

## Optimal Sampling Times for Therapeutic Drug Monitoring

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### Abstract

Therapeutic drug monitoring has evolved from simple concentration measurements to estimating the level of exposure of to the drug and making dosage recommendations. Optimal sampling strategies are commonly used in therapeutic drug monitoring to optimize drug therapy. Optimal sampling strategies aim to determine the sampling times which will produce the most accurate estimation of pharmacokinetic parameters or exposure indices. The methodology used to create optimal sampling strategies is diverse and heterogeneous. Multiple regression analysis has been surpassed by Maximum A Posteriori Bayesian (MAPB) estimation in terms of accuracy and flexibility. An optimal sampling strategy using MAPB estimation is created by either selecting sampling times from a predetermined set of sampling times or using Fisher information to calculate times with the most information on the parameters to be estimated. Validation of the strategy is required, preferably by resampling statistics for its efficient use of data.

**Keywords:** Maximum A Posteriori Bayesian; Therapeutic drug monitoring; Drug therapy

### Introduction

Therapeutic drug monitoring (TDM) is commonly used to individualize drug therapy. The goal of therapeutic drug monitoring is to optimize treatment efficacy and minimize toxicity or side effects, using measured drug concentrations. Not all drugs need to be monitored by TDM. Some criteria for TDM are: a relationship exists between drug concentrations and treatment efficacy or toxicity, a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug in individual patients and populations and availability of reliable drug assays. Some examples of drugs therapeutically monitored in clinical practice are: cyclosporine [1,2], sirolimus, tacrolimus, mycophenolic acid [3], anti-cancer agents [4], aminoglycosides [5], vancomycin [5] and antifungal agents [6].

Dosage formulation and adjustment in TDM is based on estimating one or more relevant pharmacokinetic parameters and thereby determining the level of exposure to the drug. Dosing adjustments can be made to achieve the targets set or the desired level of exposure. However, in most drug therapies, the level of exposure cannot be directly measured. For these drugs, exposure indices are used which correlate well with the exposure to the target. Traditionally, these were single blood concentration levels of the drug. However, many studies have questioned the correlation between single blood levels and drug exposure. In addition, reduced underdosing and toxicity are suggested in methods other than single level monitoring [7,8]. The area under the concentration time curve (AUC) is accepted to be better correlated with clinical efficacy than trough levels for many drugs [2,7-10]. The AUC represents the concentration-time curve over the entire dosing interval and thus the AUC represents the complete exposure to the drug. Other exposure indices have been used, such as maximum concentration [11,12], concentration level at a specific post dose interval [13] or AUC of a part of the dosing interval [11,14,15] as a measure of drug exposure. Any exposure index can be estimated using the right tools and measurements.

Therapeutic drug monitoring has evolved from the simple measuring of drug levels (peak and trough) to the practice of estimating an exposure index and hereby predicting subsequent levels of exposure and making dosage recommendations. Later the focus shifted to the minimization of the number of measurements to reduce patient burden

and costs. In neonates even to reduce morbidity due to the negative effect of repeated skin breaking and taking a relatively large amount of blood [16,17]. This minimization of the number of measurements, or samples, needed has a diverse nomenclature in the literature [18]. Some of the terminology used is: limited, optimal, minimal and sparse sampling. All of these refer to the same process of minimizing the number of samples, while maintaining adequate estimation precision. We will use "optimal sampling" for the remainder of this article. We describe the methodology used in the literature for determining optimal sampling times.

### Multiple Regression Analysis

Optimal sampling times are classically determined by multiple regression analysis (MRA) [13,19]. In an experimental setting, a large number of measurements over an interval are made in a number of patients. The dosing schedule and sampling times must be identical in all patients. Optimal sampling times are then determined by multiple regression of all sampling time points, resulting in an equation in the form of:

$$AUC = M0 + M1 \times Ct1 + M2 \times Ct2 \dots \dots + Mi \times Cti \quad (1)$$

Where AUC is the target parameter to be calculated, M0 is a constant which signifies the intercept on the y-axis. Cti are the blood concentrations measured at time ti. Mi are the associated coefficients as determined by multiple regression analysis.

The advantage of this approach is the simplicity of the resulting equation. Several disadvantages derive from the inflexibility of the method. Only in exact replicates of the dosing schedule can the equation

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be used. Also, if a sampling time is missed, the equation and all previous measurements are useless.

### Maximum A Posteriori Bayesian Estimation

Maximum A Posteriori Bayesian (MAPB) estimation [20] has been increasingly used in pharmacokinetic parameter estimation. MAPB estimation is based on Bayes' theorem: the concept that prior information can be combined with new data to produce an "A Posteriori" maximum likelihood estimate. In pharmacokinetic parameter estimation, the prior information is the distribution of pharmacokinetic parameters over a given population, usually in the form of a population pharmacokinetic model. The new data are the data obtained from the individual patient of whom the individual pharmacokinetic parameters are to be estimated. These are in the form of drug concentration measurements and possibly other patient specific data (covariates) such as height, weight, age and renal function. The general equation for MAPB estimation, assuming no covariance between parameters, is:

$$OBJ = \sum_{i=1}^n \frac{(C_{i,obs} - C_{i,pt})^2}{SD^2 C_{i,obs}} + \sum_{j=1}^m \frac{(P_{j,pop} - P_{j,pt})^2}{SD^2 P_{j,pop}} \quad (2)$$

Where n is the number of observed plasma concentrations, m is the number of parameters, Ppop and Ppt are the parameter estimates of the population model and the patients' individualized model, respectively; Cobs represents the observed plasma concentrations and Cpt represents the patients' predicted concentration; SD Ppop represents the standard deviation of the population PK model of the estimated parameter and SD Cobs represents the standard deviation of the observed plasma concentrations, or the residual error. Residual error is mostly measurement, or assay, error, but can also be influenced by model misspecification and dosing errors. Specialized software is needed for MAPB estimation. Equation (2) is called the objective function. This function must be minimized by an optimization algorithm, i.e. an mathematic algorithm searching for the minimum of the function by changing the individual pharmacokinetic estimates, Ppt in this equation. MAPB estimation is often part of an integral PK software program with more capabilities than only MAPB estimation, such as NONMEM, ADAPT [21], MW\Pharm [22], USC\*PACK and others.

### Optimal Sampling Methods Using MAPB Estimation

In general, determining optimal sampling times can be performed in two ways: selecting the optimal times from a collection of previously determined available times or by mathematical methods incorporating Fisher information [23].

#### Selecting sampling times

For this method, a dataset consisting of patient records with an identical rich sampling schedule is required. A rich sampling schedule is a schedule in which samples are taken over the entire time interval of interest. The dosing interval should be identical in all patients, but the dose or the number of the dosing interval can have any value. This dataset is usually obtained in a pharmacokinetic experiment in which few patients are sampled at (many) predetermined timepoints.

When the starting dataset is obtained, all combinations of one or more sampling times are tested for their performance in estimating pharmacokinetic parameters, often termed predictive performance. The predictive performance is determined by comparing the individual pharmacokinetic parameter estimates obtained from the tested

combination of sampling times with reference values. These reference values can be obtained by several methods, including the trapezoidal method, MAPB estimation with all available samples or non-linear least squares of all sampling times [18]. The predictive performance is quantified by determining the bias, precision or coefficient of determination of the estimates compared to the reference [18,24], where precision has some theoretical advantages [24].

#### Fisher information

The use of Fisher information [23] is a method of measuring the amount of predictive information a variable carries about a parameter. In optimal sampling the Fisher information is the amount of information about one or more pharmacokinetic parameters at the sampling times. Determinant (D)-optimality is the most often used optimality criterion using Fisher information [18]. In D-optimality, the determinant of the Fisher Information Matrix (FIM) is used. The FIM is determined by:

$$FIM = [P^T R^{-1} P] \quad (3)$$

Where P is the Jacobian matrix, PT the transpose of the Jacobian matrix and R-1 is the inverse of the variance matrix, signifying the weights attached to the measurements. The Jacobian matrix has the following form in D-optimality:

$$P = \begin{bmatrix} \frac{dC(P^*, t_1)}{dP_1} & \dots & \dots & \frac{dC(P^*, t_1)}{dP_n} \\ \vdots & \ddots & \ddots & \vdots \\ \frac{dC(P^*, t_m)}{dP_1} & \dots & \dots & \frac{dC(P^*, t_m)}{dP_n} \end{bmatrix} \quad (4)$$

Where C (P\*,tm) is the concentration of drug in a PK compartment as a function of parameter P at time t.

The determinant of the FIM is maximized by varying the sampling times. This is achieved by an optimization algorithm such as the Nelder-Mead simplex [25], although any robust global optimization algorithm can be used. When the optimal sampling times are determined a separate analysis must be performed to determine the predictive performance.

D-optimality has some disadvantages. The sampling times are dependent on the input pharmacokinetic parameters, which are usually population means or medians. Incorporating PK parameter distributions is possible by using methods like ED, EID or API optimality [26,27]. These methods maximize the expectation of some form of the detFIM over the population distribution. The simplest method of maximizing the detfim over a distribution is by Monte Carlo sampling [28].

#### Validation

Validation of the optimal sampling strategy is the process of confirming adequate accuracy of the sampling times in determining individual pharmacokinetic parameters. Validation is traditionally performed by splitting the data into two groups: a training group and a validation group [29,30]. The training group is used to determine the optimal sampling times by any of the above described methods (MRA, MAPB selection or Fisher information). With Fisher information, the training group can be used to determine the population pharmacokinetic model parameters, or population means. The validation group is then used to determine the predictive performance of the sampling strategy.

Data splitting has one main disadvantage [31]. Only a part, usually half, of the data is used to determine the optimal sampling times. When

only a small number of patients is available, resampling statistics or a Monte Carlo simulated dataset can be used for validation.

As mentioned, resampling statistics can be used for optimal sampling strategy validation. Here, a dataset is split into a training group and a validation group several times, to ensure each patient is in each group a number of times. Variation of resampling statistics are: the jackknife method, bootstrapping and cross validation [32]. This is an efficient use of patient data, as every patient is used for determining the optimal sampling strategy as well as validating the strategy.

## Conclusion

Optimal sampling strategies in pharmacokinetics have a diverse methodology. This is a result of many different available software programs and personal preferences of researchers. Using MAPB estimation has some very important advantages over multiple regression analysis, especially concerning flexibility. Selection of sampling times or using Fisher information for determining sampling times have both been used often in the literature and have produced sampling strategies with adequate precision. In the currently described methodology, only optimal sampling strategies using Fisher information can be called truly optimal. Other sampling strategies are bound to a combination of predetermined sampling times used in a pharmacokinetic experiment with rich sampling. Validation is an important part of building an optimal sampling strategy, which is, however, often omitted [18]. Resampling statistics make the most efficient use of available data for validation.

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