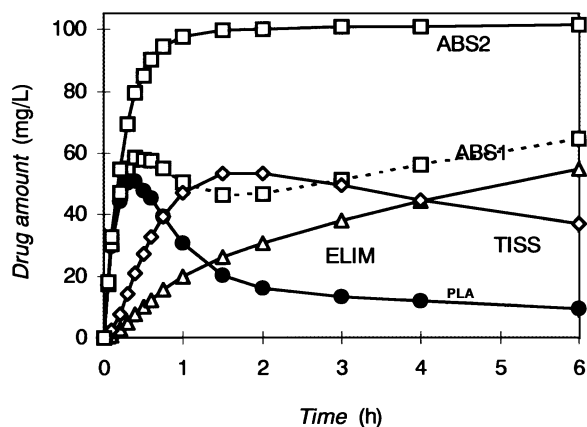


Fig. 3. Wagner–Nelson and Loo–Riegelman plot of the data of Table 3.

compartment with rate constants $k_{12} = 1.5$ and $k_{21} = 0.5$, the values of which must be obtained from a separate oral solution treatment (Columns *C5* and *C6* are only used to avoid cumbersome formulas in *TISS*)

$$C5 = RC2 * EXP(K21 * RC1)$$

$$C6 = R[-1]C + (RC1 - R[-1]C1) * (RC5 + R[-1]C5) / 2$$

$$TISS = K12 * EXP(-K21 * RC1) * RC6$$

$$ABS2 = RC2 + RC3 + RC7$$

4. Summary

Excel features are useful for handling of IVIVC problems, as illustrated in this paper by some elementary numerical integration algorithms: AUC and mean of release or plasma data, Wagner–Nelson and Loo–Riegelman absorption profiles. Subsequent papers of this series will deal with more specific problems, namely

- Part II: Distribution functions in vitro and in vivo.
- Part III: Convolution and deconvolution algorithms.
- Part IV: Generalized matrix analysis of linear compartment systems.

5. Notation

Denoting the time abscissa by t , we generally denote probability density functions (pdf) as $f(t)$ and cumulative distribution function (cdf) as $F(t)$. Regarding input, weighting and response functions, their differential profiles are denoted by $i(t)$, $w(t)$, $r(t)$; cumulative profiles by $I(t)$, $W(t)$ and $R(t)$. In mathematical equations, matrixes are denoted by bold-face letters, e.g. **A** or **Z**. Column and row vectors are denoted as **x** or **y**.

Excel-specific code is distinguished by capitalized non-serif font, e.g. **R[-1]C** as cell reference, **K12** as named range, or **= {MMULT(WTRI; WAVE)}** as array formula with named references. Range labels or names assigned to ranges, e.g. *TIME*, *PLAS*, *PDF*, *TISS*, *MEAN1*, are denoted by italic font. Note that *KE*, *K12* and *K21* are symbolic names, which cannot be used directly in formulas because of confusion with cell references, but must be substituted by appropriate references or named ranges.

Acknowledgements

The present manuscript was prepared with the assistance of J. Mysicka and Dr H. Rettig, whose contributions are gratefully acknowledged.

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