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New methods for optimizing drug dosage regimens for maximally precise individualized therapy

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Abstract

Optimal dosage individualization methods include: 1) **Nonparametric (NP),** not parametric (P) population models. P models estimate parameter means and variances. Dosage uses only central tendencies. NP models estimate entire distributions, using multiple discrete support points. Each point has a model parameter estimate, plus the probability of each point in the population.

Those support points permit 2) **Multiple Model (MM) dosage design**. A candidate regimen predicts multiple future serum concentrations. One computes the weighted squared error of its failure to hit the target, and then finds the maximally precise regimen having minimum error.

Depending on each patient, four Bayesian methods are used. **1) MM analysis is used routinely.** Support points having parameter values fitting his/her serum data well become more probable - those that do not - less so. The Bayesian posterior joint density is thus found. MM dosage design is again used. 2) For **unusual patients outside the ranges of the NP model**, a **Hybrid method** first uses a maximum aposteriori probability (MAP) procedure locating the general area, often beyond the model ranges. Extra support points (up to 10x10) augment the original NP population for subsequent MM analysis. 3) For **highly unstable patients** having changing parameter values, the **interacting multiple model (IMM)** tracks drug behavior best. Using these methods in relevant clinical situations will be demonstrated.

Biography

Roger Jelliffe MD, FCP, FAAPS, developed the first computer software for individualizing drug dosage regimens in 1967. He was the first to relate renal drug elimination to creatinine clearance. He developed the first method for estimating creatinine clearance when serum creatinine is changing. He founded the USC Laboratory of Applied Pharmacokinetics in 1973, and the USC*PACK and more recent MM-USCPACK clinical software for individualizing drug dosage regimens most precisely. His laboratory developed the Resource for Population Modeling at the San Diego Supercomputer Center, the nonparametric adaptive grid (NPAG) population modeling approach, and Multiple Model (MM) design of maximally precise dosage regimens. This is now the Bestdose clinical and Pmetrics research software. We have developed three new methods of Bayesian analysis for individual patients. This adds great capability and safety in managing unusual patients. Dr. Jelliffe's interest is now in nonlinear PK/PD population modeling of multiple interacting drug systems, optimally coordinated combination MM dosage regimens for patients, and in methods using the dose itself as an active partner to learn about the patient optimally while having to treat him/her at the same time.
He is author or co-author of 132 peer reviewed publications, has mentored over 100 visiting scientific scholars, 1 sabbatical scholar, 2 Master's Students, 3 Ph.D candidates, and 3 mini-sabbaticals.

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