Bridging studies: handling covariates models using the Prior approach

Anna Chan Kwong (1), Elisa Calvier (2), David Fabre (2), Gilles Tuffal (2), Florence Gattacceca (1), Sonia Khier (3)
(1) Aix-Marseille University INSERM, CNRS, CRCM SMARTc (2) SANOFI Montpellier (3) Montpellier University, IMAG (Alexander Grothendieck Institute).
✉ anna.chankwong@gmail.com

OBJECTIVES

The **PRIOR** subroutine in NONMEM enables the estimation of parameters and their relative standard error (RSE) on **sparse data** by **stabilizing the parameters towards prior estimates** with a penalty function on the objective function [1,2]. However, the use of an initial (prior) model that includes **covariate(s)** as well as the identification of new covariates when using the prior approach begs two questions:

1. How do we test the significance of a **covariate identified with a previous dataset (e.g. rich data) for a new dataset (e.g. sparse data) ?**
2. How can we identify **new covariates on the sparse dataset?**

METHODS

We propose a strategy to answer each question using the case example of a subcutaneously administered antibody. Figure 1 presents the datasets and models built without Priors. Population pharmacokinetic analysis was run with NONMEM® version 7.4.1. Covariate inclusion was performed with the Stepwise Covariate Modeling (SCM) tool implemented in Perl Speaks NONMEM (PSN)® version 4.7.0 [3] (forward inclusion: α = 0.05, backward deletion: α = 0.001).

Dataset A[a] → Model A = ***Model A with n covariates***
Dataset A[a] → n Model(s) A1 = ***n Model A minus 1 covariate (first step of backward deletion)***
Dataset A[a] → Model A2 = ***Pharmacostatistical Model A (no covariate)***

Dataset A[a] **+ Dataset B**[b] → Model AB (reference)

[a] dataset A: rich data from one phase I study (36 healthy volunteers, 546 samples) and one phase II study (18 patients, 154 samples)
[b] dataset B: sparse data from one phase IIb study (216 patients, 1171 samples)

Figure 1: datasets and models built without Priors

Dataset B was analyzed using models A, A1 and A2 with a "PRIOR approach" using informative priors. Covariates were handled in two different ways:

1. Assessment of the significance of the **covariates included in model A** for dataset B
Likelihood Ratio Test ($p < 0.001$, $\Delta OFV > 10.8$), as a backward deletion, between Models B and B1 (Figure 2)

Dataset B → *Model A estimated on Dataset B, with **informative prior of Model A** on all parameters* → Model B
Dataset B → *Model A1 estimated on Dataset B, with **informative prior of Model A1** on all parameters* → n Model(s) B1
Model B & n Model(s) B1 → Difference of Objective Function Value (ΔOFV)

Figure 2: datasets and models built with Priors, first strategy

2. Identification of **new covariates**:
We performed an **SCM** on the parameters estimated on dataset B only (Figure 3). The final model obtained is called **Model B2'**.

Dataset B → *Model A2 estimated on Dataset B, with **informative prior of Model A2 only on poorly estimated parameters (RSE>50%)*** → Model B2
Model B2 → SCM on parameters estimated without prior information → Model B2'

Figure 3: datasets and models built with Priors, second strategy

Covariates that were found statistically significant using strategies 1 and 2 (on dataset B) were compared to those of Model AB (pooled dataset A and B) used as a reference.

RESULTS

The pharmacostatistical Models A and AB were mono-compartmental with a first order absorption and a linear elimination. Interindividual variability was estimated on all parameters and using an ω block between clearance and volume. Model A only included the effect of age on clearance, thus model A1 (backward Step 1) and model A2 (no covariate) were the same. The results of the two strategies to handle covariates on dataset B are presented below (Table 1):

1. Assessment of the significance of the covariate included in **model A**. A drop of 2.8 points in objective function was found between **Model B** and **Model B1**, meaning that the covariate of Model A was not significant on dataset B.

2. Search for new covariates. **Model B2** had informative priors only on Ka, the absorption rate constant. Therefore, SCM was performed on clearance and volume. **Model B2'** included the same covariates as **Model AB**, except the age on clearance.

Table 1: OFV, structure and estimates of the models

Models	OFV	THETA (RSE %)								OMEGA (RSE %)				SIGMA (RSE %)
		CL_{pop}	KA_{pop}	V_{pop}	CLAGE1	CLAGE2	CLGFR	CLWT	VWT	CL	KA	V	V-CL	
Model A THETA(CL)= CL_{pop}*(AGE/36)**CLAGE	**-62.48**[a]	0.0233 (4.41%)	0.0263 (10.48%)	11.3 (3.77%)	0.279 (27.31%)	NA	NA	NA	NA	0.0989 (20.14)	0.424 (22.70%)	0.0683 (21.75%)	0.0591 (25.18)	0.0389 (6.16%)
Model A1 = **Model A2**	**-50.37**[a]	0.0237 (4.63%)	0.0278 (9.79%)	11.3 (3.81%)	NA	NA	NA	NA	NA	0.111 (20.08%)	0.360 (22.96%)	0.0694 (21.63%)	0.0596 (26.08%)	0.0395 (6.14%)
Model B THETA(CL) = CL_{pop}*(AGE/36)**CLAGE	**3633.00**[a] 4930.35[b]	0.0248 (3.12%)	0.0240 (11.78%)	11.8 (2.15%)	0.195 (22.58%)					0.120 (10.18%)	0.469 (24.16%)	0.0962 (12.20%)	0.0877 (12.58%)	0.0571 (3.99%)
Model B1	**3635.81**[a] 4939.92[b]	0.0271 (2.20%)	0.0270 (10.41%)	11.7 (2.17%)	NA	NA	NA	NA	NA	0.122 (10.10%)	0.366 (23.12%)	0.0989 (12.04%)	0.0897 (12.42%)	0.0575 (3.95%)
Model B2	**4895.36**[a] 4885.11[b]	0.0287 (2.76%)	0.0265 (11.04%)	12.1 (2.81%)	NA	NA	NA	NA	NA	0.123 (11.47%)	0.361 (22.73%)	0.106 (14.12%)	0.0975 (13.94%)	0.0706 (5.20%)
Model B2' THETA(CL)=CL_{pop}*(1 + CLGFR*(GFR - 82.44)) *(1 + CLWT*(WT - 77)) THETA(V)=V_{pop} *(1 + VWT*(WT - 77))	**4861.48**[a] 4851.23[b]	0.0285 (2.62%)	0.0264 (11.06%)	11.92 (2.61%)	NA	NA	0.00245 (25.96%)	0.00592 (25.87%)	0.00717 (21.67%)	0.106 (11.82%)	0.361 (22.77%)	0.0823 (15.26%)	0.0785 (14.92%)	0.0712 (5.20%)
Model AB (reference) THETA(CL)=CL_{pop} *(1 + CLAGE*(AGE – 66)) *(1 + CLGFR*(GFR - 84.34)) *exp(CLWT*(WT-77)) THETA(V)=V_{pop} *(1 + VWT*(WT - 77))	**4837.99**[a]	0.0295 (2.65%)	0.0260 (10.73%)	11.7 (2.13%)	0.00703 (11.64%) *ΔOFV = -48.24*	-0.00886 (30.53%)	0.00252 (23.83%) *ΔOFV = -17.14*	0.00583 (23.08%) *ΔOFV = -17.74*	0.00710 (18.61%) *ΔOFV = -26.08*	0.104 (10.17%)	0.369 (26.21%)	0.0774 (12.66%)	0.0736 (12.76%)	0.0582 (3.99%)

[a] OFV without constant (without PRIOR penalty), [b] OFV with PRIOR penalty, NA: Not Applicable, GFR: Glomerular Filtration Rate, mL/min (median = 82.44 in dataset B, 84.34 in the pooled datasets A and B); WT: weight, kg (median = 77 in all datasets). The covariate age on clearance in the Model AB was encoded as a « hockey stick », or piece-wise linear function: CLAGE was calculated with CLAGE1 when the age was below the median age of the pooled dataset (A and B), i.e., 66 years old, and with CLAGE2 when it was higher.

Table 2: distribution of the age

AGE	Mean	Median	Min	Max	SD
Dataset A	42	36	19	77	18
Dataset B	68	68	44	85	7

With both strategies to analyze dataset B, the covariate age which was included on clearance in both Models A and AB was **not** found to be statistically significant. This could be explained by the large difference in age distribution between Datasets A and B, together with a different impact of age on clearance across young and elderly subjects. Indeed, in model AB, clearance increased with age for subjects younger than 66 years old, and decreased beyond this age. This supports the results of the first strategy: the prior relation assessed on young subjects was not relevant to analyze our sparse data in elderly patients. However, the second strategy was not powerful enough to find the reducing impact of age on clearance in elderly patients.

CONCLUSION

1. **The first strategy** was useful to verify the significance of a **covariate previously included in a prior model**. In this case example, the covariate identified on the previous dataset was not found significant on the new dataset. Its impact was different between the two subpopulations from which the previous and the new datasets were sampled. Therefore, one should be very careful when using a previously identified covariate as prior on a new dataset, especially when the covariate was identified in a different population.

2. **The second strategy** allowed to build a model very close to the reference model: **new covariates** were successfully identified on parameters estimated only on the sparse dataset, except for one covariate. Of note, in the reference model, this covariate had a different impact on the two subpopulations.
To generalize our results, this approach should be performed on simulations and challenged on other molecules and on datasets of different sizes.

REFERENCES: [1] Gisleskog, P.O., Karlsson, M.O. & Beal, S.L. J Pharmacokinet Pharmacodyn (2002) 29: 473 [2] Robert J. Bauer (ICON): NONMEM 7.4: Workshop for Advanced Methods [3] https://uupharmacometrics.github.io/PsN/docs.html