A Bayesian approach to estimating the prehepatic insulin secretion rate
Andersen, Kim Emil; Højbjerre, Malene

Publication date:
2006

Document Version
Publisher’s PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

? Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
? You may not further distribute the material or use it for any profit-making activity or commercial gain
? You may freely distribute the URL identifying the publication in the public portal?

Take down policy
If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from vbn.aau.dk on: december 07, 2018
Motivation
Insulin resistance and failure of insulin secretion from the pancreas are characteristics of type II diabetes, whereby estimation of the prehepatic insulin secretion rate is vital. However, the insulin secretion rate is not directly measurable, since part of the secreted insulin is absorbed by the liver prior to entering the blood stream. Fortunately, the hormone C-peptide is co-secreted equimolarly and not absorbed by the liver, allowing for estimation of the insulin secretion rate.

Data and Model

The insulin secretion rate can be estimated from an IntraVenous Glucose Tolerance Test (IVGTT), where a bolus of glucose is administered intravenously to an individual for the purpose of recording the resulting glucose, insulin and C-peptide concentrations in plasma.

IVGTT data for a normal glucose tolerant individual are depicted below.

Extended Combined Model for Insulin and C-peptide Kinetics

The system can be described by the following set of inhomogeneous linearly coupled differential equations:

\[ \frac{d}{dt} I(t) = r(t) - K_{12} I(t) - K_{21} C_{1}(t) + K_{22}/\gamma_{2} C_{2}(t), \]

\[ I(0) = I_{0}, \]

\[ \frac{d}{dt} C_{1}(t) = r_{1}(t) - K_{12} I(t) - K_{21} C_{1}(t) + K_{22}/\gamma_{2} C_{2}(t), \]

\[ C_{1}(0) = C_{10}, \]

\[ \frac{d}{dt} C_{2}(t) = \text{extravascular C-peptide concentration at time } t, \]

\[ r_{1}(t) = \text{equimolar insulin and C-peptide secretion rate.} \]

where:

- \( I(t) \) : Insulin concentration in plasma at time \( t \)
- \( C_{1}(t) \) : C-peptide concentration in plasma at time \( t \)
- \( C_{2}(t) \) : extravascular C-peptide concentration at time \( t \)
- \( r_{1}(t) \) : equimolar insulin and C-peptide secretion rate.

The model for the insulin secretion rate is:

\[ r_{1}(t) = r(t) - K_{12} I(t) - K_{21} C_{1}(t) + K_{22}/\gamma_{2} C_{2}(t) \]

where the gamma densities are parametrized by their mean (\( \gamma_{1} \)) and variance (\( \gamma_{2} \)).

The conditional distributions in (1), (2) and (3) can be interpreted as parent-child distributions in a directed graphical model (Lauritzen, 1996) as depicted below.

Directed Acyclic Graph Illustrating Statistical Dependencies

Bayesian Inference

Represent the parameters, the latent processes and the observations as:

\[ \Omega = (\tau, K_{12}, K_{21}, K_{22}, \gamma_{1}, \gamma_{2}, \beta), \]

\[ \Psi = (I_{1}(t), C_{1}(t), C_{2}(t), \tau_{1}, \tau_{2}, \tau_{3}), \]

\[ \Phi = (p(\Omega | \Psi), p(\Psi | \Omega)), \]

where \( \tau \) = (\( \tau_{1}, \tau_{2}, \tau_{3}, \ldots, \tau_{k} \)) and \( \Lambda \) are the discretization time points (not necessarily equidistant) and \( T \subseteq \Lambda \) are actual observation time points.

The posterior distribution is proportional to

\[ p(\Omega, \Psi, \Phi) \propto p(\Omega | \Psi) p(\Psi | \Omega), \]

where \( p(\Omega | \Psi) \) and \( p(\Psi | \Omega) \) and \( p(\Omega | \Psi) \) form the likelihood.

The likelihood is easily derived from the normal distributions specified in (1), (2) and (3) and recursive factorization inherited by the directed graphical model.

We will assume a prior that the parameters are independently normally distributed (\( K_{12}, K_{21}, K_{22}, \gamma_{1}, \gamma_{2}, \beta \)) or Gamma distributed (\( \tau_{1}, \tau_{2}, \tau_{3} \)). However, regarding \( \tau \) we will assume

\[ p(\tau_{1}) \propto (\alpha_{1} - 1)p(\tau_{1})^{\alpha_{1} - 1} \]

\[ p(\tau_{2}) \propto (\alpha_{2} - 1)p(\tau_{2})^{\alpha_{2} - 1} \]

\[ p(\tau_{3}) \propto (\alpha_{3} - 1)p(\tau_{3})^{\alpha_{3} - 1} \]

Discussion

We have developed a Bayesian approach to estimate the prehepatic insulin secretion rate, where:

- A separation of gamma densities is used to realistically model the time-continuous insulin secretion rate.
- The ill-posed estimation problem is regularized using prior information.
- The extended combined model is considered as a unified model.
- Both physiological and observational variations are included.

For further details and references see: