

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

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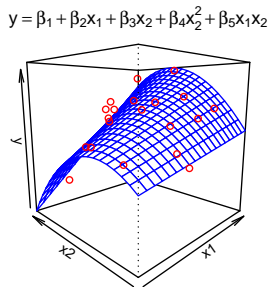
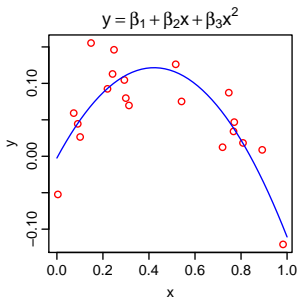
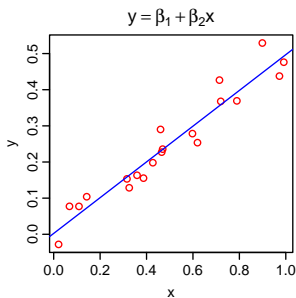
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OUTLINE

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

LINEAR MODELS ARE GREAT



- 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)
- OK, so then *why Non-Linear Least Squares (NLLS) fitting?*

WHY NLLS? – FIRST, WHAT MAKES A MODEL NON-LINEAR?

- OLS can be used to fit both linear and nonlinear *equations* that *intrinsically linear*, e.g.,
 - Straight line: $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$
 - Polynomial: $y_i = \exp(\beta_0) + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i$
- Indeed, for OLS to work, we need *intrinsic linearity* — i.e., the equation to be fitted (model) should be *linear in the parameters*
- Are these models linear in their *parameters*?
 - $y_i = \beta_0 + \beta_1 x_i^{\beta_2} + \varepsilon_i$
 - $y_i = \beta_0 e^{\beta_2 x_i} + \varepsilon_i$

NO!

SO WHAT — WHY IS INTRINSIC NON-LINEARITY A PROBLEM?

Recall what the Least Squares method does:

- Consider a predictor x , data y , n observations, and a model that we want to fit to the data:

$$f(x_i, \beta) + \varepsilon_i$$

where $\beta = (\beta_1, \beta_2, \dots, \beta_k)$ are the model's k parameters

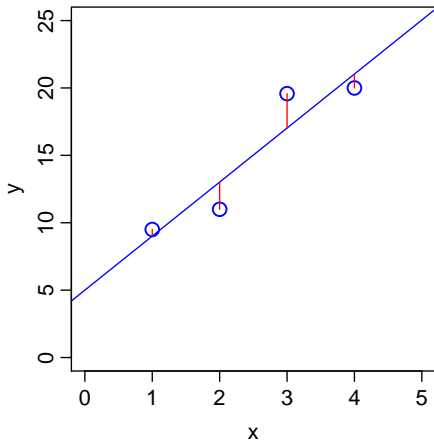
- The objective is to find estimates of values of the k parameters ($\hat{\beta}_j$) that minimize the sum (S) of squared residuals (r_i) (AKA RSS):

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

THE LEAST-SQUARES SOLUTION

OLS minimizes the *sum* of the *squared* residuals

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



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

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

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

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

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

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

INTRINSIC NON-LINEARITY DOES NOT ALLOW A ALGEBRAIC SOLUTION

- So, then, in an intrinsically non-linear model such as $y_i = \beta_0 e^{\beta_2 x_i} + \varepsilon_i$ the derivatives $\frac{\partial r_i}{\partial \beta_j}$ are naughty
- That is, they are functions of both x and the parameters β_j , so the gradient equations do not have a solution like the OLS case
- So the nice trick of solving $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$ is impossible *mathematically*

SO — ENTER NLLS

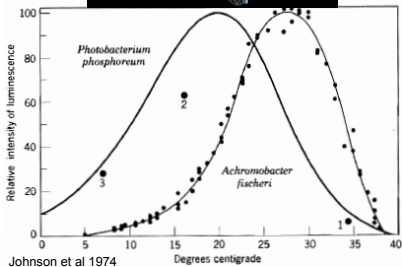
But we can use brute-force computation to find close-to-optimal least squares minimization!

- Choose initial values for the parameters we want to estimate (β_j 's)
- Then, “refine” the parameters *iteratively* by calculating $\frac{\partial r_i}{\partial \beta_j}$ *approximately* — this approximation is the *Jacobian* (the gradient), which is a matrix of the $\frac{\partial r_i}{\partial \beta_j}$'s
- Whether a refinement has taken place in any step of the iteration is determined by re-calculating the residuals at that step
- Eventually, if it all goes well, we find a combination of β_j 's that is *very close* to the desired solution $\frac{\partial S}{\partial \beta_j} = 0, j = 0, 1, 2, \dots, k$

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:
 - Logistic population growth
 - Allometric growth
 - Michaelis-Menten biochemical kinetics (two parameters V_{\max} and K_m : $v = \frac{V_{\max}[S]}{K_m + [S]}$)
 - Responses of metabolic rates to changing temperature
 - Consumer-Resource (e.g., predator-prey) functional responses
 - Time-series data (e.g., fitting a sinusoidal function)
- *Can you think of some examples?*

EXAMPLE: TEMPERATURE AND METABOLISM



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

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 vant Hoff 1884, S Arrhenius 1889)

- Surely there is more to thermal responses?
 - Oxygen limitation
 - Complexity of metabolic network
 - Hormonal regulation
- *What about alternative models?*

EXAMPLE: FUNCTIONAL RESPONSES

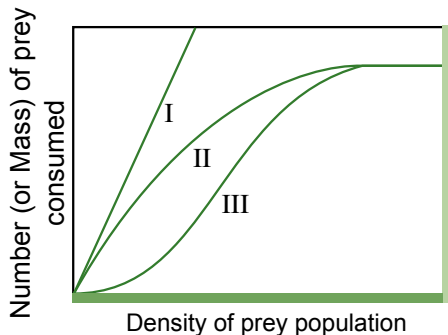
$$f(x_R) = \frac{ax_R^{q+1}}{1+hax_R^{q+1}} \text{ (Holling, 1959)}$$

x_R = Resource density (Mass / Area or Volume)

a = Search rate (Area or Volume / Time)

h = Handling time

q = Shape parameter (dimensionless)



Note that:

- NLLS fitting can yield $h < 0$, $q < 0$, or both
- $h < 0$ is biologically impossible but indicates an upward curving response
- $q < 0$ is biologically unlikely as it indicates a decline in search rate with resource density (but is useful as a measure of deviation away from a type III response)

NLLS FITTING

So the general procedure 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 you can choose between:

- 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) switches between Gauss-Newton and “gradient descent” and is more robust against starting values that are far-off-optimal — available in R through the `minpack.lm` package
<http://cran.r-project.org/web/packages/minpack.lm>
- The command is `nlsLM`

NLLS FITTING

- Once the algorithm has converged (hopefully – but you may be surprised how well it usually works), you need to get the goodness of fit measures
- First, of course, examine the fits visually
- Also, report the best-fit results, including:
 - Sums of deviations of the data points from the final model fit (final RSS)
 - R^2
 - Estimated coefficients
 - For each coefficient, standard error (can be used for CI's), t-statistic and corresponding (two-sided) p-value
- The function `summary.nls` will give you all these measures
- Remember, the precise parameter values you obtain will depend in part on the initial values chosen and the convergence criteria
- You may also want to compare multiple models.

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 error distribution is Gaussian — for example, what would the error distribution of this non-linear model be: $y_i = \beta_0 e^{\beta_2 x_i} + \varepsilon_i$
- What if the errors are not normal? — use Maximum Likelihood or Bayesian methods instead.

MORE NLLS TIPS

- You can use mixed-effects modelling with NLLS in R; the package is `nlme` <https://stat.ethz.ch/R-manual/R-devel/library/nlme/html/nlme.html> (You are probably stuck with the Gauss-Newton algorithm with `nlme` though)
- You can also use Python — look up `lmfit` <https://lmfit.github.io/lmfit-py/index.html>. python seems to have a better Levenberg-Marquardt implementation than R

READINGS AND RESOURCES

- Motulsky, Harvey, and Arthur Christopoulos. Fitting models to biological data using linear and nonlinear regression: a practical guide to curve fitting. OUP USA, 2004.
- Johnson, J. B. & Omland, K. S. 2004 Model selection in ecology and evolution. *Trends Ecol. Evol.* 19, 101–108.

WHY IS INTRINSIC NON-LINEARITY A PROBLEM?

- Our model is $f(x_i, \beta) + \varepsilon_i$
- We want to find estimates of values of the parameters ($\hat{\beta}_j$) that *minimize* the sum (S) of squared residuals (r_i) (AKA “RSS”)
$$S = \sum_{i=1}^n [y_i - f(x_i, \beta)]^2 = \sum_{i=1}^n r_i^2$$
- For this we can solve $\frac{\partial S}{\partial \beta_j} = 0, j = 0, 1, 2, \dots, k$ to find the *minimum*
- That is, we need to solve $\frac{\partial \sum_{i=1}^n r_i^2}{\partial \beta_j} = 0$
- Or, $2 \sum_{i=1}^n r_i \frac{\partial r_i}{\partial \beta_j} = 0$

WHY IS INTRINSIC NON-LINEARITY A PROBLEM?

- Thus, solving $2 \sum_{i=1}^n r_i \frac{\partial r_i}{\partial \beta_j} = 0$
boils down to finding the “gradient” $\frac{\partial r_i}{\partial \beta_j}$
- This is not a problem in linear models, because this gradient is fully solvable as the equation is *intrinsically linear*
- That is, the solution of $\frac{\partial r_i}{\partial \beta_j}$ is simple (enough)

WHY IS INTRINSIC NON-LINEARITY A PROBLEM?

- For example, if $f(x_i, \beta) + \varepsilon_i = \beta_0 + \beta_1 x_i + \varepsilon_i$
- That is, our model is $y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$ (Linear Regression)
- Then we want to solve
$$\frac{\partial S}{\partial \beta_0} = \sum_{i=1}^n \frac{\partial [y_i - (\beta_0 + \beta_1 x_i)]^2}{\partial \beta_0} = 0$$
$$\frac{\partial S}{\partial \beta_1} = \sum_{i=1}^n \frac{\partial [y_i - (\beta_0 + \beta_1 x_i)]^2}{\partial \beta_1} = 0$$

WHY IS INTRINSIC NON-LINEARITY A PROBLEM?

- And, solving

$$\frac{\partial S}{\partial \beta_0} = \sum_{i=1}^n \frac{\partial [y_i - (\beta_0 + \beta_1 x_i)]^2}{\partial \beta_0} = 0$$

$$\frac{\partial S}{\partial \beta_1} = \sum_{i=1}^n \frac{\partial [y_i - (\beta_0 + \beta_1 x_i)]^2}{\partial \beta_1} = 0$$

just boils down to solving two simultaneous equations because $\frac{\partial r_i}{\partial \beta_j}$ is simple *because* the model is intrinsically linear:

$$\begin{aligned} -n\beta_0 + \sum_{i=1}^n y_i + \beta_1 \sum_{i=1}^n x_i &= 0 \\ \sum_{i=1}^n x_i y_i - \beta_0 \sum_{i=1}^n x_i + \beta_1 \sum_{i=1}^n x_i^2 &= 0 \end{aligned}$$

- That is, we need to solve $\mathbf{Y} = \mathbf{X}\beta + \varepsilon$ (*this is what R solves when you use `lm()`*)