NUMERICAL METHODS FOR PK PARAMETER ESTIMATION pdf

1: CiteSeerX â€" Citation Query Numerical methods for solving linear least squares problems

van den Bos, A. () Numerical Methods for Parameter Estimation, in Parameter Estimation for Scientists and Engineers, John Wiley & Sons, Inc., Hoboken, NJ, USA. doi: /ch6 The Newton Method for Poisson Maximum Likelihood The Newton Method for Multinomial Maximum Likelihood The.

Constructing the Paper The next task is to construct the Weibull probability plotting paper with the appropriate y and x axes. The x-axis transformation is simply logarithmic. The y-axis is a bit more complex, requiring a double log reciprocal transformation, or: Such papers have been created by different vendors and are called probability plotting papers. To illustrate, consider the following probability plot on a slightly different type of Weibull probability paper. This paper is constructed based on the mentioned y and x transformations, where the y-axis represents unreliability and the x-axis represents time. Both of these values must be known for each time-to-failure point we want to plot. Then, given the and value for each point, the points can easily be put on the plot. Once the points have been placed on the plot, the best possible straight line is drawn through these points. Once the line has been drawn, the slope of the line can be obtained some probability papers include a slope indicator to simplify this calculation. This is the parameter , which is the value of the slope. To determine the scale parameter, also called the characteristic life , one reads the time from the x-axis corresponding to. Thus, if we enter the y axis at , the corresponding value of. Thus, using this simple methodology, the parameters of the Weibull distribution can be estimated. Determining the X and Y Position of the Plot Points The points on the plot represent our data or, more specifically, our times-to-failure data. If, for example, we tested four units that failed at 10, 20, 30 and 40 hours, then we would use these times as our x values or time values. Determining the appropriate y plotting positions, or the unreliability values, is a little more complex. To determine the y plotting positions, we must first determine a value indicating the corresponding unreliability for that failure. In other words, we need to obtain the cumulative percent failed for each time-to-failure. This is a simple method illustrating the idea. The most widely used method of determining this value is the method of obtaining the median rank for each failure, as discussed next. Median Ranks The Median Ranks method is used to obtain an estimate of the unreliability for each failure. The rank can be found for any percentage point, , greater than zero and less than one, by solving the cumulative binomial equation for. This represents the rank, or unreliability estimate, for the failure in the following equation for the cumulative binomial: The median rank is obtained by solving this equation for at: For example, if and we have four failures, we would solve the median rank equation for the value of four times; once for each failure with. This result can then be used as the unreliability estimate for each failure or the plotting position. The solution of cumulative binomial equation for requires the use of numerical methods. Beta and F Distributions Approach A more straightforward and easier method of estimating median ranks is by applying two transformations to the cumulative binomial equation, first to the beta distribution and then to the F distribution, resulting in [12, 13]: Kaplan-Meier The Kaplan-Meier estimator also known as the product limit estimator is used as an alternative to the median ranks method for calculating the estimates of the unreliability for probability plotting purposes. The equation of the estimator is given by: Probability Plotting Example This same methodology can be applied to other distributions with cdf equations that can be linearized. Different probability papers exist for each distribution, because different distributions have different cdf equations. Special scales on these plots allow you to derive the parameter estimates directly from the plots, similar to the way and were obtained from the Weibull probability plot. The following example demonstrates the method again, this time using the 1-parameter exponential distribution. All of these units fail during the test after operating for the following times in hours: The steps for using the probability plotting method to determine the parameters of the exponential pdf representing the data are as follows: Rank the times-to-failure in ascending order as shown next. Obtain their median rank plotting positions. The times-to-failure, with their corresponding median ranks, are shown next: On an exponential probability paper, plot the times on the x-axis and their corresponding rank value on the y-axis. The next figure displays an example of an exponential probability paper. The paper is simply a log-linear paper. Draw the best possible

straight line that goes through the and point and through the plotted points as shown in the plot below. At the or ordinate point, draw a straight horizontal line until this line intersects the fitted straight line. Draw a vertical line through this intersection until it crosses the abscissa. The value at the intersection of the abscissa is the estimate of the mean. For this case, hours which means that This is always at Now any reliability value for any mission time can be obtained. For example, the reliability for a mission of 15 hours, or any other time, can now be obtained either from the plot or analytically. To obtain the value from the plot, draw a vertical line from the abscissa, at hours, to the fitted line. Draw a horizontal line from this intersection to the ordinate and read.

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2: Initial exploration of numerical methods for fitting models to PK data | PAGANZ

Distributions, the numerical estimation criteria give good results. Two-Parameter Distribution: Similarly, if we consider the Normal Distribution with Parameters mean and variance, both unknown, with.

Tel , Fax , rk. This article has been cited by other articles in PMC. However, the standard error of empirical Bayes estimates of inter-subject variability is not available. The computed standard error is in general similar to the results from other post-processing methods and the degree of difference, if any, depends on the employed estimation options. Also the SE of EBE can be used for simulation considering the uncertainty in the inter-subject variability [1]. The contents of this paper are as follows. In the methods section, theoretical backgrounds for calculation of the EBE and the standard errors of EBE are overviewed along with the descriptions on the four models and the two datasets used to assess the different ways of calculating the standard of errors of EBE. In the results section, the numerical results are summarized and compared. Lastly, the discussion section concludes with a few remarks and conclusions. In addition to the inter- and intra-subject variability, there can be another level of random variability called inter-occasion variability which describes the random variability among the different treatment occasions, for example, different visits. Laplacian method L uses "Laplacian" integral approximation of the objective function using up to the second order partial derivatives. The difference of FOCE objective function with respect to the Laplacian objective function is the use of the first order partial derivatives for the linear approximation whereas the Laplacian method uses up to the second order partial derivatives [4]. INTERACTION option does not affect the output for the additive residual error model, but produces different estimates which are regarded as more accurate for other residual error models proportional error, combined additive and proportional error, power function error, etc. EBE can be used for screening covariates for the structural model development [11]. If relationships between covariates and EBEs do not exist, EBE theoretically should have no trend with the covariates. Apparent relationship between EBE and covariate indicates the necessity of further refining the structural model, for example, including that covariate in the structural model. These datasets are readily available and the use of these public datasets makes it easy to compare the results of other available methods of the future. THEO dataset has observations from 12 subjects. There are 11 observations per subject following an oral administration of mg theophylline. Therefore THEO dataset can be regarded as an intensively sampled dataset. PHENO dataset has observations from 59 neonates with multiple intravenous administrations of phenobarbital. There are 1 to 6 observations per subjects, which can be regarded as a sparsely sampled dataset Table 1. One compartment PK model with variations in the structural part or residual error model was used to fit the test datasets. All of the individual PK parameters were modeled using log-normal distribution as in Equation 1. All the models had block omega matrix, and used combined proportional and additive residual error model. The four tested models are summarized in Table 2. The model prediction F for each dataset can be calculated as follows.

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3: Searching for an optimal AUC estimation method: a never-ending task?

Numerical methods for improving sensitivity analysis and parameter estimation of virus transport simulated using sorptive-reactive processes Gilbert Bartha,, Mary C. Hillb.*

The models may be given as an explicit C t relationship or defined by differential equations. For high variability and rich sampling the optimal method is only moderately advantageous over optimal trapezoid or standard numerical approaches Gauss-Legendre or Clenshaw-Curtis quadratures. The difference between the optimal estimator and other methods becomes more pronounced with a decrease in sample size or decrease in the variability. The described estimation method may appear useful in development of limited-sampling strategies for AUC determination, as an alternative to the widely used regression-based approach. It is indicated that many alternative approaches are also possible. Electronic supplementary material The online version of this article doi: AUC, Optimal sampling theory, Limited sampling strategy , Quadrature, Estimation, Minimax, Bioequivalence Introduction The estimation of integral of a function, or area under the curve AUC , plays an important role in biomedicine including in pharmacokinetic PK or toxicokinetic studies that are designed to estimate the integral of concentration of the investigated compound in plasma or tissue taken over time in a given interval. Within the framework of linear compartmental models AUC established after an intravenous administration is used to calculate the drug clearance. Regardless of which one of the possible linear models is valid, the result is determined solely by the drug dose and AUC. This is one of the reasons for AUC to be a central concept of the so-called model-independent pharmacokinetics. Regulatory institutions use AUC as a measure of extent of absorption in order to assess a bioequivalence of different formulations of the same drug [1 â€” 3]. Many authors have addressed the problem of practical determination of AUC. A few papers contain reviews of numerous algorithms designed to estimate this parameter [4 , 5]. Their authors do not pay any particular attention to the choice of sampling times, assuming they are given a priori, maybe following a certain traditional pattern. On the other hand, several authors have investigated the optimal designs which should yield the most accurate results using specific approaches. The optimal sampling is especially important if the number of measured concentrations is limited due to ethical and economical reasons. A vast number of authors MEDLINE reports about papers [7] developed limited sampling strategies for estimating AUC either of specific drugs, for instance cyclosporine [8 , 9] or midazolam [10], or in the general situation [11]. In their original form these results are of limited usefulness, since the authors have assumed fixed values of parameters of those equations. In practice such parameters are more or less uncertain if they were certain then the exact AUC would also be known and no estimation would be necessary. The present paper extends, in several directions, the ideas of that work. Namely, the aims of this work are threefold: Find an optimal sample schedule design for trapezoid rule under parameter uncertainty. Find an optimal quadrature within the class of linear combination LC quadrature approximations [13]. This is to be achieved by simultaneous adjustment of both sampling design and coefficients weights of quadrature. Evaluate obtained quadratures for five common PK models by means of simulation. In order to reach these aims it is required to: These points would be reported in the following sections after introducing the necessary background. Let be a vector of standard primary PK parameters. True AUC may be expressed as a function of these parameters,. An estimator of an unknown quantity is a function of observations that in some way approximates that quantity. As any experiment suffers from various nuisance factors, the observations do not follow any deterministic model exactly. Thus the estimation can be imperfect. One may intuitively expect that certain estimators can perform better than others. However, if one would like to transform this intuition into a scientific method, a rigorous criterion is needed that would enable comparison of estimators. Towards this end, a statistical theory of point estimation [14] introduces a loss function to assess the precision of an estimator. A loss function is always non-negative and it should yield 0 if an estimation is exact, i. The intuition behind this concept is rather simple: The worse the estimate is, the higher the loss will be. Another important concept is that of risk function. It is defined as an expectation of a loss. The expectation is taken over a joint probability distribution of all. The expectation of a continuous random variable is defined as the first moment

of its probability density function: While this definition might appear somewhat abstract, the expectation has quite simple interpretation, due to a fundamental law of statistics: The Law of Large Numbers. If one repeatedly observes a quantity that is random, then the average result should tend to the expectation of that quantity for a rigorous formulation of that law refer to any textbook on statistics, e. Estimators may be compared on a basis of their risk. Unfortunately, there is no estimator which is better than any other estimator for any parameter vector [14]. Nonetheless, an optimal estimator in that sense called a uniformly optimal estimator could be found if some restrictions were applied to the class of considered estimators. Perhaps the most popular one is the case of unbiased estimators with quadratic loss function. They are called minimum variance unbiased estimators MVUE. There can be little benefit from MVUE in pharmacokinetics, however, as unbiased estimators do not exist for standard PK models with usual parameters or, at least, they remain unknown. Despite these problems, a good or even the best estimator, according to reasonable criteria, can be constructed in a somewhat different manner. The choice between two standard solutions depends on whether is treated as a random variable with known distribution or as an unknown parameter. In the first case an estimator that minimizes expectation of the risk over distribution is searched for. It corresponds to a Bayesian approach. In the second case a maximum possible risk is minimized. That is a minimax problem. The former approach requires a knowledge of statistical distribution of PK parameters, while in the second method one needs to only know the range of those parameters. In what follows, the latter choice is analysed in detail. Assume the integrand follows a certain PK model with a parameter vector. Thus, what is measured can be expressed by the equation: The result is therefore a random variable. It may be considered as a linear estimator of an unknown integral AUC. These authors assumed specific parameters of a multiexponential equation i. If all are independently distributed with the mean 0 and variance , then 6 Note that detailed knowledge of the statistical distribution of is not required; any distribution with existing and known variance can be accepted. One way to make known is to express it as a function of C. The heteroschedastic model with a constant coefficient of variation cv is often assumed in PK models. It will be followed in the present study. Optimal sample schedule design Using the minimax approach the minimization of the risk for a given should be replaced by minimization of the maximum risk that can be obtained for any possible vector of parameters. Thus the problem in Eq. This corresponds to the division of the loss function L by the squared. An optimum based on the above loss function let it be called relative, in contrast to an absolute function L will be analysed in the present study. The corresponding risk function will be denoted by and an expression for the required optimum takes on the form: In bioequivalence studies AUC is being compared on a logarithmic scale; equivalently the comparison focuses on ratios and not differences of AUC values. Also, in clinical application, an estimation error of 10 units is certainly more important if the true AUC equals 50 units than in a case when it is as large as In both situations use of a relative risk would be preferable over an absolute risk. It means that for each trial sampling schedule the maximization in has to be conducted and finally that sampling schedule which yielded the smallest maximum is to be chosen. An optimization is constrained on both levels: PK parameter values should stay within a reasonable range; sampling times should be arranged in ascending order and they should be included in the integration interval. This constrained optimization problem cannot be solved analytically and an application of numerical algorithms is required. The optimization seems to be one of the most difficult branches of numerical analysis. There is always the possibility that the solution found would appear suboptimal. In order to minimize this possibility, the advanced methods are required using as much information as is available. This is especially important on an inner level: The necessary information includes first and second derivatives of the inner objective in , since they describe important geometrical properties of the hypersurface along which the maximum is searched for. The first derivative, i. More details are given in a subsection on numerical methods. Optimal quadrature design Another dimension in which the described approach can be improved on is the choice of a quadrature. Trapezoid and log-trapezoid rules are the simplest approaches to determine AUC. Their drawbacks were frequently indicated [16 , 17]. In the present work not only sampling points are free parameters. Some additional freedom is allowed regarding the choice of a quadrature. This may be done by considering a certain class of quadratures parameterized in a reasonable manner. Here the class of LC methods, as previously introduced by the present author [13], will

be considered. The LC-type quadrature by definition has the form given by Eq. Surprisingly, many approaches used in pharmacokinetics belong to this class. In particular, linear trapezoidal, hyperbolic trapezoidal [18], Lagrange [19] and spline [4] methods all are of the LC type. Allowing weights vector as well as knots vector to be manipulated, results in a final statement for the minimum that should be reached by the optimal method: In this problem a maximization over is nested within a minimization in both and.

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4: Parameter Estimation - ReliaWiki

Numerical Methods for Parameter Estimation in Stochastic Systems By Cody E. Clifton Submitted to the Department of Mathematics and the Graduate Faculty of the University of Kansas.

The Wiener filter is analyzed for stationary complex Gaussian signals from an information-theoretic point of view. A dual-port analysis of the Wiener filter leads to a decomposition based on orthogonal projections and results in a new multistage method for implementing the Wiener filter using a nest A dual-port analysis of the Wiener filter leads to a decomposition based on orthogonal projections and results in a new multistage method for implementing the Wiener filter using a nested chain of scalar Wiener filters. This new representation of the Wiener filter provides the capability to perform an information-theoretic analysis of previous, basis-dependent, reduced-rank Wiener filters. This analysis demonstrates that the recently introduced cross-spectral metric is optimal in the sense that it maximizes mutual information between the observed and desired processes. A new reduced-rank Wiener filter is developed based on this new structure which evolves a basis using successive projections of the desired signal onto orthogonal, lower dimensional subspaces. The performance is evaluated using a comparative computer analysis model and it is demonstrated that the low-complexity multistage reduced-rank Wiener filter is capable of outperforming the more complex eigendecomposition-based methods. APPL , " C and R are matrices that consist of actual columns and rows, respectively, of A, and U is a generalized inverse of their intersection. Mahoney, Petros Drineas " In the first stag In the first stage the randomized stage , the algorithm randomly selects O k log k columns according to a judiciously-chosen probability distribution that depends on information in the topk right singular subspace of A. In the second stage the deterministic stage , the algorithm applies a deterministic column-selection procedure to select and return exactly k columns from the set of columns selected in the first stage. Hansen - in Computational Inverse Problems in Electrocardiology, ed. Johnston, Advances in Computational Bioengineering , " The L-curve is a log-log plot of the norm of a regularized solution versus the norm of the corresponding residual norm. It is a convenient graphical tool for displaying the trade-off between the size of a regularized solution and its fit to the given data, as the regularization parameter varies. The L-curve thus gives insight into the regularizing properties of the underlying regularization method, and it is an aid in choosing an appropriate regularization parameter for the given data. In this chapter we summarize the main properties of the L-curve, and demonstrate by examples its usefulness and its limitations both as an analysis tool and as a method for choosing the regularization parameter. What distinguishes the various regularization methods is how Show Context Citation Context Golub proposed this approach in connection w Incremental condition estimation by Christian H. Appl , " This paper presents an improved version of incremental condition estimation, a technique for tracking the extremal singular values of a triangular matrix as it is being constructed one column at a time. We present a new motivation for this estimation technique using orthogonal projections. The paper focuses on an implementation of this estimation scheme in an accurate and consistent fashion. In particular, we address the subtle numerical issues arising in the computation of the eigensystem of a symmetric rank-one perturbed diagonal 2 2 matrix. Experimental results show that the resulting scheme does a good job in estimating the extremal singular values of triangular matrices, independent of matrix size and matrix condition number, and that it performs qualitatively in the same fashion as some of the commonly used nonincremental condition estimation schemes. Condition number, singular values, incremental condition estimation. The experiments reported here were performed with real matrices. In the rst set, we chose For details, the reader is referred to the code. Test matrices 1 through 5 were designed to exercise column pivoting. Matrix 6 was designed to test the behavior of the condition estimation in the presence of clusters for the smallest singular value Matrix 6 was designed to test the behavior of the condition estimation in the presence of clusters for the smallest singular value. For the other cases, we employed the LAPACK matrix generator xLATMS, which generates random symmetric matrices by multiplying a diagonal matrix with prescribed singular values by random orthogonal matrices from the left and right. For the break1 distribution, all singular values are 1. In the arithmetic and geometric distributions, they decay from 1.

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