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

Samraat Pawar

Department of Life Sciences (Silwood Park)

Imperial College London

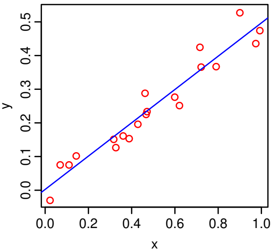
December 7, 2020

OUTLINE

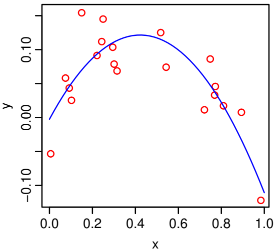
- Why Non-Linear Least Squares regression / fitting?
- The NLLS fitting method
- NLLS in `R`
- Practicals overview

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

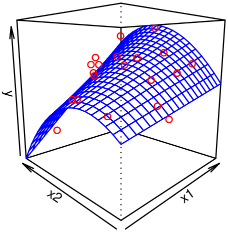
$y = \beta_1 + \beta_2 x$



$y = \beta_1 + \beta_2 x + \beta_3 x^2$



$y = \beta_1 + \beta_2 x_1 + \beta_3 x_2 + \beta_4 x_2^2 + \beta_5 x_1 x_2$



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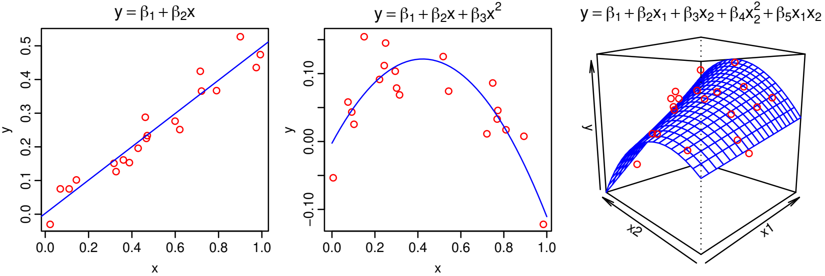

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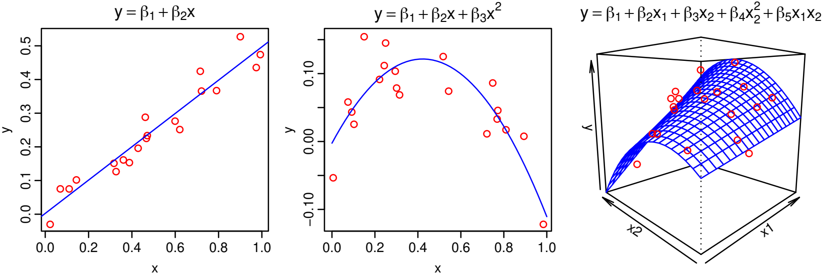

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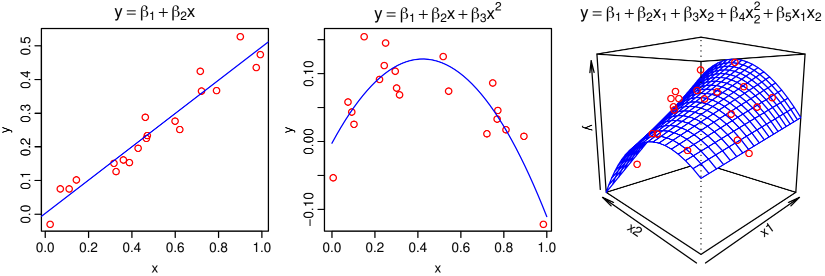

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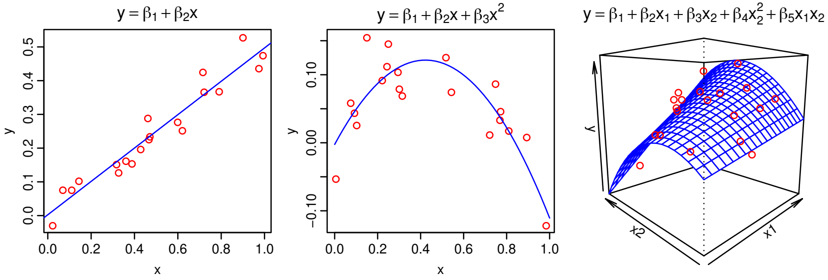

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- Linear models can *include curved responses* (e.g. Polynomial regression)

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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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Recall what the Least Squares method does:

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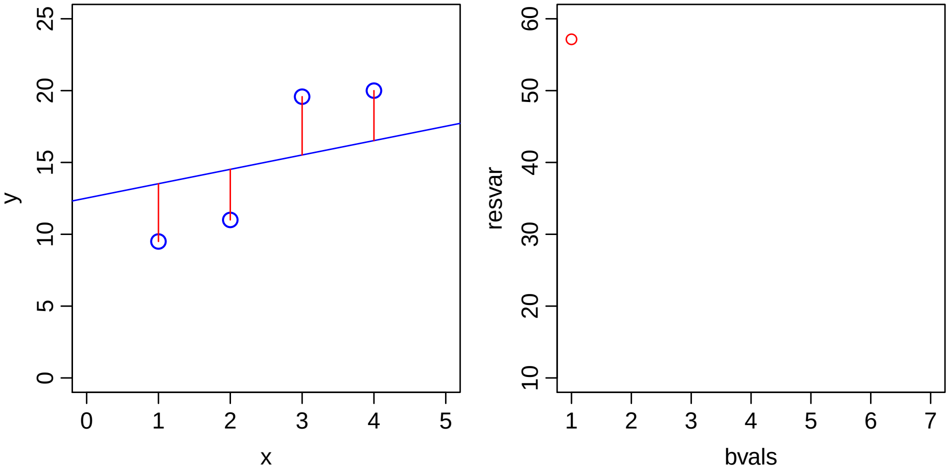
- Let's picture this using a simple (OLS) example; fitting the model $y_1 = \beta_1 x_1 + \varepsilon_1$...



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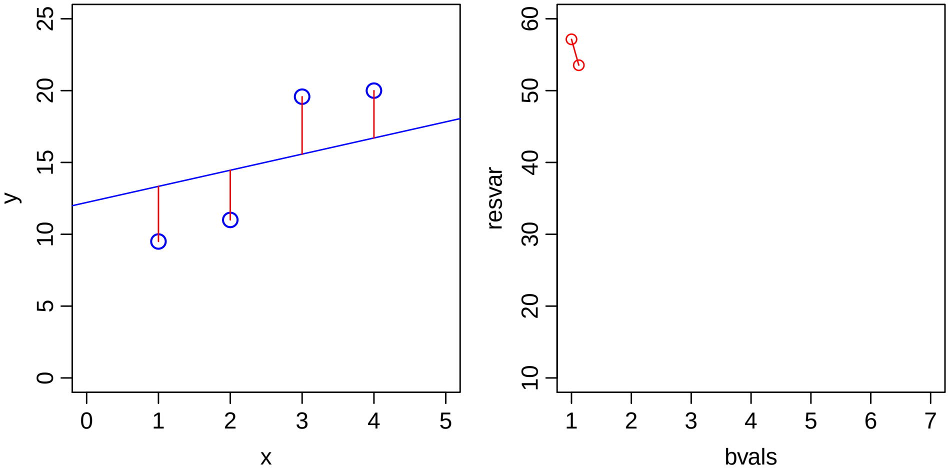
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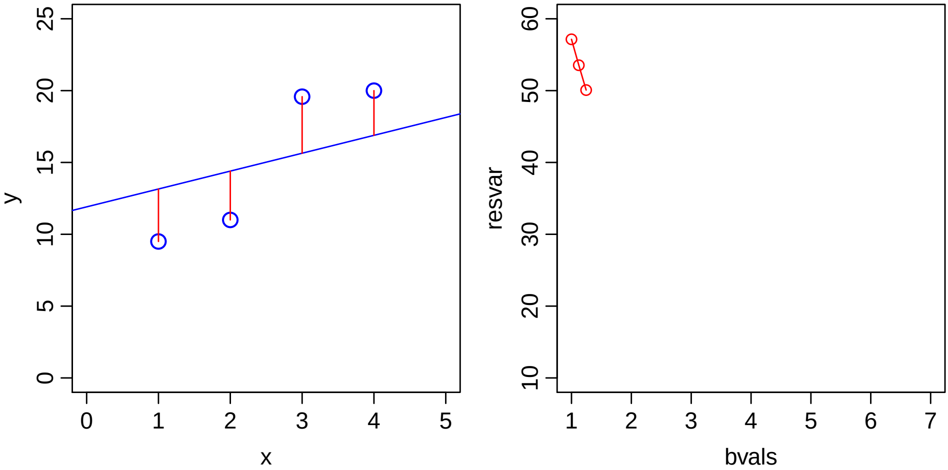

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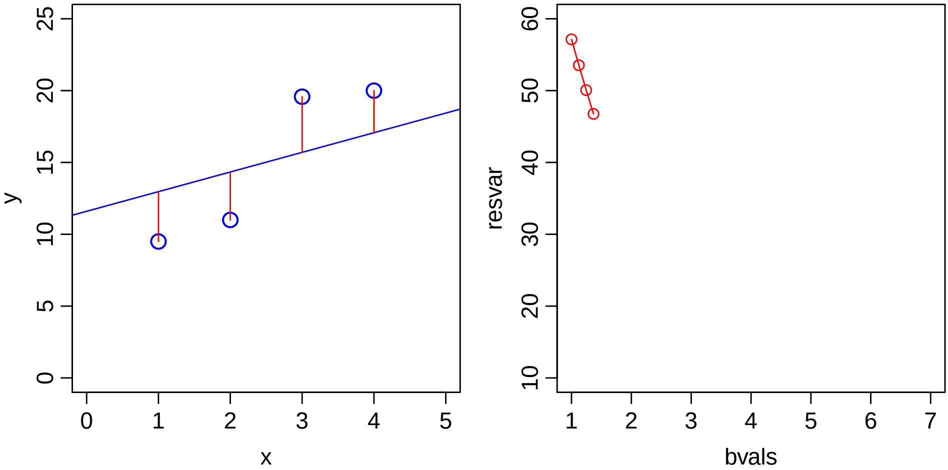
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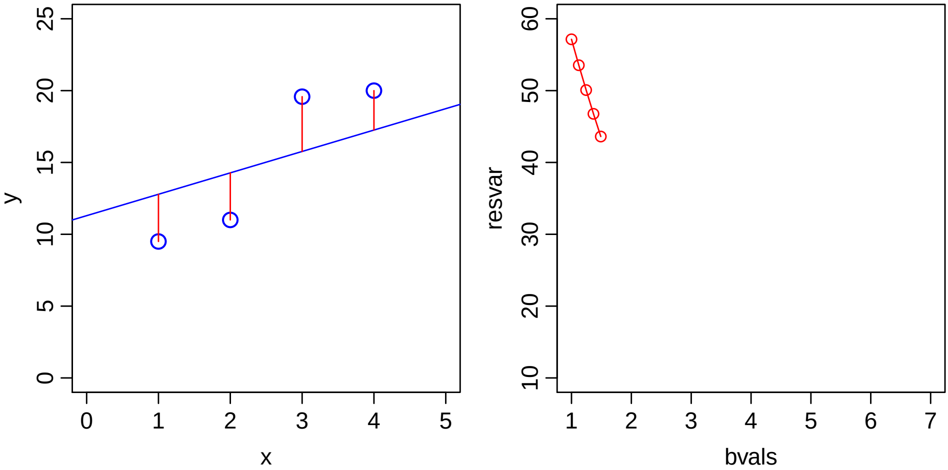

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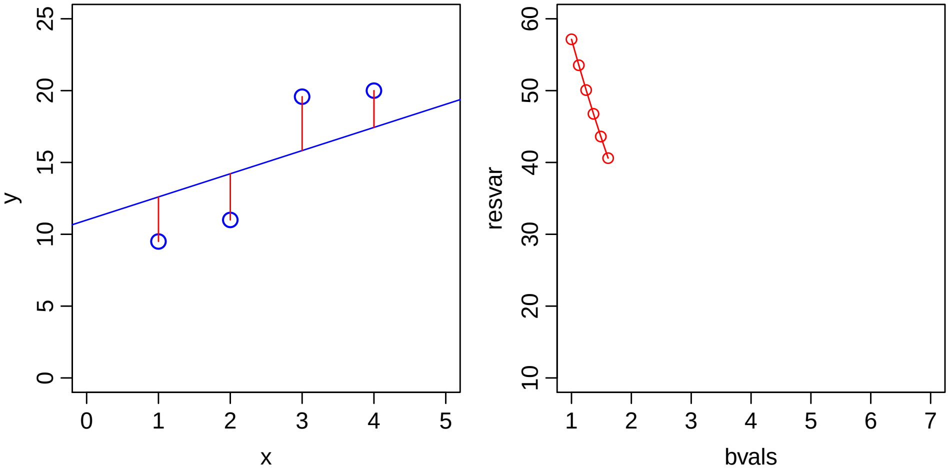

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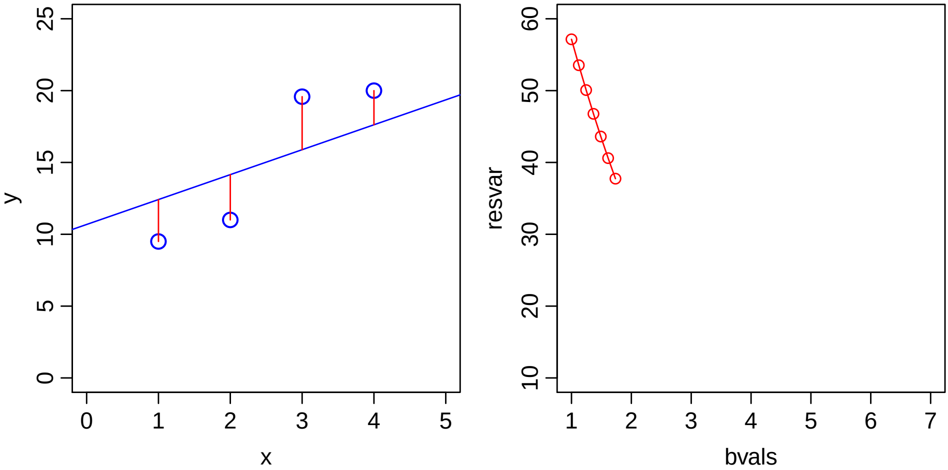

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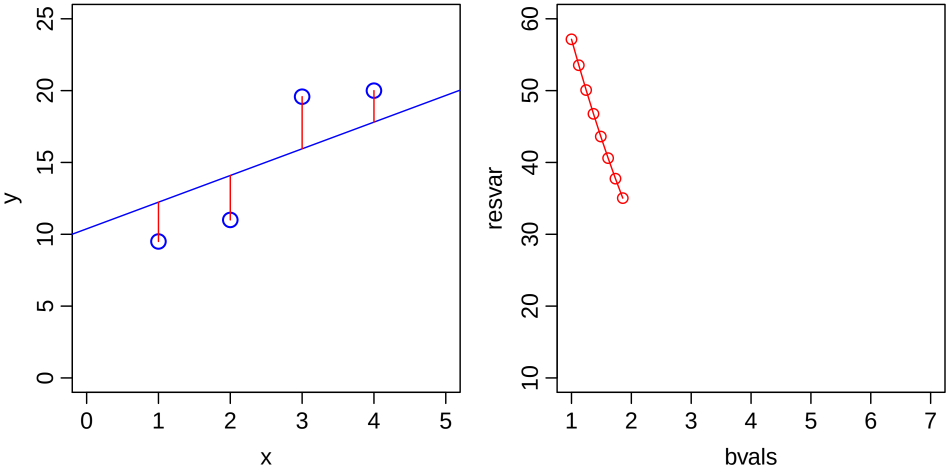

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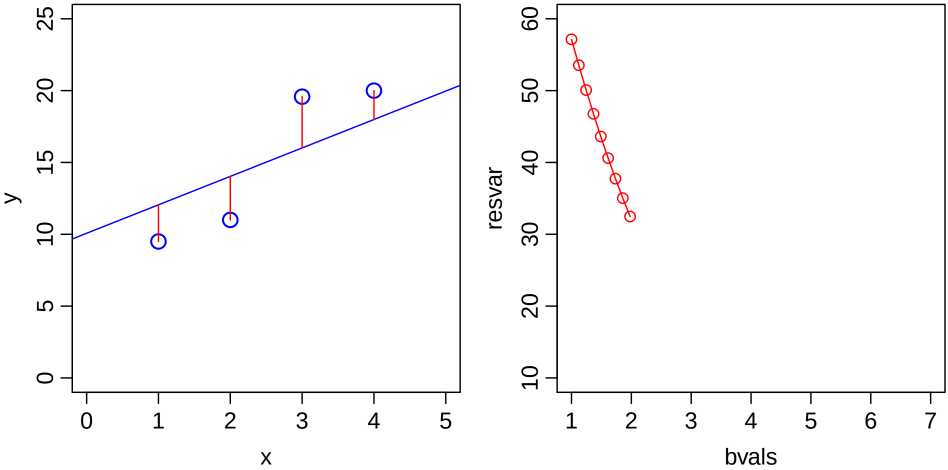

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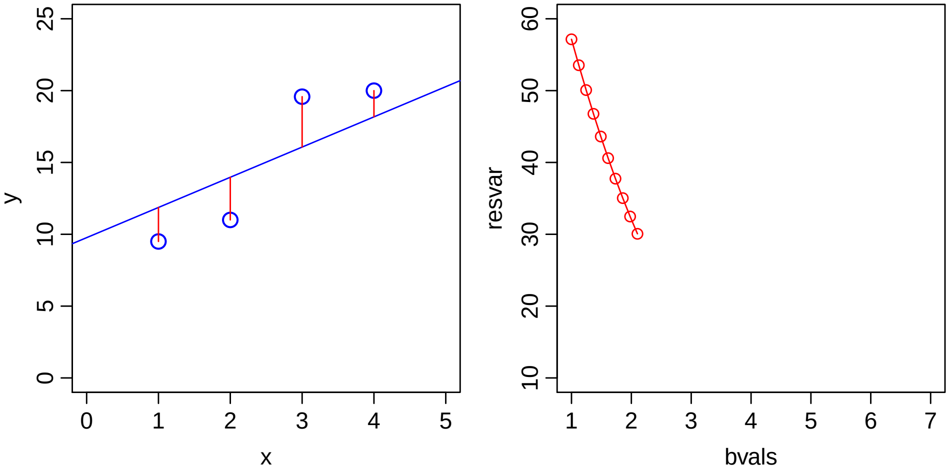

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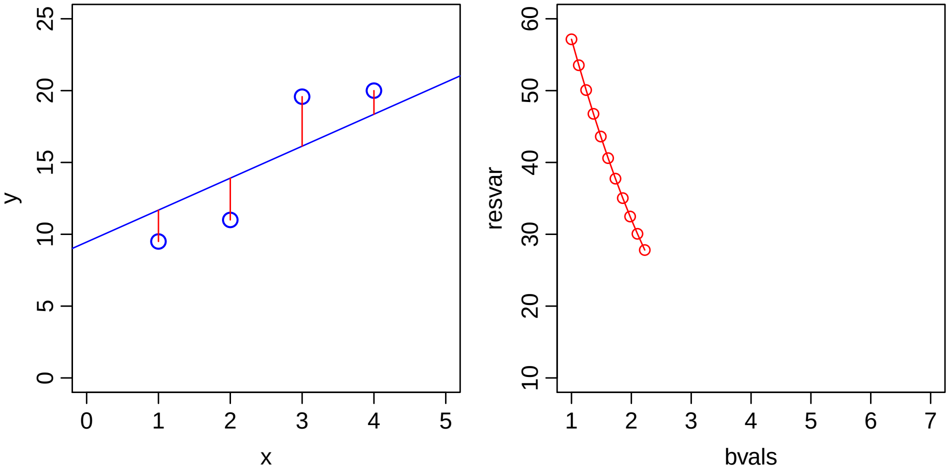

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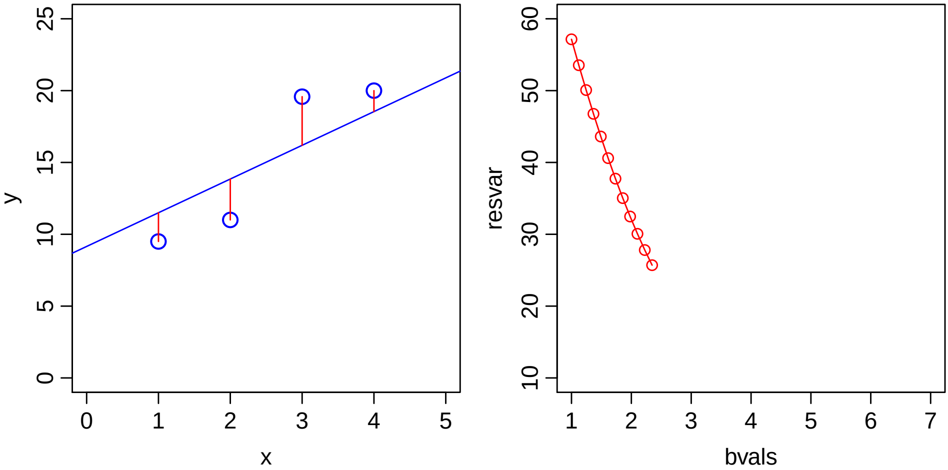

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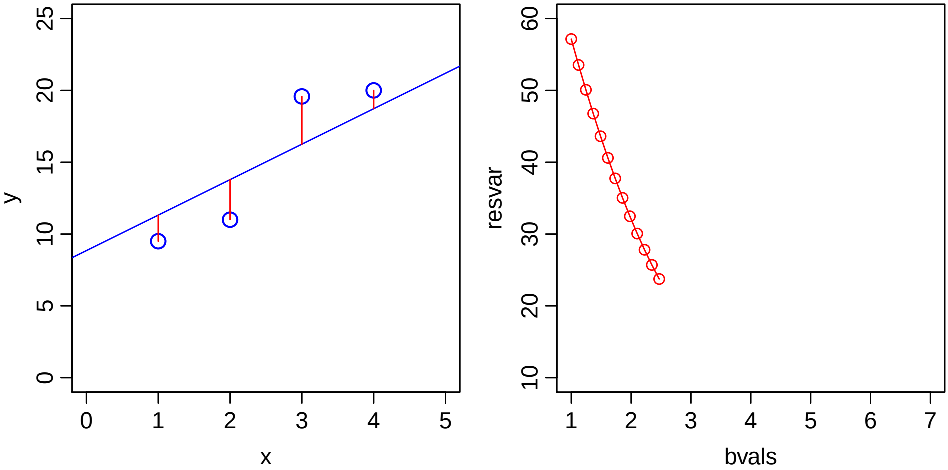

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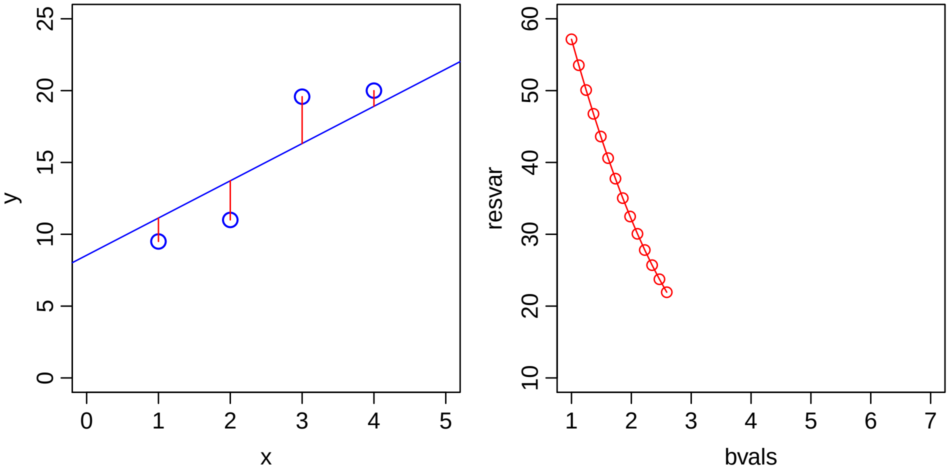
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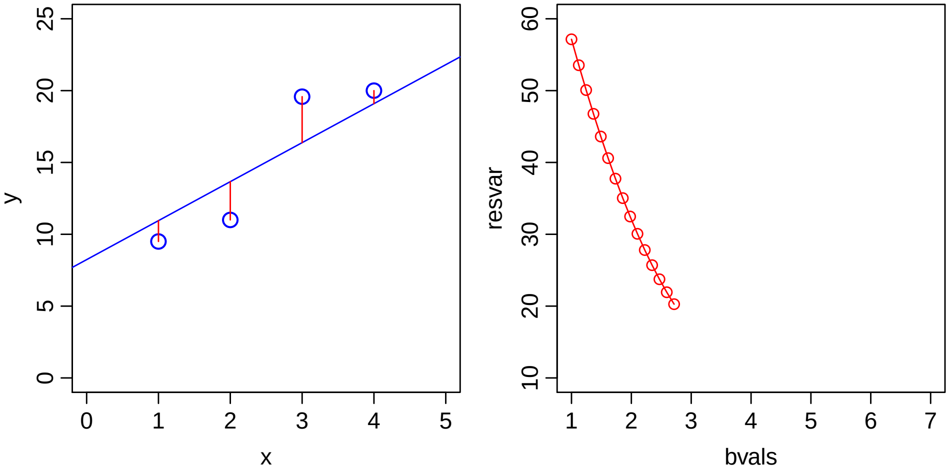

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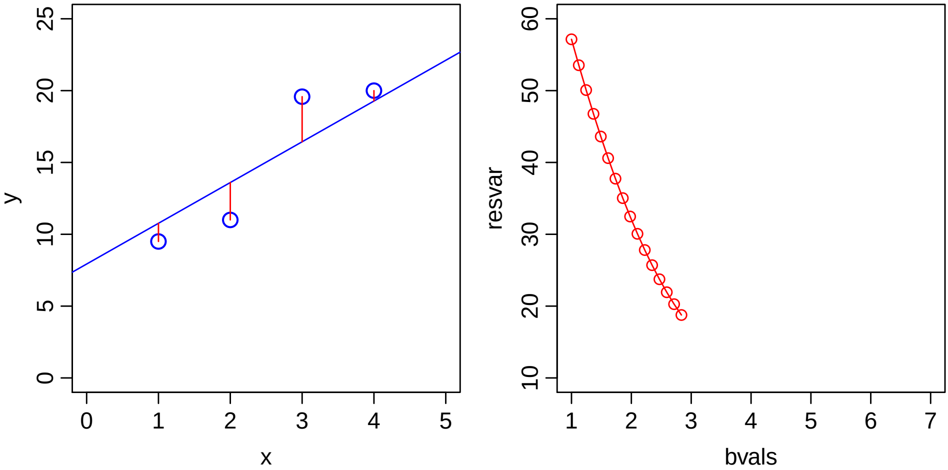
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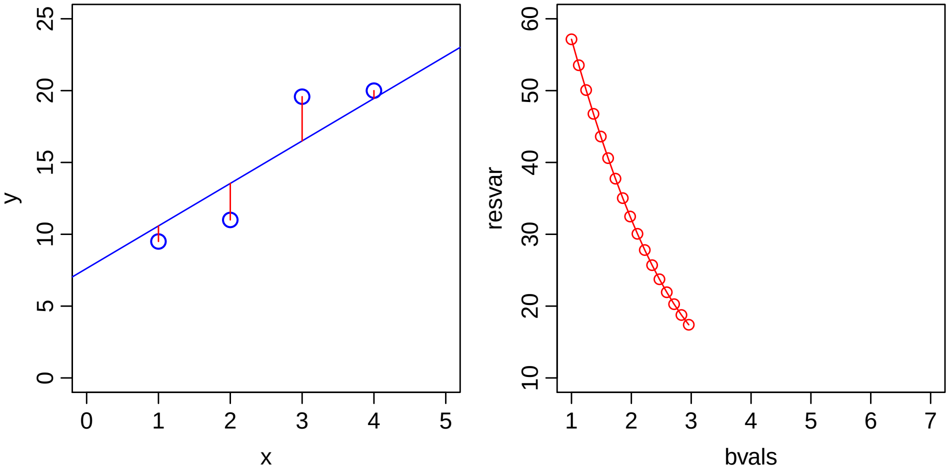

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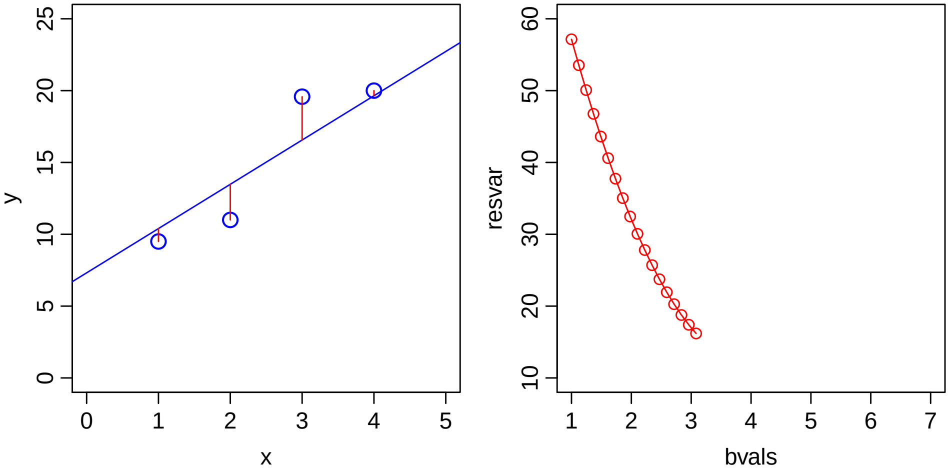

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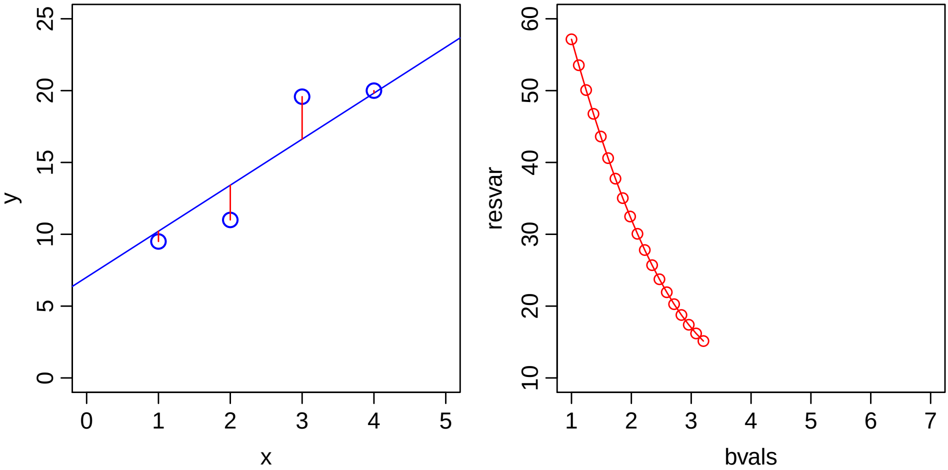

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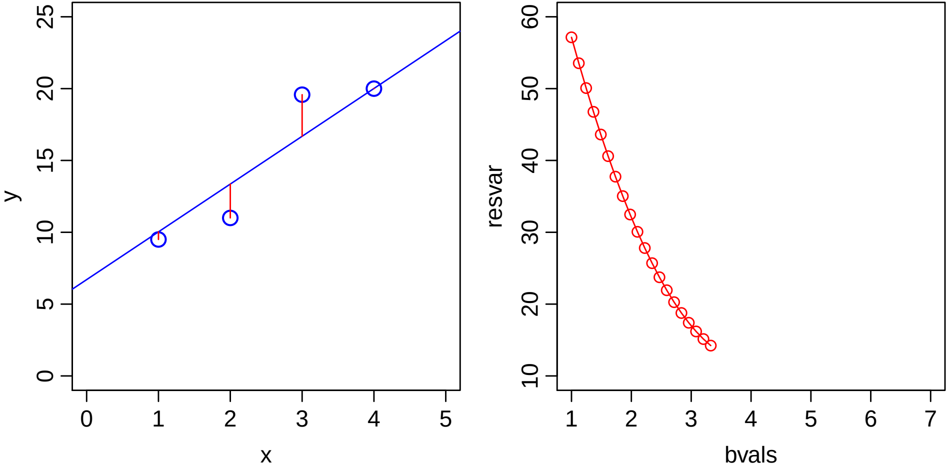

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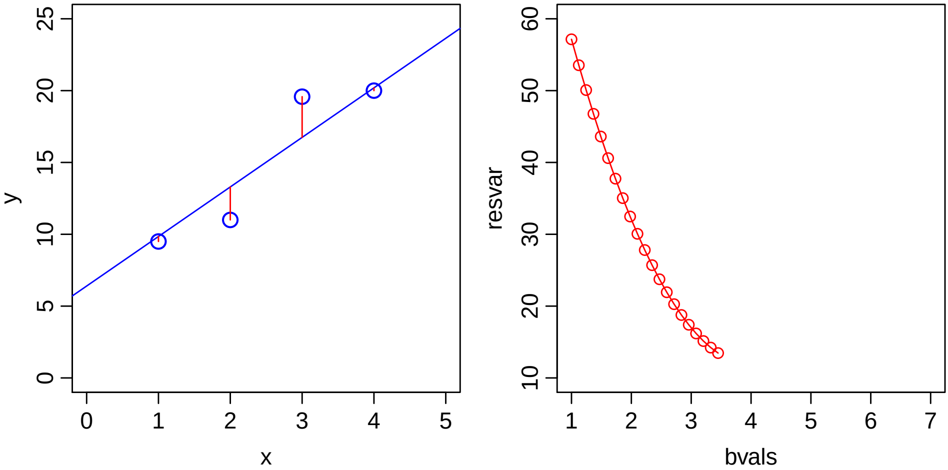

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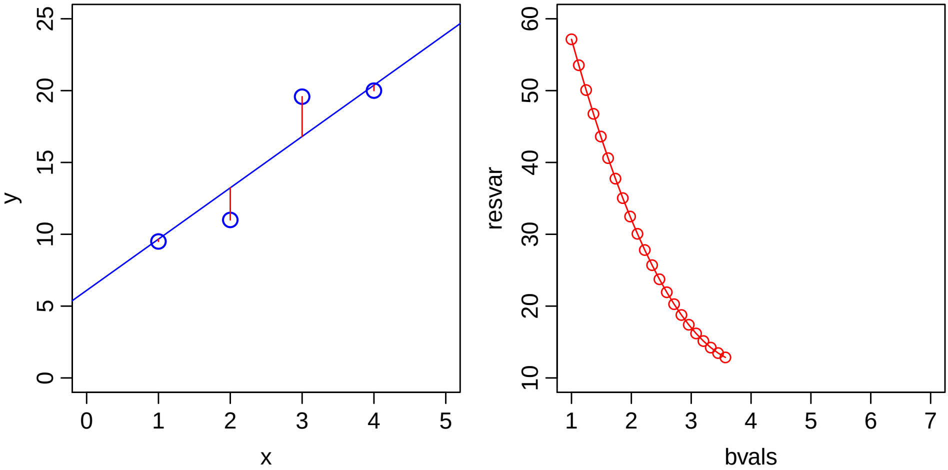

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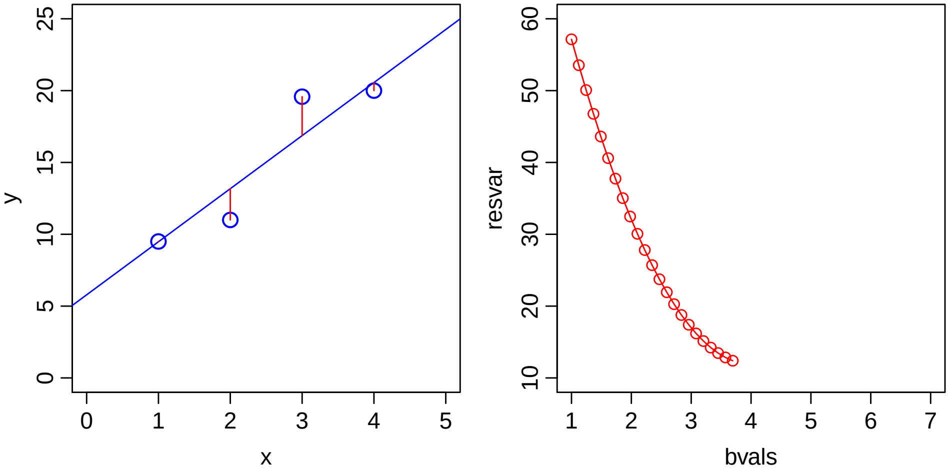

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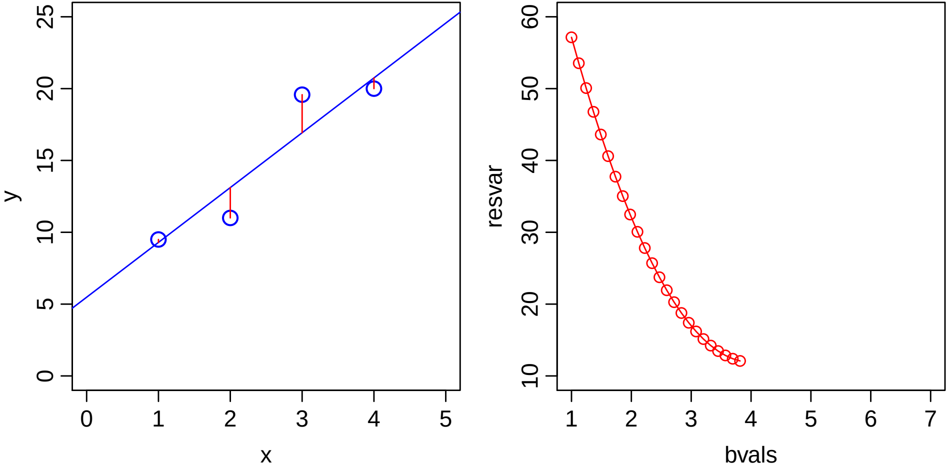
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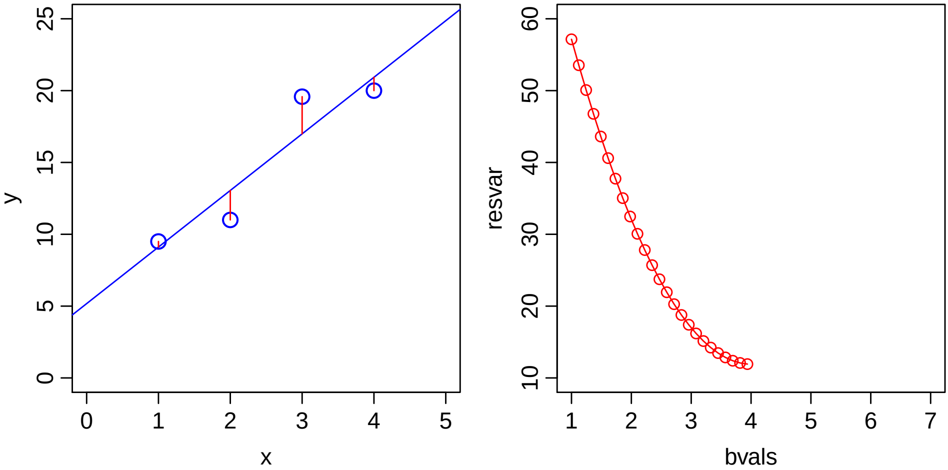

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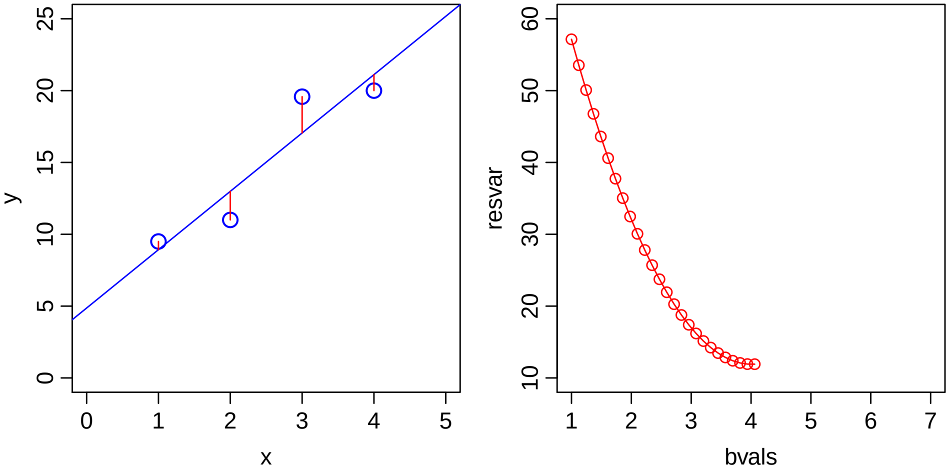

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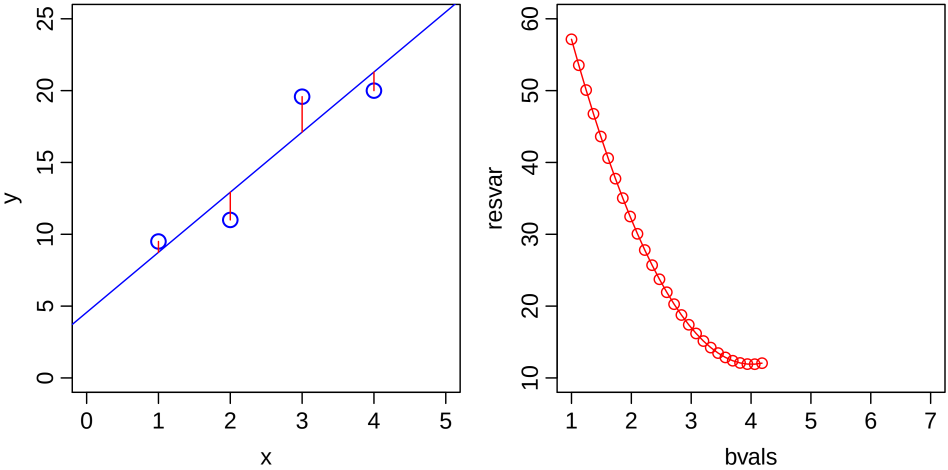

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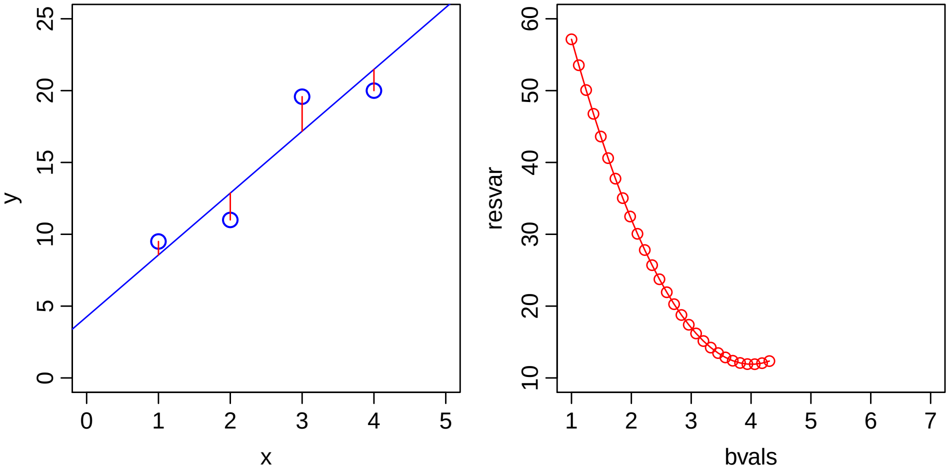

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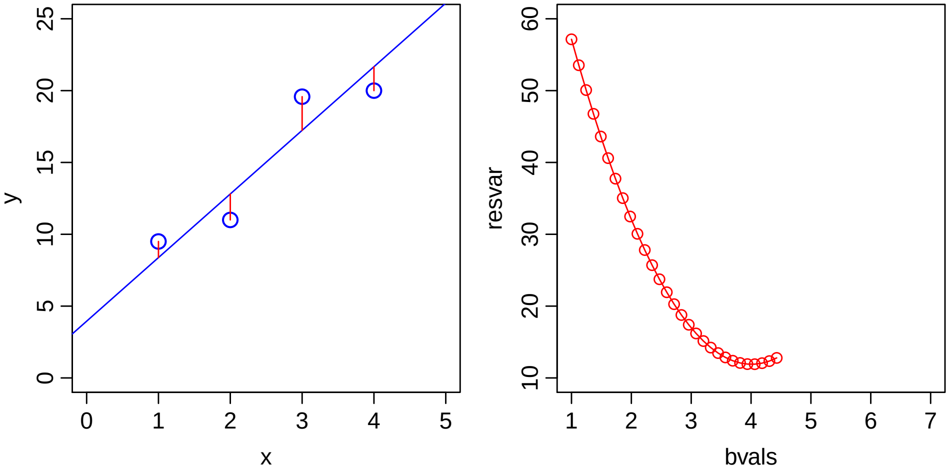

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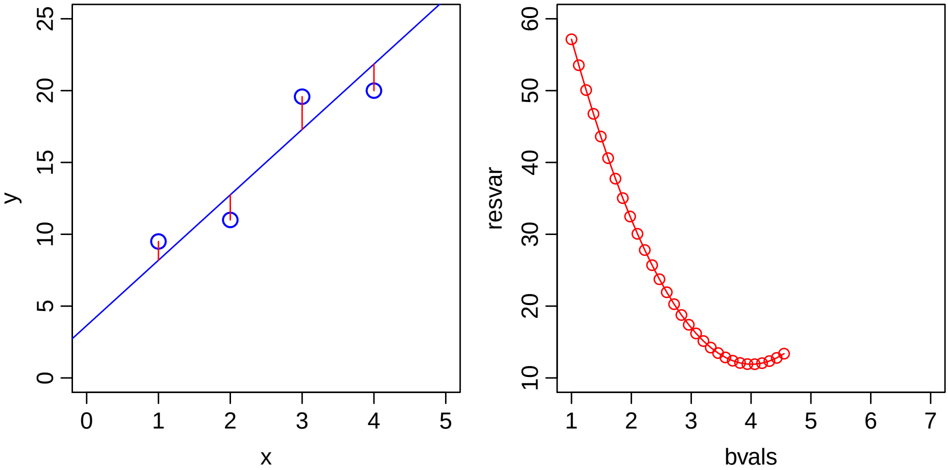

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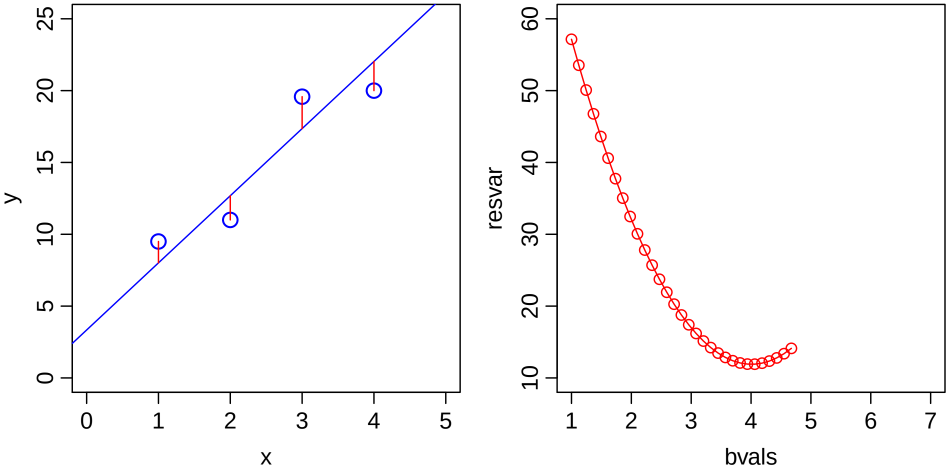

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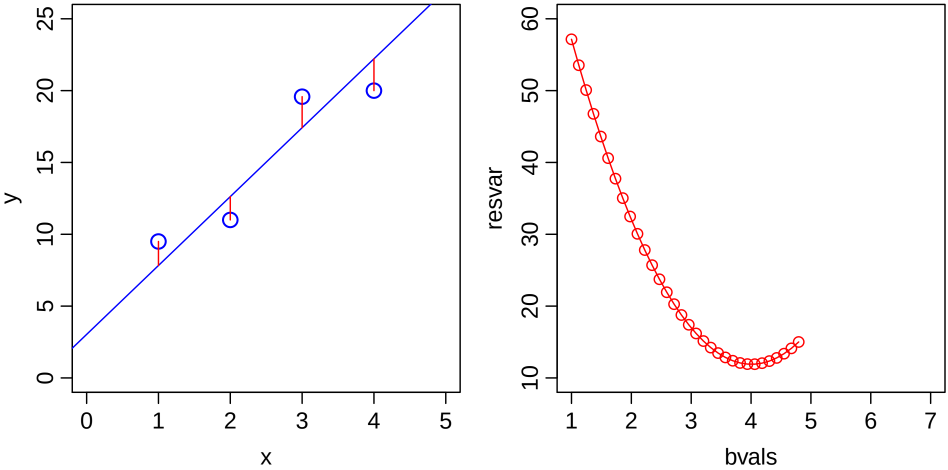

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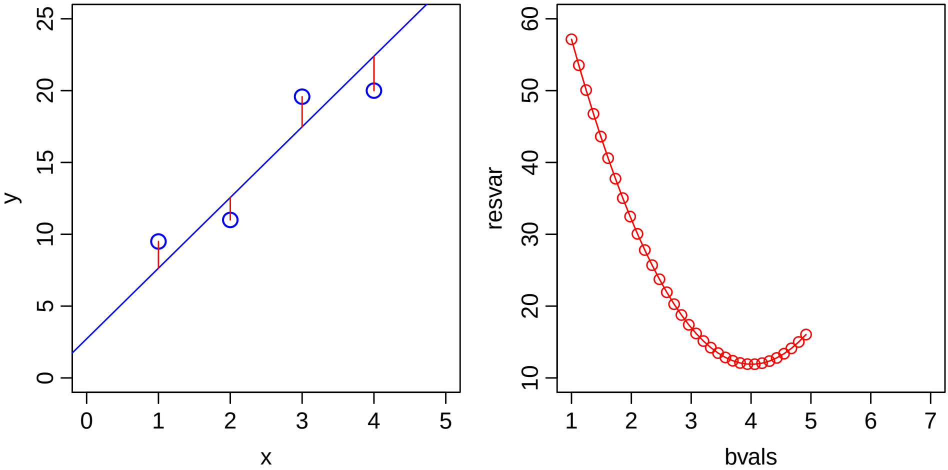

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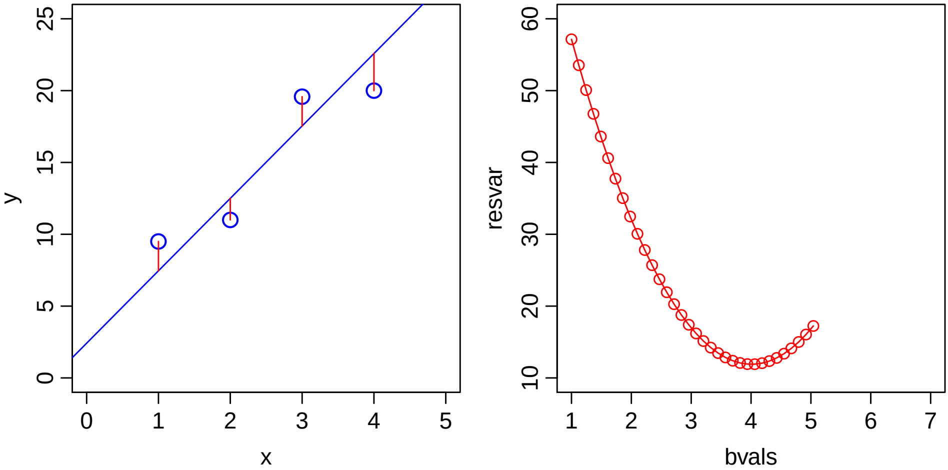

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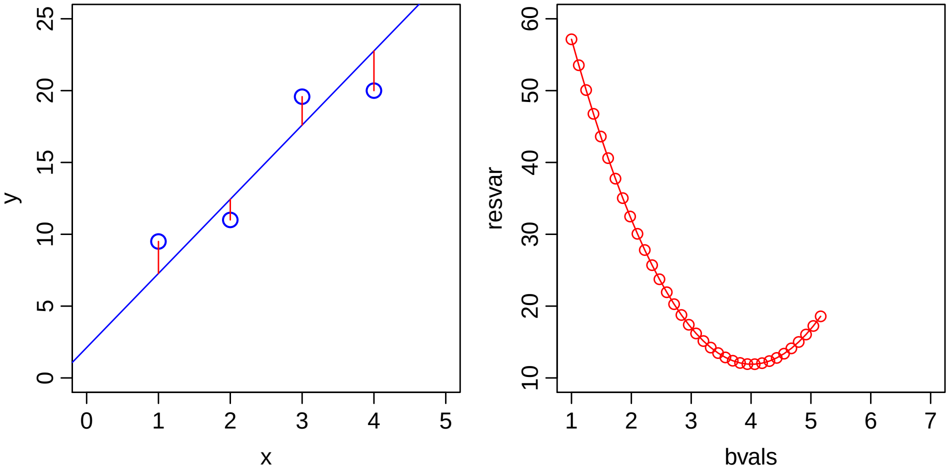

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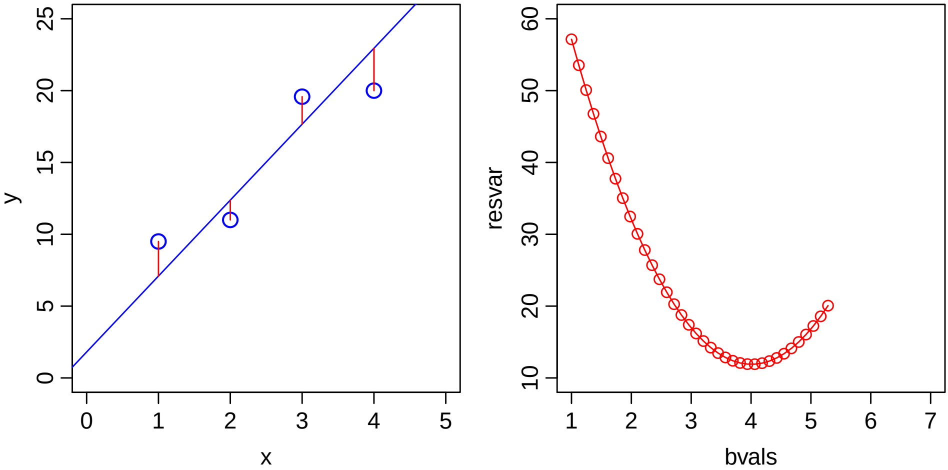

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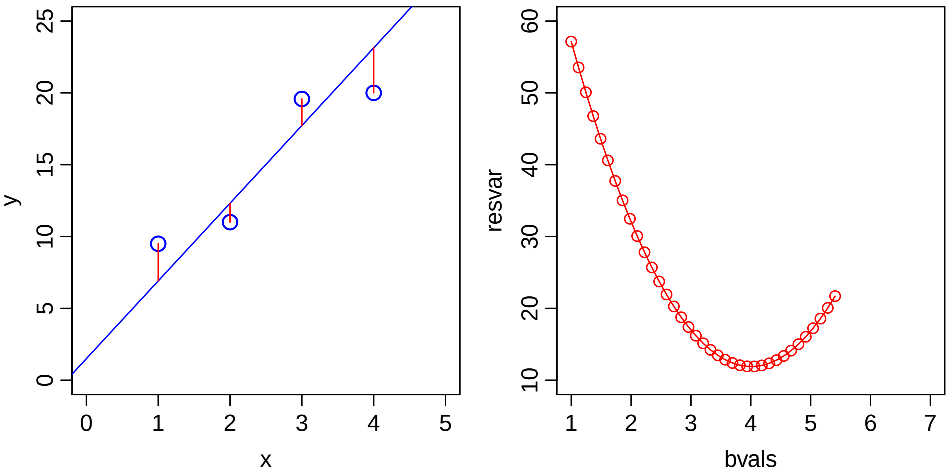

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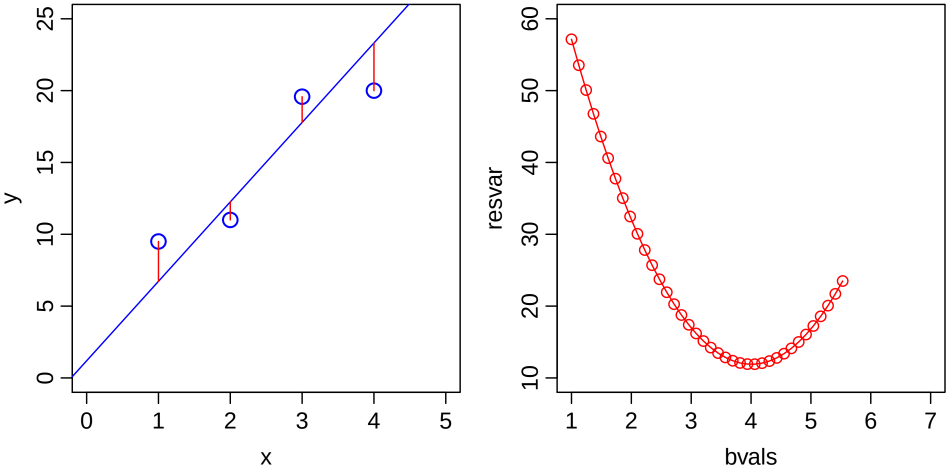
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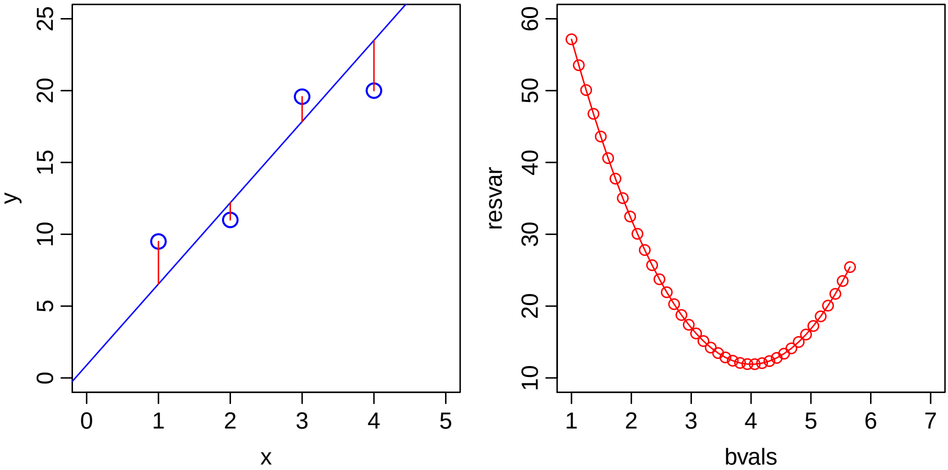

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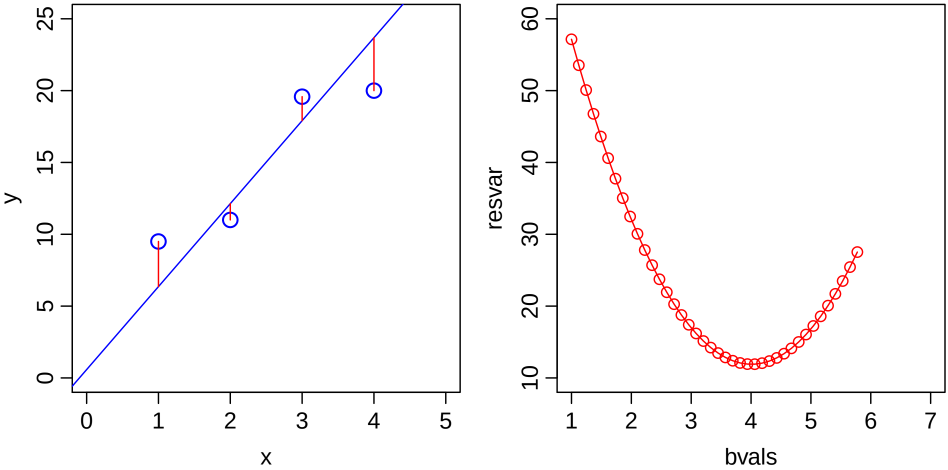
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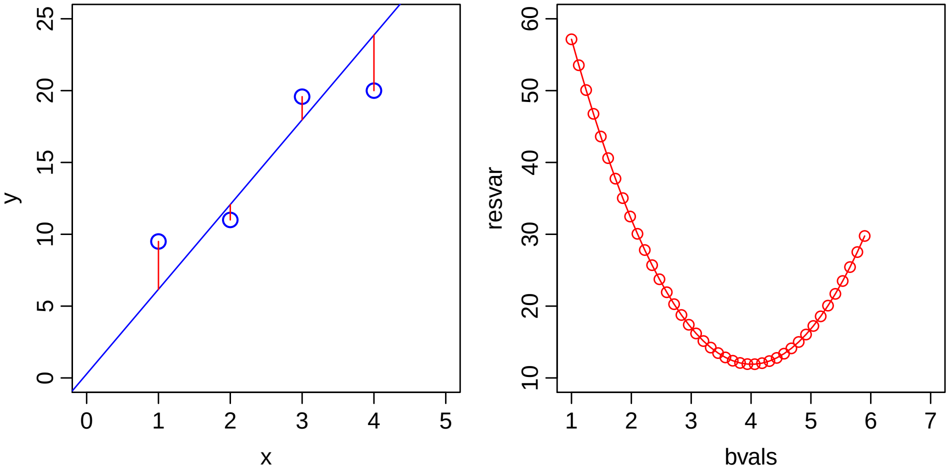

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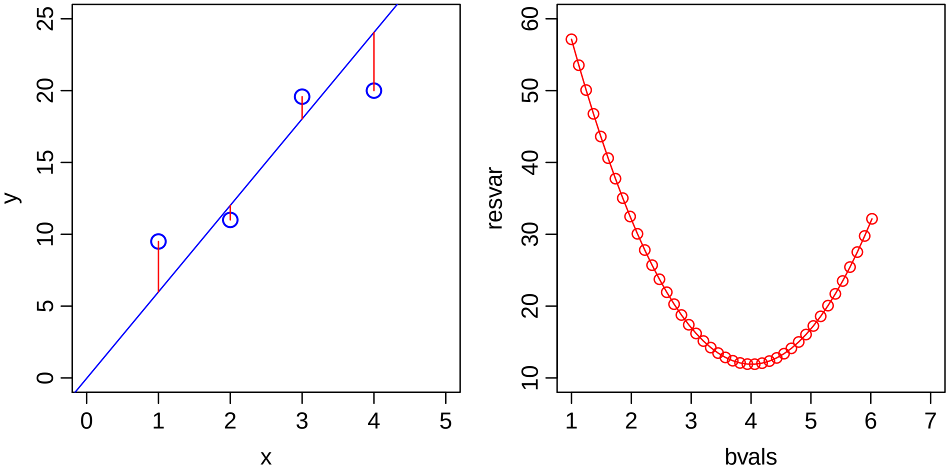

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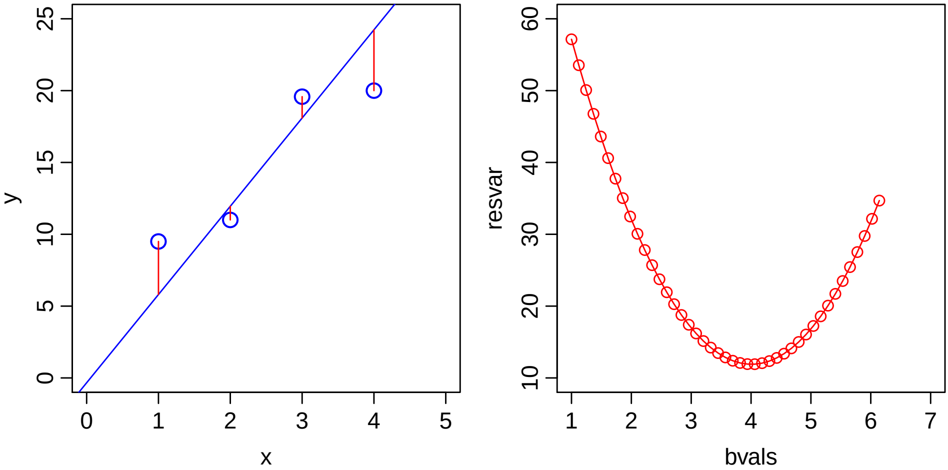

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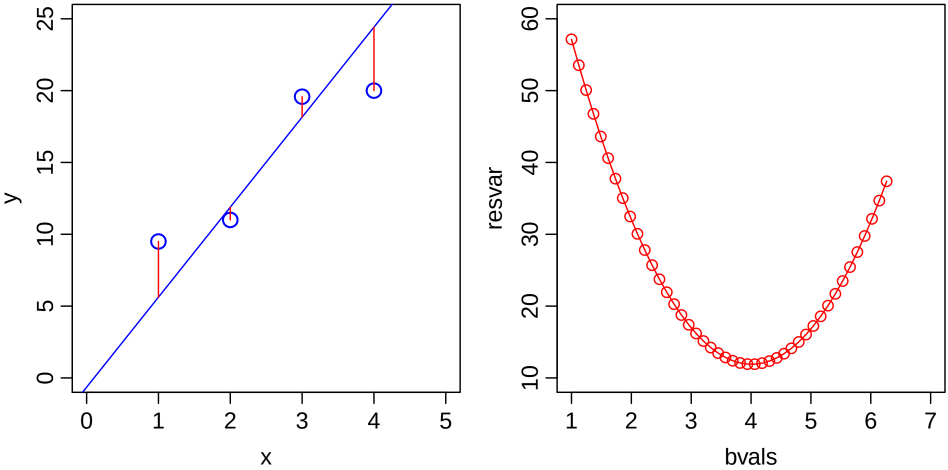

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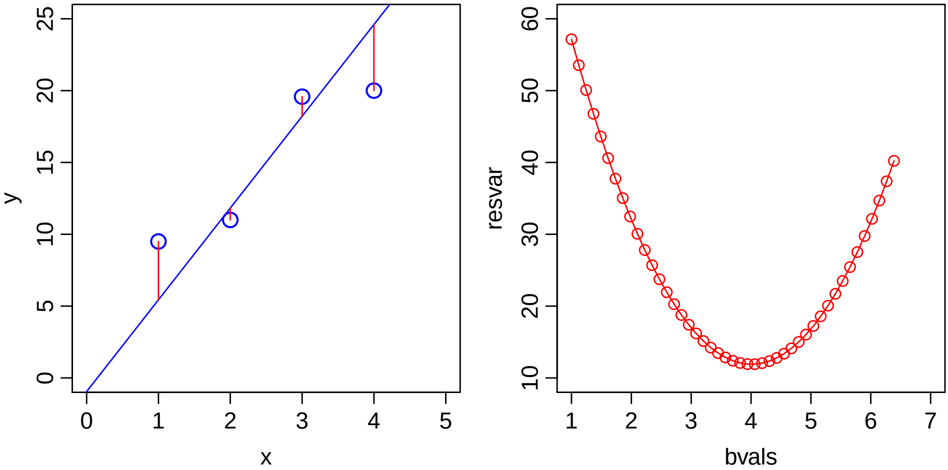

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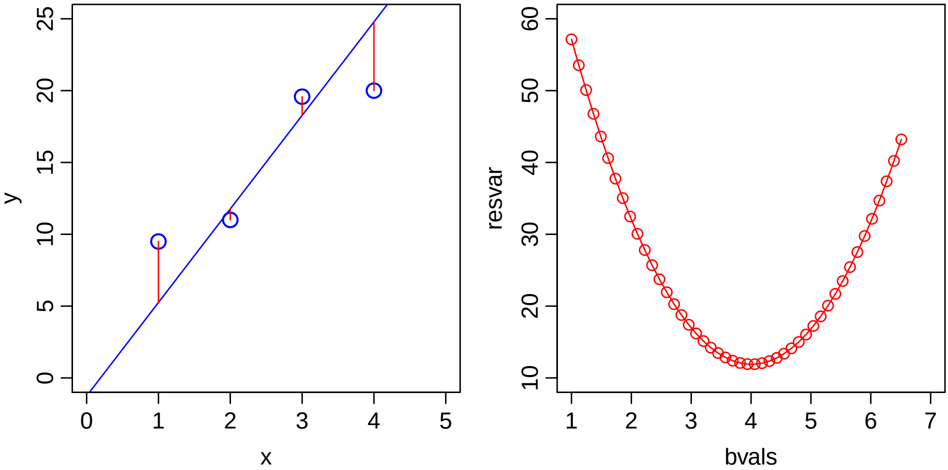

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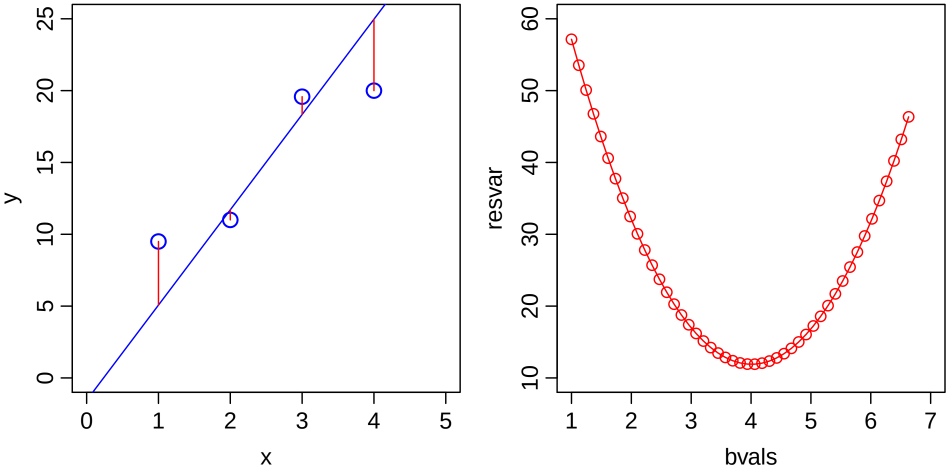

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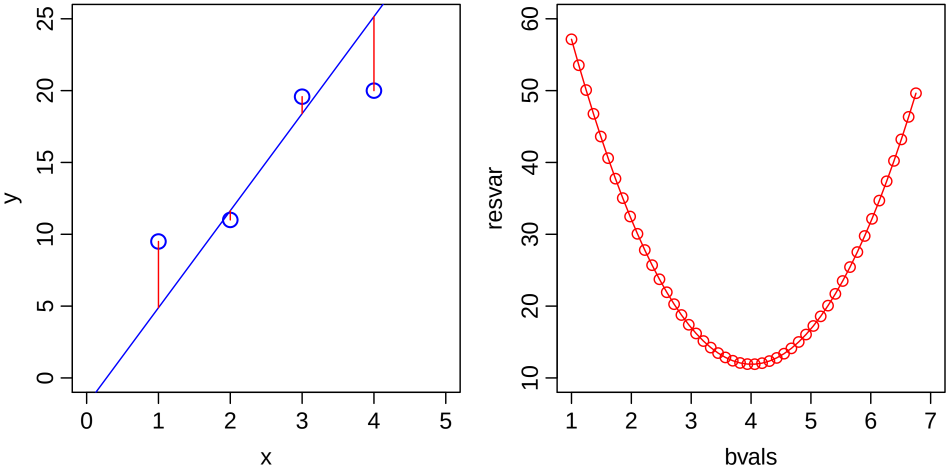

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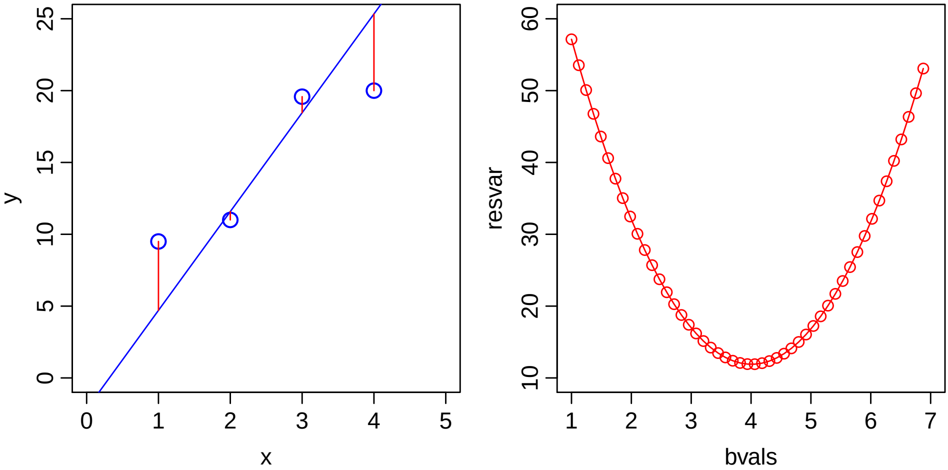

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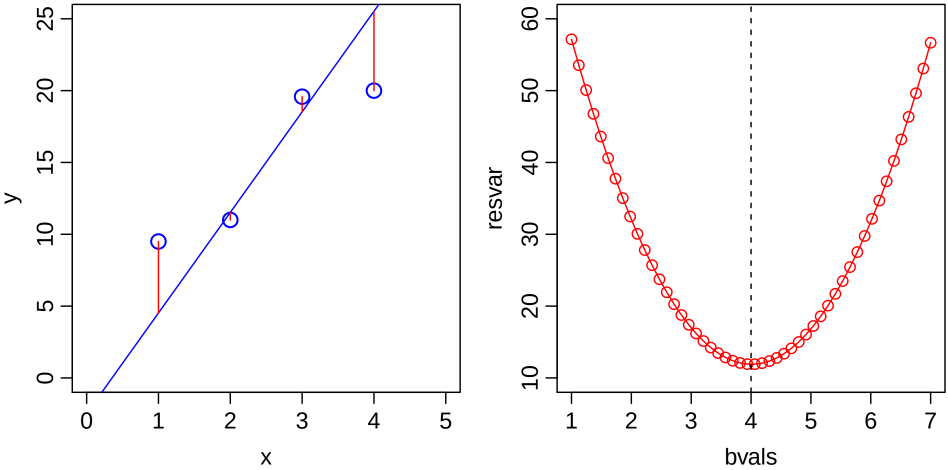
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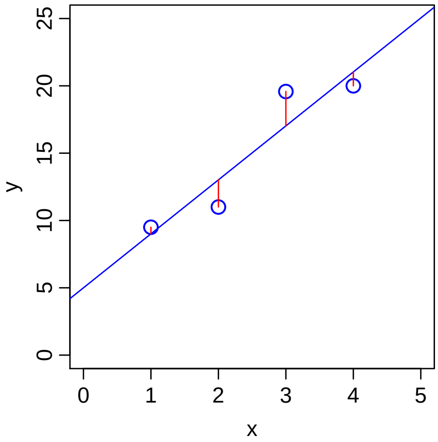
If the model is linear, the solution is easy using algebra



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

$$9.50 = 5 + 4 \times 1 + 0.50$$
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The least squares solution here is:
$\beta_0 = 5; \beta_1 = 4$

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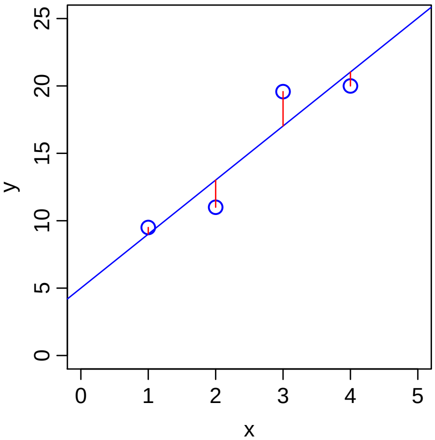

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- *This system of (linear) equations can be compactly represented (and solved using matrix algebra) as* $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$

What NLLS solves (and how)

- In an intrinsically non-linear model such as

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

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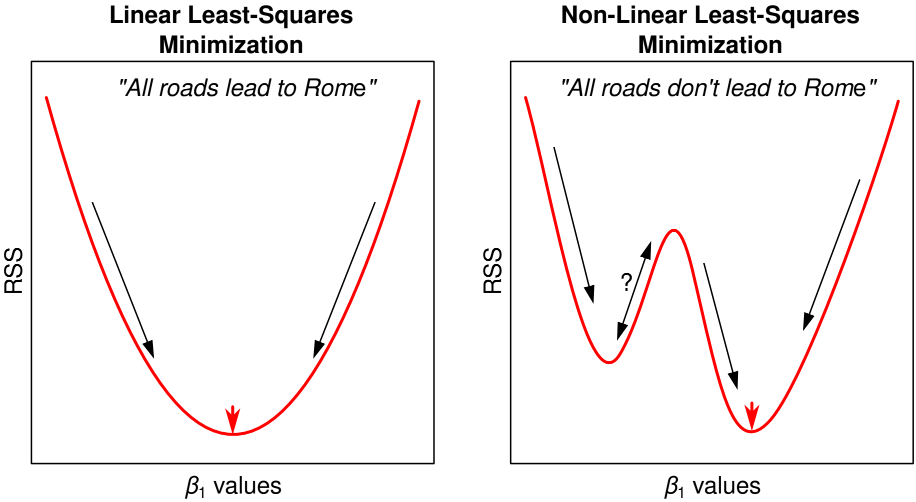
  - Eventually, if it all goes well, a combination of β_j's that is *very close* to the desired solution (where the RSS is *approximately* minimized) can be found

THE NLLS OPTIMIZATION PROCESS



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- *Can you think of some examples?*

The general procedure / algorithm is:

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5. Adjust the parameters again so that the curve comes even closer to the points (RSS decreases)
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7. 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

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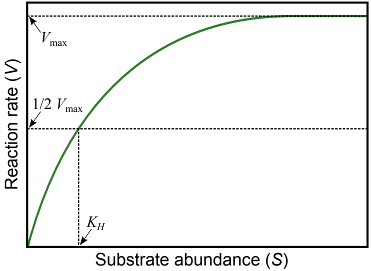
- The measurement/observation errors are Normally distributed (Gaussian)
- What if the errors are not normal? — Interpret results cautiously, and use Maximum Likelihood or Bayesian fitting methods instead

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 fir 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.