

Fitting Mathematical Models to Biological Data using Non-Linear Least-Squares Minimization (NLLS)

Samraat Pawar

Department of Life Sciences (Silwood Park)

Imperial College
London

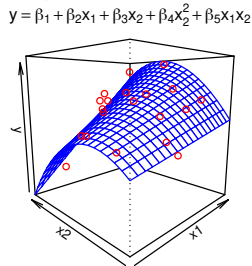
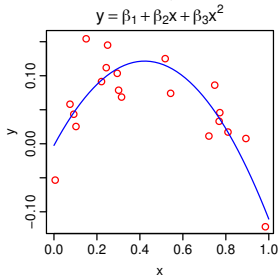
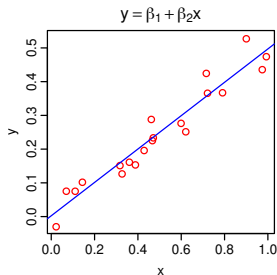
December 7, 2020

OUTLINE

- Why Non-Linear Least Squares regression / fitting?
- The NLLS fitting method
- NLLS in R
- Practicals overview

LINEAR MODELS

- Which of these are Linear Models (fitted to data)?



- These are *all* good *Linear Models* (really?!)
- The data can be modelled (aka "fitted to a mathematical model") as a *linear combination of variables and coefficients*
- Easily fitted using *Ordinary Least Squares* (OLS) regression
- Linear models can *include curved responses* (e.g. Polynomial regression)

WHAT MAKES A MODEL NON-LINEAR?

- OLS can be used to fit (model) equations that are *intrinsically linear*, e.g.,
 - Straight line: $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$
 - Polynomial (quadratic): $y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i$
 - Another quadratic: $y_i = e^{\beta_0} + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i$
- What is *intrinsic linearity*? — the equation of the model to be fitted should be *linear in the parameters* (the β 's)
- Are these models linear in their *parameters*?
 - $y_i = \beta_0 + \beta_1 x_i^{\beta_2} + \varepsilon_i$
 - $y_i = \beta_0 e^{\beta_2 x_i} + \varepsilon_i$
 - $y_i = \frac{\beta_0 x_i}{\beta_1 + x_i} + \varepsilon_i$

NO: at least one parameter (β) is non-linear (e.g. $x_i^{\beta_2}$, $e^{\beta_2 x_i}$, etc.)

WHY IS INTRINSIC NON-LINEARITY A PROBLEM FOR MDOEL FITTING?

Recall what the Least Squares method does:

- Consider data on a response variable y , a predictor (independent) variable x , and n observations.
- Say we want to fit a model to these data: $f(x_i, \beta) + \varepsilon_i$
($\beta = (\beta_0, \beta_1, \dots, \beta_k)$ are the model's $k + 1$ parameters)
- An example of $f(x_i, \beta) + \varepsilon_i$ could be: $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$
- The objective of any *least squares* method is to find estimates of values of the parameters (β_j) that minimize the sum (S) of squared residuals (r_i) (AKA RSS):

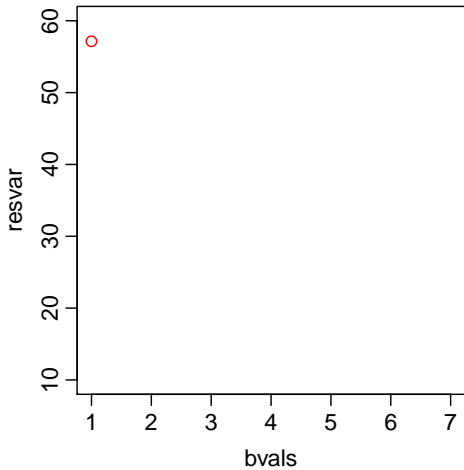
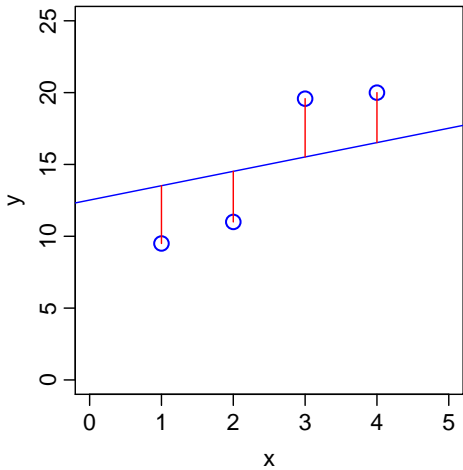
$$\text{RSS} = S = \sum_{i=1}^n [y_i - f(x_i, \beta)]^2 = \sum_{i=1}^n r_i^2$$

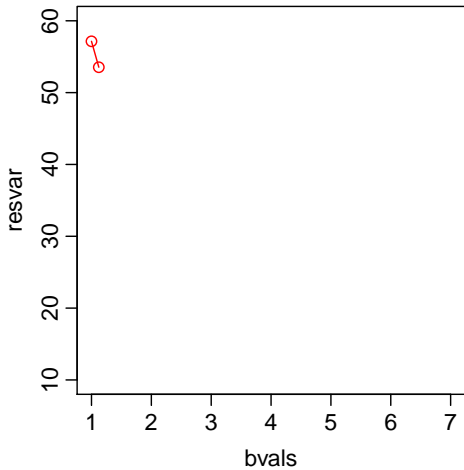
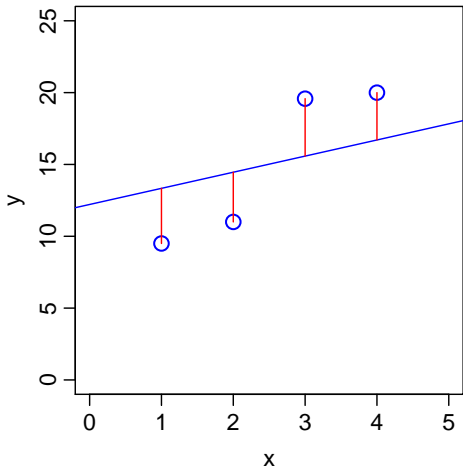
THE LEAST-SQUARES SOLUTION

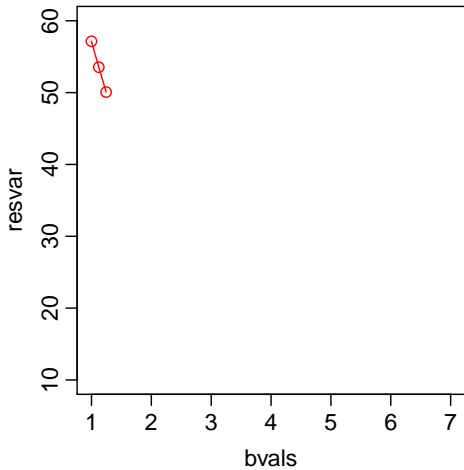
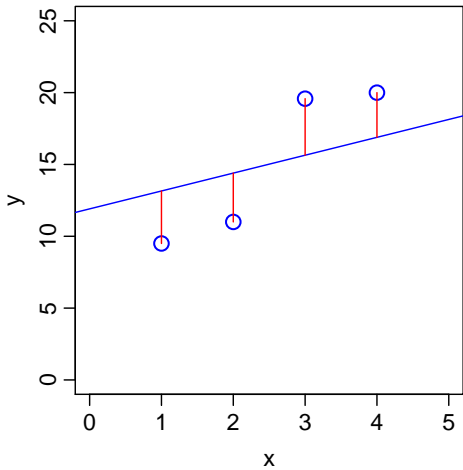
- The objective of any *least squares* method is to find estimates of values of the parameters ($\hat{\beta}_j$) that minimize the sum (S) of squared residuals (r_i) (AKA RSS):

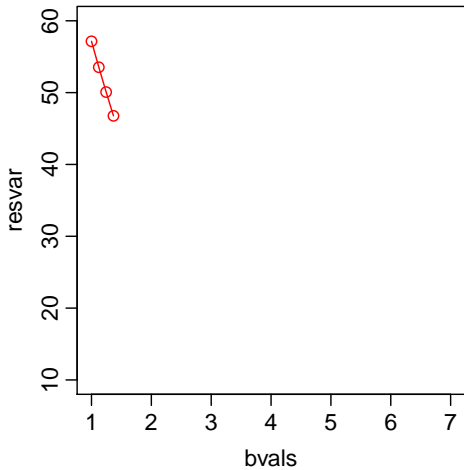
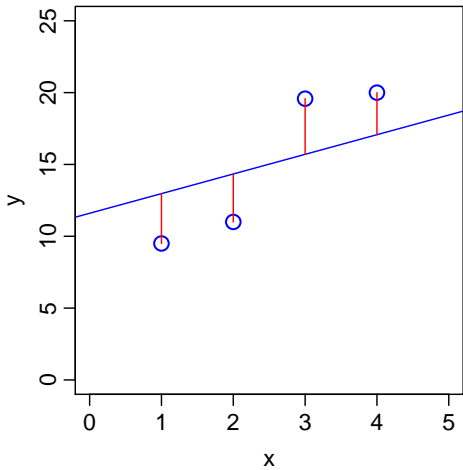
$$\text{RSS} = S = \sum_{i=1}^n [y_i - f(x_i, \beta)]^2 = \sum_{i=1}^n r_i^2$$

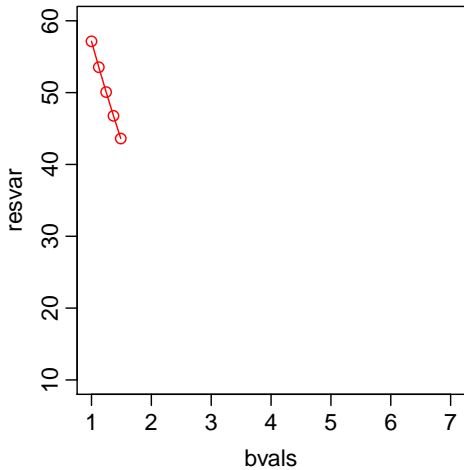
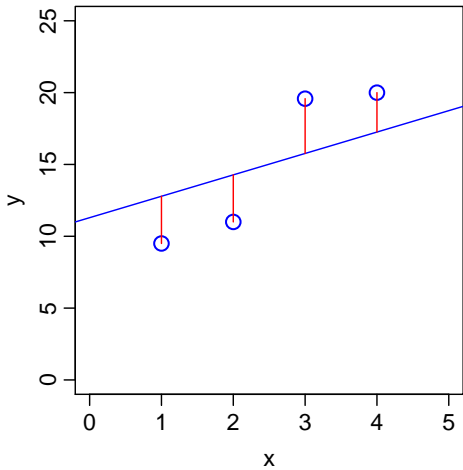
- Let's picture this using a simple (OLS) example; fitting the model $y_1 = \beta_1 x_1 + \epsilon_1 \dots$

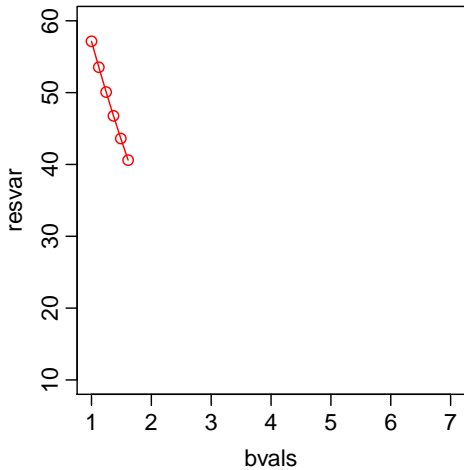
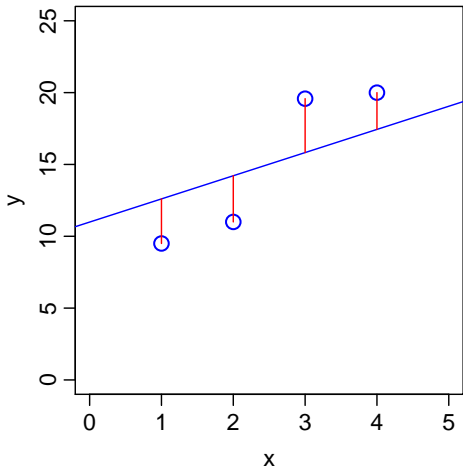


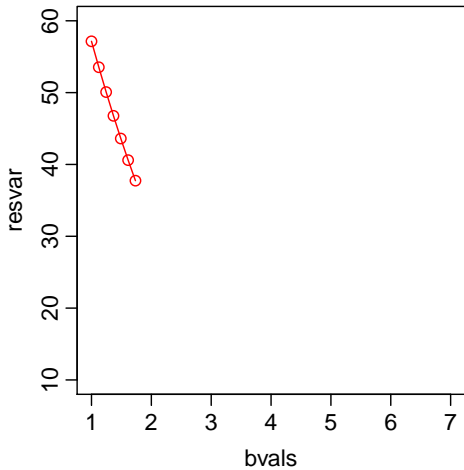
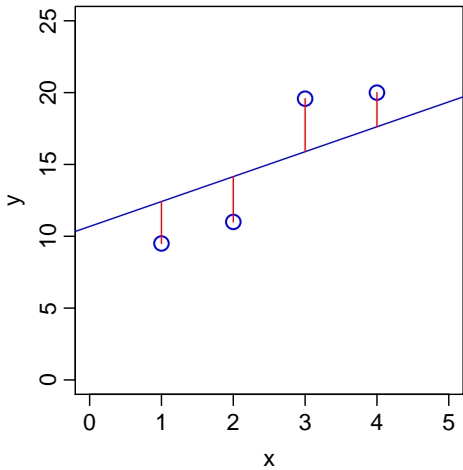


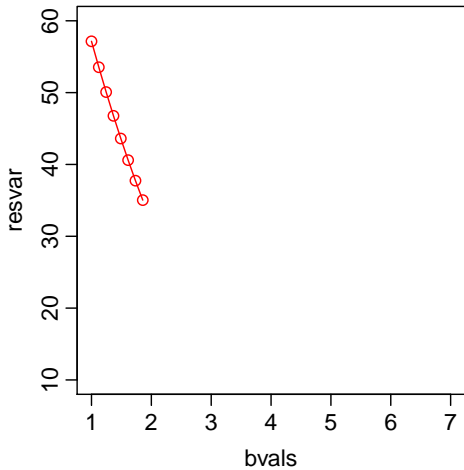
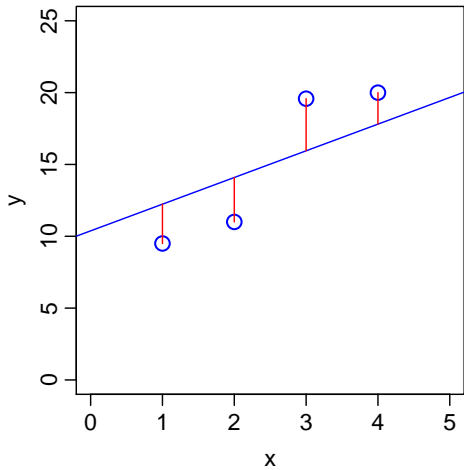


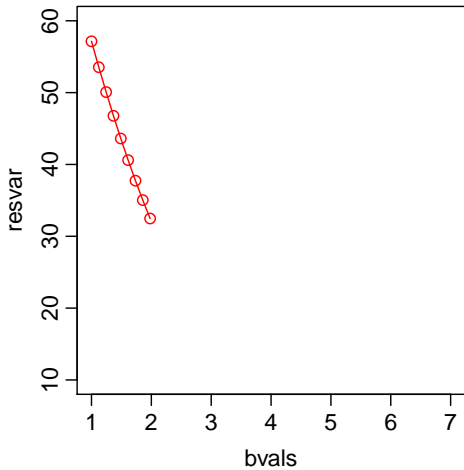
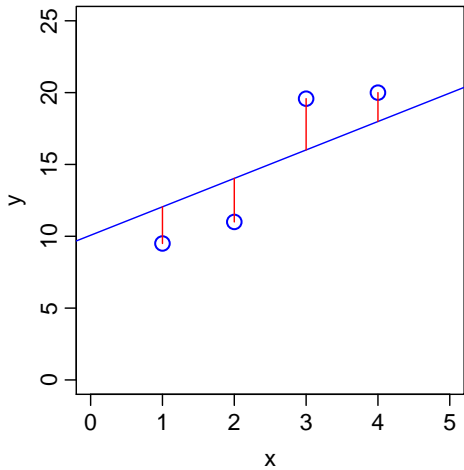


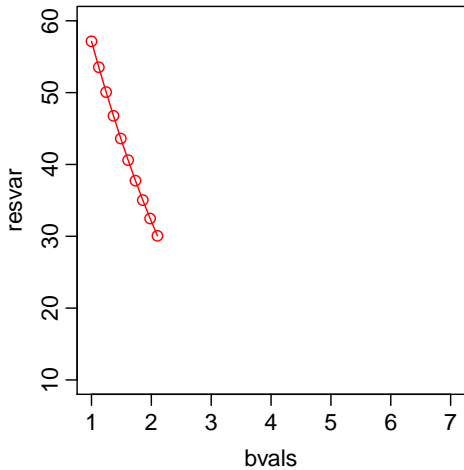
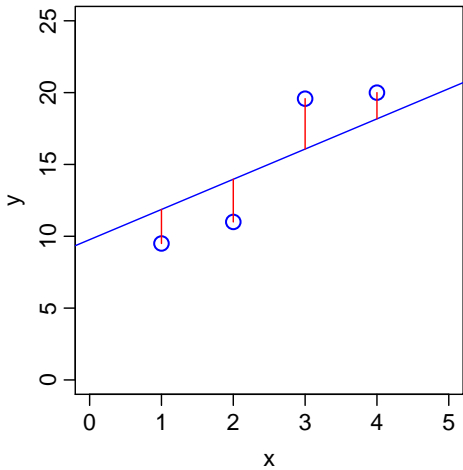


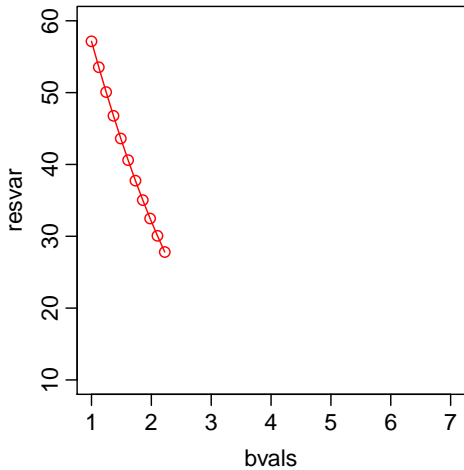
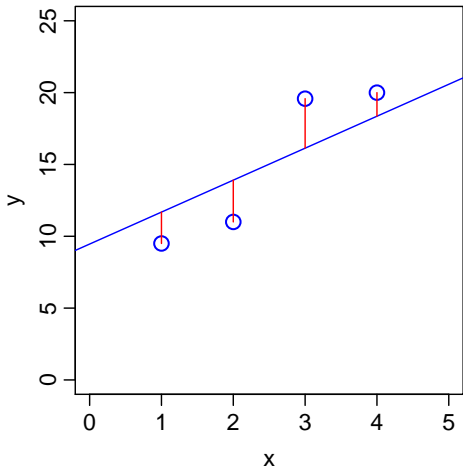


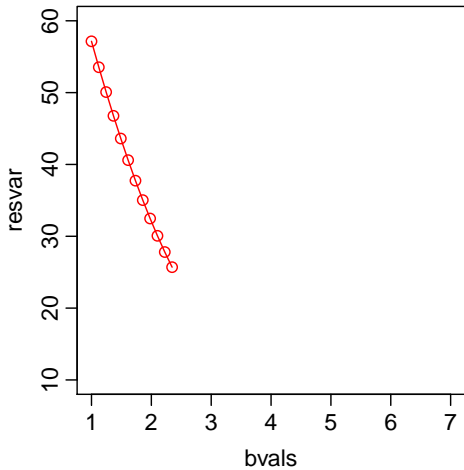
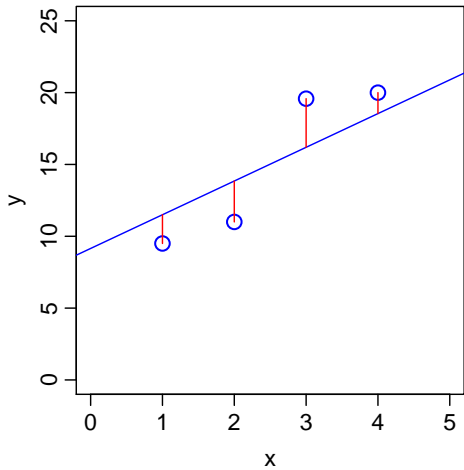


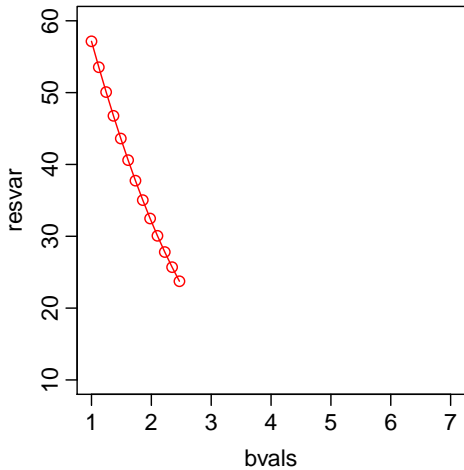
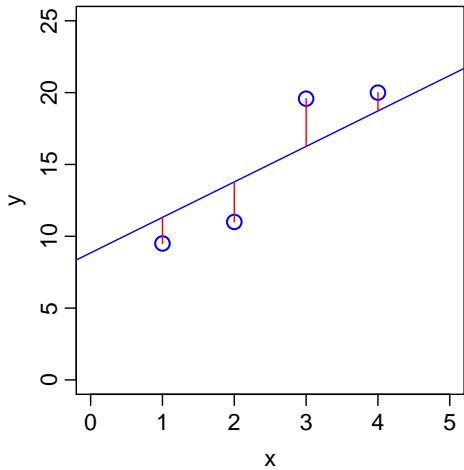


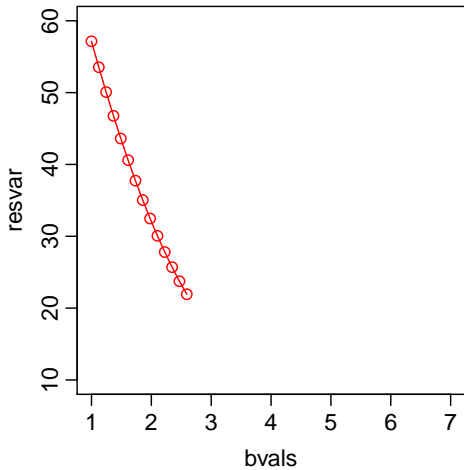
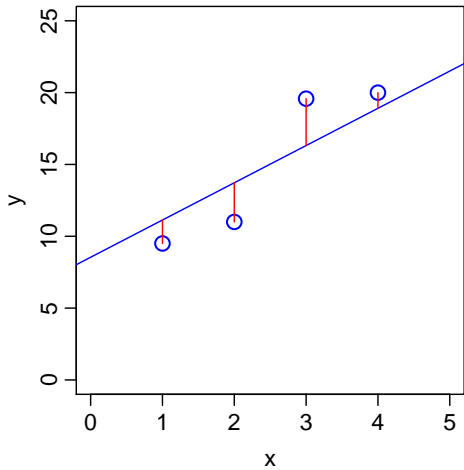


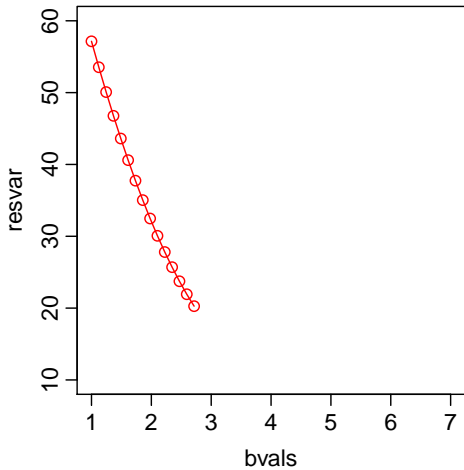
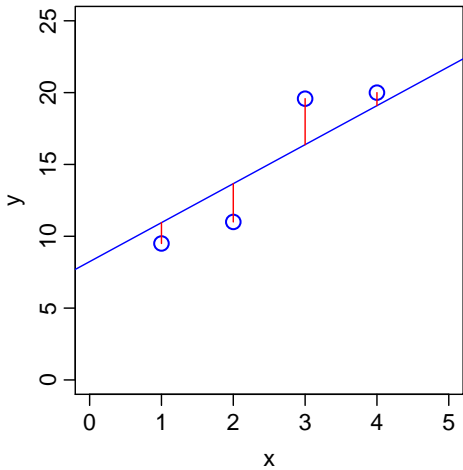


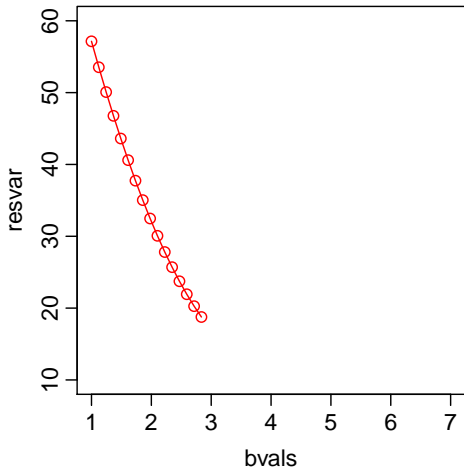
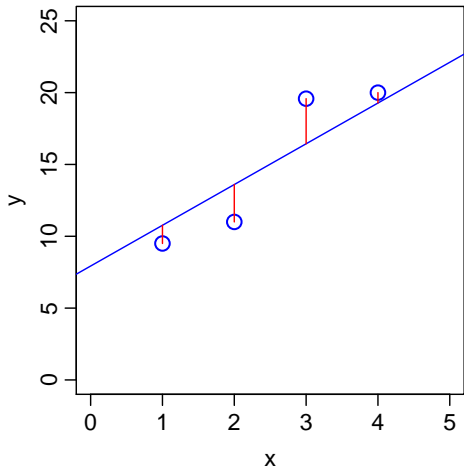


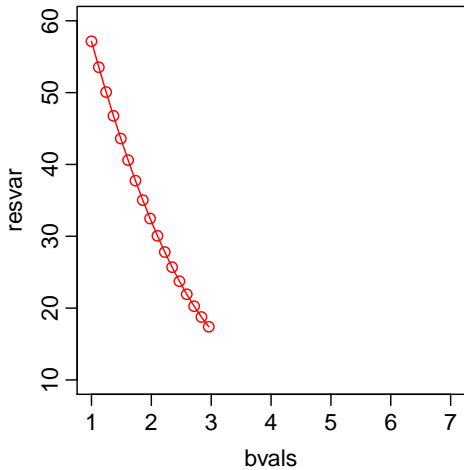
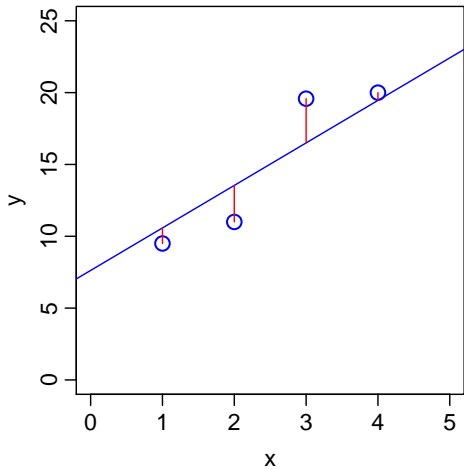


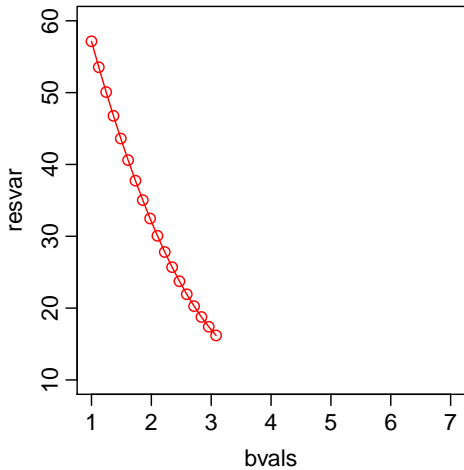
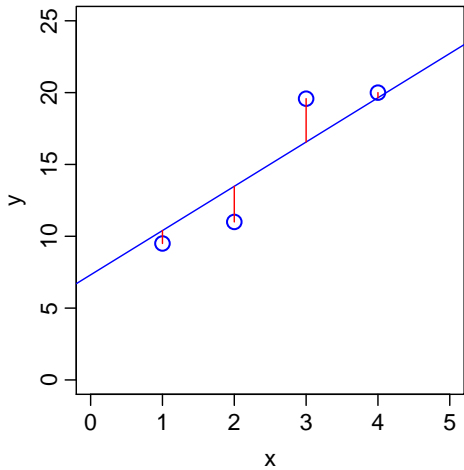


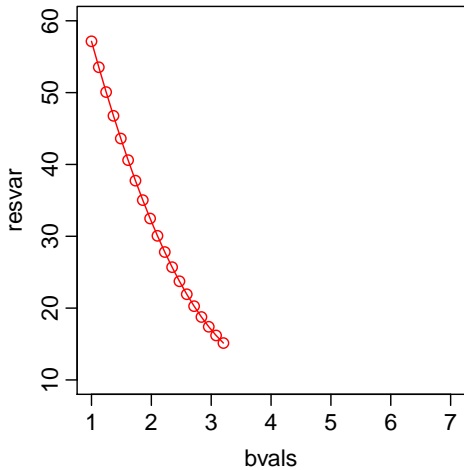
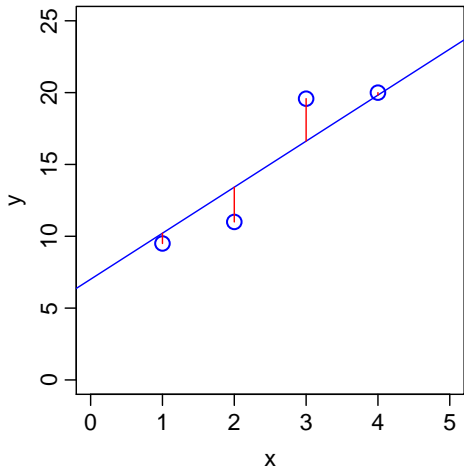


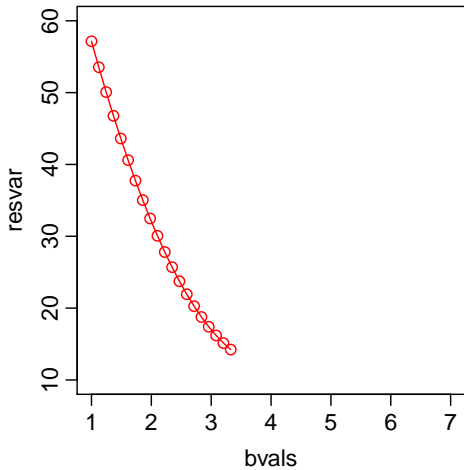
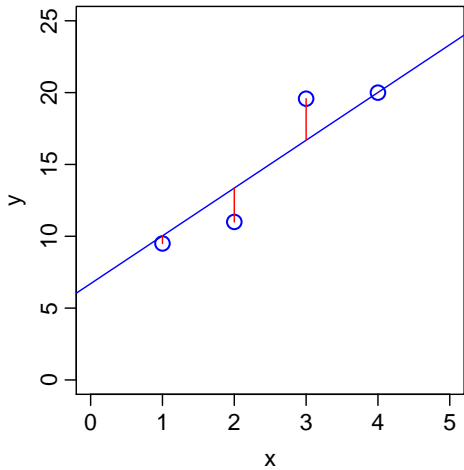


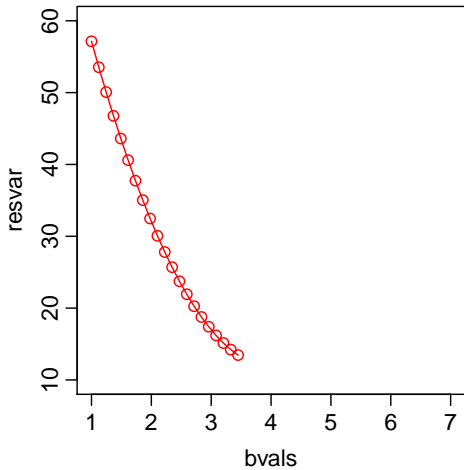
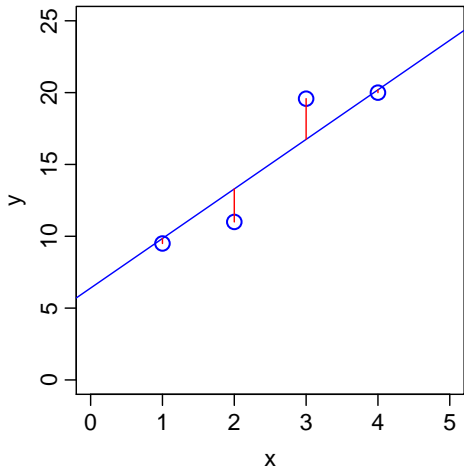


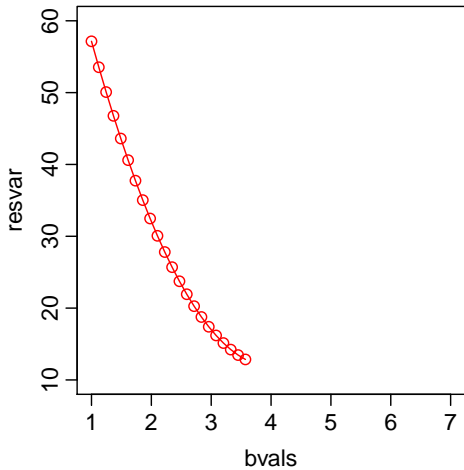
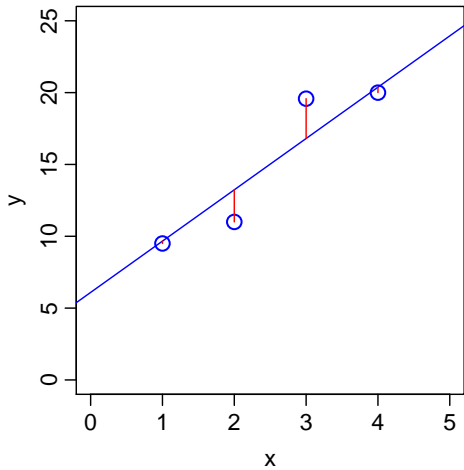


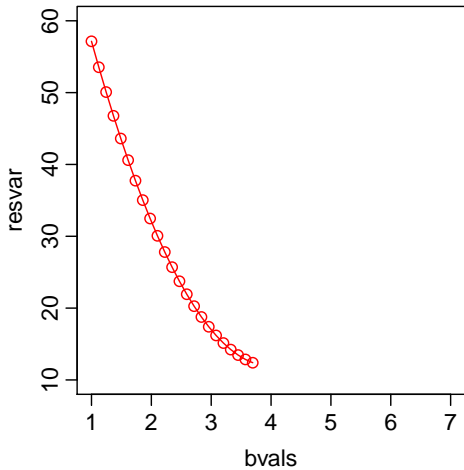
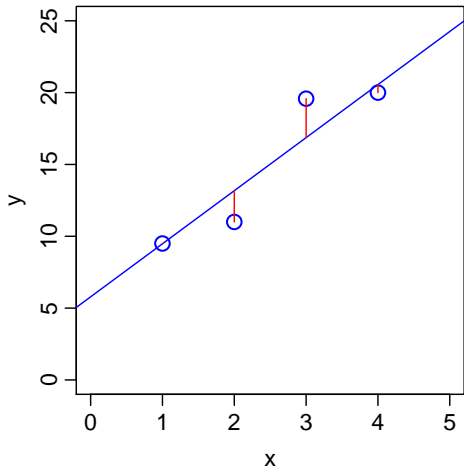


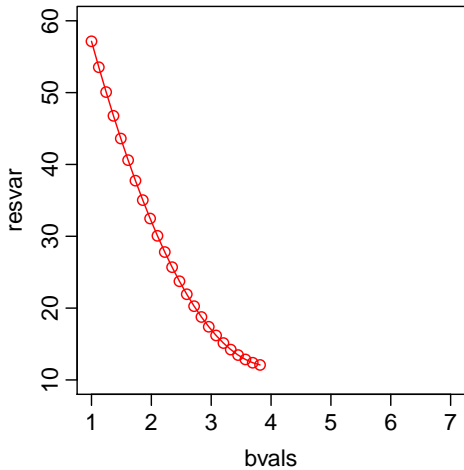
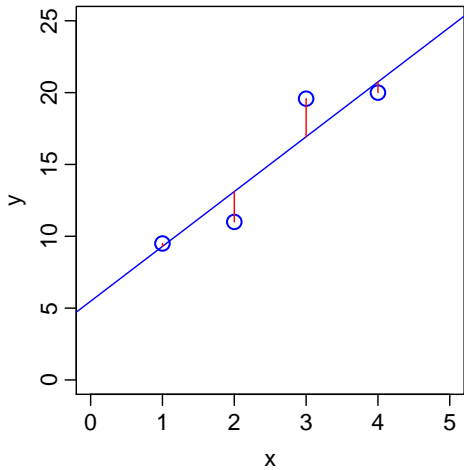


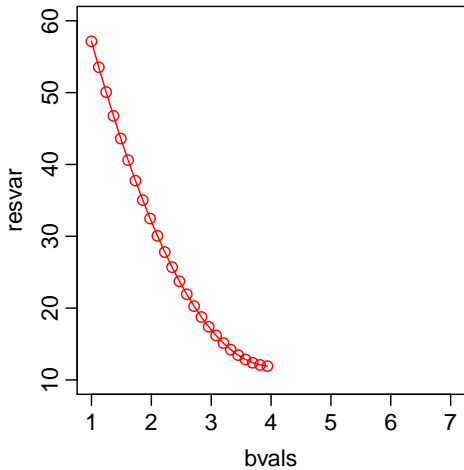
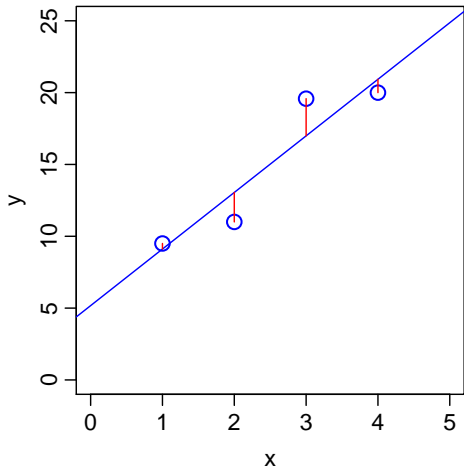


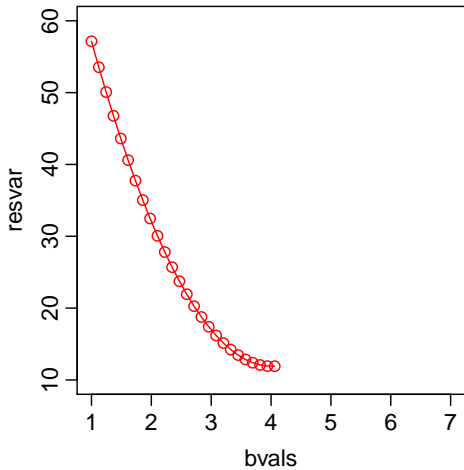
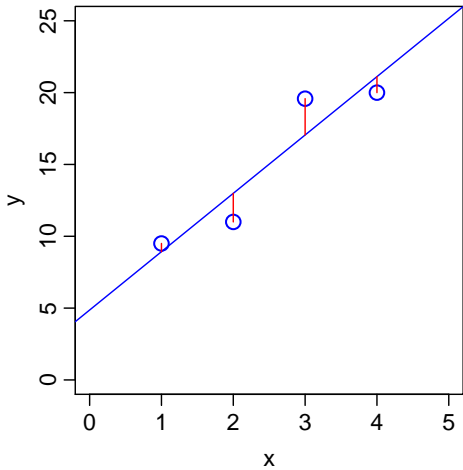


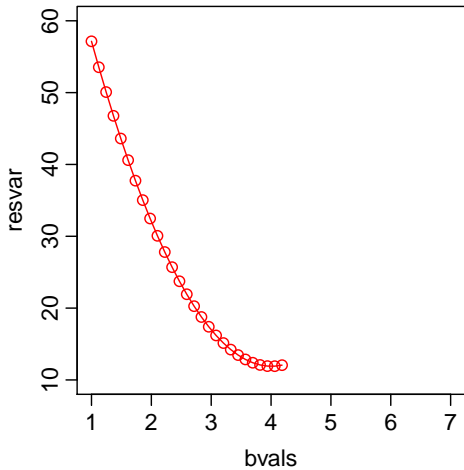
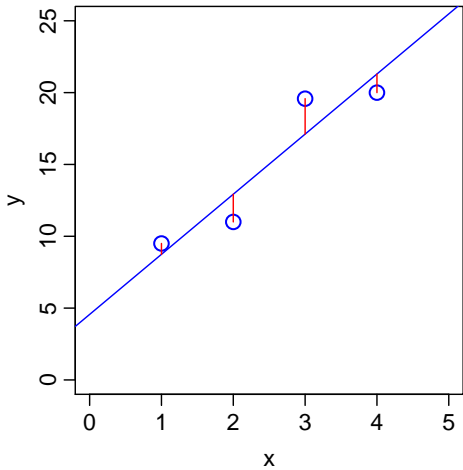


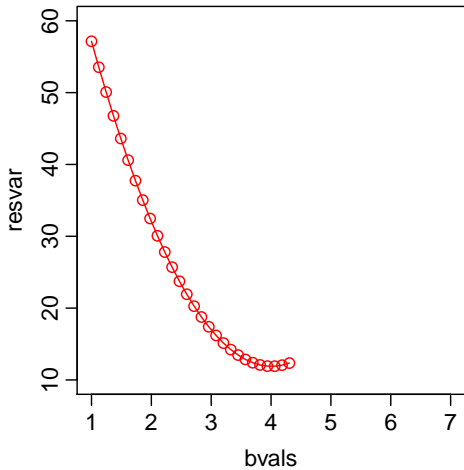
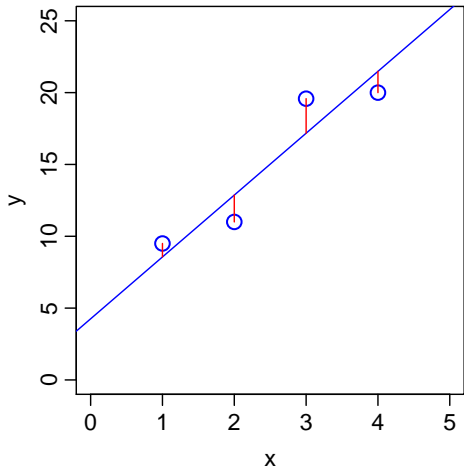


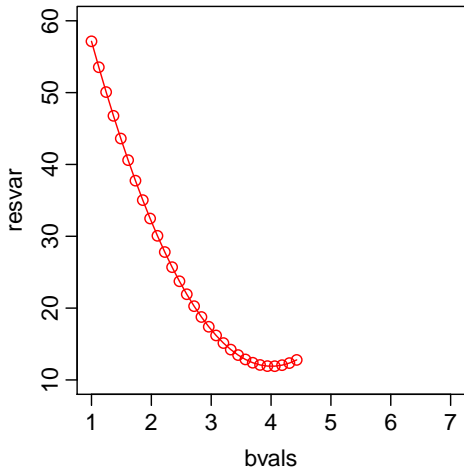
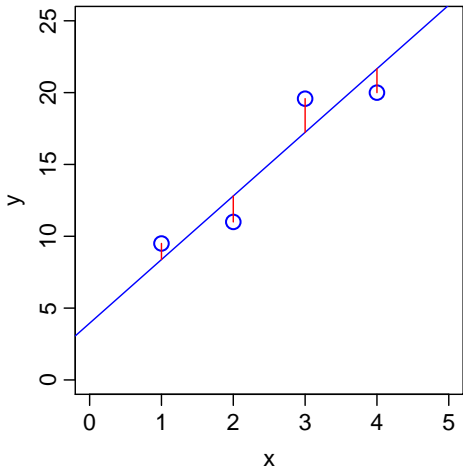


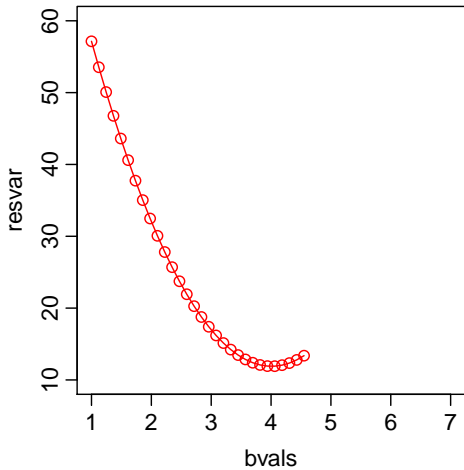
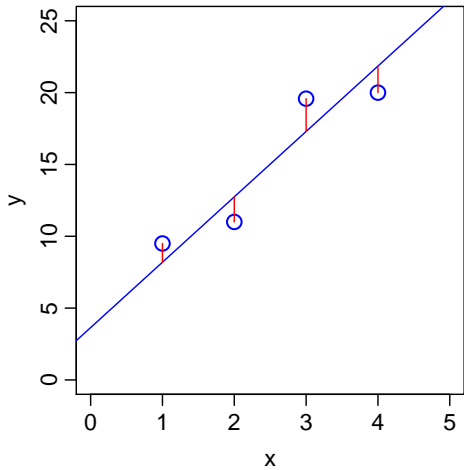


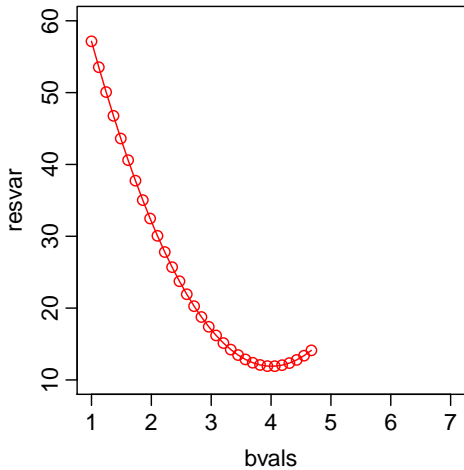
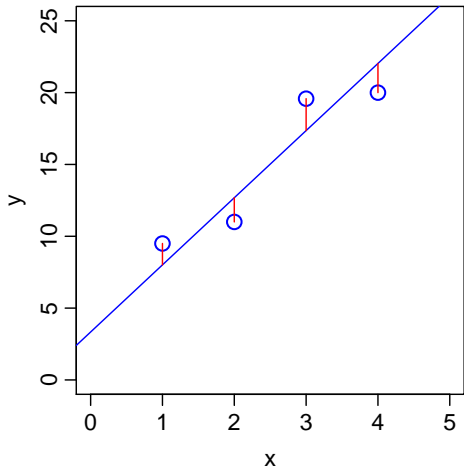


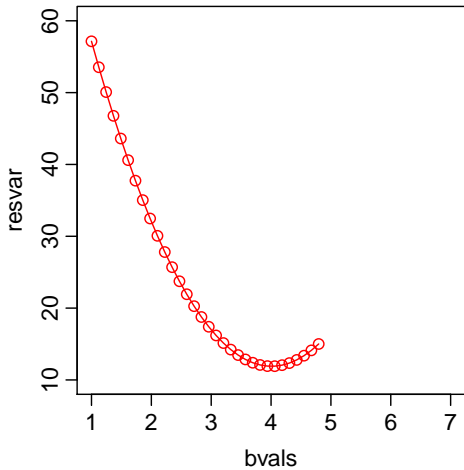
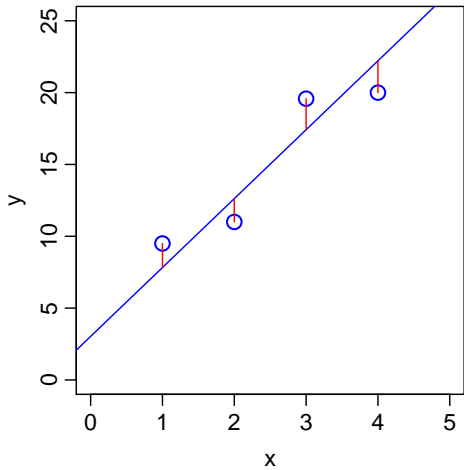


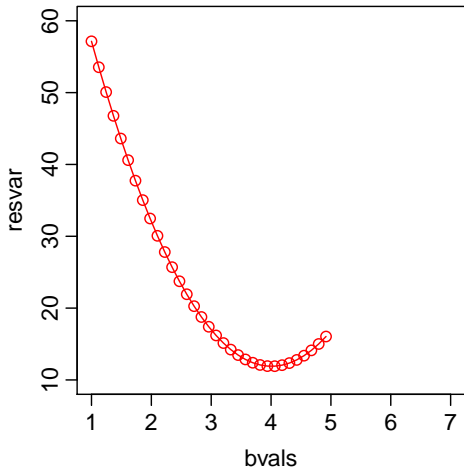
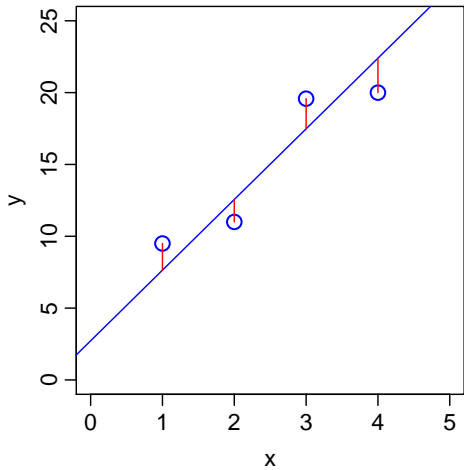


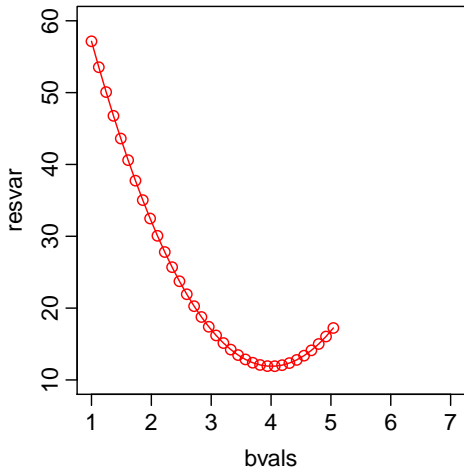
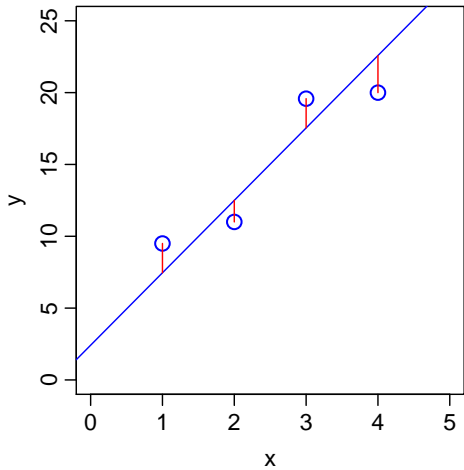


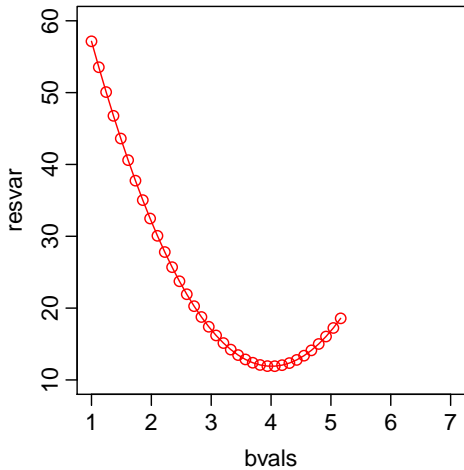
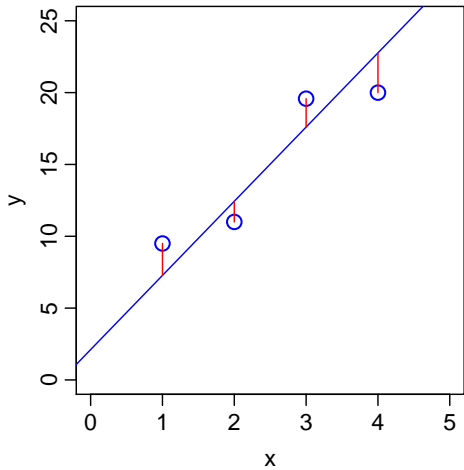


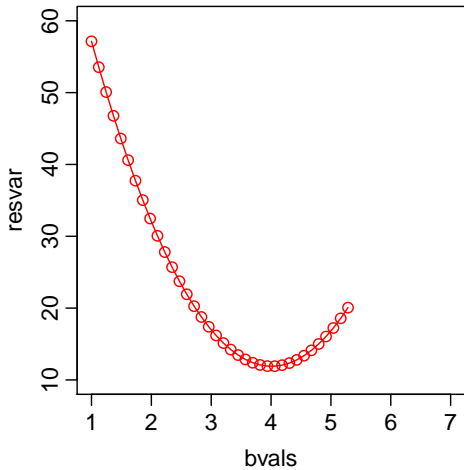
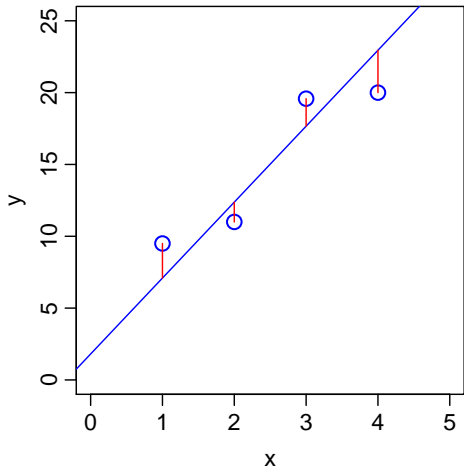


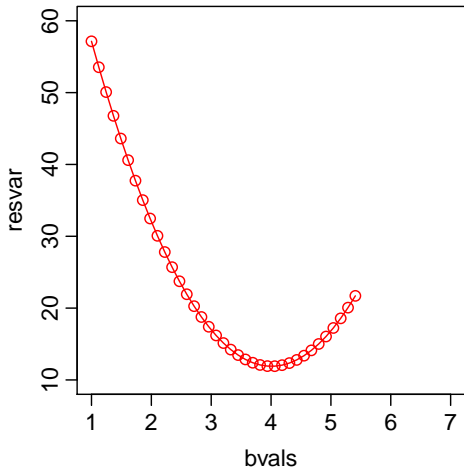
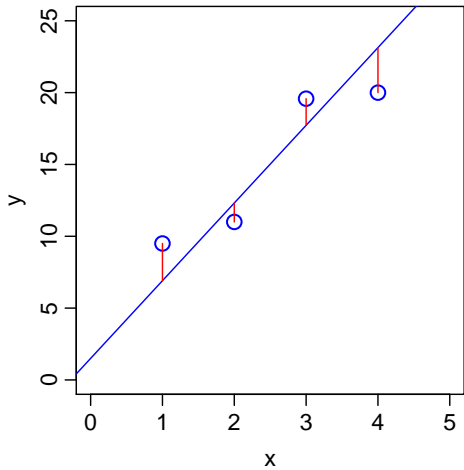


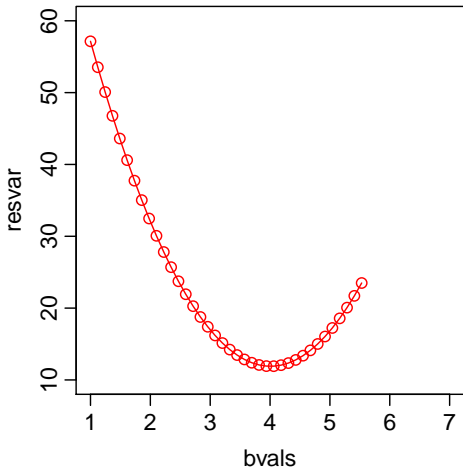
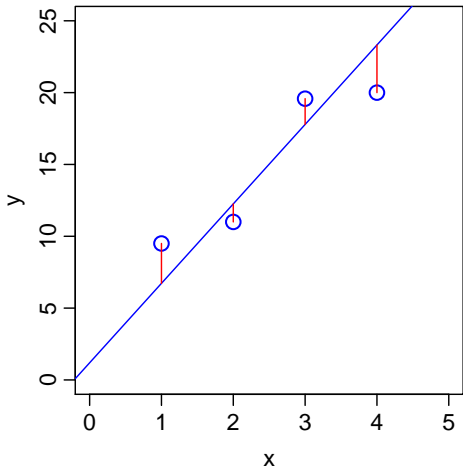


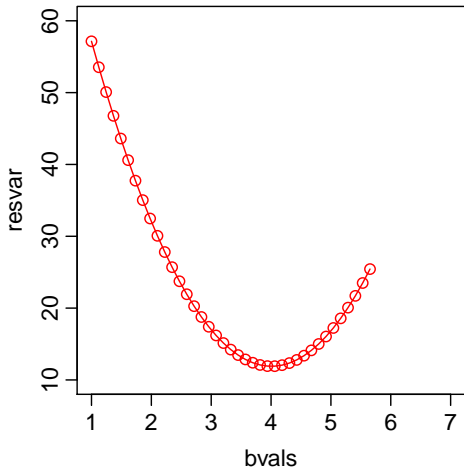
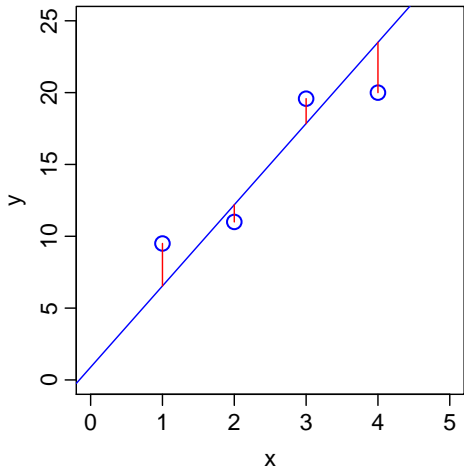


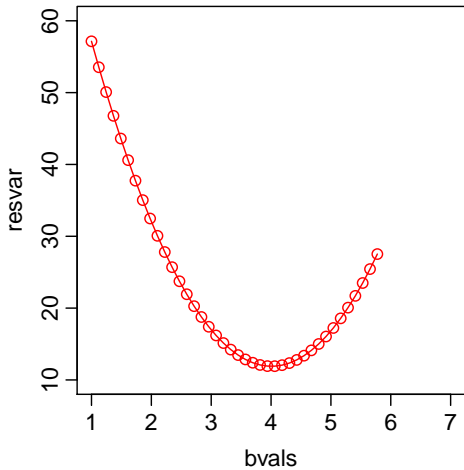
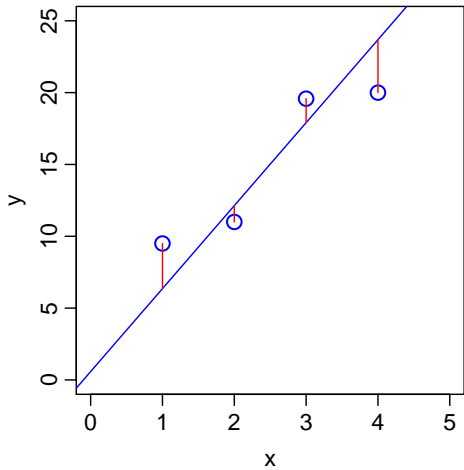


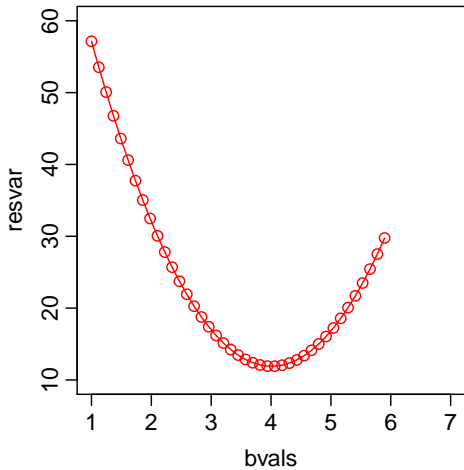
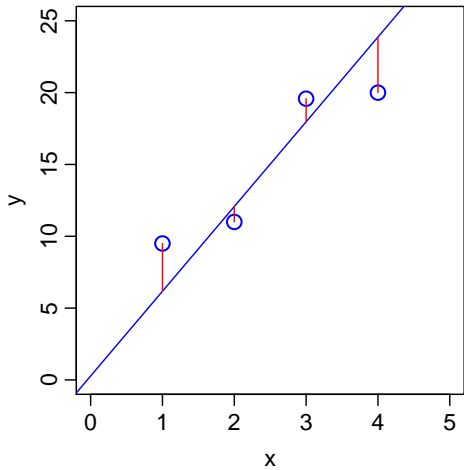


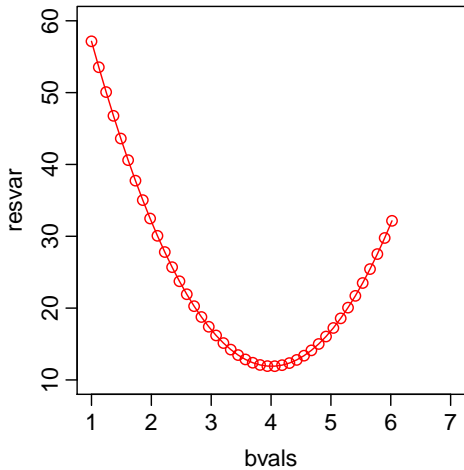
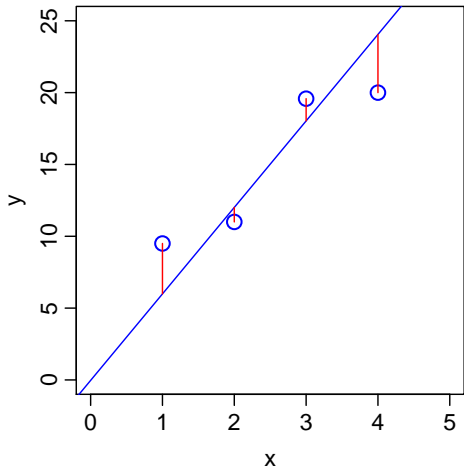


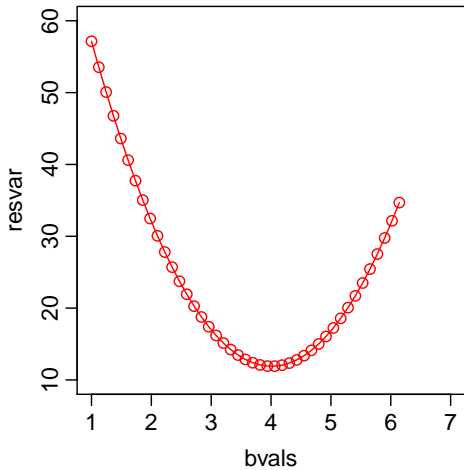
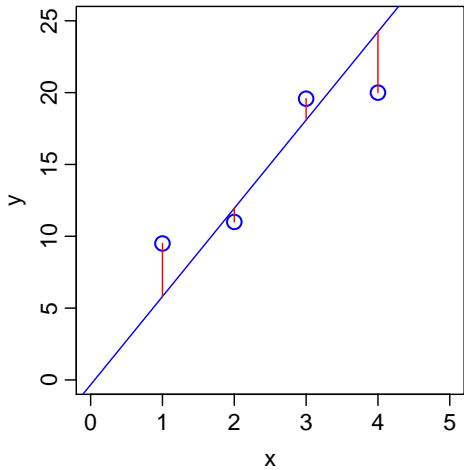


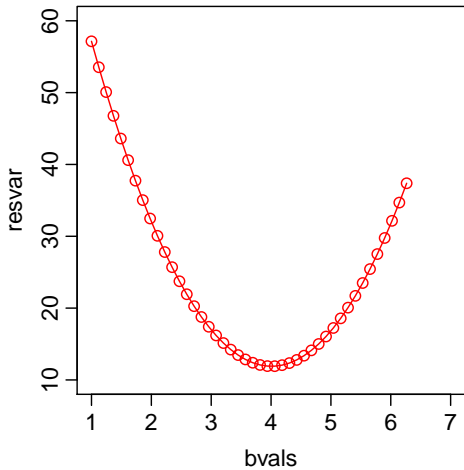
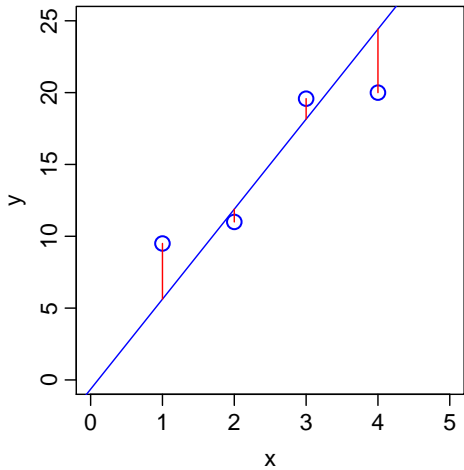


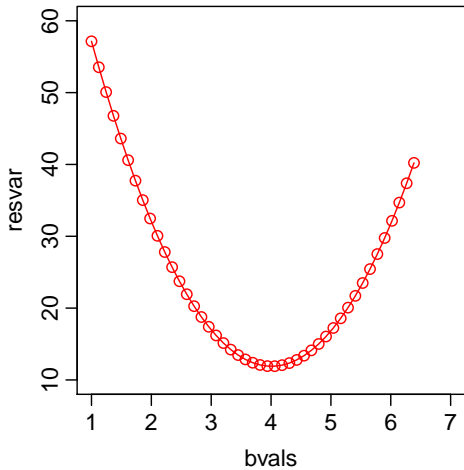
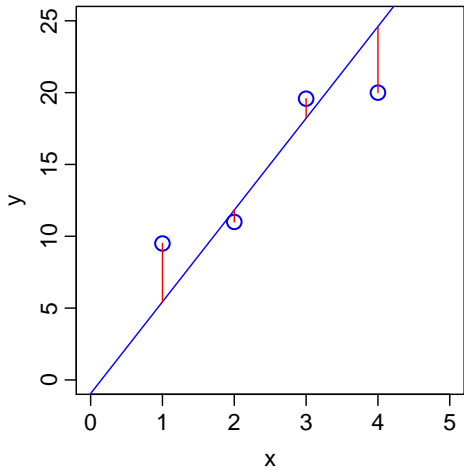


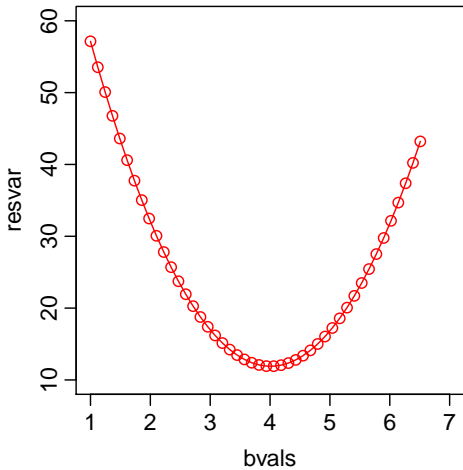
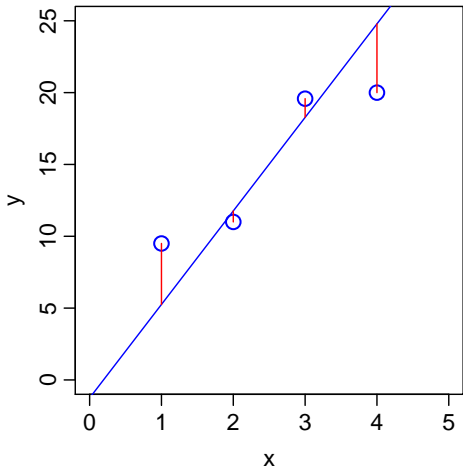


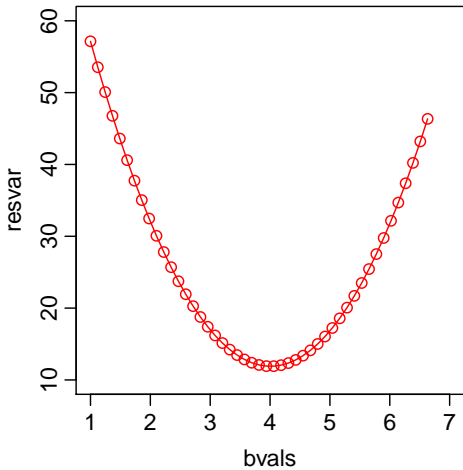
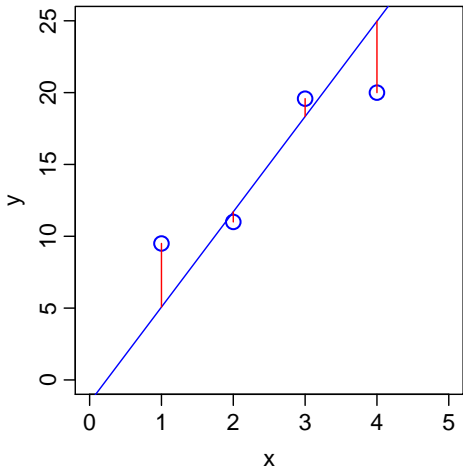


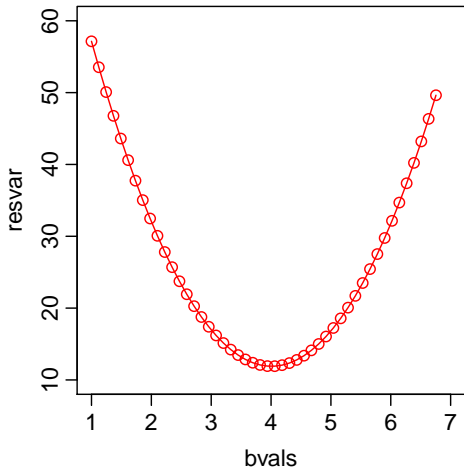
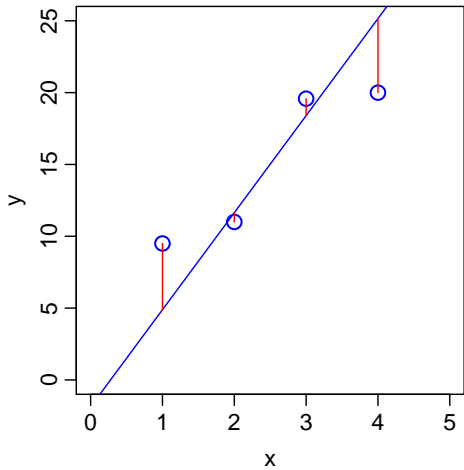


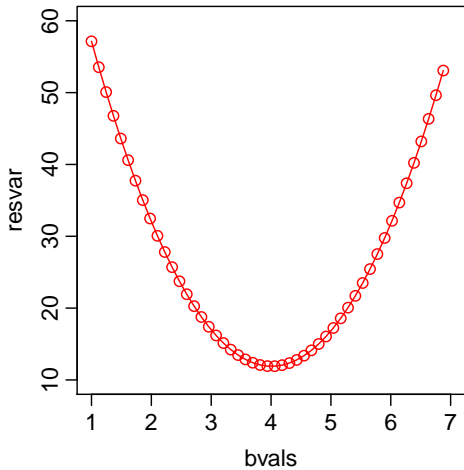
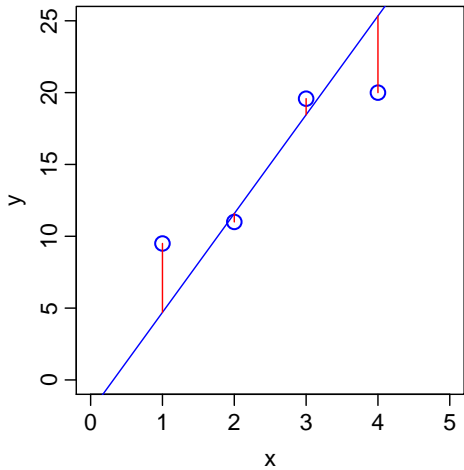


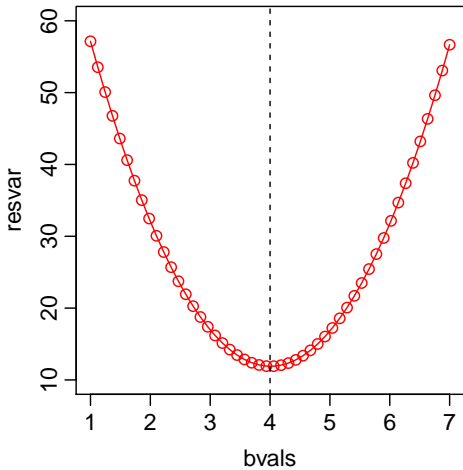
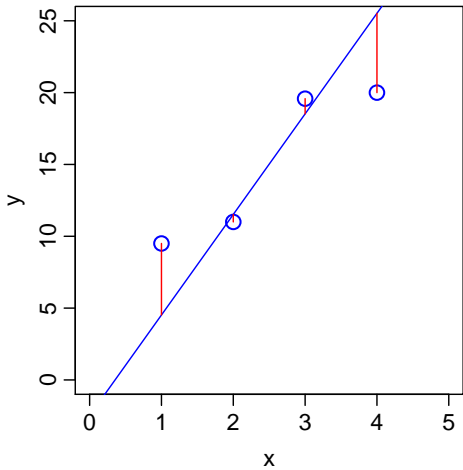




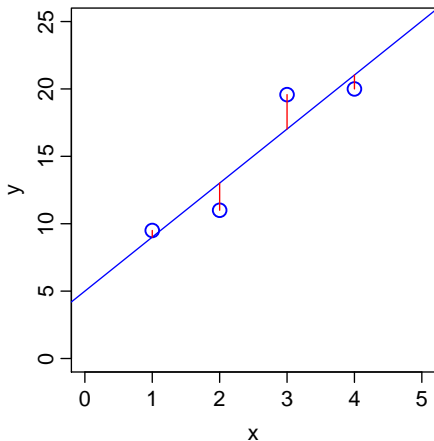








IF THE MODEL IS LINEAR, THE SOLUTION IS EASY USING ALGEBRA



$$y_1 = \beta_0 + \beta_1 x_1 + \epsilon_1$$

$$9.50 = 5 + 4 \times 1 + 0.50$$

$$11.00 = 5 + 4 \times 2 - 2.00$$

$$19.58 = 5 + 4 \times 3 + 2.58$$

$$20.00 = 5 + 4 \times 4 - 1.00$$

The least squares solution here is:

$$\beta_0 = 5; \beta_1 = 4$$

- This system of (linear) equations can be compactly represented (and solved using matrix algebra) as $\mathbf{Y} = \mathbf{X}\beta + \epsilon$

WHAT NLLS SOLVES (AND HOW)

- In an intrinsically non-linear model such as

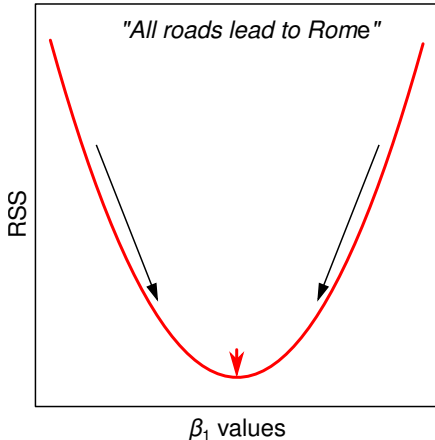
$$y_i = \beta_0 e^{\beta_2 x_i} + \varepsilon_i ,$$

the nice trick of solving $\mathbf{Y} = \mathbf{X}\beta + \varepsilon$ algebraically is impossible

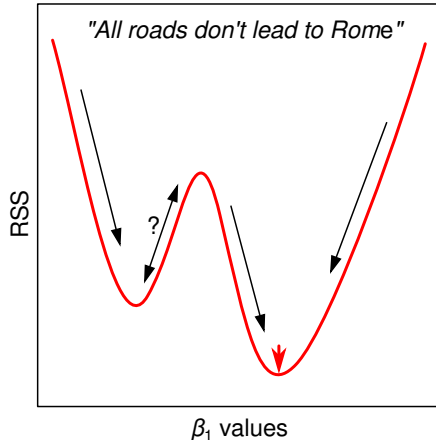
- But we can use brute-force computation to find close-to-optimal least squares minimization:
 - Choose starting (initial values for the parameters we want to estimate (β_j 's)
 - Then, adjust the parameters *iteratively* (using a specific “algorithm” that is better than searching *randomly*) such that the RSS is gradually decreased
 - Eventually, if it all goes well, a combination of β_j 's that is *very close* to the desired solution (where the RSS is *approximately* minimized) can be found

THE NLLS OPTIMIZATION PROCESS

Linear Least-Squares Minimization



Non-Linear Least-Squares Minimization



OK, FINE, WHY WOULD I EVER NEED NLLS?

- Many observations in biology are just *not* well-fitted by a linear model
- That is, the underlying biological phenomena/phenomenon are not well-described by a linear equation
- Examples:
 - Michaelis-Menten biochemical (reaction) kinetics
 - Allometric growth
 - Responses of metabolic rates to changing temperature
 - Consumer-Resource (e.g., predator-prey) functional responses
 - Individual growth
 - Population growth
 - Time-series data (e.g., fitting a sinusoidal function)
- *Can you think of some examples?*

NLLS FITTING

The general procedure / algorithm is:

- ➊ Start with an initial value for each parameter in the model
- ➋ Generate the curve defined by the initial values
- ➌ Calculate the residual sum-of-squares (RSS)
- ➍ Adjust the parameters to make the curve come closer to the data points. *This the tricky part — more on this in the next slide*
- ➎ Adjust the parameters again so that the curve comes even closer to the points (RSS decreases)
- ➏ Repeat 4–5
- ➐ Stop simulations when the adjustments make virtually no difference to the RSS

NLLS FITTING

The *tricky part* — *adjust parameters to make curve come closer to the data points* (step 4) — has two main algorithms that are generally used:

- The **Gauss-Newton** algorithm is the default in the `nls` package (part of the `stats` base package) — good in many cases, but doesn't work very well if the model is mathematically weird (the optimization landscape is difficult) and the starting values for parameters are far-off-optimal
- The **Levenberg-Marquardt (LM)** algorithm switches between Gauss-Newton and “gradient descent” and is more robust against starting values that are far-off-optimal
- the LM algorithm is available in R through the `minpack.lm` package
<http://cran.r-project.org/web/packages/minpack.lm>
- The command is `nlsLM`

NLLS FITS – ASSESSMENT AND REPORTING

- Once the NLLS fitting is done, you need to get the *goodness of fit measures*
- First, of course, examine the fits visually
- Report the goodness-fit results:
 - Sums of deviations of the data points from the final model fit (final RSS)
 - Estimated coefficients
 - For each coefficient, standard error (can be used for CI's), t-statistic and corresponding (two-tailed) p-value
- You will learn to calculate all these in the practicals
- You may also want to *compare and select between multiple competing models*
- Unlike Linear Models, R^2 values *should not* be used to interpret the quality of the fit of NLLS fit (more on this in the practicals).

NLLS ASSUMPTIONS

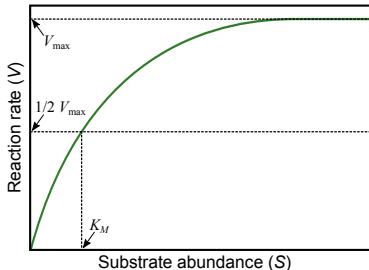
NLLS-regression has all the assumptions of OLS-regression:

- No (in practice, minimal) measurement error in explanatory variable (x -axis variable)
- Data have constant normal variance — errors in the y -axis are homogeneously distributed over the x -axis range
- The measurement/observation errors are Normally distributed (Gaussian)
- What if the errors are not normal? — Interpret results cautiously, and use Maximum Likelihood or Bayesian fitting methods instead

PRACTICAL: MICHAELIS-MENTEN BIOCHEMICAL KINETICS

$$V = \frac{V_{\max}[S]}{K_m + [S]}$$

- S = Substrate density
- V_{\max} = Maximum reaction rate (at saturating substrate concentration)
- K_M = Half-saturation constant; the S at which reaction rate reaches half of possible maximum ($= \frac{1}{2} V_{\max}$)



- You will use NLLS fitting to obtain estimates of V_{\max} and K_H
- Note that $V_{\max} \leq 0$ and $K_H \leq 0$ are physically impossible (useful for picking starting values)

READINGS

- Motulsky, Harvey, and Arthur Christopoulos. Fitting models to biological data using linear and nonlinear regression: a practical guide to curve fitting. OUP USA, 2004.