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by

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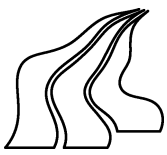

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Reconstruction of the Insulin Secretion Rate by Bayesian Deconvolution

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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 present a Bayesian methodology for the estimation of scaled densities of phase-type distributions via Markov chain Monte Carlo techniques, whereby closed form evaluation of ISR is possible. We demonstrate the methodology on simulated data concluding that the method seems as a promising alternative to existing 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. In addition, 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 a 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).

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

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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). However, 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. However, 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 demonstrate the method on simulated data concluding that phase type distributions seems like a promising tool for regularizing general ill-posed deconvolution problems in a Bayesian framework.

In Section 2 we present the mathematical convolution model of the ISR, the experimental protocol and the data. Then in Section 3 we construct the statistical model and describe the statistical methodology used. Section 4 presents a simulated data example, and a discussion of the achieved results are provided in Section 5.

2. Data and ISR Reconstruction

2.1. 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 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 and then C-peptide concentrations in plasma are collected subsequently for 240 minutes. See Figure 1 for a representative set of data for $c(t)$ and $g(t)$.

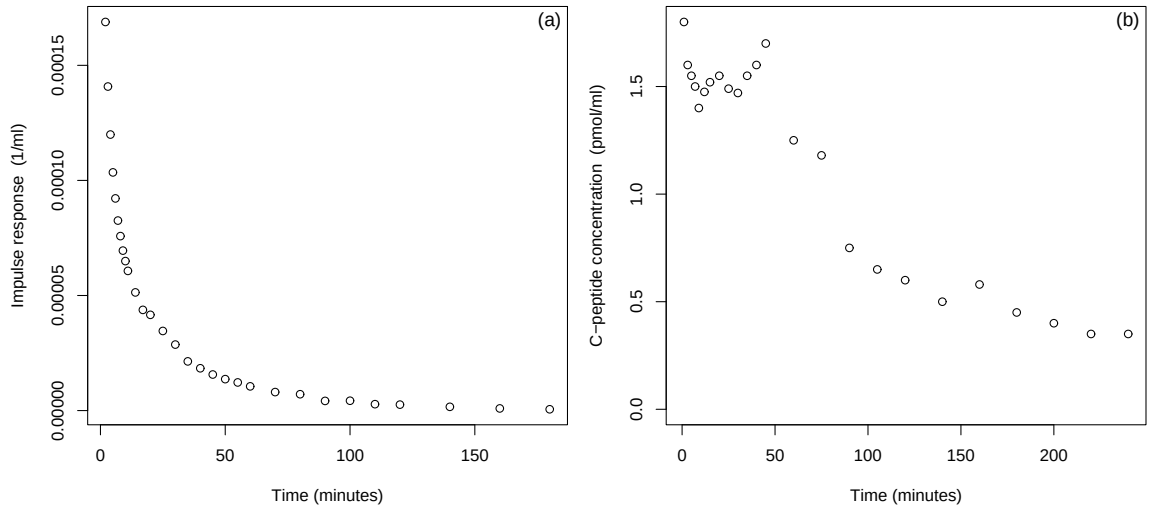

Fig. 1. Two-stage experiment performed on typical healthy subject: (a) normalized C-peptide concentrations in plasma following a C-peptide bolus injection, $g(t)$; and (b) C-peptide concentrations in plasma following a glucose bolus injection in an IVGTT, $c(t)$.

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 $\mathrm{ISR}(t)$ 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). Thus we will also assume that $\mathrm{ISR}(t)$ is on this form, i.e. $(\kappa_{\mathrm{ISR}}, \boldsymbol{\alpha}_{\mathrm{ISR}}, \boldsymbol{T}_{\mathrm{ISR}})$. Now, with both $g(t)$ and $\mathrm{ISR}(t)$ as scaled phase-type densities, then it can be shown that also $c(t)$ is a scaled phase-type density (Asmussen, 2000, Appendix 5c) with representation

$$\kappa_c = \kappa_g \kappa_{\mathrm{ISR}}, \, \boldsymbol{\alpha}_c = (\boldsymbol{\alpha}_g, \boldsymbol{0}) \text{ and } \boldsymbol{T}_c = \begin{bmatrix} \boldsymbol{T}_g & \boldsymbol{T}_g \boldsymbol{e} \boldsymbol{\alpha}_{\mathrm{ISR}} \\ \boldsymbol{0} & \boldsymbol{T}_{\mathrm{ISR}} \end{bmatrix}.$$

Thus with this reparameterization of $(\kappa_c, \boldsymbol{\alpha}_c, \boldsymbol{T}_c)$ we may assess the unknown ISR by considering the joint probability distribution of the data. This corresponds to solving a well-posed direct problem by evaluating the convolution integral (1) for given $g(t)$ and $\mathrm{ISR}(t)$. Consequently we need a methodology for the estimation of $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$ and $(\kappa_{\mathrm{ISR}}, \boldsymbol{\alpha}_{\mathrm{ISR}}, \boldsymbol{T}_{\mathrm{ISR}})$. 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 concentrations and the C-peptide impulse response. 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 plasma concentrations, $c^o(t_i)$, and C-peptide impulse response, $g^o(t_j)$, are then of the form

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

where $t_1^c, \ldots, t_n^c$ are the time points used for sampling C-peptide plasma concentrations and $t_1^g, \ldots, t_m^g$ are the time points used for sampling the C-peptide impulse response. Thus we may write

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

where $c(t)$ and $g(t)$ are scaled phase-type densities of the form specified in (2) and parameterized by the tripples $(\kappa_c, \boldsymbol{\alpha}_c, \boldsymbol{T}_c)$ and $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$, and σ_c^2 and σ_g^2 are the variances of the two random noise processes. Now, in order to assess the ISR we here exploit the reparameterization of $(\kappa_c, \boldsymbol{\alpha}_c, \boldsymbol{T}_c)$ in terms of $(\kappa_{\mathrm{ISR}}, \boldsymbol{\alpha}_{\mathrm{ISR}}, \boldsymbol{T}_{\mathrm{ISR}})$ and $(\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g)$.

For notational convenience we let $\boldsymbol{B}_g = (\kappa_g, \boldsymbol{\alpha}_g, \boldsymbol{T}_g, \sigma_g^2)$ and $\boldsymbol{B}_{\mathrm{ISR}} = (\kappa_{\mathrm{ISR}}, \boldsymbol{\alpha}_{\mathrm{ISR}}, \boldsymbol{T}_{\mathrm{ISR}}, \sigma_c^2)$ denote the system dependent parameters under reconstruction and let $\boldsymbol{\Phi}_c = (c(t_1^c), \ldots, c(t_n^c))$ and $\boldsymbol{\Phi}_g = (g(t_1^g), \ldots, g(t_m^g))$ denote the observed data. Note here that $\boldsymbol{B}_{\mathrm{ISR}}$ contains the variance of the random errors in the C-peptide concentrations. Then the likelihood function is given by

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

where the potentials are given by

$$V(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g) = \sum_{i=1}^{n} [c^o(t_i^c) - c(t_i^c)]^2 / 2\sigma_c^2$$

and

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

The classical maximum-likelihood approach to models described in such a manner is to seek the parameters $\boldsymbol{B}_{\mathrm{ISR}}$ 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 $\boldsymbol{B}_{\mathrm{ISR}}$ 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

$$\pi(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g) \propto L(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g) p(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g).$$

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 $\{(\boldsymbol{B}_{\mathrm{ISR}}^{(i)}, \boldsymbol{B}_g^{(i)})\}$ with $\pi(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g \mid \boldsymbol{\Phi}_c, \boldsymbol{\Phi}_g)$ 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 $\boldsymbol{B}_{\mathrm{ISR}}$ and $\boldsymbol{B}_g$ themselves as we are in the actual ISR time course. Implementational details of the MCMC algorithm used here are given below.

3.2. Prior Beliefs

The parameters requiring prior distributions are the functional parameters κ_{ISR}, κ_g, $\boldsymbol{\alpha}_{\mathrm{ISR}}, \boldsymbol{\alpha}_g, \boldsymbol{T}_{\mathrm{ISR}}$ and $\boldsymbol{T}_g$ and the variance parameters σ_c^2 and σ_g^2. We will denote the set of these unknown quantities by $\boldsymbol{B} = \{\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g\}$. 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 an interval. However, for the variance parameters we assume a vague inverse Gamma prior, i.e. a priori

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

Let u and v denote the dimensionality of the $\boldsymbol{\alpha}_{\mathrm{ISR}}$ and $\boldsymbol{\alpha}_g$, respectively, then the prior density for these parameters is given by

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

where e.g. $l_{\kappa_{\mathrm{ISR}}}$ denotes the end point of the interval $[0, l_{\kappa_{\mathrm{ISR}}}]$ on which κ_{ISR} 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 $\boldsymbol{T}_{\mathrm{ISR}}$ we assume a uniform prior on the negative interval $[-l_{\boldsymbol{T}_{\mathrm{ISR}}}, 0]$ whereas the off-diagonals have positive support on the corresponding positive interval $[0, l_{\boldsymbol{T}_{\mathrm{ISR}}}]$.

3.3. Parameter Updates

In order to explore the posterior distribution π properly we need specify adequate MCMC transitions. High posterior correlations between the elements of $\boldsymbol{B}_{\mathrm{ISR}}$ (and $\boldsymbol{B}_g$) implies that updating the entire vector $\boldsymbol{B}_{\mathrm{ISR}}$ in blocks is likely to be the most efficient. Similarly, the convolution integral (1) induces a high correlation between $\boldsymbol{B}_{\mathrm{ISR}}$ 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 $\boldsymbol{T}_{\mathrm{ISR}}'$. It is easy to propose a candidate as this may easily be done by first sampling the row sum followed by the off-diagonals giving a mathematical expression for the diagonal elements. However, 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 $\boldsymbol{T}_{\mathrm{ISR}}$ and $\boldsymbol{T}_g$ which is independently multivariate Gaussian with zero mean and variance $\sigma^2_{\boldsymbol{T}_{\mathrm{ISR}}}$ and $\sigma^2_{\boldsymbol{T}_g}$, respectively. Similarly, we propose new candidates $\boldsymbol{\alpha}'_{\mathrm{ISR}} = \boldsymbol{\alpha}_{\mathrm{ISR}} + \boldsymbol{\epsilon}_{\mathrm{ISR}}$ and $\boldsymbol{\alpha}'_g = \boldsymbol{\alpha}_g + \boldsymbol{\epsilon}_g$ 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 $\boldsymbol{\alpha}_g$ equal to one. Finally, candidates κ'_{ISR} and κ'_g 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 separately via an initial 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 $(\kappa_g, \kappa_{\mathrm{ISR}}, \boldsymbol{T}_g, \boldsymbol{T}_{\mathrm{ISR}}, \boldsymbol{\alpha}_g, \boldsymbol{\alpha}_{\mathrm{ISR}})$ to the candidate $(\kappa'_g, \kappa'_{\mathrm{ISR}}, \boldsymbol{T}'_g, \boldsymbol{T}'_{\mathrm{ISR}}, \boldsymbol{\alpha}'_g, \boldsymbol{\alpha}'_{\mathrm{ISR}})$ is given by

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

where

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

The updating of $\boldsymbol{B}_{\mathrm{ISR}}$ 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 $\boldsymbol{B}_{\mathrm{ISR}}$, the acceptance probability reduces to

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

for fixed $\boldsymbol{B}_g$.

In the simulation algorithm we are proposing here, 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_g^2 and σ_c^2 are also parameters that require updating. 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_g^2 and σ_c^2 are given by

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

and

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

respectively, and recognized as gamma distributions with, for example, parameters $a_g + m$ and $b_g + \sigma_g^2 V(\boldsymbol{B}_c)$. Thus if we as proposal choose this distribution, then the corresponding acceptance probability is identically equal to one. We update the variance parameters in this manner at each iteration.

4. Simulation Study

In order to assess the proposed Bayesian approach to closed-form evaluation of the ISR we conduct a simulation study in which simulated data is analysed and compared with the truth. 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) simulate data from $c(t)$ by convolving the known impulse response with the ISR. See Figure 2 for details.

4.1. Prior and Proposal Elicitation

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. These are found by conducting various pilot studies.

Appropriate proposal distributions are recovered through a semi-automated fine tuning of the simulations algorithm. Thus by starting out with arbitrary proposal variances the algorithm is run for a number of iterations and then the proposal variances are rescaled according to their corresponding acceptance probabilities.

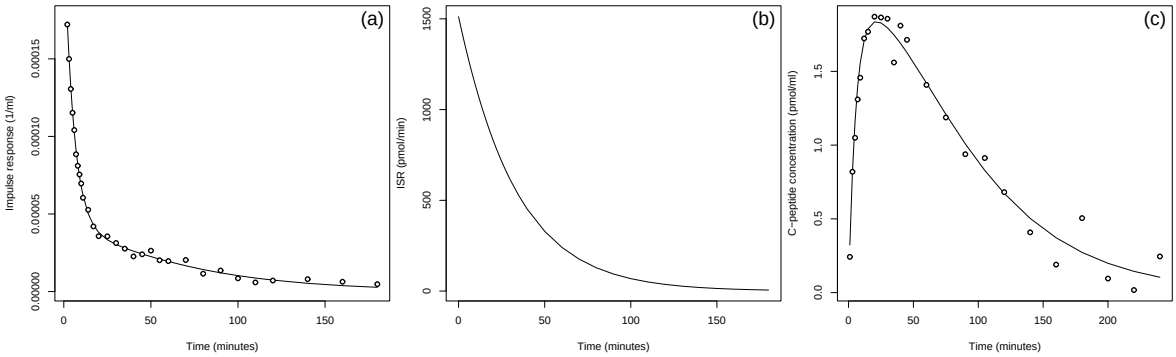

Fig. 2. Simulated two-stage experiment data: (a) C-peptide concentrations in plasma following a C-peptide bolus injection, $g(t)$; the insulin secretion rate, $\mathrm{ISR}(t)$; and (c) C-peptide concentrations in plasma following a glucose bolus injection in an IVGTT, $c(t)$.

PARAMETER	VALUE
$l_{\kappa_{\mathrm{ISR}}}$	$10\,000$
l_{κ_g}	$1\,000$
$l_{\boldsymbol{\alpha}_{\mathrm{ISR}}}$	1
$l_{\boldsymbol{\alpha}_g}$	1
$l_{\boldsymbol{T}_{\mathrm{ISR}}}$	20
$l_{\boldsymbol{T}_g}$	20
a_g	0.600
b_g	0.001
a_c	0.250
b_c	0.001
$\sigma_{\boldsymbol{\alpha}}$	0.004
$\sigma_{\boldsymbol{T}}$	0.004
σ_κ	4

Table 1. Prior distributions.

4.2. Results

MCMC methods are often 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. Thus we initially consider only the impulse response data $g^o(t)$ and apply our algorithm by letting $V(\boldsymbol{B}_{\mathrm{ISR}}, \boldsymbol{B}_g) \equiv 0$. Throughout the complete study we will assume that $u = v = 3$, i.e. $\boldsymbol{T}_c$ is a 6 by 6 matrix. 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 $\boldsymbol{B}_{\mathrm{ISR}}$. This is done in a similar manner, as we now let $W(\boldsymbol{B}_g) \equiv 0$. This iterative way of finding good starting values was conducted and each simulations algorithm was run for a small number of iterations ($N = 10\,000$).

The two configurations $\boldsymbol{B}_g$ and $\boldsymbol{B}_{\mathrm{ISR}}$ last visited in the two initial simulations serve as starting values for the final MCMC algorithm which is then run for $150\,000$ iterations. On a regular home computer with a 2800 MHz Intel Pentium 4 processor and 512 MB memory this run takes only a few hours. The Markov chain was then carefully analysed and tested for convergence so that we can be certain that the obtained chain has settled to its posterior distribution and, in addition, that we have produced a sufficiently long sample for statistical inference. However, it should be stressed here that as the configurations themselves do not have a physiological and meaningful interpretation we do not consider these. Instead we consider the convergence of the unknown time courses of $\mathrm{ISR}(t)$, $g(t)$

and $c(t)$.

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 $\boldsymbol{B}_{\mathrm{ISR}}$. From these samples the corresponding ISR was simulated and closely inspected for convergence with the spectral method of Geweke and burn-in was reached at approximately 20 000 iterations. We therefore assume that the Markov chain has settled to its stationary distribution at $50\,000$ iterations, i.e. the remaining $100\,000$ iterations are used for statistical inference, see Figure 3 for details. Here we see that the Markov chain appear to exhibit excellent mixing properties and, in addition, the remaining parameters of interest was examined with the method of Heidelberg and Welch to ensure the chain has run long enough to obtain reliable inference.

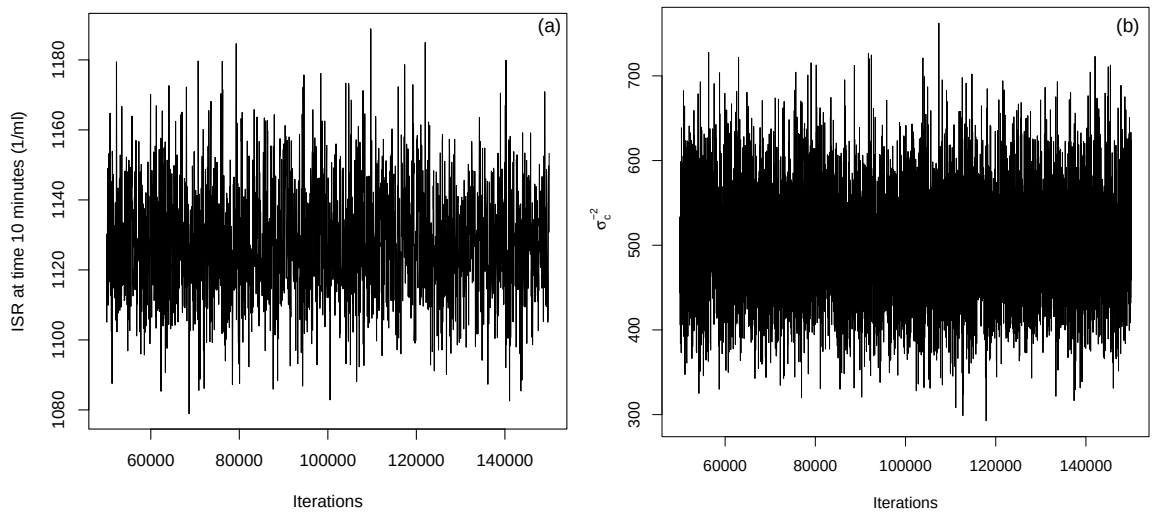

Fig. 3. Trace plots for (a) the ISR at time $t = 10$ minutes; and (b) the precisions σ_c^{-2}.

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

Note that the true curves $g(t)$, $\mathrm{ISR}(t)$ and $c(t)$ are all included in the credible intervals, which leads us to conclude that the Bayesian ISR reconstruction algorithm developed above appear very promising.

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

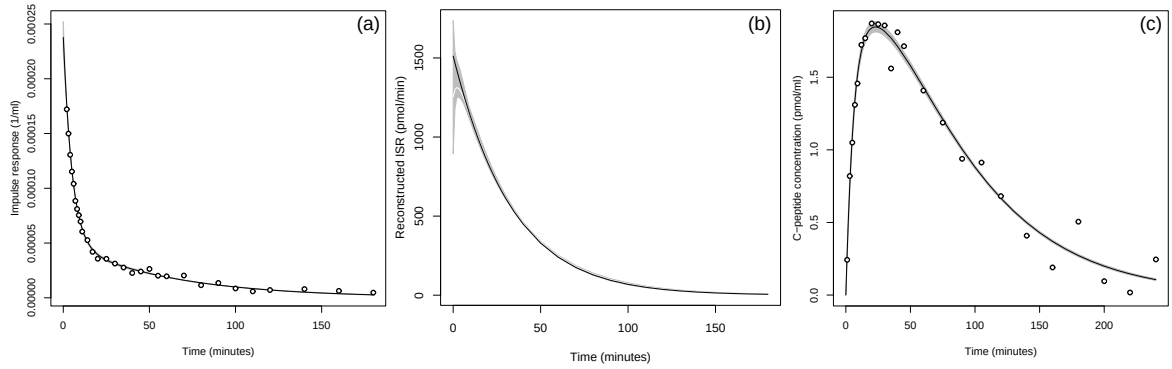

Fig. 4. Posterior mean (white line) and 95% credible intervals superimposed in gray for: (a) the impulse response; (b) the ISR; and (c) the c-peptide concentration following a glucose bolus injection in an IVGTT. Shown with black lines are the true curves.

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 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) secondly 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 an 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 and it is therefore very interesting to see our method applied to real experimental data, however, some improvements 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 and, in addition, faster convergence of the Markov chain.

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