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:

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

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

Log-Normal:

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

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

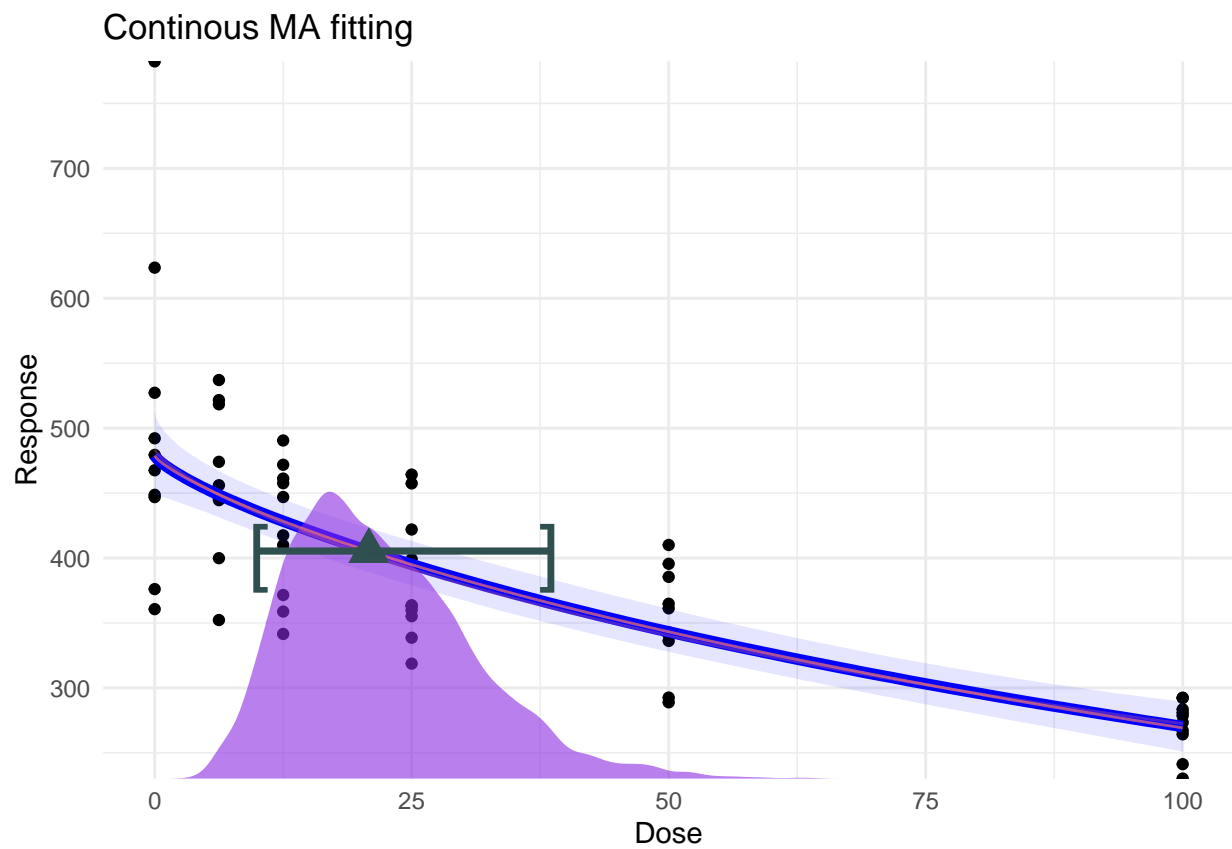Here are two generated datasets from Hill condition 2 and 8:

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## NOTE: Parameter 'c' added to prior list. It is not used in the analysis.
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##       BMD      BMDL      BMDU
## 17.392323  7.232769 30.255670
```

Continous MA fitting
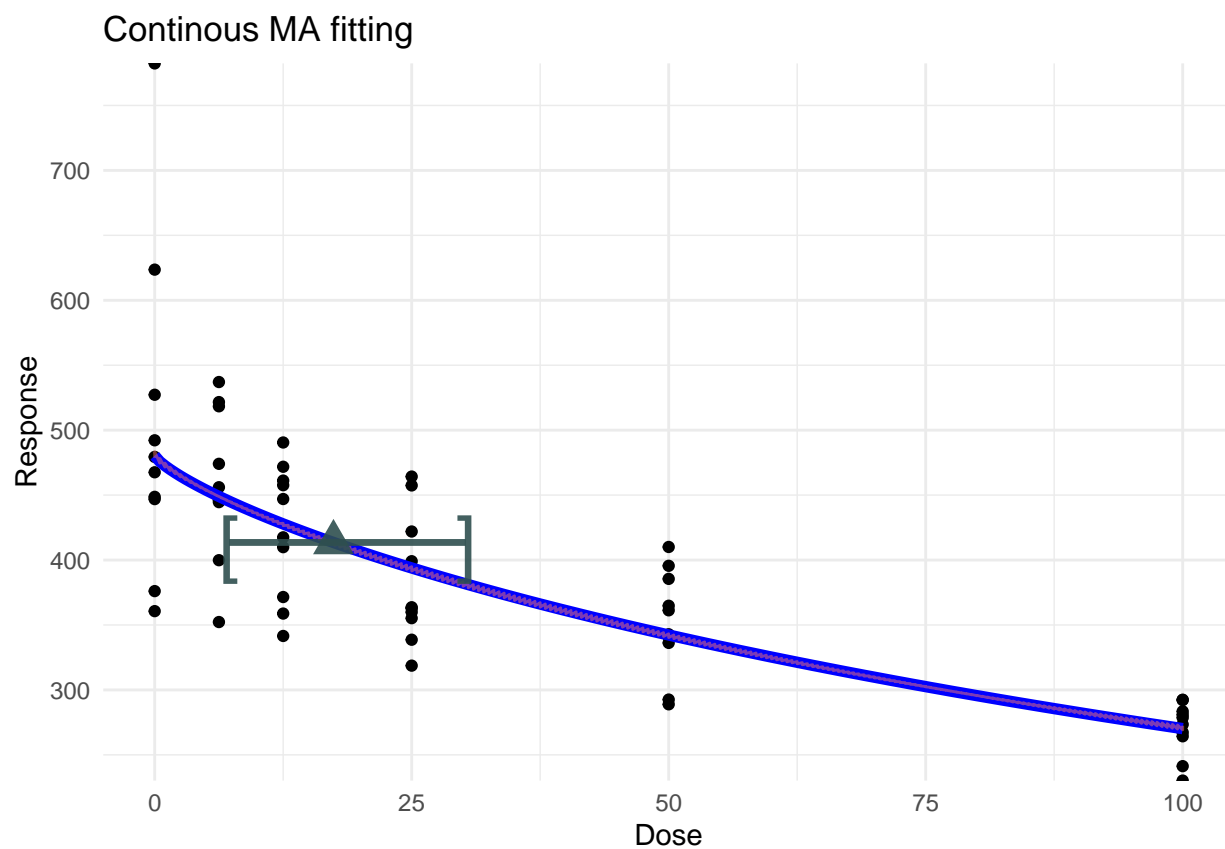

```
##        BMD      BMDL      BMDU
## 20.83957 10.16524 38.31135
```

Continous MA fitting

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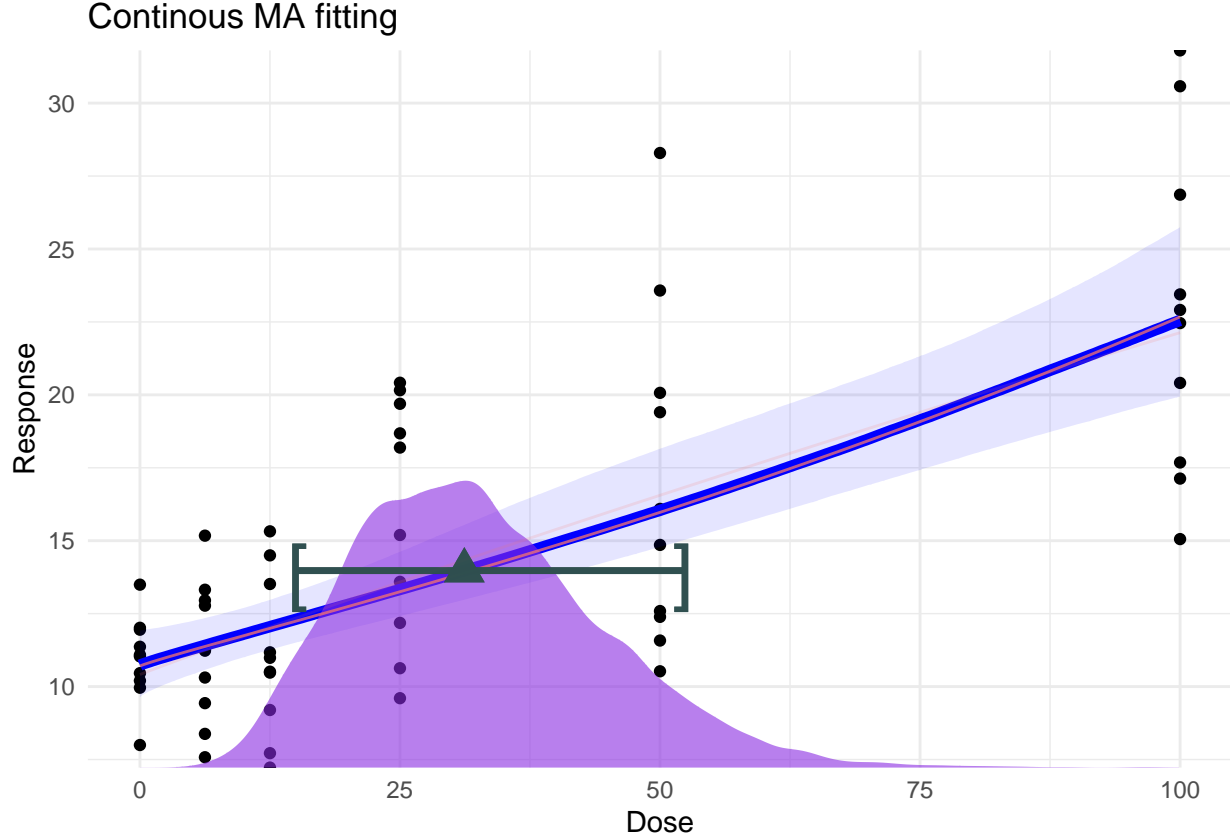
Continous MA fitting

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.
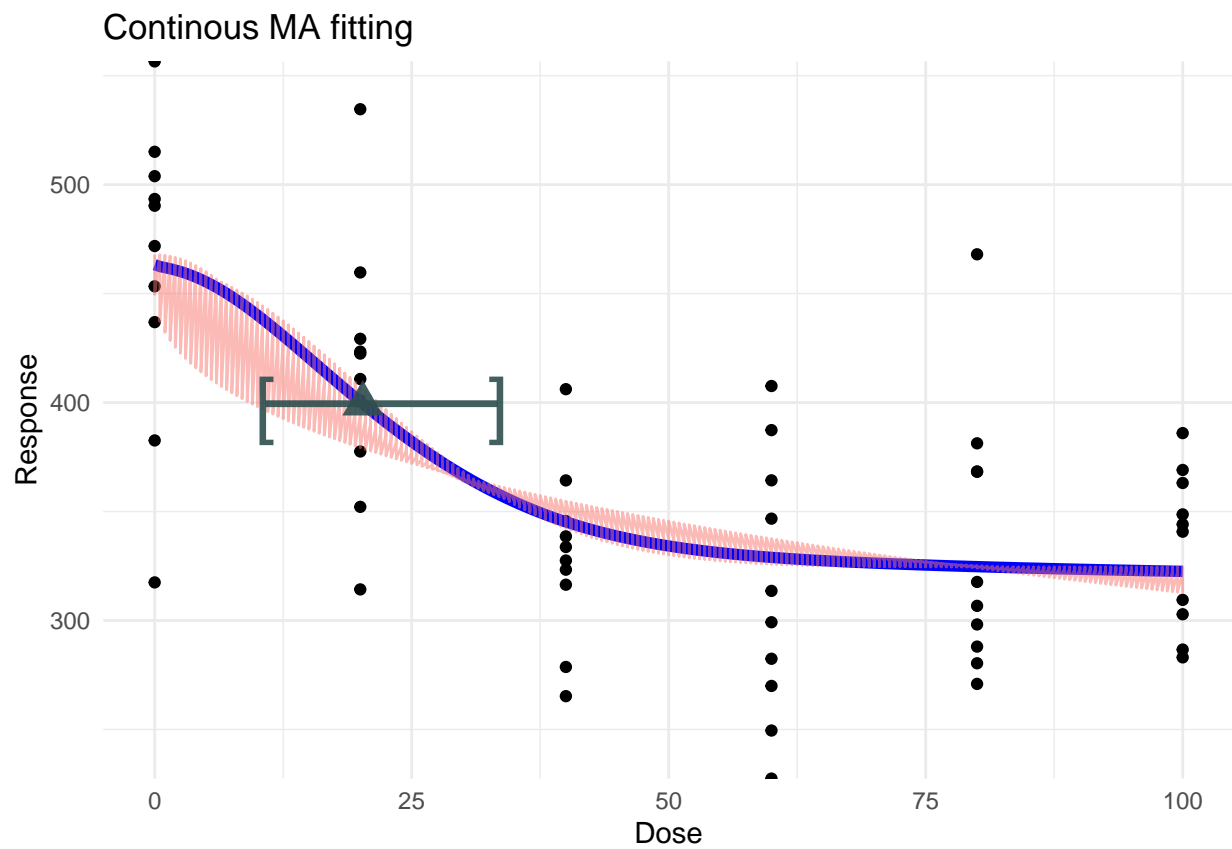
Continous MA fitting


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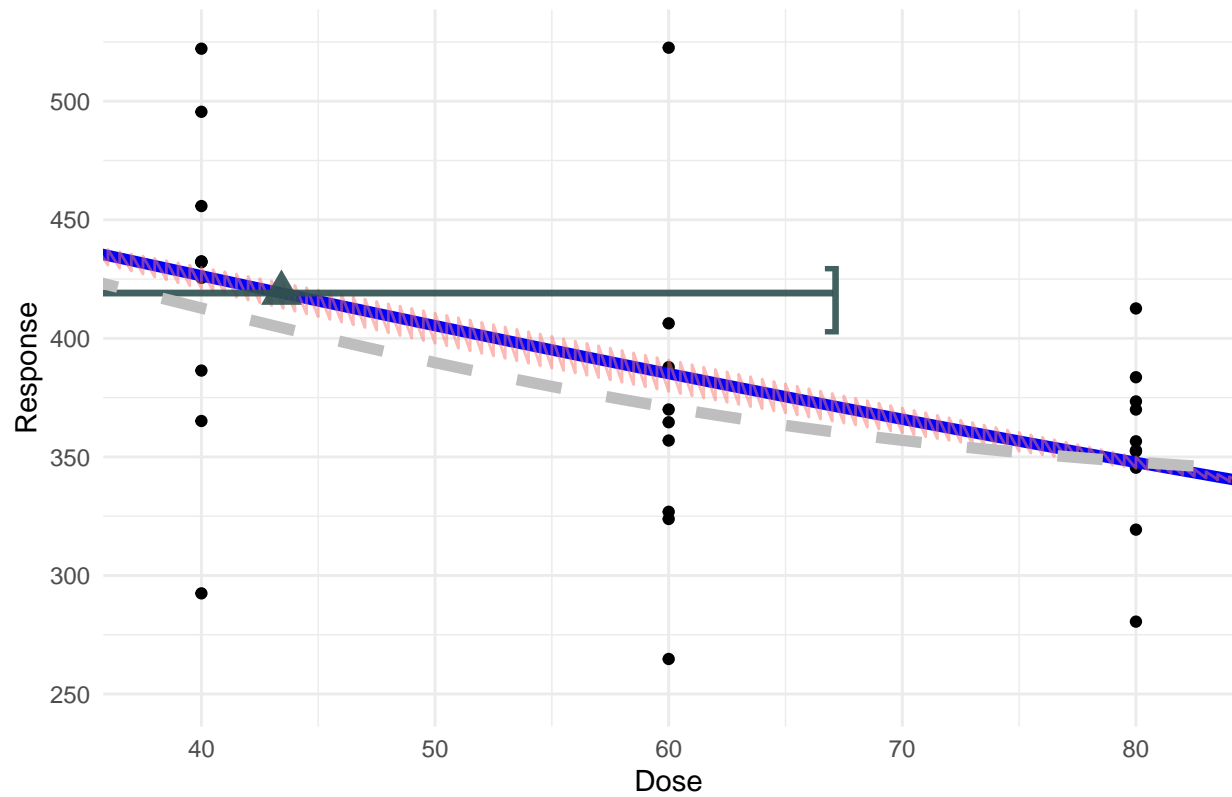
Continous MA fitting
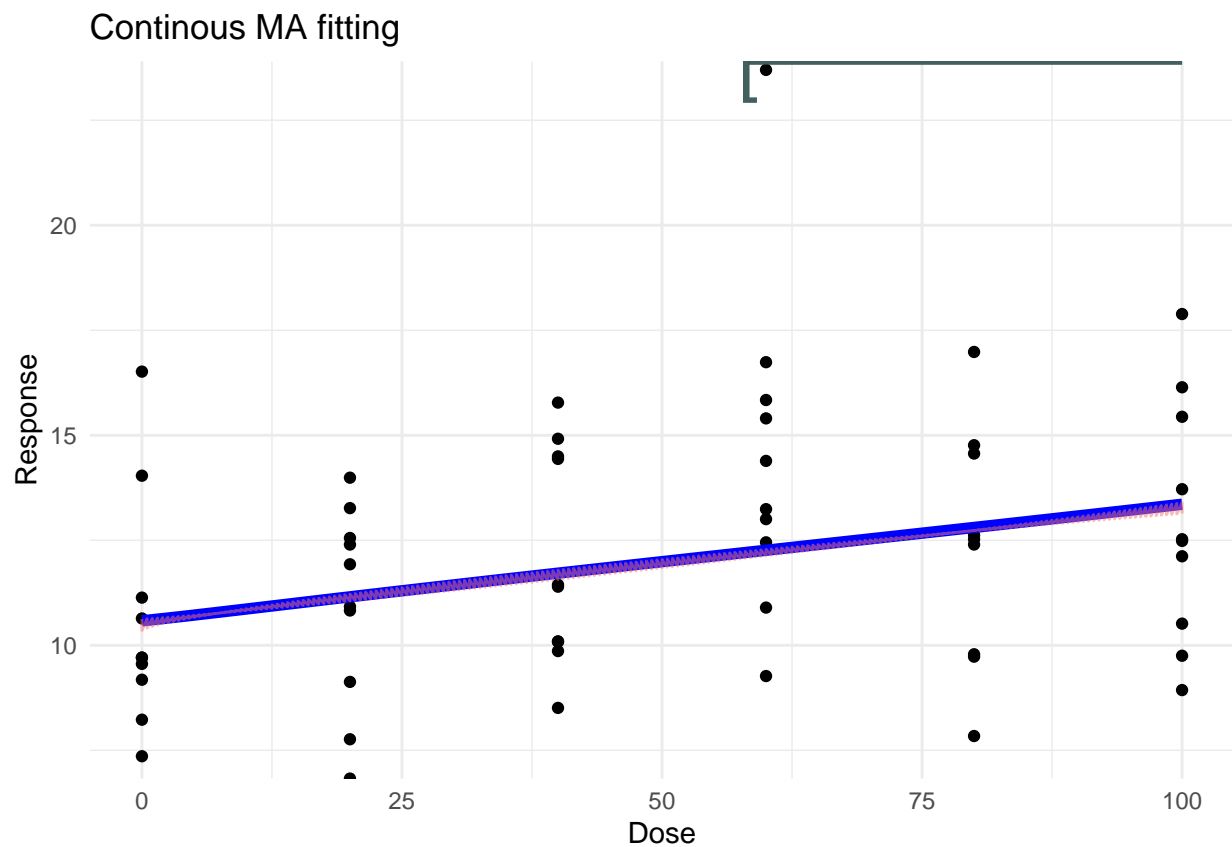

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```

```
##      BMD      BMDL      BMDU
## 43.42620 24.92417 67.04030
```
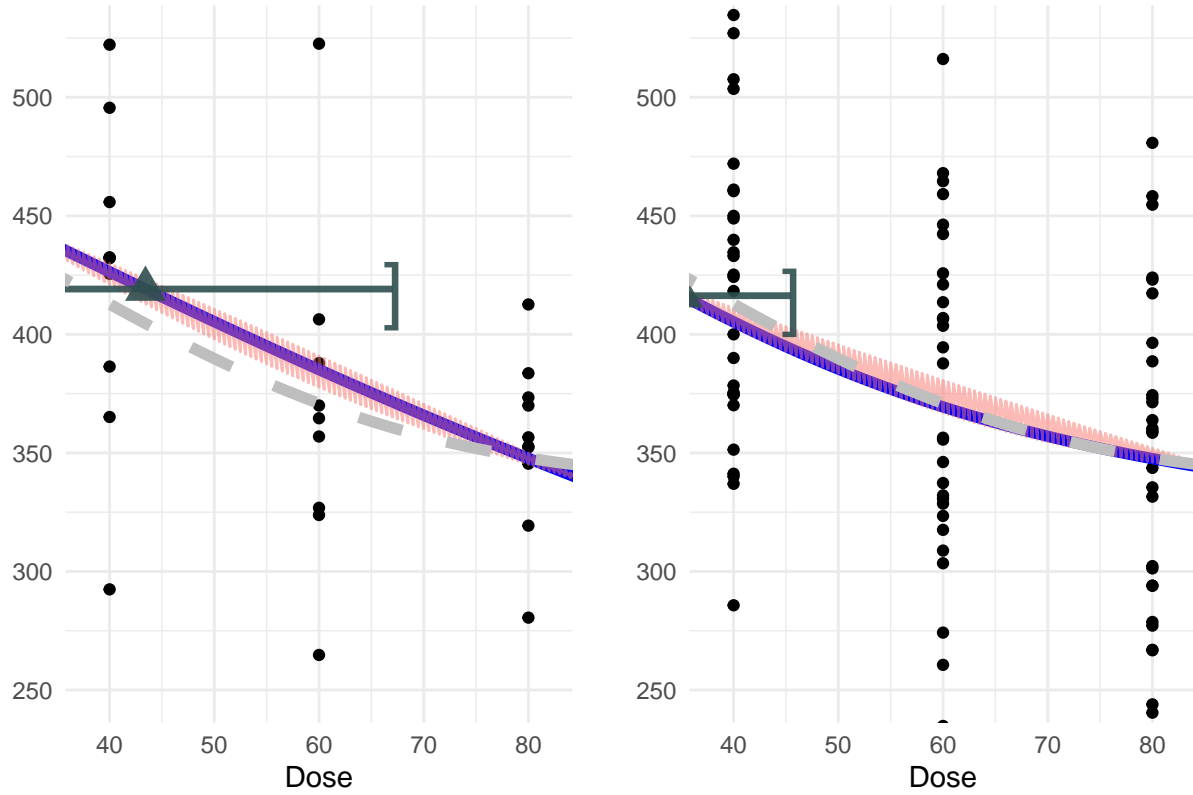
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##       BMD      BMDL      BMDU
## 35.12072 24.79565 45.45648
```

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

```
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##       BMD      BMDL      BMDU
## 111.30915   24.24588 527.03508

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##       BMD      BMDL      BMDU
## 20.78624 16.14923 26.11917
```
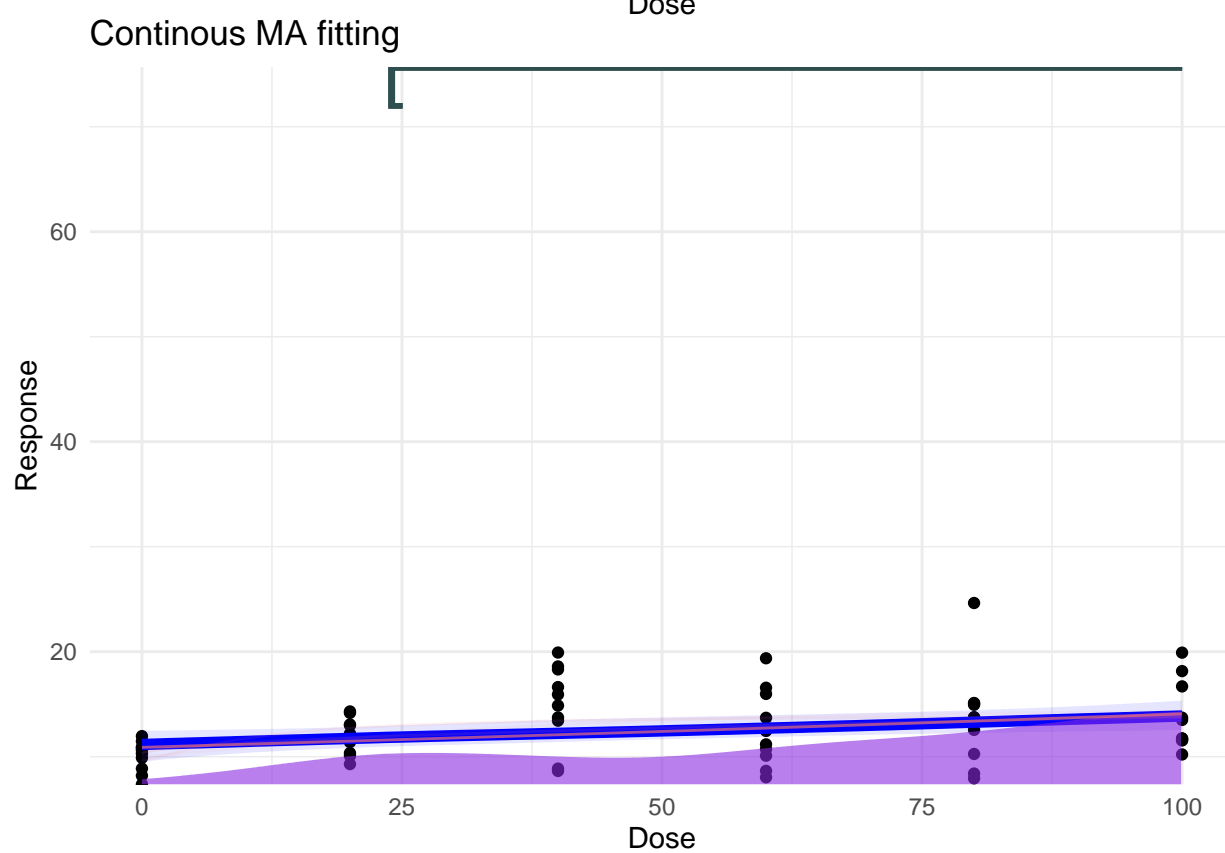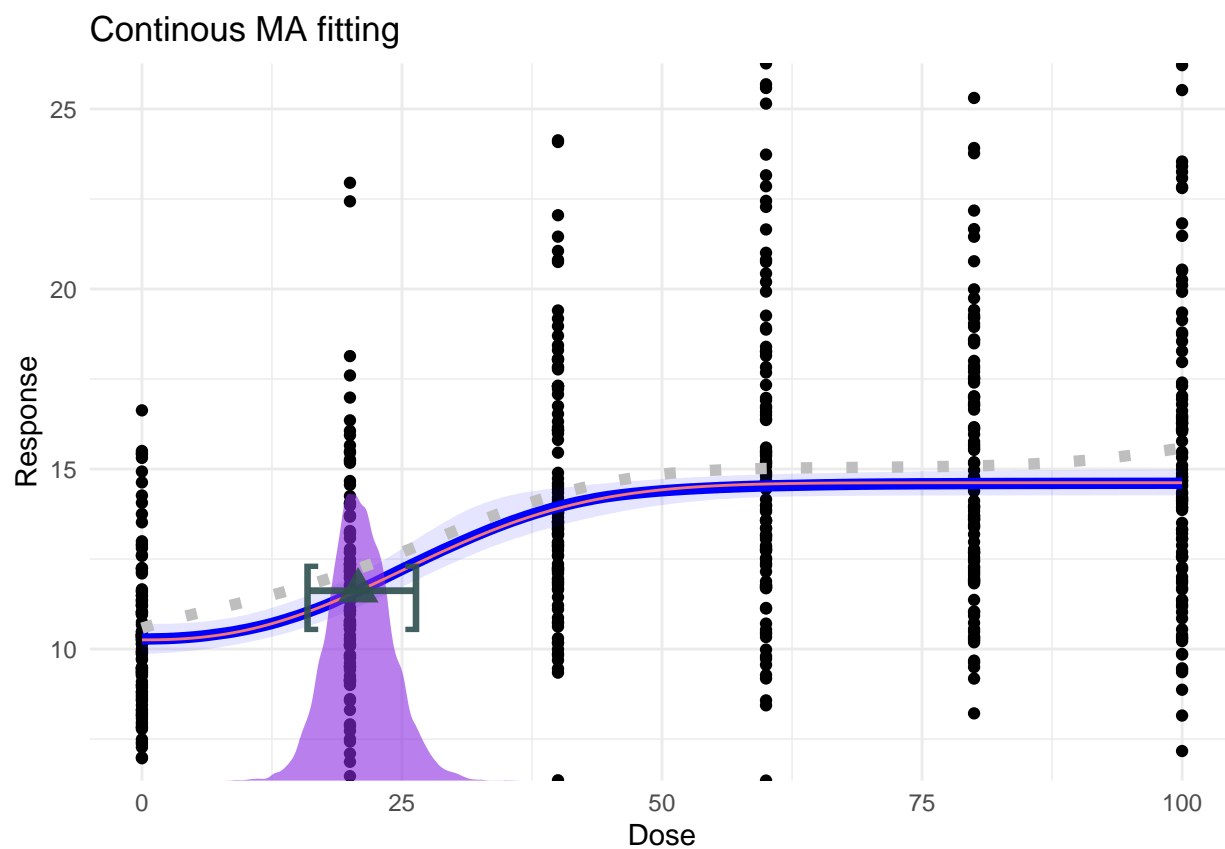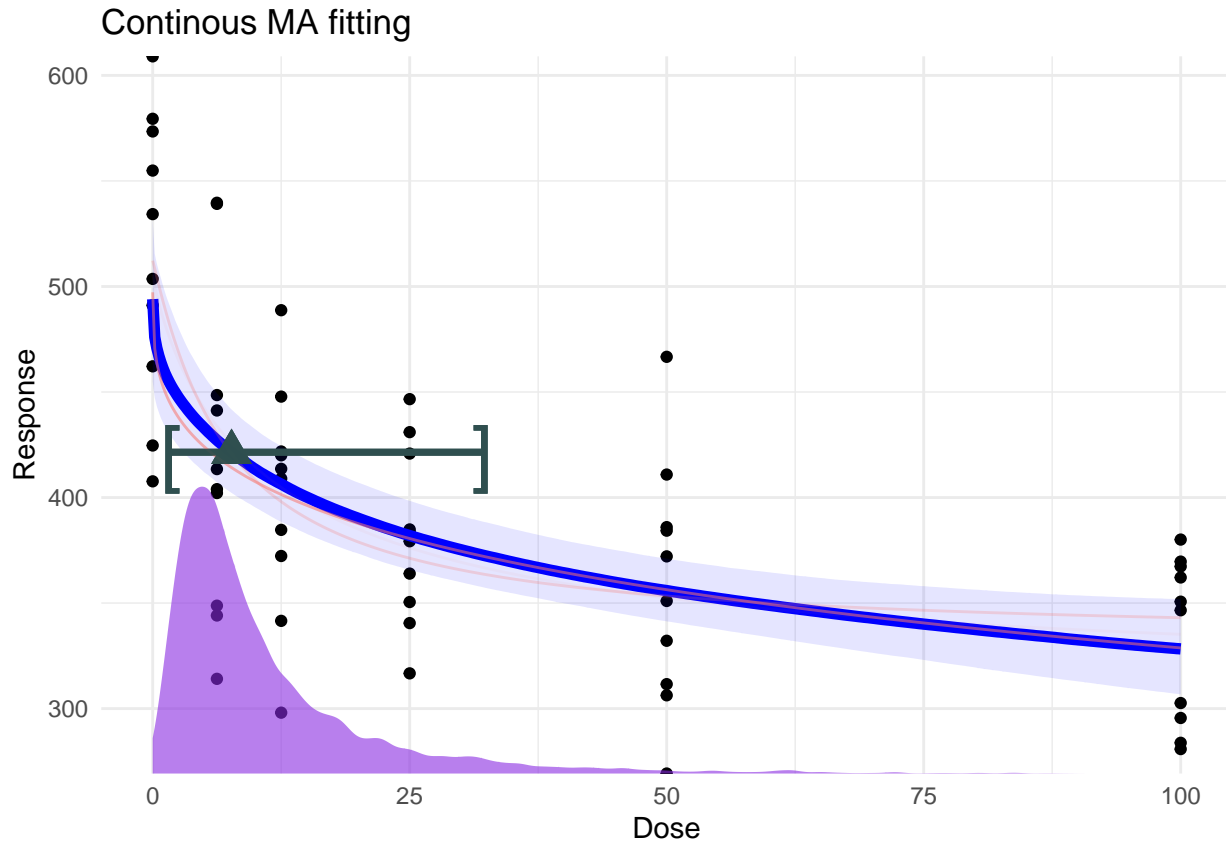
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Continous MA fitting

Continous MA fitting

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## NOTE: Parameter 'c' added to prior list. It is not used in the analysis.
```

Continous MA fitting

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

Tables of BMD values for Rel-Dev approach

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

Tables of BMD values for Hybrid approach

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