A Bayesian approach to estimating the prehepatic insulin secretion rate

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Motivation

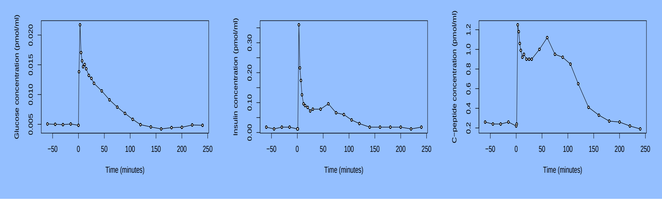
Insulin resistance and failure of insulin secretion from the pancreas are characteristics of type II diabetes, whereby estimation of the prehepatic insulin secretion rate is vital. However, the insulin secretion rate is not directly measurable, since part of the secreted insulin is absorbed by the liver 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 responding glucose, insulin and C-peptide concentrations in plasma.

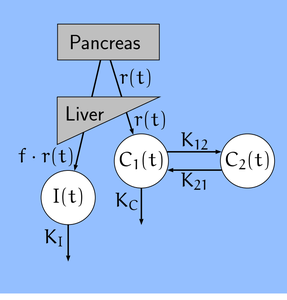
IVGTT data for a normal glucose tolerant individual are depicted below.

IntraVenous Glucose Tolerance Test (IVGTT)



The extended combined model proposed in Watanabe et al. (1998) describes the kinetics of insulin and C-peptide during an IVGTT study.

Extended Combined Model for Insulin and C-peptide Kinetics



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

$$\begin{aligned}
\dot{I}(t) &= fr(t) - K_I I(t), & I(0) &= I^b,\\
\dot{C}_1(t) &= r(t) - (K_{12}+K_C)C_1(t) + K_{21}/V_{12}C_2(t), & C_1(0) &= C_1^b,\\
\dot{C}_2(t) &= K_{12}V_{12}C_1(t) - K_{21}C_2(t), & C_2(0) &= C_2^b,
\end{aligned}$$

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.
- $r(t)$: equimolar insulin and C-peptide secretion rate.
- f: constant fraction of insulin surviving liver extraction.
- V_{12}: ratio of plasma C-peptide and plasma insulin distribution volumes.
- K_{12}, K_{21}: transfer rates between C-peptide compartments.
- K_I, K_C: elimination rates from insulin and C-peptide compartments.
- I^b, C_1^b, C_2^b: constant base levels prior to the bolus.

By considering the model in steady state it can be derived that

$$r^b = K_C C_1^b, \quad f = \frac{K_I I^b}{K_C C_1^b} \quad \text{and} \quad C_2^b = \frac{K_{12}}{K_{21}} V_{12} C_1^b,$$

where $r^b \geq 0$ denotes the basal insulin secretion rate, reducing the number of parameters to be estimated.

Current Approach

Watanabe et al. (1998) use an approach where

- kinetics parameters estimated iteratively factoring the insulin secretion rate out and succesively considering the insulin and C-peptide as known constant.
- insulin secretion rate estimated by deconvolution based on kinetics estimates and a piece-wise constant secretion rate.

Problems

- consider the secretion rate unrealistically as piece-wise constant.
- purely data-driven without error terms on observations.
- does not simultaneously consider all three differential equations.
- consider the differential equations as deterministics.
- does not consider the ill-posedness - very dependent on good initial estimates.

Our approach

A unified model with error terms on process increments and observations represented as a directed graphical model, where the ill-posed estimation problem is regularized by Bayesian inference using Markov chain Monte Carlo (MCMC) methods.

Directed Graphical Model

Using Brownian motions to model potential physiological variation and approximating the model by discretisation we obtain the following stochastic model

$$\begin{aligned}
I_{t_k} | I_{t_{k-1}}, r_{t_{k-1}}, \tau_I &\sim \mathcal{N}(h^I(I_{t_{k-1}}, r_{t_{k-1}}), \tau_I^{-1}(t_k - t_{k-1})),\\
C_{1_{t_k}} | C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}, r_{t_{k-1}}, \tau_{C_1} &\sim \mathcal{N}(h^{C_1}(C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}, r_{t_{k-1}}), \tau_{C_1}^{-1}(t_k - t_{k-1})), \quad (1)\\
C_{2_{t_k}} | C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}, \tau_{C_2} &\sim \mathcal{N}(h^{C_2}(C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}), \tau_{C_2}^{-1}(t_k - t_{k-1})),
\end{aligned}$$

where t is used as subscript and the mean structures are given as

$$\begin{aligned}
h^I(I_{t_{k-1}}, r_{t_{k-1}}) &= I_{t_{k-1}} + (t_k - t_{k-1})(f r_{t_{k-1}} - K_I I_{t_{k-1}}),\\
h^{C_1}(C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}, r_{t_{k-1}}) &= C_{1_{t_{k-1}}} + (t_k - t_{k-1})\left(r_{t_{k-1}} - (K_{12}+K_C)C_{1_{t_{k-1}}} + \frac{K_{21}}{V_{12}} C_{2_{t_{k-1}}}\right),\\
h^{C_2}(C_{1_{t_{k-1}}}, C_{2_{t_{k-1}}}) &= C_{2_{t_{k-1}}} + (t_k - t_{k-1})\left(K_{12}V_{12}C_{1_{t_{k-1}}} - K_{21}C_{2_{t_{k-1}}}\right),
\end{aligned}$$

Note that the variances depend on the length of discretization intervals.

Concerning the secretion rate r_{t_k} we model deviation from the basal level, r^b, as a scaled sum of weighted gamma densities, i.e. the rate mean structure is

$$h^r(t_k) = r^b + \kappa \sum_{k=1}^{K} w_k \frac{(m_k/\nu_k)^{m_k^2/\nu_k}}{\Gamma(m_k^2/\nu_k)} t_k^{m_k^2/\nu_k - 1} e^{-m_k/\nu_k t_k},$$

where the gamma densities are parametrized by their mean $m_k > 0$ and variances $\nu_k > 0$. Besides $\kappa > 0$, $w_k \in \mathbb{R}$ and $\sum_{k=1}^{K} w_k = 1$. The weights are not strictly positive, allowing the insulin secretion rate to fall beneath base level.

The model for the secretion process r_{t_k} is

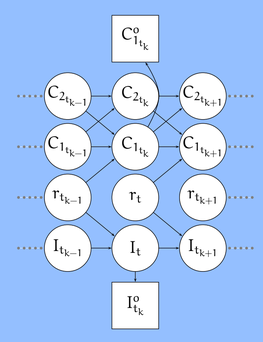
$$r_{t_k} \,|\, h^r(t_k), \tau_r \sim \mathcal{N}(h^r(t_k), \tau_r^{-1}). \quad (2)$$

Let $I^o_{t_k}$ and $C^o_{1_{t_k}}$ be the insulin and C-peptide plasma concentrations for specific time points t_k, which we model as

$$\begin{aligned}
\log I^o_{t_k} \mid I_{t_k}, \tau_{I^o} &\sim \mathcal{N}(\log I_{t_k}, \tau_{I^o}^{-1}),\\
\log C^o_{1_{t_k}} \mid C_{1_{t_k}}, \tau_{C_1^o} &\sim \mathcal{N}(\log C_{1_{t_k}}, \tau_{C_1^o}^{-1}).
\end{aligned} \quad (3)$$

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

Directed Acyclic Graph Illustrating Statistical Dependencies



Bayesian Inference

Represent the parameters, the latent processes and the observations as

$$\begin{aligned}
\Omega &= (\Upsilon, K_I, K_C, K_{12}, K_{21}, V_{12}, I^b, C_1^b, \tau_I, \tau_{C_1}, \tau_{C_2}, \tau_r, \tau_{I^o}, \tau_{C_1^o}),\\
\Psi &= \{I_{t_k}, C_{1_{t_k}}, C_{2_{t_k}}, r_{t_k}\}_{t_k \in \Lambda},\\
\Phi &= \{I^o_{t_k}, C^o_{1_{t_k}}\}_{t_k \in \mathcal{T}},
\end{aligned}$$

where $\Upsilon = (\kappa, m_1, \ldots, m_K, \nu_1, \ldots, \nu_K, w_1, \ldots, w_K)$, Λ are the discretization time points (not necessarily equidistant) and $\mathcal{T} \subseteq \Lambda$ are actual observation time points.

The posterior distribution is proportional to

$$p(\Omega, \Psi \,|\, \Phi) \propto p(\Phi \,|\, \Omega, \Psi) p(\Psi \,|\, \Omega) p(\Omega), \quad (4)$$

where $p(\Omega)$ is the prior and $p(\Psi \,|\, \Omega)$ and $p(\Phi \,|\, \Omega, \Psi)$ 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 priori that the parameters are independent normally distributed $(K_I, K_C, K_{12}, K_{21}, V_{12}, I^b, C_1^b)$ or Gamma distributed $(\tau_I, \tau_{C_1}, \tau_{C_2}, \tau_r, \tau_{I^o}, \tau_{C_1^o})$. However, regarding Υ we will assume

$$p(\Upsilon) \propto p_1(1-p_1)^{K-1} p(\kappa) \mathbb{1}(\Upsilon \in \Xi) \prod_{k=1}^{K} p(w_k) p(m_k) p(\nu_k)$$

where Ξ is the set of allowable secretion parameters, p_1 is the probability that $K = 1$ (corresponding to a geometric prior on K). Furthermore $p(\kappa)$,$p(w_k)$, $p(m_k)$ and $p(\nu_k)$ are uniform priors. Hereby the prior is the product of $p(\Upsilon)$, normal and gamma densities.

MCMC Methods

By use of MCMC methods we construct an irreducible Markov chain $\{(\Omega_1, \Psi_1), (\Omega_2, \Psi_2), \ldots\}$ with the posterior $p(\Omega, \Psi \,|\, \Phi)$ as stationary distribution.

Within model moves: K fixed

Blocked Metropolis–Hastings (Metropolis et al, 1953) random walk updates.

1. Propose Ω_j' from a symmetric proposal distribution $q(\Omega_j; \Omega_j')$.
2. Propose Ψ_j' from $p(\Psi_j \,|\, \Omega_j')$.
3. Accept the joint proposal (Ω_j', Ψ_j') with probability

$$\alpha(\Omega_j, \Psi_j; \Omega_j', \Psi_j') = \min\left\{1, \frac{p(\Phi \,|\, \Omega_j', \Psi_j') p(\Psi_j' \,|\, \Omega_j') p(\Omega_j')}{p(\Phi \,|\, \Omega_j, \Psi_j) p(\Psi_j \,|\, \Omega_j) p(\Omega_j)}\right\}.$$

Between model moves: K alters

Trans Dimensional MCMC Methods (Green, 1995).

Split model:

1. Pick (w_k, m_k, ν_k) uniformly from K existing contributions with probability $1/K$.
2. Split (w_k, m_k, ν_k) into two contributions according to the injective map

$$g : (w_k, m_k, \nu_k) \longmapsto \begin{cases} (w_k - w_{K+1}, m_k - m_{K+1}, \nu_k - \nu_{K+1}) \\ (w_{K+1}, m_{K+1}, \nu_{K+1}), \end{cases}$$

where $(w_{K+1}, m_{K+1}, \nu_{K+1})$ is picked uniformly on the product space $[-l_w, l_w] \times [0, l_m] \times [0, l_\nu]$ with probability $1/(l_w^2 l_m l_\nu)$.
The probability for performing the reverse move is $2/(K(K+1))$ and Jacobian is one. Hence the acceptance probability for a split is

$$\alpha_{\text{split}}(\Omega_j, \Psi_j; \Omega_j', \Psi_j') = \min\left\{1, \frac{p(\Phi \,|\, \Omega_j', \Psi_j') p(\Psi_j' \,|\, \Omega_j') p(\Omega_j')}{p(\Phi \,|\, \Omega_j, \Psi_j) p(\Psi_j \,|\, \Omega_j) p(\Omega_j)} \frac{2 l_w^2 l_m l_\nu}{K+1}\right\}.$$

Merge model:

1. Pick (w_k, m_k, ν_k) and (w_j, m_j, ν_j) uniformly from K existing contributions with probability $2/(K(K-1))$.
2. Merge (w_k, m_k, ν_k) and (w_j, m_j, ν_j) into one contribution according to

$$g : (w_k, m_k, \nu_k, w_j, m_j, \nu_j) \longmapsto (w_k + w_j, m_k + m_j, \nu_k + \nu_j)$$

The probability for performing the reverse move is $1/(K-1)$ and Jacobian is one. Hence the acceptance probability for a merge is

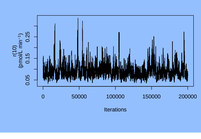
$$\alpha_{\text{merge}}(\Omega_j, \Psi_j; \Omega_j', \Psi_j') = \min\left\{1, \frac{p(\Phi \,|\, \Omega_j', \Psi_j') p(\Psi_j' \,|\, \Omega_j') p(\Omega_j') K}{p(\Phi \,|\, \Omega_j, \Psi_j) p(\Psi_j \,|\, \Omega_j) p(\Omega_j) 2}\right\}.$$

Results

We perform the following steps:

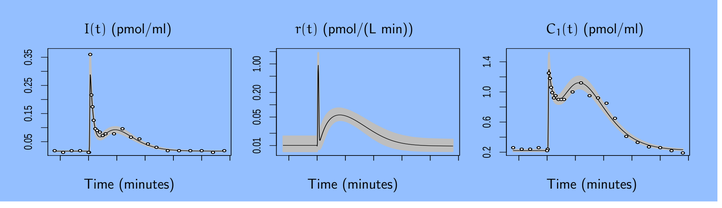
1. fine tune such that acceptance probabilities are within $(0.2; 0.4)$.
2. run a final Markov chain for 200 000 iterations after burn-in.
3. convergence is inspected by spectral method of Geweke.
4. trace plots are inspected for good mixing properties.
5. method of Heidelberg and Welch is used to ensure long enough chains.
6. prior sensitivity analysis is performed by considering marginal likelihoods.

Trace of the insulin secretion rate $r(t)$ at time $t = 10$



Posterior mean with 95 per cent credible interval for the insulin secretion rate $r(t)$ for any $t \in \Lambda$ is given below, where also posterior mean with 95 per cent credible intervals for the latent processes $I(t)$ and $C(t)$ are provided.

Posterior mean and 95 per cent credible intervals



Discussion

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

- a superposition 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:
Andersen, K.E. & Højbjerre, M. (2005). A Bayesian approach to estimating the prehepatic insulin secretion rate, Technical Report R-2005-35, Aalborg University. http://www.math.aau.dk/research/reports/R-2005-35.pdf