BMA Approach — Point Esimation

– We first average (or marginalise) the working model across the posterior distribution of a to obtain the posterior predictive distributions:

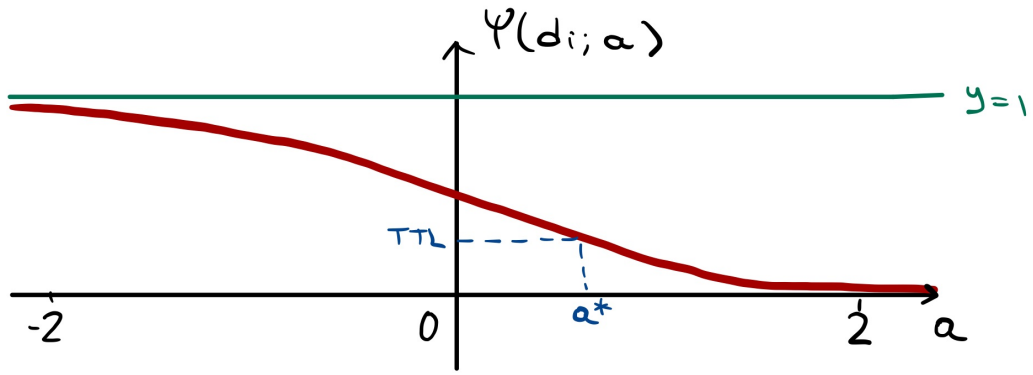
$$p_m(d_i|\Omega_j) = \int_{\mathcal{A}} \psi_m(d_i; a) f_m(a|\Omega_j) da.$$

– Then, we can apply BMA to combine each of the posterior predictive distributions corresponding to each ordering to obtain a single, combined distribution as follows,

$$p_c(d_i|\Omega_j) = \sum_{m=1}^{M} p(m) p_m(d_i|\Omega_j).$$

Escalation with Overdose Control

- Determine a^* such that $\psi_m(d_i; a^*) = \theta$.
- Compute $\Pr[\psi_m(d_i; a) > \theta] = \int_{-\infty}^{a^*} f_m(a|\Omega_j)da$



- Combine the integrals corresponding to each ordering to obtain

$$\Pr[\psi(d_i; a) > \theta] = \sum_m p(m) \Pr[\psi_m(d_i; a) > \theta]$$

- This value can then be compared to the feasibility bound c_{od}.

Prior Elicitation

- Suppose dose schedules are given the following notation:

  d_0 : Standard of Care
  d_1 : 1500mg BID
  d_2 : 1000mg TID
  d_3 : Asymmetric; 1500mg in the morning, 2000mg in the evening

- d_0 is known to be the least toxic.
- d_1 is less toxic than d_3.
- This yields the following orderings:

  $$m = 1 : d_0 \to d_1 \to d_2 \to d_3$$
  $$m = 2 : d_0 \to d_1 \to d_3 \to d_2$$
  $$m = 3 : d_0 \to d_2 \to d_1 \to d_3$$

- Denote true risk of toxicity of i-th dose as $R(d_i)$.

– Systematic approach to prior specification.

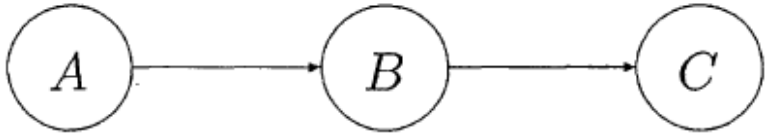


Figure: A simple discrete graphical model from Hoeting et al. (1999).

– Prior probability of existence of a particular arrow from node j to node k is denoted as $\pi_{jk} = \pi_{kj}$.
– $p(m = i) = \prod_{j,k} \pi_{jk}^{\delta_{ijk}} (1 - \pi_{jk})^{1-\delta_{ijk}}$ where δ_{ijk} indicates whether the arrow exists from j to k in the i-th model.
– Suppose that π_{jk} is prior probability of $R(d_j) > R(d_k)$ s.t. $\pi_{jk} = (1 - \pi_{kj})$.
– $p(m = i)$ can be elicited from pairwise prior probabilities.
– Depending on prior beliefs, may not be practical for settings with many possible doses (e.g. for 16 doses, ${}_{16}C_2 = 120$).

Example

$\pi_{01} = \pi_{02} = \pi_{03} = 0$
$\pi_{12} = 0.4$
$\pi_{13} = 0$
$\pi_{23} = 0.25$

$$p(m=1) = (1-\pi_{01})(1-\pi_{02})(1-\pi_{03})(1-\pi_{12})(1-\pi_{13})(1-\pi_{23})$$
$$= 1 \times 1 \times 1 \times 0.6 \times 1 \times 0.75 = 0.45$$

$$p(m=2) = (1-\pi_{01})(1-\pi_{02})(1-\pi_{03})(1-\pi_{12})(1-\pi_{13})\pi_{23}$$
$$= 1 \times 1 \times 1 \times 0.6 \times 1 \times 0.25 = 0.15$$

$$p(m=3) = (1-\pi_{01})(1-\pi_{02})(1-\pi_{03})\pi_{12}(1-\pi_{13})(1-\pi_{23})$$
$$= 1 \times 1 \times 1 \times 0.4 \times 1 \times 0.75 = 0.3$$

Simulation Study Plan

Assessment Metrics:

- Proportion of Acceptable Selections
- Proportion of Correct Selections
- Proportion of Overly Toxic Selections
- Number of treated at overly toxic doses

Scenarios

- Traditional, basic scenarios should be included as baseline/benchmark
- Scenarios where possible orderings are similar should be included, important that no potential ordering is correct
- Displays operating characteristics of BMA methods under scenarios where posterior model probabilities are likely to be similar

Example:

$$1 \to 2 \to 3 \to 5 \to 4 \to 6$$

$$1 \to 2 \to 3 \to 5 \to 6 \to 4$$

$$1 \to 2 \to 5 \to 3 \to 4 \to 6$$

True ordering: $1 \to 2 \to 3 \to 4 \to 5 \to 6$