Study and application of nonparametric and parametric population modeling for automatic subpopulation classification to CYP2D6 phenotype compounds and pediatric age groups

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Objective

Subpopulation classification is an important way to improve the decision making in drug development [1]. Existing population pharmacokinetic methods for subpopulation identification predominantly rely on heterogeneous expression or mixture modeling. If sub-populations distributions overlap, the identification of individual subpopulation based on existing methods becomes difficult and tricky. Taking CYP2D6 phenotype as examples, Dextromethorphan, Bufuralol or Imipramine has many metabolic pathways via other enzymes while Metoprolol or Desipramine or Tolterodine has less metabolic pathways [2]. Finding dosage for pediatric age sub-groups is tricky. We propose to use nonparametric combined with parametric population methods for automatic subpopulation classification to overcome the problems suffered from current methods [1, 3].

Methods

A selected proportion of CYP2D6 phenotype subpopulation is virtually sampled using physiologically based pharmacokinetic (PBPK) modeling, i.e. to create combinations of heterogeneous virtual patients. CYP2D6 metabolic compounds as above are used to generate the drug exposure with subpopulations distributions overlap. A simplified population PK model is built using parametric method for identifying the initial population distribution. Nonparametric method [4] is added on top of parametric method which reduce the number of support points and automatically determine the number of components of the mixture models to capture the subpopulation (Figure 1). Simulation such as visual predictive check (VPC) is used to confirm the subpopulation (Figure 1).

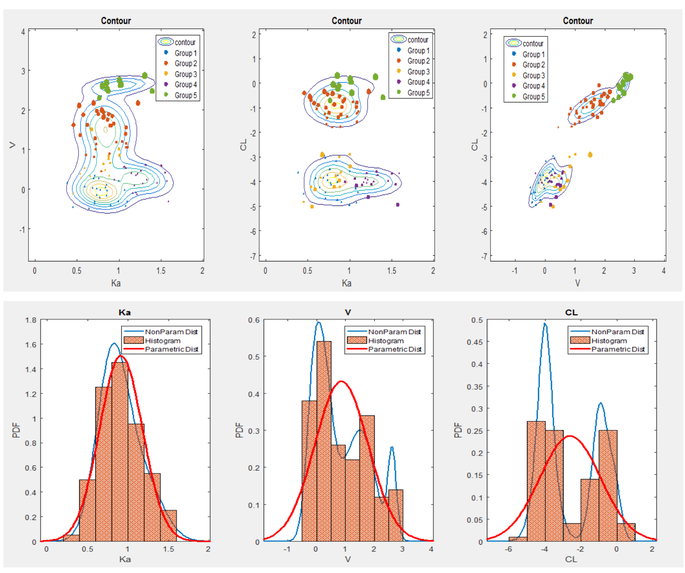
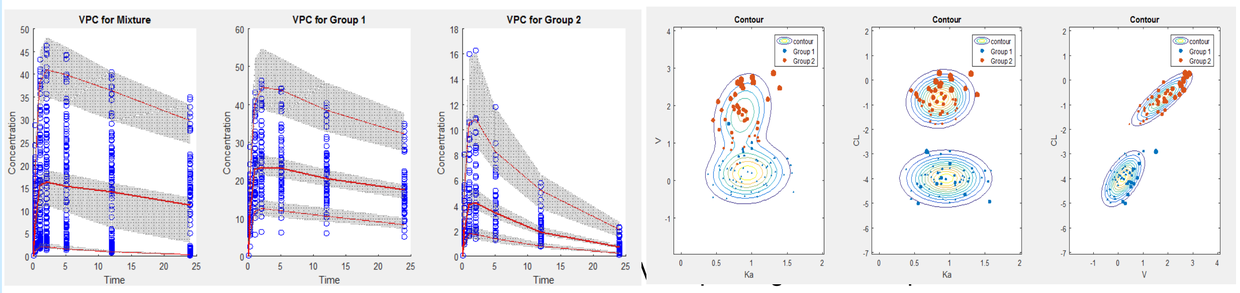


Figure 1. Automatically determine the number of components of the mixture models via nonparametric method – top left is the contour plot; bottom left is the mixture distribution; top right is the fraction of metabolism via CYP enzyme and renal clearance; bottom right is the VPC for subgroups.

By using the nearest weighted Kullback-Leibler (KL) distance as the criteria, a user can further reduce the number of mixture distribution to the expected mixture models, e.g. 2 mixture distribution (Figure 2).

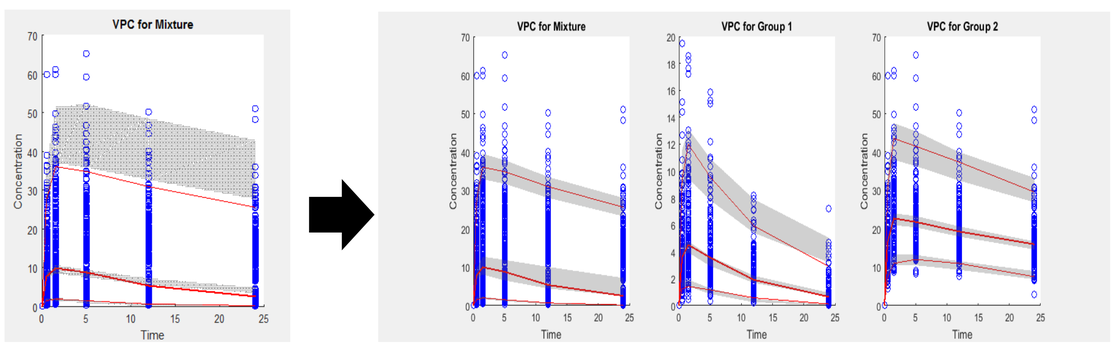


Results

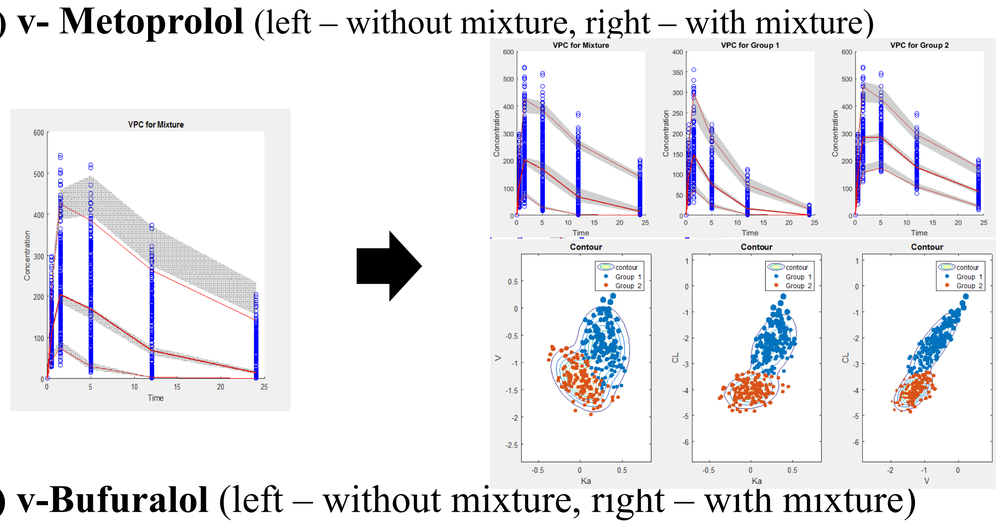
PBPK simulation using Simcyp Simulator creates CYP enzyme heterogeneous expression with overlay mixture distribution samples (Figure 1). Nonparametric method indeed converts a few hundred support points to a handful of manageable mixture distribution. The VPC plot confirmed the sub-group identification and the number of subpopulations matched the predefined PBPK subpopulation.

By creating a virtual population with 50% of EM and 50% of PM in the major metabolic pathway CYP2D6, a few virtual (v-) compounds are analyzed below.

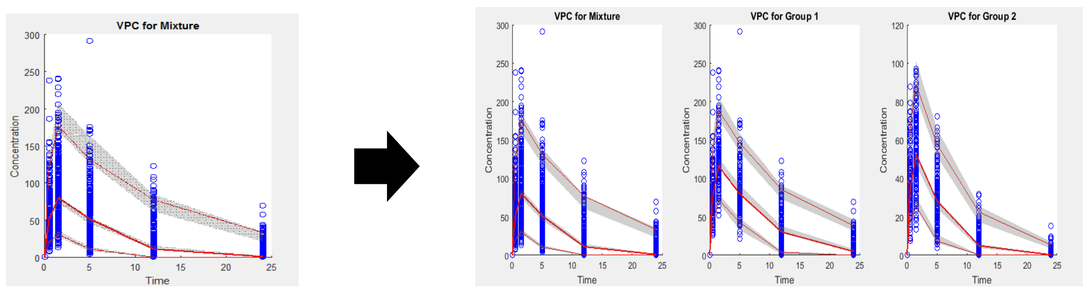
a) **v-Dextromethorphan** (left – without mixture, right – with mixture)



b) **v- Metoprolol** (left – without mixture, right – with mixture)



c) **v-Bufuralol** (left – without mixture, right – with mixture)



d) **v- Imipramine (left) v- Desipramine** (right); **v- Tolterodine** (missed)

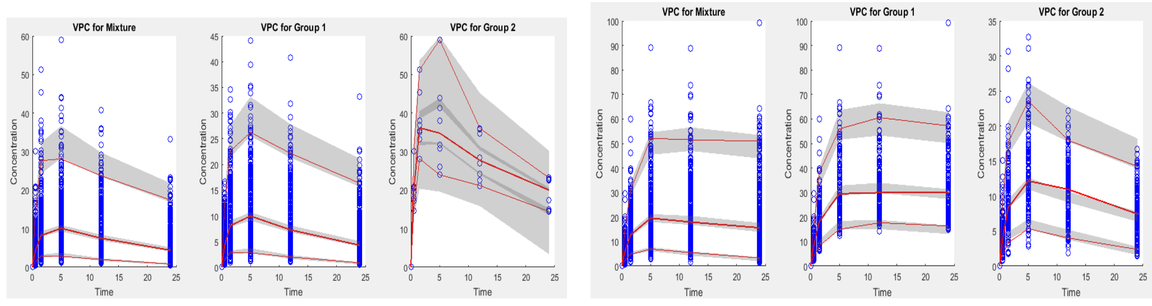
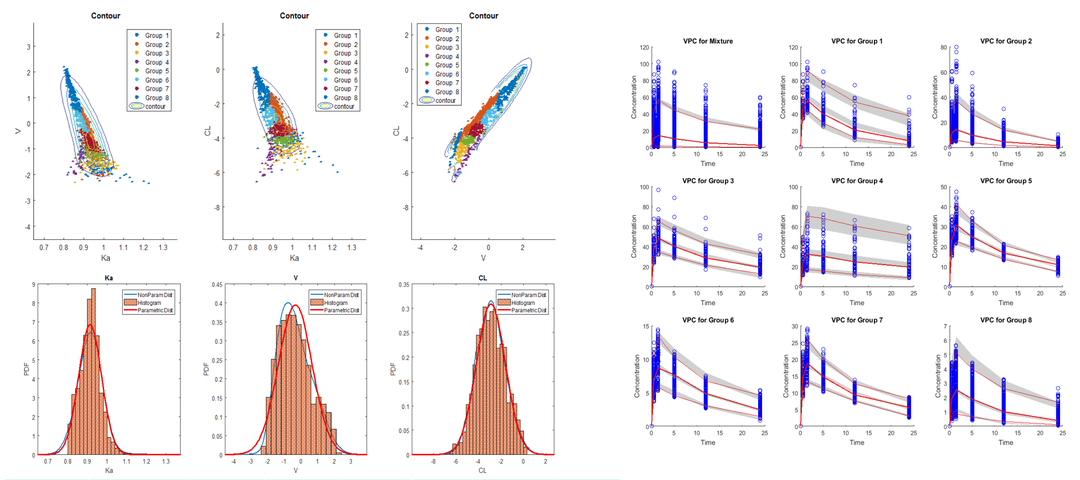


Figure 3. Virtual CYP2D6 compounds analysis

Virtual-Dextromethorphan is used for pediatric age group classification is used with the age range covered 1 month old to 25 years old (Figure 4).



Age Group	No. Subjects	Mean (years)	SE	5% tile	95%tile	Min	Max
1	74	0.127	0.038	0.092	0.229	0.085	0.277
2	541	2.17	2.529	0.202	6.859	0.086	14.205
3	91	0.247	0.114	0.116	0.456	0.095	0.937
4	75	1.229	1.206	0.242	3.839	0.221	6.060
5	108	0.589	0.567	0.211	1.999	0.101	3.273
6	168	5.550	4.002	0.396	12.241	0.396	14.826
7	143	1.771	1.548	0.252	5.706	0.201	9.1206
8	300	16.694	4.638	10.289	22.397	5.596	23.606

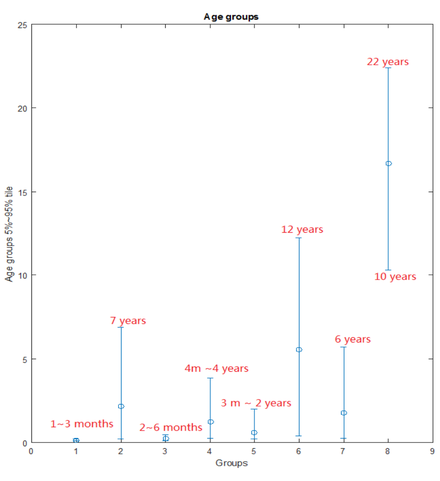


Figure 3. Pediatric age dosing groups - The virtual simulation shows the same statement as drugs.com that the age group under the age 4 years old has a lot of variation and uncertainty. It gets the confidence from the age group from age 2 years to 25 years old. Using this age group classification, it provides evidence for the age group dosing design.

Conclusions

The nonparametric methods successfully find differences in exposure in genetic subpopulations and pediatric age groups. The method can be expanded to manage the dose-titration or individual treatment in all patients based on safety and/or efficacy markers, or on Therapeutic Drug Monitoring (TDM), or gene based dosing.

References

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