Nonlinear regression

Nonlinear regression analysis

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How can we model non-linear effects?

- Polynomials tend to be very wiggly
  (use 'i=rq' or 'i=rc' in the symbol-statement)

- Splines
  piecewise interpolations, often linear or cubic

Polynomial regression

\[ Y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \cdots + \beta_p x_i^p \]

With the new covariates

\[ Z_1 = X, Z_2 = X^2, \ldots, Z_p = X^p \]

this is just a linear multiple regression

\[ Y_i = \beta_0 + \beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_p Z_p \]

The model is linear in the parameters!
How can this work?

The covariates $Z_1, \cdots, Z_p$ are of course** correlated**, but they are not **linearly** dependent.

What do we use polynomial regression for?

- as model checking for the linear model
- as a smoothing method
- rarely as a ‘final model’ for publications

Linear splines

- Subdivide age into groups, using appropriate thresholds
- Fit linear effect of age in each age group
- Make the linear pieces ‘meet’ at the thresholds

The result is a **bent line**:

Example

Oxygen consumption (from earlier exercise)

<table>
<thead>
<tr>
<th>days</th>
<th>1</th>
<th>105</th>
<th>97</th>
<th>104</th>
<th>106</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>136</td>
<td>161</td>
<td>151</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>173</td>
<td>179</td>
<td>174</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>195</td>
<td>182</td>
<td>201</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>207</td>
<td>194</td>
<td>206</td>
<td>213</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>218</td>
<td>193</td>
<td>235</td>
<td>229</td>
<td></td>
</tr>
</tbody>
</table>

We want to give a description of the oxygen consumption (**boc**) over time (**days**)

The above plot shows that **boc** as a function of **days** is certainly **not linear**.
The biologists claim that the relation between \textit{boc} and \textit{days} can be described by a relation of the form

\[ \text{boc} = \gamma \exp(-\beta/\text{days}) \]

This relation is obviously nonlinear, but may be transformed to linearity using the (natural) logarithm:

\[ \log(\text{boc}) = \log(\gamma) - \beta/\text{days} \]

With

\[ y = \log\text{boc} = \log(\text{boc}) \]
\[ x = \text{invdays} = 1/\text{days} \]
\[ \alpha = \log(\gamma) \]

we may write this equation as

\[ y = \alpha - \beta x \]

i.e., a \textit{linear relation}, just with a minus sign on the slope.

A scatter plot of these new variables

![Scatter plot](image)

The linear regression model gives us the estimates:

- intercept: \( \hat{\alpha} = \log(\hat{\gamma}) = 5.431(0.019) \)
- slope: \( \hat{\beta} = -0.808(0.039) \)

Noting that \( \text{boc}(\infty) = \gamma = \exp(\alpha) \), we find the estimate of \( \text{boc}(\infty) \) to be

\[ \exp(5.431) = 228.38 \]

with the 95% confidence interval

\[ (\exp(5.392), \exp(5.471)) = (219.6, 237.7) \]

This plot seems reasonably linear. We get

\[ \log\text{boc} = 5.431 - 0.808 \times \text{invdays} \]
Residual plot and fitted curve

Why use non-linear regression?

- Transformation is necessary to obtain variance homogeneity, but transformation destroys linearity.
- Linearity does not fit, and the transformation seems to destroy other parts of the model assumptions, e.g. the assumption of variance homogeneity.
- Theoretical knowledge (e.g. from kinetics or physiology) indicates that the proper relation is intrinsically non-linear.
- Interest is in functions of the parameters that do not enter linearly in the model (e.g. kinetic rate constants or ED$_{50}$ in dose-response studies)

Example

Quantification of the Reticuloendothelial cell system (RES) of the liver:

Concentration measurements $y_i$ over the liver, following a bolus injection of radioactive tracer

First order kinetics implies

$$c(t) = \beta (1 - e^{-\gamma t})$$

No transformation to linearity possible!

$$y_i = \beta (1 - e^{-\gamma t_i}) + \varepsilon_i, \quad \varepsilon_i \sim N(0, \sigma^2)$$
Least squares method

Minimize the sums of squares

\[ SS(\beta, \gamma) = \sum (y_i - \beta (1 - e^{-\gamma t_i}))^2 = \sum \varepsilon_i^2 \]

This requires an iterative procedure

Example: RES in the liver

Residual sum of squares, SS, as a function of only one parameter (hypothetical)

In case of linear regression:

We have to determine the minimum

Starting values:
- \( c(\infty) = \beta \approx 2000 \)
- \( \frac{dc}{dt}(0) = \beta \gamma \approx 100 \)
Residual sum of squares, SS, as a function of two parameters (hypothetical)

There may be problems with convergence of the iteration procedure and the solution may be a local minimum.

SAS program

```sas
data reticulo;
infile 'kw_res.txt';
input tid conc;
run;
proc nlin data=reticulo;
parms beta=2000
gamma=0.05;
model conc=beta*(1-exp(-gamma*tid));
run;
```

Output

<table>
<thead>
<tr>
<th>Iter</th>
<th>beta</th>
<th>gamma</th>
<th>Sum of Squares</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2000.0</td>
<td>0.0500</td>
<td>4370990</td>
</tr>
<tr>
<td>1</td>
<td>1958.6</td>
<td>0.0824</td>
<td>382995</td>
</tr>
<tr>
<td>2</td>
<td>2159.2</td>
<td>0.0769</td>
<td>26355.0</td>
</tr>
<tr>
<td>3</td>
<td>2174.2</td>
<td>0.0772</td>
<td>25286.7</td>
</tr>
<tr>
<td>4</td>
<td>2174.0</td>
<td>0.0773</td>
<td>25286.7</td>
</tr>
<tr>
<td>5</td>
<td>2174.0</td>
<td>0.0773</td>
<td>25286.7</td>
</tr>
</tbody>
</table>

NOTES: Convergence criterion met.

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>F Value</th>
<th>Pr &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>2</td>
<td>63048136</td>
<td>31524068</td>
<td>29920.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Residual</td>
<td>24</td>
<td>25286.7</td>
<td>1053.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected Total</td>
<td>26</td>
<td>63073423</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>25</td>
<td>3455129</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example

The fit becomes:

\[
\hat{\beta} = 2174.0 \pm 28.3, \text{ CI}=(2115.5, 2232.5) \\
\hat{\gamma} = 0.0773 \pm 0.0023, \text{ CI}=(0.0726, 0.0819)
\]
Residuals

Residual pattern shows **systematic behaviour**:

so the model does not fit particularly well

Asymptotic normality of parameter estimates

- The distribution of the estimates is in general unknown, we only have *approximate* normality
- The approximations may be *very poor* for small samples

Confidence regions:
- Asymptotically (i.e. for large sample sizes), the estimates are normally distributed
- The confidence areas will therefore be approximately elliptic
- For small sample sizes, this can become *extremely* misleading!

Alternative procedure

Determine confidence regions directly from the sum of squares $SS$, i.e. as those values of the parameter, which makes $SS$ sufficiently small.

Determining the cutoff

What is “sufficiently small” $SS$ to obtain a 95% confidence region?
Or: How do we determine the coverage probability for a given confidence region?

This is rather technical...

Good approximation to a $(1-\alpha)$-sized region:

$$\{\theta | SS(\theta) \leq SS(\hat{\theta})(1 + \frac{p}{n-p}F_{\alpha}(p, n-p))\}$$
For **linear** regression, the situation is:

and confidence intervals become **symmetric/elliptic**

Same model as before: 

\[ c(t) = \beta (1 - e^{-\gamma t}) \]

Simulated data, \((\beta = 1, \gamma = 1, \sigma = 0.05):\)

The design is not adequate, we only see the linear part of the concentration curve!
If we spread out the x’s:

Enlarged picture, with superimposed normal approximation:

‘Optimal’ design (in terms of a normal confidence region):

Effect of parametrization:

\[ y_i = \beta (1 - e^{-\gamma t_i}) + \varepsilon_i \]

Reparametrization:

\[ \alpha = \beta \gamma \]

\[ y_i = \frac{\alpha}{\gamma} (1 - e^{-\gamma t_i}) + \varepsilon_i \]
Parameters $\beta$ and $\gamma$:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Approx. 95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta</td>
<td>1.0559</td>
<td>0.2407</td>
<td>0.3875 - 1.7244</td>
</tr>
<tr>
<td>gamma</td>
<td>1.0376</td>
<td>0.5202</td>
<td>-0.4067 - 2.4818</td>
</tr>
</tbody>
</table>

Approximate Correlation Matrix

<table>
<thead>
<tr>
<th></th>
<th>beta</th>
<th>gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta</td>
<td>1.0000</td>
<td>-0.9592</td>
</tr>
<tr>
<td>gamma</td>
<td>-0.9592</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Parameters $\alpha$ and $\gamma$:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Approx. 95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfa</td>
<td>1.0956</td>
<td>0.3176</td>
<td>0.2138 - 1.9774</td>
</tr>
<tr>
<td>gamma</td>
<td>1.0376</td>
<td>0.5202</td>
<td>-0.4067 - 2.4818</td>
</tr>
</tbody>
</table>

Approximate Correlation Matrix

<table>
<thead>
<tr>
<th></th>
<th>alfa</th>
<th>gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfa</td>
<td>1.0000</td>
<td>0.9749</td>
</tr>
<tr>
<td>gamma</td>
<td>0.9749</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Compartment models

Differential equations ⇒ multi-exponential curves

Often only measurements from a single compartment!

Identification problems

There may be problems with the identification of parameters, even with good quality data.

This will give rise to very unprecise and extremely correlated estimates.

Compartment models yield solutions as a sum of exponential curves:

\[ f(t) = \alpha_1 \exp(-\lambda_1 t) + \alpha_2 \exp(-\lambda_2 t) \]

<table>
<thead>
<tr>
<th></th>
<th>( \alpha_1 )</th>
<th>( \lambda_1 )</th>
<th>( \alpha_2 )</th>
<th>( \lambda_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>( \frac{1}{2} )</td>
<td>11</td>
<td>( \frac{1}{7} )</td>
</tr>
<tr>
<td>2</td>
<td>11.78</td>
<td>( \frac{1}{3.1} )</td>
<td>6.06</td>
<td>( \frac{1}{9.4} )</td>
</tr>
</tbody>
</table>

Rule of thumb:
There must be a ratio of at least 5 in \( \frac{\lambda_1}{\lambda_2} \)

Example: Dose-effect

Effect of isoprenalin on heart rate

- E: Increase in heart rate
- D: Dose of isoprenalin

Michaelis-Menten relation:

\[ E = \frac{E_{\text{max}} D}{k_d + D} \]

\[ 0 \quad 1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \]

\[ 0 \quad 10 \quad 20 \quad 30 \quad 40 \quad 50 \quad 60 \]

Figure 3.4: Progress of an oral drug.
Linearization (Lineweaver-Burk)

\[
\frac{1}{E} = \frac{k_d + D}{E_{\text{max}}D} = \frac{1}{E_{\text{max}}} + \frac{k_d}{E_{\text{max}}} \frac{1}{D}
\]

Linear relation between the inverses:

\[
\frac{1}{E} = \alpha + \beta \frac{1}{D}
\]

with the reparametrisation:

\[
\alpha = \frac{1}{E_{\text{max}}} \quad \beta = \frac{k_d}{E_{\text{max}}}
\]

\[
E_{\text{max}} = \frac{1}{\alpha} \quad k_d = \beta / \alpha
\]

Ex. Isoprenalin:

\[\alpha: 0.0165 \quad (0.0004), \quad \beta: 0.0202 \quad (0.0004)\]

\[E_{\text{max}}: \quad \frac{1}{0.0165} = 60.6 \quad (57.8, 63.7)\]

\[k_d: \quad \frac{0.0202}{0.0165} = 1.22\]

Lineweaver-Burk plot

The model fits nicely

Estimates, isoprenalin

<table>
<thead>
<tr>
<th></th>
<th>(E_{\text{max}})</th>
<th>(k_d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/E linear</td>
<td>60.6</td>
<td>1.22</td>
</tr>
<tr>
<td>E, non-linear</td>
<td>62.67 (2.12)</td>
<td>1.33 (0.14)</td>
</tr>
<tr>
<td>log(E), non-linear</td>
<td>61.59 (1.82)</td>
<td>1.26 (0.08)</td>
</tr>
</tbody>
</table>
Isoprenalin following metropolol:

<table>
<thead>
<tr>
<th></th>
<th>$E_{\text{max}}$</th>
<th>$k_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/E linear</td>
<td>-228.2</td>
<td>-45.62</td>
</tr>
<tr>
<td>E, non-linear</td>
<td>56.97 (3.47)</td>
<td>5.46 (0.85)</td>
</tr>
<tr>
<td>log(E), non-linear</td>
<td>80.73 (30.93)</td>
<td>11.71 (6.09)</td>
</tr>
</tbody>
</table>

What is the difference between the two fits?

- It is not just a reparametrisation!
- We change the outcome from $E$ to $\frac{1}{E}$
- If we have constant variance on the $E$ scale, the variance on the $\frac{1}{E}$ scale will be proportional to $\frac{1}{E^2}$
- The assumption of constant variance on the $\frac{1}{E}$ scale corresponds to an assumption that the variance on the $E$ scale is proportional to $E^4$, i.e. an SD proportional to $E^2$ – which more or less corresponds to disregarding the observations with large outcomes!
If the smallest concentration is omitted:

<table>
<thead>
<tr>
<th></th>
<th>$E_{\text{max}}$</th>
<th>$k_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/E linear</td>
<td>65.19</td>
<td>7.14</td>
</tr>
<tr>
<td>E, non-linear</td>
<td>56.31 (3.04)</td>
<td>5.25 (0.74)</td>
</tr>
<tr>
<td>log(E), non-linear</td>
<td>59.49 (5.36)</td>
<td>6.06 (1.011)</td>
</tr>
</tbody>
</table>

Why non-linear regression?

- Transformation is necessary to obtain variance homogeneity, but transformation destroys linearity.
- Linearity does not fit, and the transformation seems to destroy other parts of the model assumptions, e.g. the assumption of variance homogeneity.
- Theoretical knowledge (e.g. from kinetics or physiology) indicates that the proper relation is intrinsically non-linear.
- Interest is focused on functions of the parameters, that do not enter linearly in the model (e.g. kinetic rate constants or ED$_{50}$ in dose-response studies).

Example of a typical dose-response relation, for moderate doses

We *almost* have linearity in this dose range:
For extreme doses we see a clear deviation from linearity and smaller variation in the ends.

Y axis: Probit- or logit- transformed outcome
X axis: Logarithmic transformed dose

We get a reasonable linearity on these scales.

Theoretical dose response relation:

Example from anaesthesia:

47 patients to be operated with two different anesthetics

- Halothane
- Neurolept

Y: Twitch response at the ulnar nerve (at the thumb), in %
X: Dose of muscle relaxantia

<table>
<thead>
<tr>
<th>group=halothane</th>
<th>patient</th>
<th>dose</th>
<th>response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.2</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.8</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22.2</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>34.9</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>35.9</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>35.4</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>group=neurolept</th>
<th>patient</th>
<th>dose</th>
<th>response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.9</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25.0</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24.6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>.</td>
<td>.</td>
<td>.</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>37.1</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>37.7</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>37.1</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>
Transformation to linearity

Using two different transformations:

\[ y : \text{logit}_{\text{twitch}} = \log \left( \frac{\text{twitch}}{100 - \text{twitch}} \right) \]

or

\[ y : \text{probit}_{\text{twitch}} = \text{probit} \left( \frac{\text{twitch}}{100} \right) = \Phi^{-1} \left( \frac{\text{twitch}}{100} \right) \]

\[ x : \text{logdose} = \log(\text{dose}) \]

**Linear relation:**

\[ \text{logit}_{\text{twitch}} = \alpha + \beta \text{logdose} \]

produces estimates of \( \alpha \) and \( \beta \), with corresponding standard errors (s.e.)

We get estimates of \( \alpha \) and \( \beta \) from the equation

\[ \text{logit}_{\text{twitch}} = \alpha + \beta \text{logdose} \]

**But:** What about the parameters of interest, i.e. \( \text{ED}_{50} \) and \( \text{ED}_{90} \)?

\[ \hat{\text{ED}}_{50} = \exp \left( \frac{-\hat{\alpha}}{\hat{\beta}} \right) \]

How do we calculate s.e.\((\hat{\text{ED}}_{50})\) ?

**Reparameterization:**

\[ \gamma_1 = \log(\text{ED}_{50}) \]
\[ \gamma_2 = \log(\text{ED}_{90}) \]
The model may then be written as:

\[ y = \text{logit}_{\text{twitch}} = \text{logit}(0.9) \times \frac{x - \gamma_1}{\gamma_2 - \gamma_1} = 2.197 \times \frac{x - \gamma_1}{\gamma_2 - \gamma_1} \]

or, using the \text{probit}-transformation:

\[ \text{probit}_{\text{twitch}} = \text{Probit}(0.9) \times \frac{x - \gamma_1}{\gamma_2 - \gamma_1} = 1.282 \times \frac{x - \gamma_1}{\gamma_2 - \gamma_1} \]

These functions are \text{nonlinear} in \( \gamma_1 \) and \( \gamma_2 \)!

Direct estimation of \( \gamma_1 \) and \( \gamma_2 \) using \text{non-linear regression}

Estimation

```
data twitch2;
set twitch;
logdose=log(dose);
logit_twitch=log(response/(100-response));
probit_twitch=probit(response/100);
run;
```

```
proc nlin data=twitch2; by group;
parms loged50=3.2
loged90=3.6;
model logit_twitch=probit(0.9)*(logdose-loged50)/(loged90-loged50);
run;
```

Halothane, output from logit analysis:

```
Halothane, output from logit analysis:
group=halotan
The NLIN Procedure
Dependent Variable logit_twitch

Source DF Sum of Squares Mean Square F Value Pr > F
Model 1 27.6468 27.6468 15.80 0.0016
Error 13 22.7511 1.7501
Corrected Total 14 50.3980

Approx Parameter Estimate Std Error Approx. 95\% Confidence Limits
loged50 3.2450 0.0551 3.1259 3.3641
loged90 3.5755 0.0814 3.4996 3.7513
```

Halothane, output from probit analysis:

```
Halothane, output from probit analysis:
group=halotan
The NLIN Procedure
Dependent Variable probit_twitch

Source DF Sum of Squares Mean Square F Value Pr > F
Model 1 8.3329 8.3329 14.49 0.0022
Error 13 7.4776 0.5752
Corrected Total 14 15.8105

Approx Parameter Estimate Std Error Approx. 95\% Confidence Limits
loged50 3.2473 0.0574 3.1234 3.3712
loged90 3.5984 0.0897 3.4045 3.7923
```
Halothane – results

from probit analysis:

**Estimate** of log(ED\(_{50}\)): 3.247 (0.0574)

with **confidence interval**:

\[
3.247 \pm 2.16 \times 0.0574 = 3.247 \pm 0.124 = (3.123, 3.371)
\]

**Transformed back** to the original scale:

**Estimate** of ED\(_{50}\): \(\exp(3.247) = 25.7\)

with confidence interval:

\((\exp(3.125), \exp(3.371)) = (22.7, 29.1)\)

Similarly for ED\(_{90}\):

log(ED\(_{90}\)): 3.598 (0.090)  
ED\(_{90}\): \(\exp(3.598) = 36.5\)

with confidence interval (30.5, 43.7)

The confidence interval for ED\(_{50}\) is not symmetric around 25.7!!

A more complicated nonlinear model

Ethanol elimination: Infusion until time \(t_0\):
Theoretical compartment model

- Blood compartment: $V_B, c_B$
- Peripheral compartment: $V_E, c_E$
- 1st order kinetics for interchange between compartments $k$
- 0th order elimination from blood: $v_{max}$

Letting $T = \frac{V_E^2}{k(V_B+V_E)^2}$ and $\lambda = k(\frac{1}{V_B} + \frac{1}{V_E})$, we find that until $t_0$:

$$c_B = (I_0 - v_{max})(T(1 - \exp(-\lambda t)) + \frac{t}{V_B + V_E})$$

After $t_0$:

$$c_B = (I_0 - v_{max})(T(1 - \exp(-\lambda t)) + \frac{t}{V_B + V_E}) - I_0(T(1 - \exp(-\lambda(t-t_0))) + \frac{(t-t_0)}{V_B + V_E})$$

---

```plaintext
proc nlin; by patient;
parms ve=18
vb=6.2
k=0.6
vmax=2;
v=ve+vb;
t=ve**2/(k*v**2);
lam=k*(1/vb+1/ve);
b1=I0-vmax;
if del=1 then do;
  model etanol=b1*(t*(1-exp(-lam*tid))+tid/v);
end;
if del=2 then do;
  model etanol=b1*(t*(1-exp(-lam*tid))+tid/v)
  -I0*(t*(1-exp(-lam*(tid-t0)))+(tid-t0)/v);
end;
output out=ny p=yhat r=resid;
run;
```

**Patient 9**

The NLIN Procedure
Dependent Variable etanol
Method: Gauss-Newton

<table>
<thead>
<tr>
<th>Iter</th>
<th>ve</th>
<th>vb</th>
<th>k</th>
<th>vmax</th>
<th>Sum of Squares</th>
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</table>

NOTE: Convergence criterion met.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Std Error</th>
<th>Approximate 95% Confidence Limits</th>
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<tbody>
<tr>
<td>ve</td>
<td>22.4881</td>
<td>0.5138</td>
<td>21.4402 to 23.5360</td>
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<tr>
<td>vb</td>
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<td>8.6175 to 11.0106</td>
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<td>k</td>
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<td>0.9830 to 1.2499</td>
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<td>vmax</td>
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<td>0.0163</td>
<td>2.1085 to 2.1750</td>
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</tbody>
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