Bayesian Statistics (22S:138)

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A Bayesian Approach for Population Pharmacokinetic Modeling of C-Peptide

Introduction

C-peptide (CP) is a byproduct of insulin production that is produced by the pancreas. CP level in the blood stream is an indicator of how much insulin is being produced in the body. CP is basically a protein that is made up of amino acids. When the pancreas produces insulin, it releases CP into the bloodstream in the same way that the production of heat from burning coal or wood releases smokes into the atmosphere.

The amount of CP in the blood can indicate the presence or absence of disease. For example, abnormally low amounts of C-peptide in the blood suggest the insulin production is too low (or absent) because of type I diabetes, also known as juvenile or insulin-dependent diabetes. On the other hand, abnormally high amounts of C-peptide warn of the possible presence of a tumor called an insulinoma that secretes insulin. Normal levels of C-peptide may signal that all is well. However, in a person with diabetes, a normal level of C-peptide indicates the body is making plenty of insulin but the body is just not responding properly to it and this is the hallmark of type 2 diabetes (adult insulin-resistant diabetes). C-peptide, therefore, plays a crucial diagnostic role as regards to insulin.

Project Objective

The objective of our project is to explore a Bayesian approach for the population pharmacokinetic analysis of C-peptide in order to estimate its pharmacokinetic disposition parameters in healthy volunteers.

Study Design and Data Set

The dataset that we used is obtained from an already published study. Briefly, a bolus (average mass of about 50 000 pmol) of biosynthetic CP was intravenously administered to 14 normal humans. In order to avoid the confounding effect of endogenously secreted CP, CP pancreatic secretion was suppressed through a somatostatin infusion (started two hours before the bolus administration and thereafter continued throughout the experiment). Blood samples were collected at min 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 17, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 and CP plasma concentration was measured. Permission to use the dataset has been obtained from the Resource Facility of Population Kinetics at the University of Washington.

Data Analysis and Model Design

A two-compartment model is used to fit the data. For the Bayesian population pharmacokinetic analysis, concentration-time data will be described using a three-stage hierarchical model. Concentrations will be modeled as a nonlinear function of individual-specific pharmacokinetic parameter values in the first level of the hierarchy. Distribution of these pharmacokinetic parameters around the population mean is specified in the second level of hierarchy. Priors are given in the third level of hierarchy. Analysis has been done using PKBUGS (version 1.1) and WinBUGS (version 1.3); PKBUGS is considered as an interface of the WinBUGS.

The 3-stage hierarchical model

<u>Stage I</u>: Model for the data

$$y_{ij} = f(\theta_i, x_{ij}) + \varepsilon_{ij}$$

$$\varepsilon_{ij} \sim N(0, \tau), \sigma 2 = \tau\text{-}1$$

Where;

Y_{ij}: the jth observation for the ith patient.

$f(\theta_i, x_{ij})$: the expected value of the data from the model.

θ_i: a vector of individual pharmacokinetic parameter values for the ith individual.

x_{ij}: a sampling time.

ε_{ij}: the residual difference between the expected value and the observed value, and N represents a normal distribution with zero mean and variance $\sigma 2$.

Stage II: Model between subject variability

$$\theta i \sim Np(\theta, \Omega\text{-}1)$$

where;

θ: vector of mean population pharmacokinetic parameters.

Ω: is the variance–covariance matrix of between subject random variability.

Np: represents a p dimensional multivariate normal distribution where p is the number of parameters.

Stage III: Model for the priors

$$\tau \sim Gamma(a, b)$$

$$\theta \sim Np(\mu.\text{mean}, \Sigma\text{-}1)$$

$$\Omega \sim Wip(R, \rho)$$

Where;

μ.mean: a vector of prior population mean values of the parameters.