Simultaneous fit of competing models as a model discrimination tool in a fully Bayesian approach

Lena E Friberg, Chantaratsamon Dansirikul, Stephen B Duffull

School of Pharmacy, University of Queensland, Australia

Introduction

- In Markov chain Monte Carlo (MCMC) analysis there is no "gold standard" model discrimination method (as the frequentists' likelihood ratio test), but several methods have been suggested and are commonly used (Table 1), e.g. the DIC which is based on a measure of model fit and a measure of complexity
- MCMC also allows model discrimination to be based on predictive or posterior distributions as competing models can be fitted simultaneously as a joint model with an added parameter to indicate which model is preferred[3,4]

Table 1. Proposed methods for model selection in Bayesian analysis[1,2]

	Advantages	Disadvantages
AIC (Akaike information criteria)	• Easily computed	• Not suitable for hierarchical non-linear models – how many effective parameters?
DIC (Deviance information criteria)	• Provided by WinBUGS on "the fly"	• The calculation of the number of effective parameters does not always work properly, when?
Bayes factors	• Used by some statisticians	• Determines how well the priors predict the observed data • Requires extensive extra coding • Conservative
Cross-validation	• Considered accurate	• Computationally intensive • Not suitable for small data sets
Posterior Predictive Check (PPC)	• Can be computed on "the fly"	• Need a good feature of the observed data to compare the model predictions with
Reversible Jump	• Can assess many models simultaneously	• Computationally intensive • Not feasible in WinBUGS (yet)

Aim

- To examine the use of a mixture model with a mixture population parameter to discriminate between population pharmacokinetic models in WinBUGS

Methods

Data sets

- Data sets with 1-compartment (1-c) and 2-compartment (2-c) characteristics were simulated in MATLAB (hypothetical and based on citalopram) or in NONMEM (based on sirolimus) (Table 2) in addition to the two real data sets for citalopram and sirolimus
- The 2-c hypothetical nominal simulation parameters were derived by assuming a dose of 1,000 units, a V_c of 10, α =1, β = 0.1 and $AUC_{distribution\ phase}/AUC_{total}$=0.25. The 1-c nominal parameters were derived by fitting a 1-c model through the 2-c data
- For the citalopram and sirolimus simulated data sets the nominal parameters were from priors elicited from the literature

Table 2. Data sets and analysis scenarios

		Data sets			*MCMC analysis scenarios*		
	Dosing	# of datasets/ scenario	# of subjects/ data set	# of observations/ subject	Priors[1]	Residual error variance	Residual error structure
Simulated hypothetical	single i.v.	2 x 30	20	10	high high low low flat flat	additive additive additive additive additive proportional	common independent common independent independent independent
Simulated citalopram	single p.o.	2 x 10	20	10	high high	additive additive	common independent
Simulated sirolimus	single p.o.	2 x 10	20	14	high low flat	additive additive additive	independent independent independent
Real data citalopram	single p.o.	1	26	1-12	high high	proportional proportional	common independent
Real data sirolimus	multiple p.o.	1	25	3-20	high high	proportional proportional	common independent

[1] *high*= informative, precisions ≈ 25; *low*= biological plausible ranges, precisions ≈ 0.05-0.2; *flat*=uninformative, precisions=0.0001

Model discrimination

- For each data set the two competing models (1-c and 2-c) were fit simultaneously in WinBUGS[5] as a mixture model with a mixture population parameter (*Mix*) drawn from a uniform distribution (U(0,1))

$$Model_{Mixture} = Model_{1\text{-}c} \times (1\text{-}Mix) + Model_{2\text{-}c} \times Mix$$

- Common and independent residual error structures were investigated as well as high, low and flat prior information
- Each data set was run for 10,000 iterations of which 4,000 were burn-in and discarded. Pilot runs indicated convergence for the mixture parameter
- For one scenario (flat priors, additive error, independent error structure), the 1-c and 2-c models were also fit separately and the DICs were compared

Results

Mixture model

- For the simulated data sets the true model was supported (i.e. the median of the posterior probability (evidence) for the true model was >0.5) in all but one case (1-c data, proportional error model; Fig. 1)

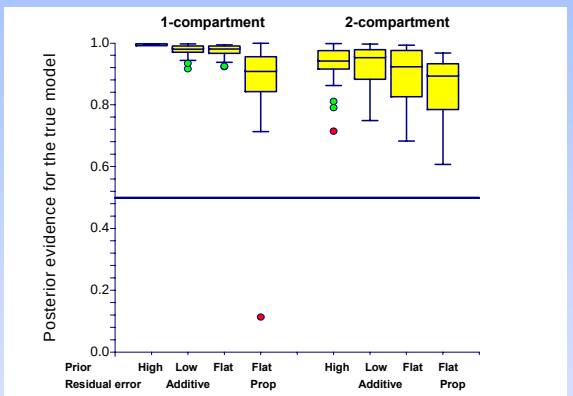

Fig. 1 Probability of choosing the true model for the hypothetical data sets (n=30) for different scenarios with independent residual error structures

- The posterior evidence for the true model was similar with common (not shown) and independent residual error structures while parameter estimates for the true model were closer to the nominal simulation values with independent residual variances
- The 1-c model was preferred for the real citalopram data (probability > 0.975) while the 2-c model was preferred for the real sirolimus data (probability > 0.975)

DIC

- Selected the true model in all cases for the 2-c data but for the 1-c data, the wrong model was selected in all cases
- For both the real citalopram data and the real sirolimus data, the DIC was in favour of the 2-c model

Discussion

- Analysing two competing models simultaneously with a mixture parameter is a promising model-selection tool in WinBUGS which can be performed on-the-fly. This dichotomous (closed) model selection method was here shown to work well
- The model selection process can also be considered as "open", i.e. by averaging over models. Then the MCMC chains need to be run for longer than for closed model selection

References

1. Spiegelhalter et al. R Statist Soc B (2002) 64: 583-639
2. Gelman et al. Bayesian Data analysis 2nd Ed. Chapman & Hall (2003)
3. Carlin and Chib. J R Statist Soc B (1995) 57: 473-484
4. Riley. AAPS Workshop on Bayesian Primer Salt Lake City, Utah (2003)
5. Spiegelhalter et al. WinBUGS Version 1.4 User Manual (2003)