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Averaged Model Based Decision Making for Dose Selection Studies

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Recent publication

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www.nature.com/psp

ORIGINAL ARTICLE

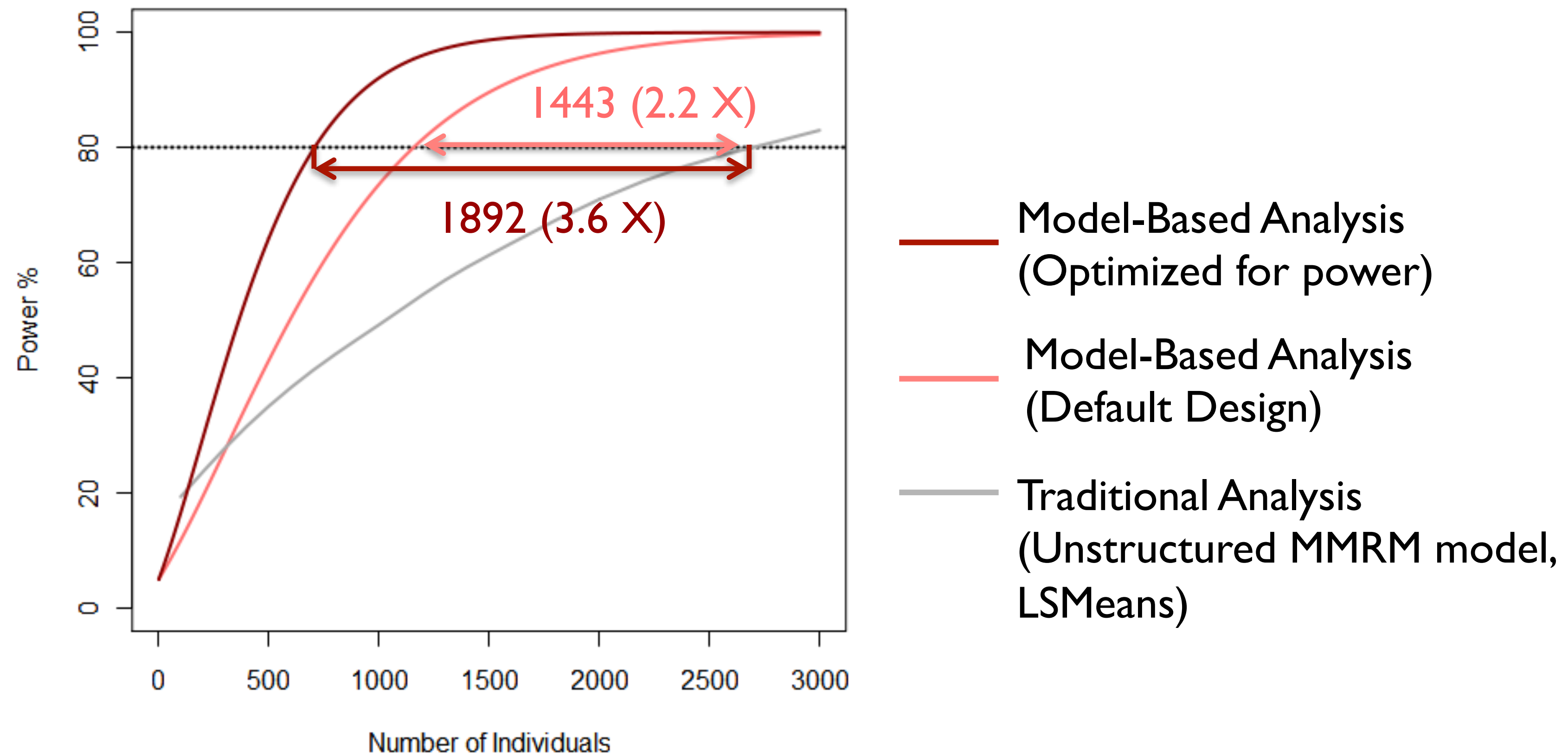
Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson¹, C Vong¹, M Bergstrand¹, EN Jonsson^{1,2} and MO Karlsson¹

Drug development struggles with high costs and time consuming processes. Hence, a need for new strategies has been accentuated by many stakeholders in drug development. This study proposes the use of pharmacometric models to rationalize drug development. Two simulated examples, within the therapeutic areas of acute stroke and type 2 diabetes, are utilized to compare a pharmacometric model-based analysis to a *t*-test with respect to study power of proof-of-concept (POC) trials. In all investigated examples and scenarios, the conventional statistical analysis resulted in several fold larger study sizes to achieve 80% power. For a scenario with a parallel design of one placebo group and one active dose arm, the difference between the conventional and pharmacometric approach was 4.3- and 8.4-fold, for the stroke and diabetes example, respectively. Although the model-based power depend on the model assumptions, in these scenarios, the pharmacometric model-based approach was demonstrated to permit drastic streamlining of POC trials.

CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:[10.1038/psp.2012.24](https://doi.org/10.1038/psp.2012.24); advance online publication 16 January 2013

Model based vs. traditional data analysis



General principle

We would like to:

- Use population pharmacometric models for longitudinal data (nonlinear mixed effects models)
- Avoid model building to avoid problems of potential model bias (pre-specified models, model averaging)
- Test for a drug effect using population model based approaches
- Incorporate uncertainty in both model structure and estimated model parameters in dose selection.

Averaged Model Based Analysis Result

Model Based Analysis of PhIIb study data recommends ____mg
with ____% probability of achieving an effect higher than the target effect.

Assumptions:

- Placebo Model reasonably describes the placebo effect.
- Dose Effect relationship can be described reasonably by at least one of the following models: linear, log-linear, emax, sigmoidal.

Model averaging

How we do it

Placebo Model

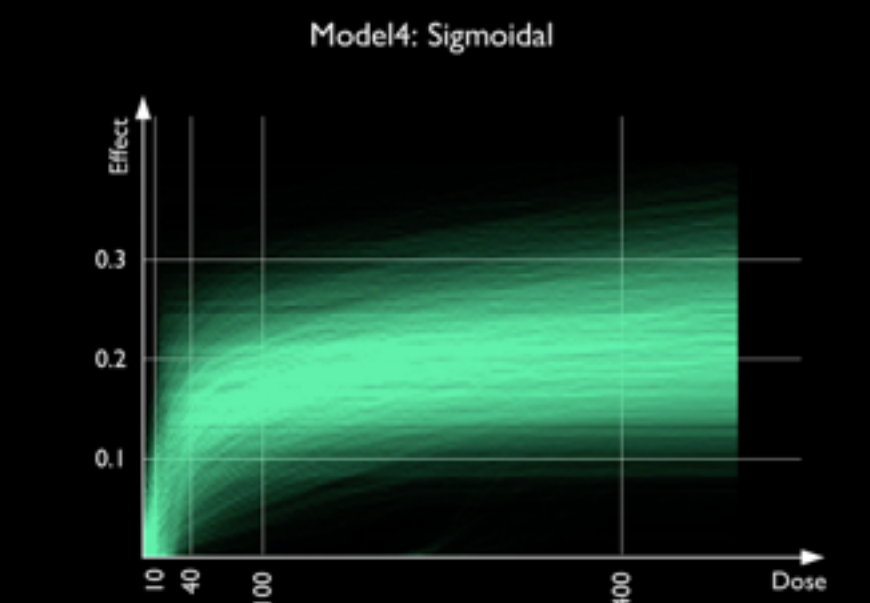
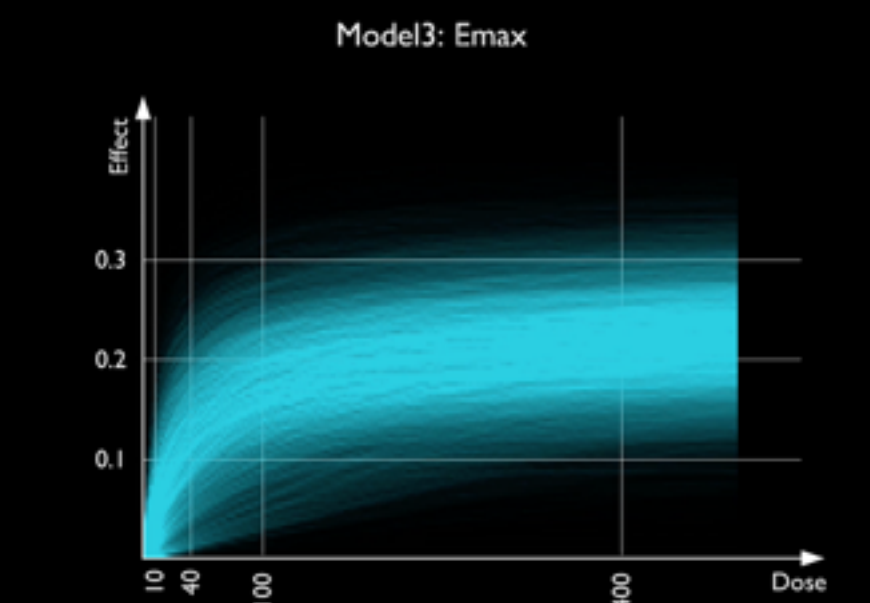
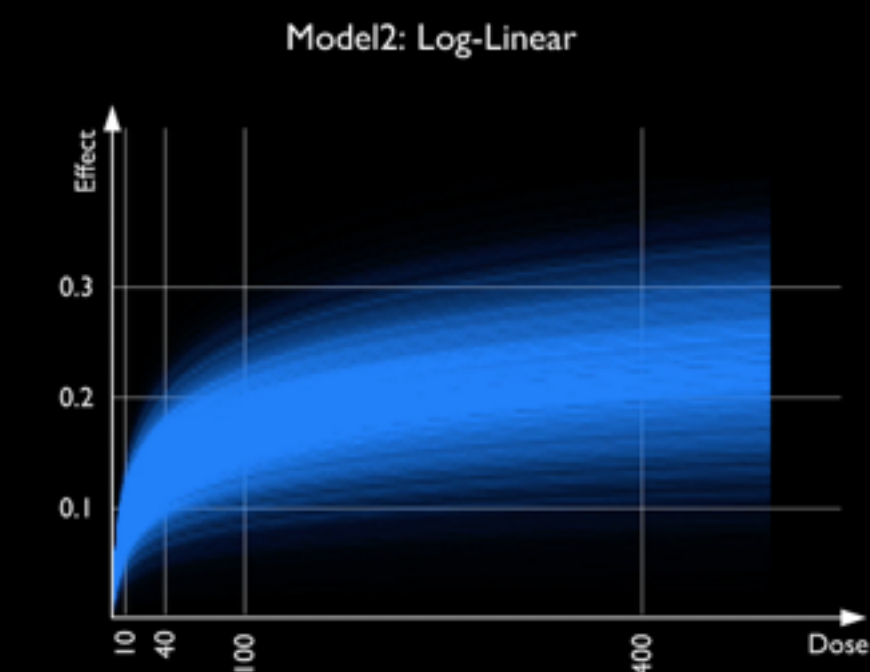
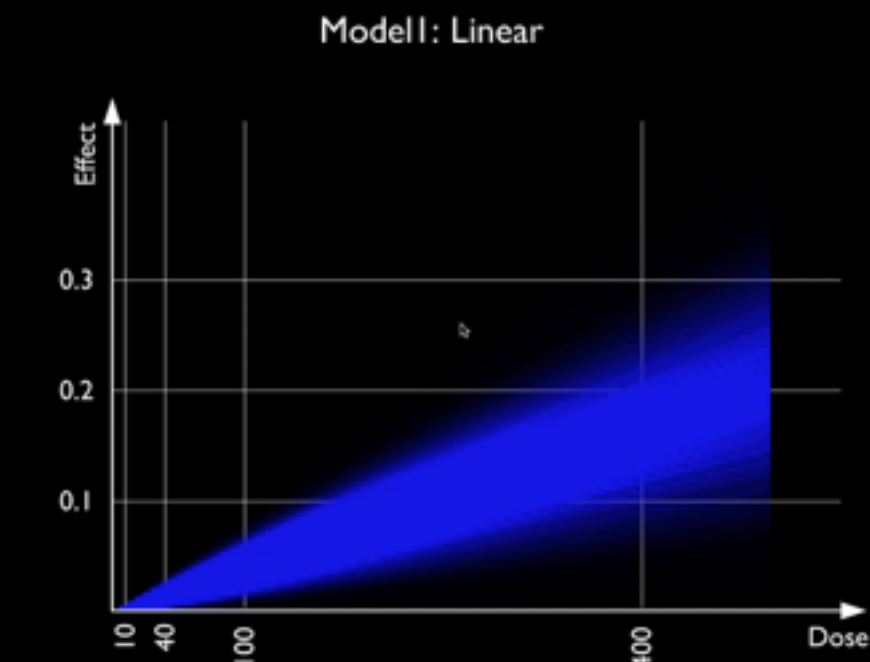
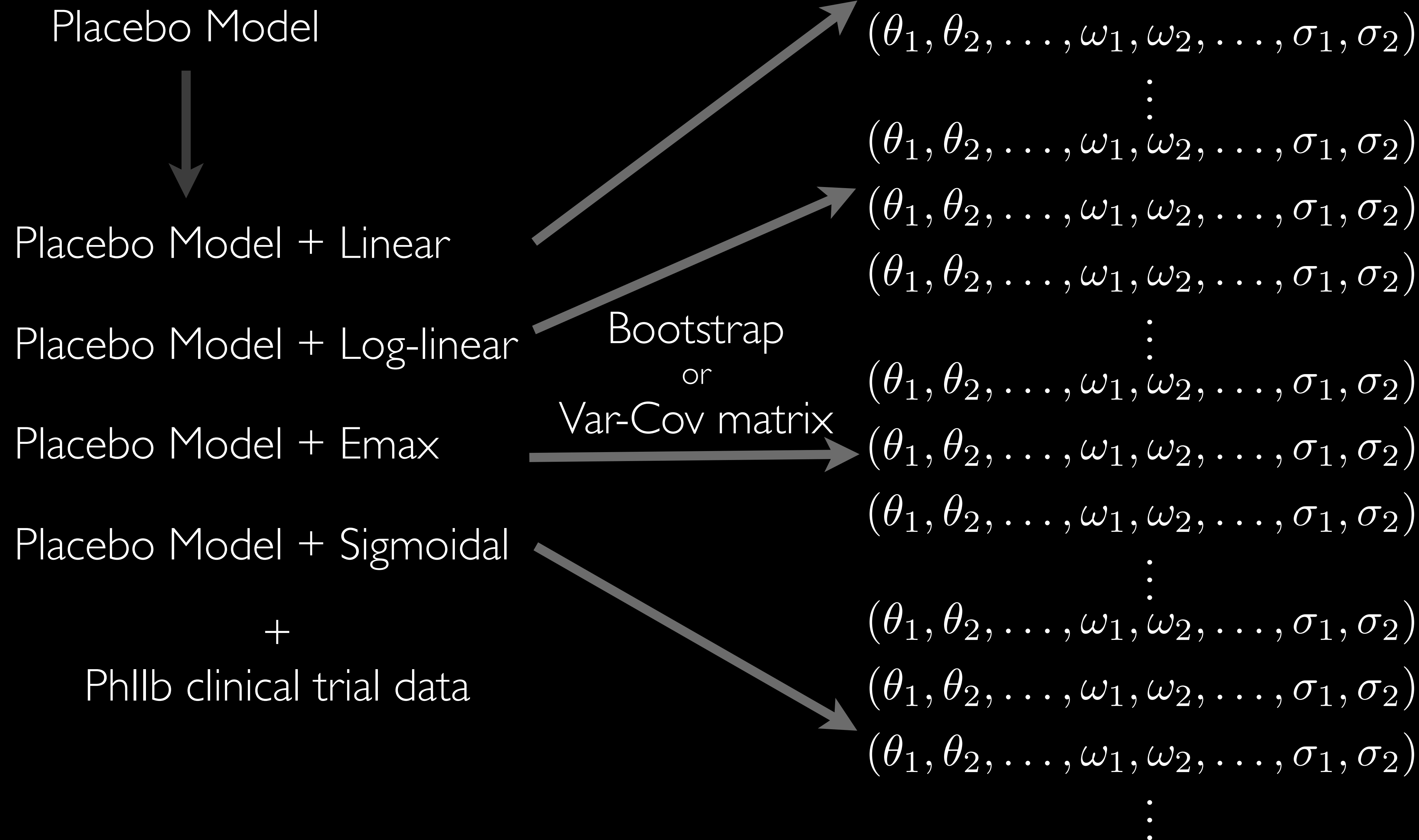


Placebo Model + D-E relationship 1

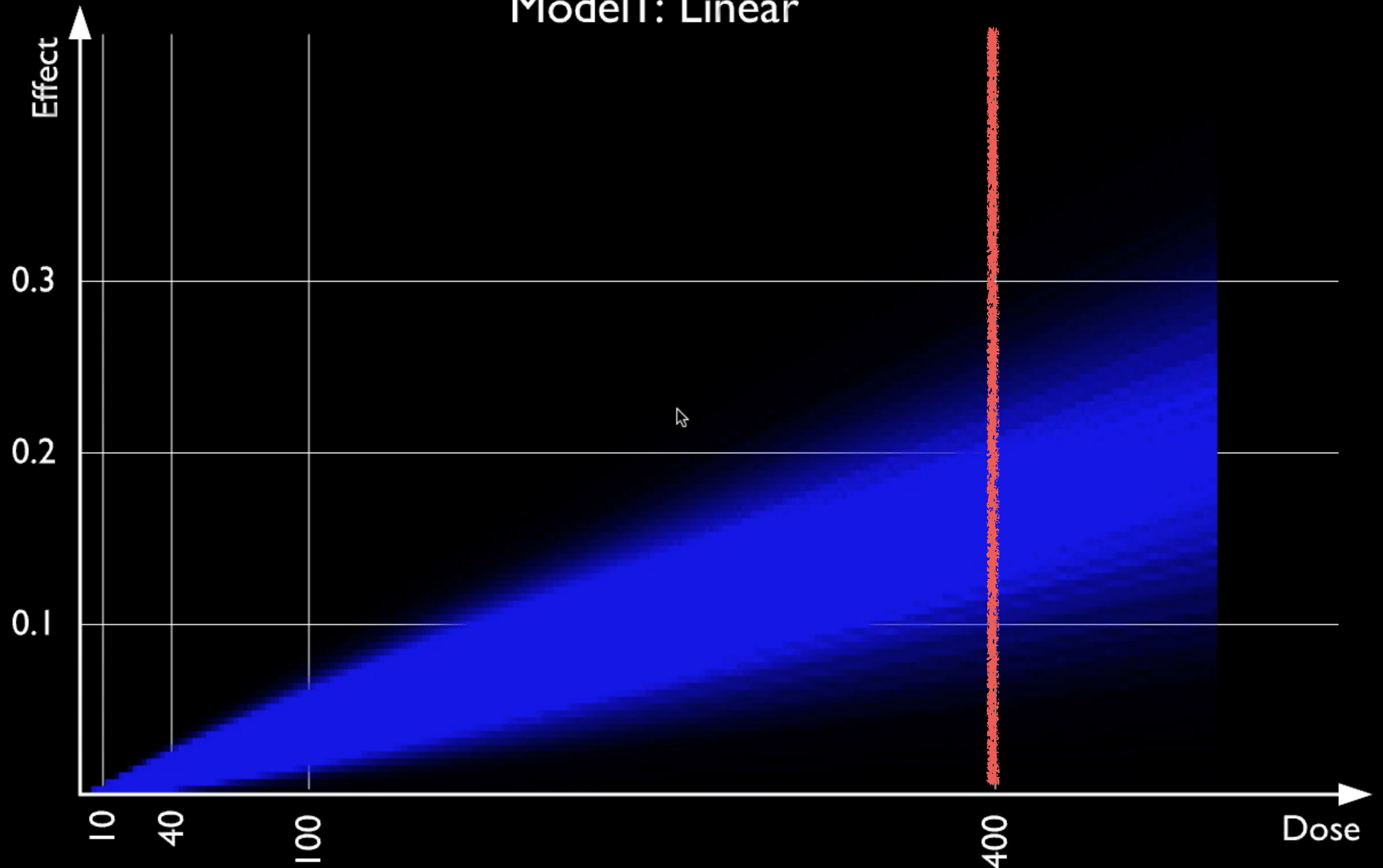
Placebo Model + D-E relationship 2

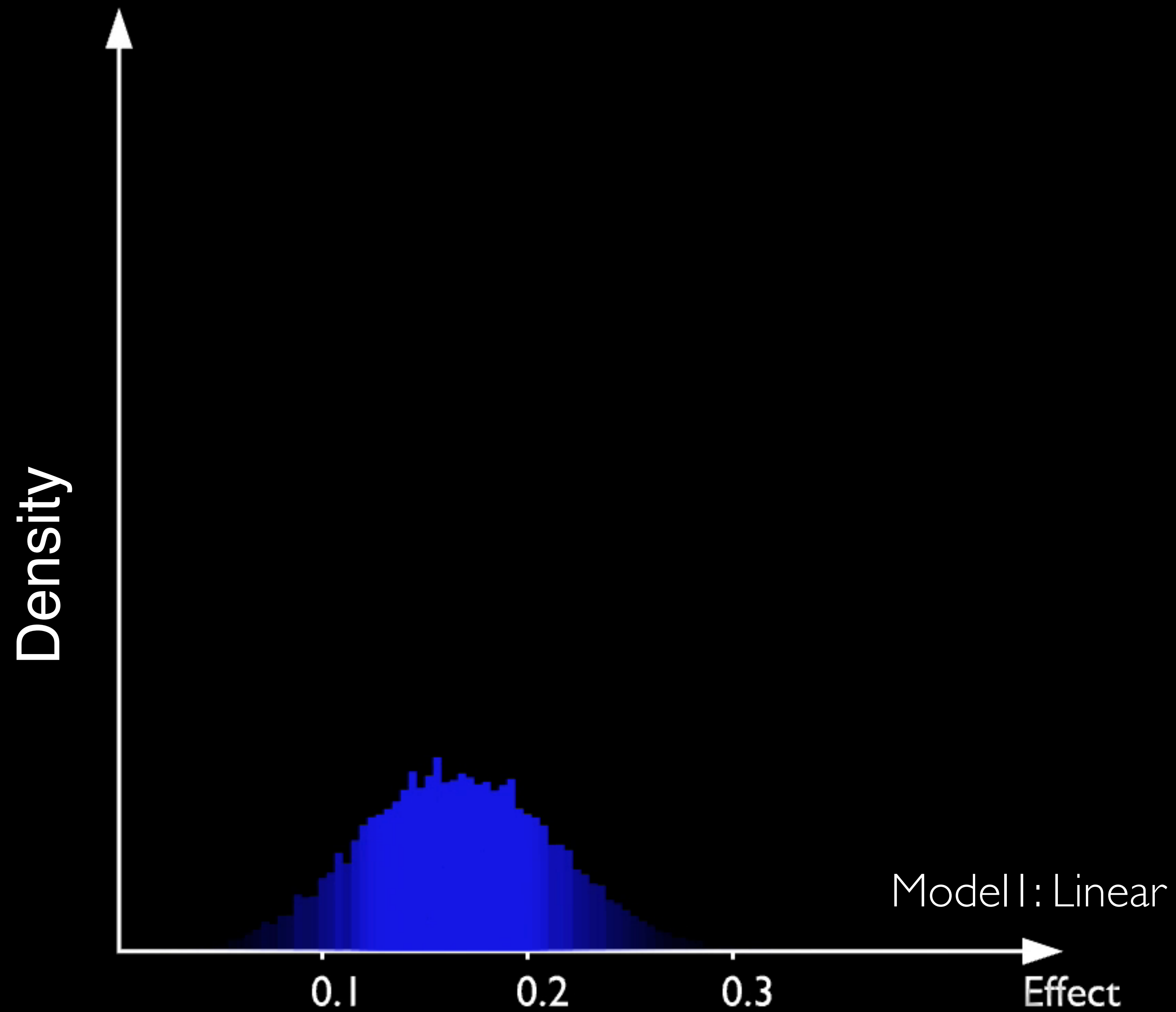
Placebo Model + D-E relationship 3

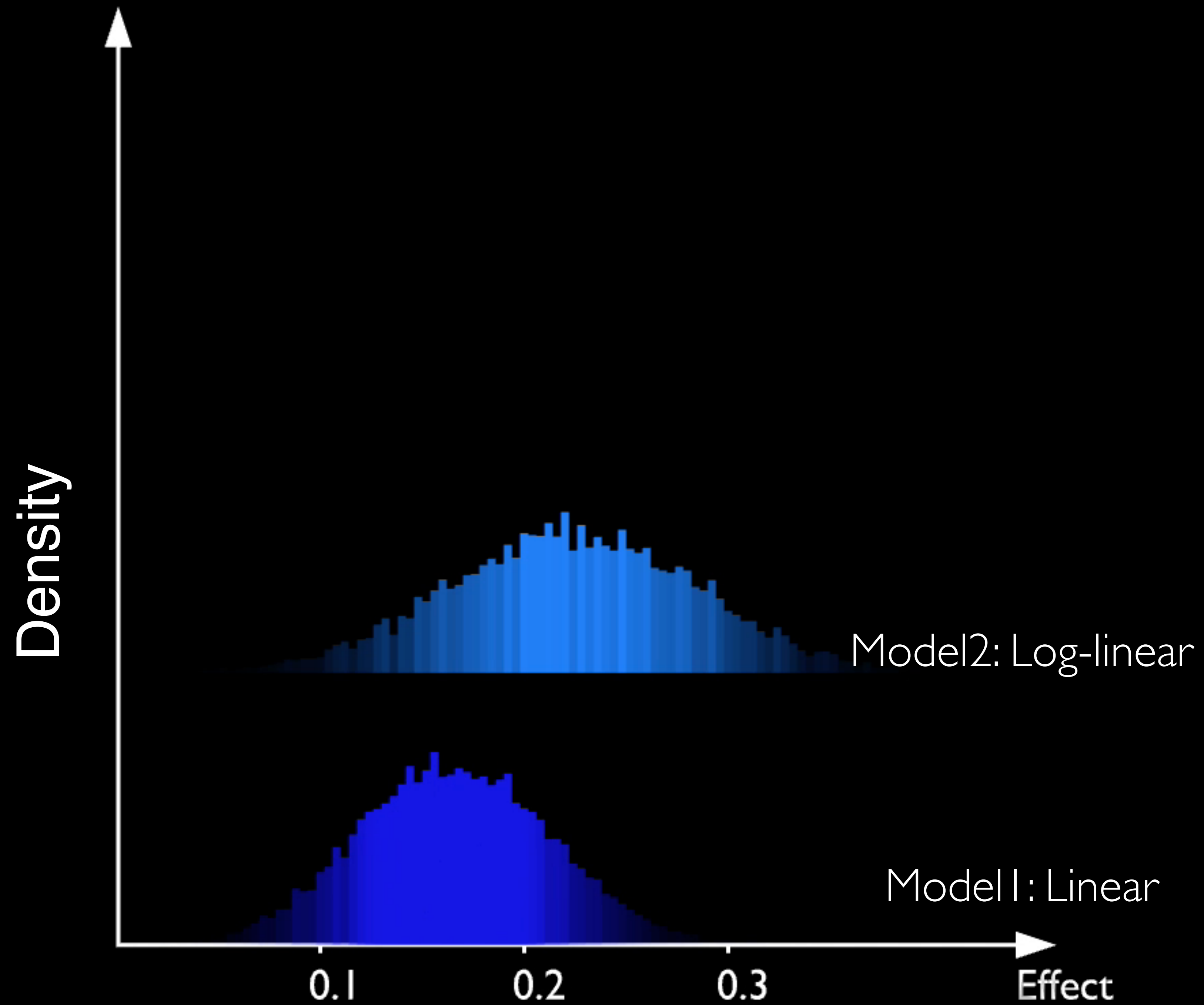
Placebo Model + D-E relationship 4

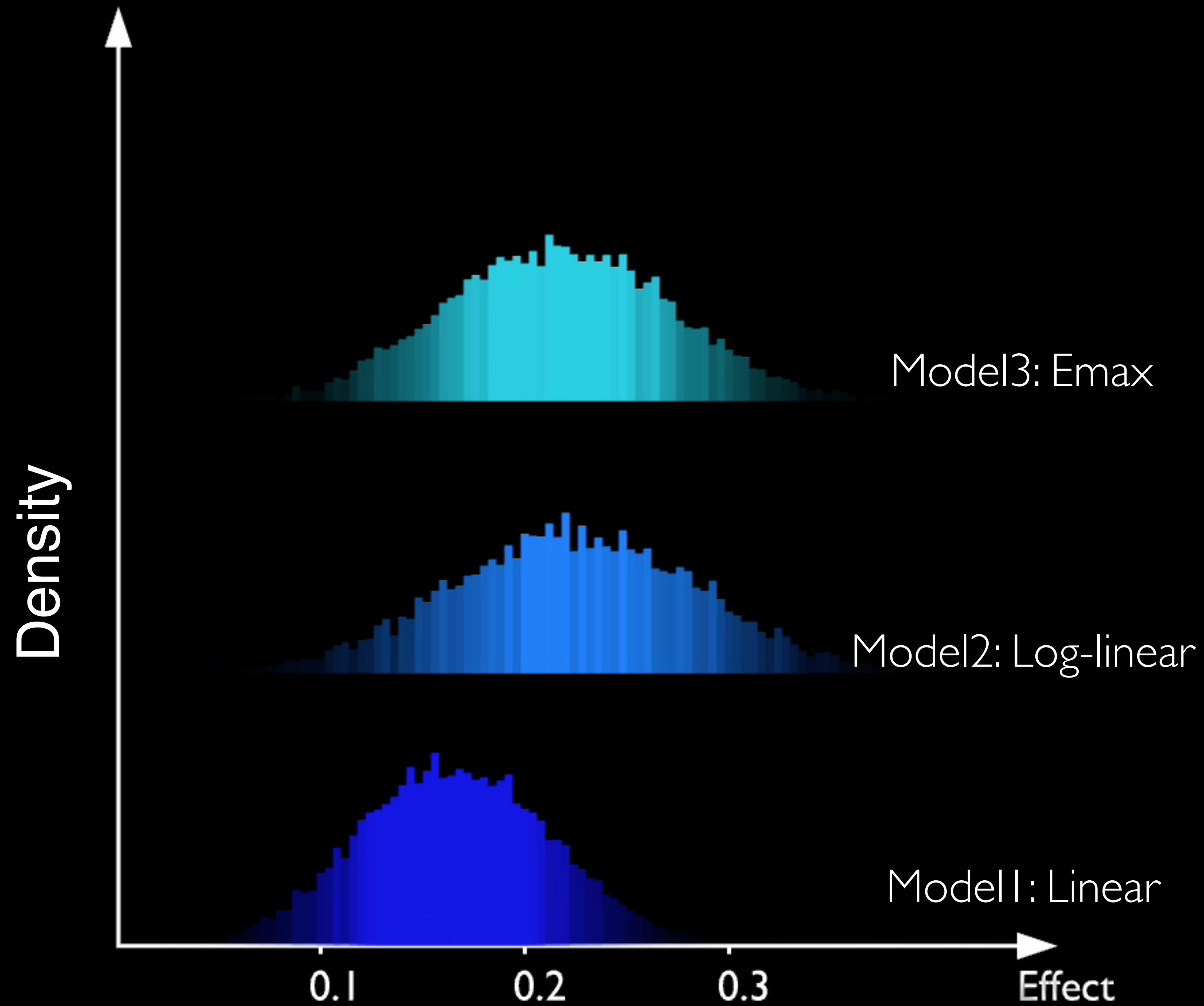


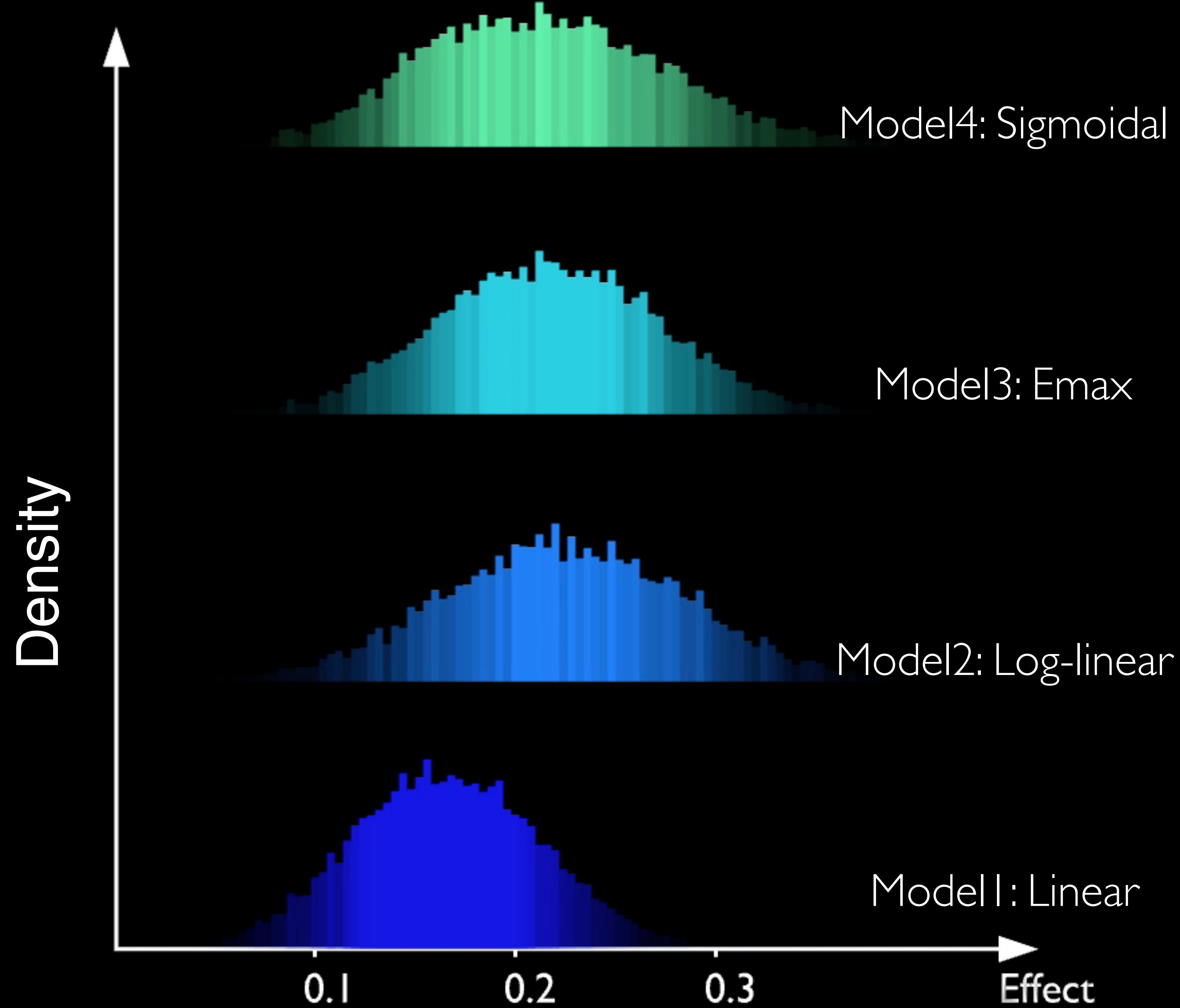
Model I: Linear

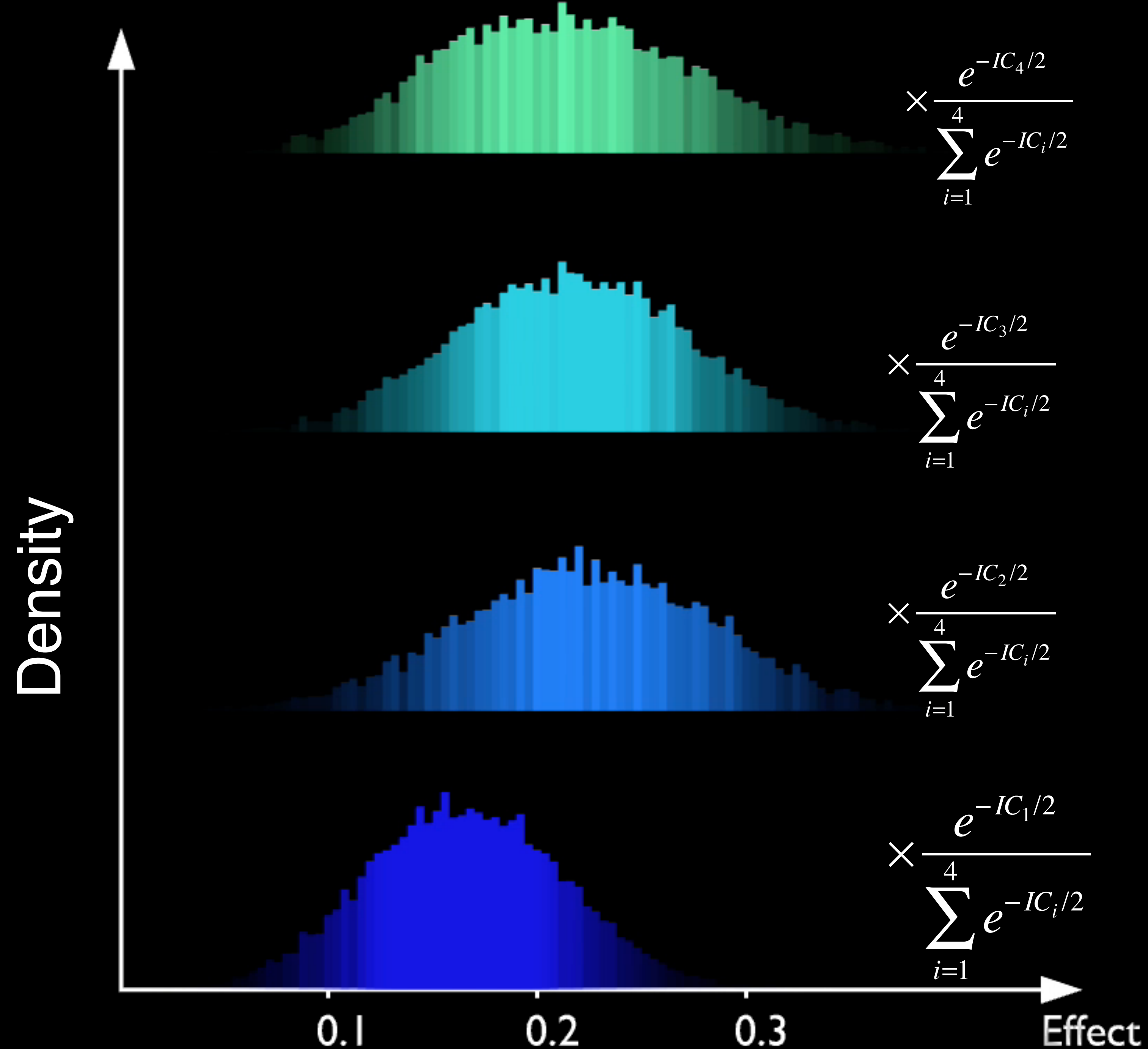




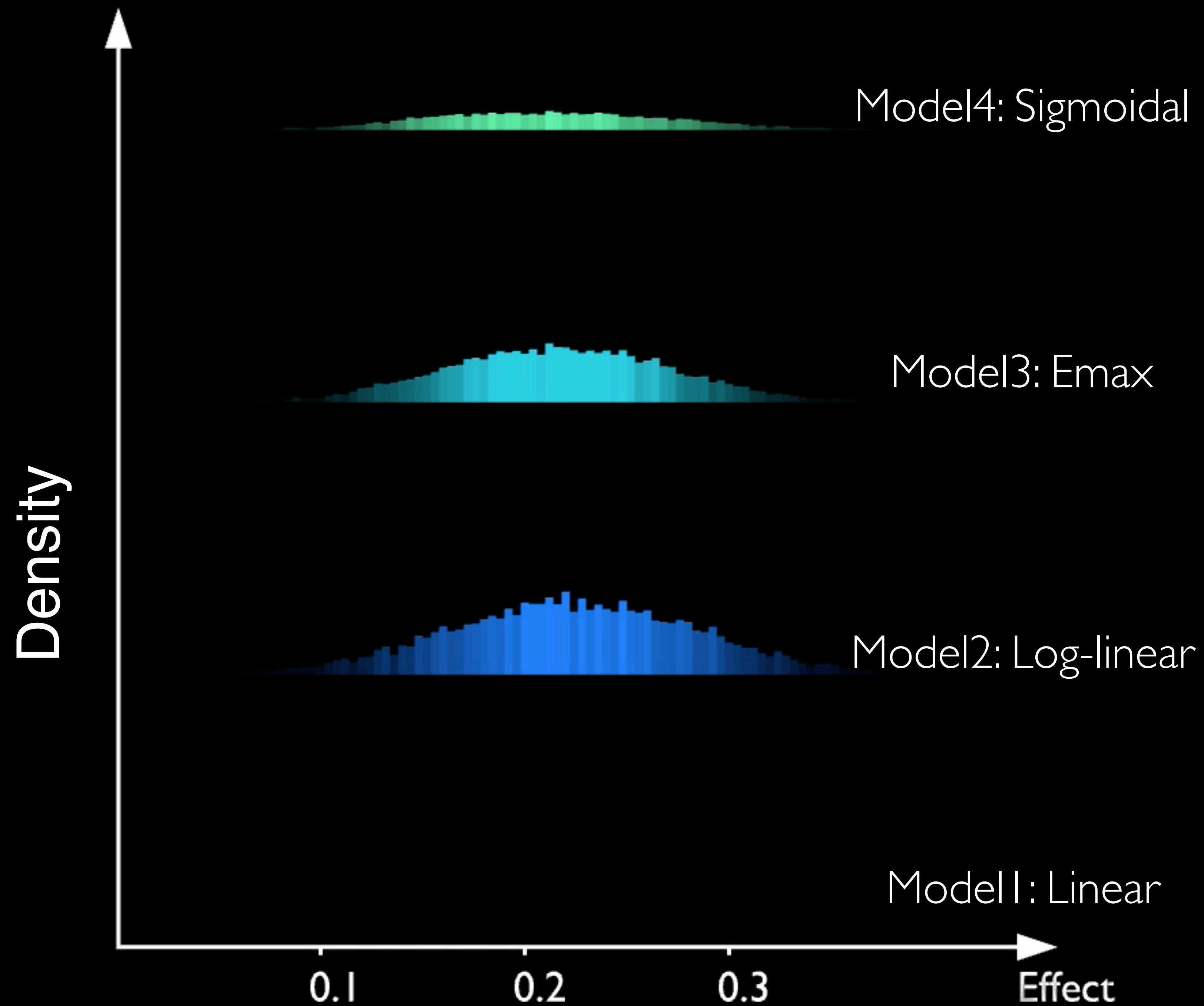


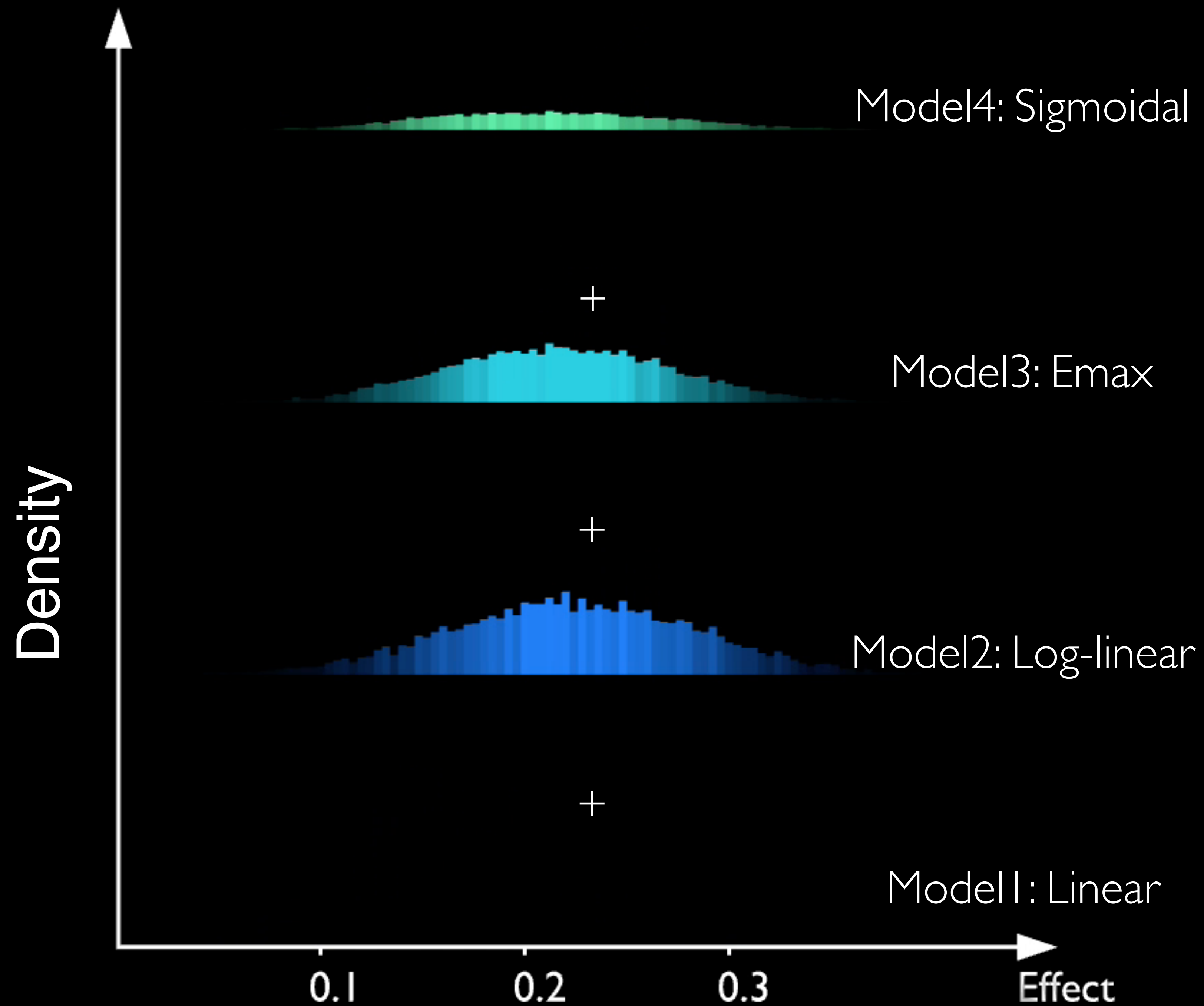


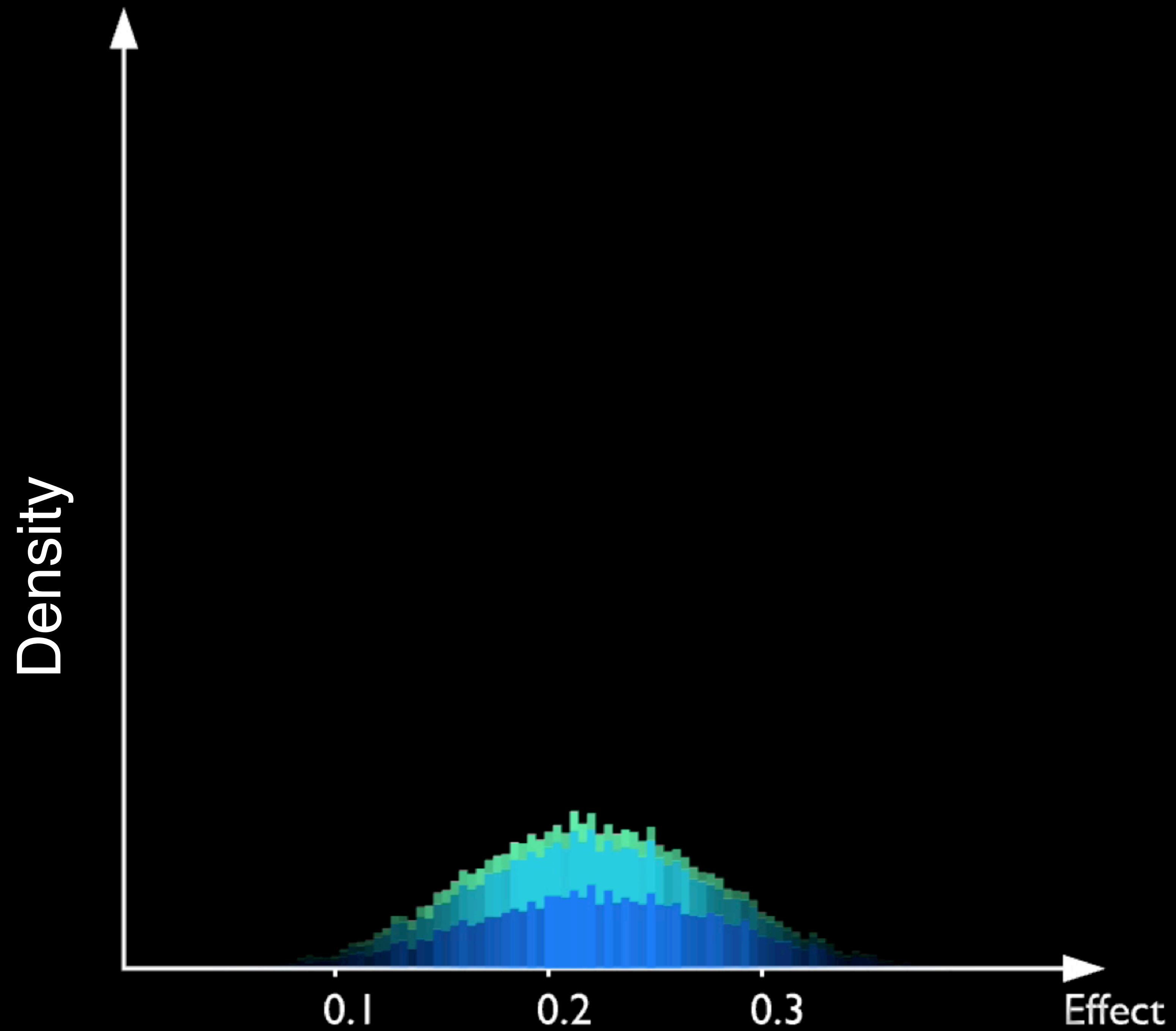


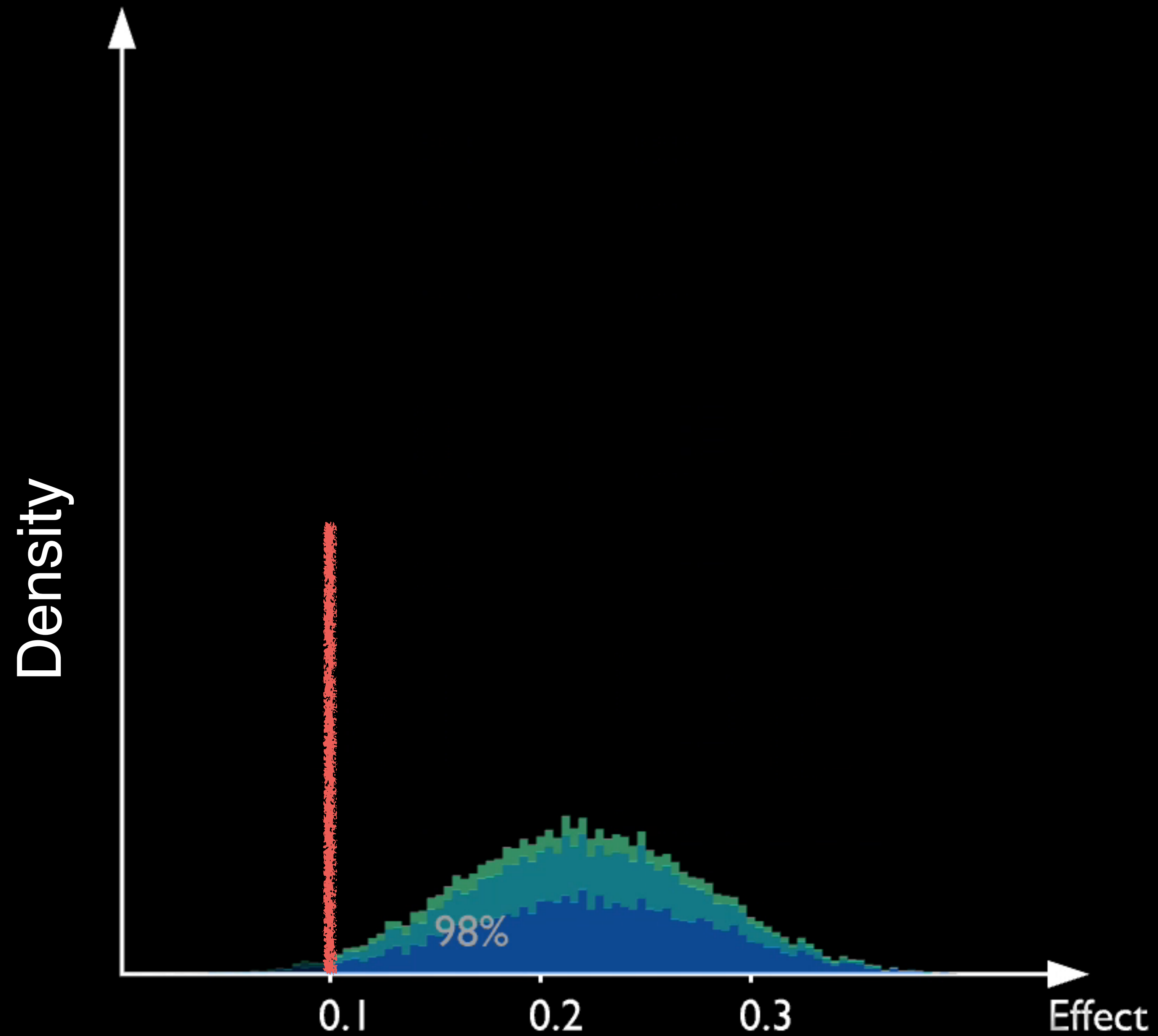


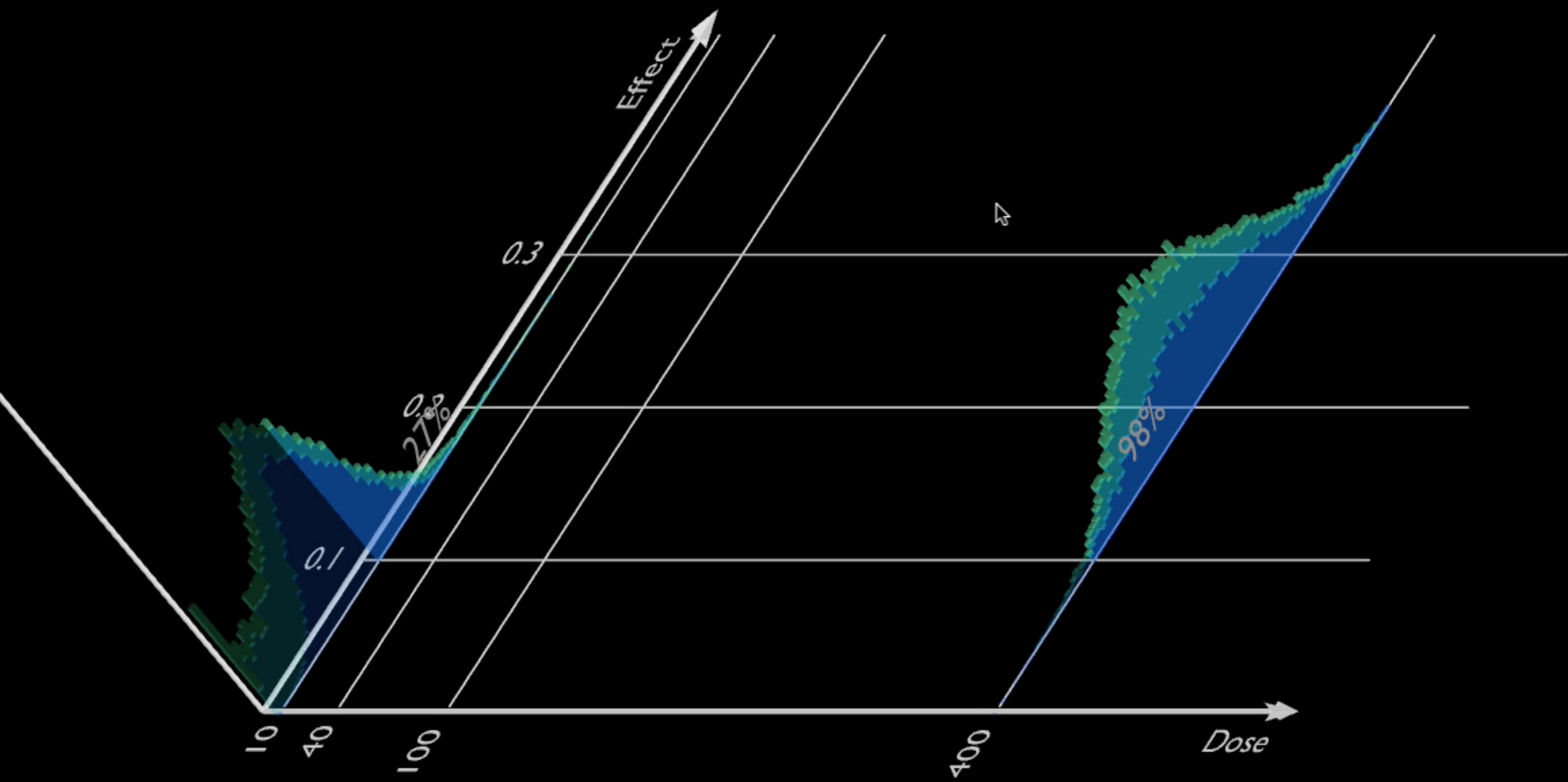
- IC can be any information criteria (in coming example we use $-2 \cdot \log(\text{likelihood})$)
- Weighting scheme proposed by Buckland et.al. 1997

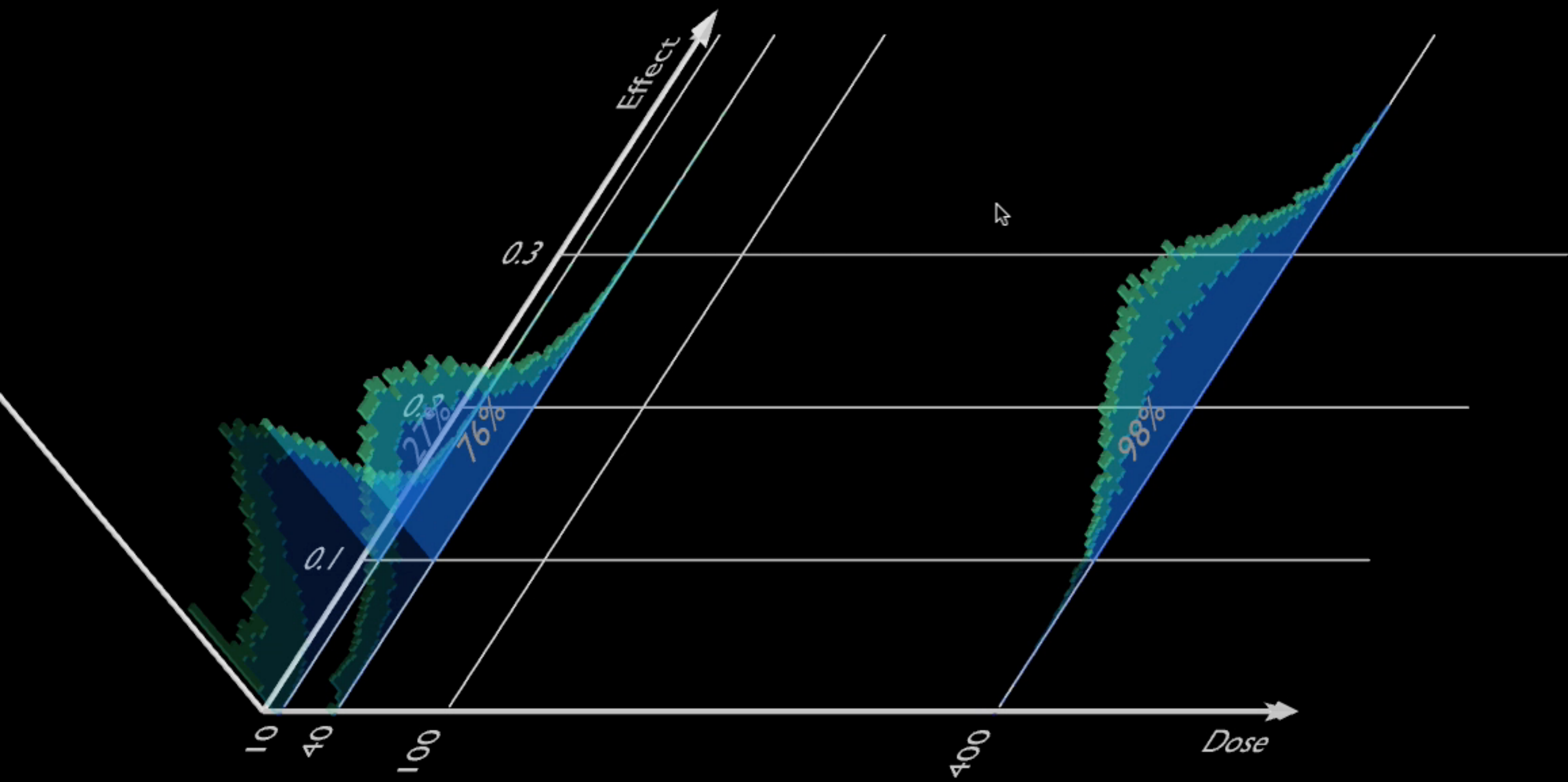


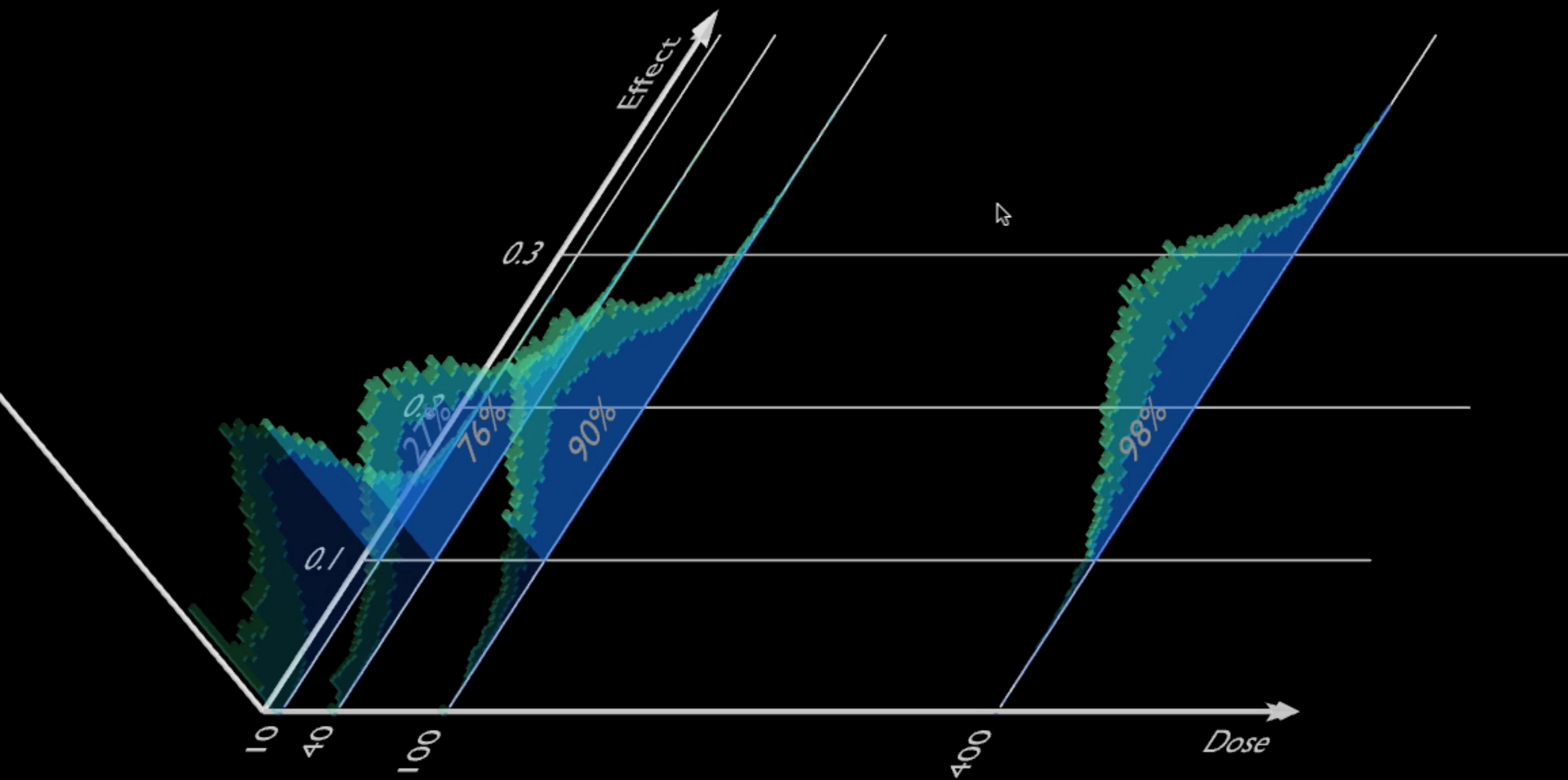




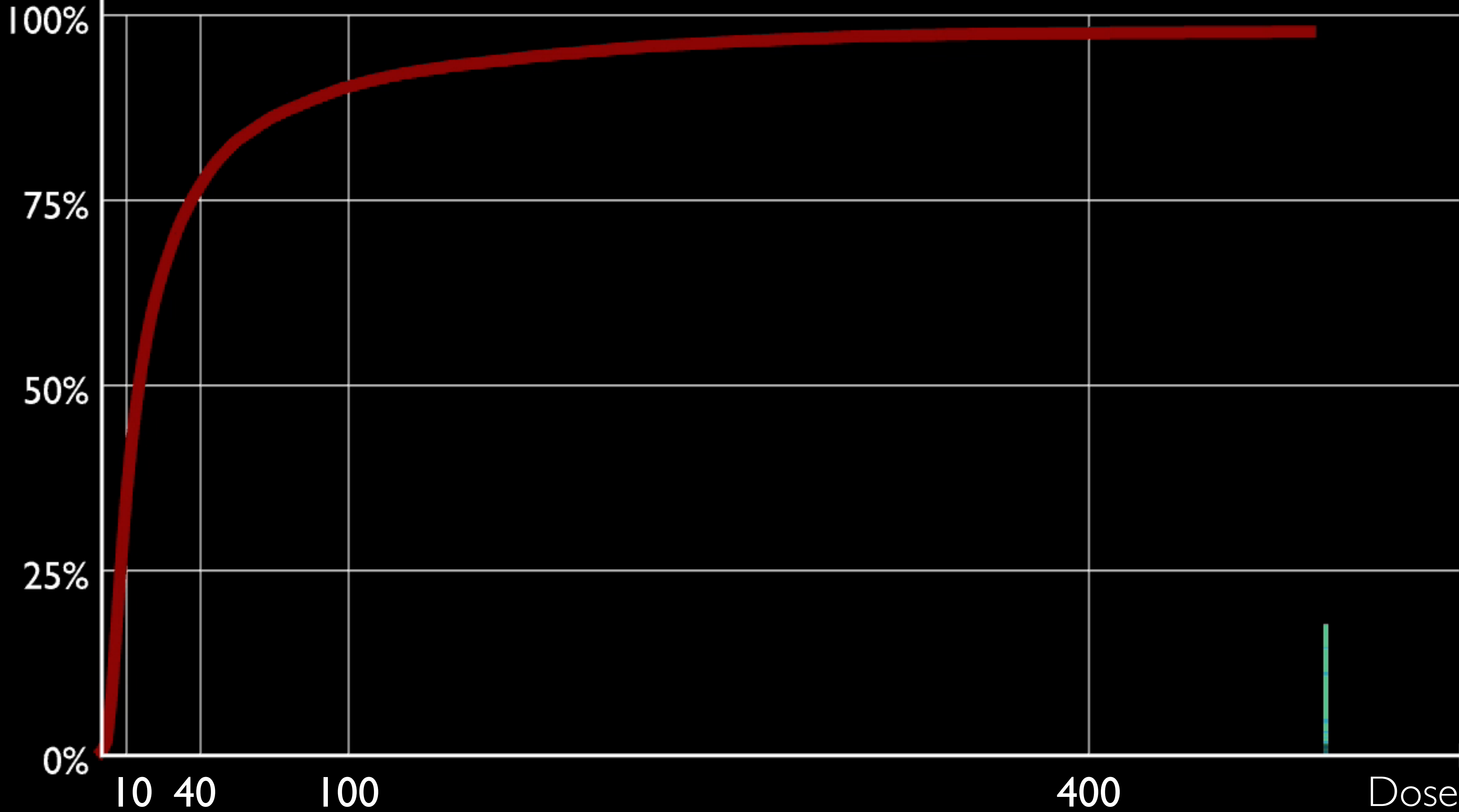




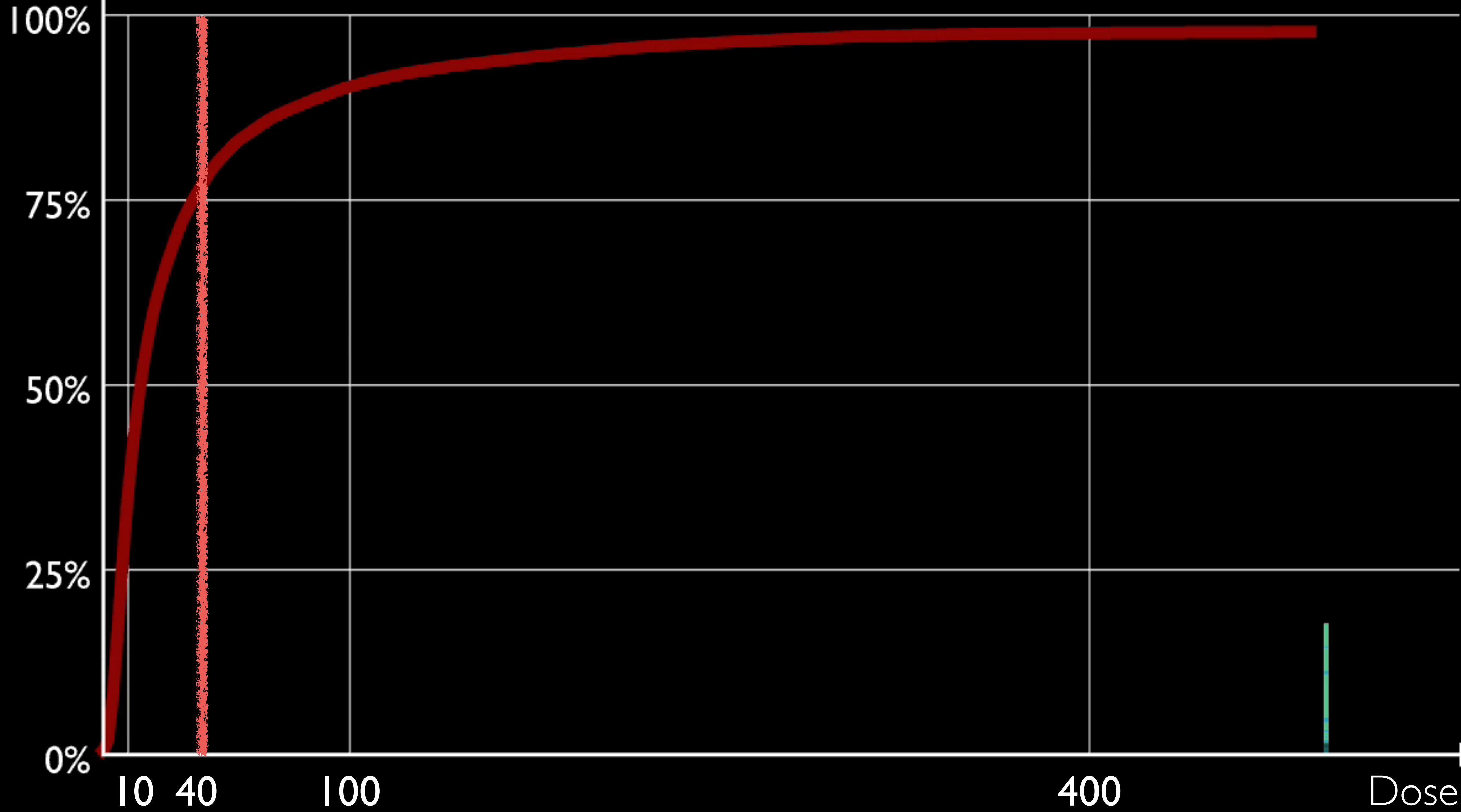




Probability of Achieving the Target Effect



Probability of Achieving the Target Effect



Averaged Model Based Analysis Result

Model Based Analysis of PhIIb study data **recommends 40mg**
with **76% probability** of achieving an effect higher than the target effect.

Assumptions:

- Placebo Model reasonably describes the placebo effect.
- Dose Effect relationship can be described reasonably by at least one of the following models: **linear**, **log-linear**, **emax**, **sigmoidal**.

Simulation Studies

based on AZD1981

AZD1981

Oral drug candidate compound for Asthma treatment.

Doses 0mg 10mg 40mg 100mg and 400mg were tested during PhIIb Study.

Target Effect : 0.1 L placebo-baseline adjusted improvement of FEV1

PhIIb study simulation data

- Step 1: Randomly choose model structure from linear, log-linear, emax, and sigmoidal.
- Step 2: Choose model parameters from reasonable ranges with appropriate constraints.
- Step 3: Add the drug effect to the placebo data.

Placebo data

ID	Time	FEV I obs
1	-1	1.96
1	0	1.77
1	1	1.99
1	2	1.83
2	-1	3.22
2	0	3.33
2	1	3.42
2	2	3.12
3	-1	1.55
3	0	1.43
3	1	1.62
3	2	1.52
3	3	1.5
3	4	1.7

Placebo data

ID	Time	FEV I obs	Simulation Dose
1	-1	1.96	400
1	0	1.77	400
1	1	1.99	400
1	2	1.83	400
2	-1	3.22	0
2	0	3.33	0
2	1	3.42	0
2	2	3.12	0
3	-1	1.55	40
3	0	1.43	40
3	1	1.62	40
3	2	1.52	40
3	3	1.5	40
3	4	1.7	40

Placebo data				
ID	Time	FEV I obs	Simulation Dose	FEV I sim dose-response
1	-1	1.96	400	FEV I obs
1	0	1.77	400	FEV I obs
1	1	1.99	400	FEV I obs+Drug Effect
1	2	1.83	400	FEV I obs+Drug Effect
2	-1	3.22	0	FEV I obs
2	0	3.33	0	FEV I obs
2	1	3.42	0	FEV I obs
2	2	3.12	0	FEV I obs
3	-1	1.55	40	FEV I obs
3	0	1.43	40	FEV I obs
3	1	1.62	40	FEV I obs+Drug Effect
3	2	1.52	40	FEV I obs+Drug Effect
3	3	1.5	40	FEV I obs+Drug Effect
3	4	1.7	40	FEV I obs+Drug Effect

Averaged Model Based Dose Selection

comparison with the traditional dose selection criterion

Traditional Dose Selection Scheme

base on study protocol of AZD1981

Choose either “go” with 10mg, 40mg, 100mg, 400mg or “stop”.

Criterion 1: p-value of pairwise ANOVA of active arm and placebo arm is less than 0.05.

Criterion 2: average of the placebo-baseline adjusted effect to be greater than 0.1 L.

Averaged Model Based Dose Selection Scheme

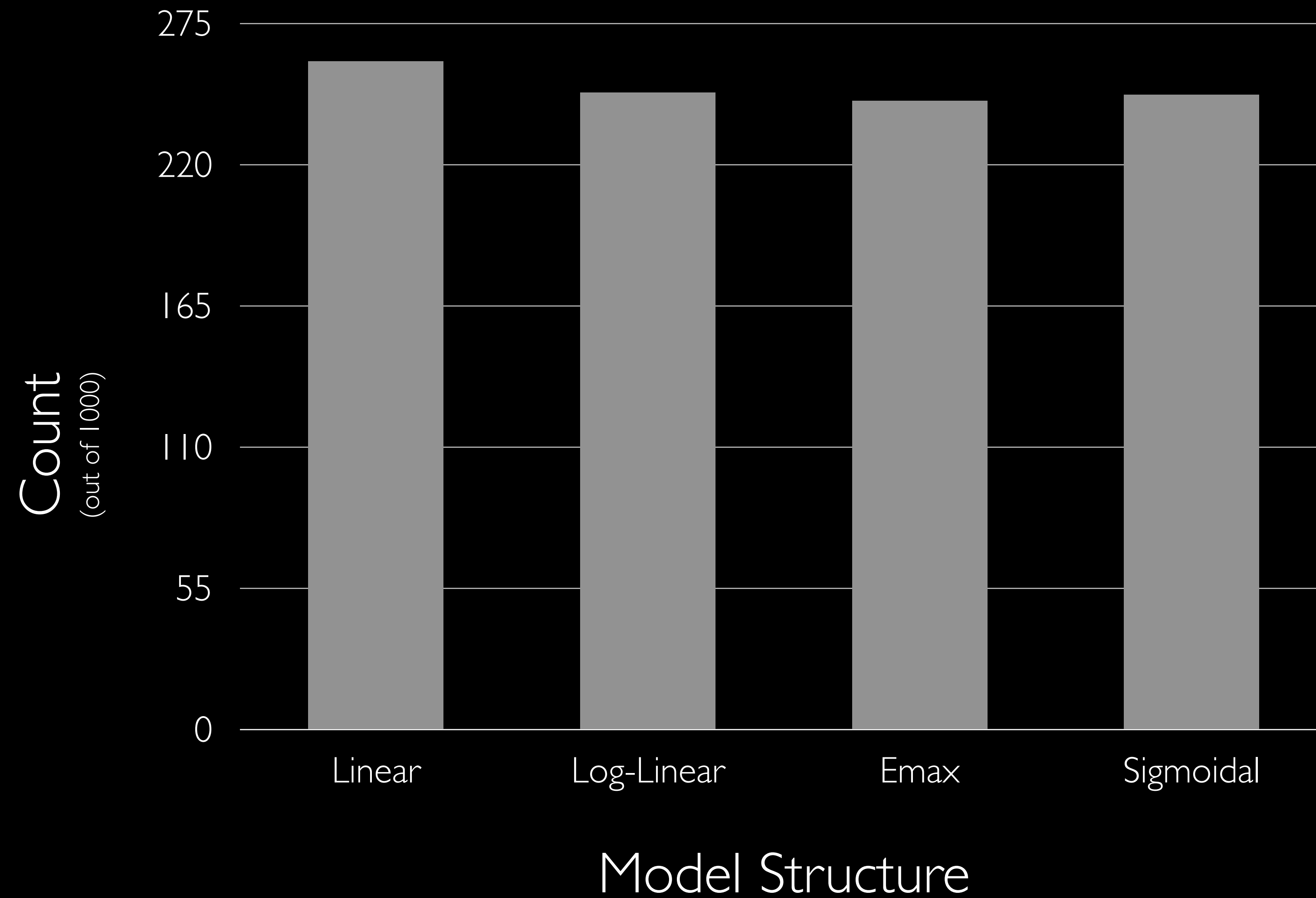
Choose either “go” with 10mg, 40mg, 100mg, 400mg or “stop”.

Criterion 1: All models have to pass the likelihood ratio test against the model without drug effect.
(if not, automatically “stop” decision).

Criterion 2: Choose the minimum dose with probability of achieving the target effect is above 50%.

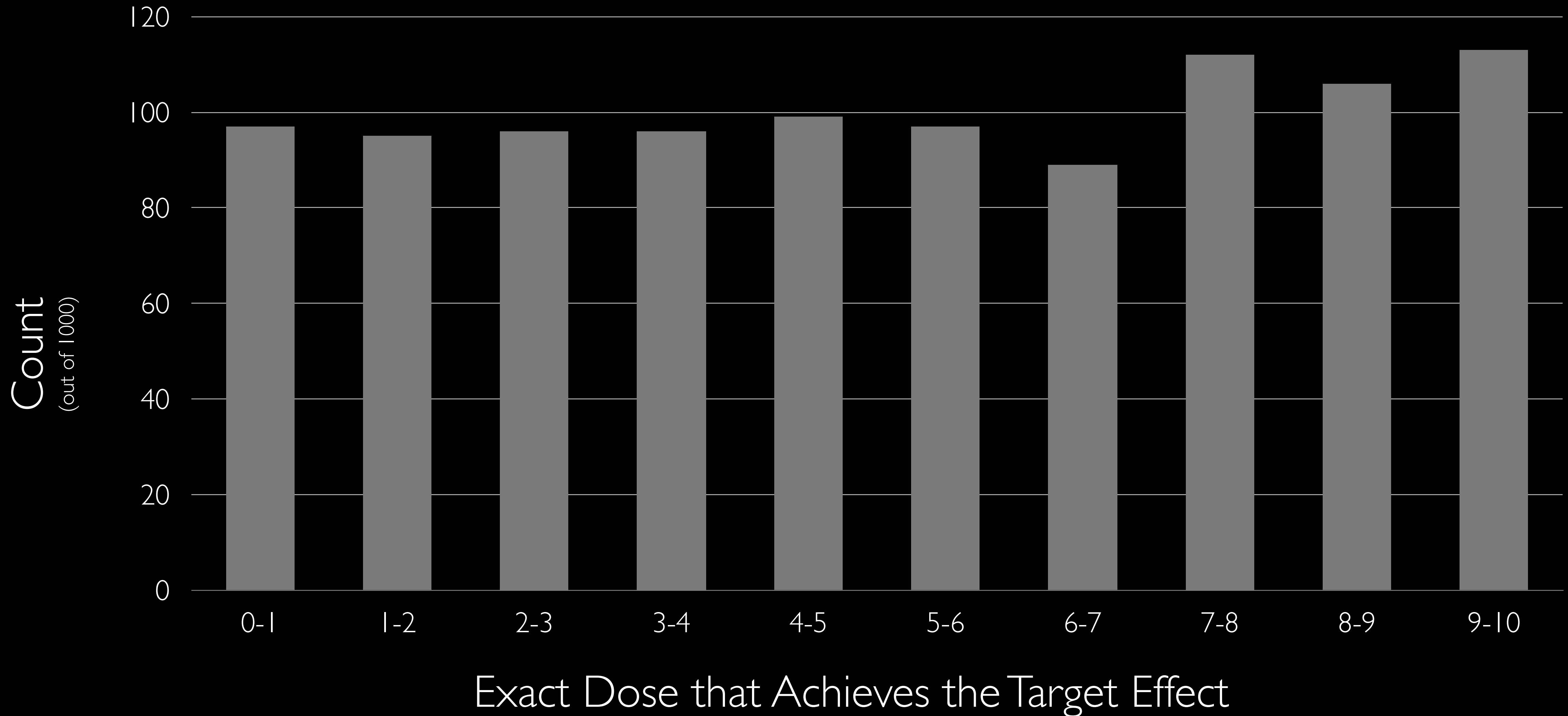
Simulation Study I

correct dose = 10mg



Simulation Study I

correct dose = 10mg



Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
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Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	582	238	60	47	73

Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	582	238	60	47	73
Averaged Model Based (with Preconditioning and Unconditional)	788	170	19	10	13

Simulation Studies 1-4

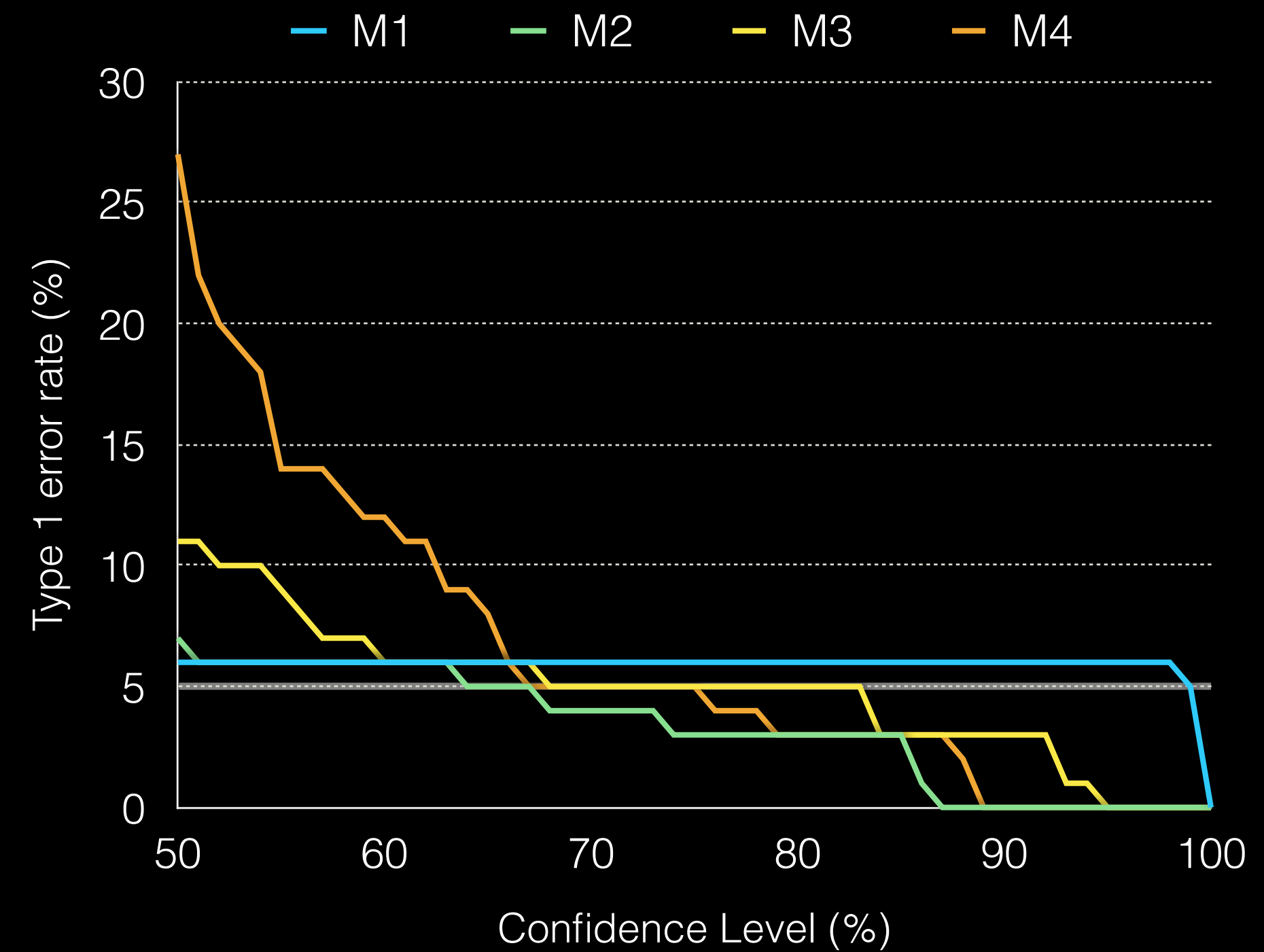
	Frequencies of making the correct dose selection	
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based
Simulation Study 1 correct dose = 10mg	35% improvement	
Simulation Study 2 correct dose = 40mg	64% improvement	
Simulation Study 3 correct dose = 100mg	38% improvement	
Simulation Study 4 correct dose = 400mg	29% improvement	

Simulation Studies 1-4

	Frequencies of making the correct dose selection	
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based
Simulation Study 1 correct dose = 10mg	41% improvement	
Simulation Study 2 correct dose = 40mg		
Simulation Study 3 correct dose = 100mg		
Simulation Study 4 correct dose = 400mg		

Type-I error rates

	Frequencies of making the correct dose selection	
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based
Simulation Study 6 correct decision = “stop”	98%	95%



Modifications

- Selection criteria for test of drug effect
- how to get uncertainty in model predictions of drug effect
- weighting principles

•Software available on the Apple App Store for Mac

•Future versions also available in PsN / xpose

Featured

Top Charts

Categories

Purchases

Updates

model
AVERAGE

Open

modelAverage 4+

Graphical user interface based model averaging framework for nonlinear mixed effect models. Recommended to be used together with NONMEM and PsN.

What's New in Version 0.1.1

Some improvements for the expression parser.
Can copy graphs and paste it as .csv file so that the calculated value can easily be used outside of this software.

Yasunori Aoki Web Site

modelAverage Support

Information

Category: Productivity
Updated: 24 September 2014
Version: 0.1.1
Price: Free
Size: 19.4 MB
Family Sharing: Yes
Developer: Yasunori Aoki
© Yasunori Aoki and Andrew C. Hooker

Rated 4+
Compatibility:
OS X 10.6.6 or later, 64-bit processor

More Apps by Yasunori Aoki

PopED lite

PopED lite
Productivity

/Users/yaoki/Documents/modelAverage_Handson

-1: Import PsN Bootstrap Raw Results Files

0: View Bootstrap Results

1: Define Endpoint

2: Define Weight and Selection Criterion

3: Probability of Achieving the Target Value

4: Dose Selection

5: Compare with Truth (For simulation studies)

Calculating probability of success using bootstrap samples 0-100.

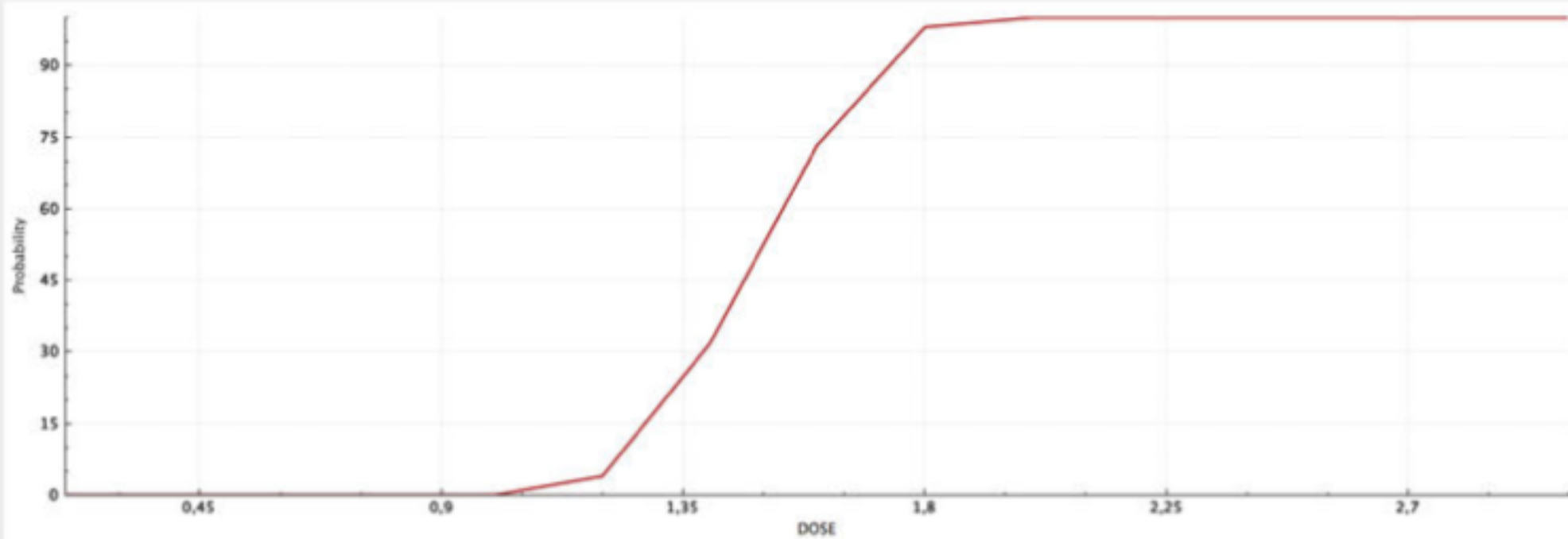
Abort Calculation

Model Selection

using using one ofv per model

Probability of (-inf < EndPoint < -2)

reCalculate





Customer Ratings

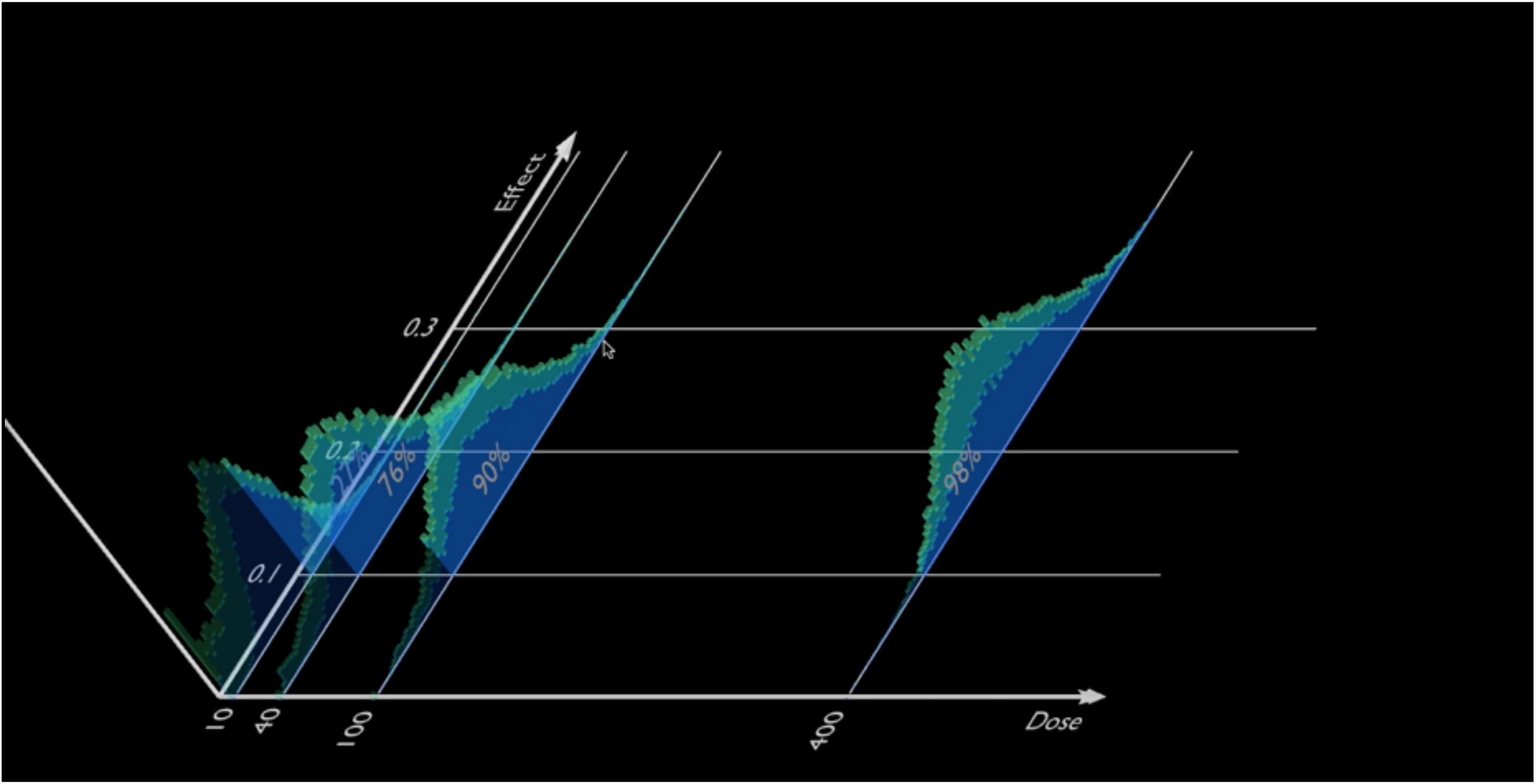
We have not received enough ratings to display an average for the current version of this application.

Rate this application: ★★★★★

Customer Reviews

Comparison to MCP-MOD

- Testing for drug effect
 - Using the likelihood ratio test for each model, instead of contrast tests
 - Allows for incorporation of covariate adjusted dosing and dose-concentration-effect modelling.
- Model averaging takes into account uncertainty in models and parameter estimates and uses predicted drug effect as the parameter of interest



Averaged Model Based Analysis Result

Model Based Analysis of PhIIb study data recommends ____mg
with ____% probability of achieving an effect higher than the target effect.

Assumptions:

- Placebo Model reasonably describes the placebo effect.
- Dose Effect relationship can be described reasonably by at least one of the following models: linear, log-linear, emax, sigmoidal.

Conclusion

	Frequencies of making the correct dose selection	
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based
Simulation Study 1 correct dose = 10mg	41% improvement	
Simulation Study 2 correct dose = 40mg		
Simulation Study 3 correct dose = 100mg		
Simulation Study 4 correct dose = 400mg		

Backup Slides

Research sponsored by
AstraZeneca R&D Mölndal Sweden

Special thanks to
Uppsala University Pharmacometrics Group

Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	582	238	60	47	73
Averaged Model Based*	543 (70%)	173 (21%)	31 (4%)	18 (2%)	26 (3%)

*The covariance steps failed for all four models on 219 simulations.

Preconditioning

a numerical linear algebra “trick” to reduce the rounding error

Original

34% of \$cov failed

with Unconditional

8.3% of \$cov failed

with Preconditioning
and
Unconditional

0.04% of \$cov failed

Numerical experiments were conducted using NONMEM7.2 with gcc4.2.1 compiler on MacOSX.

Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	582	238	60	47	73
Averaged Model Based	543	173	31	18	26

Simulation Studies 1-4

Simulation Study I

correct dose = 10mg

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	582	238	60	47	73
AMB with Preconditioning and Unconditional	788	170	19	10	13

Simulation Study 2

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	132	361	244	145	118
AMB with Preconditioning and Unconditional	155	592	137	80	36

Simulation Study 3

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	41	120	312	325	202
AMB with Preconditioning and Unconditional	29	238		228	73

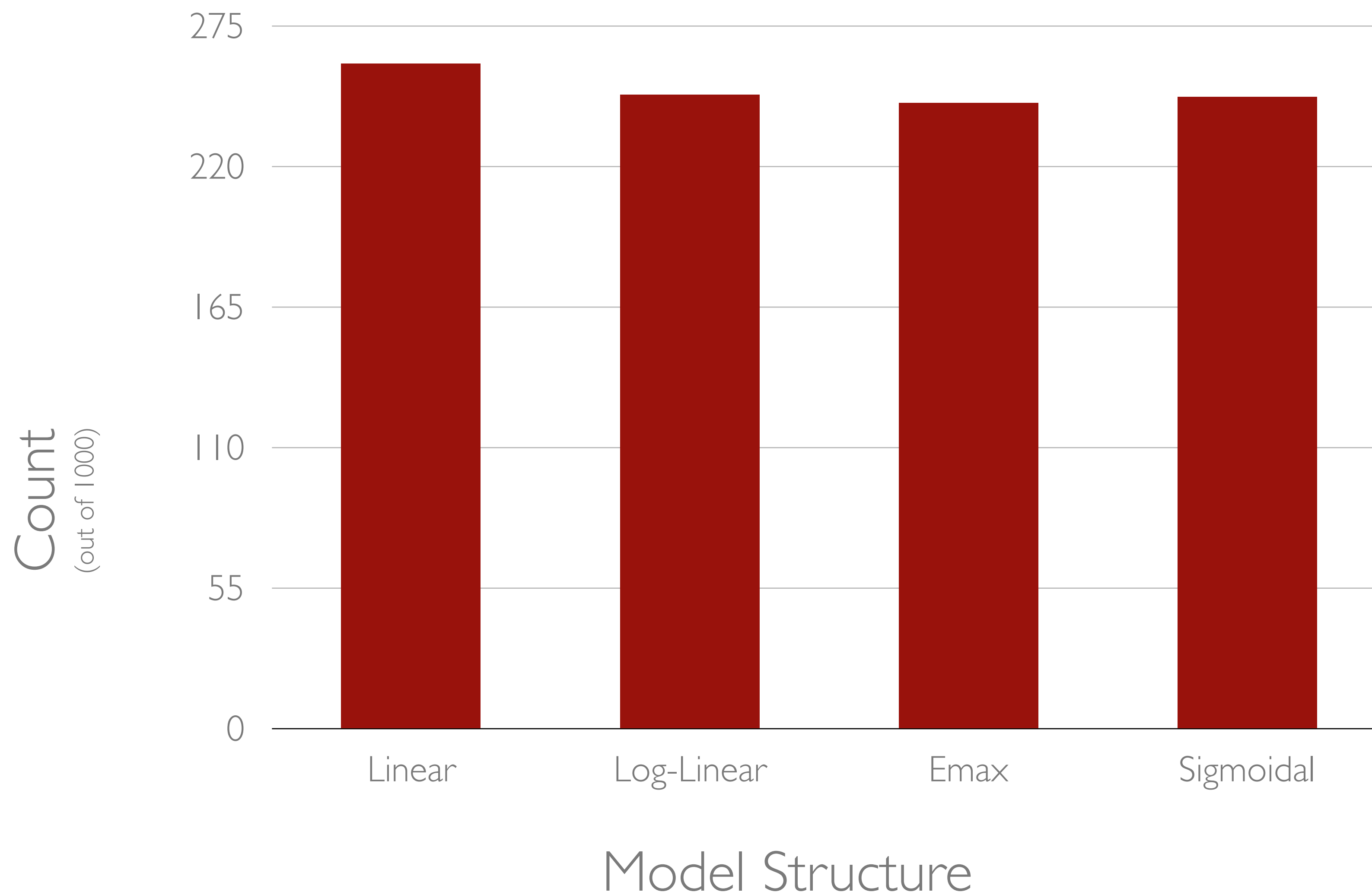
Simulation Study 4

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	18	31	84	402	465
AMB with Preconditioning and Unconditional	9	94	136	519	242

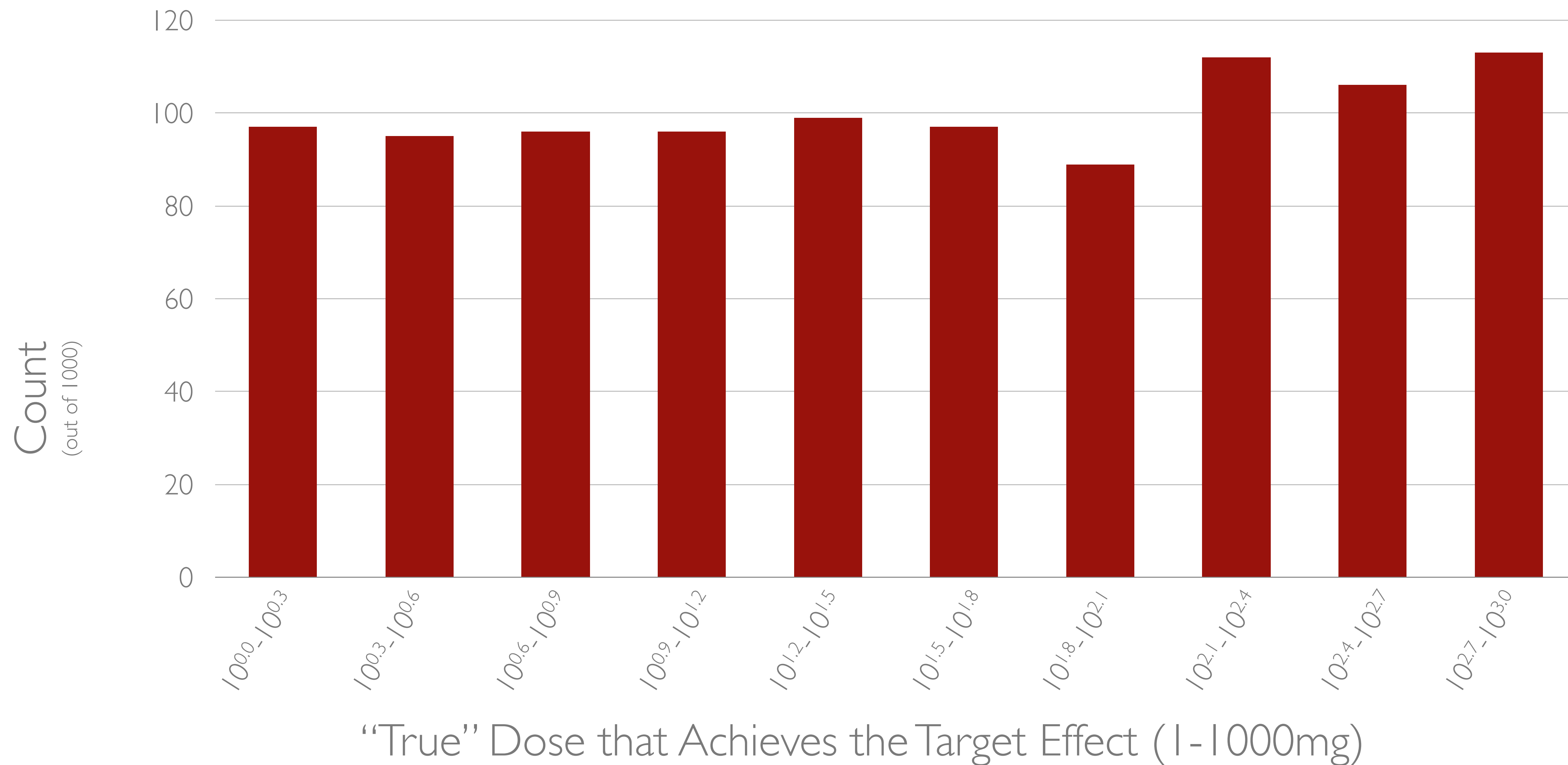
Simulation Study 0

verification of the estimated probability of achieving the target effect

Simulation Study 0



Simulation Study 0



- 0: Preferences
- 1: Manage Simulation Data Set
- 2: Design the Experiment/Clinical Trial
- 3: Simulate Data
- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

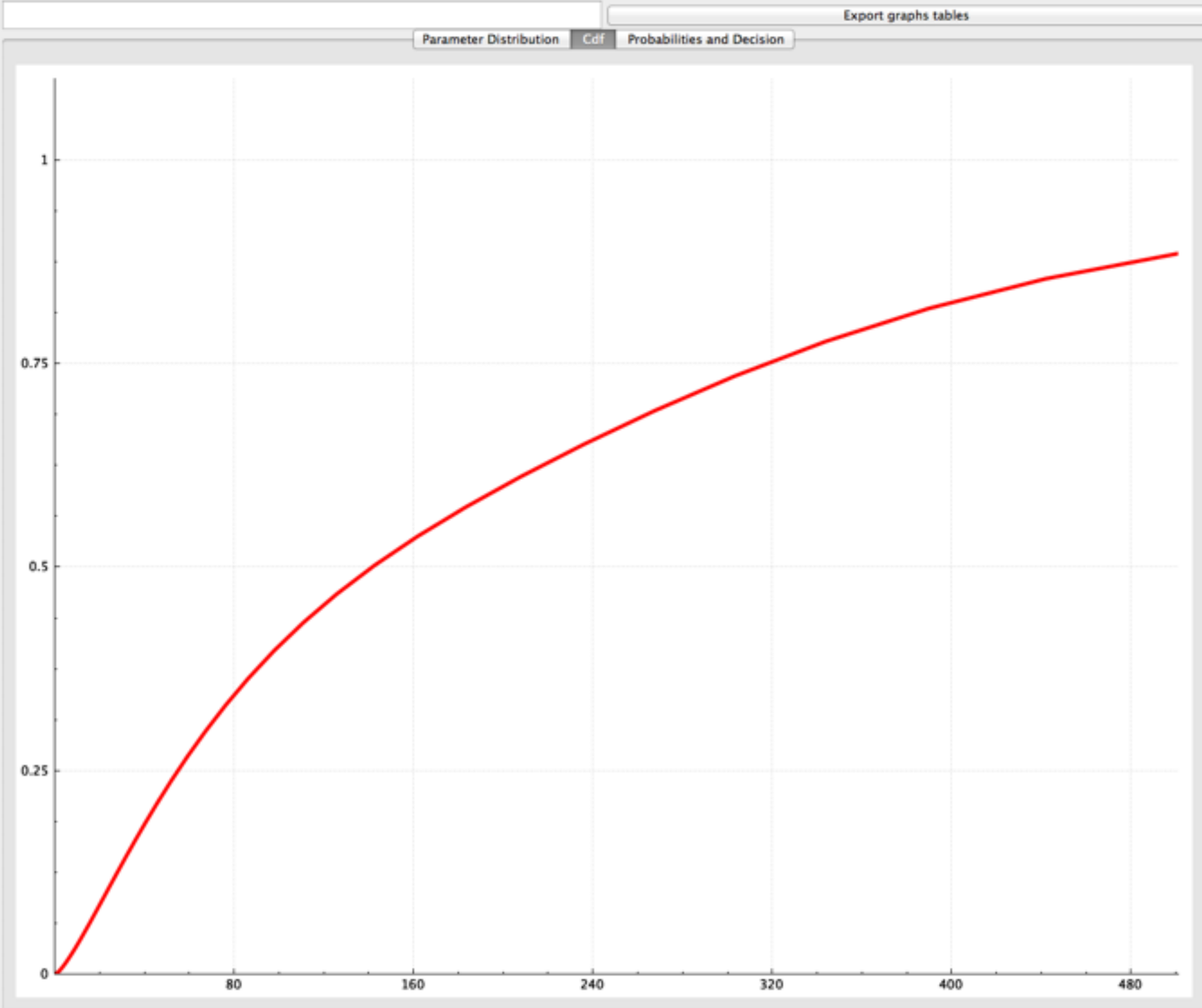
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
Simulation 1	-2364.73	-2380.24	-2381.12	-2382.22	-2380.82
Simulation 2	-2319.93	-2360.35	-2397.42	-2394.76	-2398.75
Simulation 3	-1995.79	-2184.67	-2371.49	-2363.7	-2374.1
Simulation 4	-2342.61	-2394.85	-2381.29	-2394.12	-2392.34
Simulation 5	-2380.3	-2380.4	-2384.04	-2382.56	-2383.66
Simulation 6	-2365.97	-2381.33	-2387.36	-2382.43	-2384.49
Simulation 7	-2266.27	-2388.18	-2341.5	-2386.18	-2384.22
Simulation 8	-2367.39	-2376.99	-2387.6	-2385.67	-2384.05
Simulation 9	-2388.5	-2387.25	-2388.77	-2387.52	-2385.54
Simulation 10	4114.89	-2194.57	3336.75	3842.67	
Simulation 11	-2391.64	-2389.99	-2390.47	-2388.05	-2386.44
Simulation 12	-2361.58	-2392.34	-2378.54	-2390.34	-2390.84
Simulation 13	-2354.72	-2383	-2378.53	-2386.04	-2386.03
Simulation 14	6336.36	-2213.7	5496.19	646.08	6020.75
Simulation 15	-2376.48	-2376.12	-2381.12	-2383.52	-2381.79
Simulation 16	-2387.23	-2386.49	-2386.15	-2384.23	-2382.33
Simulation 17	3086.61	-2182.69	2375.48	-2181.88	-2111.59
Simulation 18	-2354.36	-2381.11	-2364.98	-2379.11	-2378.6
Simulation 19	3128.95	-2228.73	2422.09	-2215.64	-2024.85
Simulation 20	-2369.62	-2381.51	-2385.35	-2385.73	-2384.72
Simulation 21	-2305.7	-2374.58	-2360.93	-2372.78	-2371.5
Simulation 22	-2312.36	-2321.61	-2365.04	-2378.33	-2376.7
Simulation 23	-2301.37	-2348.04	-2375.9	-2376.12	-2374.19
Simulation 24	6421.29	-2182.53	5447.89	6051.51	6071.79
Simulation 25	3423.46	-2182.23	2343.23	-2189.18	-2175.47
Simulation 26	-2387.94	-2386.51	-2387.17	-2385.59	-2383.6
Simulation 27	-2348.45	-2396.38	-2376.54	-2394.38	-2393.06
Simulation 28	-2285.95	-2378.14	-2344.32	-2376.15	-2374.24
Simulation 29	-2367.47	-2372.93	-2384.78	-2384.13	-2382.22
Simulation 30	-2199.89	-2366.34	-2290.58	-2364.5	-2363.03



- 0: Preferences
- 1: Manage Simulation Data Set
- 2: Design the Experiment/Clinical Trial
- 3: Simulate Data
- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

9 TARGETDOSE

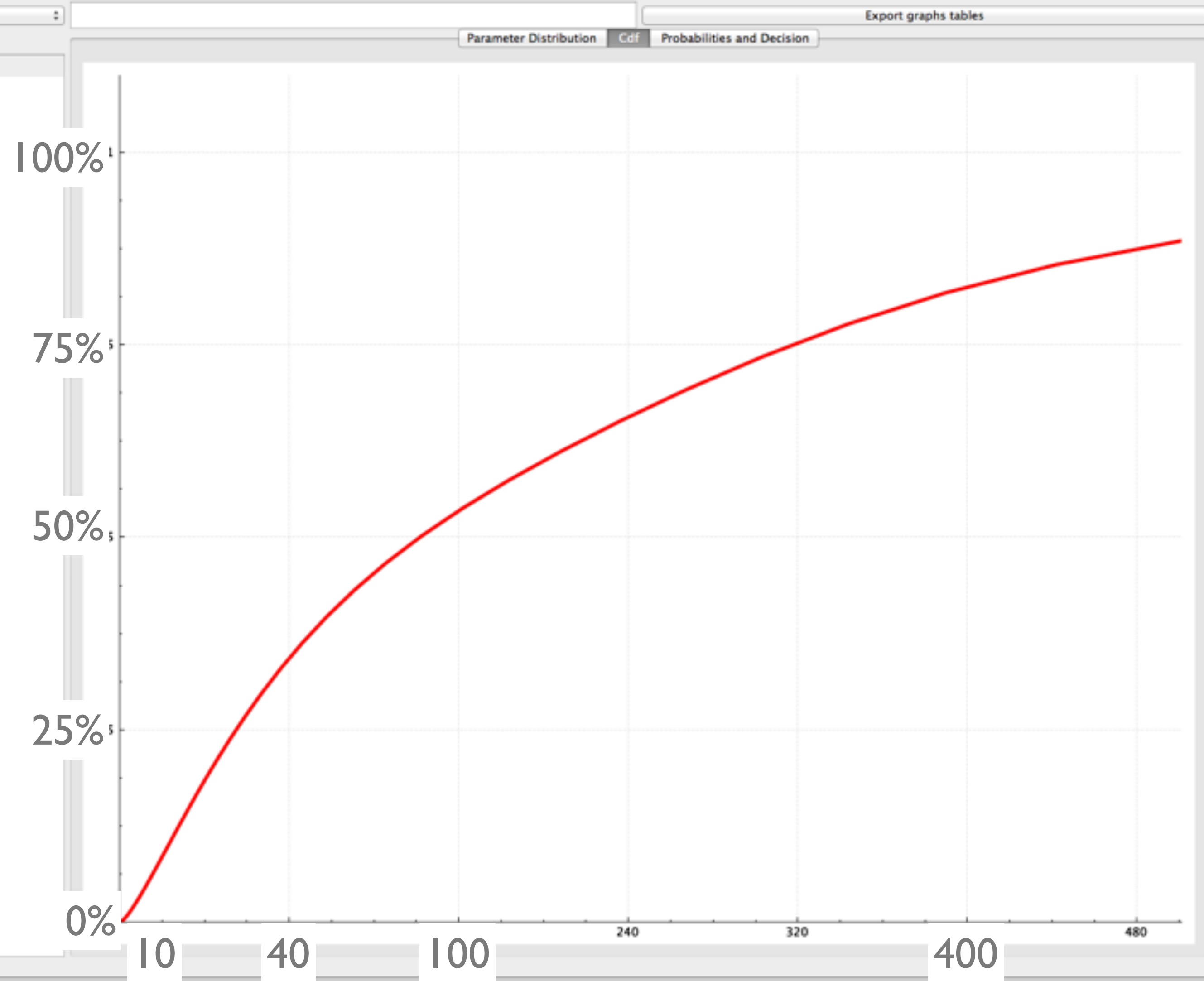
Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
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Simulation 6	-2365.97	-2381.33	-2387.36	-2382.43	-2384.49
Simulation 7	-2266.27	-2388.18	-2341.5	-2386.18	-2384.22
Simulation 8	-2367.39	-2376.99	-2387.6	-2385.67	-2384.05
Simulation 9	-2388.5	-2387.25	-2388.77	-2387.52	-2385.54
Simulation 10	4114.89	-2194.57	3336.75	3842.67	
Simulation 11	-2391.64	-2389.99	-2390.47	-2388.05	-2386.44
Simulation 12	-2361.58	-2392.34	-2378.54	-2390.34	-2390.84
Simulation 13	-2354.72	-2383	-2378.53	-2386.04	-2386.03
Simulation 14	6336.36	-2213.7	5496.19	646.08	6020.75
Simulation 15	-2376.48	-2376.12	-2381.12	-2383.52	-2381.79
Simulation 16	-2387.23	-2386.49	-2386.15	-2384.23	-2382.33
Simulation 17	3086.61	-2182.69	2375.48	-2181.88	-2111.59
Simulation 18	-2354.36	-2381.11	-2364.98	-2379.11	-2378.6
Simulation 19	3128.95	-2228.73	2422.09	-2215.64	-2024.85
Simulation 20	-2369.62	-2381.51	-2385.35	-2385.73	-2384.72
Simulation 21	-2305.7	-2374.58	-2360.93	-2372.78	-2371.5
Simulation 22	-2312.36	-2321.61	-2365.04	-2378.33	-2376.7
Simulation 23	-2301.37	-2348.04	-2375.9	-2376.12	-2374.19
Simulation 24	6421.29	-2182.53	5447.89	6051.51	6071.79
Simulation 25	3423.46	-2182.23	2343.23	-2189.18	-2175.47
Simulation 26	-2387.94	-2386.51	-2387.17	-2385.59	-2383.6
Simulation 27	-2348.45	-2396.38	-2376.54	-2394.38	-2393.06
Simulation 28	-2285.95	-2378.14	-2344.32	-2376.15	-2374.24
Simulation 29	-2367.47	-2372.93	-2384.78	-2384.13	-2382.22
Simulation 30	-2199.89	-2366.34	-2290.58	-2364.5	-2363.03

Probability of Achieving the Target Effect



- 0: Preferences
- 1: Manage Simulation Data Set
- 2: Design the Experiment/Clinical Trial
- 3: Simulate Data
- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

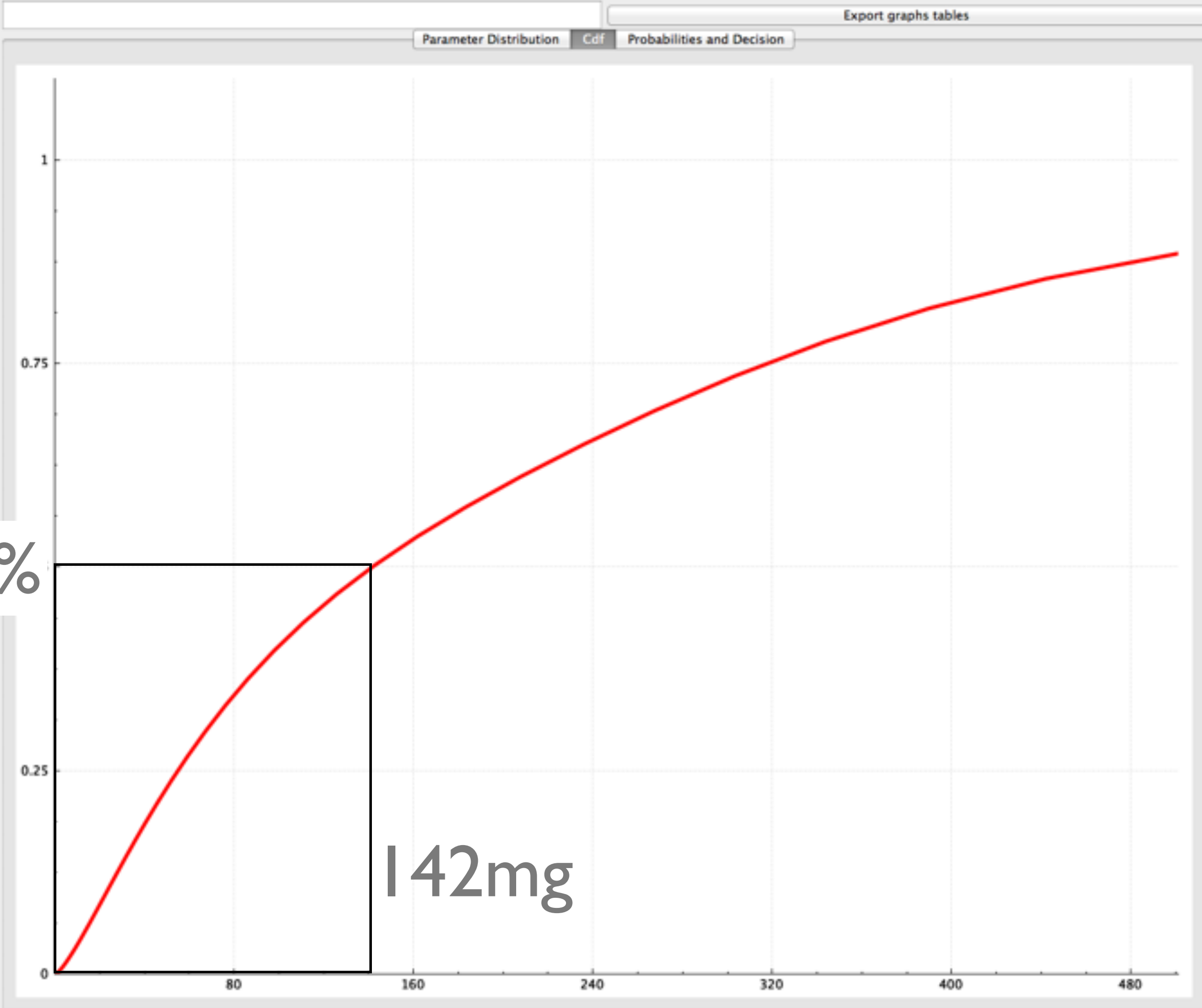
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
Simulation 1	-2364.73	-2380.24	-2381.12	-2382.22	-2380.82
Simulation 2	-2319.93	-2360.35	-2397.42	-2394.76	-2398.75
Simulation 3	-1995.79	-2184.67	-2371.49	-2363.7	-2374.1
Simulation 4	-2342.61	-2394.85	-2381.29	-2394.12	-2392.34
Simulation 5	-2380.3	-2380.4	-2384.04	-2382.56	-2383.66
Simulation 6	-2365.97	-2381.33	-2387.36	-2382.43	-2384.49
Simulation 7	-2266.27	-2388.18	-2341.5	-2386.18	-2384.22
Simulation 8	-2367.39	-2376.99	-2387.6	-2385.67	-2384.05
Simulation 9	-2388.5	-2387.25	-2388.77	-2387.52	-2385.54
Simulation 10	4114.89	-2194.57	3336.75	3842.67	
Simulation 11	-2391.64	-2389.99	-2390.47	-2388.05	-2386.44
Simulation 12	-2361.58	-2392.34	-2378.54	-2390.34	-2390.84
Simulation 13	-2354.72	-2383	-2378.53	-2386.04	-2386.03
Simulation 14	6336.36	-2213.7	5496.19	646.08	6020.75
Simulation 15	-2376.48	-2376.12	-2381.12	-2383.52	-2381.79
Simulation 16	-2387.23	-2386.49	-2386.15	-2384.23	-2382.33
Simulation 17	3086.61	-2182.69	2375.48	-2181.88	-2111.59
Simulation 18	-2354.36	-2381.11	-2364.98	-2379.11	-2378.6
Simulation 19	3128.95	-2228.73	2422.09	-2215.64	-2024.85
Simulation 20	-2369.62	-2381.51	-2385.35	-2385.73	-2384.72
Simulation 21	-2305.7	-2374.58	-2360.93	-2372.78	-2371.5
Simulation 22	-2312.36	-2321.61	-2365.04	-2378.33	-2376.7
Simulation 23	-2301.37	-2348.04	-2375.9	-2376.12	-2374.19
Simulation 24	6421.29	-2182.53	5447.89	6051.51	6071.79
Simulation 25	3423.46	-2182.23	2343.23	-2189.18	-2175.47
Simulation 26	-2387.94	-2386.51	-2387.17	-2385.59	-2383.6
Simulation 27	-2348.45	-2396.38	-2376.54	-2394.38	-2393.06
Simulation 28	-2285.95	-2378.14	-2344.32	-2376.15	-2374.24
Simulation 29	-2367.47	-2372.93	-2384.78	-2384.13	-2382.22
Simulation 30	-2199.89	-2366.34	-2290.58	-2364.5	-2363.03



- 0: Preferences
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- 2: Design the Experiment/Clinical Trial
- 3: Simulate Data
- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

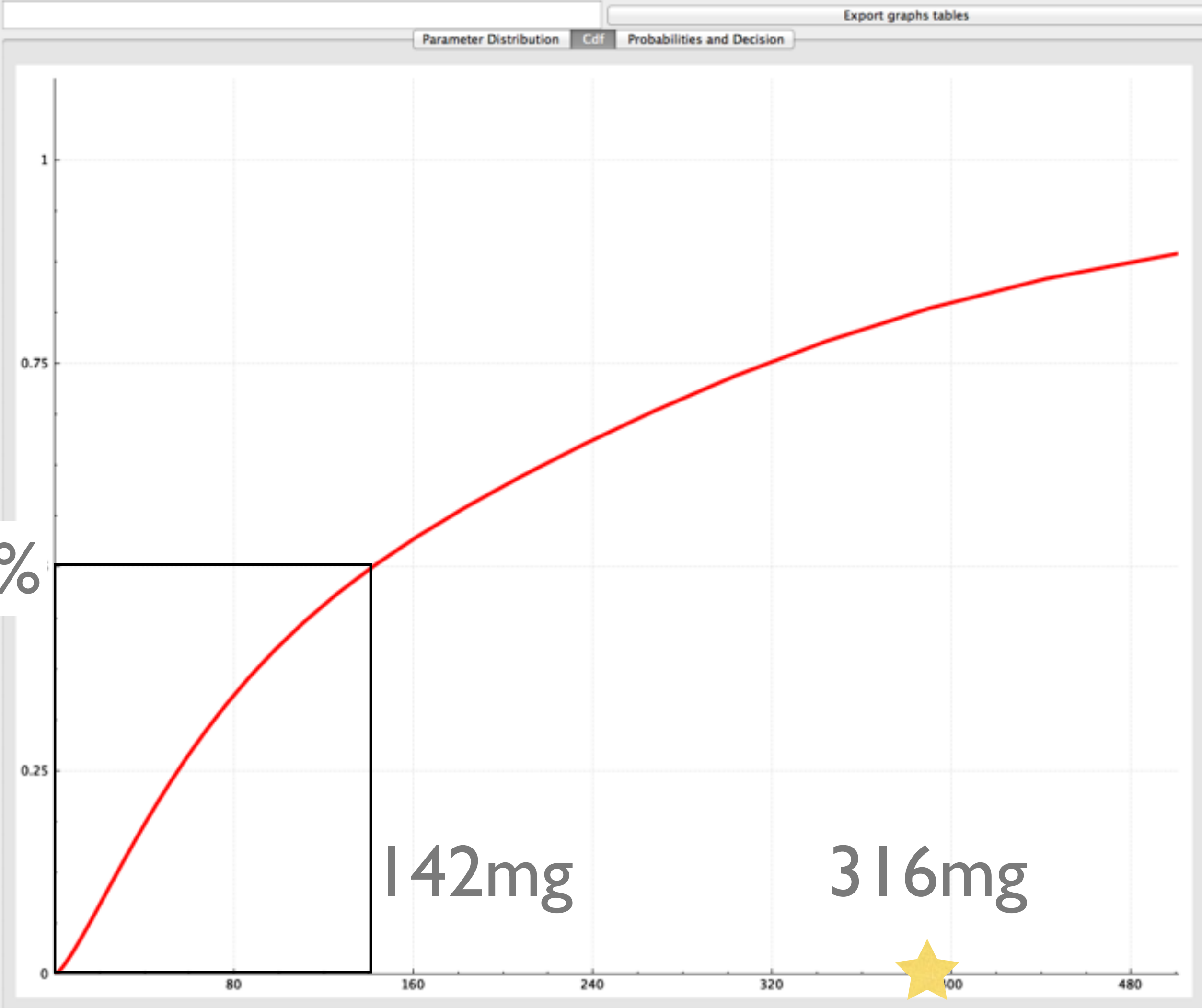
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
Simulation 1	-2364.73	-2380.24	-2381.12	-2382.22	-2380.82
Simulation 2	-2319.93	-2360.35	-2397.42	-2394.76	-2398.75
Simulation 3	-1995.79	-2184.67	-2371.49	-2363.7	-2374.1
Simulation 4	-2342.61	-2394.85	-2381.29	-2394.12	-2392.34
Simulation 5	-2380.3	-2380.4	-2384.04	-2382.56	-2383.66
Simulation 6	-2365.97	-2381.33	-2387.36	-2382.43	-2384.49
Simulation 7	-2266.27	-2388.18	-2341.5	-2386.18	-2384.22
Simulation 8	-2367.39	-2376.99	-2387.6	-2385.67	-2384.05
Simulation 9	-2388.5	-2387.25	-2388.77	-2387.52	-2385.54
Simulation 10	4114.89	-2194.57	3336.75	3842.67	
Simulation 11	-2391.64	-2389.99	-2390.47	-2388.05	-2386.44
Simulation 12	-2361.58	-2392.34	-2378.54	-2390.34	-2390.84
Simulation 13	-2354.72	-2383	-2378.53	-2386.04	-2386.03
Simulation 14	6336.36	-2213.7	5496.19	646.08	6020.75
Simulation 15	-2376.48	-2376.12	-2381.12	-2383.52	-2381.79
Simulation 16	-2387.23	-2386.49	-2386.15	-2384.23	-2382.33
Simulation 17	3086.61	-2182.69	2375.48	-2181.88	-2111.59
Simulation 18	-2354.36	-2381.11	-2364.98	-2379.11	-2378.6
Simulation 19	3128.95	-2228.73	2422.09	-2215.64	-2024.85
Simulation 20	-2369.62	-2381.51	-2385.35	-2385.73	-2384.72
Simulation 21	-2305.7	-2374.58	-2360.93	-2372.78	-2371.5
Simulation 22	-2312.36	-2321.61	-2365.04	-2378.33	-2376.7
Simulation 23	-2301.37	-2348.04	-2375.9	-2376.12	-2374.19
Simulation 24	6421.29	-2182.53	5447.89	6051.51	6071.79
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Simulation 28	-2285.95	-2378.14	-2344.32	-2376.15	-2374.24
Simulation 29	-2367.47	-2372.93	-2384.78	-2384.13	-2382.22
Simulation 30	-2199.89	-2366.34	-2290.58	-2364.5	-2363.03



- 0: Preferences
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- 2: Design the Experiment/Clinical Trial
- 3: Simulate Data
- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

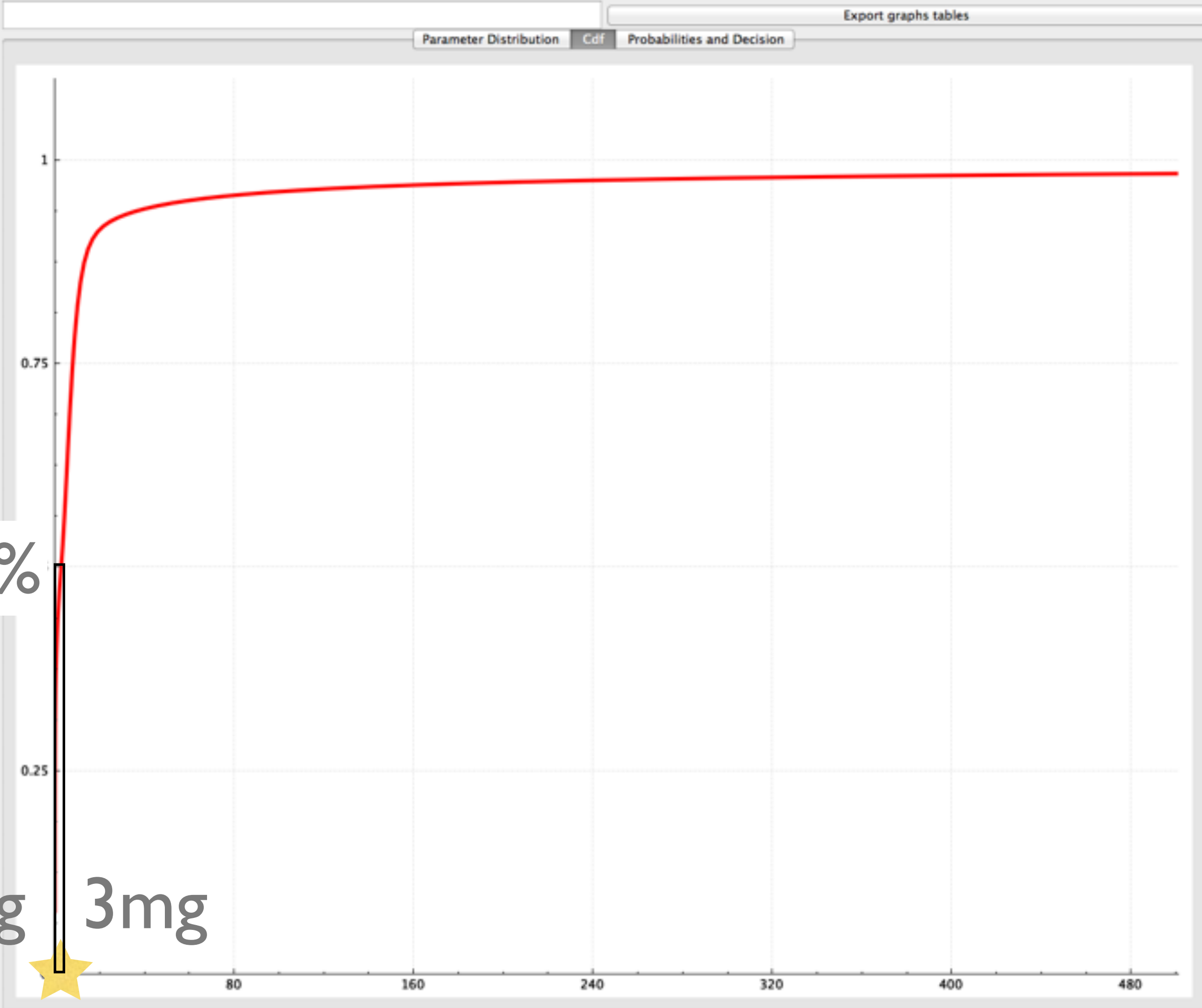
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
Simulation 1	-2364.73	-2380.24	-2381.12	-2382.22	-2380.82
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Simulation 7	-2266.27	-2388.18	-2341.5	-2386.18	-2384.22
Simulation 8	-2367.39	-2376.99	-2387.6	-2385.67	-2384.05
Simulation 9	-2388.5	-2387.25	-2388.77	-2387.52	-2385.54
Simulation 10	4114.89	-2194.57	3336.75	3842.67	
Simulation 11	-2391.64	-2389.99	-2390.47	-2388.05	-2386.44
Simulation 12	-2361.58	-2392.34	-2378.54	-2390.34	-2390.84
Simulation 13	-2354.72	-2383	-2378.53	-2386.04	-2386.03
Simulation 14	6336.36	-2213.7	5496.19	646.08	6020.75
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- 4: Estimate the Dose-Response
- 5: Visualize the Dose-Response Relationship
- 6: Model Average

Parameter

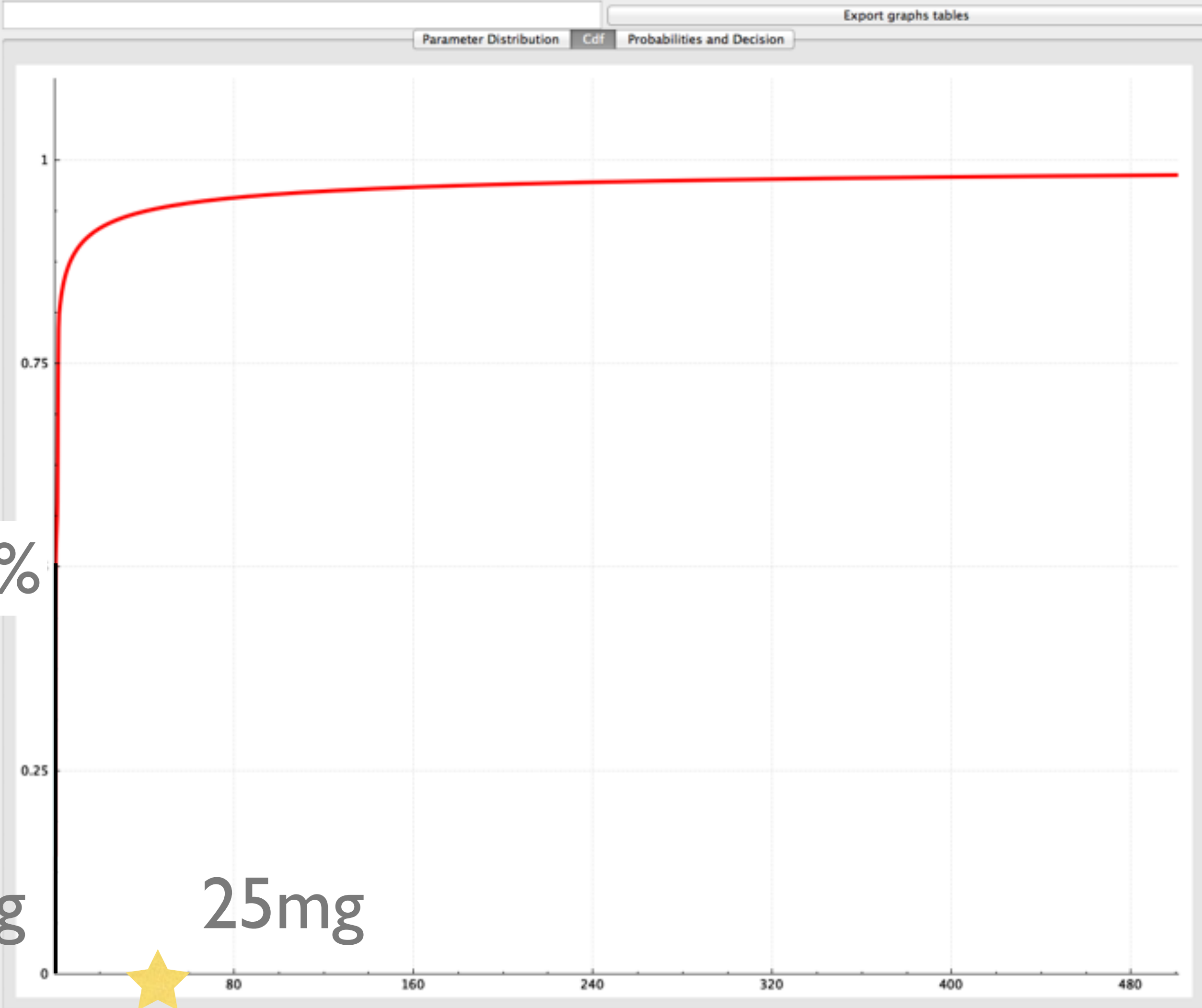
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
Simulation 1	-2364.73	-2380.24	-2381.12	-2382.22	-2380.82
Simulation 2	-2319.93	-2360.35	-2397.42	-2394.76	-2398.75
Simulation 3	-1995.79	-2184.67	-2371.49	-2363.7	-2374.1
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Parameter

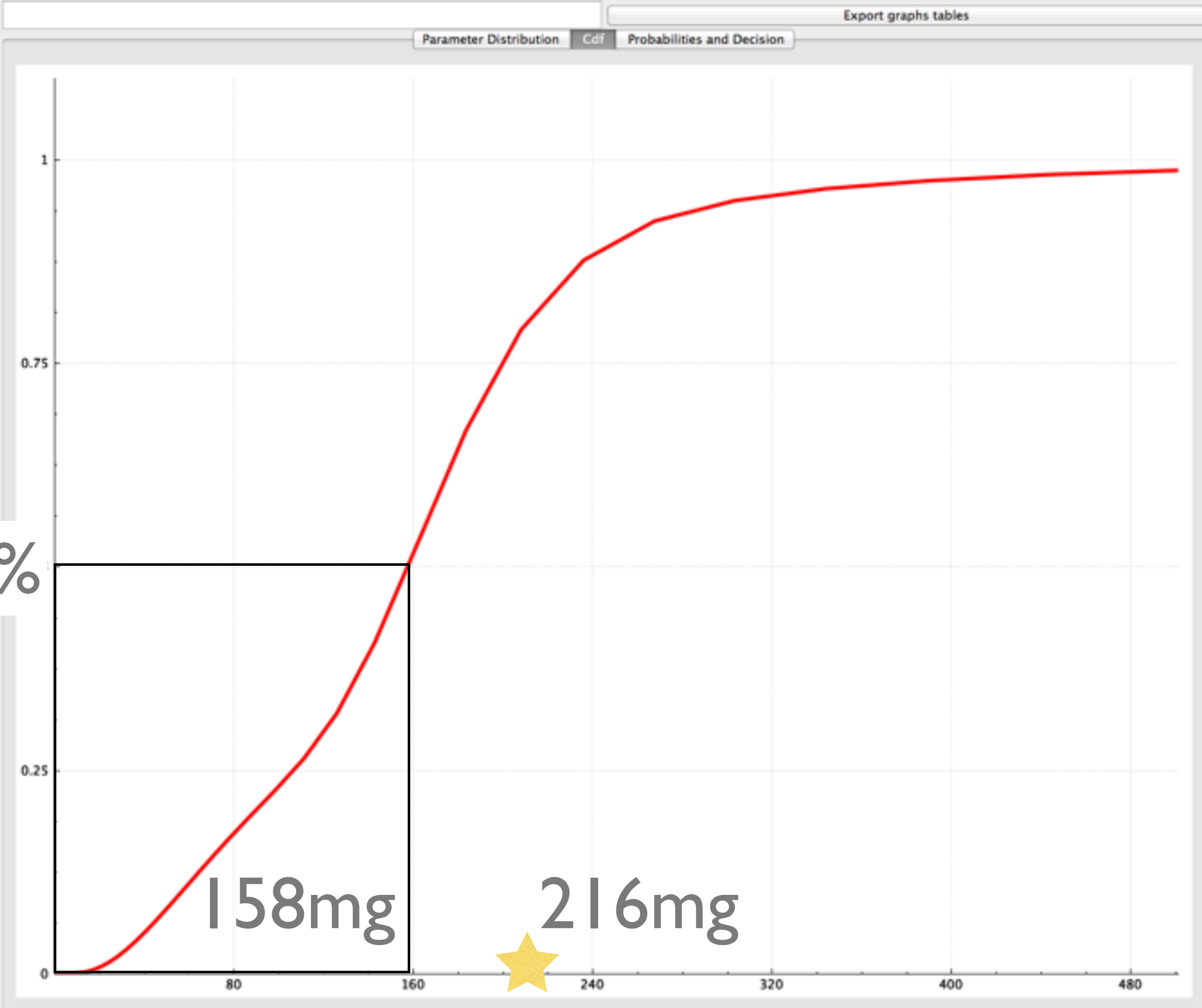
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

	Model 0	Model 1	Model 2	Model 3	Model 4
Average over	☐	☒	☒	☒	☒
Simulation 0	-2240.56	-2305.47	-2376.48	-2374.67	-2374.54
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Parameter

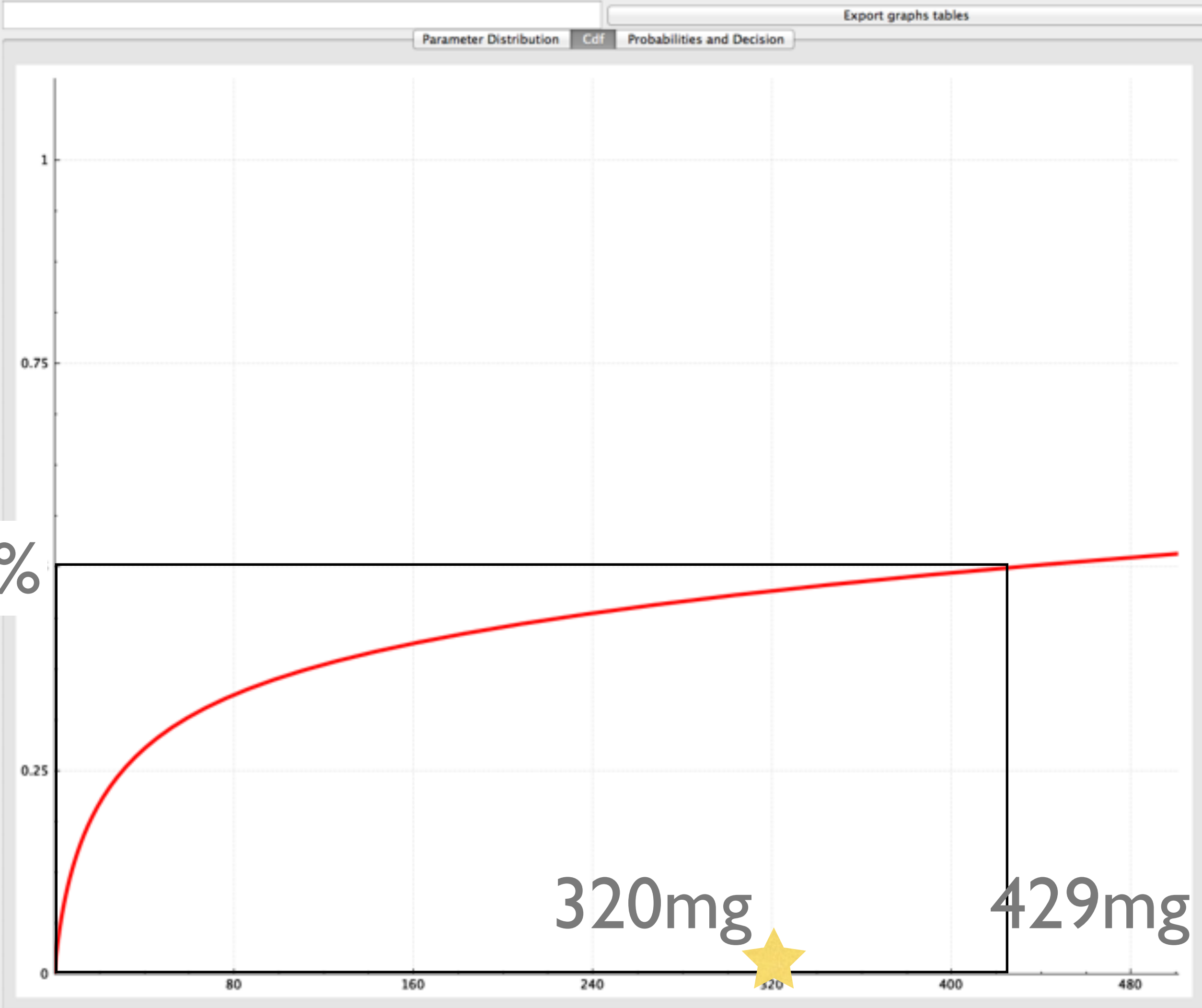
9 TARGETDOSE

Probability of the parameter to be

Less than

AIC

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Simulation 30	-2199.89	-2366.34	-2290.58	-2364.5	-2363.03



Confidence Level		50%	
Frequencies of Underdosing			

Confidence Level		50%	
Frequencies of Underdosing		493/1000	

Confidence Level	30%	50%	
Frequencies of Underdosing		493/1000	

Confidence Level	30%	50%	
Frequencies of Underdosing	662/1000	493/1000	

Confidence Level	30%	50%	70%
Frequencies of Underdosing	662/1000	493/1000	

Confidence Level	30%	50%	70%
Frequencies of Underdosing	662/1000	493/1000	319/1000



Averaged Model Based Analysis Result

Model Based Analysis recommends ____mg with ____% confidence level
of achieving an effect higher than the target effect.

Assumptions:

- Placebo Model reasonably describes the placebo effect.
- Dose Effect relationship can be described reasonably by at least one of the following models: linear, log-linear, emax, sigmoidal.

Simulation Study 5

what about the type I error?

Simulation Study 5

correct decision = STOP

There are drug effects added to placebo model, but they do not achieve the target effect within the tested dose range (i.e., 0-400mg)

hence the STOP is the right decision.

Averaged Model Based Dose Selection Scheme

Choose either “go” with 10mg, 40mg, 100mg, 400mg or “stop”.

Criterion 1: All models have to pass the likelihood ratio test against the model without drug effect.
(if not, automatically “stop” decision).

Criterion 2: Choose the minimum dose with probability of achieving the target effect is above 50%.

Simulation Study 5

correct decision = STOP

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	11	12	38	161	778
AMB with Preconditioning and Unconditional	57	68	90	287	498

Simulation Study 5

correct decision = STOP

	10 mg	40 mg	100 mg	400 mg	Stop
Study Protocol (ANOVA + Averaged Effect)	222				778
AMB with Preconditioning and Unconditional	502				498

Simulation Study 5

correct decision = STOP

Probability of achieving the TE	50%	75%	85%	90%	95%
Stop	498	731	808	860	912
Go Type I error	502	269	192	140	88

Averaged Model Based Dose Selection Scheme

Choose either “go” with 10mg, 40mg, 100mg, 400mg or “stop”.

Criterion 1: All models have to pass the likelihood ratio test against the model without drug effect.
(if not, automatically “stop” decision).

Criterion 2: Choose the minimum dose with probability of achieving the target effect is above 50%.

Averaged Model Based Dose Selection Scheme

possible revision?

Choose either “go” with 10mg, 40mg, 100mg, 400mg or “stop”.

Criterion 1: There is 95% of probability of achieving the target effect at the highest dose (i.e., 400mg).
(if not, automatically “stop” decision).

Criterion 2: Choose the minimum dose with probability of achieving the target effect is above ____%.

Estimation Models

Estimation Models

Step 1: Construct placebo model.

$$\text{FEV1} = (\text{BASE} + \text{PlaceboEffect}) \times (1 + \text{EPS}(1)) + \text{EPS}(2)$$

$$\begin{aligned} \text{BASE} = & (\text{Typical_BBASE} \times \text{EXP}(\text{ETA}(1))) \times (1 + \text{coeffNormal} \times (\text{fev1_}\% \text{of normal} - \text{mean})) \\ & \times (1 + \text{AgeSlope} \times (\text{AGE} - \text{mean})) \\ & \times \text{SexFactor} \\ & + \text{coeffWeight} \times (\text{WEIGHT} - \text{mean}) \end{aligned}$$

$$\text{PlaceboEffect} = \{\text{if placebo=false, 0 else, Typical_PlaceboEffect} + \text{ETA}(2)\}$$

Step 2: Add dose effect component.

$$\text{FEV1} = (\text{BASE} + \text{PlaceboEffect} + \text{Dose Effect Relationship}) \times (1 + \text{EPS}(1)) + \text{EPS}(2)$$

Estimation Models

Step 1: Construct placebo model.

$$FEV1 = (BASE + PlaceboEffect) \times (1 + EPS(1)) + EPS(2)$$

$$\begin{aligned} BASE = & (Typical_BBASE \times EXP(ETA(1))) \times (1 + coeffNormal \times (fev1_ \% of normal - mean)) \\ & \times (1 + AgeSlope \times (AGE - mean)) \\ & \times SexFactor \\ & + coeffWeight \times (WEIGHT - mean) \end{aligned}$$

$$PlaceboEffect = \{ \text{if placebo=false, 0 else, Typical_PlaceboEffect} + ETA(2) \}$$

Step 2: Add dose effect component.

$$\text{Model 1: } FEV1 = (BASE + PlaceboEffect + \text{linear}) \times (1 + EPS(1)) + EPS(2)$$

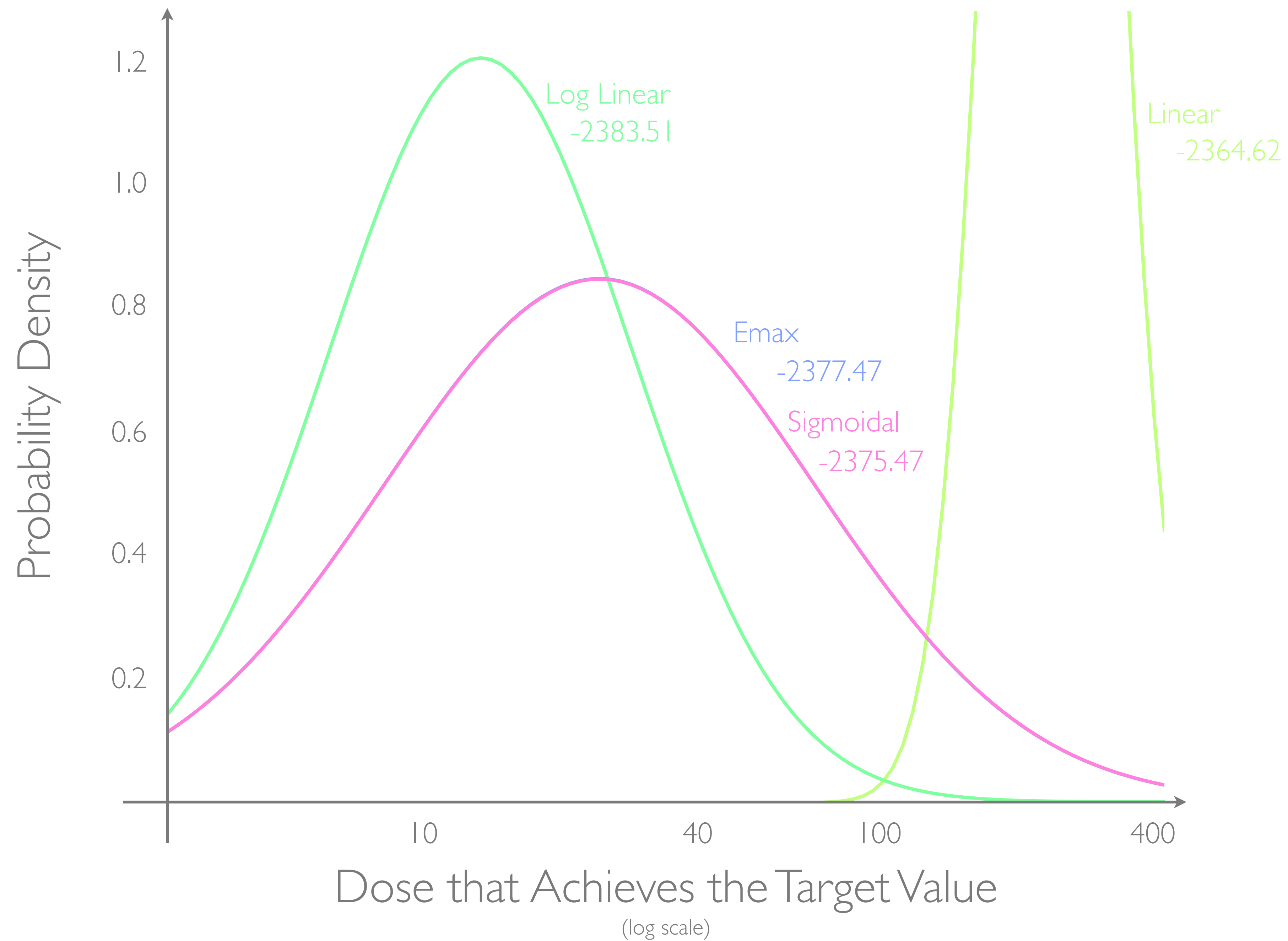
$$\text{Model 2: } FEV1 = (BASE + PlaceboEffect + \text{log-linear}) \times (1 + EPS(1)) + EPS(2)$$

$$\text{Model 3: } FEV1 = (BASE + PlaceboEffect + \text{emax}) \times (1 + EPS(1)) + EPS(2)$$

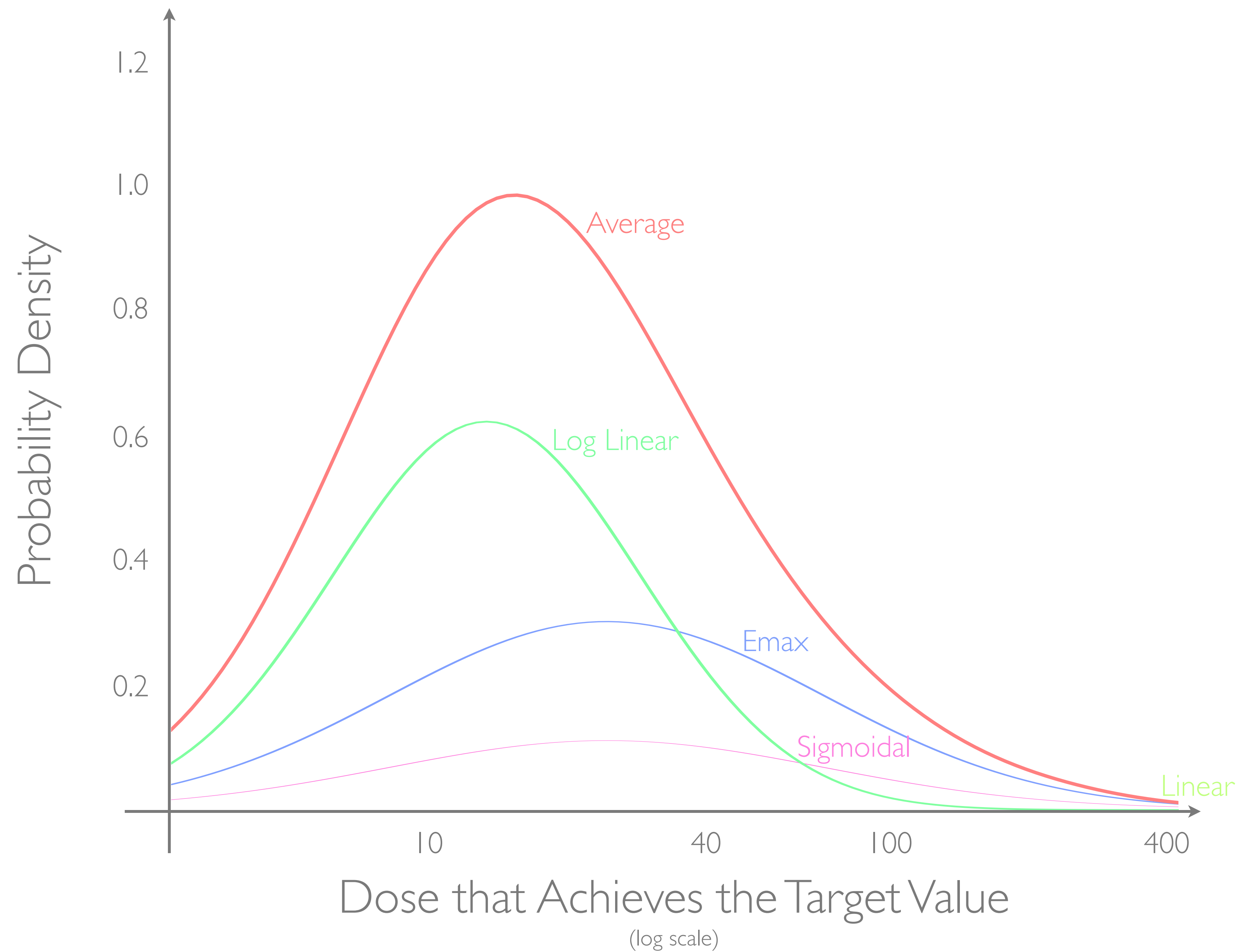
$$\text{Model 4: } FEV1 = (BASE + PlaceboEffect + \text{sigmoidal}) \times (1 + EPS(1)) + EPS(2)$$

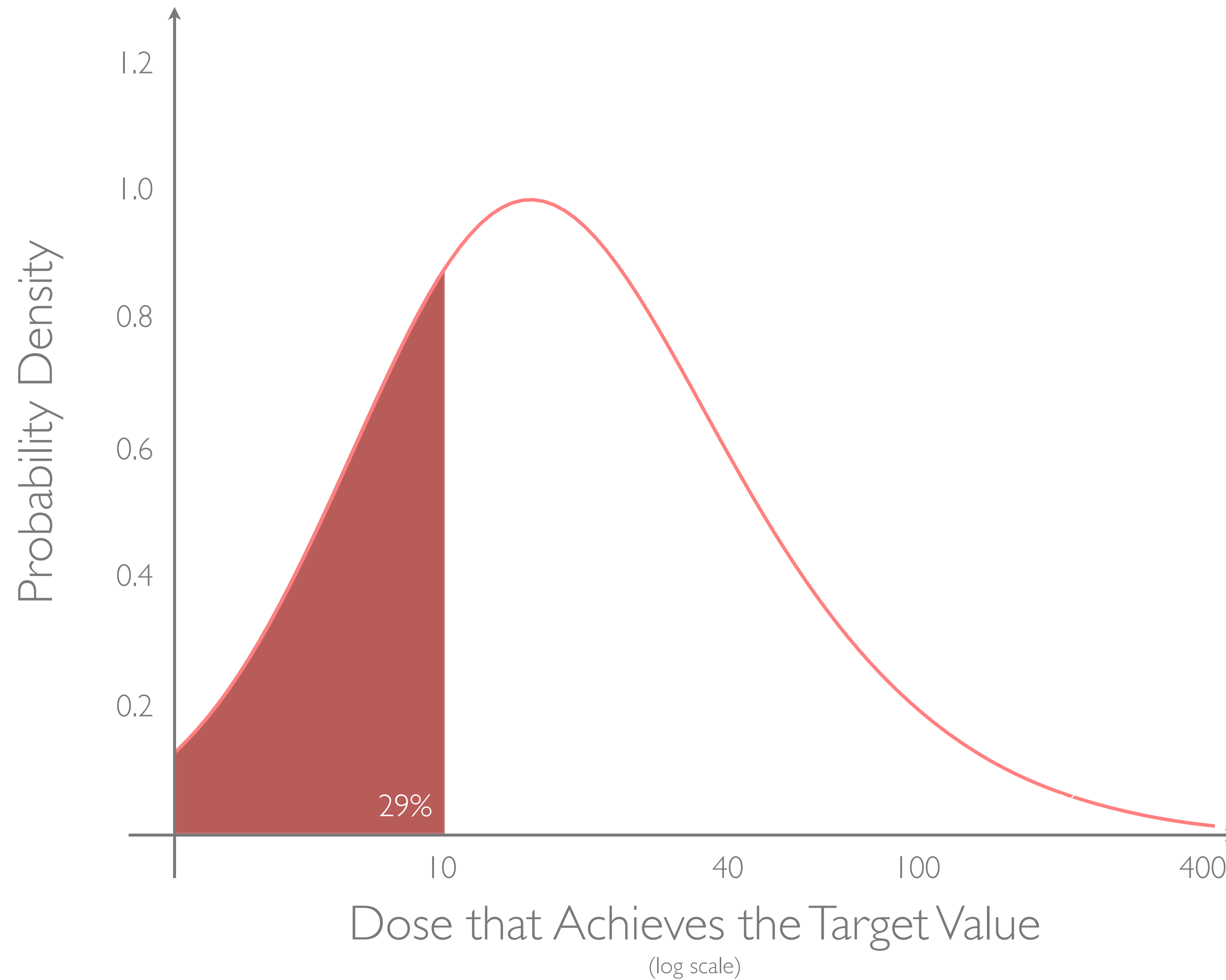
Model Averaging

using covariance matrix









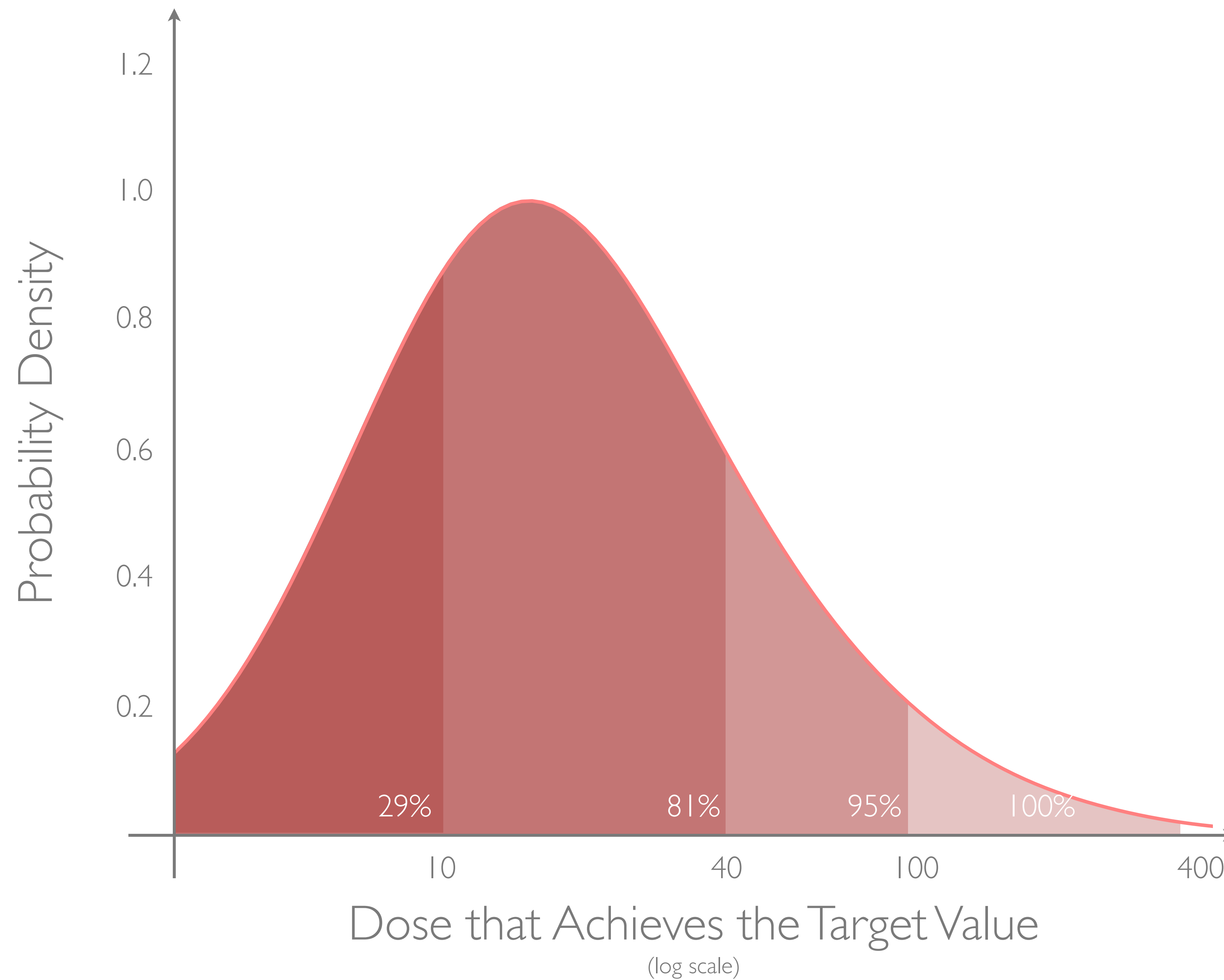
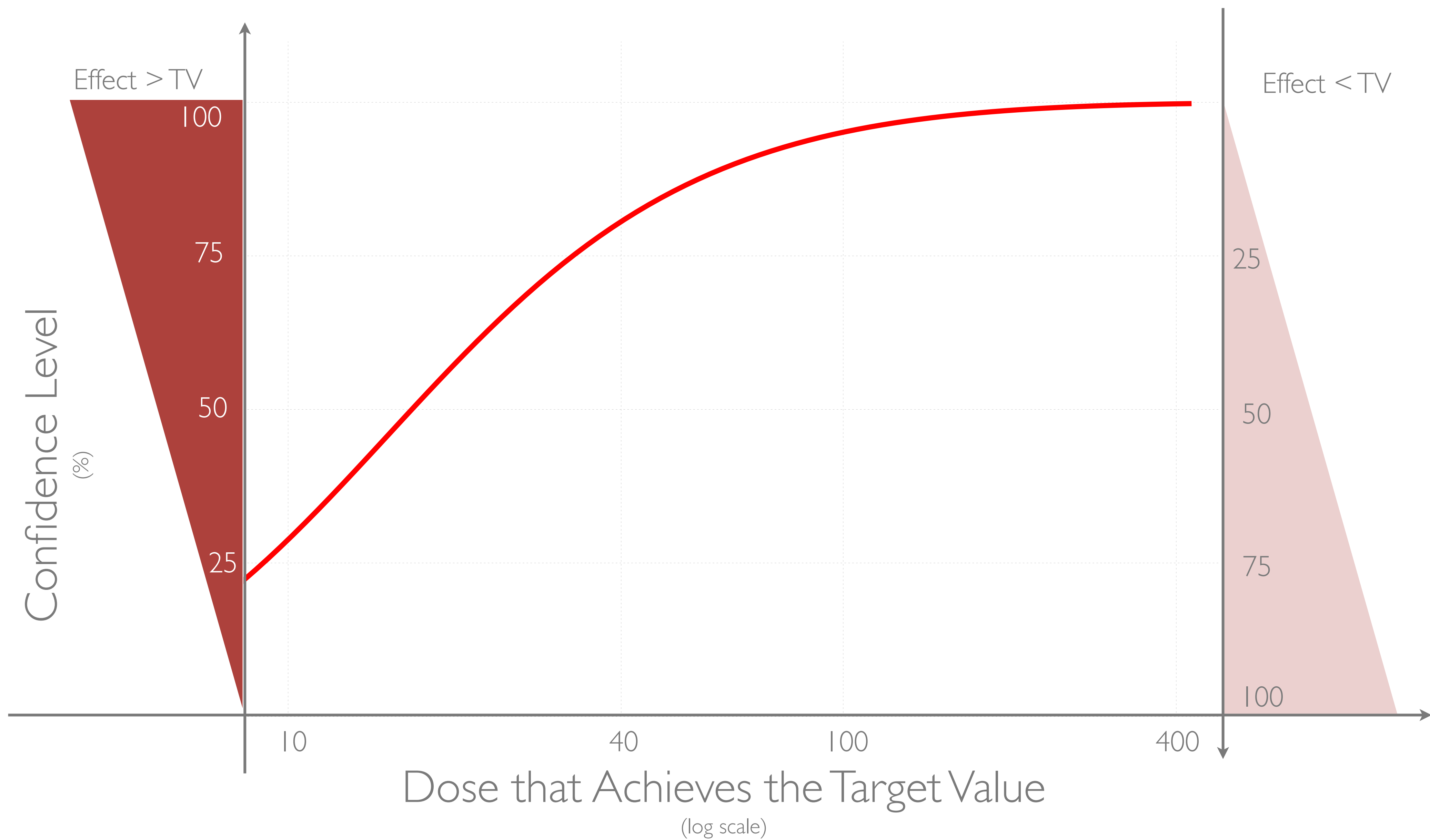


Table of Confidence Level

(Simulation Study I Simulated Data 3)

	10 mg	40 mg	100 mg	400 mg
Effect > TV	29%	81%	95%	100%
Effect < TV	71%	19%	5%	0%



Preconditioning

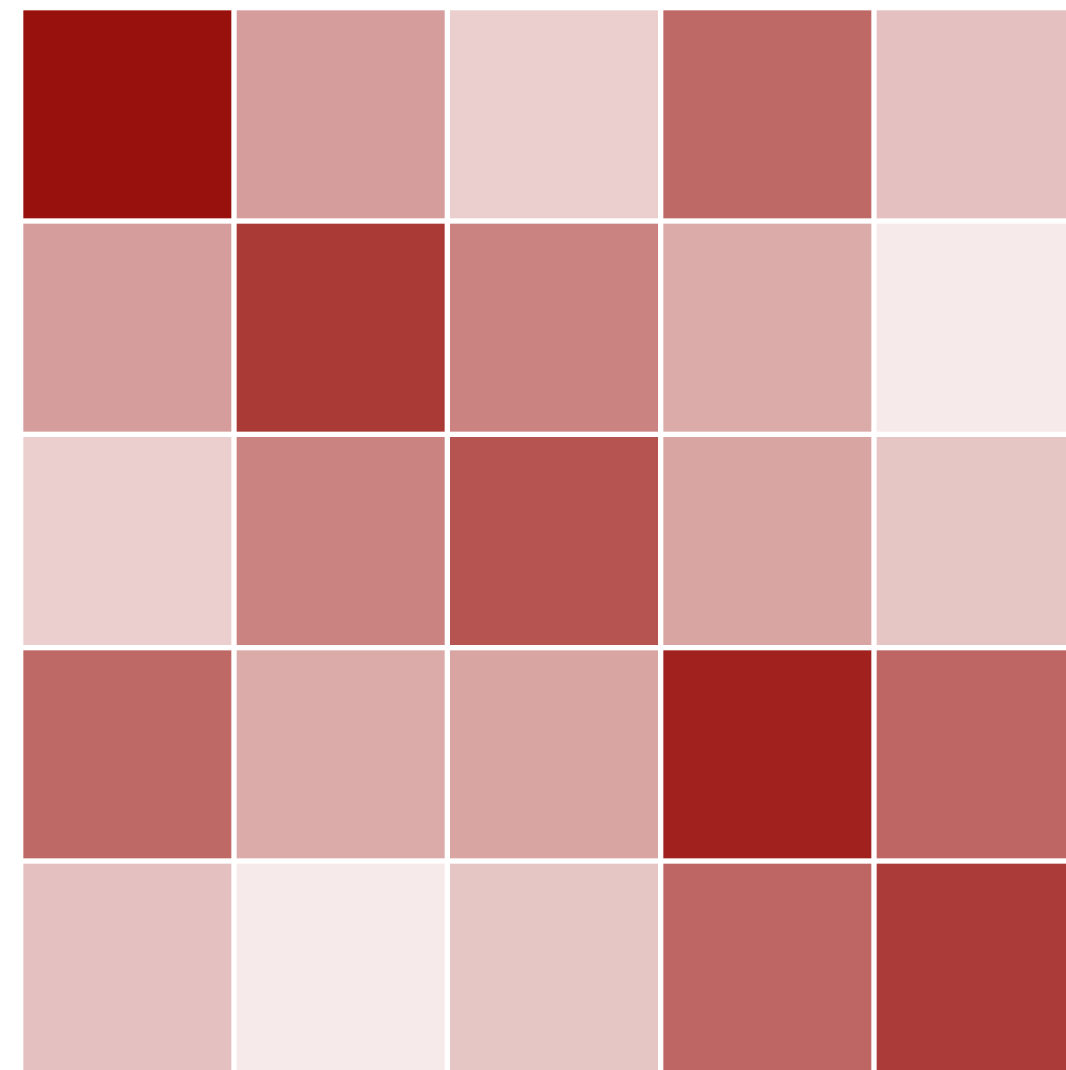
saving $\$cov$ step by providing an initial guess of var-cov matrix

Preconditioning

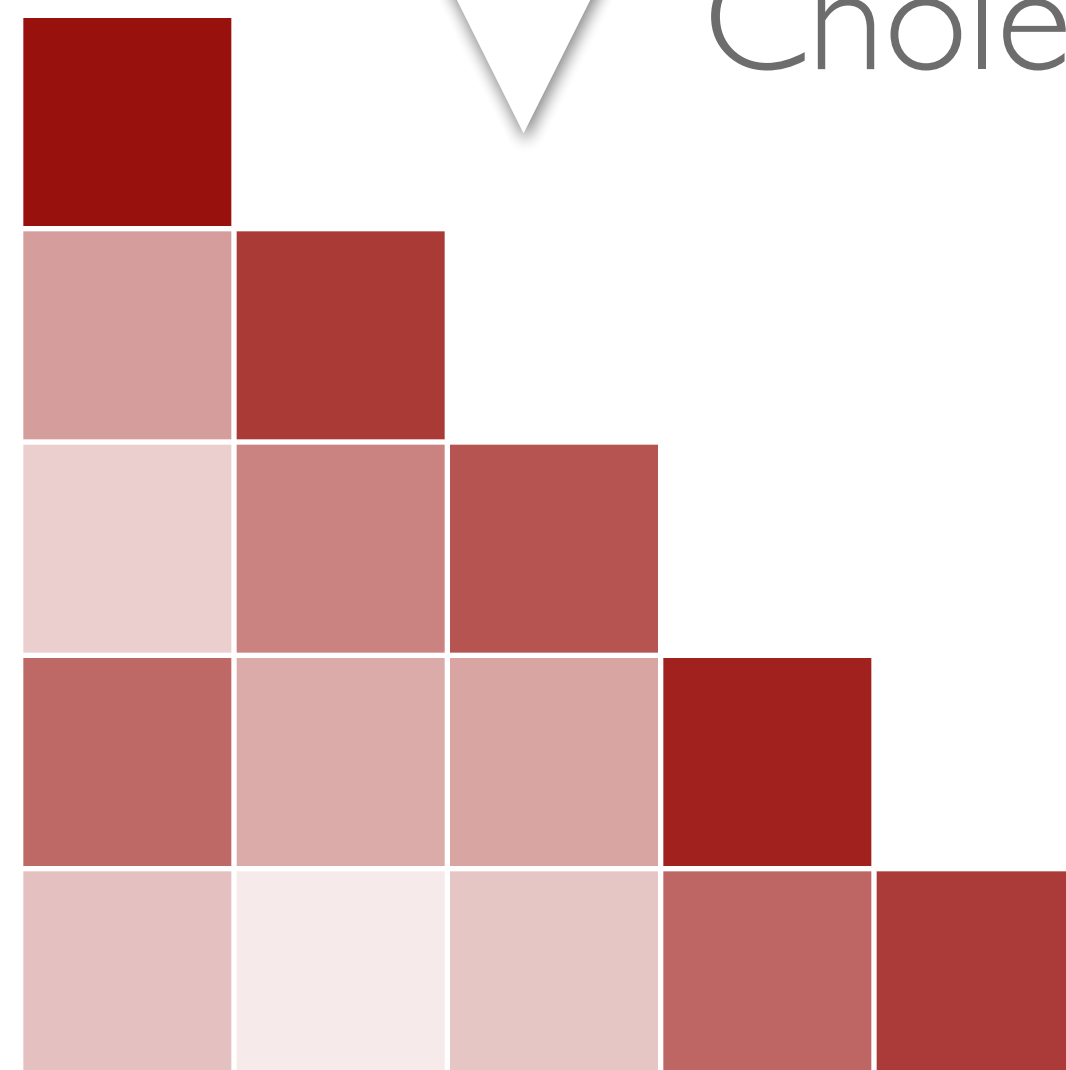
Widely used technique in the field of numerical linear algebra
(i.e., trust me there is a strong theoretical reason why it should work!!)

Linearly re-parameterize the model using the “initial guess” of the var-cov matrix to decrease the condition number of the re-parameterized model’s var-cov matrix that NONMEM is estimating.
(i.e., trick NONMEM to think var-cov matrix is almost a diagonal matrix!!)

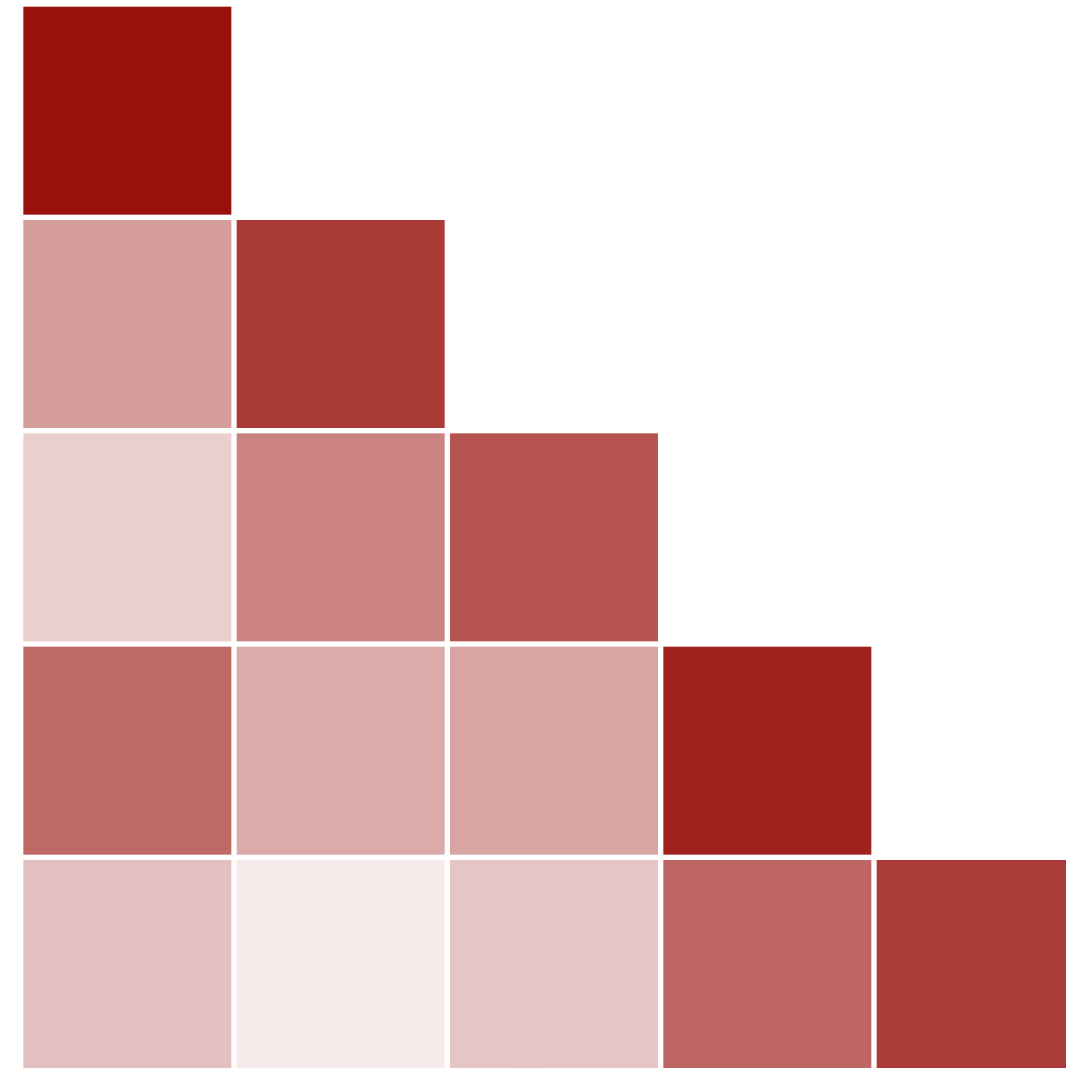
Initial Guess of var-cov matrix



LDL
or
Cholesky



L of initial guess

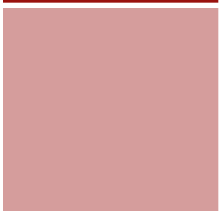
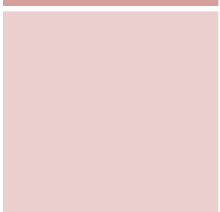
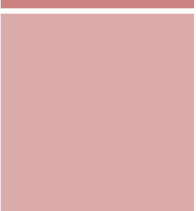
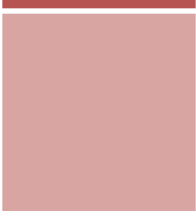
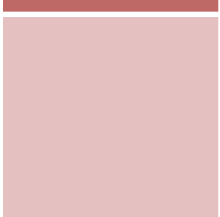
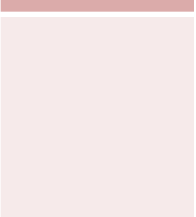
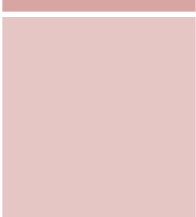
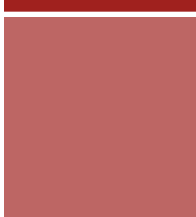


linear re-parameterization of the model

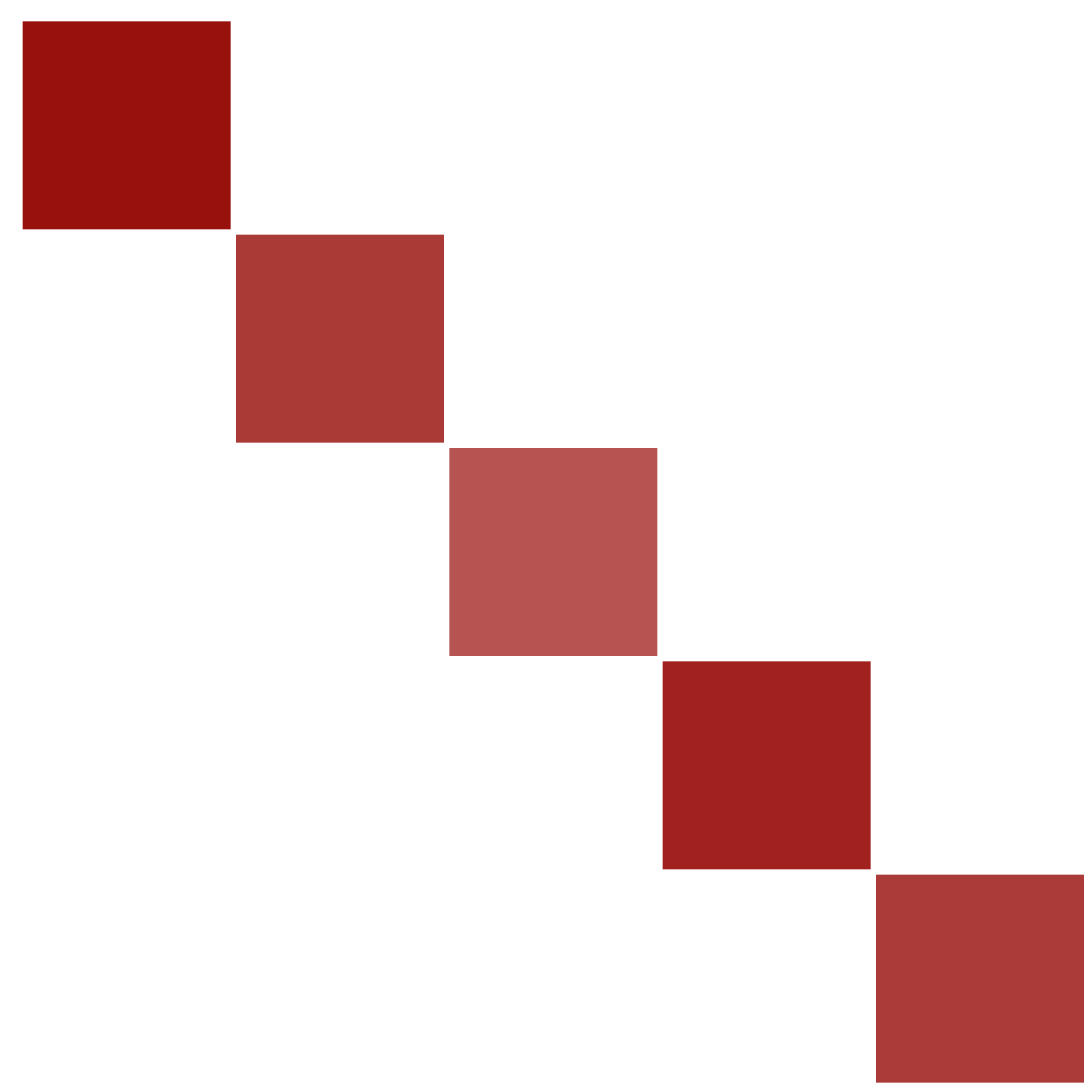
$$\begin{aligned}
 \text{Theta1_original} &= \begin{matrix} \text{Dark Red} \\ \text{Light Red} \\ \text{Very Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(1) \\
 \text{Theta2_original} &= \begin{matrix} \text{Light Red} \\ \text{Very Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(1) + \begin{matrix} \text{Dark Red} \\ \text{Light Red} \\ \text{Light Red} \\ \text{Very Light Red} \end{matrix} \times \text{THETA}(2) \\
 \text{Theta3_original} &= \begin{matrix} \text{Very Light Red} \\ \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(1) + \begin{matrix} \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \\ \text{Very Light Red} \end{matrix} \times \text{THETA}(2) + \begin{matrix} \text{Dark Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(3) \\
 \text{Theta4_original} &= \begin{matrix} \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(1) + \begin{matrix} \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(2) + \begin{matrix} \text{Light Red} \\ \text{Light Red} \\ \text{Dark Red} \end{matrix} \times \text{THETA}(3) + \begin{matrix} \text{Dark Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(4) \\
 \text{Theta5_original} &= \begin{matrix} \text{Light Red} \\ \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(1) + \begin{matrix} \text{Very Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(2) + \begin{matrix} \text{Light Red} \\ \text{Light Red} \end{matrix} \times \text{THETA}(3) + \begin{matrix} \text{Light Red} \\ \text{Dark Red} \end{matrix} \times \text{THETA}(4)
 \end{aligned}$$

Model
Parameters

What NONMEM thinks
the model parameters are...

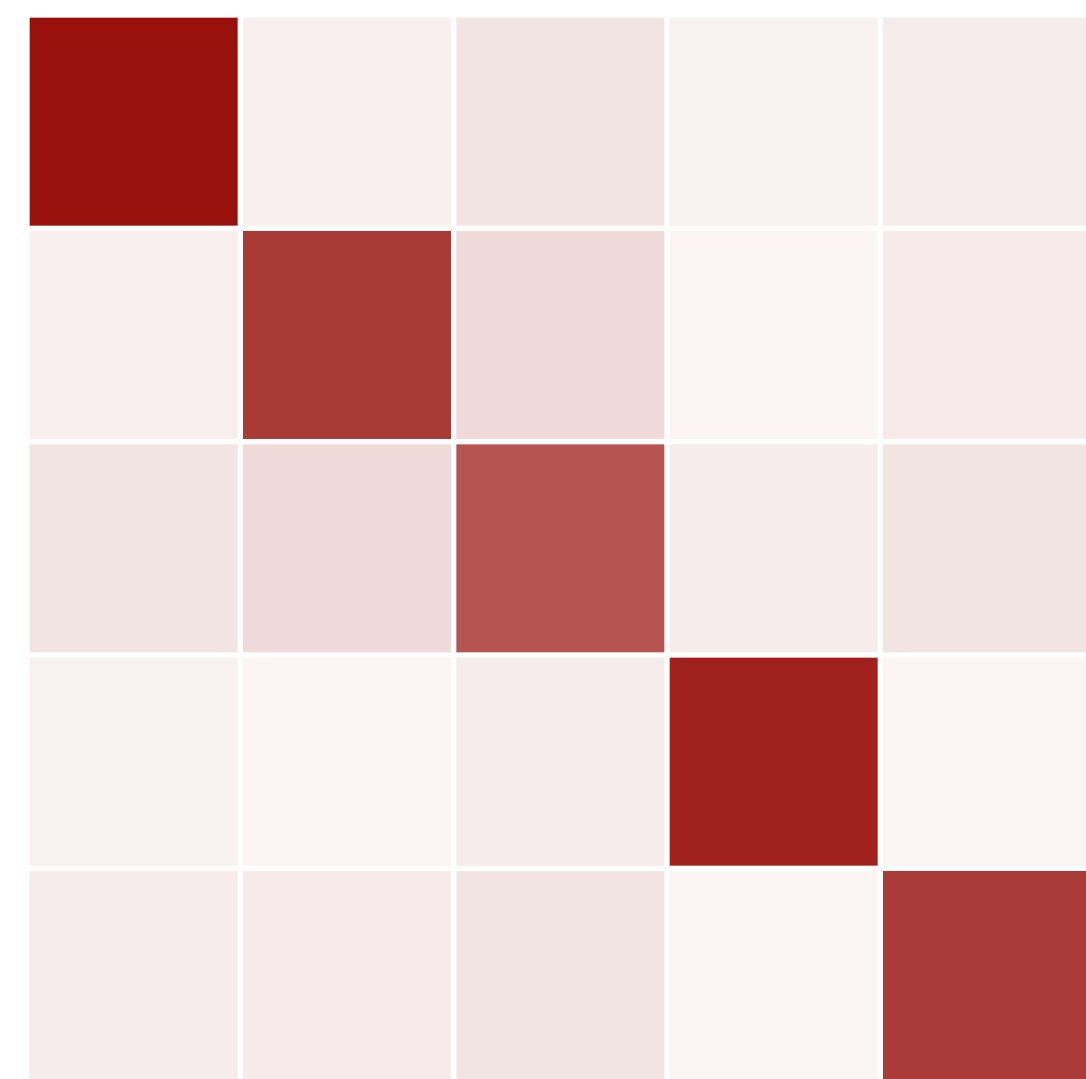
Theta1_original		x THETA(1)									
Theta2_original		x THETA(1)	+		x THETA(2)						
Theta3_original		x THETA(1)	+		x THETA(2)	+		x THETA(3)			
Theta4_original		x THETA(1)	+		x THETA(2)	+		x THETA(3)	+		x THETA(4)
Theta5_original		x THETA(1)	+		x THETA(2)	+		x THETA(3)	+		x THETA(4)

var-cov matrix for THETA



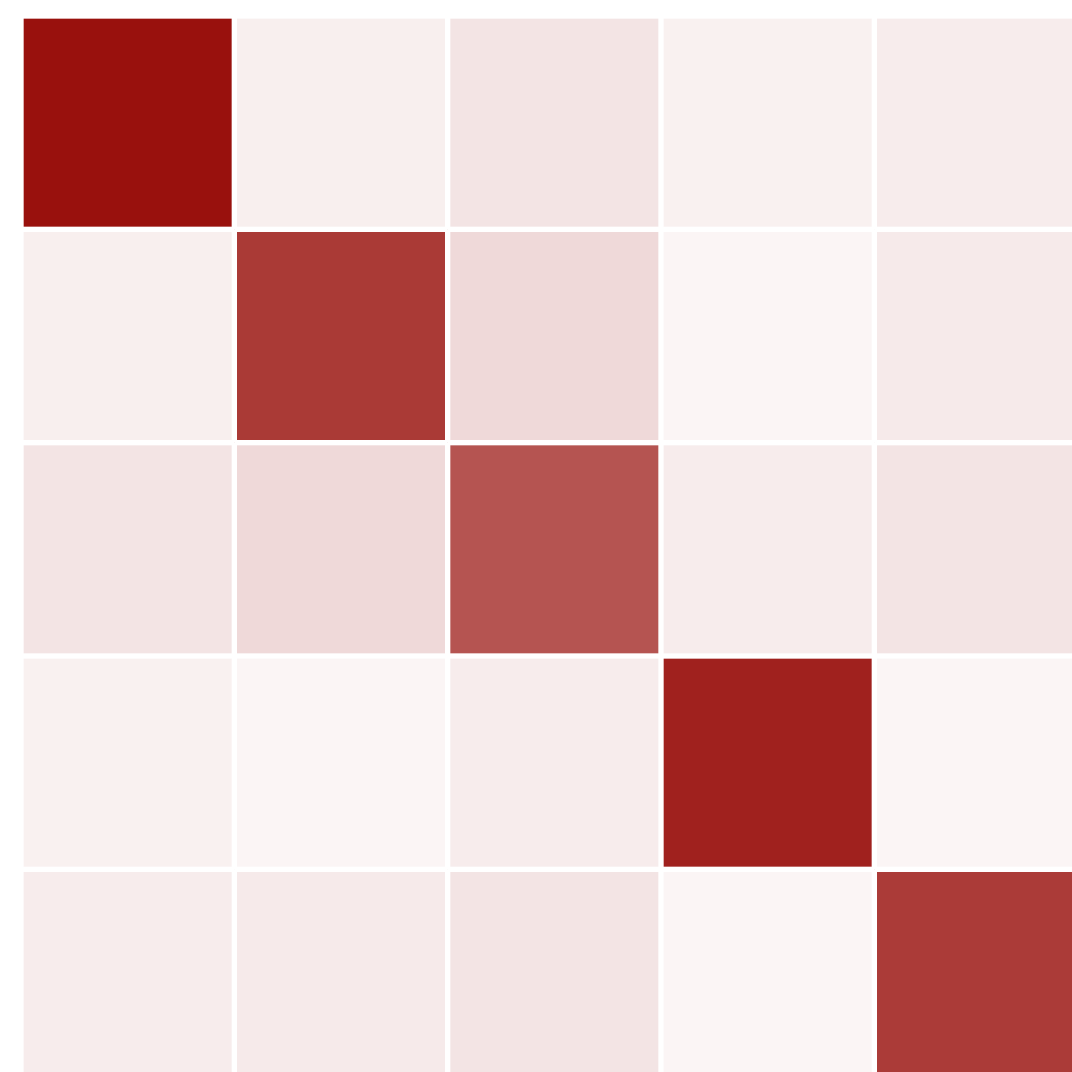
If the initial guess is perfect

var-cov matrix for THETA

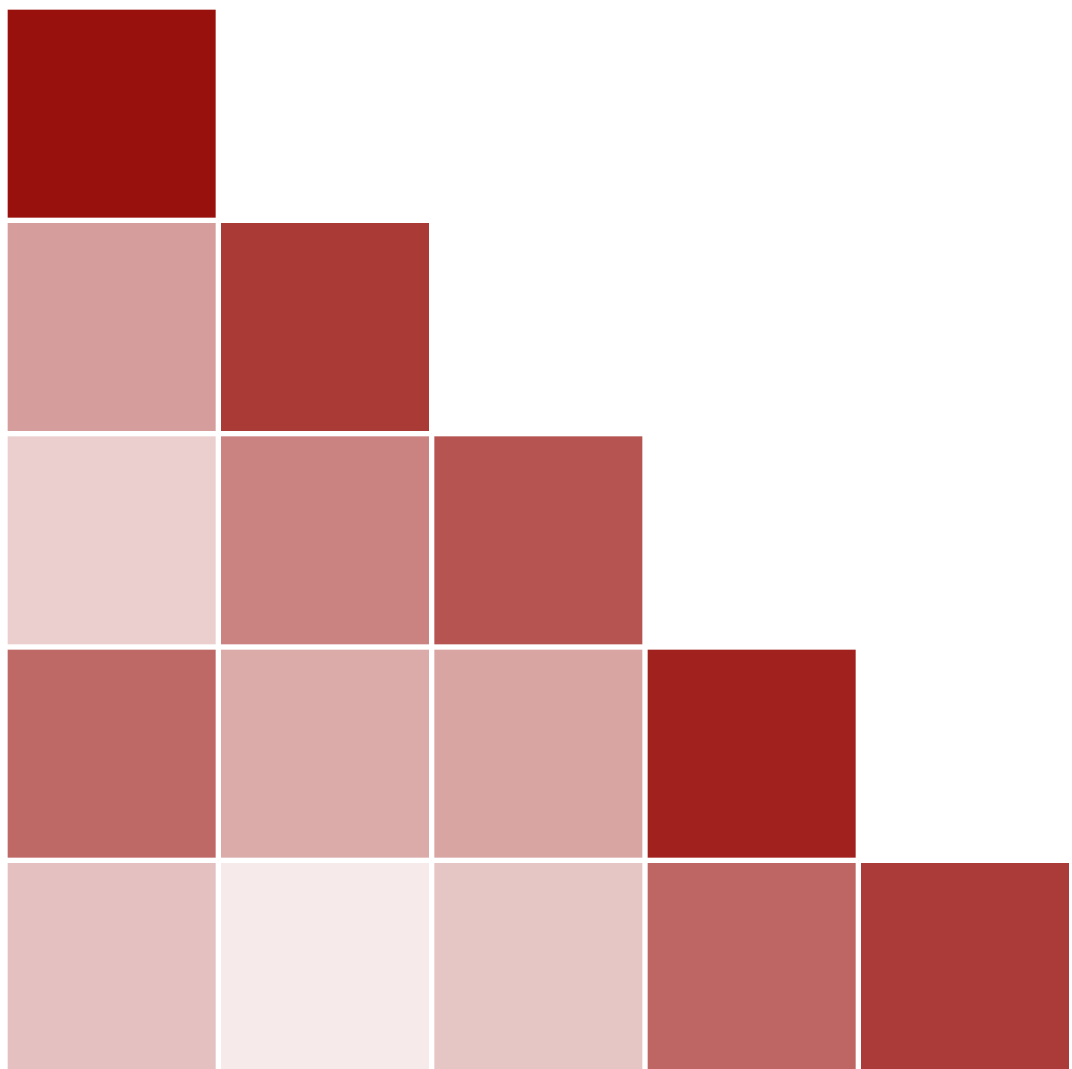


If the initial guess is good

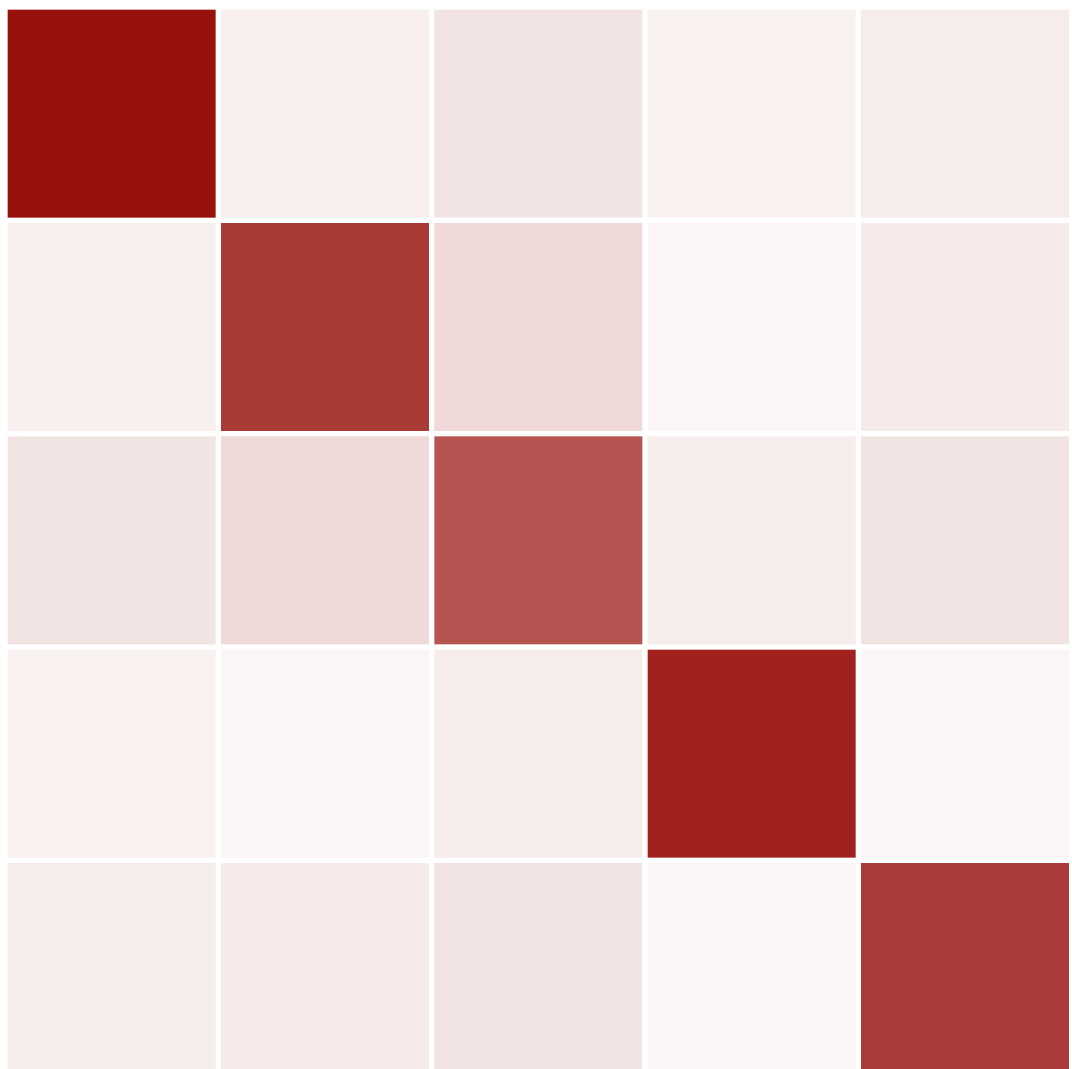
var-cov matrix
for THETA



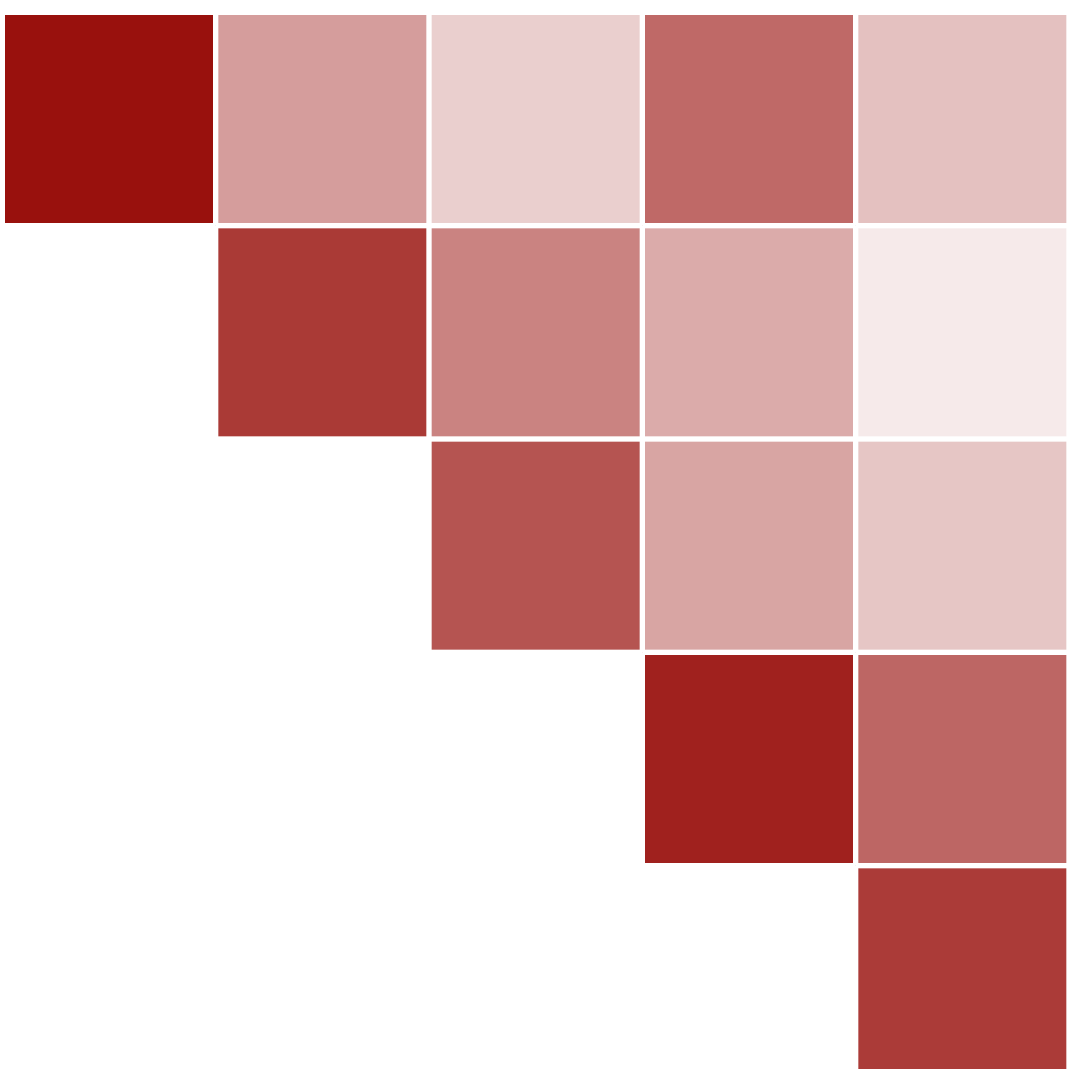
L of initial guess



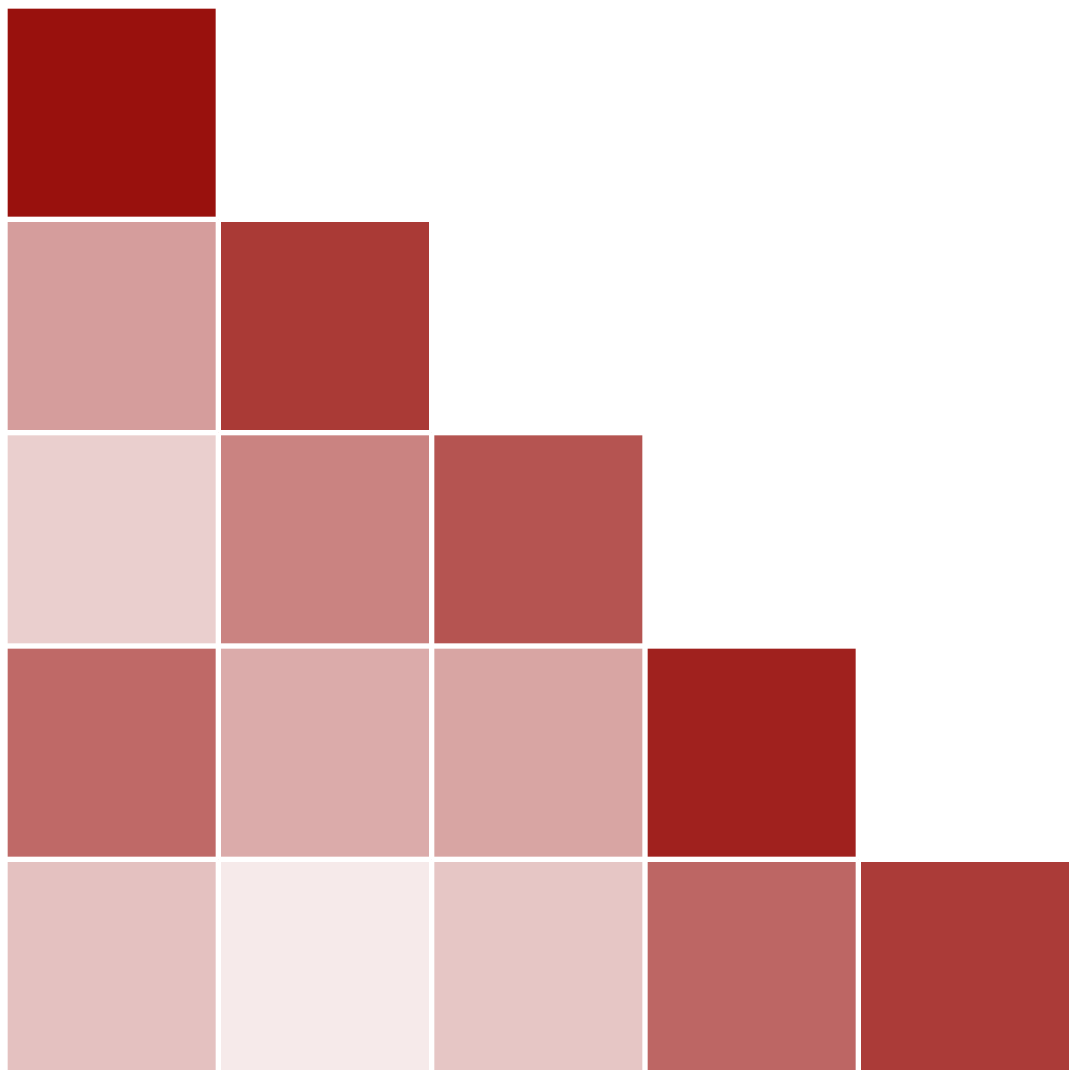
var-cov matrix
for THETA



L^T of initial guess



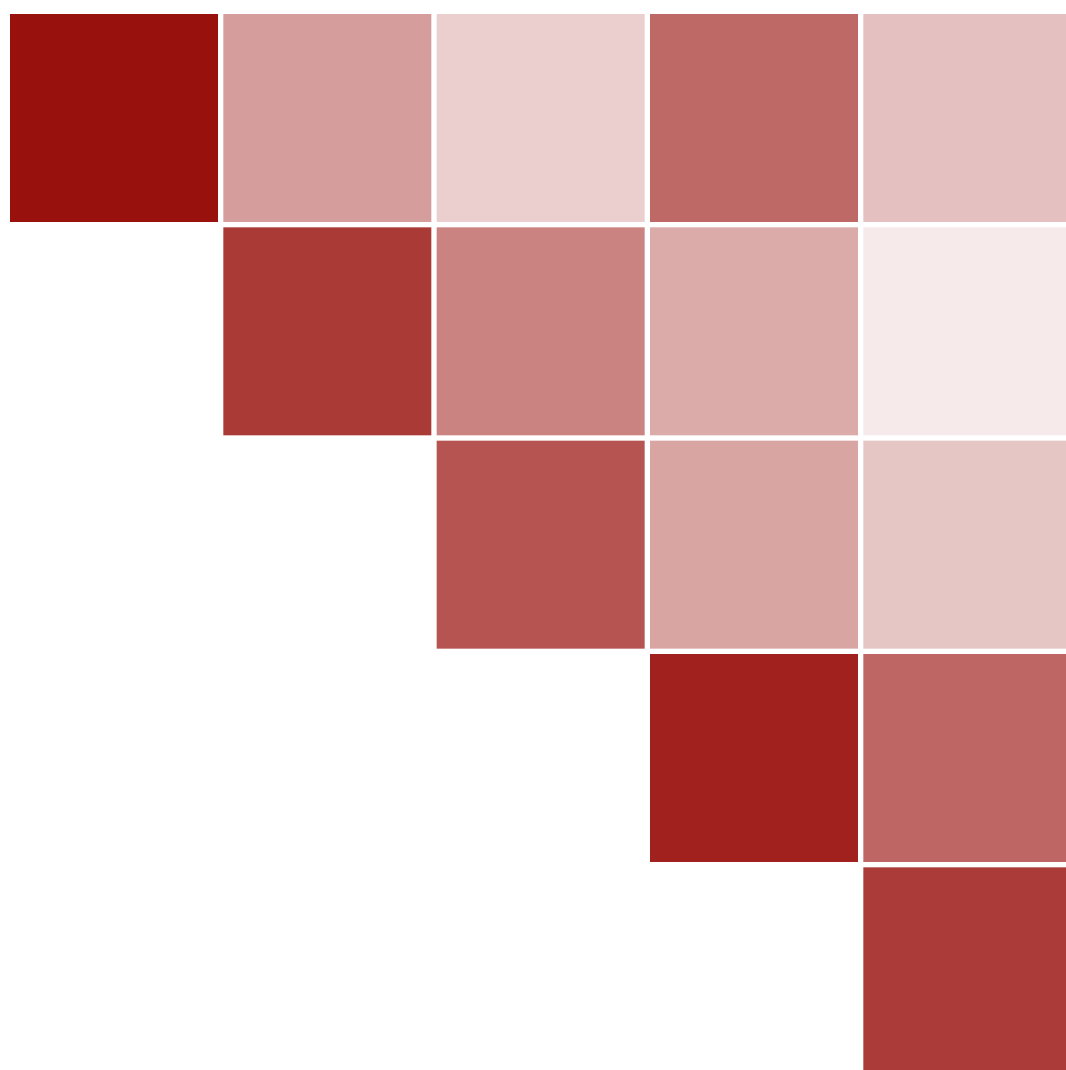
L of initial guess



var-cov matrix
for THETA

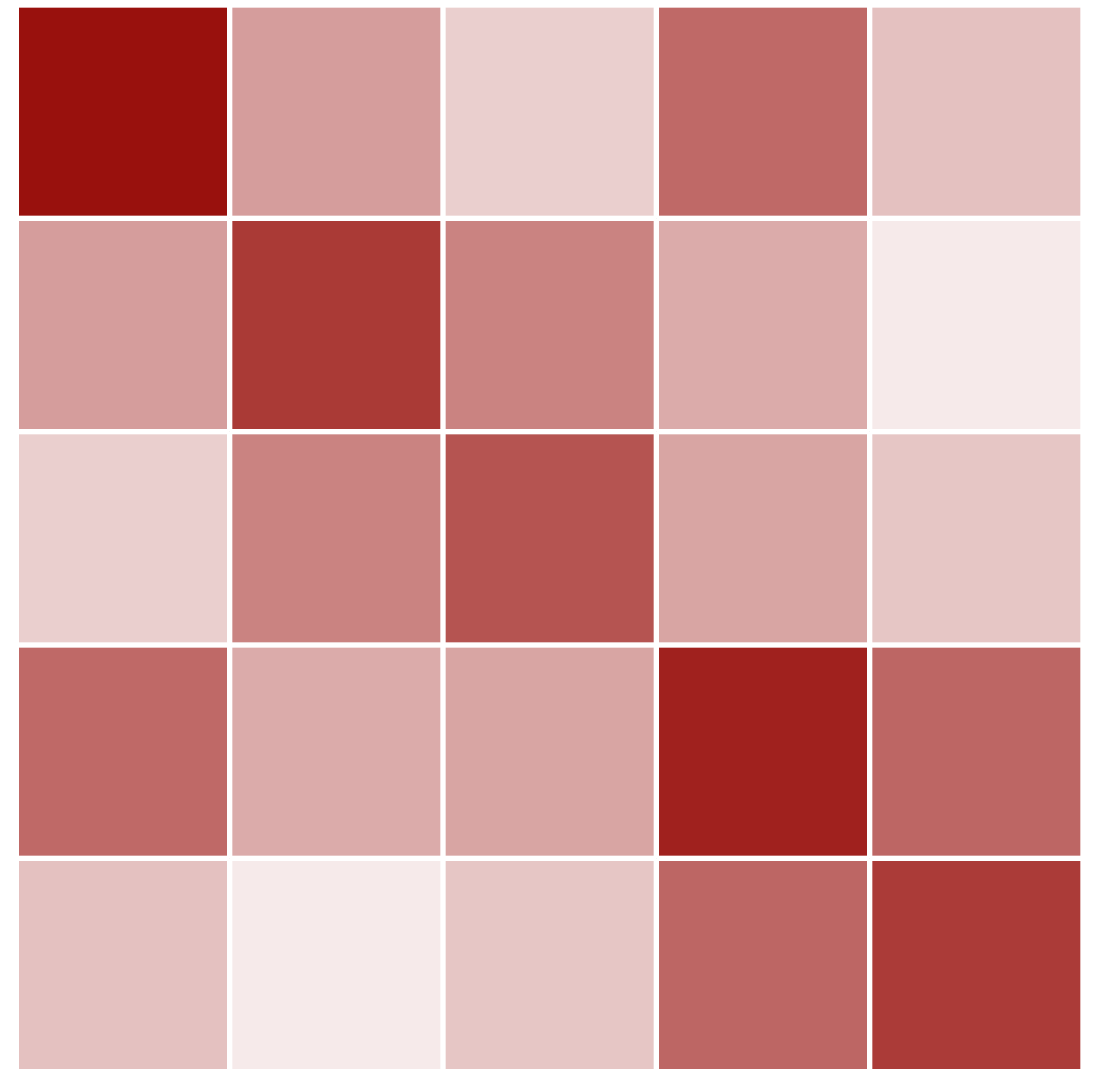


L^T of initial guess



=

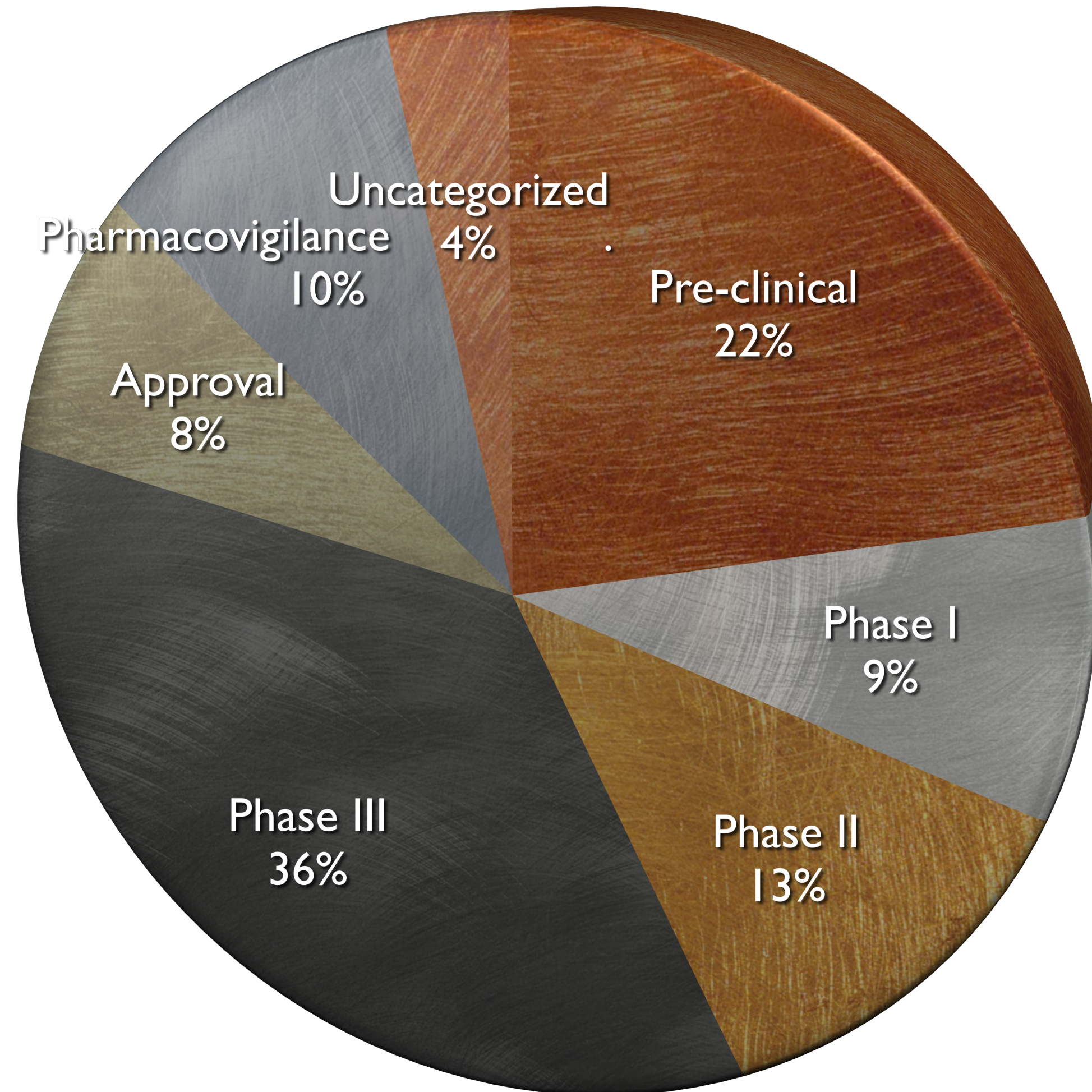
var-cov matrix
for Theta_original





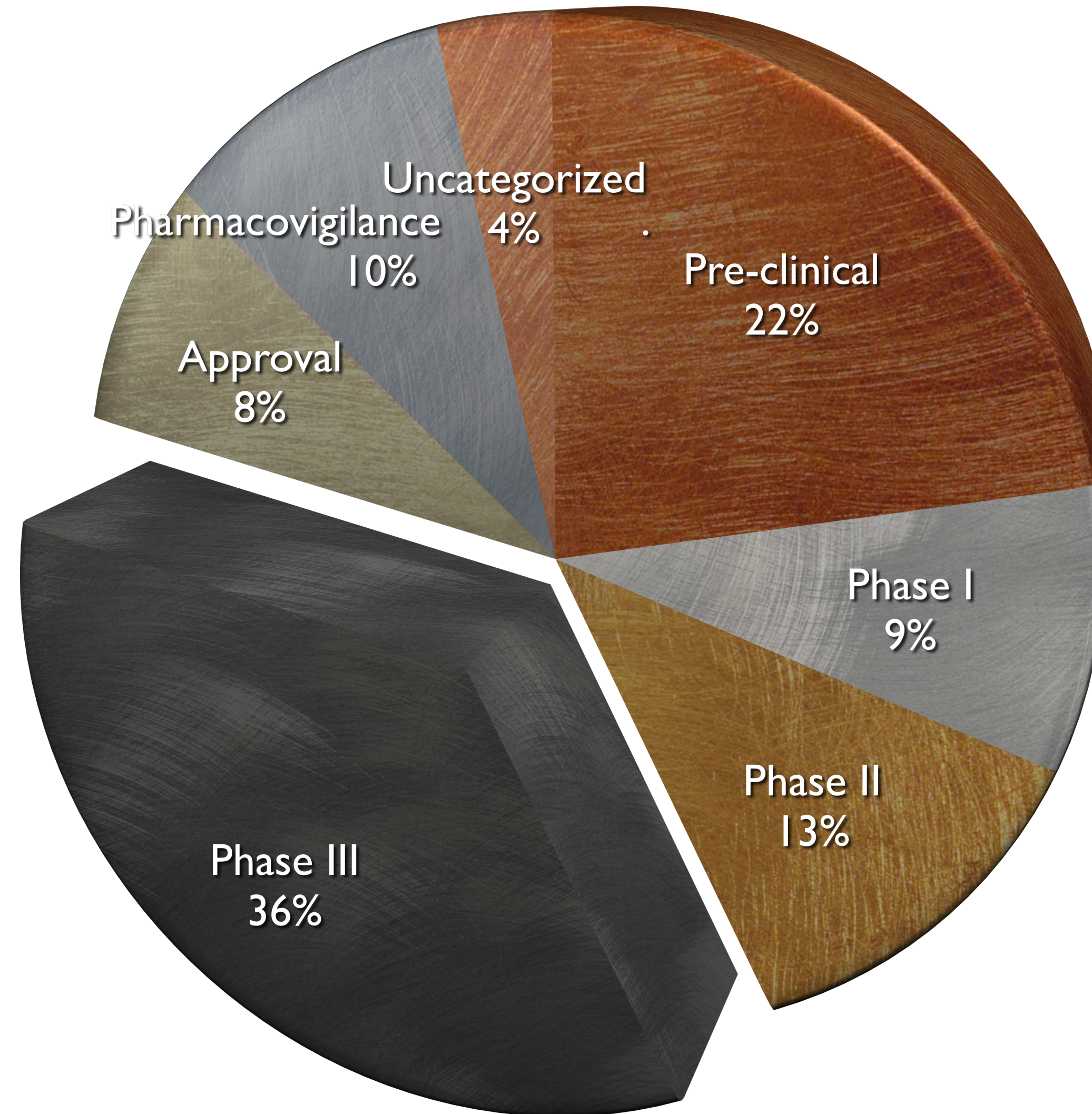
Java based programming language for visual design (e.g. infographics) artists.

Cost of Drug Development Program



Original data obtained from

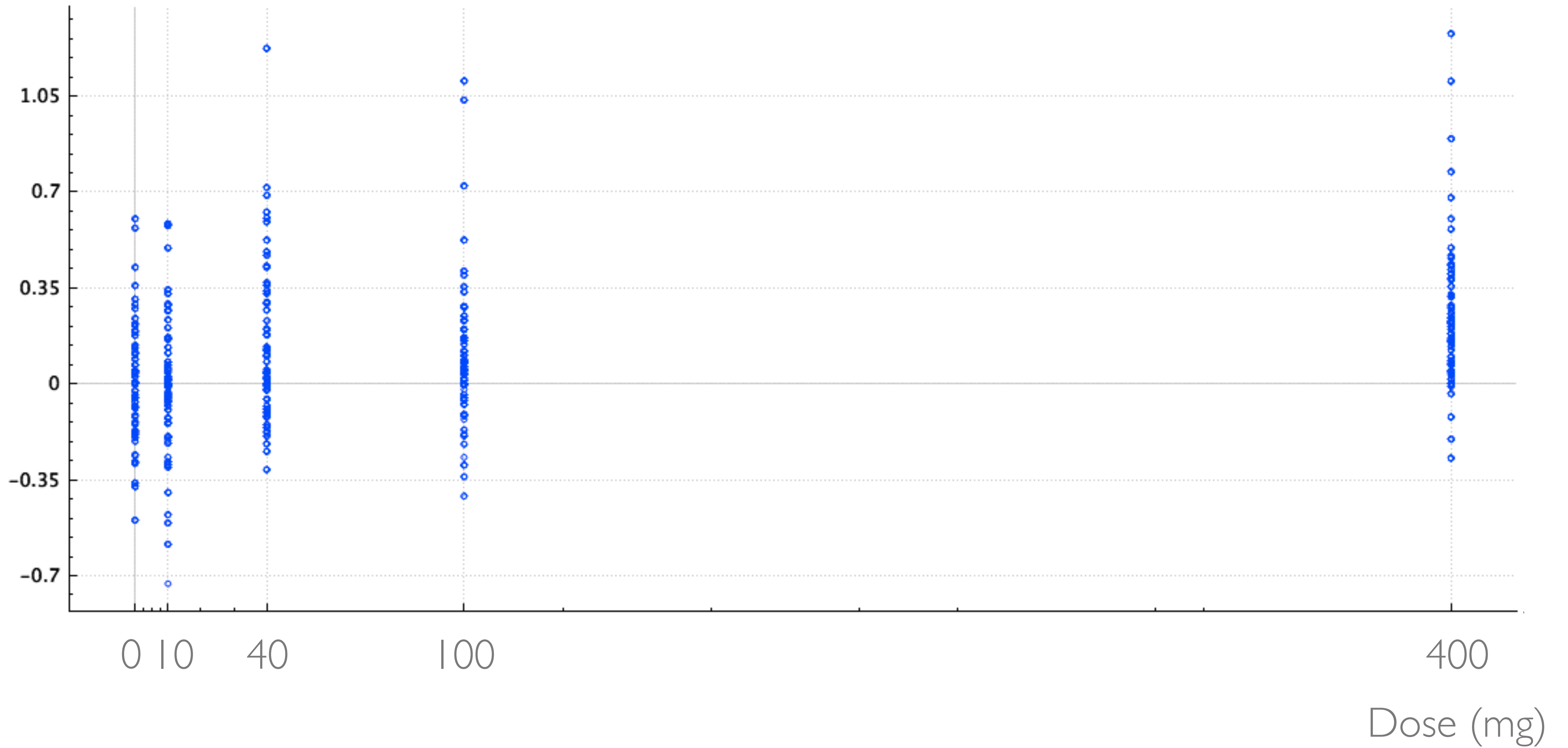
Cost of Drug Development Program



Original data obtained from

Baseline and Average Placebo adjusted FEV1 (L)

FEV1



Baseline and Average Placebo adjusted FEV1 (L)

FEV1

