Simulation Conditions for CMA

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Basic simulation conditions

We are interested in basic simulation conditions meant to mimic a typical Rat bioassayl, and the chosen endpoints are weight loss and liver weight gain. All background weights were taken from Piao et al (2013) Table 1 and the average Male/Female weight was used as well as the average of the standard deviation.

Dose-response experimental designs were based upon recommendations in FDA's Redbook 2000, which are generally standard across agencies. Here 4 and 5 dose group + control studies were designed with both even and geometrically spaced dose designs. That is dose groups were $[0, 20, 40, 60, 80, 100]$ and $[0, 6.25, 12.5, 25, 50, 100]$, for the 5 dose group studies and they were $[0, 25, 50, 75, 100]$ and $[0, 12.5, 25, 50, 100]$ for the four group studies.

Distributional Conditions

For the simulation, three different distributions were considered, the normal and the inverse-Gaussian distributions. **Normal:**

$$g(y|dose) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp(-\frac{(y - \mu[dose])^2}{2\sigma^2}) \tag{1}$$

For the body-weight conditions $\sigma = 37.5$, and for the liver weight conditions, $\sigma = 1.145$.

Log-Normal:

$$g(y|dose) = \frac{1}{y\sqrt{2\pi\sigma^2}} \exp(-\frac{(\log[y] - \mu[dose])^2}{2\sigma^2}) \tag{2}$$

For the body weight conditions $\sigma = 0.0777$, and for the liver weight conditions $\sigma = 0.107302$. These values were chosen so that the control group standard deviation matched with the other simulation conditions, which was the average SD from males and female rats in table 1 at 72 weeks from Piao et al(2013).

Inverse-Gaussian:

$$g(y|dose) = \sqrt{\frac{\lambda}{2\pi y^2}} \exp\left[\frac{\lambda(y - \mu\{dose\})^2}{2\mu(dose)^2 y}\right] \tag{3}$$

For the body-weight conditions $\lambda = 78643.17$, and for the liver weight conditions, $\lambda = 902.3632$. These values were chosen so that the control group standard deviation matched with the other simulation conditions, which was the average SD from males and female rats in table 1 at 72 weeks from Piao et al(2013).

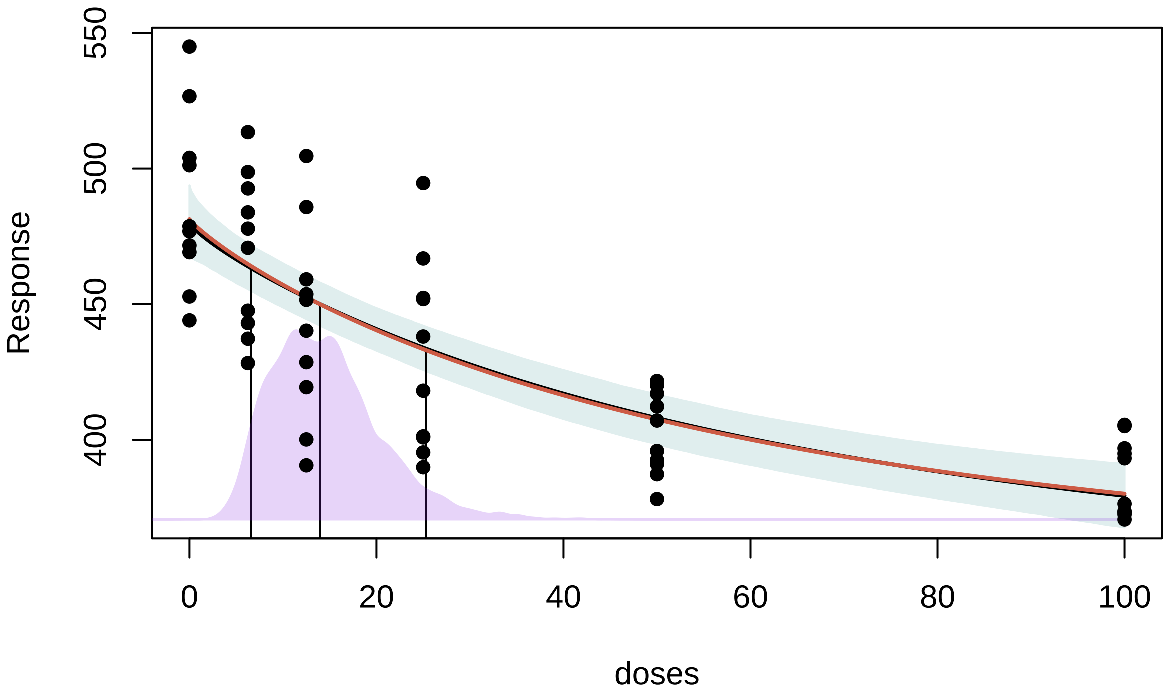
Dose-Response Conditions

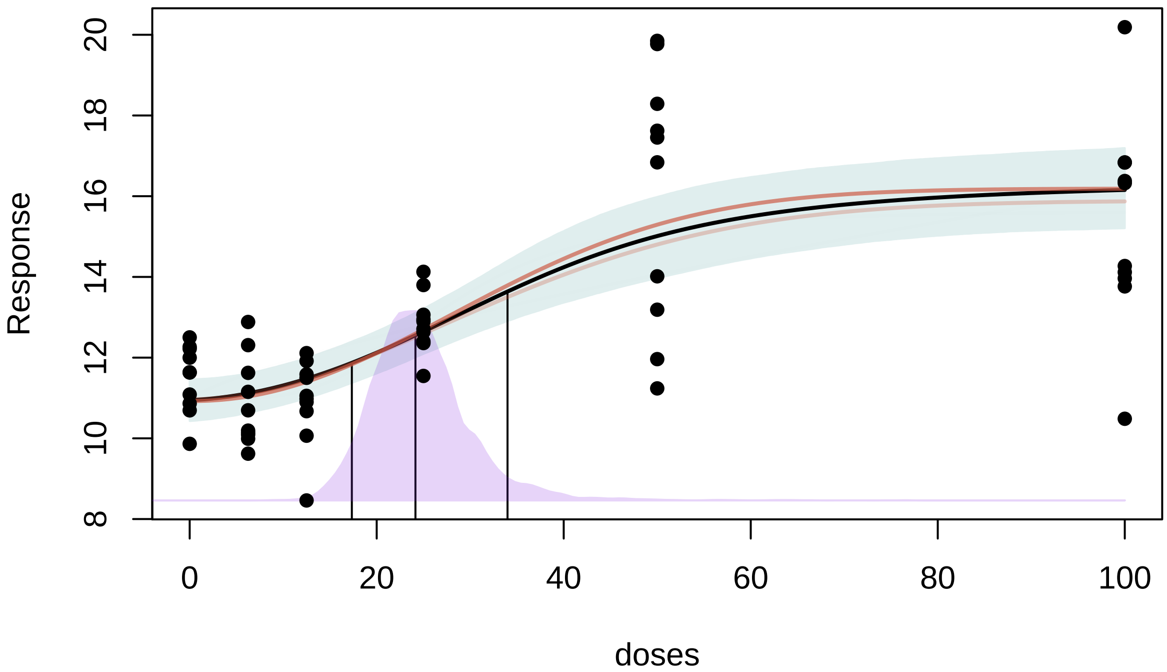
Here we define the basic dose-respone function $\mu(dose)$ for each of the data distributions specified above. ### Hill DR: The Hill mean models were used for the simulation:

$$f(dose) = a + \frac{b \times dose^d}{c^d + dose^d} \tag{4}$$

	a	b	c	d
Hill Simulation 1	481.00	-144.30	70	3.3
Hill Simulation 2	481.00	-144.30	40	1.3
Hill Simulation 3	481.00	-144.20	15	1.1
Hill Simulation 4	481.00	-144.30	50	4.0
Hill Simulation 5	10.58	5.29	70	3.5
Hill Simulation 6	10.58	5.29	25	3.0
hill Simulation 7	10.58	5.29	15	2.0
Hill Simulation 8	10.58	5.29	50	4.0

Here are two generated datasets from Hill condition 2 and 8:





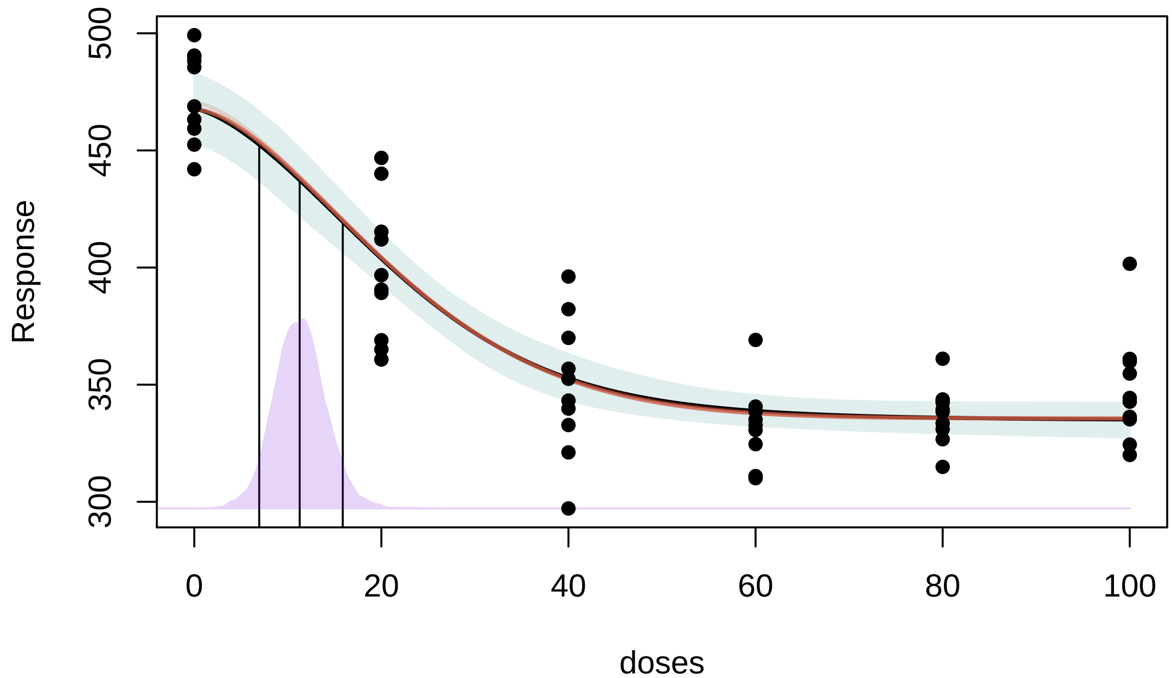
Exponential-5 DR:

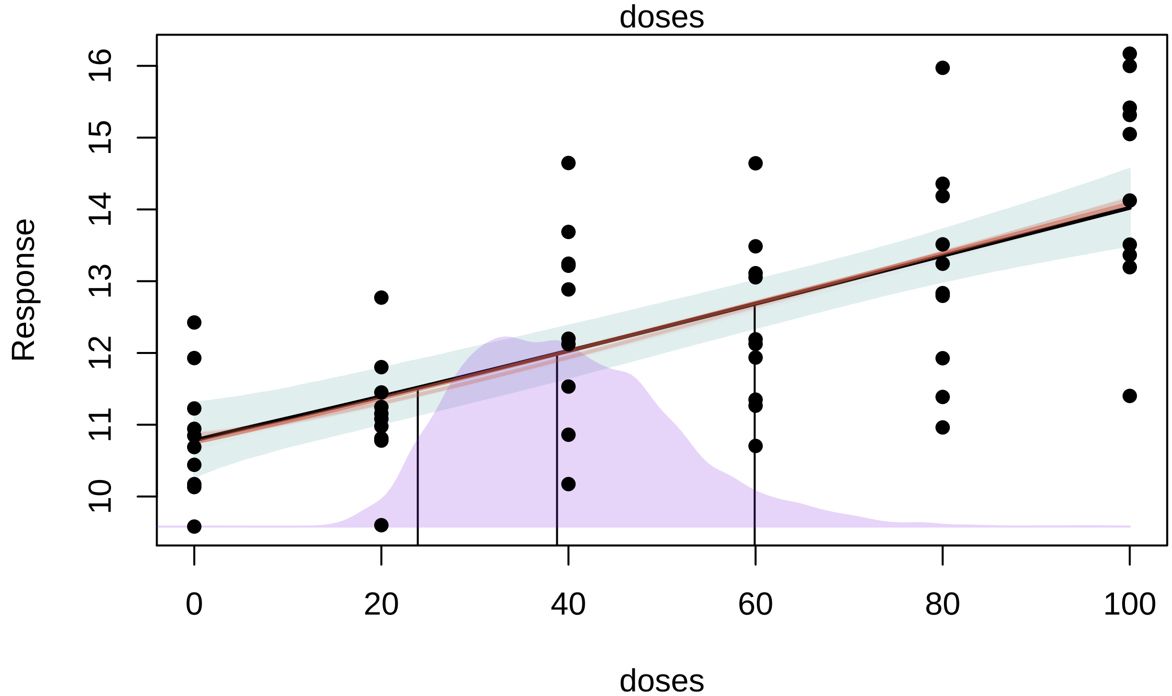
Similar to the Hill condition we looked at 8 unique datasets generated from the exponential dose-response function. The exponential-5 dose-response function that we use in the simulation is

$$\mu(dose) = a\left[c - (c-1)\exp(-\{b \times dose\}^d)\right] \tag{5}$$

	a	b	c	d
Exp-5 Simulation 1	481.00	0.05	0.699937	2.0
Exp-5 Simulation 2	481.00	0.02	0.699937	2.0
Exp-5 Simulation 3	481.00	0.01	0.699937	2.0
Exp-5 Simulation 4	481.00	0.10	0.699937	2.0
Exp-5 Simulation 5	10.58	0.05	1.500000	1.5
Exp-5 Simulation 6	10.58	0.02	1.500000	1.5
Exp-5 Simulation 7	10.58	0.01	1.500000	1.5
Exp-5 Simulation 8	10.58	0.10	1.500000	1.5

Here are two of the simulated datasets from condition 1 and 7 and fit using model averaging.


500
450
400
350
300
Response
0
20
40
60
80
100
doses


16
15
14
13
12
11
10
Response
0
20
40
60
80
100
doses