Bayesian reconstruction of the insulin secretion rate

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Bayesian Reconstruction of the Insulin Secretion Rate

Cobal 2

February 2005

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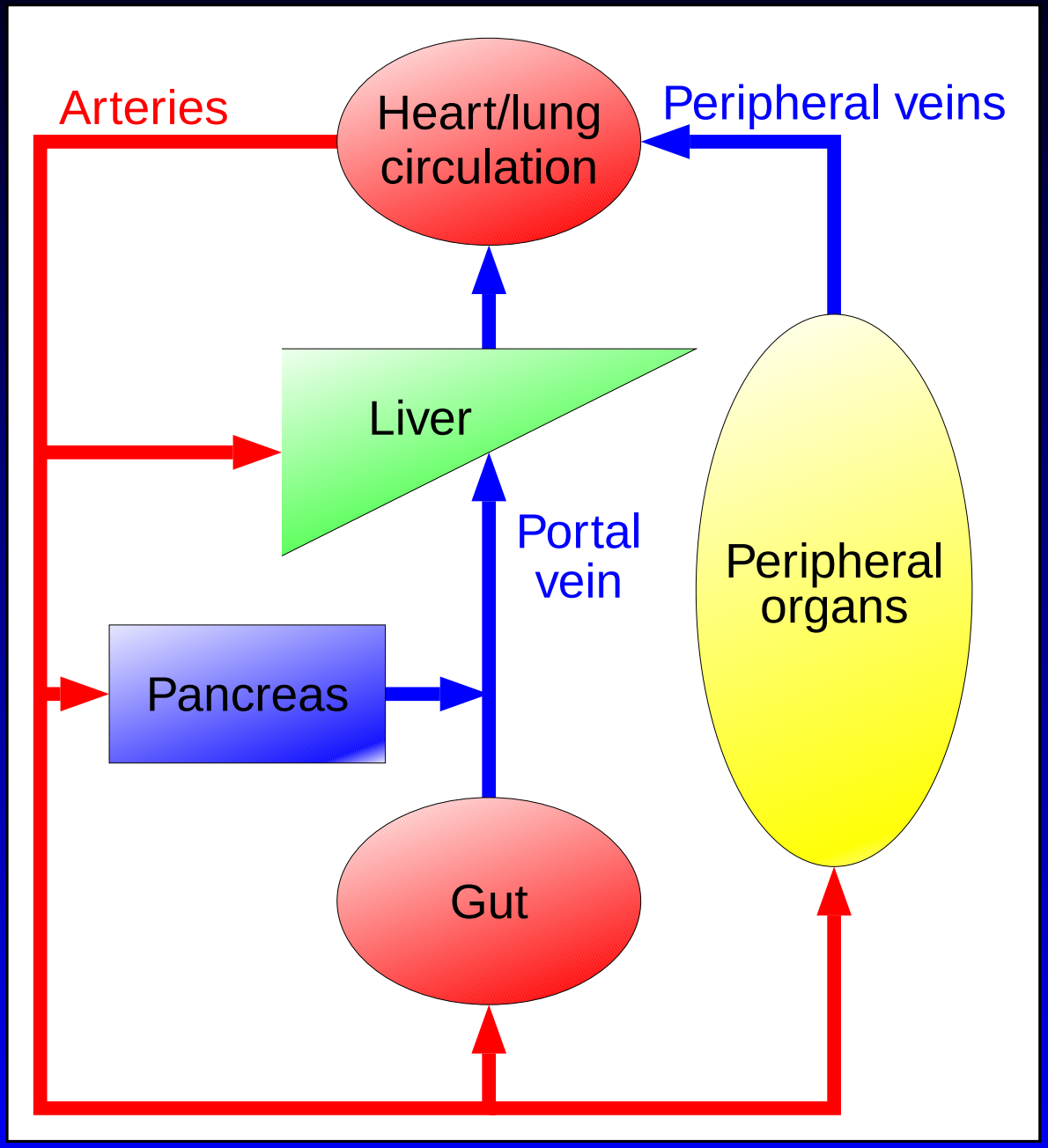
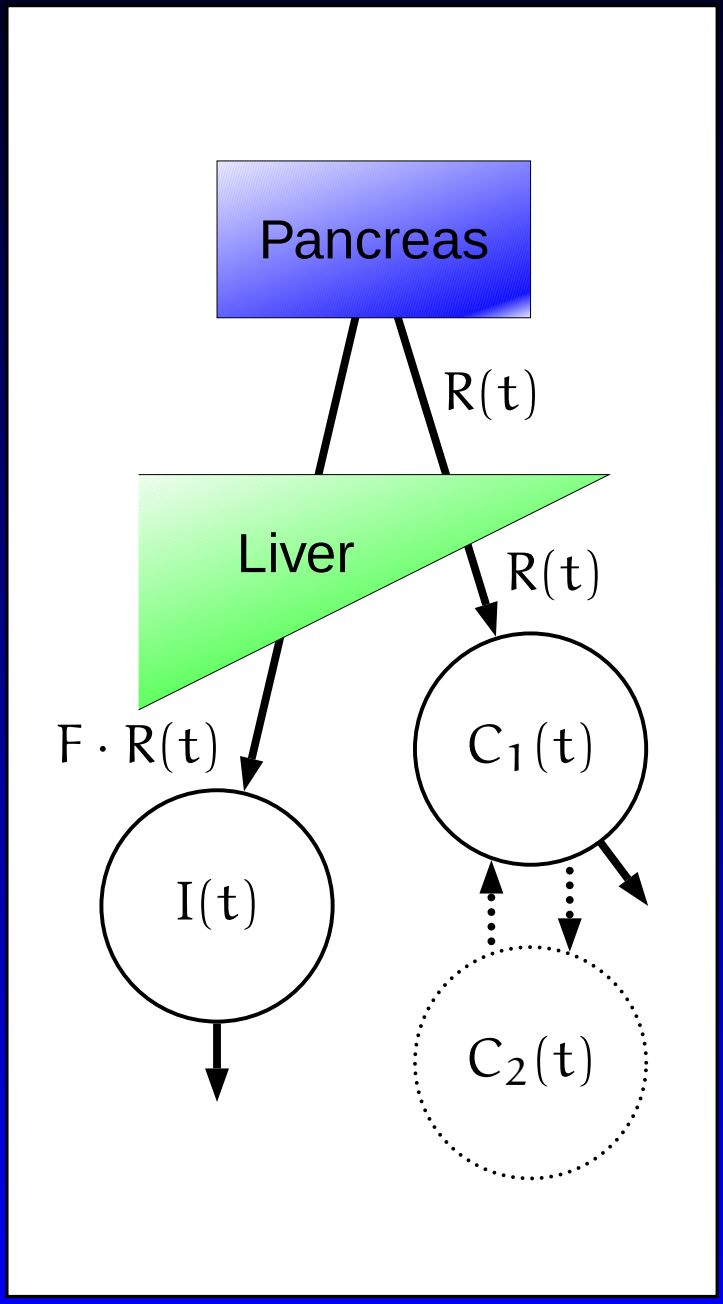
Physiological Circulation





Aim

Determine the Insulin Secretion Rate (**ISR**) allowing for

- a quantitative understanding of the glucose regulating system
- an evaluation of the therapeutic effect of e.g. a new diabetic agent

Problem

Endogenous insulin undergoes a large and variable liver extraction

Fortunately

C-peptide is co-secreted on a equimolar basis and is (almost) NOT extracted by the liver

Solution

Base assessment of ISR upon C-peptide

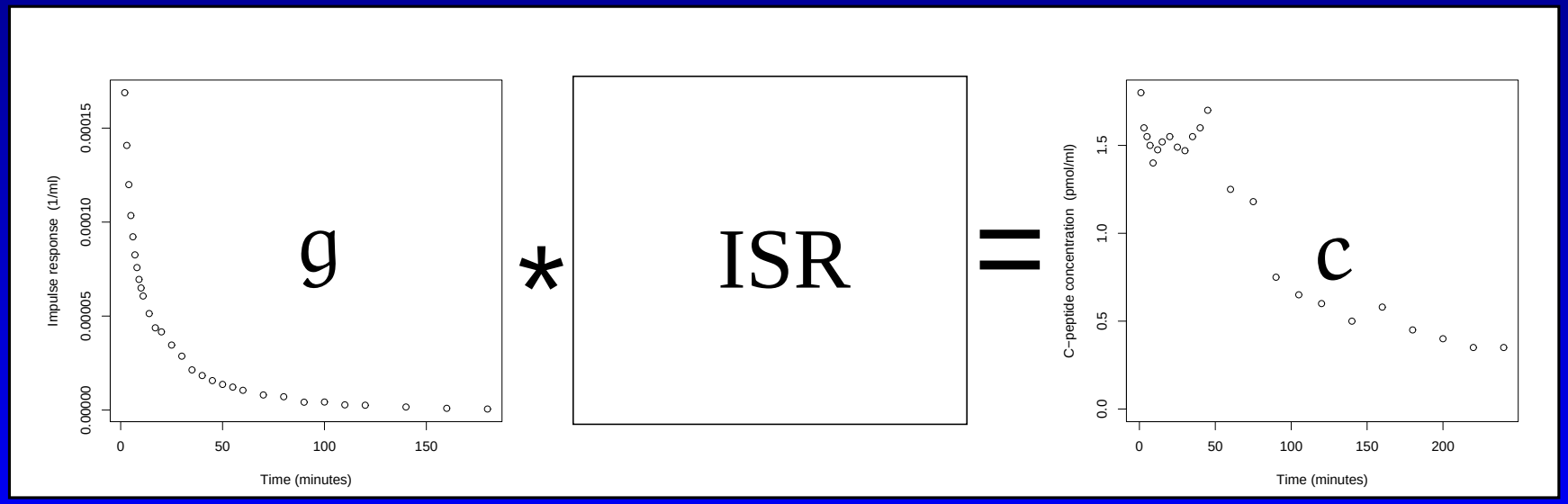
Mathematical Convolution Model vs Data

Let

- $\mathrm{ISR}(t)$ denote the insulin secretion rate [pmol/min]
- $c(t)$ denote the C-peptide concentration [pmol/ml] ← IVGTT
- $g(t)$ denote the C-peptide impulse response [ml^{-1}] ← C-peptide bolus

then it is possible to relate the unmeasurable $\mathrm{ISR}(t)$ with $c(t)$ by the convolution integral

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



Current Two Stage Approaches

Main assumptions:

Stage 1

- Imposing a sum of exponentially decaying functions $g(t) = \sum_{i=1}^{N} A_i e^{-\alpha_i t}$ on the C-peptide impulse response – treated as known

Stage 2

- Assuming ISR to be piecewise constant

Consequence:

Leads to an ill-posed inversion problem, which can be solved through proper regularisation

$$\arg\min_{c \in \mathcal{C}} \|c_{obs} - c\|^2 + \alpha \|c\|^2$$

In a stochastic setup this may be done by the use of the variance of c

Our Approach

Main idea:

- Consider both set of data simultaneously
  - unified approach
  - allowing for random deviations in e.g. the C-peptide impulse response

Solution strategy:

- Obtain flexible class of representations of $c(t)$ and $\mathrm{ISR}(t)$
- Determine their convolution properties
- Recast the problem in a Bayesian setting

In practice:

- Rescaled phasetype densities

Phasetype Distributions

Definition:

Let T denote the convergence time for a Markov chain, then T has density

$$g(t) = \boldsymbol{\alpha} e^{\mathbf{T}t}\mathbf{t}$$

where

- $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_n)$ is an n-dimensional row-vector with $\alpha_i \geq 0$ and $\sum_{i=1}^{n} \alpha_i = 1$
- $\mathbf{T}$ is an $n \times n$ intensity matrix with $T_{ii} \leq 0$ and $T_{ij} \geq 0$ subject to $\sum_{j=1}^{n} T_{ij} \leq 0$
- $\mathbf{t} = -\mathbf{T}\boldsymbol{e}$

Examples:

- Exponential
- Erlang
- Gaussian

Fundamental properties:

- Dense in the space of distributions

Scaled phasetype densities

Closed Form Convolution Models

Assumptions:

Assume that both $g(t)$ and $\mathrm{ISR}(t)$ are of scaled phasetype, i.e.

- $g(t) = \kappa_g \alpha_g e^{T_g t} t_g$
- $\mathrm{ISR}(t) = \kappa_{\mathrm{ISR}} \alpha_{\mathrm{ISR}} e^{T_{\mathrm{ISR}} t} t_{\mathrm{ISR}}$

then the convolution $g * \mathrm{ISR}$ is also of scaled phasetype

- $c(t) = (g * \mathrm{ISR})(t) = \kappa_c \alpha_c e^{T_c t} t_c$

where

- $\kappa_c = \kappa_g \kappa_{\mathrm{ISR}}$
- $\alpha_c = (\alpha_g, 0)$
- $T_c = \begin{bmatrix} T_g & T_g e \alpha_{\mathrm{ISR}} \\ 0 & T_{\mathrm{ISR}} \end{bmatrix}$

Solving the *direct* problem is **well-posed**

Statistical Model and Algorithm

Model:

Let

- $t_1^c, \ldots, t_n^c$ denote the time points used for sampling the C-peptide
- $t_1^g, \ldots, t_m^g$ denote the time points used for sampling the impulse response
- Gaussian IID distributed with variance σ_c^2 and σ_g^2

Thus

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

Naïve algorithm:

1. Simulate $g(t)$ and $c(t)$ for initial $\mathbf{B}_g = (\kappa_g, \boldsymbol{\alpha}_g, T_g, \sigma_g^2)$ and $\mathbf{B}_{ISR} = (\kappa_{ISR}, \boldsymbol{\alpha}_{ISR}, T_{ISR}, \sigma_c^2)$
2. Propose new candidates $\mathbf{B}_g'$ and $\mathbf{B}_{ISR}'$
3. Evaluate new candidates according to some object function π
4. Accept or reject new candidates according to simple rule
5. Goto 2

Likelihood Construction

Data:

Let $\Phi_c = (c^o(t_1^c), \ldots, c^o(t_n^c))$ and $\Phi_g = (g^o(t_1^g), \ldots, g^o(t_m^g))$ denote the observed data

Likelihood:

The likelihood function is given by

$$L(B_{ISR}, B_g | \Phi_c, \Phi_g) \propto \frac{\exp\{-V(B_{ISR}, B_g) - W(B_g)\}}{\sigma_c^n \sigma_g^m}$$

where the potentials are given by

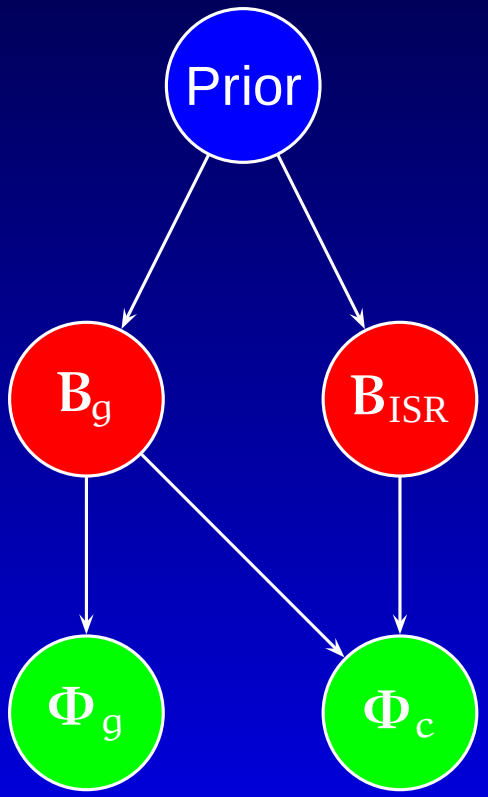
$$V(B_{ISR}, B_g) = \sum_{i=1}^{n} [c^o(t_i^c) - c(t_i^c)]^2 / 2\sigma_c^2$$

and

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

Graphical Model and Bayesian Analysis

Graphical Model:



Posterior π:

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

where the prior distribution is given by

$$\begin{aligned}
\mathrm{p}(\mathbf{B}_{ISR}, \mathbf{B}_g) &= \mathrm{p}(\kappa_{ISR}) \\
&\times \mathrm{p}(\boldsymbol{\alpha}_{ISR}) \\
&\times \mathrm{p}(\mathbf{T}_{ISR}) \\
&\times \mathrm{p}(\kappa_g) \\
&\times \mathrm{p}(\boldsymbol{\alpha}_g) \\
&\times \mathrm{p}(\mathbf{T}_g) \\
&\times \mathrm{p}(\sigma_c^2) \\
&\times \mathrm{p}(\sigma_g^2)
\end{aligned}$$

Uniform

Inverse gamma

ISR Reconstruction in Details

Blocked Random Walk Metropolis–Hastings Updating:

Random walks are used as proposals, i.e.

$$T' \sim \mathcal{N}(T, \sigma_T^2)$$
$$\alpha' \sim \mathcal{N}(\alpha, \sigma_\alpha^2) \qquad \text{Reversible by design}$$
$$\kappa' \sim \mathcal{N}(\kappa, \sigma_\kappa^2)$$

Allowable Configurations:

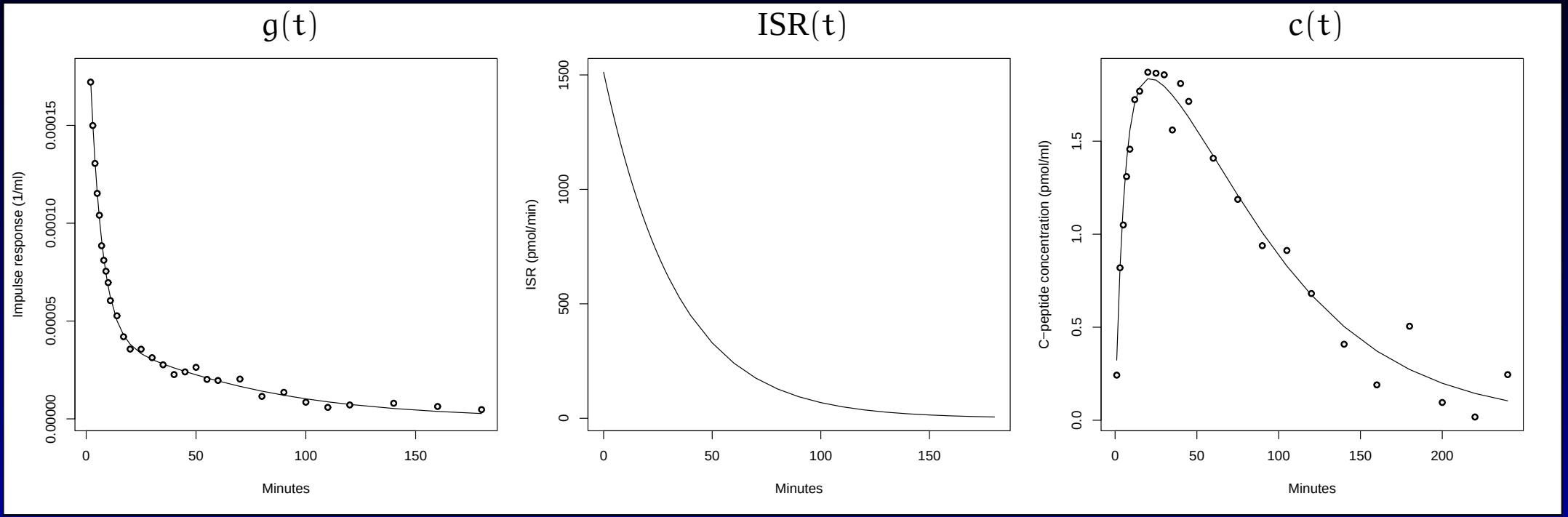
Let Ψ_T and Ψ_α denote the set of allowable matrices and vectors, i.e. the validity of the state $B = (\kappa, \alpha, T)$ is given by the indicator

$$1(B) = 1(\kappa > 0, \alpha \in \Psi_\alpha, T \in \Psi_T)$$

The proposal $(B_g', B_{ISR}') = (\kappa_g', \alpha_g', T_g', \kappa_{ISR}' \alpha_{ISR}', T_{ISR}')$ is then accepted with

$$\alpha = 1(B_g')1(B_{ISR}') \min\left(1, \exp\left\{V(B_{ISR}, B_g) - V(B_{ISR}', B_g') + W(B_g) - W(B_g')\right\}\right)$$

Simulation Study



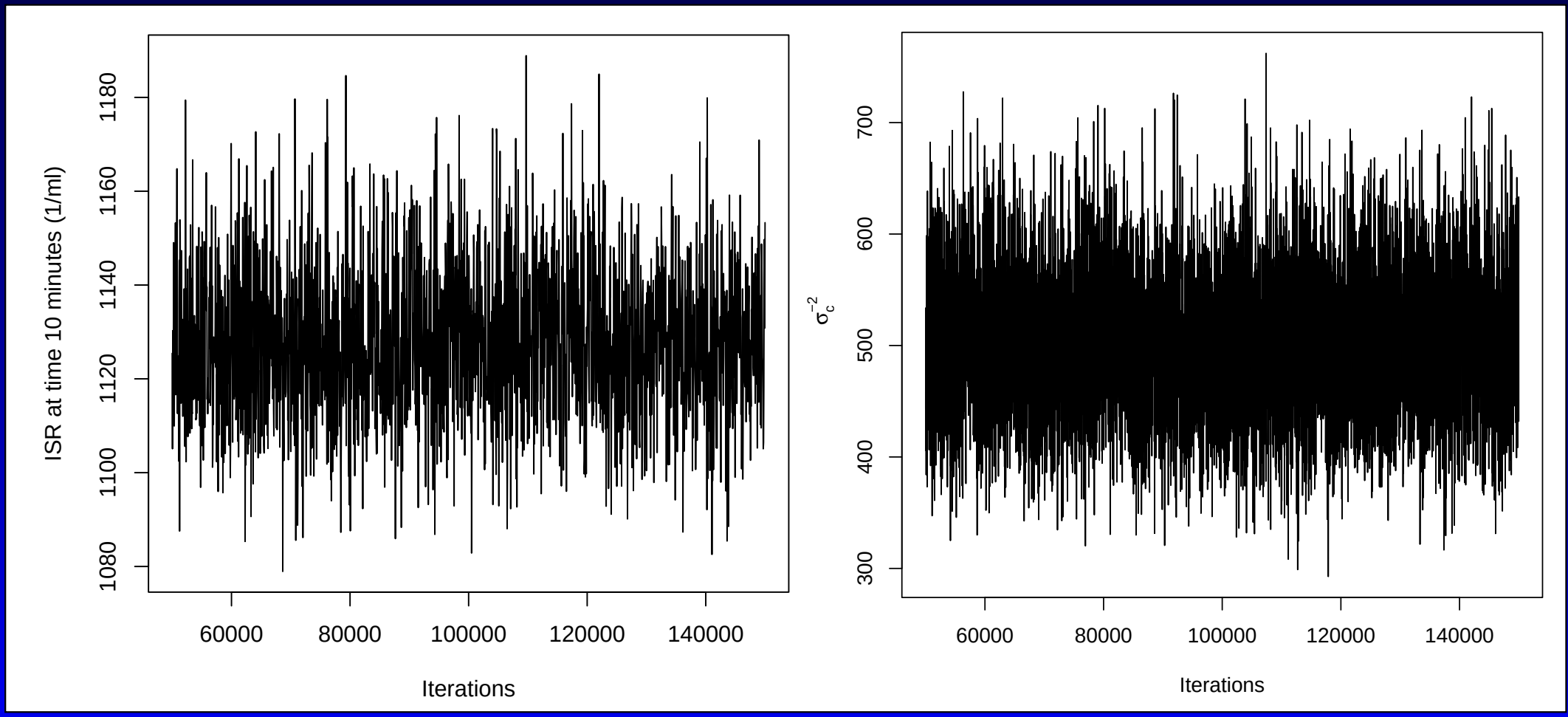
Modifications

1. Let $V(\mathbf{B}_{\text{ISR}}, \mathbf{B}_{\text{g}}) \equiv 0$ to obtain good starting values for $\mathbf{B}_{\text{g}}$
2. Keep $\mathbf{B}_{\text{g}}$ fixed and let $W(\mathbf{B}_{\text{g}}) \equiv 0$ to obtain good starting values for $\mathbf{B}_{\text{ISR}}$
3. With good initial values for $\mathbf{B}_{\text{ISR}}$ and $\mathbf{B}_{\text{g}}$ a final run for $150\,000$ iterations is conducted

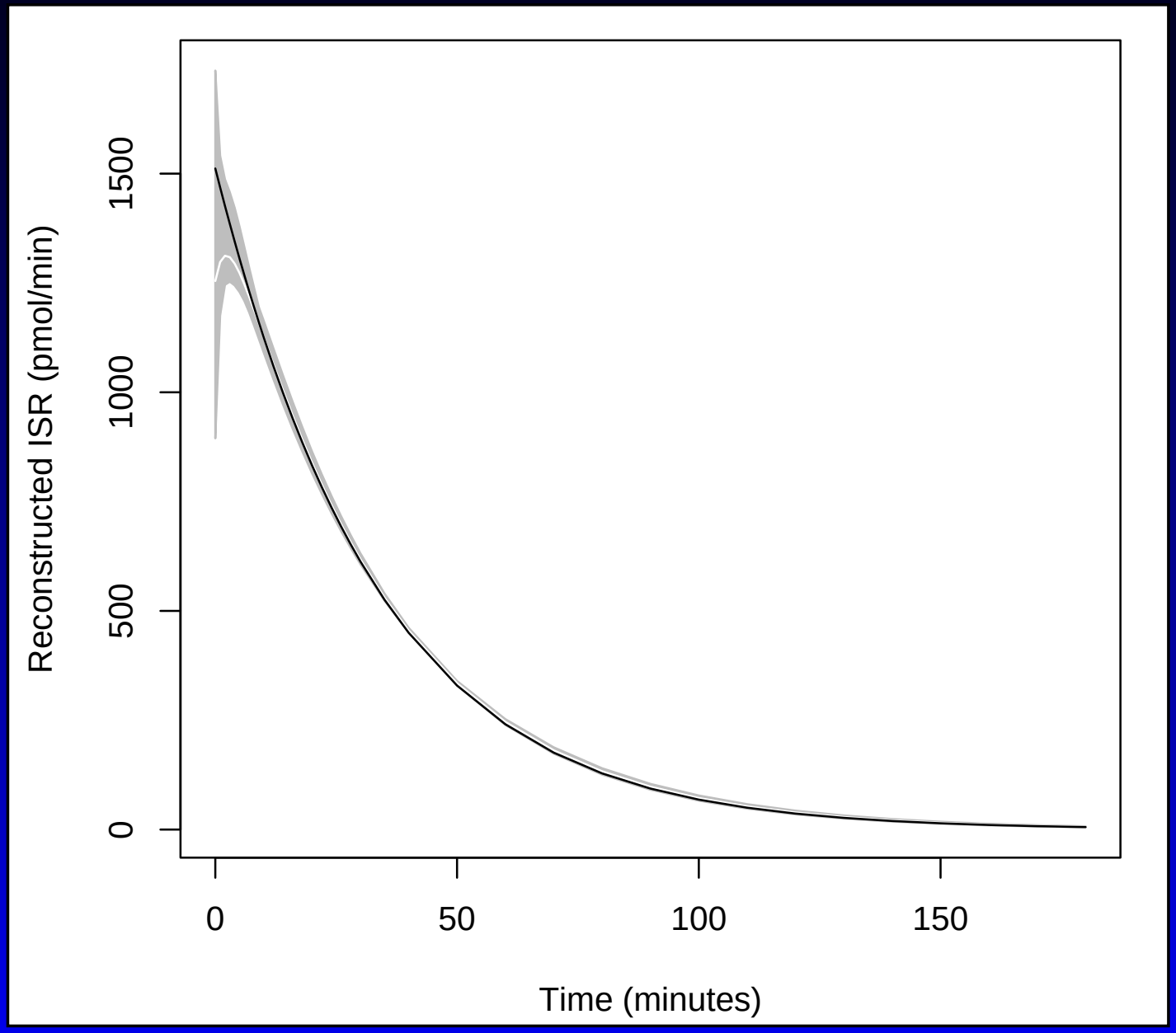
Results

Trace plots:

It is meaningless to trace the parameters as they have no physiological interpretation.



Reconstructed Insulin Secretion Rate



The NN1998 AERx Study

Inhaled Insulin Agent:

How much of an inhaled insulin agent reaches the bloodstream ?

Approach:

Experiment 1:

- ➤ Perform traditional C-peptide bolus experiment followed by an IVGTT

Experiment 2:

- ➤ Perform another IVGTT inwhich inhaled insulin is administered

>From the two experiments, we may

1. ❶ Determine the subjects endogenous insuline secretion rate
2. ❷ Determine both the endogenous and exogenous insulin
3. ❸ Subtract to find exogenous insulin

All done simultaneously

Discussion

Pros:

- Unified approach
- Possible to make closed form reconstruction of the ISR
- Quick

Cons:

- Problems with dimensionality (RJMCMC)
- Would be slow!

Future:

- Consider gamma densities as basis functions
- Convolution results in Kummer functions (confluent hypergeometric functions)
- Less ’nice’ mathematical representation
- Computationally more tractable