Meta-Analysis of Clinical Dose Response and Its Application

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Introduction

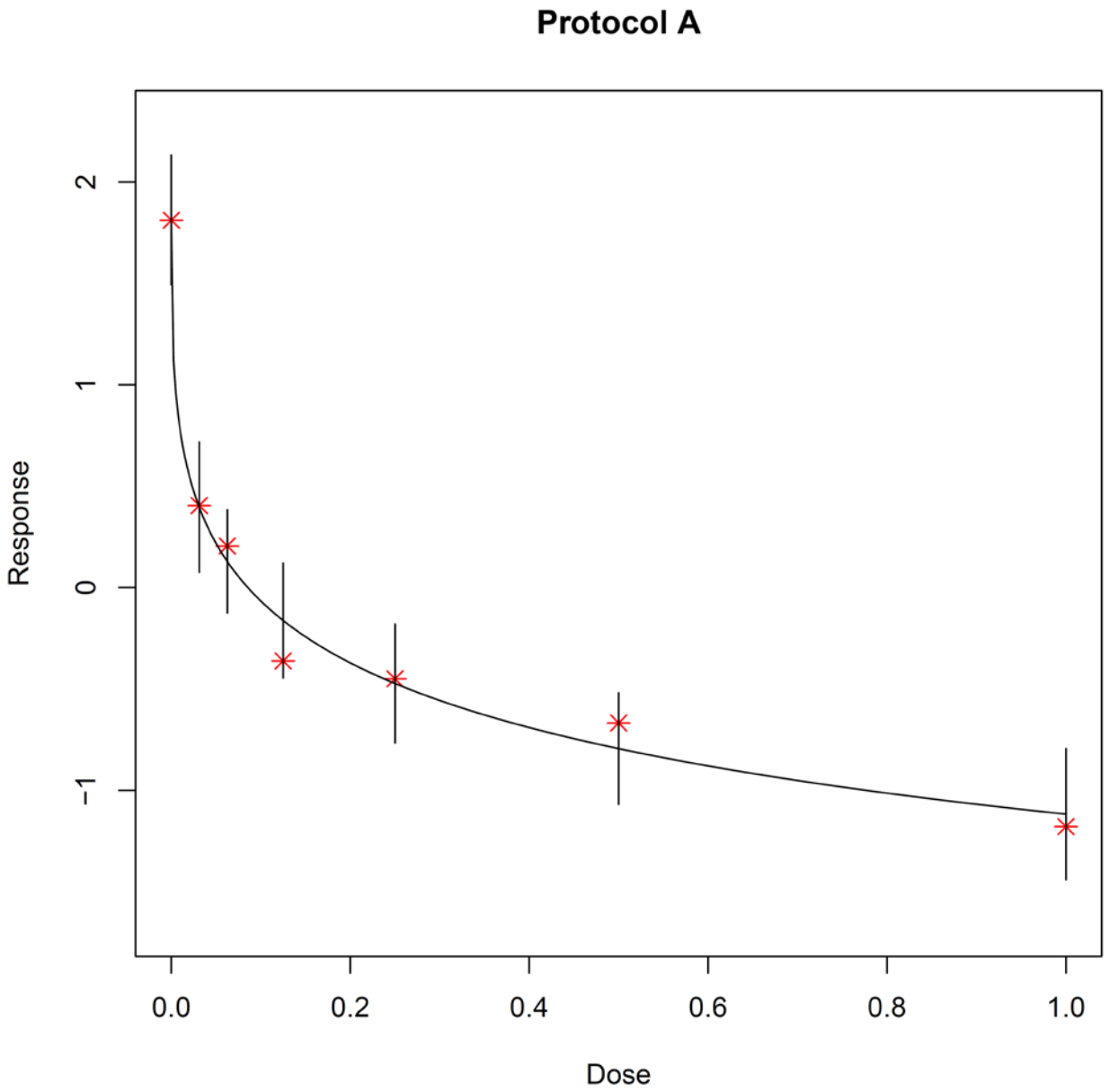
- **Numerous statistical methods for estimating dose response**
  - MCP-MOD, NDLM, Bayesian model averaging
  - Derived to be optimal under some conditions

Introduction

- **What are the relevant conditions?**
  - Meta-analysis of 225 compounds supports the Emax model from clinical pharmacology
- **Bayesian model-based dose response**
  - Empirically-based prior distribution combining dose response meta-data and compound-specific information
  - Brief example illustrating software to implement this approach and the potential for large improvements

Example

Example: Lipitor to lower LDL-c (continuous endpoint)



The Emax model in pharmacology

Dose Response Model: Emax

$$Response = E0 + \frac{Emax * Dose^{\lambda}}{ED50^{\lambda} + Dose^{\lambda}}$$

- E0 = response under placebo treatment
- Emax = maximum difference with PBO
- ED50 = dose producing half the maximum response
- The power parameter determines the steepness of the curve

Meta-analyses of dose response

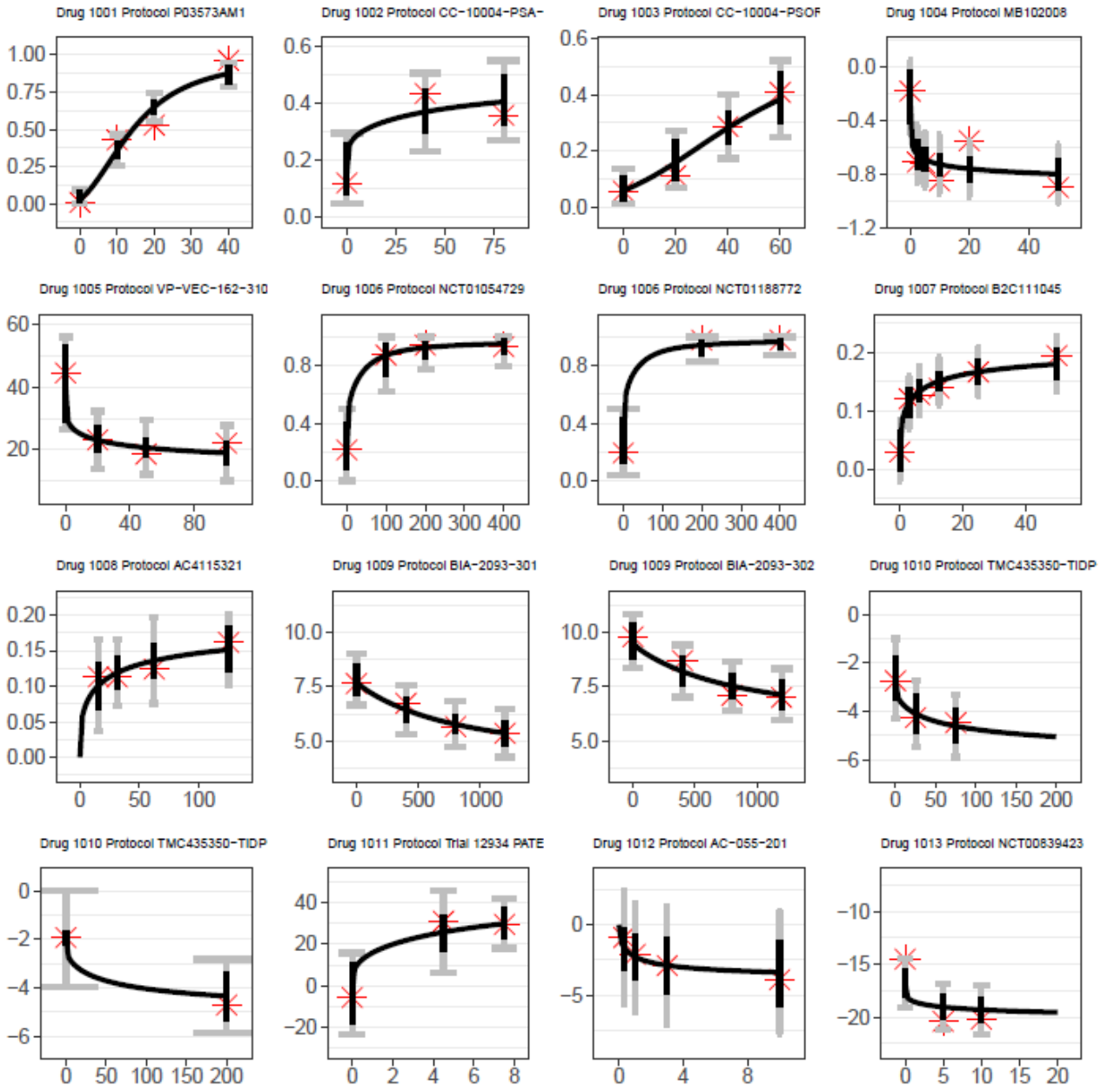
Compound sampling frame

- Approximately 225 compounds
  - Pfizer compounds 1998-2017
  - FDA approved compounds 2009-2017
  - Includes small molecule and biologics. Excludes oncology and vaccines
- Study criteria (315 studies)
  - Phase 2 studies. Phase 3 studies included if they had ≥ 2 doses and the Phase 2 endpoint was collected

Design Characteristics

- Data types
  - 63% were continuous endpoints
  - 37% were binary endpoints
- Dosing
  - Dosing summarized by total daily dosing in the meta-analyses (a few adjustments required)

FDA Approved Compounds



Detecting Model Deviations (Goodness of fit)

Model checking

- How much power do we have to detect clinically important deviations from the model?
  - Several approaches to assess model adequacy have been explored
  - The most concerning deviation is a loss of efficacy at the higher doses

Conclusions

- How much power do we have to detect non-monotone deviations from the model?
  - The proportion of compounds with clinically important (non-monotone) deviations from the model is roughly (1/100,1/10)
  - Two likely non-monotone dose response curves identified.

Quantitative Trends in the model parameters

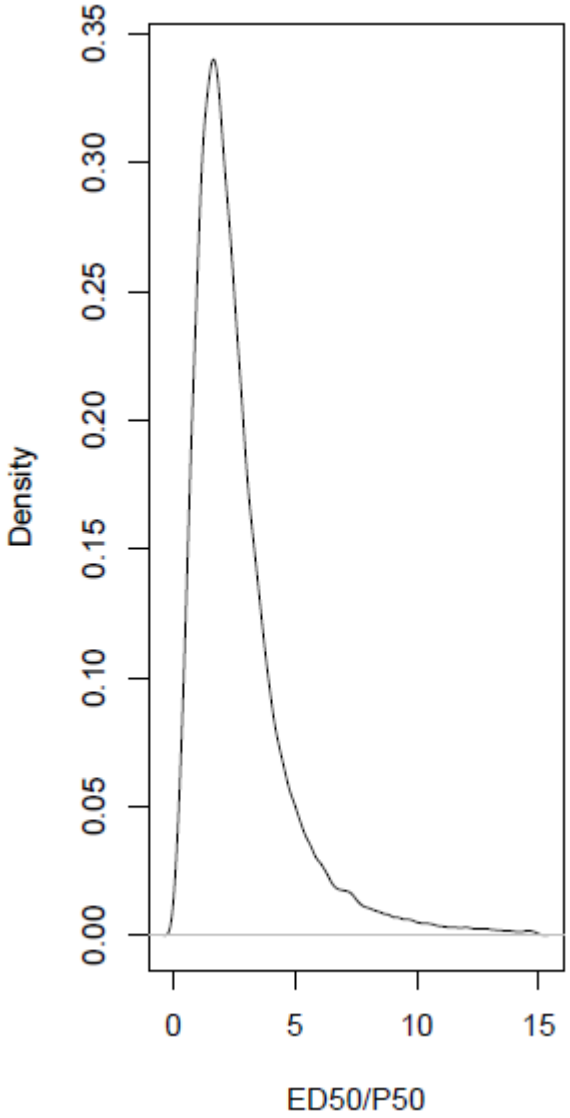
Bayesian Hierarchical Model

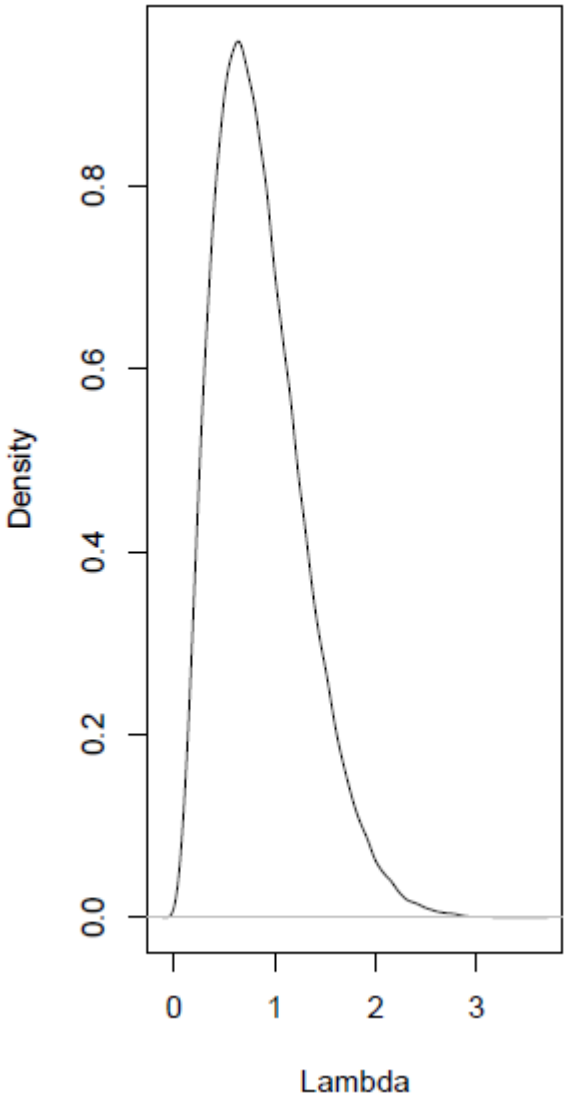
- Diffuse, but proper prior distributions were specified for the E_0, E_{max} and residual standard deviation
- The Hill parameters, λ and the, ED_{50} , have hierarchical distributions
- An Emax model on the logit scale was used for binary data, and then back-transformed

Standardization

- The ED50 requires special consideration
  - An initial prediction (explicit or implicit) of the ED_{50} is required when designing the first dose finding study. Denote it by P_{50}
  - When it is not recorded, the mid-point between the lowest two non-PBO doses in the first Phase 2 is a reasonable approximation
  - Modelling is performed on the log(ED50/P50)

Predictive Distribution for your next compound





Easy-to-remember summaries for the ED_{50}/P_{50} and λ

- Summaries
  - The ED_{50} has high probability (approx 90%) to be in ($P_{50}/10$, $10P_{50}$)
  - The λ has high probability (approx 90%) to be in (1/2, 2)

Applying the Results of the Meta-analyses

Planning a dose response study

- POC study is on-going. Results from the POC study will be available at the time of final planning
- Preliminary planning assumes the POC study is successful

Prior distribution (R package clinDR)

```
e0mu<-qlogis(0.2)
e0sd<-2

emaxmu<-qlogis(0.6)-qlogis(0.2)
emaxsd<-2

p50<-20

prior<-prior.control(epmu=e0mu,epsd=e0sd,emaxmu=emaxmu,
emaxsd=emaxsd, p50=p50, edDF = 5, binary=TRUE)
```

Initial proposed design:

```
doselev<-c(0,10,25,50)
n<-c(150,150,150,150)
```

Simulation population

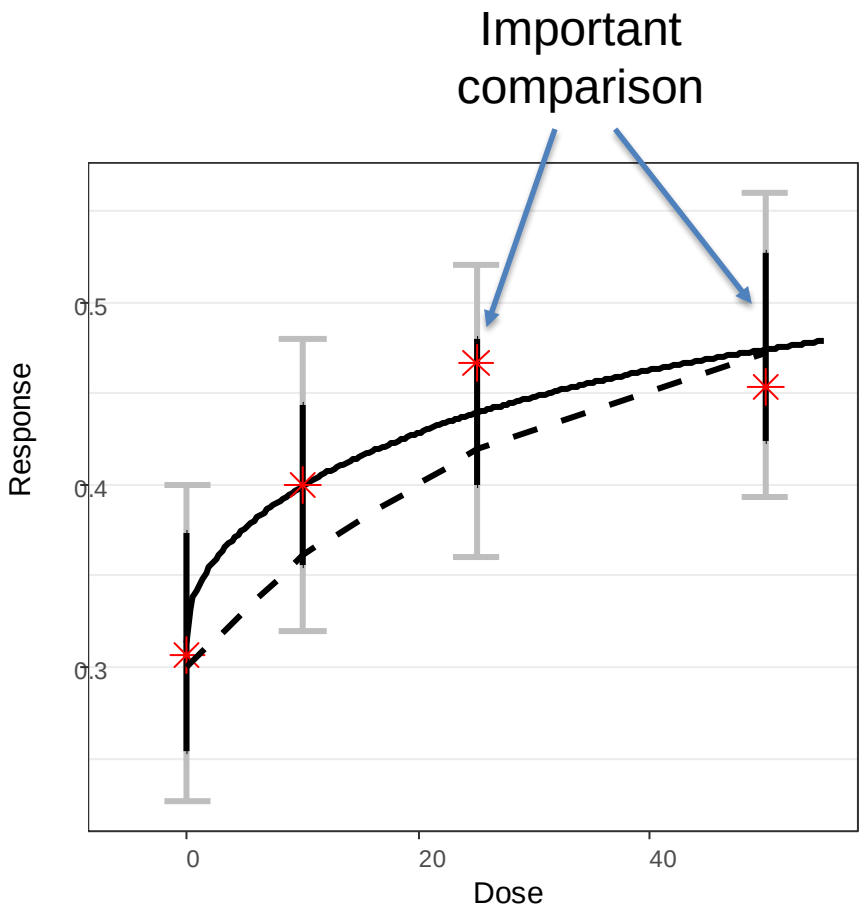
```
e0<- qlogis(0.3)
emax<-qlogis(0.60)-qlogis(0.3)
ed50<-35
lambda<-1
pop<-c(log(ed50),lambda,emax,e0)
proplev<-plogis(emaxfun(doselev,pop))

gen<-FixedMean(n,doselev,proplev,binary=TRUE,parm=pop)
```

Execute Simulation

```
D1 <- emaxsimB(nsim=5000, gen, prior, seed=12357,binary=TRUE)
plot(D1[5000])
summary(D1)
```

Simulated sample: 5000



Output of summary

Coverage probabilities for nominal 0.95 intervals [Dose-PBO]:
Bayesian Dose response modeling posterior intervals:

10	25	50
0.982	0.970	0.957

Square Root Mean Squared Error [Dose-PBO]:
Bayesian dose response modeling (est=posterior mean) :

10	25	50
0.030	0.038	0.051

RMSE Pairwise comparisons: 0.054
Efficiency: 1.12-3.24

Too large to be useful

Key comparison of two highest doses
RMSE=0.021
Efficiency: 7.53

Precise enough to be useful

Concluding Remarks

- **Consistent with expectations from clinical pharmacology, our meta-data demonstrate a dose–response relationship that is well described by the Emax function for a high percentage of compounds**

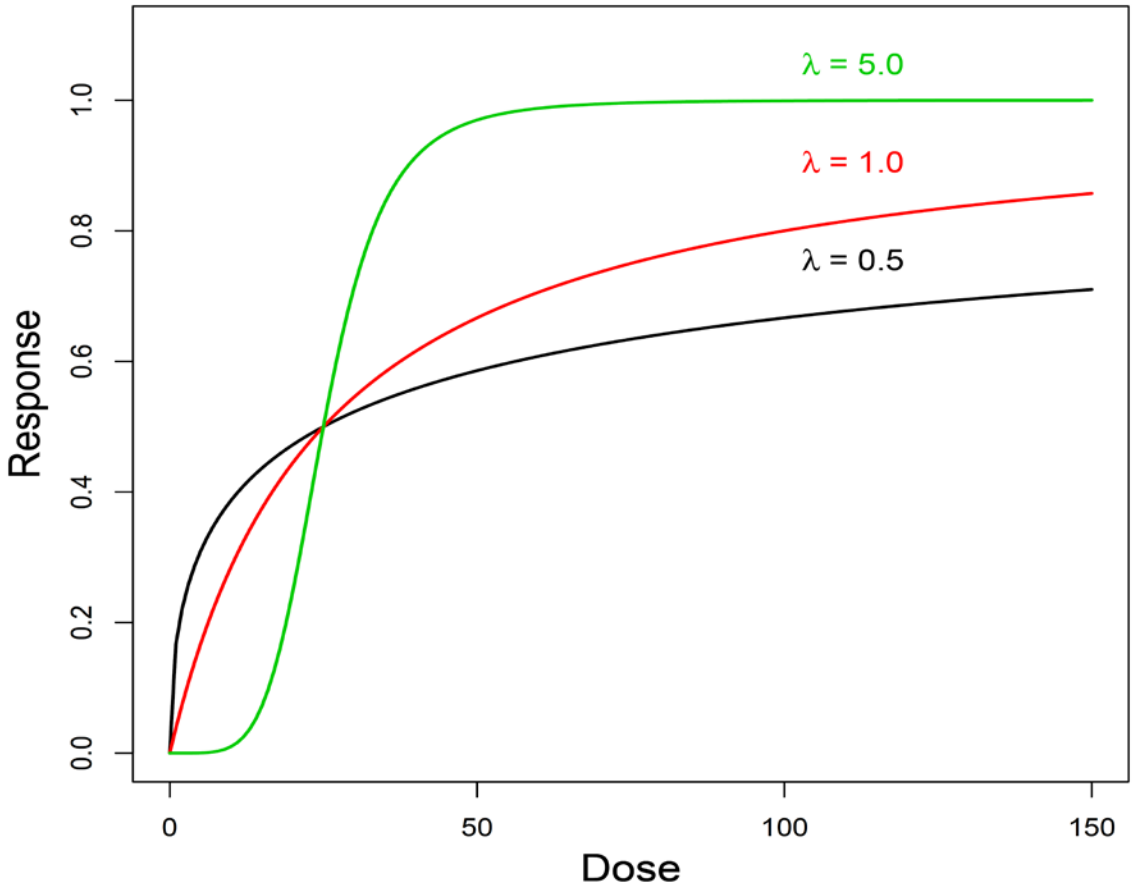
- **For design and analysis we propose to use a Bayesian Emax model**
  - Graphical and quantitative assessments of goodness of fit are always performed
  - Exceptions only for compelling reasons, for example when there are toxicities/toleration issues combined with a non-specific endpoint (e.g. global assessment of change)

Supplementary slides

References

- **Iliadis, A., and Macheras, P. (2006). Modeling in Biopharmaceutics, and Pharmacodynamics: Homogeneous and heterogeneous approaches, Springer: New York.**
- **Thomas N, Sweeney K, Somayaji V. Meta-Analysis of Clinical Dose-Response in a Large Drug Development Portfolio. *Statistics in Biopharmaceutical Research* 2014; 6: 302-317.**
- **Thomas, N., and Roy, D. (2017). Analysis of clinical dose-response in small-molecule drug development: 2009-2014. *Statistics in Biopharmaceutical Research,* Vol. 9, No. 2, 137-146. doi: 10.1080/19466315.2016.1256229.**
- **Wu, J., Banerjee, A., Jin, B. Menon, M. S., Martin, S. and Heatherington, A. (2017). Clinical dose–response for a broad set of biological products: A model-based meta-analysis. Statistical Methods in Medical Research. doi: 10.1177/0962280216684528.**

Sigmoid Emax Model



- **When λ = 1, ED90 = 9*ED50**
- **When λ = 0.5, ED90 = 81*ED50**
- **when λ = 5.0, ED90 = 1.5*ED50**

Prior density