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Reconstructing the insulin secretion rate by Bayesian deconvolution of phase-type densities

by

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R-2005-32 October 2005

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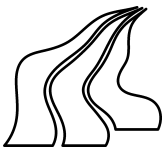

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Reconstructing the Insulin Secretion Rate by Bayesian Deconvolution of Phase-type Densities

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Summary. The rate by which the insulin is secreted from the pancreatic β-cells is not directly measurable as part of the insulin is absorbed by the liver before entering the blood stream. However, C-peptide is co-secreted equimolarly and is not absorbed by the liver, implying that reconstruction of the insulin secretion rate (ISR) can be done by solving a highly ill-posed deconvolution problem. We represent the ISR, the C-peptide concentration and the convolution kernel as scaled phase-type densities and develop a Bayesian methodology for estimating such densities via Markov chain Monte Carlo techniques. Hereby closed form evaluation of ISR is possible. We demonstrate the methodology on experimental data from healthy subjects and obtain results which are more realistic than recently reported conclusions based upon methods where the ISR is considered as piecewise constant.

Keywords: Markov chain Monte Carlo; Bayesian deconvolution; Phase-type distribution; Insulin secretion rate.

1. Introduction

The reconstruction of the pancreatic insulin secretion rate (ISR) is of vital importance for a quantitative understanding of the glucose regulating system in human beings. In particular, when developing a new insulin product for type II diabetic persons, it is necessary to understand how much insulin the patients produce themselves to assess the therapeutic effect of the synthetic insulin. Furthermore, when developing an artificial pancreas it is also a necessity to have a quantitative assessment of the true pancreatic ISR.

The endogenous insulin is secreted by the pancreatic β-cells into the portal vein, and prior to entering whole body circulation, the insulin undergoes a large and variable liver extraction. Consequently the ISR is not directly measurable as only the effect of secretion after liver absorption can be measured in plasma. Fortunately C-peptide is co-secreted with insulin on an equimolar basis and is, in contrast to insulin, not significantly extracted by the liver. Thus the ISR may be reconstructed from the time course of C-peptide concentration in plasma by solving a deconvolution problem. Such problems are often extremely ill-posed implying that even small perturbations of the data may result in unacceptably large distortions of the estimated solution (Hadamard, 1923).

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Thus deconvolution is a challenging problem and in connection with evaluation of the ISR *in vivo* it was initially proposed by Eaton et al. (1980), where a parametric approach was taken. Afterwards non-parametric approaches based upon classic Tikhonov regularization (Tikhonov, 1963*a*,*b*) have most often been studied in the literature, see e.g. Cobelli et al. (1987). It was first when Tikhonov regularization was embedded in a Bayesian methodology that adequate statistical inference on the ISR was made feasible, see e.g. Sparacino and Cobelli (1996); Pillonetto et al. (2001). These Bayesian regularization techniques impose certain regularity constraints via e.g. *a priori* knowledge and has been shown to be very robust (De Nicolao et al., 1997). However, most often ISR is estimated by assuming that it is piecewise constant leading to rather unrealistic estimates of the ISR time courses for which reliable inference is difficult to obtain.

In this paper we consider the problem of reconstructing the ISR in a Bayesian framework too. We adopt a very flexible class of functions, namely scaled density functions of phase-type distributions, to describe the ISR, the C-peptide concentrations and the kernel used in the convolution of the ISR. We develop a fully Bayesian approach based upon Markov chain Monte Carlo (MCMC) methods (Brooks, 1998; Robert and Casella, 1999) to estimate the scaled density functions, implying that the posterior mean together with corresponding credible intervals of the ISR is easily obtained by simple closed form deconvolution for phase-type distributions. We validate the method via a simulation study and demonstrate it afterwards on experimental data concluding that phase-type distributions is a promising tool for regularizing general ill-posed deconvolution problems in a Bayesian framework.

We begin in Section 2 with a presentation of the mathematical convolution model of the ISR, the experimental protocol and the data. In Section 3 we construct the statistical model and provide details of the statistical methodology used, together with a simulation study to demonstrate the utility and robustness of the proposed method. We present our results on experimental data in Section 4 and a discussion of the achieved results are provided in Section 5.

2. Data and ISR Reconstruction

2.1. Mathematical Model and Data

Let $c(t)$ denote the C-peptide concentrations in plasma (pmol/ml) at time $t \geq 0$. As described in Eaton et al. (1980) it is possible to relate $c(t)$ and the insulin secretion rate $\mathrm{ISR}(t)$ (pmol/min) by the convolution integral

$$c(t) = \int_{-\infty}^{t} g(t-\tau)\,\mathrm{ISR}(\tau)\,d\tau, \tag{1}$$

where $g(t)$ is the C-peptide impulse response (1/ml). Thus, if $c(t)$ and $g(t)$ are known, then $\mathrm{ISR}(t)$ can be estimated by deconvolution.

Typically $c(t)$ and $g(t)$ are determined by performing a two-stage experiment. In the first part of the experiment, the C-peptide impulse response $g(t)$ is recovered by suppressing the endogenous pancreatic secretion of C-peptide and then applying a bolus of biosynthetic C-peptide. Subsequently C-peptide concentrations in plasma are collected at several time points

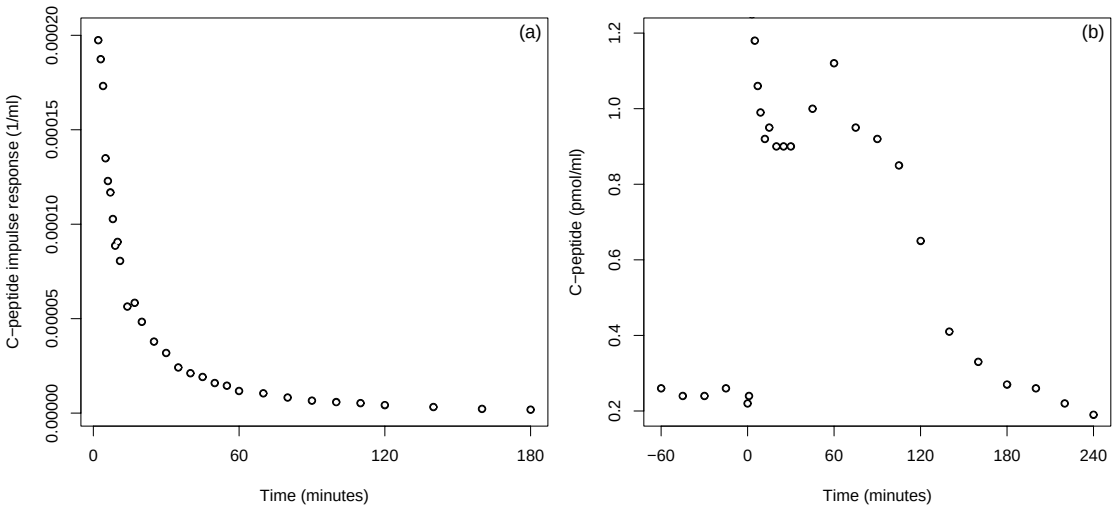

Fig. 1. Two-stage experiment performed on typical healthy subject (Subject 1): (a) normalized C-peptide concentrations in plasma following a C-peptide bolus injection, $g(t)$; and (b) C-peptide concentrations in plasma following a glucose bolus injection in an IVGTT, $c(t)$.

within a 180 minutes time interval, and afterwards normalized according to the amount of C-peptide injected to obtain $g(t)$. In the latter part of the experiment, the same subject's basal C-peptide concentrations are observed 60 minutes prior to a standard Intravenous Glucose Tolerance Test (IVGTT), in which a bolus of glucose is administered intravenously into the blood and then C-peptide concentrations in plasma are collected subsequently for 240 minutes. See Figure 1 for a representative set of experimental data for $g(t)$ and $c(t)$.

2.2. ISR Reconstruction

The most employed approach to solving the deconvolution problem is based on a discretization of the integral in (1). Thus by imposing a sum of N exponentially decaying functions on the C-peptide impulse response, i.e.

$$g(t) = \sum_{i=1}^{N} A_i e^{-\alpha_i t}$$

and assuming ISR(t) to be piecewise constant, (1) becomes an ill-posed matrix-vector problem which needs proper regularization. This problem has been addressed in Sparacino and Cobelli (1996) and further extended in Pillonetto et al. (2001). Here the deconvolution problem is stated in a stochastic context so that regularization may be done by solving a linear minimum variance estimation problem in which the degree of fit of the solution is balanced with a regularizing function measuring its 'appropriateness'. The use of linear minimum variance estimations allows for analytical computation of confidence intervals, however, the solution is still based on piecewise constant functions. In this paper we develop a method evaluating and assessing via credible intervals the reliability of a time-continuous ISR by the use of MCMC methods.

2.3. ISR Reconstruction by Phase-type Distributions

Eaton et al. (1980) introduce the sum of exponential functions presented above for describing $g(t)$. We will extend this approach by using the parametric form of a scaled density function of a phase-type distribution (Asmussen, 2000), i.e. we will assume that $g(t)$ is described by

$$g(t) = \kappa_g \boldsymbol{\alpha}_g \exp(\boldsymbol{T}_g t)\boldsymbol{t}_g, \tag{2}$$

where κ_g is a positive scaling factor, $\boldsymbol{\alpha}_g$ is an n-dimensional row-vector of non-negative values with sum 1 and $\boldsymbol{T}_g$ is an $n \times n$ matrix with negative diagonal elements and positive off-diagonal elements so that the row sums are negative. Further, $\boldsymbol{t}_g = -\boldsymbol{T}_g \boldsymbol{e}$ with $\boldsymbol{e}$ being an n-dimensional vector of ones. Recall that the matrix-exponential $\exp(\boldsymbol{K})$ is defined for any quadratic matrix $\boldsymbol{K}$ by the standard series expansion $\sum_0^\infty \boldsymbol{K}^n/n!$. We will for simplicity denote the representation of $g(t)$ by the triple $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$.

A fundamental property of phase-type distributions is denseness, which implies that any density function on $(0, \infty)$ can be approximated arbitrarily close by a density function of a phase-type distribution (Asmussen, 2000, Appendix 5d). It will therefore be an appealing approach to assume that also $\mathrm{ISR}(t)$ is on this form, however, since a basal insulin secretion occurs also for $t \leq 0$ we need to take this effect into account. Consequently we let $\mathrm{ISR}(t) = \mathrm{ISR}_b + \widetilde{\mathrm{ISR}}(t)$, where $\widetilde{\mathrm{ISR}}(t)$ denotes the ISR relative to the baseline ISR_b, which is here assumed constant. Assuming $\widetilde{\mathrm{ISR}}(t) \equiv 0$ for $t \leq 0$ it is easy to show, that

$$c(t) = \kappa_g \,\mathrm{ISR}_b + \int_0^t g(t-\tau)\widetilde{\mathrm{ISR}}(\tau)\, d\tau$$

as the scaled phase-type density $g(t)$ integrates to κ_g. Since $\widetilde{\mathrm{ISR}}(t)$ has support only on $(0, \infty)$ we may represent it arbitrarily well by a scaled phase-type density, say $(\kappa_{\widetilde{\mathrm{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}}, \boldsymbol{T}_{\widetilde{\mathrm{ISR}}})$. Denote by $\tilde{c}(t)$ the C-peptide concentrations adjusted for the basal insulin (C-peptide) secretion, i.e.

$$\tilde{c}(t) = c(t) - \kappa_g \,\mathrm{ISR}_b = \int_0^t g(t-\tau)\widetilde{\mathrm{ISR}}(\tau)\, d\tau.$$

With both $g(t)$ and $\widetilde{\mathrm{ISR}}(t)$ as scaled phase-type densities it can be shown that also $\tilde{c}(t)$ is a scaled phase-type density (Asmussen, 2000, Appendix 5c) with representation

$$\kappa_{\tilde{c}} = \kappa_g \kappa_{\widetilde{\mathrm{ISR}}}, \quad \boldsymbol{\alpha}_{\tilde{c}} = (\boldsymbol{\alpha}_g, \boldsymbol{0}) \quad \text{and} \quad \boldsymbol{T}_{\tilde{c}} = \begin{bmatrix} \boldsymbol{T}_g & \boldsymbol{T}_g \boldsymbol{e} \boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}} \\ \boldsymbol{0} & \boldsymbol{T}_{\widetilde{\mathrm{ISR}}} \end{bmatrix}. \tag{3}$$

Consequently the C-peptide concentrations may be represented by

$$c(t) = \begin{cases} \kappa_g \,\mathrm{ISR}_b & \text{for } t \leq 0, \\ \kappa_g \,\mathrm{ISR}_b + \kappa_{\tilde{c}} \boldsymbol{\alpha}_{\tilde{c}} \exp(\boldsymbol{T}_{\tilde{c}} t)\boldsymbol{t}_{\tilde{c}} & \text{otherwise.} \end{cases} \tag{4}$$

Note that the observations prior to administering the bolus is also taken into account. Observe that $c(t)$ is reparameterized by ISR_b, $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$ and $(\kappa_{\widetilde{\mathrm{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}}, \boldsymbol{T}_{\widetilde{\mathrm{ISR}}})$, and that ISR can be found in terms of ISR_b, $(\kappa_{\widetilde{\mathrm{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}}, \boldsymbol{T}_{\widetilde{\mathrm{ISR}}})$ as

$$\mathrm{ISR}(t) = \mathrm{ISR}_b + \kappa_{\widetilde{\mathrm{ISR}}} \boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}} \exp(\boldsymbol{T}_{\widetilde{\mathrm{ISR}}} t)\boldsymbol{t}_{\widetilde{\mathrm{ISR}}}. \tag{5}$$

Hence we may assess the unknown ISR by estimating ISR_b, $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$ and $(\kappa_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{T}_{\widetilde{\text{ISR}}})$ from the joint probability distribution of the data. In particular, this means that the highly ill-posed inverse deconvolution problem in (1), where the $\text{ISR}(t)$ is determined by deconvolving $c(t)$ with $g(t)$, is reformulated as a well-posed direct problem. Consequently we only need a methodology for the estimation of the unknown quantities ISR_b, $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$ and $(\kappa_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{T}_{\widetilde{\text{ISR}}})$. This methodology is developed in a Bayesian framework as described in the following section.

3. Statistical Model and Methodology

We begin by obtaining the likelihood function of the joint model of the C-peptide impulse response, $g(t)$, and the C-peptide concentrations, $c(t)$. We assume that the errors on both these entities are independently Gaussian distributed with mean zero and homogeneous variance, say σ_c^2 and σ_g^2, respectively. The corresponding observed C-peptide impulse response, $g^o(t)$, and C-peptide plasma concentrations, $c^o(t)$, are then of the form

$$\begin{aligned} g^o(t) &= g(t) + \epsilon_g(t), \quad t = t_1^g, \ldots, t_m^g, \\ c^o(t) &= c(t) + \epsilon_c(t), \quad t = t_1^c, \ldots, t_n^c, \end{aligned}$$

where $g(t)$ and $c(t)$ are scaled phase-type densities of the form specified by (2) and (4), respectively, and $t_1^g, \ldots, t_m^g$ are the time points used for sampling the C-peptide impulse response and $t_1^c, \ldots, t_n^c$ are the time points used for sampling C-peptide plasma concentrations. Note that some of the C-peptide plasma concentrations are recorded at negative time points t_i^c. Also note that we do not impose any constraints on the sampling scheme such as equidistant sampling points, etc. We may reformulate our statistical model as

$$\begin{aligned} g^o(t) &\sim \mathcal{N}(g(t), \sigma_g^2), \quad t = t_1^g, \ldots, t_m^g, \\ c^o(t) &\sim \mathcal{N}(c(t), \sigma_c^2), \quad t = t_1^c, \ldots, t_n^c, \end{aligned}$$

where σ_g^2 and σ_c^2 are the variances of the two independent random noise processes $\epsilon_g(t)$ and $\epsilon_c(t)$.

In order to assess the ISR need to estimate ISR_b, $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$ and $(\kappa_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{T}_{\widetilde{\text{ISR}}})$. For notational convenience we let

$$\boldsymbol{B}_g = (\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g, \sigma_g^2) \quad \text{and} \quad \boldsymbol{B}_{\text{ISR}} = (\text{ISR}_b, \kappa_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{T}_{\widetilde{\text{ISR}}}, \sigma_c^2)$$

denote the system dependent parameters under reconstruction and let $\boldsymbol{\Phi}_g = (g^o(t_1^g), \ldots, g^o(t_m^g))$ and $\boldsymbol{\Phi}_c = (c^o(t_1^c), \ldots, c^o(t_n^c))$ denote the observed data. Note here that $\boldsymbol{B}_{\text{ISR}}$ contains the basal insulin secretion and the variance of the random noise process inherent in the C-peptide concentrations.

The conditional independence assumptions for system parameters, $\boldsymbol{B}_g$ and $\boldsymbol{B}_{\text{ISR}}$, the non-observable process means, $g(t)$ and $c(t)$, and the observed data $g^o(t)$ and $c^o(t)$, can be illustrated by the directed graphical model (Lauritzen, 1996) depicted in Figure 2.

The likelihood function is then given by

$$L(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g) \propto \frac{\exp\{-V(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g) - W(\boldsymbol{B}_g)\}}{\sigma_c^n \sigma_g^m}, \tag{6}$$

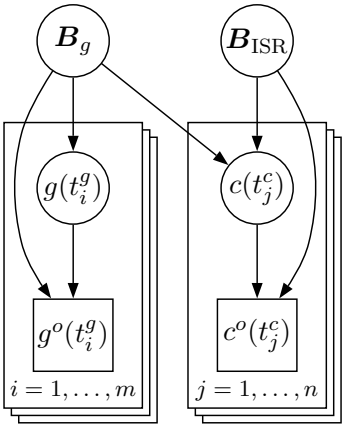

Fig. 2. A directed graphical model illustrating the conditional independencies among the system parameters, $\boldsymbol{B}_g$ and $\boldsymbol{B}_{\text{ISR}}$, the process means, $g(t_i^g)$ and $c(t_j^c)$, and the data $g^o(t_i^g)$ and $c^o(t_j^c)$, where $i = 1, \ldots, m$ and $j = 1, \ldots, n$.

where the potentials are given by

$$V(\boldsymbol{B}_g) = \sum_{i=1}^{m} [g^o(t_i^g) - g(t_i^g)]^2 / 2\sigma_g^2.$$

and

$$W(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g) = \sum_{j=1}^{n} [c^o(t_j^c) - c(t_j^c)]^2 / 2\sigma_c^2$$

The classical maximum-likelihood approach to models described in such a manner is to seek the parameters $\boldsymbol{B}_{\text{ISR}}$ and $\boldsymbol{B}_g$ that maximizes the likelihood function. However, maximizing the above derived likelihood function is not straightforward and we will therefore recast the problem in a Bayesian framework.

3.1. Bayesian Analysis

The Bayesian approach involves constructing a posterior distribution for the model parameters $\boldsymbol{B}_{\text{ISR}}$ and $\boldsymbol{B}_g$ as a product of the joint probability distribution of the data and the prior distributions representing our *a priori* beliefs about the parameters before having observed any data. Thus the posterior distribution is given by

$$\pi(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g) \propto L(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g) p(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g), \tag{7}$$

where $L(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g)$ and $p(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g)$ denotes the likelihood in (6) and the prior distribution, respectively.

In order to obtain reliable inference about the unknown parameters of interest, we will exploit MCMC methods which provide an alternative integration technique whereby posterior inference is conducted by using a random sample from the posterior. These random draws are obtained by constructing a Markov chain $\{(\boldsymbol{B}_{\text{ISR}}^{(i)}, \boldsymbol{B}_g^{(i)})\}$ with $\pi(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g)$ as stationary distribution. MCMC sampling was first introduced by Metropolis et al. (1953) and was subsequently adapted by Hastings (1970).

Note that we are not in particular interested in the parameters $\boldsymbol{B}_{\text{ISR}}$ and $\boldsymbol{B}_g$ themselves as we are in the actual ISR time course given by (5). Implementational details of the MCMC algorithm used here are given below.

3.2. Prior Beliefs

The parameters requiring prior distributions are the functional parameters ISR_b, $\kappa_{\widetilde{\text{ISR}}}$, κ_g, $\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_g$, $\boldsymbol{T}_{\widetilde{\text{ISR}}}$ and $\boldsymbol{T}_g$ and the variance parameters σ_c^2 and σ_g^2. As we have no prior beliefs about each of these functional parameters, we will assume that they are independent and adopt a simple uniform prior for each parameter on some pre-specified closed interval. However, for the variance parameters we assume a vague inverse Gamma prior, i.e. a priori

$$\begin{aligned}\sigma_c^{-2} &\sim \Gamma(a_c, b_c)\\ \sigma_g^{-2} &\sim \Gamma(a_g, b_g).\end{aligned}$$

Now, let u and v denote the dimensionality of $\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}$ and $\boldsymbol{\alpha}_g$, respectively, then the joint prior density for these unknown parameters of interest is given by

$$\begin{aligned}p(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g) &= p(\text{ISR}_b)p(\kappa_{\widetilde{\text{ISR}}})p(\kappa_g)p(\boldsymbol{\alpha}_{\widetilde{\text{ISR}}})p(\boldsymbol{\alpha}_g)p(\boldsymbol{T}_{\widetilde{\text{ISR}}})p(\boldsymbol{T}_g)p(\sigma_c^{-2})p(\sigma_g^{-2})\\ &= \left(l_{\text{ISR}_b} l_{\kappa_{\widetilde{\text{ISR}}}} l_{\kappa_g} l^u_{\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}} l^v_{\boldsymbol{\alpha}_g} l^{u^2}_{\boldsymbol{T}_{\widetilde{\text{ISR}}}} l^{v^2}_{\boldsymbol{T}_g}\right)^{-1} p(\sigma_c^{-2})p(\sigma_g^{-2}),\end{aligned}$$

where e.g. l_{ISR_b} denotes the end point of the interval $[0, l_{\text{ISR}_b}]$ on which ISR_b is assumed to be uniformly distributed a priori, and $p(\sigma_c^{-2})$ and $p(\sigma_g^{-2})$ are gamma densities. Note that for the diagonal elements of $\boldsymbol{T}_{\widetilde{\text{ISR}}}$ we assume a uniform prior on the negative interval $[-l_{\boldsymbol{T}_{\widetilde{\text{ISR}}}}, 0]$ whereas the off-diagonals have positive support on the corresponding positive interval $[0, l_{\boldsymbol{T}_{\widetilde{\text{ISR}}}}]$.

3.3. Parameter Updates

In order to explore the posterior distribution π in (7) properly we need specify adequate MCMC transitions. High posterior correlations between the elements of $\boldsymbol{B}_{\text{ISR}}$ (and $\boldsymbol{B}_g$) implies that updating the entire vector $\boldsymbol{B}_{\text{ISR}}$ (and $\boldsymbol{B}_g$) in blocks is likely to be the most efficient. Similarly, the convolution integral (1) induces a high correlation between $\boldsymbol{B}_{\text{ISR}}$ and $\boldsymbol{B}_g$, implying that a blocking of these two vectors within a single MCMC transition also would be efficient. Thus we suggest updating the unknown quantities in two different steps.

To obtain a Markov chain with good mixing properties an appropriate proposal distribution must be specified. First one must consider the problem of proposing allowable candidate matrices $\boldsymbol{T}'_g$ and $\boldsymbol{T}'_{\widetilde{\text{ISR}}}$. However, it is easy to propose a candidate as this may be done by first sampling the row sum followed by the off-diagonals giving a mathematical expression for the diagonal elements. Nevertheless, this candidate may be arbitrarily far from the state the Markov chain is currently visiting leading to very small acceptance probabilities. Alternatively we suggest using a random walk Metropolis proposal for $\boldsymbol{T}_g$ and $\boldsymbol{T}_{\widetilde{\text{ISR}}}$ which is independently multivariate Gaussian with zero mean and variance $\sigma^2_{\boldsymbol{T}_g}$ and $\sigma^2_{\boldsymbol{T}_{\widetilde{\text{ISR}}}}$, respectively. Similarly, we propose new candidates $\boldsymbol{\alpha}'_g = \boldsymbol{\alpha}_g + \boldsymbol{\epsilon}_g$ and $\boldsymbol{\alpha}'_{\widetilde{\text{ISR}}} = \boldsymbol{\alpha}_{\widetilde{\text{ISR}}} + \boldsymbol{\epsilon}_{\widetilde{\text{ISR}}}$ by

simulating the first $u-1$ (and $v-1$) Gaussian variates with mean zero and variance $\sigma^2_{\boldsymbol{\alpha}}$ from which the last variate can be determined as the random perturbation should sum to zero maintaining the sum of the elements $\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}$ equal to one. Note that the elements of $\boldsymbol{\alpha}_g$ are non-negative, since $g(t)$ is strictly positive, whereas the elements of $\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}$ are allowed to be negative, since $\text{ISR}(t)$ should be able to be less than ISR_b. Finally, candidates κ'_g and $\kappa'_{\widetilde{\text{ISR}}}$ for the remaining components are proposed by a random walk Metropolis proposal which is Gaussian with zero mean and variance σ^2_κ. The variance parameters introduced here will later be determined via a fully automated pilot-tuning simulation. Note, however, that the disadvantage of this approach is the risk of proposing invalid candidates.

Now, let $\boldsymbol{\Psi}_{\boldsymbol{T}}$ and $\boldsymbol{\Psi}_{\boldsymbol{\alpha}}$ denote the set of allowable matrices and allowable vectors in the scaled phase-type density. Then if we let the indicator

$$\mathbb{1}(\boldsymbol{B}_g) = \mathbb{1}(\kappa_g > 0, \boldsymbol{T}_g \in \boldsymbol{\Psi}_g, \boldsymbol{\alpha}_g \in \boldsymbol{\Psi}_{\boldsymbol{\alpha}})$$

denote the validity of the state $\boldsymbol{B}_g$, then the acceptance probability for the fully blocked update for the transition from $(\text{ISR}_b, \kappa_g, \kappa_{\widetilde{\text{ISR}}}, \boldsymbol{T}_g, \boldsymbol{T}_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_g, \boldsymbol{\alpha}_{\widetilde{\text{ISR}}})$ to the proposed candidate $(\text{ISR}'_b, \kappa'_g, \kappa'_{\widetilde{\text{ISR}}}, \boldsymbol{T}'_g, \boldsymbol{T}'_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}'_g, \boldsymbol{\alpha}'_{\widetilde{\text{ISR}}})$ is given by

$$\alpha = \mathbb{1}(\boldsymbol{B}'_g)\mathbb{1}(\boldsymbol{B}'_{\widetilde{\text{ISR}}}) \min(1, A),$$

where

$$A = \exp\{V(\boldsymbol{B}_g) - V(\boldsymbol{B}'_g) + W(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g) - W(\boldsymbol{B}'_{\text{ISR}}, \boldsymbol{B}'_g)\}.$$

The updating of $\boldsymbol{B}_{\text{ISR}}$ and $\boldsymbol{B}_g$ in separate blocks are done similarly. However, note that when updating $\boldsymbol{B}_g$ the acceptance probability is similar to the full acceptance probability, whereas for updating $\boldsymbol{B}_{\text{ISR}}$, the acceptance probability reduces to

$$A = \exp\{W(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g) - W(\boldsymbol{B}'_{\text{ISR}}, \boldsymbol{B}_g)\}$$

for fixed $\boldsymbol{B}_g$.

In the simulation algorithm we suggest that the fully blocked updating mechanism is exploited in combination with the separate block updating. It should be noted here, that the former updating mechanism only requires one expensive likelihood computation as opposed to the latter.

The moves that we have so far described deal with exploring the state space of π concerning the system parameters. However, the error variances σ^2_g and σ^2_c are also parameters that require updating, which we propose doing by a Gibbs update. Thus we assume a priori that the precisions, i.e. the inverse variances, are independently gamma distributed with parameters (a_g, b_g) and (a_c, b_c), in which case the posterior conditional densities for σ^2_g and σ^2_c are given by

$$\pi(\sigma_g^{-2} \mid \boldsymbol{\Phi}_g) \propto \sigma_g^{2(a_g+m-1)} \exp\{-\frac{b_g}{\sigma^2_g} - V(\boldsymbol{B}_g)\}$$

and

$$\pi(\sigma_c^{-2} \mid \boldsymbol{\Phi}_c) \propto \sigma_c^{2(a_c+n-1)} \exp\{-\frac{b_c}{\sigma^2_c} - W(\boldsymbol{B}_{\text{ISR}}, \boldsymbol{B}_g)\},$$

respectively, and recognized as gamma distributions with, for example, parameters $a_g + m$ and $b_g + \sigma^2_g W(\boldsymbol{B}_c)$. Thus if we choose this distribution as proposal, then the corresponding

PARAMETER	VALUE
$l_{\widetilde{\mathrm{ISR}}_b}$	1
$l_{\kappa_{\widetilde{\mathrm{ISR}}}}$	10 000
l_{κ_g}	1 000
$l_{\boldsymbol{\alpha}_{\widetilde{\mathrm{ISR}}}}$	10
$l_{\boldsymbol{\alpha}_g}$	1
$l_{\boldsymbol{T}_{\widetilde{\mathrm{ISR}}}}$	20
$l_{\boldsymbol{T}_g}$	20
a_g	0.600
b_g	0.001
a_c	0.250
b_c	0.001

Table 1. Prior distributions.

acceptance probability is identically equal to one. We update the variance parameters in this manner at each iteration.

3.4. Simulation Study

In order to assess the proposed Bayesian approach to closed-form evaluation of the ISR we conduct a brief simulation study in which several simulated data sets are analysed and the estimated ISR is compared with the true ISR. Thus we construct an artificial set of data for a given ISR by: (1) simulating data from the impulse response function $g(t)$; and (2) simulating data from $c(t)$ by convolving the known impulse response with the known ISR. In order to conduct the simulation study we need specify adequate prior and proposal distributions. The priors are specified according to Section 3.2, see Table 1 for details.

It is well-known that MCMC methods often are very computer intensive and obviously obtaining good initial values may be of crucial means for the speed of convergence of the simulations algorithm. Therefore we make a minor modification of the reconstruction methodology described above to obtain good starting values. In addition this also allows for recovering appropriate proposal distributions which in turn leads to adequate performance of the MCMC scheme.

We therefore propose a fully-automated fine tuning of the simulations algorithm, which proceeds as follows: (1) consider initially the impulse response data $g^o(t)$ only and apply our algorithm with $W(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g) \equiv 0$. For any parameter with a mean acceptance ratio less than 0.2, we halve the current proposal variance. For any parameter with a mean acceptance ratio greater than 0.5, we multiply the current proposal variance by 1.5. This process is continued until three consecutive runs have all mean acceptance ratios within (0.25; 0.4), see Gelman et al. (1996). Note that the last visited state serves as initial state for the next run; (2) having found an adequate configuration $\boldsymbol{B}_g$ describing the data $g^o(t)$ we now keep $\boldsymbol{B}_g$ fixed and consider finding a good initial value for $\boldsymbol{B}_{\mathrm{ISR}}$ and in addition recover adequate proposal variances following the above procedure with $V(\boldsymbol{B}_g) \equiv 0$.

Thus by starting out with arbitrary proposal variances the algorithm is run for a number of iterations ($N = 10\,000$ worked well) and then the proposal variances are rescaled according to their corresponding acceptance probabilities. However, the achieved proposal variances

only work well whenever one block is updated independently of the other. Thus we need to do one last fine tuning of our algorithm where also the entire block is updated. Thus we have two sets of proposal variances to choose between depending on the used updating mechanism. This iterative way of both finding good starting values and achieving adequate proposal variances was conducted for each simulated data set and then a final run of 250 000 iterations were done. For all data sets we found very good agreement between the estimated ISR and the true ISR whenever the dimensionality of the true $\boldsymbol{\alpha}_{\widetilde{\text{ISR}}}, \boldsymbol{T}_{\widetilde{\text{ISR}}}, \boldsymbol{\alpha}_g, \boldsymbol{T}_g$ and their corresponding estimates are equal. However, in order to assess the robustness of our proposed methodology simulation studies were performed with wrongly specified dimensionality. It appeared that the simulation algorithm performed well whenever the dimensionality was greater than the actual dimensionality, whereas slightly poorer results were obtained for the opposite situation.

4. Results

In this section, we consider the performance of our approach on seven healthy young male subjects, see Figure 1 for the data recorded for subject 1. The data for all seven subjects are shown in Figure 4. The simulations algorithm proposed and discussed in detail in Section 3 is applied to the seven subjects, i.e. for each subject the simulations scheme a fully automated fine tuning of the proposal variances for the two blocked updating mechanisms and, in addition, also finds proposal variances for the entire blocked update. For each subject we let $u = v = 6$ be fixed and sample random values of $\boldsymbol{B}_g$ and $\boldsymbol{B}_{\text{ISR}}$ from the prior as initial states, i.e. $\boldsymbol{T}_{\widetilde{\text{ISR}}}$ and $\boldsymbol{T}_g$ are both 6×6 matrices whereby $\boldsymbol{T}_{\tilde{c}}$ becomes a 12×12 matrix. The final run is then initiated with the obtained proposal distributions and run for 500 000 iterations.

Many sophisticated methods for testing the convergence of an MCMC simulations algorithm have been proposed in the literature. Here we apply the spectral method of Geweke (1992) implemented in the CODA package (Best et al., 2003) for R/Splus to test for convergence of the Markov chain. Furthermore, ensuring that the algorithm has been run for sufficiently many iterations so that a sample for reliable statistical inference is obtained we propose the Heidelberger and Welch's convergence criteria (Heidelberger and Welch, 1981). See Brooks and Gelman (1998) and Brooks and Guidici (2000) for a general review of diagnostic techniques for MCMC simulation.

The output from the MCMC simulation algorithm consists of samples from $\boldsymbol{B}_g$ and $\boldsymbol{B}_{\text{ISR}}$. From these samples the corresponding ISR was simulated and closely inspected for convergence with the spectral method of Geweke and it was found, as expected, that burn-in was reached at the very beginning of the chain for all seven subjects. We therefore assume that the final seven Markov chains have been initiated in their stationary distributions, i.e. all 500 000 iterations are used for statistical inference, see Figure 3 for details. Here we see that the Markov chain appear to exhibit excellent mixing properties. In addition, the parameters of interest was also examined with the method of Heidelberg and Welch to ensure that the chain has run long enough to obtain reliable inference.

Shown in Figure 3(a) is the visited states of the ISR at time $t = 10$ minutes. From these

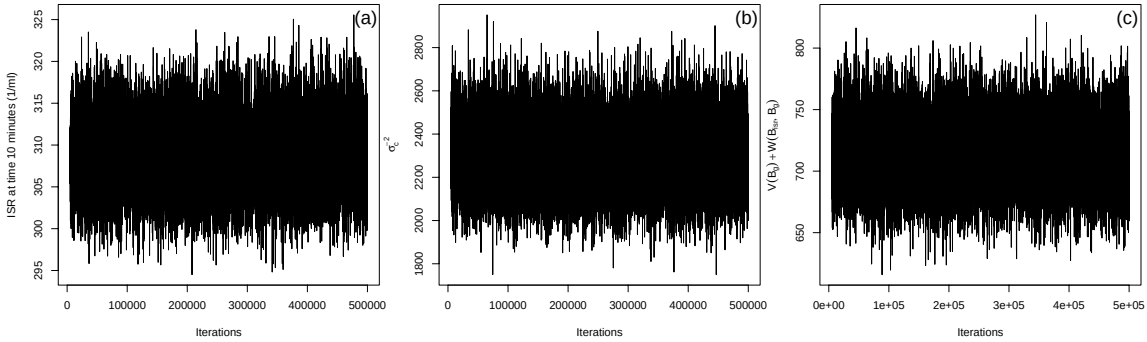

Fig. 3. Trace plots for subject 1: (a) the ISR at time $t = 10$ minutes; (b) the precisions σ_c^{-2}; and (c) the sum of the posterior potentials $W(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g) + V(\boldsymbol{B}_g)$.

we may construct the mean ISR and corresponding 95 per cent credible intervals. See Figure 4 where 95 per cent credible intervals are superimposed for $g(t)$, $\mathrm{ISR}(t)$ and $c(t)$ with corresponding posterior mean curves. .

From Figure 3 we see that the proposed simulation algorithm provides realistic time-continuous estimates of the ISR compared to Sparacino and Cobelli (1996), where the same data has been analysed in a setting with ISR considered as piecewise constant. We observe similar patterns for all seven subjects as the ISR is characterized by a pronounced first phase insulin secretion and then followed by a moderate second phase insulin secretion. For some of the subjects, e.g. subject 5, few of the observations are not close to the estimated C-peptide time-course, especially during the first phase insulin secretion. This might be improved by increasing the dimensionality of the phase-type distributions involved. In this connection Trans Dimensional MCMC methods (Green, 1995) is a feasible technique in order to estimate the needed dimensionality.

5. Discussion

In this paper we have demonstrated a Bayesian technique for solving highly ill-posed deconvolution problems by introducing a very flexible class of parametric functions derived from phase-type distributions. The method seems as a promising alternative to traditional two-stage techniques for reconstructing the ISR, as we in our approach combine the recorded data to achieve a closed form ISR evaluation technique, rather than a piecewise constant function. The approach has been assessed for various sets of simulated and experimental data and performed well in all cases.

The approach may be of outmost importance as it allows for assessing the therapeutic effect of new insulin products under evaluation. For example, the effect of an inhaled insulin drug on Type II diabetics may be assessed in a two-stage approach: (1) initially an ISR evaluation is performed by deconvolution; then (2) an insulin test with the new drug is performed. The result can now be compared to the subjects endogenous insulin obtained by convolution, from which one may evaluate the new drugs actual effect.

Also in the process of developing an artificial pancreas quantitative assessment of the pancreatic ISR is of great importance. In this situation it seems more reasonable to extend the

analysis to a population-based model and thereby achieve an impression of the over-all ISR in the healthy population. In addition it would also be interesting to see how the ISR differs between a normal and a diabetic population.

In all cases quantitative assessment of the pancreatic ISR is of great importance however, some improvements of the proposed method may be called for. The method should be extended to a population-based method to assess the ISR for e.g. the healthy population. Besides we have fixed the dimensionality of the involved matrices and vectors. However, by using sophisticated MCMC techniques allowing for transdimensional jumps (Green, 1995) we may obtain even better model fitting. This may require use of further advanced techniques such as simulated tempering) to reach faster convergence of the Markov chain.

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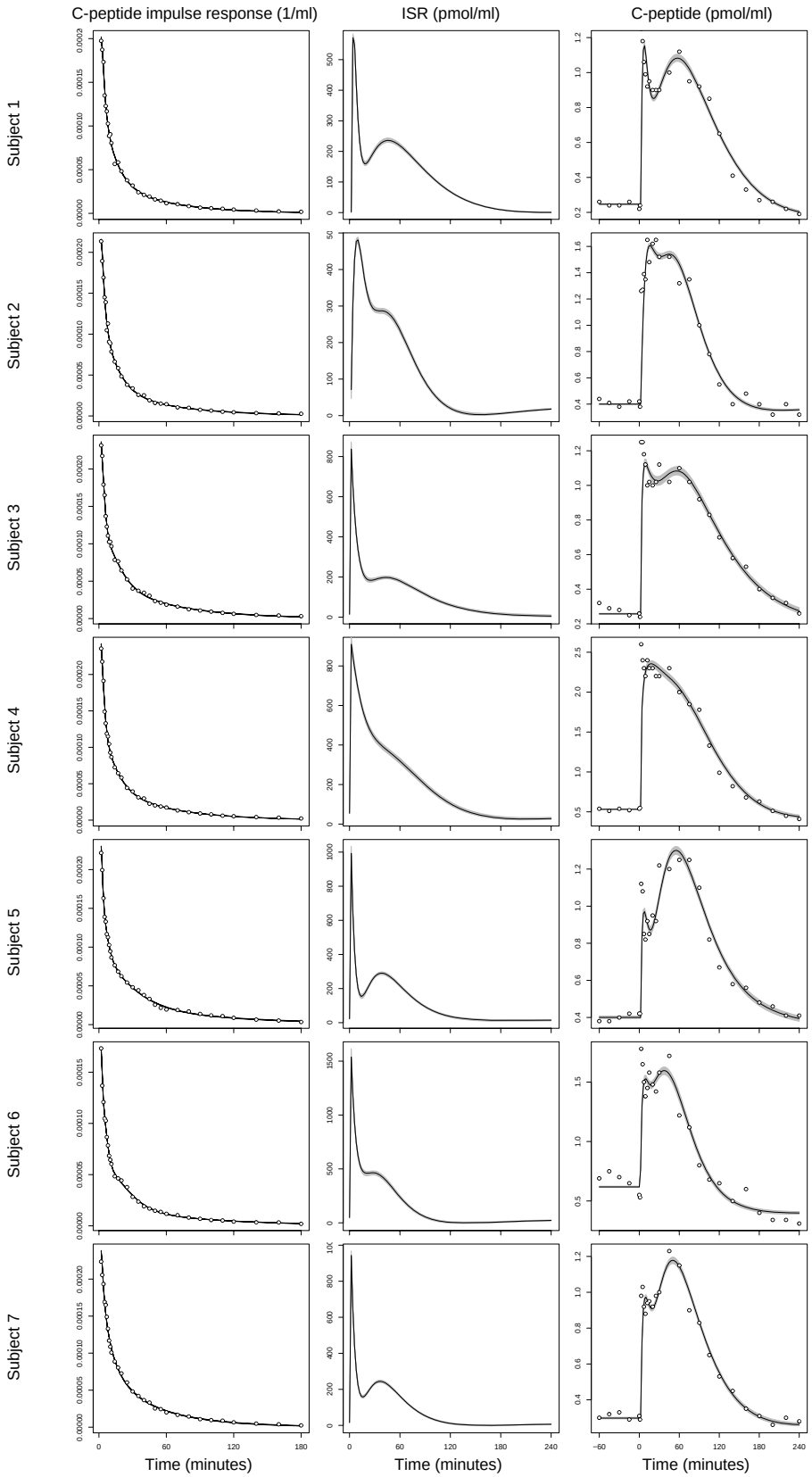

Fig. 4. Posterior mean (black line) and 95% credible intervals superimposed in gray from top to bottom for the seven subjects and from left to right for the impulse response; the ISR; and the c-peptide concentration following a glucose bolus injection in an IVGTT.