Minimum-χ^2-estimation of pharmacokinetic parameters

Karl-Ernst Biebler
Institute for Biometry and Medical Informatics
Ernst-Moritz-Arndt-University Greifswald
17487 Greifswald, Germany

Abstract
Parameter estimation in the pharmacokinetics requires a probability theoretical model. One often uses a regression formula with a random error term. Another approach is developed here. Random variable is the residence time of a drug molecule in the individual. Its probability distribution is derived from the pharmacokinetic model via the related ordinary differential equations. The related parameter estimation is calculated according to the varied minimum-χ^2-method from the measured concentration values. The applicability of this procedure was examined for certain classic compartment models. Examples and counterexamples are given. If the varied minimum-χ^2-estimation exists, it is uniquely determined and consistent. The test of Pearson then can be used for the model choice.

Key Words: Pharmacokinetics, compartment model, residence time distribution, minimum-χ^2 parameter estimation

1. Introduction

If a mathematical model is formulated for the change of the concentrations of drugs in an organism over time, then it is to be biochemically, physiologically, etc. verified in a technical context. The a-posteriori selection of a model can't do without a mathematical characterization of the decision rule and the related calculation methods. Well-founded rules for decisions should be formulated. The judgment of the compatibility of measurements with a function chosen for the description of them is a generally formulated task. For experimental evaluations, statistical methods are preferred in which experimental planning (in the statistical sense), parameter estimation and tests of goodness of fit infer the ideal problem solution.

The typical pharmacokinetic experiment consists in drug concentration measurements cm_i at an individual at different times $t_i, i = 1, \dots, r$. So an individual kinetics is looked at. In a population kinetic context, samples $cm_{ij},\ i = 1, \dots, r,\ j = 1,2,3$ of j such individual kinetics are evaluated. It is clever to measure they at the same t_i for each individual. The statistical methods found in literature about parameter estimation and model choice, respectively, refer mainly to regression models

$$CM_i = \mathrm{c}(t_i) + \varepsilon_i, \qquad i = 1, \dots, r.$$

Here $CM_1, \dots, CM_r$ is a random vector, its realizations $cm_{1j}, \dots, cm_{rj}$ are the measured concentrations at times t_i and $c(t)$ is a model function. The error terms ε_i are understood as random variables. It is well known, that the ordinary Least-squares-method is a best linear unbiased estimator for the parameters of a linear model function, e.g. $(t) = b_0 + b_1 t + b_2 t^2$, whenever the error terms are uncorrelated, homoscedastic and have expec-

tation zero. This is no longer true, when the model function is proper nonlinear in its parameters. Such functions are typical of the pharmacokinetics, e.g. $c(t) = b_0\ exp(b_1 t)$. The Maximum-likelihood-method (ML-method) allows the parameter estimation in such situations and is preferred because of its asymptotic properties concerning efficiency, unbiasedness and normality. It requires the knowledge of the probability distribution of the random vector $(CM_1, \dots, CM_r)$. The parameters to be estimated have to be parameters of this distribution. Usually normal distributions are presupposed. An error variance model is required besides that. The ADAPT software package [10] offers a comfortable environment for modeling, parameter estimation and simulation experiments in pharmacokinetics. Weighted Least-square-estimation, ML estimation, Generalized-least-square-estimation and Bayesian estimation are there available to calculate model parameters from a set of individual kinetics. Considerable numerical efforts are involved in these procedures. The specific pharmacokinetic models, measurement plans and error models are mathematically developed and explained in the user manual of ADAPT. Further commercial software packages to the pharmacokinetics are in use. There is an extensive literature to regression models and related ML parameter estimations in general.

The typical pharmacokinetic experiment consists in drug concentration measurements cm_i at an individual at different times $t_i, i = 1, \dots, r$. So an individual kinetics is looked at. In a population kinetic context, samples $cm_{ij},\ i = 1, \dots, r,\ j = 1,2,3$ of j such individual kinetics are evaluated. It is clever to measure they at the same t_i for each individual. The statistical methods found in literature about parameter estimation and model choice, respectively, refer mainly to regression models

$$CM_i = \mathrm{c}(t_i) + \varepsilon_i, \qquad i = 1, \dots, r.$$

Here $CM_1, \dots, CM_r$ is a random vector, its realizations $cm_{1j}, \dots, cm_{rj}$ are the measured concentrations at times t_i and $c(t)$ is a model function. The error terms ε_i are understood as random variables. It is well known, that the ordinary Least-squares-method is a best linear unbiased estimator for the parameters of a linear model function, e.g. $(t) = b_0 + b_1 t + b_2 t^2$, whenever the error terms are uncorrelated, homoscedastic and have expectation zero. This is no longer true, when the model function is proper nonlinear in its parameters. Such functions are typical of the pharmacokinetics, e.g. $c(t) = b_0\ exp(b_1 t)$. The (ML)-method allows the parameter estimation in such situations and is preferred because of its asymptotic properties concerning efficiency, unbiasedness and normality. It requires the knowledge of the probability distribution of the random vector $(CM_1, \dots, CM_r)$. The parameters to be estimated have to be parameters of this distribution. Usually normal distributions are presupposed. An error variance model is required besides that.

The ADAPT software package [10] offers a comfortable environment for modeling, parameter estimation and simulation experiments in pharmacokinetics. Weighted Least-square-estimation, ML-estimation, Generalized-least-square-estimation and Bayesian estimation are there available to calculate model parameters from a set of individual kinetics. Considerable numerical efforts are involved in these procedures. The specific pharmacokinetic models, measurement plans and error models are mathematically developed and explained in the user manual of ADAPT. Further commercial software packages to the pharmacokinetics are in use. There is an extensive literature to regression models and related ML parameter estimations in general.

Nonparametric statistical procedures that make as few assumptions as possible necessary, may serve for the selection of models due to the judgment of the error terms. This includes sign and rank tests which are recommended for the application in the pharmacokinetics and compared with other decision criteria in [17]. With look at regression models

one can watch in the literature concerning pharmacokinetics, the errors ε_i are presupposed to be stochastically independent. Variance equality is usually accepted. Hypothesis examination is carried out by means of methods which are justified for linear statistical models with regard to suppositions of normal distributions. In [2] , [3], [17] and [23] the variance of the residuals is judged with the F-test. This test is here for the choice of models mathematically not well-founded, but for the situation however practicable. The different nature of observed time courses of concentration is discussed regarding an analysis of variance in [14]. The sum S of weighted quadratic residuals, as well as the number m of parameters to be estimated have influence on the criteria of goodness of fit by Akaike [1] and Schwarz [20]. The Akaike criterion was applied to pharmacokinetic examples by [24]. Normally distributed residuals were assumed. The authors came to the conclusion that for the observed data sets the Akaike and F-test both lead to the same model selection. The same criteria are compared in [16], on the basis of Monte-Carlo simulations though. There are further empirical methods of the model choice. Here for example the models are linearized and graphic representations are judged.

In this contribution another approach is proposed concerning the simultaneous parameter calculation and model choice for the classical pharmacokinetic compartment models. The residence time of a pharmaceutical molecule is considered a random variable. Its probability distribution is derived from the differential equation defining the respective compartment model. In comparison to regression attempts, assumptions on the distribution and properties of error terms are not necessary. The measured concentrations cm_i are not a direct observation of residence times. Therefore the standard ML-method is not applicable. Instead one gets the estimates of parameters from the varied Minimum-χ^2-method. This allows the application of the classical χ^2-test of goodness of fit from K. Pearson for the model choice. The proofs of the below formulated propositions are omitted here. One will find it in a book which is just prepared for publication [5].

2. Compartment models

In the medicine compartment models are used e.g. in pharmacokinetics (the first monograph on pharmacokinetics is [12]) and in urea kinetics (e.g. [19]) to describe the time course of the concentrations of the substance being in observation. The method is taken from chemical reaction kinetics.
The so-called One-compartment-model for iv bolus administration describes the time course of a substance administered rapidly at time zero, $t = 0$, to a body, which is regarded to be a single homogeneous compartment. The related differential equation is the diffusion equation

$$\frac{d}{dt}c(t) = -k_{el}c(t)$$

with time $t \geq 0$, elimination constant $k_{el} > 0$ and initial value $c(0) = c^0$. The unique solution to this homogeneous linear differential equation with constant coefficient is $c(t) = c^0 exp(-k_{el}t)$.
The inhomogeneous linear problem, the so-called One-compartment-model with first order input,

$$\frac{d}{dt}c(t) + k_{el}c(t) = -k_i c_i^o exp(-k_i t)\,, \quad k_{el} > 0\,, k_i > 0, c_i^0 > 0,$$

c_i^0 is here the value of the first order input function at time equals zero, has the unique solution

$c(t) = c_i{}^0 k\ t\ e^{-kt}$ for $k_i = k_{el} = k$ and

$c(t) = \frac{c_i k_i}{k_{el} - k_i}\ [e^{-k_i\, t} - e^{-k_{el}\, t}]$ for $k_i \neq k_{el}$, abbreviated

$c(t) = A\ [e^{-a\, t} - e^{-b\, t}]$.

The so-called system parameters a, b, A are functions of the model parameters $k_{el} > 0$, $k_i > 0$ and the initial condition $c_i^0 > 0$.
The Two-compartment model of the pharmacokinetics is given by the differential equation system

$$\frac{d}{dt} C(t) = K\ C(t) + I(t)$$

with the transposed compartments concentration functions vector $C(t) = [c_1(t), c_2(t)]^T$, the transposed compartments input functions vector $I(t) = [I_1(t), I_2(t)]^T$, and the model parameters matrix

$$K = \begin{pmatrix} -(k_{10} + k_{12}) & k_{21} \\ k_{12} & -(k_{20} + k_{21}) \end{pmatrix}.$$

Here the model parameters $k_{ij} > 0$ are the transfer parameters from compartment *i* to compartment *j* and k_{i0} the compartments elimination parameters. For simplicity, we consider the situation $I(t) = [0,0]^T$, i.e. there is iv bolus drug administration only in the compartment number one and the initial conditions are $c_1(0) = c^0$ and $c_2(0) = 0$. The solutions to this so-called Two-compartment-model for iv bolus administration arise with the known standard methods. To specify the Two-compartment-models for iv bolus administration, for the model parameters we write 0 for $k_{ij} = 0$ and k_{ij} for $k_{ij} \neq 0$ in the following and call it $(k_{10}, k_{12}, k_{20}, k_{21})$ -Two-compartment-model for iv bolus administration. There are 16 different such Two-compartment-models for iv bolus administration depending on whether the model parameters are different from zero. Models which, however, contain compartments with output but without input are left out as well the trivial model with model parameters all zero. Nine models remain in the consideration. Among them are $(k_{10}, 0,0,0)$ and $(0, k_{12}, k_{20}, 0)$, the One-compartment-model for iv bolus administration and the One-compartment-model with first order input, respectively. Additionally, the solutions to the differential equation system require case distinctions. The relations between the model parameters and the system parameters, calculable from the data, get complicated with that [4].

3. Residence time distributions related to compartment models

The parameters of the above established compartment models shall be calculated as well as the goodness of fit shall be judged with statistical methods. The measurements of an individual kinetics serve as data. So a probability theoretical model of the drug disposition process which corresponds with the compartment model is needed.
Every non-negative continuous real function with integral equals 1 over the whole set of real numbers defines a probability distribution. Probability densities can be produced

from suitable solutions to differential equations this way. Well known is the Pearson family of probability distributions [13]. A probabilistic model of the drug disposition process which corresponds with the deterministic compartment model in a canonical way is sought. Random variable is the residence time of a drug molecule. Its probability distribution has to be defined. Does a solution to the Two-compartment-model for iv bolus administration generate the associated residence time distribution? Statistical parameter estimations and tests are possible in these cases.
Residence time distributions and their connection to compartment models were studied under different points of view ([15], [22], [4], [6], [25], for example). A complete description of the residence time distributions associated to the Two-compartment-model for iv bolus administration one will find in [5]. In this contribution we restrict ourselves to examples.

Definition 1
Let $c(t) = c(t; a, b, A, B)$ be a function that corresponds with one of the observed compartment models, is dependent on system parameters a, b, A, B and is integrable on the whole set of nonnegative real numbers. Then

$$f_c(t) = \frac{c(t)}{AUC}$$

with

$$AUC = \int_0^\infty c(t)dt < \infty$$

denotes the standardized concentration-time function of $c(t)$. Δ

Not every function $c(t)$ associated with a compartment model can be assigned a standardized function $f_c(t)$. The function $c(t) = Aexp(at) + B$ is among the solutions of a two-compartment model and only locally integrable.

The duration of presence, synonymously: residence time, of a drug molecule in an organism is regarded to be a random variable X.

Definition 2
With respect to a compartment model, let $m_e(t)$ denote the drug quantity of applied dose DOS eliminated from the organism up to time t. The probability distribution of X is defined as

$$F_X(t) = Prob(X < t) = \frac{m_e(t)}{DOS} \ ,$$

the density is denoted by $f_X(t)$. Mass and concentration are in the relation $m(t) = Vc(t)$. The distribution volume V is regarded as constant. Δ

Agreement: Densities and distributions are defined on the whole set of real numbers per definitionem. Followingly we ignore the extension with zero of these functions $F_X(t)$ and $f_X(t)$, respectively, on the negative real numbers because of a simpler notation.

We consider now as examples the simplest cases.

Proposition 1
For a One-compartment-model for iv bolus administration, the residence time of a drug molecule is exponentially distributed,

$$f_X(t) = f_c(t) = \ k_{el}\, e^{-k_{el}\, t} \ .$$

Δ

Proposition 2
The following is valid under the assumption $k_i \neq k_{el}$ for the One-Compartment model with first order input:

1. The random variable X has the distribution function

$$F_X(t) = 1 - \frac{k_{el} k_i}{k_{el} - k_i} \left[\frac{e^{-k_i\, t}}{k_i} - \frac{e^{-k_{el}\, t}}{k_{el}} \right] \ .$$

2. $f_X(t) = f_c(t)$ is valid for the density function.

3. $f_X(t)$ is the linear combination of the densities of two exponential distributions. Δ

Proposition 3
The following is valid under the assumption $k_i = k_{el} = k$ for the One-Compartment model with first order input:

1. The random variable X is Gamma distributed and has the distribution function

$$F_X(t) = 1 - \ (1 + kt) e^{-k\, t} \ .$$

2. The following is valid for the density function:

$$f_X(t) = f_c(t) = \ k^2 t e^{-k\, t} \ .$$

Δ

The proofs of these propositions are straightforward. Calculate the solutions to the differential equation system according to the given conditions, calculate the standardized concentration-time functions according to the definition, calculate the probability distributions according to the definition. Use the mass balance equation $DOS = m(t) + m_e(t)$.
From a systematic of the case distinctions one obtains explicit the residence time distributions related to the Two-compartment-model for iv bolus administration. They exist as functions of the concentration course in the drug administration compartment for the models $(k_{10}, 0,0,0\ )$, $(0, k_{12}, k_{20}, 0\ )$, $(0, k_{12}, k_{20}, k_{21}\ )$, $(k_{10}, k_{12}, 0, k_{21}\ )$. The residence time distribution densities are linear combinations of the standardized concentration-time functions $f_{c_1}(t)$ and $f_{c_2}(t)$ for the models $(k_{10}, k_{12}, k_{20}, 0\ )$ and $(k_{10}, k_{12}, k_{20}, k_{21}\ )$. One will be able to find more details in [5]. A sufficient condition for the coincidence of residence time density and standardized concentration-time function gives

Proposition 4
The residence time X of a molecule in an organism is a continuous distributed random variable with density $f_X(t)$. Elimination of the pharmaceutical is only carried out in the observation compartment. Quantity and concentration in the observation compartment are

connected by the equation $m(t) = Vc(t)$ and V is a constant distribution volume. The elimination can be described by $m'_e(t) = m_{el}(t)$. Here k_{el} is an elimination constant. Then the following is valid: For every density $f_X(t)$, a time course of concentration $c(t)$ exists such that $f_X(t) = f_c(t)$.

Δ

Not every one of the Two-compartment-models for iv bolus administration corresponds with a residence time distribution. It should be stressed that the distribution functions are independent from the applied drug quantity DOS and that the densities correspond with the observable time courses of concentration.

The correspondence of residence time density and standardized concentration-time functions is fundamentally based on the qualities of the pharmacokinetic model: Consider a so-called elimination process of 0-th order $c'(t) = -k_{el},\ c(0) = c^0$. In our context, the solution only applies to the interval $[0, c^0/k_{el}]$ where it is not negative. One goes over of the concentration-time-course to the mass-time-function by introducing the constant distribution volume V. The residence time distribution $F_X(t) = V\ k_{el}/DOS$ one obtains via the mass balance equation. It is dependent from DOS. In addition, $f_X(t) \neq f_c(t)$.

4. Parameter estimation: The varied Minimum-χ^2-method

The calculation of the parameters of a pharmacokinetic model is now formulated as a statistical problem of density parameters estimation. The random variable X is the residence time of a drug molecule in an organism. The parameters of its probability distribution can be estimated from samples. It is necessary to know its relations to the pharmacokinetic model for the interpretation of results. The residence times of the applied drug molecules shall serve as a concrete sample. To obtain a sample therefore indicates supplying the organism with a number of molecules and registering the residence time of every molecule. Four points of view require discussion with regard to the sampling method:

1. It must be assumed that the residence times of the single molecules are stochastically independent. This prerequisite is necessary to be able to use basic statements of the statistical estimation theory. On the other hand it is also essential for a theory of distribution processes at a molecular level, see [22] and in a more general setting [8]. One surely will accept the independence at low drug concentrations. Saturation as known for drug transporters or metabolizing enzymes can be an argument against independence. Pharmacologists have to decide the acceptance of the assumption at the end.
2. A measurement cm_i of concentration at t_i isn't realization of the residence time of a molecule. It has a summarizing character. Therefore, standard maximum-likelihood methods can't be used for parameter estimations. These require knowledge of the numerical values that the residence time takes on in a concrete sample. Residence times of single molecules are not available from the classical pharmacokinetic experiment.
3. The molecules however aren't actually detected one by one when a concentration is measured. Certain units of mass are counted. The precision of the method of measurement is contemplated here. According to this, the sample size N is con-

sidered to be the integral multiple of the unit of administered drug mass. Such a specification is also found in kinetics of chemical reactions: The equations formulated for molecules are only the model of thought for the relation between the amounts of substances that are, for example, measured in Mol.
4. If the last measurement of concentration yields an observed value considerable above zero, then the lifetime of a part of the elements of the sample wouldn't be recorded by the observation. However, transition to a truncated distribution is possible. This requires an interpretation of results with respect to the truncation.

From the observation of the concentration-time course one gets residence time data in grouped form. The standard statistic for evaluation of such data is the χ^2-statistic. Two problems can be processed with that, parameter estimation and model choice as a statistical test. As is well known, using the same data twice in subsequent statistical procedures is problematic. It is an advantage of the χ^2-test that merely a loss of degrees of freedom arises here.
Let n be the cell number and m the number of parameters to be estimated. The asymptotic distribution of the χ^2-test statistic is the χ^2-distribution with $n - m - 1$ degrees of freedom if the parameters were estimated according to the varied Minimum-χ^2-method. This is also right for the ML-estimated parameters if this estimation is based on the group frequencies of grouped data. The χ^2-test statistic does not have any limiting χ^2-distribution in general, when the ML-estimation of the parameters stems from the original sample data [7]. A direct comparison of χ^2-estimation and ML-estimation for medium sample situations can be carried out with simulation studies. The Minimumχ^2-estimation is a special kind of the minimum distance estimation method and has a very welcome robustness property: Accepted the real but unknown watched residence time distribution $G(t)$ is not member of the distribution family which was developed from the compartment model. That means the proposed model is incorrect. Then a minimum distance estimator is a consistent estimator for the specific parameter, which selects the best approximation of $G(t)$ in the parametric distribution family [18]. So the robustness ensures a certain compensation of the model error. This must be taken into consideration since the data also contain information about disturbance variables as well as measuring errors.
The varied Minimum-χ^2-method is chosen here for the construction of parameter estimates in connection with pharmacokinetic models. This corresponds with the interpretability of the pharmacokinetic experiment as a sample procedure, makes propositions concerning the qualities of possible estimators, and permits the use of the statistical test theory for the treatment of the problem concerning the selection of a model. The varied Minimumχ^2-method is explained in such a way now as it is needed for the Two-compartment-models for iv bolus administration. As calculation example an One-compartment-model for iv bolus administration was selected for the sake of simplicity.
$f_X(t; \alpha_1, \dots, \alpha_m)$ denotes the density of the continuous random variable X which is dependent on parameters α_j. $I_1, \dots, I_n$ with $m < n$ is a disjoint partition of the real range of X. The associated probabilities are $p_i = P(X \in I_i)$ with $p_1 + \cdots + p_n = 1$ and $p_i = p_i(\alpha_1, \dots, \alpha_m)$. B_i is the number of observations in I_i and

$E_i = Np_i$ is the number of realizations of X in I_i expected with regard to f_X in a sample of size N. If

$$\chi^2 = \chi^2(\alpha_1, \dots, \alpha_m) = \sum_{i=1}^{n} \frac{(B_i - E_i)^2}{E_i}$$

reaches a minimum at $(\hat{\alpha}_1, \dots, \hat{\alpha}_m)$, then $(\hat{\alpha}_1, \dots, \hat{\alpha}_m)$ is called a Minimum-χ^2-estimate for $(\alpha_1, \dots, \alpha_m)$. Suppose p_i is differentiable with regard to α_j.

$$\frac{\partial}{\partial \alpha_j} \chi^2(\hat{\alpha}_1, \dots, \hat{\alpha}_m) = 0, \quad j = 1, \dots, m \,,$$

are necessary conditions that $(\hat{\alpha}_1, \dots, \hat{\alpha}_m)$ is an extreme value of χ^2. The following simpler system of equations can be obtained when the denominator of χ^2 is viewed as a constant:

$$\sum_{i=1}^{n} \frac{(B_i - E_i)}{E_i} \frac{\partial p_i}{\partial \alpha_j} = 0, \qquad j = 1, \dots, m; \;\; m < n \;\; .$$

Its' solutions yields the so-called varied Minimum-χ^2-estimates of the parameters. The problem of parameter estimation in Two-compartment-models for iv bolus administration is now examined with regard to this method. The measuring times $t_1, \dots, t_r, \; r \geq 2$, yield a partition $I_i = [t_i, t_{i+1})$ of $[t_i, t_{i+1})$ in $r - 1$ intervals as well as the set of nonnegative real numbers in $r + 1$ intervals. The latter are the ones mentioned before as well as $[0, t_1)$ and $[t_r, \infty)$. The number B_i of drug molecules observed in I_i is proportional to the integral over the interval $[t_i, t_{i+1})$ of the observed concentration-time function $c(t)$. An approximation is required to more accurately denote the observed function $c(t)$ from the measurements $cm_i, \; i = 1, \dots, r$, on hand. Interpolating cubic spline functions are suitable for this. The number E_i of expected realizations in I_i of X arises from the knowledge of $f_X(t)$ and is calculated as

$$E_i = Np_i = N \int_{t_i}^{t_{i+1}} f_X(t) dt \;\; .$$

The sample size N can be obtained by the area under the spline function. E_0 or E_∞ and B_0 or B_∞ correspond with the intervals $[0, t_1)$ and $[t_r, \infty)$, respectively.
Two problems need to be solved in order to be able to estimate the parameters of the residence time distribution of interest by means of the Minimum-χ^2-method.
First, an incomplete observation of the process influences the parameter estimation. This is expected when $P(X < t_1) + P(X > t_r)$ has a noteworthy magnitude. A way out could be the consideration of truncated densities. But this leads to a modification of the pharmacokinetic model.
Second**,** if $f_X(t)$ represents a linear combination of the densities of two standardized $c(t)$-functions, then the expected values E_i aren't only dependent on one of

the two functions $c_j(t)$ anymore. In these cases, the observations of only one of the courses $c_1(t)$, or $c(t)$, isn't enough to indicate the realizations of the random variable. The number of drug molecules observed in a single compartment isn't proportional to the number of molecules present in the organism. The estimation of parameters via the Minimum-χ^2-method isn't possible for Two-compartment-models for iv bolus administration with elimination from both compartments. This gives a probability-theoretical look to the significance of the mammillary models with regard to the residence time concept. The problem itself was already addressed by [11]. Mammilary models have all input into a central compartment and all loss occurring from the central compartment. These models are extremely common in pharmacokinetics. So the exclusion of models with elimination from both compartments does not seem to be overly restrictive.

Proposition 5
Of the Two-compartment-models for iv bolus administration, exactly the models $(k_{10}, 0,0,0)$, $(0, k_{12}, k_{20}, 0)$, $(0, k_{12}, k_{20}, k_{21})$ and $(k_{10}, k_{12}, 0, k_{21})$ are estimatable with regard to the varied Minimumχ^2-method. Δ

5. Model selection by the varied Minimum-χ^2-method

A fundamental theorem is consulted for the characterization of the statistical qualities of the varied Minimumχ^2-estimator in connection with Two-compartment-models for iv bolus administration. It dates back to R.A. Fisher, E.A. Pearson, J. Neyman and H. Cramer. Bibliographical references as well as a proof can be found already in [9].

Theorem ([9, pages 427-434]
n real functions and $p_1(\alpha_1, \dots, \alpha_m)$, …, $p_n(\alpha_1, \dots, \alpha_m)$ of $m < n$ variables $\alpha_1, \dots, \alpha_m$ are given. Let the following be true for all points $(\alpha_1, \dots, \alpha_m)$ of a non-degenerated subset $\mathcal{R}$ of $\mathbb{R}^m$:

1. $\sum_{i=1}^{n} p_i(\alpha_1, \dots, \alpha_m) = 1$.

2. $p_i(\alpha_1, \dots, \alpha_m) > 0$ for all $= 1, \dots, n$.

3. All p_i have continuous partial derivatives $\frac{\partial}{\partial \alpha_j} p_i$ and $\frac{\partial^2}{\partial \alpha_j \partial \alpha_k} p_i$, $j, k = 1, \dots, m$.

4. The matrix $J = \left(\frac{\partial p_i}{\partial \alpha_j} \right)$, $i = 1, \dots, n$ and $j = 1, \dots, m$, has rank m.

Let X be a random variable, $I_1, \dots, I_n$ a disjoint partition of its range, and $p_i^0 = p_i^0(\alpha_1^0, \dots, \alpha_m^0) = P(X \in I_i)$ with $\alpha^0 = (\alpha_1^0, \dots, \alpha_m^0)$ an inner point of $\mathcal{R}$. For N realizations of X denotes B_i the number of its values in I_i , $B_1 + \dots + B_n = N$. Then the system of equalities

$$\sum_{i=1}^{n} \frac{(B_i - E_i)}{E_i} \frac{\partial}{\partial \alpha_j} p_i = 0, \qquad j = 1, \dots, m \ ,$$

has a unique solution $\hat{\alpha} = (\hat{\alpha}_1, \dots, \hat{\alpha}_m)$. It converges in probability to α^0 for $\to \infty$. The random variable χ^2 calculated with $\hat{p}_i = p_i(\hat{\alpha}_1, \dots, \hat{\alpha}_m)$,

$$\chi^2 = \sum_{i=1}^{n} \frac{(B_i - N\hat{p}_i)^2}{N\hat{p}_i} \quad ,$$

is asymptotically χ^2-distributed with $n - m - 1$ degrees of freedom. Δ

This theorem is fundamental for the proofs of the following propositions.

Proposition 6
For the Two-compartment-models $(k_{10}, 0,0,0)$, $(0, k_{12}, k_{20}, 0)$ and $(0, k_{12}, k_{20}, k_{21})$, the parameters of the associated residence time distributions are estimated consistently and uniquely via the varied Minimum-χ^2-method. The compatibility of measurements with accompanying concentration-time-functions of the respective model can then be judged with Pearson's χ^2-test of goodness of fit. Δ

Conjecture: Also for the Two-compartment-model $(k_{10}, k_{12}, 0, k_{21})$ the Pearson test is applicable. However, we do not have any proof at present.

Proposition 7
Let the residence time distribution that is truncated at the first and last measurements be assigned to the One-compartment-model for iv bolus administration. It's parameter k_{10} is estimated consistently and uniquely via the varied Minimum-χ^2-method. The compatibility of the measurements and the function $c(t) = c^0 exp(-k_{10}t)$ on the observation interval $[t_1, t_r)$ can then be judged with the χ^2-test of goodness of fit. The number of degrees of freedom is $r - 2$. Δ

6. Example

An example will illustrate the test of goodness of fit in connection with the parameter estimation. The model function $c(t) = c^0 exp(-k_{10}t)$ is chosen and truncation is carried out at t_1 and t_r. Next, the function values are calculated for $c^0 = 250$ and $k_{10} = 0.5$ at measuring times $t_i = i,\ i = 1, \dots, 10$. For even i, these results are alternatively increased or decreased by *PV* percent of their values. With these "measurements", the model parameter k_{10} was estimated with regard to the varied Minimum-χ^2-method with reference to the residence time distribution with truncation. The corresponding χ^2-value CHI was calculated. The critical values for the respective significance levels 0.05 and 0.01 of the tests here are $\chi^2_{8,0.05} = 15.51$ and $\chi^2_{8,0.01} = 20.09$. For $PV = 50$, by the varied Minimum-χ^2-estimation result $\hat{k}_{10} = 0.5738$ and $CHI = 15.96$. This $PV = 50$ is the smallest PV-value such that CHI exceed the critical χ^2-test value. It is recognizable at which fluctuation of the measurements the test of goodness of fit rejects the compatibility with the best fitted model function (see also Figure 1).

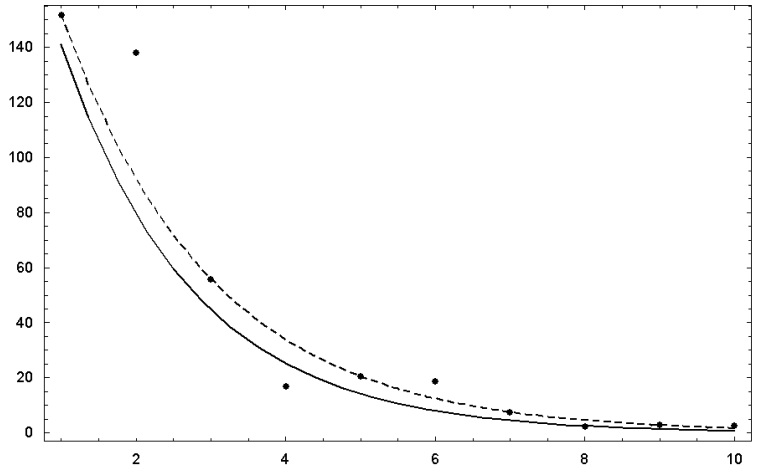

Figure 1: Varied Minimum-χ^2-estimation and Pearson's test of goodness of fit.
Dotted line: model function $c(t) = 250\ exp(-0.5\ t)$; single points: data; $PV = 50$.
The estimated $\hat{k}_{10} = 0.5738$ defines a model function (solid line) not fitting the data, $CHI = 15.96 > \chi^2_{8,0.05} = 15.51$, (see text).

7. Averaging

The problem of averaging proper nonlinear functions is of special interest in a population kinetic context. The described varied Minimum-χ^2-method offers particularly the possibility of calculating average kinetics. Individual kinetics $c^{\ell}(t), \ell = 1, \dots, k$ deliver each B_i^{ℓ} observed and E_i^{ℓ} expected numbers of realizations of residence times in the respective intervals I_i (see the explanations of the varied Minimum-χ^2-estimation above). The following process to determine the varied Minimumχ^2-averaged kinetic $c_{av}(t)$ of the given individual kinetics $c^{\ell}(t)$ can then be proposed:

1. Chose a system of knots $t_i,\ i = 1,2,\dots,r,$ and **fix** it for all measurements!

2. Calculate the parameter $(\hat{\alpha}_1, \dots, \hat{\alpha}_m)$ of the varied Minimum-χ^2-averaged kinetic $c_{av}(t)$ as the solution to

$$\sum_{\ell=1}^{k} \sum_{i=1}^{n} \frac{\left(B_i^{\ell} - E_i^{\ell}\right)}{E_i^{\ell}} \frac{\partial p_i}{\partial \alpha_j} = 0, \qquad j = 1, \dots, m;\ \ m < n\,.$$

The requirement of a system of fixed knots $t_i, i = 1,2,\dots,r,$ for all measurements is a necessary condition for the proposed averaging method. This way the averaging is similar to the situation one meets at the classical χ^2-test of homogeneity.
As an example, two kinetics

$$c^{(1)}(t) = A^{(1)} exp\left(-k_{10}^{(1)} t\right)$$

and

$$c^{(2)}(t) = A^{(2)} exp\left(-k_{10}^{(2)} t\right)$$

are varied Minimum-χ^2- averaged (see Figure 2).

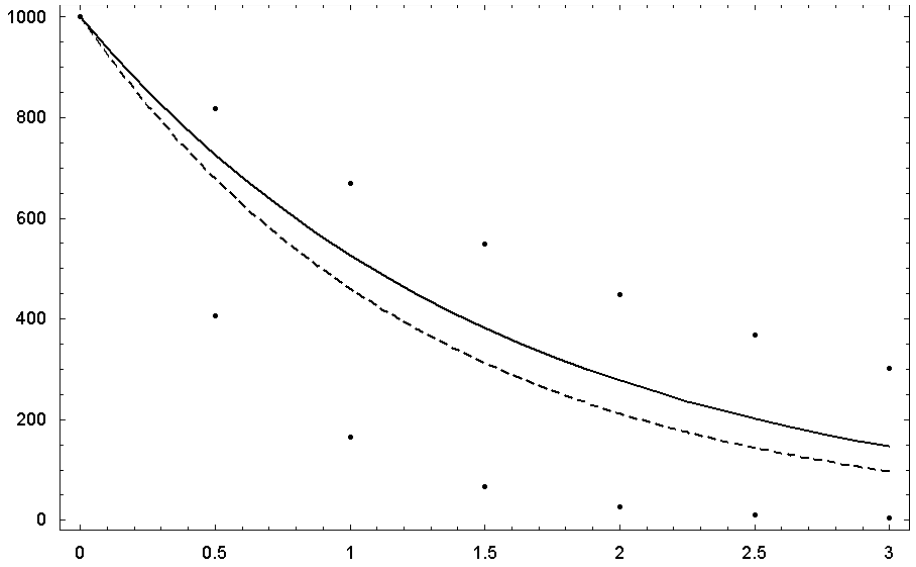

Figure 2: Illustration of the varied Minimum-χ^2-averaging (solid line) of two individual kinetics (single dots). The method-of-least-squares - averaged curve (dotted line) is given for comparison. Explanations can be found in the text.

References

[1] Akaike, H., 1974. A new look at the statistical model identification. IEEE Trans Autom Control AC 19, 716-723.

[2] Bardsley, W.G., McGinley, P.B., 1987. The use of nonlinear regression analysis and the F-test for model discrimination with dose-response curves and ligand binding data. J theor biol 126, 183-201.

[3] Bartfai, T., Mannersik, B., 1972. A procedure based on statistical criteria for discrimination between steady state kinetic models. FEBS lett 26, 252-256.

[4] Biebler, K.E., 1989. Beiträge zur Pharmakokinetik. Thesis. Ernst-Moritz-Arndt-Universität Greifswald. Germany.

[5] Biebler, K.E., Wodny, M., to appear. Splines and Compartment Models - An Introduction. 295 p.

[6] Cheng, H., Gillespie, W.R., Jusko, W.J., 1994. Mean residence time concepts for nonlinear pharmacokinetic systems (review article). Biopharmaceutics and Drug Disposition 15, 627-641.

[7] Chernoff, H., Lehmann, E.L., 1954. The Use of Maximum Likelihood Estimates in χ^2-Tests for Goodness of Fit. The Annals of Mathematical Statistics 25, 579-586.

[8] Clifford, P., Green, N.J.B., 1994. Diffusion kinetics in microscopic nonhomogeneous systems. Weiss, G. H. (ed.), Contemporary problems in statistical physics. Philadelphia, PA: SIAM. 1-40 (1994).

[9] Cramer, H., 1946. Mathematical methods of statistics. Princeton.

[10] D'Argenio, D.Z., Schumitzky A., Wang, X., 2009. ADAPT 5 Users Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles.

[11]DiStefano, J.J. 3rd, 1982. Noncompartmental vs. compartmental analysis: some bases for choice. Am.J.Physiol. 243. R1-6.
[12] Dost, F.H., 1953. Der Blutspiegel. Leipzig.
[13] Elderton, W.P., Johnson, N.L., 1969. Systems of frequency curves. Cambridge University Press.
[14] Gladigan, V., Vollmer, K.O., 1977. Beschreibung des pharmakokinetischen Verhaltens von Etozelin und dessen Hauptmetaboliten. Arzneimittelforsch/Drug res 27, 1786.
[15] Jacquez, J.A., 1985. Compartmental Analysis in Biology and Medicine, The University of Michigan, MI, 1985
[16] Ludden, T., Beal, S., Sheiner, L., 1994. Comparison of the Akaike Information Criterion, the Schwarz criterion and the F-test as guides to model selections. J Pharmacokinetic Biophram 22, 431-445.
[17] Meier, J., Rettig, H., Hess., H., 1981. Biopharmazie: Theorie und Praxis der Pharmakokinetik. Berlin/Heidelberg/New York.
[18] Parr, W.C., 1981. Minimum distance estimation: a bibliography. Communications in Statistics. Theory and Methods 10:12, 1205-1224.
[19] Sargent, J.A., Gotch, F.A., 1980. Mathematic modeling of dialysis therapy. Kidney Int. 10 Suppl, 2-10.
[20] Schwarz, G., 1978. Estimating the dimension of a model. Ann statist., 461-464.
[21] Steinijans, V., 1982. Double exponential concentration-time curves: a mathematical approach to certain time-dependencies in repetitive-dose studies. Pharmacokinetics during drug development: data analysis and evaluation techniques, ed.: J Bozler Stuttgart, 191-203.
[22] Veng-Pedersen, P., 1991. Stochastic interpretation of linear pharmacokinetics: A linear system analysis approach. J. pharmaceut. sci. 80,621-631.
[23] Wagner, J.G., 1975. Do you need a pharmacokinetic model, and if so, which one? J pharmacokin biophar 3, 457-480.
[24] Yamaoka, K., Nakagawa, T., Uno, T., 1978. Statistical moments in pharmacokinetics. J pharmacokin biopharm 6, 547-557.
[25] Yu, J., Wehrly, T.E., 2004. An approach to the residence time distribution for stochastic multi-compartment models. Mathematical Biosciences 191, 185-205.