

**Title:** A Simple Method for Approximating Population Pharmacokinetic Parameters

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**Objectives:** Population PK models are useful for describing time-concentration data, but often there is little time and no budget to engage corporate or external experts to analyze data and determine these values. The analysis often involves rather specialized software such as Nonmem, SAS NL MIXED, or the nlme package in R/S. In a recent engagement, we needed a reasonable set of parameters to facilitate trial simulation methods development, and wanted to see if a simple method could be used to approximate population PK model without having to teach scientists, not specializing in PK modeling, a new programming language or to buy specialized software. Because MS-Excel is often used to contain and transmit data, we utilized the MS-Excel's Visual Basic macro functions to generate and test model parameters. The first step was to create a system to fit concentration curves and provide a matrix of patient-specific parameters for a PK model. These parameters and their distributions were the starting point to create population PK parameter estimates, by ensuring the mean and variance data for resampled cohorts matched actual data well. The resulting population parameters were shown to generate profiles matching clinical trial data not used in their fitting and estimation. These parameters were then used to develop an approach to trial simulation. Of course, for rigorous trial simulation, we used a more standard approach with appropriate software mentioned above, so the outcome of our simple method is compared with those more rigorous approaches. We asked 1) are the estimates from this approximation close to those from the more rigorous methods, 2) are those estimates useful, 3) are the approximations useful as a starting point for the rigorous methods (is convergence better or faster), and 4) are the resampled values of the approximate methods yield similar results to the more rigorous methods?

**Methods:** For individualized PK model parameters, we generated a series of macros in Excel utilizing time by concentration data to provide pharmacokinetic model parameters for a standard two-compartment model. The fittings were done to optimize the sum of the weighted square errors. These optimizations were done using the Solver feature (based on Generalized Reduced Gradient method) of Microsoft Excel. The system functions with either single dose or multiple doses of drug. The motivating problem was with multiple doses during the day displaying different kinetics. The individual peaks for each dose were determined by classic "peak stripping" techniques. For the population PK, the individual parameter values with the variance estimates from a small data set were used to generate a large random population. The mean and variance of the random population were then compared to original to determine if the variability from the random population matched the variability from the small dataset. The model parameters that were generated were compared to the literature and those generated using Nonmem and R.

**Results:** Published data for glyburide (1-3) and metformin (4-5) were selected to use as supply data for comparative examples. We also generated an idealized data set under several reasonable assumptions. Two sets of data were generated from the published literature and used to estimate both individual and population pharmacokinetic parameters for each drug. The resulting individual pharmacokinetic parameters generated by the worksheet were not significantly different than either the literature parameters or those generated by Nonmem. The population pharmacokinetic parameters generated by the system for these examples were comparable to published model parameters and those generated by Nonmem or nlme.

**Conclusions:** The system provided a simple method to fit individual PK model parameters using concentration data. The system utilized either single dose data or multiple dose data and provided reasonable PK model parameters for each dataset tested. The population PK model parameters generated by the system also provided reliable parameters and variance information. This method provides an approximate estimate of PK model parameters that could be used in initial trial simulations, or in quick evaluation of designs for additional

experiments. It has the advantage of utilizing standard worksheet software for those users who do not have access to experts, or time to learn how to use specialized software. We caution that this is an approximation, which may help give reasonable starting estimates for the software usually required for regulatory submission.

**References:**

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