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 $\sigma = 77.5$, and for the liver weight conditions, $\sigma = 2.28$.

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 $\sigma = 0.158$, and for the liver weight conditions $\sigma = 0.209$. These values were chosen so that the control group standard deviation was approximatly the same as 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 $\lambda = 18528.14$, and for the liver weight conditions, $\lambda = 227.8176$. 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:

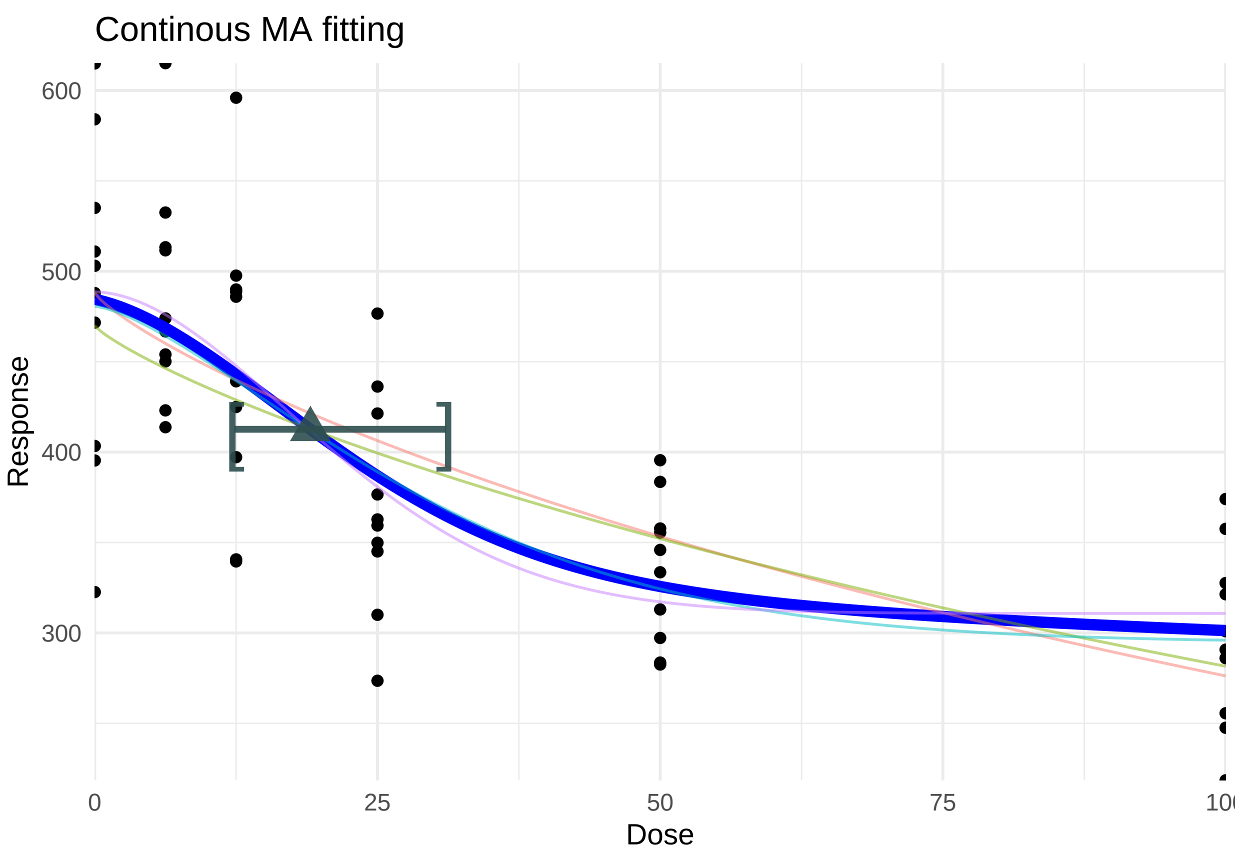
The Hill mean models were used for the simulation:

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

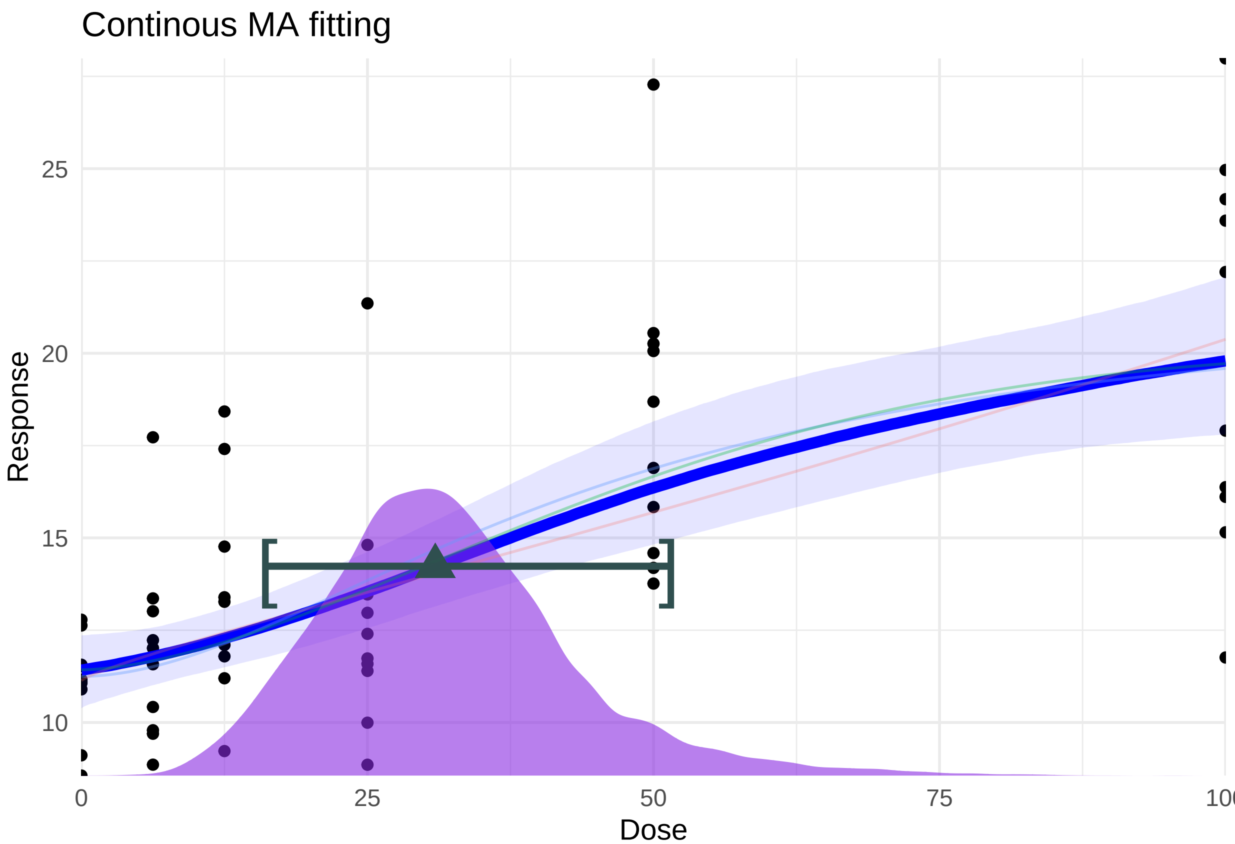
	a	b	c	d
Hill Simulation 1	481.00	-250.3	70	3.3
Hill Simulation 2	481.00	-250.3	40	1.3
Hill Simulation 3	481.00	-250.2	15	1.1
Hill Simulation 4	481.00	-250.3	50	4.0
Hill Simulation 5	10.58	9.7	70	3.5
Hill Simulation 6	10.58	9.7	25	3.0
Hill Simulation 7	10.58	9.7	15	2.0
Hill Simulation 8	10.58	9.7	50	4.0

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

```
##      BMD     BMDL     BMDU
## 19.06732 12.33703 31.07930
```




```
##      BMD     BMDL     BMDU
## 19.08490 10.77855 38.50136
```



Exponential-5 DR:

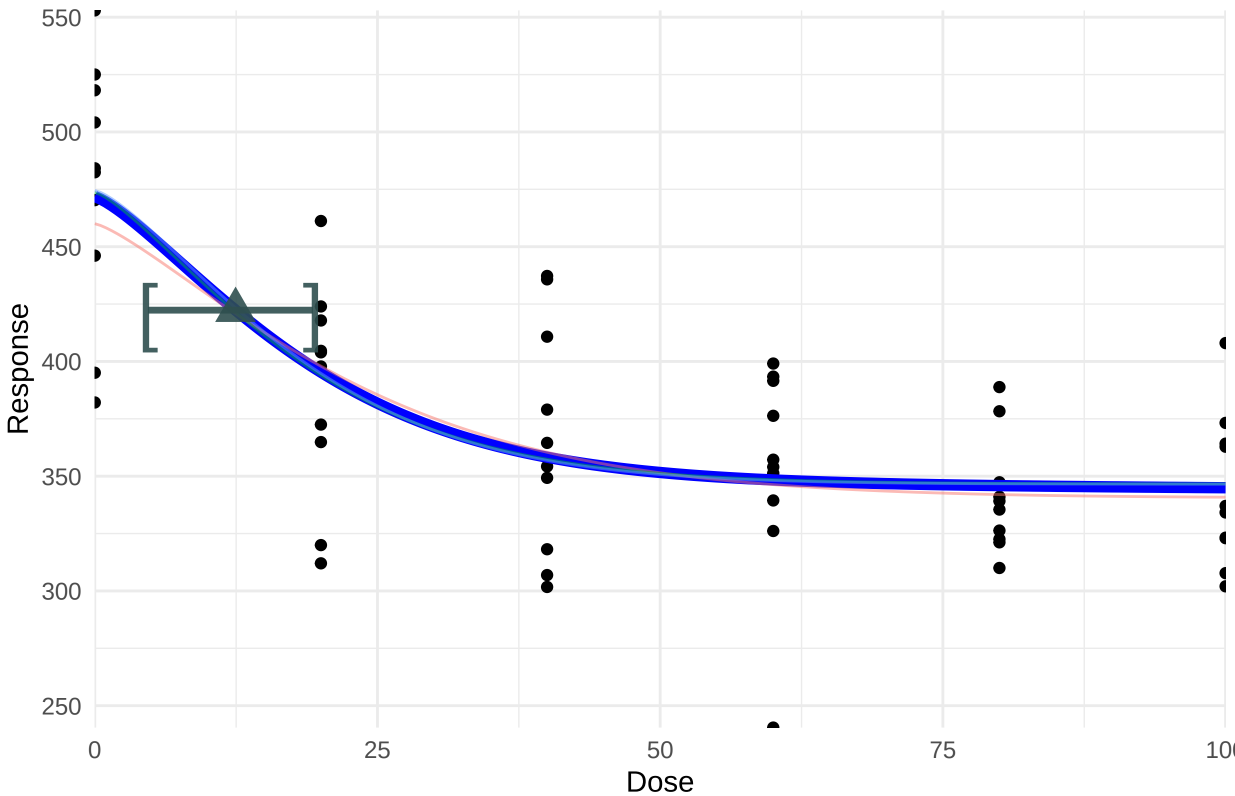
Similar to the Hill condition we looked at 8 unique datasets generated from the exponential dose-response function. The exponential-5 dose-response function that we use in the simulation is

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

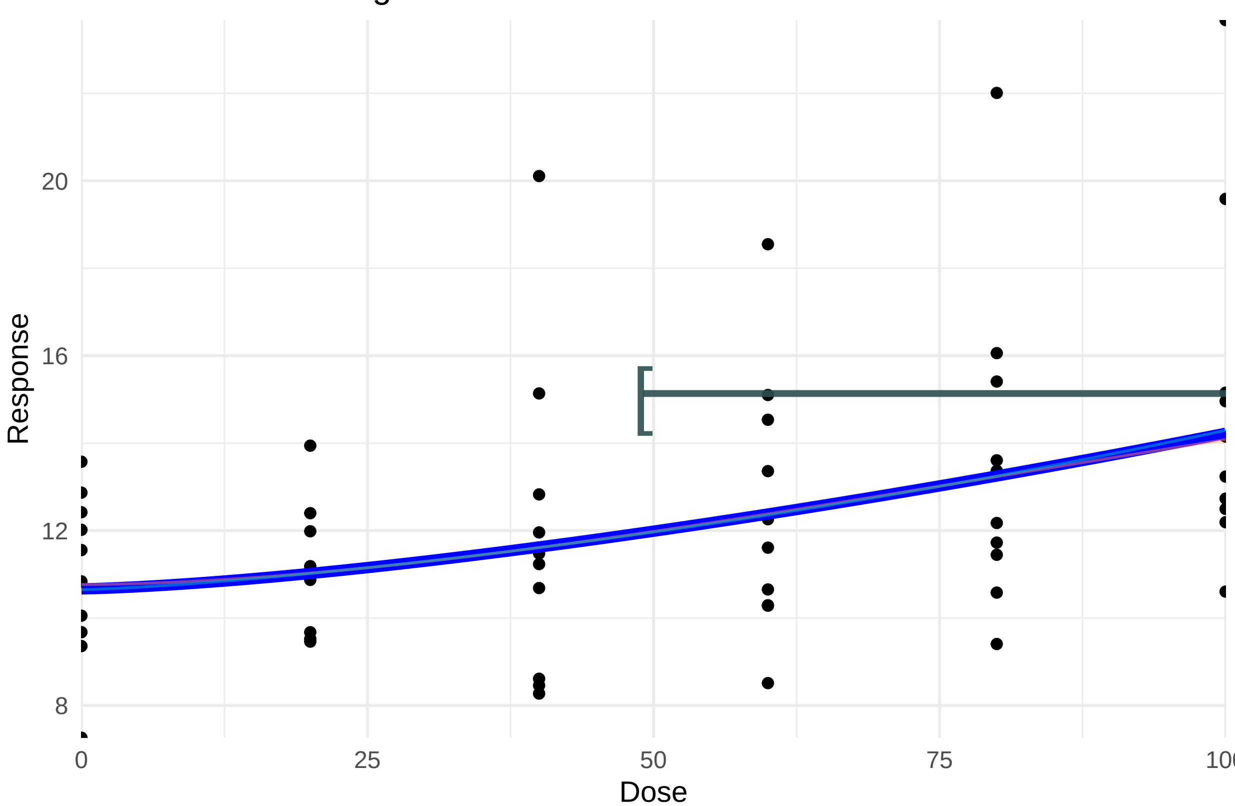
	a	b	c	d
Exp-5 Simulation 1	481.00	0.05	0.70	2.0
Exp-5 Simulation 2	481.00	0.02	0.70	2.0
Exp-5 Simulation 3	481.00	0.01	0.70	2.0
Exp-5 Simulation 4	481.00	0.10	0.70	2.0
Exp-5 Simulation 5	10.58	0.05	1.75	1.5
Exp-5 Simulation 6	10.58	0.02	1.75	1.5
Exp-5 Simulation 7	10.58	0.01	1.75	1.5
Exp-5 Simulation 8	10.58	0.10	1.75	1.5

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

Continous MA fitting

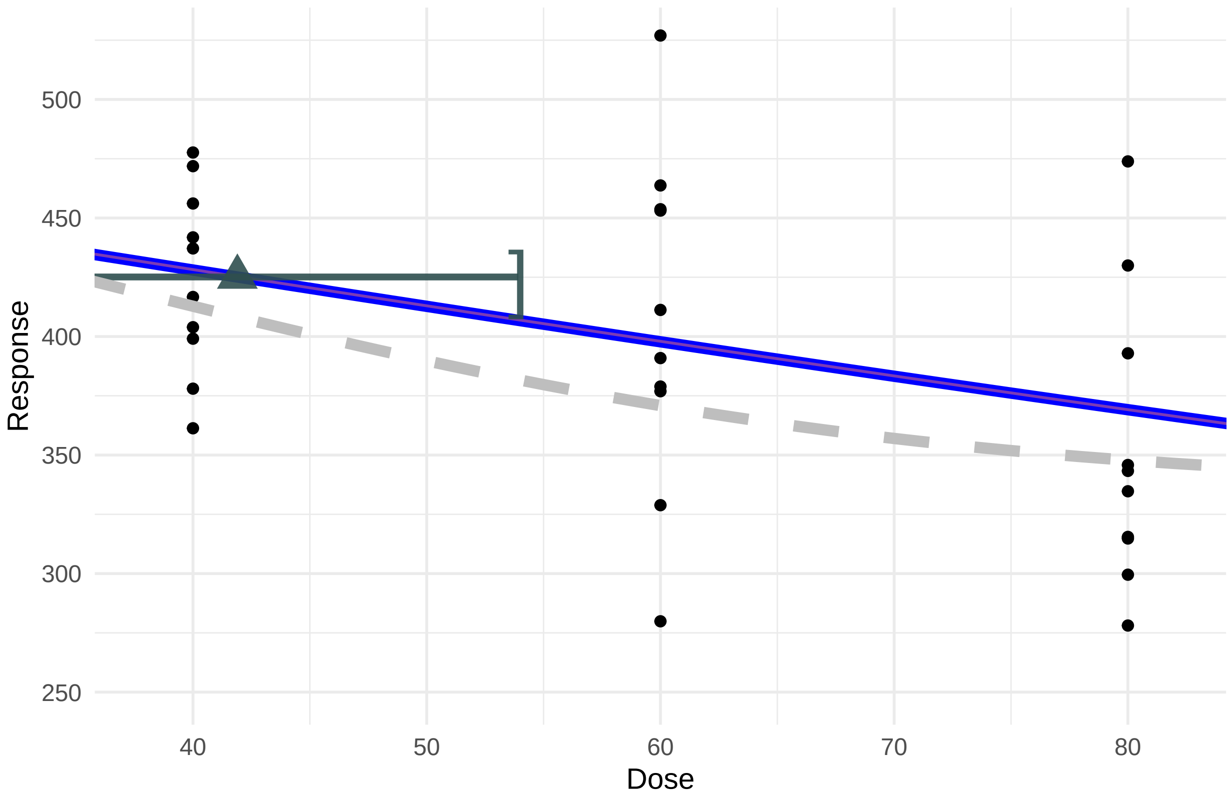


Continous MA fitting

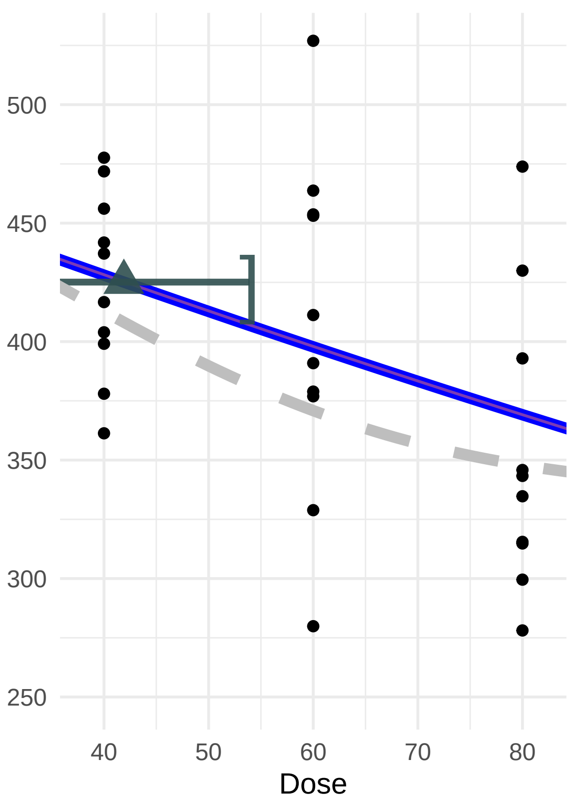


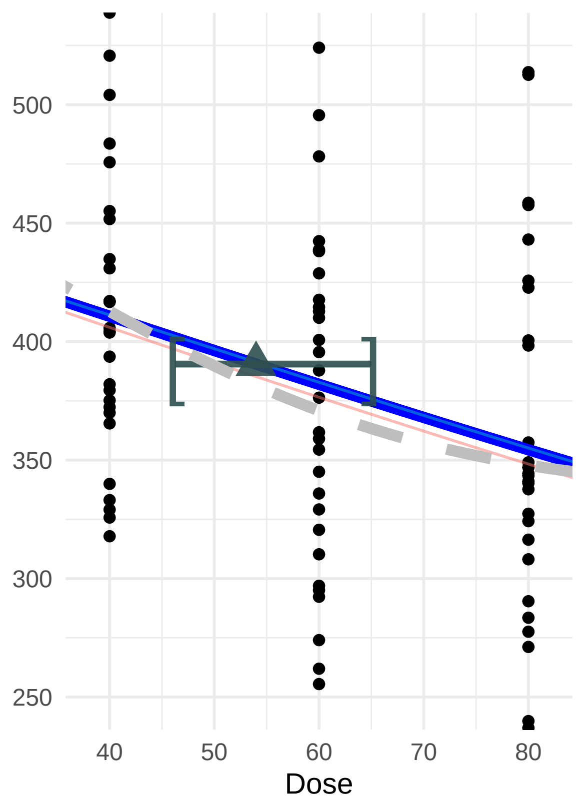

```
##        BMD       BMDL       BMDU
```

```
## 41.89854 27.88508 53.92031
```




```
##       BMD      BMDL      BMDU
## 53.98598 46.21798 64.98342
```





I-Spline DR:

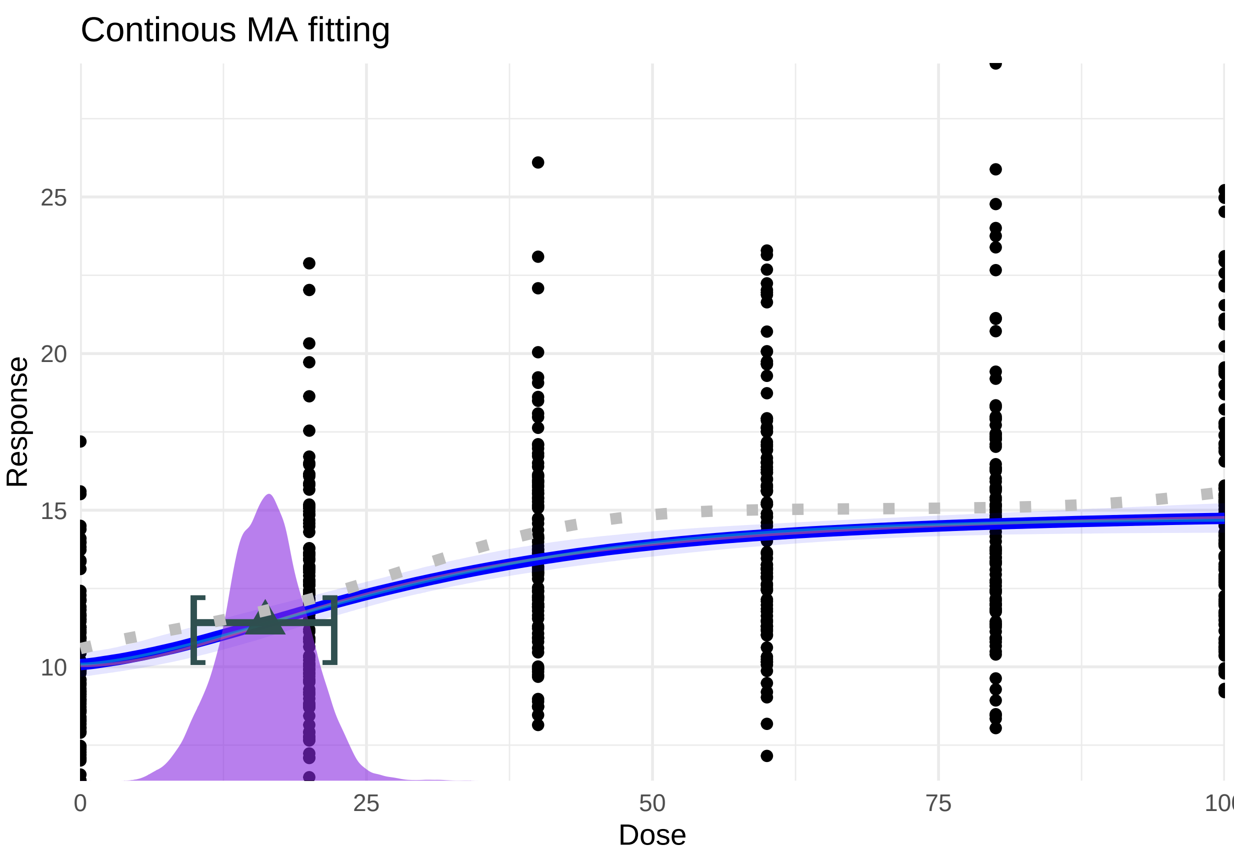
Further, we consider 4 dose-response functions that are not considered in the parametric model suite. These functions are representable as I-spline (monotone splines) functions. In this case,

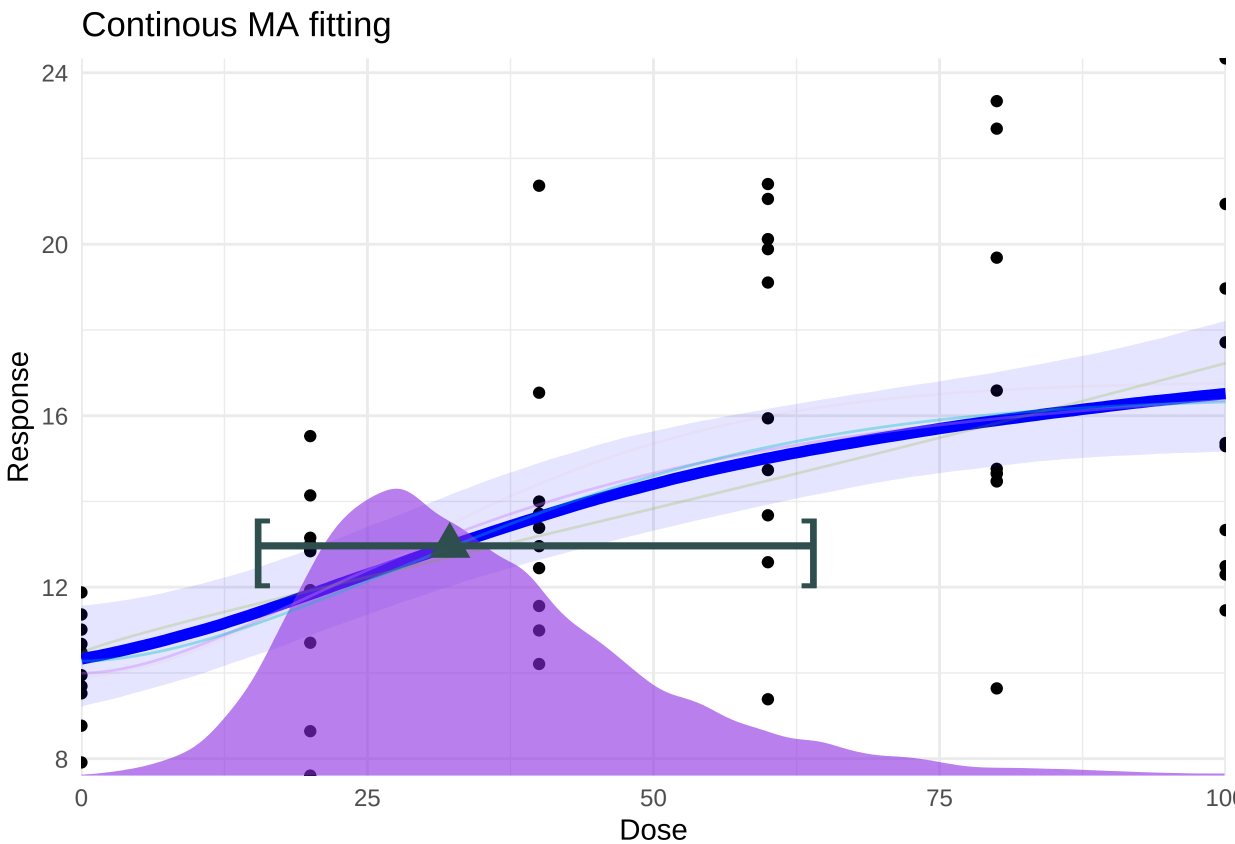
$$\mu(dose) = b_0 \sum_{i=1}^{8} b_i is(dose) \tag{6}$$

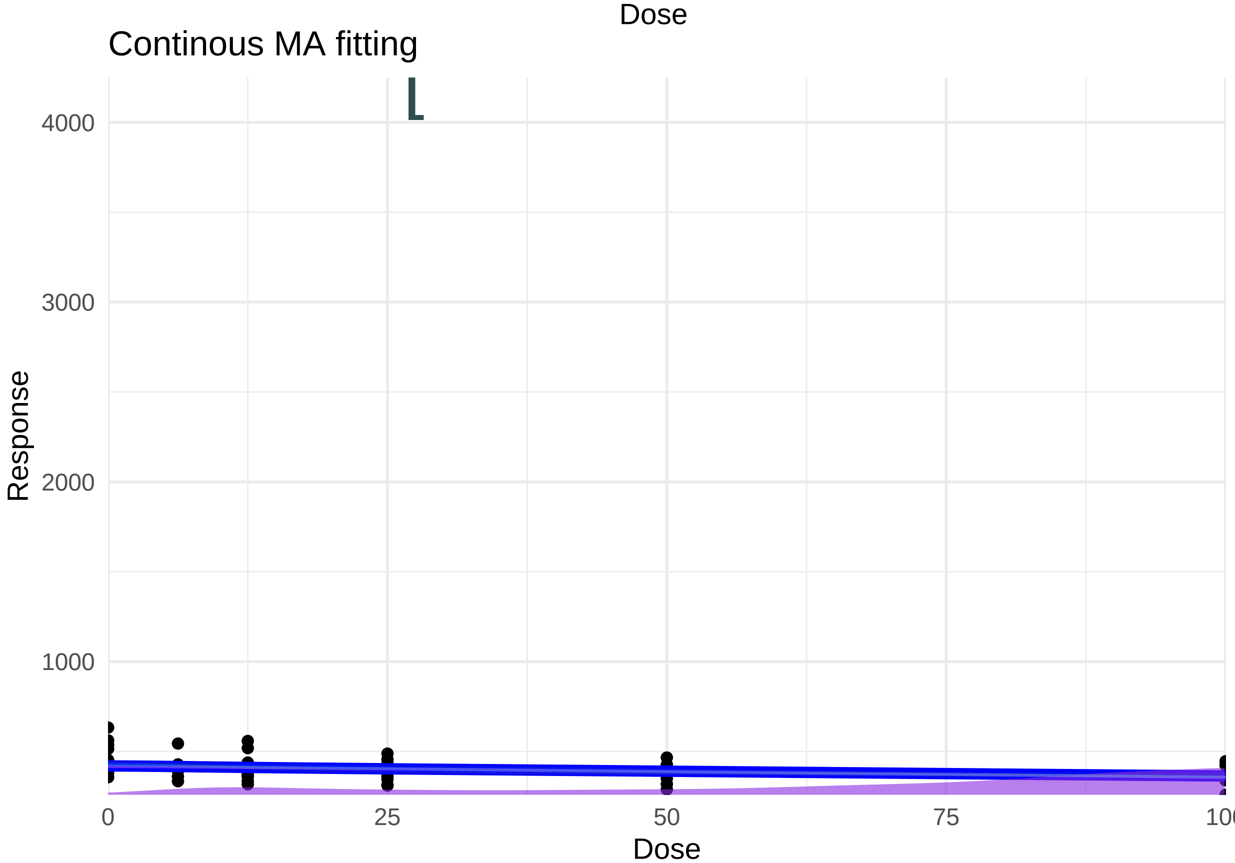
	b1	b2	b3	b4	b5	b6	b7	b8
iSpline Simulation 1	0.155	0.141	0.058	0.674	0.184	0.928	1.607	1.045
iSpline Simulation 2	0.678	0.323	3.356	0.103	0.009	0.088	0.344	0.100
iSpline Simulation 3	-45.715	-53.669	-14.267	-8.066	-1.620	-1.800	-1.800	-1.800
iSpline Simulation 4	-11.957	-19.991	-39.345	-16.390	-2.819	-4.580	-0.835	-0.700

```
##      BMD     BMDL     BMDU
## 32.19130 15.60615 63.81175
```

```
##      BMD     BMDL     BMDU
## 16.15496 10.06757 22.01796
```







Computed true BMD values

For the simulation, the BMD is computed using the standard deviation (SD), relative deviation (RD), and hybrid (HB) approaches. Each method requires the specification of the benchmark response (BMR). For the standard deviation, a $BMR = 1$ is used. For the relative deviation, a $BMR = 0.1$ is used. Finally, for the hybrid approach the $BMR = 0.05$ with the tail probability being 0.025.

Tables of BMD values for SD approach

```
## [1] 6006.2500 6006.2500 6006.2500 6006.2500    5.1984    5.1984    5.1984
## [8]    5.1984
```

Table 4: Hill Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Hill Simulation 1	54.90	54.91	54.90
Hill Simulation 2	21.59	21.60	21.59
Hill Simulation 3	7.24	7.25	7.24
Hill Simulation 4	40.92	40.93	40.92
Hill Simulation 5	49.97	49.97	49.97
Hill Simulation 6	16.87	16.87	16.87
hill Simulation 7	8.31	8.31	8.31
Hill Simulation 8	37.23	37.23	37.23

Table 5: Exponential-5 Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Exp-5 Simulation 1	17.55	17.56	17.55
Exp-5 Simulation 2	43.87	43.89	43.87
Exp-5 Simulation 3	87.75	87.79	87.75
Exp-5 Simulation 4	8.77	8.78	8.77
Exp-5 Simulation 5	13.65	13.65	13.65
Exp-5 Simulation 6	34.13	34.13	34.13
Exp-5 Simulation 7	68.25	68.25	68.25
Exp-5 Simulation 8	6.83	6.83	6.83

Table 6: I-Spline Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
I-Spline Simulation 1	88.55	88.55	88.55
I-Spline Simulation 2	26.50	26.50	26.50
I-Spline Simulation 3	17.12	17.14	17.12
I-Spline Simulation 4	48.49	48.54	48.49

Table 7: Hill Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Hill Simulation 1	45.30	45.30	45.30
Hill Simulation 2	13.25	13.25	13.25
Hill Simulation 3	4.07	4.07	4.07
Hill Simulation 4	34.92	34.92	34.92
Hill Simulation 5	38.41	38.41	38.41
Hill Simulation 6	12.41	12.41	12.41
Hill Simulation 7	5.25	5.25	5.25
Hill Simulation 8	29.58	29.58	29.58

Table 8: Exponential-5 Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Exp-5 Simulation 1	12.73	12.73	12.73
Exp-5 Simulation 2	31.83	31.83	31.83
Exp-5 Simulation 3	63.67	63.67	63.67
Exp-5 Simulation 4	6.37	6.37	6.37
Exp-5 Simulation 5	7.36	7.36	7.36
Exp-5 Simulation 6	18.39	18.39	18.39
Exp-5 Simulation 7	36.79	36.79	36.79
Exp-5 Simulation 8	3.68	3.68	3.68

Table 9: I-Spline Simulation BMDs for standard deviation BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
I-Spline Simulation 1	64.86	64.86	64.86
I-Spline Simulation 2	14.27	14.27	14.27
I-Spline Simulation 3	9.15	9.15	9.15
I-Spline Simulation 4	27.79	27.79	27.79

Table 10: Hill Simulation BMDs for Hybrid BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Hill Simulation 1	41.49	57.19	42.61
Hill Simulation 2	10.61	23.94	11.35
Hill Simulation 3	3.13	8.18	3.39
Hill Simulation 4	32.48	42.32	33.20
Hill Simulation 5	40.08	54.81	38.90
Hill Simulation 6	13.04	18.79	12.60
Hill Simulation 7	5.65	9.78	5.37
Hill Simulation 8	30.70	40.37	29.91

Table 11: Exponential-5 Simulation BMDs for Hybrid BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
Exp-5 Simulation 1	11.03	18.84	11.52
Exp-5 Simulation 2	27.57	47.09	28.79
Exp-5 Simulation 3	55.13	94.18	57.59
Exp-5 Simulation 4	5.51	9.42	5.76
Exp-5 Simulation 5	8.12	17.11	7.58
Exp-5 Simulation 6	20.31	42.78	18.95
Exp-5 Simulation 7	40.62	85.56	37.89
Exp-5 Simulation 8	4.06	8.56	3.79

```
## [1]    5.1984    5.1984 6006.2500 6006.2500
```

Table 12: I-Spline Simulation BMDs for Hybrid BMD across the three different distributional conditions.

	Normal	Log-Normal	Inverse-Gaussian
I-Spline Simulation 1	70.97	72.03	66.76
I-Spline Simulation 2	16.06	16.41	14.80
I-Spline Simulation 3	6.93	6.49	7.54
I-Spline Simulation 4	22.15	20.99	23.74