

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

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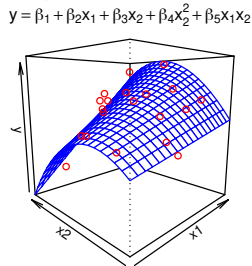
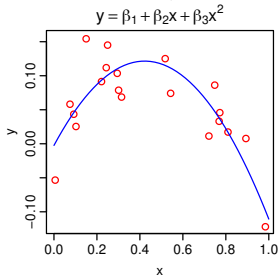
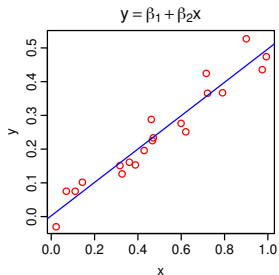
December 7, 2020

OUTLINE

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

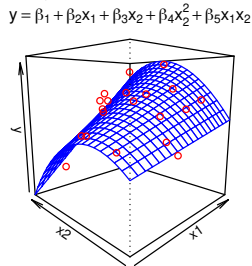
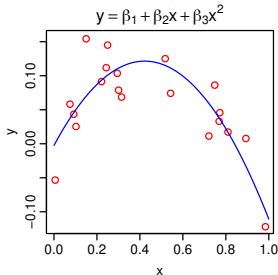
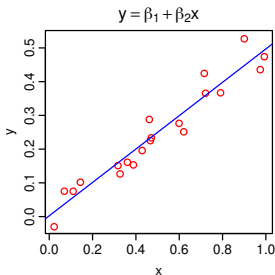
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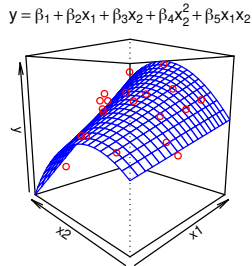
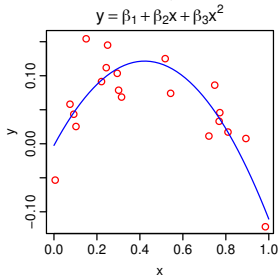
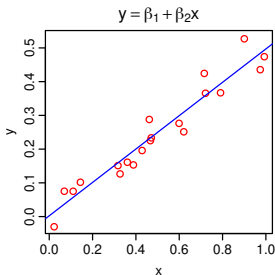
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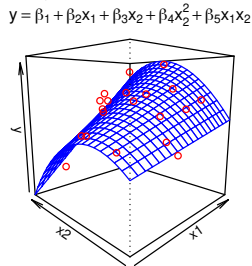
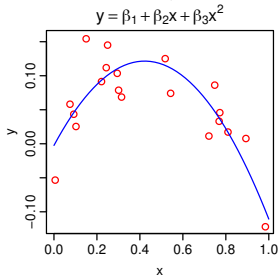
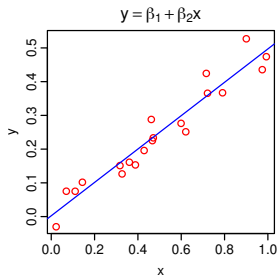
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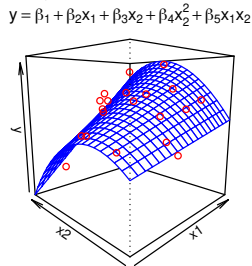
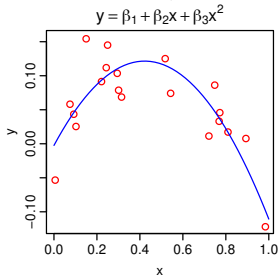
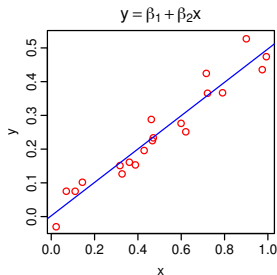
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- Linear models can *include curved responses* (e.g. Polynomial regression)

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

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- 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):

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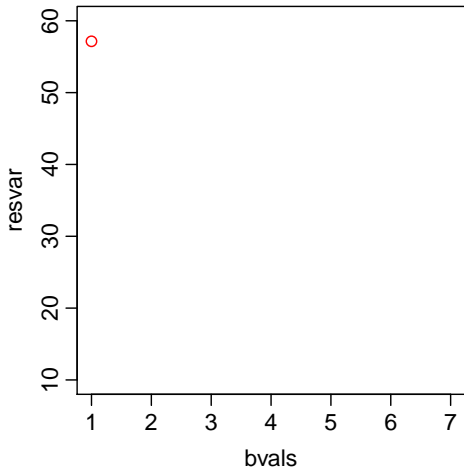
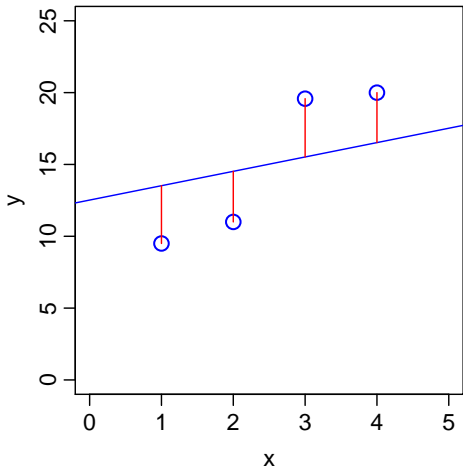
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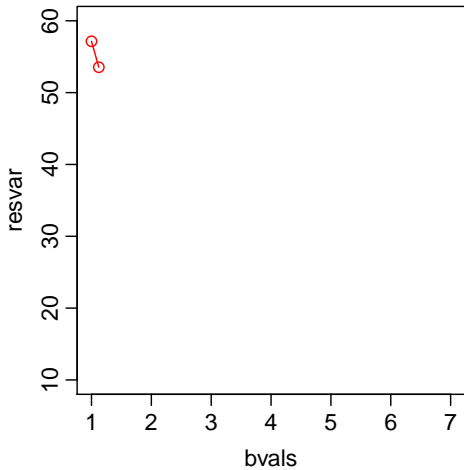
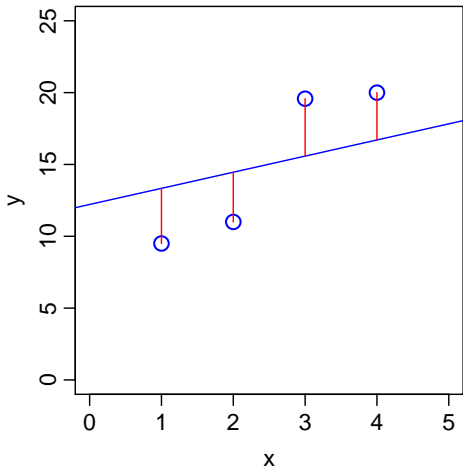
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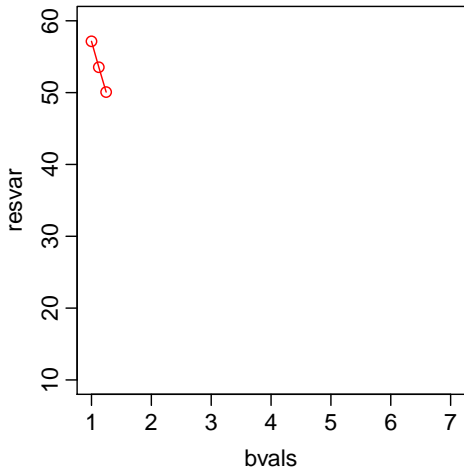
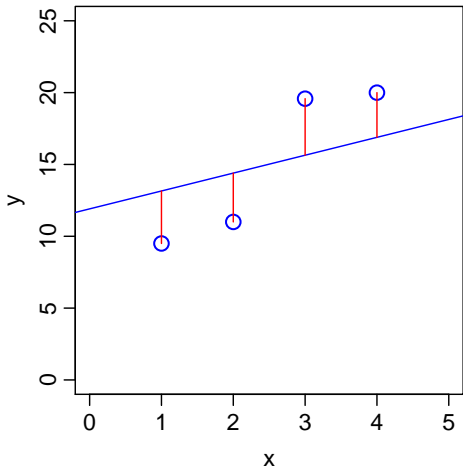
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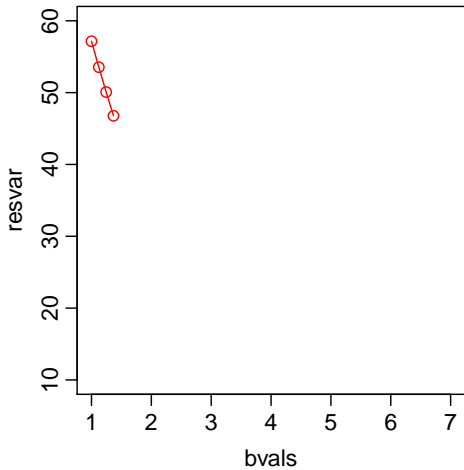
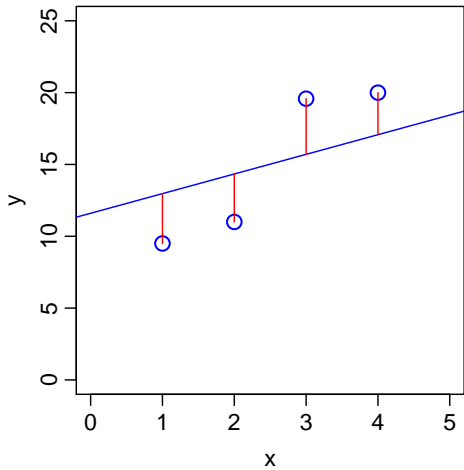
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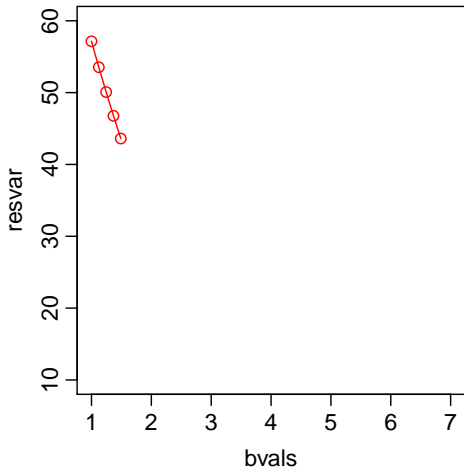
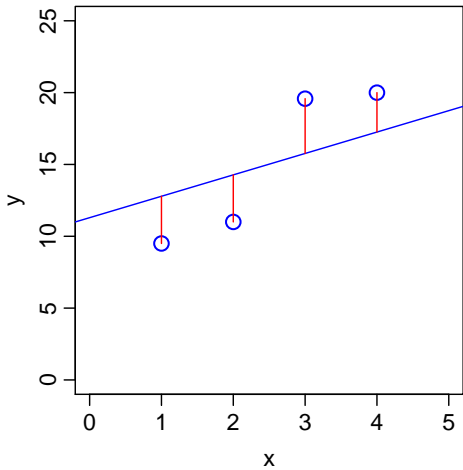
- Let's picture this using a simple (OLS) example; fitting the model $y_1 = \beta_1 x_1 + \epsilon_1 \dots$

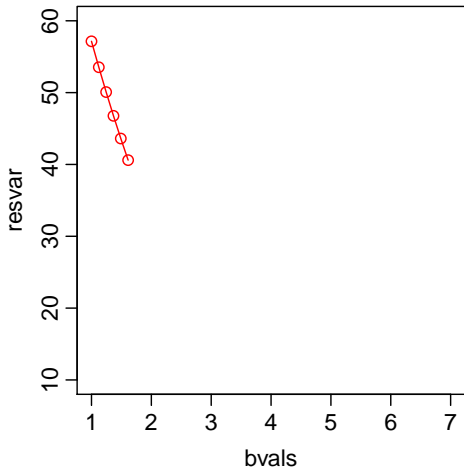
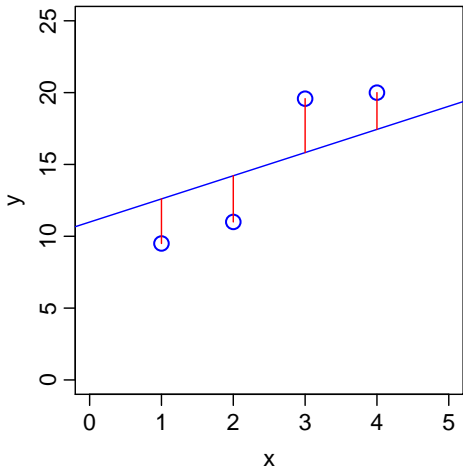


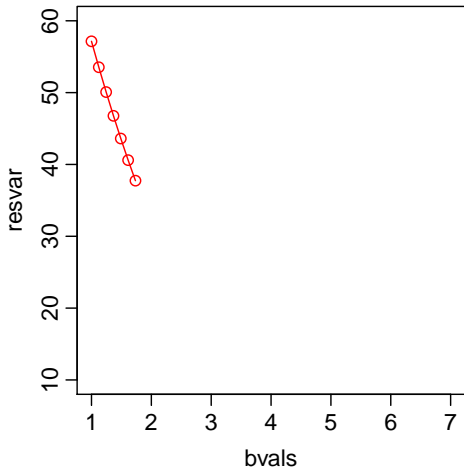
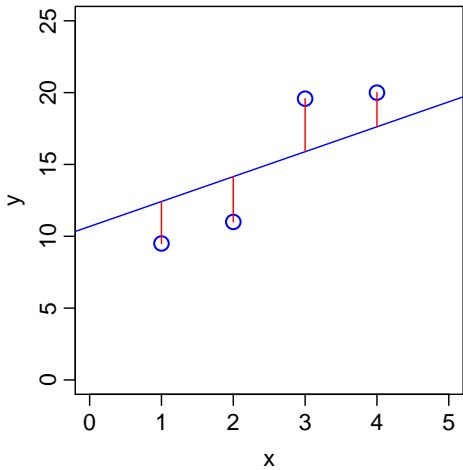


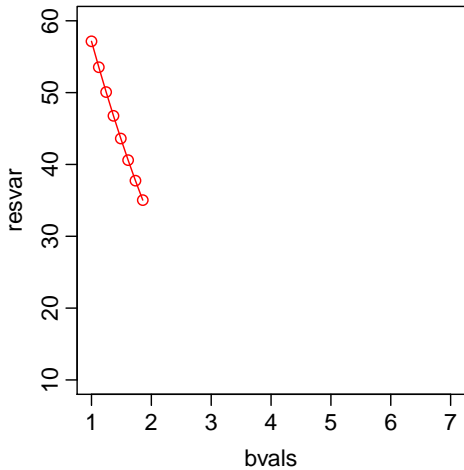
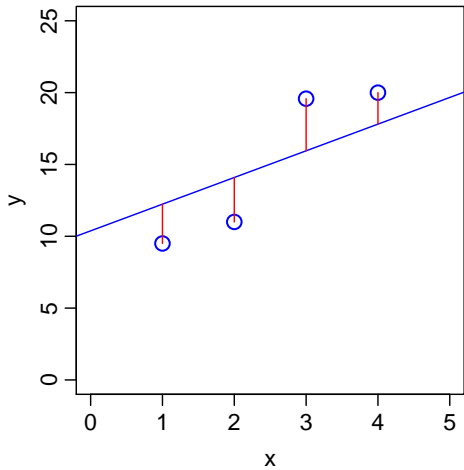


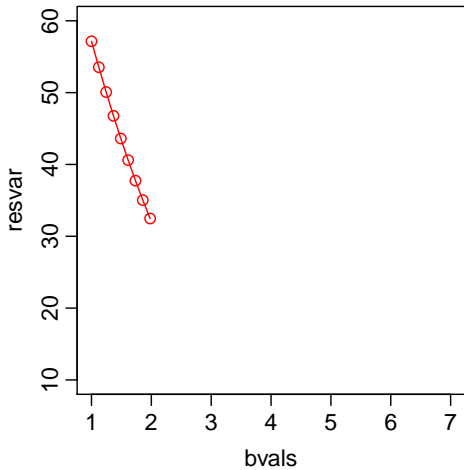
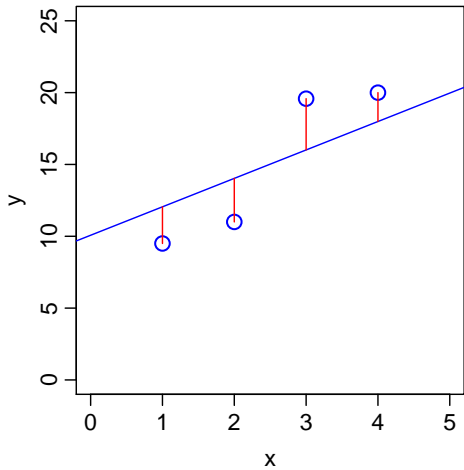


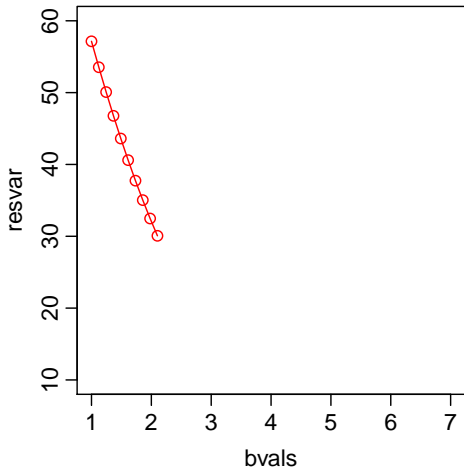
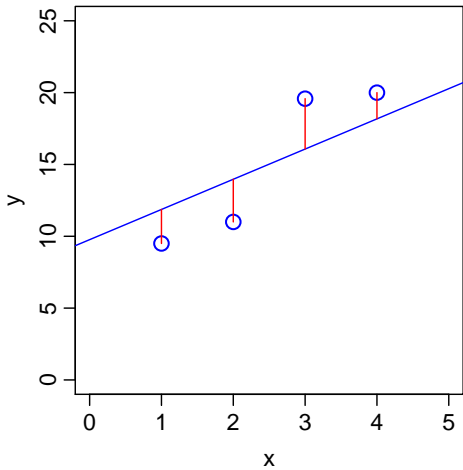


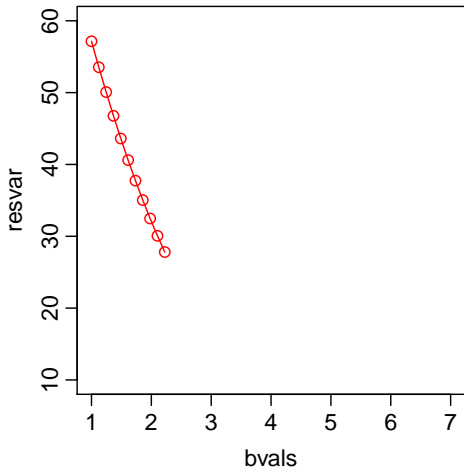
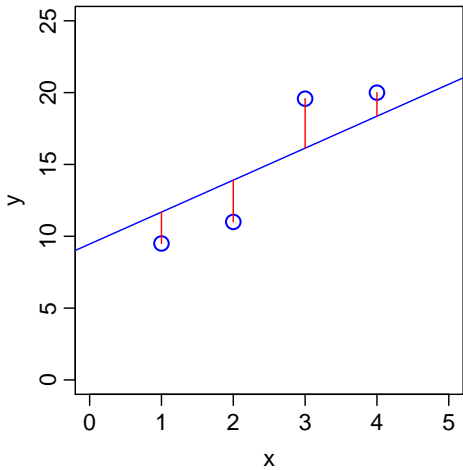


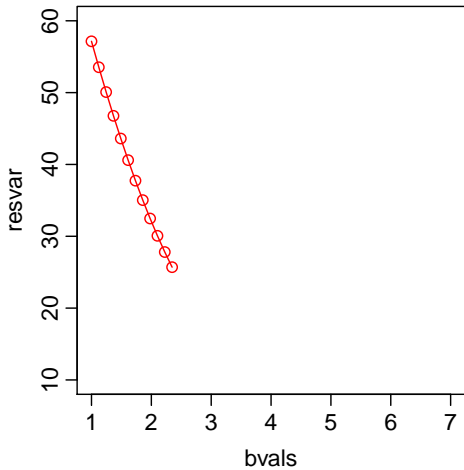
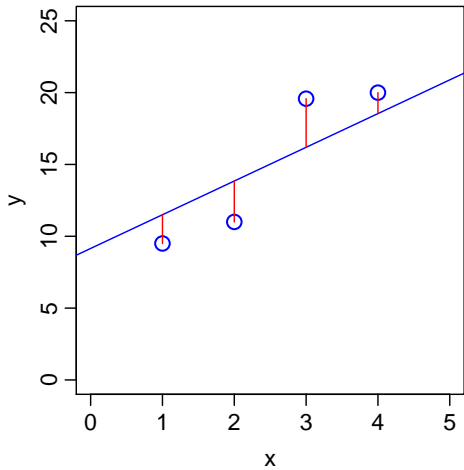


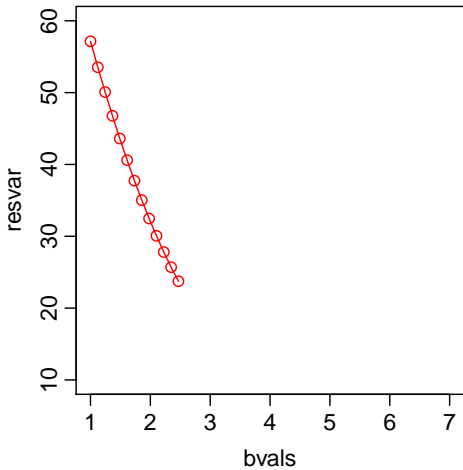
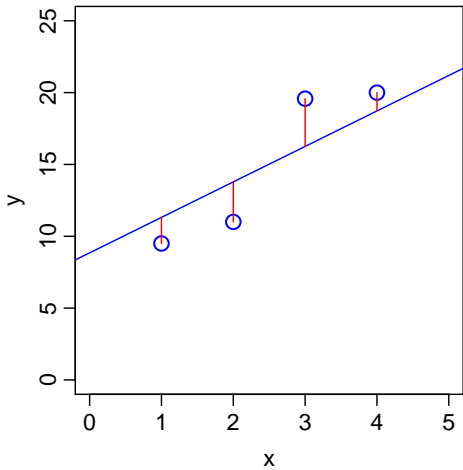


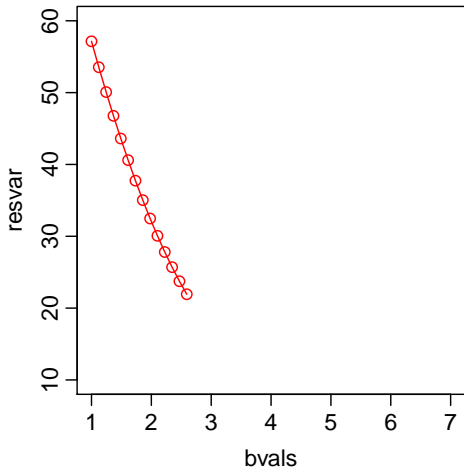
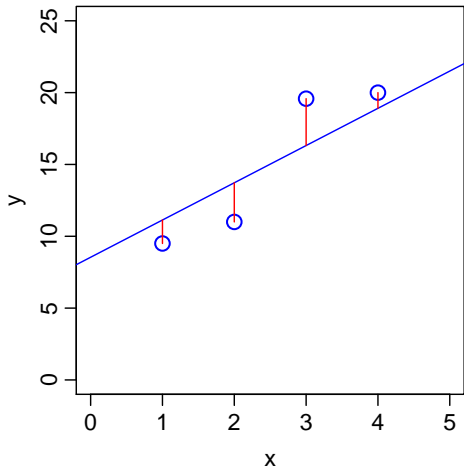


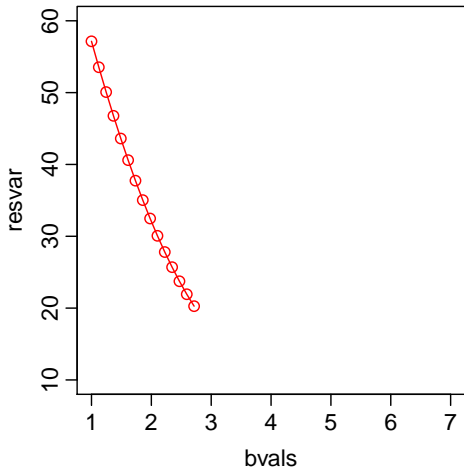
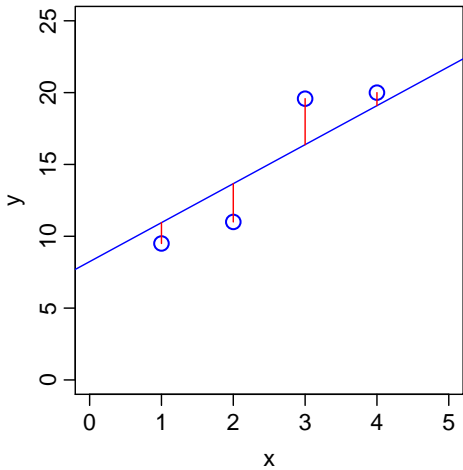


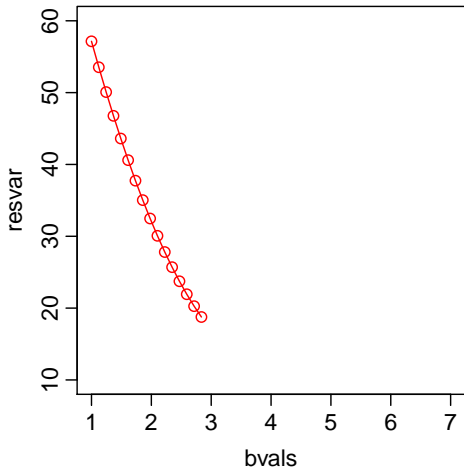
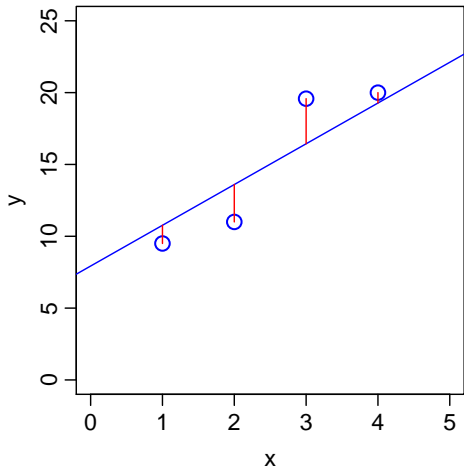


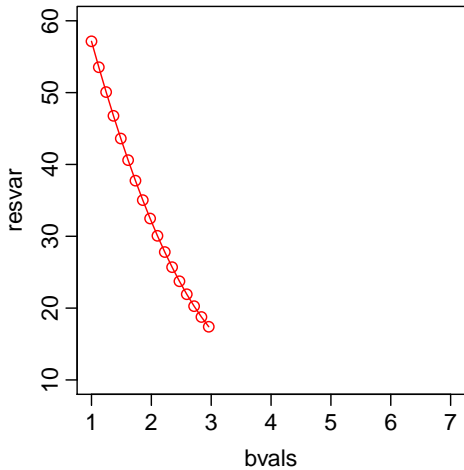
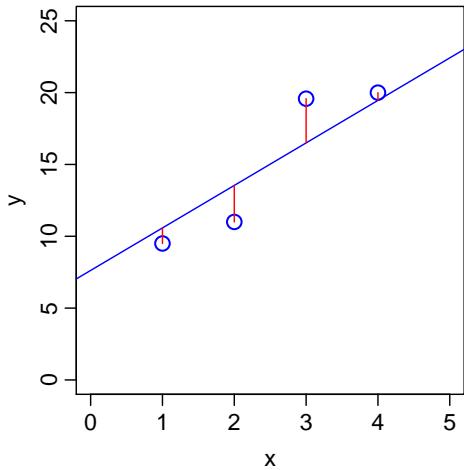


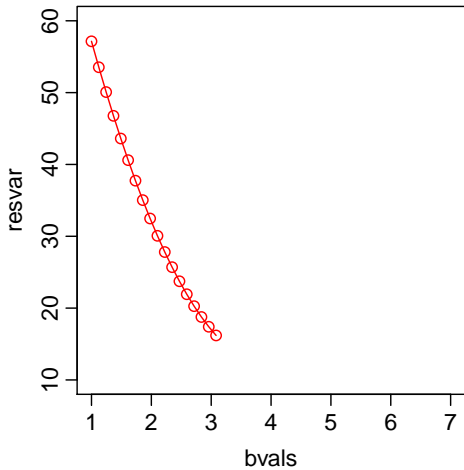
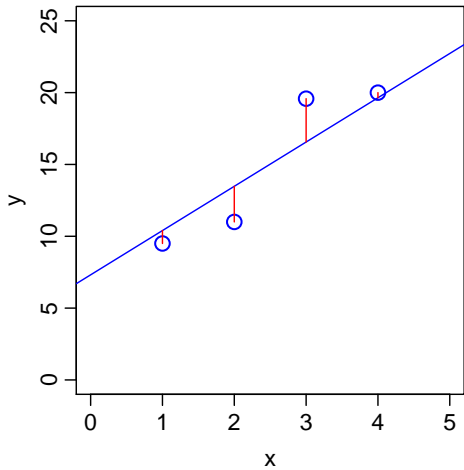


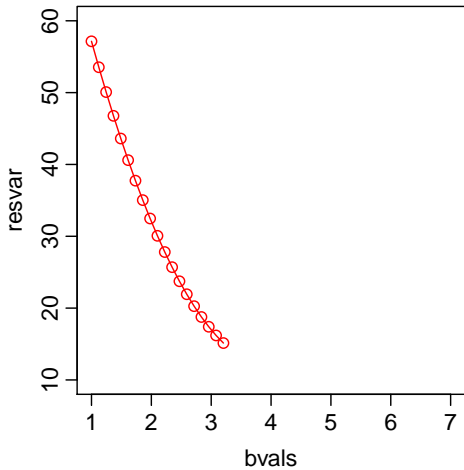
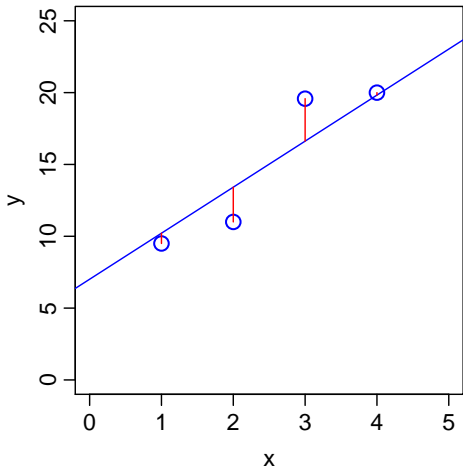


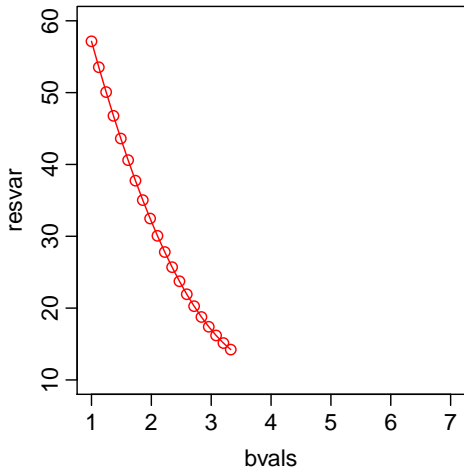
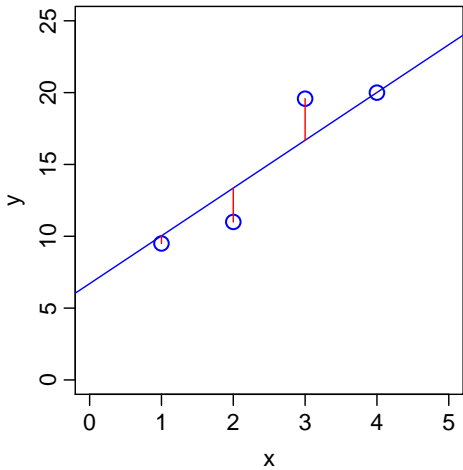


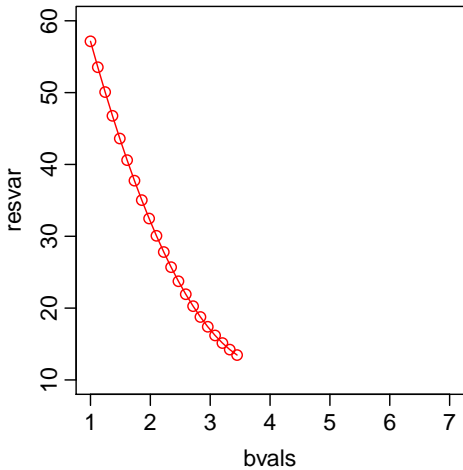
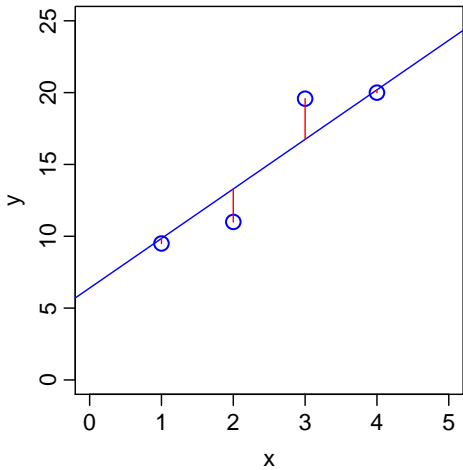


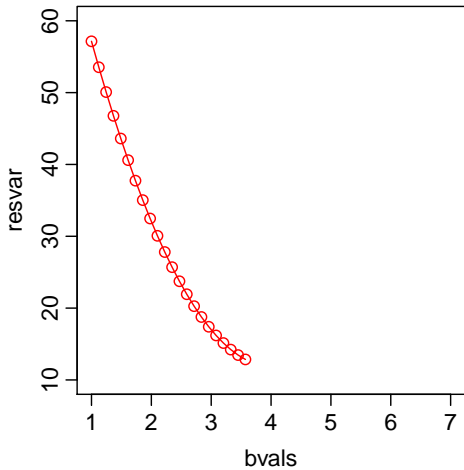
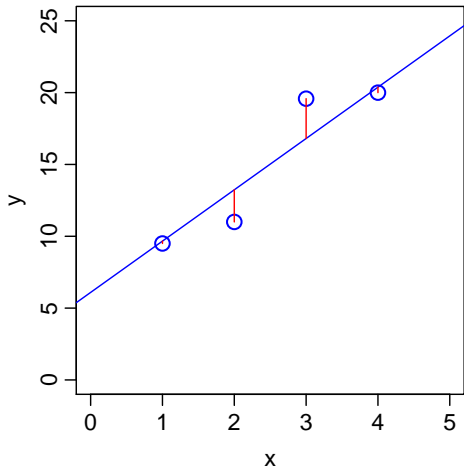


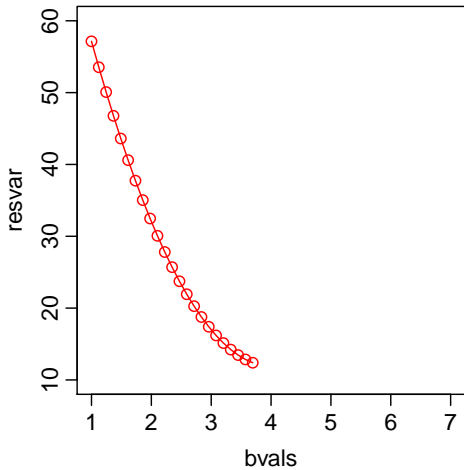
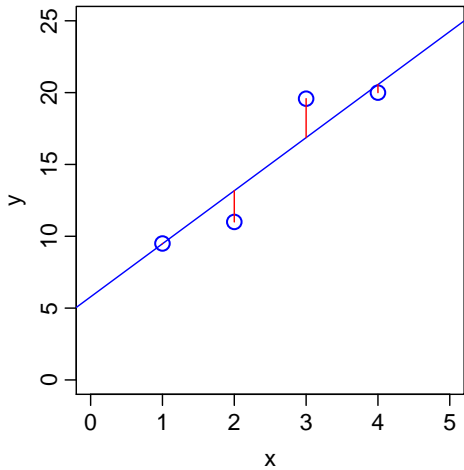


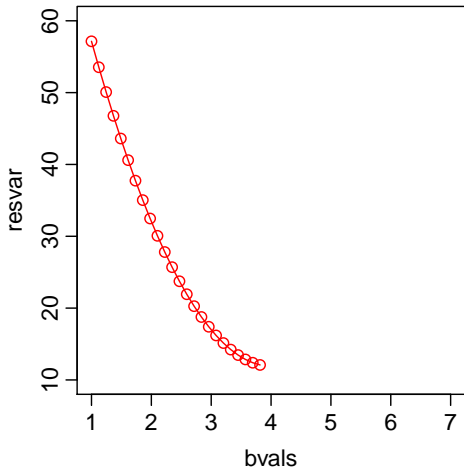
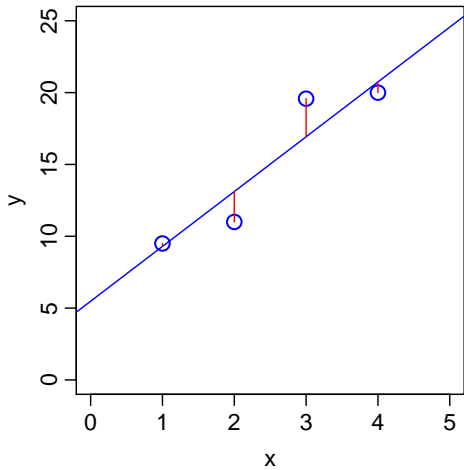


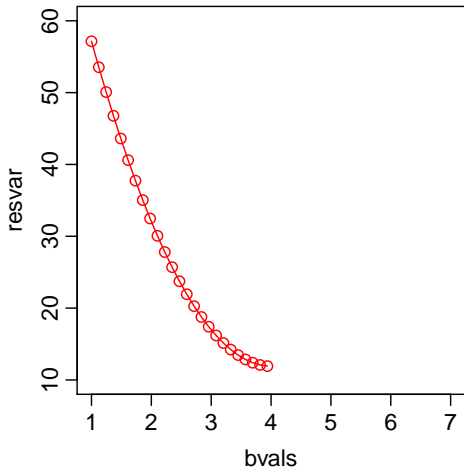
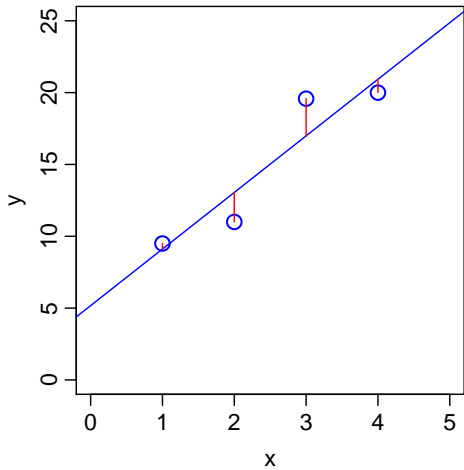


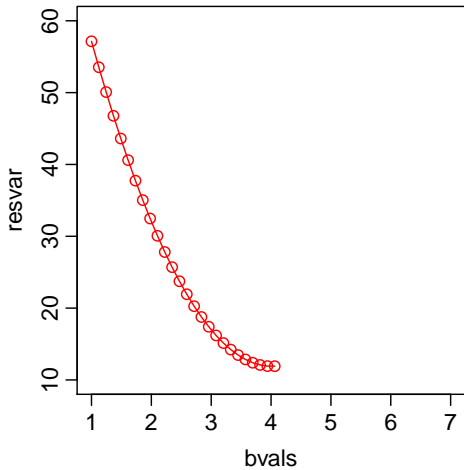
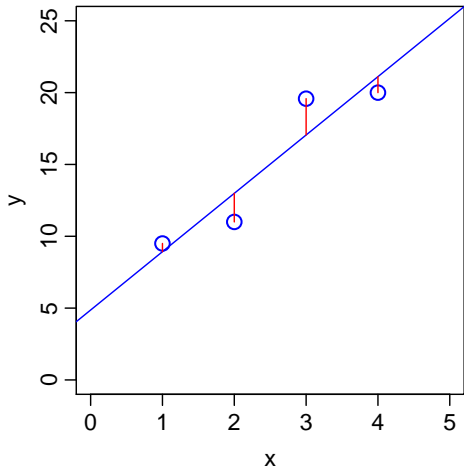


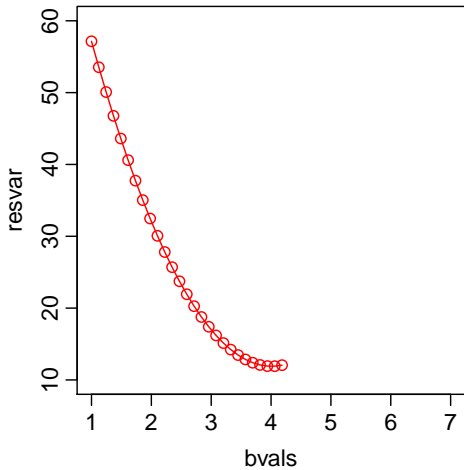
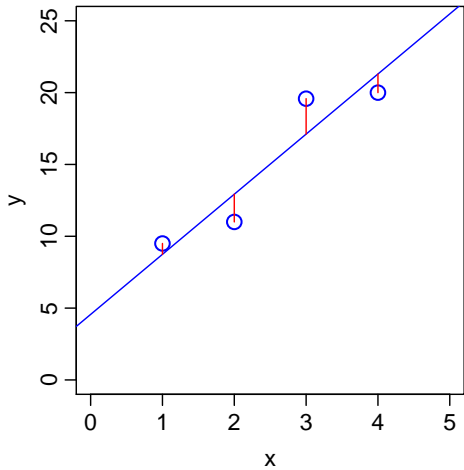


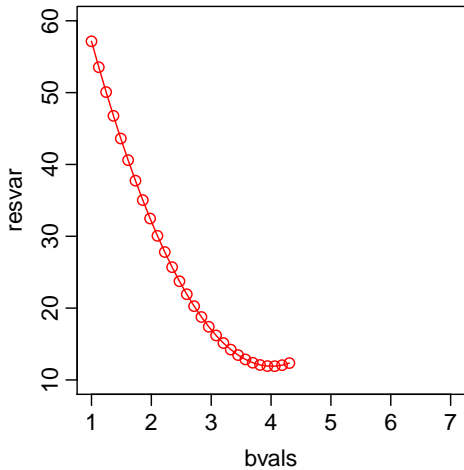
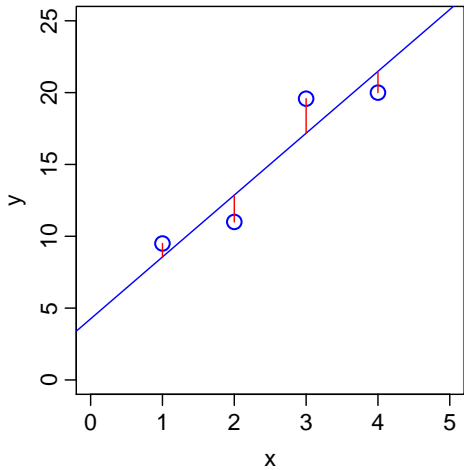


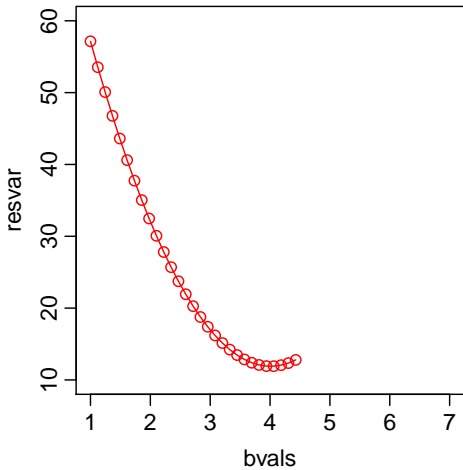
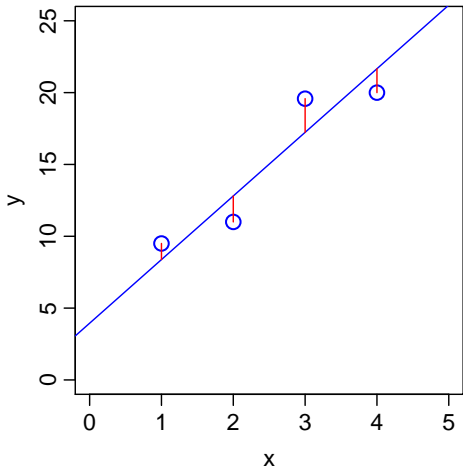


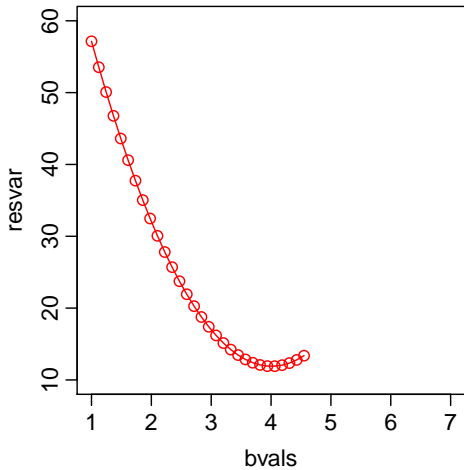
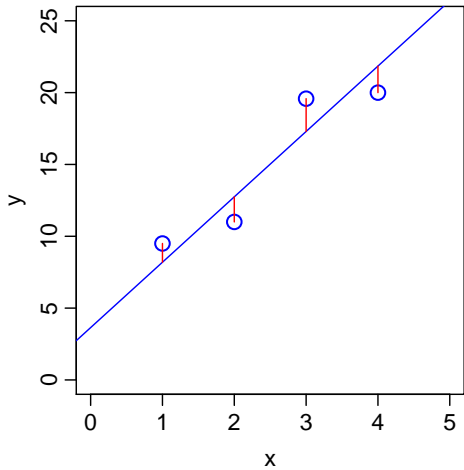


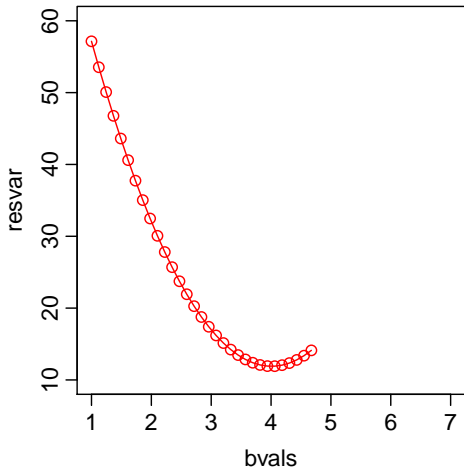
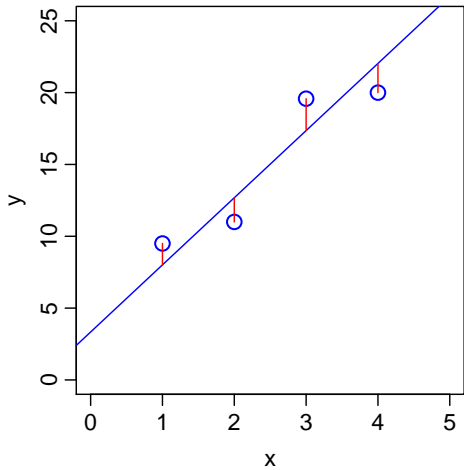


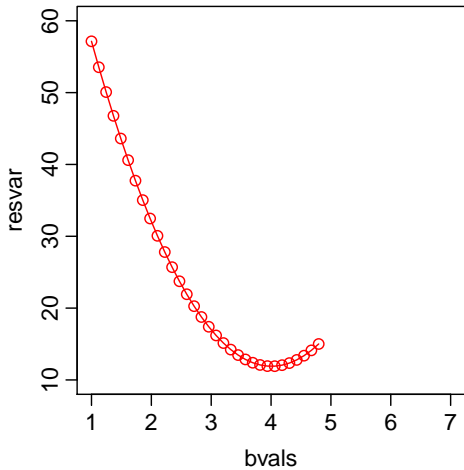
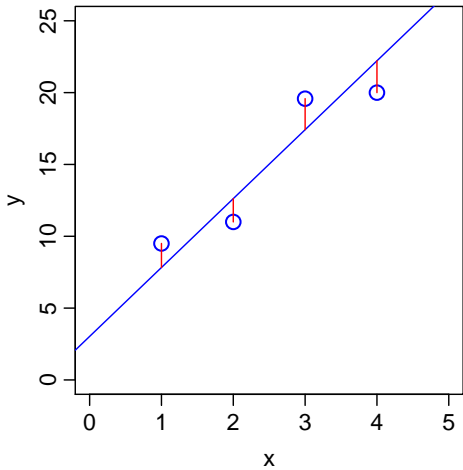


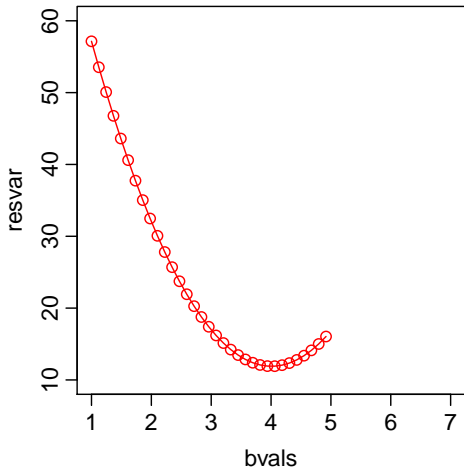
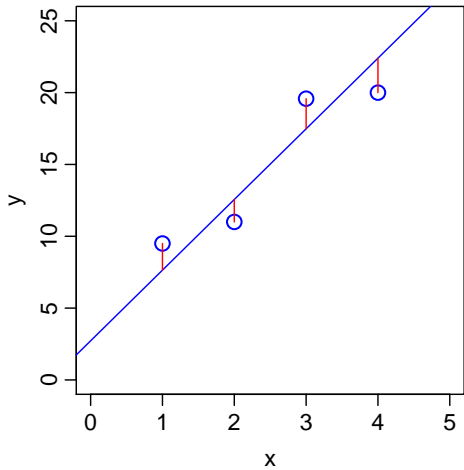


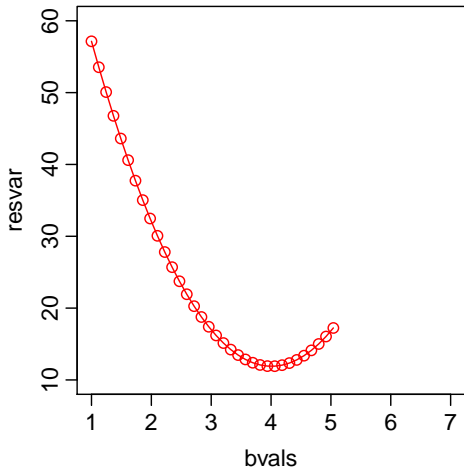
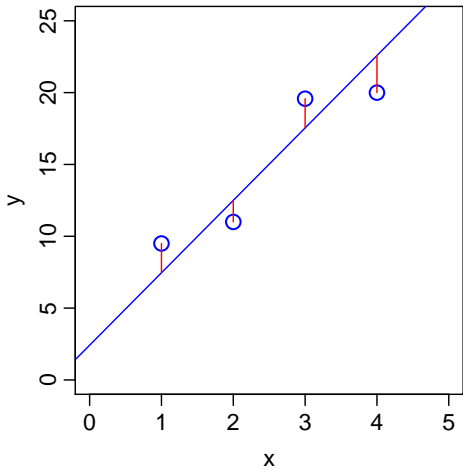


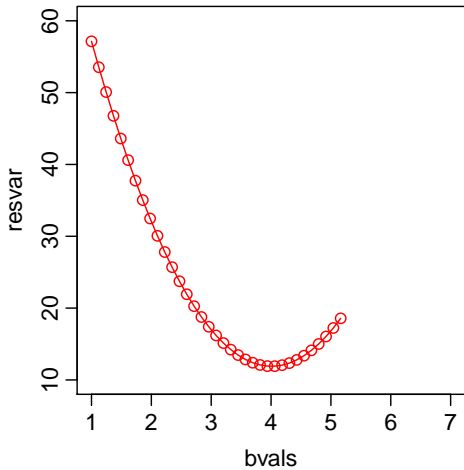
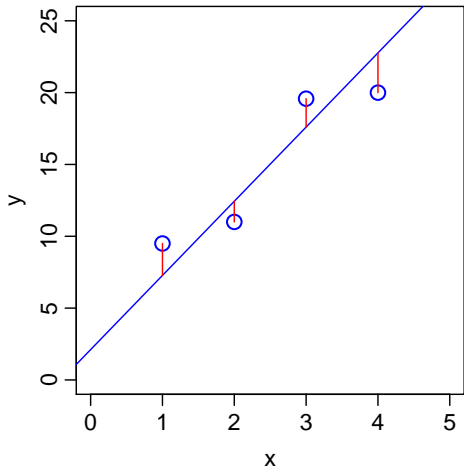


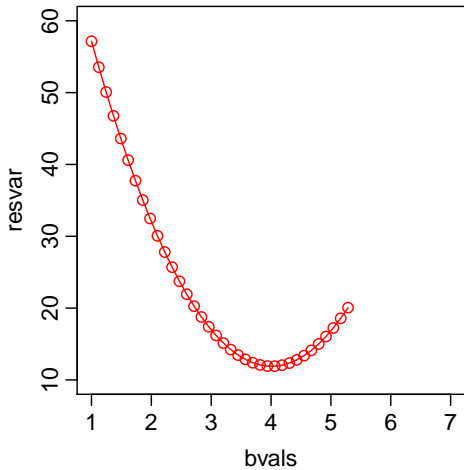
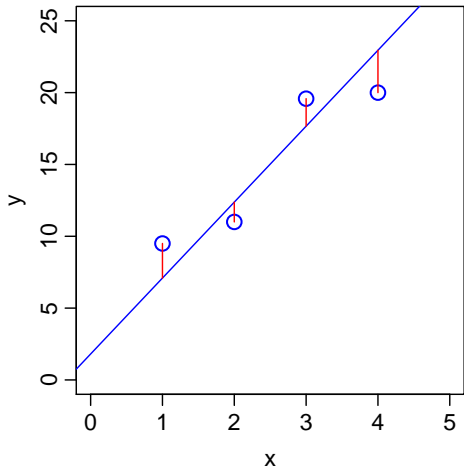


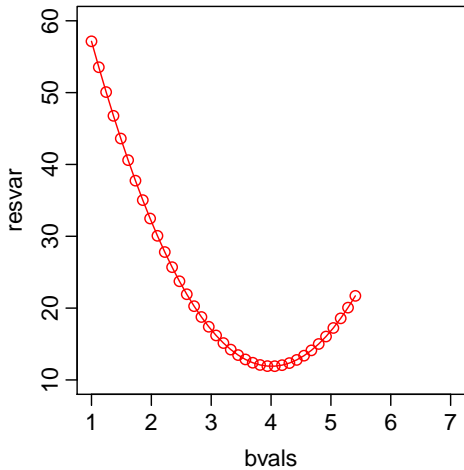
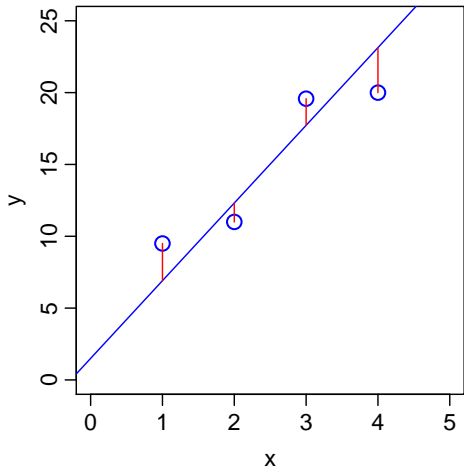


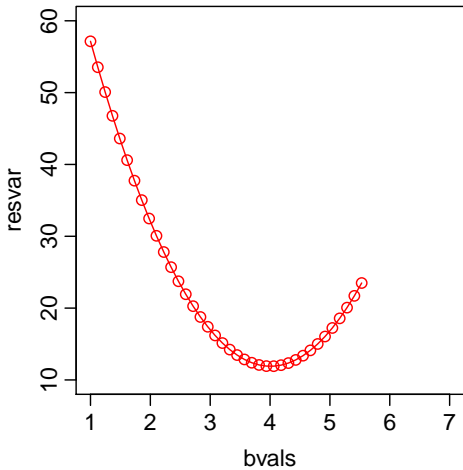
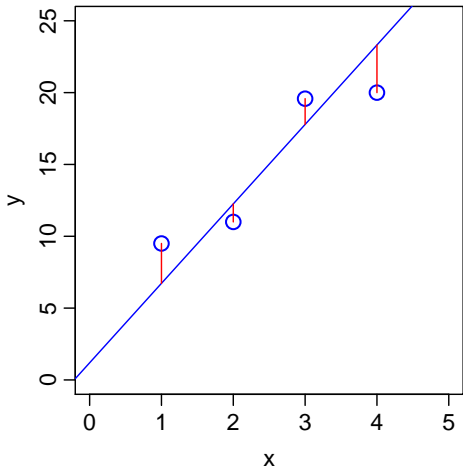


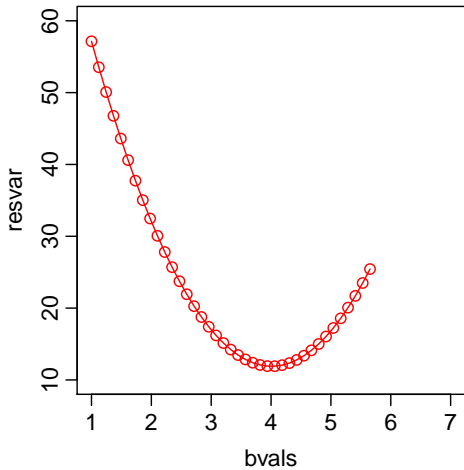
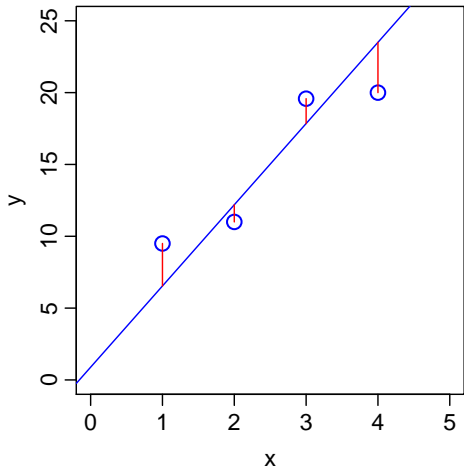


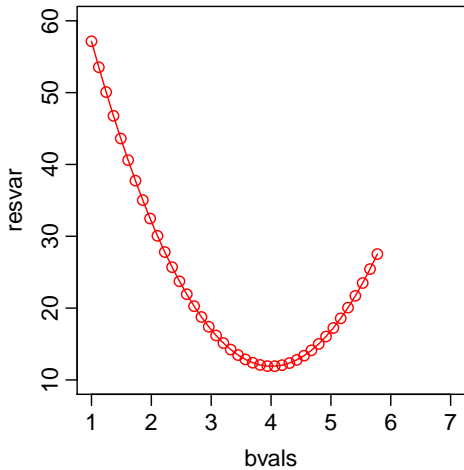
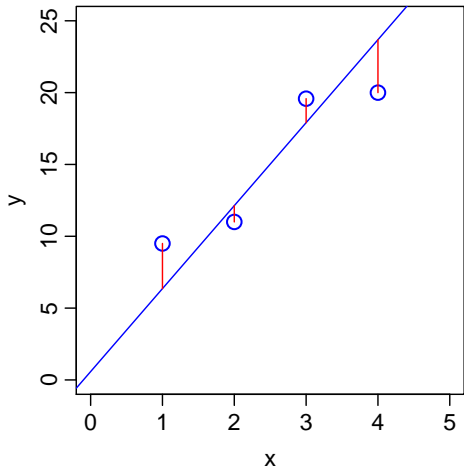


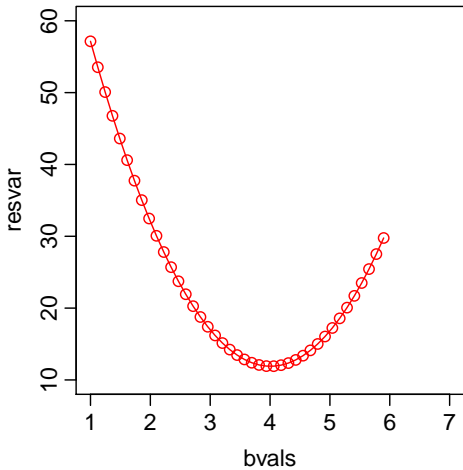
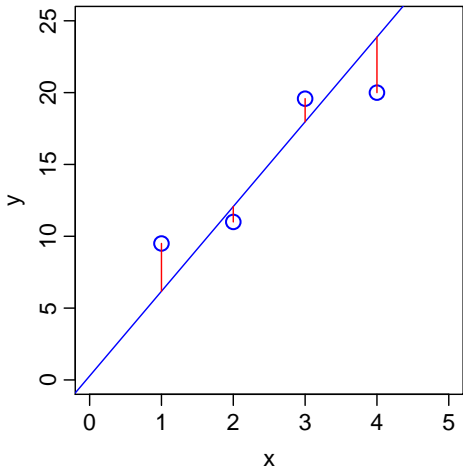


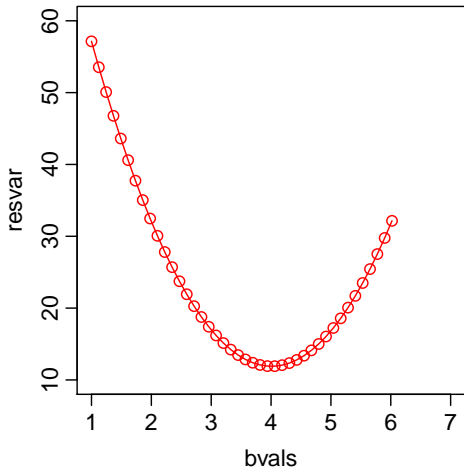
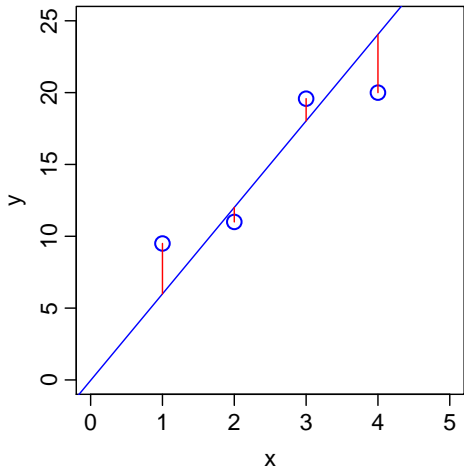


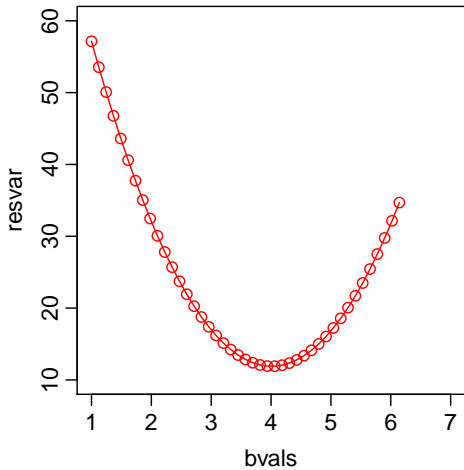
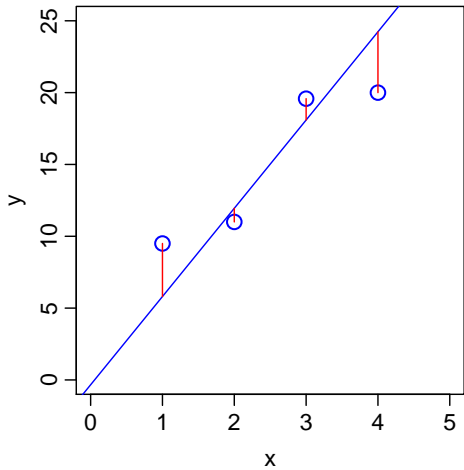


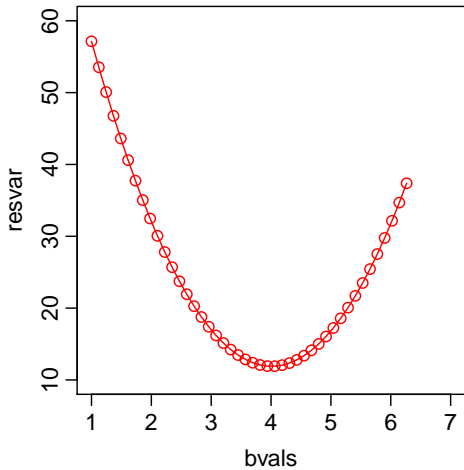
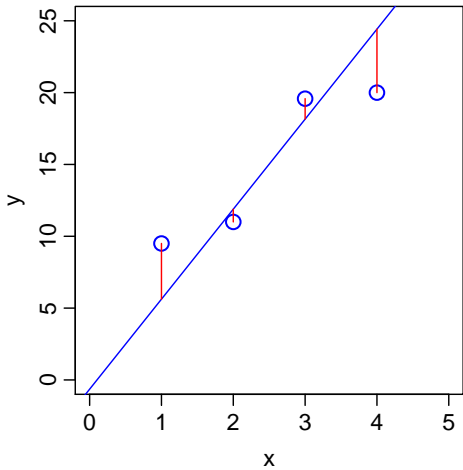


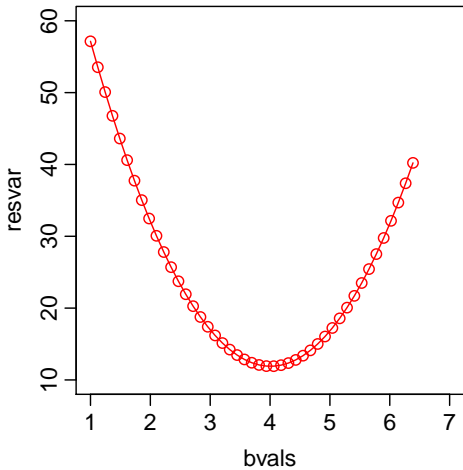
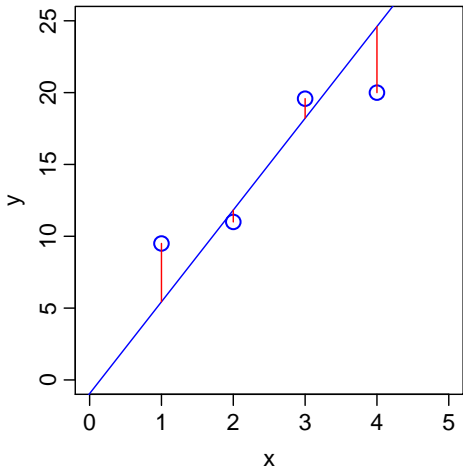


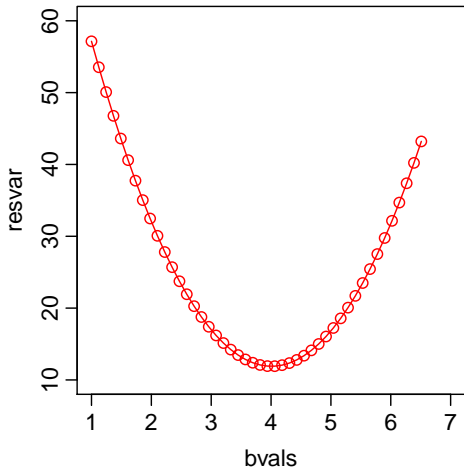
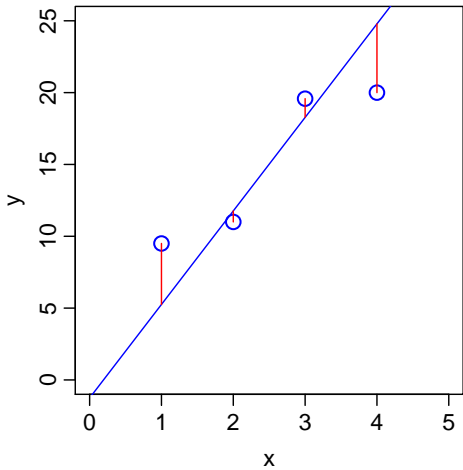


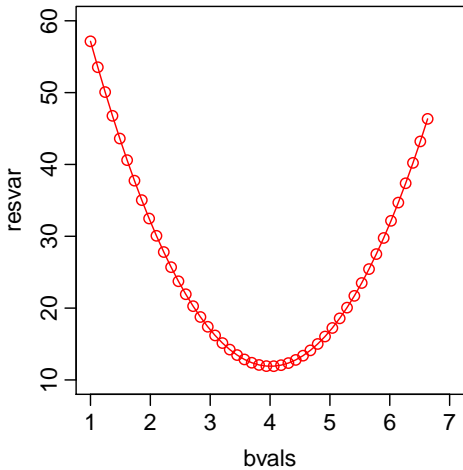
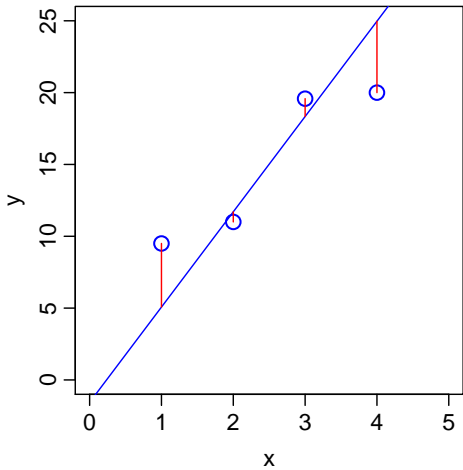


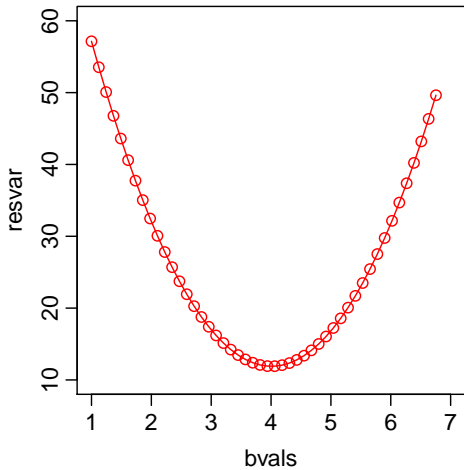
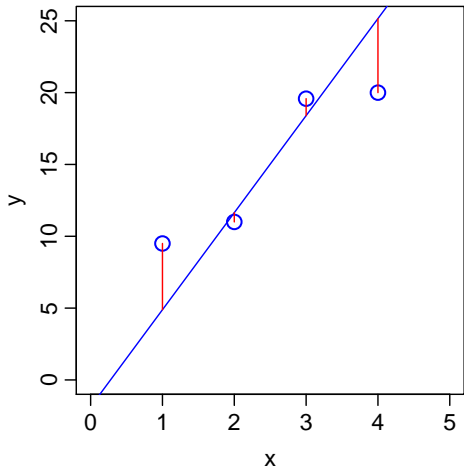


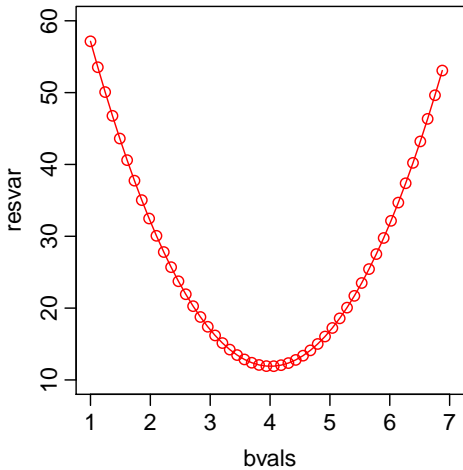
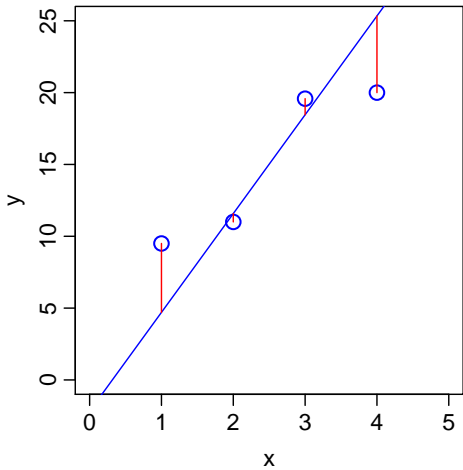


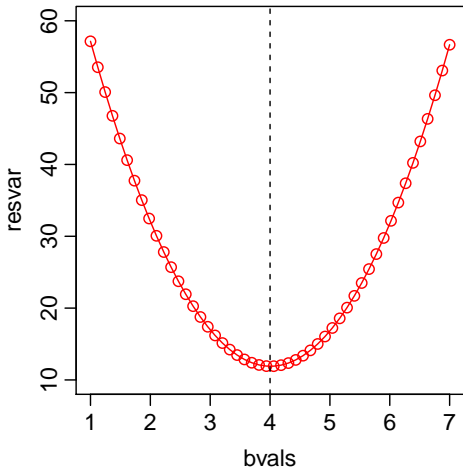
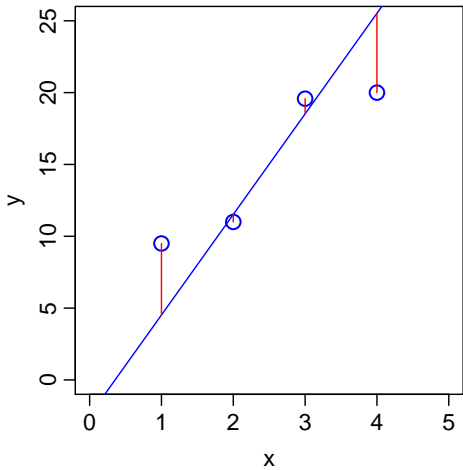




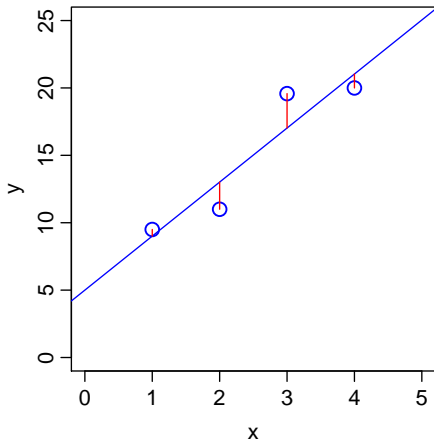








IF THE MODEL IS LINEAR, THE SOLUTION IS EASY USING ALGEBRA



$$y_1 = \beta_0 + \beta_1 x_1 + \varepsilon_1$$

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

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

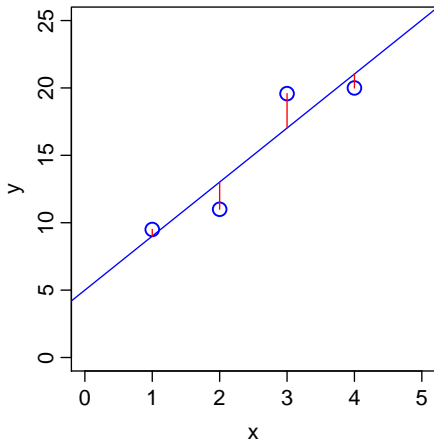
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The least squares solution here is:

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

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- In an intrinsically non-linear model such as

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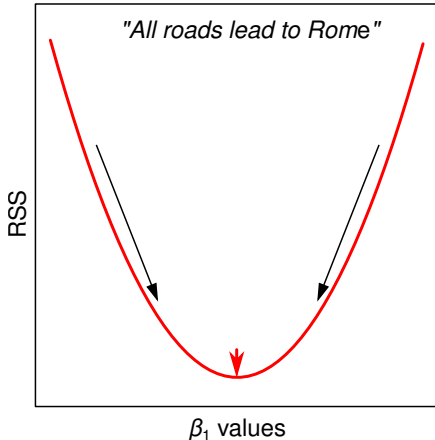
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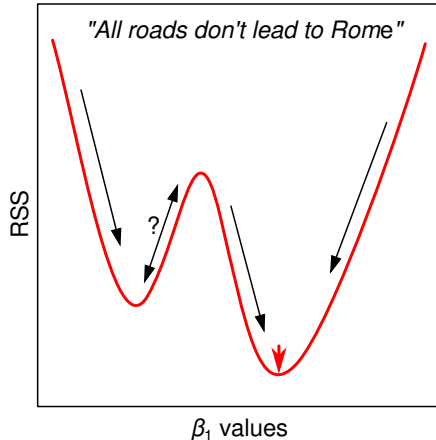
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 - Eventually, if it all goes well, a combination of β_j 's that is *very close* to the desired solution (where the RSS is *approximately* minimized) can be found

THE NLLS OPTIMIZATION PROCESS

Linear Least-Squares Minimization



Non-Linear Least-Squares Minimization



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- *Can you think of some examples?*

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- 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

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- 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).

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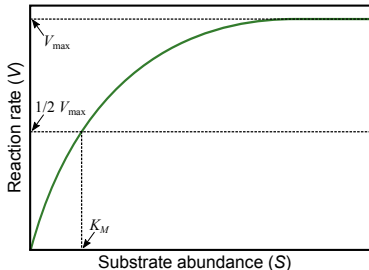
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- The measurement/observation errors are Normally distributed (Gaussian)
- What if the errors are not normal? — Interpret results cautiously, and use Maximum Likelihood or Bayesian fitting methods instead

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.