Estimation of Parameter Values

Nutrition Models Workshop

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Outline

- Nutrition models are VERY diverse
  - Combination of empirical, mechanistic, dynamic and static models
  - Regression, linear and nonlinear mixed models, differential equations

- Today: Main approaches for estimating parameters in a variety of models
  - Some mathematical description
  - Idea is for you to understand the reasoning and challenges of different approaches

- One exercise/demonstration in the end
  - Fit model with two approaches

Introduction

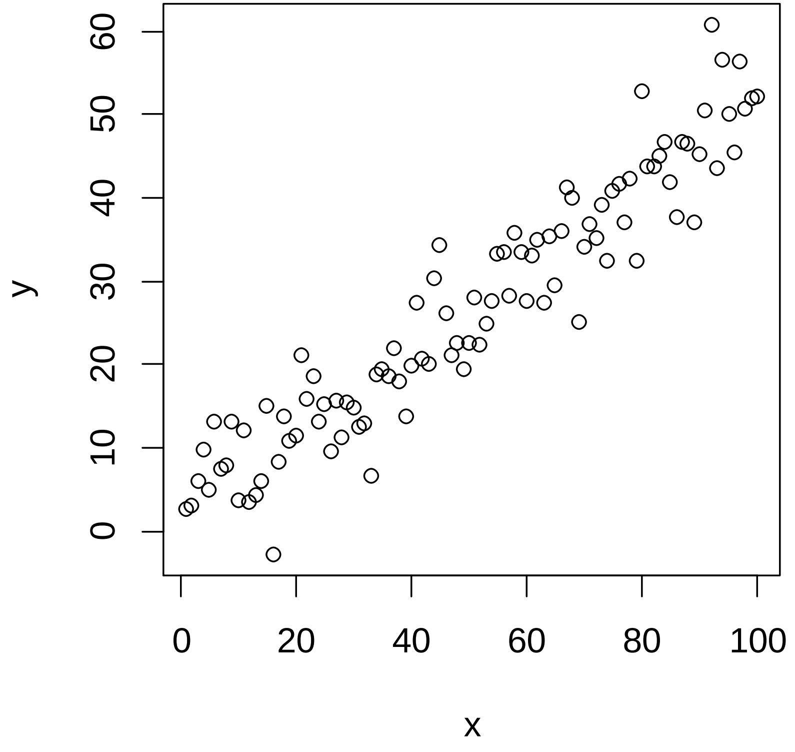
- Different types of models have been used for nutrition modeling
  - Compartmental, regression, meta-analysis, nonlinear mixed models, …..

- One feature is common to almost all these models
  - Parameters are needed to describe the system
  - Quantify relationship between variables

Introduction

- Simple example: linear regression

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



- Y_i is the response variable for the *i*th observation
- x_i is the predictor variable in the *i*th observation
- β_0 is the intercept
- β_1 is the slope
- ε_i is the error, $E[\varepsilon_i] = 0$, $Var[\varepsilon_i] = \sigma^2$ and ε_i are independent
- $i = 1, \ldots, n$

In matrix notation: $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$

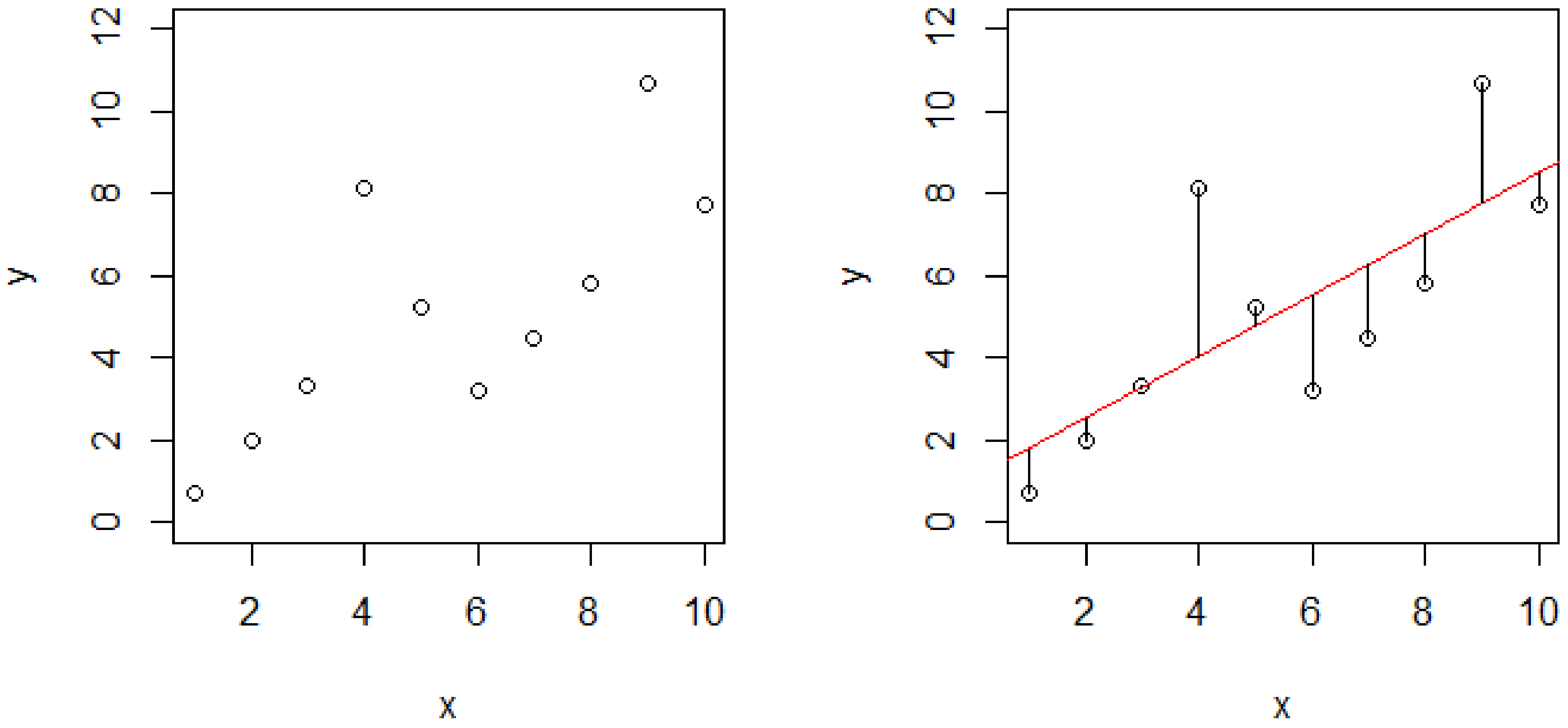
$$\begin{bmatrix} Y_1 \\ \vdots \\ Y_n \end{bmatrix} = \begin{bmatrix} 1 & x_1 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix} + \begin{bmatrix} \varepsilon_1 \\ \vdots \\ \varepsilon_n \end{bmatrix}$$

Introduction

- In practice, parameter true values are unknown
  - Estimators from a sample

- Parameters have to be optimal in some sense
  - Least square estimators minimize squared errors
  - Maximum likelihood estimators maximize the likelihood function

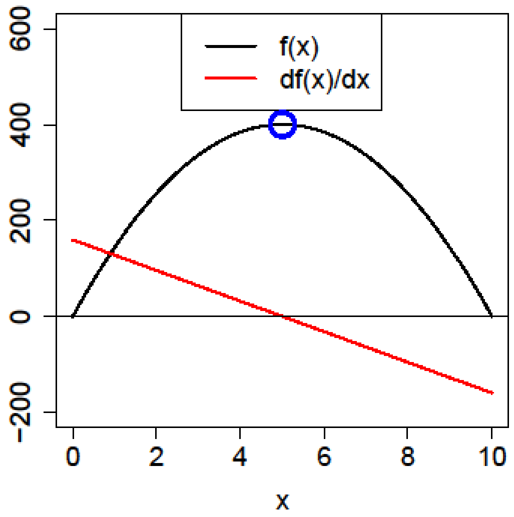
Least Squares Estimators



Least Square Estimators

- The least squares estimators minimize the square errors: $Q = \sum_{i=1}^{n} \left[Y_i - (\beta_0 + \beta_1 x_i) \right]^2$
- How do we get them???
- We can find points of minimum and maximum of a function using derivatives.

For example for $f(x) = 160x - 16x^2$



Set derivative to zero and "solve" for x:

$$160 - 32x = 0$$
$$x = 5$$

Second derivative test: -32

Least Squares Estimators

$$\frac{\partial Q}{\partial \beta_0} = -2\sum_{i=1}^{n}\left(Y_i - \beta_0 - \beta_1 x_i\right)$$

$$\frac{\partial Q}{\partial \beta_0} = -2\sum_{i=1}^{n} x_i\left(Y_i - \beta_0 - \beta_1 x_i\right)$$

Setting these partial derivatives to zero, we construct the normal equations

$$\sum_{i=1}^{n} Y_i = nb_0 + b_1 \sum_{i=1}^{n} X_i$$

$$\sum_{i=1}^{n} X_i Y_i = b_0 \sum_{i=1}^{n} X_i + b_1 \sum_{i=1}^{n} X_i^2$$

Least Squares Estimators

- The least square estimators are the solutions to the normal equations

$$b_1 = \sum_{i=1}^{n}\left(x_i - \bar{x}\right)\left(Y_i - \bar{Y}\right) / \sum_{i=1}^{n}\left(x_i - \bar{x}\right)^2$$

$$b_0 = \bar{Y} - b_1 \bar{x}$$

- The concept extends to multiple regression

$$Q = \sum_{i=1}^{n}\left[Y_i - \left(\beta_0 + \beta_1 x_{i1} + \beta_{p-1} x_{i,p-1}\right)\right]^2$$

  - General form of the least squares estimators: $\mathbf{b} = \left(\mathbf{X}^{\mathrm{T}}\mathbf{X}\right)^{-1}\mathbf{X}^{\mathrm{T}}\mathbf{Y}$

Least Squares Estimators

- Estimates of the uncertainty associated with these parameters

- Estimator of the error's variance

$$MSE = \frac{1}{n-p}\sum_{i=1}^{n}\left[Y_i - \left(b_0 + b_1 x_{i1} + \cdots + b_{p-1} x_{i,p-1}\right)\right]^2$$

- Estimated variance-covariance matrix of the parameters

$$MSE\left(\mathbf{X}^{\mathrm{T}}\mathbf{X}\right)^{-1}$$

Nonlinear Models

- So far, we can estimate parameters in linear models

- Many phenomena in biology are nonlinear
  - For example, reaction velocity vs. substrate concentration in an enzymatic reaction
  - Before we start with nonlinear models, let's clarify

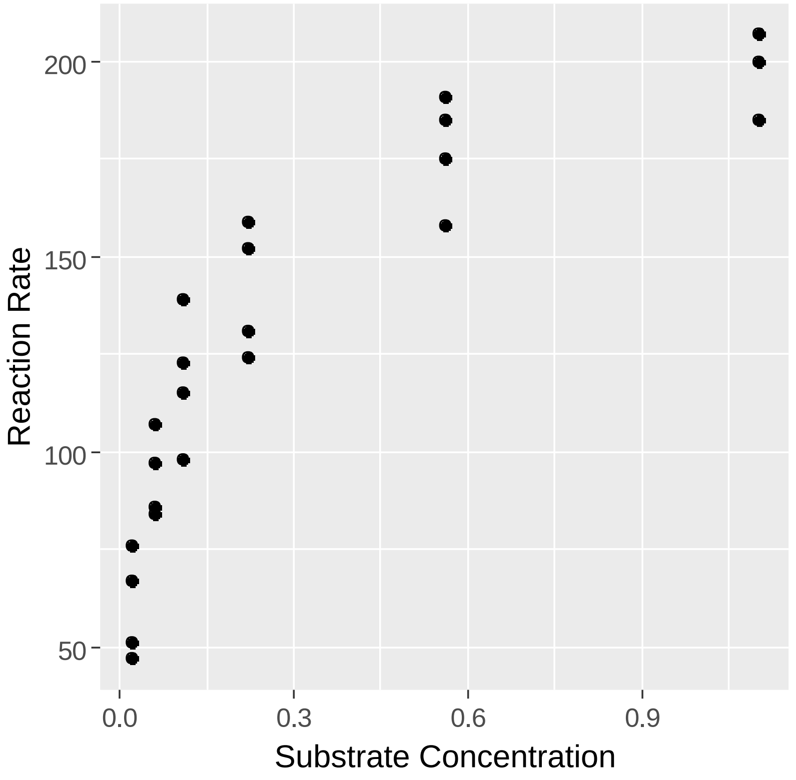
$$Y_i = \frac{\theta_1}{1+\theta_2 \exp\left(\theta_3 x_i\right)} + \varepsilon_i$$ is a <u>nonlinear</u> model

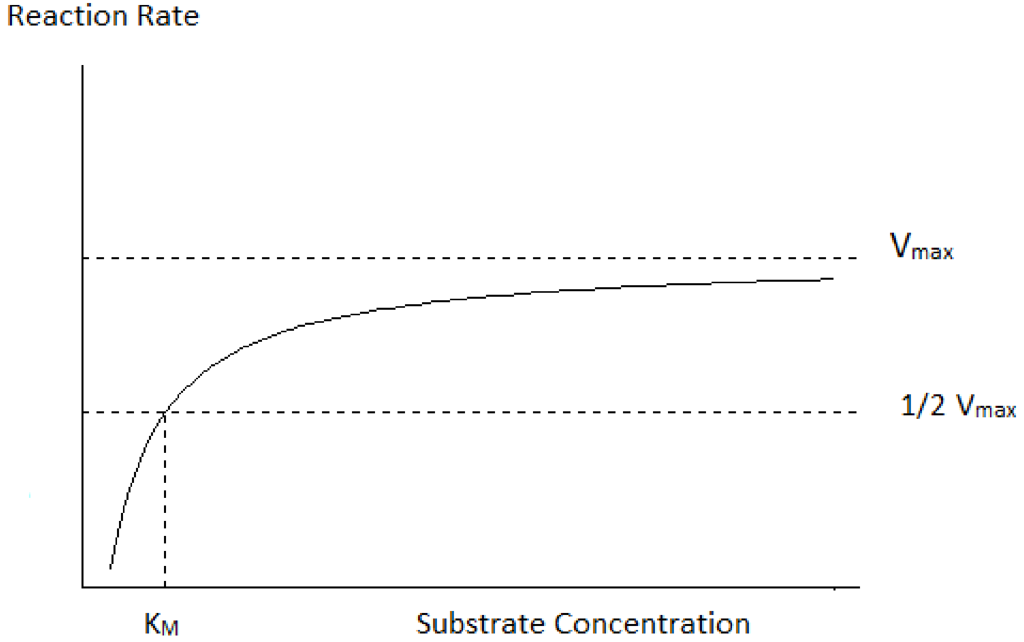
$$Y_i = \beta_0 + \beta_1 x_i + \beta_2 x_i^2 + \varepsilon_i$$ is a <u>linear</u> model

Nonlinear Models

Michaelis-Menten Kinetics

$$v = \frac{V_{\max}[S]}{K_M + [S]}$$





Nonlinear Regression

$$Y_i = f\left(x_i, \boldsymbol{\theta}\right) + \varepsilon_i$$

f is the nonlinear function describing the relationship between Y and x

Michaelis-Menten example: $y_i = \dfrac{V_{\max} x_i}{K_M + x_i} + \varepsilon_i \quad \Rightarrow f\left(x_i, \boldsymbol{\theta}\right) = \dfrac{V_{\max} x_i}{K_M + x_i}$

- y_i is the reaction rate for the *i*th observation
- x_i is the associated substrate concentration

$\boldsymbol{\theta} = \left(V_{\max}, K_M\right)^{\mathrm{T}}$ are the parameters to be estimated

- ε_i is the error, $E[\varepsilon_i] = 0$, $Var[\varepsilon_i] = \sigma^2$ and independent
- $i = 1, \ldots, n$

Least Squares Estimators

- For the simple linear regression model, least squares minimize

$$Q = \sum_{i=1}^{n} \left[Y_i - \left(\beta_0 + \beta_1 x_i \right) \right]^2$$

- For the nonlinear regression, the idea is the same: minimize

$$Q = \sum_{i=1}^{n} \left[Y_i - f\left(x_i \right) \right]^2$$

Least Squares Estimators

- Solution to the normal equations are often difficult to obtain analytically

- Numerical Algorithms
  - For example, Gauss-Newton
  - Require initial values to initialize numerical procedures

Gauss-Newton

- Default in PROC NLIN and `nls()`
- Approximate the nonlinear model with linear terms
- Taylor series expansion and least squares as for linear regression
- Denote the least squares estimates $\mathbf{g}$ and the initial values $\mathbf{g}^{(0)} = \left(g_0^{(0)}, g_1^{(0)}, \cdots, g_{p-1}^{(0)}\right)$
- Approximation around starting values:

$$f\left(x_i, \boldsymbol{\theta}\right) \approx f\left(x_i, \mathbf{g}^{(0)}\right) + \sum_{k=0}^{p-1} \left[\frac{\partial f\left(x_i, \boldsymbol{\theta}\right)}{\partial \theta_k}\right]_{\boldsymbol{\theta}=\mathbf{g}^{(0)}} \left(\theta_k - g_k^{(0)}\right)$$

Gauss-Newton

- Model approximation

$$Y_i - f\left(x_i, \mathbf{g}^{(0)}\right) \approx \sum_{k=0}^{p-1} \left[\frac{\partial f\left(x_i, \boldsymbol{\theta}\right)}{\partial \theta_k} \right]_{\boldsymbol{\theta}=\mathbf{g}^{(0)}} \left(\theta_k - g\right)_k^{(0)} + \varepsilon_i$$

- It is a linear model!

- Estimate parameters by least squares: $\mathbf{b}^{(0)} = \left(\mathbf{D}^{(0)\mathrm{T}}\mathbf{D}^{(0)}\right)^{-1} \mathbf{D}^{(0)\mathrm{T}}\mathbf{Y}^{(0)}$

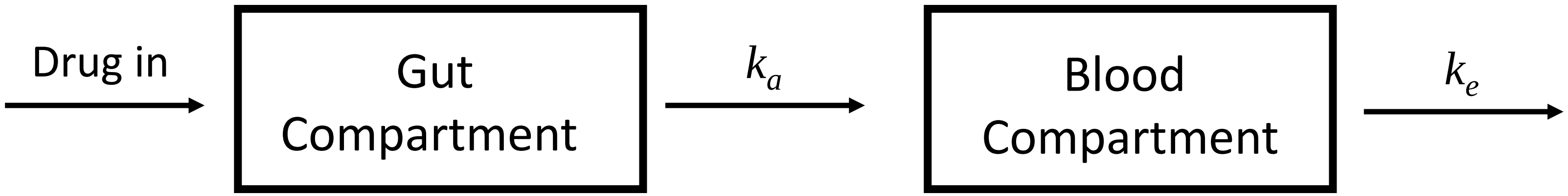
- Update: $\mathbf{g}^{(1)} = \mathbf{g}^{(0)} + \mathbf{b}^{(0)}$

Gauss-Newton

- Evaluation criteria: $SSE^{(0)} = \sum_{i=1}^{n}\left(Y_i - f_i^{(0)}\right)^2$
- Start the process again with $\mathbf{g}^{(1)}$ as the initial values
- Repeat procedure until $SSE^{(s+1)} - SSE^{(s)}$ is negligible
- Estimate of error's variance: $MSE = \sum_{i=1}^{n}\left[Y_i - f\left(x_i, \mathbf{g}\right)\right]^2 / n - p$
- Other methods available, e.g. Nelder-Mead and Marquardt

Compartmental Models

- Traditionally used in nutritional modeling
  - Roots on pharmacokinetics and differential calculus



Compartmental Models

- Functional forms described in terms of differential equations
  - Instead of the “integrated form”

- Strategy for parameter estimation
  - Expected mean represented by a compartmental model f
  - If f cannot be obtained analytically, it has to be solved numerically
    - Euler, Runge-Kutta4, lsoda
  - Can use nonlinear least squares but have to numerically solve f at iteration
  - Modern software estimate using maximum likelihood

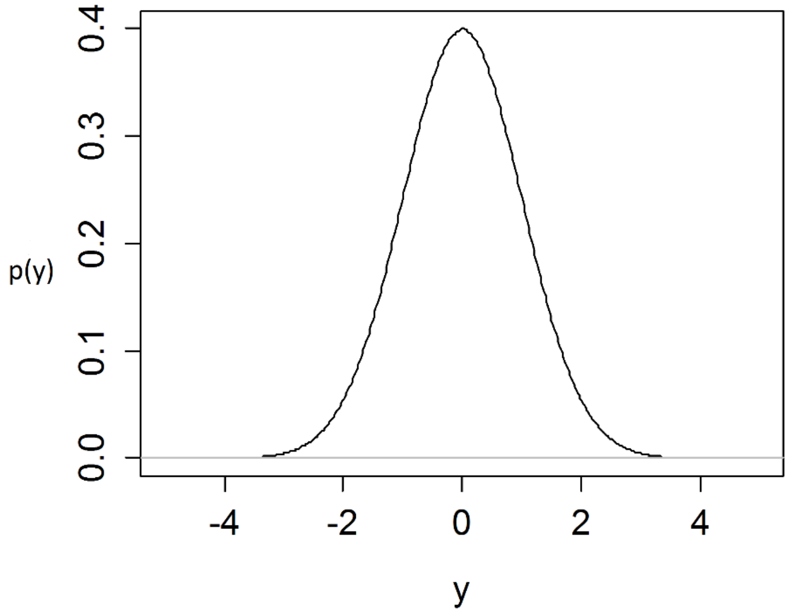
Maximum Likelihood Estimation

- Another strategy for parameter estimation

- For regression models with independent $\varepsilon_i \sim N\left(0, \sigma^2\right)$, estimators coincide with least squares estimators

- Estimators maximize the likelihood function
  - Parameter values that are in best agreement with the data

Maximum Likelihood Estimation



$$p\left(y \mid \mu, \sigma^2\right) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(y-\mu)^2}{2\sigma^2}\right)$$

- $p\ (y \mid \mu\ \sigma^2)$ is the density function: How likely y is at each value
- The likelihood function is: $L\left(\mu, \sigma^2 \mid y_1, \ldots, y_n\right) = p\left(y_1 \mid \mu, \sigma^2\right) \times\ \ldots\ \times p\left(y_n \mid \mu, \sigma^2\right)$
  – "How likely the whole data is with that set of parameters values"
  – MLE: "maximize the likelihood of getting the observed data"

Maximum Likelihood Estimation

- Linear Regression Example: $Y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$

$$L\left(\beta_0, \beta_1, \sigma^2 \mid y_1, \ldots, y_n\right) = \left(\frac{1}{\sqrt{2\pi\sigma^2}}\right)^n \exp\left[-\frac{1}{2\sigma^2}\sum_i \left(y_i - \beta_0 - \beta_1 x_i\right)^2\right]$$

- It is easier to work with the log-likelihood

$$\log L\left(\beta_0, \beta_1, \sigma^2 \mid y_1, \ldots, y_n\right) = -\frac{n}{2}\log\left(2\pi\right) - \frac{n}{2}\log\left(\sigma^2\right) - \frac{1}{2\sigma^2}\sum_i \left(y_i - \beta_0 - \beta_1 x_i\right)^2$$

- To find parameters that maximize the likelihood we…
  - Take the derivative with respect to each parameter and set to zero. Also need second derivative test

Mixed Models

- Modern mixed modeling relies heavily on likelihood methods
- Extension of (non)linear models with both fixed and random effects
- Probably the “type” of model you need to analyze your data or construct your nutrition model
- There’s a whole workshop on mixed models in this meeting

Nonlinear Mixed Models

- Nonlinear functional forms
  - Michaelis-Menten, logistic, exponential, Gompertz, …
- Random effects that "enter the model" nonlinearly
- Allow you to model nonlinear clustered, logitudinal data
  - Records from the same animal, treatment means from the same study

Nonlinear Mixed Models

$$y_{ij} = f\left(x_{ij}, \boldsymbol{\theta}_i\right) + \varepsilon_{ij}$$

- y_{ij} is the jth record on the ith “subject” or cluster
- x_{ij} is the associated predictor variable
- $\boldsymbol{\theta}_i$ is the vector of subject specific parameters

$$\boldsymbol{\theta}_i = \underbrace{\boldsymbol{\beta}}_{\text{“Fixed”}} + \underbrace{\mathbf{b}_i}_{\text{“Random”}} \qquad \mathbf{b}_i \sim N(\mathbf{0}, \boldsymbol{\Psi})$$

- ε_{ij} is the random error $\sim N(0, \sigma^2)$

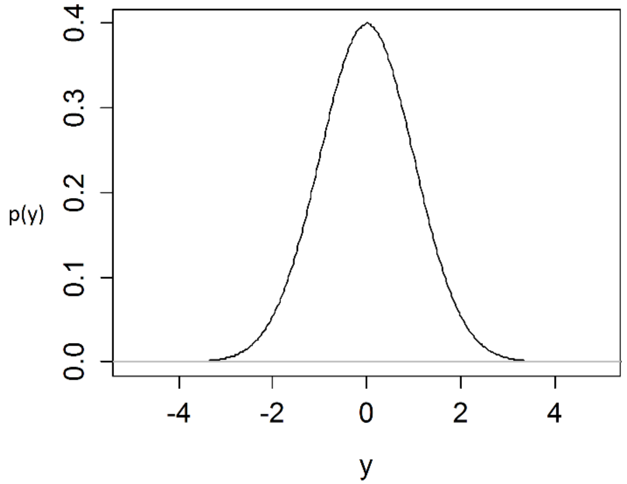
Nonlinear MM Maximum Likelihood

- There is more than one source of variability
  - Between subjects and within subjects

- To represent the generative process of the data we need to take both into account
  - Joint density of the response and the random effects

Maximum Likelihood

- For the linear regression



$$p\left(y \mid \mu, \sigma^2\right) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{\left(y-\mu\right)^2}{2\sigma^2}\right)$$

- The likelihood function is: $L\left(\mu, \sigma^2 \mid y_1, \ldots, y_n\right) = p\left(y_1 \mid \mu, \sigma^2\right) \times \ \ldots \ \times p\left(y_n \mid \mu, \sigma^2\right)$

- For the nonlinear mixed model, we need to compute the marginal density of the responses: $p\left(\mathbf{y} \mid \boldsymbol{\beta}, \sigma^2, \boldsymbol{\Psi}\right) = \int p\left(\mathbf{y} \mid \mathbf{b}, \boldsymbol{\beta}, \sigma^2\right) p\left(\mathbf{b} \mid \boldsymbol{\Psi}\right) d\,\mathbf{b}$

Maximum Likelihood

- Bad news from a estimation perspective
- The likelihood function to estimate the parameters requires integrating the joint density with respect to the random effects
- The integral often does not have a closed form expression
- Approximation of the likelihood function

Exercise

- Let's go back to the compartmental model

$$\begin{cases} \dfrac{dy_1}{dt} = -k_a y_1 \\ \dfrac{dy_2}{dx} = k_a y_1 - k_e y_2 \end{cases}$$

- y_1 is the amount of drug in the gut compartment
- y_2 is the amount of drug in the blood compartment
- k_a is the absorption rate (1/hr)
- k_e is the elimination rate (1/hr)

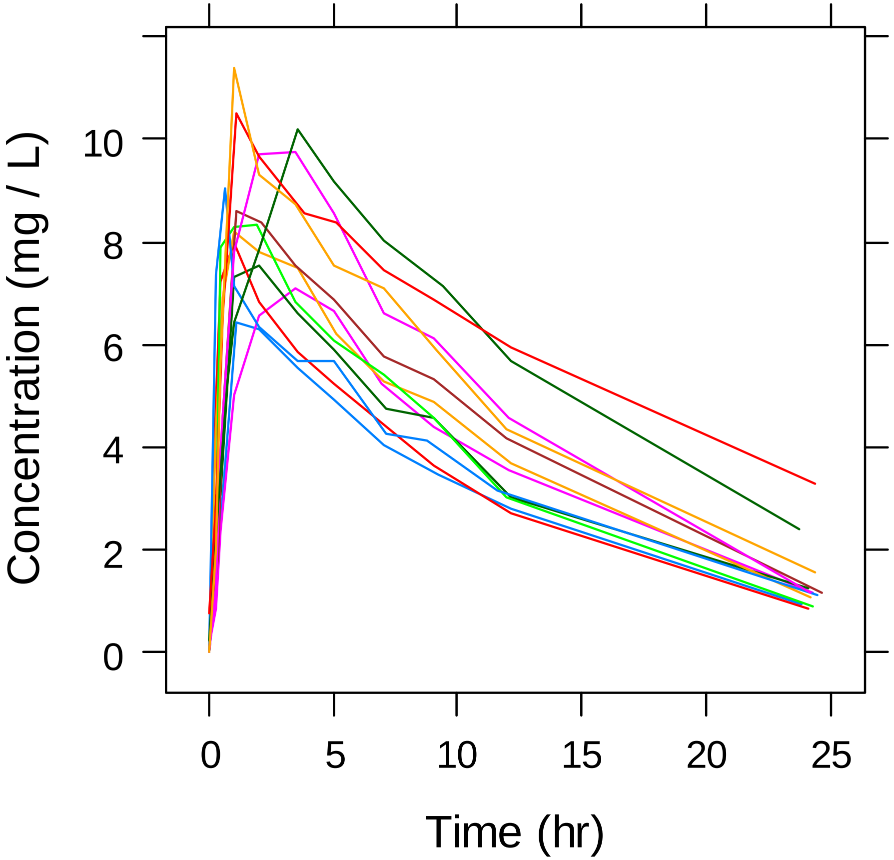
Exercise

- Data from Davidian and Giltinan (1995)

- 12 subjects received a single oral dose of theophylline
  - Anti-asthmatic drug
  - Single oral dose at time zero

- Measurements of blood concentrations of drug at 11 time points over a 25 hour period

Exercise



Exercise

- We only observe data from the second compartment
- The differential equation for the second compartment can actually be solved analytically
- We will estimate the parameters in two different ways
  - Analytical solutions: nonlinear mixed model
  - Numerical solutions for differential equations in a mixed model framework

Exercise

- The analytical solution to the second differential equation is

$$C(t) = \frac{Dose\ k_e k_a}{Cl\left(k_a - k_e\right)}\left[\exp\left(-k_e t\right) - \exp\left(-k_a t\right)\right]$$

- As a nonlinear mixed model

$$C_{ij} = \frac{Dose_i\ k_e k_{a,i}}{Cl_i\left(k_{a,i} - k_e\right)}\left[\exp\left(-k_e t_{ij}\right) - \exp\left(-k_{a,i} t_{ij}\right)\right] + \varepsilon_{ij}$$

$$\varepsilon_{ij} \sim N\left(0, \sigma^2\right) \quad \text{and} \quad \begin{bmatrix} Cl_i \\ k_{a,i} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{Cl}^2 & 0 \\ 0 & \sigma_{k_a}^2 \end{bmatrix}\right)$$

Exercise

- All three parameters must be positive
- Reparameterize model with parameters on a log scale

$$C(t) = \frac{Dose\,\exp\left(lk_e + lk_a - lCl\right)}{\exp\left(lk_a\right) - \exp\left(lk_e\right)} \left\{\exp\left[-\exp\left(lk_e\right)t\right] - \exp\left[-\exp\left(lk_a\right)t\right]\right\}$$

where

$$lk_e = \log\left(k_e\right) \quad , \quad lk_a = \log\left(k_a\right) \quad \text{and} \quad lCl = \log\left(Cl\right)$$

Exercise

- First method
  - Fit nonlinear mixed model in R

Exercise

- Second method
  - Nonlinear mixed model but solve differential equations numerically: lsoda solver

$$
\begin{cases}
\dfrac{dy_1}{dt} = -k_a y_1 \\
\dfrac{dy_2}{dx} = k_a y_1 - k_e y_2 \\
y_1\left(0\right) = Dose \\
y_2\left(0\right) = 0
\end{cases}
$$

- Observation Equation: $C\left(t\right) = \dfrac{y_2\left(t\right)}{Cl} k_e$

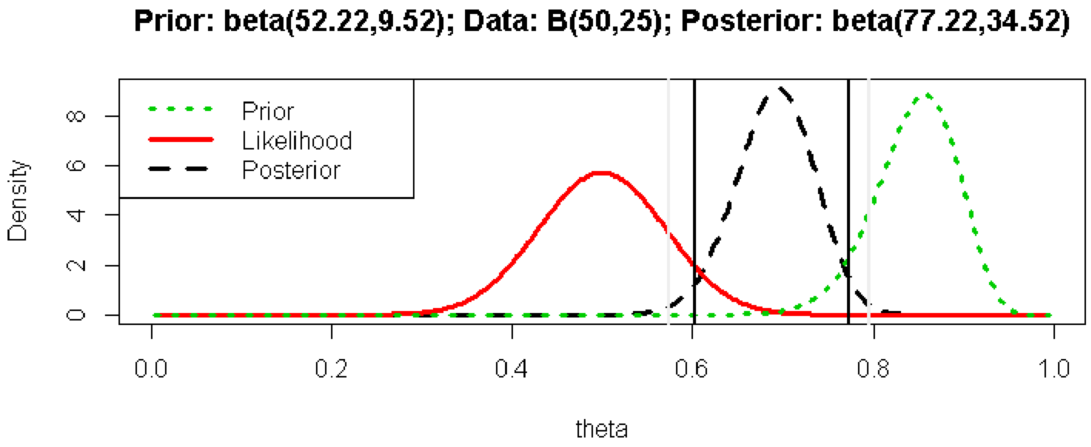
Bayesian Inference

- Combines prior information with new data: update of knowledge

- All parameters are treated as random variables
  - Prior distributions for parameters
  - Inference is based on the posterior distribution
  - Bayes theorem

$$p(\boldsymbol{\theta} \mid \mathbf{y}) \propto g(\boldsymbol{\theta}) L(\boldsymbol{\theta} \mid \mathbf{y})$$

Posterior Prior Data



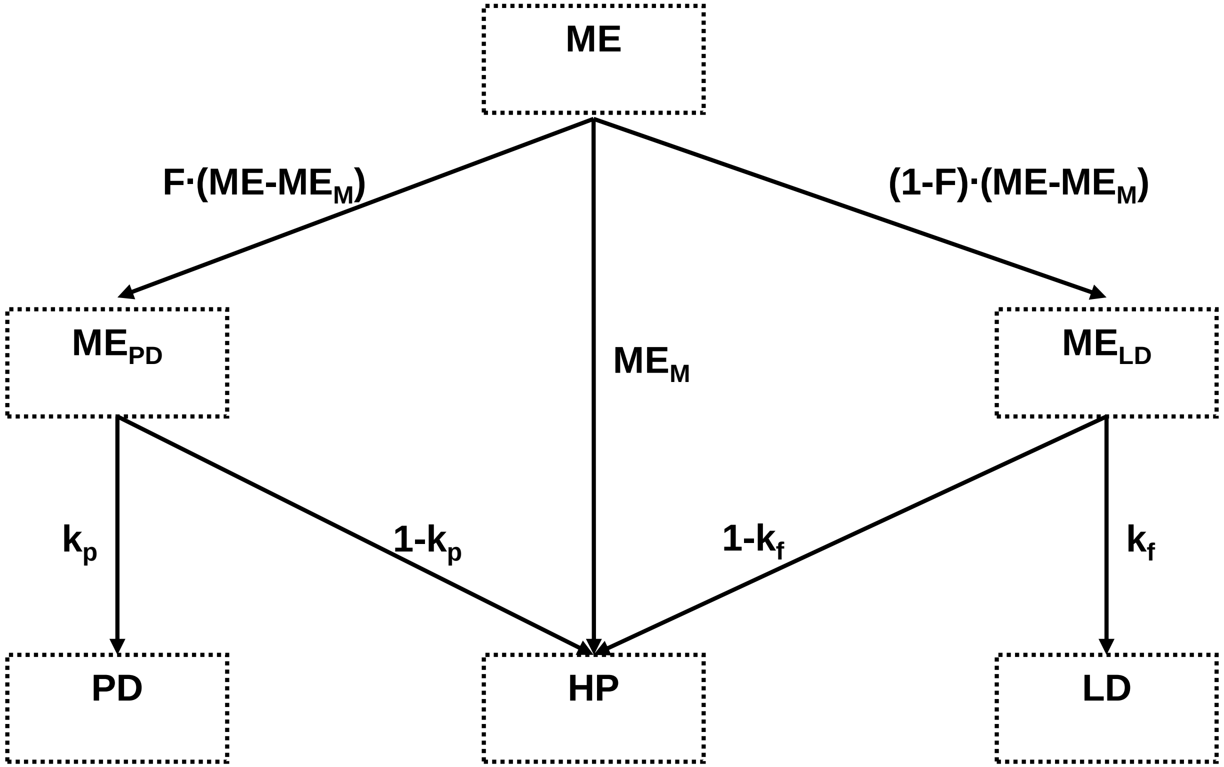
From: https://www.r-bloggers.com/the-beta-prior-likelihood-and-posterior/

Bayesian Inference

- Inference based on posterior
  - Combines prior information with the observed data
  - Particularly suited for models built with many parameters that good biological knowledge is available
  - Many freely software available
  - Including with differential equations “solvers”
  - We don’t have to have a known or tractable posterior: Markov Chain Monte Carlo (MCMC)

Example of a Multivariate Nonlinear Model

- From Strathe et al. (2012). J. Agri. Sci. 150:764-774



Courtesy of A. B. Strathe and adapted after van Milgen and Noblet (1999)

Example for a Multivariate Nonlinear Model

Multivariate Model:

$$PD = \frac{PD_{max}}{BW_{PDmax}} BW \cdot \log\left(\frac{BW_{PDmax} \cdot \exp(1)}{BW}\right)$$

$$LD = k_f \left(ME - a \cdot BW^b - PD / k_p\right)$$

Priors from literature

partial efficiencies k_p *and* k_f

k_f	k_p	Reference
0·72–0·88	0·52–0·63	Strathe *et al.* (2010a)*
0·75	0·56	van Milgen *et al.* (2000)*
0·77–0·82	0·58–0·60	van Milgen & Noblet (1999)*
0·84	0·62	Noblet *et al.* (1999)†
0·76	0·54	NRC (1998)†
0·60	0·52	Tess *et al.* (1984)†
0·74	0·56	ARC (1981)†

* Partial efficiencies derived from multivariate modelling approaches.

$$k_p \sim N\left(0.60,\ 0.10^2\right) \quad \text{and} \quad k_f \sim N\left(0.80,\ 0.10^2\right)$$

Credible Intervals for the Posterior

b	0·60 (0·56–0·66)	0·61 (0·
k_p	0·59 (0·53–0·65)	0·58 (0·
k_f	0·78 (0·72–0·85)	0·76 (0·

From Strathe et al. (2012). J. Agri. Sci. 150:764-774