DEVELOPMENT OF A PARZEN-BASED SOFTWARE FOR NON-PARAMETRIC BAYESIAN APPROACH TO POPULATION PHARMACOKINETICS

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The Bayesian approach to population pharmacokinetics has gained a noteworthy consideration among bio-statisticians. The underlying idea is simple: each individual is considered to be drawn at random from some suitable population, where the kinetics of a specific drug is assumed to follow a given, parametric, model. As a consequence, before any measurement takes place (including the observation of co-variates such as age, sex, etc.) the individual pharmacokinetic parameters are independently and identically distributed according to some (unknown) prior probability density function.
Based on these concepts, the state-of-the-art methodology is a parametric modelization of the population distribution, joining identification of both individual and population (meta)-parameters. However, an incorrect model of the population distribution adversely affects (i.e. biases) the estimate of the individual parameters, also.
For this reason, we replaced the parametric model of the population distribution with a non-parametric evaluation based on the Parzen method.
The non-parametric techniques do not assume a particular form of density function but usually estimate one, and the Parzen approach is proved to be asymptotically unbiased and uniformly consistent. Therefore it converges uniformly in probability to the true population, also in case of asymmetric or multi-modal distribution.
Our work was focused about the following steps: first, we implemented equation systems that describe classical compartment models, to estimate the main pharmacokinetic indices of each subject. Then, we made an error model that can either accept a well-known value or calculate it by data, both with homo- or hetero-scedastic (log-normal) error algorithms.
The third step was the realization of a module to calculate the function describing the population distribution. Based on the Parzen method, the algorithm is completely data-driven, model-independent and non parametric, useful to analyze the non-linear population PK problems.
For these reasons, we created a plug-in for the software package Matlab 6$^{(R)}$, employing the editor and the optimization routines of the program, with the aim to develop an easy interface and a flexible tool, useful for early parameters identification in any kind (rich, poor) of time-concentration data.
Preliminary testing of our plug-in were performed employing 5-Fluorouracil, Ceftriaxone and Clodronate data, with 1-compartment, 1st order, I.V. or IM model and error estimate. We obtained good and encouraging outcomes, both regarding technical aspects (elaboration time, software crash absence) and, especially, parameter and population distribution estimates. Furthermore, comparing the individual Volume and K10 estimates with the results obtained with WinNonLin 3.0 using the same models, we found very similar values, with an average maximal discrepancy of 20%.
In conclusion, the development of a module based on the Parzen method seems to be a useful and tool for non-parametric approach in pharmacokinetic modelling. Software users

insert each patient's time-concentration and dose data, then choose a compartmental model and a type of error management. Matlab(R) calculates individual PK parameters and produces a graph to describe the population distribution. In addition, our plug-in can easily be adapted to pharmacodynamic studies.

References

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