



*Tutorials and worked examples for simulation,
curve fitting, statistical analysis, and plotting.*
<http://www.simfit.org.uk>

Constrained nonlinear regression involves the attempt to locate a local minimum of some objective function which is a function of the variable parameters to be estimated given the fixed data and weights supplied by the user.

In SIMFIT the following definitions are used

- y_1, y_2, \dots, y_n : The observations
- x_1, x_2, \dots, x_n : Values of the independent variable
- w_1, w_2, \dots, w_n : The assumed weights
- $\Theta = \theta_1, \theta_2, \dots, \theta_m$: The parameters to be estimated
- g_1, g_2, \dots, g_n : The function values evaluated at x, Θ

where it is assumed that, for errors ϵ ,

$$y = g(x, \Theta) + \epsilon,$$

and the appropriate objective function to be minimized is the weighted sum of squared residuals divided by the number of degrees of freedom, that is

$$\begin{aligned} f(\Theta) &= \frac{WSSQ}{n - m} \\ &= \frac{1}{n - m} \sum_{i=1}^n w_i (y_i - g_i)^2. \end{aligned}$$

If the weights are reasonably accurate and the errors are normally distributed with zero means this should be an approximately chi-squared variable of order unity at the solution point and, in addition, if sensible starting estimates have been supplied the parameters should also be of order unity at the solution point.

Now the basis of constrained nonlinear regression is that the objective function should be approximately quadratic at the solution point, and that therefore a well-defined local minimum should have contours at the solution point that are approximately elliptical.

To demonstrate a case where this condition is realized then consider fitting the test data file `exfit.tf2` using a one-exponential model in the form

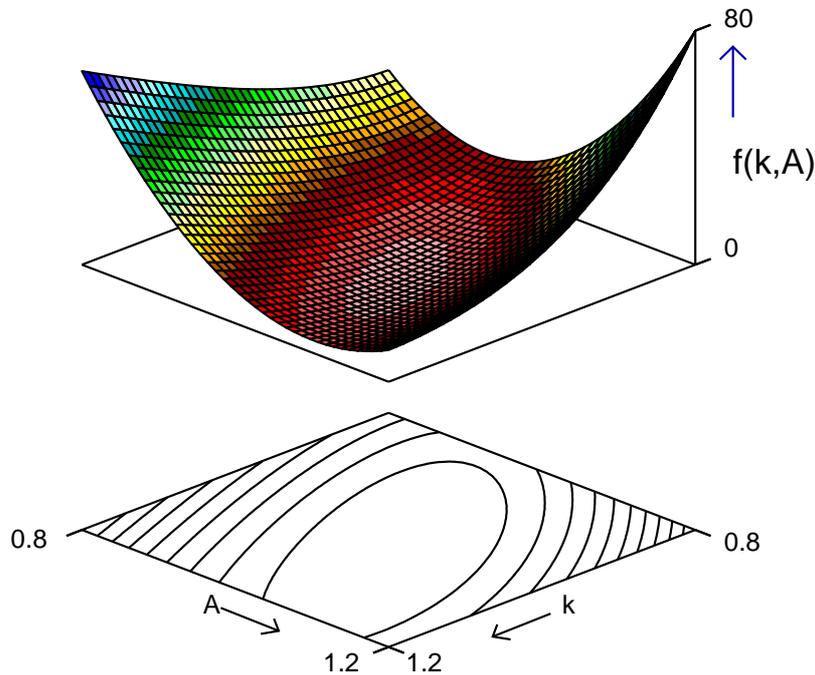
$$g(x, A, k) = A \exp(-kx)$$

using program **qfit** and noting that starting estimates are indicated on this data file as follows

```
begin{limits}
0.0 0.5 3.0
0.0 1.5 3.0
0.0 0.0 0.0
end{limits}
```

so that the EXPERT mode can be used. After fitting, the option to view the objective function at the solution point can be chosen to obtain the following plot.

WSSQ/NDOF = f(k,A)



As a more complicated example consider fitting the data in test file `qnfitt_data.tf4` using the model defined in `qnfitt_model.tf4` which defines the double Michaelis-Menten model in the following way, first in parameter form then in the more familiar enzyme kinetic form

$$\begin{aligned}
 g(x, \Theta) &= \frac{\theta_3 x}{\theta_1 + x} + \frac{\theta_4 x}{\theta_2 + x} \\
 &\equiv \frac{Vmax_1 S}{Km_1 + S} + \frac{Vmax_2 S}{Km_2 + S}.
 \end{aligned}$$

Three important points should be noted.

1. Complications with more than two parameters

There are now more than two parameters so the objective function and contours can be plotted in several ways to display the surface as a function of just two parameters.

2. Ambiguity with the model

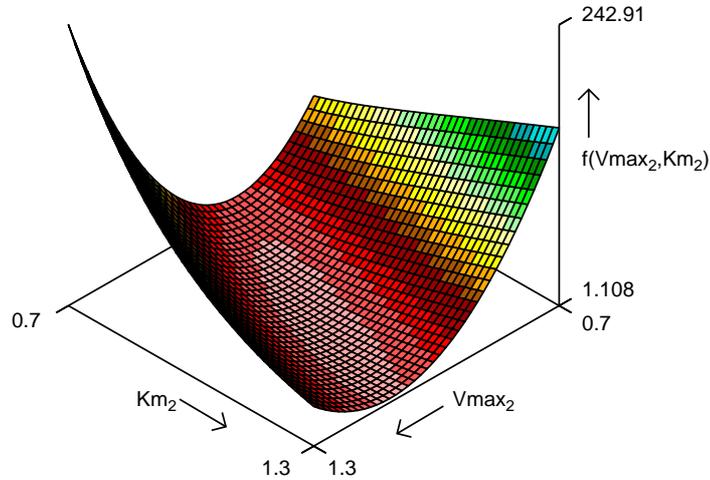
The model is ambiguous in that the pairs $Vmax_1, Km_1$ and $Vmax_2, Km_2$ are not uniquely defined. In other words, the parameter estimates will refer to these pairs in arbitrary order, depending only on the starting estimates and limits set.

3. Elongated valleys

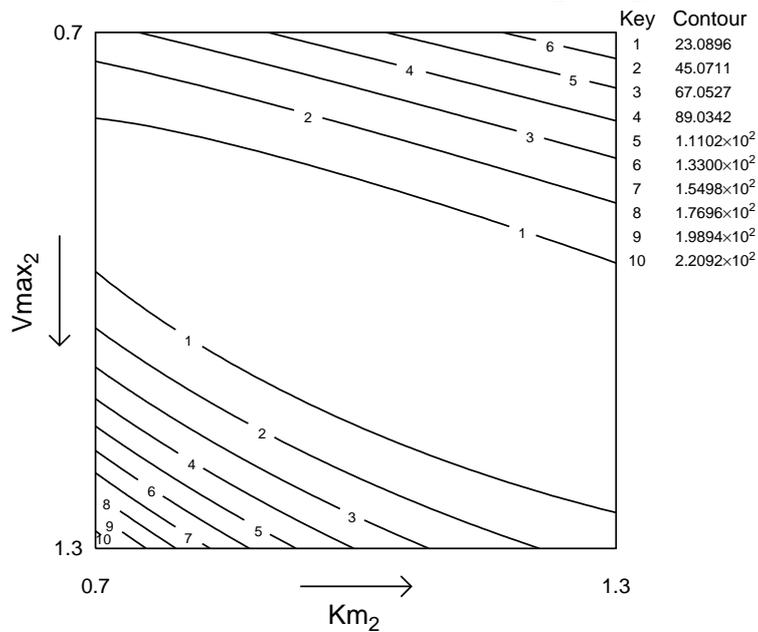
The eccentricity of the elliptical contours at the solution point will be exaggerated if the order of magnitude of the parameters chosen and the range chosen to display the plots are not comparable.

The point is that the contours are stretched with the chosen pair of parameters as will be seen in the next plot, and this is what happens when more than two parameters are estimated namely, long valleys leading to the solution point makes convergence to the local minimum increasingly difficult.

Surface for WSSQ/NDOF = $f(V_{max_2}, Km_2)$



Contours for WSSQ/NDOF = $f(V_{max_2}, Km_2)$



This can also be confirmed by observing the eigenvalues and condition number of the internal Hessian matrix which, for this example, were as follows.

Eigenvalues of the internal Hessian matrix

5.07548E-01 1.45150E+01 1.88722E+02 3.44715E+03, Condition number = 6.79178E+03

The condition number is the ratio of largest to smallest eigenvalue, which reflects the ratio of the longest valley to the shortest. This value will clearly be distorted in cases where not all the estimated parameters are of comparable size in internal coordinates.