

## 1.0 Abbreviations, Background and Objectives

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NOTE: Population kinetics look at measures of variability but clinical dose adjustments need a single value for the respective parameters in the individual case.

The naïve user is unable to look behind the apparent black box of population approaches. Contrasting to that, we want to present pharmacokinetics and pharmacodynamics in a transparent way, so that every clinician will be able to understand and to use the equations for calculations by the own hardware or even by mind. This book also is based on a mathematical approach more than on a mechanistic, physical or physiological approach. As pharmacokinetics and pharmacodynamics illustrate, mathematics applies also inside the body to the individual patient. “Mathematics is the alphabet of nature” [Galileo Galilei 1564 – 1642].

Mathematical sciences are more general than physical sciences. The mechanistic approach looks for the causal sequence of events. Mathematics are dealing not on primary cause and secondary consequences. Mathematics is a kind of abstraction from the reality, it is the deductive logic of premise and proof. The big potential of the mathematical approach is that it is able to focusing on the essential relation and their correlation – namely equations and functions. Mechanics are based on physics and empirical experience that is real or fictive experimentation. Mathematics is not based on laws but stating such laws.

In clinical life, as intended also in our book, pharmacokinetics (PK) and pharmacodynamics (PD) are used instrumental to improve drug therapy. For this purpose, pharmacokinetics and pharmacodynamics best should be presented in general and transmissible terms. The case of kidney failure gives a paradigm for other fields of application. Kidney failure states one important example of how individual disease influences the response to drug therapy. The kidney patients exemplarily show how pharmacokinetic theory can be used to produce the same pharmacodynamic response in the individual patient as in those patients with normal renal function. The reason and the purpose of our approach will be to compile a reader on individualized drug dosing tools by means of pharmacokinetic and pharmacodynamic principles.

We want to present both, pharmacokinetics and pharmacodynamics as transparent and comprehensible disciplines in medical science. When physicians understand the principles they can apply them by themselves to any individual case better than by relying on general guidelines and package inserts or product information. Practically, drug dosing adjustment in patients with renal impairment often is derived from information in tables and pharmacological compendiums [Aronoff 2005]. However, recommendations for drug dosing adjustment differ between different books [Vidal 2005]. One reason for these differences is that most recommendations are not based on a generally accepted concept integrating pharmacokinetics and pharmacodynamics.

The aim of the present book is to derive a general concept for drug dosing adjustment in renal impairment integrating pharmacokinetics and pharmacodynamics. Background information is provided that allows for reassessment of suggested dosing regimens as well as the development of specifically modified regimens. In addition, the general drug dosing rules could be applied in situations of impaired drug elimination due to reasons other than renal impairment provided that individual pharmacokinetic predictions are possible. Several practically oriented chapters try a linking between theory and practice.

### *Epistemology*

To make the present approach transparent and to explain the concept that is behind this textbook, some debates in pharmacokinetic theory will be traced back to classical positions and controversies in history and epistemology. For this purpose, short methodological statements will be placed before the respective chapters.

### *Common Principles*

Since drugs were given to produce an effect, it is obvious that pharmacokinetics is a required but not yet sufficient tool for drug dose decision. It is not only the kinetics but also the dynamics that must be considered when deciding on the appropriate adjustment of the dose (D) or the administration interval (Tau). Pharmacokinetics (PK) must be supplemented by pharmacodynamics (PD) to derive the individualized dose adjustment (= D/Tau).

$$\frac{D_{standard}}{Tau_{standard}} \rightarrow PK + PD \rightarrow \frac{D_{individual}}{Tau_{individual}}$$

One drug level ( $C_{indiv}$ ) can be used with the mean value and standard deviation (SD) of population parameters ( $P_{pop}$ ) as an a priori knowledge for the individual parameter estimate using the Bayesian objective function that minimizes the weighted differences. In analogy to an Aristotelian syllogism, the major general premise is stated and then the minor specific premise is added – thus, the conclusion can be deduced.

Premise 1: general parameters =  $P_{pop}$

Premise 2: individual concentration =  $C_{indiv}$

Conclusion: individual parameters =>  $P_{indiv}$

This is the logical basis of the Bayesian forecasting usually applied to derive the population parameters from clinical studies. From population parameters ( $P_{pop}$ ) the population-derived concentration can be predicted ( $C_{pop}$ ). The population-derived concentration can be stated also as the target for pharmacokinetic or therapeutic drug monitoring. From Bayesian theorem of conditional probability the objective function can be derived. The objective function looks for a minimum of differences (MIN).

$$MIN = \sum \frac{(C_{indiv} - C_{pop})^2}{SD_C^2} + \sum \frac{(P_{indiv} - P_{pop})^2}{SD_P^2}$$

First the logic goes bottom-up. The individual case is not only the origin of medical science but finally also the end. The second step is the top-down way. Medicine is the science of individuality [Michel Foucault 1963]. It remains a debate whether the methods to synthesize (= population kinetics) are also best applied when individualization is at stake (= inference).

In an individual case several concentrations can be measured =  $C_{indiv}$

From several individual cases the common parameters of a drug can be derived =  $P_{pop}$

This drug is characterized by specific parameters in an individual case =  $P_{indiv}$

The direct bottom-up way is the therapeutic drug monitoring (TDM). Based on therapeutic drug monitoring (TDM) by measurements of concentrations the dose can be adjusted to

variable clinical conditions. By such individual parameter estimates, every drug can be made applicable to every patient based on the individual conditions. But the interpretation of TDM needs top-down knowledge, namely pharmacokinetic and pharmacodynamics principles.

NOTE: For an individual prediction one single but precise value for the respective parameter is needed not an estimate of the overall variability.

Also pharmacogenetics (PG) can be integrated into this common concept, and be figured out as specific pharmacokinetic (PK) and pharmacodynamic (PD) parameter values for the individual patient. While pharmacogenetics gives categorical information (yes or no, the one or the other allele), pharmacokinetics and pharmacodynamics can be used to transform and to parameterize this discrete category into continuous variables. Thus, pharmacogenetics will be used for precision medicine while pharmacokinetics and pharmacodynamics are required to make proposals for an individualized therapy.

$$\text{Pharmacogenetics} \rightarrow \left[ \begin{array}{c} \text{Pharmacokinetics} \\ + \\ \text{Pharmacodynamics} \end{array} \right] \rightarrow \text{individual phenotype}$$

The main problem with drug kinetics arises after multiple dosing. This was the starting line for what has been introduced as “Pharmakokinetik” by Friedrich Hartmut Dost.

### Friedrich Hartmut Dost

Die wiederholte Verabreichung eines Heilmittels stellt das älteste, einfachste und daher auch heute noch am meisten verbreitete Verfahren dar, um zu einer verlängerten Wirkung zu gelangen. Wir können bei den folgenden, ins einzelne gehenden Betrachtungen von der Voraussetzung ausgehen, daß sowohl die Invasions- als auch die Eliminationsfunktionen jeweils einfachen Exponentialfunktionen folgen; denn wir haben schon früher dargelegt, daß die denkbaren Abweichungen von diesem Gesetz in Wirklichkeit nur gering sind. Nur die lineare Elimination des Alkohols beim Menschen werden wir auch hier wiederum einer gesonderten Darstellung unterziehen, da ihr eine große praktische Bedeutung zukommt, obwohl diese Eliminationsform bisher den einzigen Ausnahmefall in der gesamten Pharmakokinetik darstellt. Hingegen scheidet die hyperbolische Elimination von Antikörpern nach aktiver Immunisierung, da es sich hierbei um einen endogenen Stoff handelt, an dieser Stelle aus unserem Interessenkreis aus.

Figure 1. Friedrich Hartmut Dost was the first to coin the term “Pharmakokinetik”. Pharmacokinetics originates from analysis of repetitively administered drugs. DER BLUTSPIEGEL. Thieme, Leipzig. 1953: 244.

The main problems arise with drugs repetitively administered. But any drug that produces a therapeutic action may also exert adverse effects. Thus, pharmacokinetics and pharmacodynamics also apply to single dose regimens.

## 2.0 Basic Concepts in Pharmacokinetics

NOTE: Pharmacokinetics and pharmacodynamics can be seen as the proof of the axiom presumed for all physical medicine: Mathematical laws are valid also in an individual patient.

A kind of dogmatic controversy exists about the right way to derive, to present and to teach pharmacokinetics. The one way are the model based and mechanism-based approaches that can be distinguished from another way, the more abstract and mathematical approach. Mechanistic theory is the cause and consequence reasoning underlying the model-based approaches. This is more empirical and can be subjected to experimental falsification. The mathematical approach could be considered to be an approach of pure logical thinking. Here mainly the plausibility of axioms and the correctness of the derivations are of interest. Causality is one-directional, linear, vertical and hierarchical. Mathematical derivations are bi-directional, time-invariant, horizontal, reversible and recursive. Mechanical causality will assume on-dimensional thinking from A to B. Mathematical abstraction can move in a multi-dimensional space of equalities. This will impact on the bi-directional correlation of pharmacokinetics and pharmacodynamics where pharmacokinetics clearly is the cause and pharmacodynamics the consequence. With dose adjustment, however, both become complementary since pharmacokinetics will help to avoid toxic overdosing but pharmacodynamics will be needed to avoid inefficient underdosing.

Mathematics is not a one-dimensional cause and consequence but a recursive thinking. Mathematical theories are not only based on premise and conclusion but on a multi-granular logic. It is an advantage of the mathematical thinking that consequence can change the position and firm as a premise while the cause can be derived as a syllogistic conclusion. Mechanism based thinking is concerned with the specific appearance of the problem. The mathematical approach is interested in the general solution of a problem. Mechanistic thinking is bottom-up but mathematical thinking is top-down.

Mechanism based models are more easily comprehensible. This is physics, that can be perceived with our senses and physicians need to trust their senses. But mathematics, according to Maimonides, is just the other source of truth. Mathematics cannot be seen, cannot be heard, not be tasted, not be smelled not be touched. Mathematics is a purely intellectual abstraction. But mathematics can be explained and be learned by the 10 fingers that represent a natural abacus. Galileo Galilei stated that "mathematics is the alphabet of the nature". Accordingly, one could say that physics is the book of the nature but mathematics is not only the alphabet but also the grammar. Mathematics states the rules that nature should obey – but not always does nature follow these rules.

There are three basic principles and natural laws applicable to pharmacokinetics and pharmacodynamics: The one is the exponential solution to differential equations and the other is the law of mass action and the third is the power function.

### *Exponential function*

Differential equations apply when a change is considered. If there is a dependent variable that changes with an independent variable, this change is proportional to the variable for many natural processes (growth, radiation...). Thus the change is a function of the variable and a proportionality constant. This might be stated as a plausible and intuitively evident primary assumption in many natural processes.

$$\frac{dy}{dx} = -k \cdot y$$

While the absolute change of the variable depends on the value of this variable, it is typical for exponential functions that the relative change is constant.

$$-\frac{dy/dx}{y} = k$$

In pharmacokinetics the independent variable is the time  $t$  and the dependent variable is the concentration  $C$ . Rearrangement will allow to integrate this function.

$$\frac{dC}{dt} = -Ke \cdot C$$

$$\frac{dC}{C} = -Ke \cdot dt$$

The integrated or antiderivative function uses the natural logarithms.

$$\ln(C) = -Ke \cdot t$$

The natural logarithm ( $\ln x = \text{logarithmus numeralis}$ ), the decadic logarithm ( $\lg x$ ) or decimal logarithm ( $\log_{10}$ ) and the exponential function are defined as follows.

$$\log_{10}(x) = \lg(x)$$

$$\log_e(x) = \ln(x)$$

$$\ln(x) = 2.3025851 \cdot \lg(x)$$

$$\lg(x) = 0.4342945 \cdot \ln(x)$$

Since the natural logarithm is the inverse exponential function and the exponential function is the anti-logarithmic function of the  $\ln(x)$ , we use the natural logarithm in pharmacokinetics.

$$y = \ln(x)$$

$$\exp(y) = x$$

In analogy to the logarithm  $\ln(x)$  we choose the spread sheet writing for exponential functions  $\exp(x)$ . The exp function uses the Euler's constant  $e$  where it holds ( $e = 2.71828$ ).

$$e^x = \exp(x)$$

## 2.0 Basic Concepts in Pharmacokinetics

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$$\ln(\exp[x]) = x$$

$$\exp(\ln[x]) = x$$

The integration can be separated into two processes, one for each side.

$$\int \frac{dC}{C} = \ln(C)$$

$$\int -Ke \cdot dt = -Ke \cdot t$$

$$\ln(C) = -Ke \cdot t + \text{const.}$$

The integration constant can be identified by the initial concentration at time zero.

$$\text{const.} = \ln(C_0)$$

$$\ln(C) - \ln(C_0) = -Ke \cdot t$$

$$\ln\left(\frac{C}{C_0}\right) = -Ke \cdot t$$

The logarithm is the undue exponential function and the exponential is the reverse logarithmic function.

$$\exp\left[\ln\left(\frac{C}{C_0}\right)\right] = \exp(-Ke \cdot t)$$

The exponential function is the antilog version of an integrated differential equation.

$$\frac{C}{C_0} = \exp(-Ke \cdot t)$$

$$C = C_0 \cdot \exp(-Ke \cdot t)$$

$$C = \frac{C_0}{\exp(Ke \cdot t)}$$

### *Half-life*

For the condition that a concentration is one half of a previous concentration, the half-life can be derived as a determinant where the half-life is no longer only a time variable but a pharmacokinetic parameter ( $t_{1/2} = T_{1/2}$ ).

$$\frac{C_2}{C_1} = \frac{1}{2}$$

$$\frac{1}{2} = \exp(-Ke \cdot t_{1/2})$$

## 2.0 Basic Concepts in Pharmacokinetics

$$2 = \exp(Ke \cdot t_{1/2})$$

$$\ln(2) = Ke \cdot t_{1/2}$$

$$T_{1/2} = \frac{\ln(2)}{Ke}$$

The natural logarithm from 2 is constant ( $\ln(2) \approx 0.693$ ).

$$T_{1/2} = \frac{0.693}{Ke}$$

$$C_2 = C_1 \cdot \exp\left(-\ln(2) \cdot \frac{t_2 - t_1}{T_{1/2}}\right)$$

$$C_2 = C_1 \cdot \exp\left(-0.693 \cdot \frac{t_2 - t_1}{T_{1/2}}\right)$$

This rule applies to any concentration – the half-life, therefore, is a constant for any exponential function.

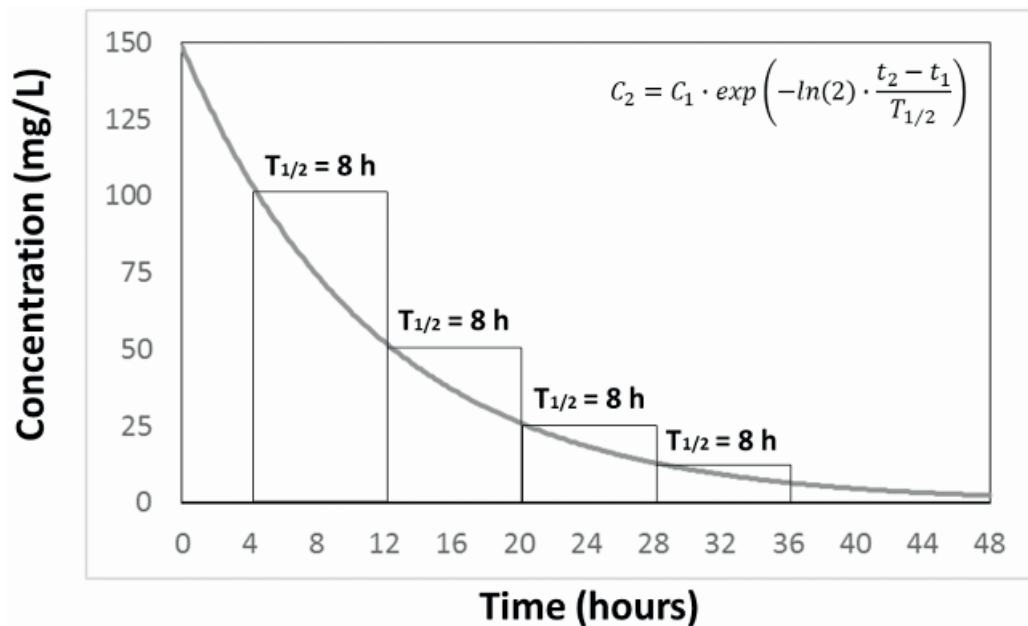


Figure 2. For an exponential concentration decline, the half-life is a constant.

It is important to note, that also for the amount in the body ( $A$ ) a differential equation can be stated where the volume is constant ( $A = C \cdot V$ ). The decrease in this amount is proportionate to the actual amount. The proportionality constant corresponds also the elimination rate constant  $Ke$  stated for the concentration decline.

$$\frac{dA}{dt} = -Ke \cdot A$$

$$A = A_0 \cdot \exp(-Ke \cdot t)$$

Considering intravenous bolus injection, the initial amount is the dose ( $A_0 = D$ ) and the elimination rate constant reflects the half-life.

$$A = D \cdot \exp\left(-0.693 \cdot \frac{t}{T_{1/2}}\right)$$

Thus, the half-life is the same for both, the concentration decline and for the eliminated amount. This relationship applies for drugs following one-compartment characteristics. In case of more complex pharmacokinetics, the relationship still applies for the terminal phase of the concentration-time curve.

#### *The 1-exp function*

An important extension of the differential equation yields the most general version of the 1-exp function. As one practical example, the 1-exp function has been used to describe drug dissolution by the Noyes-Whitney formula [Noyes 1897]. Here the dissolution constant is  $K$ .

$$\frac{dC}{dt} = K \cdot (C_{max} - C)$$

$$\frac{dC}{C_{max} - C} = K \cdot dt$$

$$\frac{dC}{C - C_{max}} = -K \cdot dt$$

The final concentration is  $C_{max}$  and the initial concentration is  $C_0$ .

$$\ln(C - C_{max}) - \ln(C_0 - C_{max}) = -K \cdot t$$

$$\ln \frac{C - C_{max}}{C_0 - C_{max}} = -K \cdot t$$

If the initial concentration is zero ( $C_0 = 0$ ), one obtains a solution for the dissolution process that is an example of a general 1-exp function.

$$C = C_{max} \cdot [1 - \exp(-K \cdot t)]$$

$$C = C_{max} \cdot \left[1 - \exp\left(-0.693 \cdot \frac{t}{T_{1/2}}\right)\right]$$

A further extension of the 1-exp function is the Weibull function with a sigmoidal shape of the curve [Weibull 1951]. The Weibull function looks similar to the Douglas version of the sigmoidal 1-exp function that can be used to describe nonlinear sigmoidal and saturation kinetics [Dokumetzidis 2006].

$$\frac{C}{C_{\infty}} = 1 - \exp(-a \cdot t^b)$$

The original version considered the mass of the drug in dilution that can be expressed also as a concentration to make it applicable to pharmacokinetics.

### *Order of kinetics*

The differential equation can have different specifications. Based on the form of the differential equation, the zero order kinetics ( $C^0 = 1$ ) ...

$$\frac{dC}{dt} = K \cdot C^0$$

$$\frac{dC}{dt} = K$$

... can be distinguished from first order kinetics ( $C^1 = C$ ) ...

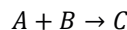
$$\frac{dC}{dt} = K \cdot C^1$$

$$\frac{dC}{dt} = K \cdot C$$

It is typical for first order kinetics that a half-life can be stated. The half-life is the inverse rate constant. We use the symbol  $T_{1/2}$  (and not  $t_{1/2}$ ) since the half-life is considered to be a parameter such as clearance (Cl) or volume (Vd) and not a variable such as time (t) and this holds not only for first-order kinetics.

$$T_{1/2} = \frac{\ln(2)}{K}$$

First order kinetics must be distinguished from second order kinetics. Second order kinetics will result when two reaction partners form a product.



$$\frac{dC}{dt} = K \cdot C^2$$

The differential form and the integrated version of second order kinetics are rarely needed in pharmacokinetics [<https://chem.libretexts.org>].

$$\frac{dC}{dt} = K \cdot [A] \cdot [B]$$

$$\frac{A}{B} = \frac{A_0}{B_0} \cdot \exp[(A_0 - B_0) \cdot K \cdot t]$$

## 2.0 Basic Concepts in Pharmacokinetics

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Second order kinetics are more complicated to analyze. The half-life of a second order process depends on the initial concentration and is inversely proportional to the initial concentration.

$$T_{1/2} = \frac{1}{K \cdot C_0}$$

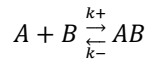
If the initial concentration is higher, the half-life will be shorter. The concentration-dependence of the half-life here in the second order kinetics is just contrasting to the concentration-dependence of the half-life which can be seen with the zero order part of capacity-limited Michaelis-Menten kinetics. The half-life from capacity-limited Michaelis-Menten kinetics is prolonged if the concentrations are high. If the half-life rises when concentrations rise, this indicates Michaelis-Menten kinetics. One can call this the MM half-life, where  $(1 / \ln(2) = 1.44)$ .

$$T_{1/2 MM} = \frac{K_m + 0.75 \cdot C}{1.44 \cdot V_{max}}$$

The strengths and weaknesses of the half-life parameter will matter all over the whole textbook here.

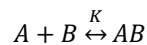
### *Law of mass action*

The second basic law in pharmacokinetics is the law of mass action. The law of mass action in its most simple form can be derived from the equilibrium condition. The molecules A and B are in equilibrium with the complex AB [Ferner 2015].



The equilibrium constant (K) holds for the equilibrium condition.

$$K = \frac{k+}{k-}$$



$$\frac{A \cdot B}{AB} = K$$

The law of mass action can be used to describing saturable plasma binding of drugs (PB%). Since there is a binding maximum, the general hyperbolic function can be derived for the free concentration ( $A = C_{free}$ ).

$$AB = B_{max} - A$$

$$A = \frac{B_{max}}{1 + \frac{B}{K}}$$

## 2.0 Basic Concepts in Pharmacokinetics

$$C_{free} = \frac{PB\%_{max}}{1 + \frac{C_{bound}}{K}}$$

Similarly, the law of mass action has been used to derive equations describing enzyme action and saturable Michaelis-Menten kinetics. The law of mass action allows to analyze the receptor-mediated reversible effect-concentration correlation. The law of mass action is also the basis for the hyperbolic and the 1-exp approach to nonlinear saturation kinetics.

### Power functions and polynomials

In a double logarithmic graph, some processes look linear. Here a power function often can be found and fitted.

$$\ln(y) = a + b \cdot \ln(x)$$

$$\ln(y) = a + \ln(x^b)$$

If the intercept is zero ( $a = 0$ ) the power dependence is log-proportional.

$$y = x^b$$

More frequently no theoretical mode is presupposed but only the empirical form of a power function is encountered. Here the parameters are in the product and power mode.

$$C = a \cdot t^b$$

$$\ln(C) = \ln(a) + b \cdot \ln(t)$$

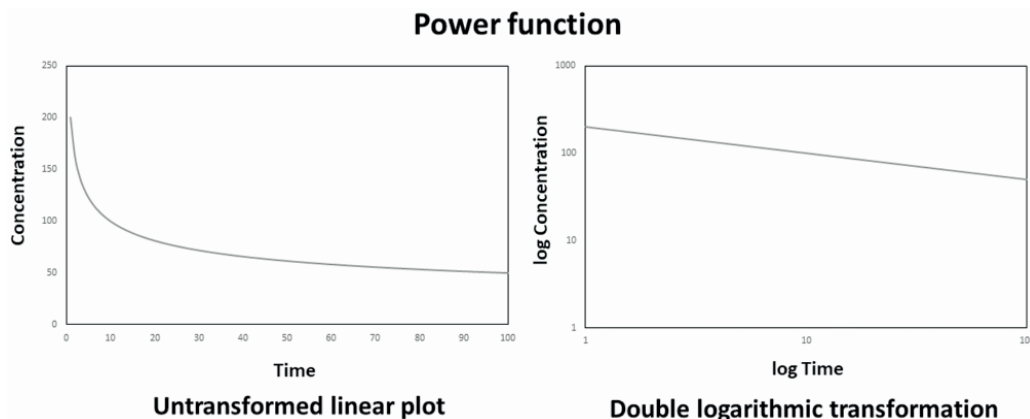


Figure 3. The arithmetic and untransformed concentration decline looks convex. However, this is not a multi-exponential kinetics but a power function. After double logarithmic transformation a linearization can be demonstrated. The parameters are  $a = 200$  and  $b = -0.3$  of the lines in both diagrams.

Such power functions – frequently with exponent 0.75 – are used for allometric scaling [Calvier 2017]. A power function has also been fitted to the complex elimination kinetics of amiodarone [Tucker 1984]. Also the dependence of gentamicin volume of distribution on

body weight could be fitted to a power function better than to a linear function. The power function corresponds to the obvious experience with gentamicin much better because a linear dependence would imply that a negative volume could result for very low weight. A power function has also been used to derive an equation for enzyme kinetics. Polynomials are also power functions. The polynomials are sometimes used to find a formal solution for a complex problem.

$$y = \sum_0^n a_i \cdot x^i = a_0 \cdot x^0 + a_1 \cdot x^1 + a_2 \cdot x^2 \dots + a_n \cdot x^n$$

Such polynomials are composites of several regular power functions. Cubic spline functions are frequently used and correspond to third order polynomials.

$$y = a + b \cdot x + c \cdot x^2 + d \cdot x^3$$

Such a cubic spline can empirically be fitted to complex data with nonlinear appearance.

### *Mathematics and medicine*

The mathematical world happens somewhere separate from the real world. Already Platon (428/427 – 348/347 BC) discussed on the idea that the mathematical cosmos exists different and separate from the real world. The time makes the difference. The real world is subjected to changes and nonstationary conditions. Mathematics – more than physics and other natural sciences – looks time-invariant and eternal. To overcome this difference in temporality, the mathematical logic has been made more applicable to reality by introducing the multimodal logics or temporal logic.

But how can mathematics and reality interact and communicate. The other great Greek philosopher, Aristoteles (384 – 322 BC) stated that all being must be understood as a plurality (“το ον λεγεται πολλαχοι”). Plurality means that the real world consists of multiple singular cases. Because of the plurality of entities, a multitude of possibilities exists in one and the same subject simultaneously. The number of possibilities outruns the number of events. If one of the possibilities comes to reality – and medicine tells us this truth – this event will dominate all the other possibilities. One disease can result into death ending all potential options.

Mathematics reflects on that what is common to these individual beings, on abstraction from real entities, on generalizability. The most generic but universal essence of the real world forms the cosmos of algorithms, equations, functions, relations and numbers. Mathematics represents the universality to that every single person participates. Numbers and their relations constitute the essential figures that are common to all different being. Mathematics is part of us.

This view corresponds to experience with medical science and case-based decision-making in clinical practice. Diseases become manifest only in an individual patient [Michel Foucault 1996]. The patients are different not the diseases. The disease is an always uniform entity – otherwise medicine as science would be impossible. The presentation of a disease will be modified by the respective singular case different from all other and all previous cases.

## 2.0 Basic Concepts in Pharmacokinetics

The reality is one-dimensional, linear and irreversible following the law of cause and consequence. Before one consequence will happen, one cause can induce a multitude of possible events. Always more than one consequence can come into action but only one of them will find the way into reality. Only one of the potential consequences will be selected and can ensue [Carl Friedrich von Weizsäcker 1992 p 106]. Which one happens can be a matter of chance. One cause, multiple possibilities but one consequence characterize reality. At the same time, more than one mechanism can be enacted causing one consequence. Thus, a blended causality results. Multiplicity and chance give reality sometimes a chaotic appearance. However, not indeterminism but unpredictability and uncertainty will follow from blended causality.

Mathematics, however, is multi-dimensional, following the referential logic of inference and deduction. Mathematics exists as multiple worlds – or at least as two worlds since for example, the linear world and the circular world are incommensurable. The real world presents as chaotic, but the mathematical cosmos looks regular, clear and surprisingly well structured. This magic order can be illustrated by a simple example: The sequence of squared numbers follows an obvious law. The difference between two squared numbers corresponds to the sum of the two first + one.

Table 1. The twice plus one law for the difference between two successive squared numbers.

| Number n | Order of numbers ni | Square of number | Order of squares SQi | Sum            | Sum + 1 | Difference SQn - SQn-1 |
|----------|---------------------|------------------|----------------------|----------------|---------|------------------------|
| 1        | n1                  | 1                | SQ1                  | n1 + n1 = 2    | 3       | SQ2 - SQ1 = 3          |
| 2        | n2                  | 4                | SQ2                  | n2 + n2 = 4    | 5       | SQ3 - SQ2 = 5          |
| 3        | n3                  | 9                | SQ3                  | n3 + n3 = 6    | 7       | SQ4 - SQ3 = 7          |
| 4        | n4                  | 16               | SQ4                  | n4 + n4 = 8    | 9       | SQ5 - SQ4 = 9          |
| 5        | n5                  | 25               | SQ5                  |                |         |                        |
| ...      |                     |                  |                      |                |         |                        |
| 16       | n16                 | 256              | SQ16                 | n16 + n16 = 32 | 33      | SQ17 - SQ16 = 33       |
| 17       | n17                 | 289              | SQ17                 |                |         |                        |

This tabulated observations can be transformed into a rule and conclusively be formalized. All this tabulated material can be put into one line: an equation. Thus, a somewhat – in former times – complicated calculation of squares can be simplified to an algebraic addition by the sequence of operations more easy to perform.

$$n_i^2 - n_{i-1}^2 = n_{i-1} + n_{i-1} + 1$$

Accordingly, the difference between  $17^2$  and  $16^2$  will be predicted with  $16 + 16 + 1 = 33$  and this prediction can easily be approved by an algebraic calculation. Thus, the square value of 256 can be predicted with  $225^2 = 255^2 + 255 + 255 + 1 = 65025 + 511 = 65536$ . This predictive equation has no other meaning and this equation probably will be completely useless. But it illustrates the astonishing lawful order behind such mathematical relations. Some people might call this order also beauty and are able to see real magic esthetics in such an abstract formula. The real world might be compared with a well-tempered keyboard. The practical advantage from well-tempered tuning results that any piece of music can be played in any key.