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A Bayesian Approach to Bergman's Minimal Model

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Motivation

Diabetes is associated with a number of abnormalities of insulin metabolism ranging from an absolute deficiency of the hormone to a combination of insulin deficiency and resistance causing an inability to metabolise glucose from the blood at normal rates.

Three factors are recognised to play an important role for glucose disposal.

Important Factors for Glucose Disposal

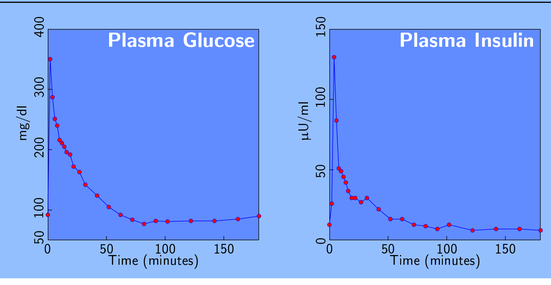
Insulin sensitivity	Glucose effectiveness	Pancreatic responsiveness
The capability of insulin to increase glucose uptake in muscles, liver and adipose tissue	The ability of glucose to enhance its own disappearance at basal insulin level	The ability of the pancreatic β-cells to secrete insulin in response to glucose stimuli

Failure of any of these factors may lead to impaired glucose tolerance, or, if severe, to overt diabetes and assessment of them may improve classification, prognosis and therapy of the disease.

Bergman's Minimal Model

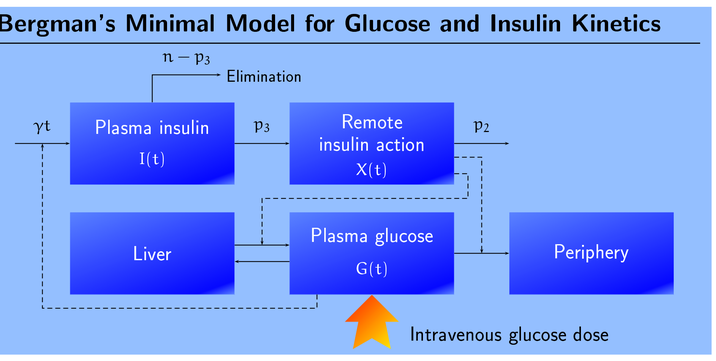
Quantitative assessment of the factors were made possible by the 'minimal model' (Bergman et al., 1979). The 'minimal model' is based upon an analysis of frequently sampled intravenoues glucose tolerance (FSIVGTT) data, where a dose of glucose (usually 0.3 g. of glucose per kg. body weight) is administered intravenously over a 60 seconds period to overnight-fasted subjects. Data from a single experiment is shown below.

Frequently Sampled Intravenous Glucose Tolerance Test



The minimal model is based upon a compartmental analysis of the glycaemic system.

Bergman's Minimal Model for Glucose and Insulin Kinetics



The feedback effect illustrated above may be decomposed into two independent components:

- The effect of glucose to enhance insulin secretion
- The effect of insulin to accelerate glucose uptake,

which by careful compartmental analysis leads to

$$\begin{aligned} \dot{I} &= -nI + \gamma(G-h)^{+}t, & I(0) &= I_0, \\ \dot{G} &= -p_1(G-G_b) - XG, & G(0) &= G_0, \\ \dot{X} &= -p_2X + p_3(I-I_b), & X(0) &= 0. \end{aligned} \tag{1}$$

The metabolic portrait of a single individual is determined by the four parameters:

The Integrated Metabolic Portrait

Insulin sensitivity	Glucose effectiveness	Pancreatic responsiveness
$S_I = \frac{p_3}{p_2}$	$S_G = p_1$	$\phi_1 = \frac{I_{max} - I_b}{n(G_0 - G_b)}$, $\phi_2 = \gamma \times 10^4$

What can be done?

Current Approach

- does not simultaneously take all three differential equations into account
- does not consider the ill-posedness of the estimation problem
  - ❖ very dependent on good initial parameter estimates

but are reasonably fast, though not reliable.

Our Approach

- takes all three differential equations into account
- adequately models the *a priori* information
  - ❖ efficient regularisation of the estimation problem
- provides a solution given in terms of probability distributions
  - ❖ allows for statistical inference

Statistical Model

Assume that physiologic variation and discretisation error can be modelled by random white noise processes; ϵ_t^G, ϵ_t^X and ϵ_t^G. Then by discretisation the non-linear coupled differential equations in (1) become

$$G_{t+1} = (1 - \Delta t p_1 - \Delta t X_t)G_t + \Delta t p_1 G_b + \epsilon_t^G \quad \Rightarrow \quad G_{t+1} \mid \mu_{t+1}^G, \tau_G \sim \mathcal{N}(\mu_{t+1}^G, \tau_G^{-1}),$$

$$X_{t+1} = (1 - \Delta t p_2)X_t + \Delta t p_3(I_t - I_b) + \epsilon_t^X \quad \Rightarrow \quad X_{t+1} \mid \mu_{t+1}^X, \tau_X \sim \mathcal{N}(\mu_{t+1}^X, \tau_X^{-1}),$$

$$I_{t+1} = (1 - \Delta t n)I_t + \gamma(G_t - h)^{+}\Delta t + \epsilon_t^I. \quad \Rightarrow \quad I_{t+1} \mid \mu_{t+1}^I, \tau_I \sim \mathcal{N}(\mu_{t+1}^I, \tau_I^{-1}).$$

Statistical Dependencies

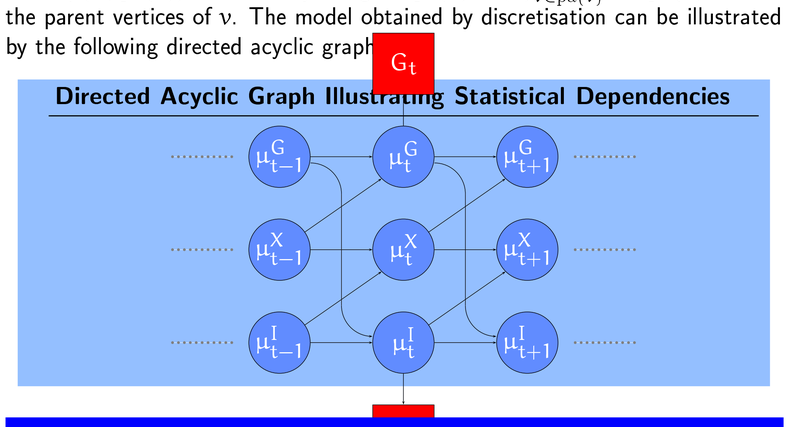
Graphical Model

Directed graphical models (Lauritzen, 1996) represent conditional independence structures of a statistical model through an appropriate factorisation of the density w.r.t. a graph. The vertices V represent the components of the model and missing links respresent conditional independence assumptions. More precisely, the density of V admits the *recursive factorisation* given as

$$p(V) = \prod_{v \in V} p(v \mid \mathrm{pa}(v)),$$

where $p(v \mid \mathrm{pa}(v))$ is the density of v given $\mathrm{pa}(v) = (v)_{v \in \mathrm{pa}(v)}$ and $\mathrm{pa}(v)$ denotes the parent vertices of v. The model obtained by discretisation can be illustrated by the following directed acyclic graph

Directed Acyclic Graph Illustrating Statistical Dependencies



Simulation Based Inference

Let $\Theta = (p_1, p_2, \ldots, G_{\text{unobs}}, X_{\text{unobs}}, I_{\text{unobs}})$ denote all unobserved vertices, where

$$\begin{aligned} G_{\text{unobs}} &= \{\text{all unobserved } G_t\text{'s}\} = G \setminus G_{\text{obs}} \\ X_{\text{unobs}} &= \{\text{all } X_t\text{'s}\} \\ I_{\text{unobs}} &= \{\text{all unobserved } I_t\text{'s}\} = I \setminus I_{\text{obs}} \end{aligned}$$

then inference about Θ is made by exploring the posterior distribution

$$p(\Theta \mid \Phi) \propto p(\Theta)L(\Phi \mid \Theta),$$

where the observed data $\Phi = (G_{\text{obs}}, I_{\text{obs}})$ enters trough the *likelihood function* $L(\Phi \mid \Theta)$ and the *a priori* information is modelled by the *prior density* $p(\Theta)$.

Samples from the posterior are obtained by Markov chain Monte Carlo techniques (Metropolis et al., 1953) by successively simulating values from the full conditionals

$$p(v \mid V \setminus v) \propto p(v \mid \mathrm{pa}(v)) \prod_{w\,:\,v \in \mathrm{pa}(w)} p(w \mid \mathrm{pa}(w)), \quad v \in \Theta.$$

Hereby an irreducible Markov chain $\{\Theta_0, \Theta_1, \ldots\}$ with state space Θ and with stationary distribution $p(\Theta \mid \Phi)$ is constructed. See Robert and Casella (1999) for an introduction to MCMC techniques.

Implementation

The Metropolis–Hastings Algorithm

1. Propose a candidate v' from the proposal distribution $q(v, v')$.
2. Accept with probability

$$\alpha(v, v') = 1 \wedge \frac{p(v' \mid V \setminus v')q(v', v)}{p(v \mid V \setminus v)q(v, v')}.$$

Updating e.g. X_t

Note how the density $p(X_t \mid \Phi, \Theta \setminus \{X_t\})$ factorises into

$$p(X_t \mid \Phi, \Theta \setminus \{X_t\}) \propto p(X_t \mid X_{t-1}, I_{t-1})p(X_{t+1} \mid X_t, I_t)p(G_{t+1} \mid G_t, X_t).$$

The required conditional densities are

$$X_t \mid X_{t-1}, I_{t-1}, \tau_X \sim \mathcal{N}((1 - \Delta t p_2)X_{t-1} + \Delta t p_3(I_{t-1} - I_b), \tau_X^{-1})$$

$$G_t^I \mid G_{t-1}, X_{t-1}, \tau_G \sim \mathcal{N}((1 - \Delta t p_1 - \Delta t X_{t-1})G_{t-1} + \Delta t p_1 G_b, \tau_G^{-1})$$

Now, propose a new candidate X_t' from a symmetric proposal distribution

$$X_t' \mid X_t, \sigma^2 \sim \mathcal{N}(X_t, \sigma^2),$$

then the acceptance probability α becomes

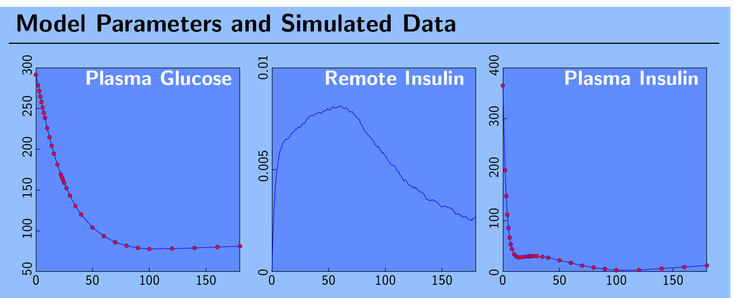
$$\alpha(X_t, X_t') = 1 \wedge \frac{p(X_t' \mid X_{t-1}, I_{t-1})p(X_{t+1} \mid X_t', I_t)p(G_{t+1} \mid G_t, X_t')}{p(X_t \mid X_{t-1}, I_{t-1})p(X_{t+1} \mid X_t, I_t)p(G_{t+1} \mid G_t, X_t)}.$$

Simulated Data Example

Simulating Data

In order to investigate the performance of our Bayesian approach to Bergman's minimal model we simulated experimental data from a normal glucose tolerant person. The model parameters and data obtained are given below

Model Parameters and Simulated Data

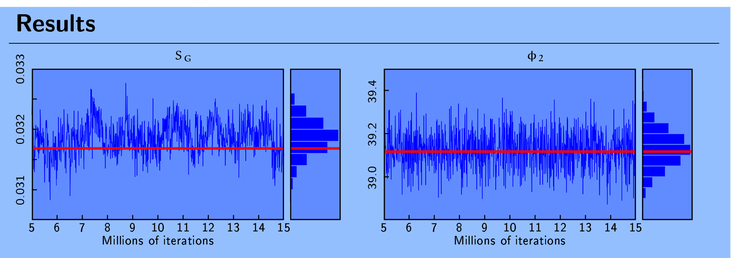


Parameter	'Truth'	Parameter	'Truth'	Parameter	'Truth'
p_1	0.0317	G_b	90.0000	γ	$3.912 \cdot 10^{-3}$
p_2	0.0123	I_b	7.0000	n	0.2659
p_3	$4.892 \cdot 10^{-6}$	h	79.0353		

Results

The Markov chain were run for 15 million iterations. Below is shown summary statistics for the latter 10 million iterations.

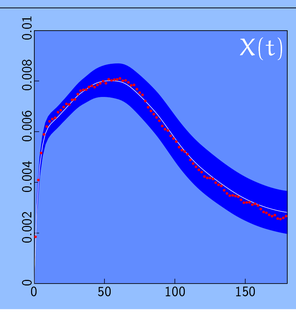
Results



Parameter	'Truth'	Posterior Mean	95 % CI Lower	95 % CI Upper
S_G	0.0317	0.0319	0.0312	0.0325
S_I	3.9653	4.1209	3.2485	4.9934
ϕ_2	39.1169	39.1301	38.9589	39.3012
n	0.2659	0.2661	0.2658	0.2664
G_b	90.0000	90.1281	88.2466	92.0097
I_b	7.0000	6.9753	6.7812	7.1295
h	79.0353	79.0107	78.9065	79.1149

Moreover, the active insulin process may be efficiently assessed.

Assessment of the Active Insulin Process



Discussion

What has been done ?

We have developed a Bayesian method

- to regularise an ill-posed estimation problem and
- assess the metabolic properties of a single individual from all three differential equations simultanesously

What needs to be done ?

- Better mixing
  - ❖ Better proposals
  - ❖ Simulated tempering
  - ❖ MCMCMC-techniques

Future work

- Real data
- Not only allow for physiological variation/discretisation error, but also take measurement error into account
- Extend approach to the oral glucose tolerance test procedure
- Extensions to normal populations ➠ inference on e.g. normal metabolic properties.
- Prior sensitivity analysis

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