Wednesday, Feb 7

Linear Versus Nonlinear Models

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 $x_{i1}, x_{i2}, \dots, x_{ik}$ *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 and thus not a linear model.

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 = 0, beta1 = 0))
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 the starting values. For a *linear* model we (usually) do not need to provide good starting values so zeros work just fine. 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))
```

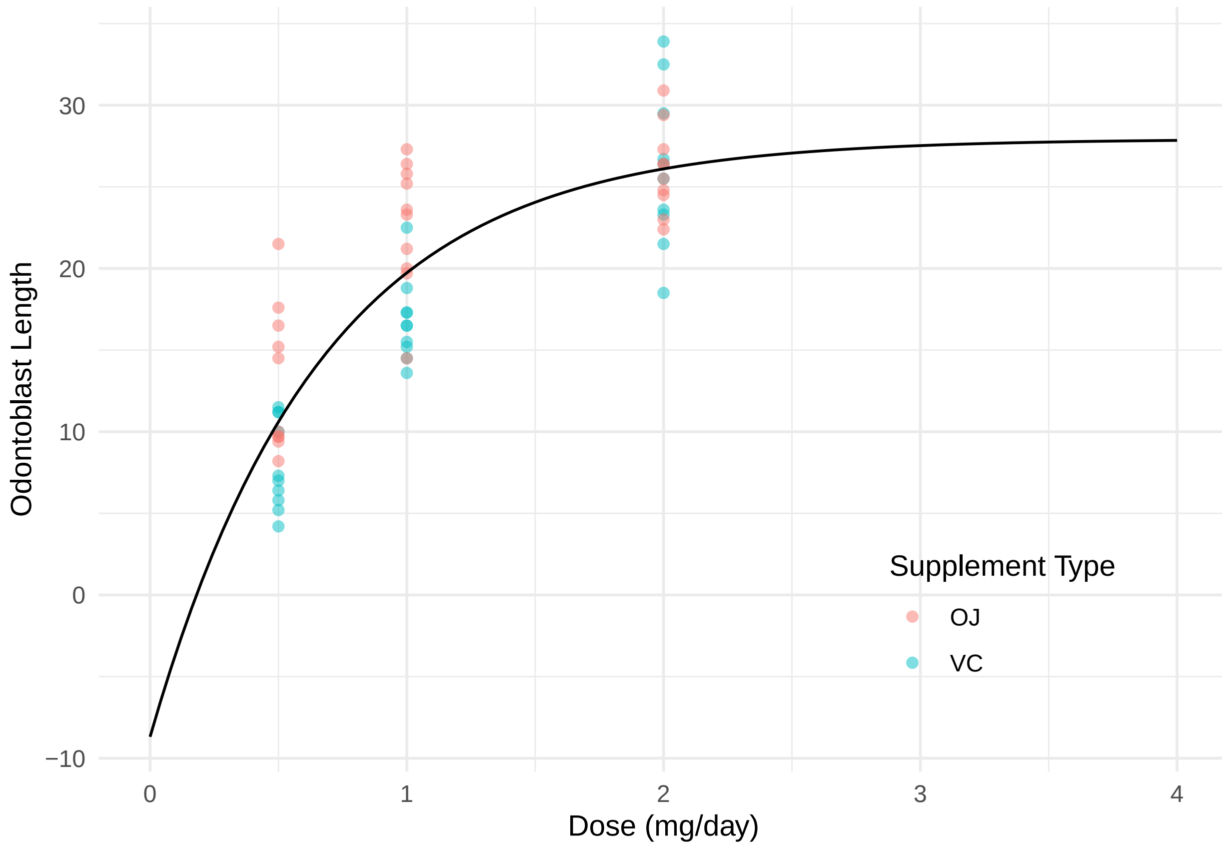
```
Error in nlsModel(formula, mf, start, wts, scaleOffset = scOff, nDcentral = nDcntr): singular gradient m
```

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)
```

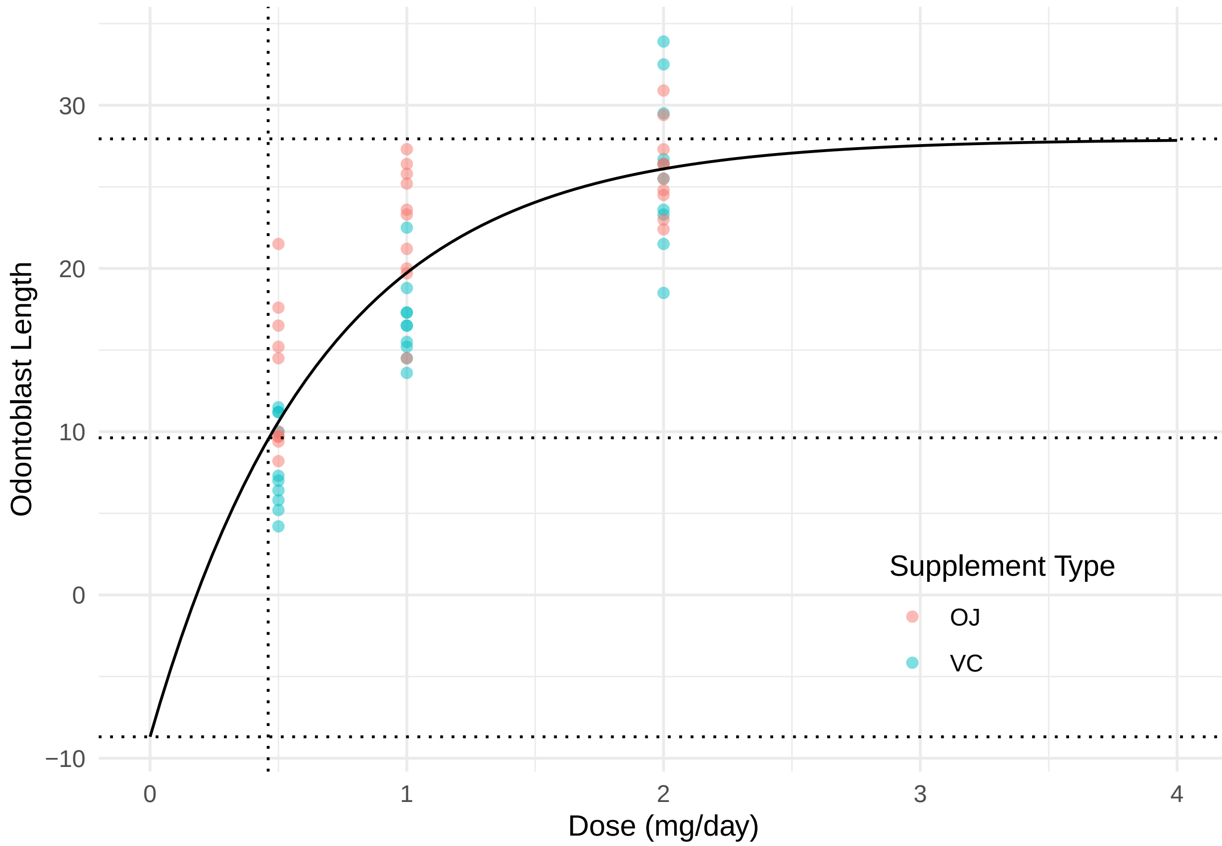


We can add some annotation if desired to highlight the interesting quantities.

```
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).

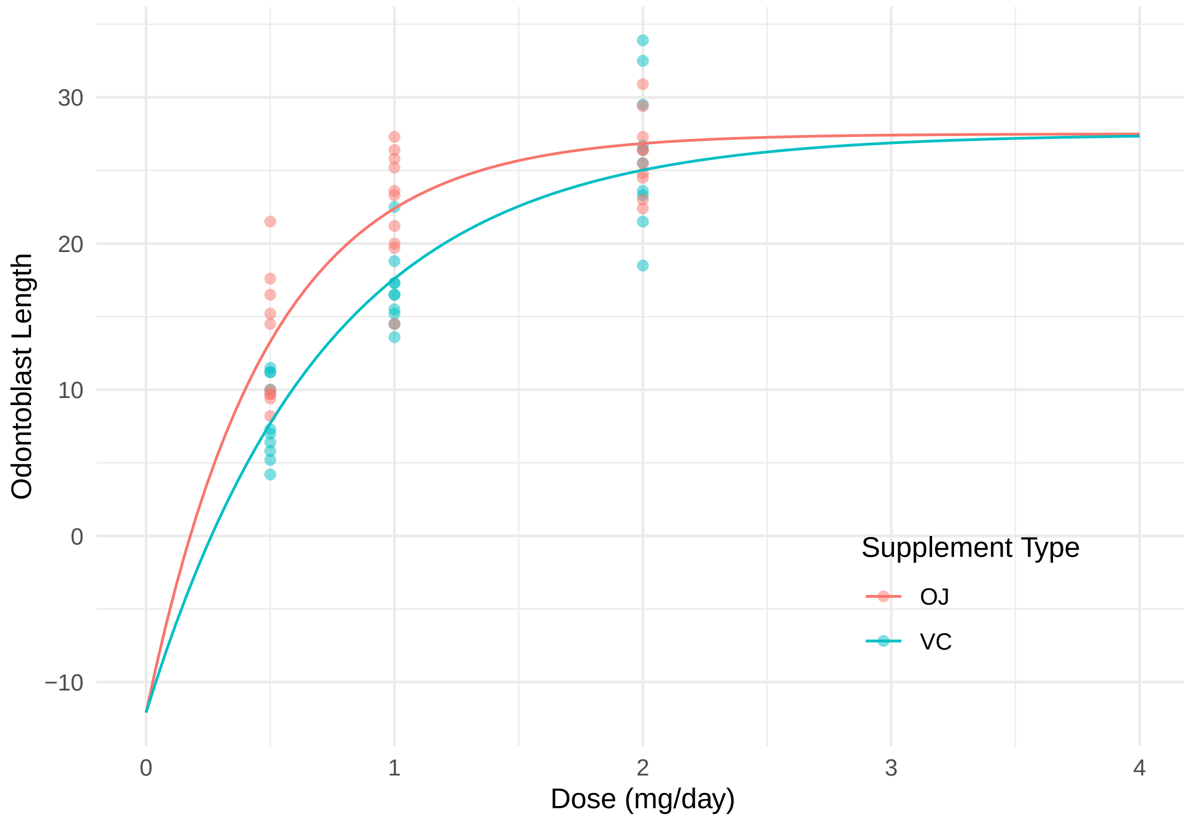
```
m <- nls(len ~ b0 + b1*2^(-dose/((supp == "OJ")*hoj + (1 - (supp == "OJ"))*hvc)),
  data = ToothGrowth, start = c(b0 = 28, b1 = -37, hoj = 0.46, hvc = 0.46))
summary(m)$coefficients
```

```
    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(
```

```r
  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* $h_{\text{VC}} - h_{\text{OJ}}$?

```r
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
```

```r
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.

```r
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 $h + \delta$.

```r
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`).

```r
confint(m)
```

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

```r
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.

```r
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).

```r
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
```

This effectively causes `lincon` to use four sets of coefficients to make inferences about each parameter: `c(1,0,0,0)`, `c(0,1,0,0)`, `c(0,0,1,0)`, and `c(0,0,0,1)`.

Estimating a Linear Model with `nls`

We can use `nls` to estimate a linear model. Consider the following linear model.

```r
m.whiteside <- lm(Gas ~ Insul + Temp + Insul:Temp, data = MASS::whiteside)
summary(m.whiteside)$coefficients
```

```
                Estimate Std. Error t value  Pr(>|t|)
(Intercept)       6.8538    0.13596  50.409 7.997e-46
InsulAfter       -2.1300    0.18009 -11.827 2.316e-16
Temp             -0.3932    0.02249 -17.487 1.976e-23
InsulAfter:Temp   0.1153    0.03211   3.591 7.307e-04
```

This can be written as

$$E(G_i) = \beta_0 + \beta_1 d_i + \beta_2 t_i + \beta_3 d_i t_i,$$

where G_i is gas consumption, t_i is temperature, and d_i is defined as

$$d_i = \begin{cases} 1, & \text{if the } i\text{-th observation is after insulation,} \\ 0, & \text{otherwise.} \end{cases}$$

Thus we can also write the model case-wise as

$$E(G_i) = \begin{cases} \beta_0 + \beta_2 t_i, & \text{if the } i\text{-th observation is before insulation,} \\ \beta_0 + \beta_1 + (\beta_2 + \beta_3) t_i, & \text{if the } i\text{-th observation is after insulation.} \end{cases}$$

Here are a few different ways to estimate this model using `nls`.

```
m1 <- nls(Gas ~ b0 + b1*(Insul == "After") + b2*Temp + b3*(Insul == "After")*Temp,
  data = MASS::whiteside, start = c(b0 = 0, b1 = 0, b2 = 0, b3 = 0))
summary(m1)$coefficients
```

```
   Estimate Std. Error t value  Pr(>|t|)
b0   6.8538    0.13596  50.409 7.997e-46
b1  -2.1300    0.18009 -11.827 2.316e-16
b2  -0.3932    0.02249 -17.487 1.976e-23
b3   0.1153    0.03211   3.591 7.307e-04
```

```
m2 <- nls(Gas ~ ifelse(Insul == "Before", b0 + b2*Temp,
  b0 + b1 + (b2 + b3)*Temp), data = MASS::whiteside,
  start = c(b0 = 0, b1 = 0, b2 = 0, b3 = 0))
summary(m2)$coefficients
```

```
   Estimate Std. Error t value  Pr(>|t|)
b0   6.8538    0.13596  50.409 7.997e-46
b1  -2.1300    0.18009 -11.827 2.316e-16
b2  -0.3932    0.02249 -17.487 1.976e-23
b3   0.1153    0.03211   3.591 7.307e-04
```

```
m3 <- nls(Gas ~ case_when(
  Insul == "Before" ~ b0 + b2*Temp,
  Insul == "After"  ~ b0 + b1 + (b2 + b3)*Temp),
  data = MASS::whiteside,
  start = c(b0 = 0, b1 = 0, b2 = 0, b3 = 0))
summary(m3)$coefficients
```

```
   Estimate Std. Error t value  Pr(>|t|)
b0   6.8538    0.13596  50.409 7.997e-46
b1  -2.1300    0.18009 -11.827 2.316e-16
b2  -0.3932    0.02249 -17.487 1.976e-23
b3   0.1153    0.03211   3.591 7.307e-04
```

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.

```r
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
```

```r
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
```

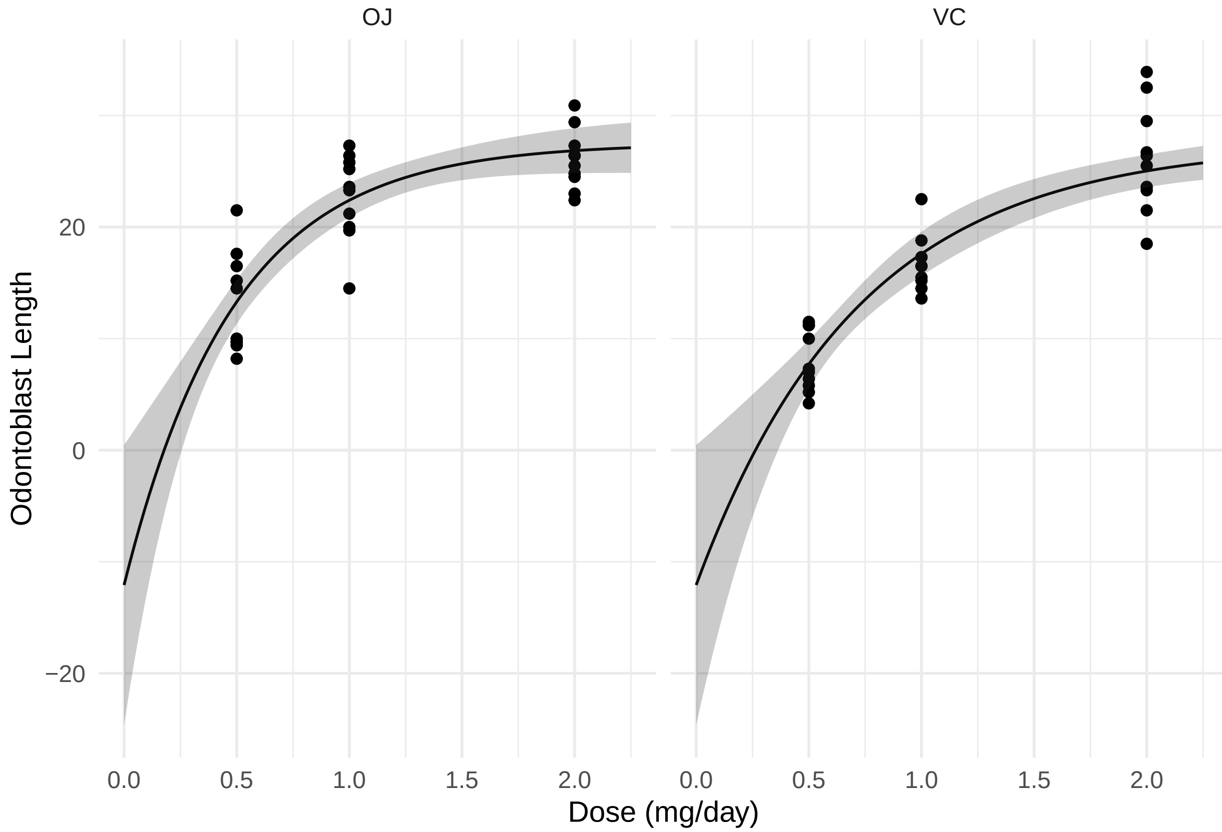
The intervals are confidence intervals by default. Prediction intervals can be obtained using `interval = prediction` (as you would with the `predict` function with a linear model).

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.

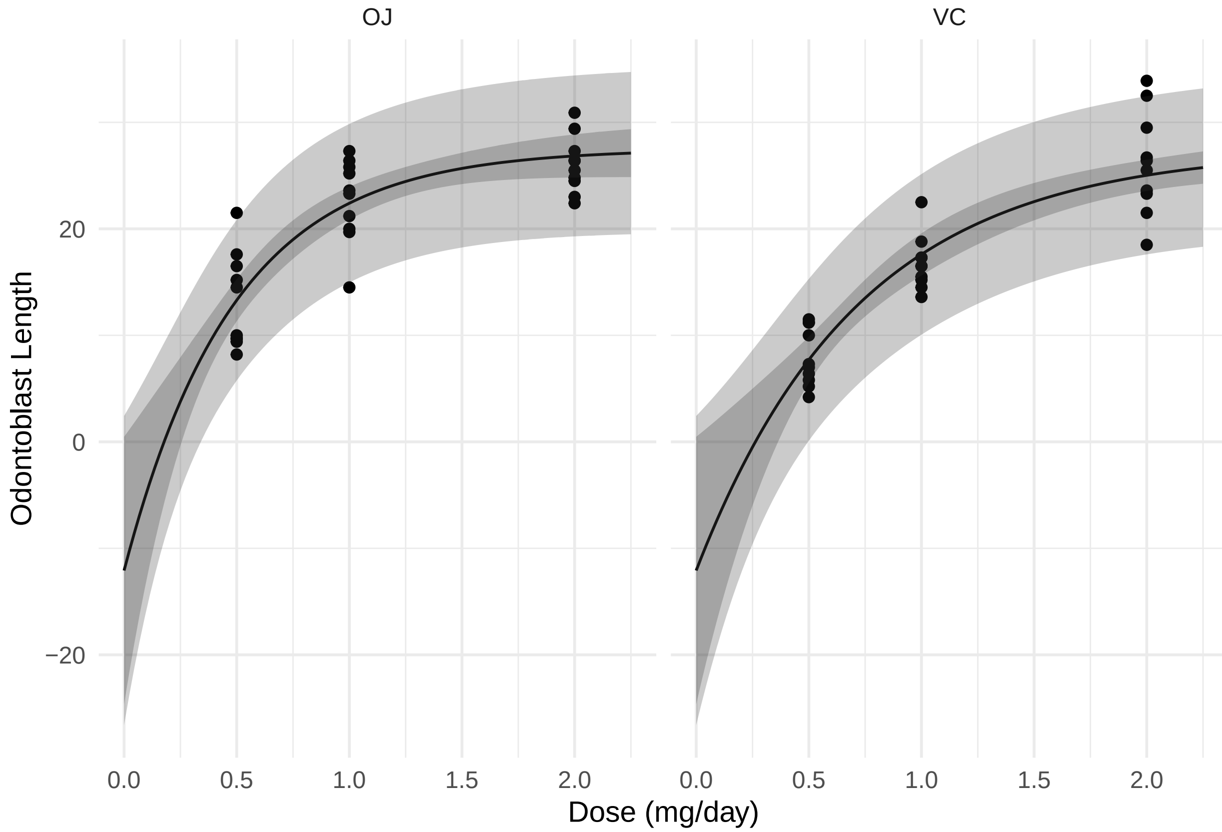
The `nlsint` function is also useful for plotting confidence and/or prediction intervals.

```r
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)