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- Development of **physiologically-based pharmacokinetic (PBPK) models** for the analysis of clinical PK data is an approach with progressively increasing impact due to the significant advantages it offers (e.g. prediction of tissue concentrations, extrapolation).
- **Bayesian approaches** are particularly useful for **population data analyses with PBPK models**, as often the fitted data are insufficient to inform the estimation of all model parameters and **prior knowledge** needs to be utilised.
- PBPK models are **high-dimensional differential equations systems** (often stiff) with a considerable number of parameters and thus Bayesian analyses are challenging.
- In NONMEM 7, an algorithm for MCMC Bayesian analysis is available. **The purpose of this work is to employ and evaluate the performance of the Bayesian MCMC method in NONMEM in the specific context of PBPK modelling.**

- **Diazepam population PK data** that have been previously [1] successfully analysed in WinBUGS with a whole-body PBPK model (Figure 1) were re-analysed with the Bayesian MCMC method in NONMEM 7.3 and parameter estimates between the two platforms were compared.
- **Diazepam plasma concentrations** were available for **12 individuals** after a 7mg IV infusion. **Prior information from pre-clinical species** (rat) was utilised to facilitate the estimation of the tissue partition coefficients (KPs) [1].
- Additional **practical issues** regarding application of the MCMC algorithm in NONMEM for Bayesian PBPK modelling were also explored (e.g. **selection of subroutine, assessment of chain convergence**)
- Finally, the NONMEM generated **posterior distributions** were superimposed with the **maximum a posteriori (MAP)** point estimates (FOCE-I in conjunction to the prior functionality) [2] to assess the degree of agreement.

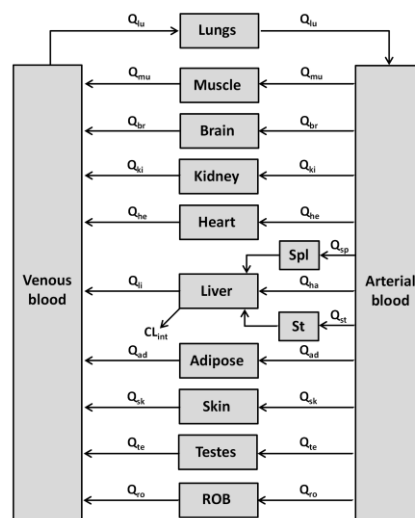


Figure 1: Schematic structure of a whole-body PBPK model for diazepam. Different organ/tissues are represented as different compartments connected by perfusing blood.

- **Comparable results** were obtained across **NONMEM** and **WinBUGS** (Table 1, Figure 4) providing further confidence for use of the former in Bayesian PBPK analyses of population data.
- **Selection of the differential equation solver** (subroutine) was particularly critical for the computation time of the analysis. **ADVAN13 exhibited the best performance** (0.6 sec / iteration), followed by ADVAN8 (0.9 sec / iteration), ADVAN9 (9.7 sec / iteration) and ADVAN6 (>30 sec / iteration).
- **MCMC convergence** (Figure 2) in such a complex model should be ideally assessed with **multiple-chain diagnostics** (e.g. Rubin-Gelman). Substantial auto-correlation was observed and long chains had to be run to assure convergence.
- **Only the model parameters to which the plasma output is sensitive were substantially updated from the priors** (Figures 3 & 5)
- **The modes of the NONMEM generated posterior densities can be very accurately captured by MAP estimation** in the same platform (Figure 3) with significant reductions in computation time.

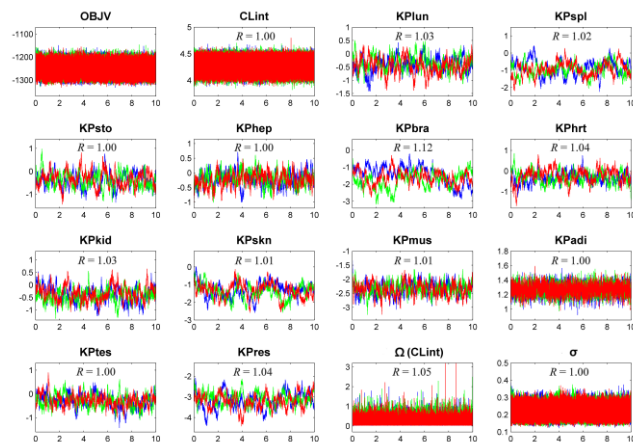


Figure 2: Trace plots of the 3 MCMC chains run for the Bayesian analysis in NONMEM. Parameter values (log-transformed) are plotted against iteration number (x100,000). The potential scale reduction factor from the Gelman-Rubin diagnostic (R) is also reported for each parameter.

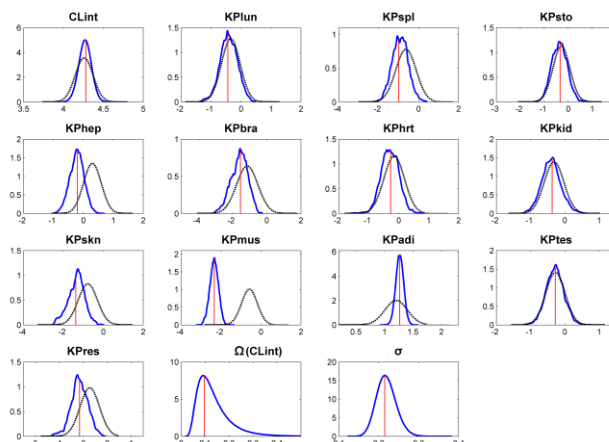


Figure 3: Posterior marginal probability density (blue solid line) for each model parameter after Bayesian analysis in NONMEM, superimposed with the prior probability density (black dotted line). Red vertical lines represent the location of the MAP point estimate in the same platform.

Table 1: Parameter values of the model across different platforms

Parameter	Prior mean (SD)	WinBUGS mean (CV) ^(a)	NONMEM _{MCMC} mean (CV) ^(b)	NONMEM _{MAP} estimate (CV) ^(c)
Structural model ^(d)				
CL _{int} (L/h)	71.3 (7.99)	75.0 (7%)	71.8 (8%)	72.2 (8%)
KL _{int} (Lungs)	0.75 (0.24)	0.70 (21%)	0.69 (29%)	0.64 (30%)
KP _{int} (Splanchnic)	0.60 (0.33)	0.48 (25%)	0.43 (42%)	0.37 (43%)
KP _{int} (Stomach)	0.80 (0.29)	0.76 (25%)	0.73 (35%)	0.71 (33%)
KP _{int} (Liver)	1.41 (0.43)	0.66 (33%)	0.83 (24%)	0.82 (23%)
KP _{int} (Brain)	0.39 (0.27)	0.31 (19%)	0.23 (47%)	0.22 (52%)
KP _{int} (Heart)	0.91 (0.32)	0.82 (28%)	0.78 (31%)	0.77 (31%)
KP _{int} (Kidney)	0.76 (0.22)	0.71 (21%)	0.70 (30%)	0.69 (28%)
KP _{int} (Skin)	0.52 (0.26)	0.38 (18%)	0.28 (41%)	0.25 (38%)
KP _{int} (Muscle)	0.61 (0.25)	0.19 (6%)	0.10 (22%)	0.09 (23%)
KP _{int} (Adipose)	3.41 (0.68)	3.01 (9%)	3.06 (7%)	3.04 (7%)
KP _{int} (Testes)	0.79 (0.23)	0.77 (21%)	0.77 (27%)	0.76 (28%)
KP _{int} (Rest of body)	0.07 (0.03)	0.07 (43%)	0.05 (36%)	0.04 (33%)
IV^(e)				
CL _{int}	0.5 ^(f)	0.16 (25%)	0.14 (34%)	0.10 (5%)
Res^(g)				
		0.26 (6%)	0.22 (11%)	0.22 (7%)

	0.2/0.2 (2/0)	0.2/2 (2/0)	0.2/2 (2/2)
(a)	refer to the posterior distribution determined in WinBUGS by Gueorgieva et al [11]		
(b)	refer to the posterior distribution determined in NONMEM in the current work		
(c)	Maximum <i>a posteriori</i> (MAP) estimates from Langdon et al [2]		
(d)	Structural model parameters are reported in the domain of physiological interest and not in the domain of the estimated log-transformed parameter		
(e)	reported as variance		
(f)	non-informative prior assigned		

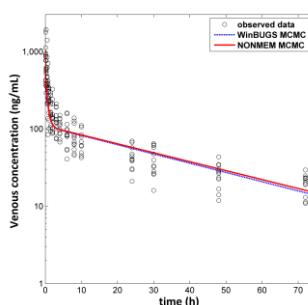


Figure 4: Model-predicted typical venous concentration-time profiles obtained after the Bayesian analysis in WinBUGS [1] (blue dotted line) and NONMEM (red solid line).

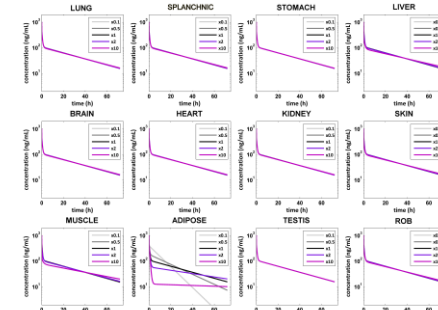


Figure 5: Sensitivity of the diazepam plasma concentration profiles on numerical perturbations of the tissue partition coefficients of the model.

1. Gueorguieva *et al.* J Pharmacokinet Pharmacodyn (2006) 33(5):571-594.
2. Langdon *et al.* Eur J Clin Pharmacol (2007) 63(5):485-498.