MULTIPLE MODEL (MM) DOSAGE DESIGN: ACHIEVING TARGET THERAPEUTIC GOALS WITH MAXIMUM PRECISION.

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ABSTRACT

Dosage regimens based on parametric population models use single values to describe each parameter distribution. When a target goal is selected, the regimen to achieve it assumes that it does so exactly. In contrast, MM dosage design is based on nonparametric (NP) population models which have up to one set of parameter values for each subject studied in the population. With this more likely model, multiple predictions are possible. Using these NP models, one can compute the MM dosage regimen which specifically minimizes the predicted weighted squared error with which a target goal can be achieved.

With feedback from serum concentrations, each set of parameter values in the NP prior has its probability recomputed. Using that revised model, the new regimen to achieve the target with maximum precision is again computed. A new Interacting Multiple Model (IMM) sequential Bayesian method now estimates posterior densities when parameter values have been changing during the analysis. A new clinical software package is in development.

INTRODUCTION: SET INDIVIDUALIZED TARGET GOALS FOR EACH PATIENT

Therapeutic ranges of serum drug concentrations are overall ranges in which most patients, but not all, do well. One must always evaluate each individual patient clinically,, whatever the serum concentration is.

A better approach is to evaluate each patient's individual clinical need for that drug, and to select an estimated risk of toxicity which is felt on clinical grounds to be justified by the patient's need. One then selects a target therapeutic goal. One then wants to hit the target goal with the greatest possible precision, thus maximizing efficacy and holding toxicity within selected bounds.

Individualized drug therapy thus begins by setting specific individualized target goals. The clinical task is to select, and then to hit, a target goal as precisely as possible. As the regimen is given, the clinical task is then to observe the patient's response, to reevaluate whether the target goal was hit precisely or not and was correctly chosen or not. An adjusted dosage regimen is then developed to hit the revised target goal most precisely.

THE NEED FOR PHARMACOKINETIC AND DYNAMIC (PK/PD) MODELS

PK/PD models store past experience with the behavior of drugs, and are the tool to apply that past experience to the care of future patients. The dosage regimen to achieve the selected target goal is computed and given. The patient is then monitored both clinically and by measuring serum concentrations. The serum concentrations are used to make an individualized model of the behavior of the drug. One can see what the probable serum concentrations were at all other times when they where not measured. One can also see the computed concentrations of drugs in a peripheral nonserum compartment or in various effect compartments. These cannot be seen or inferred at all without such models. By comparing the clinical behavior of the patient with the behavior of the patient's model, one can evaluate the patient's clinical sensitivity to the drug, and can adjust the target goal appropriately.

CURRENT BAYESIAN INDIVIDUALIZATION OF DRUG DOSAGE REGIMENS

In the Maximum Aposteriori Probability (MAP) Bayesian approach to individualization of drug dosage, parametric population models are used as the Bayesian priors. The credibility of these models (their parameter variances) is then evaluated in relationship to that of the measured serum concentrations as they are obtained. Having made

the patient's Bayesian posterior individualized model, one then uses it to reconstruct the behavior of the drug in the patient during his therapy to date. One can examine a plot of this behavior over the duration of the past therapy. One can specifically evaluate the clinical sensitivity of the patient to the drug by comparing the patient's clinical behavior with that of the patient's individualized model. In that way, one can evaluate whether the initial target goal was well chosen or not. One can choose a different goal if needed, and once again one can compute the dosage regimen to achieve it.

CRITIQUE OF THE MAP BAYESIAN APPROACH

The weakness of the MAP Bayesian procedure is that the models it uses have only single point estimates of the various pharmacokinetic parameters. Because of that, there is only one version of either the individualized model, or of the population model itself. The regimen developed to achieve the target goal must simply be assumed to do so exactly.

THE SEPARATION PRINCIPLE

The separation principle states that whenever control of a system is separated first, into obtaining single point parameter estimates for the model, and second, of using those single point estimates to control the system, the task is often achieved in a suboptimal manner. This is a significant problem with the above MAP Bayesian fitting and dosage design. The way around this problem is by incorporating improved NP population models, and in using MM dosage regimens specifically designed to be maximally precise.

POPULATION MODELS IN CLINICAL THERAPEUTICS

When a parametric population model is used as the Bayesian prior to design an initial dosage regimen, one has only a single value for each parameter. Only one prediction of future concentrations is made. The regimen must simply be assumed to hit the target goal exactly.

However, as shown in Figure 1, when a lidocaine infusion regimen based on mean parameter values was given to each of the actual 81 diverse NP population support points from which the mean values were obtained, a wide distribution of predicted serum concentrations was seen, due to the diversity in the NP population model. Using that NP population model, one can make 81 predictions of concentrations from any candidate dosage regimen. Based on these multiple models, one can develop the regimen which specifically minimizes the predicted weighted squared error in the achievement of the target goal.

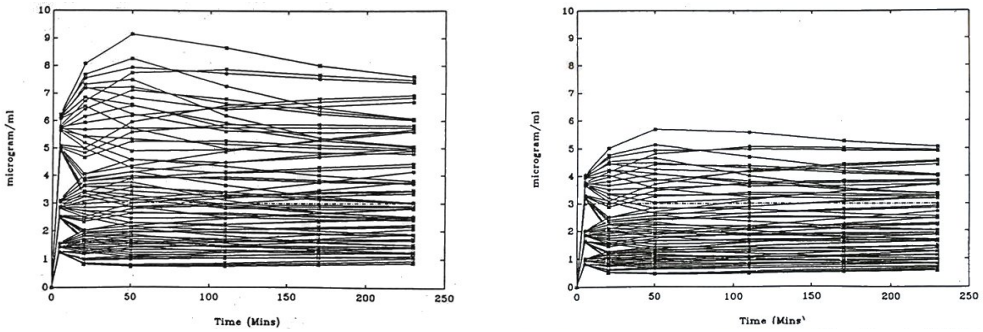

Figure 1 (Left). Result when a lidocaine infusion based on population mean parameter values was given to the 81 diverse support points from which the population mean values were obtained. Great diversity in the predicted responses is seen.
Figure 2 (Right). Predicted response of the 81 support points (models) when the regimen obtained by multiple model dosage design was given. The target was achieved with visibly greater, and optimal, precision

As shown in Figure 2, the MM lidocaine infusion regimen visibly decreased the error in the achievement of the target therapeutic goal The MM approach circumvents the pitfalls of the separation principle. This is the strength of the combination of NP population models with MM dosage design.

OBTAINING MULTIPLE MODEL BAYESIAN POSTERIORS

The MM Bayesian approach, using the NP joint densities, preserves the multiple sets of population parameter values, but recomputes their Bayesian posterior probability, based upon the serum concentrations obtained. Those sets of parameter values that predicted the measured concentrations well become more probable. Those that predicted them less well become less so. When the regimen for the next cycle is developed, these revised models are used to develop it. The regimen is again specifically designed to achieve the desired target goal with maximum precision (minimum weighted squared error). One can see by the narrowed bandwidth of the new predictions exactly what one has learned from the serum data.

SEQUENTIAL BAYESIAN APPROACHES

Three other Bayesian approaches have been used by us to incorporate feedback from serum concentration data. The first is the sequential MAP Bayesian approach, in which the MAP posterior parameter values are sequentially updated after each of several serum concentration data points in a cluster are obtained. However, at the end of each full feedback cycle, this method has learned no more with respect to developing the next new dosage regimen than if it had fitted all the data at once. The second approach is the sequential MM Bayesian one. Here the MM Bayesian posterior joint density is also sequentially updated after each data point. Still, at the end of each feedback cycle, this procedure also has learned no more with respect to developing the next dosage regimen than if all the data in that cluster were fitted at once. A third approach is the interacting multiple model (IMM) sequential Bayesian approach. This method permits the true patient being sought for actually to jump from one model support point to another during the sequential Bayesian analysis. Because of this, the IMM method permits detection of unsuspected changes in pharmacokinetic parameter densities during the sequential analysis. It provides an improved method to track changing parameter densities and behavior of unstable patients during their clinical course. Using carefully simulated models in which the true parameter values changed during the data collection, the integrated total error in tracking a simulated patient was similar for the above sequential MAP and sequential MM Bayesian procedures. However, the integrated total error of the sequential IMM procedure was only about half that of the other two methods.

CLINICAL APPLICATIONS

Nonparametric population parameter joint densities, MM dosage design and IMM Bayesian posterior joint densities offer significant improvements in tracking the behavior of drugs in patients during their care, especially when they are unstable and their models have changing parameter values. The MM dosage regimens are specifically designed to achieve target goals with maximum precision. These methods now make mathematically optimal use of all information contained in the past population data, coupled with whatever current data of feedback may be available about a particular patient up, to that point in time, to develop that patient's most precise next dosage regimen. A clinical version of this software, which runs on PC's in Windows, is now in development.

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