Appendix C

A Collection of Self-Starting Nonlinear Regression Models

We have mentioned several self-starting nonlinear regression models in the text. In this appendix we describe each of the self-starting models included with the nlme library. For each model we give the model formula, a description of the parameters, and the strategy used to obtain starting estimates.

C.1 SSasymp—The Asymptotic Regression Model

The asymptotic regression model is used to model a response y that approaches a horizontal asymptote as $x \to \infty$. We write it as

$$y(x) = \phi_1 + (\phi_2 - \phi_1) \exp[-\exp(\phi_3) x], \tag{C.1}$$

so that ϕ_1 is the asymptote as $x \to \infty$ and ϕ_2 is $y(0)$. These parameters are shown in Figure C.1. The parameter ϕ_3 is the logarithm of the rate constant. We use the logarithm to enforce positivity of the rate constant so the model does approach an asymptote. The corresponding half-life $t_{0.5} = \log 2/\exp(\phi_3)$ is illustrated in Figure C.1.

C.1.1 *Starting Estimates for* SSasymp

Starting values for the asymptotic regression model are obtained by:

1. Using `NLSstRtAsymptote` to get an estimate $\phi_1^{(0)}$ of the asymptote.
2. Regressing $\log(|y - \phi_1^{(0)}|)$ on t. The estimated slope is $-\exp(\phi_3^{(0)})$.

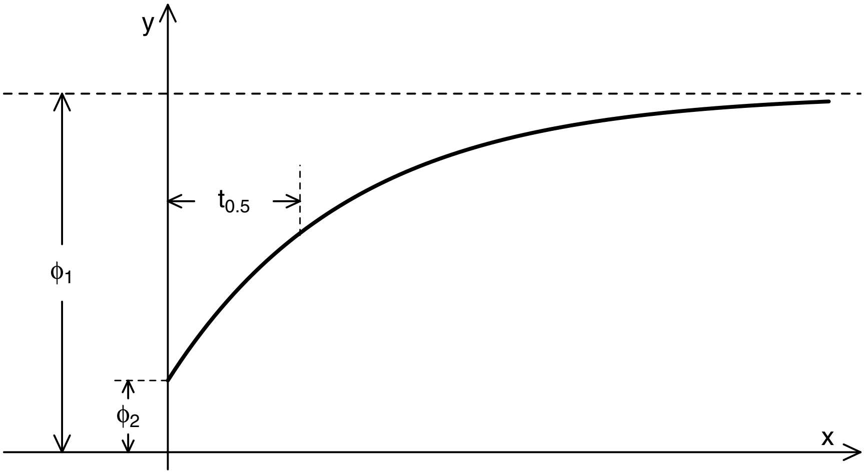

FIGURE C.1. The asymptotic regression model showing the parameters ϕ_1, the asymptotic response as $x \to \infty$, ϕ_2, the response at $x = 0$, and $t_{0.5}$, the half-life.

3. Using an algorithm for partially linear models (Bates and Chambers, 1992, §10.2.5) to refine estimates of ϕ_1, ϕ_2, and ϕ_3 in

$$y(x) = \phi_1 + (\phi_2 - \phi_1)\exp[\exp(\phi_3)x].$$

   Because ϕ_1 and ϕ_2 occur linearly in the model expression, the least squares fit iterates over a single parameter.

These estimates are the final nonlinear regression estimates.

C.2 `SSasympOff`—Asymptotic Regression with an Offset

This is an alternative form of the asymptotic regression model that provides a more stable parameterization for the `CO2` data. It is written

$$y(x) = \phi_1\{1 - \exp[-\exp(\phi_2) \times (x - \phi_3)]\}. \qquad \text{(C.2)}$$

As in `SSasymp`, ϕ_1 is the asymptote as $x \to \infty$. In this formulation ϕ_2 is the logarithm of the rate constant, corresponding to a half-life of $t_{0.5} = \log 2/\exp(\phi_2)$, and ϕ_3 is the value of x at which $y = 0$. The parameters ϕ_1, $t_{0.5}$, and ϕ_3 are shown in Figure C.2.

C.2.1 Starting Estimates for `SSasympOff`

First we fit `SSasymp` then we transform the parameters to the formulation used in `SSasympOff`. If *omega* is the vector of parameters from `SSasymp` and

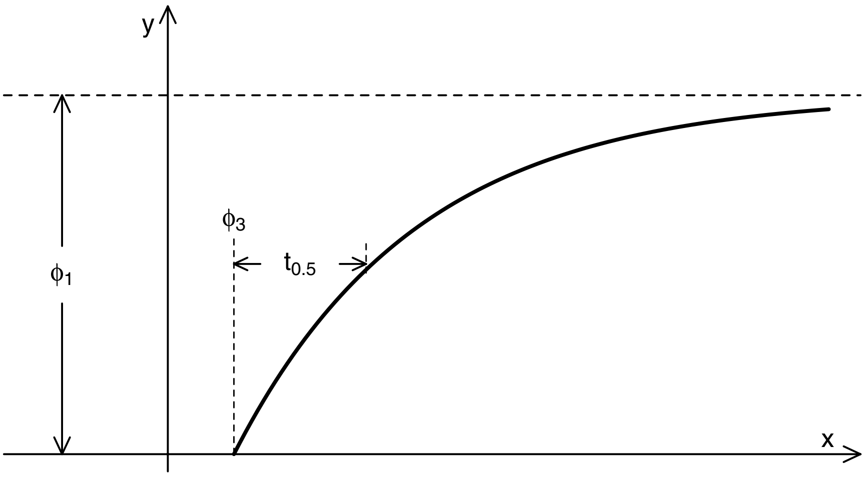

FIGURE C.2. The asymptotic regression model with an offset showing the parameters ϕ_1, the asymptote as $x \to \infty$, $t_{0.5}$, the half-life, and ϕ_3, the value of x for which $y = 0$.

$\boldsymbol{\phi}$ is the vector of parameters for `SSasympOff`, the correspondence is

$$\begin{aligned}\phi_1 &= \omega_1,\\ \phi_2 &= \omega_3,\\ \phi_3 &= \exp(-\omega_3)\log[-(\omega_2 - \omega_1)/\omega_1].\end{aligned}$$

These estimates are the final nonlinear regression estimates.

C.3 `SSasympOrig`—Asymptotic Regression Through the Origin

This form of the asymptotic regression model is constrained to pass through the origin. It is called the BOD model in Bates and Watts (1988) where it is used to model Biochemical Oxygen Demand curves. The model is written

$$y(x) = \phi_1[1 - \exp(-\exp(\phi_2)x]. \tag{C.3}$$

As in `SSasympOff`, ϕ_1 is the asymptote as $x \to \infty$ and ϕ_2 is the logarithm of the rate constant, corresponding to a half-life of $t_{0.5} = \log 2/\exp(\phi_2)$. The parameters ϕ_1 and $t_{0.5}$ are shown in Figure C.3.

C.3.1 Starting Estimates for `SSasympOrig`

Starting values for this regression model are obtained by:

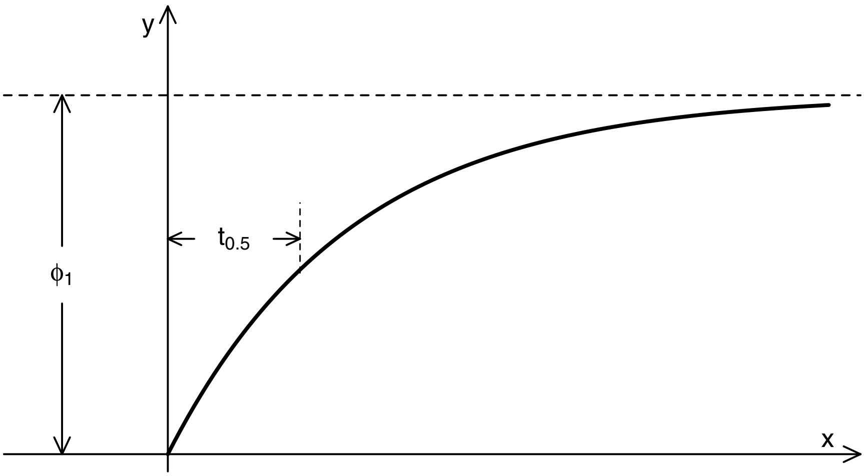

FIGURE C.3. The asymptotic regression model through the origin showing the parameters ϕ_1, the asymptote as $x \to \infty$ and $t_{0.5}$, the half-life.

1. Using `NLSstRtAsymptote` to get an estimate $\phi_1^{(0)}$ of the asymptote.
2. Obtaining an initial estimate of ϕ_2 as

$$\phi_2^{(0)} = \log \text{abs} \sum_{i=1}^{n} \left[\log(1 - y_i/\phi_1^{(0)})/x_i \right] /n.$$

3. Using an algorithm for partially linear models to refine the estimates of ϕ_1 and ϕ_2. Because ϕ_1 occurs linearly in the model expression, the least squares fit iterates over a single parameter.

These estimates are the final nonlinear regression estimates.

C.4 `SSbiexp`—Biexponential Model

The biexponential model is a linear combination of two negative exponential terms

$$y(x) = \phi_1 \exp\left[-\exp(\phi_2)x\right] + \phi_3 \exp\left[-\exp(\phi_4)x\right]. \tag{C.4}$$

The parameters ϕ_1 and ϕ_3 are the coefficients of the linear combination, and the parameters ϕ_2 and ϕ_4 are the logarithms of the rate constants. The two sets of parameters (ϕ_1, ϕ_2) and (ϕ_3, ϕ_4) are *exchangeable*, meaning that the values of the pairs can be exchanged without changing the value of $y(x)$. We create an identifiable parameterization by requiring that $\phi_2 > \phi_4$.

A representative biexponential model, along with its constituent exponential curves, is shown in Figure C.4.

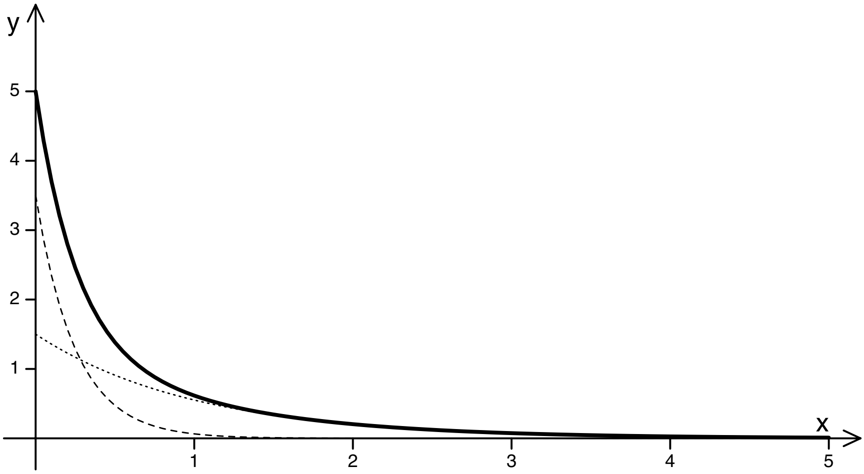

FIGURE C.4. A biexponential model showing the linear combination of the exponentials (solid line) and its constituent exponential curves (dashed line and dotted line). The dashed line is $3.5\exp(-4x)$ and the dotted line is $1.5\exp(-x)$.

C.4.1 Starting Estimates for `SSbiexp`

The starting estimates for the biexponential model are determined by *curve peeling*, which involves:

1. Choosing half the data with the largest x values and fitting the simple linear regression model
$$\log\operatorname{abs}(y) = a + bx.$$
2. Setting $\phi_3^{(0)} = \exp a$ and $\phi_4^{(0)} = \log\operatorname{abs}(b)$ and calculating the residuals $r_i = y_i - \phi_3^{(0)}\exp[-\exp(\phi_4^{(0)})x_i]$ for the half of the data with the smallest x values. Fit the simple linear regression model
$$\log\operatorname{abs}(r) = a + bx.$$
3. Setting $\phi_2^{(0)} = \log\operatorname{abs}(b)$ and using an algorithm for partially linear models to refine the estimates of ϕ_1, ϕ_2, ϕ_3, and ϕ_4. Because the model is linear in ϕ_1 and ϕ_3, the only starting estimates used in this step are those for ϕ_2 and ϕ_4 and the iterations are with respect to these two parameters.

The estimates obtained this way are the final nonlinear regression estimates.

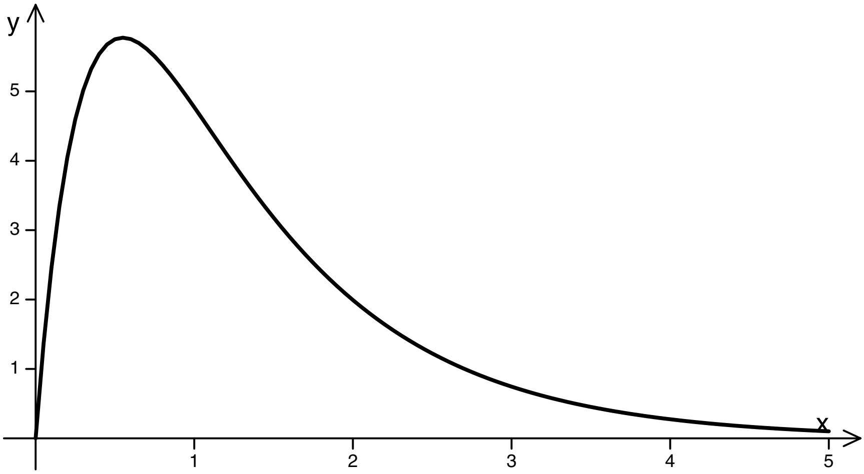

FIGURE C.5. A sample response curve from a first-order open-compartment model. The parameters correspond to an elimination rate constant of 1, an absorption rate constant of 3, and a clearance of 0.1. The dose is 1.

C.5 `SSfol`—First-Order Compartment Model

This model is derived from a compartment model in pharmacokinetics describing the concentration of a drug in the serum following a single oral dose. The model is based on first-order kinetics for the absorption of the drug from the digestive system and for the elimination of the drug from the circulatory system. Because the drug is eliminated from the circulatory system, the system of compartments is called an open system, and the model is a first-order open compartment model. It is written

$$y(x) = \frac{D\exp(\phi_1)\exp(\phi_2)}{\exp(\phi_3)\left[\exp(\phi_2)-\exp(\phi_1)\right]}\left\{\exp\left[-\exp(\phi_1)x\right]-\exp\left[-\exp(\phi_2)x\right]\right\}, \tag{C.5}$$

where D is the dose, ϕ_1 is the logarithm of the elimination rate constant, ϕ_2 is the logarithm of the absorption rate constant, and ϕ_3 is the logarithm of the clearance.

A sample response curve from a first-order open compartment model is shown in Figure C.5

C.5.1 *Starting Estimates for `SSfol`*

The starting estimates for the `SSfol` model are also determined by curve peeling. The steps are:

1. Determine the position of the maximum response. Fit the simple linear regression model

$$\log(y) = a + bx$$

to the data with x values greater than or equal to the position of the maximum response. Set $\phi_1^{(0)} = \log \text{abs}(b)$ and $\phi_2^{(0)} = \phi_1^{(0)} + 1$.

2. Use an algorithm for partially linear models to fit the nonlinear regression model

$$y(x) = k\{\exp[-\exp(\phi_1)x] - \exp[-\exp(\phi_2)x]\}$$

refining the estimates of ϕ_1 and ϕ_2.

3. Use the current estimates of ϕ_1 and ϕ_2 and an algorithm for partially linear models to fit

$$y(x) = kD\frac{\exp[-\exp(\phi_1)x] - \exp[\exp(\phi_2)x)]}{\exp(\phi_1) - \exp(\phi_2)}.$$

Set $\phi_3 = \phi_1 + \phi_2 - \log k$.

These estimates are the final nonlinear regression estimates.

C.6 `SSfpl`—Four-Parameter Logistic Model

The four-parameter logistic model relates a response y to an input x via a sigmoidal or "S-shaped" function. We write it as

$$y(x) = \phi_1 + \frac{\phi_2 - \phi_1}{1 + \exp\left[\left(\phi_3 - x\right)/\phi_4\right]}. \tag{C.6}$$

We require that $\phi_4 > 0$ so the parameters are:

- ϕ_1 the horizontal asymptote as $x \to \infty$
- ϕ_2 the horizontal asymptote as $x \to -\infty$
- ϕ_3 the x value at the inflection point. At this value of x the response is midway between the asymptotes.
- ϕ_4 a scale parameter on the x-axis. When $x = \phi_3 + \phi_4$ the response is $\phi_1 + (\phi_2 - \phi_1)/(1 + e^{-1})$ or roughly three-quarters of the distance from ϕ_1 to ϕ_2.

These parameters are shown in Figure C.6

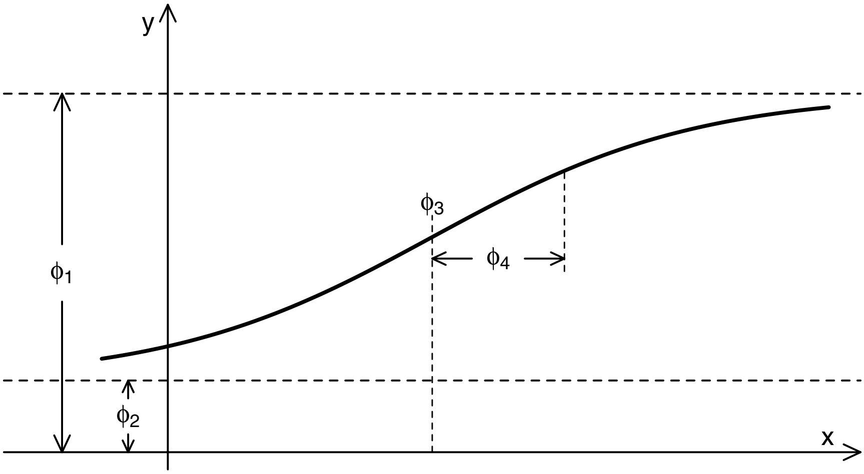

FIGURE C.6. The four-parameter logistic model. The parameters are the horizontal asymptote ϕ_1 as $x \to -\infty$, the horizontal asymptote ϕ_2 as $x \to \infty$, the x value at the inflection point (ϕ_3), and a scale parameter ϕ_4.

C.6.1 Starting Estimates for `SSfpl`

The steps in determining starting estimates for the `SSfpl` model are:

1. Use `NLSstClosestX` to determine $\phi_3^{(0)}$ as the x value corresponding a response at the midpoint of the range of the responses.

2. Use an algorithm for partially linear models to fit A, B, and ℓ while holding ϕ_3 fixed in the nonlinear regression model
$$y(x) = A + \frac{B}{1 + \exp[(\phi_3 - x)/\exp\ell]}.$$
The purpose of this fit is to refine the estimate of ℓ, the logarithm of the scale parameter ϕ_4. We start ℓ at zero.

3. Use the refined estimate of ℓ and an algorithm for partially linear models to fit
$$y(x) = A + \frac{B}{1 + \exp[(\phi_3 - x)/\exp\ell]}$$
with respect to A, B, ϕ_3 and ℓ. The estimates are then $\phi_1 = A$, $\phi_2 = A + B$, $\phi_4 = \exp\ell$ and ϕ_3.

These estimates are the final nonlinear regression estimates.

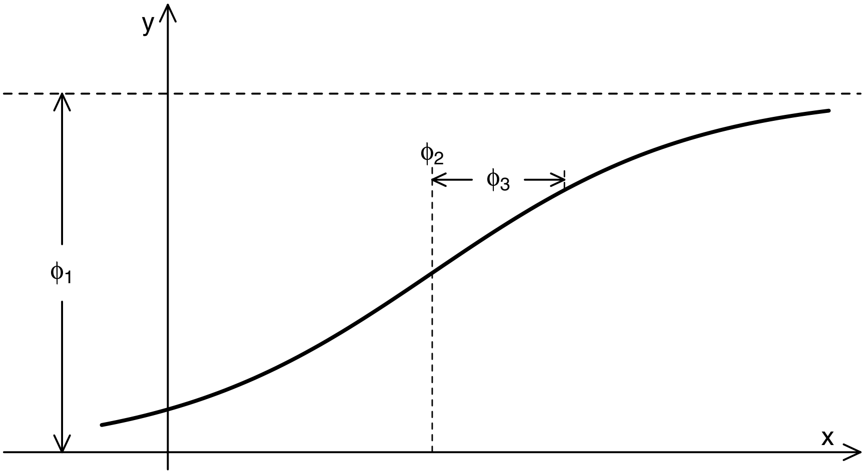

FIGURE C.7. The simple logistic model showing the parameters ϕ_1, the horizontal asymptote as $x \to \infty$, ϕ_2, the value of x for which $y = \phi_1/2$, and ϕ_3, a scale parameter on the x-axis. If $\phi_3 < 0$ the curve will be monotone decreasing instead of monotone increasing and ϕ_1 will be the horizontal asymptote as $x \to -\infty$.

C.7 `SSlogis`—Simple Logistic Model

The simple logistic model is a special case of the four-parameter logistic model in which one of the horizontal asymptotes is zero. We write it as

$$y(x) = \frac{\phi_1}{1 + \exp\left[(\phi_2 - x)/\phi_3\right]}. \tag{C.7}$$

For this model we do not require that the scale parameter ϕ_3 be positive. If $\phi_3 > 0$ then ϕ_1 is the horizontal asymptote as $x \to \infty$ and 0 is the horizontal asymptote as $x \to -\infty$. If $\phi_3 < 0$, these roles are reversed. The parameter ϕ_2 is the x value at which the response is $\phi_1/2$. It is the inflection point of the curve. The scale parameter ϕ_3 represents the distance on the x-axis between this inflection point and the point where the response is $\phi_1/\left(1 + e^{-1}\right) \approx 0.73\phi_1$. These parameters are shown in Figure C.7.

C.7.1 Starting Estimates for `SSlogis`

The starting estimates are determined by:

1. Scaling and, if necessary, shifting the responses y so the transformed responses y' are strictly within the interval $(0, 1)$.

2. Taking the logistic transformation

$$z = \log[y'/(1 - y')]$$

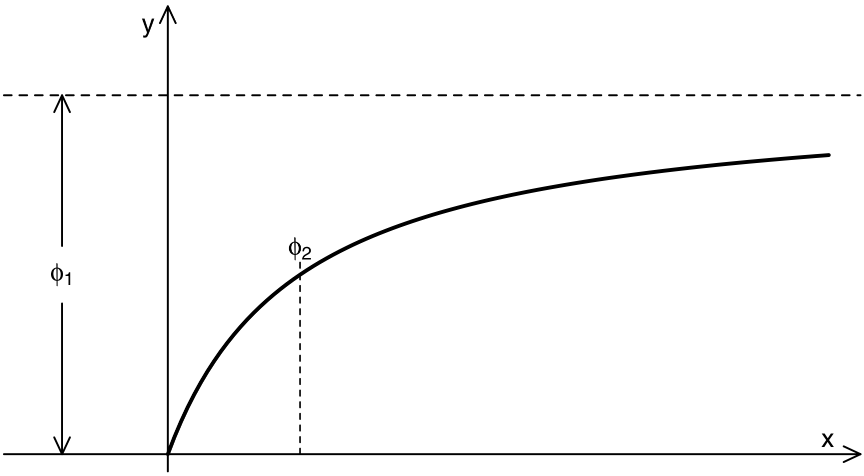

FIGURE C.8. The Michaelis–Menten model used in enzyme kinetics. The parameters are ϕ_1, the horizontal asymptote as $x \to \infty$ and ϕ_2, the value of x at which the response is $\phi_1/2$.

and fitting the simple linear regression model

$$x = a + bz.$$

3. Use $\phi_2^{(0)} = a$ and $\phi_3^{(0)} = b$ and an algorithm for partially linear models to fit

$$y = \frac{\phi_1}{1 + \exp[(\phi_2 - x)/\phi_3]}.$$

The resulting estimates are the final nonlinear regression estimates.

C.8 `SSmicmen`—Michaelis–Menten Model

The Michaelis–Menten model is used in enzyme kinetics to relate the initial rate of an enzymatic reaction to the concentration of the substrate. It is written

$$y(x) = \frac{\phi_1 x}{\phi_2 + x}, \tag{C.8}$$

where ϕ_1 is the horizontal asymptote as $x \to \infty$ and ϕ_2, the Michaelis parameter, is the value of x at which the response is $\phi_1/2$.

These parameters are shown in Figure C.8

C.8.1 Starting Estimates for `SSmicmen`

The starting estimates are obtained by:

1. Fitting a simple linear regression model

$$\frac{1}{y} = a + b\frac{1}{x}$$

for the inverse response as a function of the inverse of x.

2. Setting $\phi_2^{(0)} = \text{abs}(b/a)$ and using an algorithm for partially linear models to fit

$$y = \frac{\phi_1 x}{\phi_2 + x}.$$

The resulting estimates are the final nonlinear regression estimates.