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# Model Averaging and assessing uncertainty

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# 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.

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# Model Averaging

how we do it

Placebo Model

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



Placebo Model

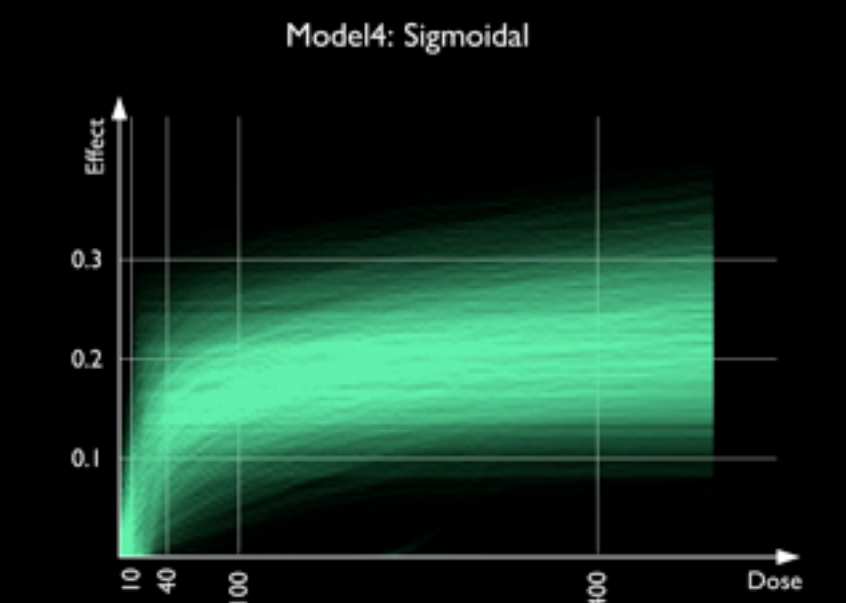
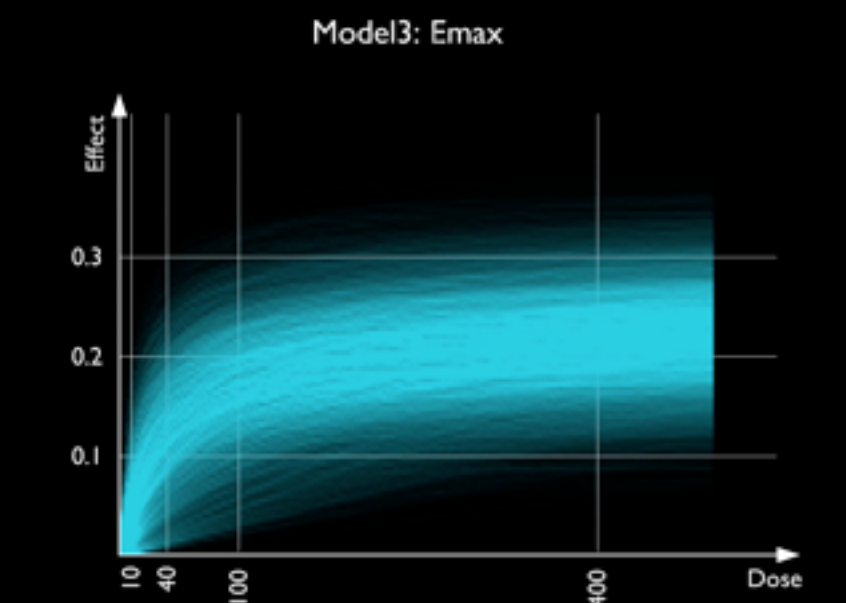
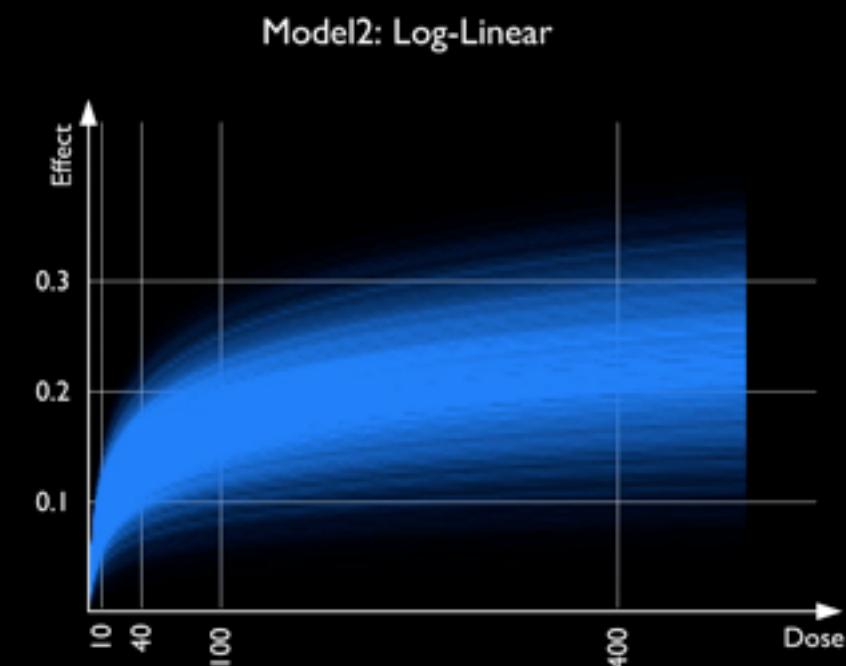
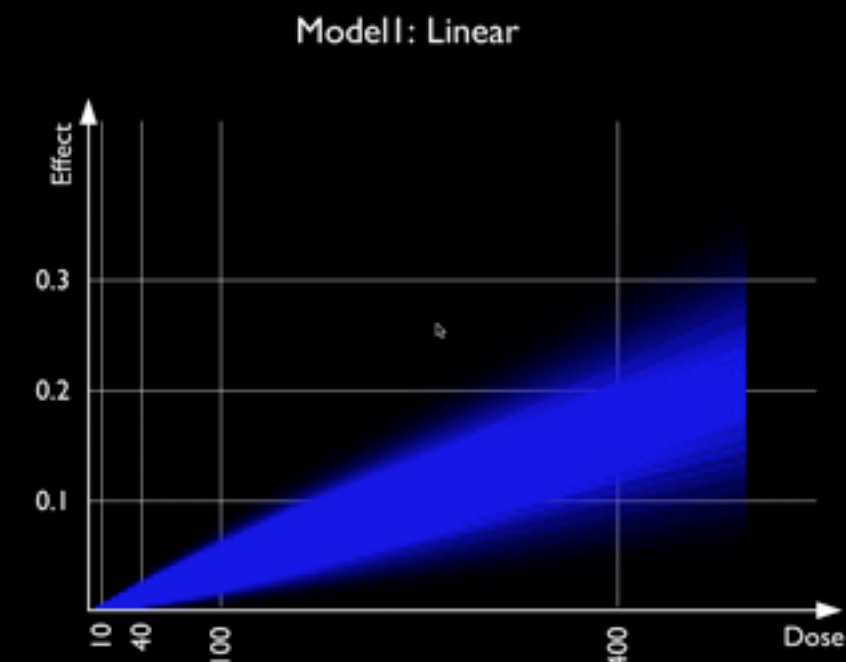


Placebo Model + Linear

Placebo Model + Log-linear

Placebo Model + Emax

Placebo Model + Sigmoidal



Placebo Model



Placebo Model + Linear

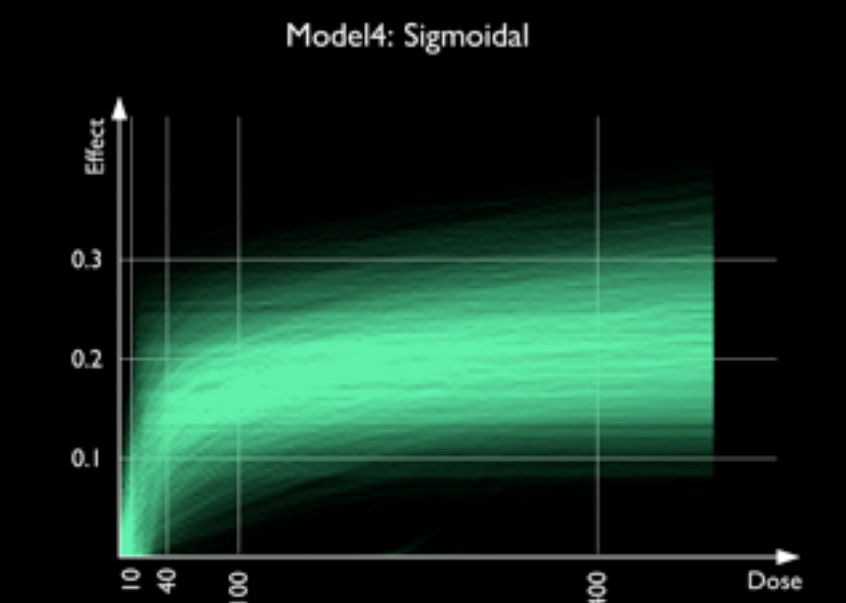
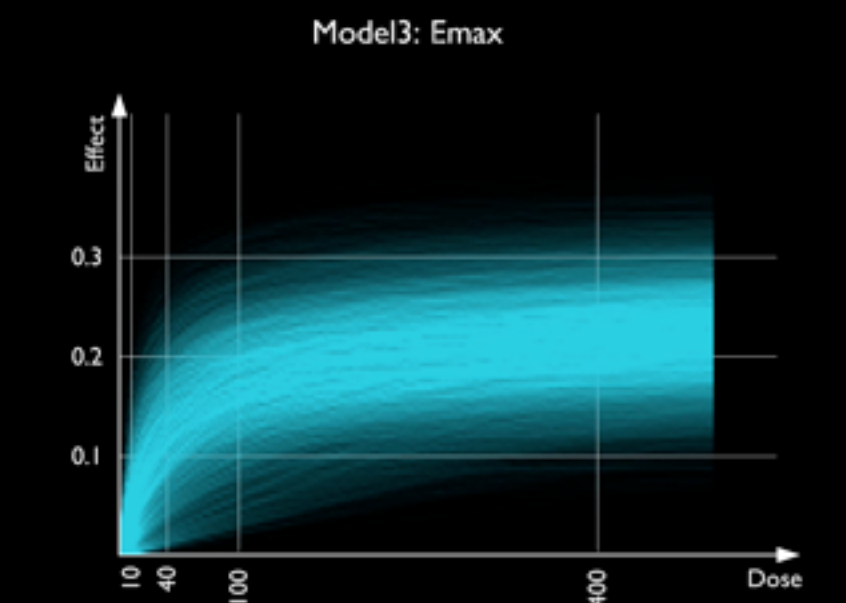
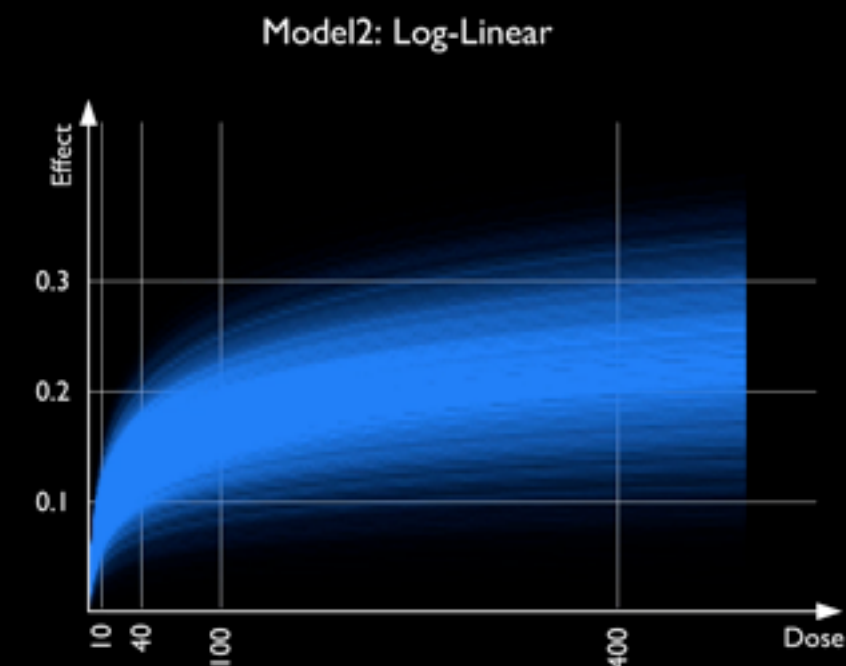
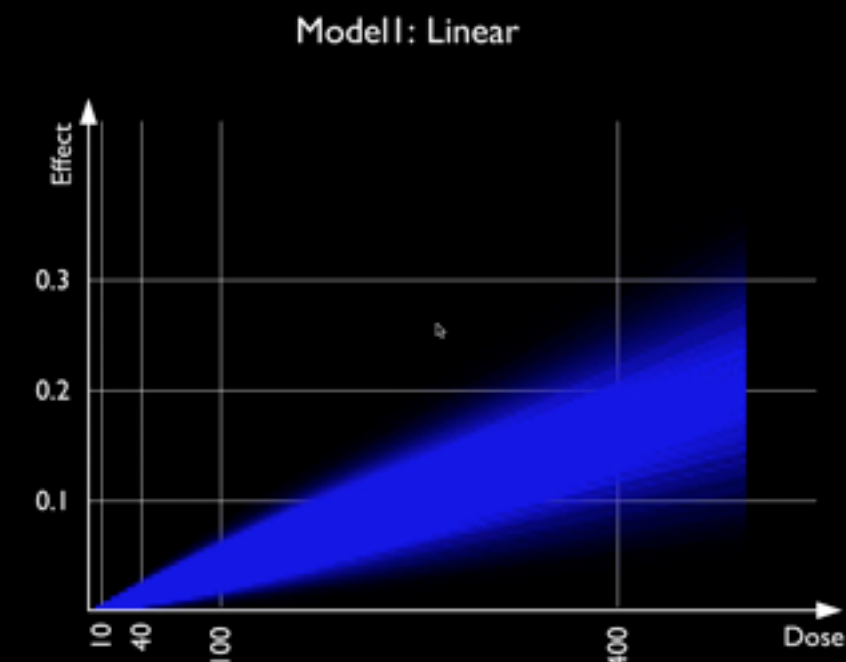
Placebo Model + Log-linear

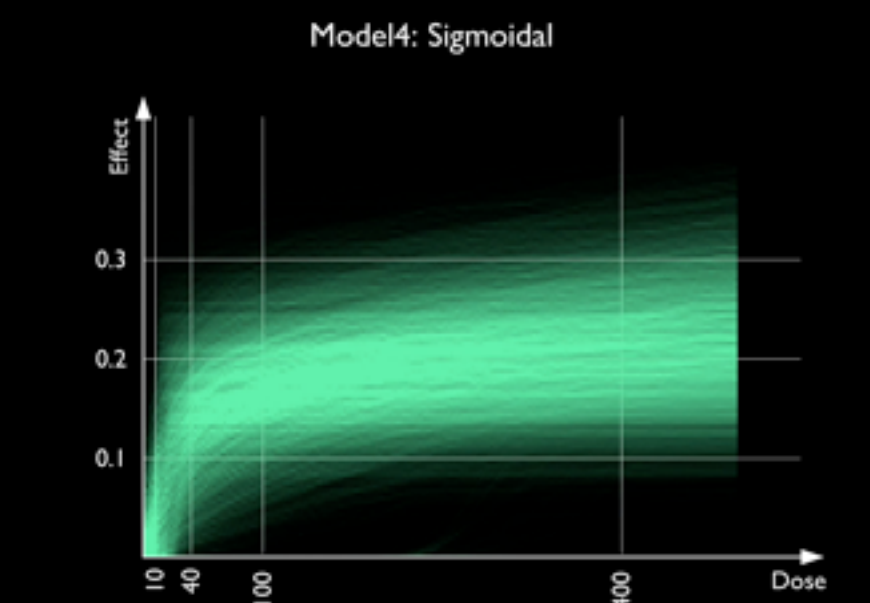
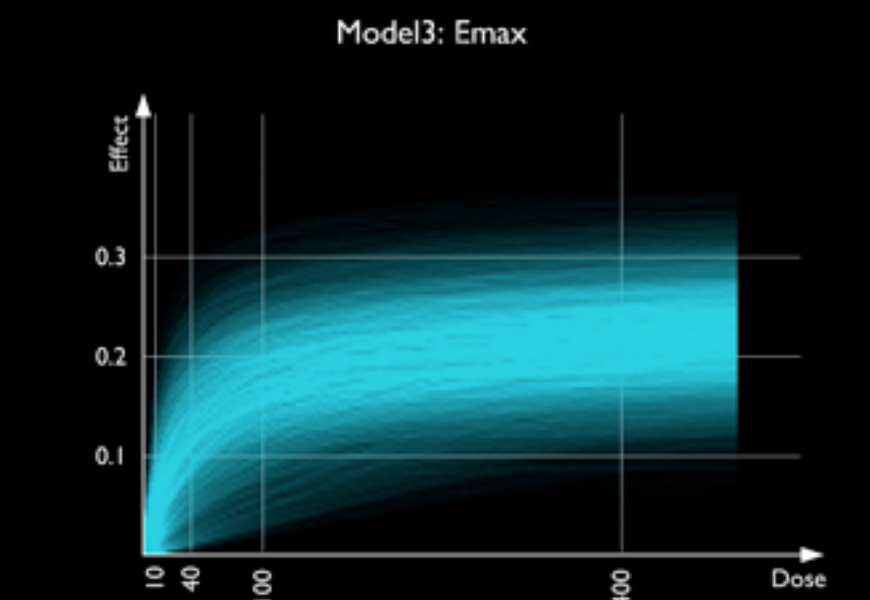
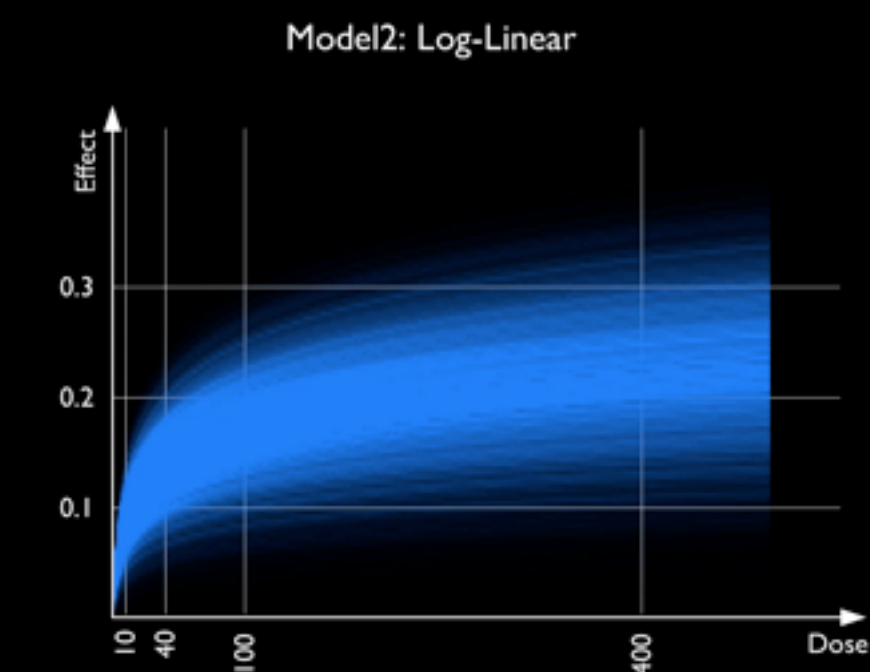
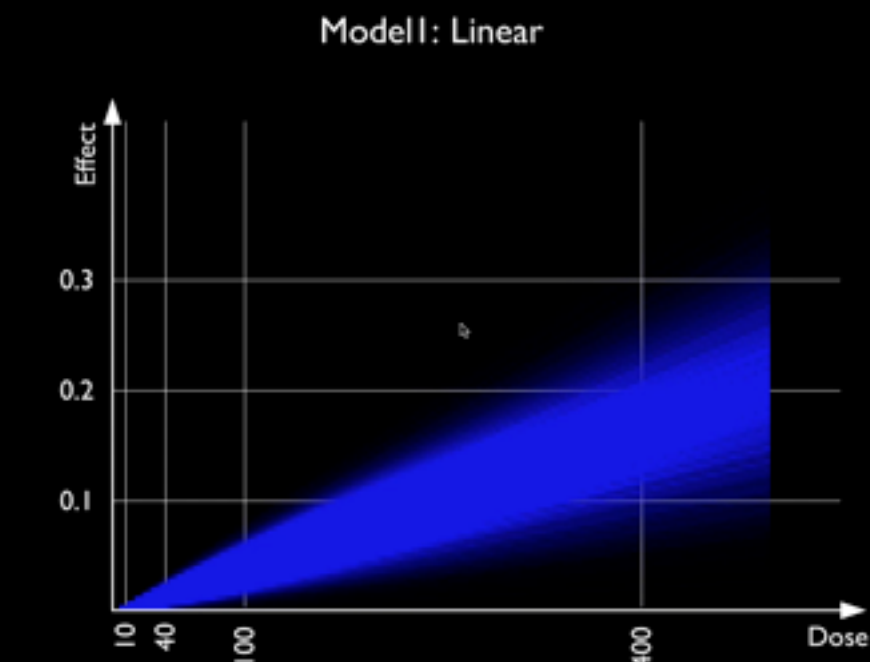
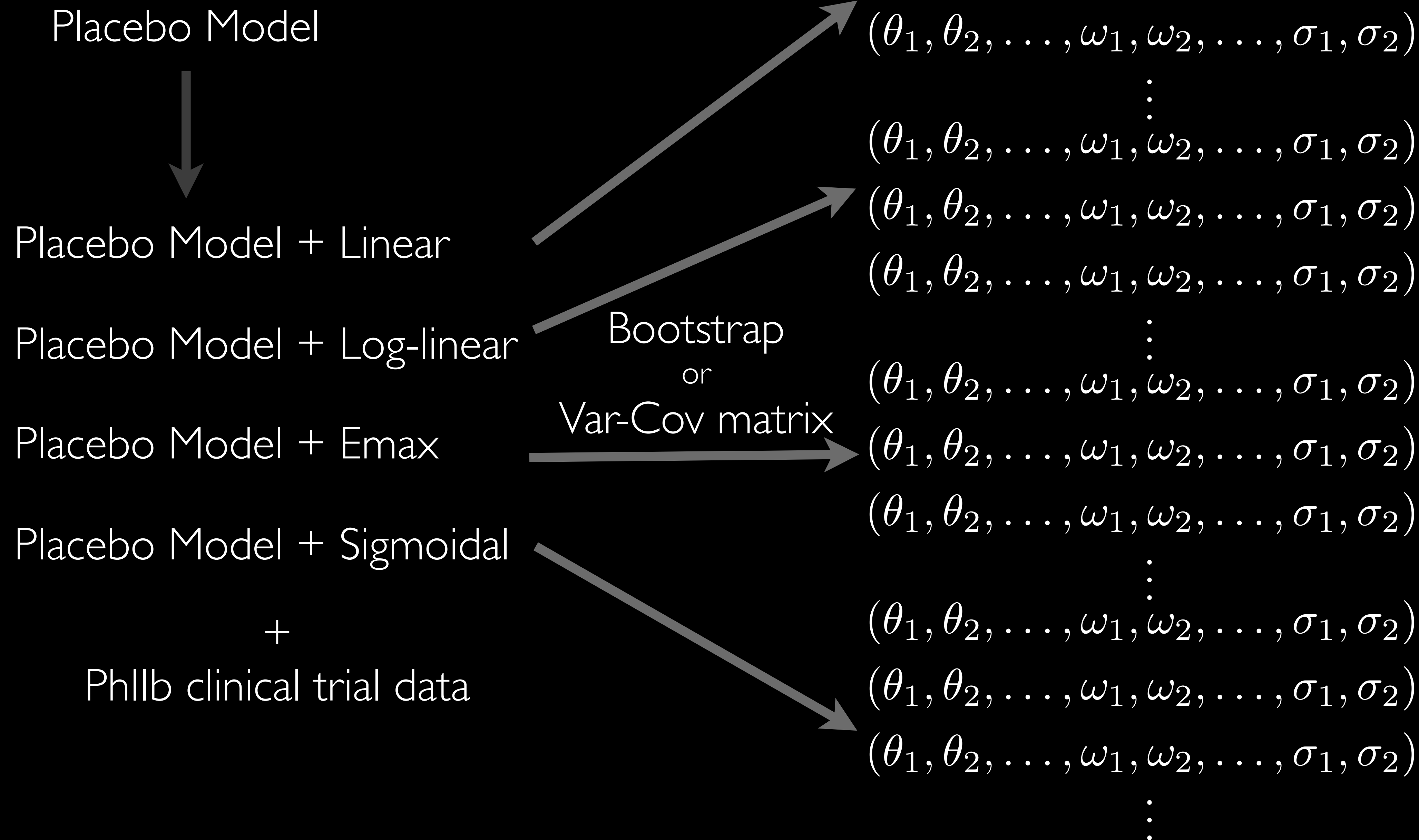
Placebo Model + Emax

Placebo Model + Sigmoidal

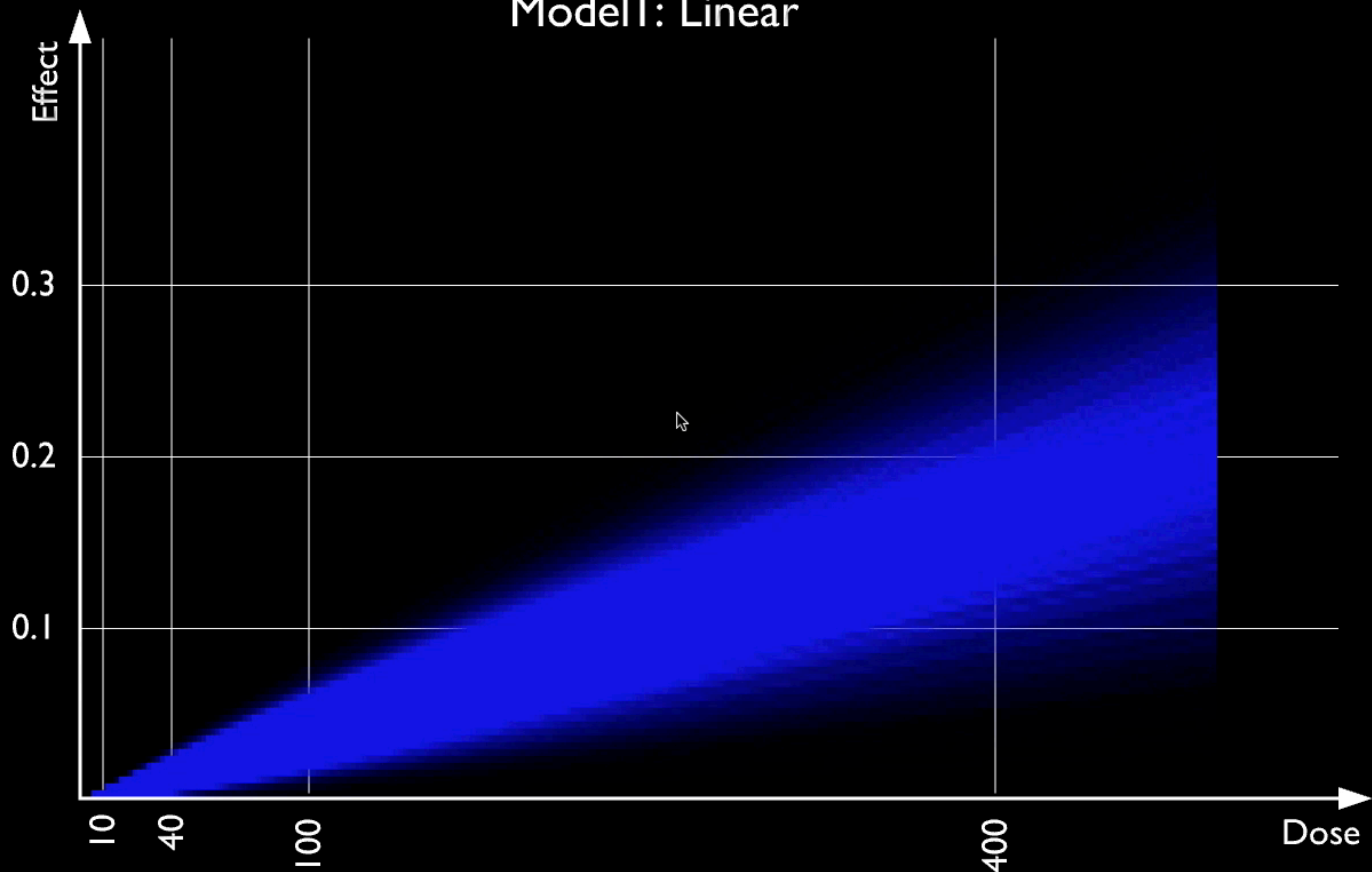
+

PhIIb clinical trial data



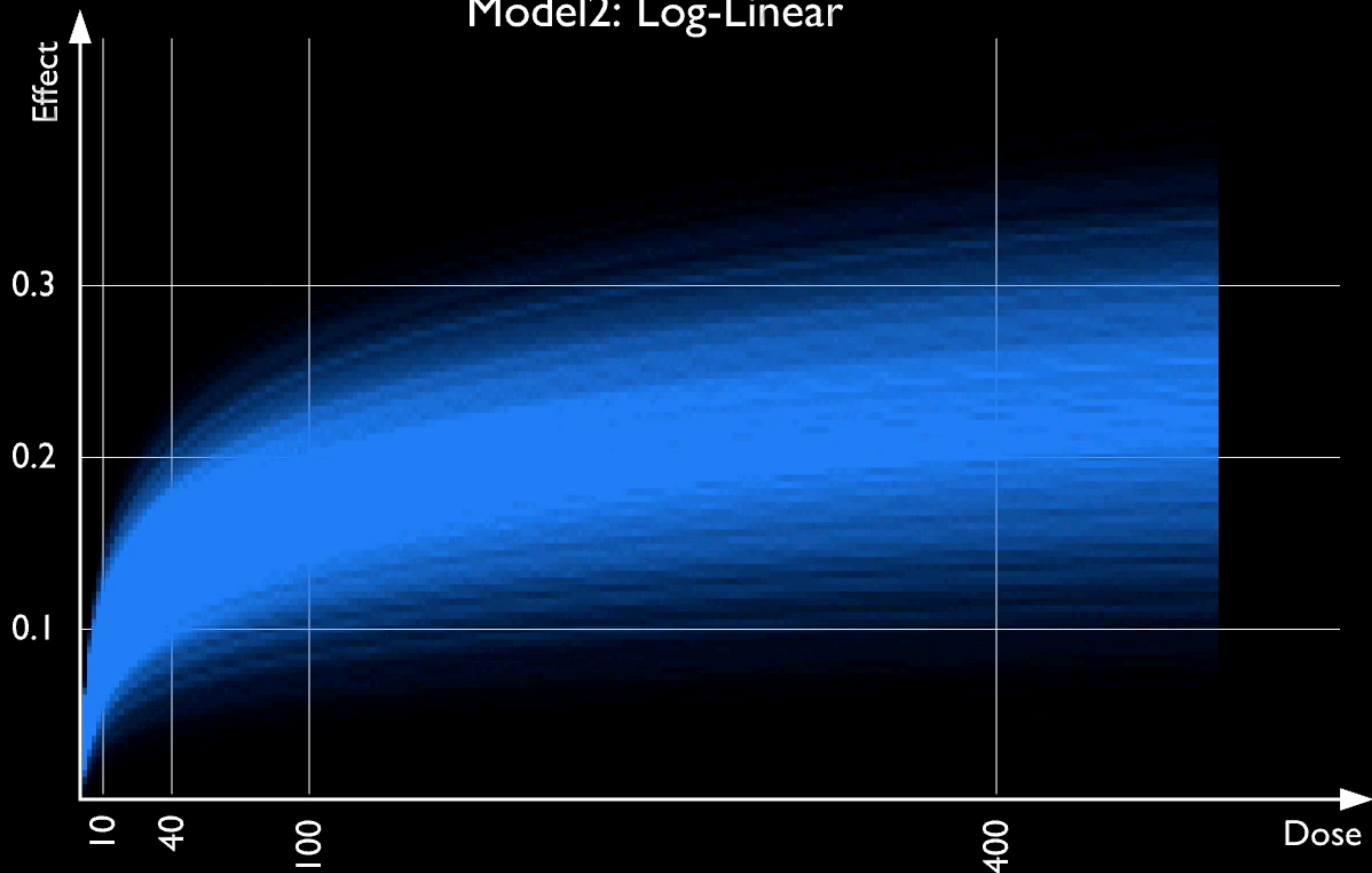


Model I: Linear

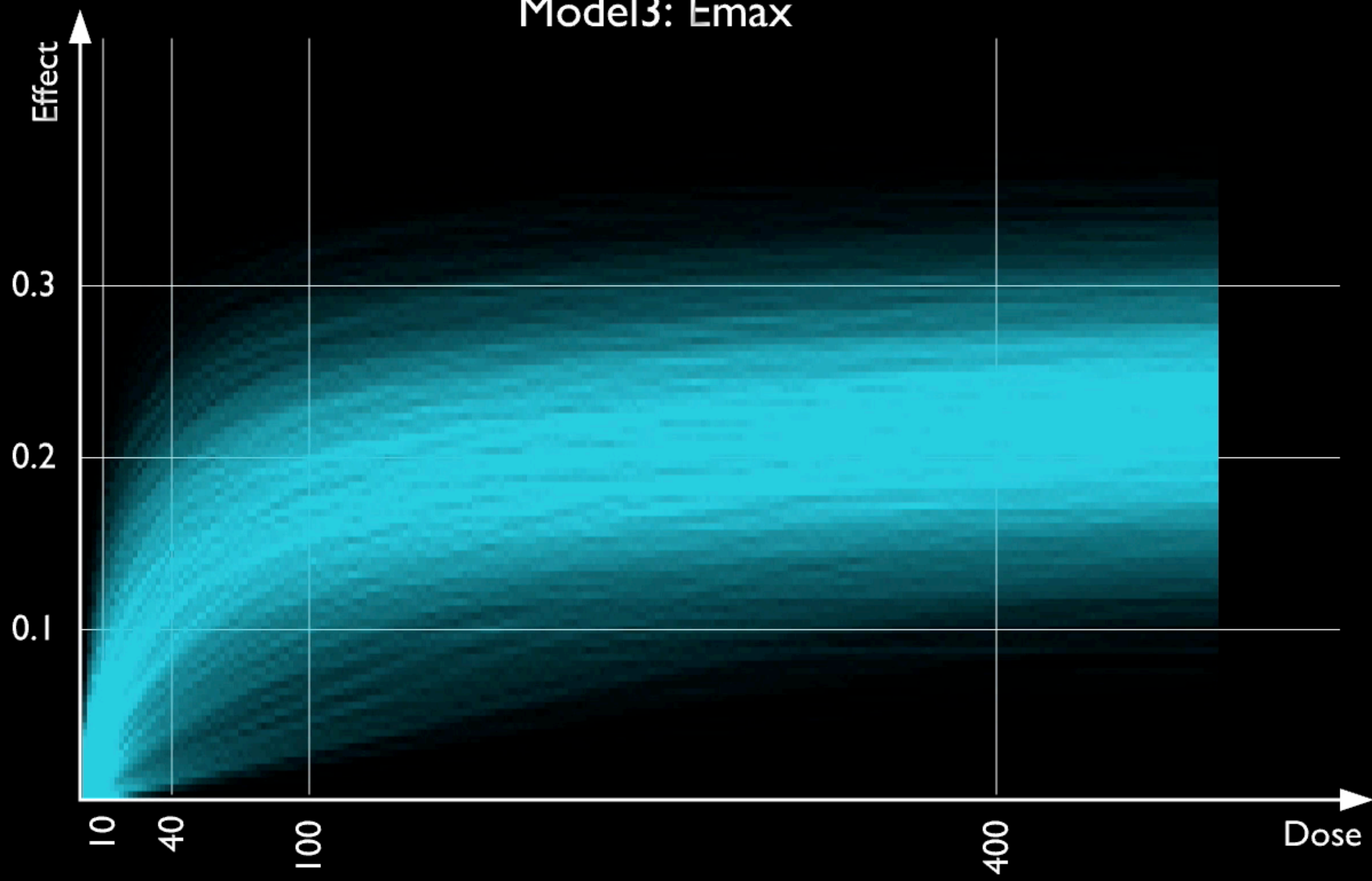




Model2: Log-Linear

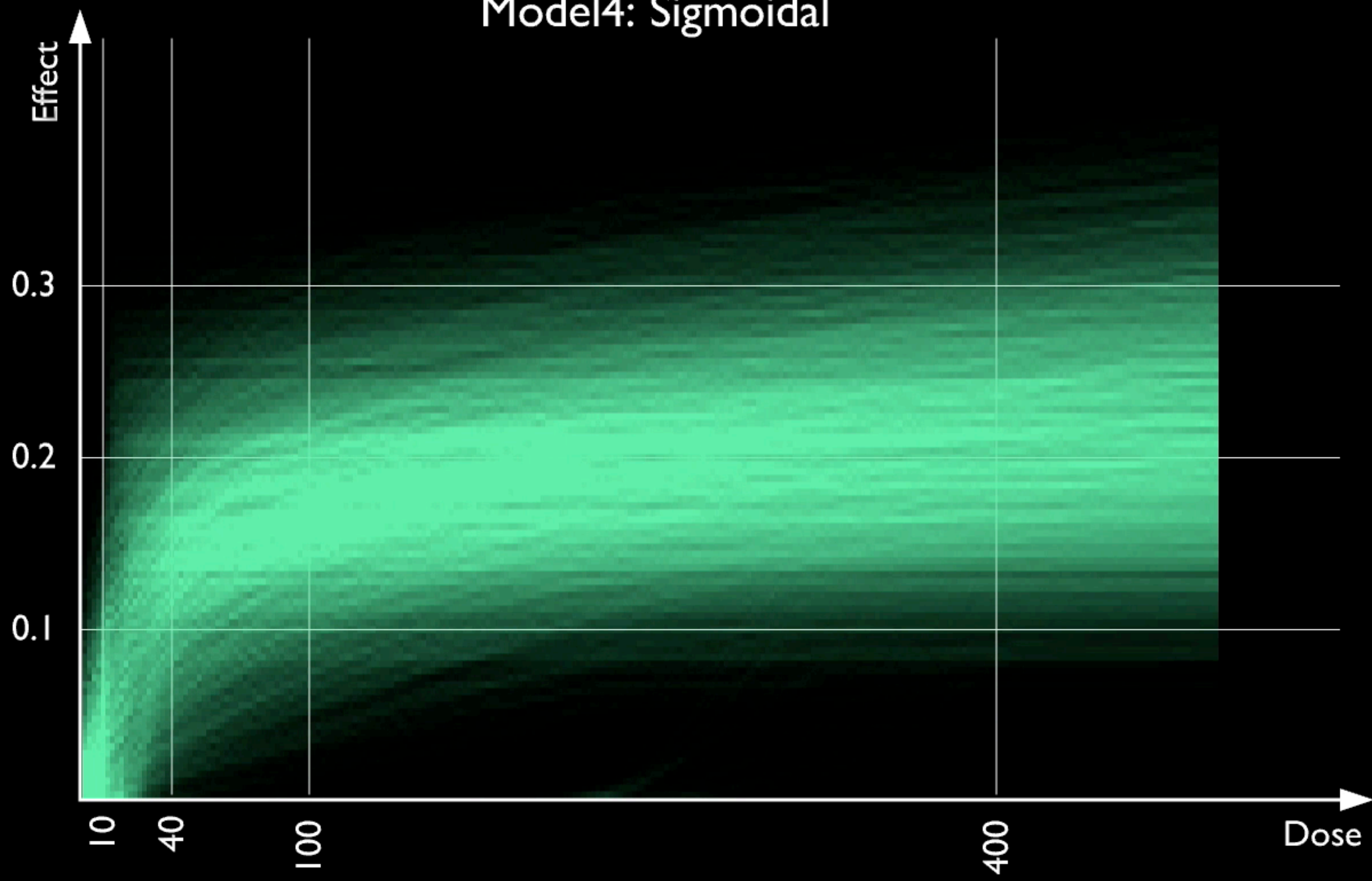


Model3: Emax

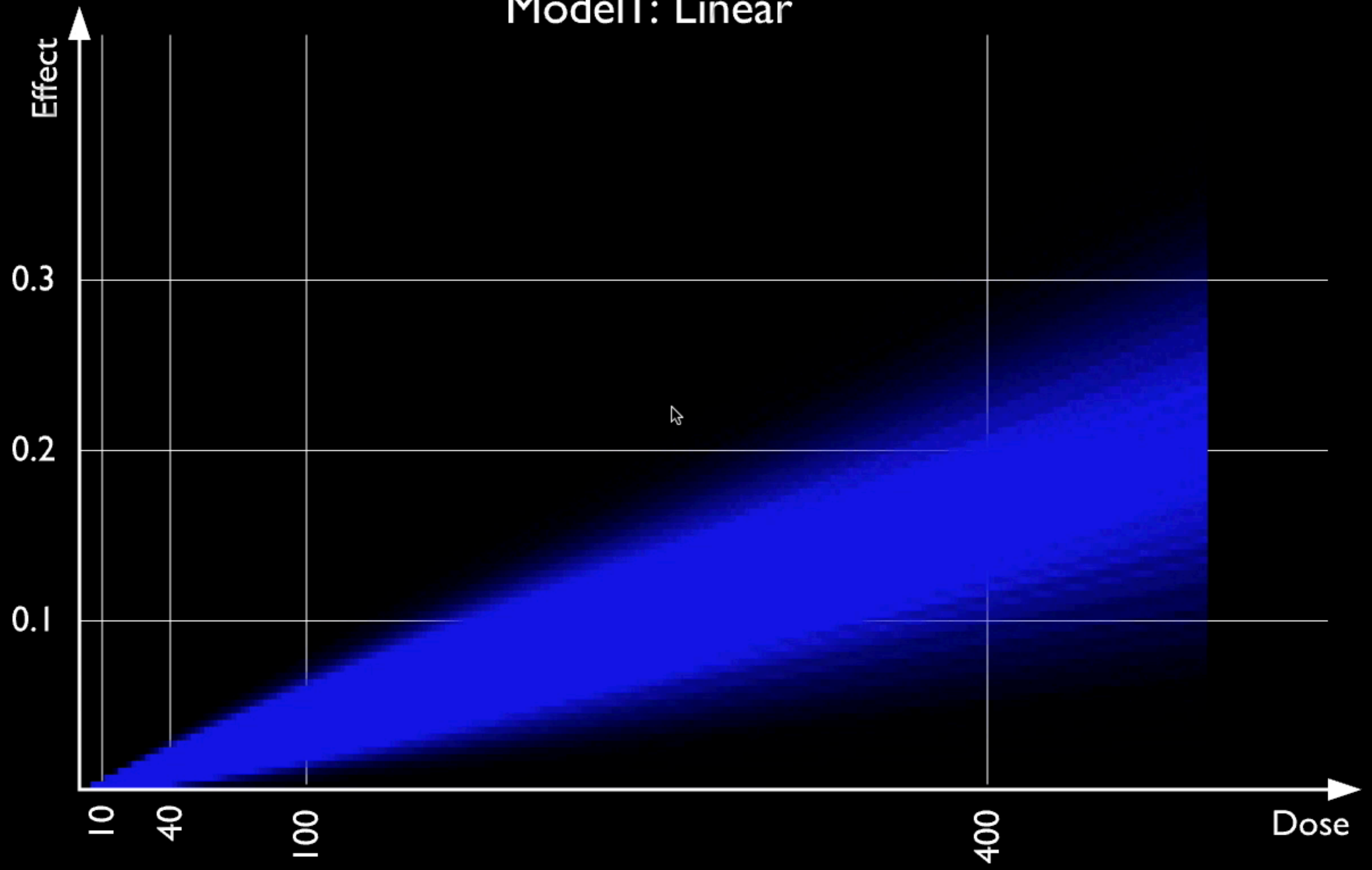




Model4: Sigmoidal

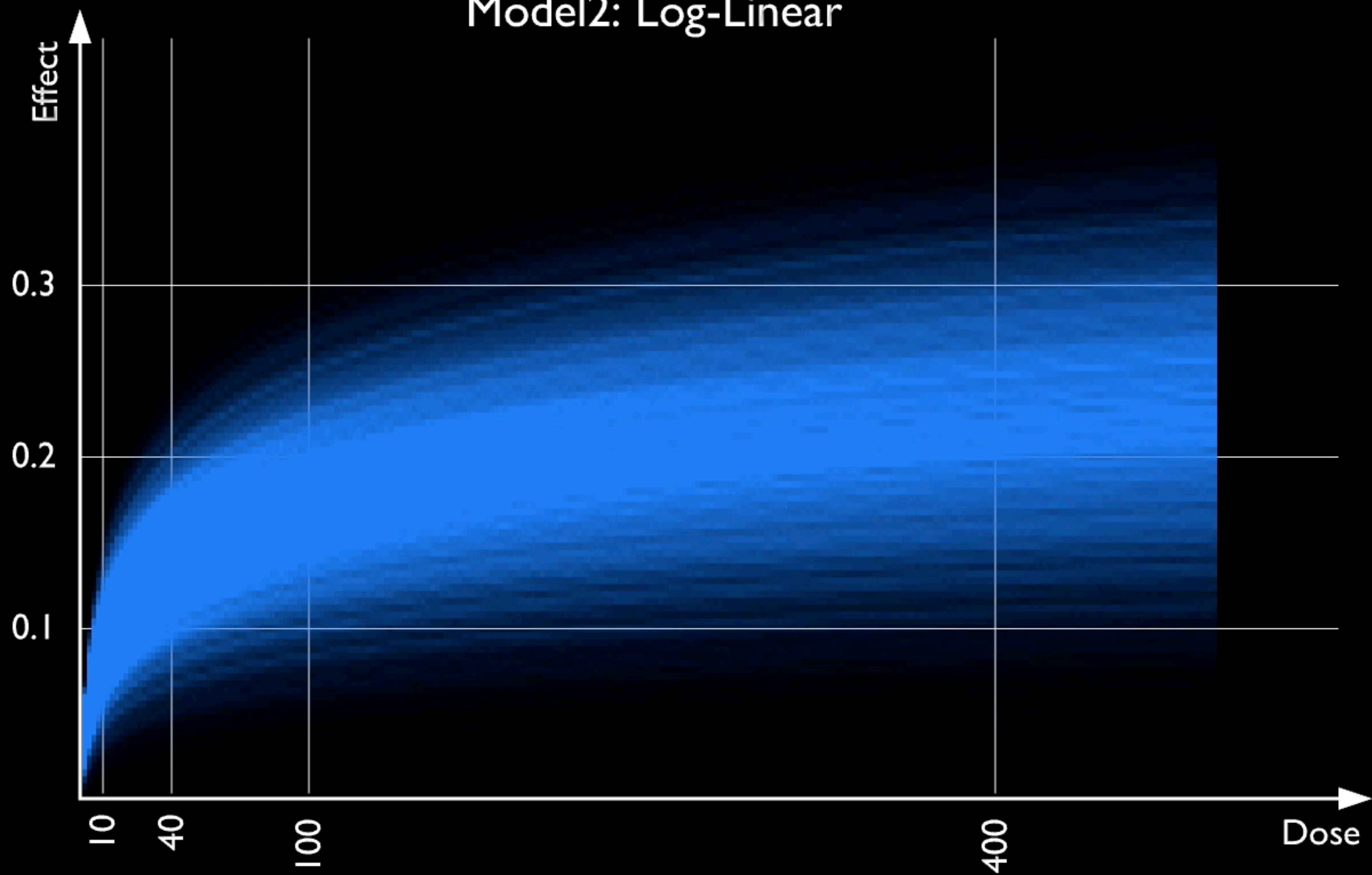


Model I: Linear

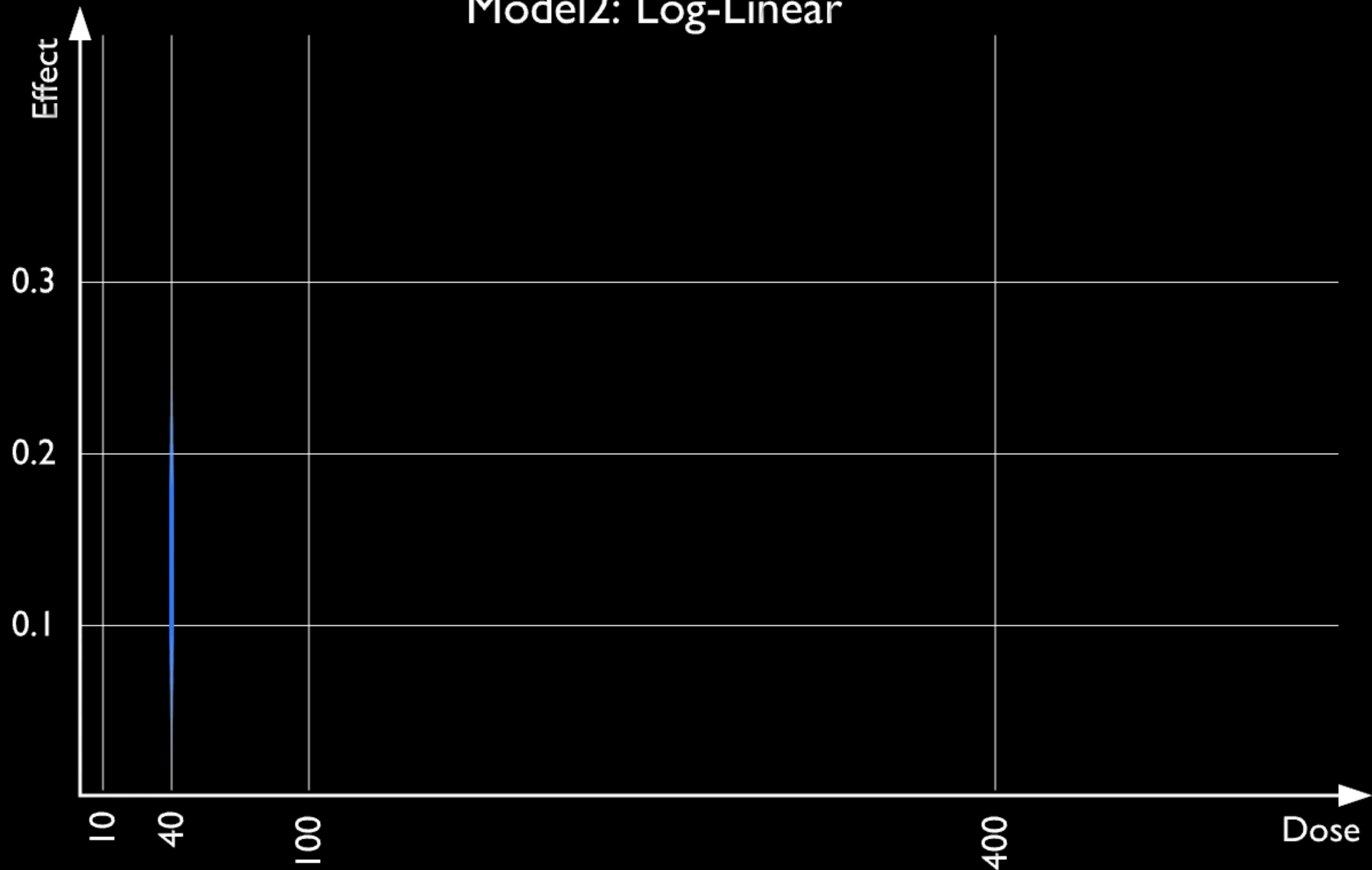




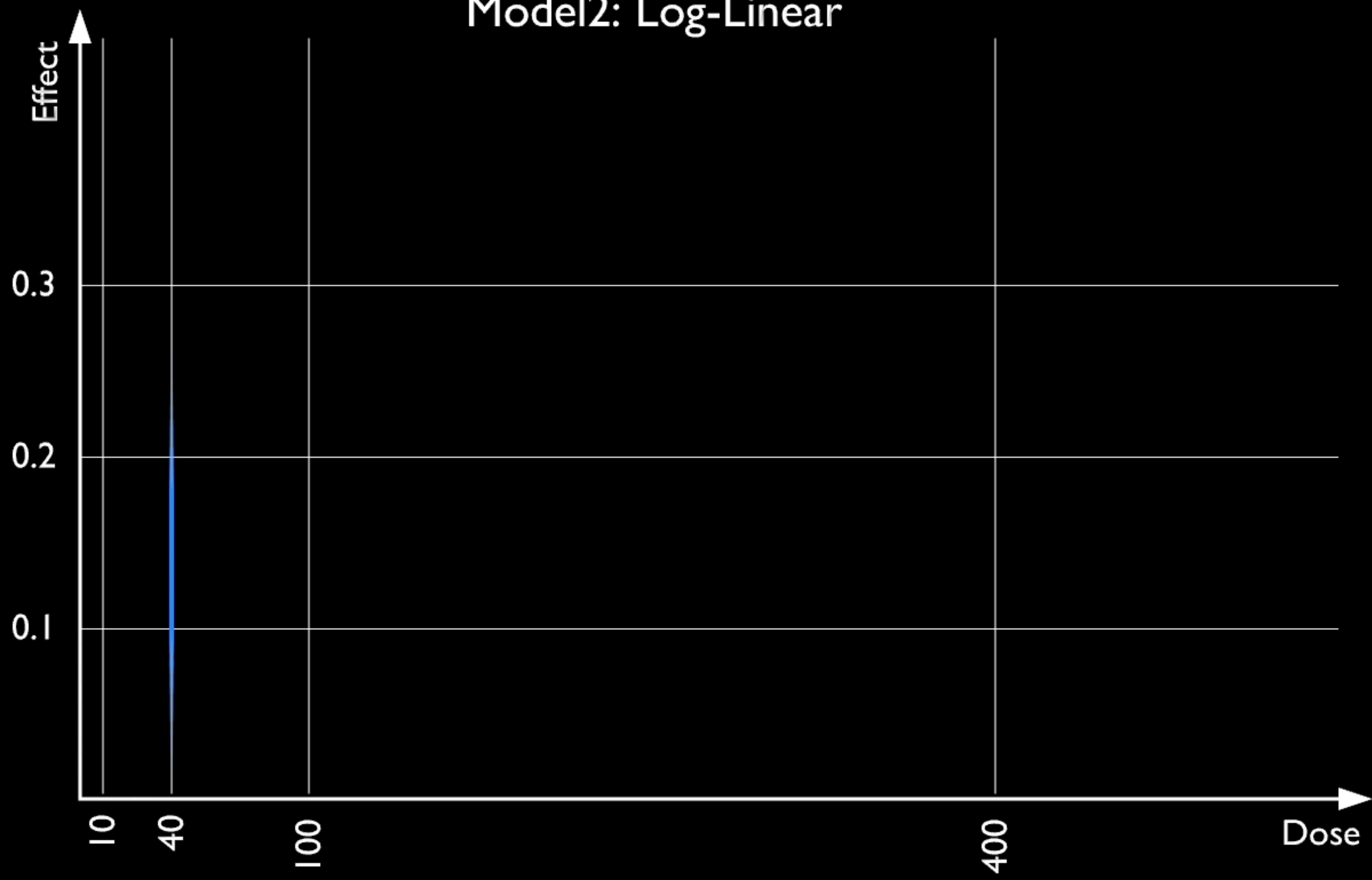
Model2: Log-Linear



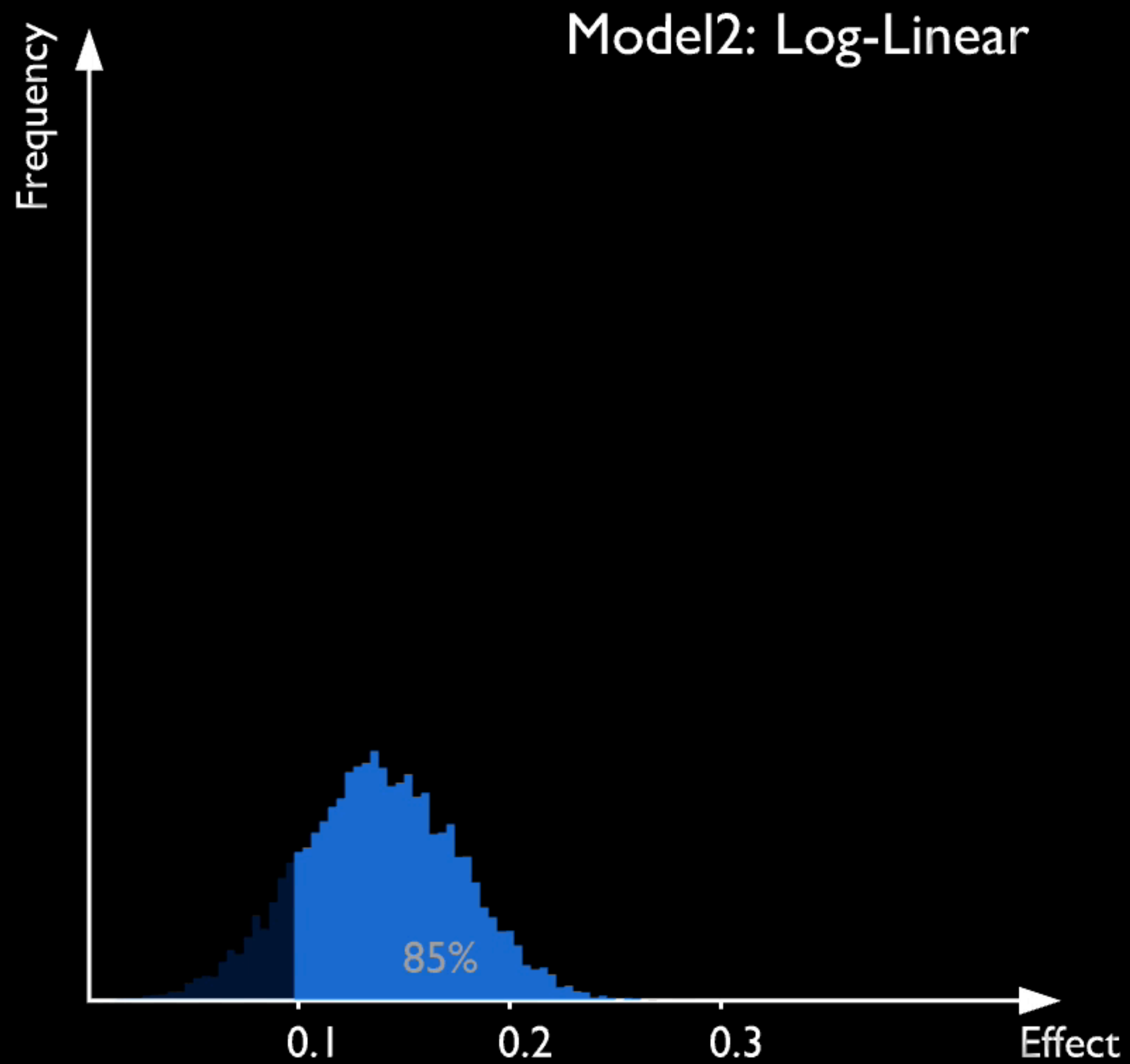
Model2: Log-Linear



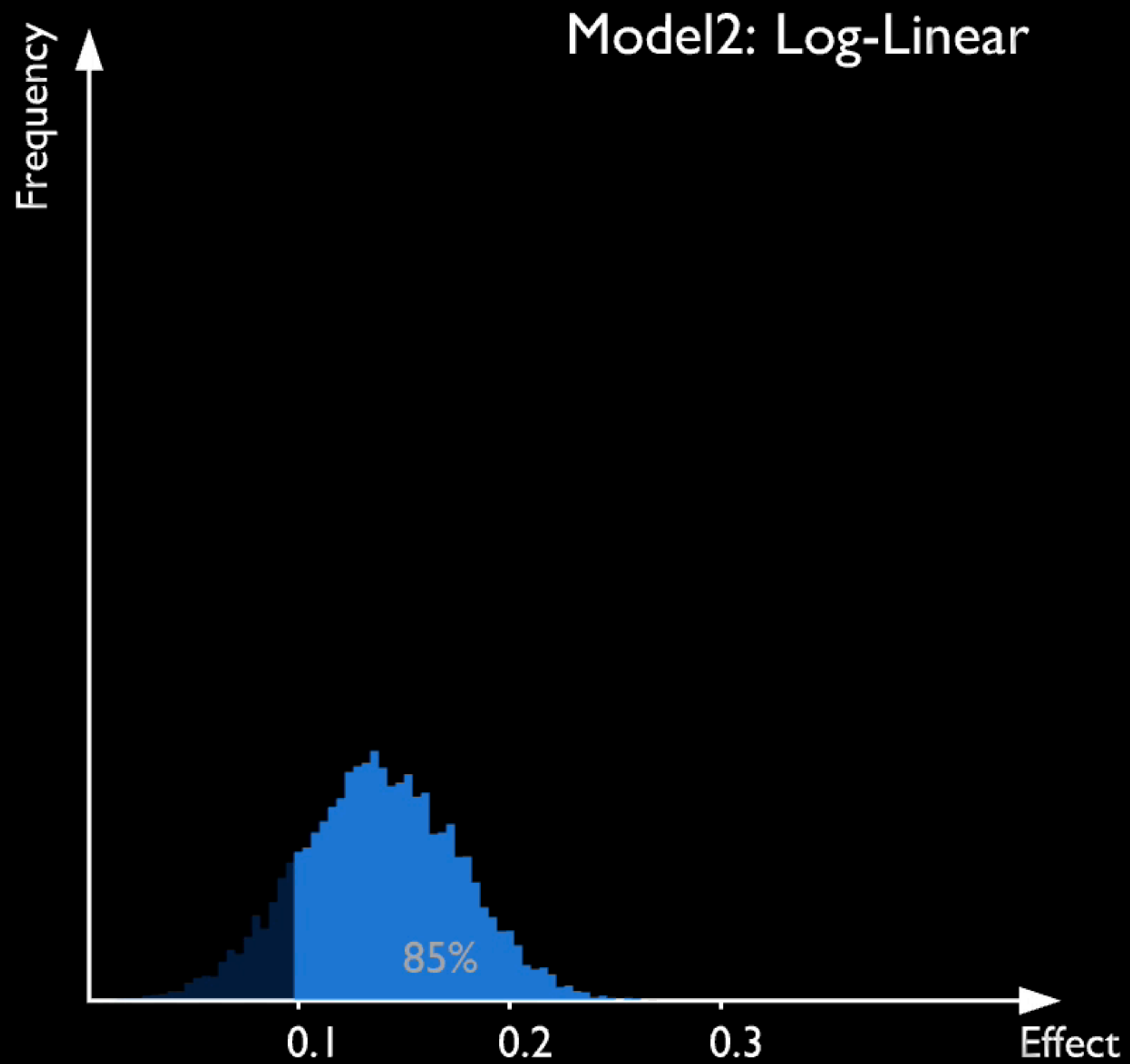
Model2: Log-Linear



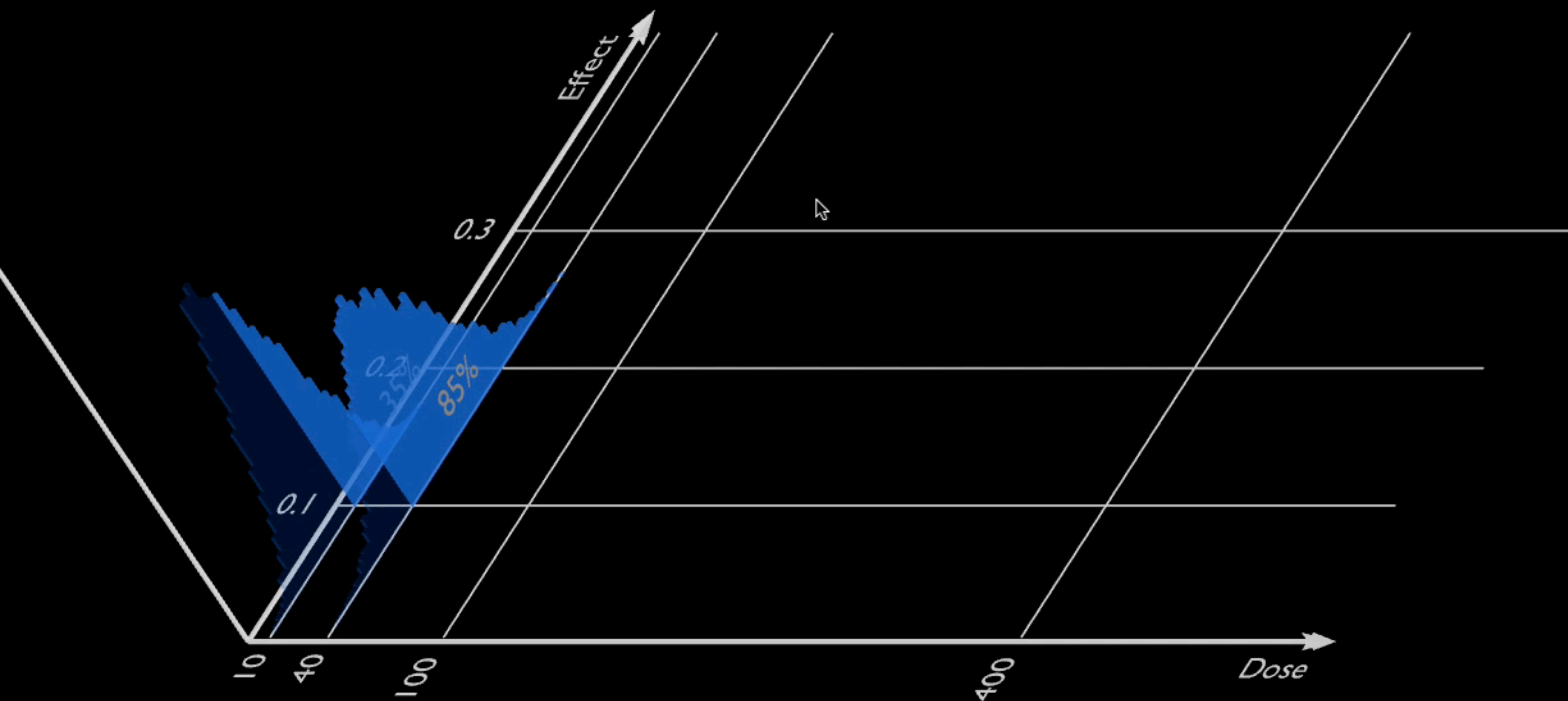
Model2: Log-Linear



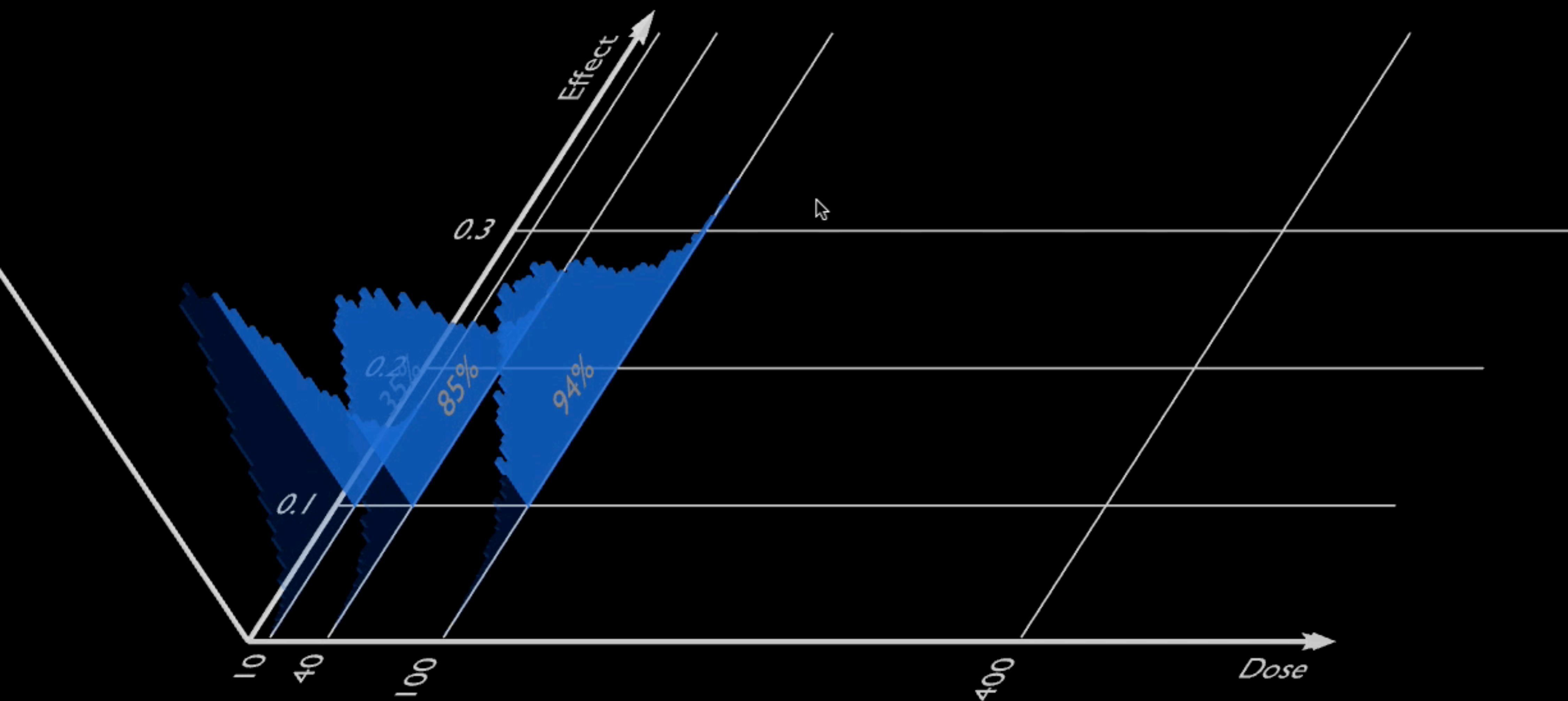
Model2: Log-Linear



## Model2: Log-Linear

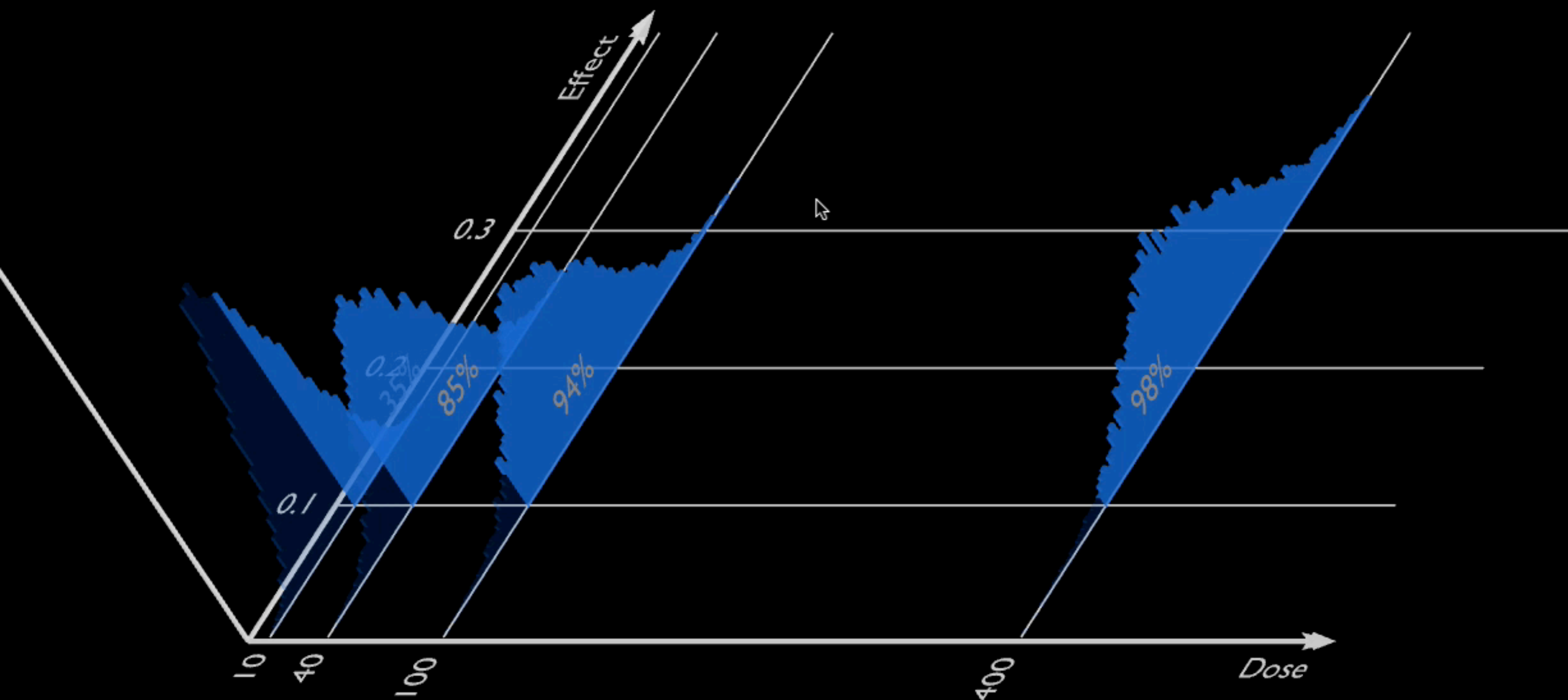


## Model2: Log-Linear



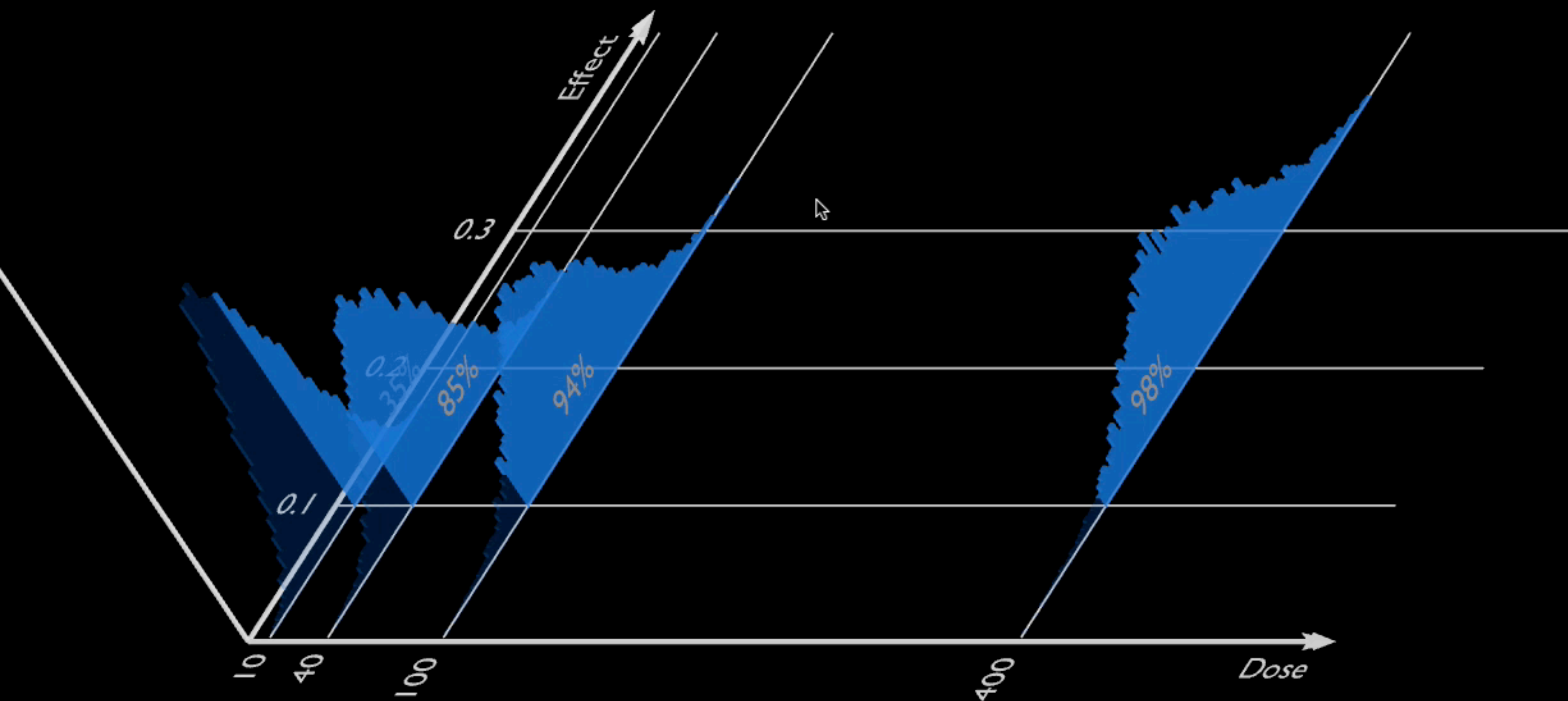


## Model2: Log-Linear

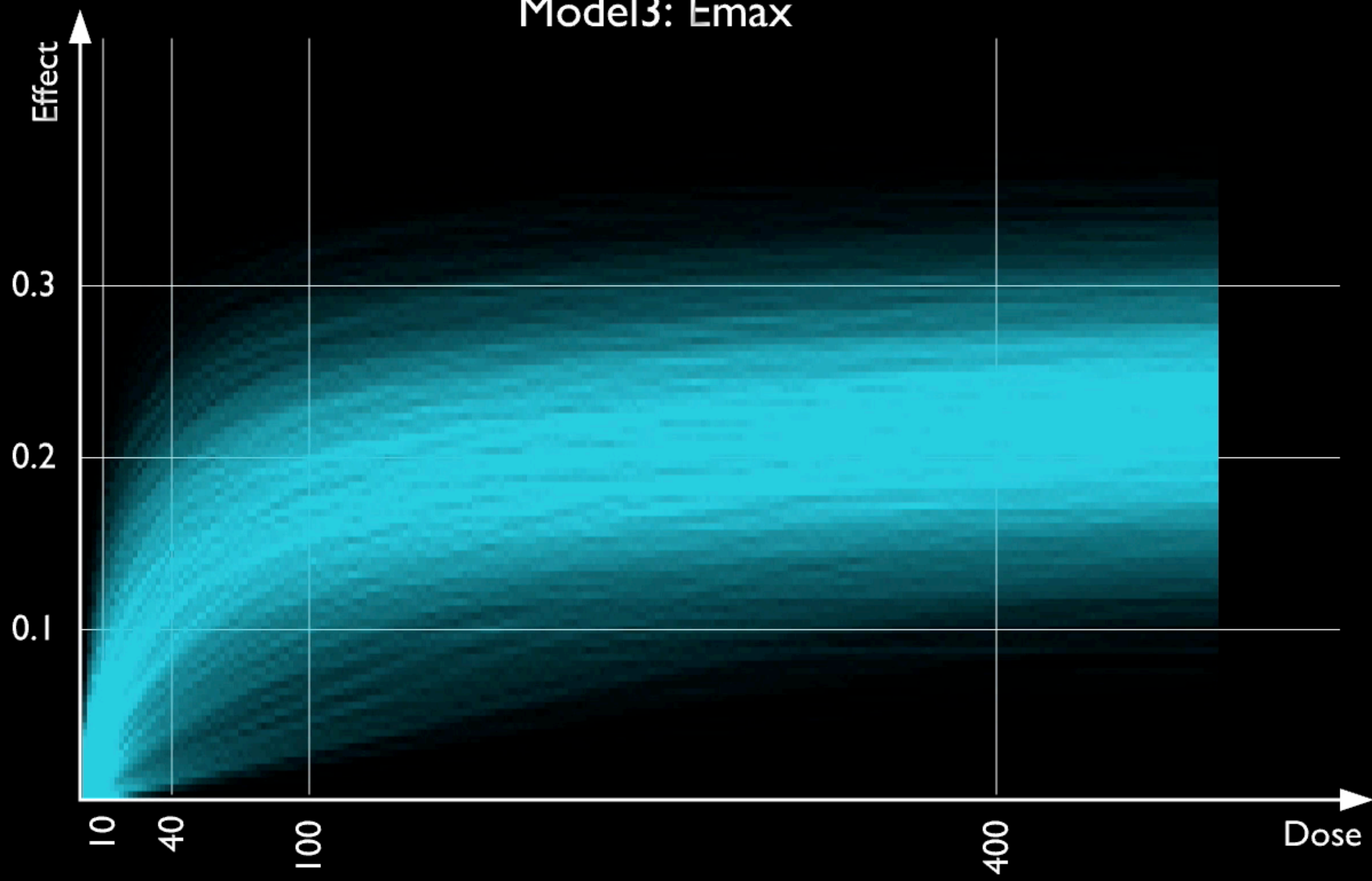




## Model2: Log-Linear

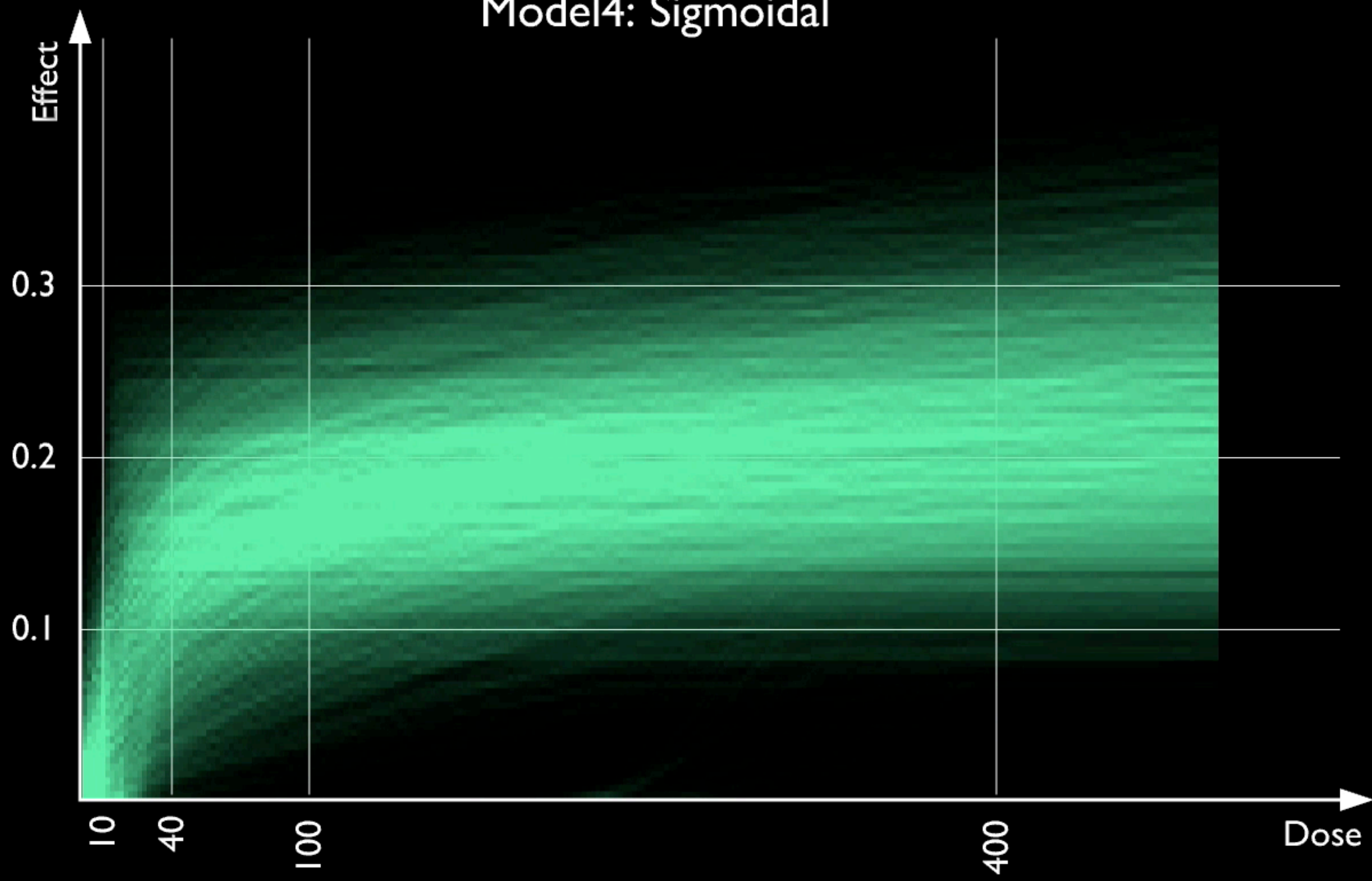


Model3: Emax

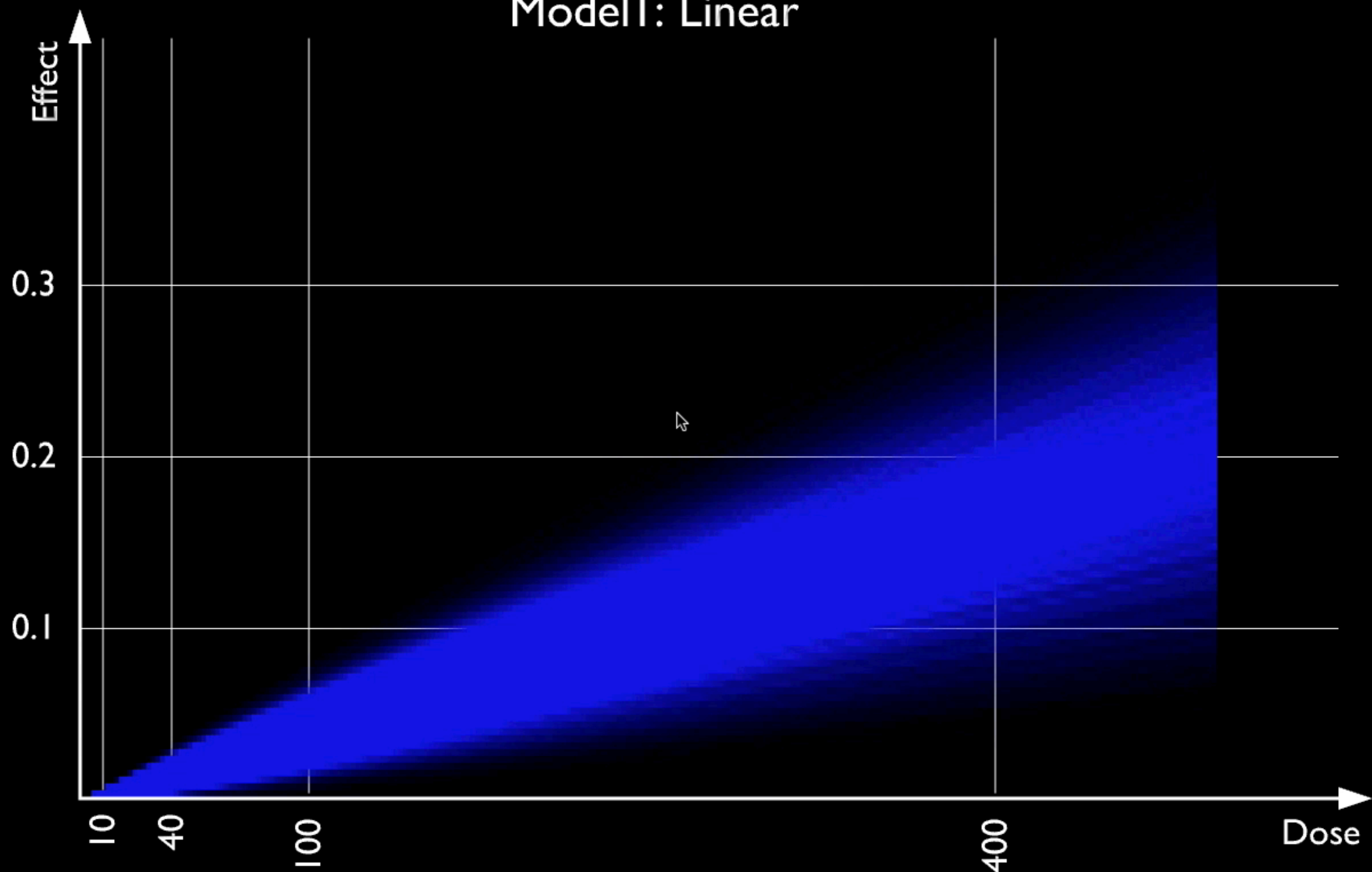




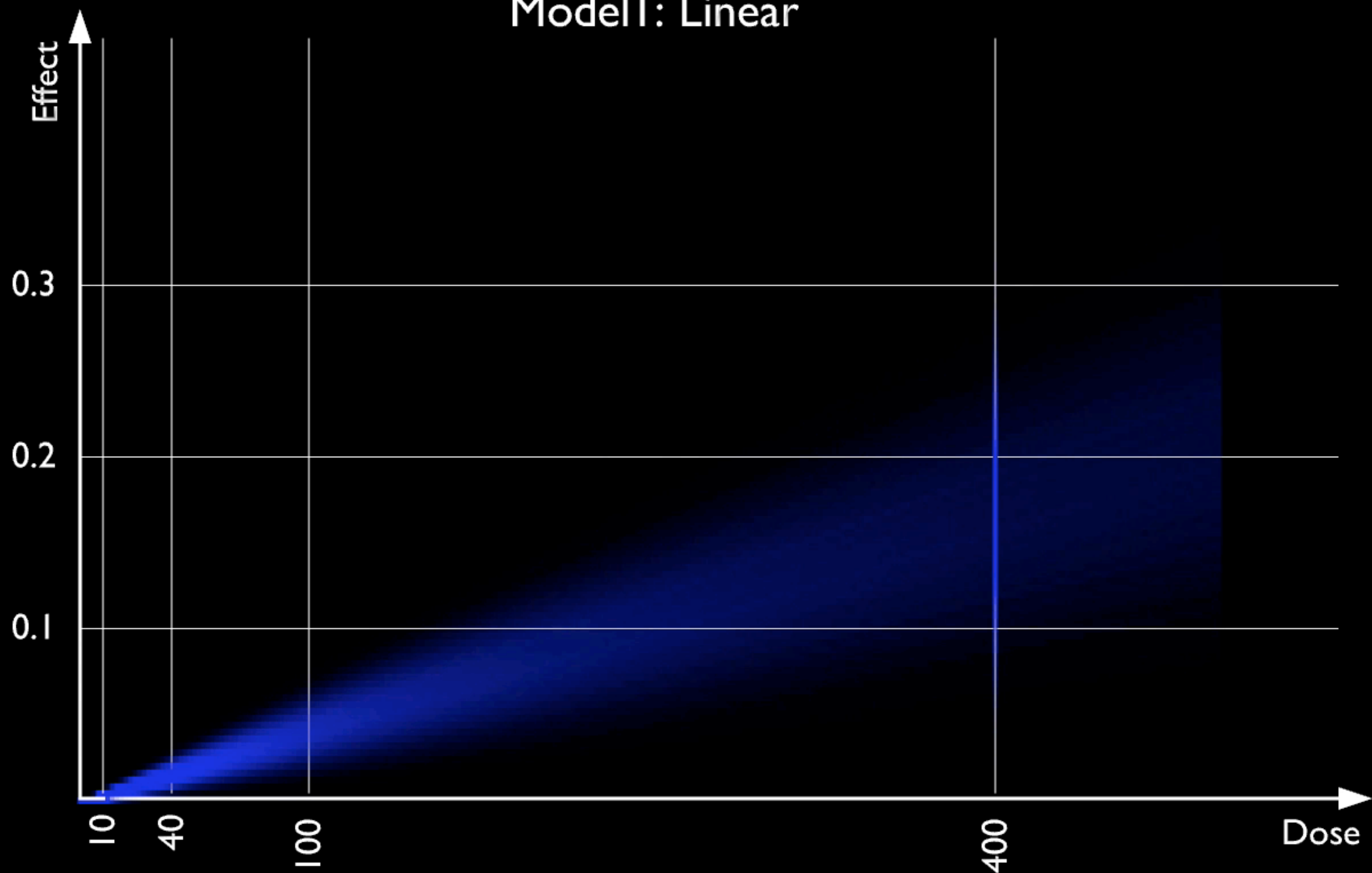
Model4: Sigmoidal

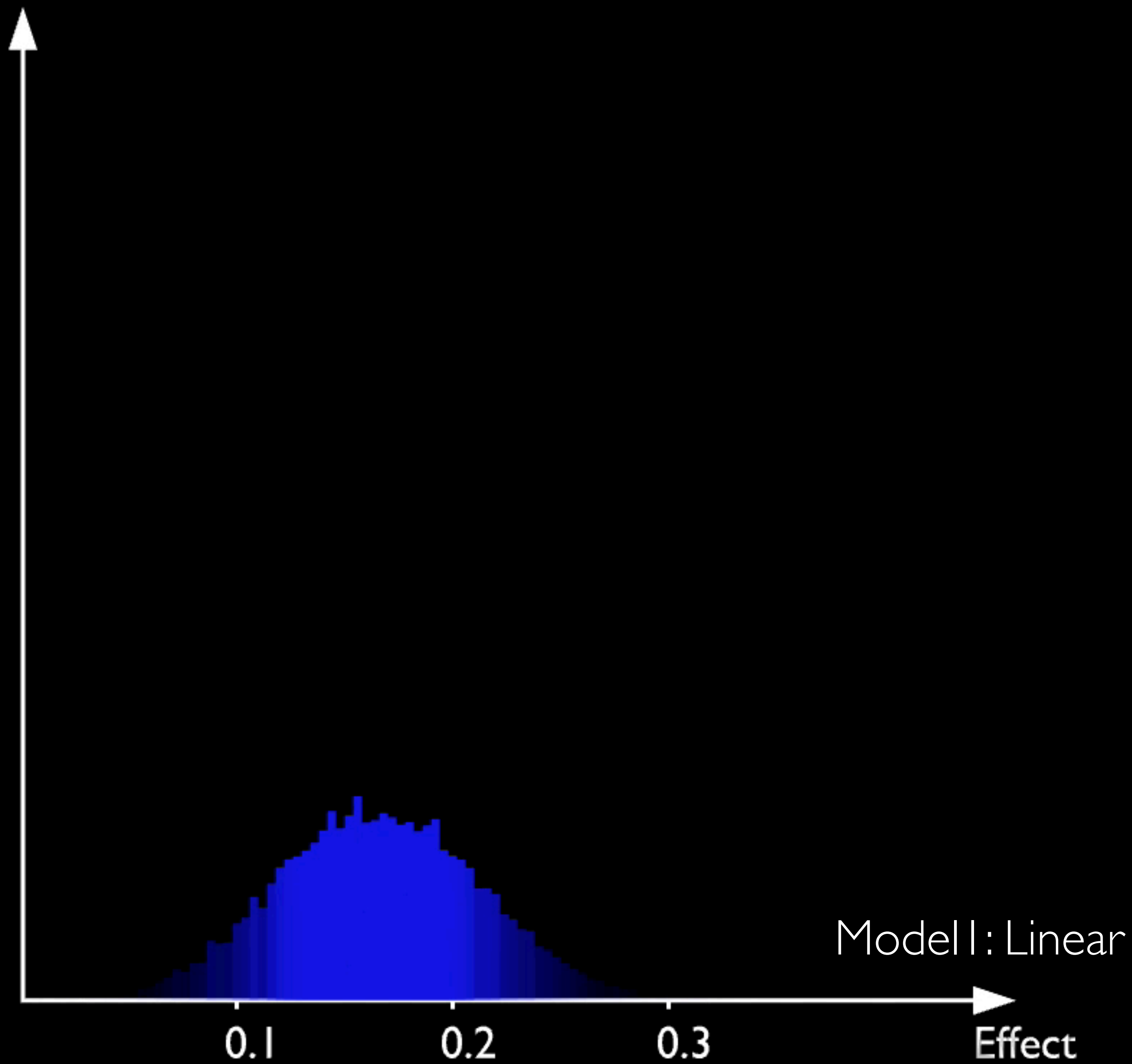


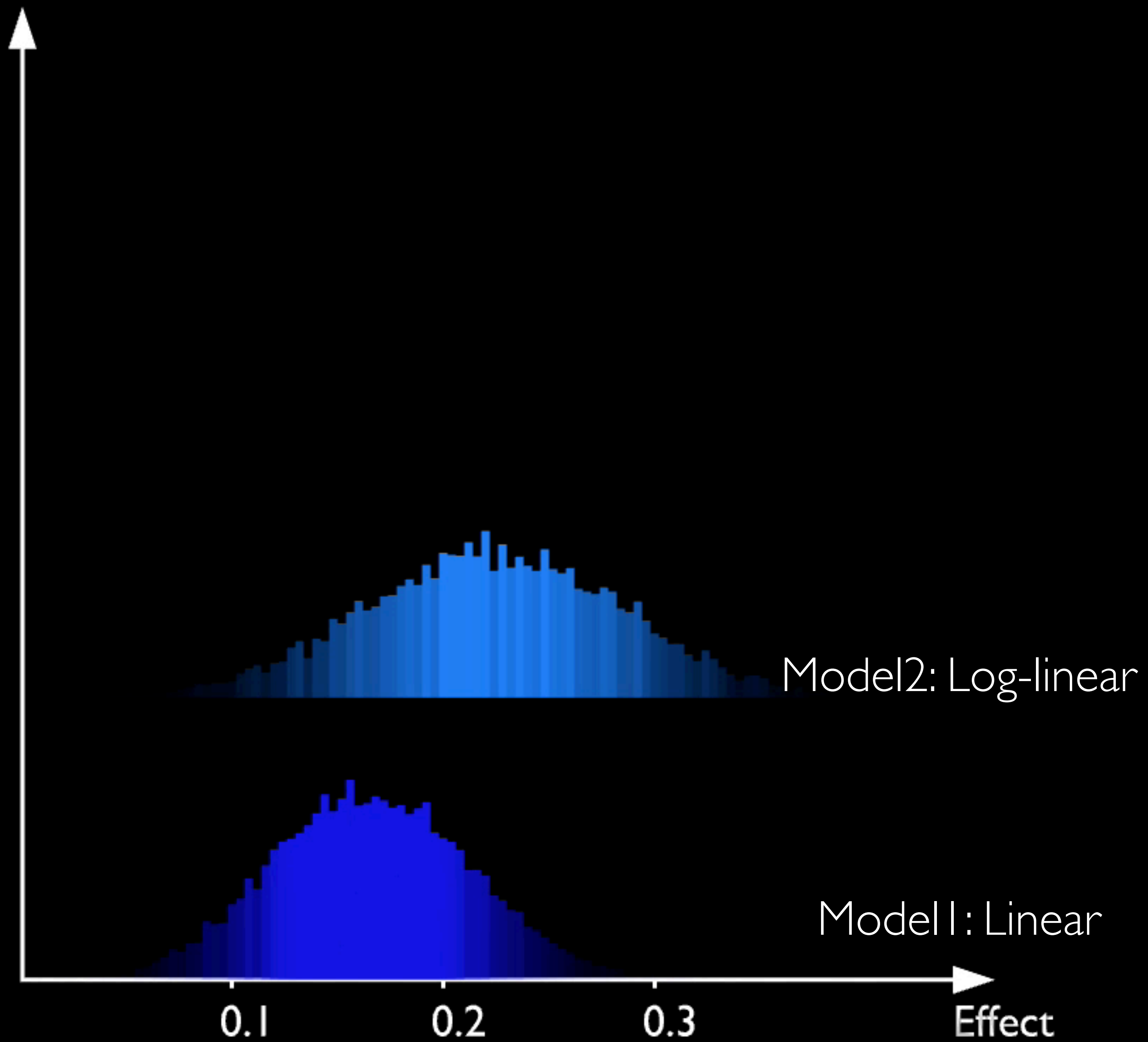
Model I: Linear

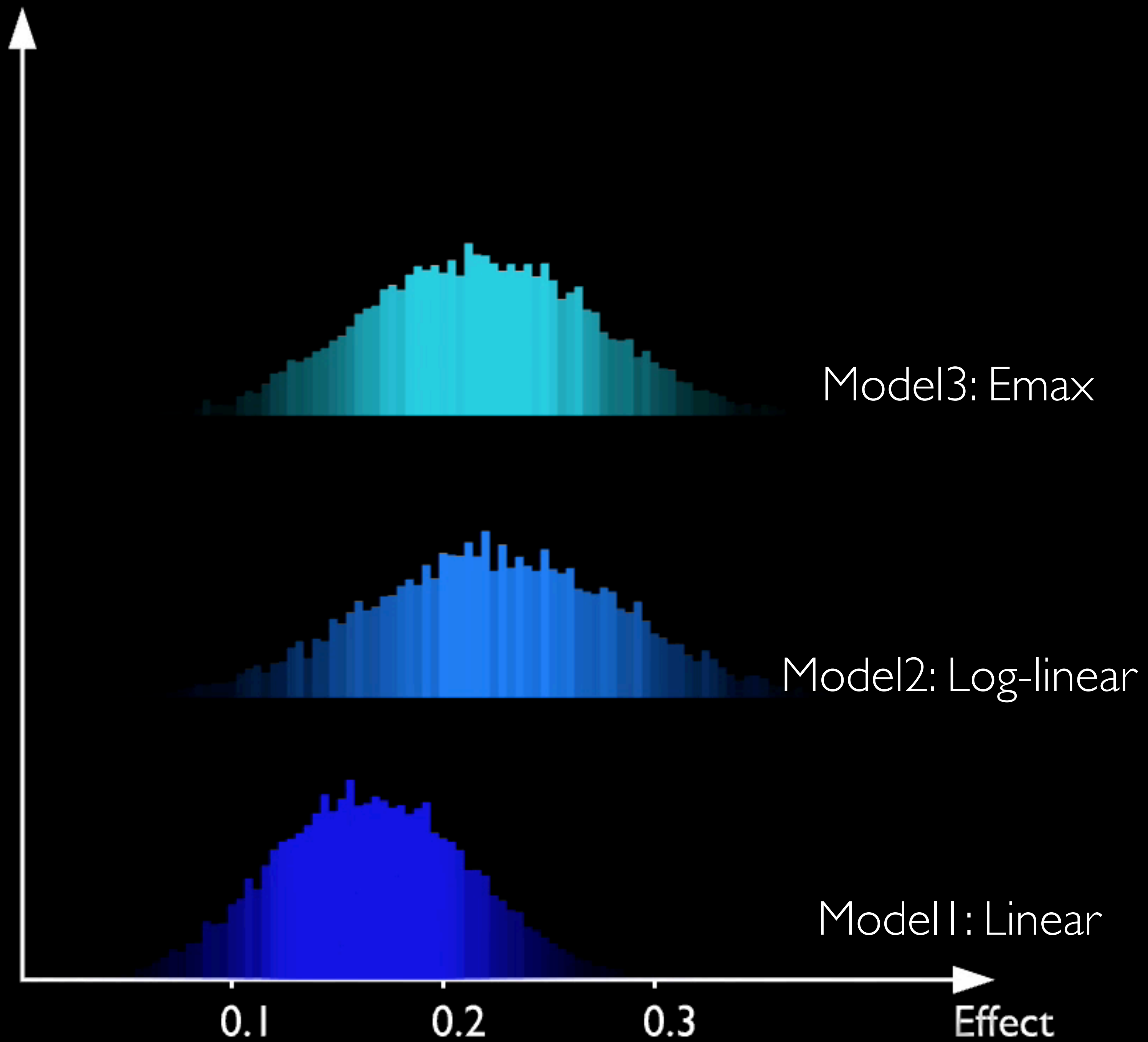


Model I: Linear

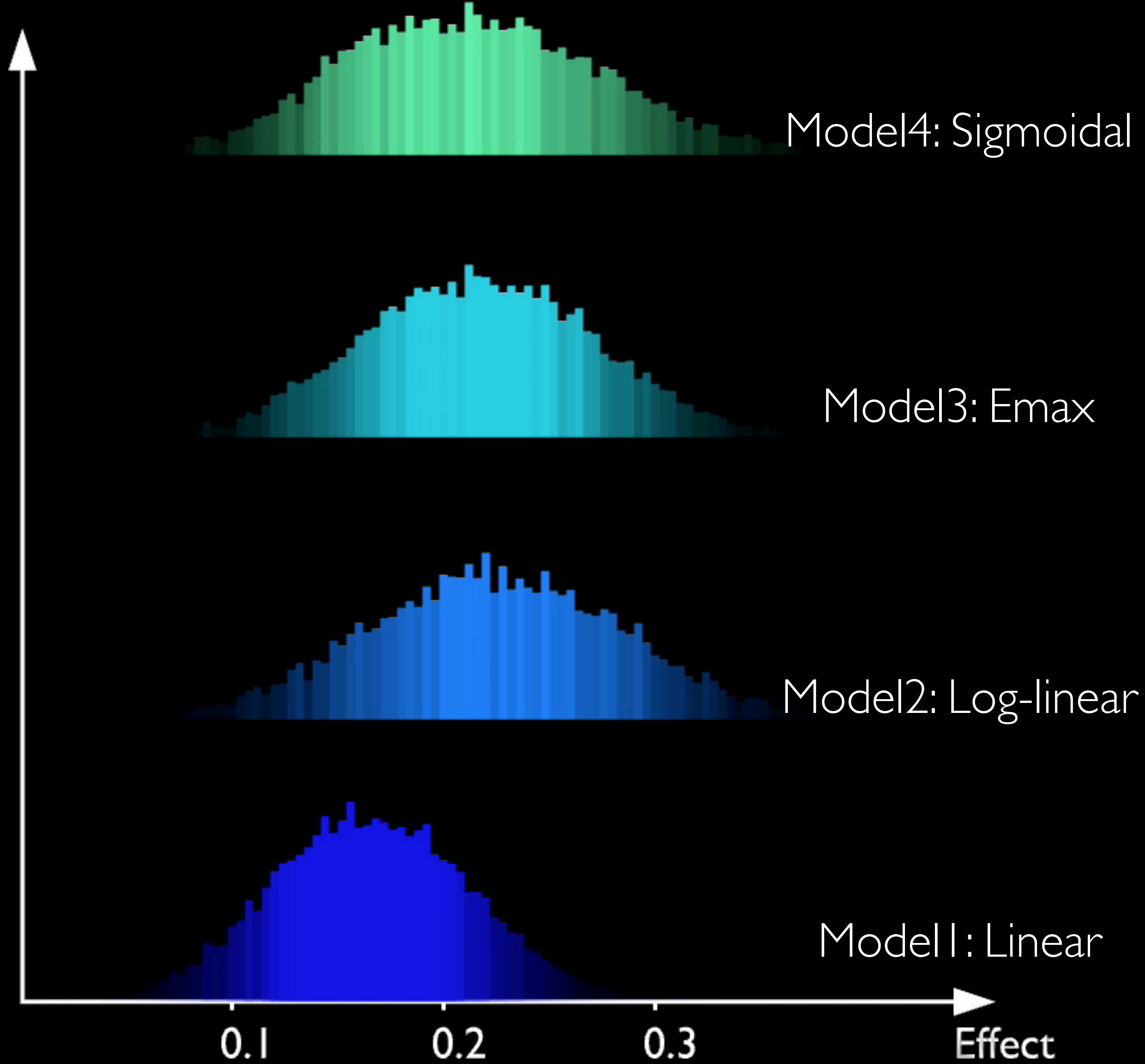


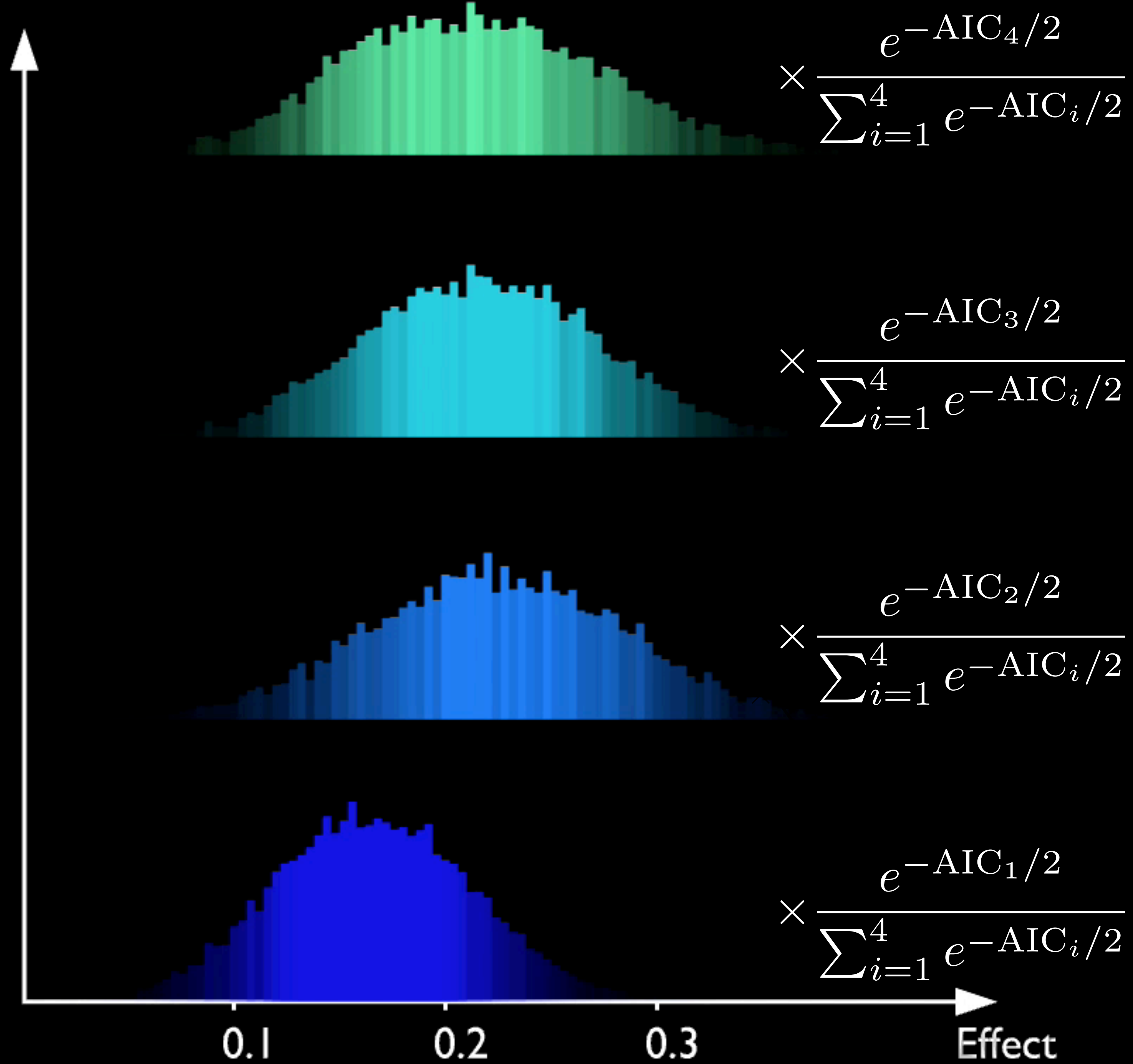


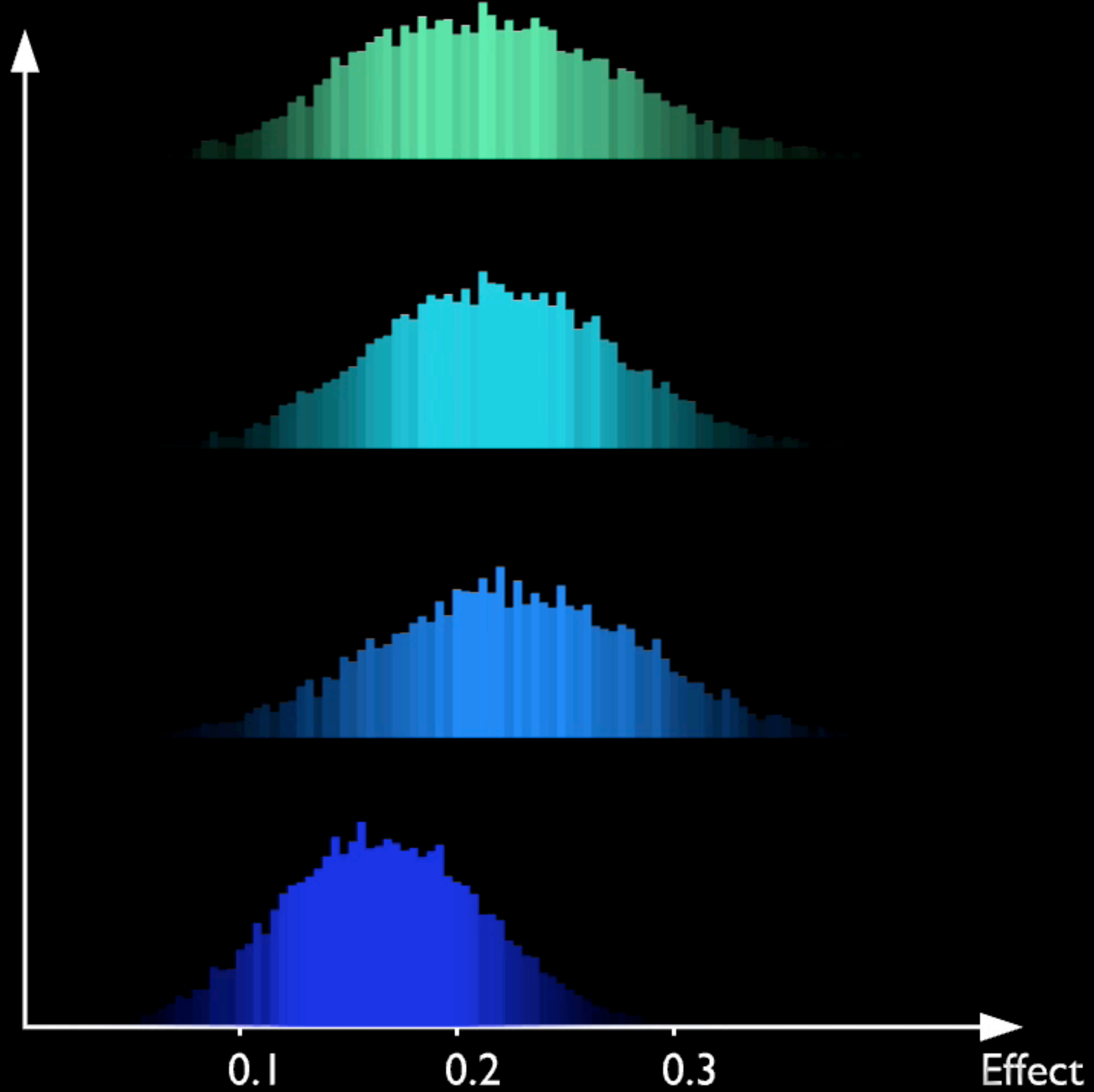


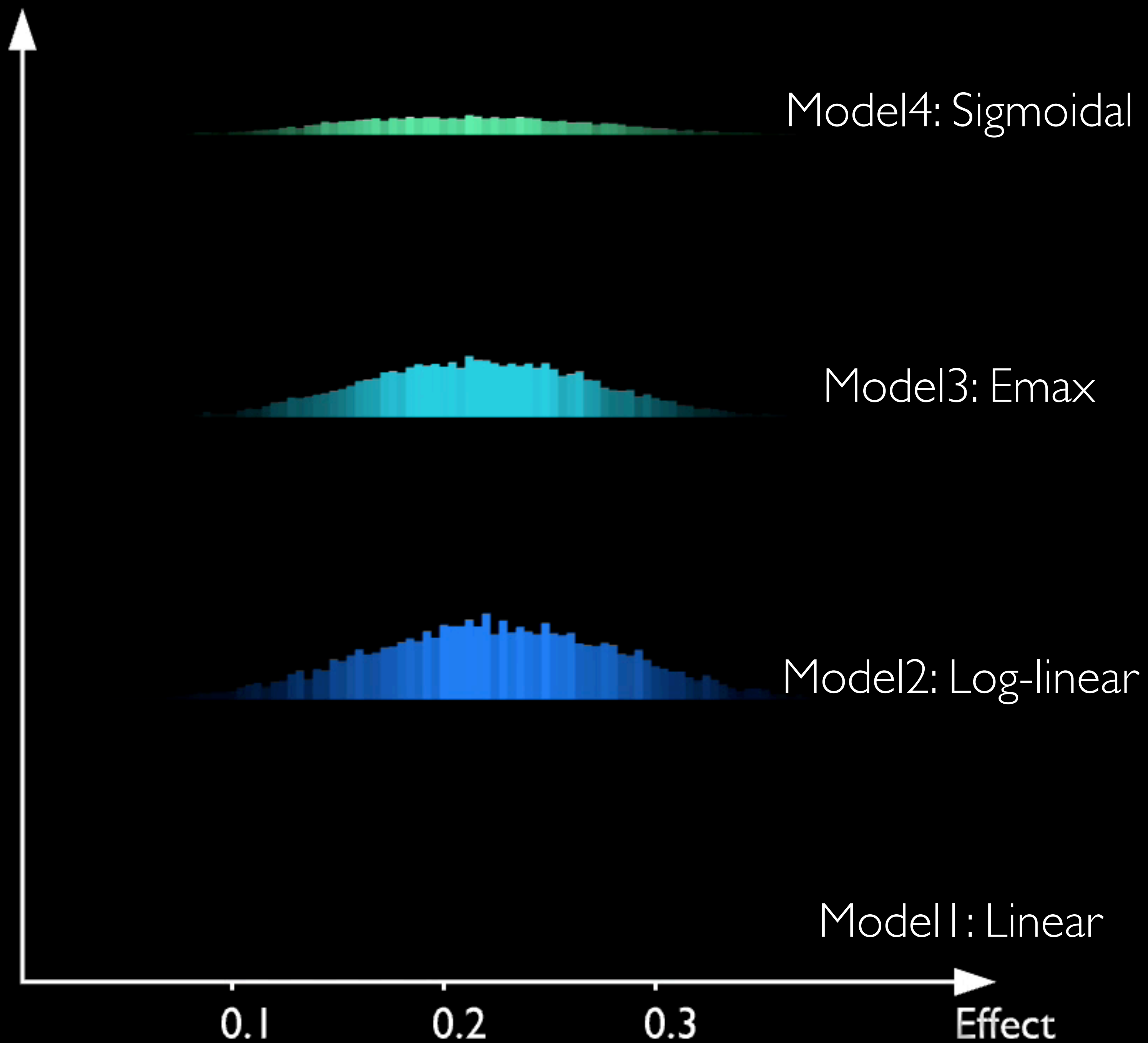


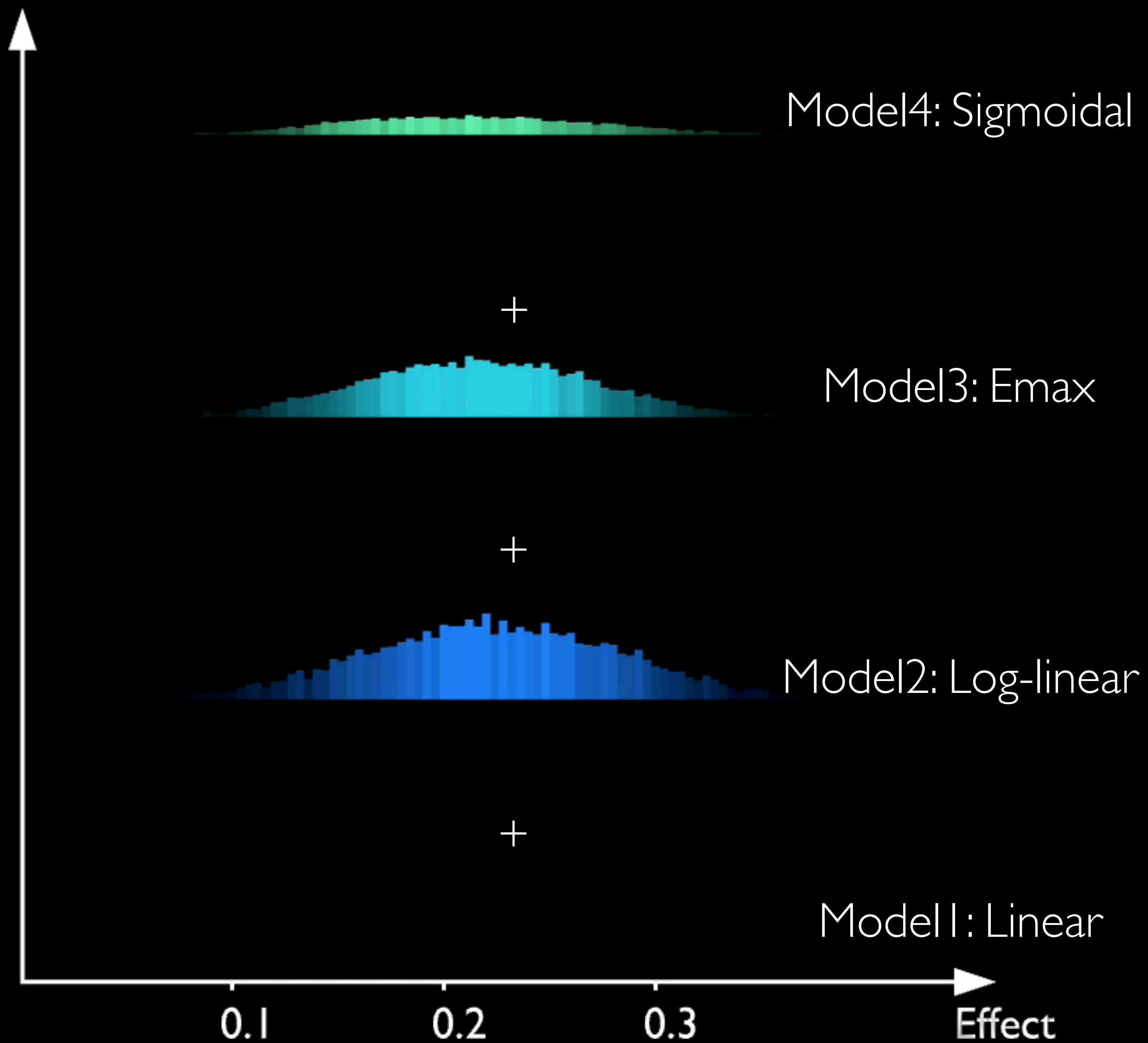


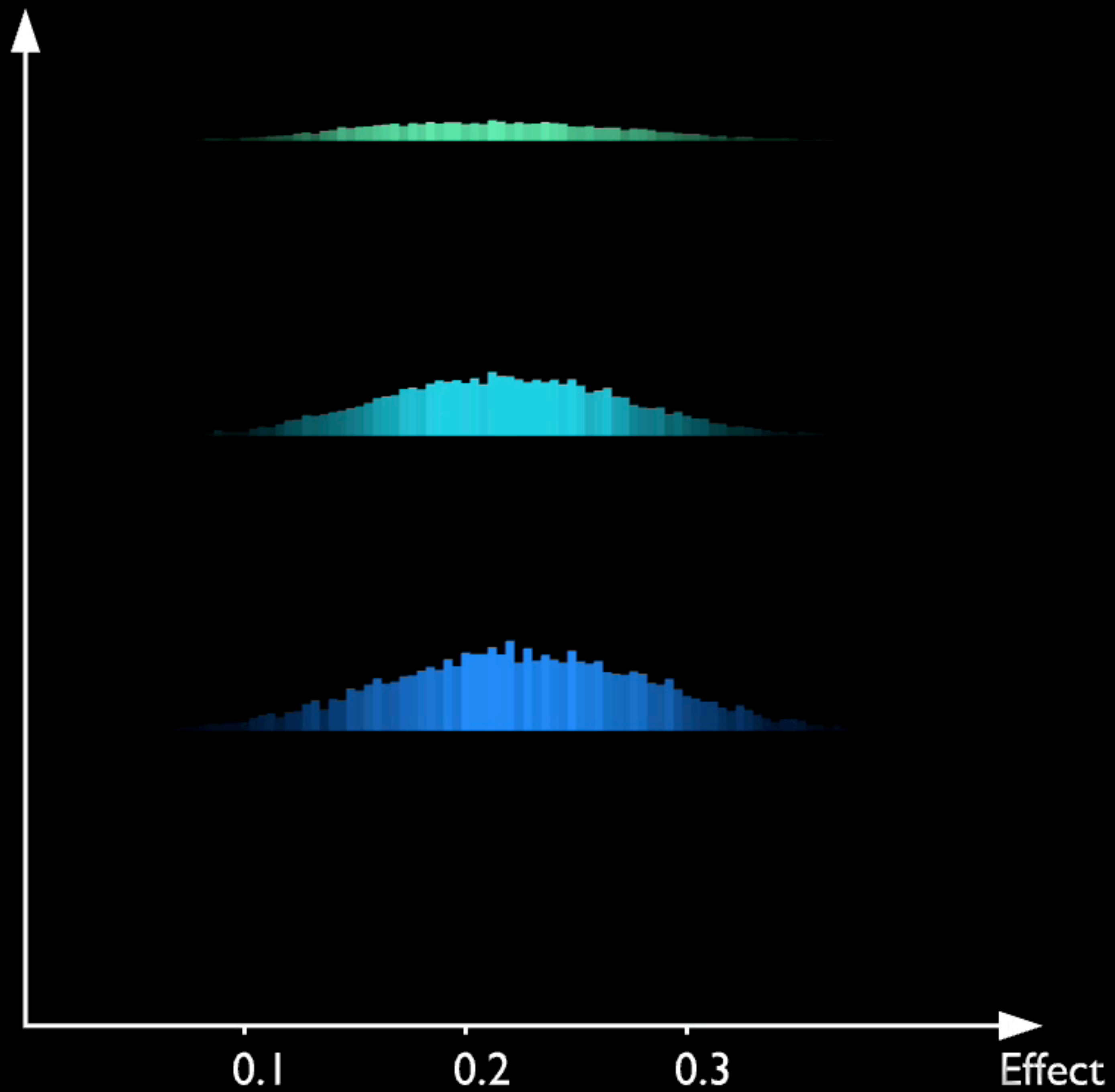


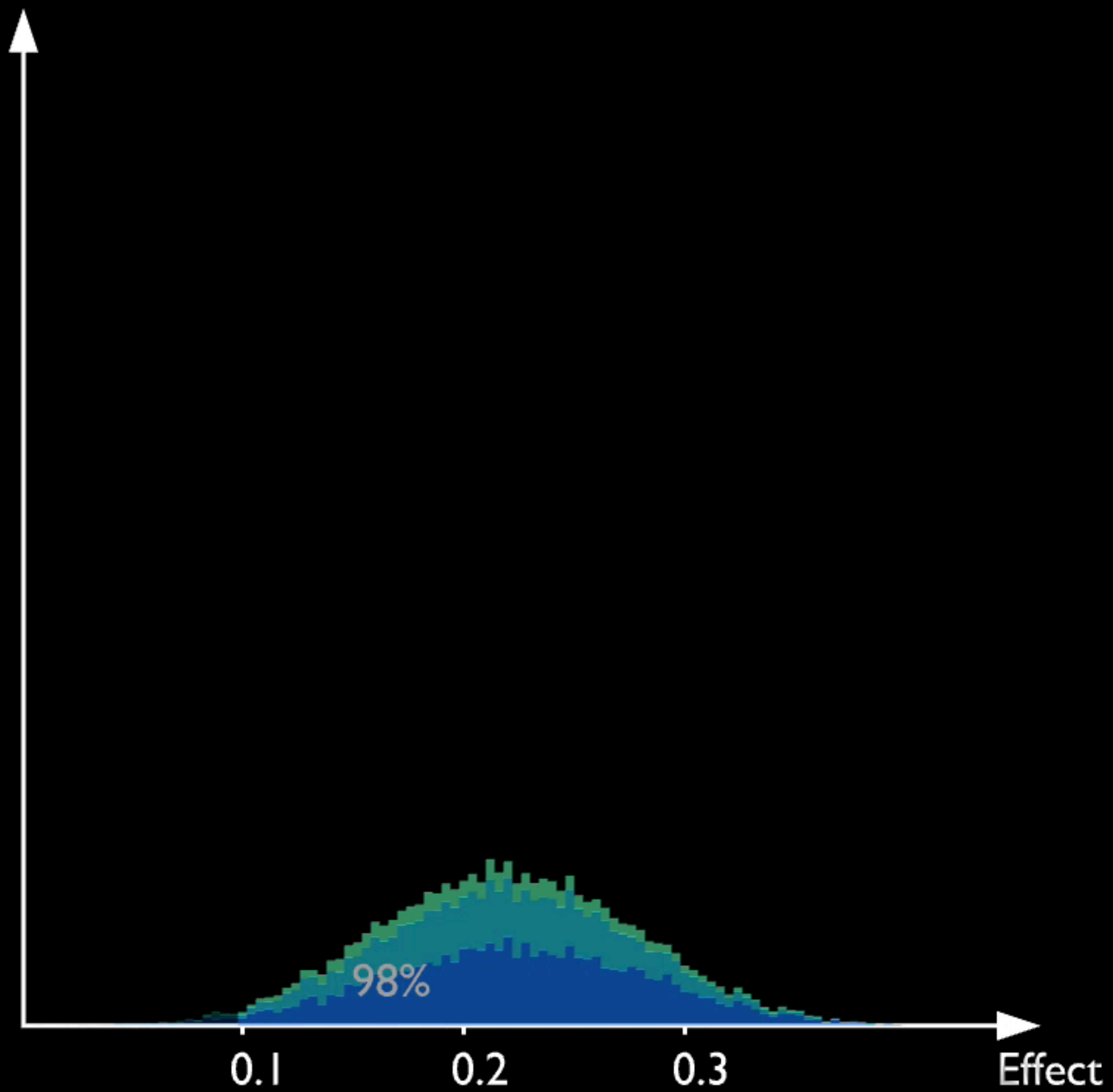


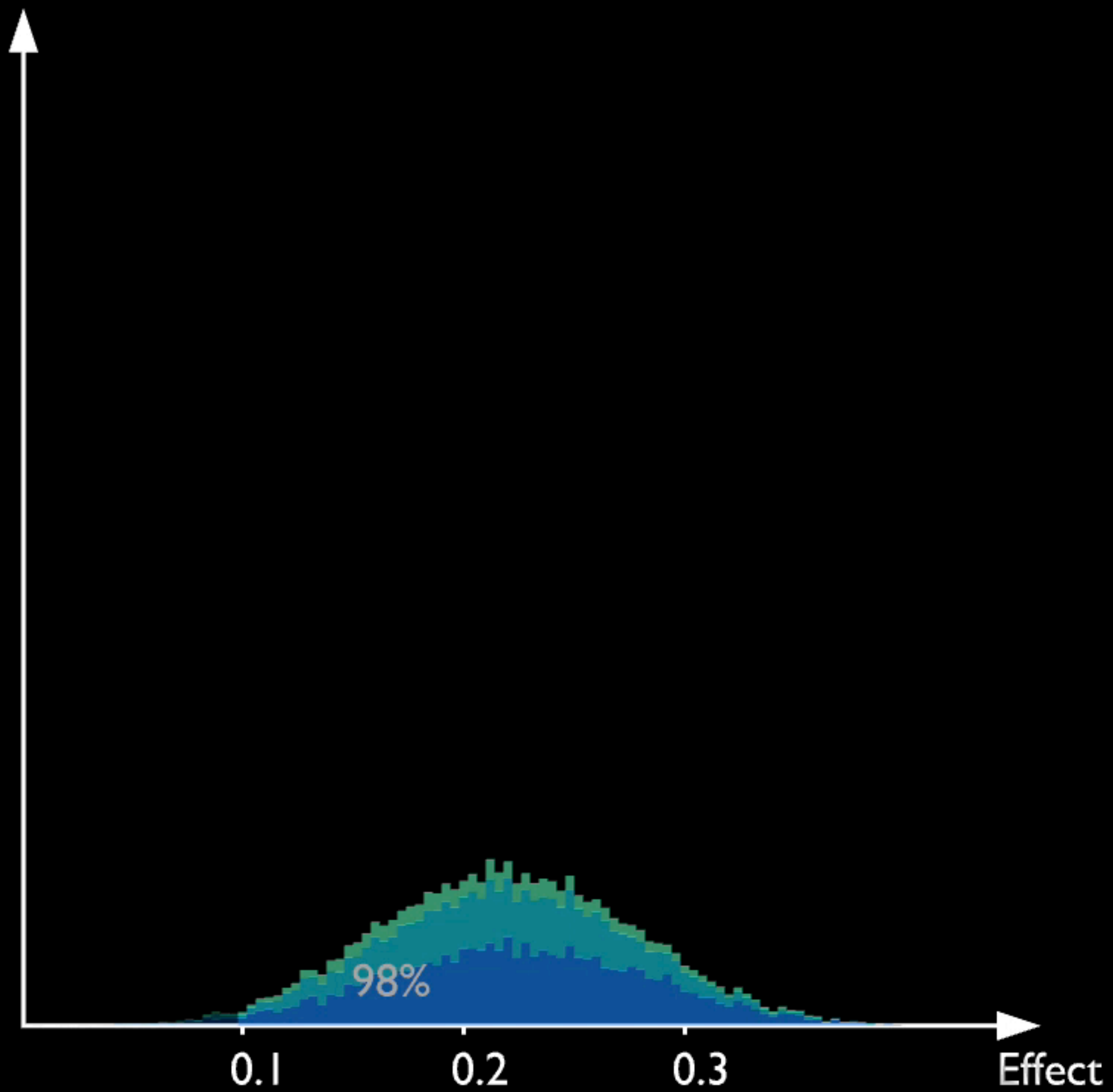




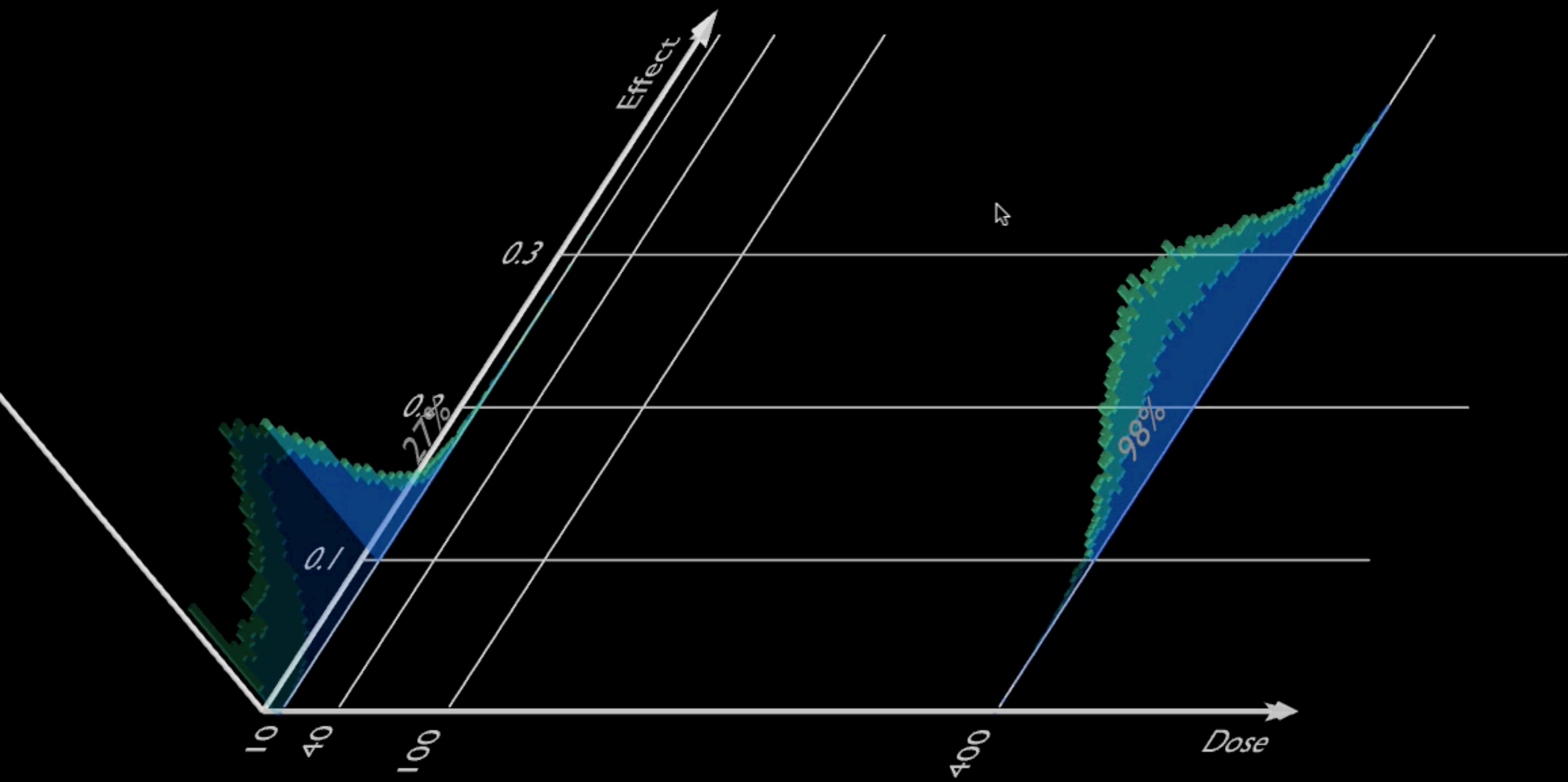


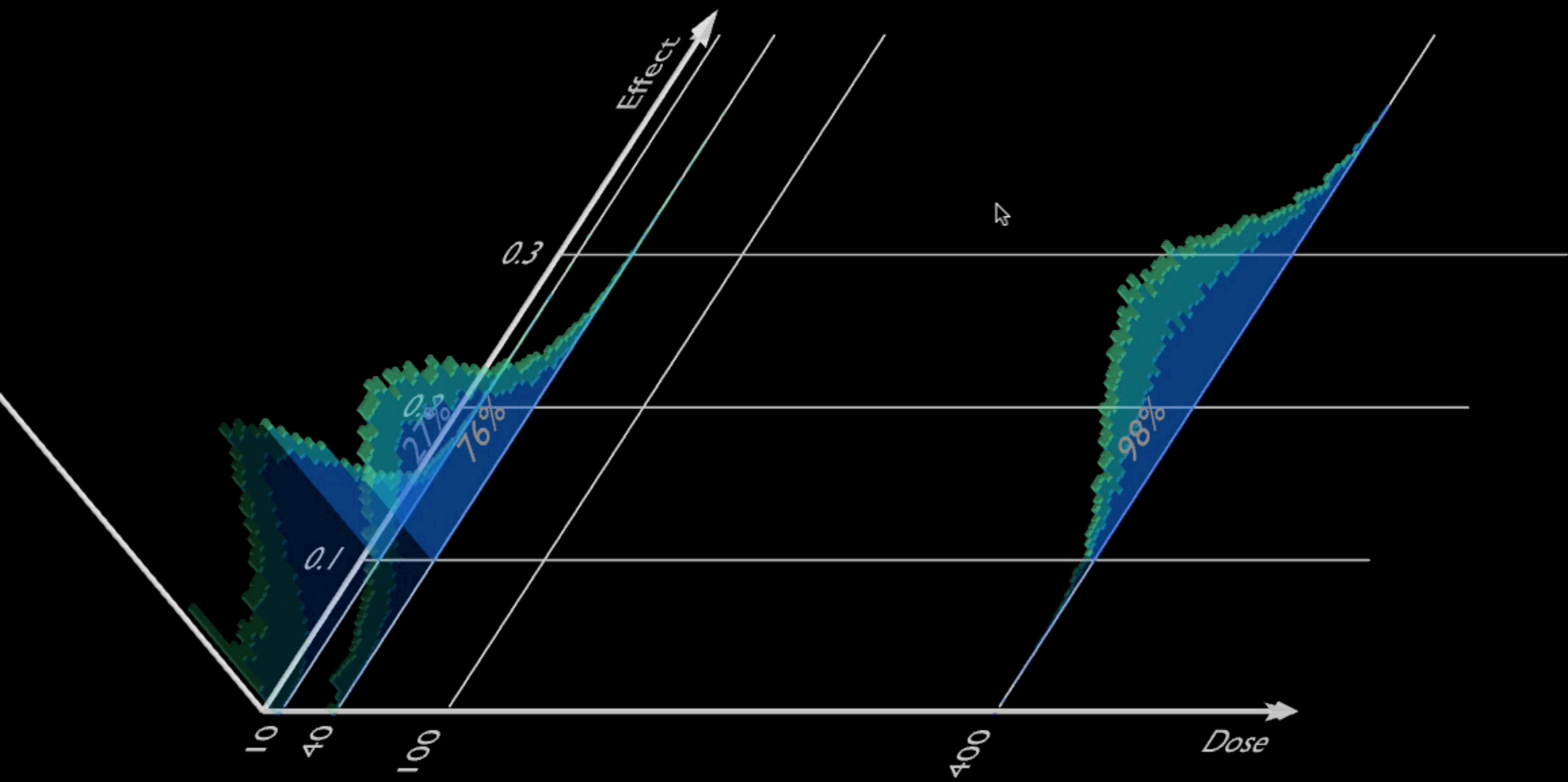


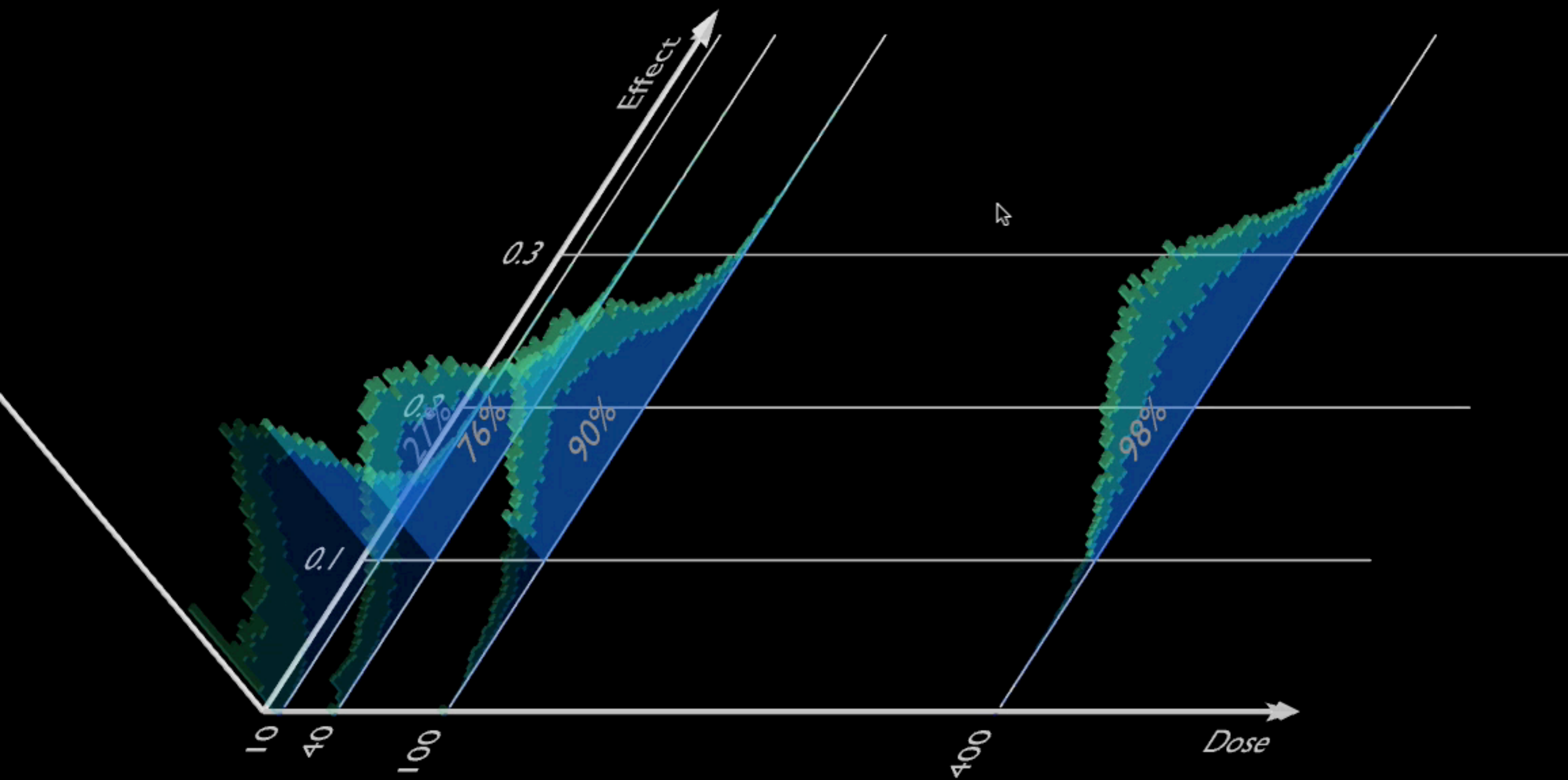




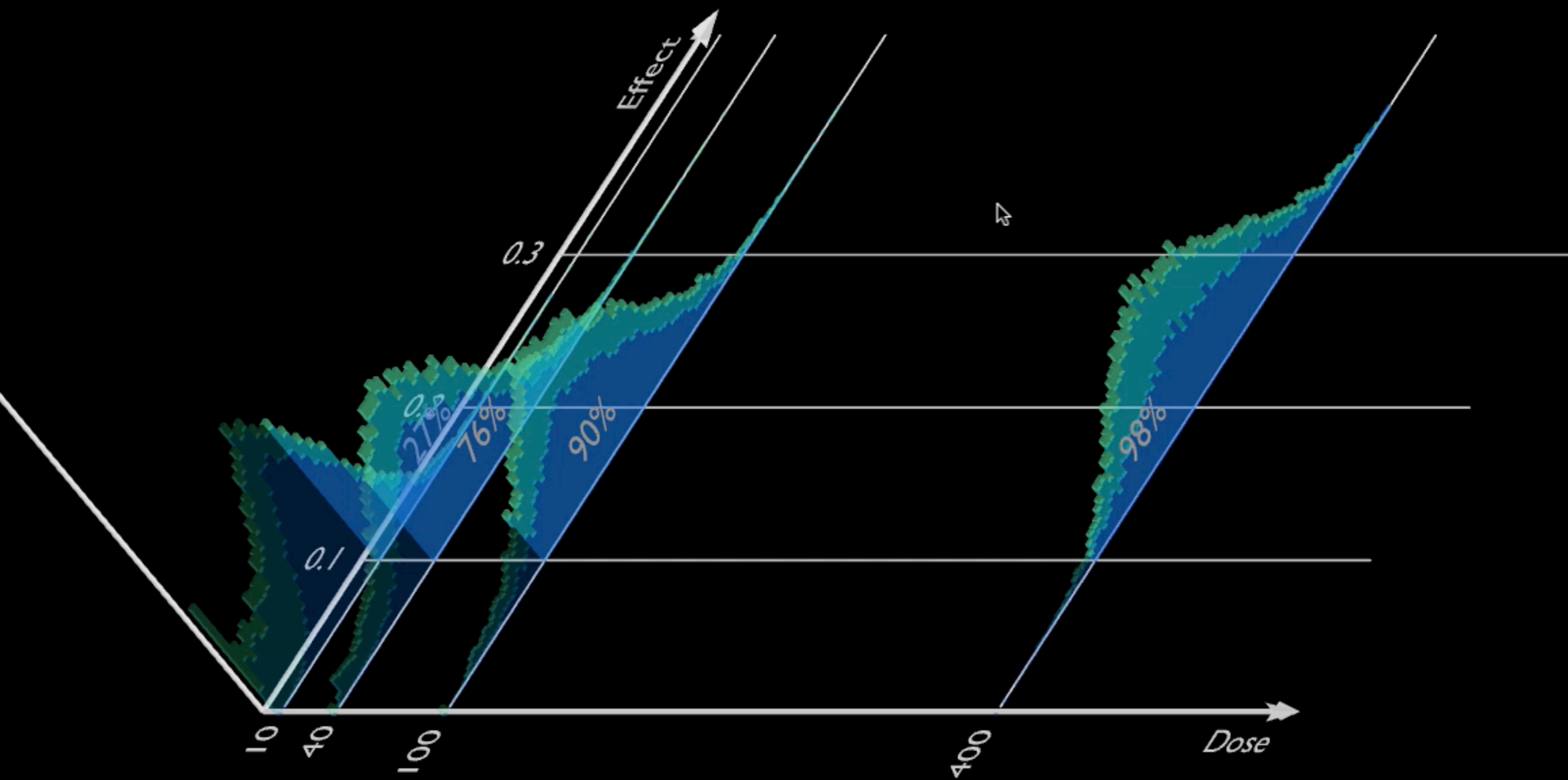


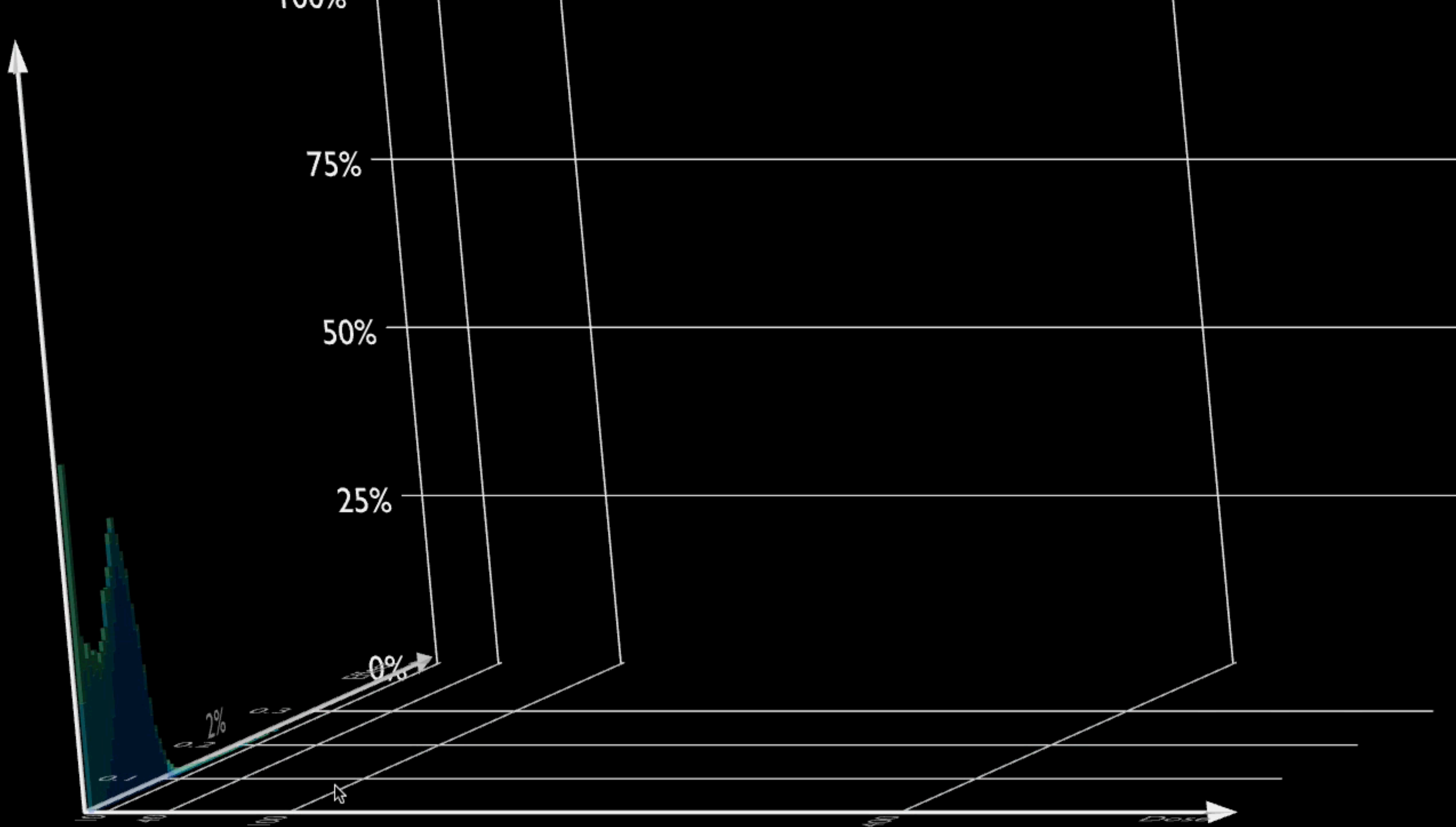




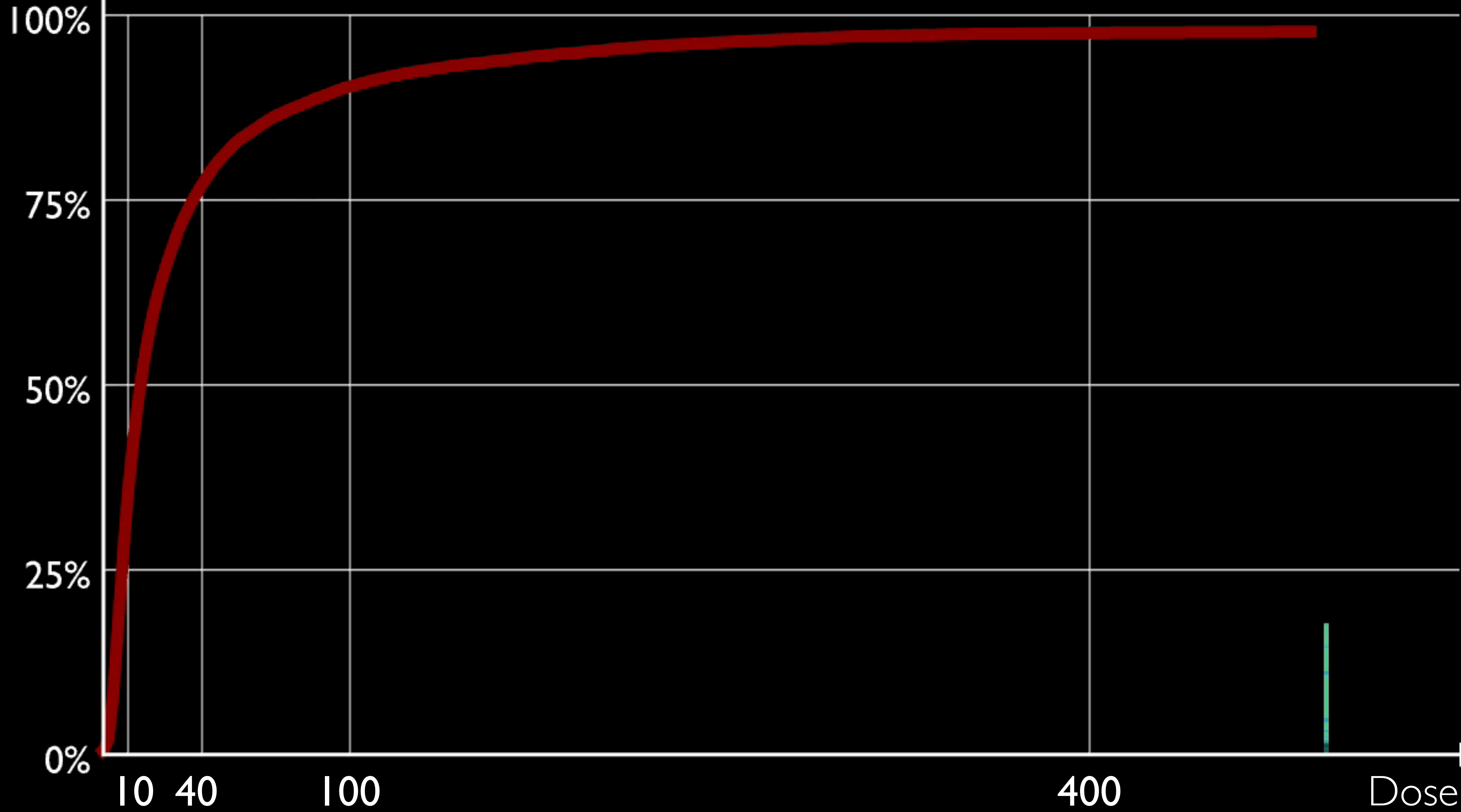




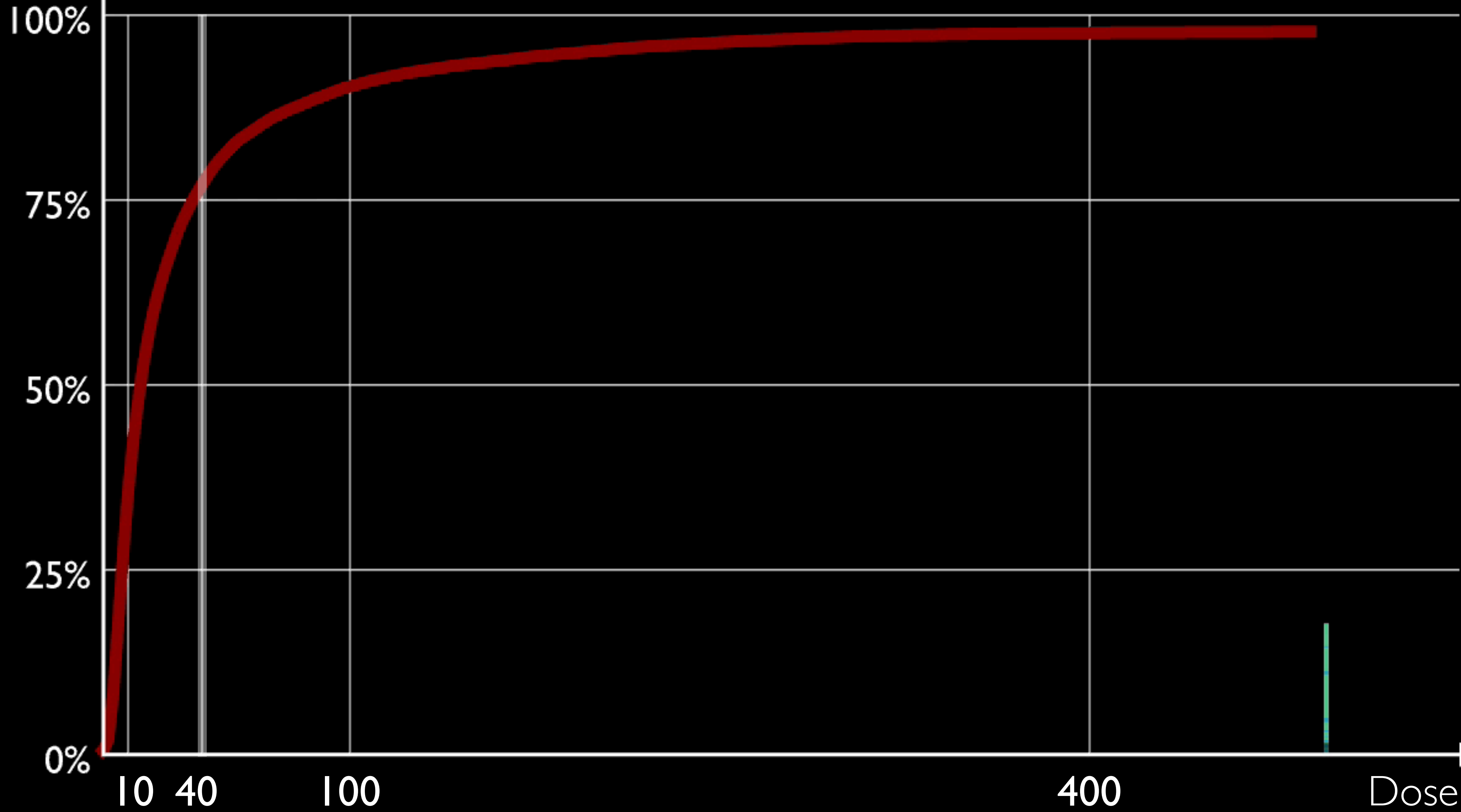




Probability of Achieving the Target Effect



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:

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# Four ways to Average/Select Model

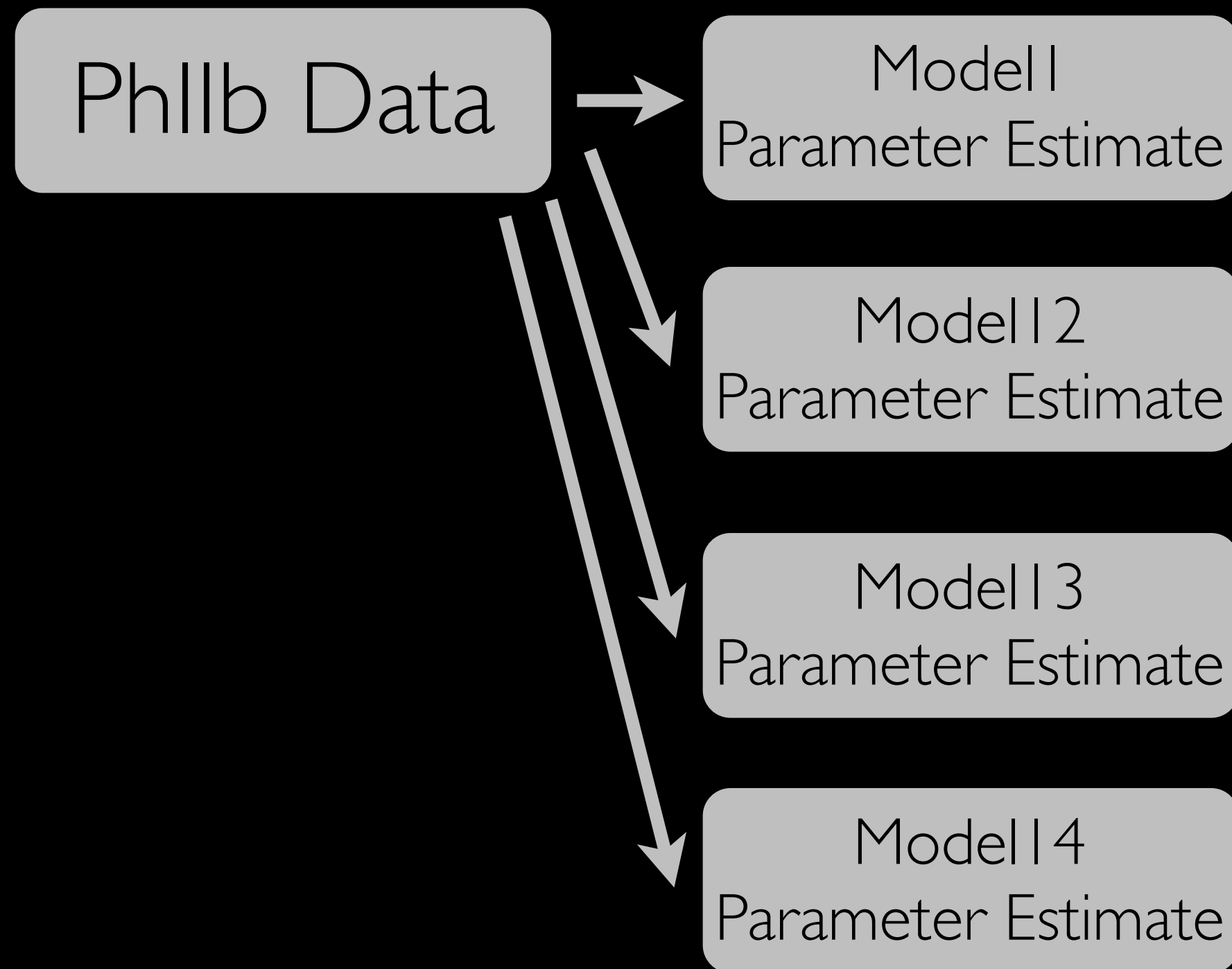
let's get bit more technical

# Method 1: Regular Model Selection

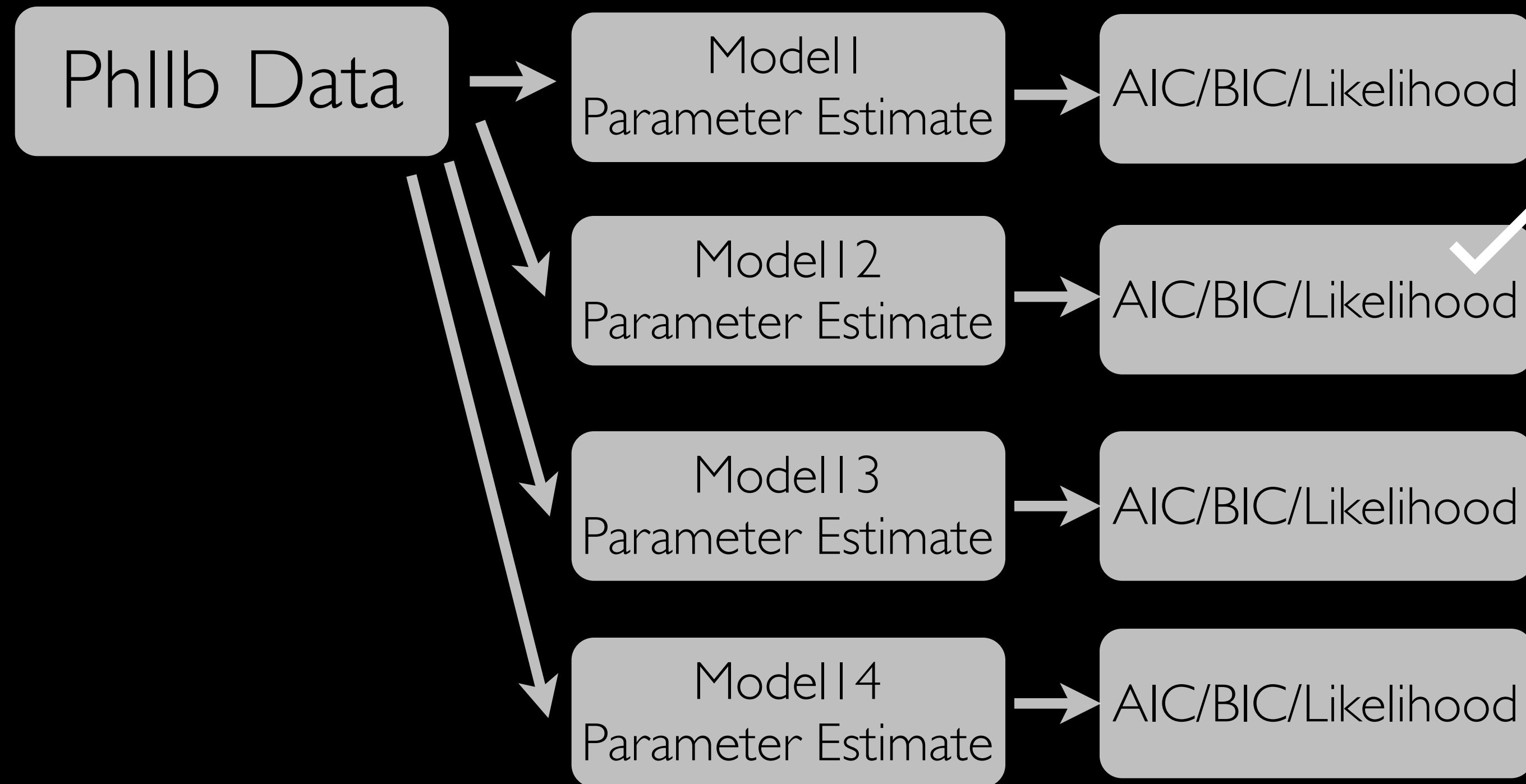
# Method 1: Regular Model Selection

Phllb Data

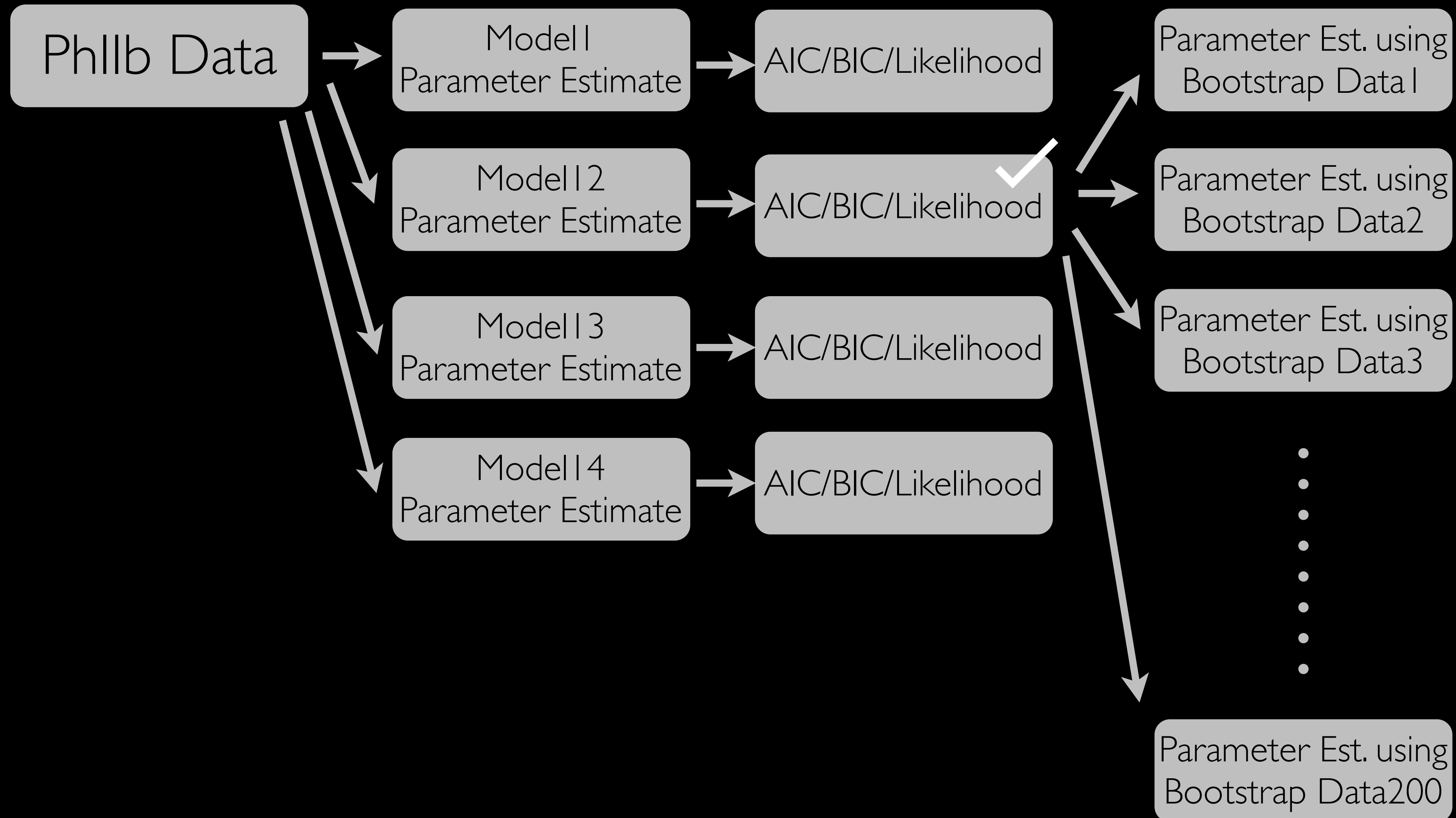
# Method I: Regular Model Selection



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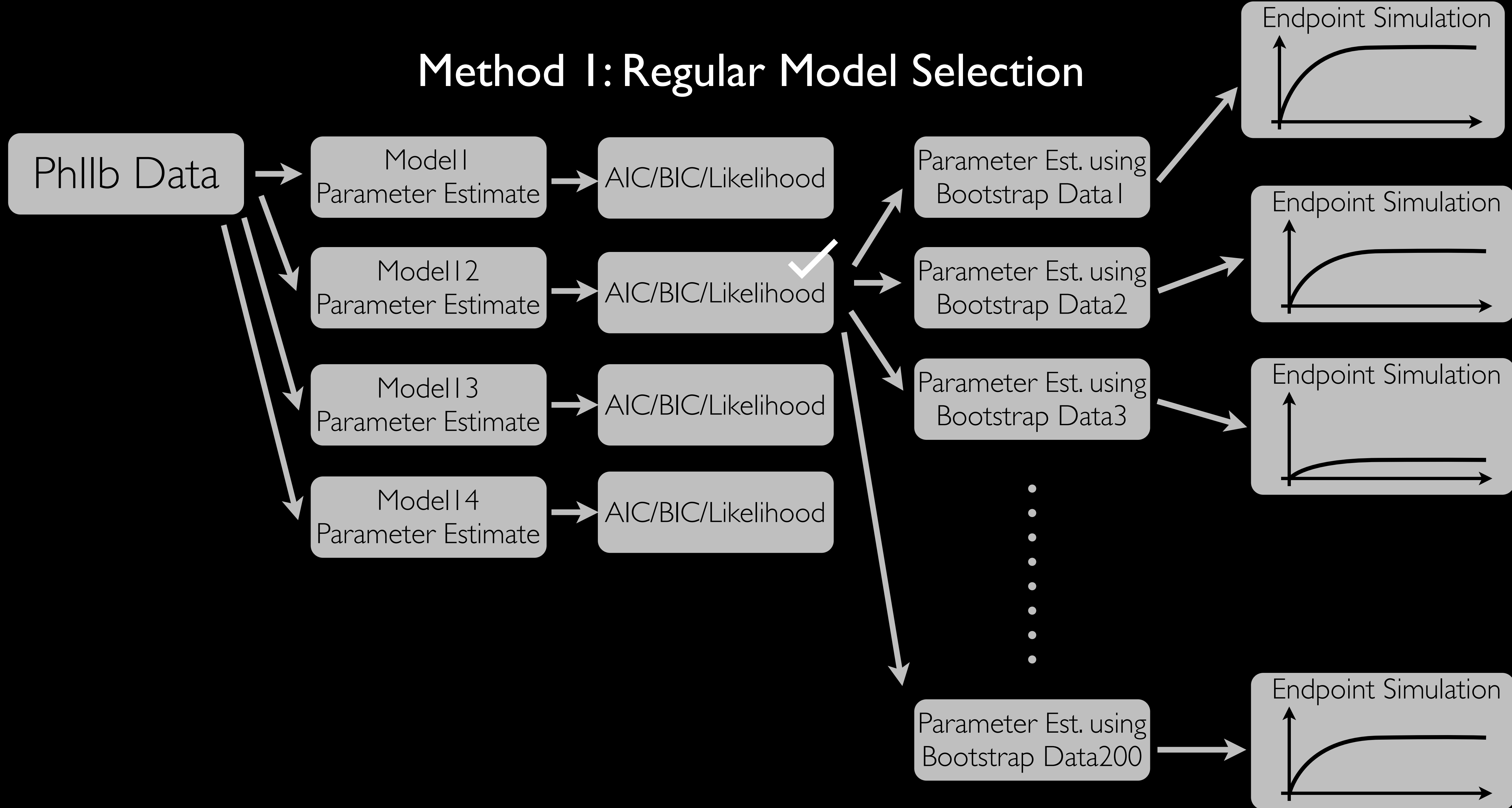


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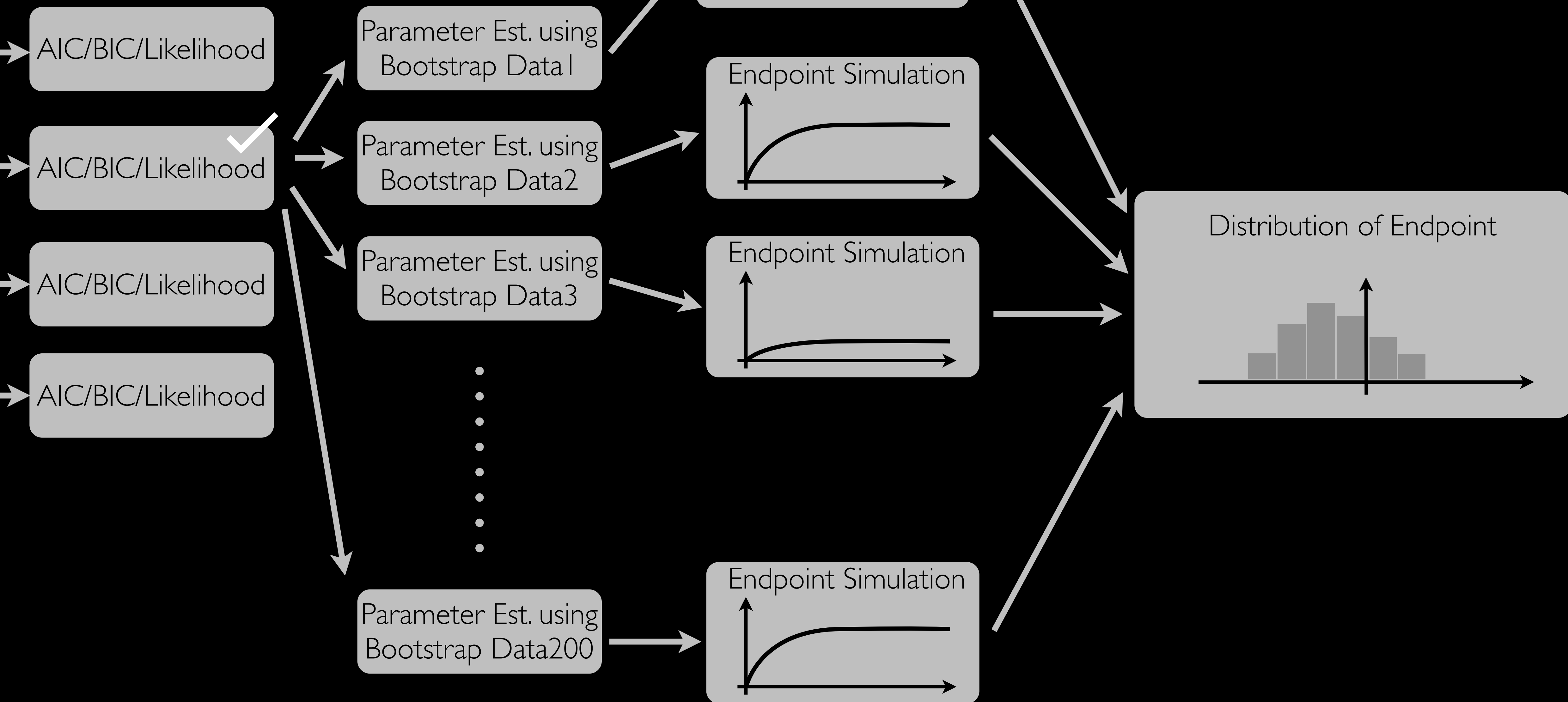




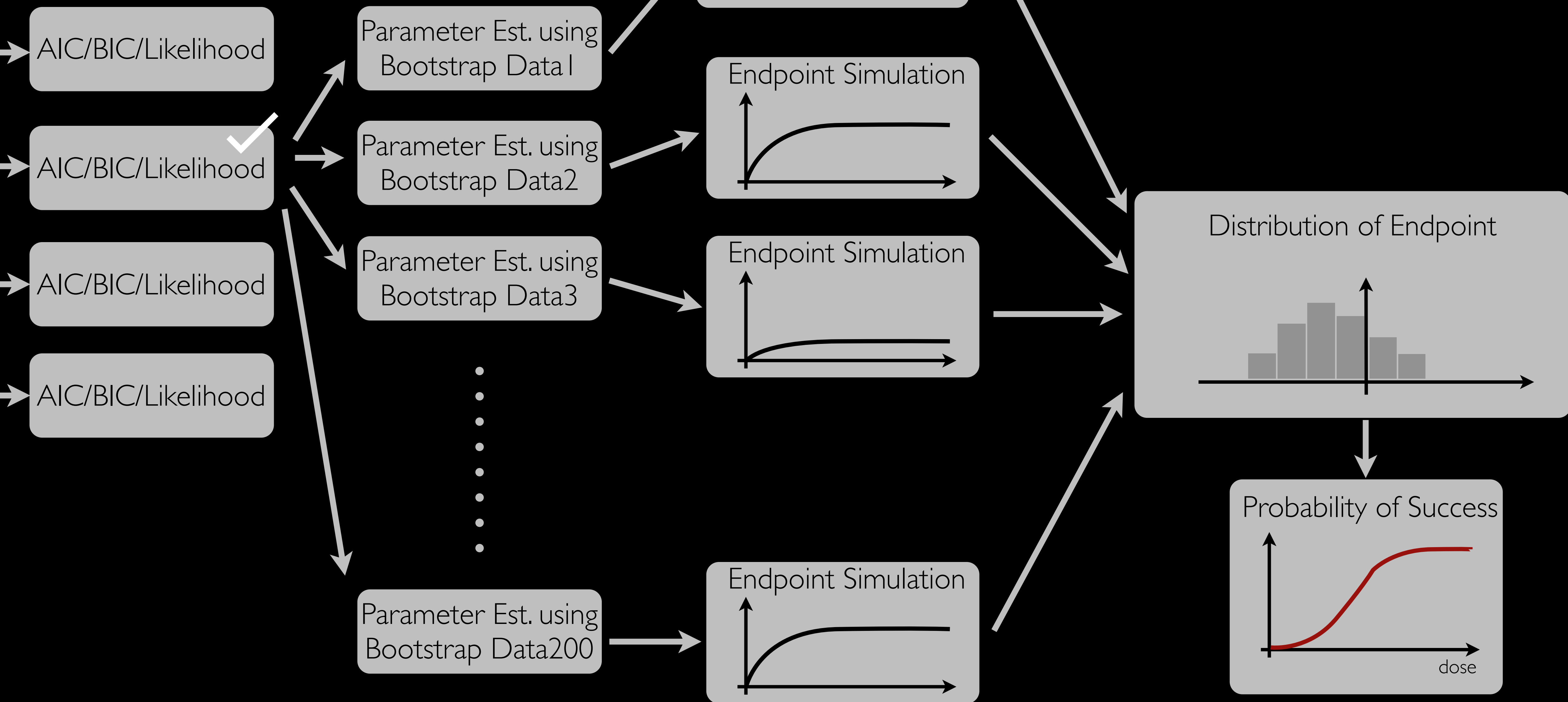
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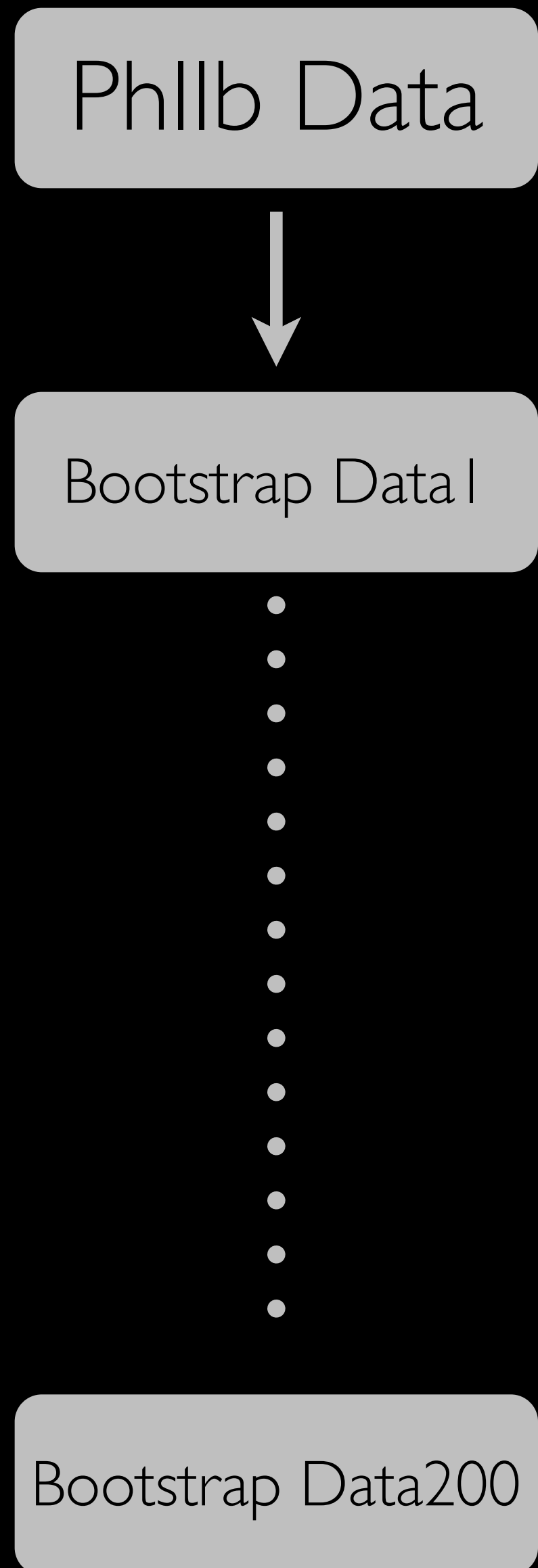


Method 2: Model Selection using bootstrap ofv

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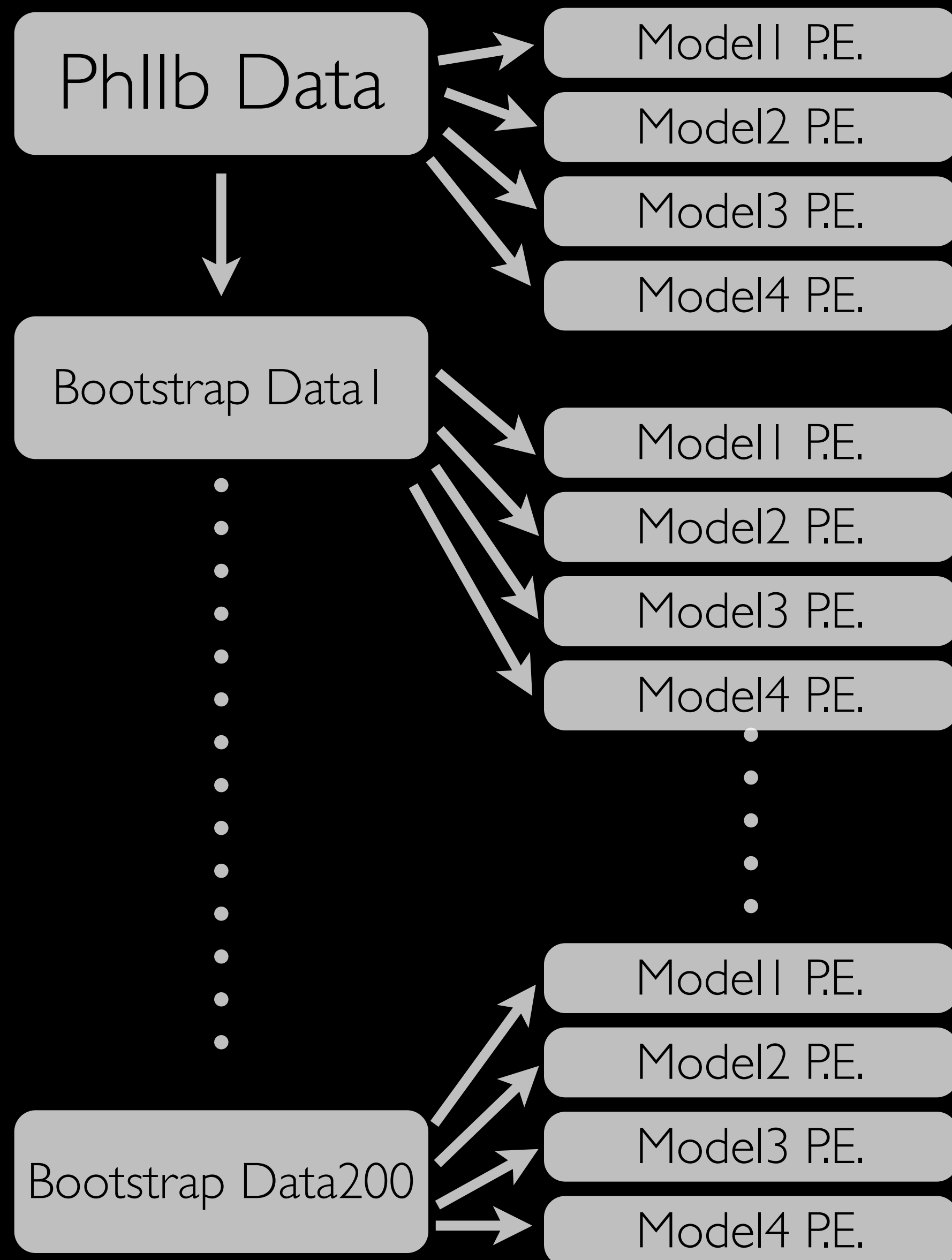
Phllb Data

## Method 2: Model Selection using bootstrap of v

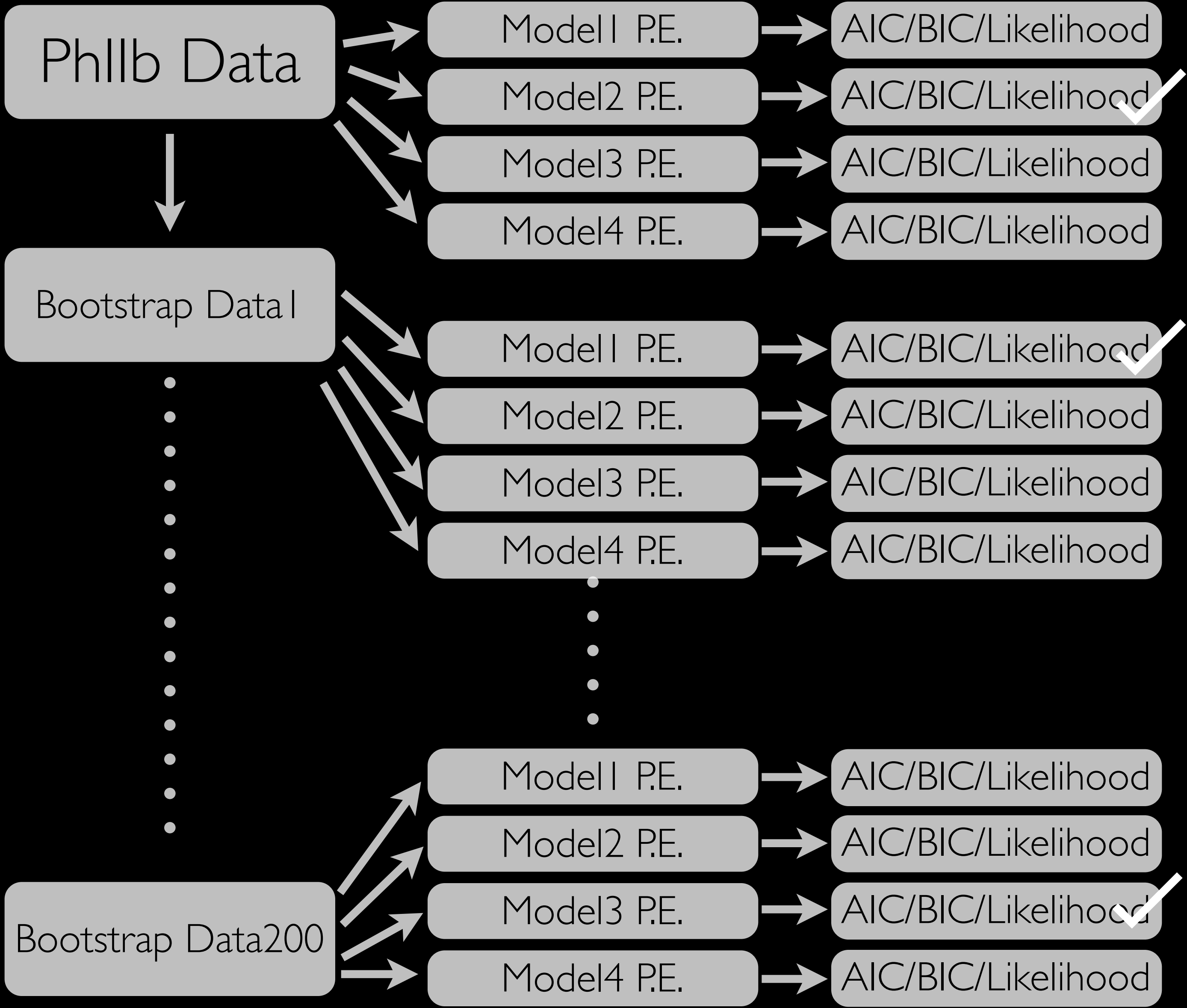




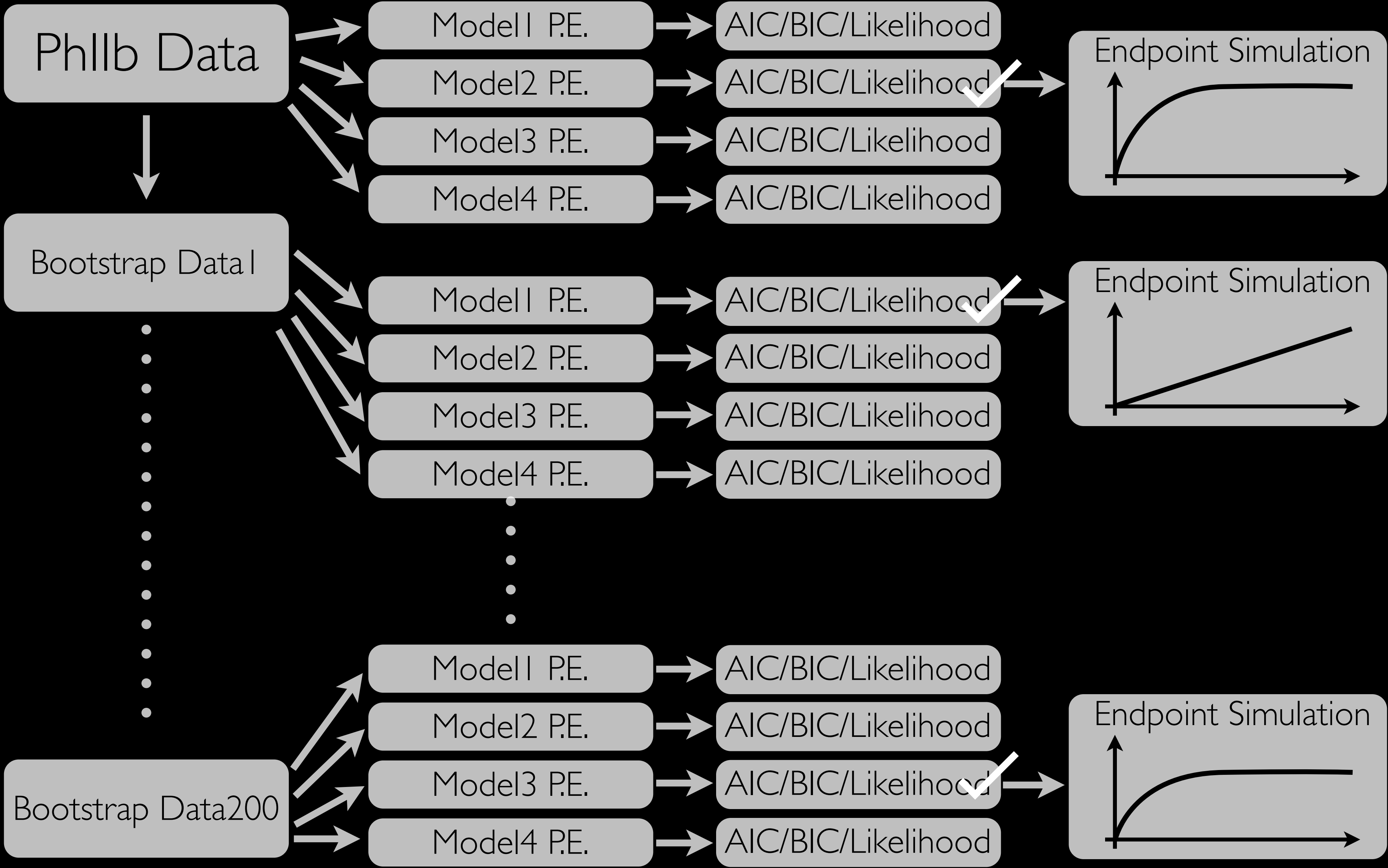
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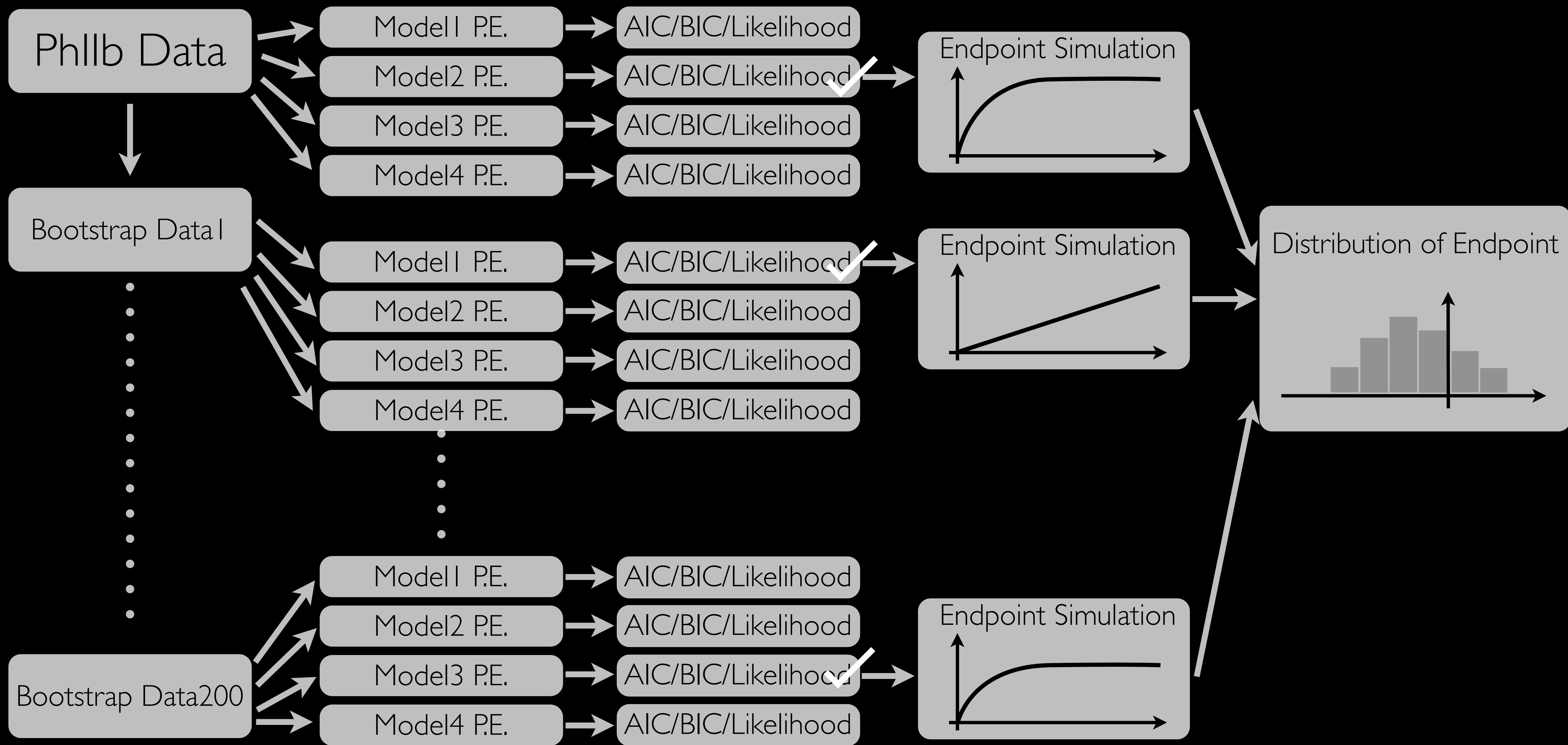
# Method 2: Model Selection using bootstrap of v



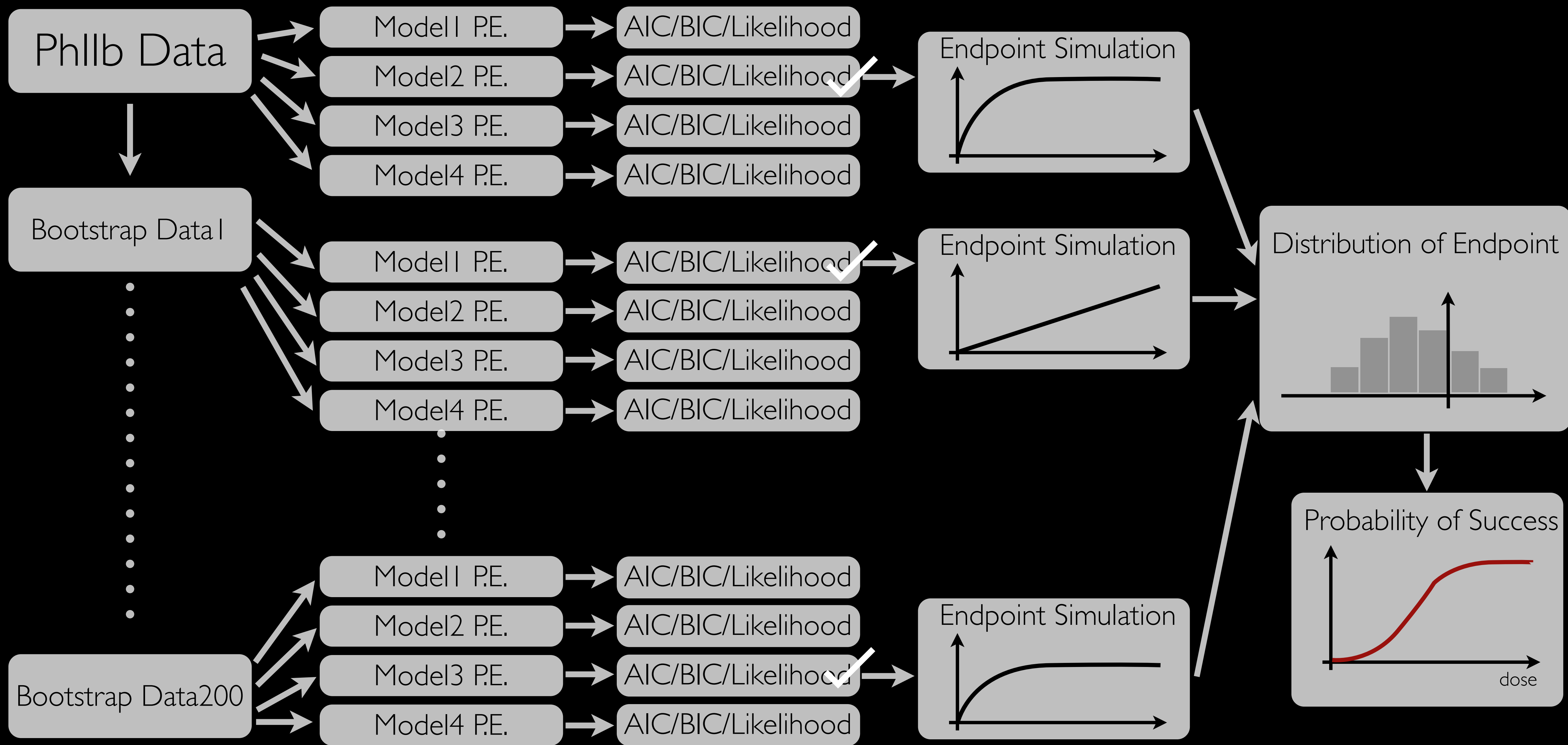
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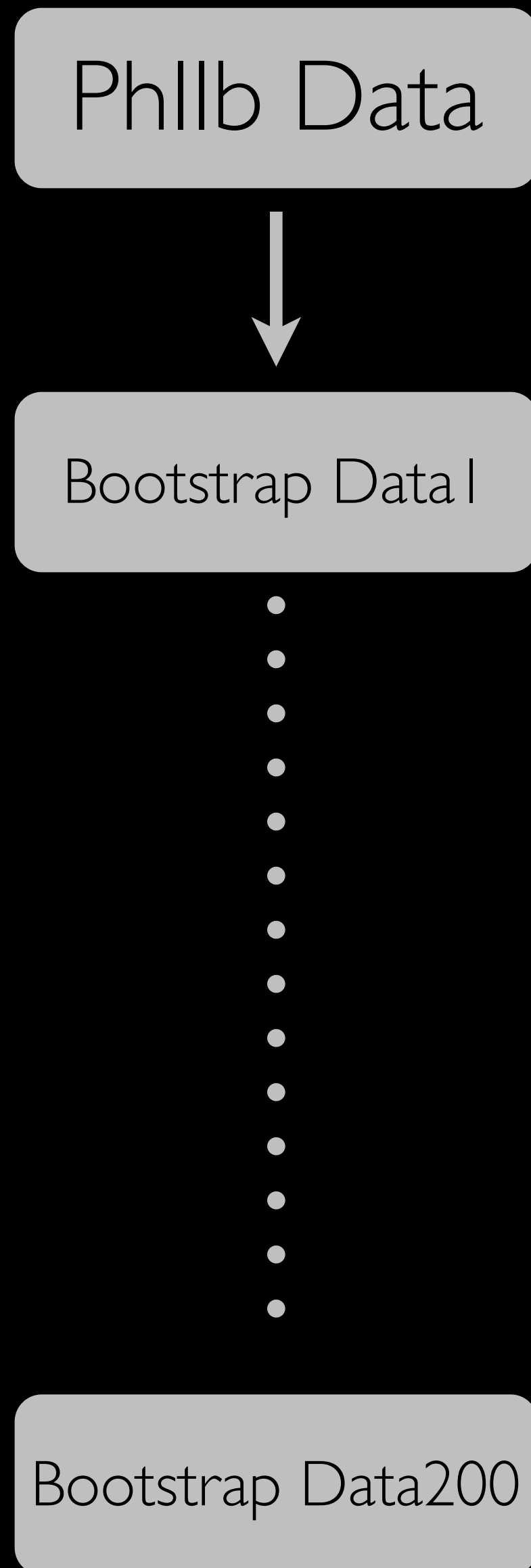
Method 3: Model Average (as shown before)



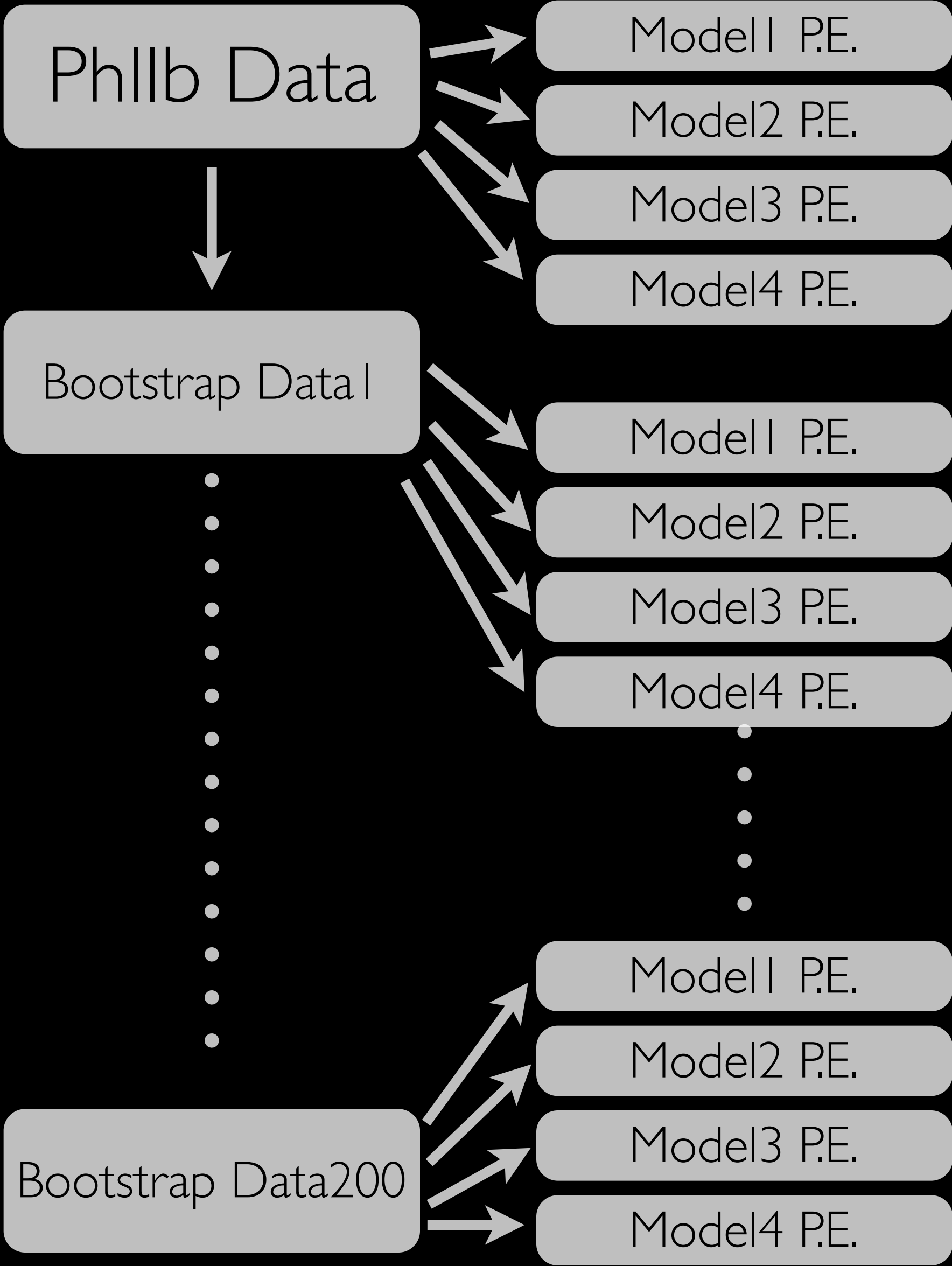
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Phllb Data

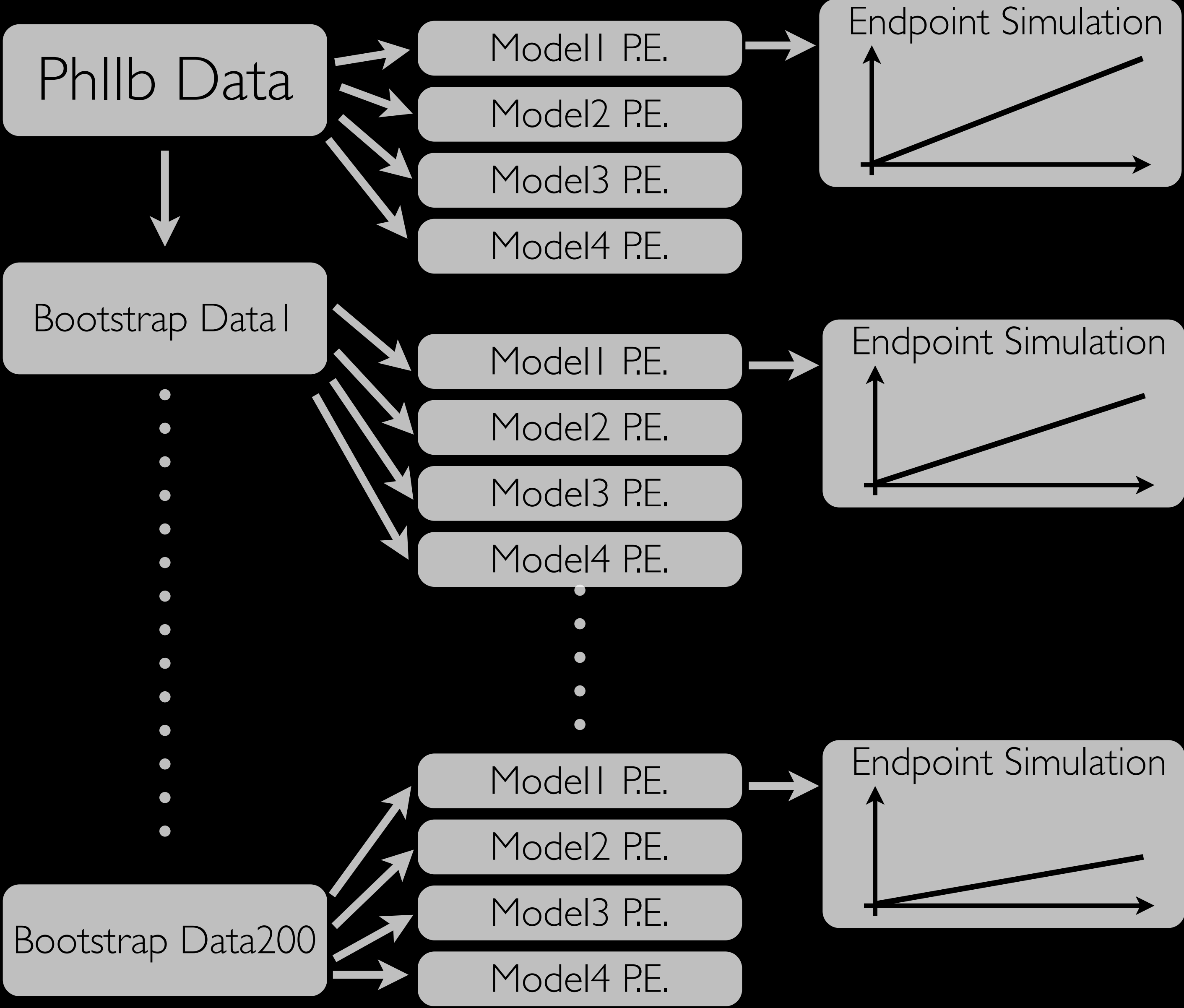
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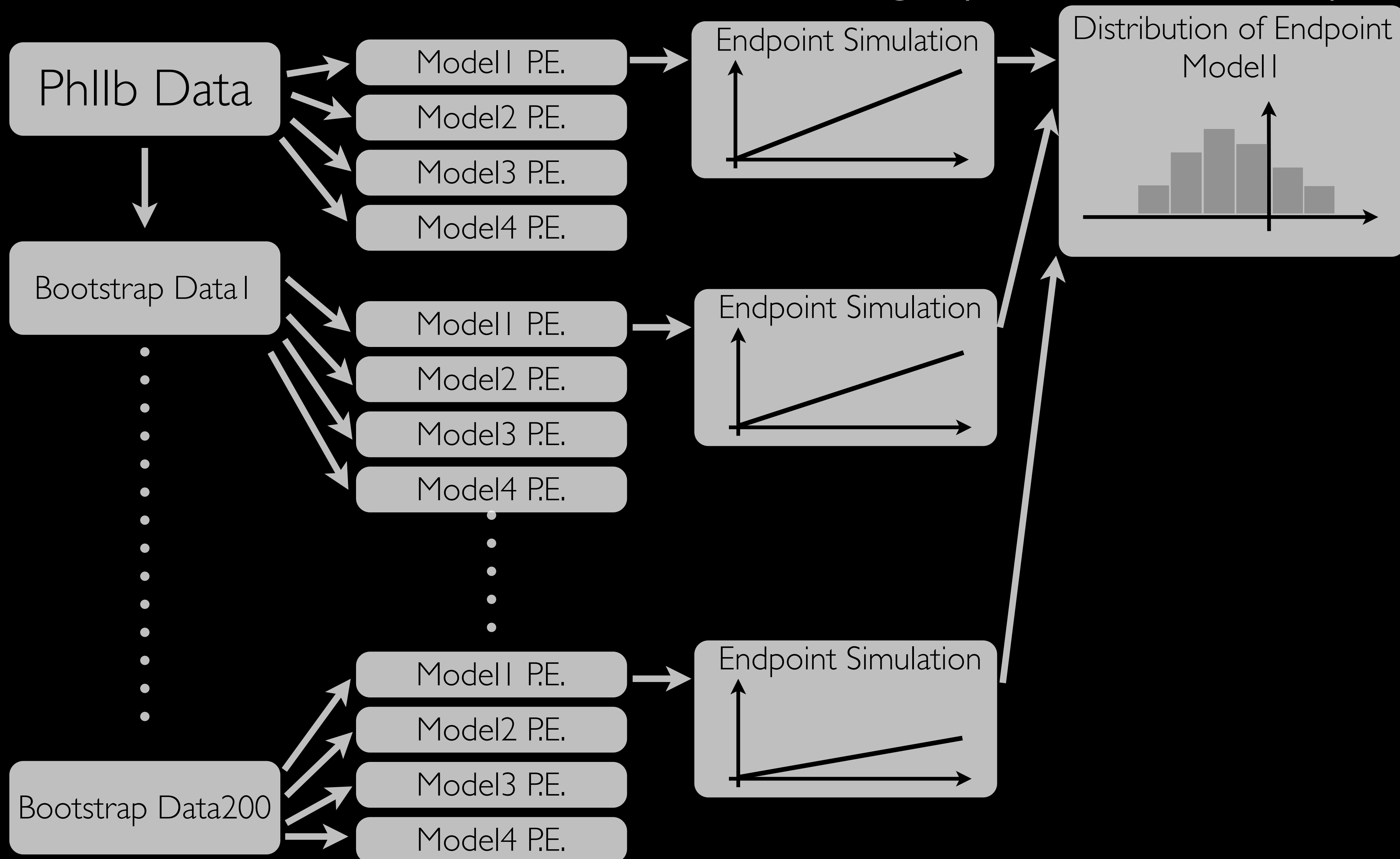
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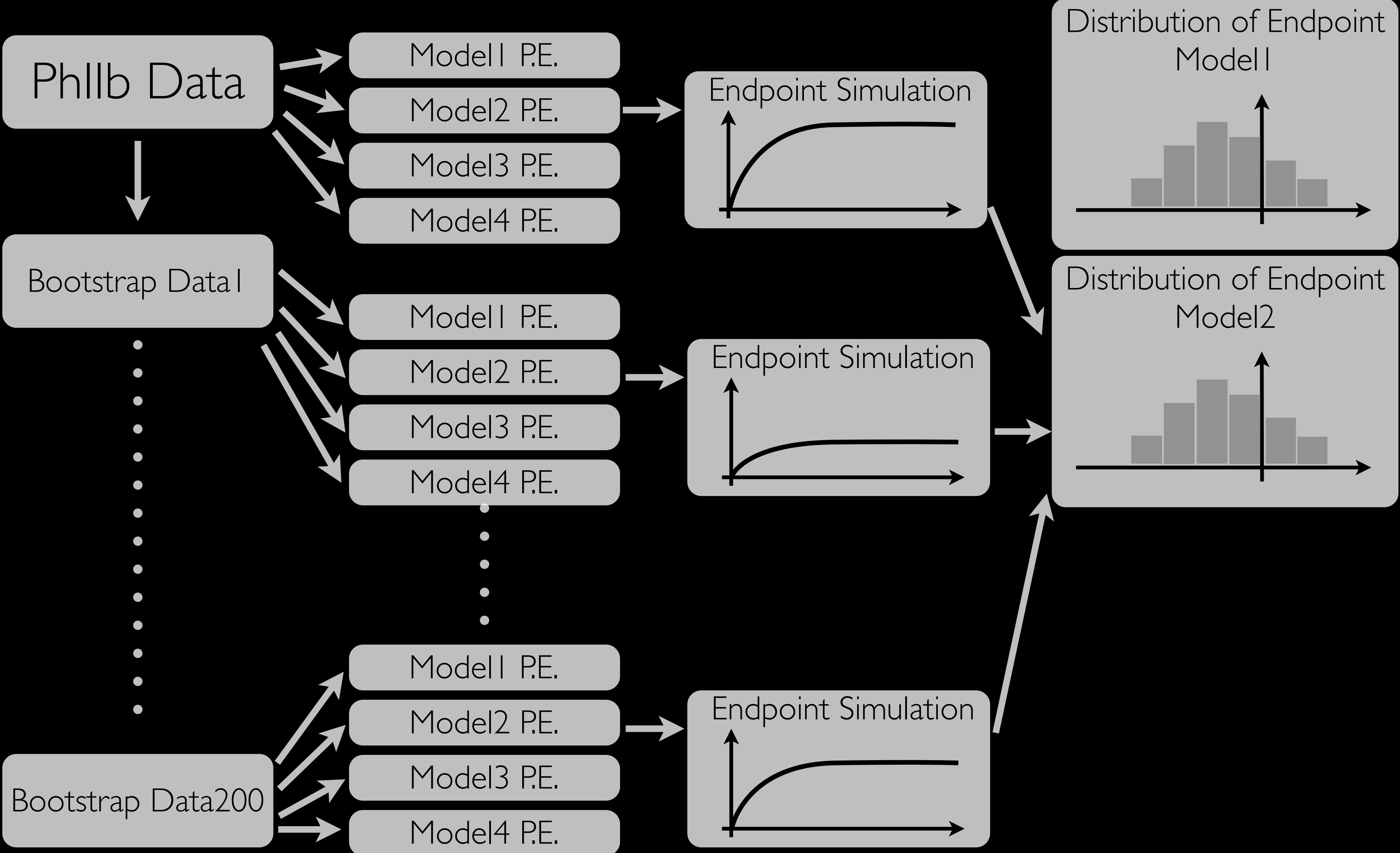
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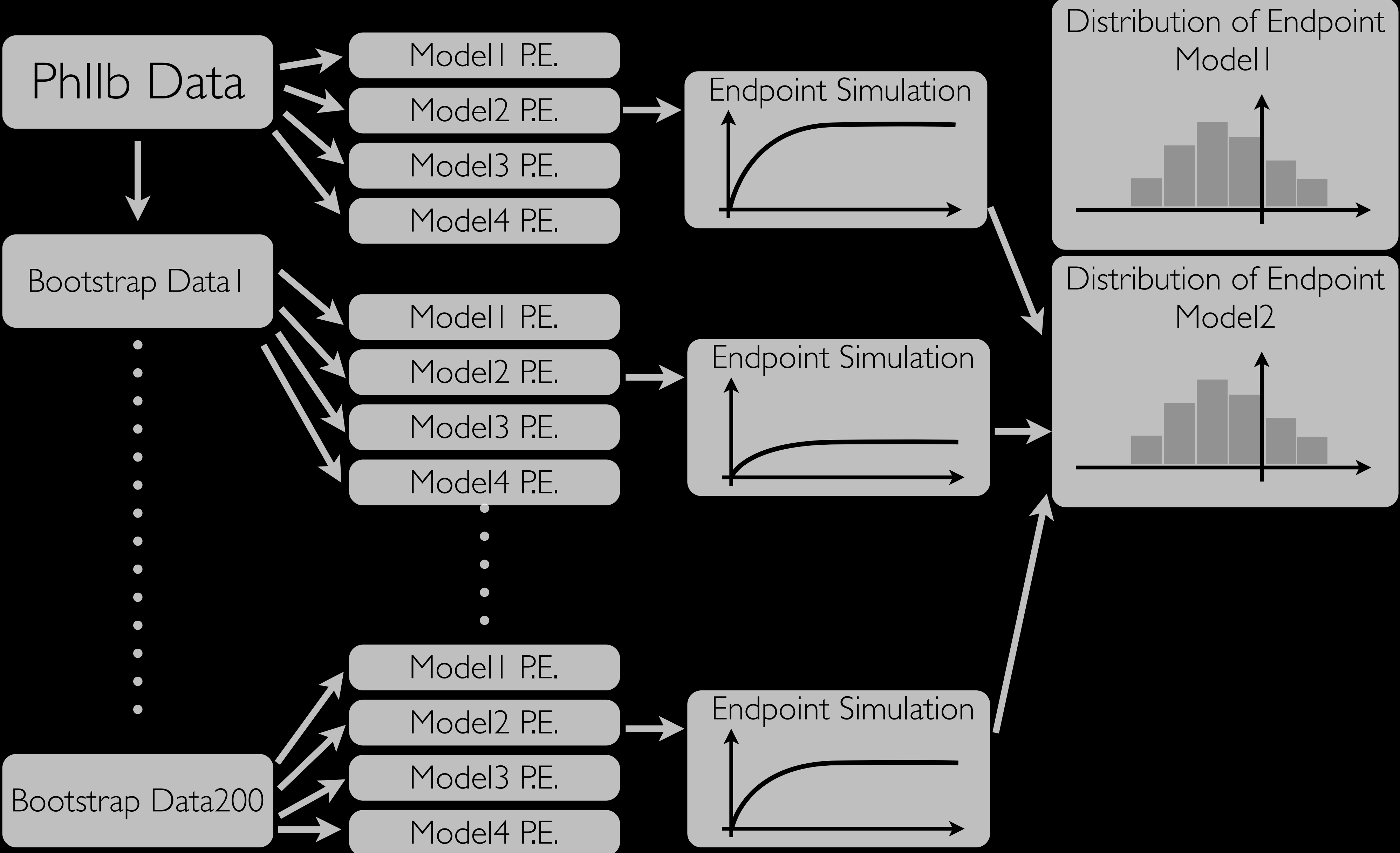
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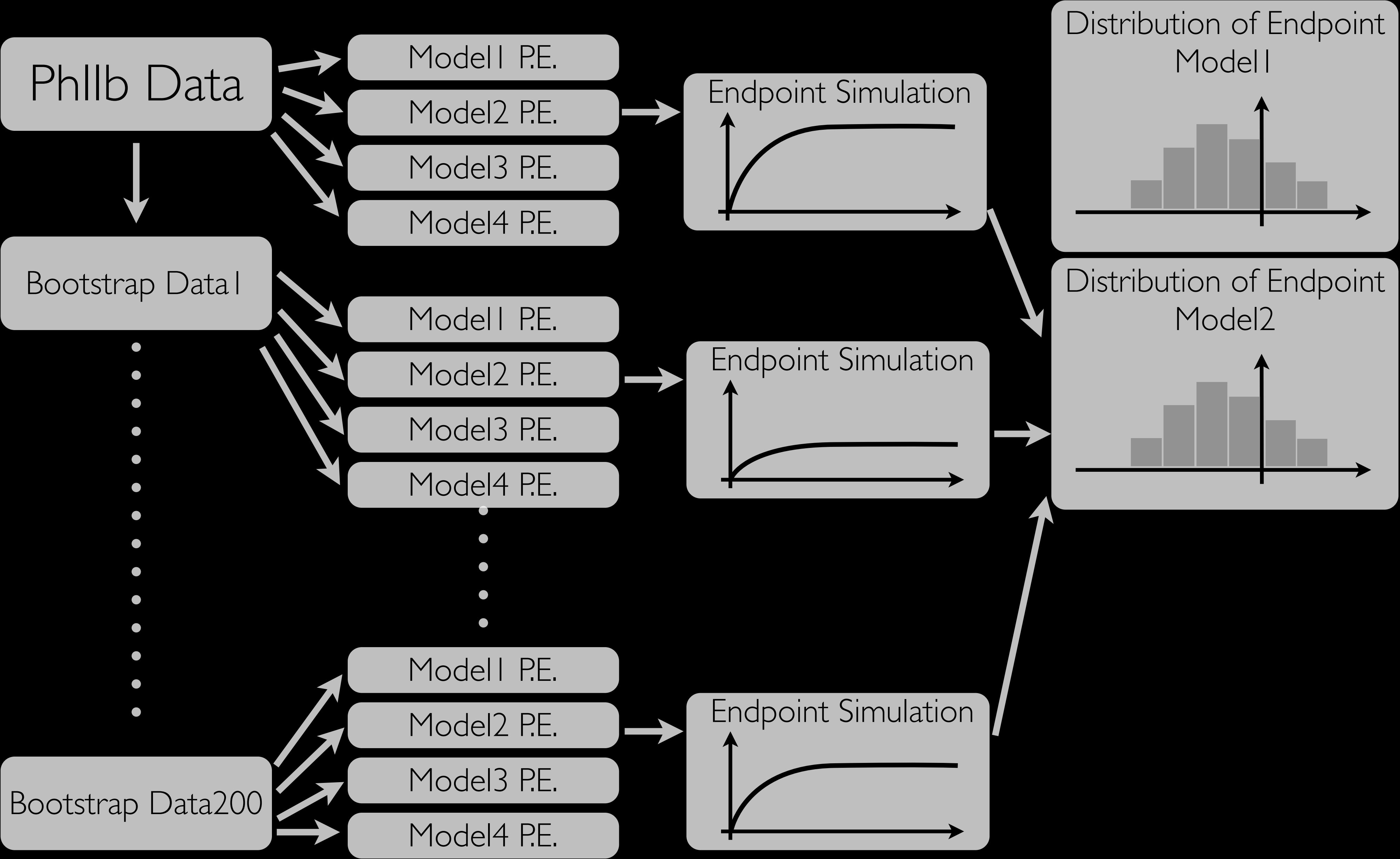
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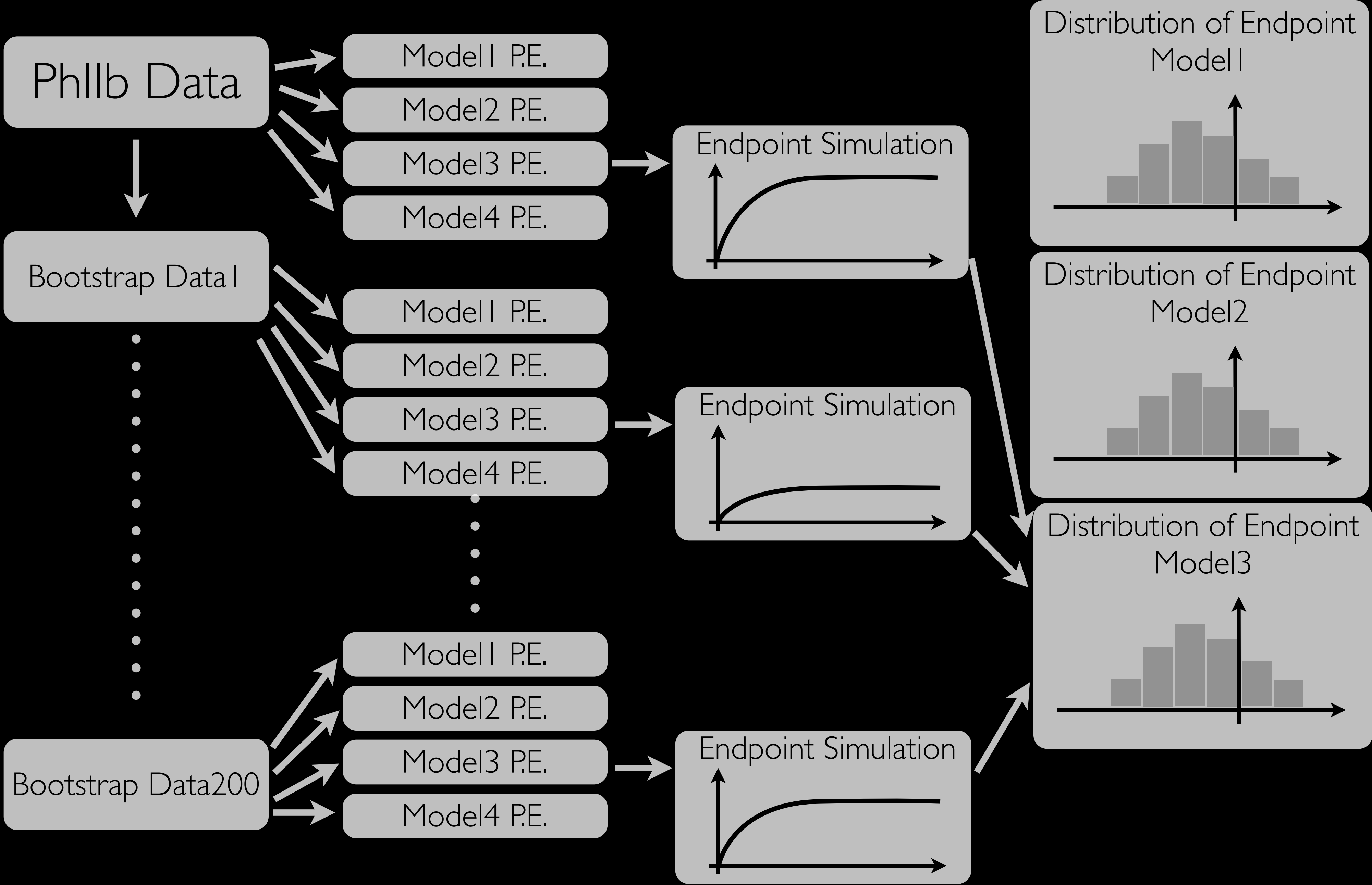


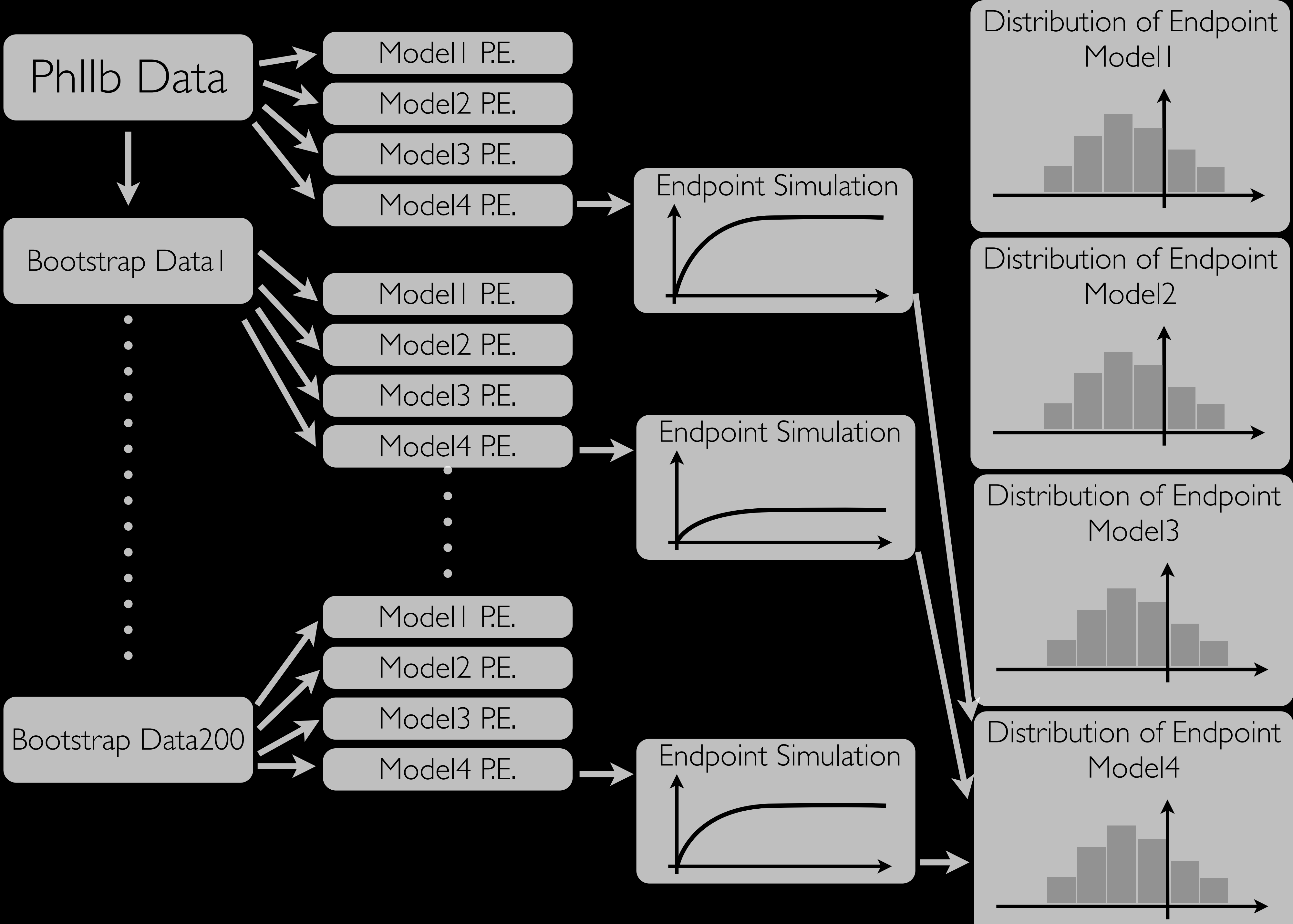
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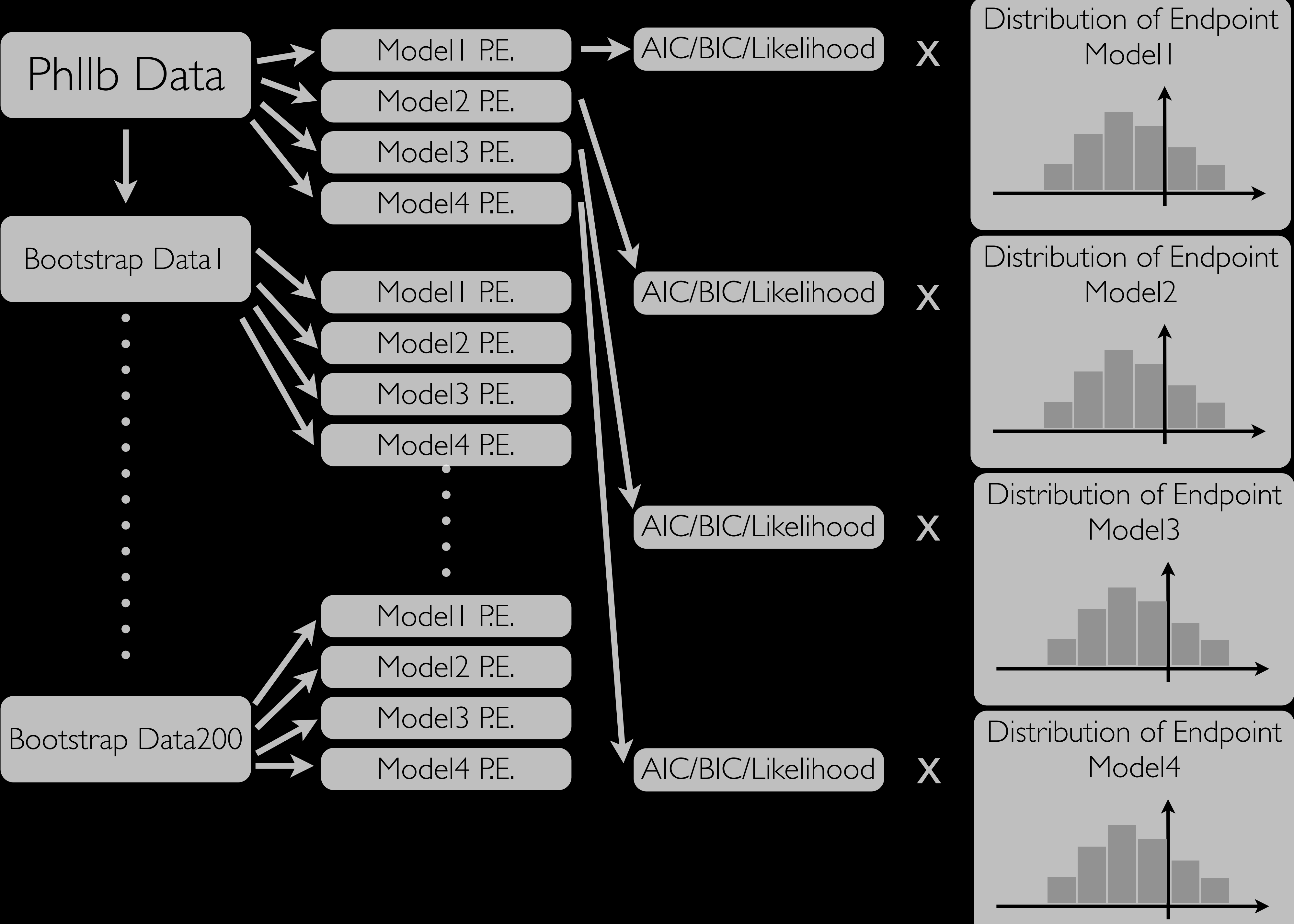


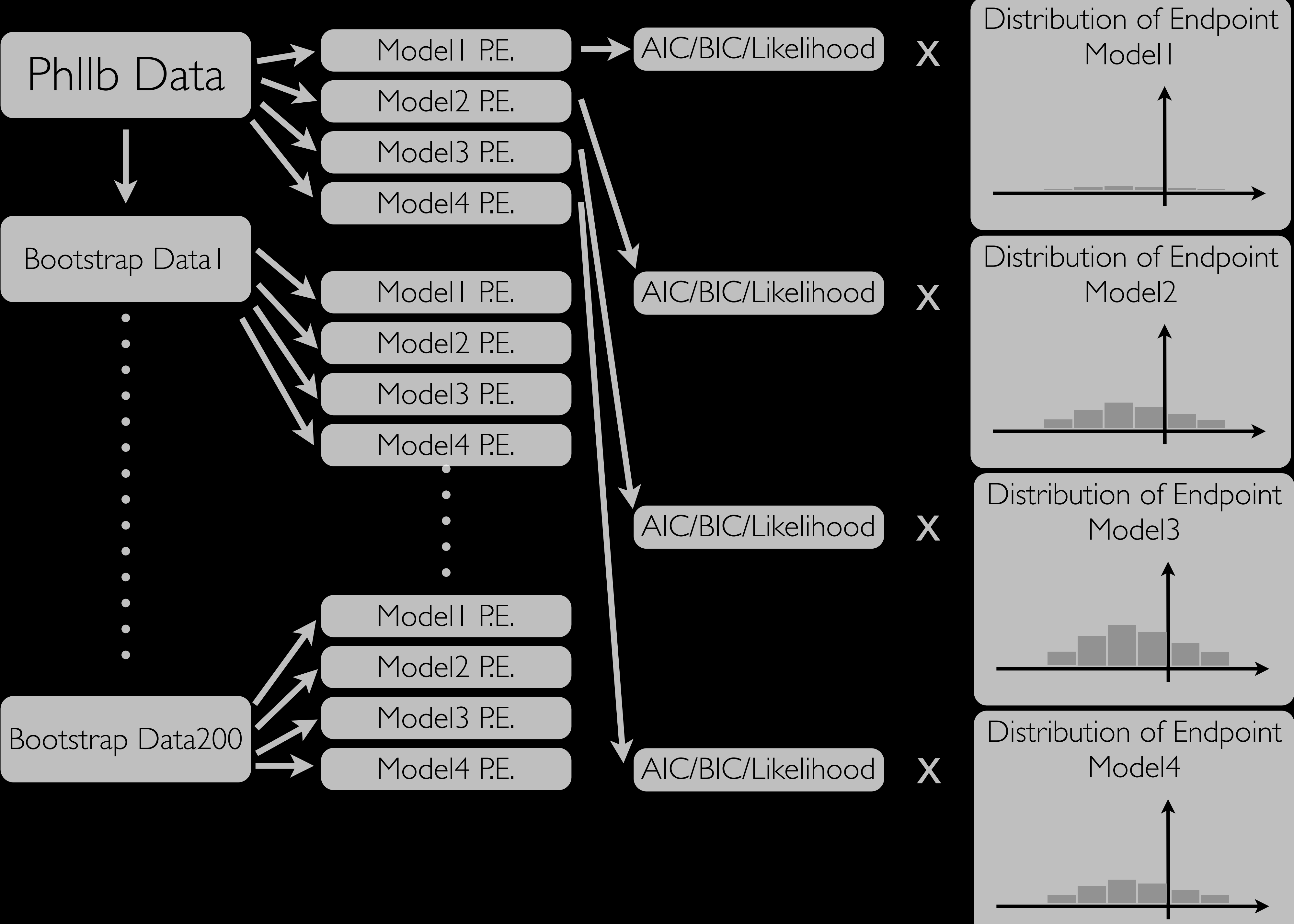


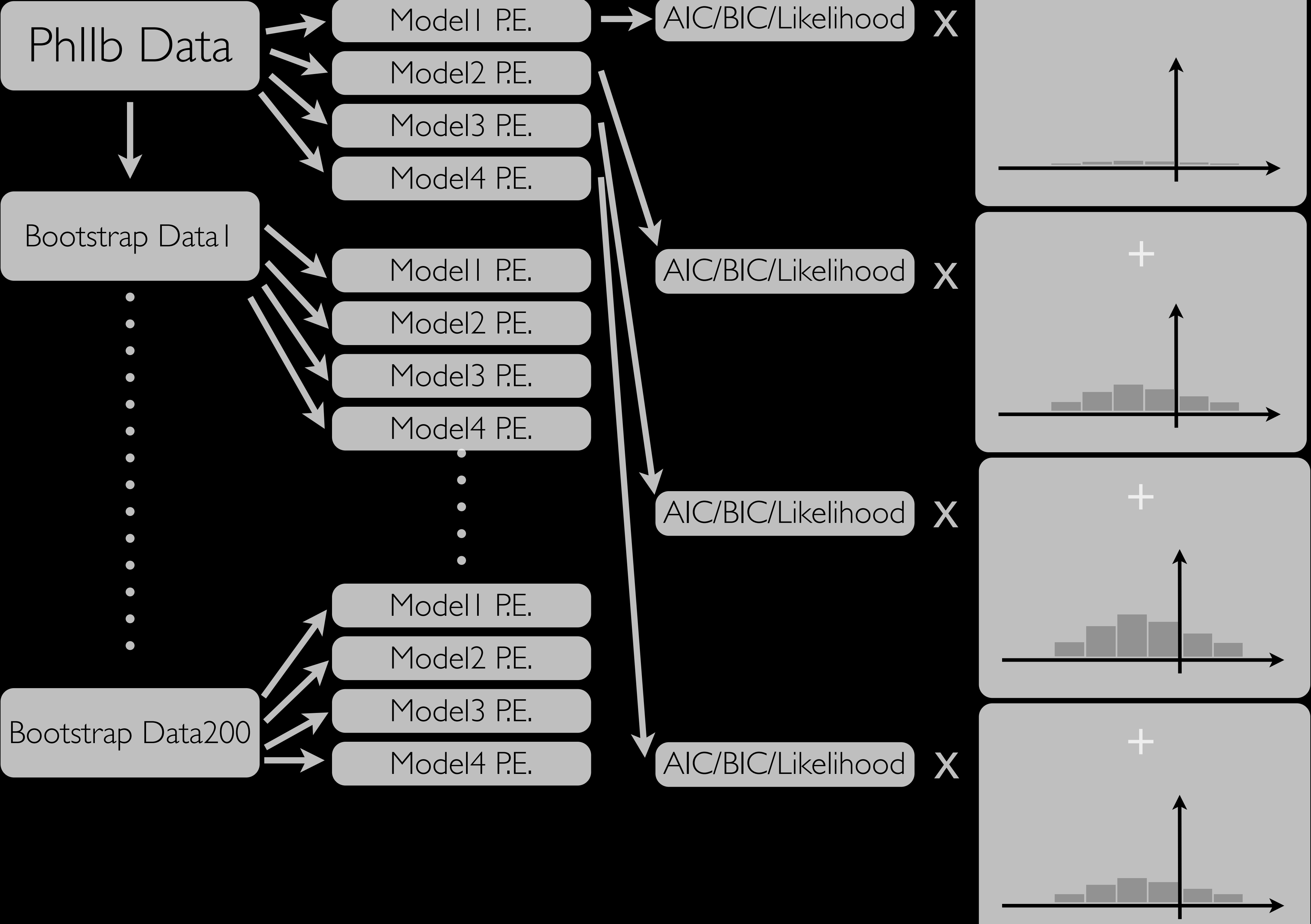


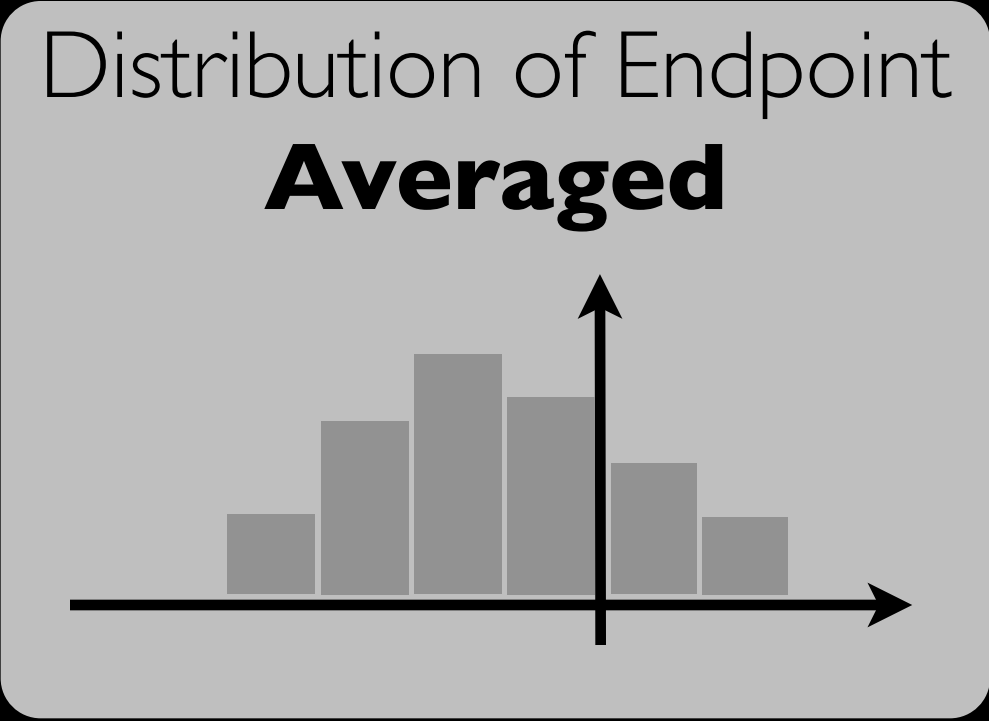
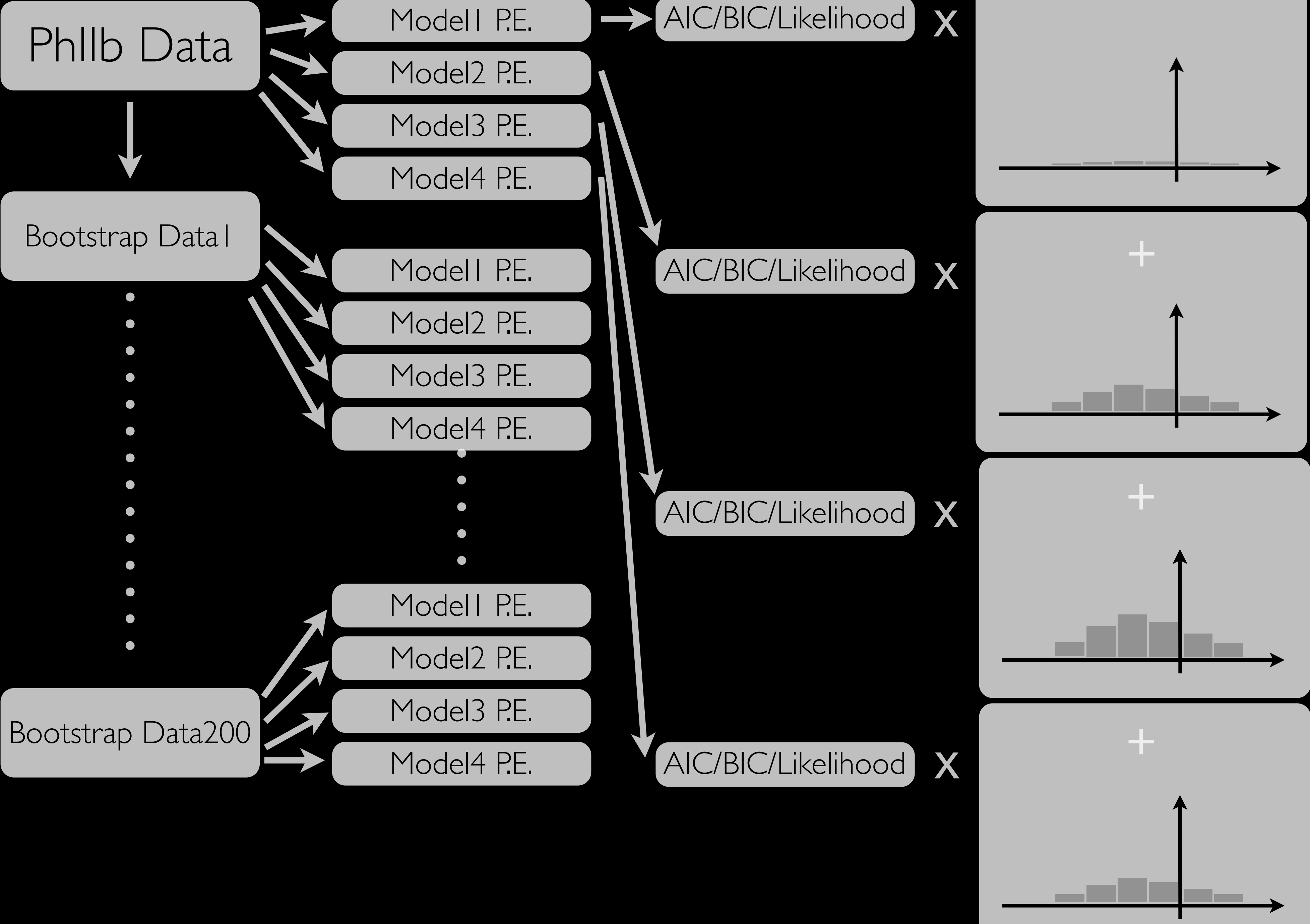




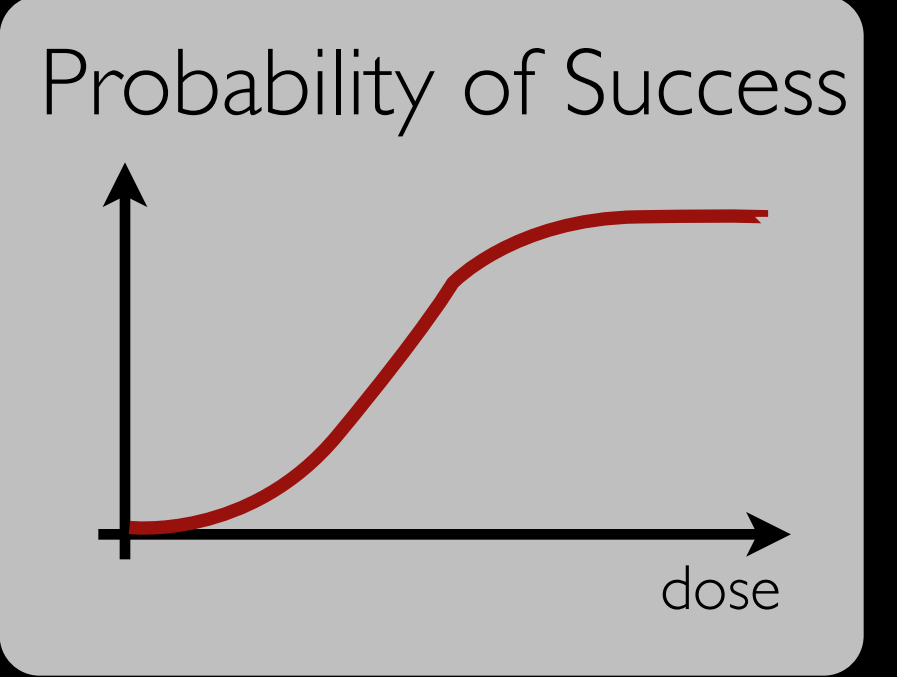
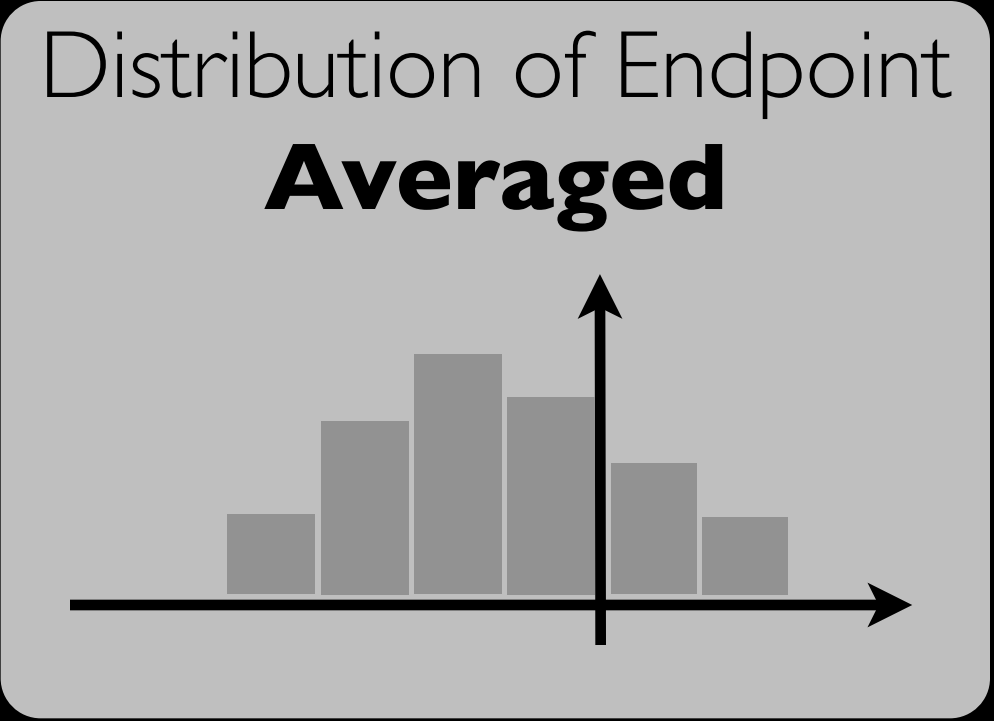
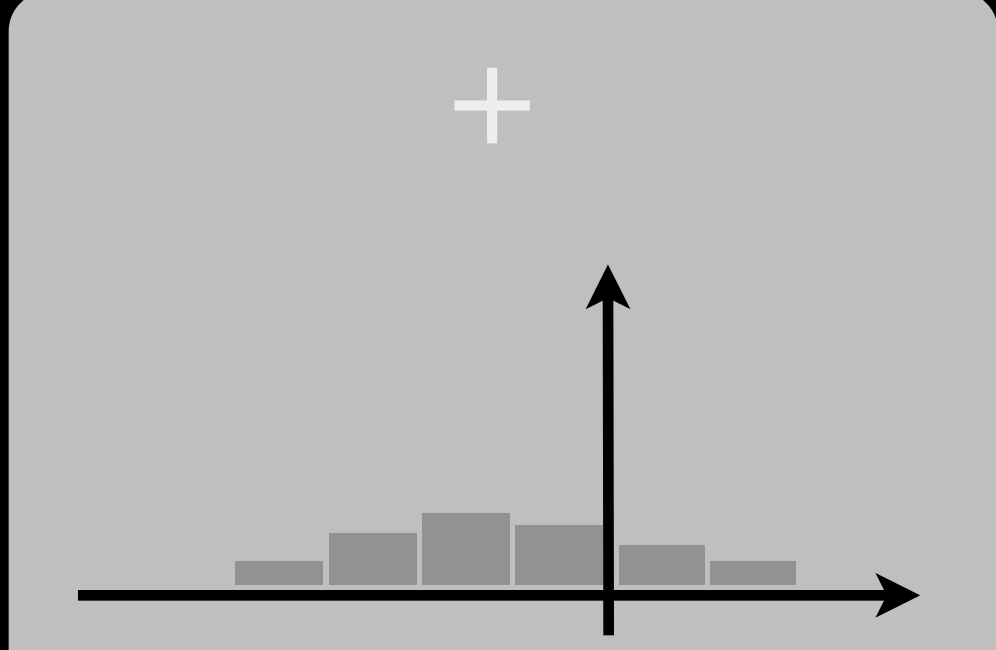
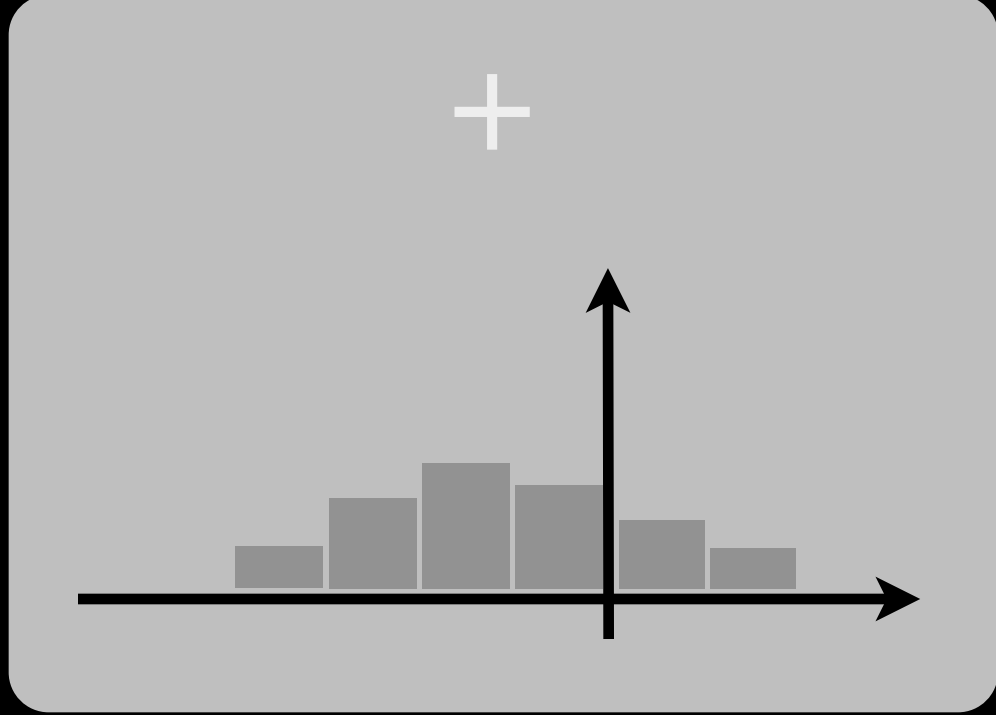
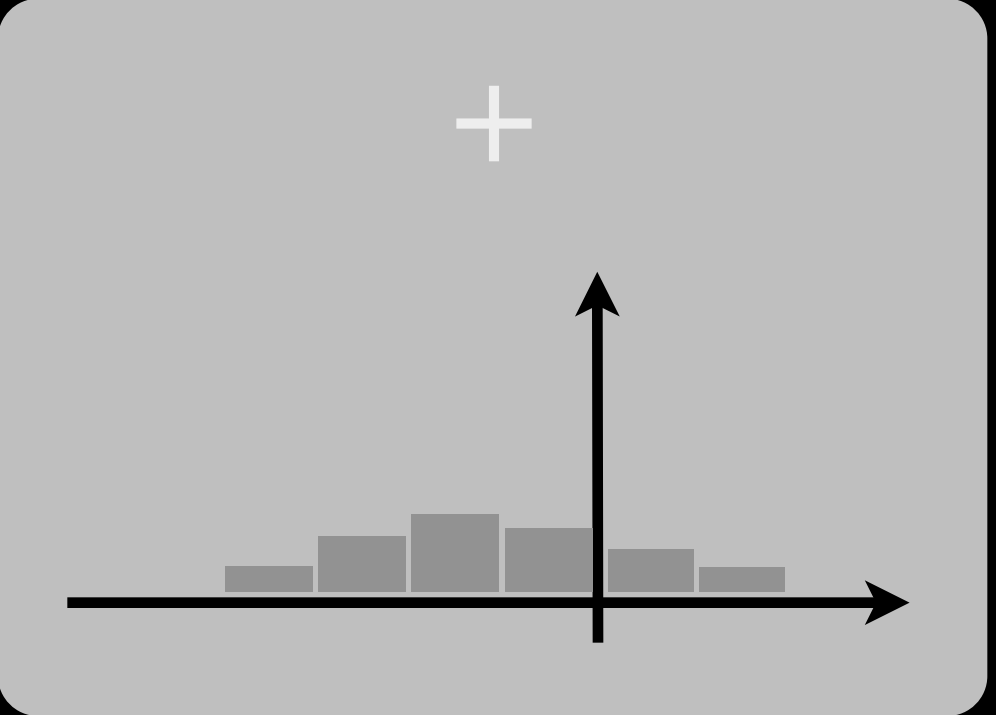
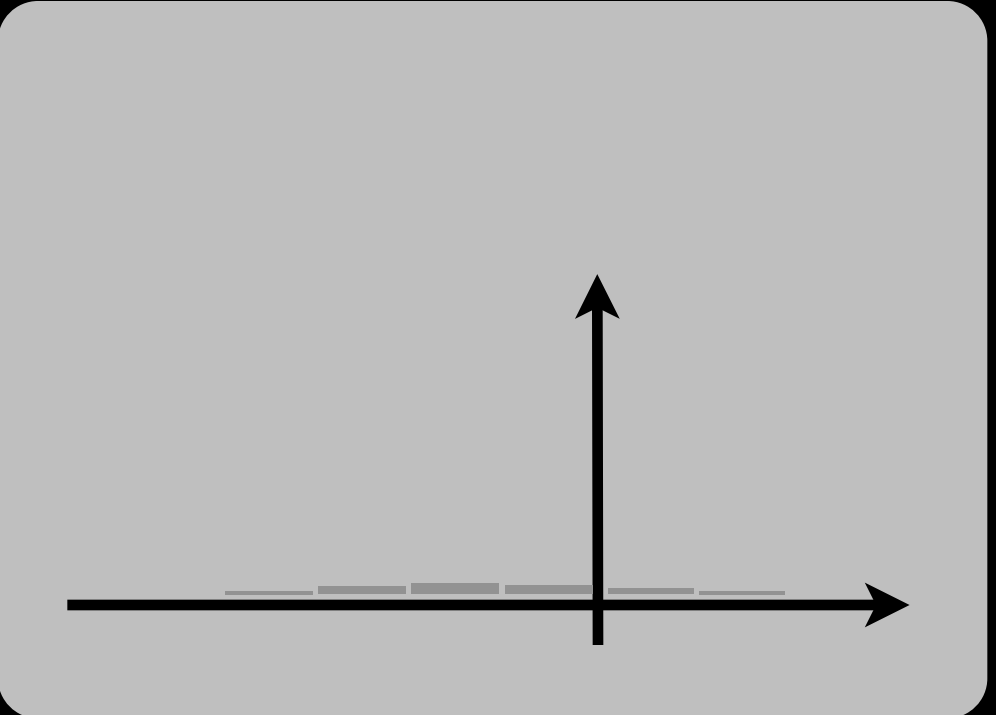
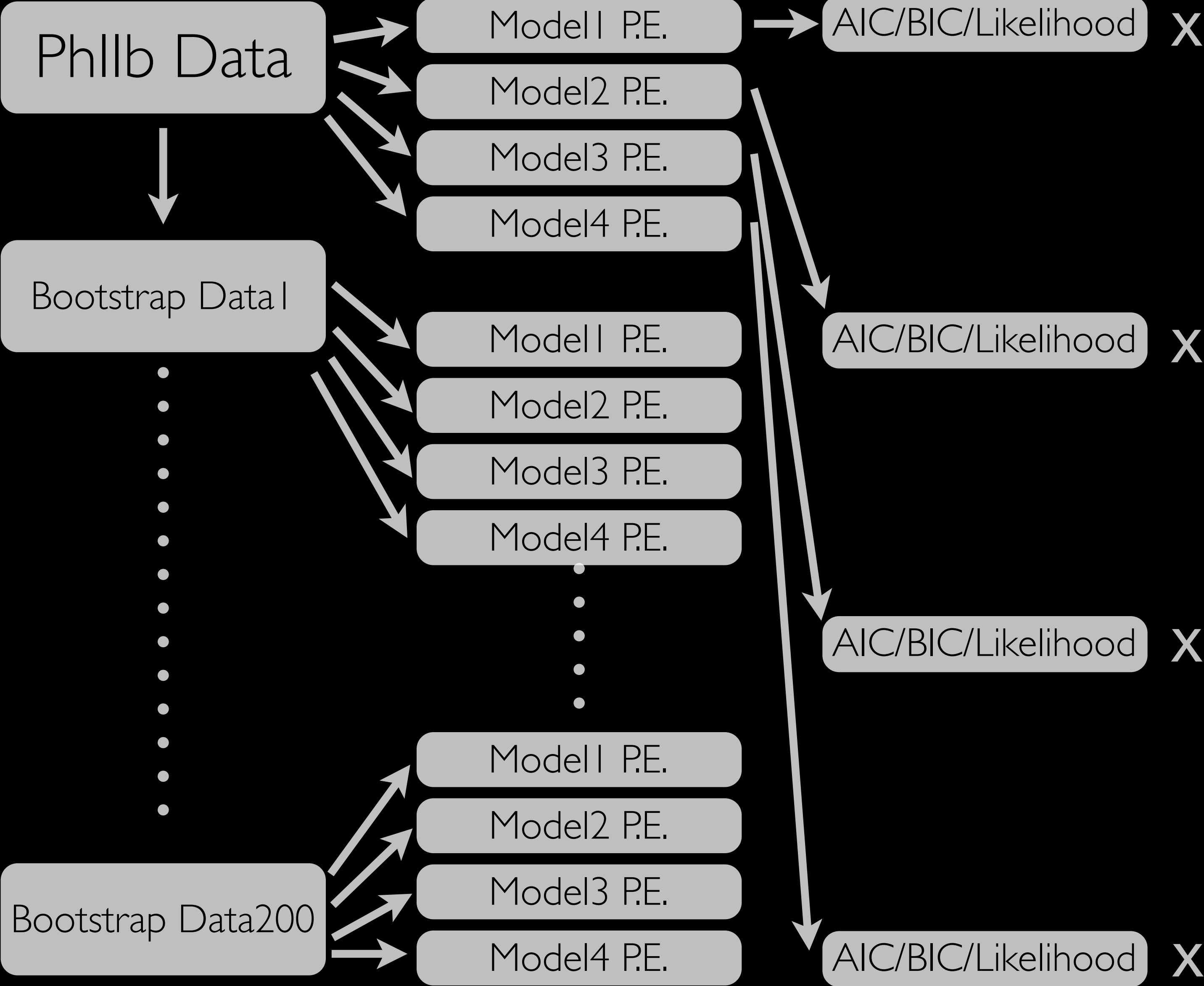










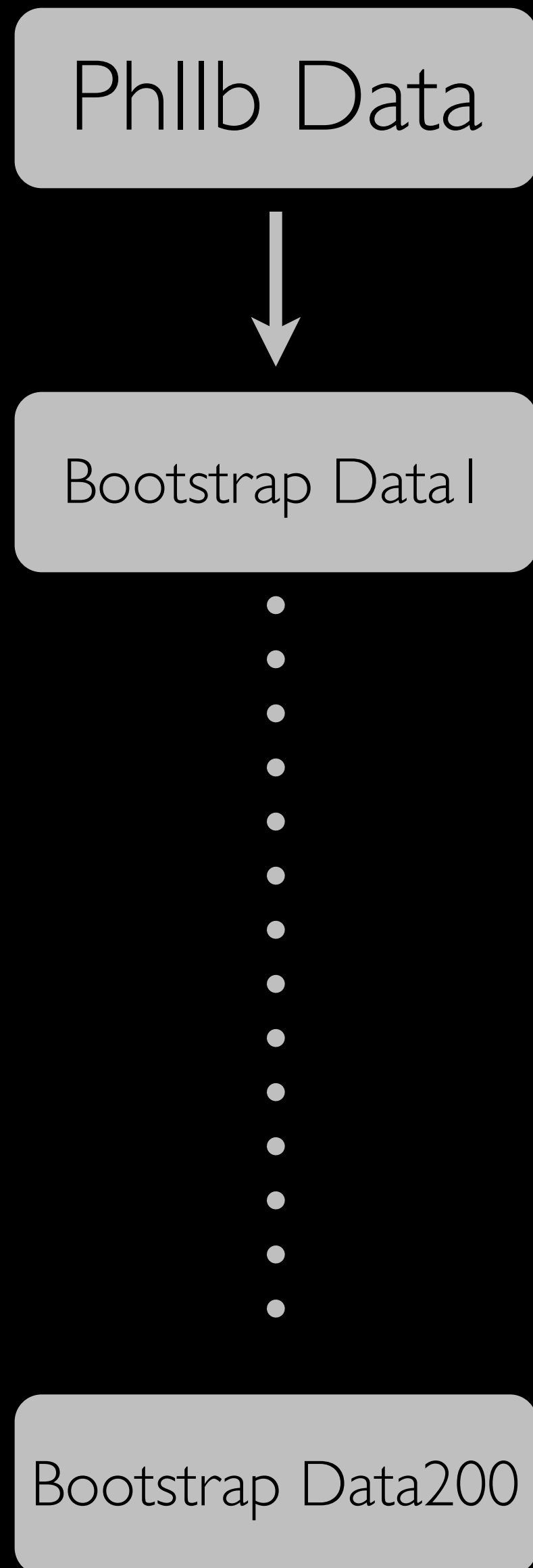


Method 4: Model Average using bootstrap ofv

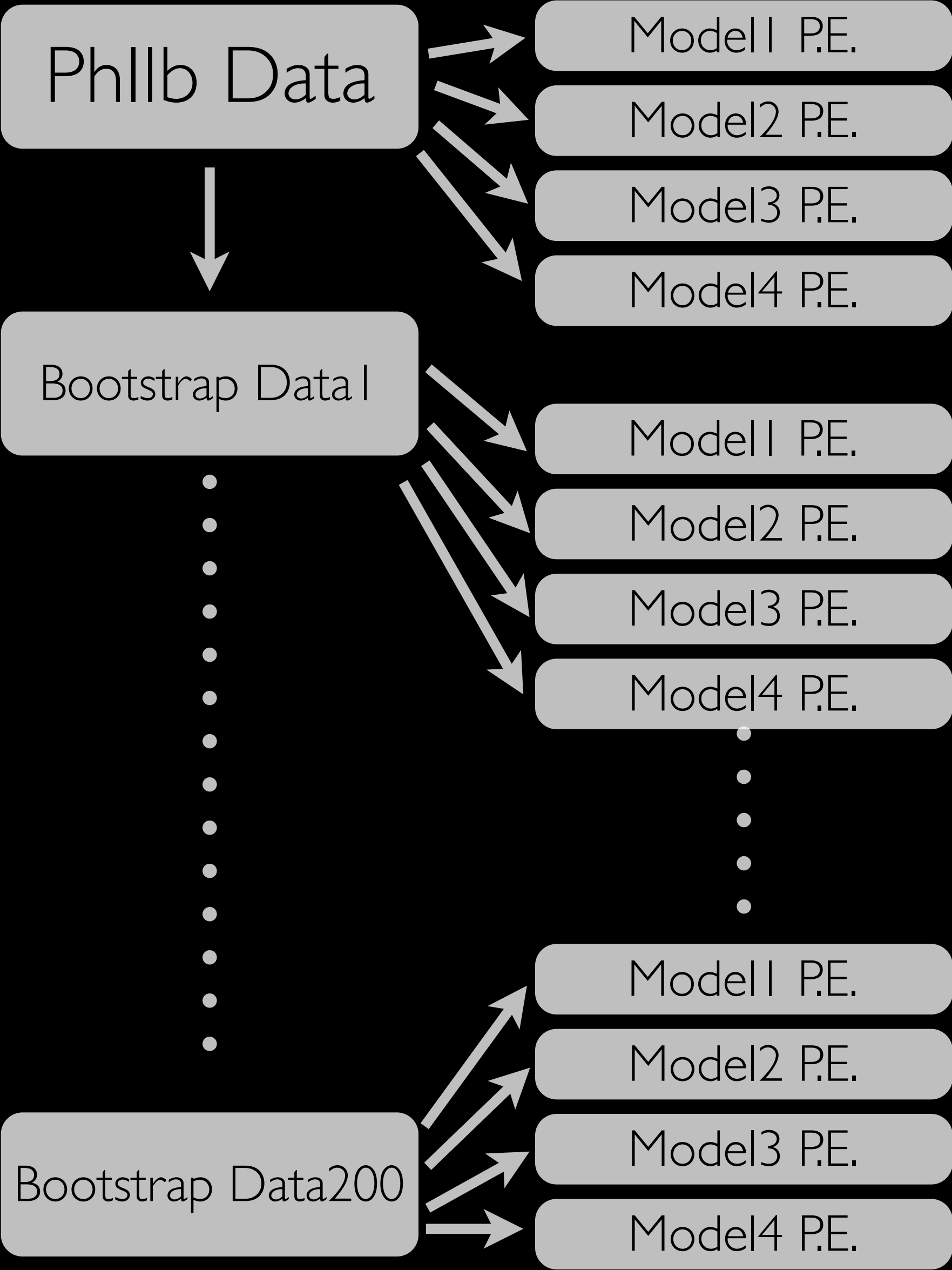
## Method 4: Model Average using bootstrap ofv

Phllb Data

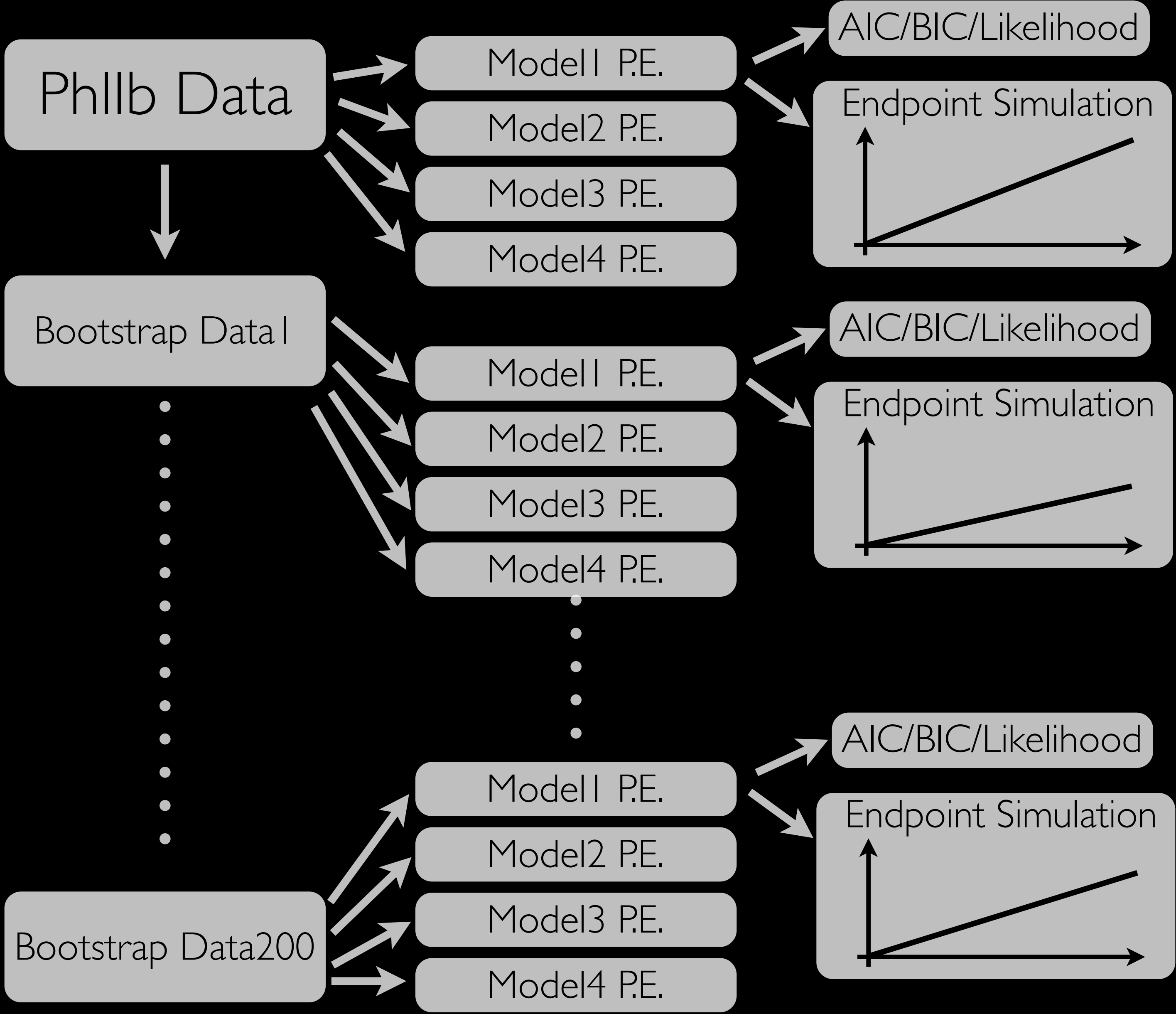
## Method 4: Model Average using bootstrap of v



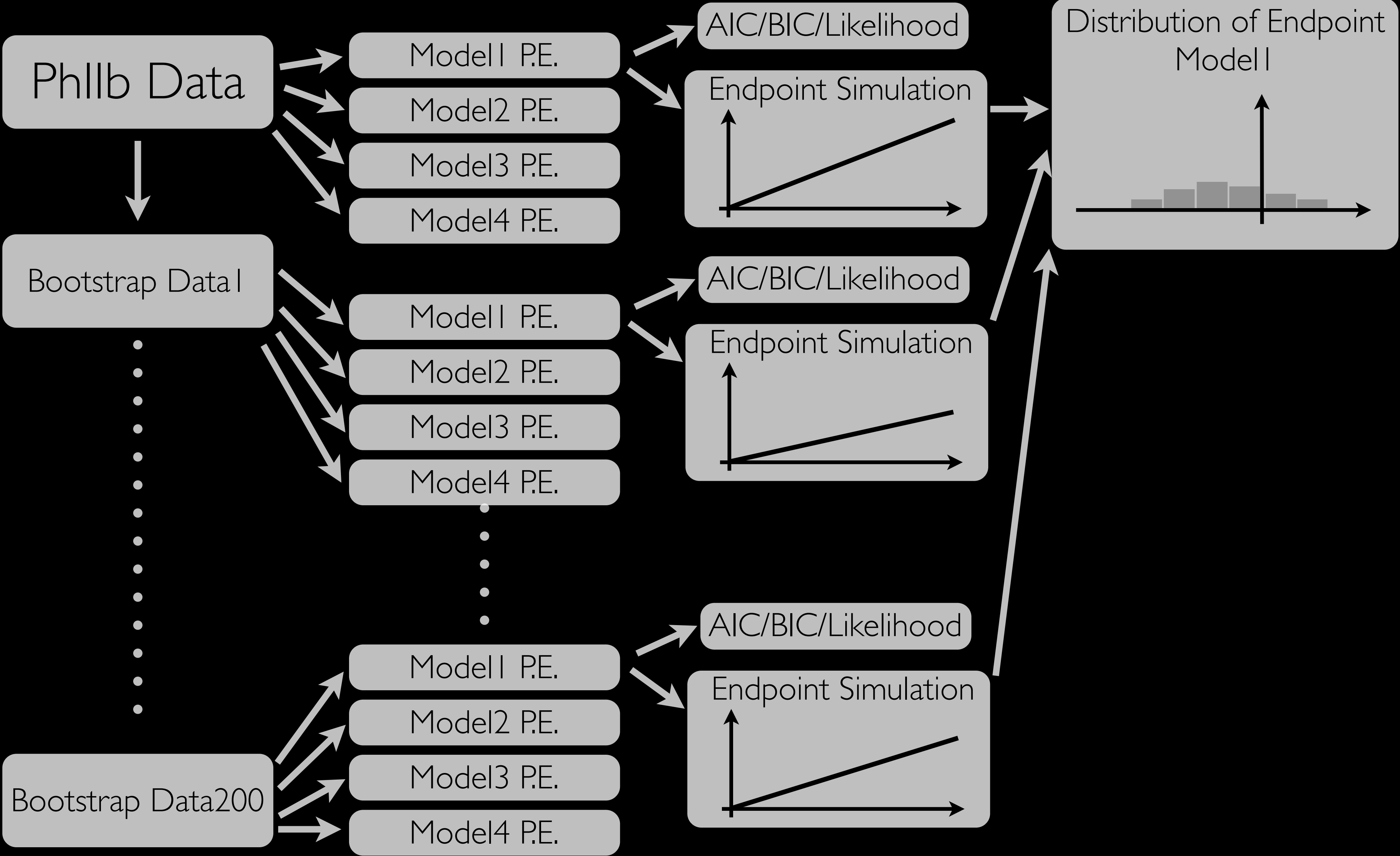
# Method 4: Model Average using bootstrap of v



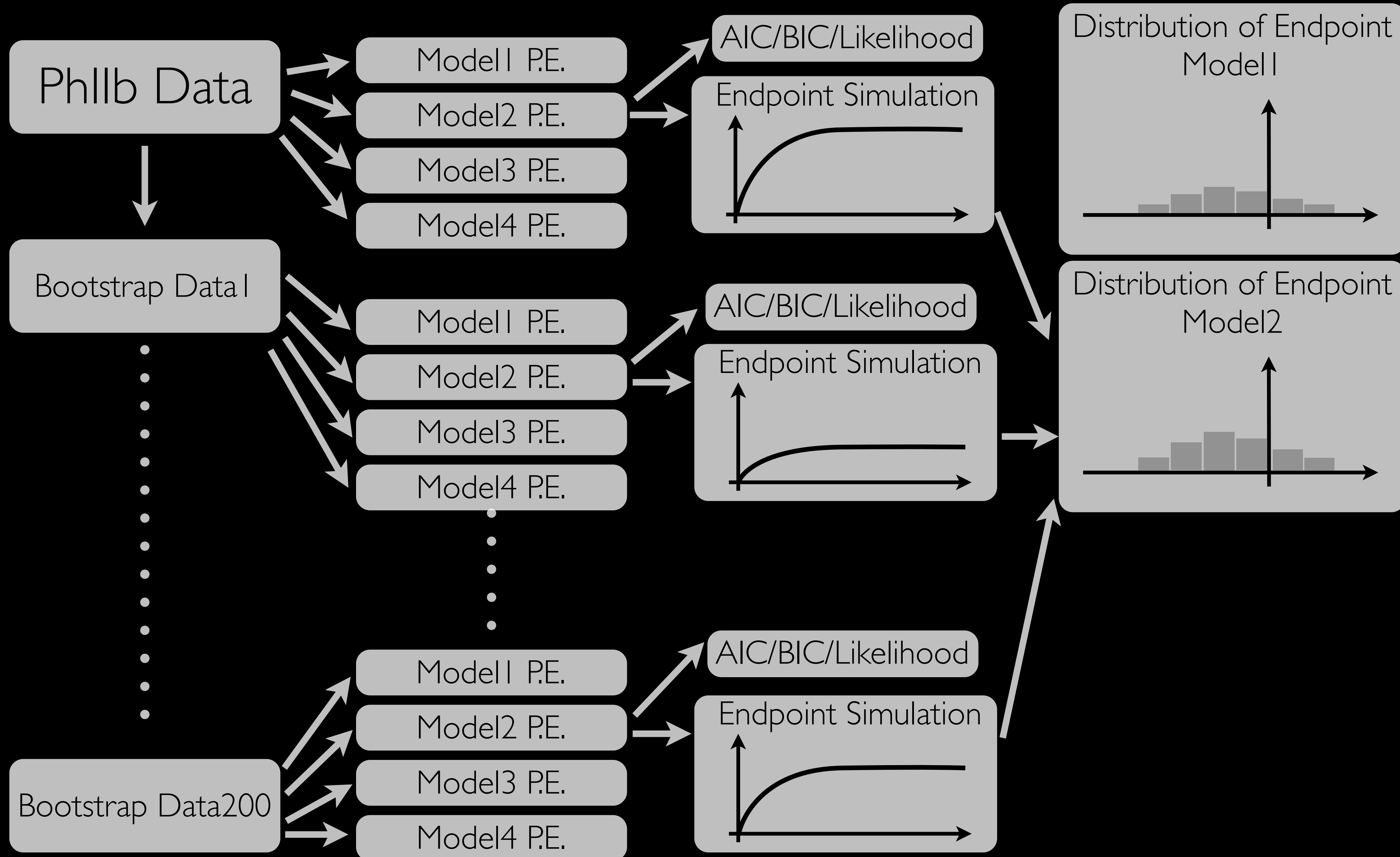
# Method 4: Model Average using bootstrap of v



# Method 4: Model Average using bootstrap of v

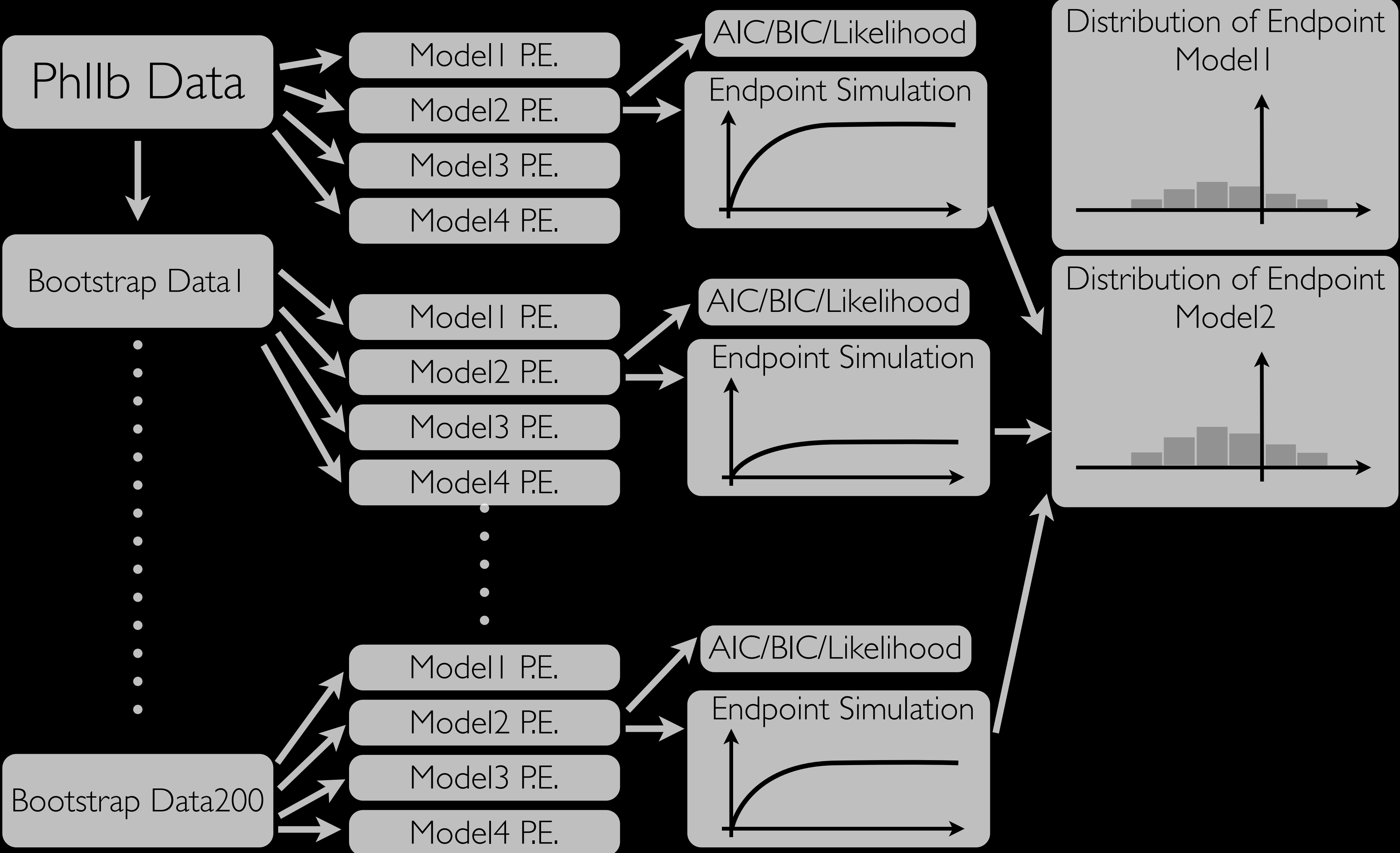


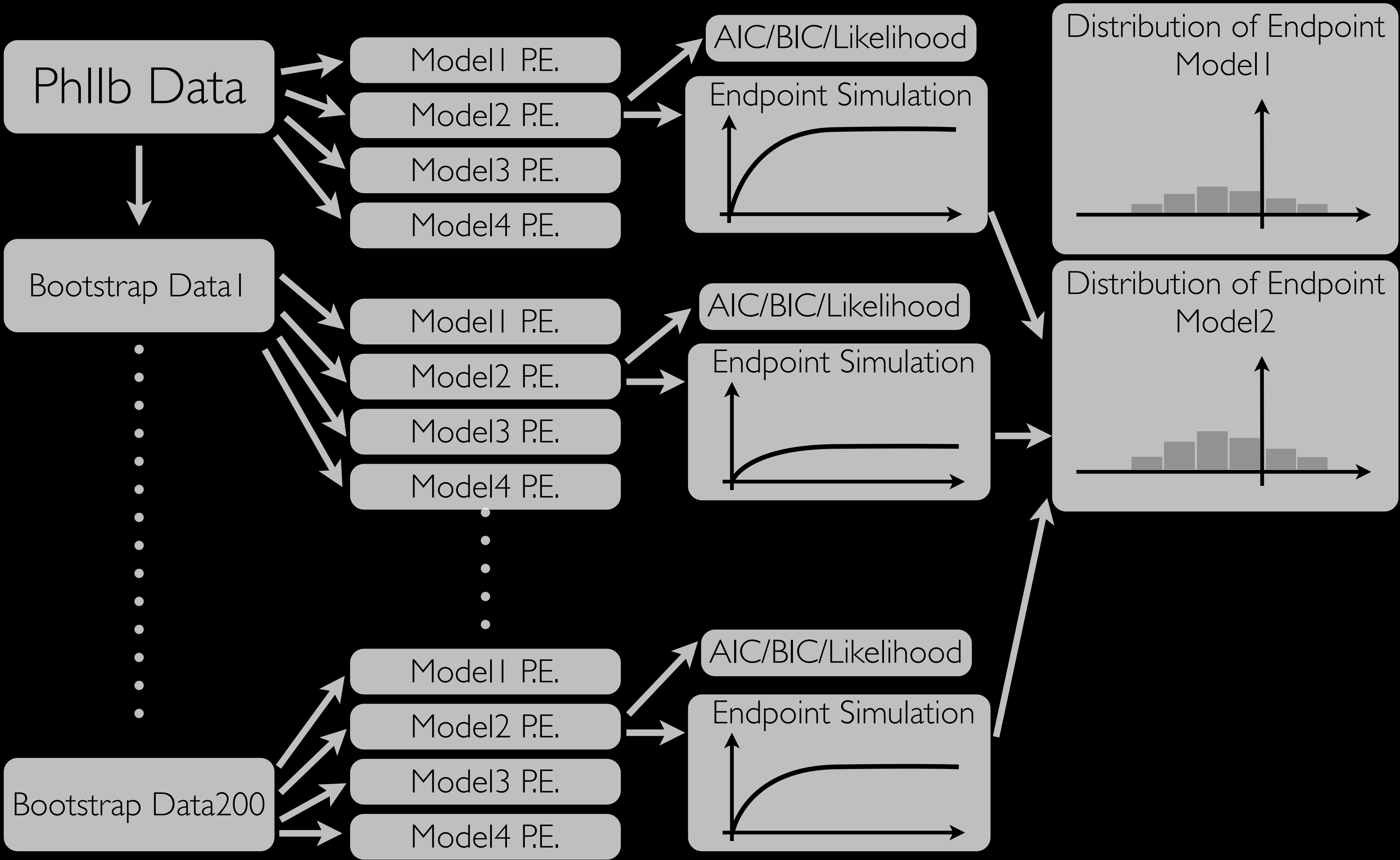
# Method 4: Model Average using bootstrap of v

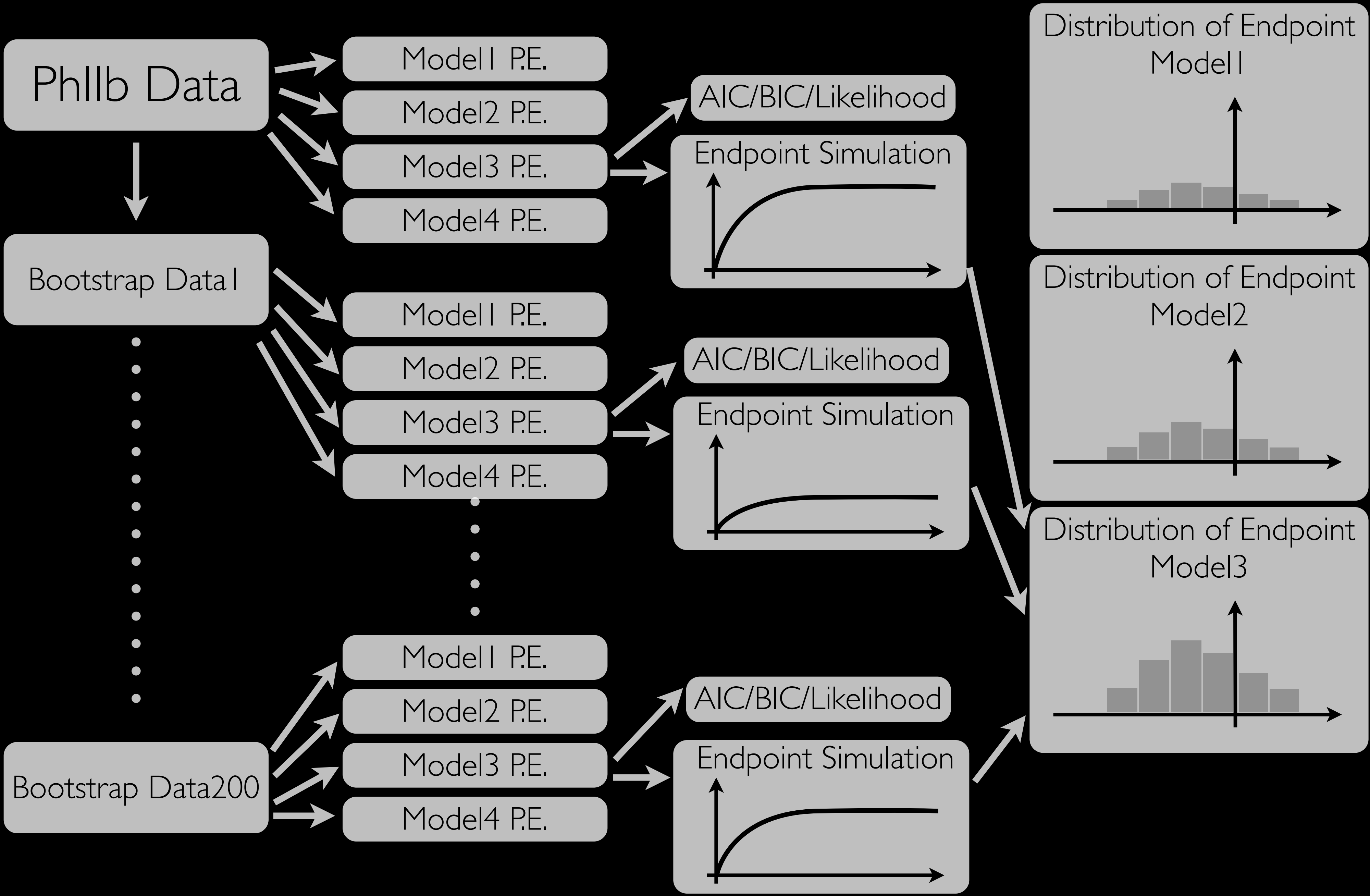


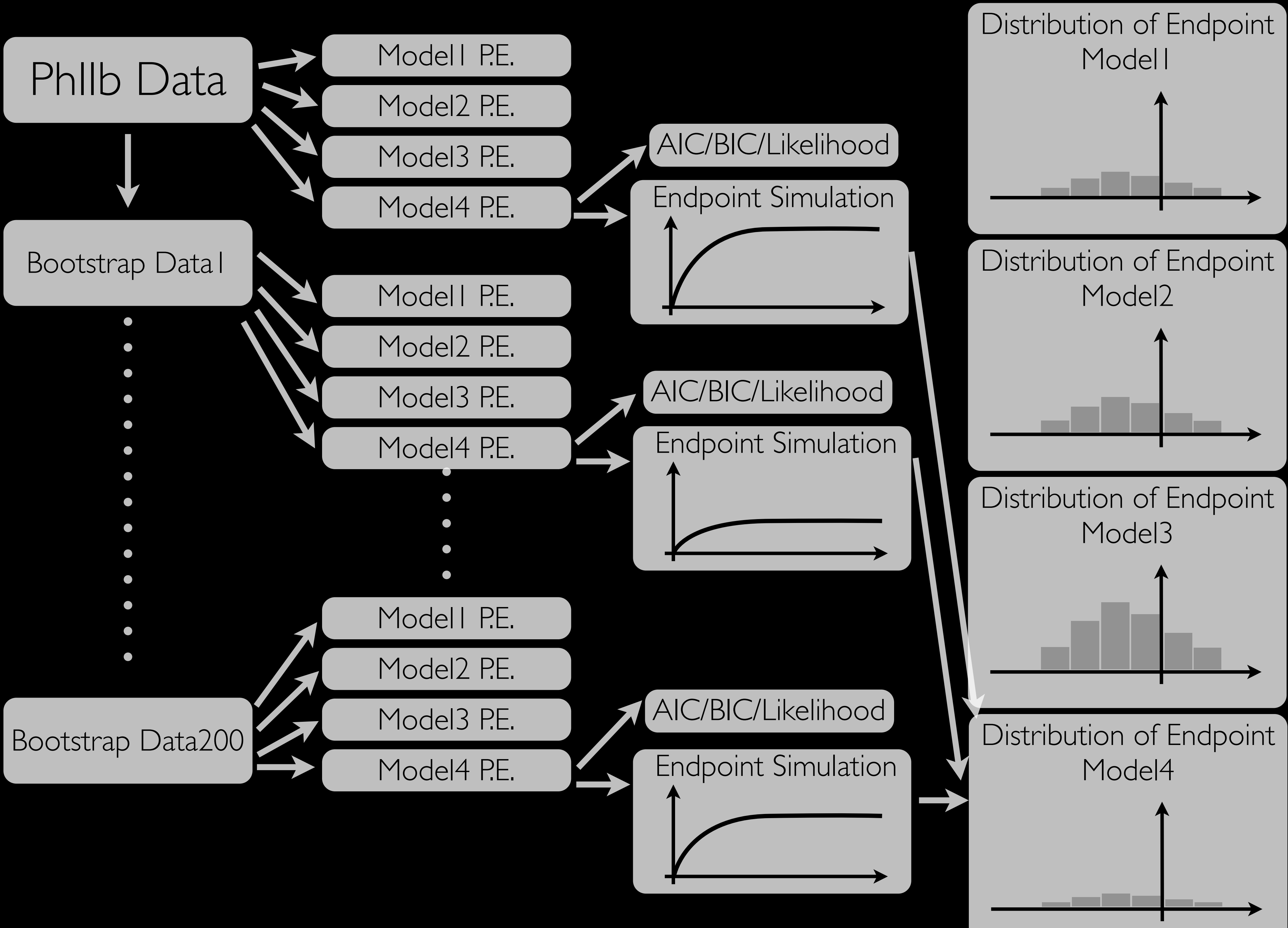


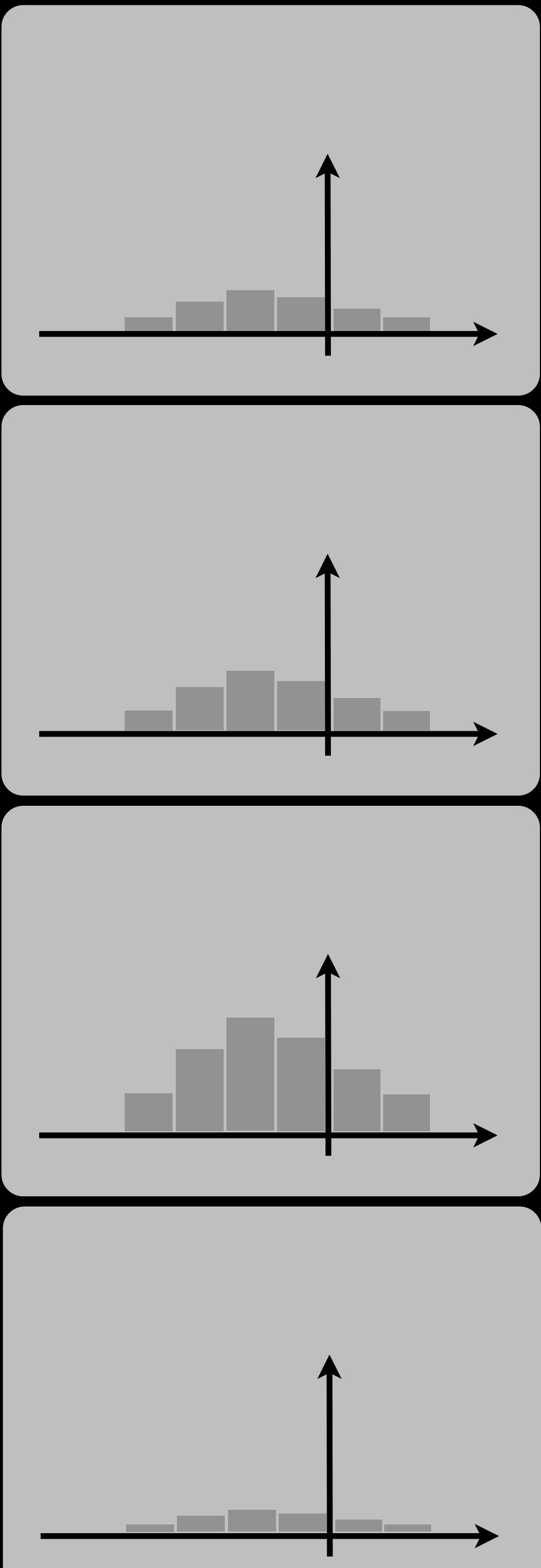
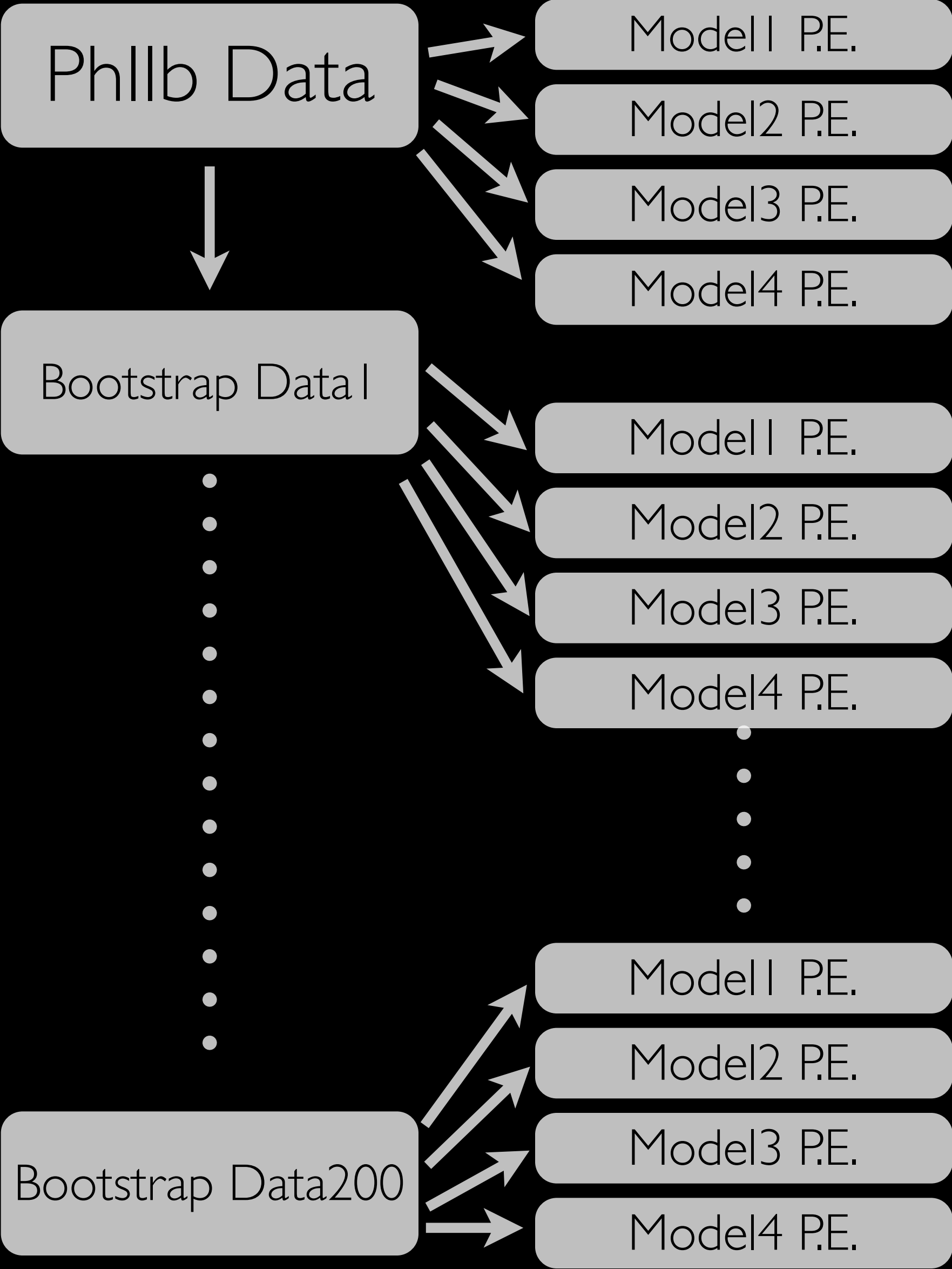
# Method 4: Model Average using bootstrap of v

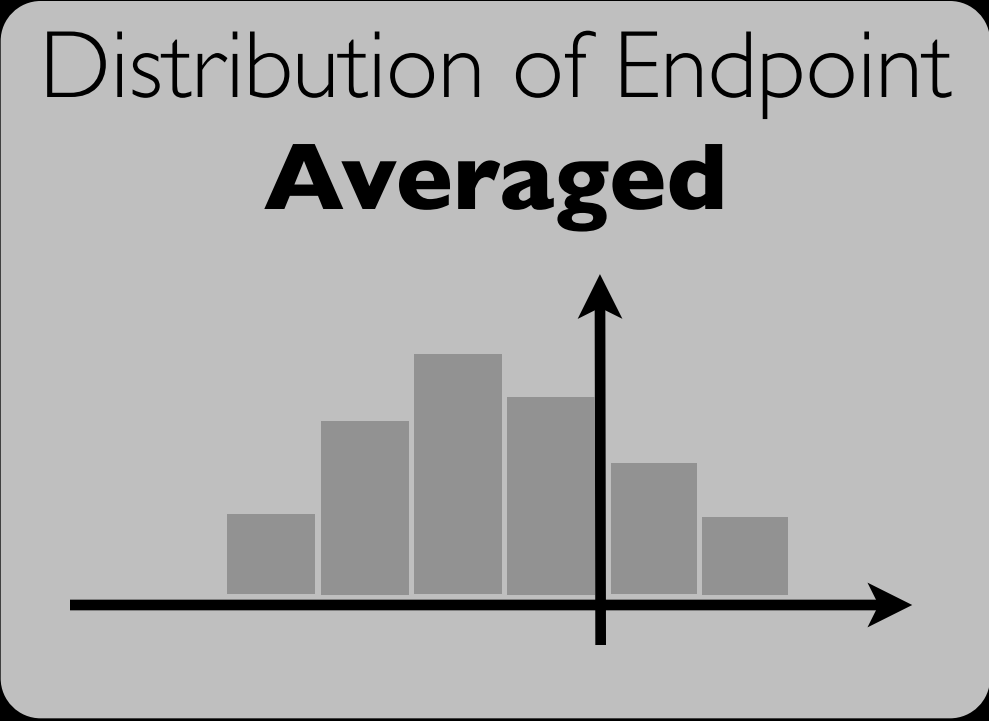
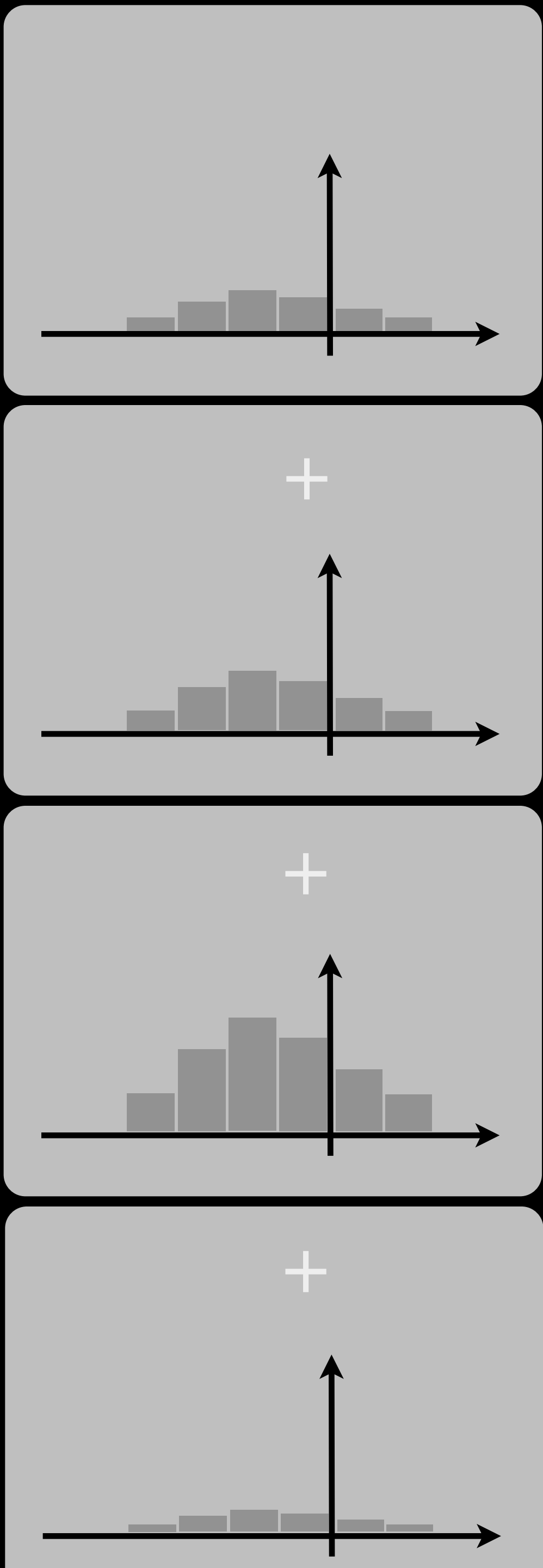
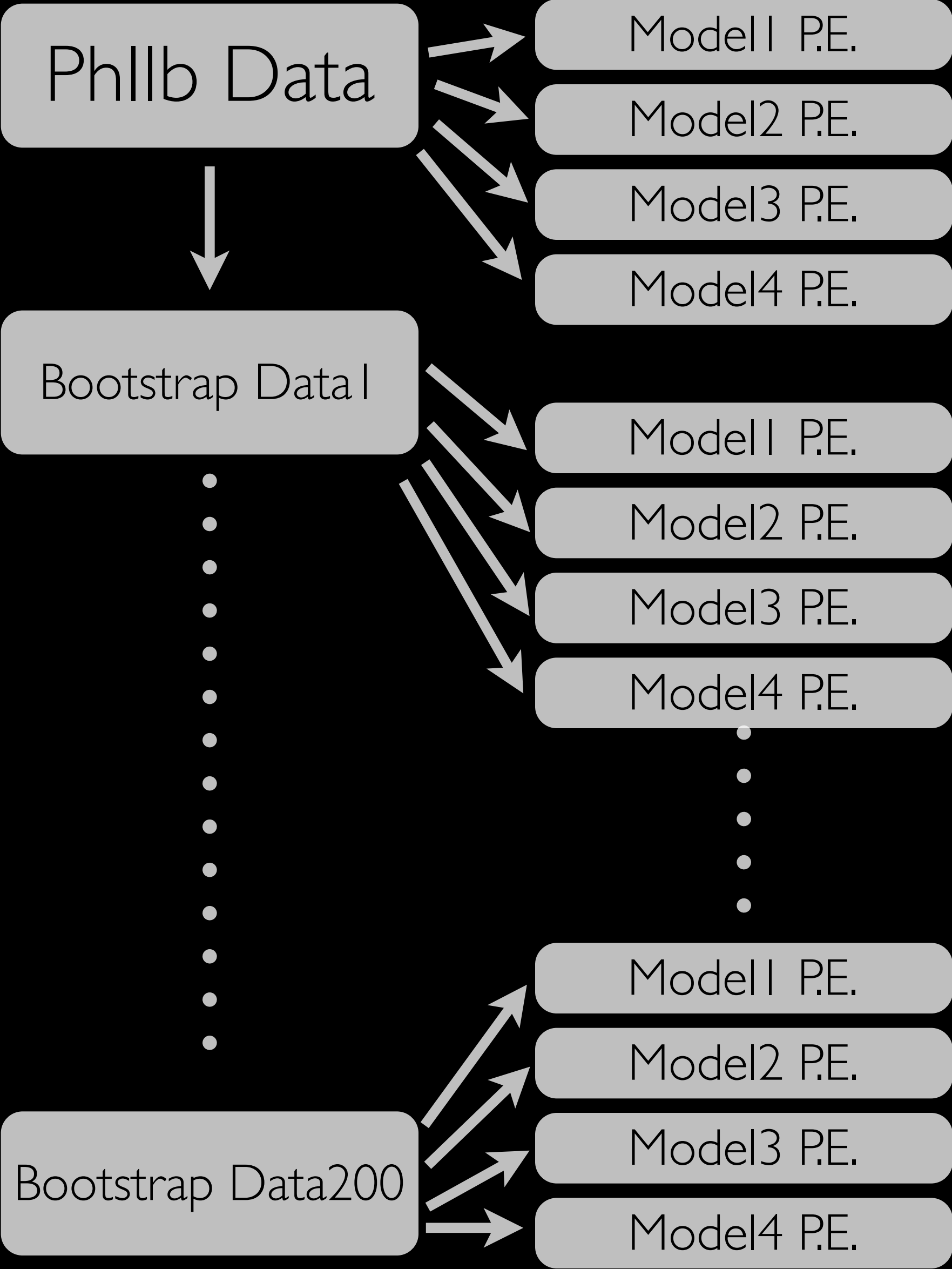


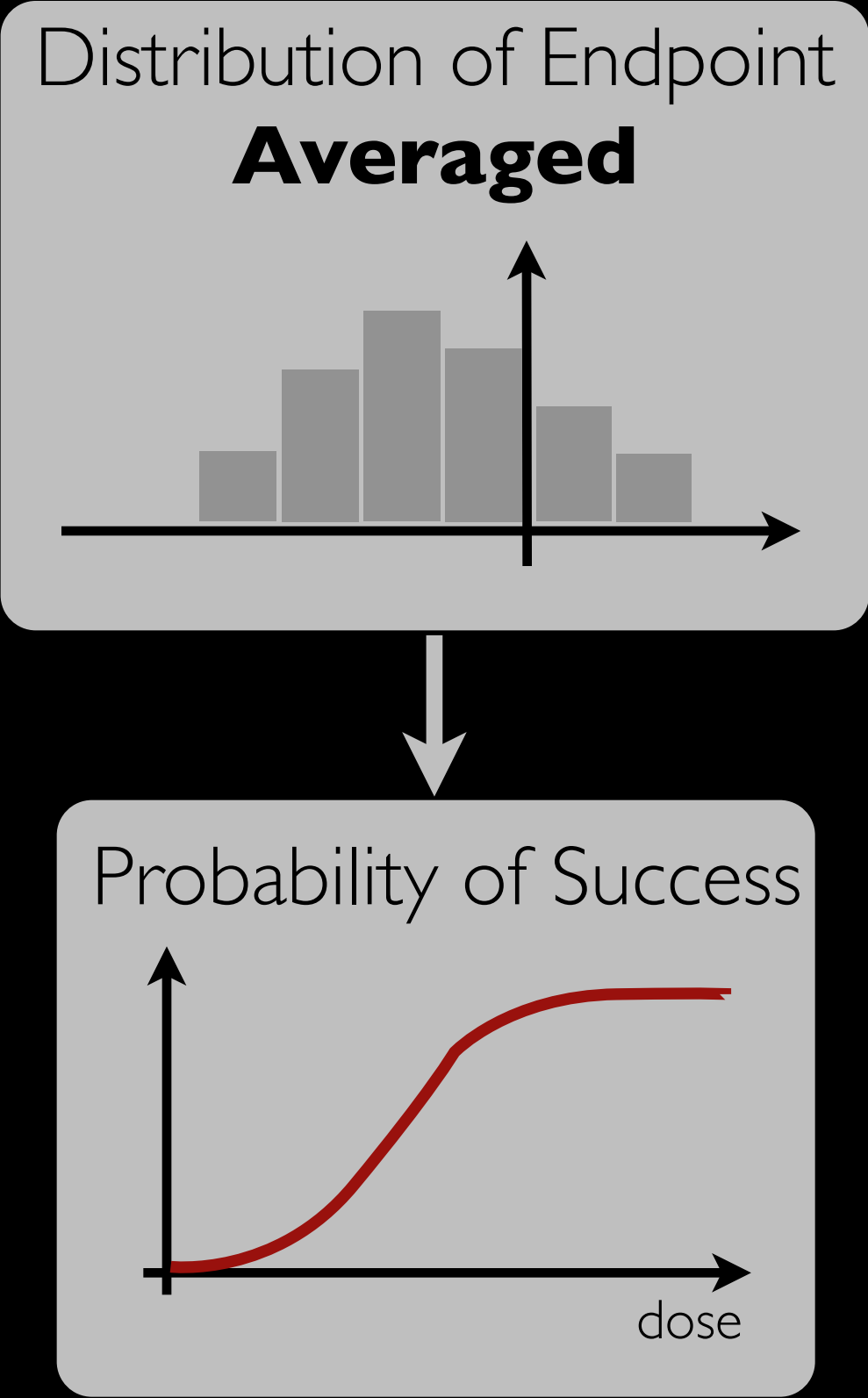
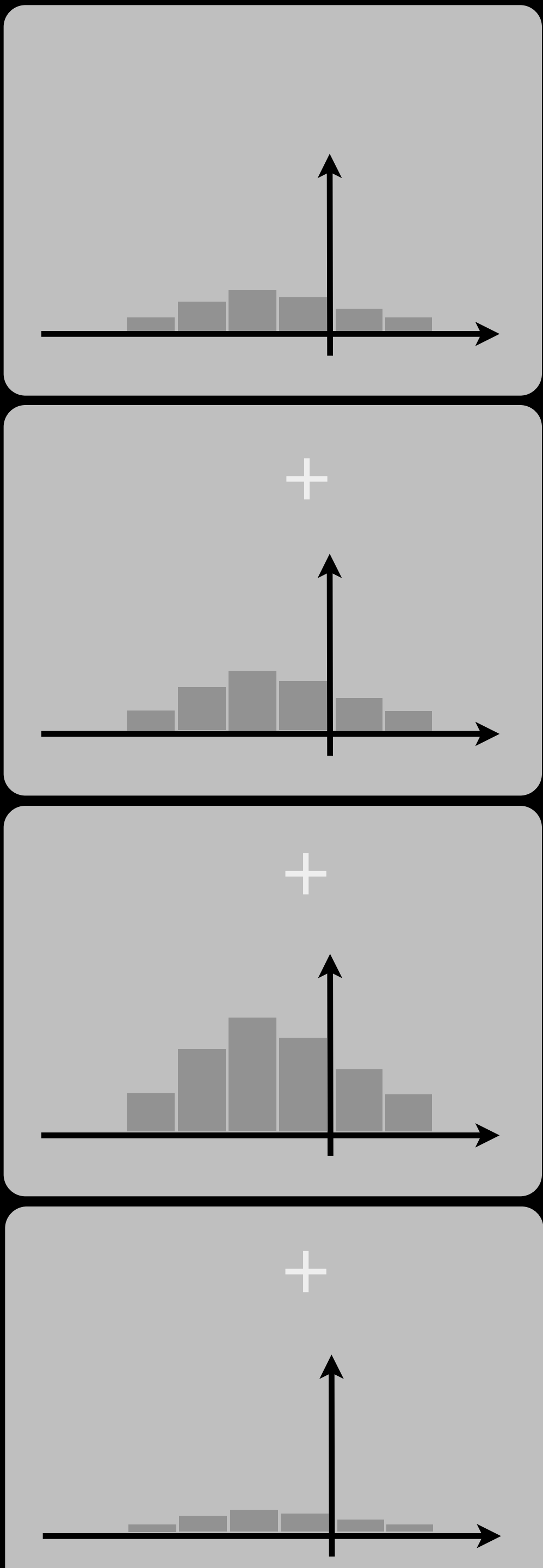
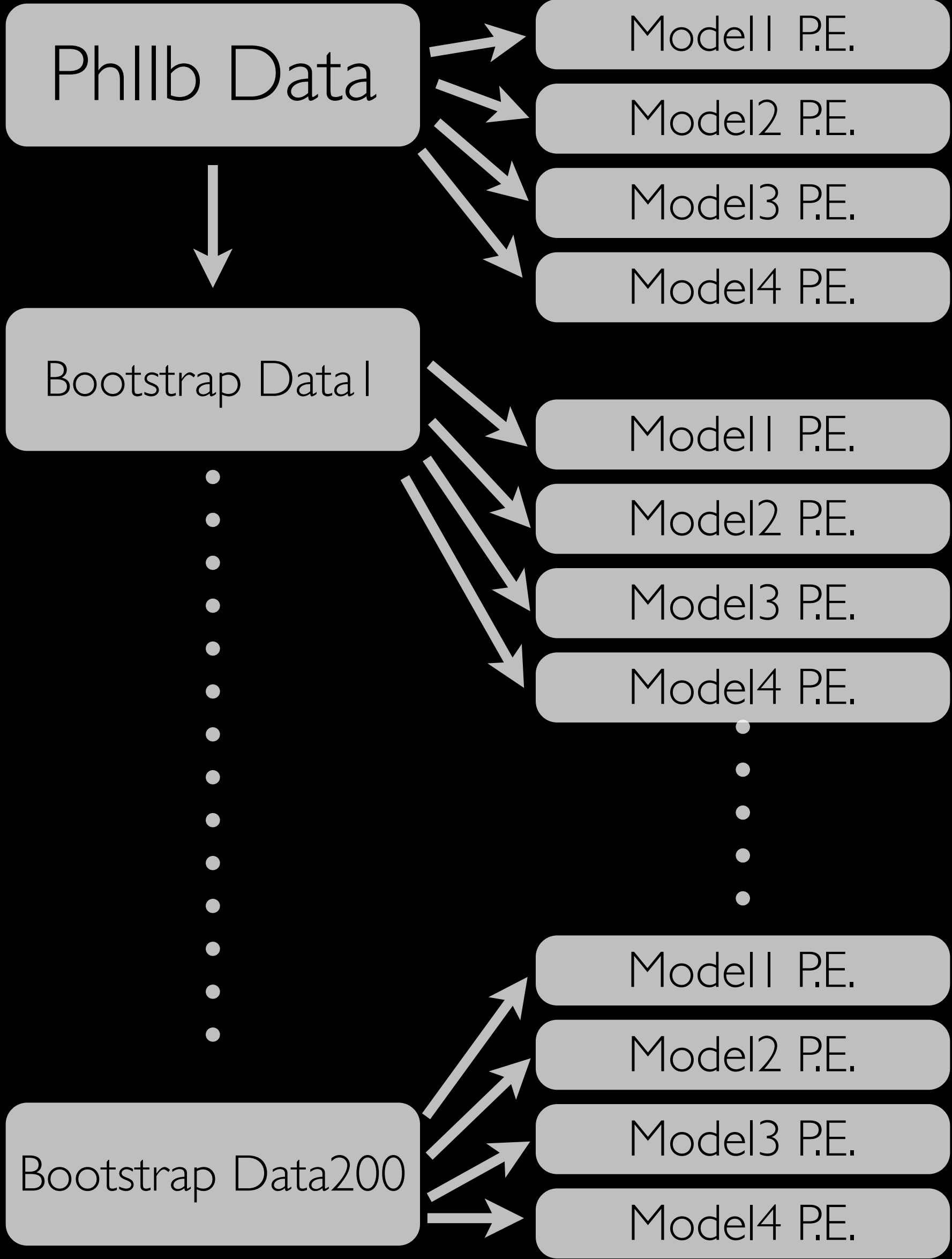












Method 1: Regular Model Selection

Method 2: Model Selection using bootstrap ofv

Method 3: Model Average

Method 4: Model Average using bootstrap ofv



# modelAVERAGE

how we really do it



Search



Safari



Mail



Contacts



Calendar



Reminders



Notes



Maps



Messages



FaceTime



Photo Booth



Game Center



iTunes



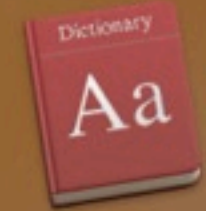
iBooks



App Store



Preview



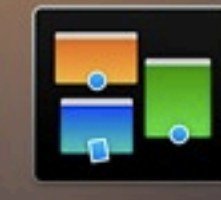
Dictionary



Calculator



Other



Mission Control



Dashboard



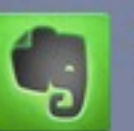
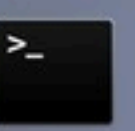
System Preferences



Evernote



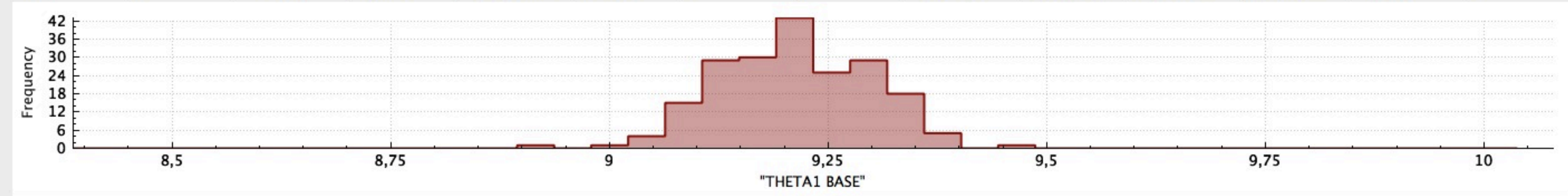
modelAverage





Model 2

subprob_est_time	subprob_cov_time	"ofv"	"THETA1 BASE"	"THETA2 KOUT"	"THETA3 SLOPE"	"THETA4 EC50"	"THETA5 N"	"PROP ERROR 0"	"PBO EFFEC"	"IIV_BASELIN"	"IIV_PBO"	"IIV_EPS"	"BASELIN"
38.75	0	-9753.63	9.21984	0.0245874	0.299814	0	0	0.0907407	-0.0114112	0.172151	0.115924	0.266482	1
53.41	0	-10102.1	9.21275	0.0233805	0.323846	0	0	0.0881727	-0.00299201	0.162075	0.107846	0.284367	1
27.56	0	-9962.86	9.32552	0.0249556	0.314884	0	0	0.0872191	-0.00750507	0.16621	0.122651	0.281789	1
25.87	0	-9894.26	9.11308	0.0239727	0.292489	0	0	0.0902133	-0.0131262	0.175322	0.113726	0.293043	1
29.23	0	-9921.2	9.20421	0.0266959	0.301725	0	0	0.0906381	-0.0121621	0.174569	0.102336	0.288807	1
29.02	0	-9817.47	9.2074	0.024392	0.295292	0	0	0.0864052	-0.022206	0.174814	0.116634	0.269815	1
59.32	0	-9706.24	9.31012	0.0251683	0.278968	0	0	0.0916674	-0.0271408	0.160535	0.109109	0.272152	1
43.14	0	-9607.13	9.17157	0.0233103	0.322375	0	0	0.0912243	-0.00825754	0.178226	0.123393	0.28465	1
61.66	0	-9659.28	9.25528	0.0268703	0.271775	0	0	0.0907535	-0.0228801	0.184382	0.112496	0.242804	1
43.72	0	-9637.9	9.21498	0.025106	0.324947	0	0	0.0867816	-0.00427276	0.176597	0.122591	0.279262	1
39.7	0	-9830.72	9.23614	0.0271309	0.253071	0	0	0.0916995	-0.0215288	0.156628	0.102853	0.262329	1



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)



/Users/yaoki/Documents/modelAverage\_Handson

-1: Import PsN Bootstrap Raw Results Files

0: View Bootstrap Results

1: Define Endpoint

Possible doses (independent variables) (e.g., 1,2,3,4,5 or 0:1:10 => 0,1,2,3,4,5,6,7,8,9,10)

0.2:0.2:3

Endpoint Definitions

EndPoint Definition	
model0_placebo	$\text{THETA1} \cdot \exp(\text{THETA8} \cdot \text{ETA1}) \cdot ((\text{THETA7} + 1 + \text{THETA9} \cdot \text{ETA2}) / (1 + 0) - 1)$
model1_linear	$\text{THETA1} \cdot \exp(\text{THETA8} \cdot \text{ETA1}) \cdot ((\text{THETA7} + 1 + \text{THETA9} \cdot \text{ETA2}) / (1 + \text{THETA3} \cdot \text{Dose}) - 1)$
model2_loglinear	$\text{THETA1} \cdot \exp(\text{THETA8} \cdot \text{ETA1}) \cdot ((\text{THETA7} + 1 + \text{THETA9} \cdot \text{ETA2}) / (1 + \text{THETA3} \cdot \log(\text{Dose} + 1))) \dots$
model3_emax	$\text{THETA1} \cdot \exp(\text{THETA8} \cdot \text{ETA1}) \cdot ((\text{THETA7} + 1 + \text{THETA9} \cdot \text{ETA2}) / (1 + \text{THETA3} \cdot \text{Dose} / (\text{Dose} \dots$
model4_sigmoidal	$\text{THETA1} \cdot \exp(\text{THETA8} \cdot \text{ETA1}) \cdot ((\text{THETA7} + 1 + \text{THETA9} \cdot \text{ETA2}) / (1 + \text{THETA3} \cdot \text{Dose}^{\text{THETA} \dots$

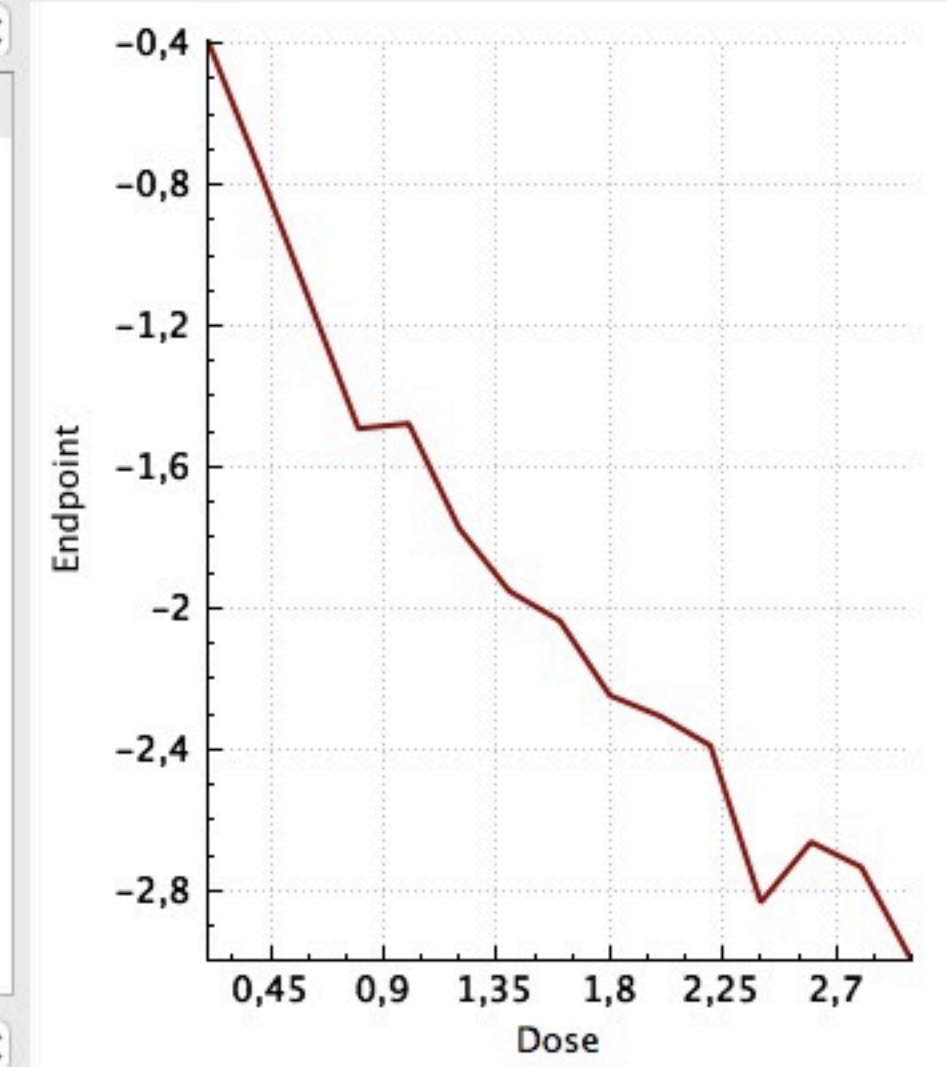
OmegaBlock

Number of Etas

2

1		2	
1	1	0	
2	0	1	

Mean of the Population 100



Note: THETA(1) ETA(1) need to be written as THETA1 ETA1, can also use COL1 for 1st column of raw results file

Raw Results Column Labels:

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	"model"	"problem"	"subproblem"	"covariance..."	"minimizati..."	"covariance..."	"covariance..."	"estimate_n..."	"rounding_..."	"zero_gradi..."	"final_zero_..."	"hessian_re..."	"s_matrix_s..."	"significant"

2: Define Weight and Selection Criterion

3: Probability of Achieving the Target Value

4: Dose Selection

5: Compare with Truth (For simulation studies)

/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

Weight expression (assumes ofv is at 20th column, leave blank to exclude the model)

☒ in log scale

Weight Definition in log scale	
model0_placebo	(ofv+0)/(0-2)
model1_linear	(ofv+2)/(0-2)
model2_loglinear	(ofv+2)/(0-2)
model3_emax	(ofv+4)/(0-2)
model4_sigmoidal	(ofv+6)/(0-2)

Relative weight

	model0_placebo	model1_linear	model2_loglinear	model3_emax	model4_sigmoida
1	2.61348e-77	0.316755	0.0997088	0.412692	0.170844
2	1.02462e-81	0.54941	0.0148203	0.292098	0.143672
3	3.75444e-87	0.459451	0.0405881	0.361205	0.138755
4	4.05529e-72	0.539819	0.0257539	0.31174	0.122687
5	9.61023e-87	0.305135	0.151493	0.389274	0.154098
6	8.73824e-79	0.592775	0.0174443	0.281039	0.108742
7	7.22762e-69	0.580501	0.0268703	0.279099	0.113531
8	9.29944e-82	0.488208	5.90094e-06	0.1796	0.332186

3: Probability of Achieving the Target Value

4: Dose Selection

5: Compare with Truth (For simulation studies)



/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

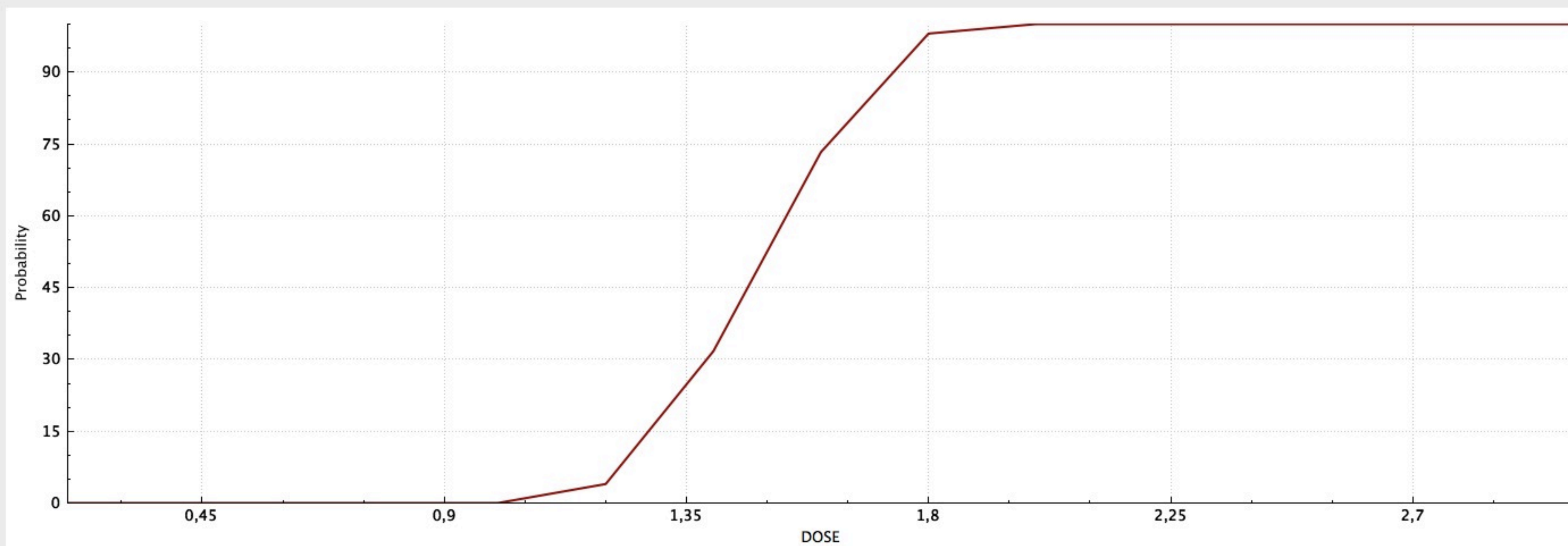
Model Selection

using

using one ofv per model

Probability of (  < EndPoint <  )

reCalculate

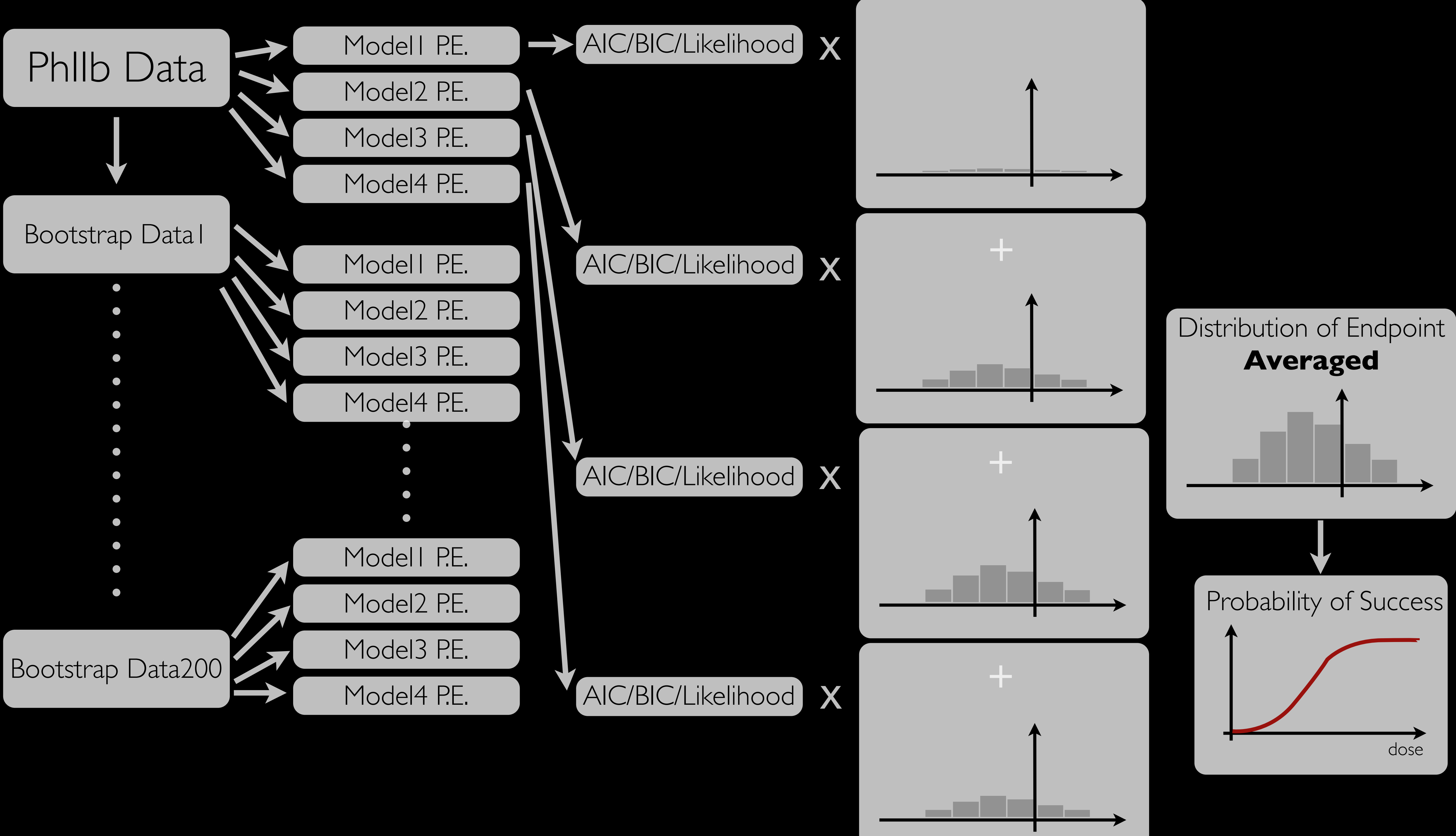


4: Dose Selection

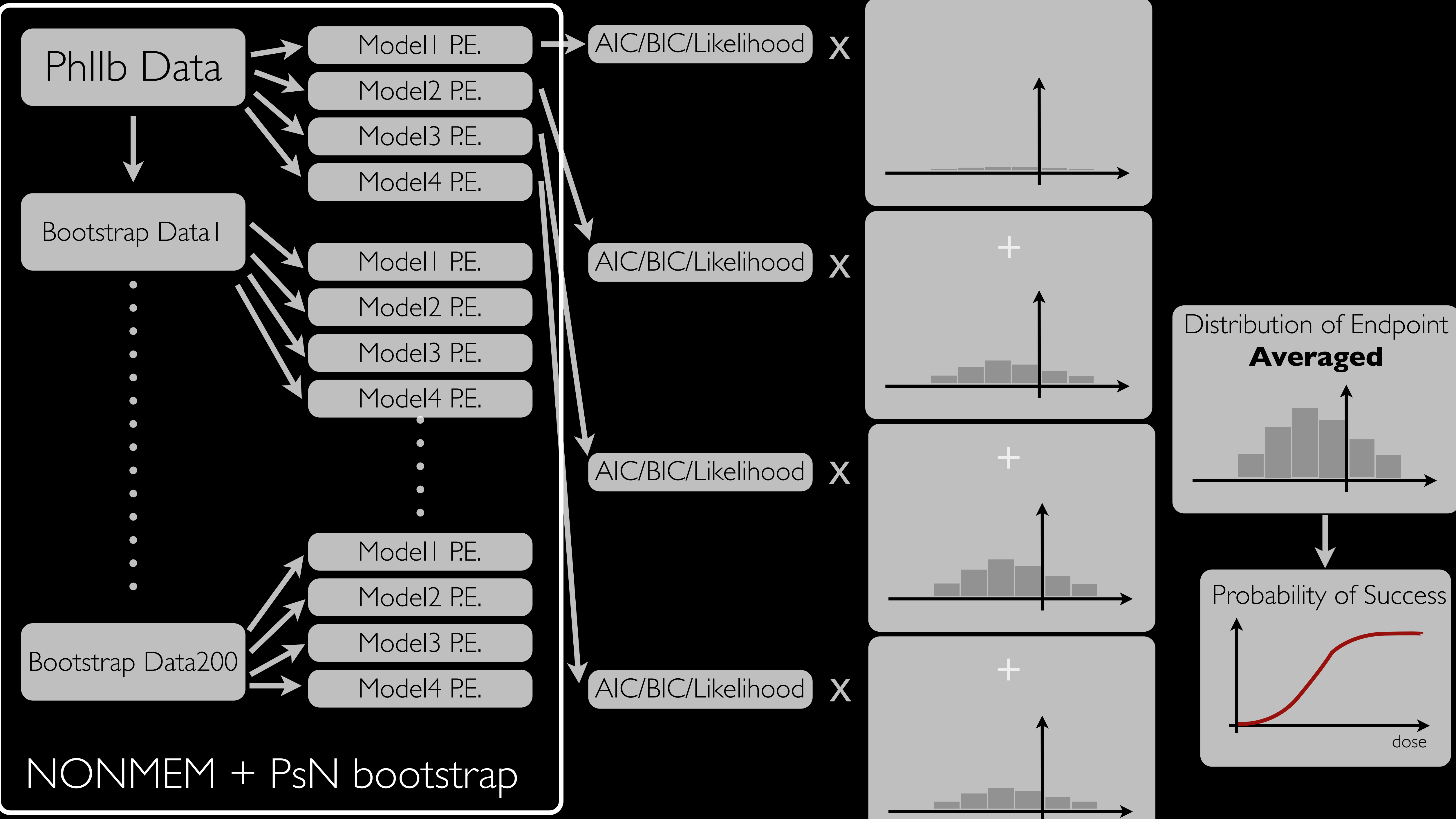
5: Compare with Truth (For simulation studies)

Calculating probability of success using bootstrap samples 0-100.

Abort Calculation







Ph11b Data

Bootstrap Data 1

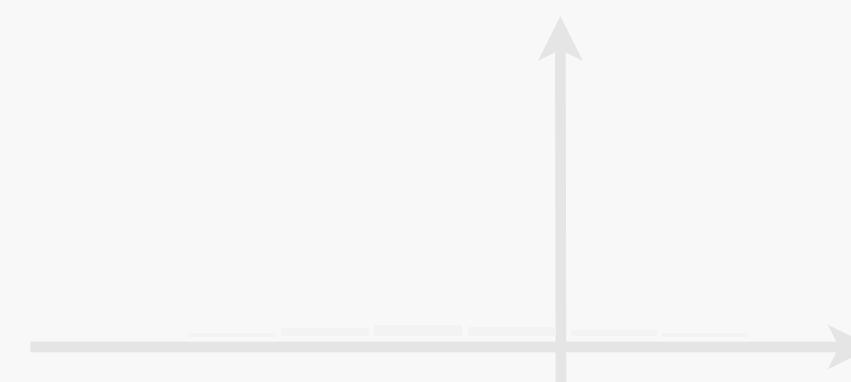
Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

AIC/BIC/Likelihood X



Model1 P.E.

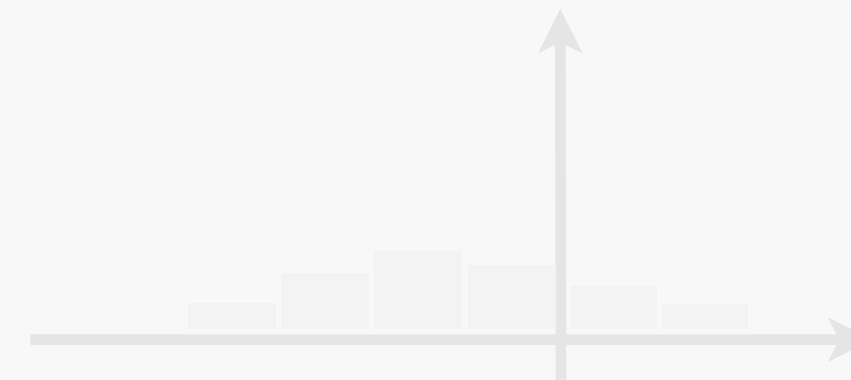
Model2 P.E.

Model3 P.E.

Model4 P.E.

AIC/BIC/Likelihood X

+



Model1 P.E.

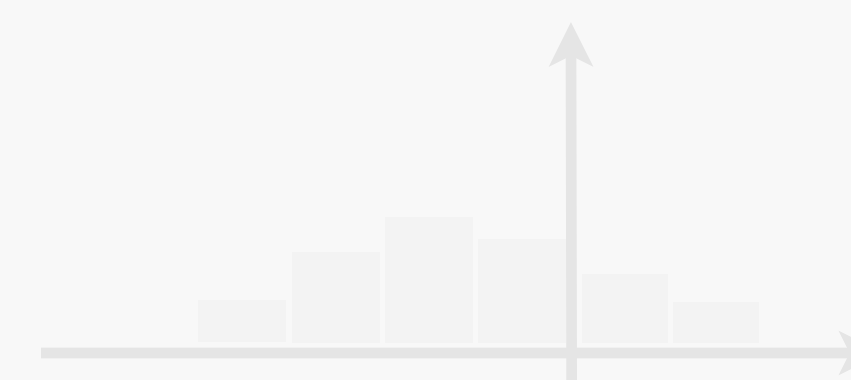
Model2 P.E.

Model3 P.E.

Model4 P.E.

AIC/BIC/Likelihood X

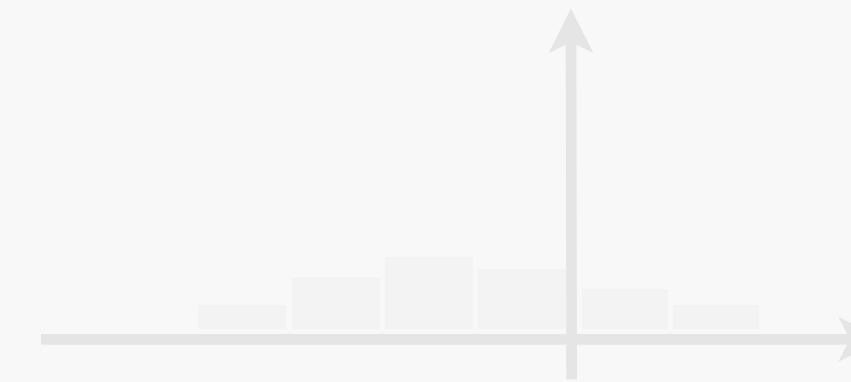
+



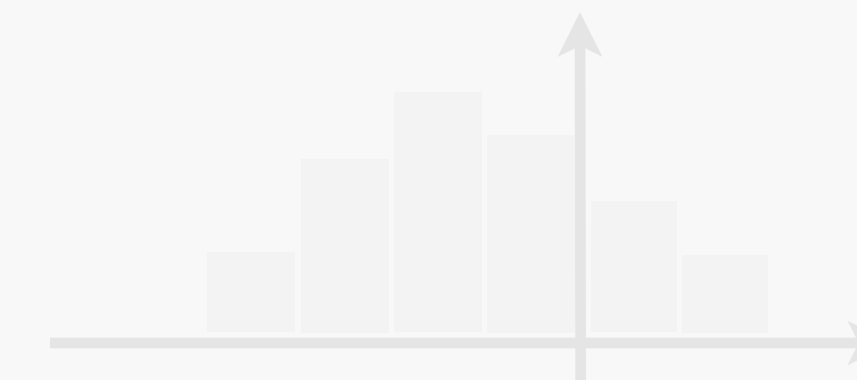
Bootstrap Data200

AIC/BIC/Likelihood X

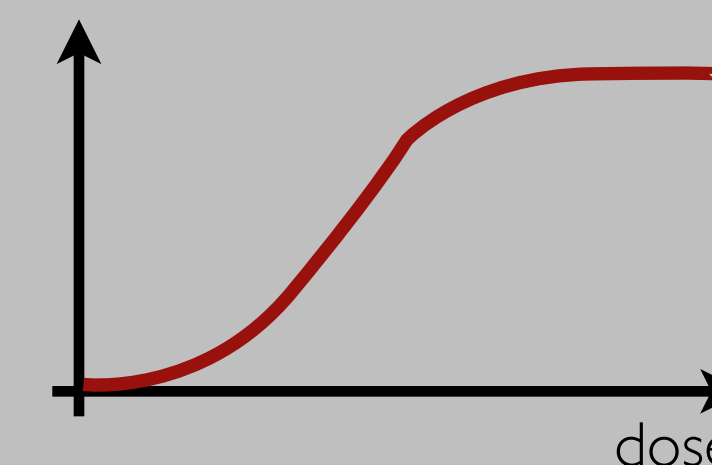
+



Distribution of Endpoint  
**Averaged**



Probability of Success



NONMEM + PsN bootstrap

Ph11b Data

Bootstrap Data I

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

model  
AVERAGE

Distribution of Endpoint  
**Averaged**

Probability of Success

dose

NONMEM + PsN bootstrap

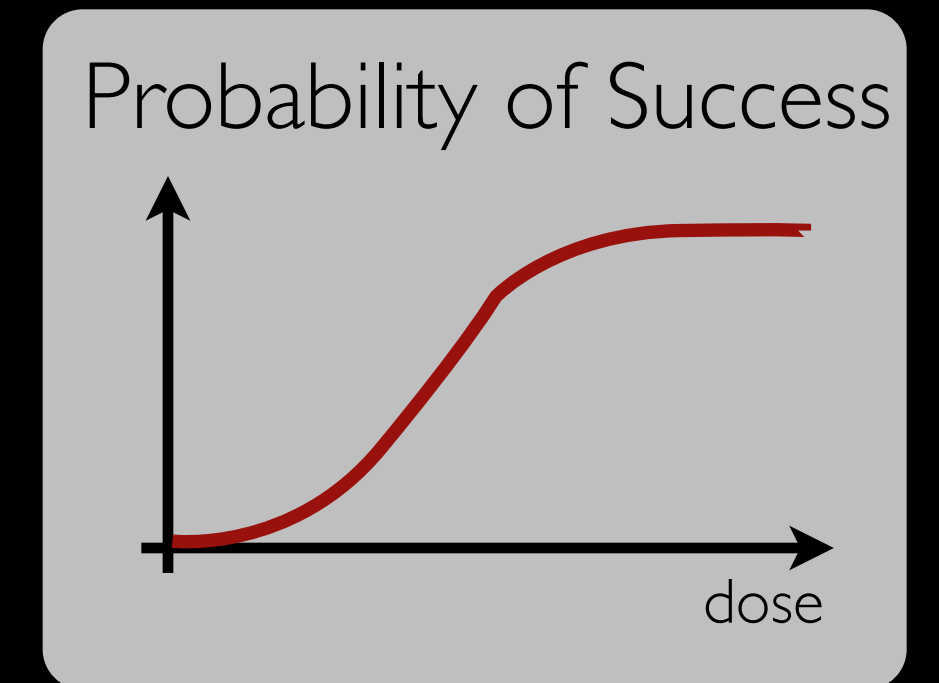
## PsN bootstrap

Raw\_results\_model1.csv  
Raw\_results\_model2.csv  
Raw\_results\_model3.csv  
Raw\_results\_model4.csv

input  
→



output  
→



Two important things to remember

## Two important things to remember

All PsN bootstraps of the candidate models must be run with the same seed.

Ph11b Data

Bootstrap Data I

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

Model1 P.E.

Model2 P.E.

Model3 P.E.

Model4 P.E.

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

AIC/BIC/Likelihood X

model  
AVERAGE

Distribution of Endpoint  
**Averaged**

Probability of Success

dose

NONMEM + PsN bootstrap

## Two important things to remember

All PsN bootstraps of the candidate models must be run with the same seed.



## Two important things to remember

All PsN bootstraps of the candidate models must be run with the same seed.

We assume the end-point (or the primary efficacy variable) can be expressed in terms of THETAs and ETAs appear in NONMEM code.

Two minor notes

## Two minor notes

THETA(I) need to be written as THETA I and ETA(I) need to be written as ETA I.

## Two minor notes

THETA(1) need to be written as THETA1 and ETA(1) need to be written as ETA1.

Minus numbers cannot be handled so for example -1 needs to be written as (0-1).