Bayesian meta-analysis model for chemical risk assessment

Witold Więcek

11 July 2019

This work, funded by a grant from European Food Safety Authority, was done in collaboration with Dr Jean-Lou Dorne (EFSA), Dr Nadia Quignot (Certara) and Dr Billy Amzal (Certara).

This is work in progress – all comments are appreciated!

Uncertainty factors (UFs) in chemical risk assessment

reference value $\times$ uncertainty factor $=$ recommended intake

- reference value $=$ no-observed-adverse-effect, lowest-observed-adverse-effect, benchmark dose
- uncertainty factor $=$ extrapolation between species, across groups (e.g. from general population to neonates, extensive to poor metabolisers)

EFSA guidelines for UFs

- Data should be used to determine chemical-specific UFs.
- When data not available, default values used.
- Default UFs divided into inter-species and between toxicokinetics and toxicodynamics;
  - in humans UF of 3.16 used for TK and another 3.16 for TD ($3.16 = \sqrt{10}$)
  - inter-species UF is 10 ($2.5 \cdot 4$)

Default values can help when either no data is available or there is no time to conduct analysis.

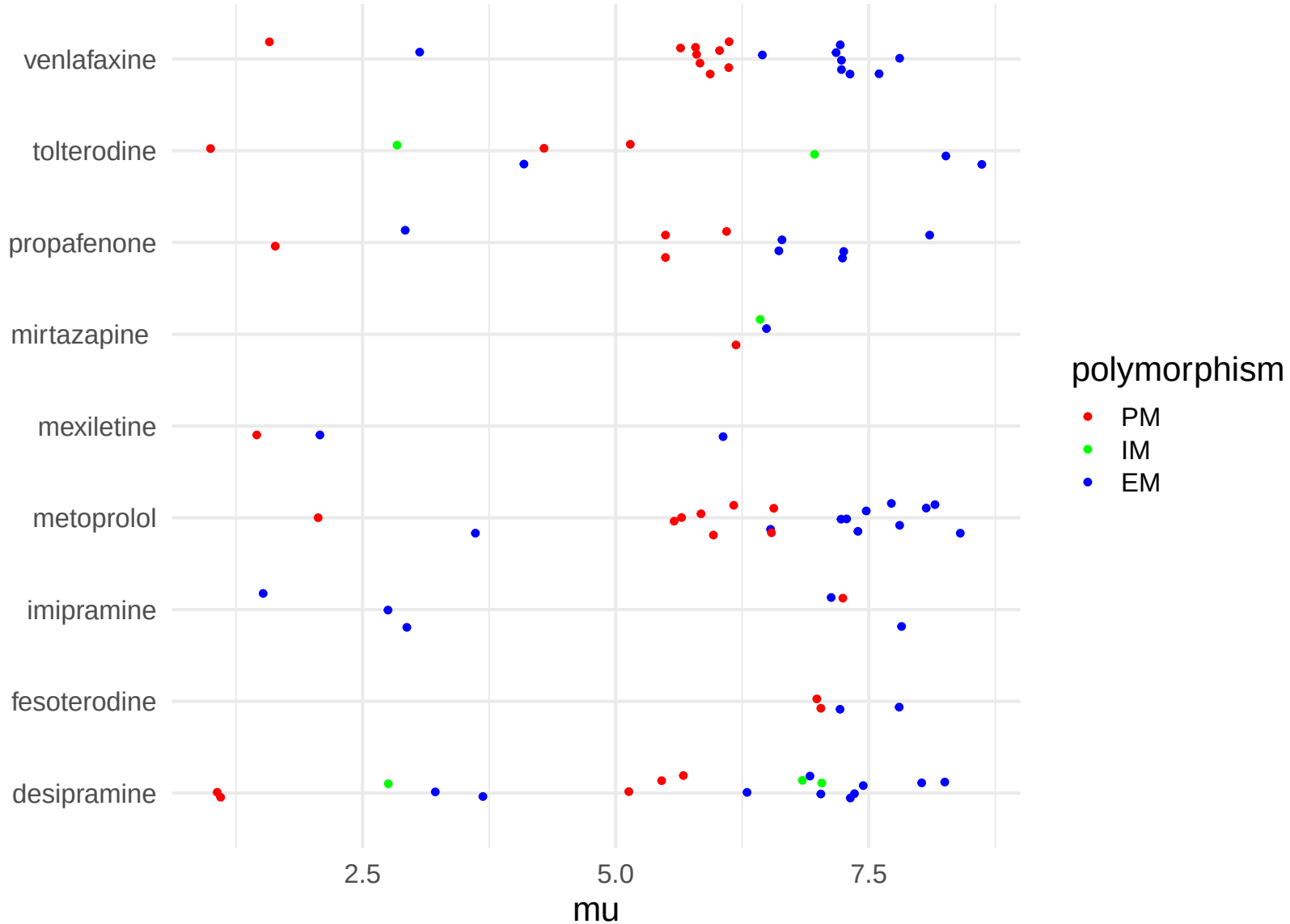
Informing the TK UFs with data

Objective: determine UFs for toxicokinetics using only summary-level data on TK parameters (AUC, clearance)

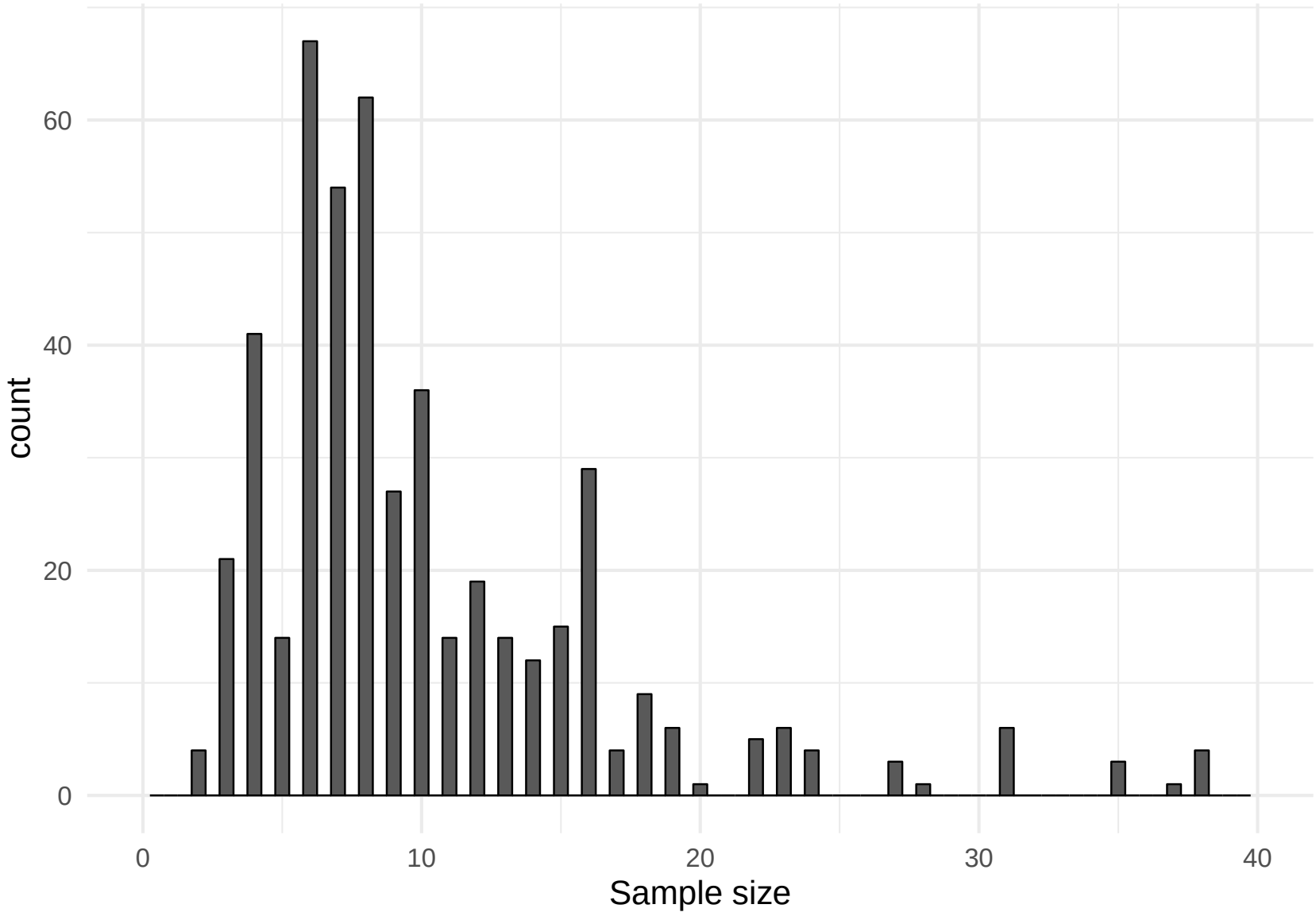
- We focus on differences due to polymorphic metabolism
- This model used in CYP2D6, CYP3A4 (incl. mixtures), CYP 2C9, 2C19, renal clearance
  - Datasets are typically a few hundred study arms
  - Large databases available, e.g. from previous literature reviews
- Here I present smaller exmaple for clearance in CYP2D6 enzyme
  - CYP2D6 has 3 phenotypes: PM, IM, EM.
  - The ratios of PM and EM are the most important.

Data: means

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

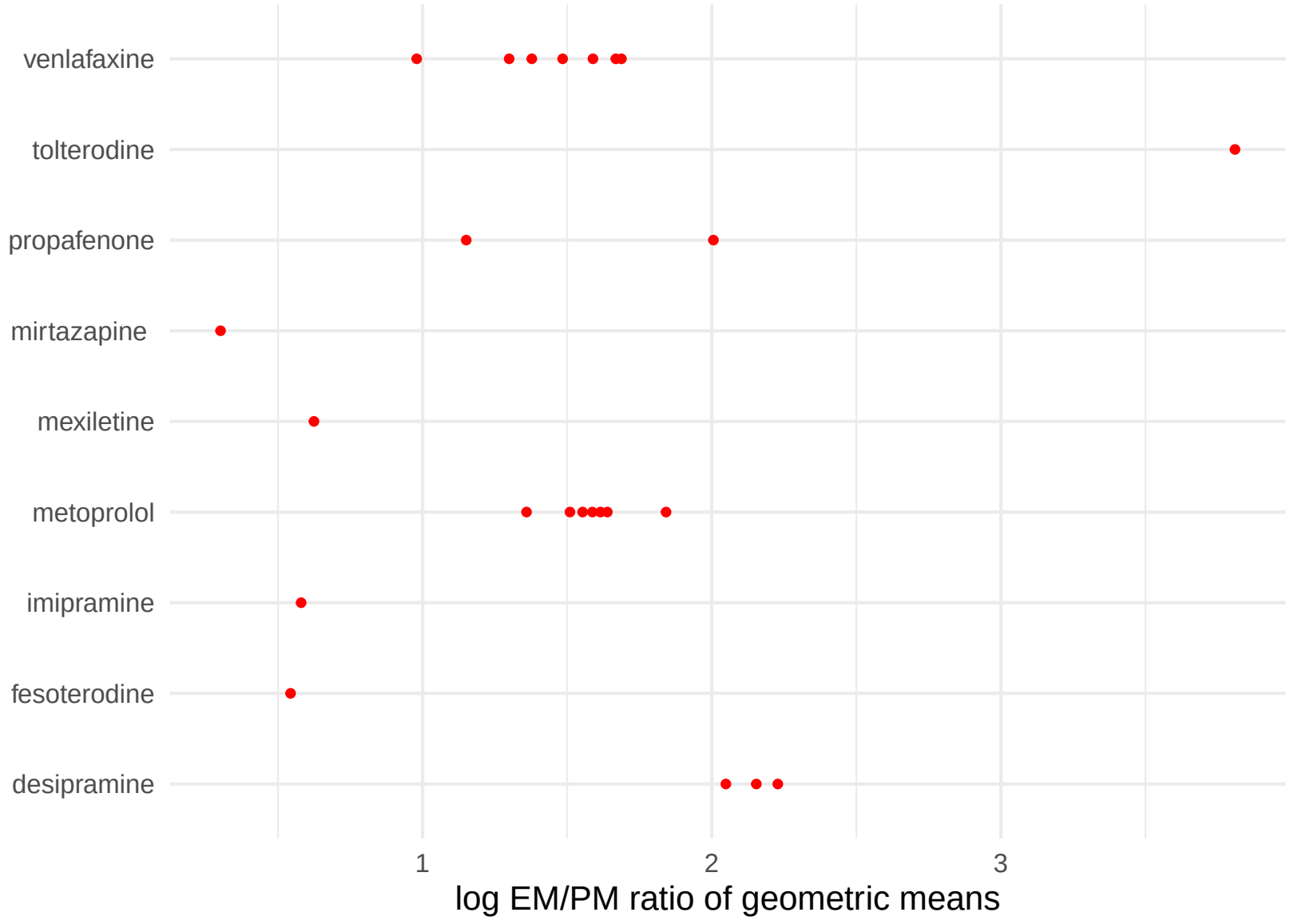


Data: sample sizes

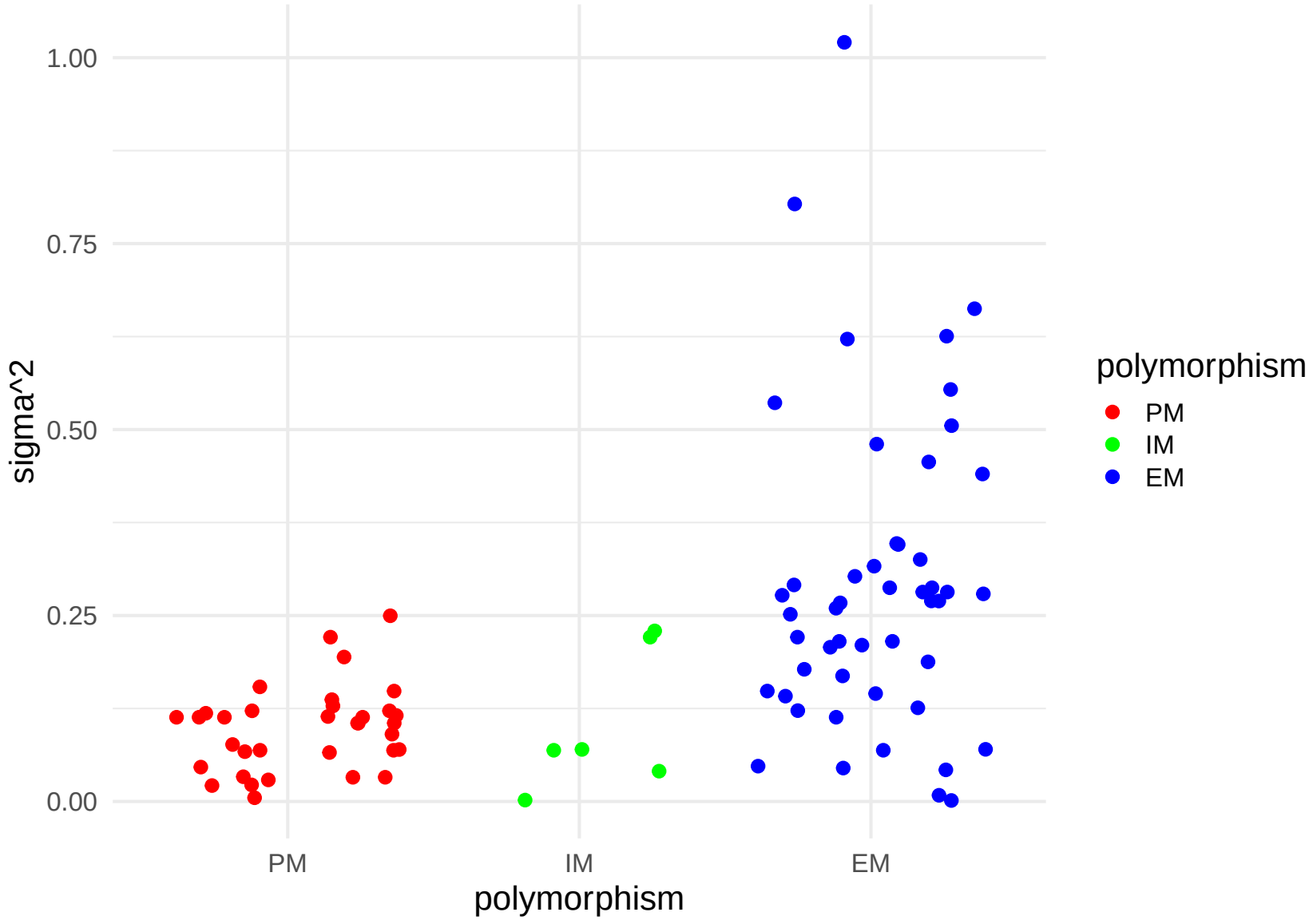


Based on a larger CYP2D6 lit review (more than 81 rows).

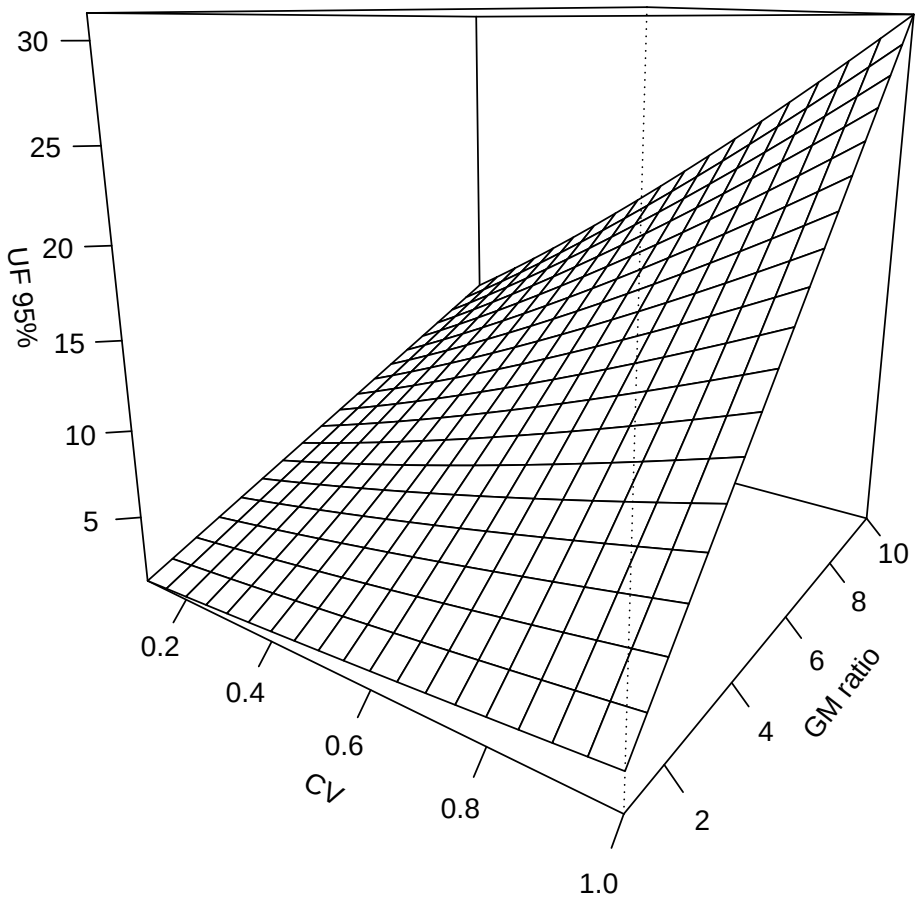
Data: ratios


venlafaxine
tolterodine
propafenone
mirtazapine
mexiletine
metoprolol
imipramine
fesoterodine
desipramine
1
2
3
log EM/PM ratio of geometric means

Data: variances



Both ratios of means and variance determine UFs



CV = coefficient of variation

Data:

- small samples
- polymorphism impacts both means and variances
- ratios of means are variable
- a few more problems that we will mention at the end

Advantage of using Bayesian models

- Can use informative priors
- Well-suited to inference on hierarchical models
- Allows us 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; we used Stan
  - Code in the links at the end
  - Can directly calculate UF using `generated quantities`

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;

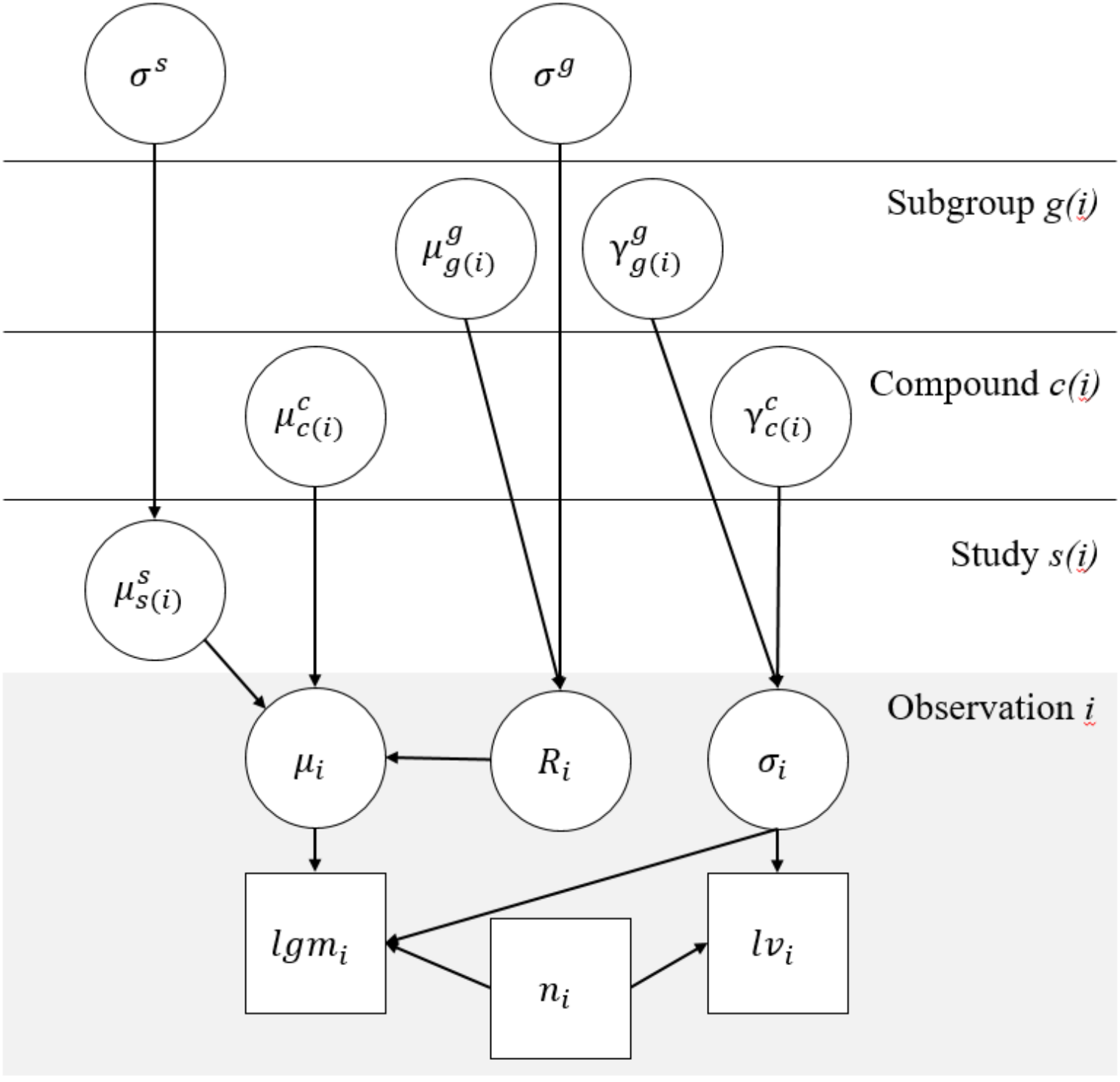
$$lgm_i \sim \mathcal{N}(\mu_i, \frac{\sigma_i}{\sqrt{n_i}})$$

$$lv_i \sim \Gamma(\frac{n_i - 1}{2}, \frac{n_i - 1}{2\sigma_i^2})$$

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

$$\mu_i = \mu^c_{c(i)} + \mu^s_{s(i)} + log(R_i),$$

$$log(\sigma_i) = \gamma^c_{c(i)} + \gamma_{g(i)}.$$


σ^s
σ^g
Subgroup *g(i)*
$\mu^g_{g(i)}$
$\gamma^g_{g(i)}$
Compound *c(i)*
$\mu^c_{c(i)}$
$\gamma^c_{c(i)}$
Study *s(i)*
$\mu^s_{s(i)}$
Observation *i*
μ_i
R_i
σ_i
lgm_i
n_i
lv_i

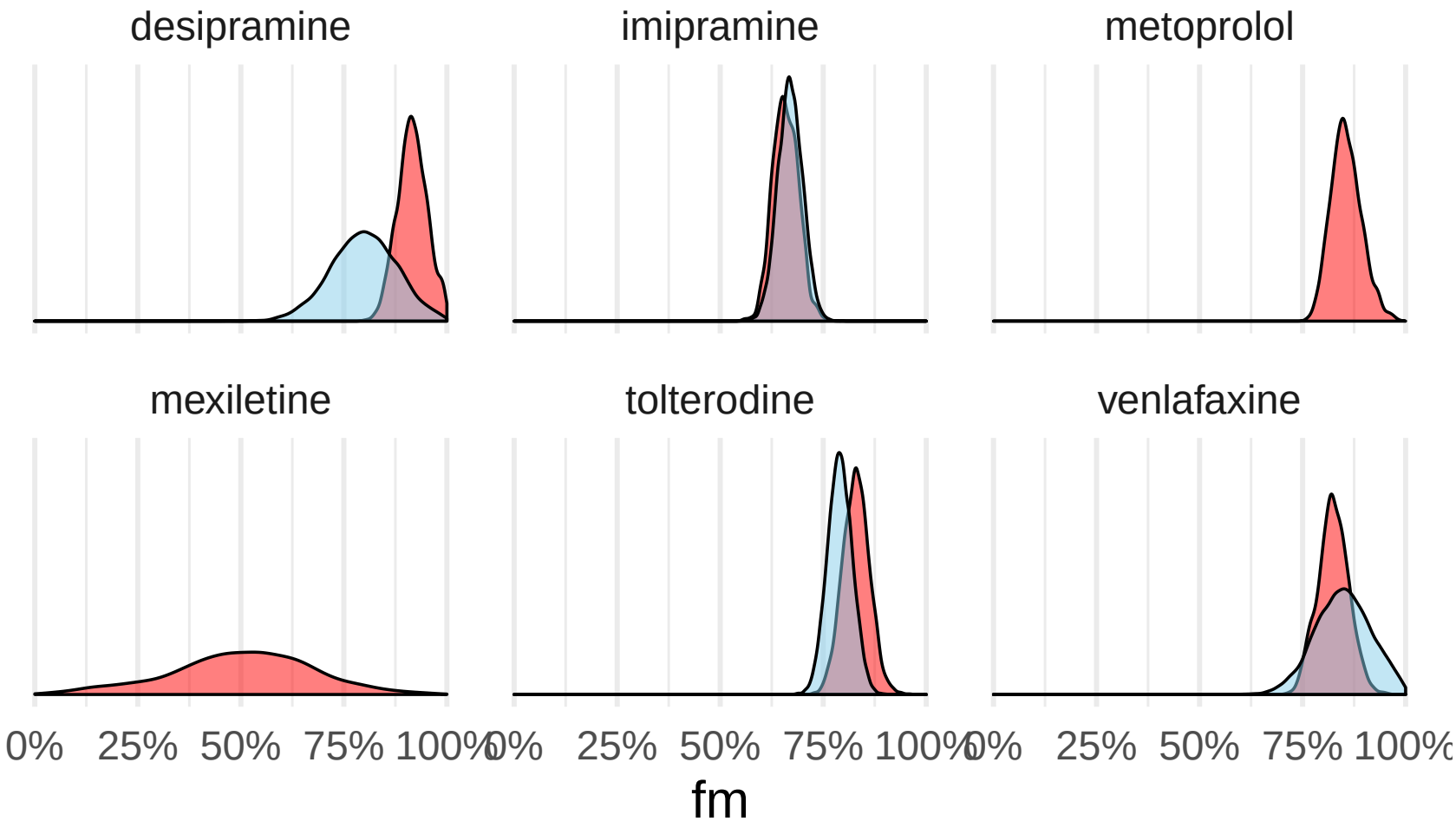
Variability in ratios and informative priors

Biologically plausible formula for ratios (PM to EM in clearance):

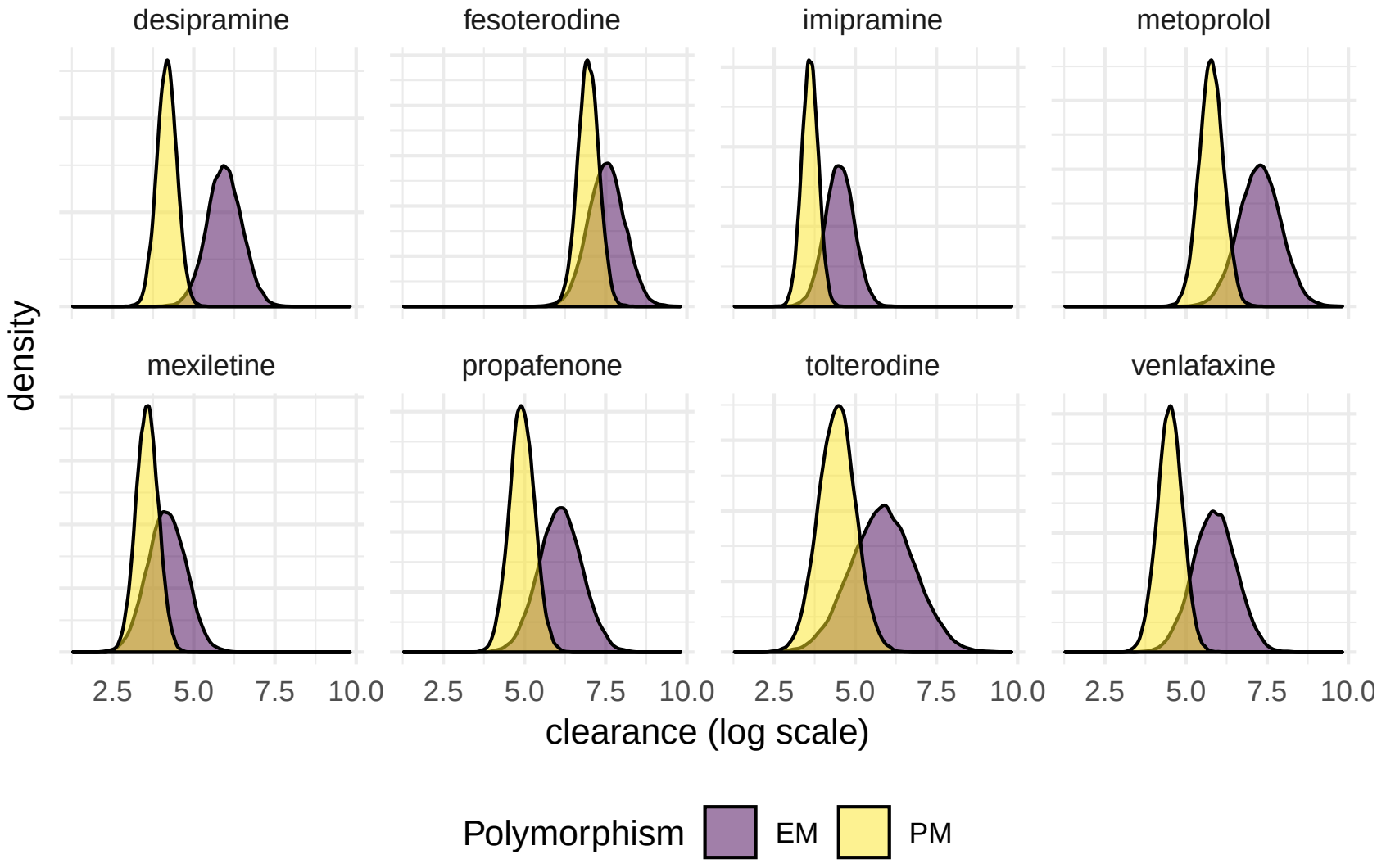
$$R_i = EF_i \cdot fm_{d(i)} + 1 - fm_{d(i)}$$

- fm = fraction metabolised, compound-specific
- EF = enzyme functioning, population-specific
  - There is a large variation in genotypes within the phenotype
- Data for TK are based on *in vivo* studies while for fm, we can define priors based on *in vitro* data

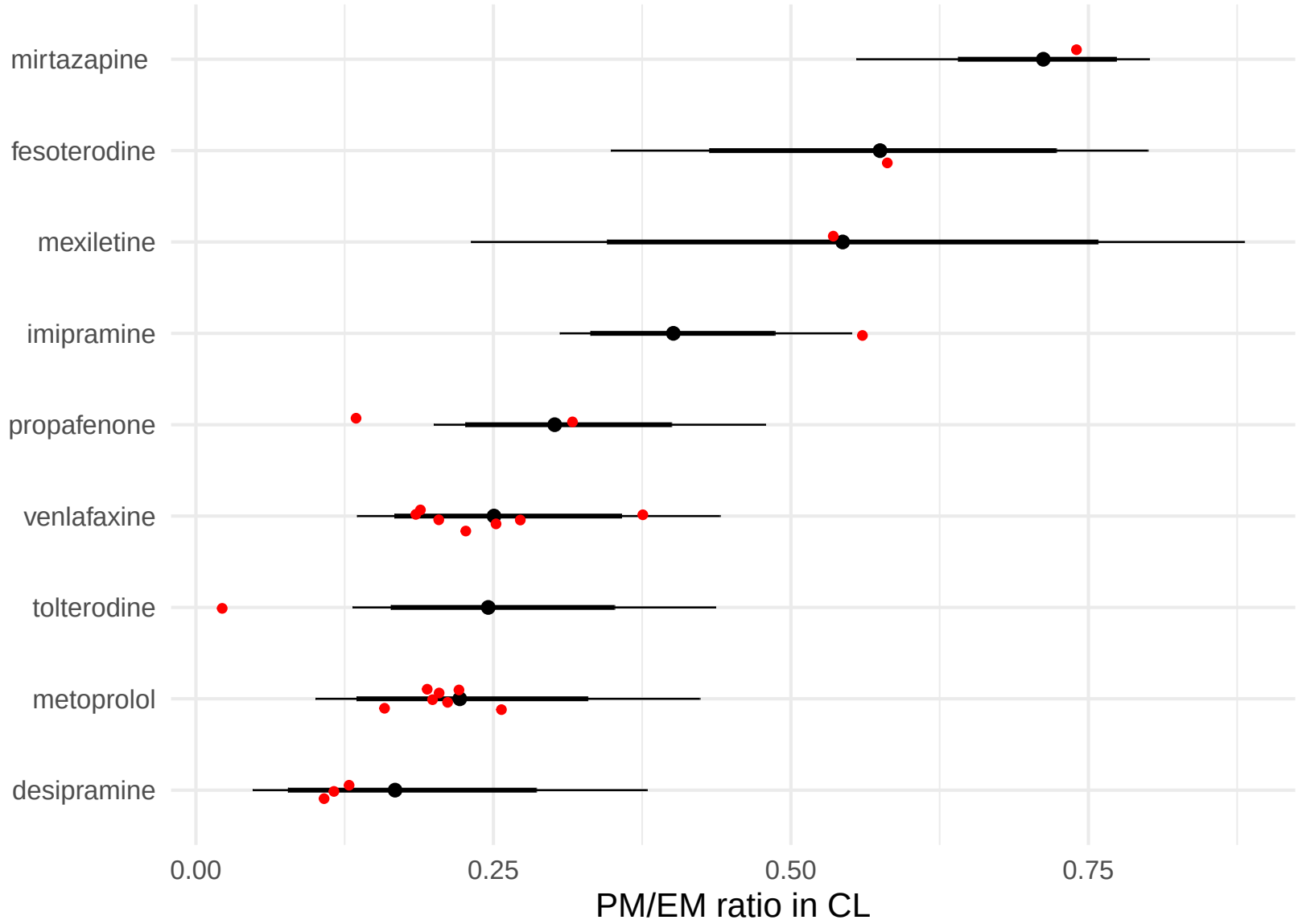
Result: fraction metabolised



Result: distribution of clearance



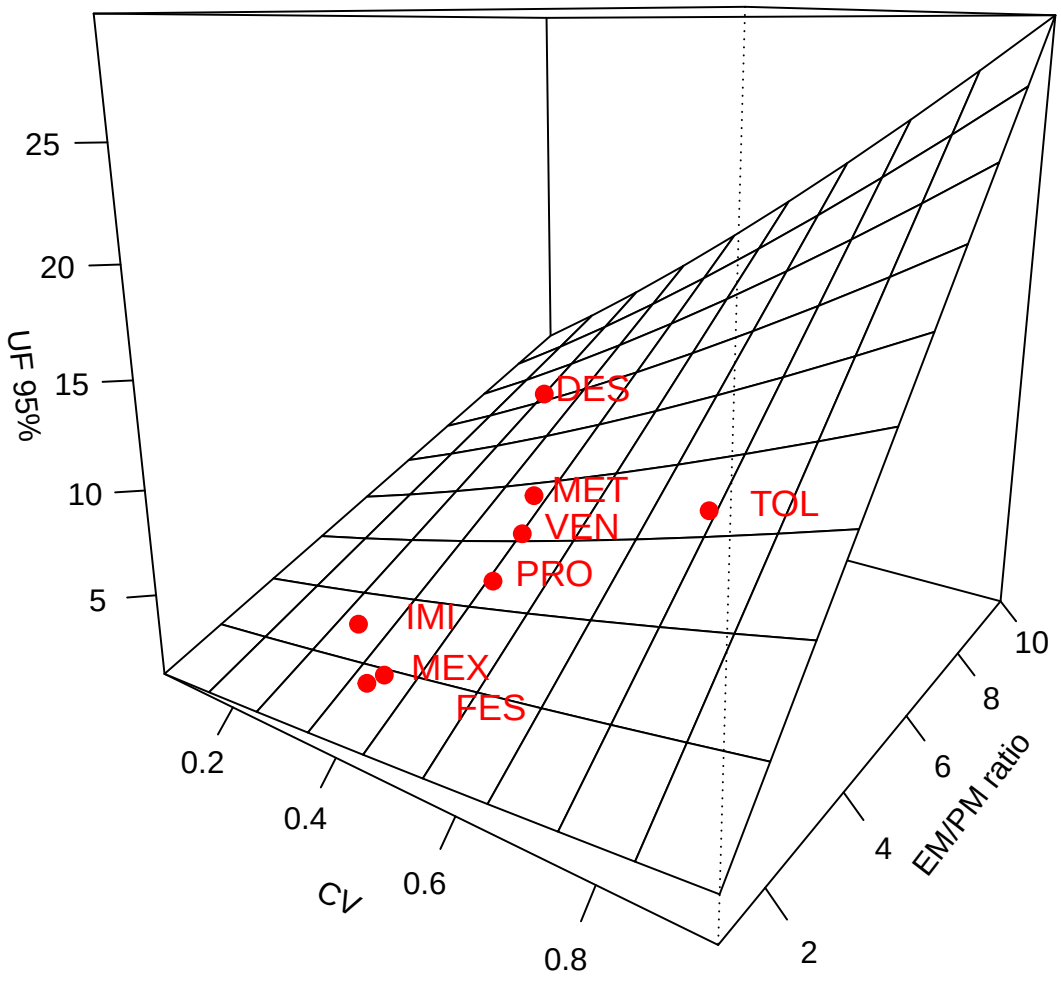
Result: ratios



Results of the CYP2D6 case study

Compound	mu_EM	mu_PM	PM/EM	sig_EM	sig_PM	UF 95
desipramine	5.9	4.2	0.17	0.53	0.31	12.2 (6, 18.8)
fesoterodine	7.5	7.0	0.58	0.56	0.32	3.1 (2.3, 4)
imipramine	4.5	3.6	0.40	0.44	0.26	3.9 (3.1, 4.6)
metoprolol	7.3	5.8	0.22	0.64	0.37	9.1 (5.8, 12.5)
mexiletine	4.2	3.6	0.55	0.59	0.34	3.6 (2.3, 5.1)
propafenone	6.1	4.9	0.30	0.66	0.38	6.5 (4.7, 8.3)
tolterodine	5.8	4.4	0.25	0.97	0.56	11.2 (7, 15.3)
venlafaxine	5.9	4.5	0.25	0.66	0.38	7.9 (5.4, 10.6)

Result: UFs


UF 95%
25
20
15
10
5
DES
MET
VEN
PRO
IMI
MEX
FES
TOL
0.2
0.4
0.6
0.8
c_V
2
4
6
8
10
EM/PM ratio

Odds & ends

- Individual-level data can be used directly in the model
- We prepared a generic Stan implementation (links at the end)
- Published literature use many different measures of dispersion
  - SE and SD often confused for each other
- Cross-validation is difficult
- Same meta-analysis problems pop-up in economic data (log-normal distributions)

Thanks!

witold.wiecek@certara.com

Slides available at `wwiecek.github.io/`