A FULL MODEL ESTIMATION APPROACH FOR COVARIATE EFFECTS: INFERENCE BASED ON CLINICAL IMPORTANCE AND ESTIMATION PRECISION

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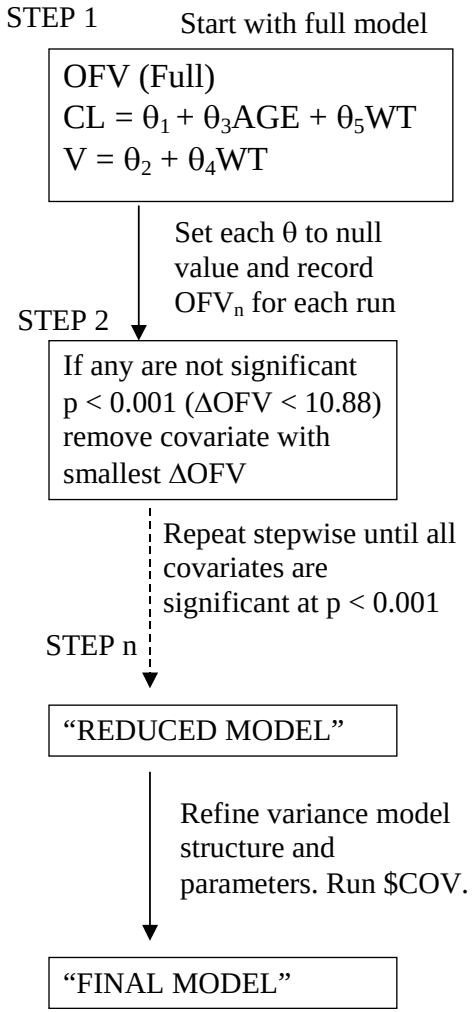
Introduction

- Covariate model building for population PK (PD) models has typically been conducted as an exploratory stepwise regression exercise characterized by varying degrees of scientific thought about inclusion of potential predictor variables.

- Stepwise forward/backward comparisons, based on the likelihood ratio test, are made across multiple models, each expressing different covariate-parameter combinations.

- Stepwise methods are commonly employed for covariate model building in population PK, despite the compute-intensive nature and well-documented problems associated with these methods.

Stepwise Backward Elimination



What happens when a covariate effect is statistically "significant", but not clinically important?

If a covariate effect is not statistically "significant", does this mean that there is no effect?

Problems with "Stepwise" Regression

http://www.pitt.edu/~wpilib/98sort.html (see topics 167, 168 & 169 on stepwise methods).

- Based on methods (e.g. F tests for nested models) that were intended to be used to test pre-specified hypotheses; Statistical tests are badly biased.
- Regression coefficients are typically over-estimated.
- Confidence intervals are falsely narrow.
- Severe problems in the presence of correlated or collinear predictors (estimation bias, interpretation difficulties).
- Adjustments for multiple comparisons must be considered.

Problems with "Stepwise" Regression (2)

- NONMEM likelihood approximations can result in (grossly) incorrect p-values, even when model is known.
- Reconciling "statistically significant" effects with clinically important effects is challenging.
- Resulting models may be predictive, but often are difficult to interpret scientifically.
- Lack of statistical "significance" does not necessarily indicate lack of effect.
- Automated methods allow us to not think about the problem.

An Alterative: Full Model Estimation of Covariate Effects

- Covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing
- Enables direct assessment of clinical importance of covariate effects, based on effect size and estimation precision
- Also provides some explanation for the apparent absence of a covariate effect (true lack of an effect vs. lack of information about that effect)

Parsimony Principle

"All things being equal, choose the simpler model."

- Stepwise reduced models do not allow for inferences about "non-significant" covariate effects and are, therefore, not "equal" to the full model.

- For the purpose of making inferences about covariate effects, the full model is the most parsimonious model.

Procedure

1. Develop stable base model using standard goodness of fit diagnostics.
2. Thoughtful consideration is given to potential covariate-parameter relationships.
3. Full covariate model is constructed and checked for goodness of fit and remaining trends.
4. Point estimates and 95% confidence intervals are obtained for covariate effects.
5. Inferences are made, based on covariate effect size and precision of parameter estimates.

Guiding Factors for Selection of Covariates for the Full Model

- Scientific or clinical interest
- Mechanistic plausibility
- Prior knowledge about covariate effects
- Exploratory graphics (view trend & shape of covariate-parameter relationships)
- Avoiding simultaneous inclusion of collinear/correlated predictors

Stable Parameterization of Full Model

$$TVP = \theta_n \cdot \prod_{1}^{m} \left(\frac{cov_{mi}}{ref_m} \right)^{\theta_{(m+n)}} \cdot \prod_{1}^{p} \theta_{(p+m+n)}^{\mathrm{cov}_{pi}}$$

where: the typical value of a model parameter (*TVP*) is described as a function of *m* individual continuous covariates (cov_{mi}) and *p* individual categorical (0-1) covariates (cov_{pi}) such that θ_n is an estimated parameter describing the *TVP* for an individual with covariates equal to the reference covariate values ($cov_{mi} = ref_m$, $cov_{pi} = 0$); $\theta_{(m+n)}$ and $\theta_{(p+m+n)}$ are estimated parameters describing the magnitude of the covariate-parameter relationships

Full Model Goodness of Fit

- Assess full model goodness of fit through typical diagnostic plots.
- Explore remaining trends between random effects (ETAs) and all covariates in the population PK database.
- Modify/improve full model as needed to remove any remaining trends in diagnostic plots.
  - Modify shape of covariate-parameter relationship.
  - Include additional predictors.

Point and Interval Estimates to Guide Inferences about Covariate Effects

- Obtain full model parameter estimates and 95% confidence intervals (via non-parametric bootstrap, log-likelihood profile, etc.).
- Point and interval estimates can be used to assess clinical relevance of covariate effects and how precisely effects are estimated.
- Understand why some covariates appear to have no impact on the model goodness of fit:
  - truly no effect
  - insufficient information (data) to estimate effect

Categorizing Covariate Effects

- **Clinically Important (CI):** Point estimate and 95% confidence interval of covariate effect parameter results in clinically important change in PK (e.g. greater than +/- 30% of null value).

- **Not Clinically Important (NCI):** 95% confidence interval of covariate effect parameter lies within a pre-defined, unimportant effect size (e.g. within +/- 30% of null value).

- **Insufficient Information (II):** 95% confidence interval of covariate effect is broad and spans across values of covariate effect that are both clinically important and not clinically important.

An Example

- POP PK-PD data for DRUG A were analyzed using NONMEM and a covariate model was constructed using a full model estimation approach.
- Covariate-parameter relationships were described with a power model and were chosen based on scientific interest, mechanistic plausibility and exploratory graphics, with care to avoid collinearity in predictors.
- Parameters of the full model were estimated and 95% confidence intervals were obtained by non-parametric bootstrap.
- Inferences about clinical importance of covariate effects were then based on point and interval estimates.
- No hypothesis testing was conducted.

Table 1: Summary of Covariates

	Sex		Cancer Type				Race					
	Male	Female	Lung	Breast	CGM	Other	Caucasian	Black	Native American	Asian	Hispanic	Other[b]
Number[a]	224	227	229	78	72	72	407	26	1	3	9	5
Percentage	49.7	50.3	50.8	17.3	16	16	90.2	5.8	0.2	0.7	2	1.1

	Age (yrs)	Weight (kg)	Height (cm)	Baseline Hemoglobin (mg/dL)	Baseline Albumin (mg/dL)	Baseline Creatinine (mg/dL)	Ideal Body Weight (kg)	Body Surface Area (m^2)	Baseline Creatinine Clearance (mL/min)	Truncated Creatinine Clearance (mL/min)
Minimum	28	38.6	135	8.7	2.2	0.1	29.4	1.31	28.8	28.8
Maximum	87	129	193	17.8	5	1.6	86.8	2.5	973	150
Mean	56.9	72.8	169	13.1	3.64	0.745	62.7	1.83	113	107
Median	57	72.3	169	13.2	3.6	0.7	61.6	1.82	106	106

All Subjects (N = 451)

Table 2: Continuous Covariate Correlations

	Age (yrs)	Weight (kg)	Height (cm)	Baseline Hemoglobin (mg/dL)	Baseline Albumin (mg/dL)	Baseline Serum Creatinine (mg/dL)	Ideal Body Weight (kg)	Body Surface Area (m^2)	Truncated Creatinine Clearance (mL/min)	Maximum Dose (mg)
Age (yrs)	1	0	0.04	0.05	-0.16	0.28	0.07	0.02	-0.52	-0.06
Weight (kg)	0	1	0.5	0.13	0.01	0.21	0.51	0.94	0.49	0.82
Height (cm)	0.04	0.5	1	0.08	-0.08	0.19	0.99	0.76	0.25	0.49
Baseline Hemoglobin (mg/dL)	0.05	0.13	0.08	1	0.19	0.11	0.13	0.13	0.06	0.12
Baseline Albumin (mg/dL)	-0.16	0.01	-0.08	0.19	1	0.12	-0.09	-0.03	-0.06	-0.03
Baseline Serum Creatinine (mg/dL)	0.28	0.21	0.19	0.11	0.12	1	0.22	0.23	-0.62	0.1
Ideal Body Weight (kg)	0.07	0.51	0.99	0.13	-0.09	0.22	1	0.76	0.24	0.49
Body Surface Area (m^2)	0.02	0.94	0.76	0.13	-0.03	0.23	0.76	1	0.46	0.81
Truncated Creatinine Clearance (mL/min)	-0.52	0.49	0.25	0.06	-0.06	-0.62	0.24	0.46	1	0.48
Maximum Dose (mg)	-0.06	0.82	0.49	0.12	-0.03	0.1	0.49	0.81	0.48	1

Full Covariate Model

PK Model

$$
\begin{aligned}
CL_i &= \theta_{CL} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{CL\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{CL\sim AGE}} \cdot \exp^{\eta_{CL}} \\
V1_i &= \theta_{V1} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{V1\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{V1\sim AGE}} \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{V1\sim BALB}} \cdot \exp^{\eta_{V1}} \\
Q_i &= \theta_{Q} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{Q\sim BSA}} \cdot \exp^{\eta_{Q}} \\
V2_i &= \theta_{V2} \cdot \left(\frac{BSA_i(m^2)}{1.8(m^2)}\right)^{\theta_{V2\sim BSA}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{V2\sim AGE}} \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{V2\sim BALB}} \cdot \exp^{\eta_{V2}} \\
CP_i &= A1_i / V1_i
\end{aligned}
$$

PD Model

$$
\begin{aligned}
SLPRBC_i &= \theta_{SLPRBC} \cdot \left(\frac{MDOS_i(mg)}{6800(mg)}\right)^{\theta_{SLPRBC\sim MDOS}} \cdot \left(\frac{AGE_i(yrs)}{60(yrs)}\right)^{\theta_{SLP\sim AGE}} \\
&\quad \cdot \left(\frac{BALB_i(g/dL)}{3.5(g/dL)}\right)^{\theta_{SLP\sim BALB}} \cdot \exp^{\eta_{SLPRBC}} \\
CRBC_i &= SLPRBC_i \cdot CP_i \\
INTp50_i &= \theta_{INTp50} \cdot \exp^{\eta_{INTp50}} \\
SLPP50_i &= \theta_{SLPP50} \cdot (\theta_{SLPP50\sim CA2})^{CA2} \cdot (\theta_{SLPP50\sim CA3})^{CA3} \cdot (\theta_{SLPP50\sim CA4})^{CA4} \cdot \exp^{\eta_{SLPP50}} \\
p50_i &= INTp50_i + SLPP50_i \cdot CRBC_i
\end{aligned}
$$

Results

- Covariate effects were estimated with a wide range of precisions (Table 3).
- Clinically important (**CI**) covariate effects included BSA on central volume and age on clearance (Tables 3 & 4).
- Point estimates for some effects, such as BSA on inter-compartmental clearance (Table 3), were small but estimates were poorly defined (**II**).
- Other covariate effects had minimal impact but were well-defined (**NCI**), such as the relative PD slope for CATP2 and the age and dose effects on SLPRBC (Tables 3 & 4).
- These latter three effects would have been dropped as "non-significant" in a stepwise regression approach.

Table 3: Covariate Parameter Estimates

Continuous covariates (null=0)

Categorical covariates (null=1)

Parameter	Typical Value (95% CI)	Covariate Classification
CL (L/hr)[a,b]	1.88 (1.29, 2.1)	
$\theta_{CL\sim BSA}$	0.528 (-1.18, 1.93)	II
$\theta_{CL\sim AGE}$	-1 (-1.76, -0.497)	CI
V1 (L)[a,c]	10.5 (9.04, 11)	
$\theta_{V1\sim BSA}$	1.15 (0.491, 1.47)	CI
$\theta_{V1\sim AGE}$	-0.282 (-0.49, -0.133)	II
$\theta_{V1\sim BALB}$	0.357 (0.0236, 0.759)	II
Q (L/hr)	2.58 (1.67, 7.95)	
$\theta_{Q\sim BSA}$	0.199 (-1.8, 5.24)	II
V2 (L)[b,c]	18.1 (7.38, 43.7)	
$\theta_{V2\sim BSA}$	2.62 (-3.6, 3.84)	II
$\theta_{V2\sim AGE}$	0.524 (-0.602, 3.74)	II
$\theta_{V2\sim BALB}$	-2.35 (-3.56, 3.89)	II
SLPRBC	0.982 (0.956, 1.03)	
$\theta_{SLPRBC\sim MDSA}$	-0.125 (-0.22, -0.0222)	NCI
$\theta_{SLPRBC\sim AGE}$	-0.109 (-0.197, 0.0267)	NCI
$\theta_{SLPRBC\sim BALB}$	0.367 (-0.0528, 0.618)	II
INTp50	26.9 (26.6, 27)	
SLPp50	0.0193 (0.0167, 0.0218)	
$\theta_{SLPp50\sim CATP2}$	1.11 (0.946, 1.3)	NCI
$\theta_{SLPp50\sim CATP3}$	1.28 (1, 2.07)	II
$\theta_{SLPp50\sim CATP4}$	0.854 (0.464, 1.12)	II

Table 4: Effects on PK-PD Parameters

Parameter	Covariate	Lower[a]	Median[b]	Upper[c]
CL (L/hr)	BSA (m^2)	1.68	1.89	2.11
CL (L/hr)	**Age (years)**	**3.05**	**1.98**	**1.49**
V1 (L)	**BSA (m^2)**	**8.21**	**10.6**	**13.4**
V1 (L)	Age (years)	12	10.7	9.83
V1 (L)	Albumin (mg/dL)	9.47	10.6	11.5
Q (L/hr)	BSA (m^2)	2.47	2.58	2.69
V2 (L)	BSA (m^2)	10.3	18.5	31.7
V2 (L)	Age (years)	14	17.6	20.5
V2 (L)	Albumin (mg/dL)	35.7	16.9	10
SLPRBC	Maximum Dose (mg)	1.04	0.983	0.936
SLPRBC	Age (years)	1.04	0.988	0.957
SLPRBC	Albumin (mg/dL)	0.883	0.992	1.08

[a]Parameter estimate at lower bound of observed 95% variability interval for specified covariate

[b]Parameter estimate at observed median for specified covariate

[c]Parameter estimate at upper bound of observed 95% variability interval for specified covariate

Conclusions/Discussion

- Unlike stepwise regression, the full model estimation approach directly addresses the clinical importance of covariate effects while providing some explanation for the apparent absence of an effect (e.g. true lack of an effect vs. lack of information about that effect).
- Stepwise regression/hypothesis testing methods are not necessary to make useful inferences about covariate effects.
- Instead of spending computing time on stepwise covariate testing, resources can be spent on more productive efforts, such as the evaluation of model performance for intended modeling purposes.

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http://www.pitt.edu/~wpilib/98sort.html (see topics 167, 168 & 169 on stepwise methods).

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