A NEW VARIANT OF THE EM-ALGORITHM FOR POPULATION PHARMACOKINETIC ANALYSIS

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Pharmacokinetics of the anti-inflammatory dipyrone drug are studied using the population approach. Experimental data from a Phase I study are analysed. We present a finite mixture model for nonlinear repeated measurement data The EM algorithm converges to a local maximum of the likelihood function-the particular solution is determined by the starting values. A method proposed by Böhning, 2003) to reduce this dependence on starting values is to wait until the algorithm seems to have converged in the sense of there being little progress in the likelihood, and then swap out one of the components, replacing it with the component θ' for which the gradient of the likelihood function $\Delta_{\theta'}(\Theta)$ is maximal (where Θ represents the current estimates). Finding the maximum of the gradient for this potentially high dimensional nonlinear problem is performed. using stochastic optimisation with simulated annealing The component to be removed from Θ is chosen so that the new likelihood is maximal. This procedure can be iterated so as to hopefully discover many of the locally optimal solutions. Finally the predictive performance of this model is compared with a standard nonlinear mixed-effects model using the .623 estimator (Efron and Tibshirani, 1993) for the mean squared error of prediction.