A Bayesian Approach to Berman's Minimal Model

Andersen, Kim Emil; Højbjerre, Malene

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A Bayesian Approach to Bergman’s Minimal Model
Kim E. Andersen and Malene Højbjerg
Department of Mathematical Sciences, Aalborg University and Novo Nordisk A/S, Denmark

Motivation

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

Three factors are recognized to play an important role for glucose disposal,

**Important Factors for Glucose Disposal**

1. Insulin availability
2. Insulin sensitivity
3. Exogenous carbohydrates

Failure of any of these factors may lead to impaired glucose tolerance, or, conversely, 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 the feedback effect illustrated above may be decomposed into two independent components:

1. The effect of glucose to enhance insulin secretion
2. The effect of insulin to increase glucose uptake, which may be explained analytically back to

\[
\begin{align*}
1 & = \text{dilution} + \gamma G - \beta I \\
\hat{G} & = -g \text{dilution} + \gamma X - \delta I
\end{align*}
\]

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

**The Integrated Metabolic Portrait**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma)</td>
<td>.67</td>
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</tr>
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</tbody>
</table>

Statistical Model

Assume that physiological variation and diabetogenic error can be modeled by random walk processes \(\xi(t)\) and \(\eta(t)\). Then by linearity the non-linear coupled differential equations in \(G\) become

\[
\begin{align*}
G_{t+1} &= G_t + \xi_t + \eta_t \\
X_{t+1} &= X_t + \xi_t + \eta_t
\end{align*}
\]

**Statistical Dependencies**

**Graphical Model**

Directed graphical models (Lauritzen, 1996) represent conditional independence structure of a statistical model through an appropriate factorization of the density \(p(\theta_1, \ldots, \theta_p)\), a graph. The network captures the strength of the model and making links target conditional independence statements. More precisely, the density of \(V\) admits the econometric factorization given at

\[
p(V) = \prod_{v \in \mathcal{V}} p(v|\mathcal{P}(v)),
\]

where \(p(v|\mathcal{P}(v))\) is the density of \(v\) given \(\mathcal{P}(v)\) and \(p(v)\) denotes the prior of \(v\). The model obtained by discretization can be illustrated by the following directed acyclic graph.

Simulation Based Inference

Let \(\theta = (\theta_1, \theta_2, \ldots, \theta_p)\) denote all unknown versions, where

\[
\begin{align*}
G_{\text{min}}(\theta) &= \text{all unknown } G - G_{\text{min}} \text{ data} \\
X_{\text{min}}(\theta) &= \text{all unknown } X - I_{\text{min}} \text{ data}
\end{align*}
\]

then inference about \(\theta\) is made by exploring the posterior distribution

\[
p(\theta|\mathcal{D}) = p(\theta) p(\mathcal{D}|\theta).
\]

where the observed data \(\mathcal{D} = (G_{\text{min}}, X_{\text{min}})\) enters through the likelihood function \(L(\theta, \mathcal{D})\), and the a priori information is modeled by the prior density \(p(\theta)\). Sample from the posterior are obtained by Markov chain Monte Carlo techniques (Metropolis et al., 1953) by successively simulating values from the full conditionals

\[
p(v|\mathcal{P}(v)), v \in \mathcal{V},
\]

Hereby an irreducible Markov chain \((\mathcal{V}, \theta, \theta', \ldots)\) with state space \(\theta\) and with stationary distribution \(p(\theta)|\mathcal{D}\) is constructed. See Robert and Casella (1999) for an introduction to MCMC technique.

Implementation

The Metropolis−Hastings Algorithm

1. Propose a candidate \(v^*\) from the proposal distribution \(q(v^*|v)\).
2. Accept with probability

\[
a(v|v^*) = \min\left(1, \frac{q(v|v^*)}{q(v^*|v)}\right).
\]

Updating \(G\):

Note how the density \(p(\theta|\mathcal{D}) \propto p(\theta) p(\mathcal{D}|\theta)\) factorizes into

\[
p(\theta|\mathcal{D}) \propto p(\theta) p(G_{\text{min}}|\theta) p(X_{\text{min}}|\theta).
\]

The required conditional densities are

\[
G_{\text{min}}|\theta, \mathcal{D}, X_{\text{min}} \quad X_{\text{min}}|\theta, \mathcal{D}, G_{\text{min}} \quad \mathcal{D} = \text{data} \quad \mathcal{P}(v) = \text{parents of } v
\]

Now, propose a new candidate \(G_{\text{min}}^*\) from a symmetric proposal distribution

\[
X_{\text{min}}|G_{\text{min}}^*, \mathcal{D} \quad G_{\text{min}}|X_{\text{min}}^*, \mathcal{D}
\]

then the acceptance probability \(a\) becomes

\[
a(G_{\text{min}}, X_{\text{min}}|G_{\text{min}}^*, X_{\text{min}}^*) = \frac{p(G_{\text{min}}^*|X_{\text{min}}^*, \mathcal{D}) p(X_{\text{min}}^*|G_{\text{min}}^*, \mathcal{D})}{p(G_{\text{min}}|X_{\text{min}}, \mathcal{D}) p(X_{\text{min}}|G_{\text{min}}, \mathcal{D})}.
\]

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 parameter and data are given below

**Model Parameters and Simulated Data**

<table>
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**Results**

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

**Assessment of the Active Feedback Process**

What has been done?

We have developed a Bayesian method

* to regulate an individual’s simulation problem
* to assess the metabolic properties of a single individual from all three differential equation simultaneously

What needs to be done?

**Better mixing**
* Better proposal
* Simulated tempering
* MCMC techniques

Future work

**Real data**

Not only allow for physiological variation/diabetogenic error, but also take measurement error into account

**External approach to the glucose tolerance test procedure**

Extension to normal populations inference on e.g. normal metabolic properties

**Pilot sensitivity analysis**

References


