Predicting Phase III Success Using a Combination of Phase II Results and Historical Reference Data

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Quantitative Sciences

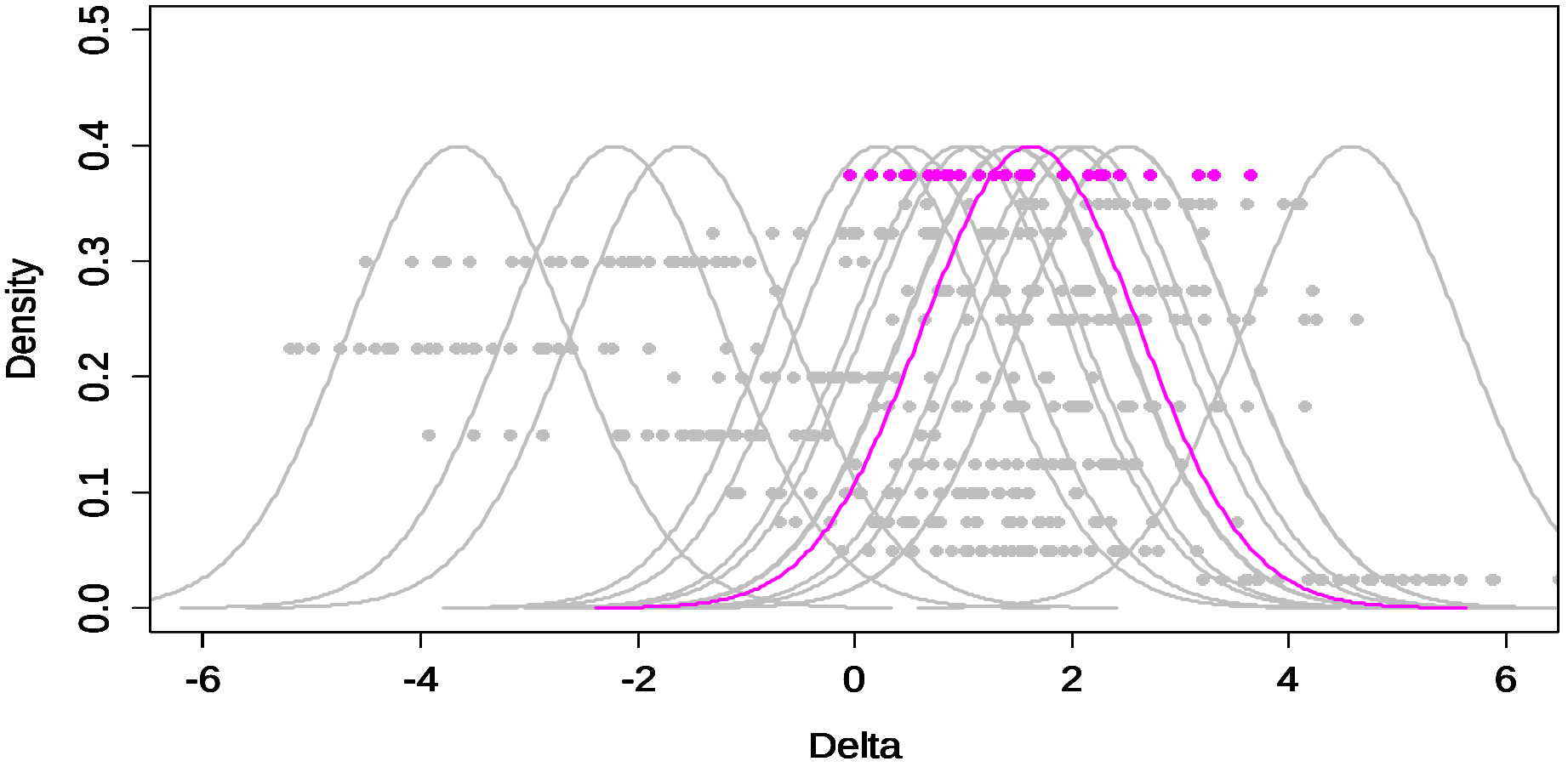
Introduction/Background

- It is common for dry-eye programs to fail in late stage development
- Therefore, many experts in this therapeutic area tend to be skeptical about the likelihood of reproducibility
- Our dry-eye project team would like to base milestone decisions on quantitative predictions of phase 3 success
- This presentation will describe a method for doing quantitatively what the experts have done qualitatively and describe why conventional p-value based decisions should be avoided

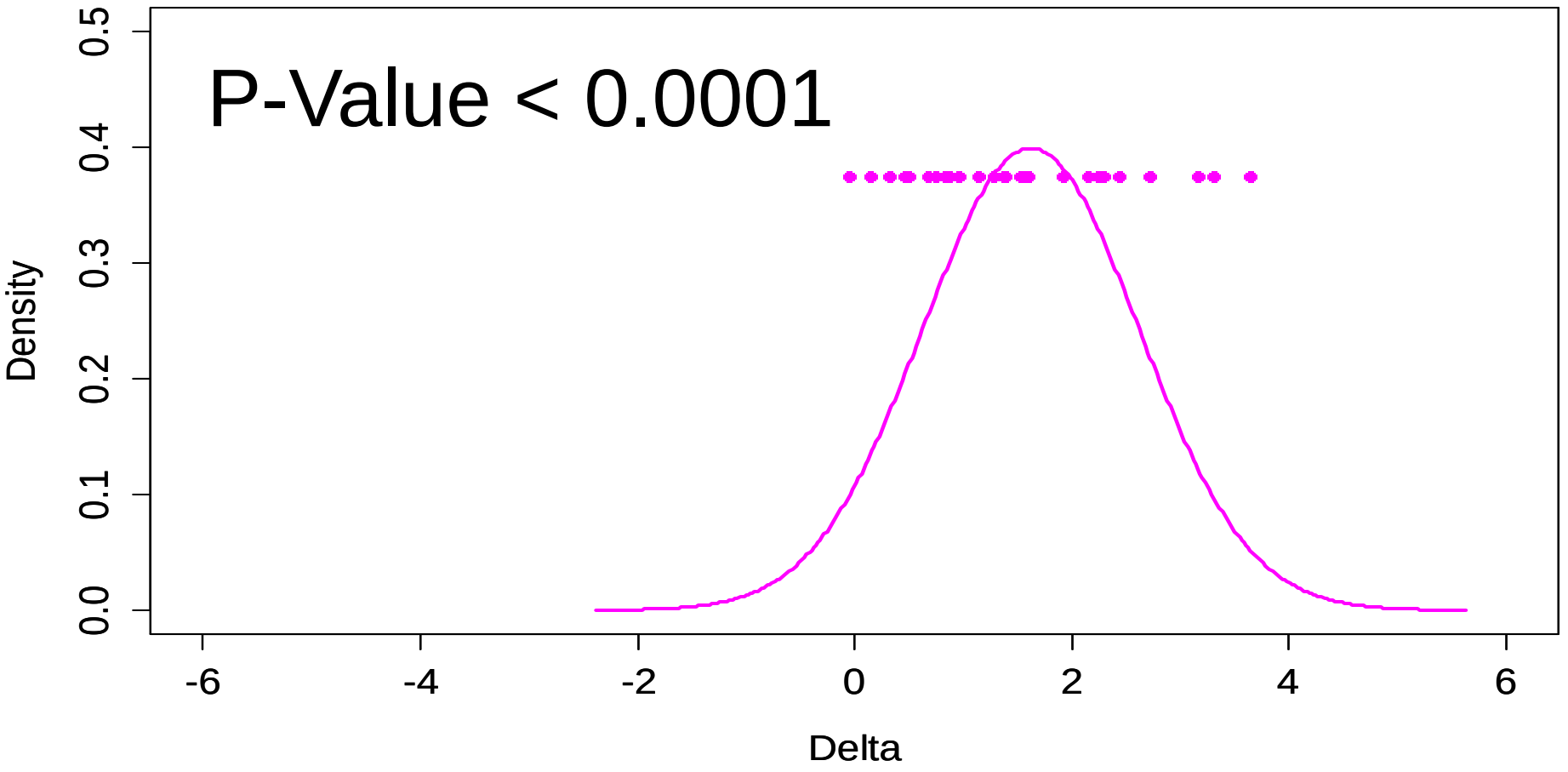
Outline

- Historic data and meta-analyses basics
- Importance of inter-study variability
- Simple meta-analysis model
- Case study with more innovative model
- Practical considerations
- A simulation study
- Conclusions

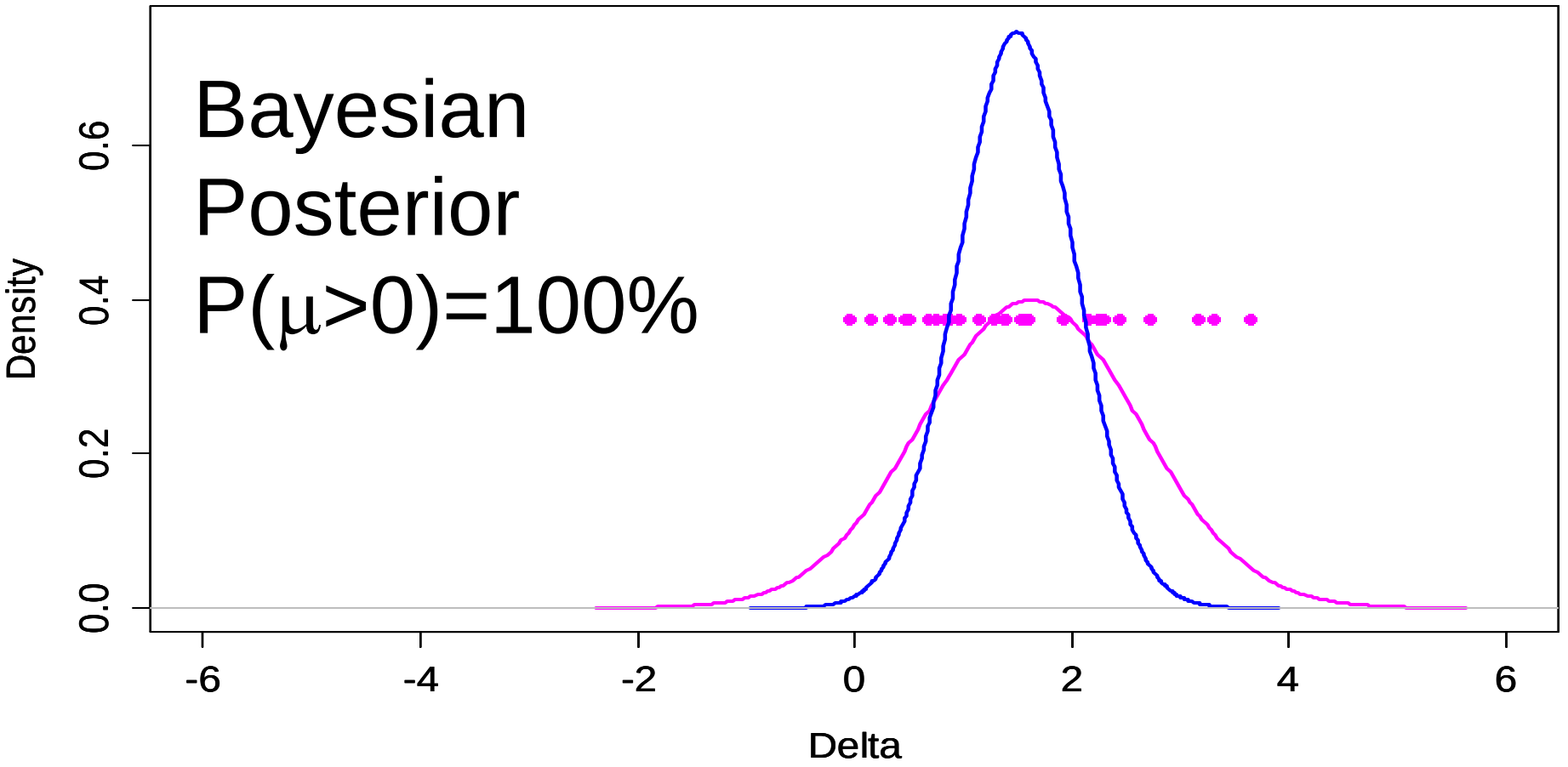
Meta-Analysis Basics



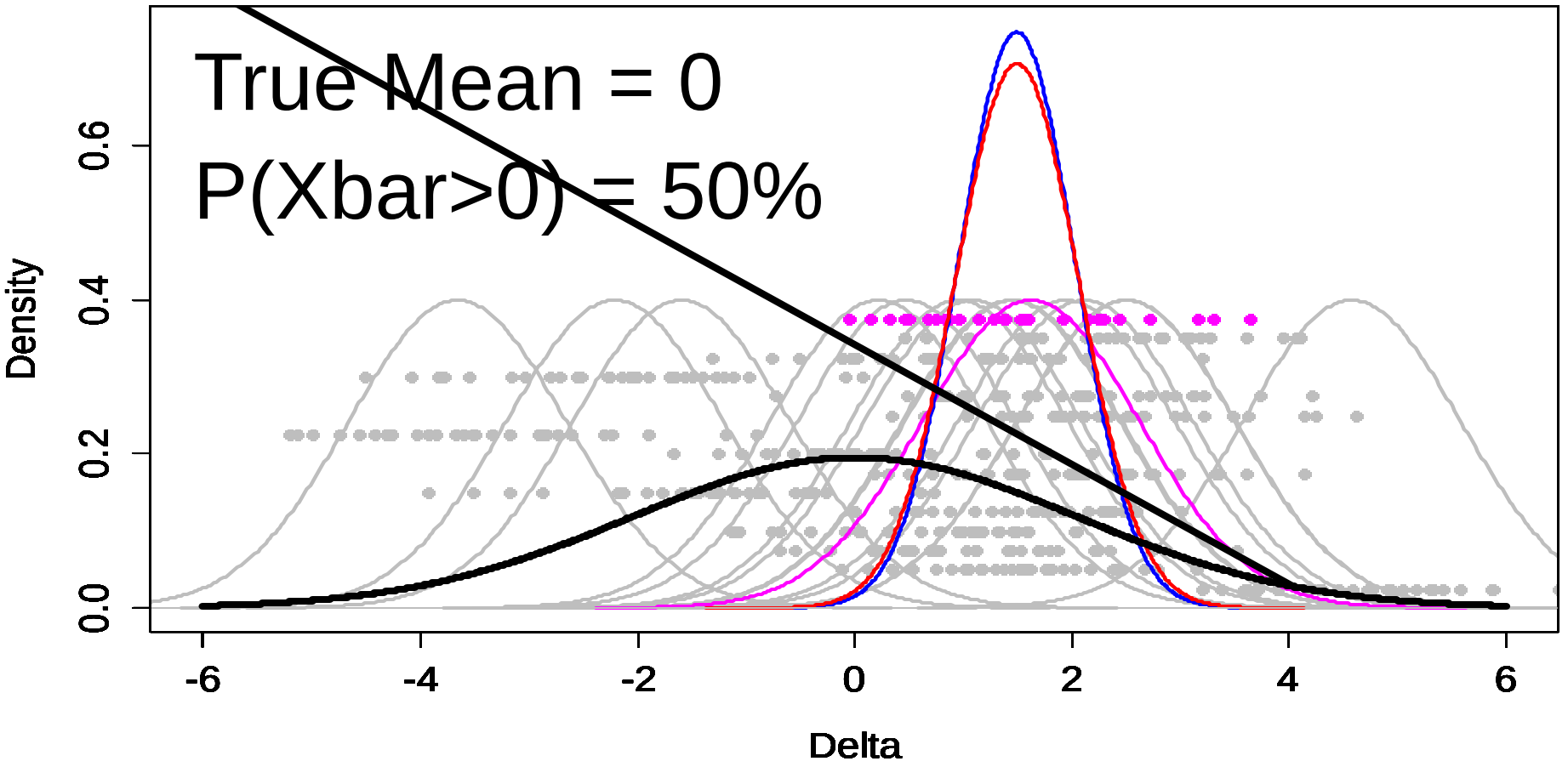
Ignoring the Historic Data



Bayesian Methods (Ignoring Historic Data)



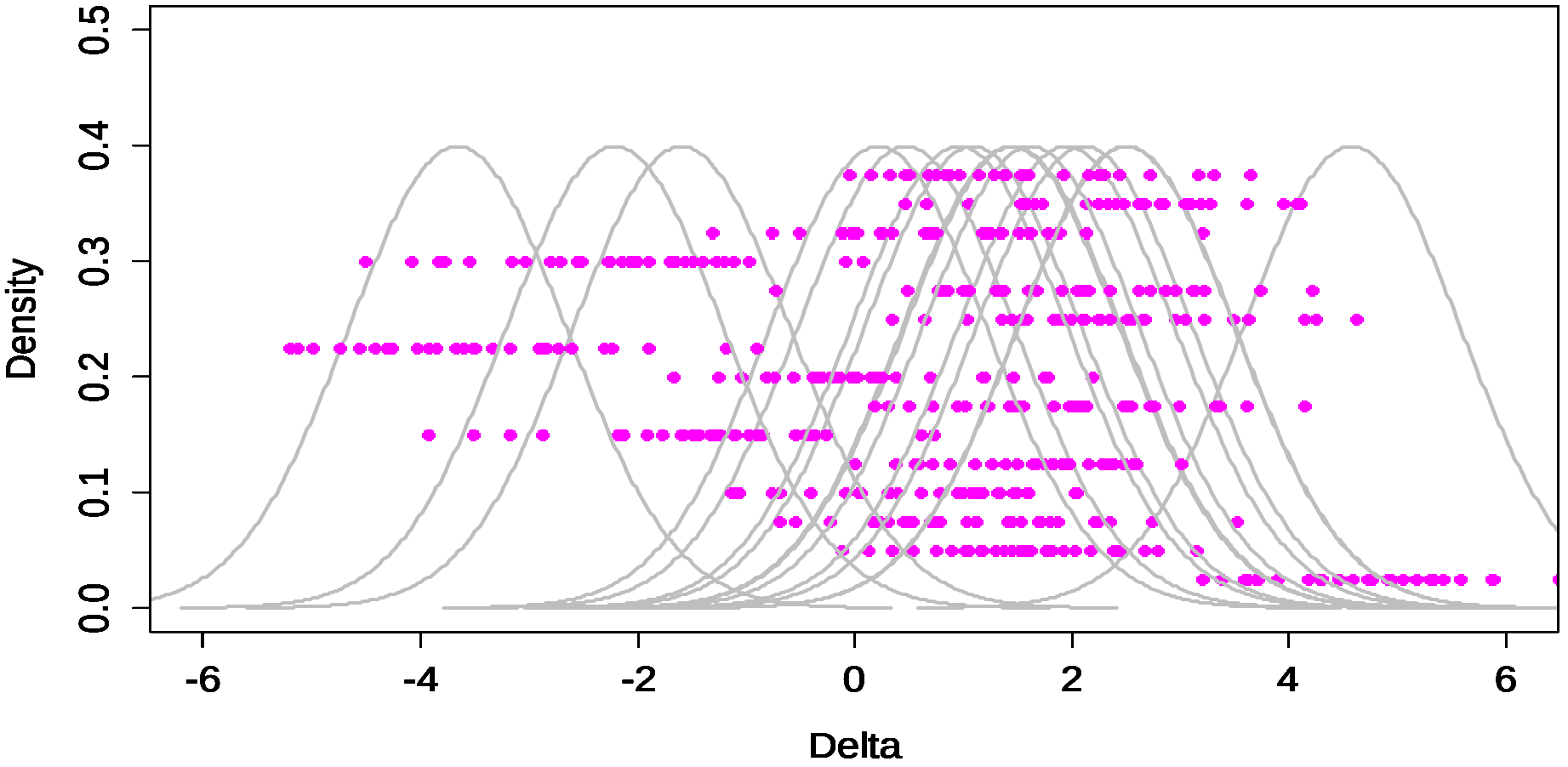
Importance of inter-study variability



“How to” Fix the Problem?

- Incorporate historic data via a formal meta-analysis
- This will provide estimates of inter and intra study variability

Historical Data for 15 Studies N=30 per Study



Random Effect Meta-analysis Model

- A simple formulation of this problem is the following Random Effect Model

$$y_{ij} = \mu + \gamma_i + \varepsilon_{ij}$$

- Where μ is the population mean, γ is a random effect for study and ε is a random (within-study) error term
- We use a Bayesian construct

$$\gamma_i \sim N\left(0, \sigma_B^2\right) \qquad \mu \sim N\left(\mu_0, \kappa_0 \sigma_W^2 + \sigma_B^2\right)$$

$$\varepsilon_{ij} \sim N\left(0, \sigma_W^2\right) \qquad \tau_X \equiv \frac{1}{\sigma_X^2} \sim G\left(Shape, Rate\right)$$

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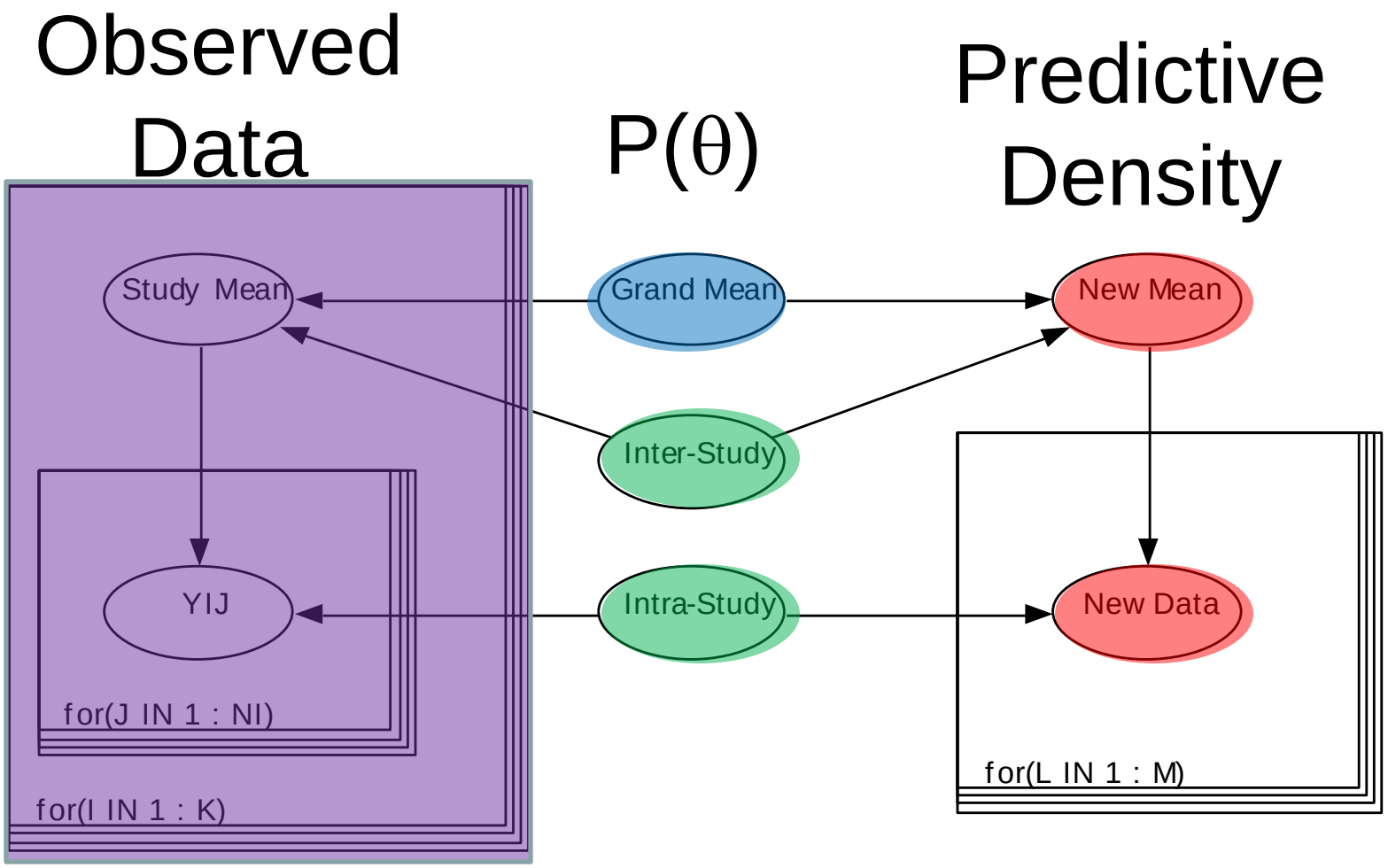
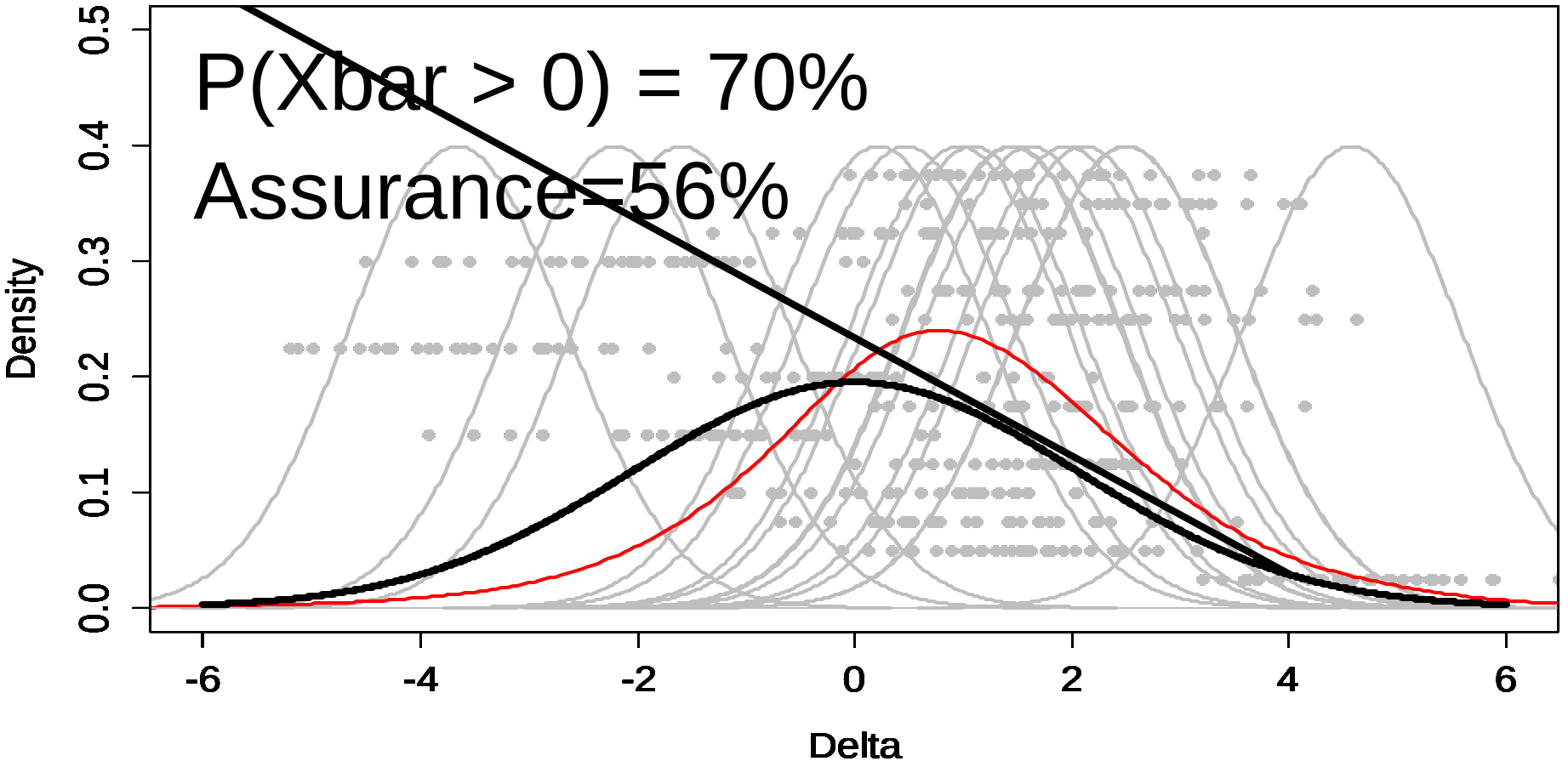
Observed Data for Multiple Studies (Normal MCMC)



Incorporating Inter-Study Variability

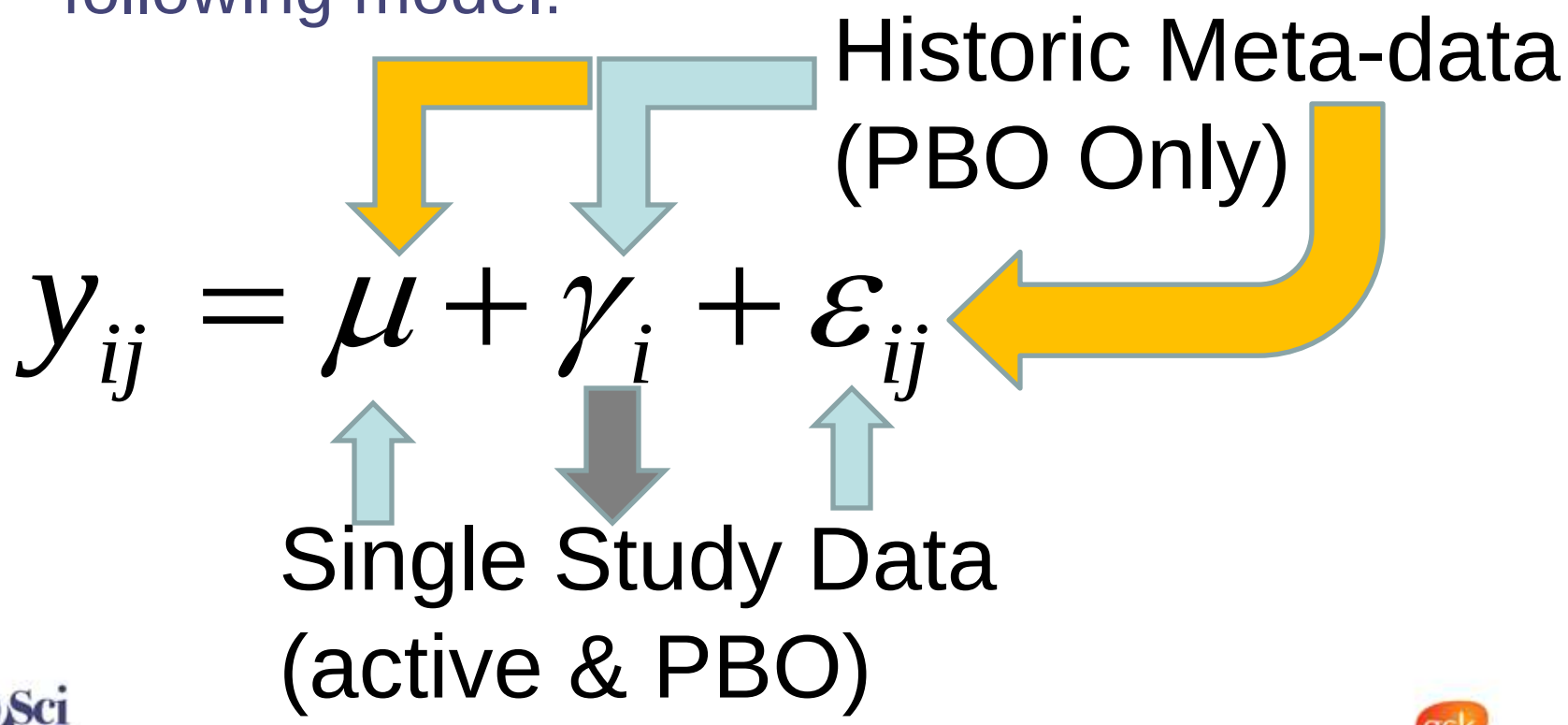


Potential for Innovation

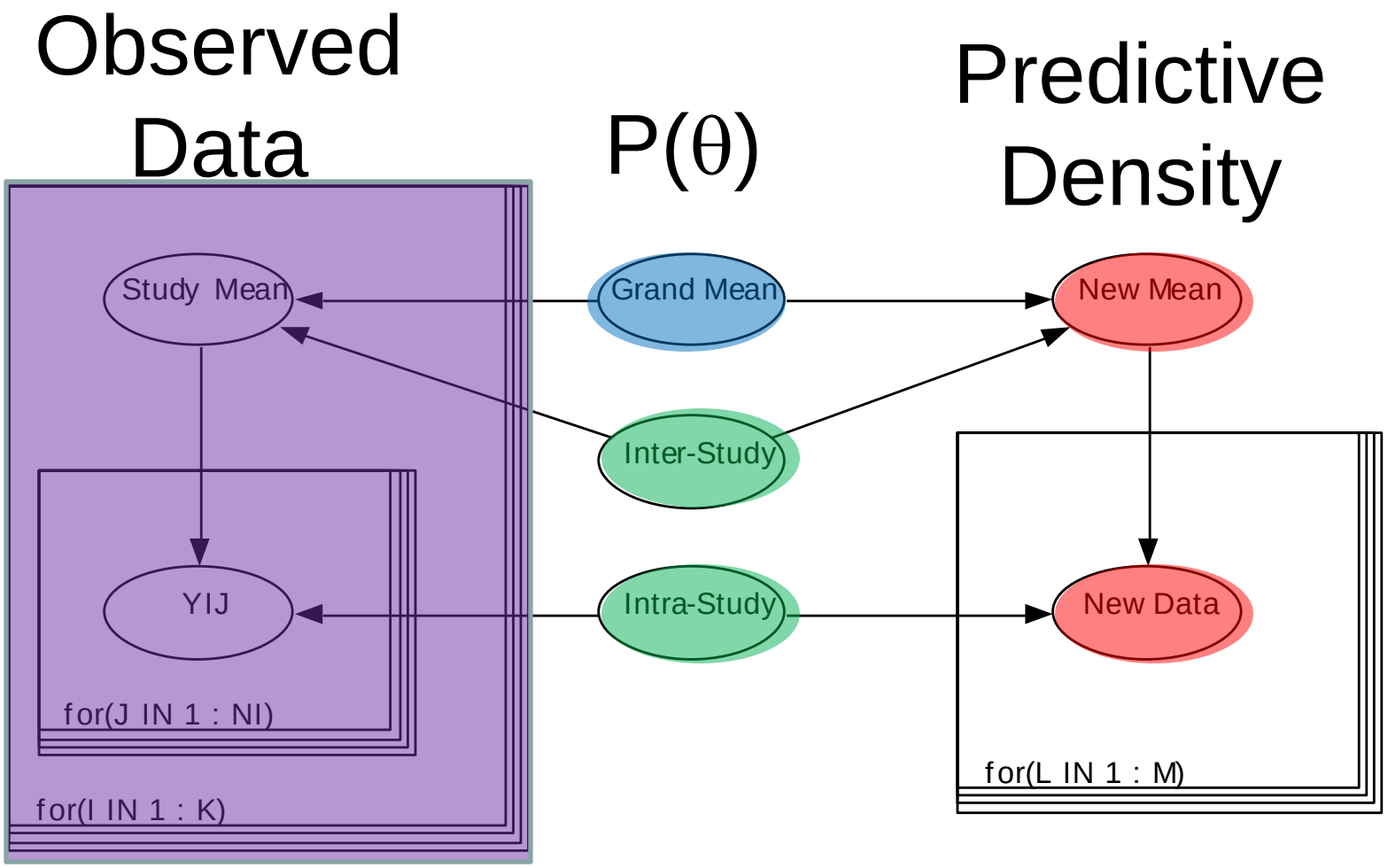
- Estimate the degree of inter-study variability at or before the POC
  - In the absence of full meta-analysis data
  - Without running replicate clinical trials
- Use these estimates to make corrected inferences in the POC
- Build predictive models and guide decision criteria that are more consistently correct
- Inform seamless development programs that are more consistently correct

Hierarchical Assurance Model

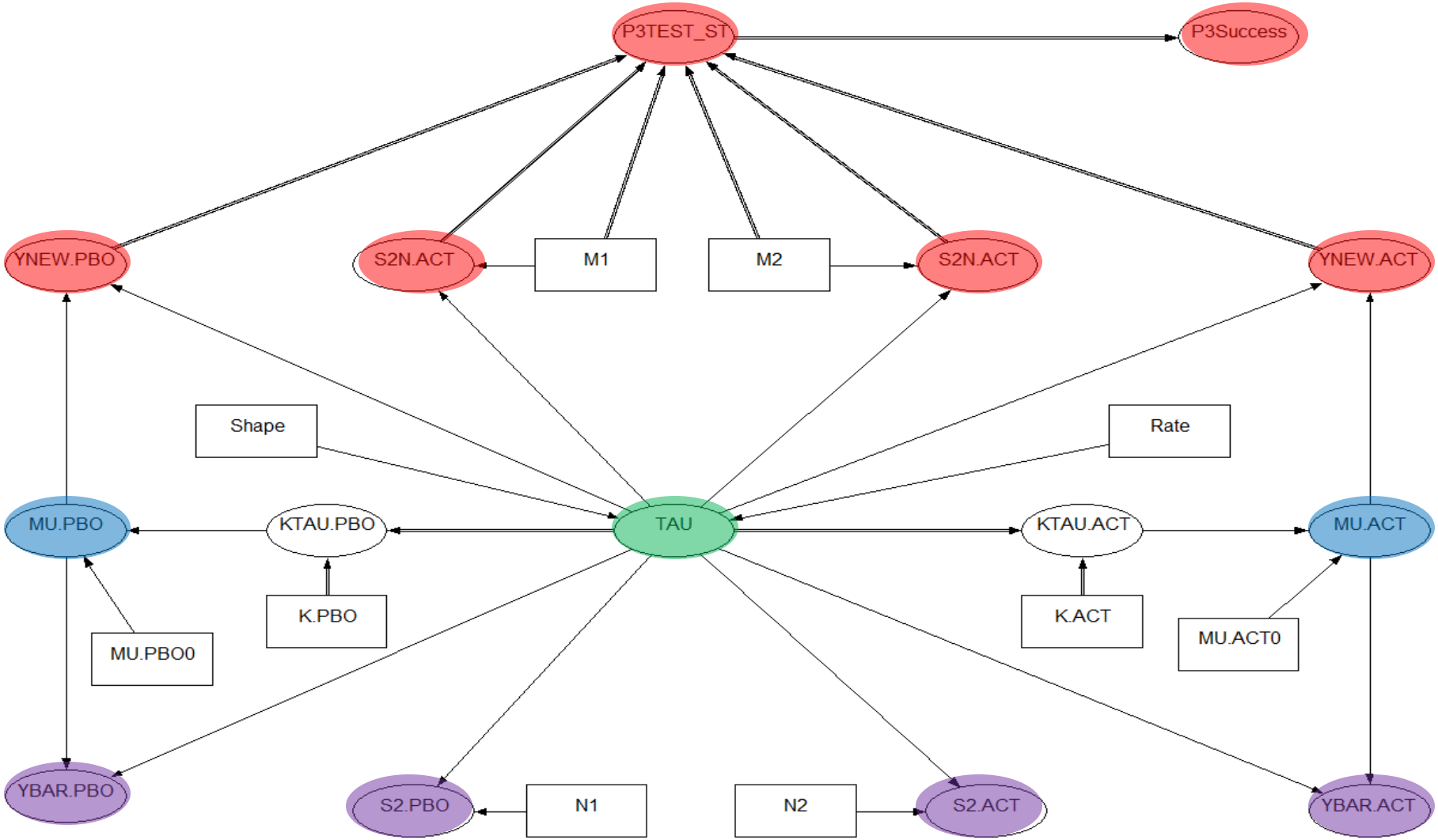
- Given single study data for the investigational drug product (no historical data), and historical data for the placebo combine them in the following model:



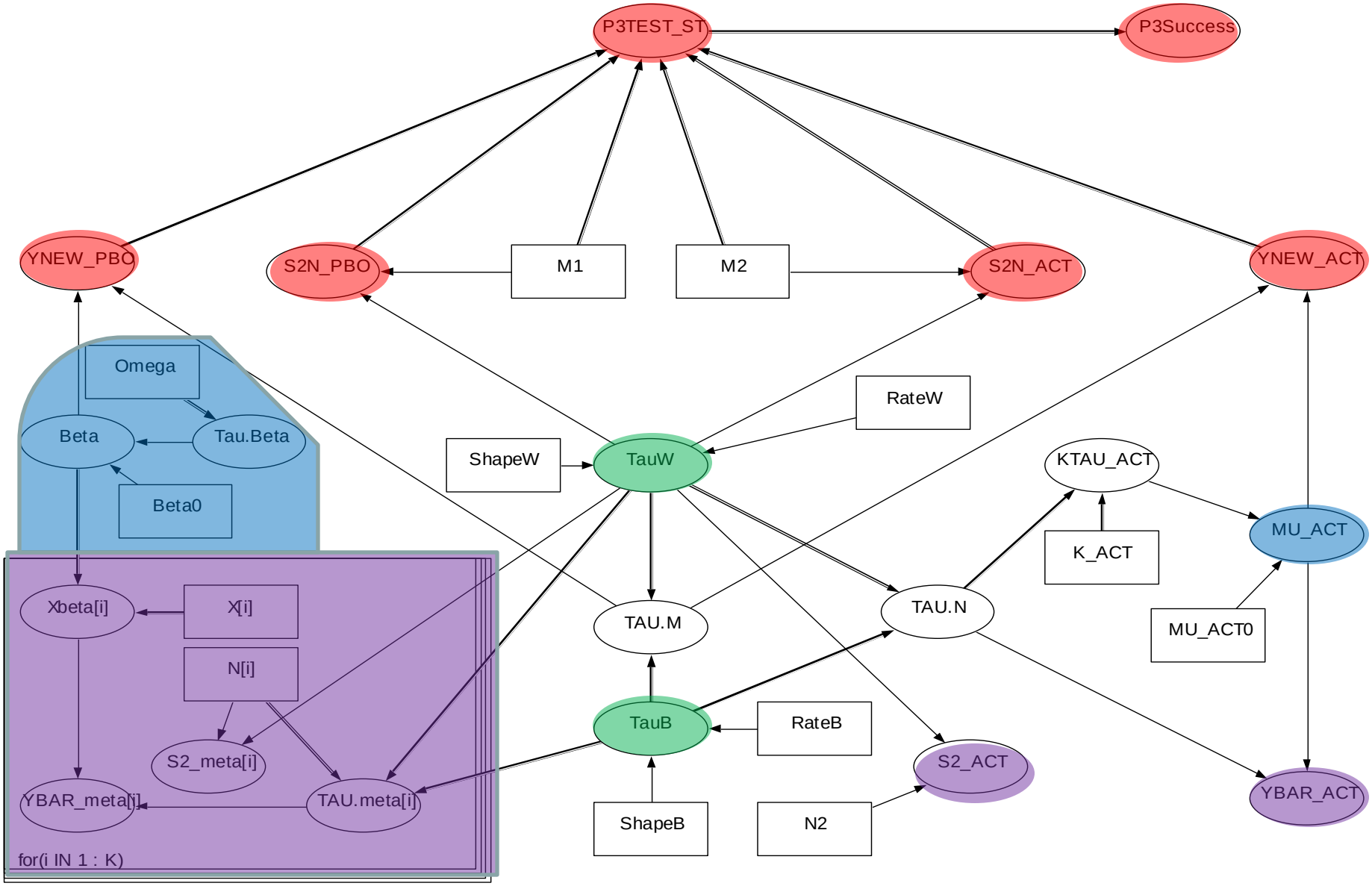
Meta Analysis Model



Single Study Model (Broken into two groups)



Hierarchical Assurance Model



Single study Data

Single Study Data for Dry-Eye example		
	Placebo	Active Treatment
Sample Mean	-0.50	-3.0
S2	16.1	15.8
Planned P3 Sample Size	100	100

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Naïve Assurance Estimate

Historical Placebo Data

Historical Placebo Data for Dry-Eye				
Study	Phase	N per group	Sample Mean	Sample S^2
1	2	103	-1.8	4.12
2	3	176	-0.48	1.13
3	2	58	1.5	8.12
4	2	93	-1.58	4.65
5	3	103	-3.0	11.33
6	2	47	-2.0	11.75
7	3	292	-1.95	26.28
8	2	142	-3.5	7.10
9	3	95	-4.8	10.45

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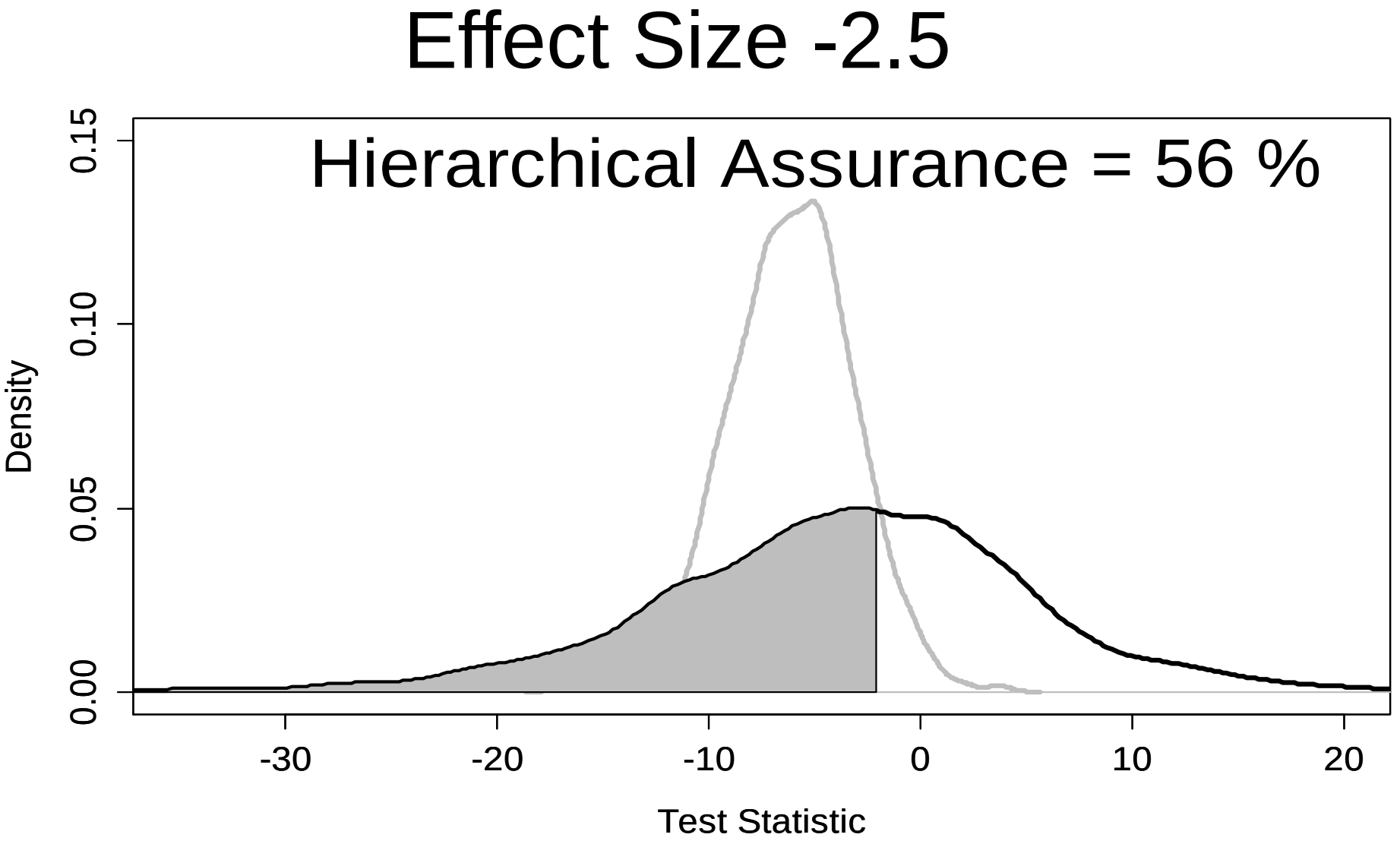
Hierarchical Assurance Result



Parameter Estimates

Parameter Estimates from Hierarchical Assurance Model for the Dry-Eye Example				
Parameter	Estimate	Standard Error	Lower 95% CI	Upper 95% CI
Bias	-0.69	0.73	-2.29	0.58
Intra-Study Variability	11.89	0.51	10.89	12.92
Inter-Study Variability	3.65	2.56	1.15	10.54
Treatment Effect	-2.00	2.14	-6.41	2.10
Posterior probability that the active treatment is superior to placebo (delta < 0) is 84.2%				

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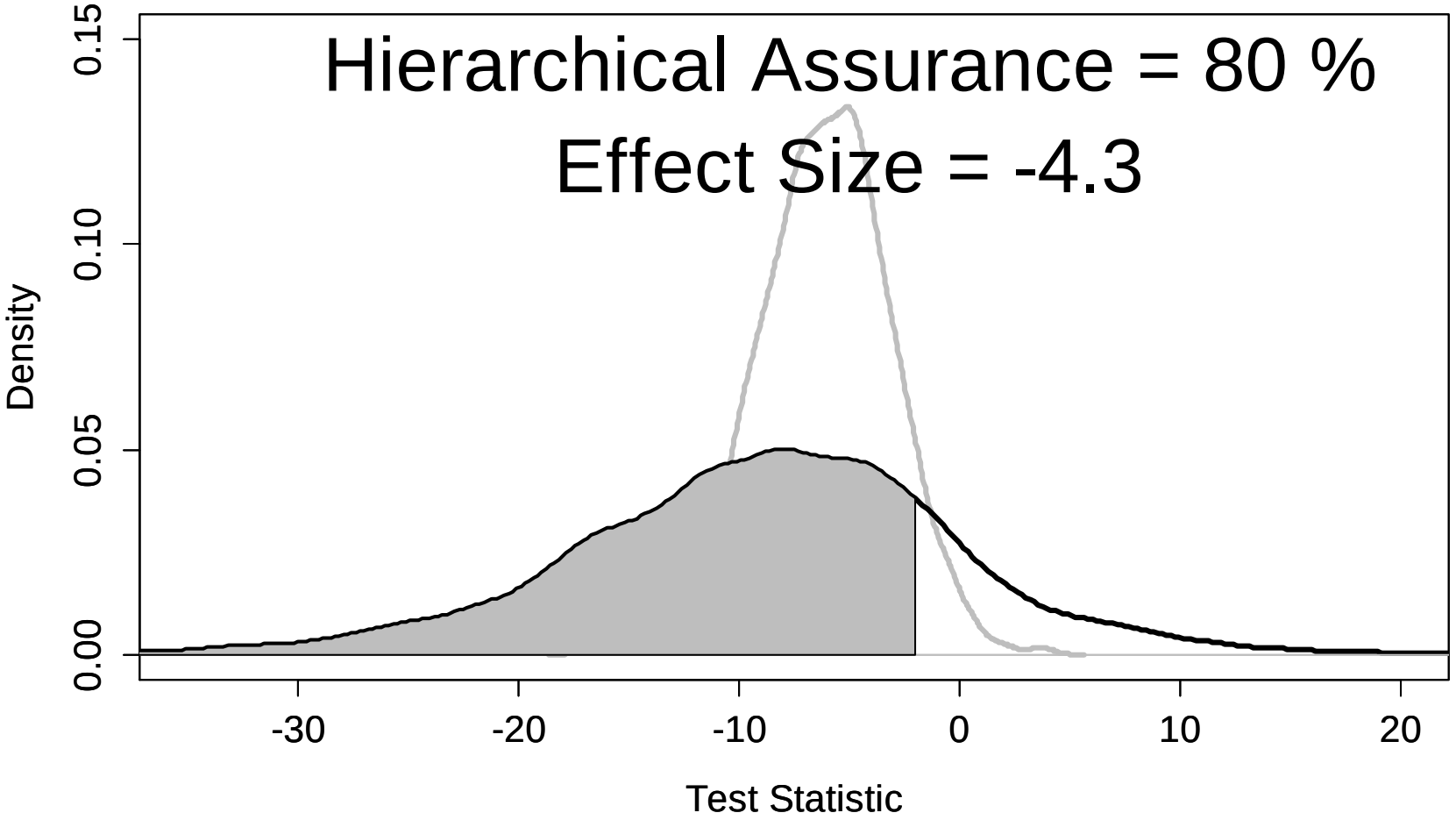
Effect Size Needed to Reach 80% Assurance



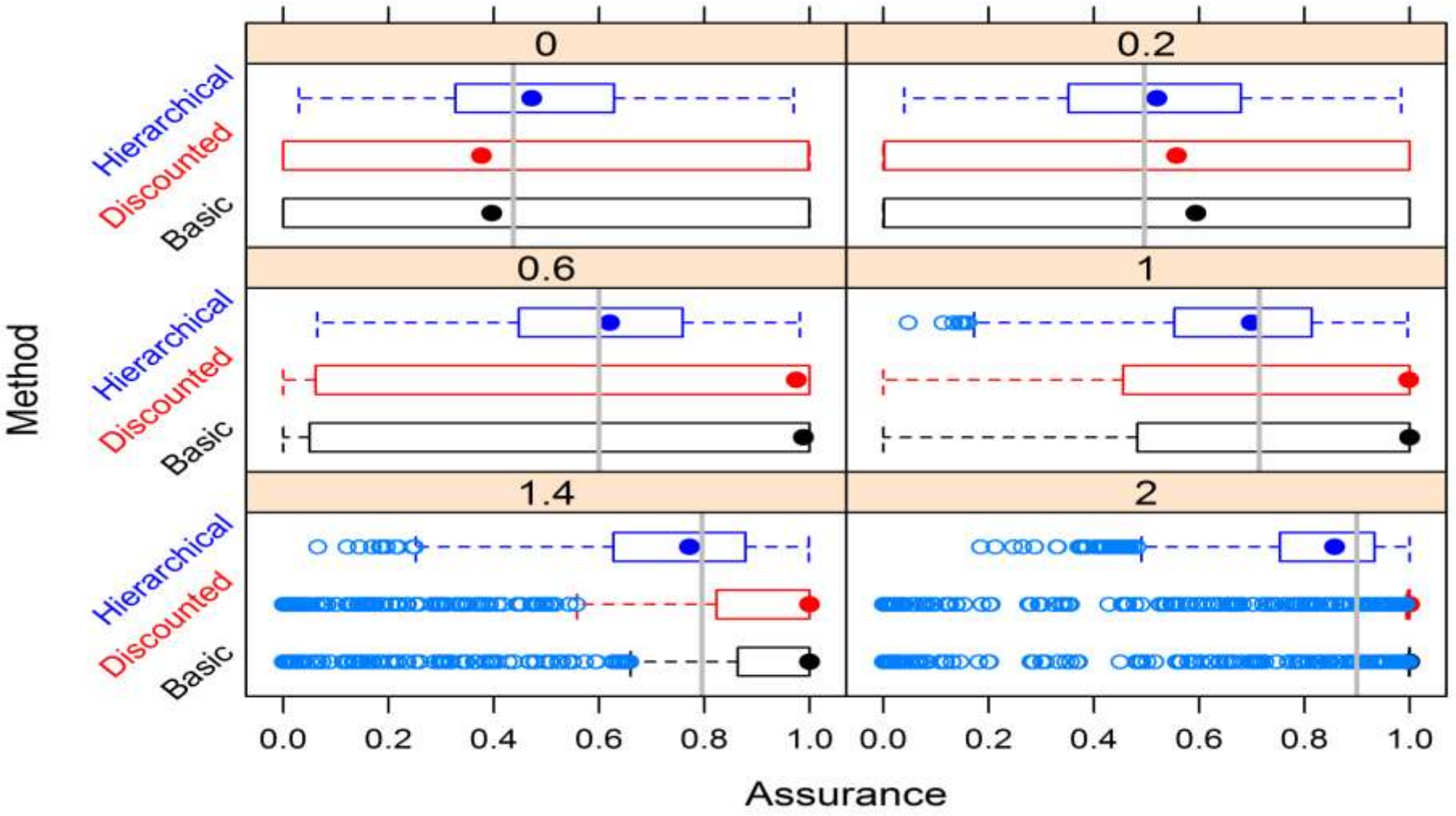
Practical Considerations

- It is helpful to specify the model in terms of sufficient statists, since subject level historical data are often inaccessible
- Involve project team members in the selection of studies to be included in the historical data set
- Try to build a robust set of historical studies that does not include reporting bias

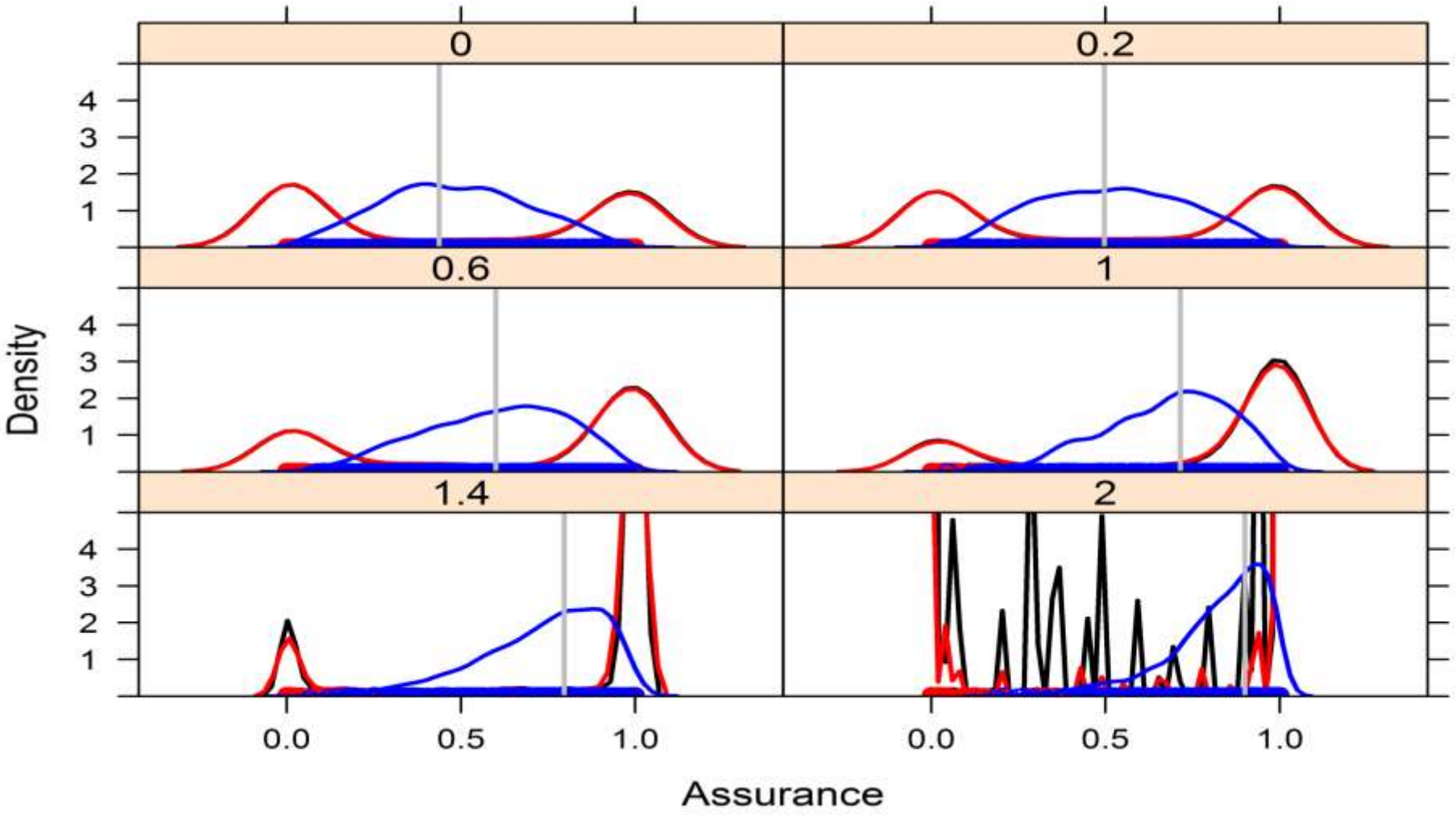
Hierarchical Model Simulations

- Large Inter-Study Variability & Moderate Bias
- Negligible Inter-Study Variability & Large Bias
- Negligible Inter-Study Variability & No Bias
- Historical Data were simulated in conjunction with one Phase 2 study and one Phase 3 study
  - Phase 2 incorporated in the model
  - Phase 3 used to determine ‘true’ success probability

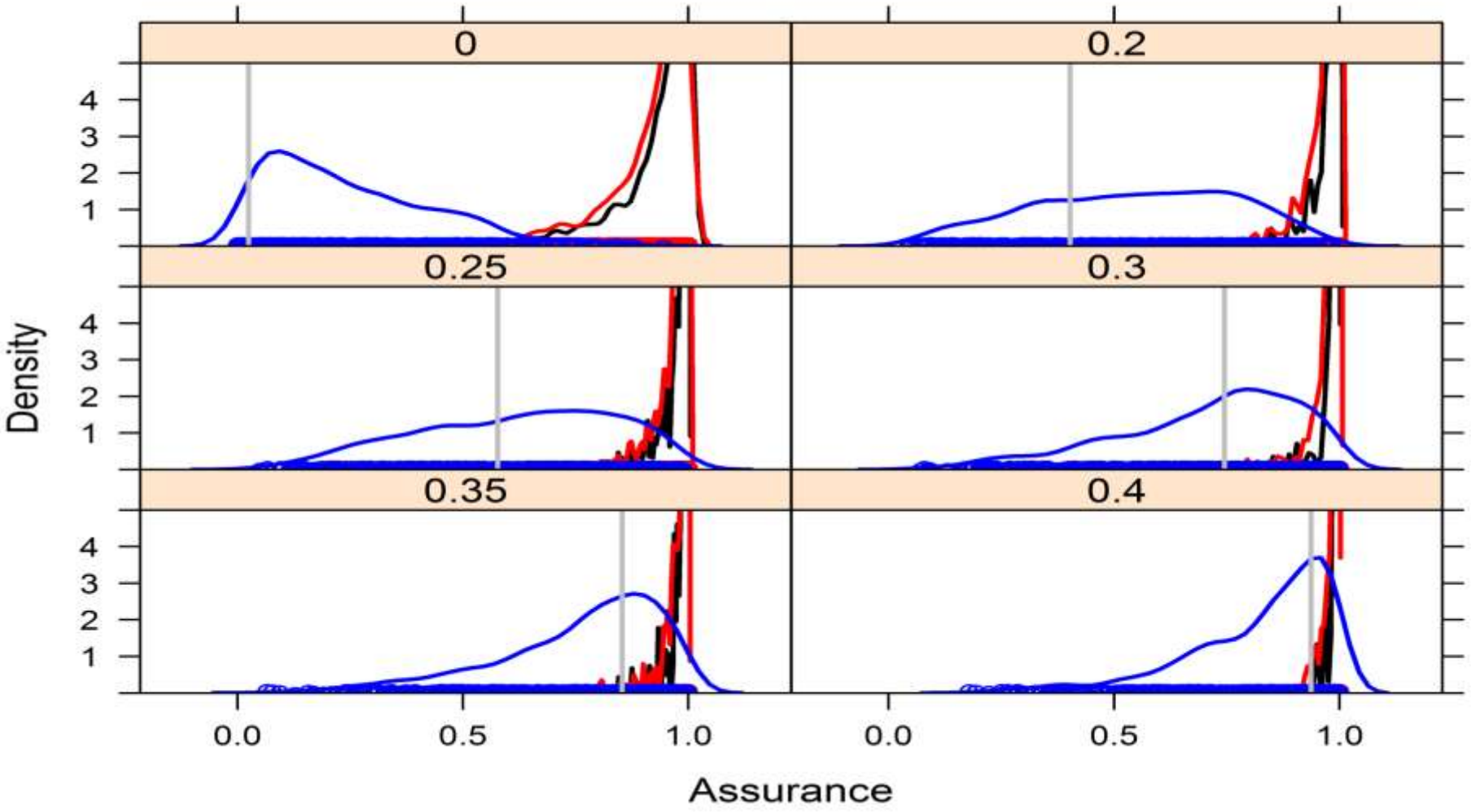
Simulation Results Scenario 1 (Large Inter-Study)



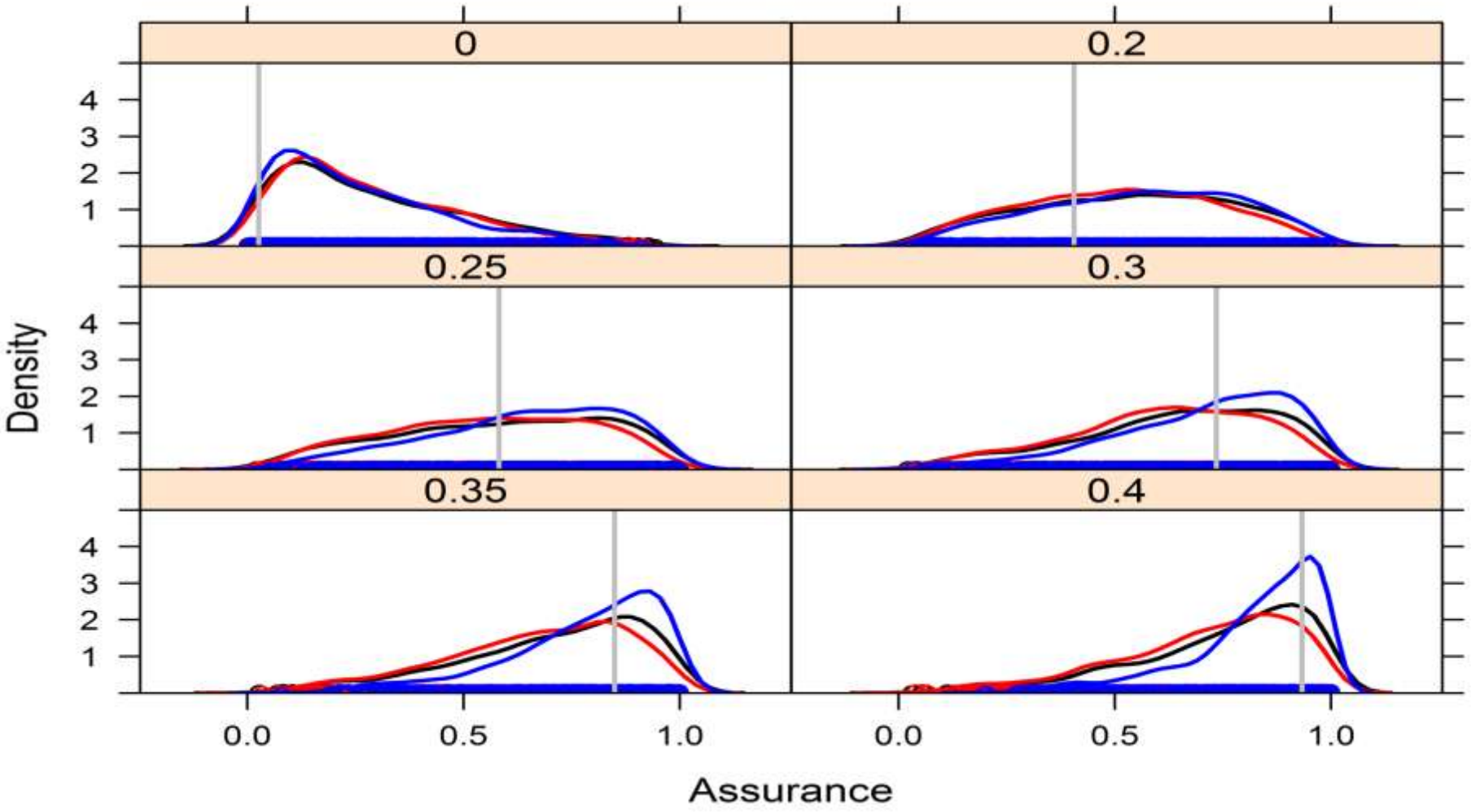
Simulation Results Scenario 1 (Large Inter-Study)



Simulation Results Scenario 2 (Large Bias)



Simulation Results Scenario 3
(No Inter-Study Variance & No Bias)



Potential Applications

- Go/No Go Criteria
- Futility and/or Adaptive Allocation
- Study Design
- Business Development Opportunities
- General Portfolio Management
- Much Much More

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Conclusions

- Inter-Study Variability can cause our inferences and predictions to be wrong more often that we expect
- There are solutions that can be used to bring our rate of being wrong back to a controllable level
- The benefits of applying these solutions early in the development process are quite substantial
- Clinical statisticians have a unique opportunity to enhance the way drugs are developed if we can build some alignment and a greater understanding of how inter-study variability can be controlled for early in the development process

Acknowledgements

- Bob Noble
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