Wednesday, Feb 8

Nonlinear Regression

A *nonlinear* regression model is any model that *cannot* be written as

$$E(Y_i) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots + \beta_k x_{ik},$$

such that $x_{i1}, x_{i2}, \ldots, x_{ik}$ *do not depend on any unknown parameters*. A linear model must be *linear in the parameters*.

Example: Let's consider an exponential model for the `ToothGrowth` data, ignoring supplement type for now, such that

$$E(Y_i) = \beta_0 + \beta_1 2^{-d_i/h}$$

where Y_i is length and d_i is dose. If h is specified (say $h = 1$) we have a linear model that we can write as

$$E(Y_i) = \beta_0 + \beta_1 x_i,$$

where $x_i = 2^{-d_i/1}$. We can estimate this model in the usual way using `lm`.

```
m <- lm(len ~ I(2^(-dose/1)), data = ToothGrowth)
summary(m)$coefficients
```

```
               Estimate Std. Error t value  Pr(>|t|)
(Intercept)       35.14      1.555   22.60 1.942e-30
I(2^(-dose/1))   -33.61      2.988  -11.25 3.303e-16
```

But suppose we want to treat h as an *unknown parameter* to be *estimated* like β_0 and β_1? This would not be a linear model. We can write the model as

$$E(Y_i) = \beta_0 + \beta_1 x_i,$$

where $x_i = 2^{d_i/h}$, but now x_i depends on an unknown parameter (h) and so the model is not linear in the parameters.

Nonlinear Regression

The `nls` function can be used to estimate a *nonlinear* regression model (the `nls` stands for "nonlinear least squares"). But its arguments are a little different from `lm`.

1. The model must be written *mathematically* rather than *symbolically*. And this requires that we know the correct operators/functions in R corresponding to the desired mathematical operators/functions.
2. The *starting values* of the parameter estimates must be provided. This does two things: it identifies what parts of the model formula are parameters, and it provides initial values for an algorithm to use to solve the least squares optimization problem.

Example: First we will replicate the results for the *linear* model where h is known/specified, but now using `nls`.

```
m <- nls(len ~ beta0 + beta1*2^(-dose/1), data = ToothGrowth,
  start = list(beta0 = 32, beta1 = -33))
summary(m)$coefficients
```

```
      Estimate Std. Error t value  Pr(>|t|)
beta0    35.14      1.555   22.60 1.942e-30
beta1   -33.61      2.988  -11.25 3.303e-16
```

Note that the results are identical to what was obtained using `lm`. Now consider a *nonlinear* model where h is also an unknown parameter.

```
m <- nls(len ~ beta0 + beta1*2^(-dose/h), data = ToothGrowth,
  start = list(beta0 = 32, beta1 = -33, h = 1))
summary(m)$coefficients
```

```
      Estimate Std. Error t value  Pr(>|t|)
beta0  27.9366     2.1482  13.005 1.062e-18
beta1 -36.6251     6.1143  -5.990 1.493e-07
h       0.4632     0.1459   3.174 2.422e-03
```

Specifying "good" starting values is important. What if we don't provide good starting values?

```
m <- nls(len ~ beta0 + beta1*2^(-dose/h), data = ToothGrowth,
  start = list(beta0 = 0, beta1 = 0, h = 1))
```

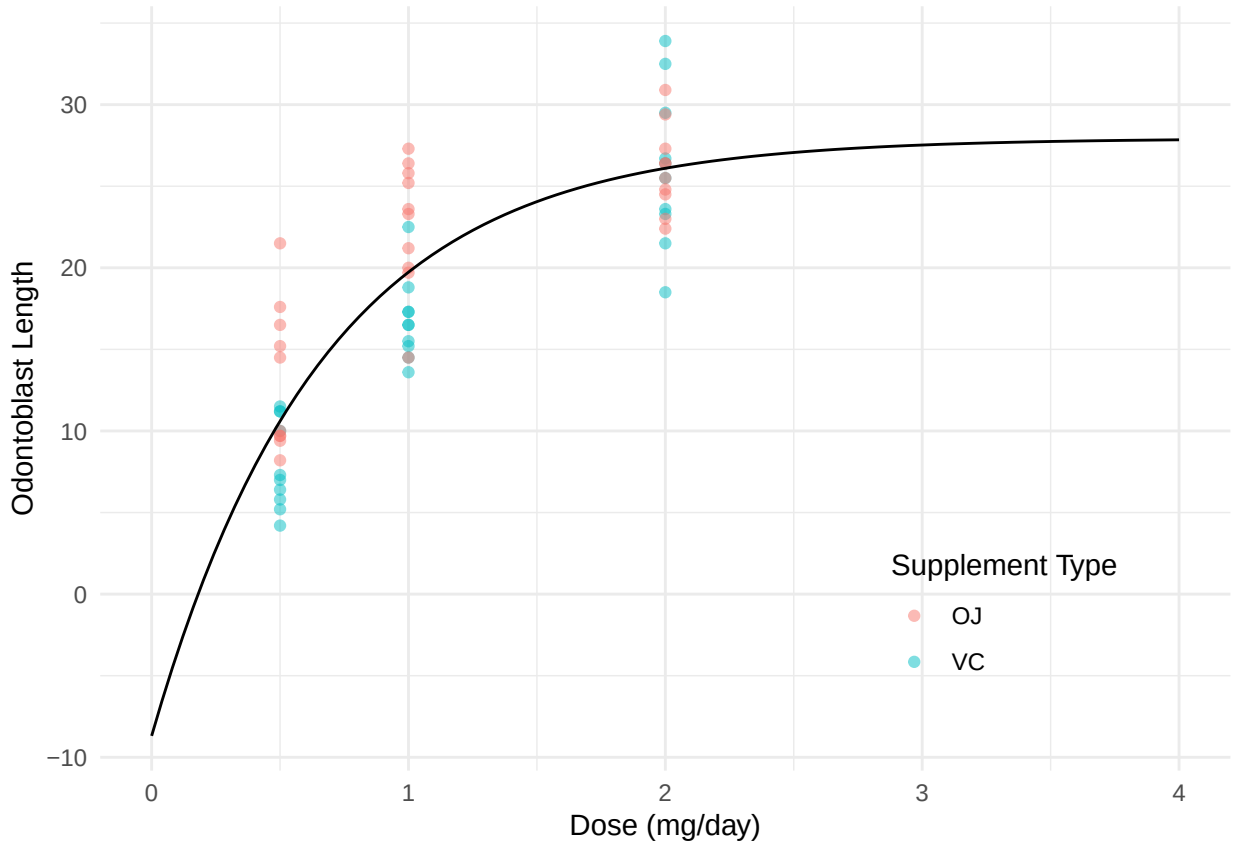
```
Error in nlsModel(formula, mf, start, wts, scaleOffset = scOff, nDcentral = nDcntr): singular gradient m
```

How do we find good starting values? One approach is to use an approximate model like we did here that is linear. Another approach is to "eyeball" the estimates from a plot.

We can plot the model in the usual way.

```
d <- expand.grid(dose = seq(0, 4, length = 100))
d$yhat <- predict(m, newdata = d)

p <- ggplot(ToothGrowth, aes(x = dose, y = len)) +
  geom_point(aes(color = supp), alpha = 0.5) +
  geom_line(aes(y = yhat), data = d) +
  labs(x = "Dose (mg/day)", y = "Odontoblast Length",
    color = "Supplement Type") +
  theme_minimal() + theme(legend.position = c(0.8,0.2))
plot(p)
```

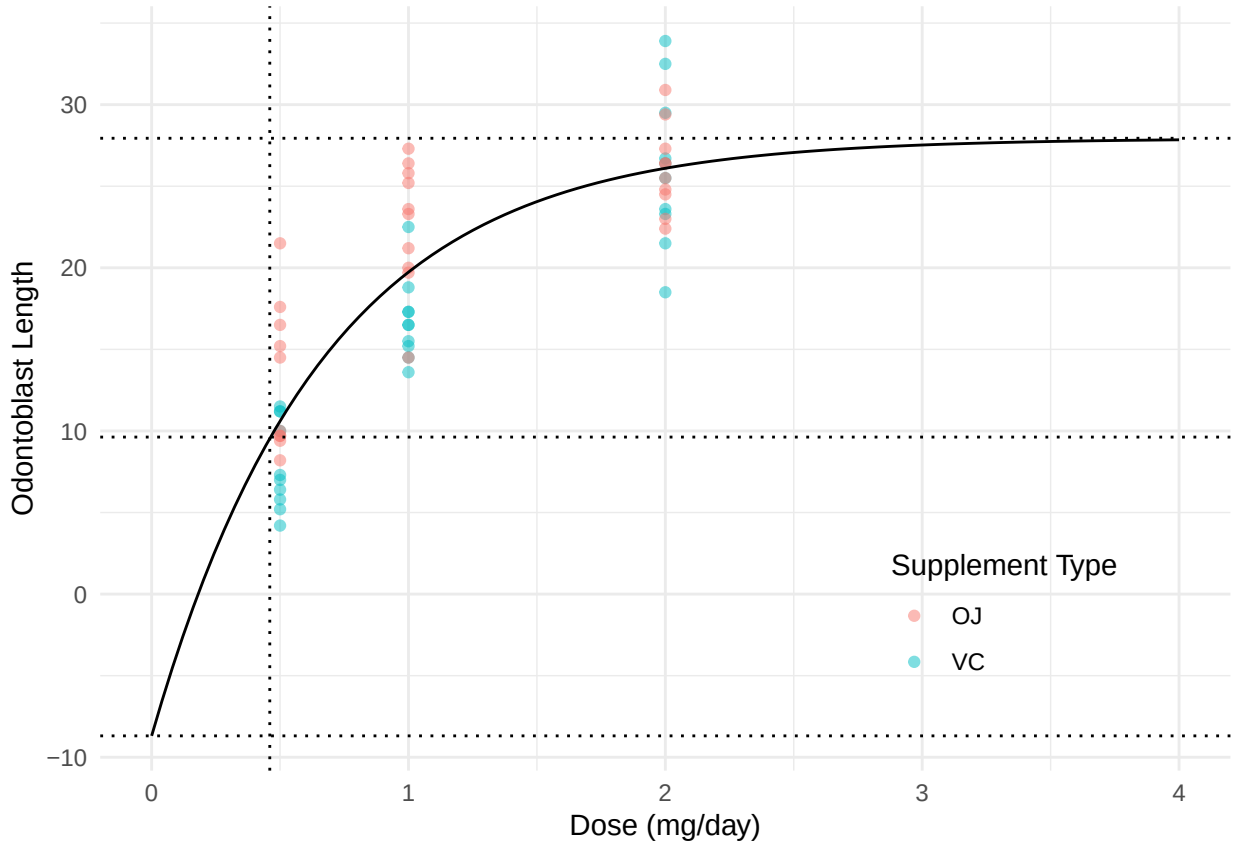


We can add some annotation if desired to highlight the interesting quantities.

```
summary(m)$coefficients
```

```
      Estimate Std. Error t value  Pr(>|t|)
beta0  27.9366     2.1482  13.005 1.062e-18
beta1 -36.6251     6.1143  -5.990 1.493e-07
h       0.4632     0.1459   3.174 2.422e-03
```

```
p <- p + geom_hline(yintercept = 27.94, linetype = 3) # asymptote (b0)
p <- p + geom_hline(yintercept = 27.94 - 36.63, linetype = 3) # intercept (b0 + b1)
p <- p + geom_hline(yintercept = 27.94 - 36.63/2, linetype = 3) # half-way (b0 + b1/2)
p <- p + geom_vline(xintercept = 0.46, linetype = 3) # half-life (h)
plot(p)
```



Recall that the "intercept" is $\beta_0 + \beta_1$. We can make inferences concerning this quantity using `lincon`.

```
m <- nls(len ~ beta0 + beta1*2^(-dose/h), data = ToothGrowth,
  start = list(beta0 = 32, beta1 = -33, h = 0.75))
lincon(m, a = c(1,1,0)) # 1*b1 + 1*b2 + 0*h = b1 + b2
```

```
          estimate    se  lower upper tvalue df pvalue
(1,1,0),0   -8.688 7.562 -23.83 6.455 -1.149 57 0.2554
```

Does this make sense?

We can also replicate the estimates of the asymptote (β_0) and half-life (h) parameters using `lincon`.

```
cbind(summary(m)$coefficients, confint(m))
```

```
      Estimate Std. Error t value  Pr(>|t|)     2.5%   97.5%
beta0  27.9366     2.1482  13.005 1.062e-18  24.7232  37.229
beta1 -36.6251     6.1143  -5.990 1.493e-07 -57.3146 -28.105
h       0.4632     0.1459   3.174 2.422e-03   0.2647   1.135
```

```
lincon(m, c(1,0,0)) # asymptote (beta0)
```

```
          estimate    se lower upper tvalue df    pvalue
(1,0,0),0    27.94 2.148 23.63 32.24     13 57 1.062e-18
```

```
lincon(m, c(0,0,1)) # half-life (h)
```

```
          estimate     se lower  upper tvalue df   pvalue
(0,0,1),0   0.4632 0.1459 0.171 0.7554  3.174 57 0.002422
```

Note the difference in the confidence intervals (particularly for h). Here `confint` and `lincon` using different

kinds of confidence intervals: `confint` uses "profile-likelihood" intervals and `lincon` uses "Wald" intervals. We will discuss profile-likelihood confidence intervals later, but note here that typically they are more accurate.

The `emmeans` and `contrast` functions cannot (yet) be applied to a `nls` object. We must rely on something like `lincon` or clever parameterization (see below).

Now consider the model

$$E(Y_i) = \begin{cases} \beta_0 + \beta_1 2^{-x_i/h_{\text{OJ}}}, & \text{if the supplement type is OJ,} \\ \beta_0 + \beta_1 2^{-x_i/h_{\text{VC}}}, & \text{if the supplement type is VC,} \end{cases}$$

where x_i is dose. There are several ways we can handle case-wise models with `nls`: indicator variables, the `ifelse` function, and the `case_when` function.

1. We could write the model as

$$E(Y_i) = \beta_0 + \beta_1 2^{-x_i/(o_i h_{\text{OJ}} + v_i h_{\text{VC}})},$$

where o_i and v_i are indicator variables for the OJ and VC supplement types, respectively. In R we can program these indicator variables as `supp == "OJ"` and `supp == "VC"`, respectively. These will return `TRUE` or `FALSE`, but will be interpreted as 1 or 0, respectively, if used in a calculation. Here is how we can write this model in `nls`.

```
m <- nls(len ~ b0 + b1*2^(-dose/((supp == "OJ")*hoj + (supp == "VC")*hvc)),
  data = ToothGrowth, start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46))
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

We could actually get away with one indicator variable if we are a little clever (and we are).

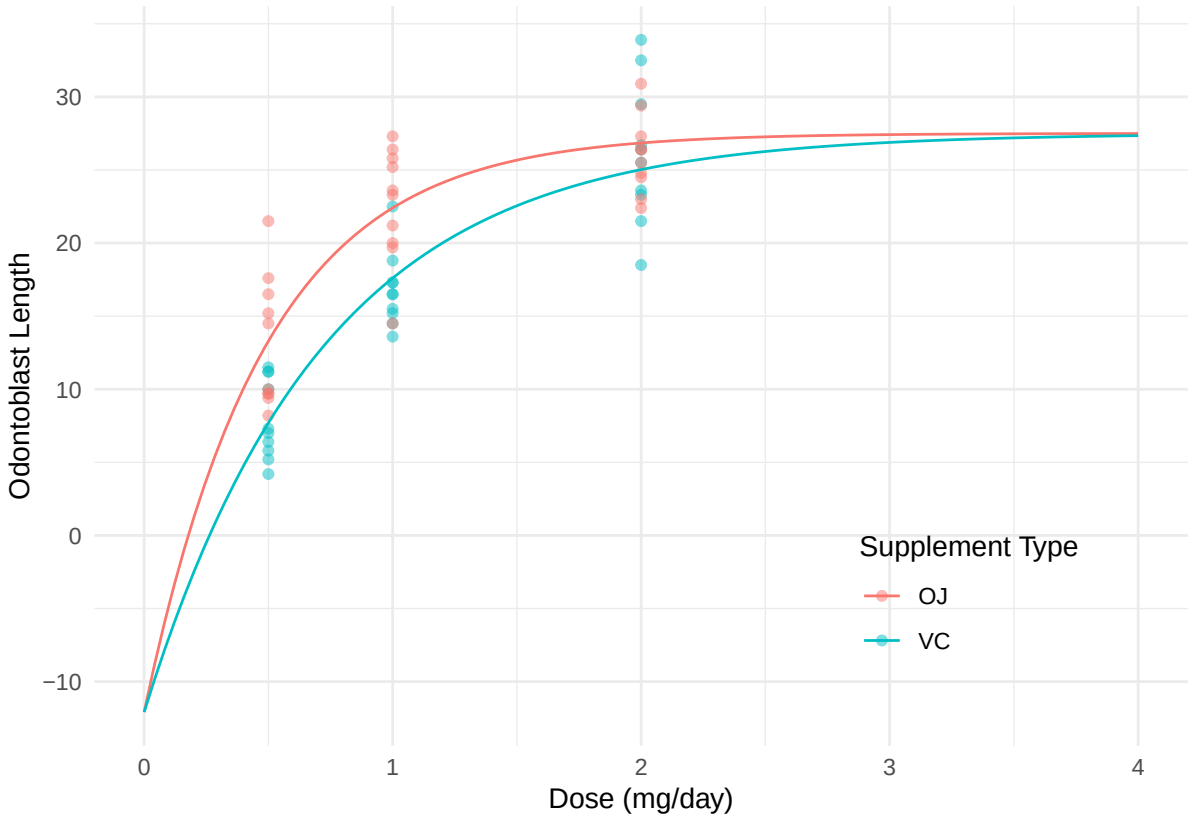
```
m <- nls(len ~ b0 + b1*2^(-dose/((supp == "OJ")*hoj + (1 - (supp == "OJ"))*hvc)),
  data = ToothGrowth, start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46))
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

Here is a plot of the model with the data.

```
d <- expand.grid(dose = seq(0, 4, length = 100), supp = c("OJ","VC"))
d$yhat <- predict(m, newdata = d)

p <- ggplot(ToothGrowth, aes(x = dose, y = len, color = supp)) +
  geom_point(alpha = 0.5) +
  geom_line(aes(y = yhat), data = d) +
  labs(x = "Dose (mg/day)", y = "Odontoblast Length",
    color = "Supplement Type") +
  theme_minimal() + theme(legend.position = c(0.8,0.2))
plot(p)
```



2. When there are only two cases it can be convenient to use `ifelse`.

```
m <- nls(len ~ b0 + b1*2^(-dose/ifelse(supp == "OJ", hoj, hvc)),
  start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46),
  data = ToothGrowth)
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

Here is another way we could write that using `ifelse`.

```
m <- nls(len ~ ifelse(supp == "OJ", b0 + b1*2^(-dose/hoj), b0 + b1*2^(-dose/hvc)),
  start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46),
  data = ToothGrowth)
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

3. When there are more than two cases using `ifelse` can be tedious because we have to use nested `ifelse` functions. An easier approach is to use the `case_when` function from the **dplyr** package.

```
library(dplyr) # for case_when
m <- nls(len ~ case_when(
```

```
  supp == "OJ" ~ b0 + b1*2^(-dose/hoj),
  supp == "VC" ~ b0 + b1*2^(-dose/hvc),
), data = ToothGrowth, start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46))
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

Ultimately it may be a matter of which is easiest to code.

Suppose we want to compare the two supplement types by making inferences about the *difference* $h_{\text{VC}} - h_{\text{OJ}}$?

```
summary(m)$coefficients
```

```
    Estimate Std. Error t value  Pr(>|t|)
b0   27.5018    1.39516  19.712 7.258e-27
b1  -39.5856    5.47238  -7.234 1.422e-09
hoj   0.3382    0.06978   4.846 1.036e-05
hvc   0.5001    0.11208   4.462 3.963e-05
```

```
lincon(m, a = c(0,0,-1,1)) # 0*b0 + 0*b1 - 1*hoj + 1*hvc = hvc - hoj
```

```
             estimate      se   lower  upper tvalue df   pvalue
(0,0,-1,1),0    0.162 0.05532 0.05115 0.2728  2.928 56 0.004927
```

But suppose we parameterize the model as

$$E(Y_i) = \begin{cases} \beta_0 + \beta_1 2^{-x_i/h}, & \text{if the supplement type is OJ,} \\ \beta_0 + \beta_1 2^{-x_i/(h+\delta)}, & \text{if the supplement type is VC,} \end{cases}$$

so that h is the half-life parameter for OJ, $h + \delta$ is the half-life parameter for VC, and δ is the difference between them.

```
m <- nls(len ~ case_when(
  supp == "OJ" ~ b0 + b1*2^(-dose/h),
  supp == "VC" ~ b0 + b1*2^(-dose/(h + delta))
  ), data = ToothGrowth, start = c(b0 = 28, b1 = -37, h = 0.46, delta = 0))
summary(m)$coefficients
```

```
      Estimate Std. Error t value  Pr(>|t|)
b0     27.5018    1.39516  19.712 7.258e-27
b1    -39.5856    5.47238  -7.234 1.422e-09
h       0.3382    0.06978   4.846 1.036e-05
delta   0.1620    0.05532   2.928 4.927e-03
```

Same model, different parameterization. Now we do not need to use `lincon` to obtain inferences for the difference between the two half life parameters, although we would need to use it to obtain inferences for the half life parameter for VC which is $h + \delta$.

```
lincon(m, a = c(0, 0, 1, 1))
```

```
            estimate     se  lower  upper tvalue df    pvalue
(0,0,1,1),0   0.5001 0.1121 0.2756 0.7247  4.462 56 3.963e-05
```

Interestingly using `confint` on these models "chokes" when trying to compute the profile-likelihood confidence interval for δ, although we can fix it by increasing the maximum number of iterations used in the estimation process (which is also used by `confint`).

```
confint(m)
```

```
Error in prof$getProfile(): number of iterations exceeded maximum of 50
```

```
m <- nls(len ~ b0 + b1*2^(-dose/ifelse(supp == "OJ", h, h + delta)),
    data = ToothGrowth, start = c(b0 = 28, b1 = -37, h = 0.46, delta = 0),
    control = nls.control(maxiter = 1000))
confint(m)
```

```
           2.5%    97.5%
b0     25.18143  30.8451
b1    -53.75676 -31.4127
h       0.23541   0.5268
delta   0.08001   0.2929
```

Alternatively we can easily compute a Wald confidence interval.

```
lincon(m, a = c(0,0,0,1)) # 0*b0 + 0*b1 + 0*h + 1*delta = delta
```

```
            estimate      se   lower  upper tvalue df   pvalue
(0,0,0,1),0    0.162 0.05532 0.05115 0.2728  2.928 56 0.004927
```

Actually if you omit the `a` argument `lincon` will return inferences for the model parameters like those given by `summary` and `confint` (but using Wald confidence intervals).

```
lincon(m)
```

```
      estimate      se     lower    upper tvalue df    pvalue
b0     27.5018 1.39516  24.70701  30.2967 19.712 56 7.258e-27
b1    -39.5856 5.47238 -50.54805 -28.6231 -7.234 56 1.422e-09
h       0.3382 0.06978   0.19838   0.4779  4.846 56 1.036e-05
delta   0.1620 0.05532   0.05115   0.2728  2.928 56 4.927e-03
```

Treating a quantitative variable as a factor is viable if there are not too many distinct values of the variable and there are replicates of some of the values. Given the difficulty of finding a reasonable model for these data, what would be the advantages and disadvantages of treating dose as a categorical variable (i.e., factor)?

1. It allows us to avoid having to specify/assume a particular mathematical relationship between the explanatory variable and the expected response.
2. It can result in more parameters (six versus four in the nonlinear model above). Models with more parameters can result in larger standard errors and thus less precise inferences because a model with more parameters relies more heavily on the data for its estimation.
3. It does not give us as much insight into the relationship between the explanatory variable and the expected response, and we cannot make inferences based on unobserved values of the explanatory variable.

Estimated Expected Responses With `nls`

The `predict` function produces the estimated expected response for any combination of explanatory variables. For example,

```
d <- expand.grid(supp = c("VC","OJ"), dose = c(0.5, 1, 1.5, 2))
d$yhat <- predict(m, newdata = d)
d
```

```
  supp dose   yhat
1   VC  0.5  7.705
2   OJ  0.5 13.297
```

```
3   VC  1.0 17.602
4   OJ  1.0 22.405
5   VC  1.5 22.551
6   OJ  1.5 25.673
7   VC  2.0 25.026
8   OJ  2.0 26.845
```

However `predict` does not provide standard errors or confidence intervals for estimating expected responses based on `nls`, and we cannot use `contrast` with `nls`. But we can use the function `nlsint` from the **trtools** package to get approximate standard errors and confidence or prediction intervals from a `nls` object.

```
library(trtools)
nlsint(m, newdata = d)
```

```
     fit     se    lwr    upr
1  7.705 1.0885  5.525  9.886
2 13.297 0.9857 11.322 15.272
3 17.602 0.9868 15.625 19.579
4 22.405 0.7711 20.860 23.949
5 22.551 0.8758 20.796 24.305
6 25.673 0.7342 24.202 27.144
7 25.026 0.7322 23.559 26.493
8 26.845 1.0098 24.823 28.868
```

```
cbind(d, nlsint(m, newdata = d))
```

```
  supp dose   yhat    fit     se    lwr    upr
1   VC  0.5  7.705  7.705 1.0885  5.525  9.886
2   OJ  0.5 13.297 13.297 0.9857 11.322 15.272
3   VC  1.0 17.602 17.602 0.9868 15.625 19.579
4   OJ  1.0 22.405 22.405 0.7711 20.860 23.949
5   VC  1.5 22.551 22.551 0.8758 20.796 24.305
6   OJ  1.5 25.673 25.673 0.7342 24.202 27.144
7   VC  2.0 25.026 25.026 0.7322 23.559 26.493
8   OJ  2.0 26.845 26.845 1.0098 24.823 28.868
```

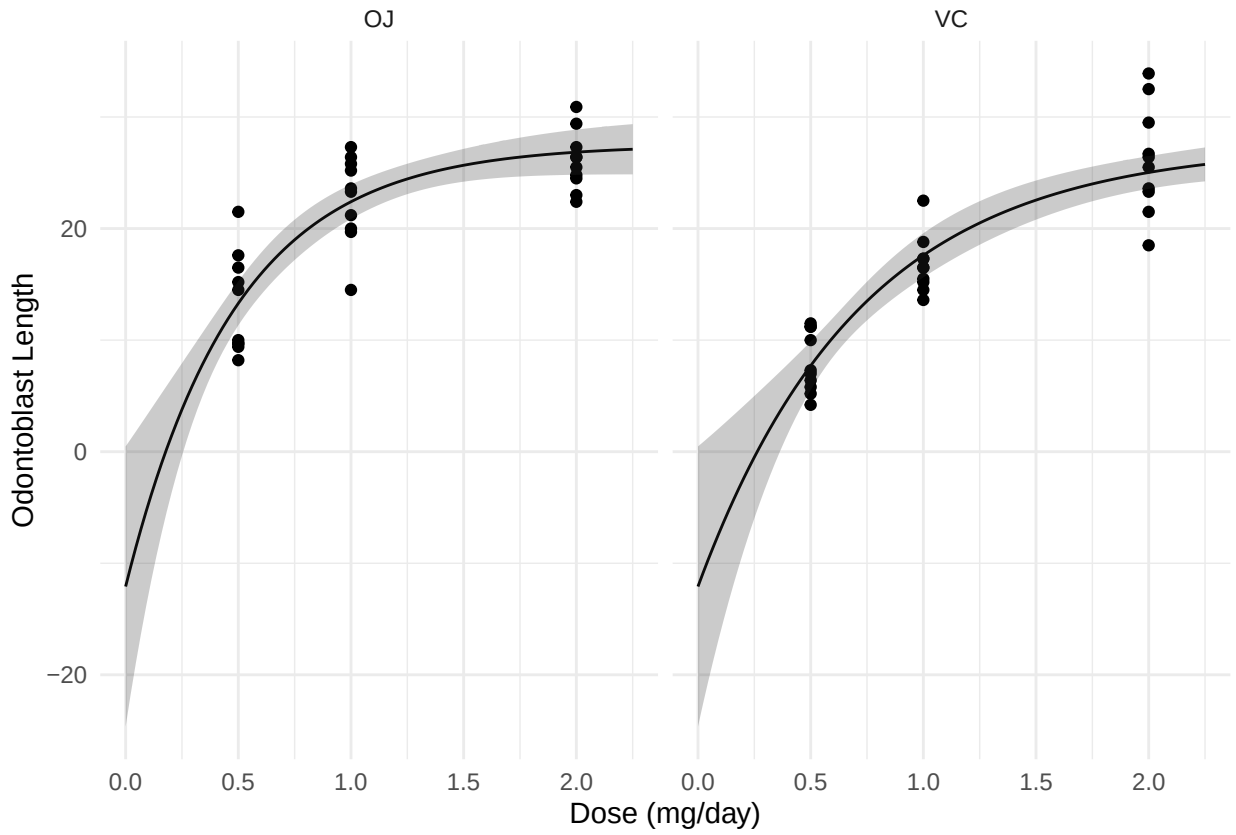
The intervals are confidence intervals by default. Prediction intervals can be obtained using `interval = prediction` (as you would with the `predict` function with a linear model).

The reason why `predict` does not provide standard errors and thus confidence intervals for a `nls` object is that the estimated expected response is *not* a linear function of the model parameters in a nonlinear model. The `nlsint` function uses what is called the *delta method* to come up with an approximate standard error. We will discuss the delta method later.

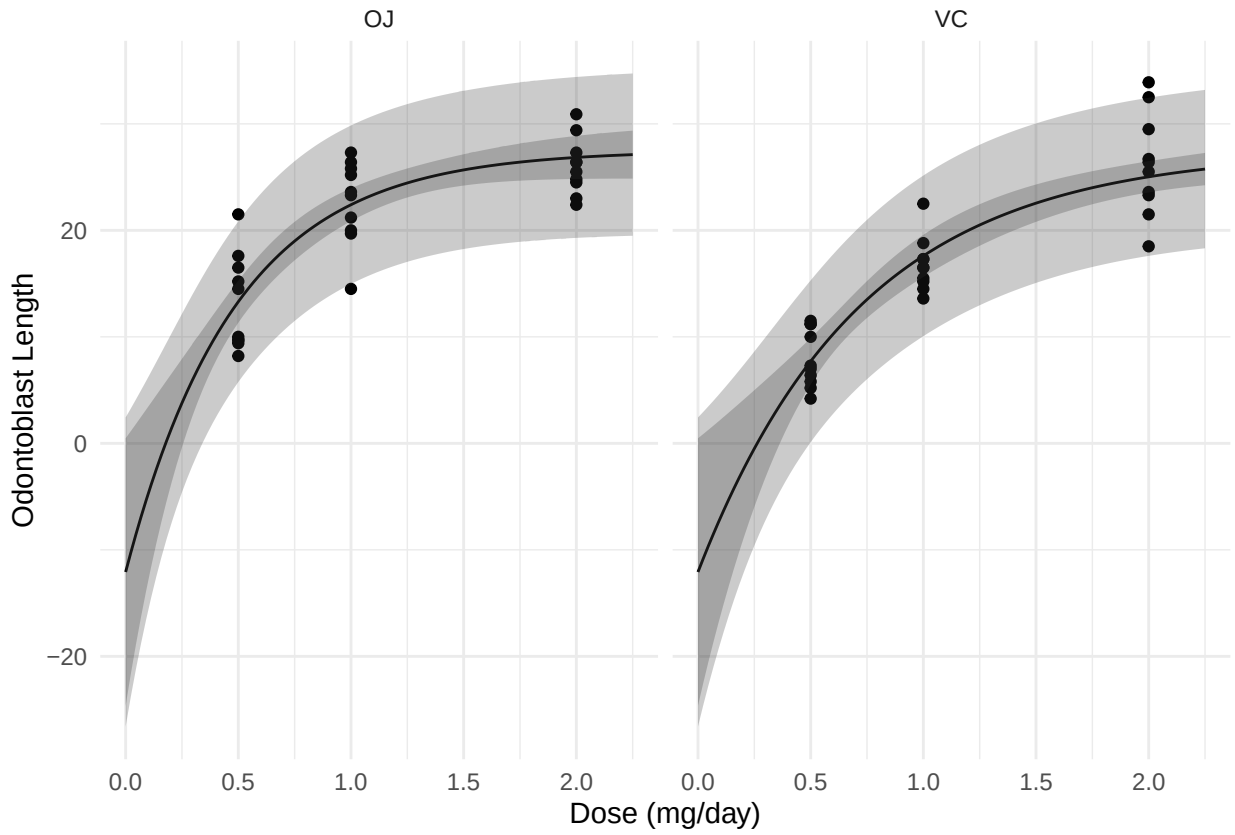
The `nlsint` function is also useful for plotting confidence and/or prediction intervals.

```
d <- expand.grid(supp = c("OJ", "VC"), dose = seq(0, 2.25, length = 100))
d <- cbind(d, nlsint(m, newdata = d))

p <- ggplot(ToothGrowth, aes(x = dose, y = len)) +
  geom_point() + facet_wrap(~ supp) + theme_minimal() +
  geom_line(aes(y = fit), data = d) +
  geom_ribbon(aes(x = dose, ymin = lwr, ymax = upr, y = NULL),
    alpha = 0.25, data = d) +
  labs(x = "Dose (mg/day)", y = "Odontoblast Length")
plot(p)
```




```
d <- expand.grid(supp = c("OJ", "VC"), dose = seq(0, 2.25, length = 100))
d <- cbind(d, nlsint(m, newdata = d, interval = "prediction"))
p <- p + geom_ribbon(aes(x = dose, ymin = lwr, ymax = upr, y = NULL),
  alpha = 0.25, data = d)
plot(p)
```


OJ
VC
Odontoblast Length
20
0
−20
0.0
0.5
1.0
1.5
2.0
Dose (mg/day)