Determination of the minimum effective dose for correlated dose-response data using Bayesian variable selection (BVS) models.

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Motivating example.

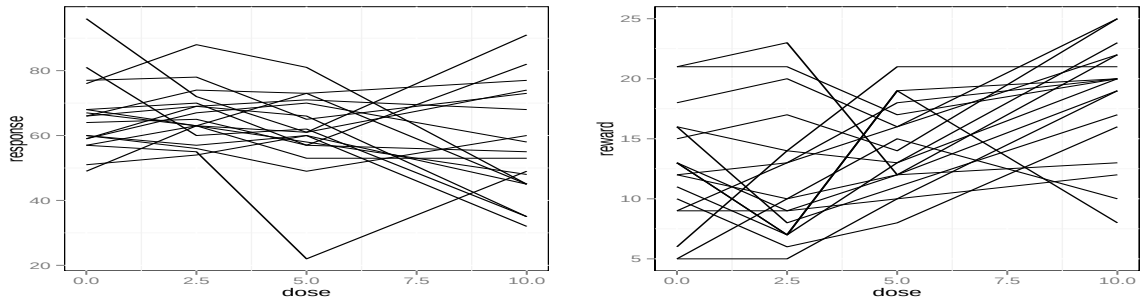
- An experiment to test activity of three doses of an active anti-depressant as compared to a control group in mice.

DRL-72 protocol.

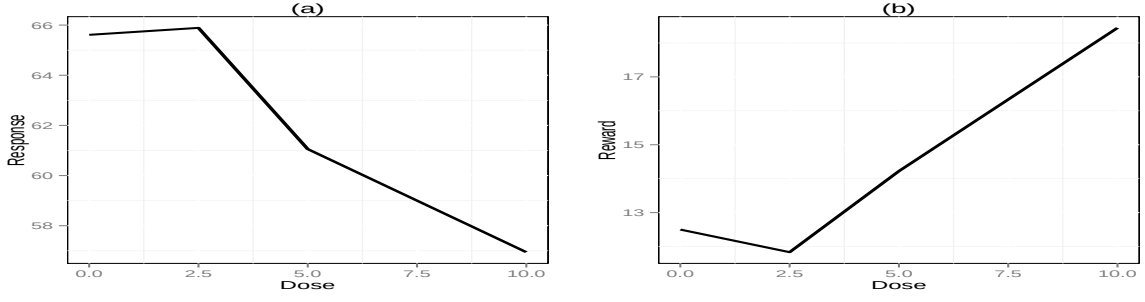
- **In the training phase**, a placebo is administered and mice are trained to press a lever for which they obtain a reward in return.
- **In the experimental phase**, each of the four doses (0.0mg/kg, 2.5 mg/kg, 5.0 mg/kg and 10.0 mg/kg) is administered and the mouse observed for 60 seconds.
- If 72 seconds have elapsed since the last lever pressing, the mouse obtains a reward.
- The **number of times the rat presses the lever (response)** and **the number of rewards** it obtains within the 60 seconds schedule are recorded.
- This sequence is repeated for all four doses being administered.

The resulting dataset.

Individual mice data for the number of responses and number of rewards obtained across the four dose levels.



Average number of responses and the average number of rewards obtained from 18 mice in the DRL-72 experiment.



We do not impose a monotonicity constraint on the dose-outcome profiles.

Our modelling goal.

- Identify the lowest dose that results in a significant change in the two outcomes -**the minimum effective dose (MED)**.
- Classical methods e.g. ANOVA requires adjusting for multiple testing say with *False discovery rate (FDR)*.
- Alternatively, fit sequence of models for the dose-response profiles of interest and compare the different model fit statistics.

Disadvantages of classical model selection.

- Number of models to test a function of dose.
- Classical model selection strategies do not account for the fact that the best model is known with some uncertainty.

Classical hierarchical model formulation.

Let;

n_{ij} be the average number of times the rat presses the lever.

Y_{ij} be the average number of rewards obtained.

$$Y_{ij}|n_{ij} \sim Bin(n_{ij}, \pi_{ij})$$

$$n_{ij} \sim Pois(\lambda_{ij})$$

$$\log(\lambda_{ij}) = \alpha_0 + \sum_{j=1}^{3} \gamma_j X_j + a_i$$

$$\text{logit}(\pi_{ij}) = \beta_0 + \sum_{j=1}^{3} \delta_j X_j + b_i$$

- α_0 and β_0 are the effects of the control dose (0.0mg/kg),
- γ_j and δ_j are the log(relative risk) and log(odds ratio),
- (j=1,2,3) for 2.5mg/kg, 5mg/kg and 10mg/kg respectively;
- a_i and b_i are the random intercepts .

Bayesian priors and hyper-priors.

Priors

$\alpha_0 \sim N(0.0, \tau_a)$

$\beta_0 \sim N(0.0, \tau_b)$

$\delta_j \sim N(0.0, \tau_d)$

$\gamma_j \sim N(0.0, \tau_g)$

$$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, D\right), \quad D = \begin{pmatrix} \sigma_a^2 & \sigma_{ab} \\ \sigma_{ab} & \sigma_b^2 \end{pmatrix}$$

Hyperpriors

$\tau_a; \tau_b; \tau_d; \tau_g \sim Gamma(0.001, 0.001)$

$D^{-1} \sim Wishart(R_D, k)$

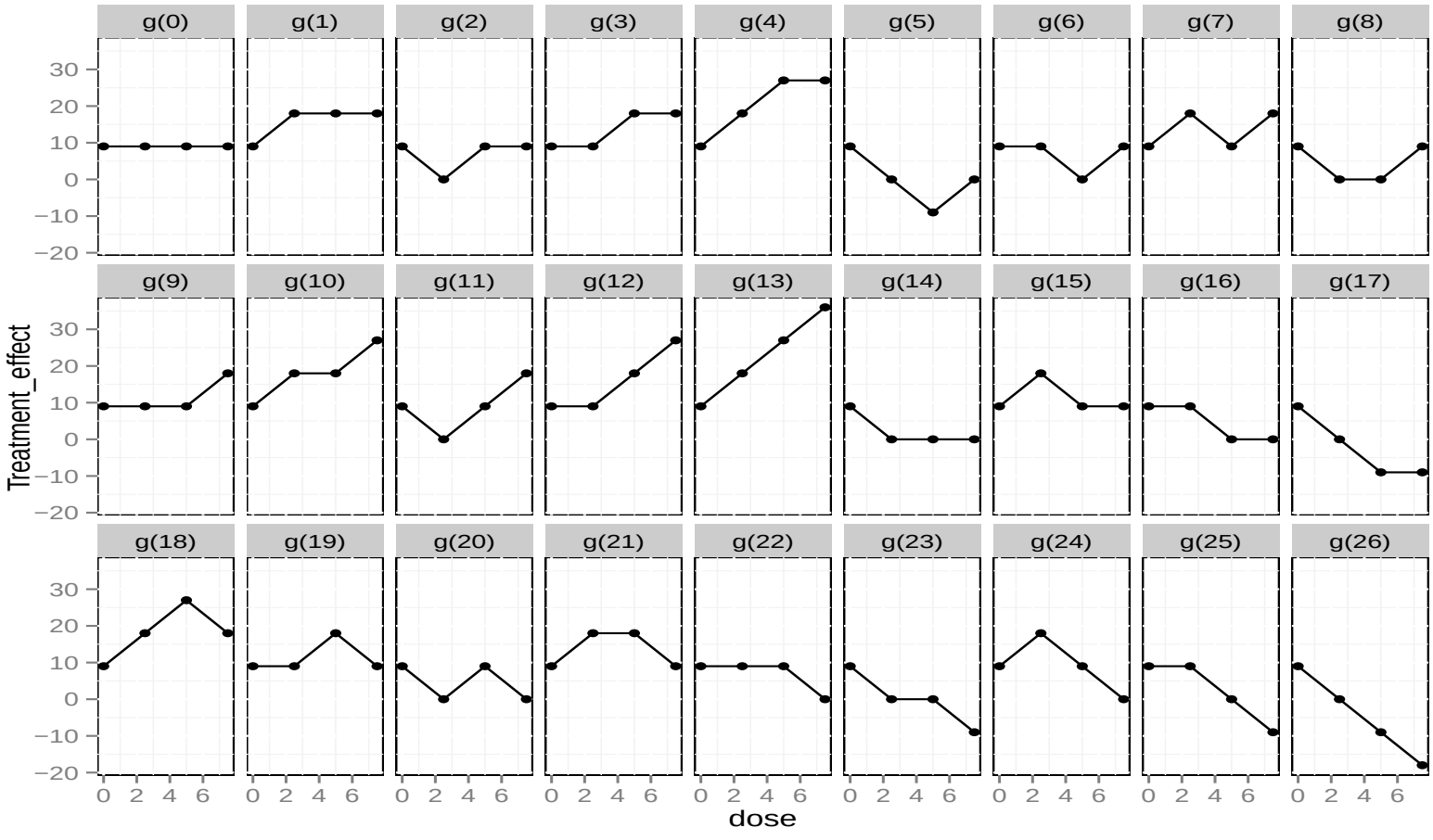
Results: Joint hierarchical model.

GLMM estimates for log(RR) and log(OR) with the corresponding 95% confidence intervals.

	log(RR)		log(OR)	
Contrast	**Estimate**	**95% CI**	**Estimate (SE)**	**95% CI**
Dose 0.0 Effect	4.1378	(4.07, 4.2)	-1.3201	(-1.5, -1.14)
2.5mg vs. 0.0mg	0.0042	(-0.08, 0.09)	-0.0732	(-0.3, 0.16)
5.0mg vs. 0.0mg	-0.072	(-0.16, 0.02)	0.2765	(0.05, 0.5)
10mg vs. 0.0mg	-0.1417	(-0.23, -0.05)	0.7687	(0.55, 0.99)
Random Effects Matrix				
$\hat{\rho}$	-0.9789 (0.0221)	(-1.03, -0.93)		
$\sigma^2_{Poisson}$	0.0206 (0.0054)	(0.01, 0.03)		
$\sigma^2_{Binomial}$	0.295 (0.0649)	(0.16, 0.43)		

Illustration of unconstrained models.

For a four dose experiment with three active doses, there are 27 unconstrained dose-outcome profiles.



Bayesian variable selection.

- Bayesian variable selection (BVS) provides a tool for *model selection* and *inference* simultaneously.
- BVS sccounts for the uncertainty in model selection given a set of *a priori* known models.
- For each parameter, we compute the **posterior inclusion probability.**
- The **posterior model selection probability** for each model in the set is also obtained.
- The model with the highest posterior selection probability is the most probable model given the data.

Bayesian variable selection model formulation.

n_{ij} be the average number of times the rat presses the lever.
Y_{ij} be the average number of rewards obtained.

$$Y_{ij}|n_{ij} \sim Bin(n_{ij}, \pi_{ij})$$
$$n_{ij} \sim Pois(\lambda_{ij})$$
$$\log(\lambda_{ij}) = \alpha_0 + \sum_{j=1}^{3} W_j \gamma_j X_j + a_i$$
$$\text{logit}(\pi_{ij}) = \beta_0 + \sum_{j=1}^{3} Z_j \delta_j X_j + b_i$$
$$W_j \sim dbern(\psi_j)\ Z_j \sim dbern(\upsilon_j)$$
$$\psi_j \sim dunif(0,1)\ \upsilon_j \sim dunif(0,1)$$

- α_0 and β_0 are the effects of the control dose (0.0mg/kg),
- γ_j and δ_j are the log(relative risk) and log(odds ratio),
- (j=1,2,3) for 2.5mg/kg, 5mg/kg and 10mg/kg respectively;
- a_i and b_i are the random intercepts .

BVS indicator variables and their priors.

$$W_j = \begin{cases} 1 \text{ if } \gamma_j \text{ is included in the model} \\ 0 \text{ if } \gamma_j \text{ is not included in the model} \end{cases}$$

$$Z_j = \begin{cases} 1 \text{ if } \delta_j \text{ is included in the model} \\ 0 \text{ if } \delta_j \text{ is not included in the model} \end{cases}$$

$$W_j \sim dbern(\psi_j) \; Z_j \sim dbern(\upsilon_j)$$

$$\psi_j \sim dunif(0,1) \; \upsilon_j \sim dunif(0,1)$$

Bayesian priors and hyper-priors.

$$\alpha_0 \sim N(0.0, \tau_a); \; \beta_0 \sim N(0.0, \tau_b)$$

$$\delta_j \sim N(0.0, \tau_d); \; \gamma_j \sim N(0.0, \tau_g)$$

$$\tau_a; \tau_b; \tau_d; \tau_g \sim Gamma(0.001, 0.001)$$

$$\begin{pmatrix} a_i \\ b_i \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, D \right), \; D = \begin{pmatrix} \sigma_a^2 & \sigma_{ab} \\ \sigma_{ab} & \sigma_b^2 \end{pmatrix}$$

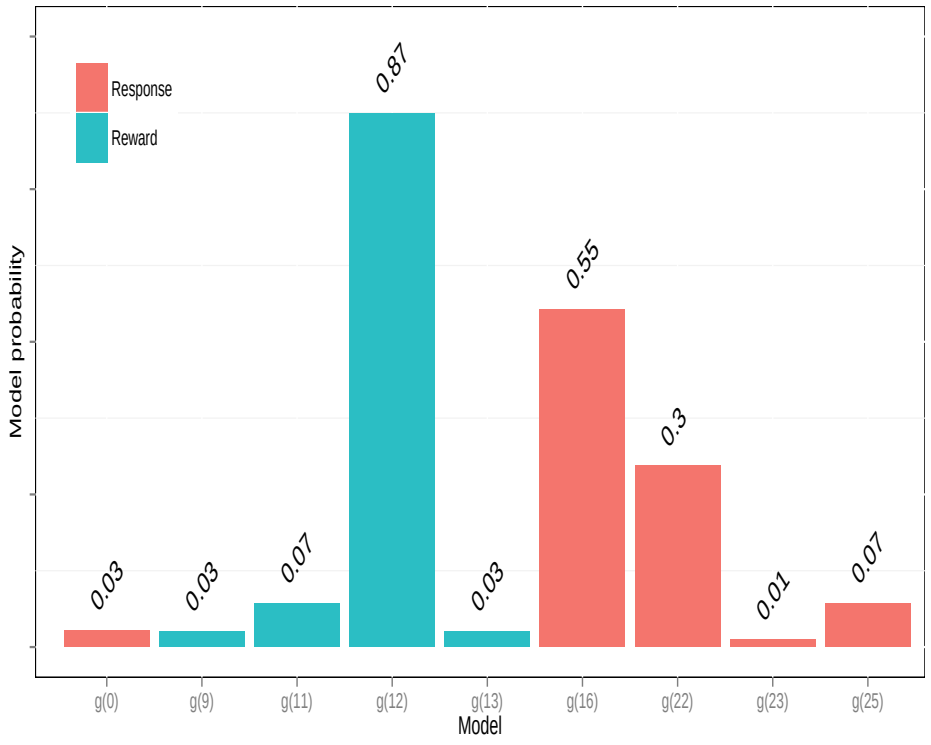
Parameter estimation.

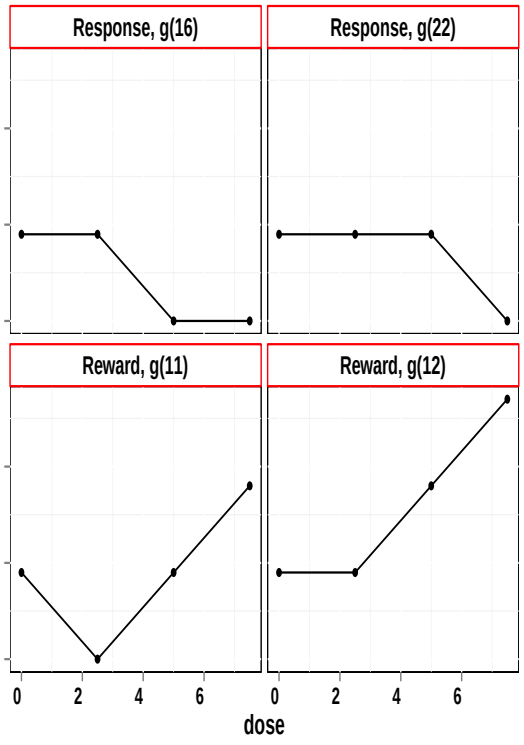
- Bayesian estimation is based on MCMC as implemented in WinBUGS.
- The posterior parameter estimates are the model-averaged estimates of the individual model estimates.
- There is shrinkage of the BVS estimates to the average of the estimated $\hat{\mu}_r$ in all the **R** models.

$$\hat{\mu}_{BVS} = \sum_{r=0}^{R} \bar{P}(g_r|data)\hat{\mu}_r$$

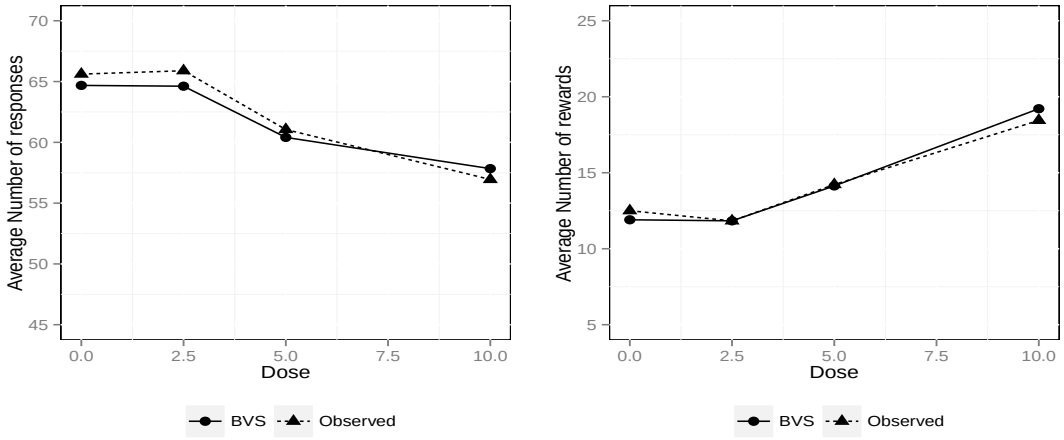
- $\bar{P}(g_r|data)$ are weights- the average number of times each parameter was included in the models.

Posterior model selection probability.





BVS shrinkage of parameter estimates to the mean.



Model	Dose	Est (cl)
log(RR)	0	4.1687 (4.092, 4.245)
	2.5	-0.001 (-0.0155, 0)
	5	-0.0691 (-0.1608, 0)
	10	-0.1121 (-0.1866, 0)
log(OR)	0	-1.4909 (-1.749, -1.241)
	2.5	-0.006 (-0.1339, 0.0128)
	5	0.3034 (0, 0.4898)
	10	0.7929 (0.6112, 0.969)

Posterior inclusion probabilities ψ_{ij} and υ_{ij} for W_j and Z_j respectively.

The mean of the selection indicator is given by $\bar{W} = \frac{1}{T}\sum_{i=1}^{T} W_i; \bar{Z} = \frac{1}{T}\sum_{i=1}^{T} Z_i$, where T is the number of simulations.

Model	Parameter	Inclusion Probability	Mean of Selection Indicator
RR	γ_1	0.348	0.045
	γ_2	0.553	0.653
	γ_3	0.466	0.393
OR	δ_1	0.366	0.1
	δ_2	0.657	0.971
	δ_3	0.666	1

Estimated parameters for the variance of random effects for response and rewards and the correlation between the two outcomes.

Parameter	Estimate
$\sigma^2_{Poisson}$	0.0171
$\sigma^2_{Binomial}$	0.2275
$\hat{\rho}$	-0.9879

Reduced model parameter estimates.

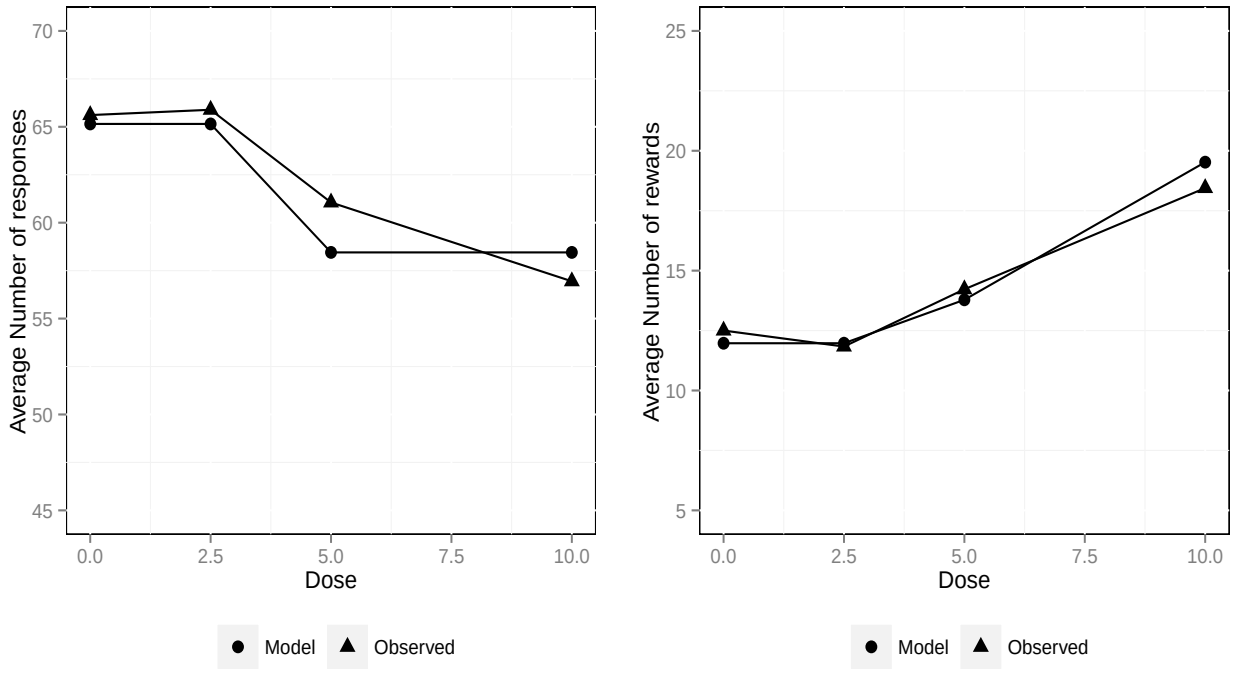
Fit the profiles suggested by the most probable model for response and reward jointly.

Param	dose	Estimate	cl
OR	0	4.176	(4.102, 4.248)
	2.5	-	-
	5	-0.1085	(-0.167, -0.0499)
	10	-	-
RR	0	-1.4927	(-1.737, -1.243)
	2.5	-	-
	5	0.3156	(0.1352, 0.4923)
	10	0.8033	(0.6297, 0.975)

The random effects matrix for the joint model is shown below;

Parameter	Estimate
$\sigma^2_{Poisson}$	0.0173
$\sigma^2_{Binomial}$	0.2275
ρ	-0.9882

Fitted average profile for response and rewards.



Conclusions.

- Bayesian variable selection provides a tool for model selection that accounts for model uncertainty.
- BVS parameter estimates are the model-averaged estimates of the set of all models.
- Weights are the posterior proportion of models for which each parameter was included.
- The most probable model enables us to compare different hypothesis in order to determine the minimum effective dose.