A Novel Covariate Search Method adapted for PKPD Models with Nonparametric Parameter Distributions

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Background

- Nonparametric (NONP) models are an attractive alternative to parametric models, especially when data arise from different sub-populations
- However, methodology[1] for screening covariates given discrete distribution of model parameters is limited in scope and no convenient statistical test can be applied to discriminate between competing NONP models

Objectives

To develop a new covariate modeling approach adjusted for nonparametric parameter distributions

To evaluate the performance of the method when based on FOCE-NONP parameter estimates in NONMEM in terms of:

- ❑ **Type-I error rate of covariate inclusion**
- ❑ **Statistical power**
- ❑ **Bias/Imprecision in regression estimates**

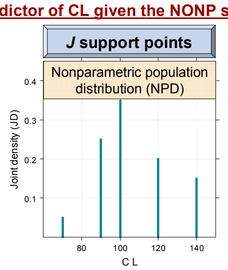
Method principle

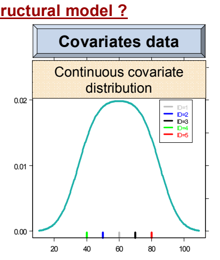
A Perl script automates the 3-step process involving NONMEM, PsN[2], and GAM package in R[3]

- **Hypothesis: Is Age an informative predictor of CL given the NONP structural model ?**

Graphical example:
Gaussian population J = 5 IDs
Continuous covariate (e.g. Age)

NONMEM
➔ NONP estimation





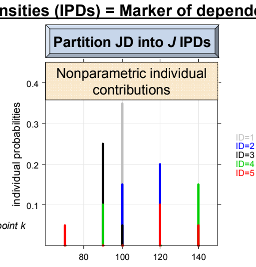
- **Step 1: Obtain individual probability densities (IPDs) = Marker of dependency between support points**

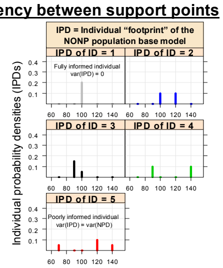
PsN
(NONP subroutine)

$$\begin{cases} JD_k = \sum_{i=1}^{J} IPD_{ik} \\ IPD_{ik} = \dfrac{JD_k \times L_{ik}}{\sum_{k=1}^{J} JD_k \times L_{ik}} \end{cases}$$

JD_k – Population joint density for support point k
IPD_{ik} – Individual probability density for support point k
L_{ik} – Individual likelihood for support point k (computed from $_iOFV$ in NONMEM)

PsN output: ***JxJ unique IPDs***





- **Step 2: Second-stage regression model of covariates on support points given *IPDs***

R
(GAM package)

Regression by weighted GAM

$$CL_i = f(AGE_i) + \varepsilon_i * h(IPD_{ik})$$

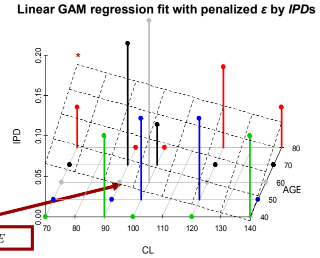
$$\begin{cases} h(IPD_{ik}) = IPD_{ik} & (1) \\ h(IPD_{ik}) = IPD_{ik} \times \left(1 - \dfrac{var(IPD_{ik})}{var(NPD_k)}\right) & (2) \end{cases}$$

Two weighting functions h can be considered, (2) being designed for sparse data to account for η-shrinkage

GAM output: $\hat{\beta}$ ***and*** AIC_{trial}

$CL = Intercept + \beta \text{ x } AGE$

Linear GAM regression fit with penalized ε by *IPDs*



* Regression plan represents a weighted linear regression CL ~ AGE

- **Step 3: Calibration of the covariate method**

➔ Aim: Obtain a likelihood-based statistical criterion ($AIC_{\alpha=0.05}$) for decision-making

R
(GAM package)

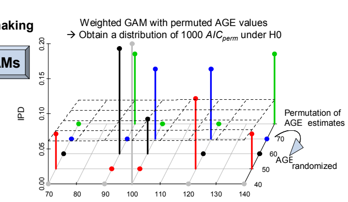
1000 permutation tests + weighted GAMs

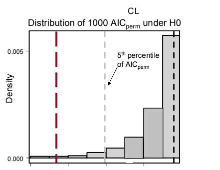
$$\begin{cases} H0: \beta = 0 \\ H1: \beta \neq 0 \end{cases}$$ with P-value calibrated to user-defined value (α=0.05)

GAM output: **1000 AIC_{perm} ➔ $AIC_{\alpha=0.05}$**

Decision rule:
if $AIC_{trial} < AIC_{\alpha=0.05}$
Age significant predictor of CL

NONMEM ($NONP)
with Age on CL





Hypothesis-testing scenarios

PK Model:

one-compartment: random effect on CL, V (30% CV), RV (10 % CV)

Simulated Data:

- informative data (3 DVs/ ID, 100 IDs)
- 1000 simulated datasets per hypothesis-testing scenario (NM 6.2)

8 hypothesis-testing scenarios:

- continuous covariate: CL ~ f(AGE) - Correlation strength: β_{true}= {0, -0.006, -0.008, -0.010}
- categorical covariate: CL ~ f(SEX) - Correlation strength: β_{true}= {0, -0.150, -0.175, -0.200}

Estimates of statistical power & type-I error rate of covariate inclusion:

- apply stochastic simulation followed by estimation (SSE) subroutine in PsN
- apply nonparametric covariate method by weighted GAM on each dataset
- reference methodology = parametric covariate modeling by likelihood ratio tests (LRTs)

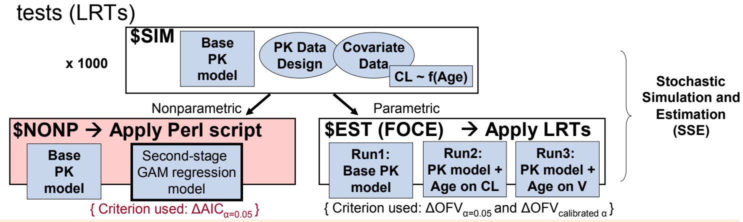


Figure 1. *Hypothesis-testing scheme for computation of statistical power & type-I error rate of covariate inclusion (Age on CL) for both parametric and nonparametric PK models (scenarios 1 to 4 with varying β_{true})*

Results

Scenario Number	Covariate Type	β_{true}	Tests	Criteria	Type-I error (α)	Statistical Power	$\hat{\beta}$	ME (β)	RMSE (β)
1	Continuous (Age)	0	LRT (FOCE)	$\Delta OFV_{nominal\ \alpha=0.05}$	6.8%(CL) / 6.1%(V)		0	$< 10^{-4}$	$< 10^{-3}$
			GAM (NONP)	ΔAIC (1)	6.2%(CL) / 5.3%(V)		0	$< 10^{-4}$	$< 10^{-3}$
2		-0.006	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	5.1%	58.9%	-0.006	$< 10^{-4}$	$< 10^{-3}$
			GAM (NONP)	ΔAIC (1)	4.4%	62.4%	-0.006	$< 10^{-3}$	$< 10^{-3}$
3		-0.008	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	5.5%	82.2%	-0.008	$< 10^{-5}$	$< 10^{-3}$
			GAM (NONP)	ΔAIC (1)	5.7%	84.3%	-0.008	$< 10^{-3}$	$< 10^{-3}$
4		-0.010	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	5.1%	95.4%	-0.010	$< 10^{-4}$	$< 10^{-3}$
			GAM (NONP)	ΔAIC (1)	5.6%	96.1%	-0.010	$< 10^{-3}$	$< 10^{-3}$
5	Categorical (Sex)	0	LRT (FOCE)	$\Delta OFV_{nominal\ \alpha=0.05}$	5.8%(CL) / 4.6%(V)		0	0.005	0.07
			GAM (NONP)	ΔAIC (1)	5%(CL) / 4.6%(V)		0	0.002	0.06
6		-0.150	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	6.3%	62.1%	-0.145	0.005	0.06
			GAM (NONP)	ΔAIC (1)	5.4%	61.6%	-0.144	0.006	0.06
7		-0.175	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	4.7%	80.0%	-0.175	$< 10^{-3}$	0.06
			GAM (NONP)	ΔAIC (1)	4.6%	79.7%	-0.176	-0.001	0.06
8		-0.200	LRT (FOCE)	$\Delta OFV_{calibrated\ \alpha}$	5.4%	89.1%	-0.198	0.002	0.05
			GAM (NONP)	ΔAIC (1)	5.2%	89.5%	-0.203	-0.003	0.06

(1) ΔAIC obtained with a weighting function h accounting for *IPD*s only – Similar estimates were obtained with (2) (data not shown)

Table 1. *Estimates of type-I error rate and statistical power for covariate inclusion on CL obtained with LRT and the proposed covariate methodology. Estimates of regression coefficients β, MEs and RMSEs are also displayed*

- **Type-I error rate:**
  - Adequate calibration of the NONP covariate methodology (close to α=5%)
  - Asymptotically approaching α=5% as No. of SSE samples increases (data not shown)
  - LRT: actual type-I error rate inflated compared to nominal α
- **Statistical power:** - Similar performance as LRT for Gaussian data
- **Regression estimates:** - Little bias (*ME*s) and similar imprecision (*RMSE*s) as LRT

Conclusions

- **A new, calibrated, covariate identification technique intended for nonparametric PKPD models is available**
- **It presents as good statistical and estimation properties as LRT for Gaussian type-data regardless of the characteristics of the relationship and of the covariate distribution of interest**
- **Although computationally demanding, this approach presents the advantage of not relying on nominal *P*-value and benefits from the robust framework of nonparametric data analysis**

References:
1. Mentré, Mallet. Handling covariates in population pharmacokinetics. *Int J Biomed Comp.* (1994)
2. Perl-speaks-NONMEM (PsN software): http://psn.sourceforge.net
3. R Development Core Team: http://www.R-project.org