Bayesian meta-analysis for pharmacokinetic parameters

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Witold Więcek

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Introduction

Objective: characterise inter-group differences in PK parameters (AUC, clearance, Cmax) using summary-level PK data only from many drugs

Use case: deriving uncertainty factors (UFs) for chemical risk assessment

- Original motivation for UFs: where compound-specific data not available, default values must be used to extrapolate
- The model applicable in any context where we extrapolate PK across different subgroups
- Especially useful when comparing more than means only

Real-world example

UFs for PK parameters due to polymorphic metabolism for CYP2D6 enzyme.

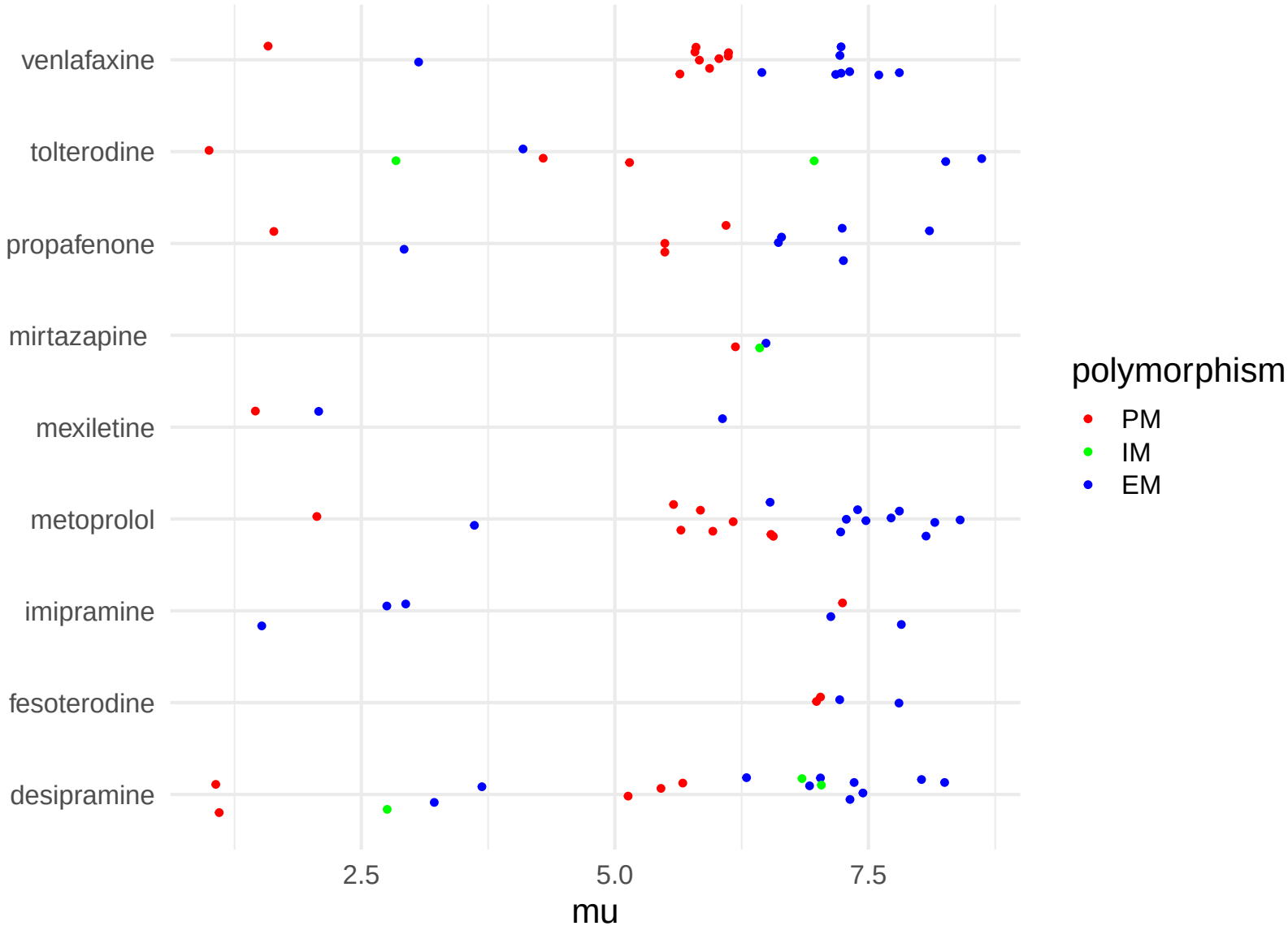
- Compare poor metabolisers, PM, vs extensive metabolisers, EM.
- Data based on pre-existing literature review. 81 studies of 9 drugs.

Issues:

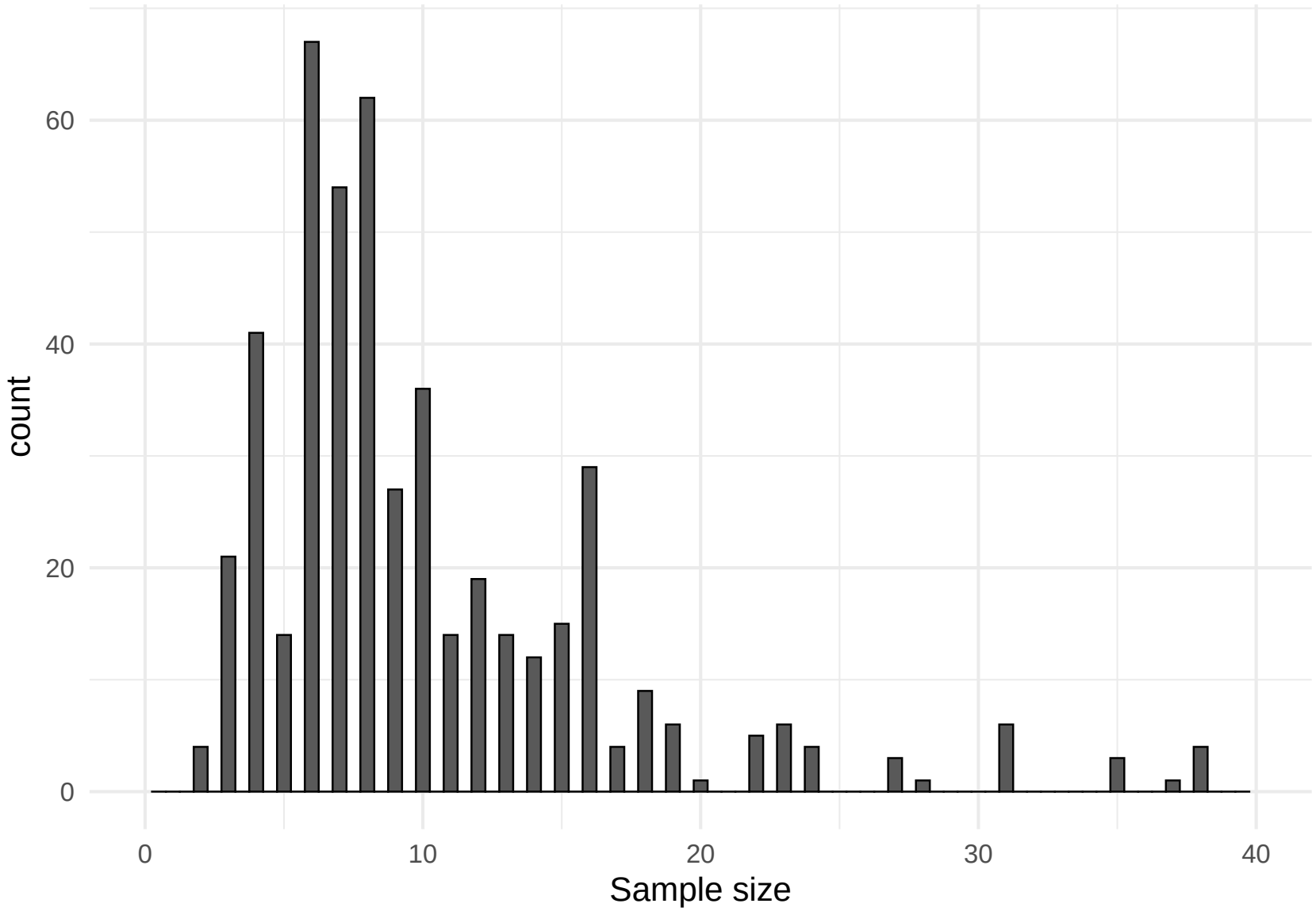
1. True variances are unknown (small samples)
2. Both means and variances may be impacted
3. Ratios of PK parameters vary across studies
4. Want to incorporate prior information

Data: geometric means

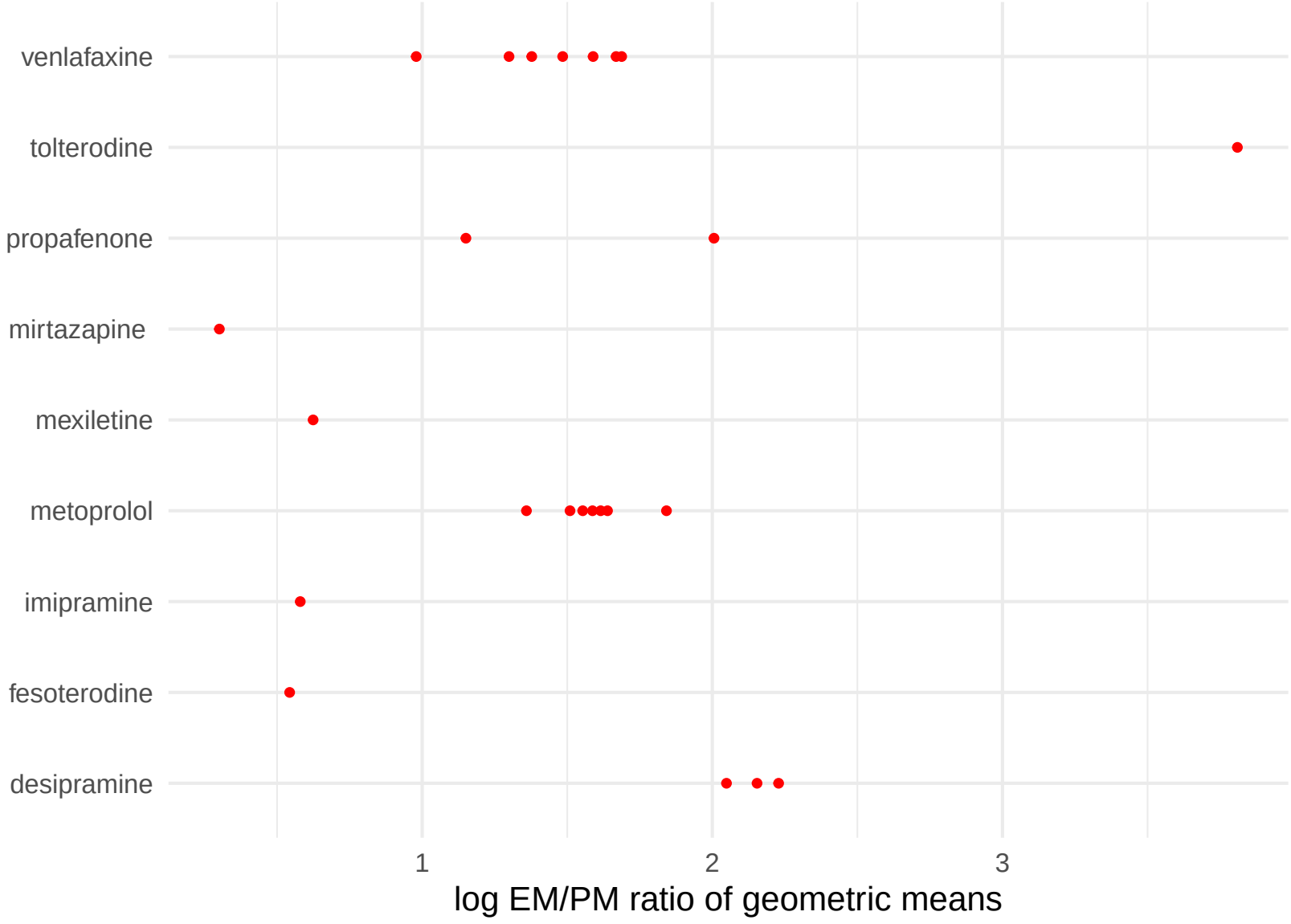
Means (logged) for clearance in a subset containing 81 study arms, 9 drugs metabolised by CYP2D6.



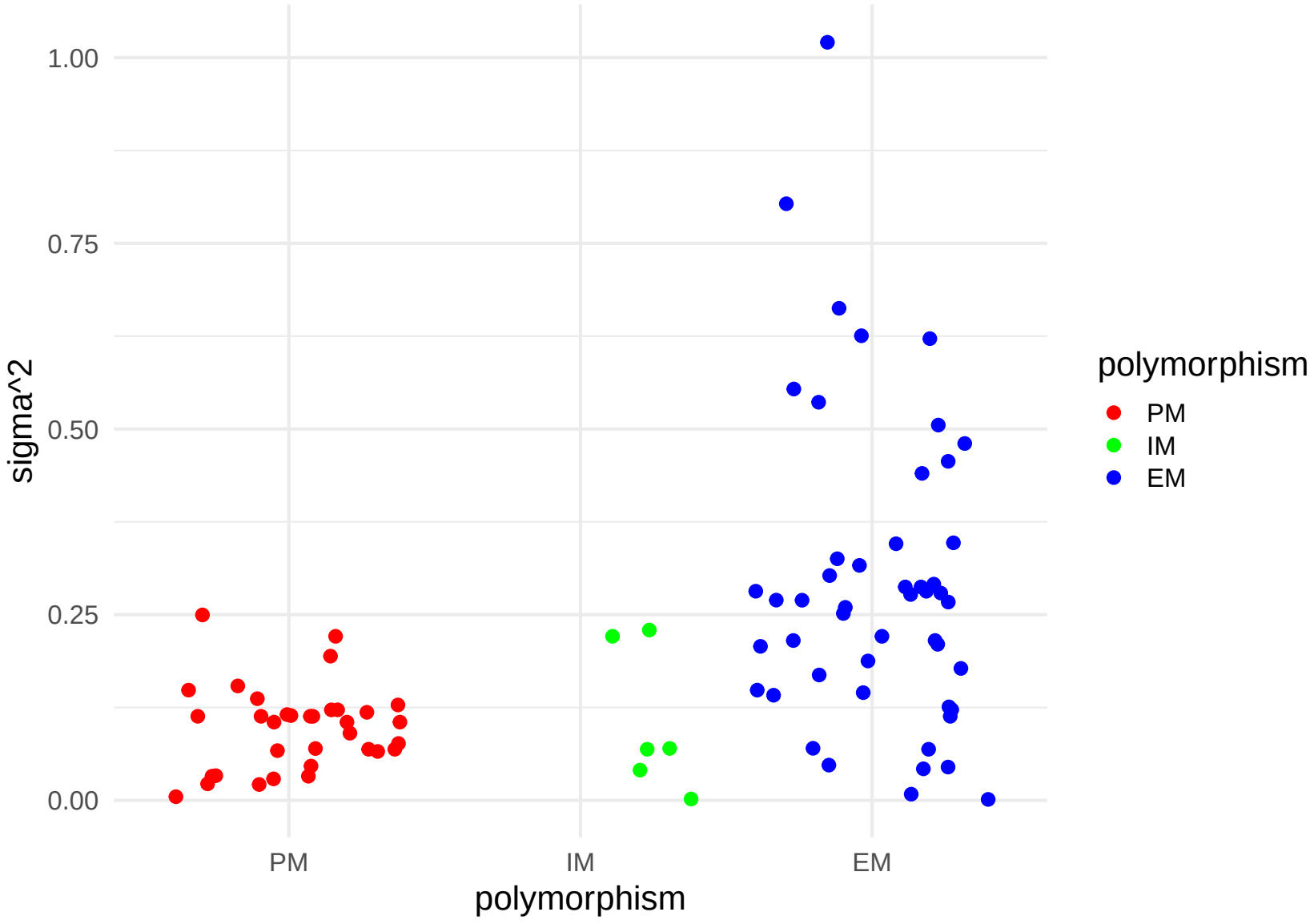
Small sample sizes



Variable (geometric mean) ratios of EM to PM



Variances depend on subgroup



Generic Bayesian model

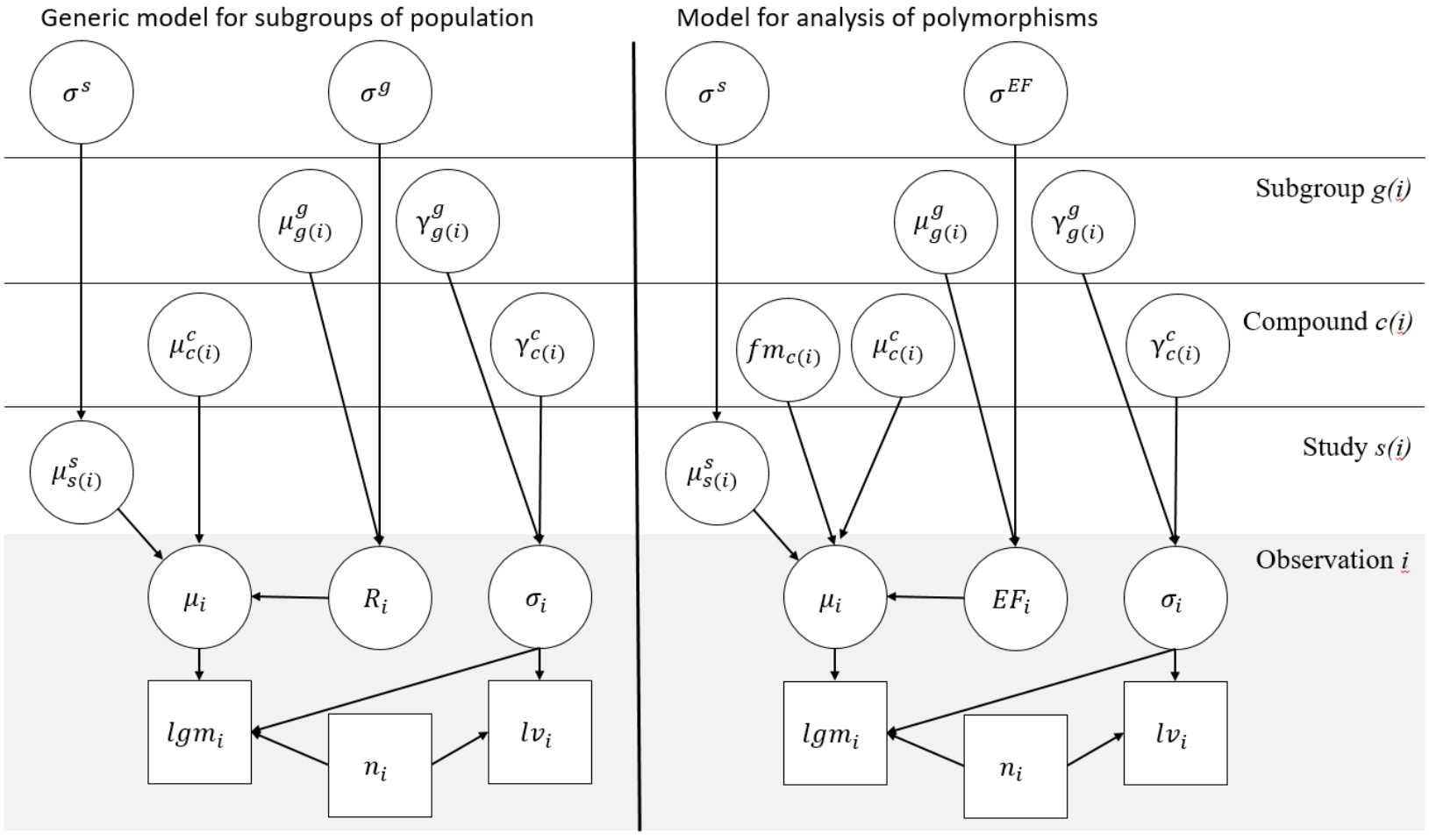
We model both the true means and true SDs: μ_i's and σ_i's.

For observation i with sample mean and variance (on log scale) lgm and lv and sample size n;

$$lgm_i \sim \mathcal{N}(\mu_i, \frac{\sigma_i}{\sqrt{n_i}})$$
$$lv_i \sim \Gamma(\frac{n_i - 1}{2}, \frac{n_i - 1}{2\sigma_i^2})$$

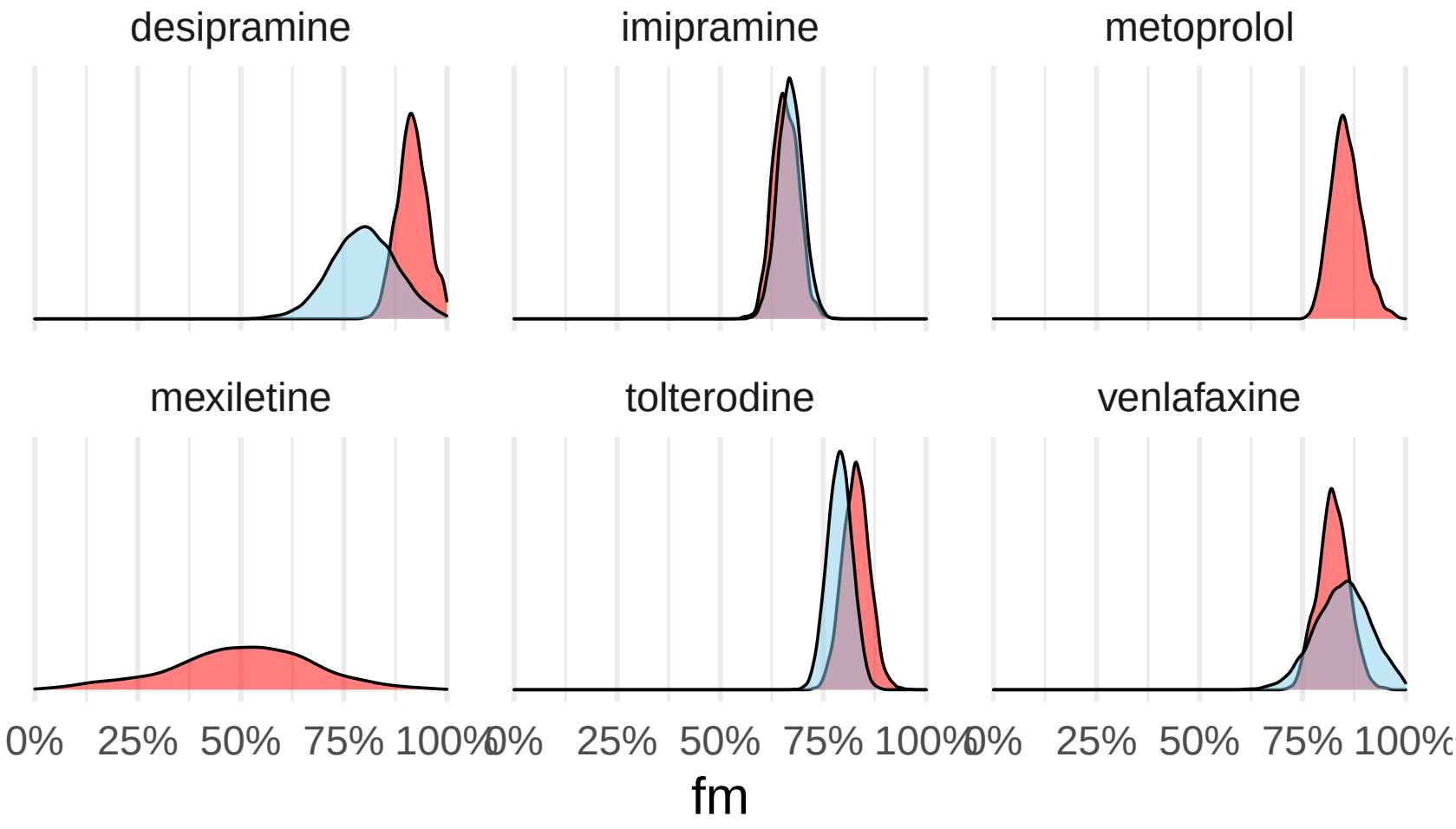
$c(i)$, compound (drug), $s(i)$, study, $g(i)$, group (polymorphism)

$$\mu_i = \mu^c_{c(i)} + \mu^s_{s(i)} + log(R_i),$$
$$log(\sigma_i) = \gamma^c_{c(i)} + \gamma_{g(i)}.$$

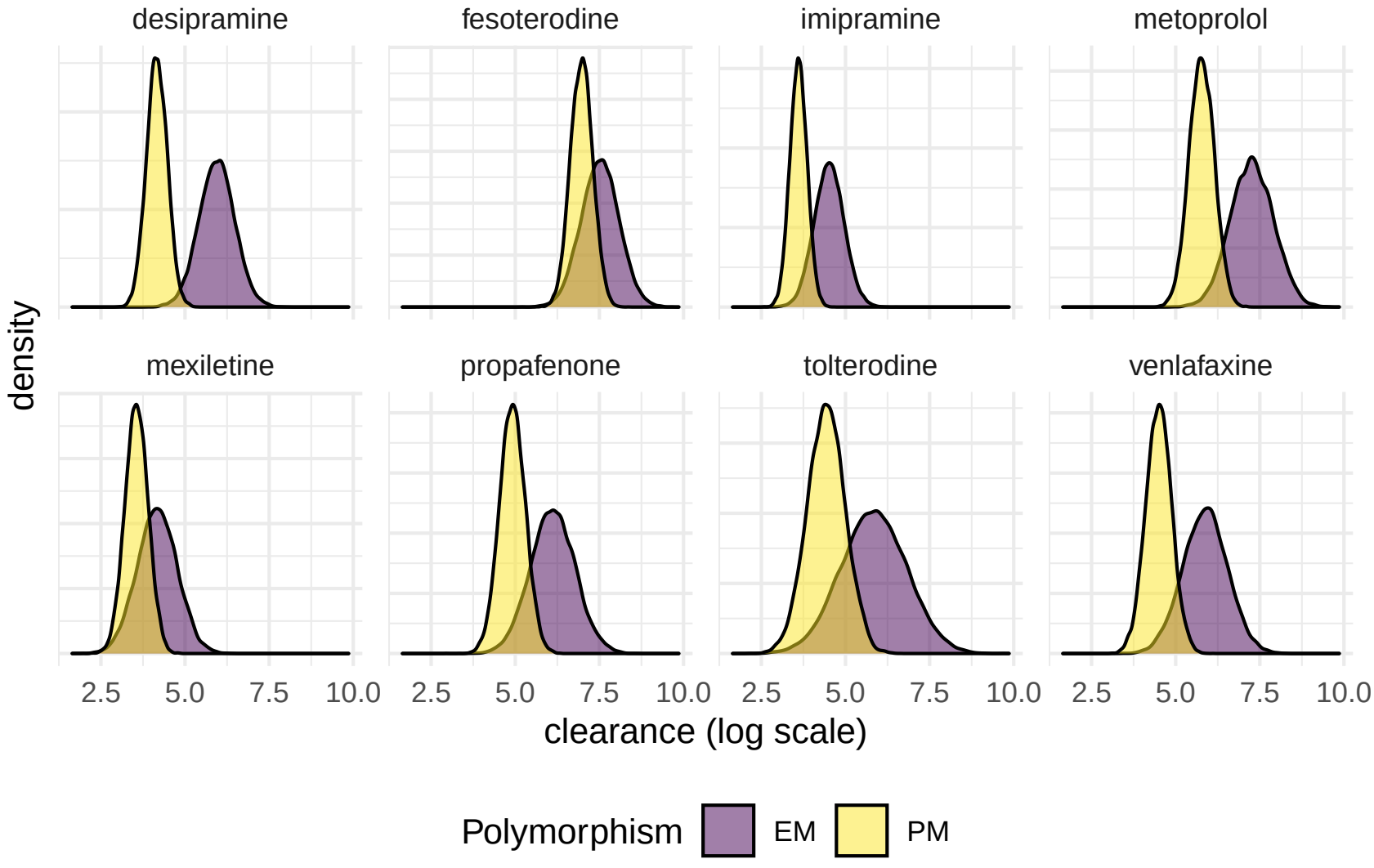


For model of polymorphisms we use $R_i = EF_i \cdot fm_{d(i)} + 1 - fm_{d(i)}$ with informative priors on fraction metabolised fm.

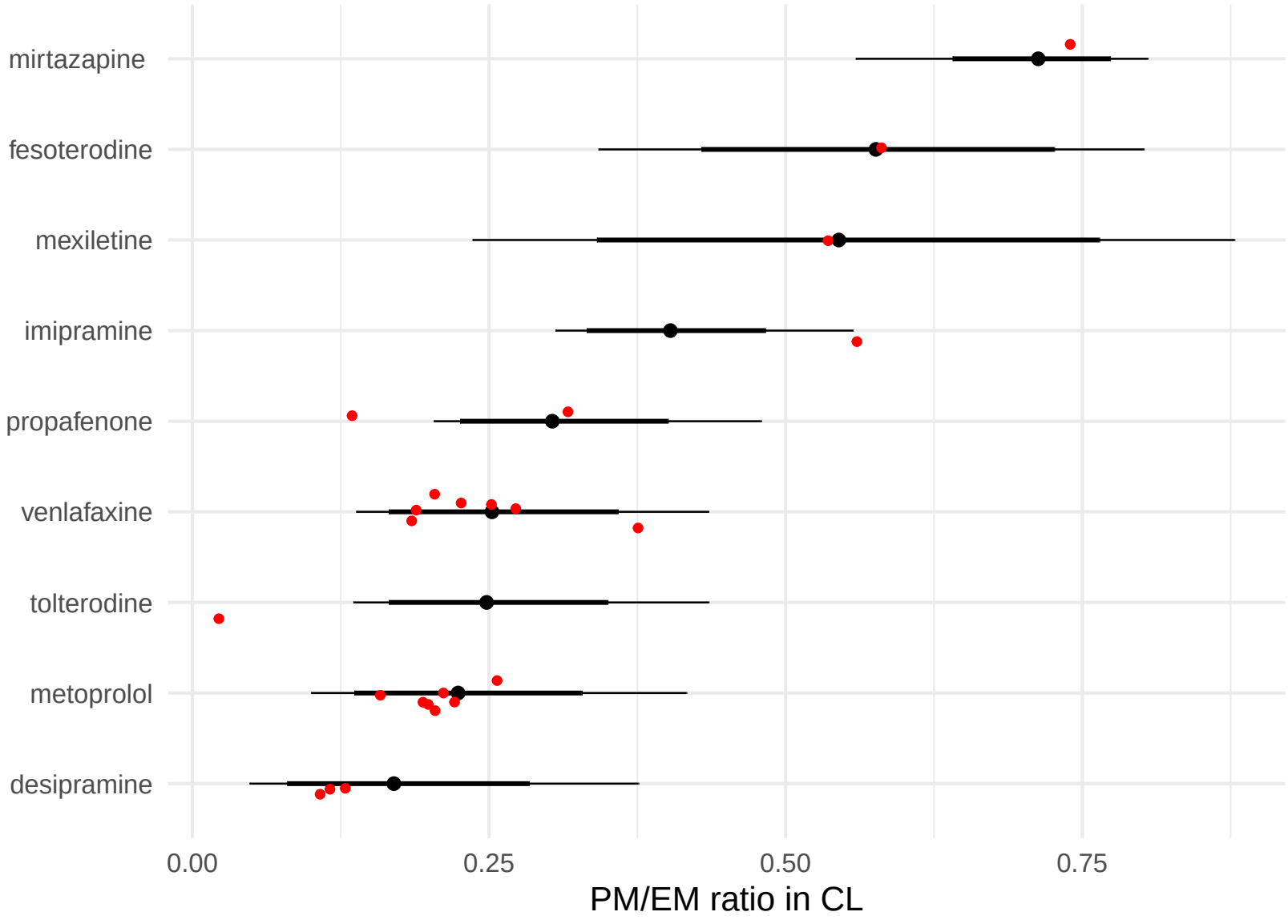
Comparing prior to posterior: fraction metabolised



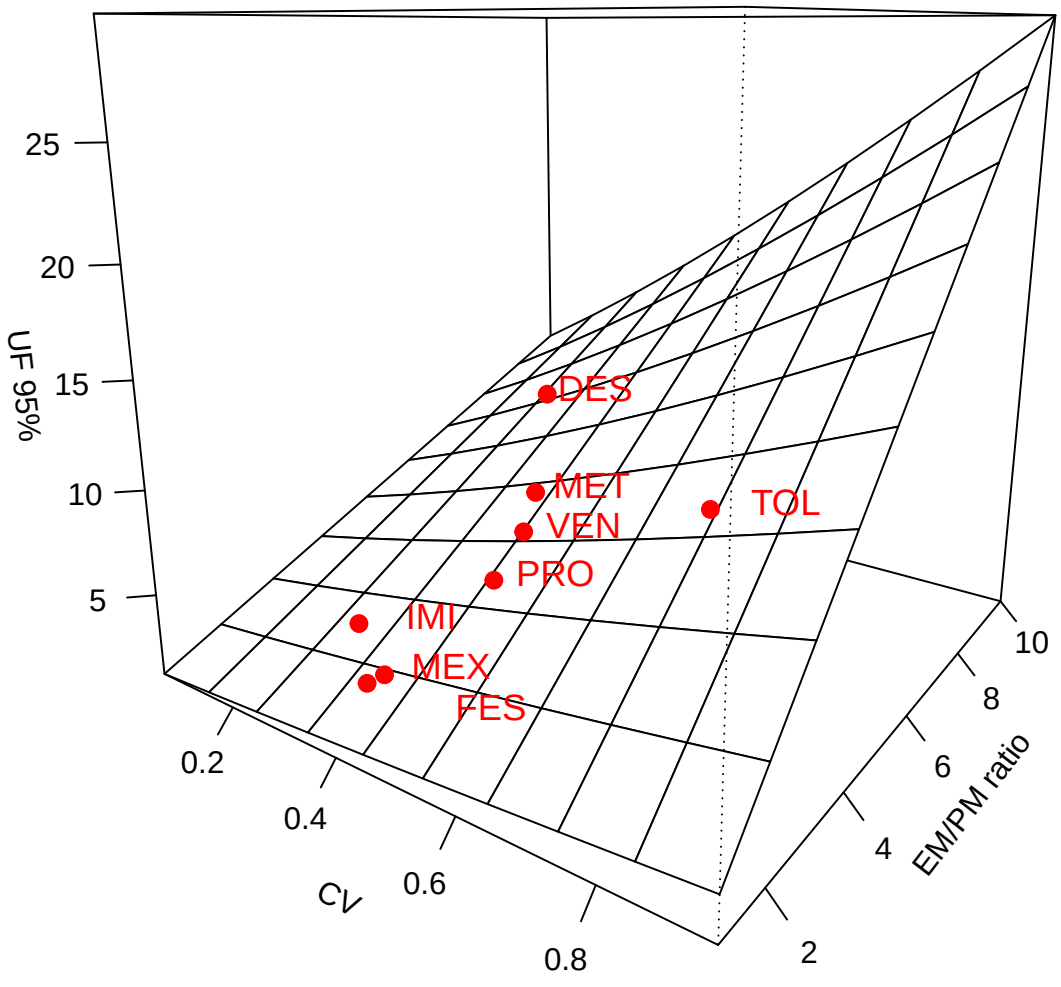
Bayesian posterior: distribution of clearance



Ratios: Bayesian posteriors (black) vs data (red)



Result: UFs depending on both variance and means



Why did we use Bayesian methods?

- Allowed us to use informative priors
  - In our case extra data on fraction metabolised *fm*
- Well-suited to inference on hierarchical models
- We could use it to generalise predictions on different levels
  - e.g. a new population for a known drug, a hypothetical drug
- Easy to implement the model (incl. model for σ) in MCMC

Thank you!

Generic code and more info: `wwiecek.github.io/`, including references to publications

Contact: `witold.wiecek@certara.com`