NEW ADVANCES IN NONPARAMETRIC PK/PD POPULATION MODELING

R. Leary, R. Jelliffe, A. Schumitzky, and M. Van Guilder. San Diego Supercomputer Center, UCSD and Laboratory of Applied Pharmacokinetics, USC School of Medicine, Los Angeles, USA.

The nonparametric (NP) maximum likelihood (ML) method of PK/PD population modeling has several advantages relative to parametric approaches, notably the guarantee of asymptotic statistical consistency and, perhaps most importantly, the ability to discover unsuspected sub-populations, of fast and slow metabolizers, for example, without further aid. The NPEM program in the USC*PACK collection of PK/PD software, is a widely used implementation of this approach. However, the specific approach used in NPEM had several functional limitations. For example, for large models, it was difficult to achieve high resolution due to limitations on the maximum grid sizes that are computationally feasible, even on supercomputers. Similarly, the computation of confidence limits via bootstrap procedures, and the separation of intra- from inter-individual variability were not feasible with NPEM on current generation computers.

We have developed a new Non-Parametric Adaptive Grid (NPAG) approach that removes these limitations, while preserving the fundamental mathematical advantages of the NPEM methodology. Rather than optimizing over a single large grid, NPAG performs a sequence of optimizations over successively refined smaller grids, at each stage using a primal-dual interior point algorithm that is much faster than the EM algorithm used by NPEM. The sequential NPAG approach also permitted incorporation of an expanded maximum likelihood scope that separates intra- from inter-individual variability. NPAG also essentially eliminates the discretization error that limited the resolution of NPEM. Finally, computational efficiency relative to NPEM is enhanced, often by factors of 100 or more. This now permits the multiple runs necessary for application of a bootstrap technique to compute confidence limits.

Supported by NIH grant RR11526