

Pharmacogenomics and Individualized Dosage Regimens

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Abstract

Objectives: To describe relationships between genetic testing and variations in gene expression over time in a patient and how best to use this information in planning, monitoring, and adjusting maximally precise dosage regimens.

Methods: The structure of optimally precise Bayesian adaptive control is briefly reviewed, to show the context in which genetic/genomic information can be used.

Results: Population pharmacokinetic / pharmacodynamic (PK/PD) models often have parameter distributions with significant genetically determined subpopulations, such as fast and slow metabolizers. The assumed normal or lognormal distributions are often not present. Mixture models to describe bimodal distributions have become popular.

Pharmacogenetics, from the 1950's, examines monogenic variations in drug behavior. Pharmacogenomics, from the 1990's,, is based on high-throughput omics technologies [1]. It describes multi-gene or genome-wide variations. Association studies correlate genomic and drug effect variation in individuals and populations. Unfortunately, only about 3% of published human genomics studies presently focus beyond discovery-oriented applications [2]. Pharmacogenomic variation must be integrated into nonparametric population modeling and maximally precise stochastic Bayesian adaptive control. This permits identification of subpopulations which convert raw data into maximally precise individualized dosing regimens. Pharmacogenomics, pharmacogenetics, population modeling, and Bayesian adaptive control approaches have not intersected meaningfully to date. Currently used covariates need to be reconsidered in light of genomic variations. However, most genetic variation appears to be determined by individual variation, not race [3].

Conclusions: Optimally precise Bayesian adaptive control sets the structure to include human genetic/genomic information to optimize therapy [4]. As genomics, pharmacometrics, and adaptive control are rapidly coalescing, there is much to be learned in all fields.

NON-PARAMETRIC (NP) POPULATION MODELS

- The theorems of Lindsay, Mallet, and Caratheodory prove the most likely parameter distribution is a discrete joint density with up to one support point per subject, weighted by its probability.
- The NP distribution is not set by any equation, only by the data.
- NP algorithms can discover, locate, and quantify unsuspected subpopulations (e.g. genetic).
- NP likelihoods are exact. Behavior is statistically consistent such that results asymptotically approach the truth.
- NP distributions permit Multiple Model (MM) dosage regimen design, with multiple weighted predictions per patient.

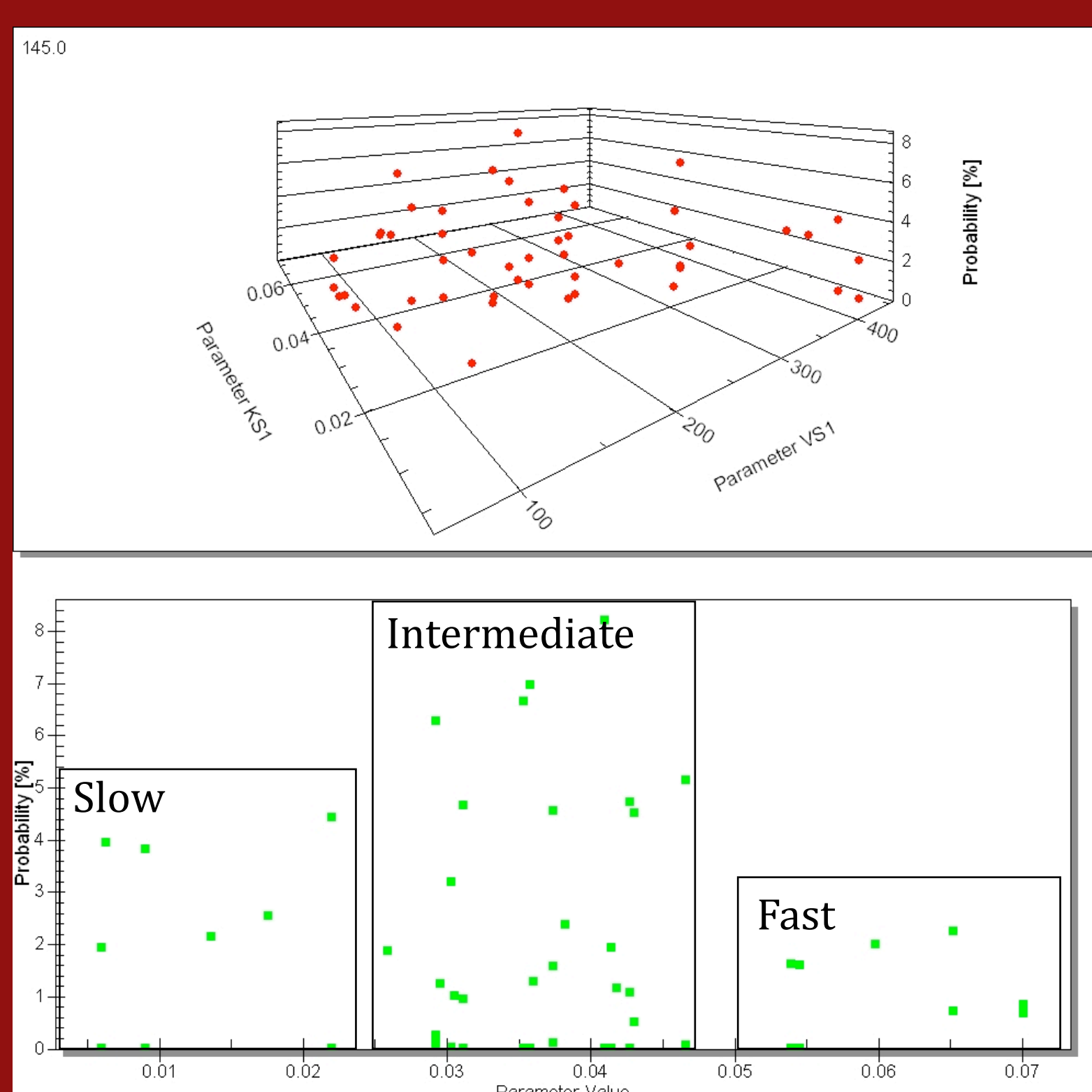


Figure 1 - An example NP population model of the HIV drug efavirenz, simulated based on published parameter values [5,6], and including different genetically determined metabolizer subgroups.

References

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MULTIPLE MODEL (MM) DOSAGE DESIGN

- Use a prior with discrete multiple models - an NPEM or NPAG model.
- Give a candidate regimen to each model.
- Predict results with each model.
- Compute weighted squared error of failure to hit target goal.
- Find the regimen hitting target with minimal weighted squared error.
- GOOD FOR PATIENTS WHOSE PARAMETERS ARE WITHIN WELL SUPPORTED REGIONS OF THE MODEL (Figure 2).

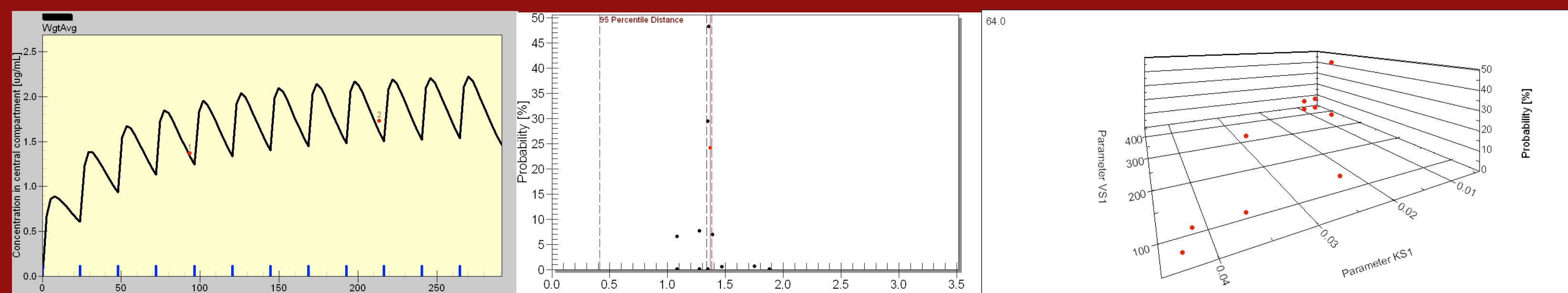


Figure 2 - Good observed vs. predicted (Left) with multiple predictions clustering around observed (Center), and Bayesian posterior model (Right) compared with prior model in Figure 1, now showing that most points have an extremely low posterior probability and contribute little to controlling this patient.

HYBRID BAYESIAN-MM (HB-MM) UPDATING

- Start with MAP Bayesian, with the ability to change the relative standard deviation of prior parameter estimates, i.e. controlling how informative the prior model is.
- Add support point "patch" around MAP Bayesian estimate, augmenting pop model in the area where the patient is now known to be.
- Then do MM Bayesian on the augmented pop model, controlling the weight (probability) of the patch relative to the remainder of the model.
- GOOD FOR PATIENTS WHOSE PARAMETERS ARE OUTSIDE WELL SUPPORTED REGIONS OF THE MODEL (Figures 3 and 4).

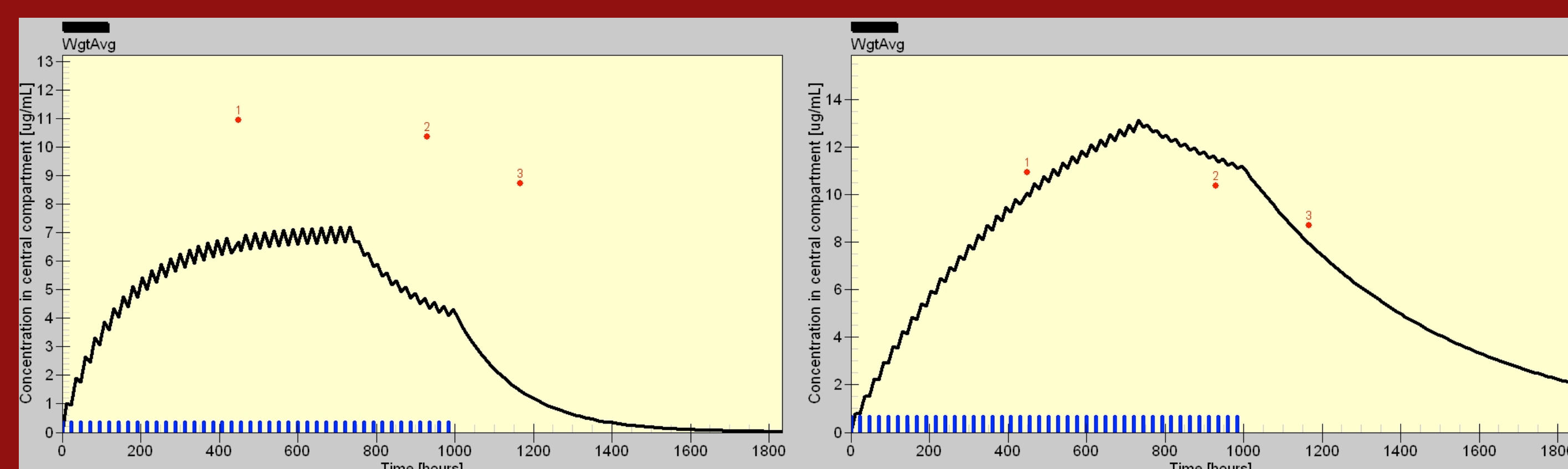


Figure 3 - Poor MM observed vs. predicted (Left) and much better HB-MM (Right). MM dose recommendation to achieve 48-hour trough of 2 mg/L was 260 mg when patient had observed concentration of 10 mg/L 19 hours after a 200 mg dose! HB-MM recommended dose to achieve the same trough concentration was 100 mg every 48 hours - much more reasonable.

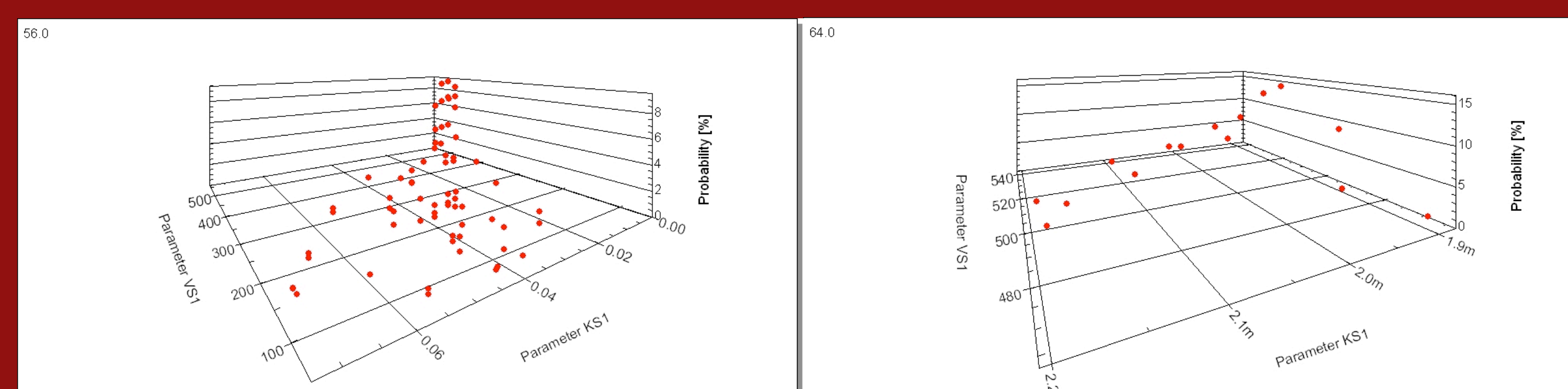


Figure 4 - Prior model (refer to Figure 1) now augmented with patch points at very low values for the elimination rate constant, Ks1 (Left) and the Bayesian posterior model showing the only probable points for this patient to be the patched points, far below the range of the original model. The patient was subsequently shown to have a slow metabolizing polymorphism, but phenotypically was much more severe than would be predicted from the genotype alone.

Conclusions

- Optimally precise MM adaptive control sets the structure to include human genetic/genomic covariate information to optimize therapy
- Our Hybrid Bayesian MM method has even greater potential to control outlier patients.
- Phenotypic expression (i.e. drug concentrations) may be poorly predicted despite genotypic information; however MM methods may better account for all pharmacokinetic covariates, known and unknown.

Acknowledgements/Declarations

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