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

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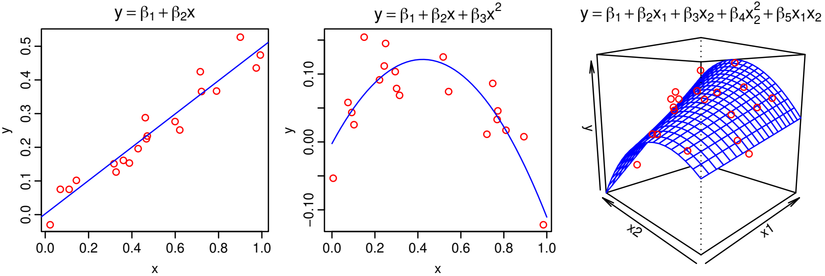
Outline

- Why NLLS?
- The NLLS fitting method
- Practicals (in `R`) overview

WHY NLLS?

- These are *all* good *Linear Models* (really?!):



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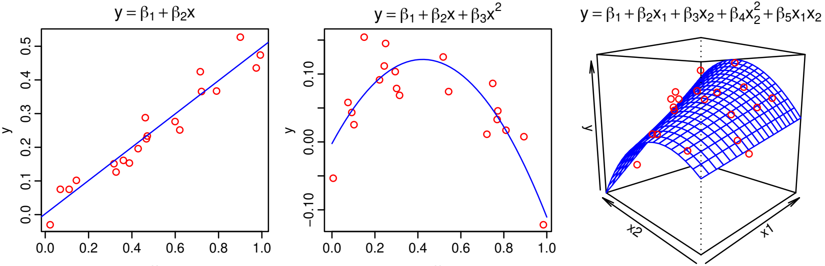

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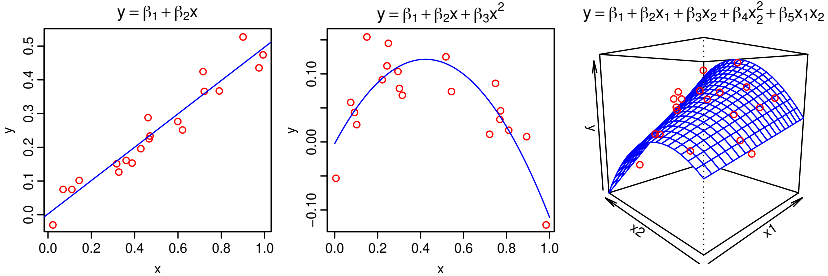

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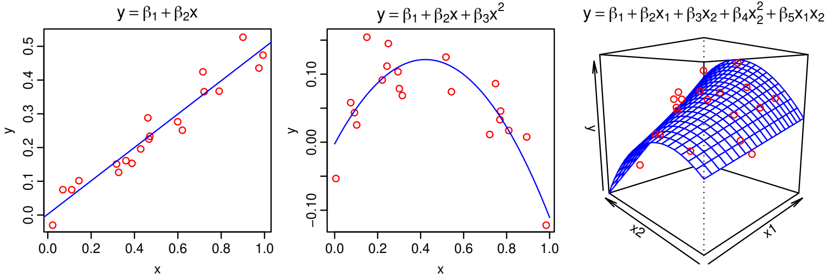

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- Easily fitted using *Ordinary Least Squares* (OLS)
- Linear models can *include curved responses* (e.g. Polynomial regression)

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  In all of these, at least one parameter (a β) is non-linear (e.g., $x_i^{\beta_2}$, $e^{\beta_2 x_i}$, etc.)

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- Consider data on a response variable y, a predictor (independent) variable x, and n observations.

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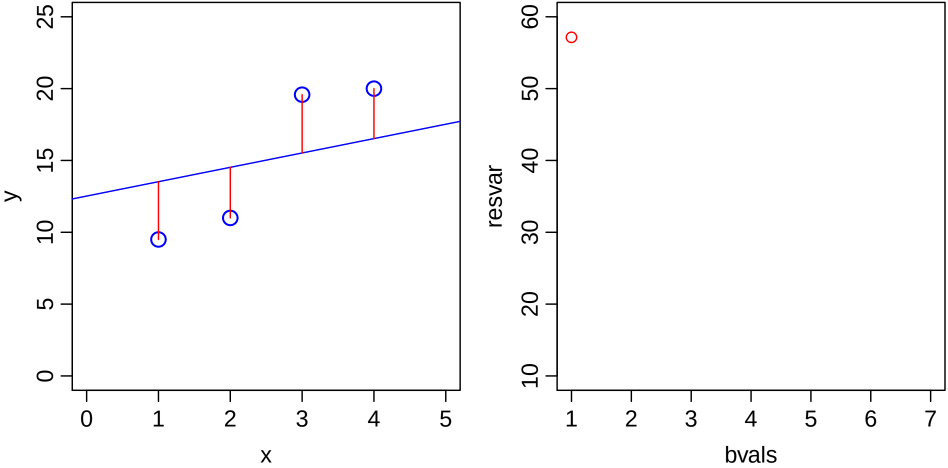
- Let's picture this using a simple (OLS) example; fitting the model $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$...



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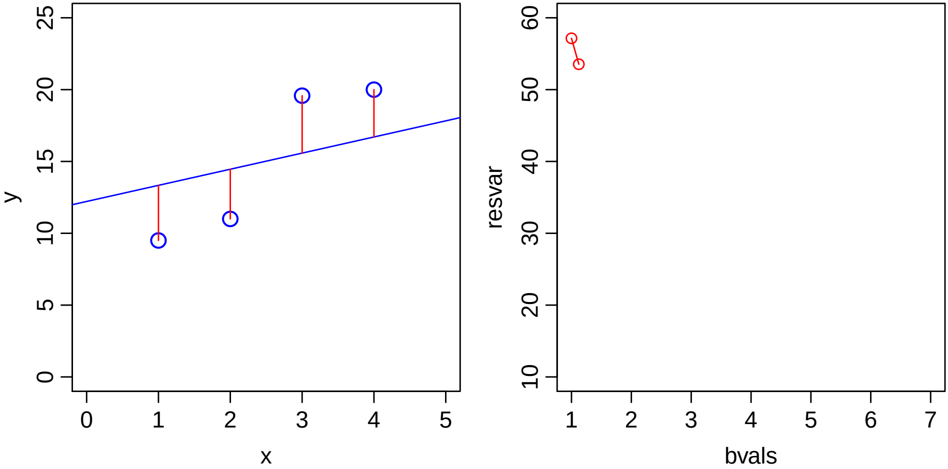

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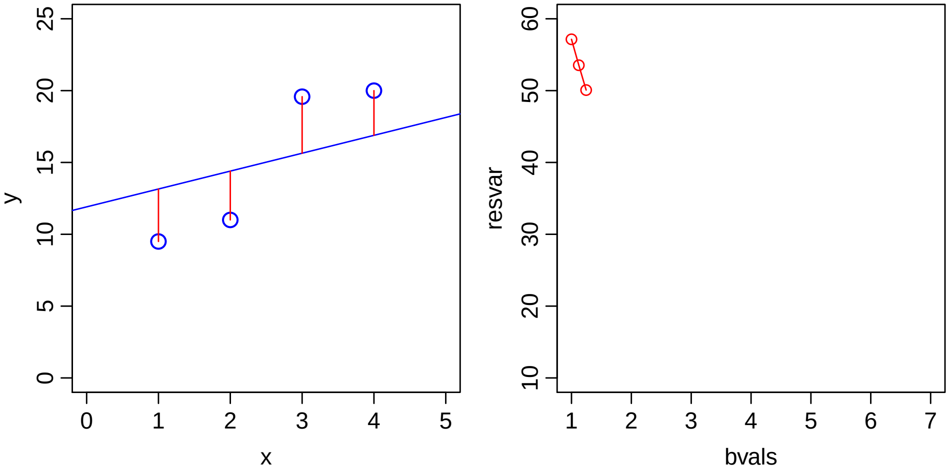

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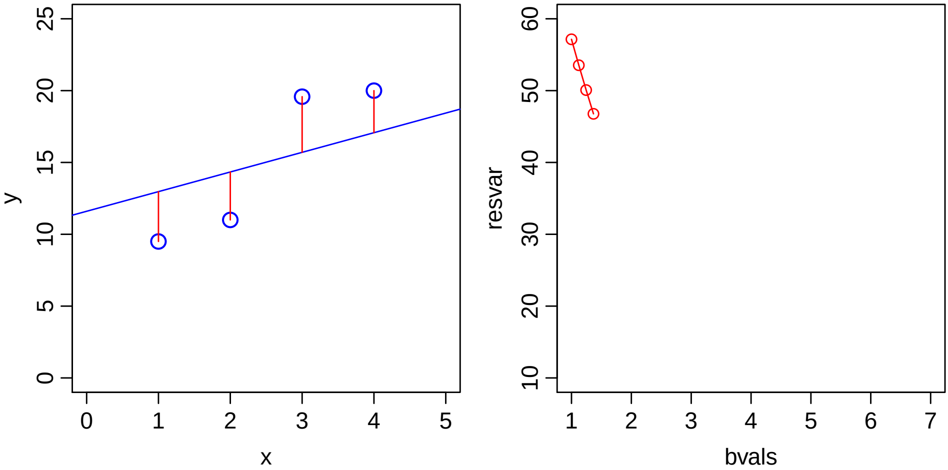

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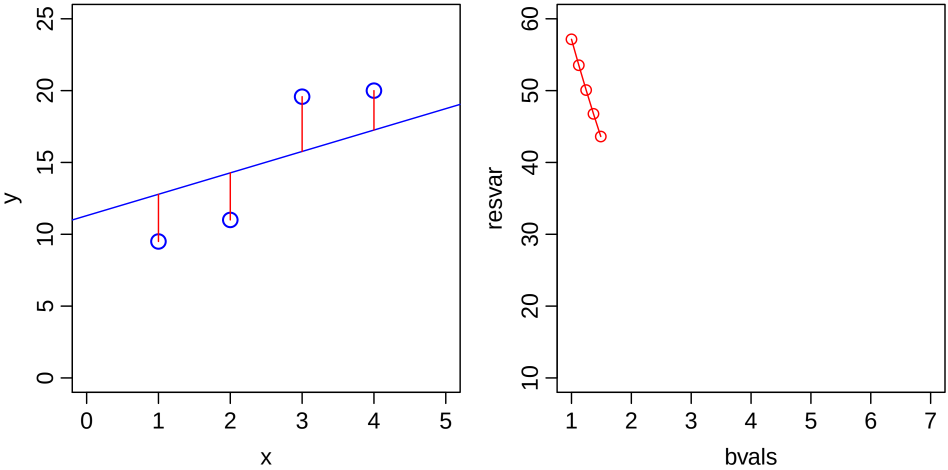

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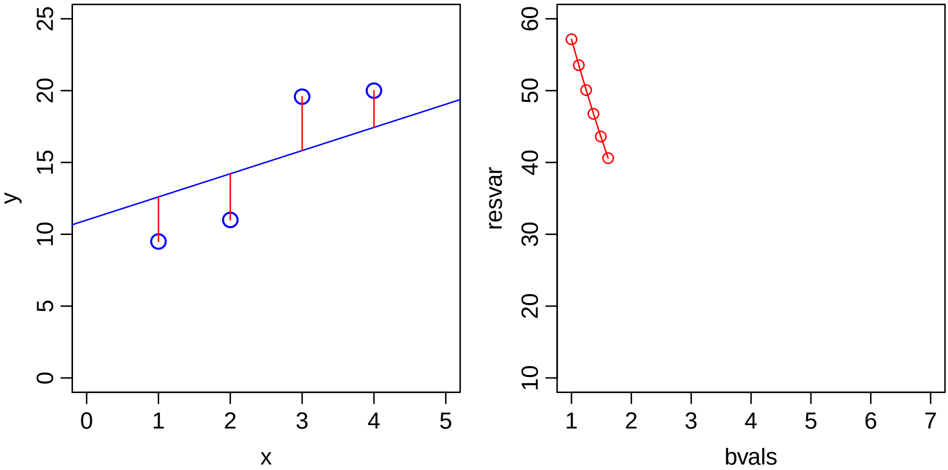

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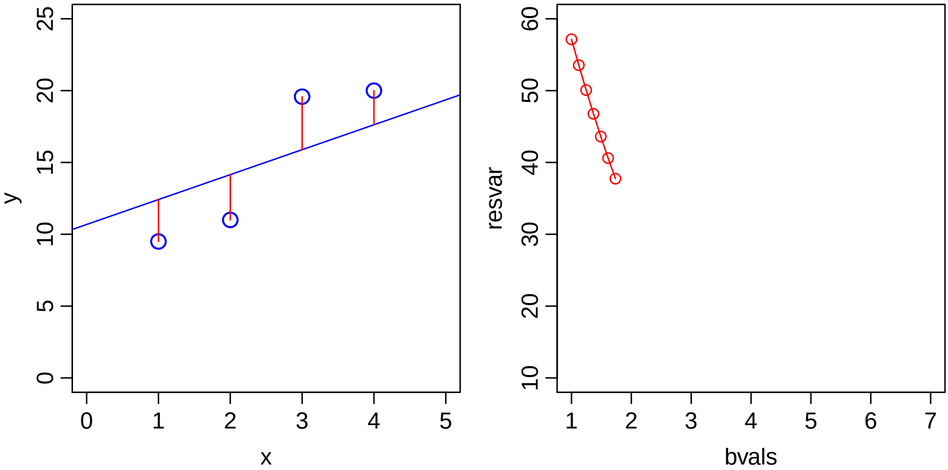

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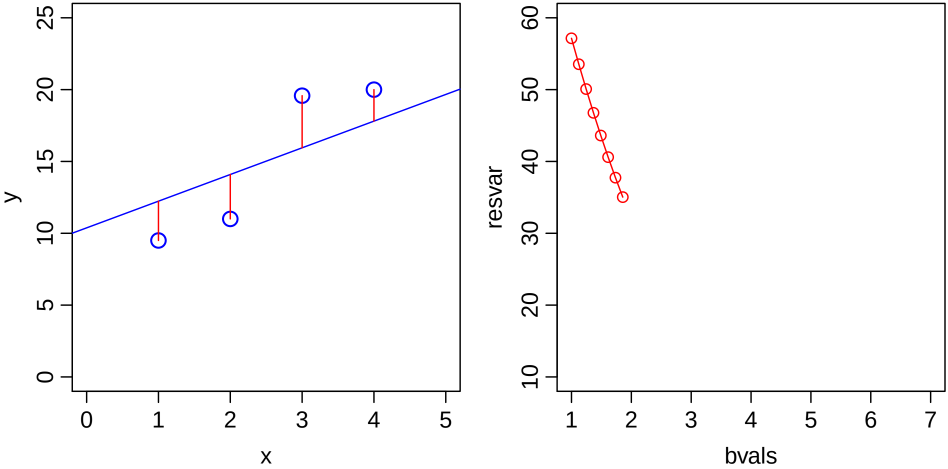

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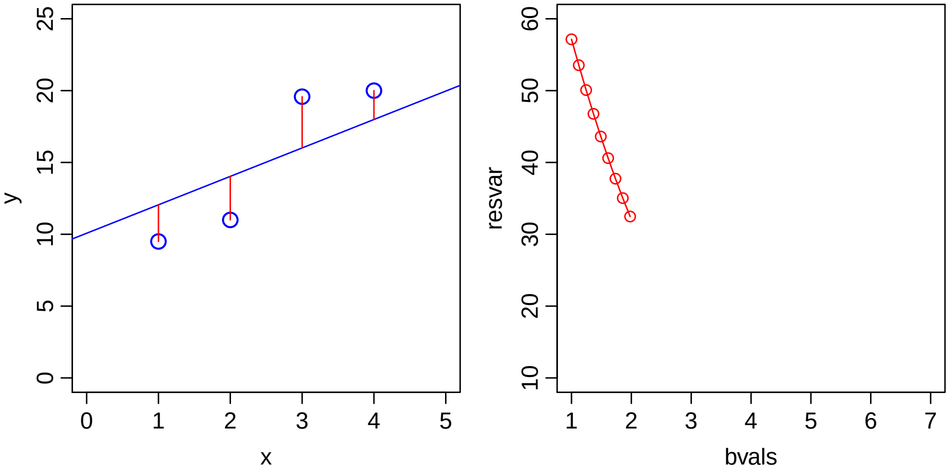

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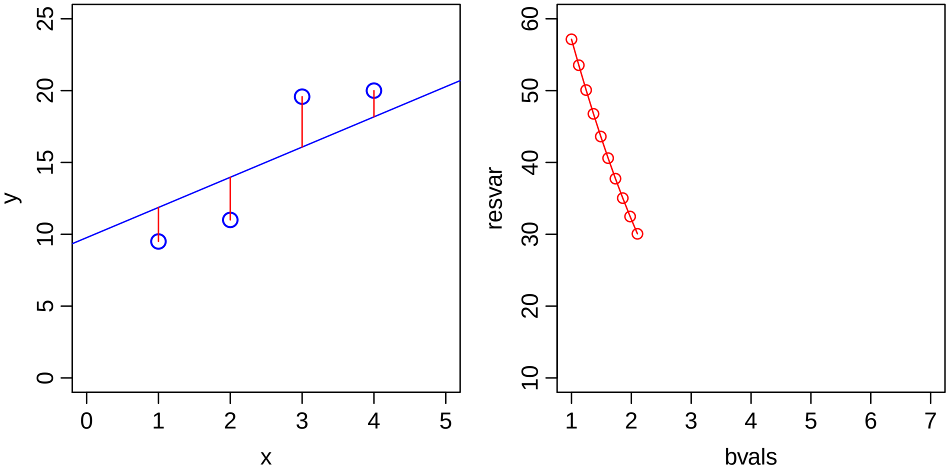

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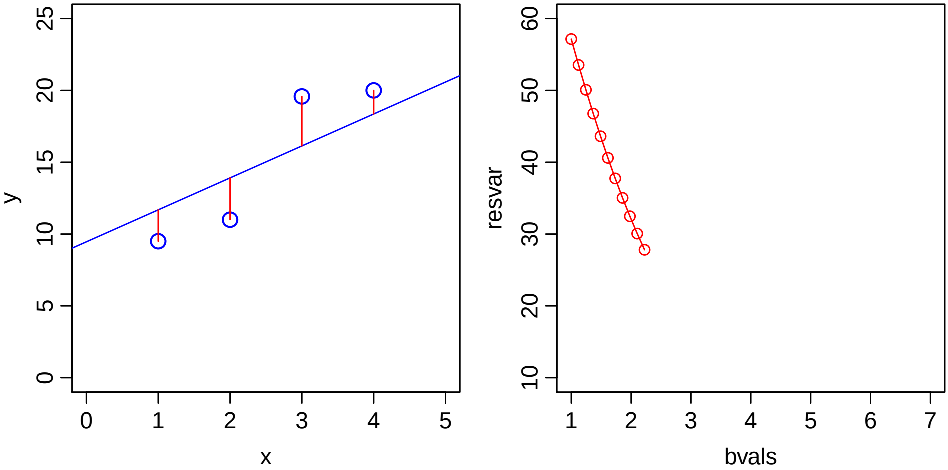

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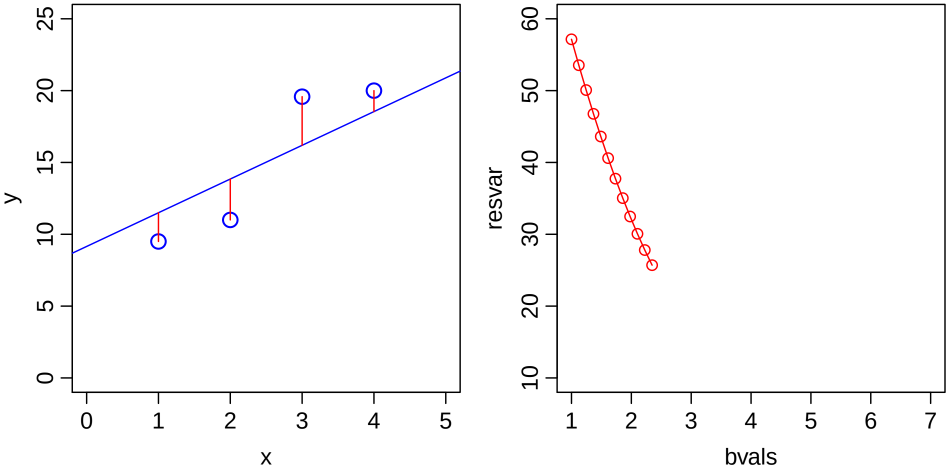

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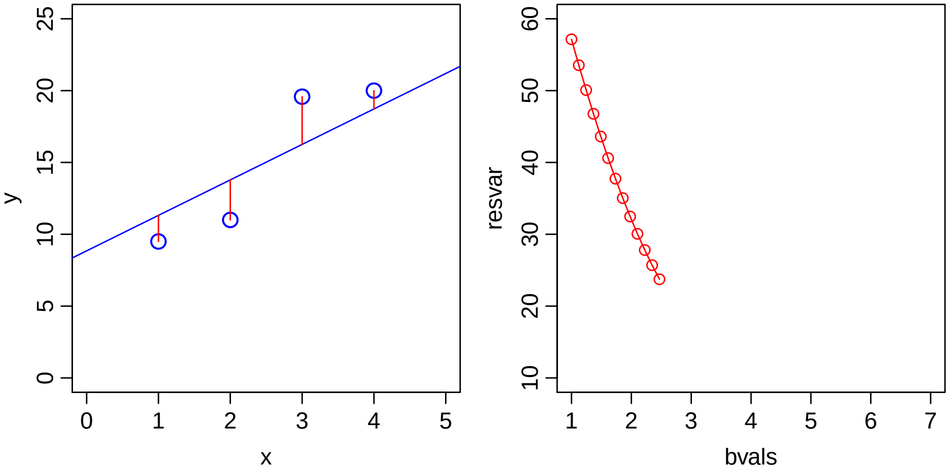

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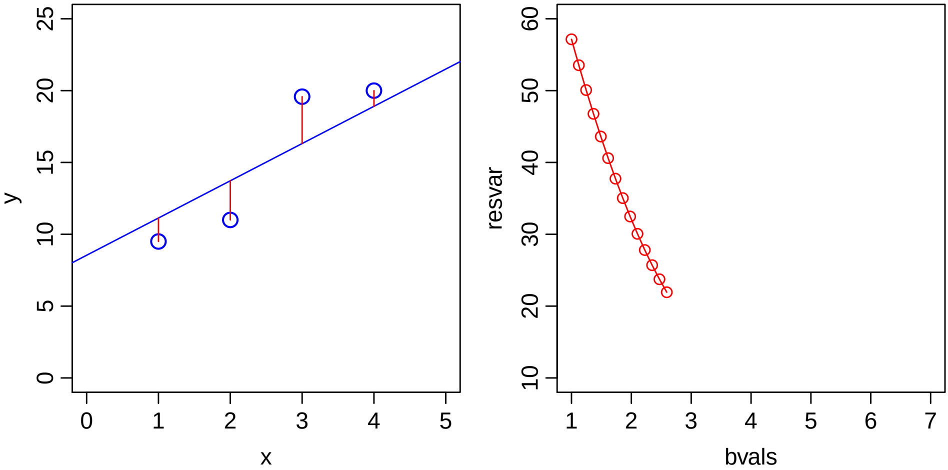

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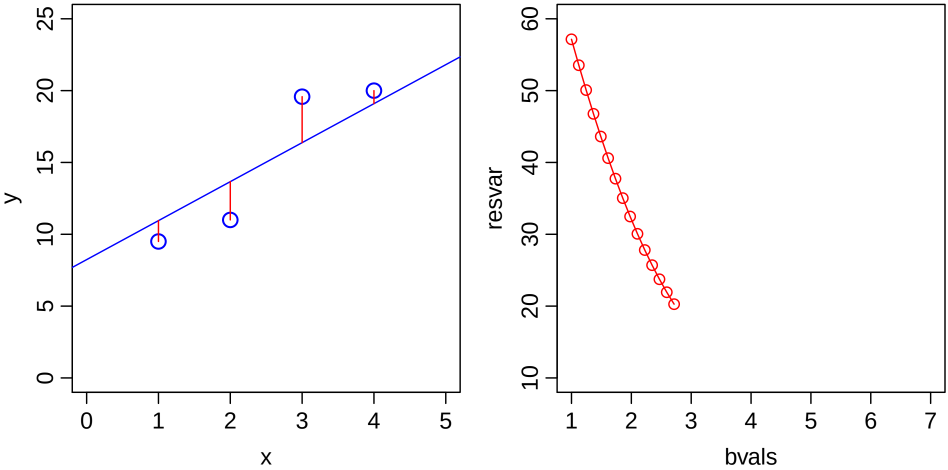

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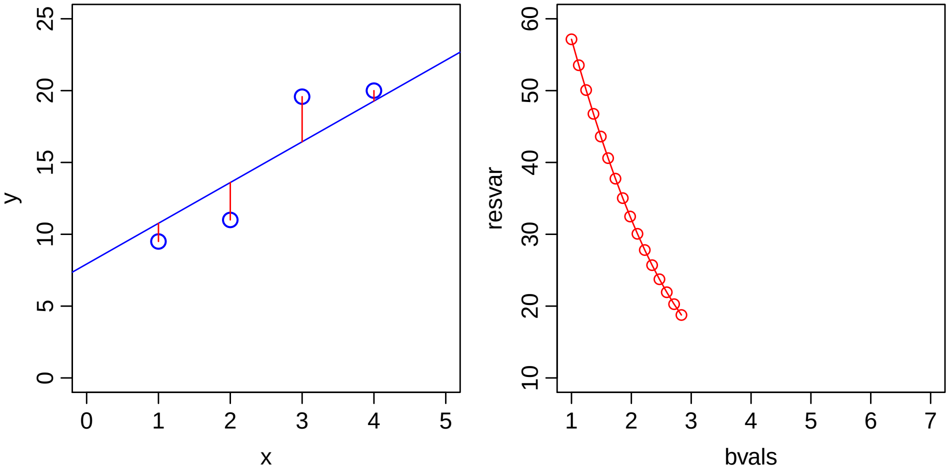

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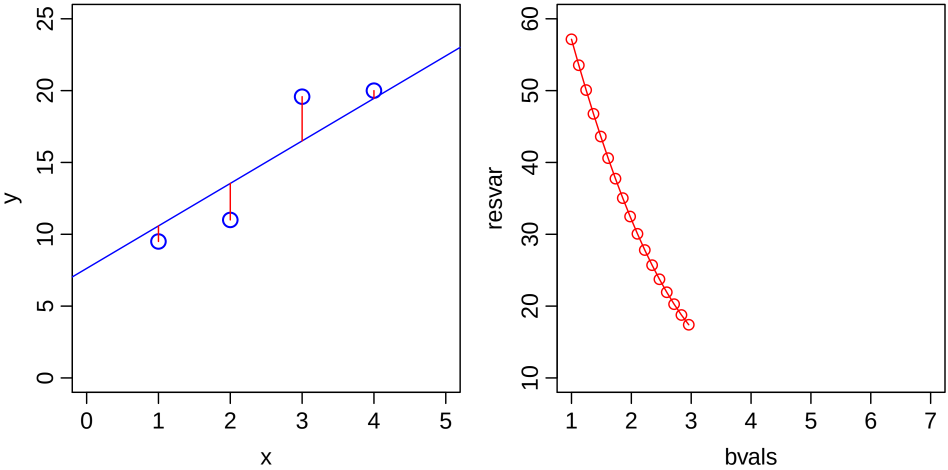

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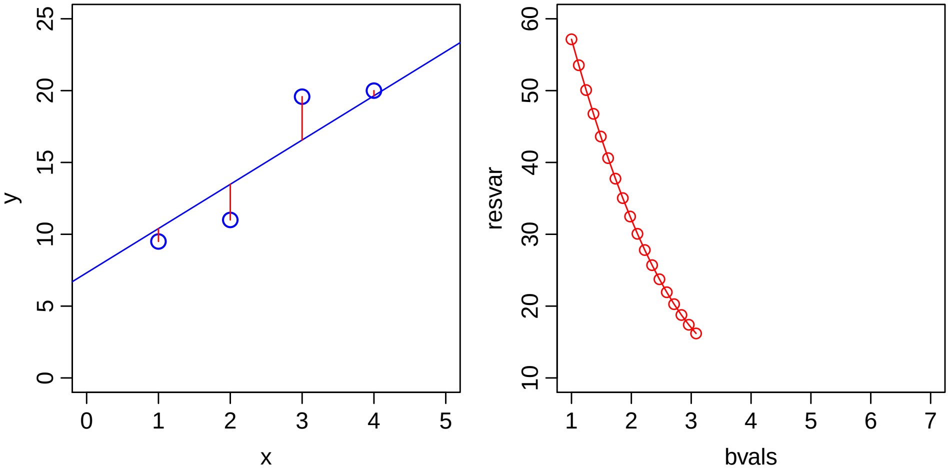

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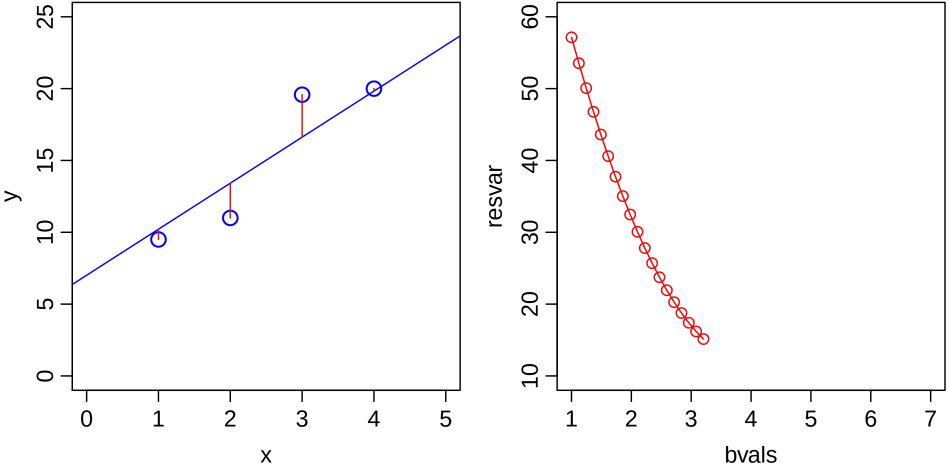

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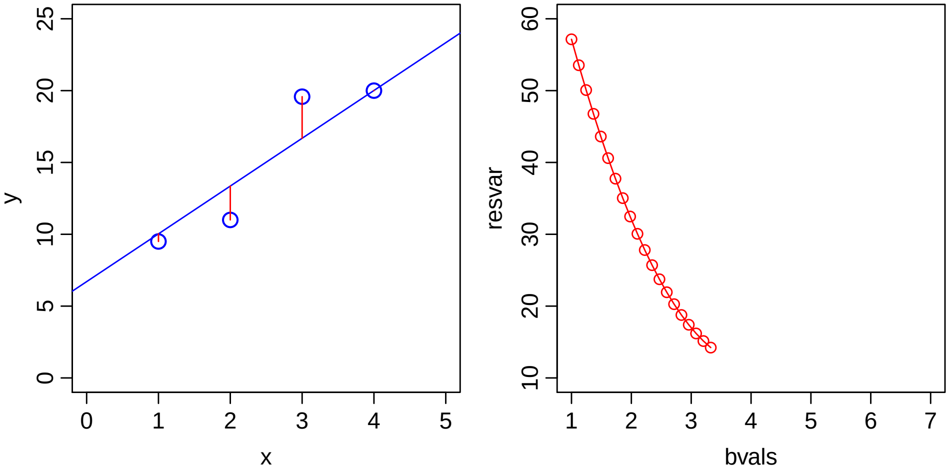
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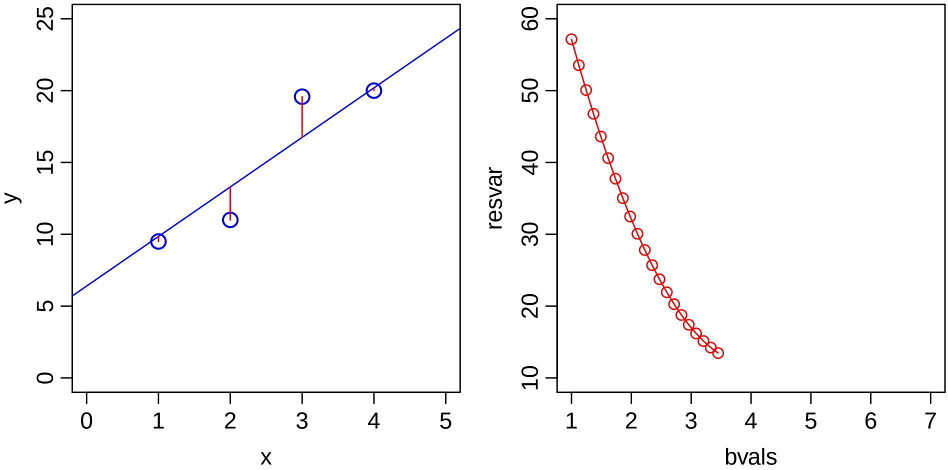

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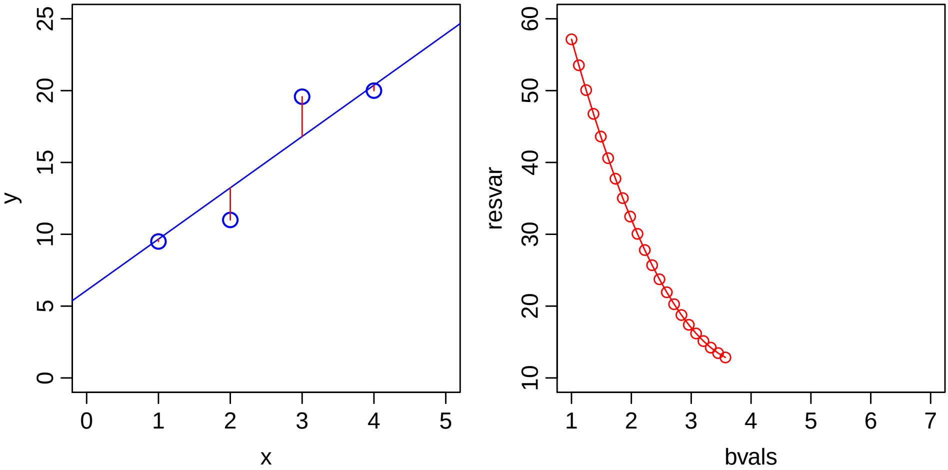

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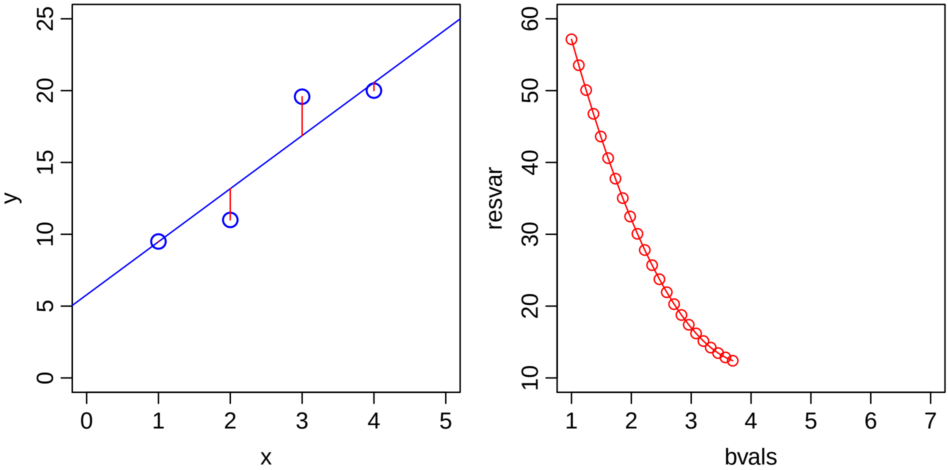
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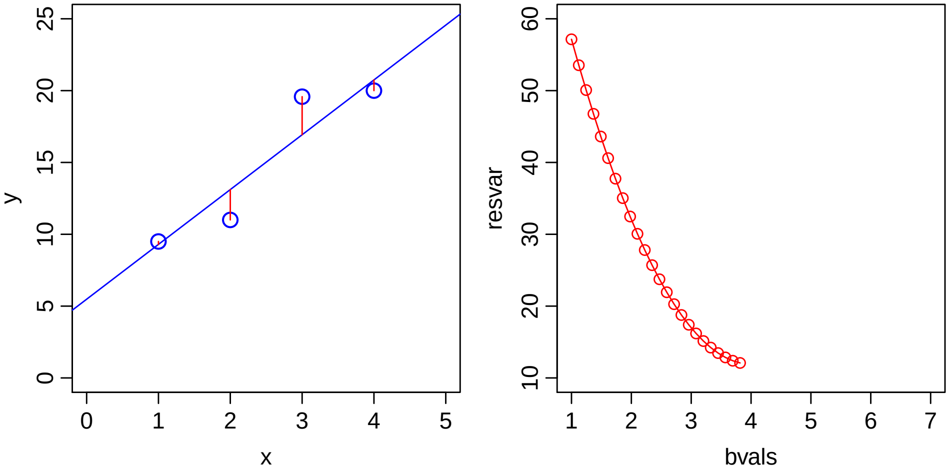

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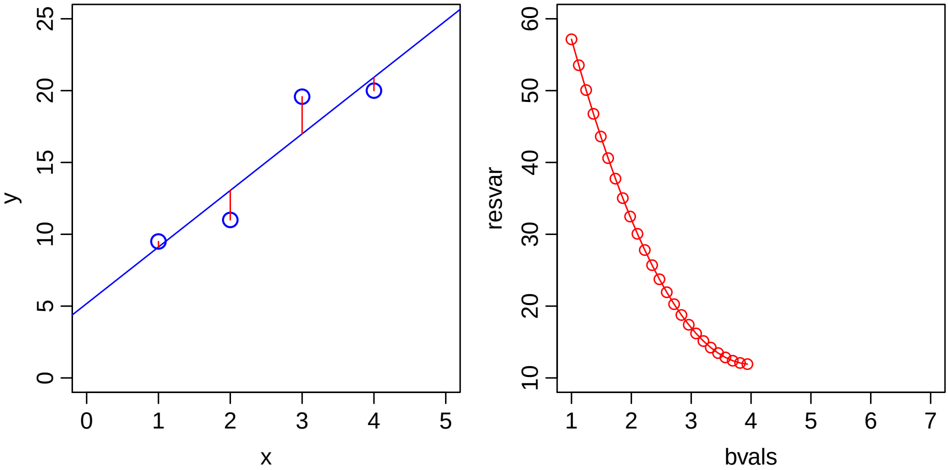

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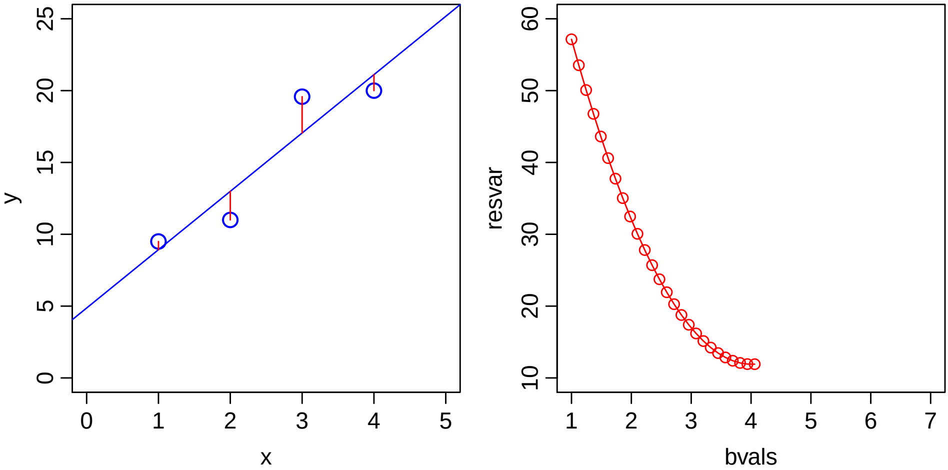

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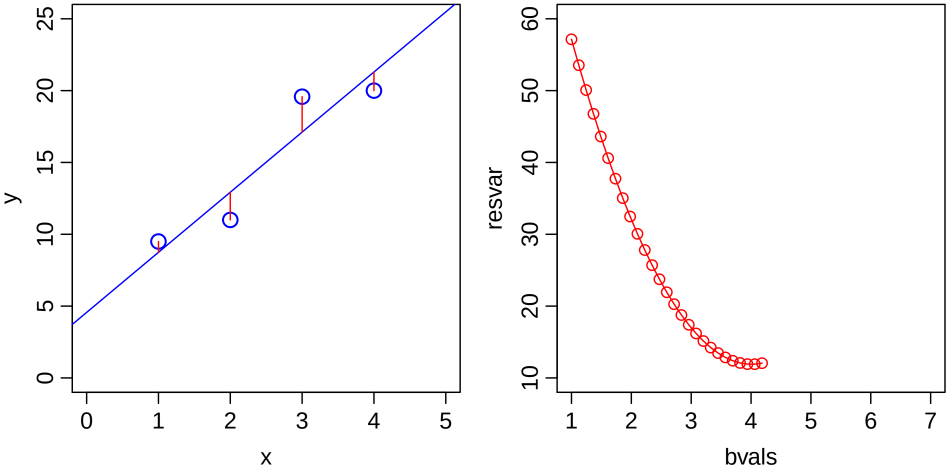

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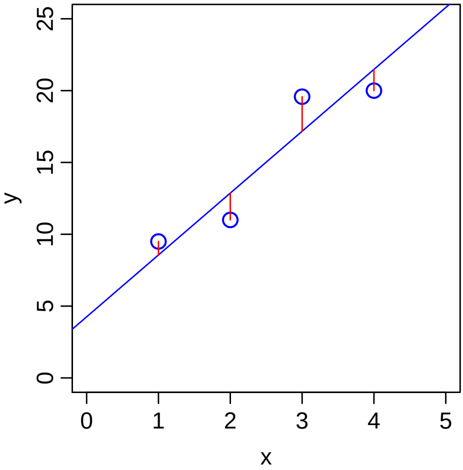

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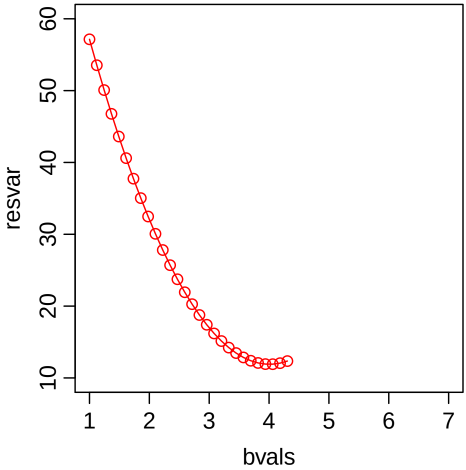

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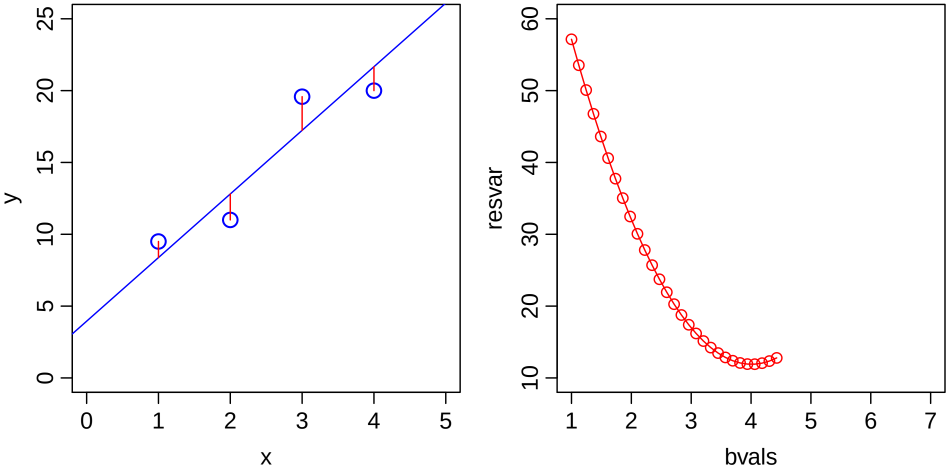

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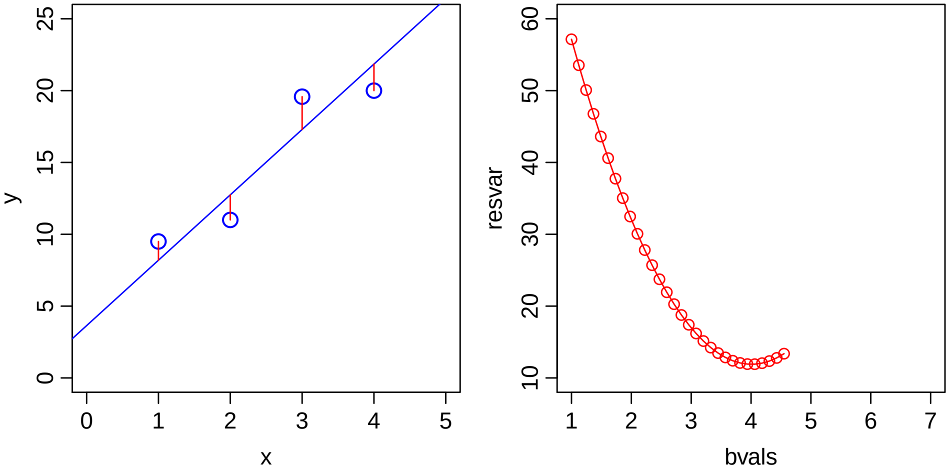
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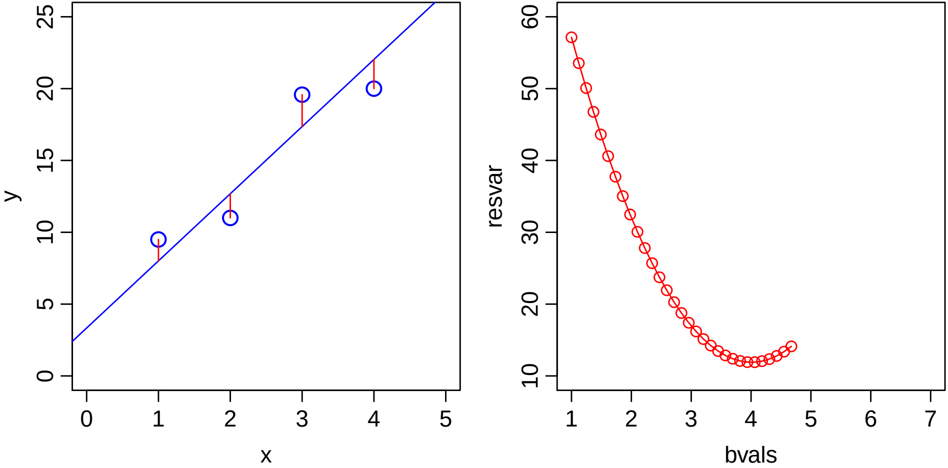

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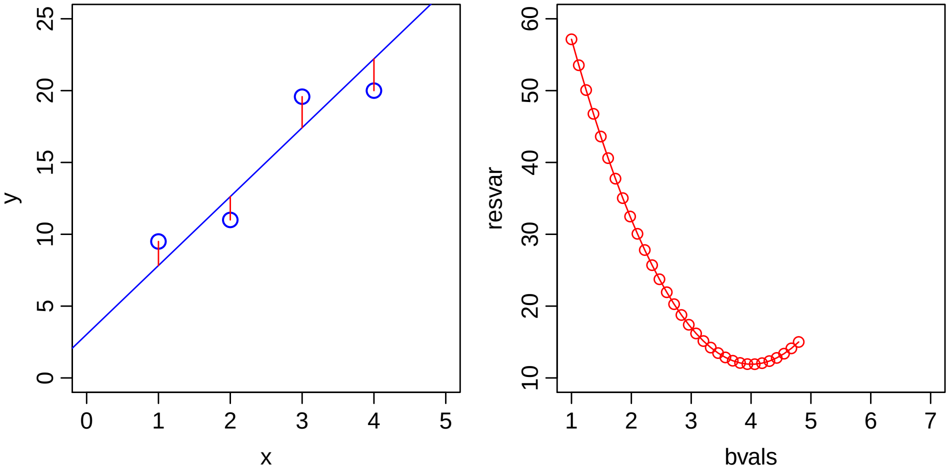

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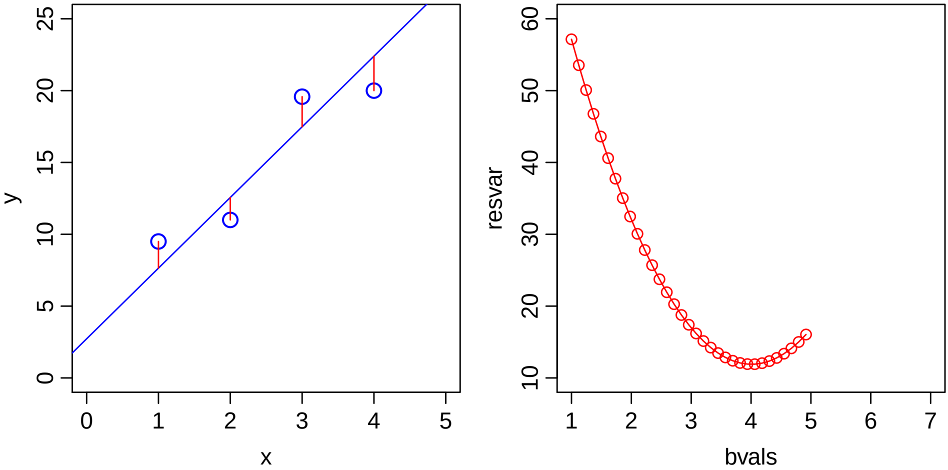

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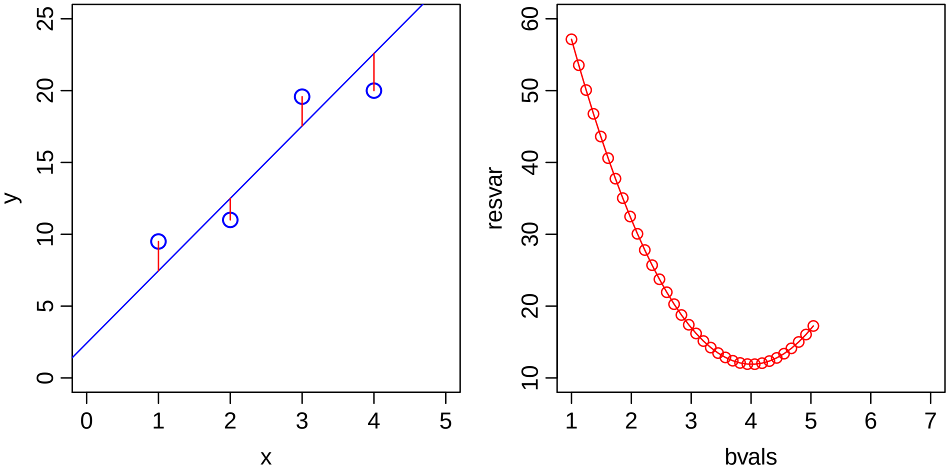

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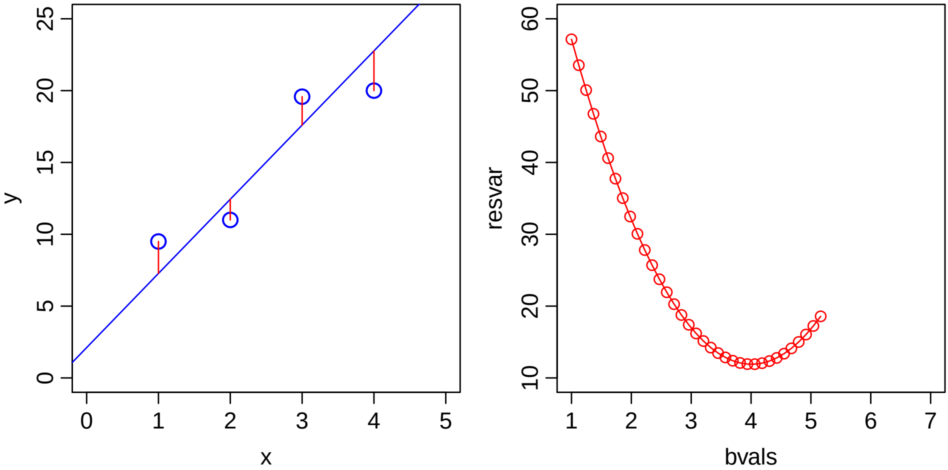
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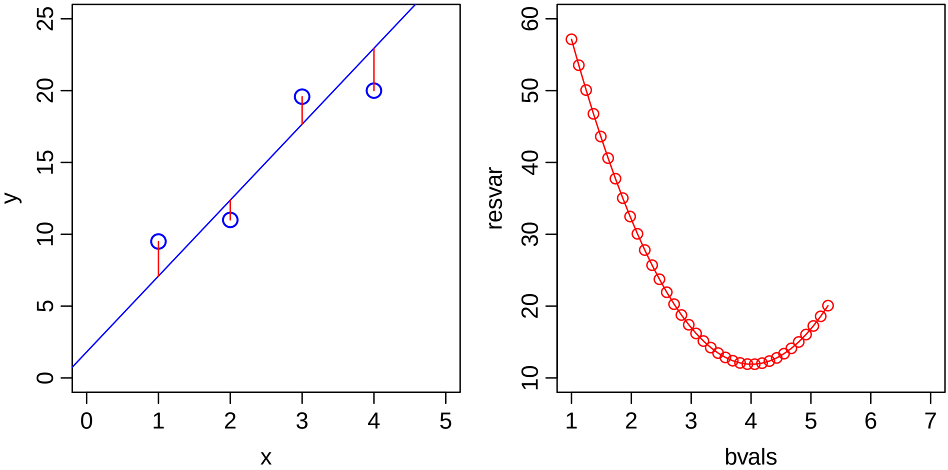

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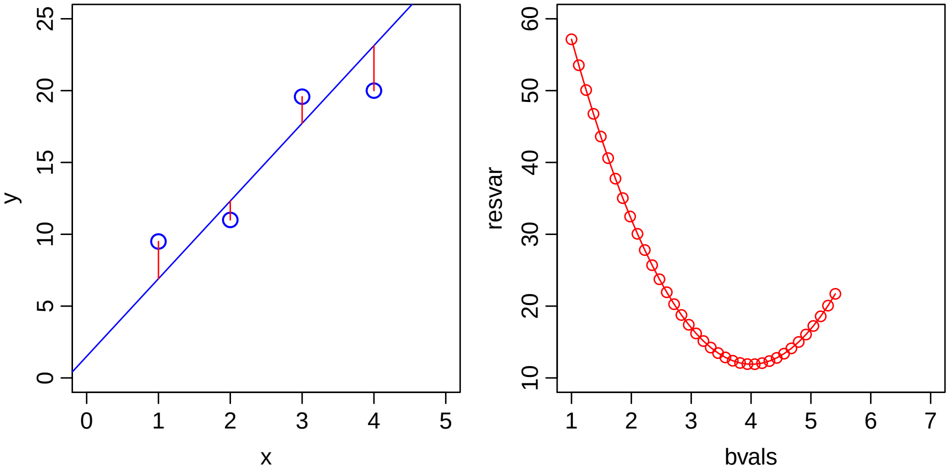

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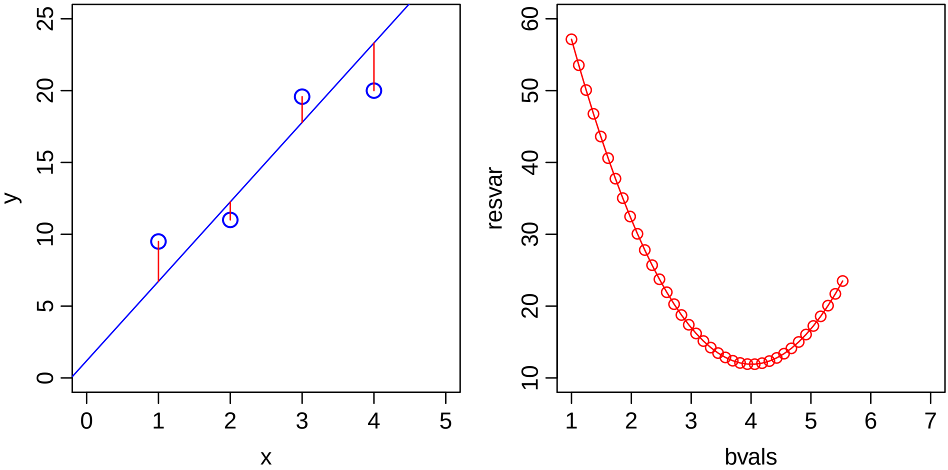

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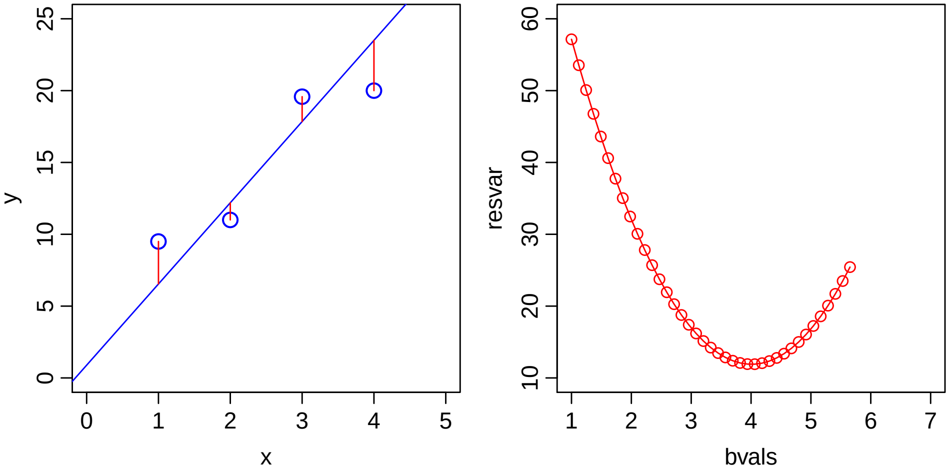
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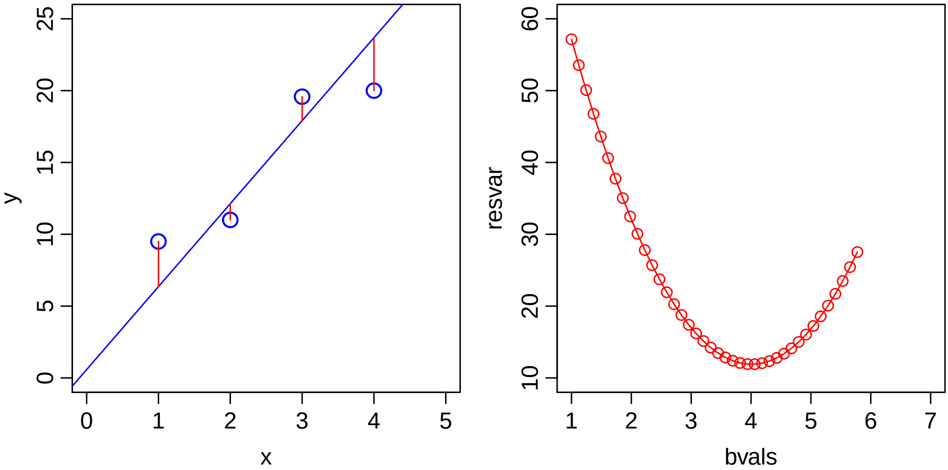

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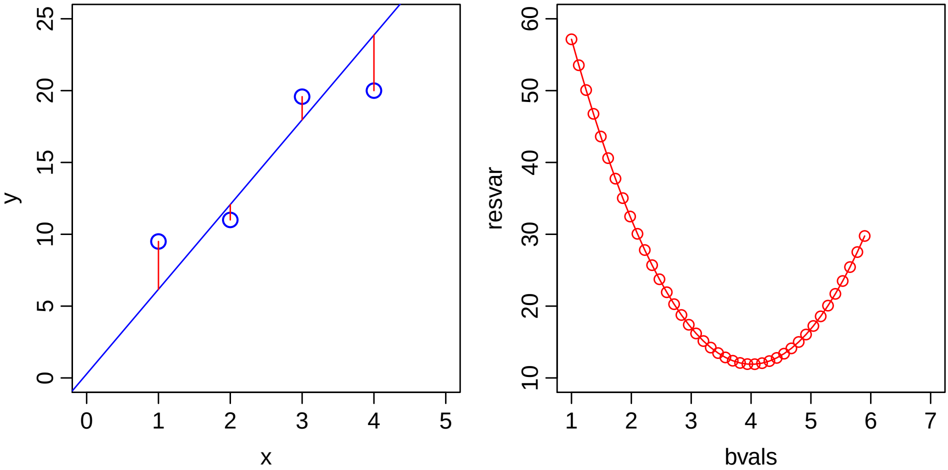
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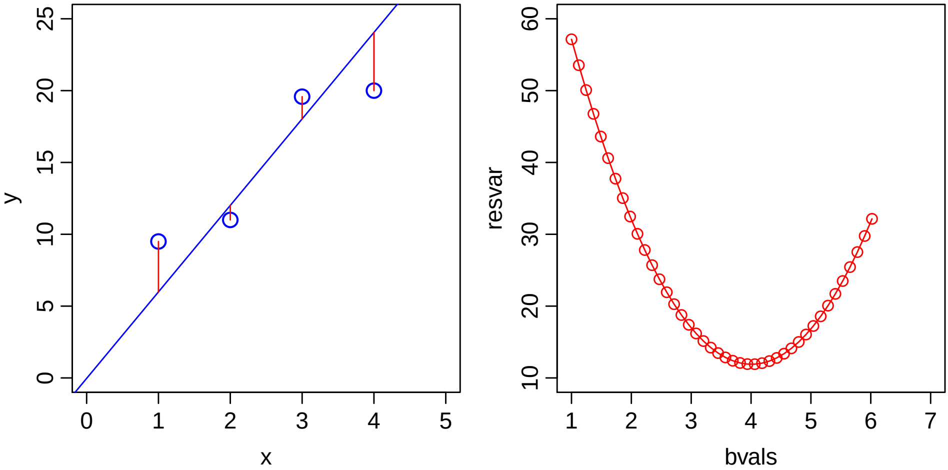

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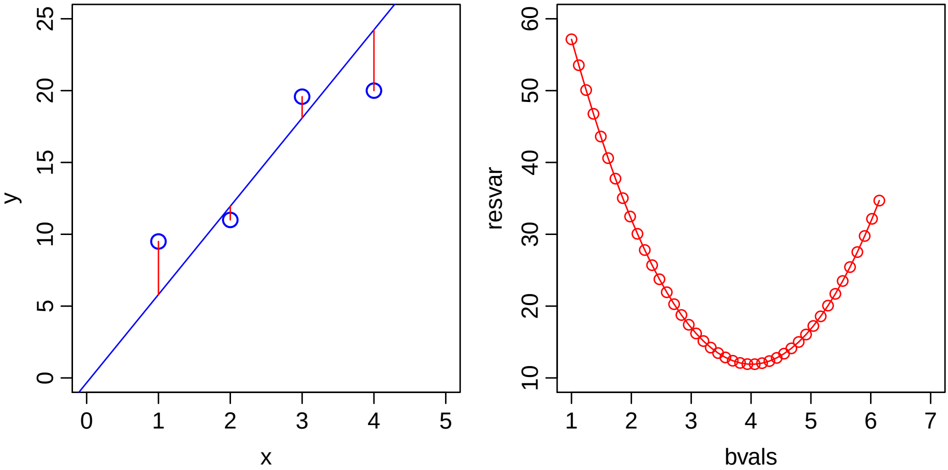

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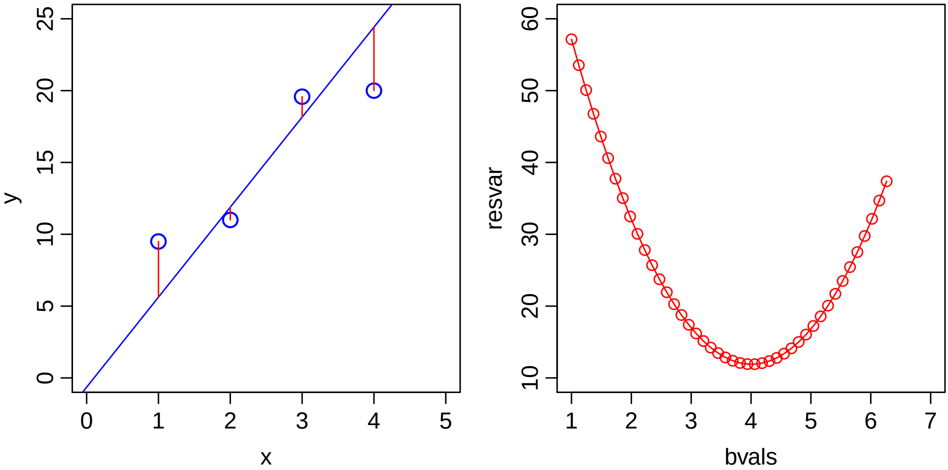

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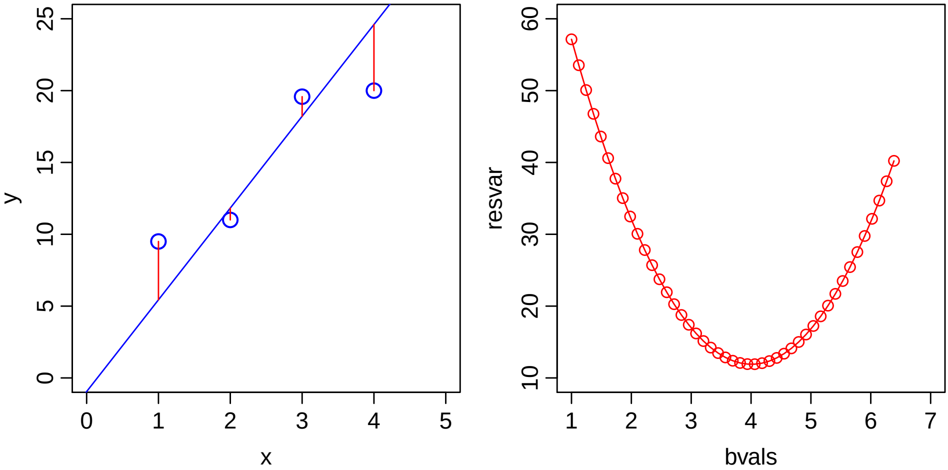

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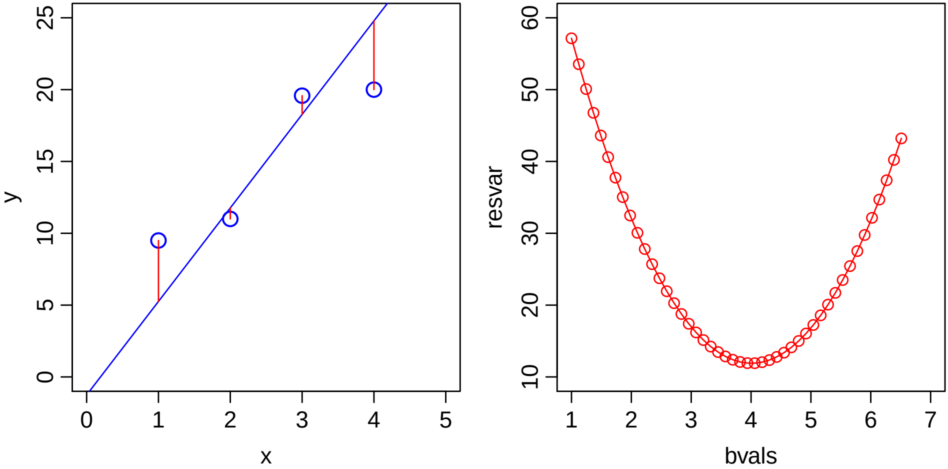

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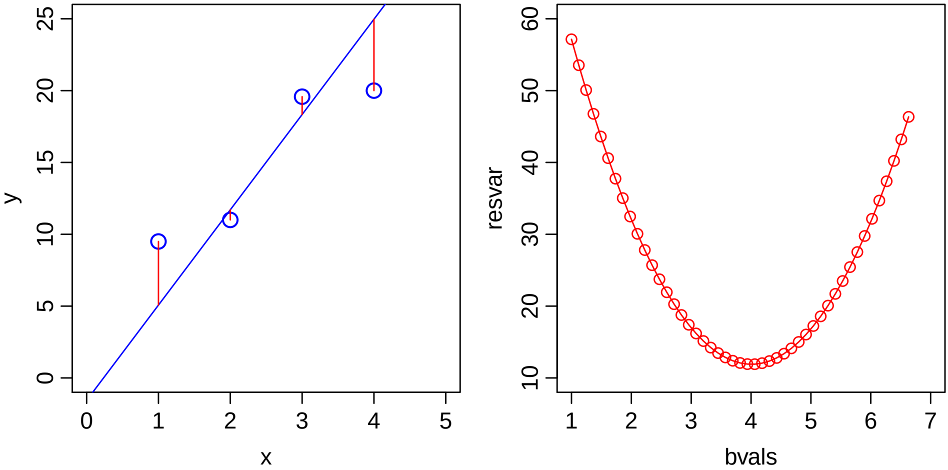

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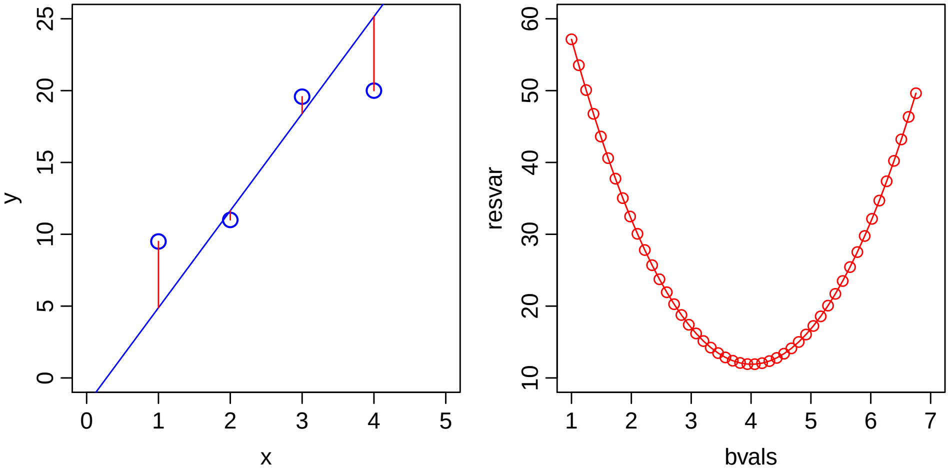

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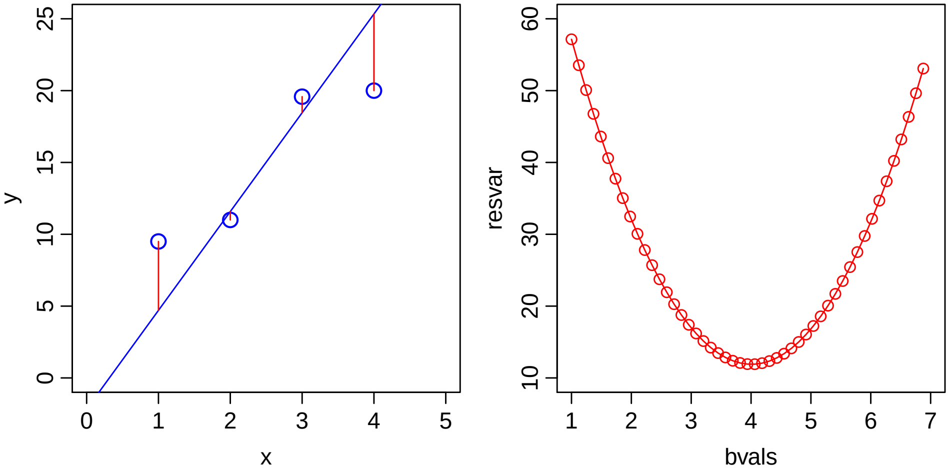

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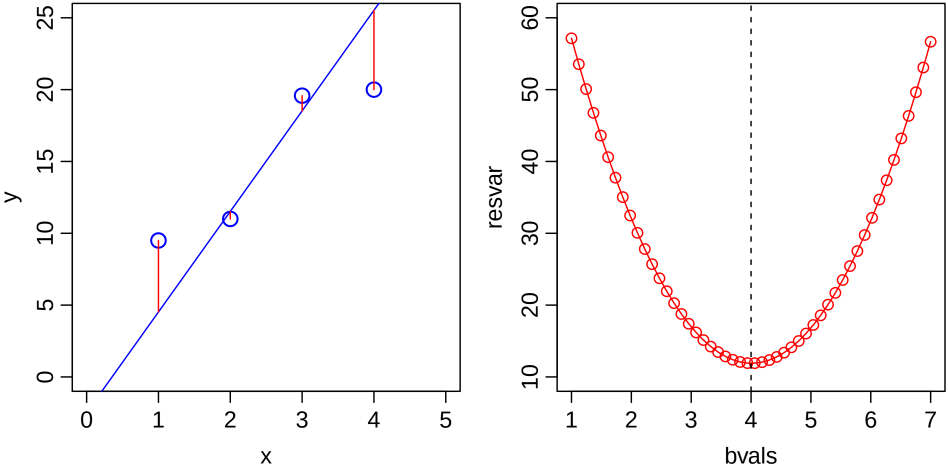

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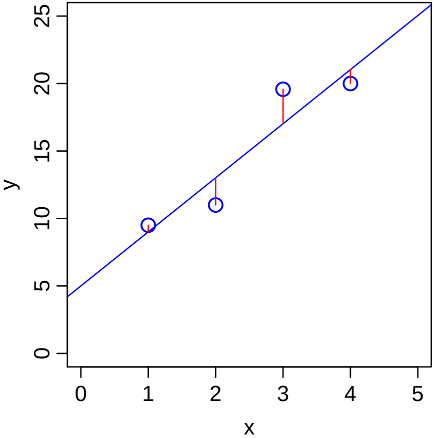
IF THE MODEL IS LINEAR, THE LEAST-SQUARE SOLUTION IS EXACT



$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

$$\begin{aligned} 9.50 &= 5 + 4 \times 1 + 0.50 \\ 11.00 &= 5 + 4 \times 2 - 2.00 \\ 19.58 &= 5 + 4 \times 3 + 2.58 \\ 20.00 &= 5 + 4 \times 4 - 1.00 \end{aligned}$$

The least squares solution here is: $\beta_0 = 5; \beta_1 = 4$

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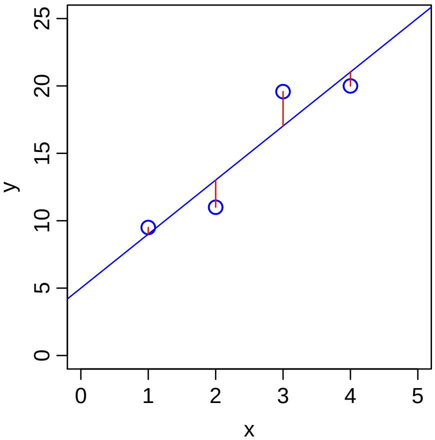

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- *This system of (linear) equations can be compactly represented (and solved using matrix algebra) as* $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$

INTRINSIC NON-LINEARITY MAKES LEAST-AQUARES MODEL FITTING DIFFICULT

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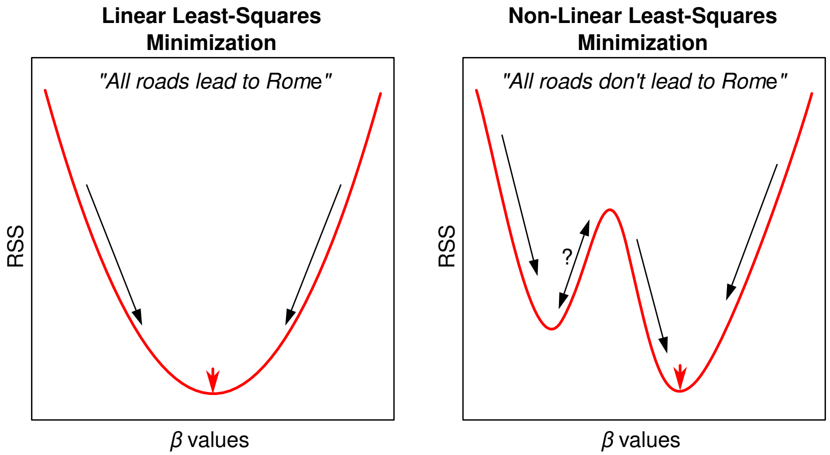

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- *Can you think of some examples?*

NON-LINEAR MODEL EXAMPLE: TEMPERATURE AND METABOLISM

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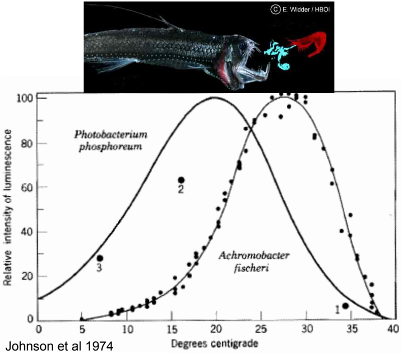

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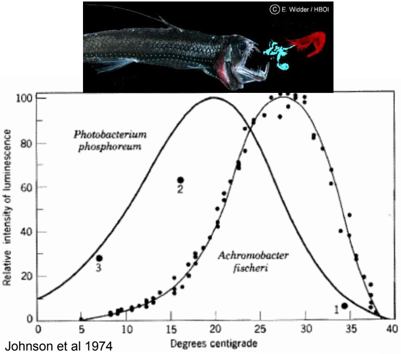

$$B = B_0 \boxed{e^{-\frac{E}{kT}}} f(T, T_{pk}, E_D)$$

T = temperature (K)
k = Boltzmann constant (eV K^{-1})
E = Activation energy (eV)
T_{pk} = Temperature of peak performance
E_D = Deactivation energy (eV)
(J H van't Hoff 1884, S Arrhenius 1889)

The NLLS Fitting Method

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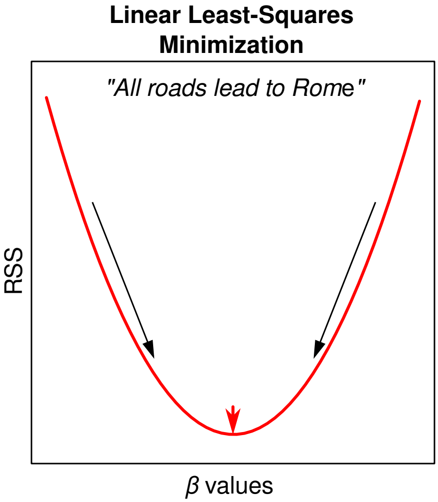
    - Then, adjust the parameters *iteratively* (using a specific "algorithm" that is better than searching *randomly*) such that the RSS is gradually decreased
    - Eventually, if it all goes well, a combination of β_j's that is *very close* to the desired solution (where the RSS is *approximately* minimized) can be found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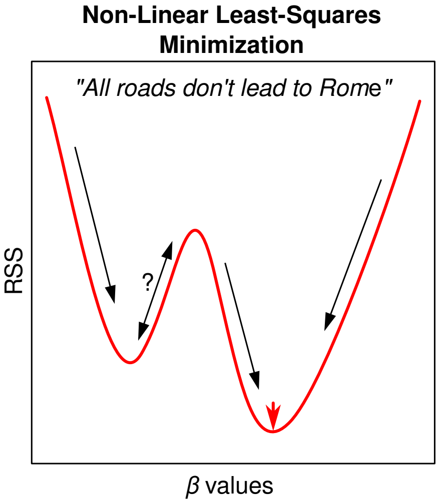
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7. Stop simulations when the adjustments make virtually no difference to the RSS

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- The **Levenberg-Marquardt** algorithm switches between Gauss-Newton and "gradient descent" and is more robust against starting values that are far-off-optimal and is more reliable in most scenarios.

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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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- What if the errors are not normal? — Interpret results cautiously, and use Maximum Likelihood or Bayesian fitting methods instead

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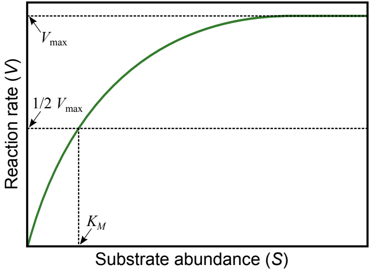
  - It offers additional features like the ability to "bound" parameters to realistic values

NLLS Fitting Practicals

- We will start with NLLS fitting of the Michaelis-Menten model of biochemical reaction 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_M

- Note that $V_{\max} \leq 0$ and $K_M \leq 0$ 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.