Using meta-analyses to guide statistical methodology for clinical dose response studies

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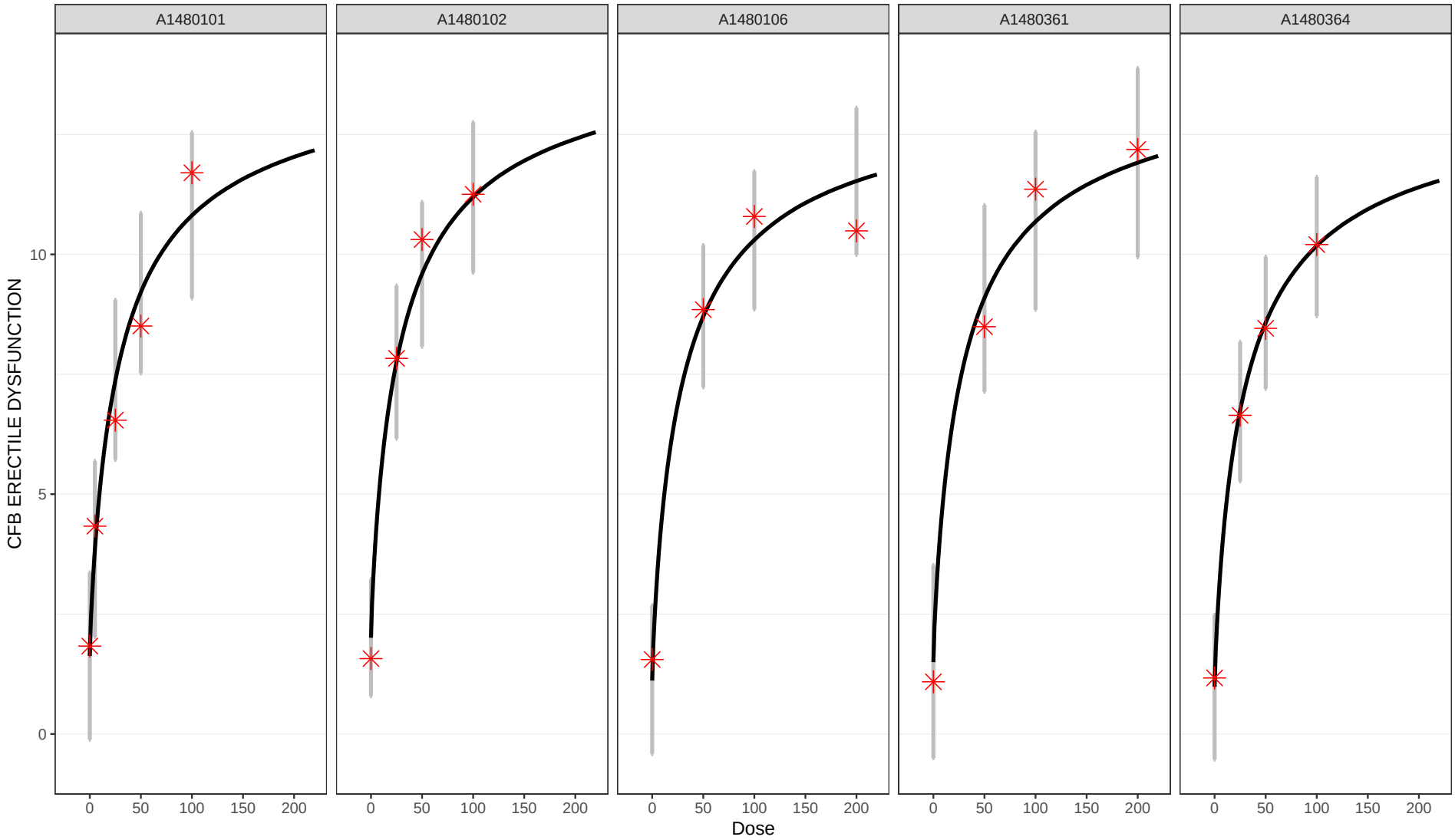
Empirical basis for dose response modeling

- Many methods have been proposed for dose response analysis
  - Most are optimal for some metric and set of conditions
  - What are the relevant conditions?
- Data extracted from dose response studies for approximately 200 compounds (400 studies, Pfizer and other sponsors)
  - Many therapeutic areas. Main exclusions: oncology and vaccines
  - Small molecules and biologics
  - Total daily(small molecules) and total weekly (biologics) dosing used to measure dose. Very few adjustments for different regimens within drug were required
  - Continuous and binary endpoints
  - Focus here is on efficacy at the sponsor-specified landmark time point
- All data and software for the examples are available in R package *clinDR* on CRAN

PDE5 inhibitor for erectile dysfunction



Study designs

Dosing designs

Number of drugs	Number of Doses
39	3
82	4
44	5
37	6
14	7
6	8
8	>8

Table: Number of doses (including placebo) per drug.

144 compounds with one study, 54 with 2 studies, 14 with 3 studies, and 18 with >3 studies

Dosing designs(cont)

- The 25^{th}, 50^{th} and 75^{th} percentiles of the ratio of the highest dose to the lowest (non-placebo) dose is 3, 6, and 15
- Most dosing spacing ratios were approximately 2 or 3 fold: 16% of spacing ratios were < 1.5, 77% were in $(1.5, 3.5)$, 7% were > 3.5
- Most compounds evaluated with a single regimen (168 with 1 regimen, 54 with 2 regimens, 8 with > 2 regimens)
- Most studies use equal sample size allocation across dose groups. More common to reduce size of the placebo group rather than increase it

Model for dose response curves

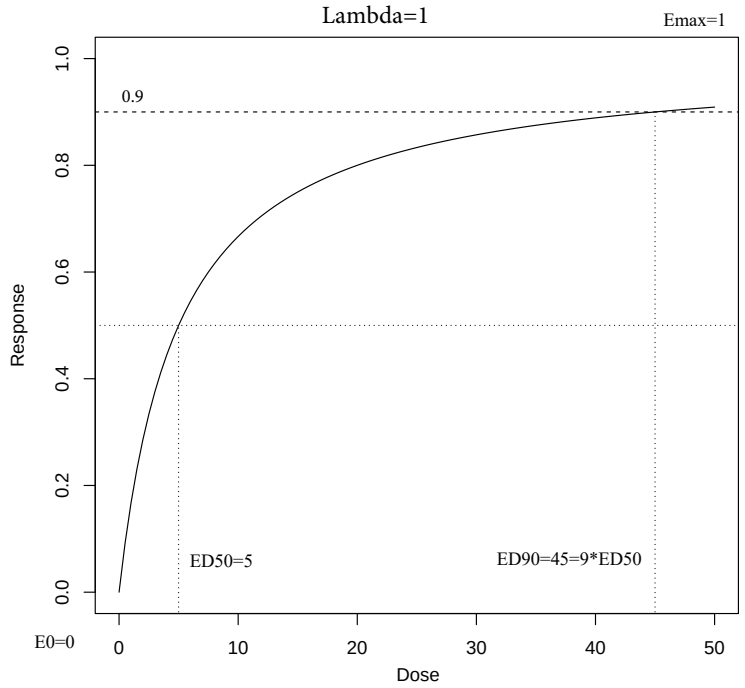
Emax Models

$$\mathrm{E}(Y \mid d) = \mathrm{E}_0 + \frac{\mathrm{E}_{\max} d^{\lambda}}{d^{\lambda} + \mathrm{ED}_{50}^{\lambda}}$$

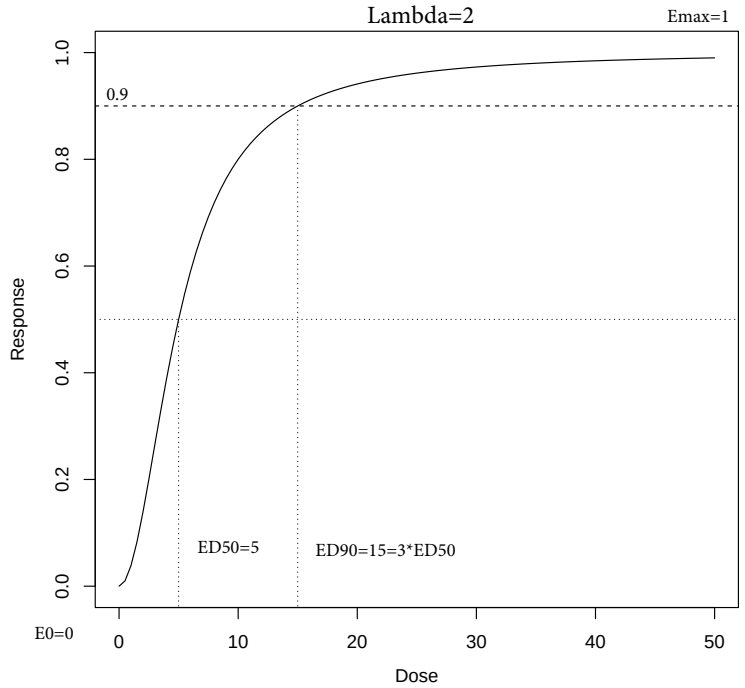
- Ubiquitous in pharmacology
- Not unique given limitations of clinical dose response data
- The Emax model is typically applied to binary data on the logit scale:

$$\mathrm{logit}\left(P(Y \mid d)\right) = \mathrm{E}_0 + \frac{\mathrm{E}_{\max} d^{\lambda}}{d^{\lambda} + \mathrm{ED}_{50}^{\lambda}}$$

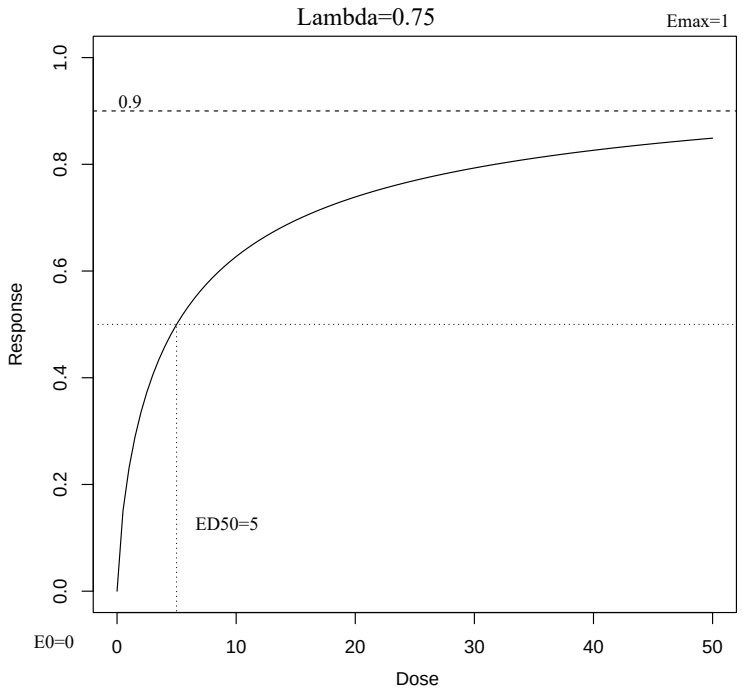
Hyperbolic Emax Model



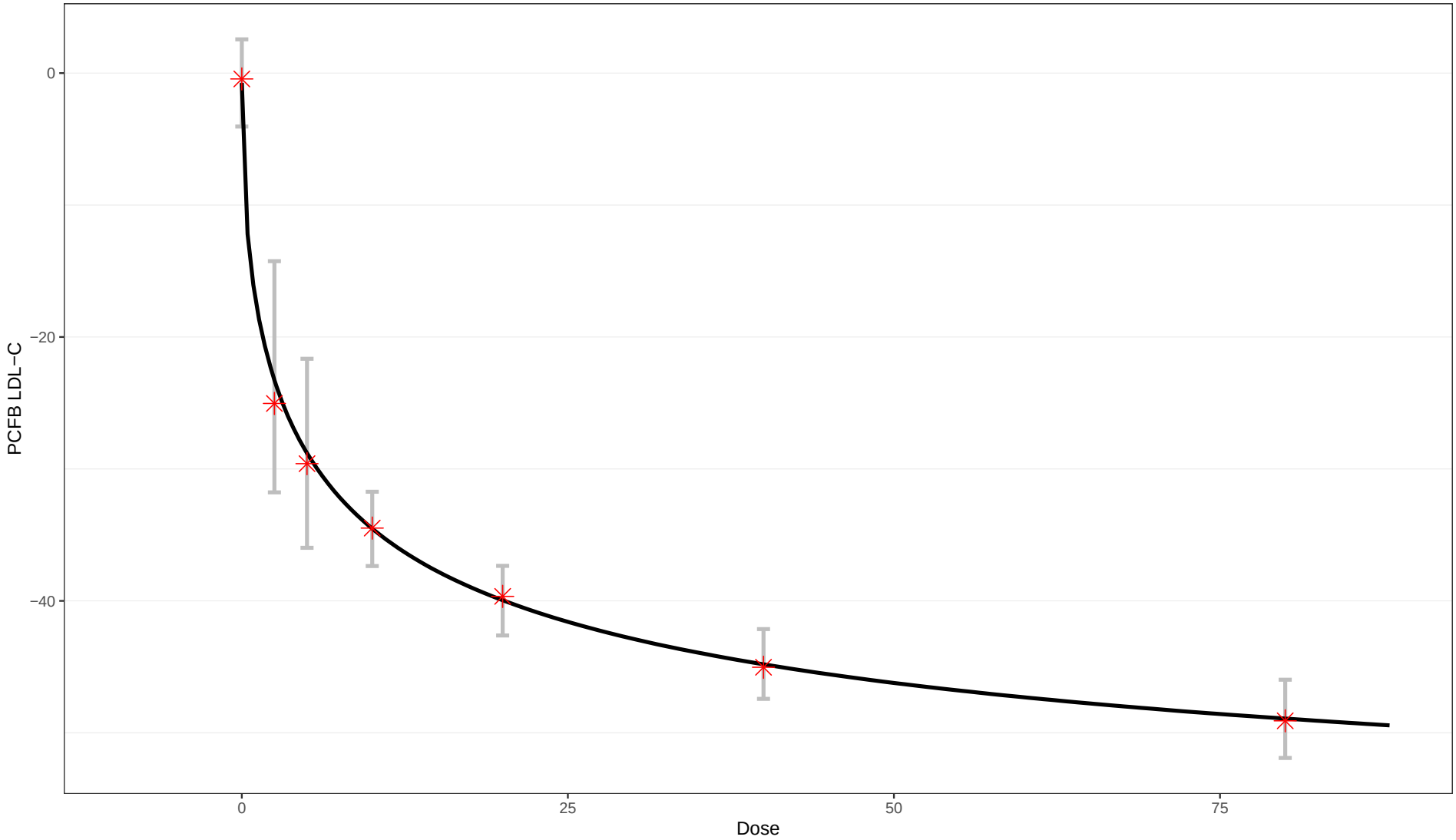
Sigmoid Emax Model



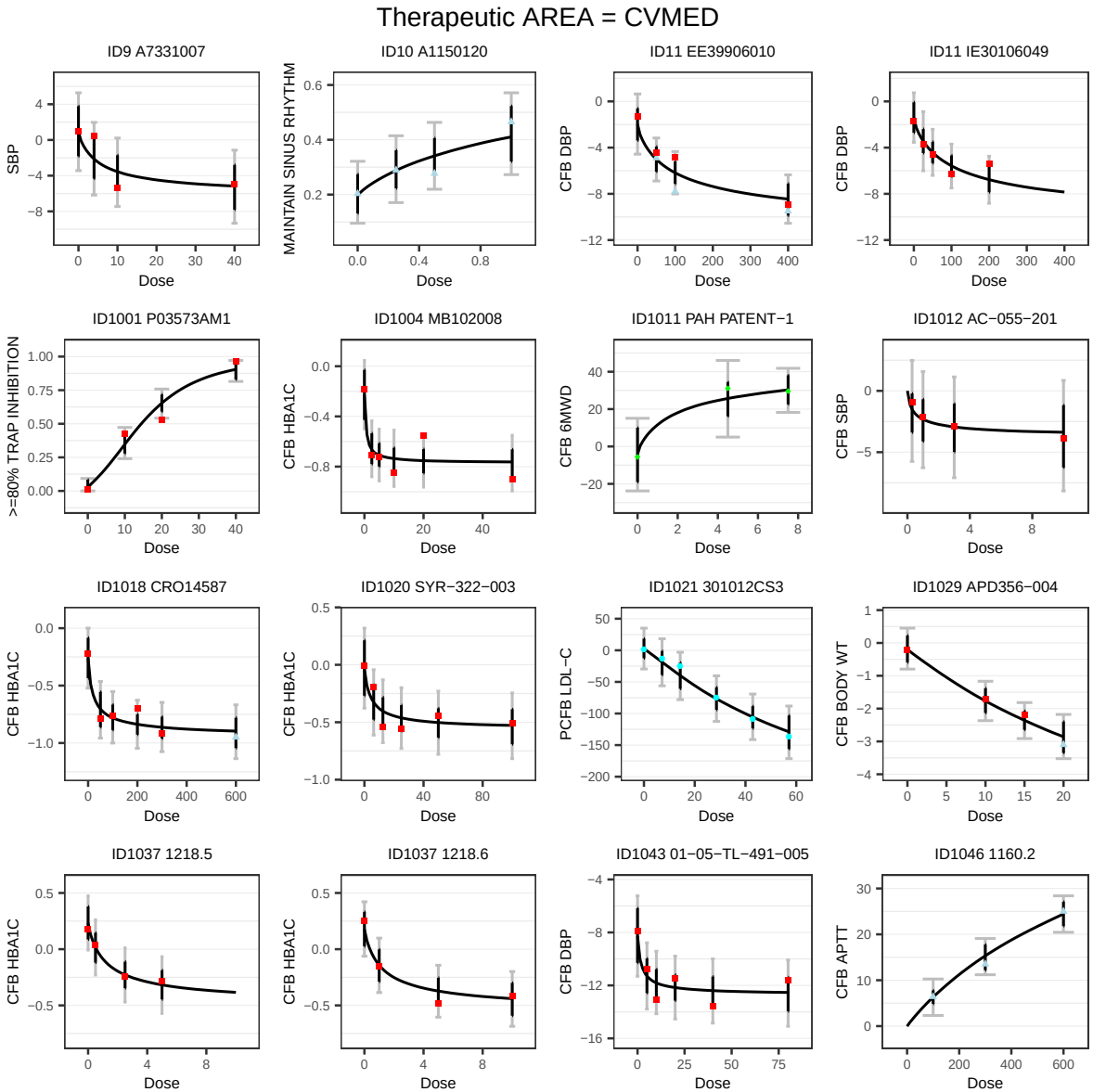
Emax Model with lower λ value



Statin to reduce low density cholesterol (Mandema, 2005)



Meta-data examples, 24 pages (FDA submission), data in *clinDR*



Modeling meta-data to create a prior distribution for future compounds

Improving model estimation: prior distribution for the model parameters

- Goal is to form empirically-based prior distribution using routinely available information
- Prior distributions based on meta-data
  - Prior distributions for the ED_{50} and λ are derived from a hierarchical model fit to the meta-data. The prior for the ED_{50} also includes compound-specific information
- Prior distributions based on compound-specific information
  - The prior distribution for the placebo-response is study-specific. It may be diffuse or based on compound-specific historical data, which have well-researched issues
  - (Maximal) Drug effect is compound specific. The most common approach is to use a diffuse prior only imposing biological plausibility, with prior studies included through the likelihood rather than the prior distribution

Hierarchical model for meta-data

$$\mathrm{E}\left(Y_{ijk} \mid d_{ijk}\right) = \mathrm{E}_{0jk} + \frac{\mathrm{E}_{\mathrm{max}_j} d_{ijk}^{\lambda_j}}{\mathrm{ED}_{50j}^{\lambda_j} + d_{ijk}^{\lambda_j}}$$

- The i, j, k index patient, drug, and study. For continuous endpoints, there is also a residual standard deviation, σ_j.
- The distribution of $(\mathrm{ED}_{50j}, \lambda_j)$ across compounds is modeled (hierarchical)
- The distributions of each E_{0jk} and $\mathrm{E}_{\mathrm{max}_j}$ across compounds are not modeled. They are assigned independent (somewhat diffuse) distributions.

Hierarchical distribution for the λ

$$\log(\lambda_j) \sim t_5(\mu_\lambda, \sigma_\lambda)$$

- The prior distribution for μ_λ is normal centered at 0 with low probability for $\mu_\lambda > \log(4.0)$
- The prior distribution for σ_λ is a folded Cauchy or uniform based on recommendations from literature
- Several different priors were evaluated. There was some sensitivity, but it is not pronounced

Hierarchical distribution for the ED_{50}

- The ED_{50} vary between nano-grams and deci-grams
- An initial prediction (explicit or implicit) of the ED_{50} is required to design the first dosing study. Denote it by P_{50}
  - There are many data sources for the prediction: pre-clinical data, PK data, mechanistic biomarkers from Phase 1b, etc
  - The P_{50} explain much of the variation in the ED_{50} across compounds. The P_{50} were approximately calibrated in the meta-data
  - A P_{50} is routinely computed by clinical pharmacologists (Pfizer). Empirical observation shows it is reliably approximated by the mid-point between the two lowest (non-placebo doses) in the first dose response study. We use this approximation when a formal estimate is not supplied. The approximation does not need to be precise

Hierarchical distribution for the ED_{50} (cont)

$$\log(\mathrm{ED}_{50j}/\mathrm{P}_{50j}) \sim t_5\left(\mu_{\mathrm{ED}_{50}}, \sigma_{\mathrm{ED}_{50}}\right)$$

equivalently

$$\log(\mathrm{ED}_{50j}) \sim t_5\left(\mu_{\mathrm{ED}_{50}} + \log(\mathrm{P}_{50j}), \sigma_{\mathrm{ED}_{50}}\right)$$

- The prior distributions for $\mu_{\mathrm{ED}_{50}}$ and $\sigma_{\mathrm{ED}_{50}}$ are formed similar to those for λ_j

Posterior predictive distribution of $(\lambda, \mathrm{ED}_{50})$ for a new compound

Conditional on the hierarchical parameters

$$\log(\lambda) \mid (\mu_\lambda, \sigma_\lambda) \sim t_5\,(\mu_\lambda, \sigma_\lambda)$$

$$\log(\mathrm{ED}_{50}/\mathrm{P}_{50}) \mid (\mathrm{P}_{50}, \mu_{\mathrm{ED}_{50}}, \sigma_{\mathrm{ED}_{50}}) \sim t_5\left(\mu_{\mathrm{ED}_{50}}, \sigma_{\mathrm{ED}_{50}}\right)$$

The $(\mu_\lambda, \sigma_\lambda, \mu_{\mathrm{ED}_{50}}, \sigma_{\mathrm{ED}_{50}})$ are unknown but estimated from the meta-data using MCMC (10,000).

The posterior predictive distribution $(\lambda, \mathrm{ED}_{50})$ can be simulated by drawing from the conditional distributions for each set of $(\mu_\lambda, \sigma_\lambda, \mu_{\mathrm{ED}_{50}}, \sigma_{\mathrm{ED}_{50}})$

Meta-analytical prior (MAP) distribution of $(\lambda, \mathrm{ED}_{50})$

- Schmidli et al (2014) called the posterior predictive distribution the MAP and showed that it can be applied to a new compound without directly combining its data with the meta-data
- The reference suggest approximating the MAP by a mixture of normal distributions
- Exploration of the predictive prior showed that the t_5 distribution when averaged over the hyper-parameters could be adequately approximated by a new re-scaled t_5 distribution
- The scale of the approximating t_5 distribution was conservatively expanded to ensure support across all of the distributions resulting from the sensitivity analyses
- The prior distribution for $(\lambda, \mathrm{ED}_{50})$ only requires the clinical team to specify the P_{50}

Summary of the prior distribution for the$(\lambda, \mathrm{ED}_{50})$

- A rough 80% interval for lambda is $(1/2, 2)$
- A rough 80% interval for a future ED_{50} is $(\mathrm{P}_{50}/10, 10 * \mathrm{P}_{50})$

Prior distribution for the E_0 and E_{max} of a future compound

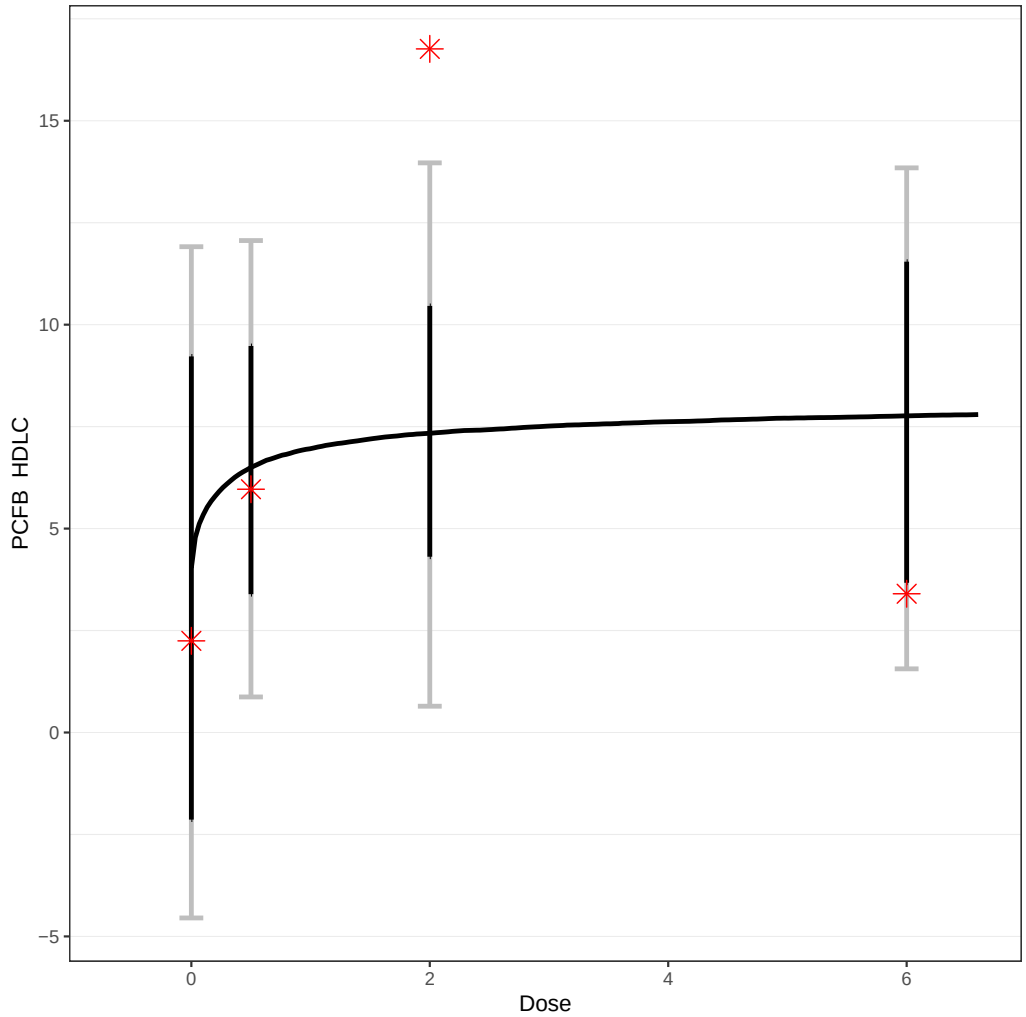
- E_0
  - The placebo data in the future study is informative for E_0. The E_0 is usually the easiest parameter to estimate
  - TA-specific historical placebo data may add additional information
  - The placebo data from the many TA's in the meta-data are not very informative and it is not obvious how to use it
- E_{max}
  - An informative prior distribution will be difficult to defend externally
  - Compounds in the meta-data have proven efficacy. Even an accurate distribution for them is not an appropriate prior distribution for an unproven new compound
  - Informative priors for the E_{max} is not common practice

Checking model fit

Posterior predictive checks

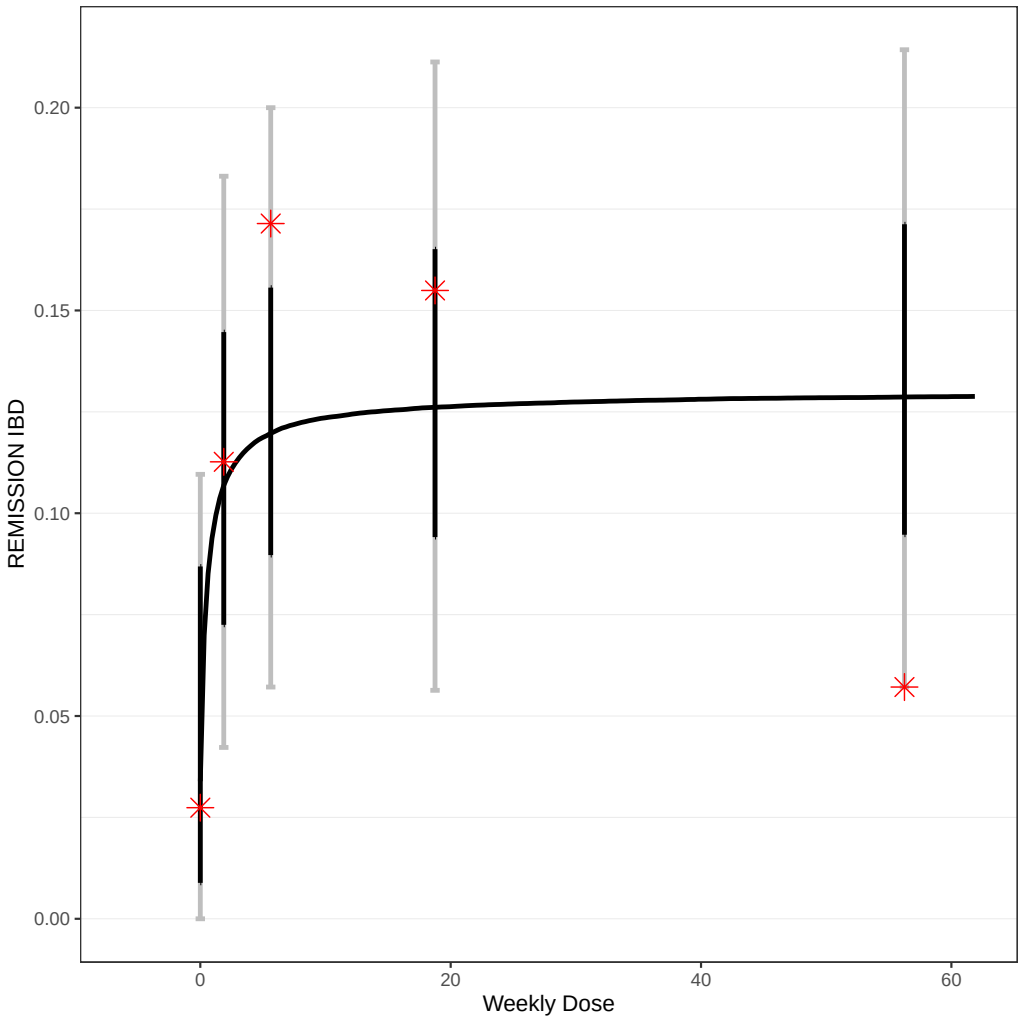
- Posterior predictive check for non-monotonicity
  - Assuming the Emax model is correct, compute the probability in a future hypothetical study with the same design that the difference between the sample means from the best lower dose versus the highest dose will exceed the difference in the actual data
  - Small predictive 'fit' probabilities imply the data are unlikely to have been produced from an Emax curve
  - Two compounds in the meta-data have confirmed non-monotone response
- Using the common 0.05 cutoff, the check has limited power to detect a 50% loss in efficacy at the highest dose. Applied to the meta-data, it rules out appreciable non-monotonicity in $>$ 10% of compounds. Approximately half of flagged compounds are false positives, approximately half of non-monotone curves are missed.

Small molecule drug with non-monotone response: PPAR-α to raise HDL



GOF=0.004. Two studies with similar trends in Nissen et al., 2007

Biological to treat ulcerative colitis with non-monotone response



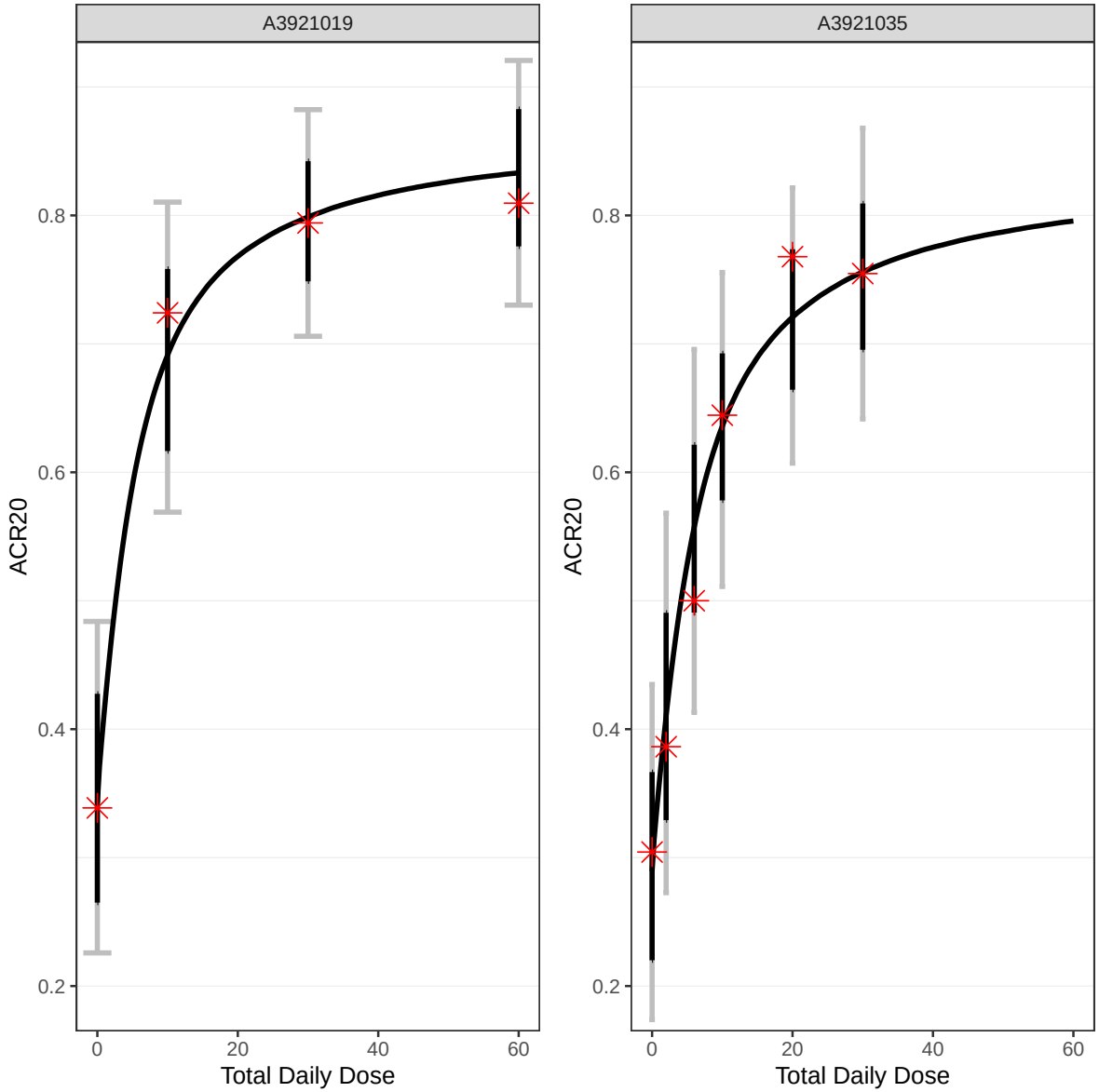
GOF=0.038. Confirmed with mechanistic biomarker data

Example of dose selection

Compound to treat rheumatoid arthritis

- Primary endpoint is binary ACR20
- Diffuse prior distributions for $\mathrm{E}_0, \mathrm{E}_{\mathsf{max}}$. Default priors for $\log(\mathrm{ED}_{50}/\mathrm{P}_{50})$ and $\log(\lambda)$
- Bayesian Emax model fit using R package *clinDR* producing MCMC posterior draws of the parameters
- Two dose response studies, because the first did not test low enough doses $(0, 10, 30, 60)$

Example of a compound to treat rheumatoid arthritis



Dose selection table

	Population Responder Rates			Phase 3 Sample Responder Rates		
Total Dose	Mean Diff	Probability Diff> 0.2	Probability Diff> 0.3	Mean Diff	Probability Diff> 0.2	Probability Diff> 0.3
2 mg	0.12	0.1	0	0.11	0.1	0.01
4 mg	0.21	0.58	0.07	0.18	0.39	0.06
6 mg	0.27	0.89	0.31	0.23	0.65	0.17
8 mg	0.31	0.98	0.6	0.27	0.81	0.33
10 mg	0.35	1	0.8	0.3	0.9	0.48
12 mg	0.37	1	0.9	0.32	0.94	0.58
14 mg	0.39	1	0.95	0.33	0.96	0.66
16 mg	0.4	1	0.97	0.34	0.97	0.72
18 mg	0.41	1	0.98	0.35	0.98	0.76
20 mg	0.42	1	0.99	0.36	0.99	0.8
30 mg	0.46	1	1	0.38	0.99	0.89

Conclusions

- Meta-data provide an empirical basis for a dose response model for most compounds. Model checking is always performed, but the model should not be changed without substantial evidence
- The meta-data also provide an empirical basis for a Bayesian prior distribution
- The Bayesian model has very good operating characteristics (not discussed)
- Five additional years of data will be complete by the end of 2023. Opportunity to expand data collection and natural time to update/change methodology possibly including longitudinal data

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