Adaptive incorporation of animal data into phase I trials: a robust Bayesian meta-analytic approach

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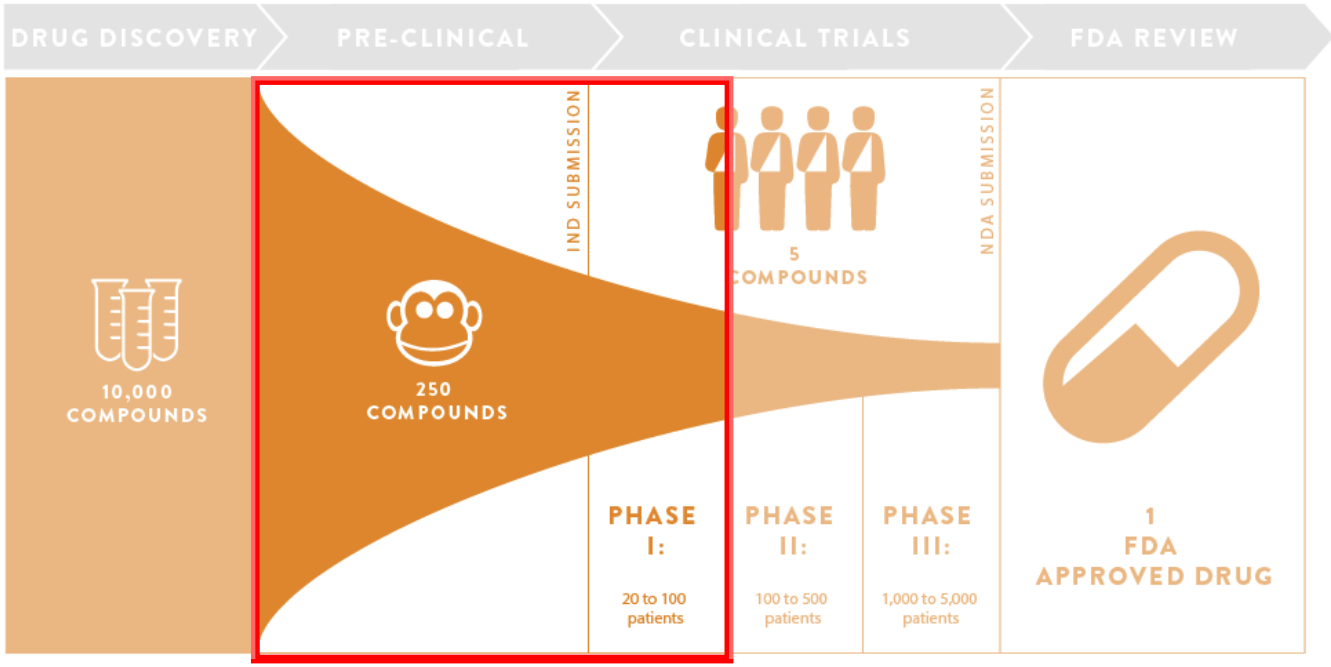
Medical and Pharmaceutical Statistics Research Unit

IDEAS Improving drug development

Motivation



- ⋆ Current approaches use preclinical data only to determine a maximum starting dose
- ⋆ **Goal:** Formal **incorporation of preclinical data** into phase I first-in-man trials

Problem formulation

Context:

- ⋆ Let i label the historical animal studies, $i = 1, \ldots, M$
- ⋆ J_i doses for evaluation: $d_{i1}, \ldots, d_{iJ_i}$
- ⋆ binary endpoint: toxicity or no-toxicity

Two-parameter logistic regression model: for $j = 1, \ldots, J_i$,

$$\text{logit}(p_{ij}) = \theta_{1i} + \exp(\theta_{2i}) \log(d_{ij}/d_{\text{Ref}}),$$

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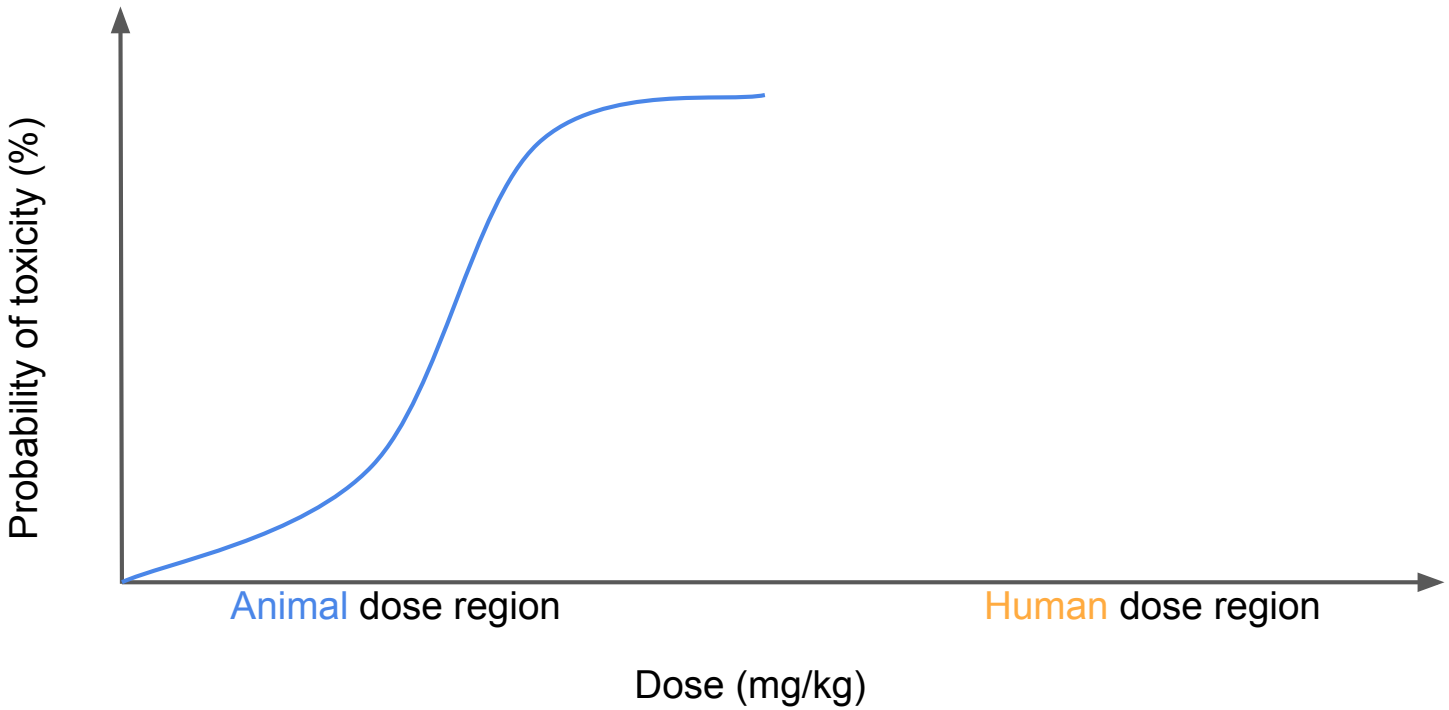
- ⋆ **Historical data** $\Rightarrow$ predict for **new** dose-toxicity parameters $\boldsymbol{\theta}_{i\star} = (\theta_{1i}, \theta_{2i})$
  - ▸ Exchangeability: $\boldsymbol{\theta}_{i\star}, \boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_M | \boldsymbol{\mu}, \Psi \sim \text{BVN}(\boldsymbol{\mu}, \Psi)$
- ⋆ Main **challenge** for using **historical animal data** $\Rightarrow$ **new** $\boldsymbol{\theta}_{i\star}$ **in a human trial**
  - ▸ the "interesting" region may be defined on very different dose intervals

Translating an animal dose-toxicity curve



⋆ **Solution**: translate the animal dose-toxicity data onto a common scale

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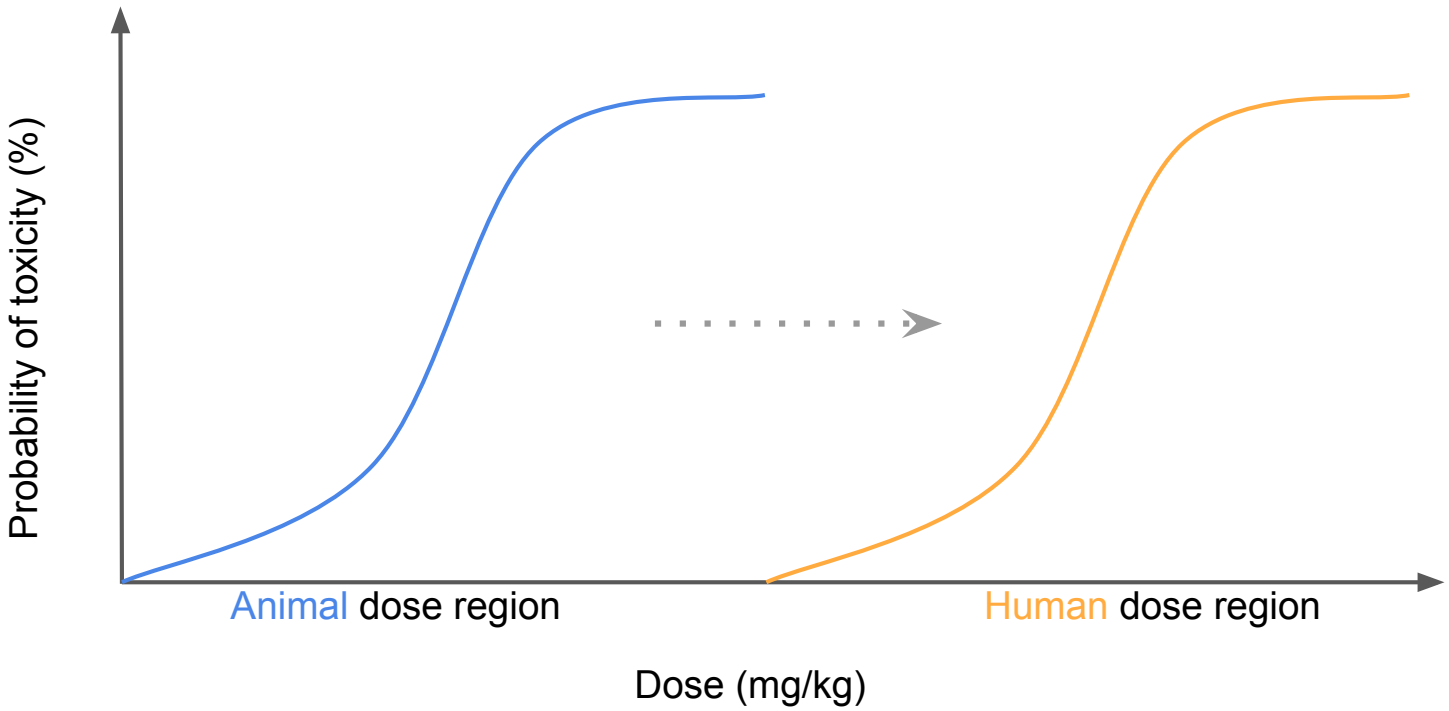

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Hierarchical modelling (I)

Thus, for M **historical animal studies**,

$$\text{logit}(p_{ij}) = \theta_{1i} + \exp(\theta_{2i}) \log(\delta_{\mathcal{A}_i} d_{ij} / d_{\text{Ref}}),$$

where $\delta_{\mathcal{A}_i}$ index the species used in historical study $i = 1, \ldots, M$.

Let $i^\star$ label the **new first-in-man trial**. We have

$$\text{logit}(p_{i^\star j}) = \theta_{1i^\star} + \exp(\theta_{2i^\star}) \log(d_{i^\star j} / d_{\text{Ref}}).$$

This translation parameter $\delta_{\mathcal{A}_i}$ leads to a feasible assumption of exchangeability:

$$\boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_M, \boldsymbol{\theta}_{i^\star} | \boldsymbol{\mu}, \Psi \sim \text{BVN}(\boldsymbol{\mu}, \Psi)$$

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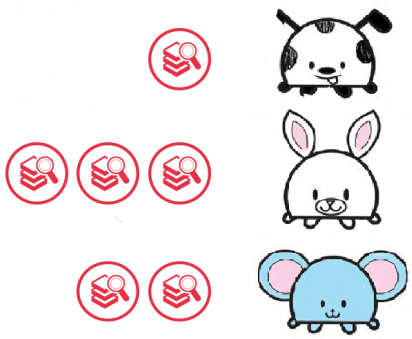
However, knowing $\mathcal{A}_i \in \{S_1, \ldots, S_K\}$,
what if predictability of the human toxicity may vary across animal species?

Hierarchical modelling (II)

Q: What if the predictability of human toxicity varies across animal species?

For illustrative purpose, assume $M = 6$ and $K = 3$.



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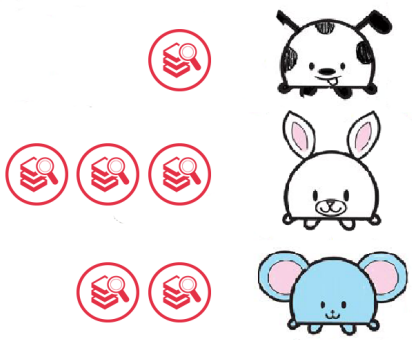

$$\begin{aligned}
\boldsymbol{\theta}_1 | \boldsymbol{\mu}_{S_1}, \Psi &\sim \text{BVN}(\boldsymbol{\mu}_{S_1}, \Psi), \\
\boldsymbol{\theta}_2, \boldsymbol{\theta}_3, \boldsymbol{\theta}_4 | \boldsymbol{\mu}_{S_2}, \Psi &\sim \text{BVN}(\boldsymbol{\mu}_{S_2}, \Psi), \\
\boldsymbol{\theta}_5, \boldsymbol{\theta}_6 | \boldsymbol{\mu}_{S_3}, \Psi &\sim \text{BVN}(\boldsymbol{\mu}_{S_3}, \Psi).
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$\star$ K random-effects distributions for sharing info between studies

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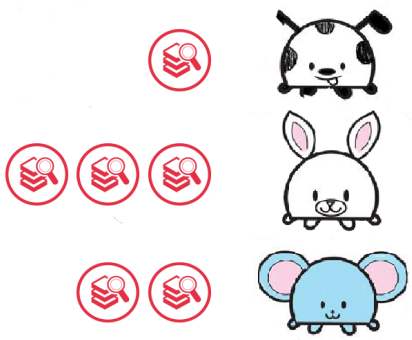

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Moreover,

$$\boldsymbol{\mu}_{S_1}, \boldsymbol{\mu}_{S_2}, \boldsymbol{\mu}_{S_3} | \boldsymbol{m}, \Sigma \sim \text{BVN}(\boldsymbol{m}, \Sigma).$$

- ⋆ K random-effects distributions for sharing info between studies
- ⋆ One 'supra-species' random-effects distribution for sharing info across species

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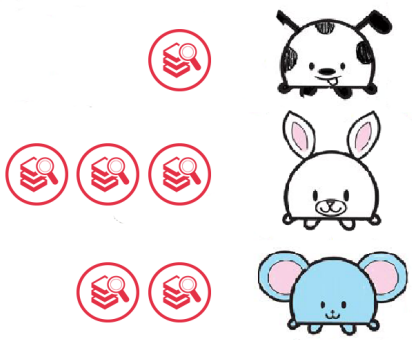

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- ⋆ K random-effects distributions for sharing info between studies
- ⋆ One 'supra-species' random-effects distribution for sharing info across species
- ⋆ This model accounts for both between-study and between-species heterogeneity

Robust borrowing of information from animals to humans

Relating the new parameters $\theta_{i\star}$ with historical parameters θ_is:

- $\star$ Permitting borrowing from each animal species S_k, we define

$$\theta_{i\star}|\mu_{S_k}, \Psi \sim \text{BVN}(\mu_{S_k}, \Psi) \quad \text{with prior probability } w_{S_k}.$$

- $\star$ For the purpose of robustification, we stipulate

$$\theta_{i\star} \sim \text{BVN}(\boldsymbol{m}_0, R_0) \quad \text{with prior probability } w_R,$$

where $w_R = 1 - \sum^{K} w_{S_k}$.

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Our hierarchical model is completed by specifying priors for the hyperparameters

- $\star$ Weakly informative priors for the population means in μ_{S_k}, $\boldsymbol{m}$
- $\star$ Half-normal priors for the variance parameters in Ψ, Σ
- $\star$ Uniform priors for the correlation coefficients in Ψ, Σ

Practical dose conversion

One common practice for dose conversion is to perform *Allometric scaling*.

- ⋆ Normalise body weight (BW) to body surface area (BSA)
- ⋆ FDA fomulated the calculation of human equivalent dose (HED)

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \frac{(\text{BW}/\text{BSA})_{\mathcal{A}}}{(\text{BW}/\text{BSA})_{\mathcal{H}}}$$

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- ⋆ Uncertainty usually surrounds the translation factor when treated as a fixed constant
- ⋆ We consider a **log-normal prior**, $\delta_{\mathcal{A}_i} \sim LN(\lambda, \gamma^2)$

Prior specification for $\delta_{\mathcal{A}_i}$

Species	BW (kg)		BSA (m^2)	HED in mg/kg		HED in mg/m^2	
	Reference	Working range		λ	γ	λ	γ
Mouse	0.02	(0.011, 0.034)	0.007				
Rabbit	1.80	(0.900, 3.000)	0.150				
Dog	10	(5, 17)	0.500				

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Specifying $\delta_{\mathcal{A}_i} \sim LN(\lambda, \gamma)$ based on an optimiser:

1. BW is commonly modelled using log-normal distribution in Biometrics literature
2. We then calibrate the log-normal distributions so that the 2.5th, 50th and 97.5th percentiles are in good agreement with the reference and working range
3. BSA is assumed to have negligible variation in adult animals and humans
4. Find the log-normal distributions for both $(\text{BW/BSA})_{\mathcal{A}}$ and $(\text{BW/BSA})_{\mathcal{H}}$
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Rabbit	1.80	(0.900, 3.000)	0.150	-1.127	0.290	2.485	0.274
Dog	10	(5, 17)	0.500	-0.616	0.301	2.996	0.286

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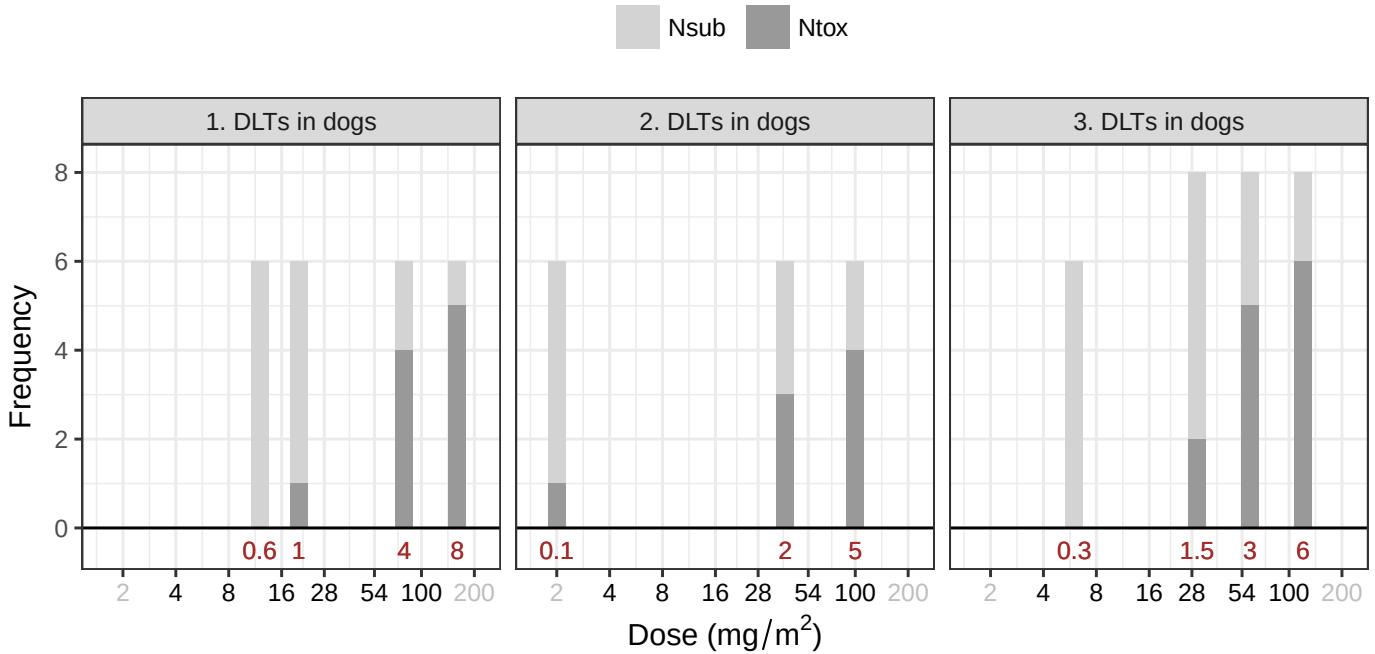
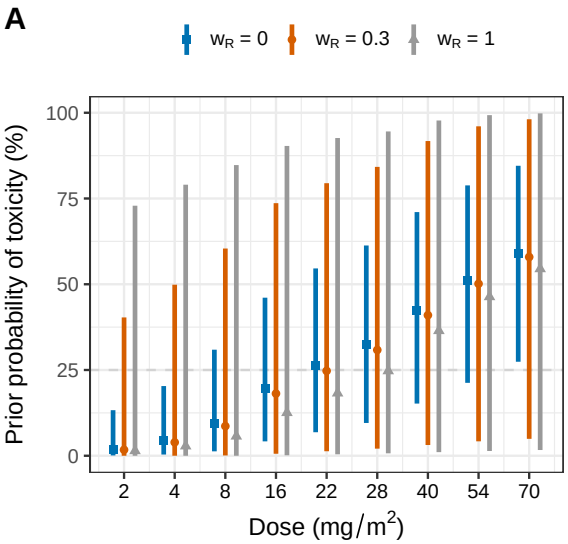
Simulation setting

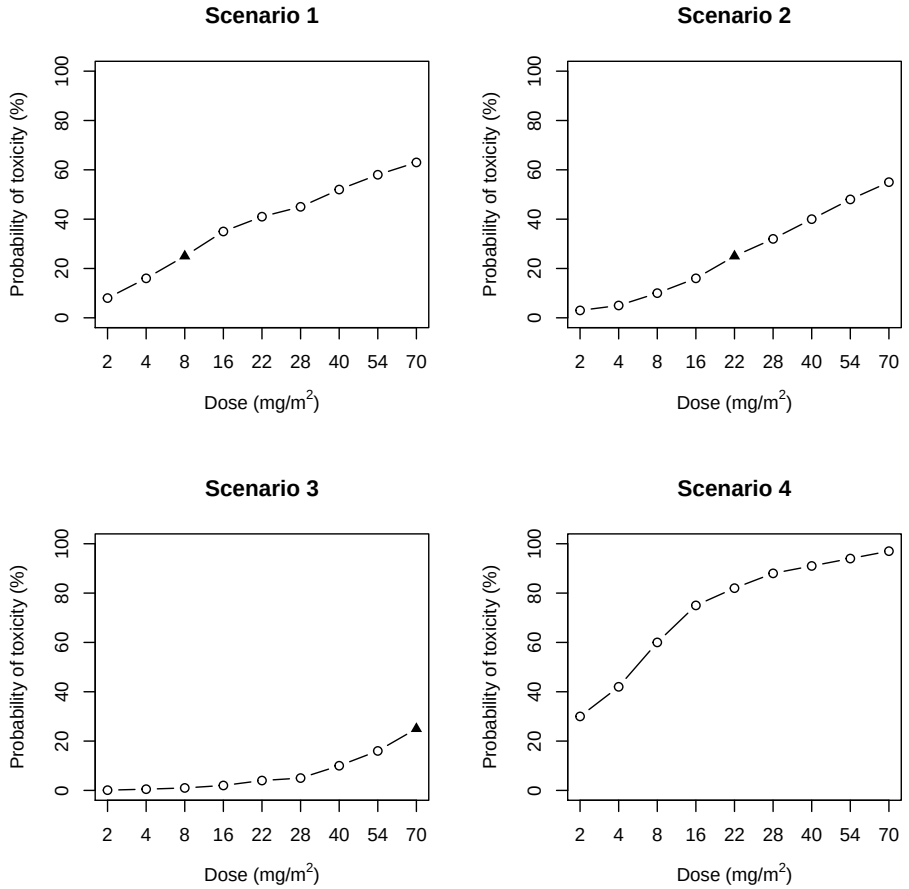
An anti-cancer therapy AUY922 is to be evaluated with a phase I first-in-man trial.

- ⋆ **Aim:** augment the phase I trial with animal data to estimate the target dose, TD25
- ⋆ Historical animal data were collected from 3 dog studies
- ⋆ Available human doses include 2, 4, 8, 16, 22, 28, 40, 54, 70 mg/m^2



Prior and toxicity scenarios





- ⋆ Simulated 2000 phase I dose-escalation trials (15 cohorts of 3 patients per trial)
- ⋆ Interim dose recommendations using animal & accumulating human toxicity data

Analysis models

We are interested in 4 analysis models for the comparison

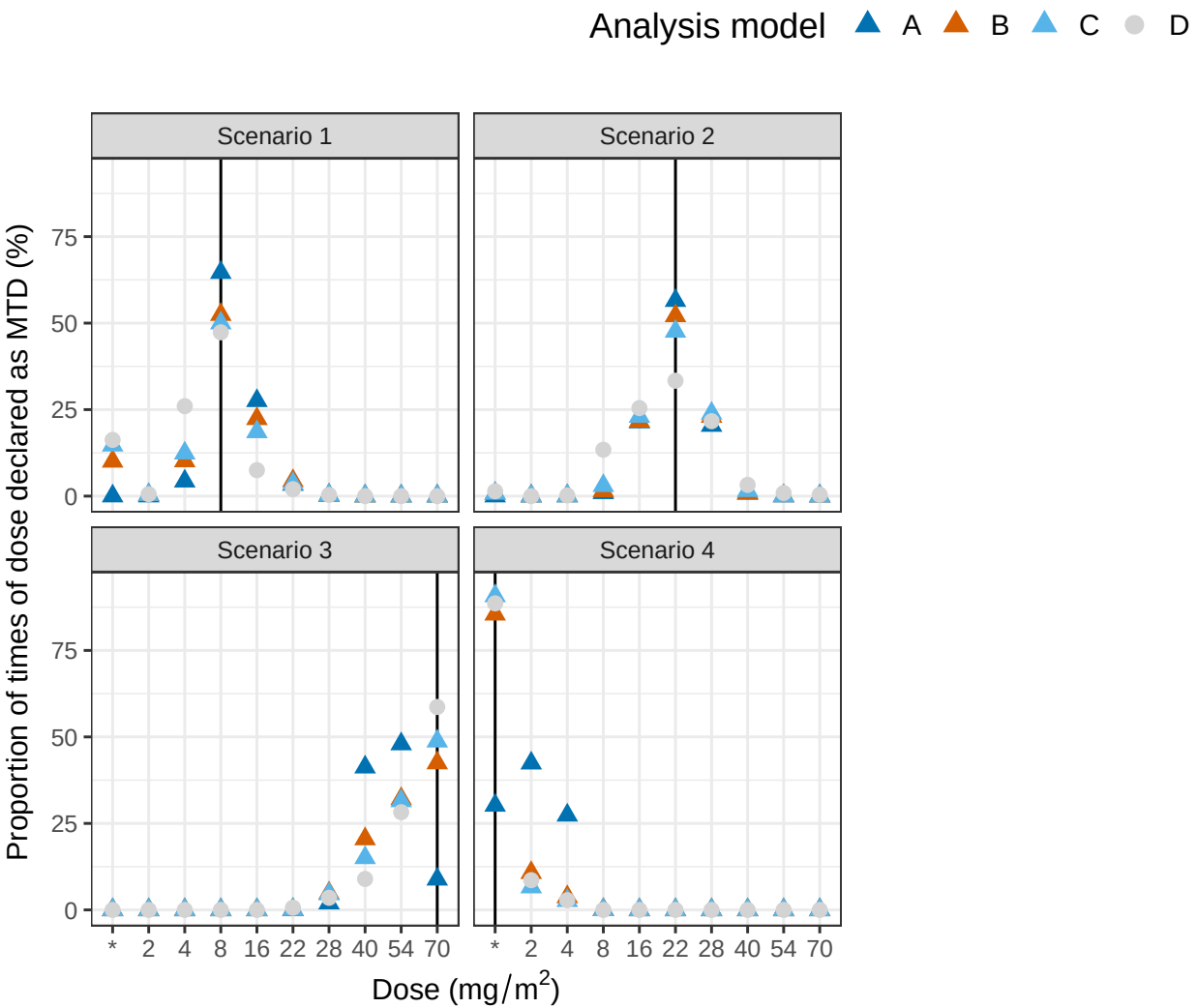
(i) Model A: Fully exchangeability between $\boldsymbol{\theta}_i$s and $\boldsymbol{\theta}_{i^\star}$ ($w_R = 0$)

(ii) Model B: High level of prior confidence in exchangeability assumption ($w_R = 0.3$)

(iii) Model C: Prior ambivalence about exchangeability assumption ($w_R = 0.5$)

(iv) Model D: No borrowing of information from preclinical data ($w_R = 1$)

Simulation results



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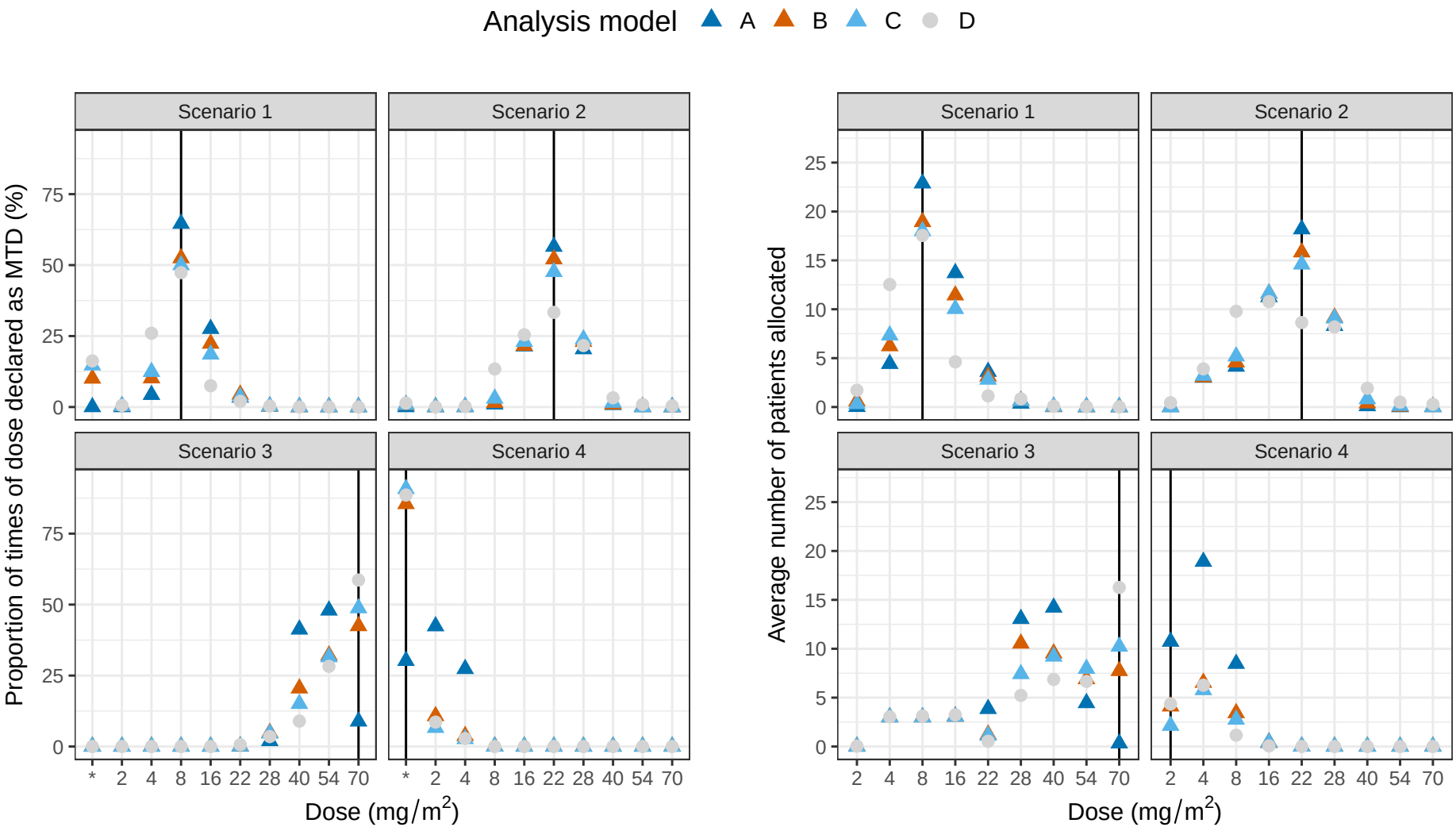

Conclusion

- ⋆ We proposed a Bayesian meta-analytic approach for data augmentation
- ⋆ By introducing the possibility of non-exchangeability, our proposal can
  - ▸ alleviate potential prior-data conflict
  - ▸ allow for robust borrowing of information from animals to humans
- ⋆ Dose-escalation procedure based on the proposed model is safe and ethical
- ⋆ It is not limited to a particular setup, but can be applied more broadly
  - ▸ synthesising data that have been recorded on a different measurement scale.

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Funding acknowledgement

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