Bayesian model discrimination for glucose-insulin homeostasis

Andersen, Kim Emil; Brooks, Stephen P.; Højbjerre, Malene

Publication date:
2007

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Andersen, K. E., Brooks, S. P., & Højbjerre, M. (2007). Bayesian model discrimination for glucose-insulin homeostasis. Poster session presented at COBAL 2, San José del Cabo, Mexico.

Bayesian Model Discrimination for Glucose-Insulin Homeostasis

Cobal 2

February 2005

Kim E. Andersen*, Stephen P. Brooks** and Malene Højbjerre*

*Department of Mathematical Sciences, Aalborg University, Denmark

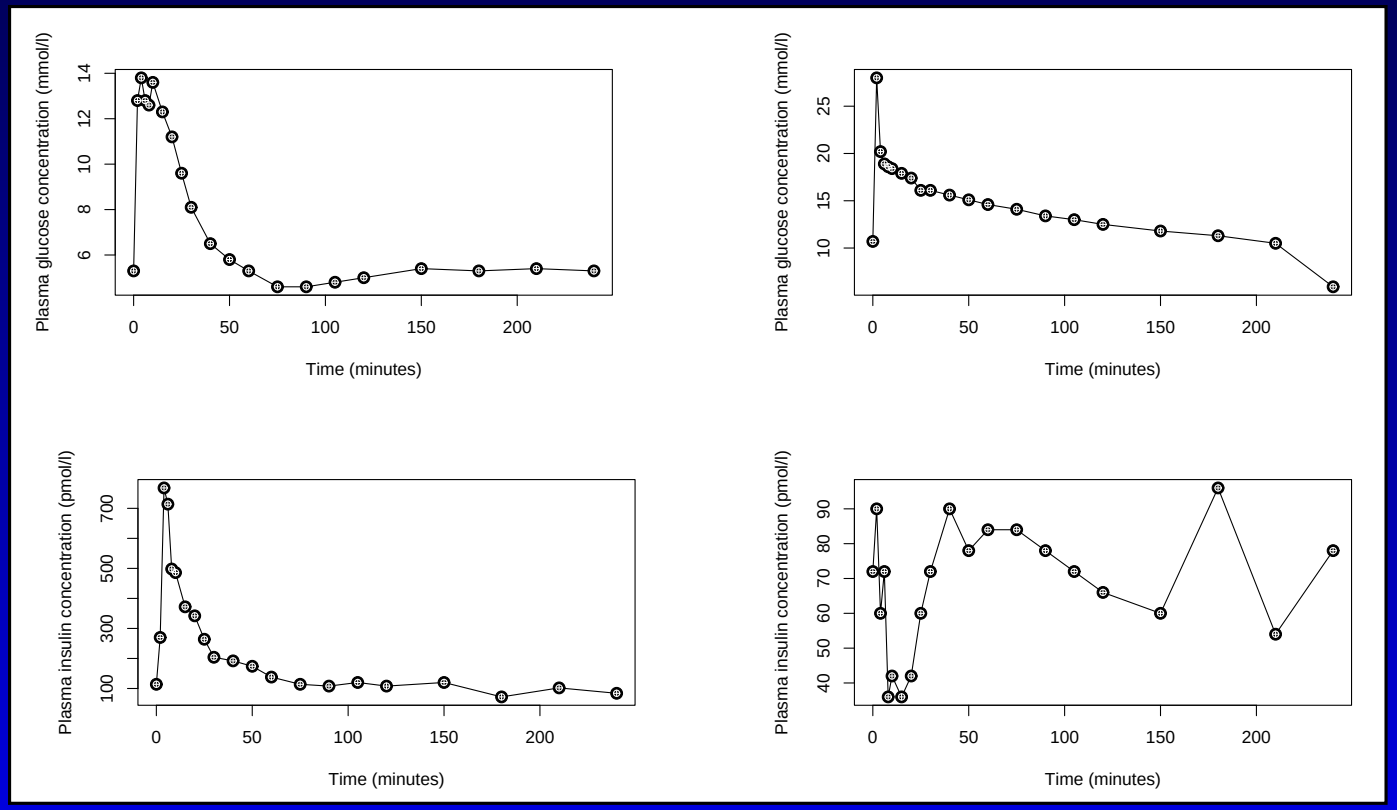
**Statistical Laboratory, University of Cambridge, UK

Data

IVGTT: Intra-Venous Glucose Tolerance Test

Sampling of glucose and insulin concentrations in plasma following an intravenous glucose injection.

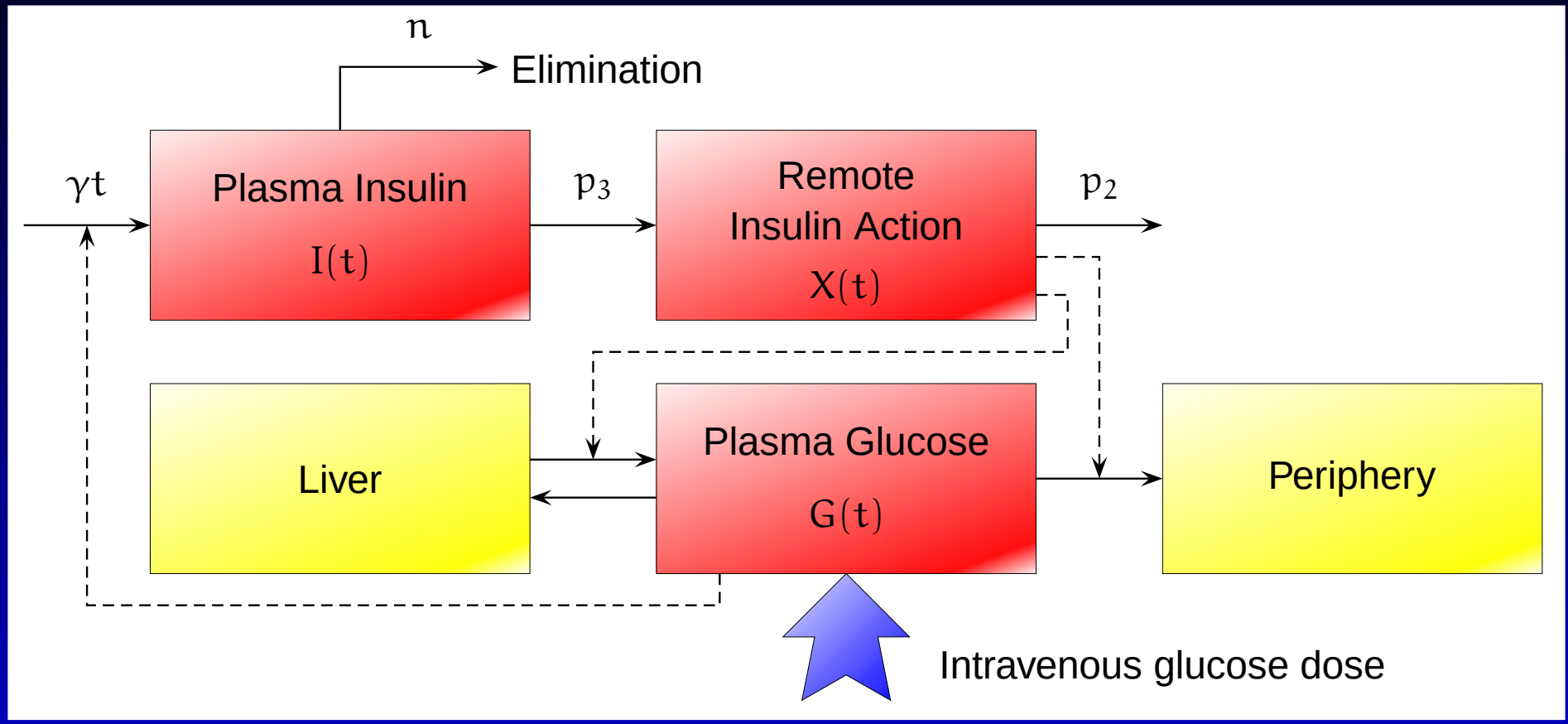
Healthy | Type II diabetic



Data on the human body's response to increased blood sugar levels.

Models – The Minimal Model

The Minimal Model: Bergman et al (1979) and Toffolo et al (1980)



$$
\begin{aligned}
G_1: \quad \dot{G}(t) &= -p_1(G(t) - G_b) - X(t)G(t) & G(0) &= G_0 \\
\dot{X}(t) &= -p_2 X(t) + p_3(I(t) - I_b) & X(0) &= 0 \\
I_2: \quad \dot{I}(t) &= -n(I(t) - I_b) + \gamma J_+(G(t) - h)t & I(0) &= I_0
\end{aligned}
$$

Models – The Minimal Model

Parameters of Interest in the Minimal Model:

insulin sensitivity: $S_I = p_3/p_2$

glucose effectiveness: $S_G = p_1$

pancreatic responsiveness: $\varphi_1 = (I_0 - I_b)/[n(G_0 - G_b)]$

$\varphi_2 = \gamma \times 10^4$

Current Approach:

Iterative nonlinear least squares technique (MINMOD PROGRAMME)

- not a unified system (the insulin is treated as known).
- S_I estimated close to zero with negative confidence intervals.
- φ_1 and φ_2 not estimated (the insulin is treated as known).
- the positive truncation J is physiologically questionable.
- the multiplicative effect of time t is difficult to justify biologically.
- no account of individual variability or process error.

Alternative models and/or other approaches are called for.

Models – Variations on the Minimal Model

Variations on the Minimal Model:

Three additional variants of the insulin component:

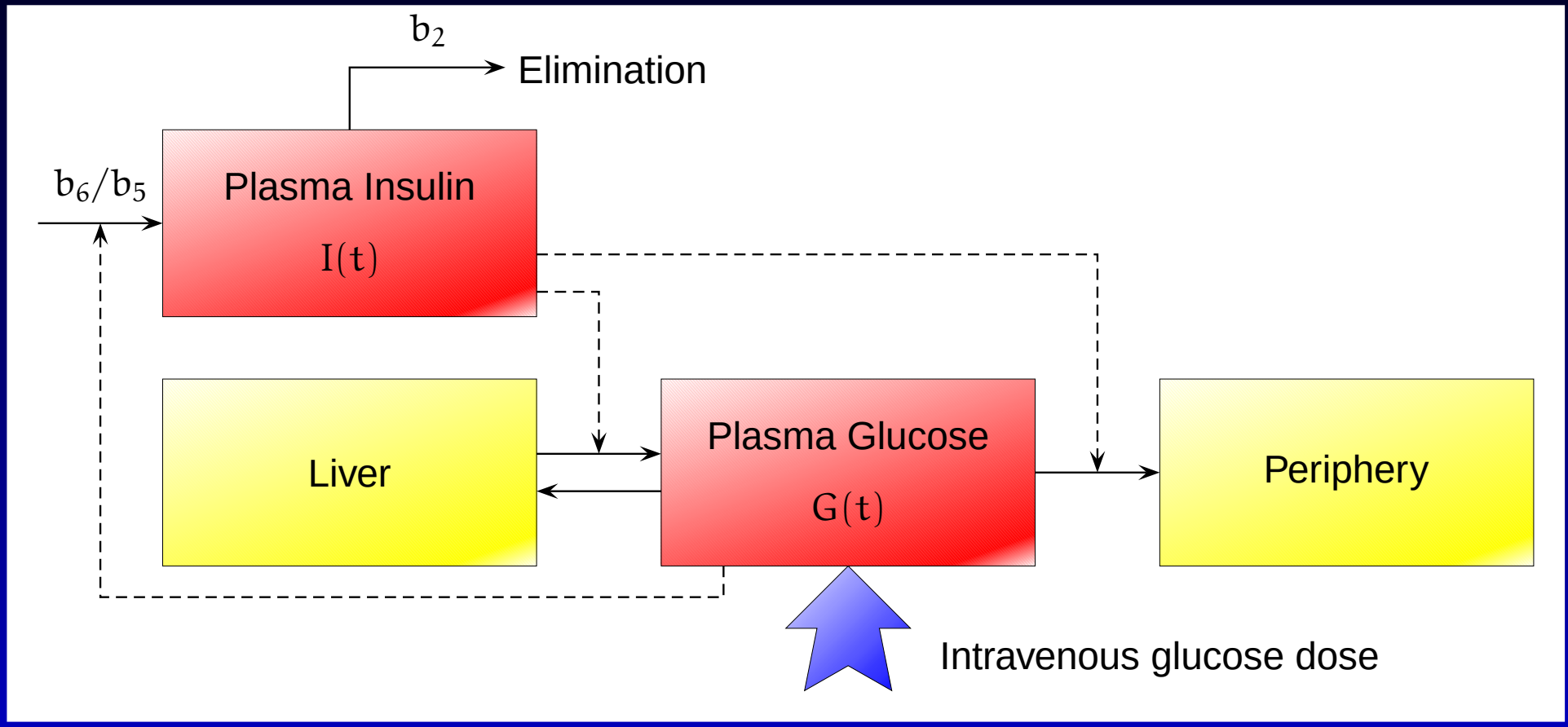
$$I_2: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma J_+(G(t) - h) \qquad I(0) = I_0$$

$$I_3: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h)t \qquad I(0) = I_0$$

$$I_4: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h) \qquad I(0) = I_0$$

Models – The de Gaetano & Arino Model

The GA Model: De Gaetano & Arino (2000)



$$G_2: \quad \dot{G}(t) = -b_1 G(t) - b_4 I(t) G(t) + b_7 \qquad G(0) = G_b + b_0$$

$$I_5: \quad \dot{I}(t) = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)\, ds \qquad I(0) = I_b + b_3 b_0$$

where $G(t) \equiv G_b$ for $t \in [-b_5, 0)$.

Models – The de Gaetano & Arino Model

Parameters of interest:

insulin sensitivity:	$S_I = b_4$
glucose effectiveness:	$S_G = b_1$
pancreatic responsiveness:	$\varphi_1 = b_3/b_2$
	φ_2 not estimated under the GA model

Reformulating the models

Same approach as Andersen & Højbjerre (2005):

- The glucose and insulin concentrations are log-transformed (same scale - common variance).
- The DE's are discretised.
- Impose random errors both on the system and the measurements.
- Extend to population modelling.

↓

A stochastic state space modelling framework that allows for likelihood constructions.

You may flip this page if you dare

Reformulating the Models

Log-Transformation:

$$g(t) = \log G(t), \qquad x(t) = \log X(t) \qquad \text{and } i(t) = \log I(t)$$
$$\dot{g}(t) = \dot{G}(t)/G(t), \qquad \dot{x}(t) = \dot{X}(t)/X(t) \qquad \text{and } \dot{i}(t) = \dot{I}(t)/I(t)$$

Reparameterizing by S_I, S_G, φ_1, φ_2 , b_0 and b_3.

Log-Transformed Minimal Model:

$$G_1: \dot{g}(t) = -S_G(1 - G_b\, e^{-g(t)}) - e^{x(t)} \qquad g(0) = \log(G_b + b_0)$$
$$\dot{x}(t) = -p_2(1 - S_I(e^{i(t)} - I_b)e^{-x(t)}) \qquad x(0) \to -\infty$$
$$I_1: \quad \dot{i}(t) = -\frac{b_3}{\varphi_1}(1 - e^{-i(t)} I_b) + 10^{-4} e^{-i(t)} \varphi_2 J_+ (e^{g(t)} - h)t \qquad i(0) = \log(I_b + b_3 b_0)$$

Discretised Log-transformed Minimal Model

$\Lambda = \{t_1, t_2, \ldots, t_{|\Lambda|}\}$ and new notation: $g(t_k) = g^s_{t_k}$, $x(t_k) = x^s_{t_k}$ and $i(t_k) = i^s_{t_k}$

$$g^s_{t_k} = g^s_{t_{k-1}} - (t_k - t_{k-1})\left(S_G\,(1 - G_b\, e^{-g^s_{t_{k-1}}}) + e^{x^s_{t_{k-1}}}\right) + \epsilon^{g^s}$$
$$x^s_{t_k} = x^s_{t_{k-1}} - (t_k - t_{k-1})p_2\left(1 - S_I(e^{i^s_{t_{k-1}}} - I_b)e^{-x^s_{t_{k-1}}}\right) + \epsilon^{x^s}$$
$$i^s_{t_k} = i^s_{t_{k-1}} - (t_k - t_{k-1})\left(\frac{b_3}{\varphi_1}(1 - e^{-i^s_{t_{k-1}}} I_b) - 10^{-4} e^{-i^s_{t_{k-1}}} \varphi_2 J_+ (e^{g^s_{t_{k-1}}} - h)t_{k-1}\right) + \epsilon^{i^s}$$

where ϵ^{g^s}, ϵ^{x^s} and ϵ^{i^s} follows $\mathcal{N}(0, \nu^{-1}(t_k - t_{k-1}))$.

Reformulating the Models

System processes:

$$g^s_{t_k} \mid g^s_{t_{k-1}}, x^s_{t_{k-1}}, \nu \sim \mathcal{N}(f^g_{t_{k-1}}, \nu^{-1}(t_k - t_{k-1}))$$

$$x^s_{t_k} \mid x^s_{t_{k-1}}, i^s_{t_{k-1}}, \nu \sim \mathcal{N}(f^x_{t_{k-1}}, \nu^{-1}(t_k - t_{k-1})), \quad t_k \in \Lambda$$

$$i^s_{t_k} \mid i^s_{t_{k-1}}, g^s_{t_{k-1}}, \nu \sim \mathcal{N}(f^i_{t_{k-1}}, \nu^{-1}(t_k - t_{k-1}))$$

where

$$f^g_{t_{k-1}} = g_{t_{k-1}} - (t_k - t_{k-1})\left(S_G(1 - G_b\, e^{-g_{t_{k-1}}}) + e^{x_{t_{k-1}}}\right)$$

$$f^x_{t_{k-1}} = x_{t_{k-1}} - (t_k - t_{k-1})p_2\left(1 - S_I(e^{i_{t_{k-1}}} - I_b)e^{-x_{t_{k-1}}}\right)$$

$$f^i_{t_{k-1}} = i_{t_{k-1}} - (t_k - t_{k-1})\left(\frac{b_3}{\varphi_1}(1 - e^{-i_{t_{k-1}}} I_b) - 10^{-4} e^{-i_{t_{k-1}}} \varphi_2 J_+ (e^{g_{t_{k-1}}} - h)t_{k-1}\right)$$

Observed processes:

$$g^o_{t_k} \mid g^s_{t_k}, \nu^{-1}_{g^o} \sim \mathcal{N}(g^s_{t_k}, \nu_{g^o})$$

$$i^o_{t_k} \mid i^s_{t_k}, \nu^{-1}_{i^o} \sim \mathcal{N}(i^s_{t_k}, \nu_{i^o}), \quad t_k \in \mathcal{T} \subseteq \Lambda$$

The other models can be reformulated similarly.

Population Modelling

System processes for individual j in model m:

$$\Phi^s_{jm} = \begin{cases} \{g^s_{jmt_k}, x^s_{jmt_k}, i^s_{jmt_k}\}_{t_k \in \Lambda} & \text{for } m = 1,\ldots,5, \quad (G_1 \times I_1, \ldots, I_5) \\ \{g^s_{jmt_k}, i^s_{jmt_k}\}_{t_k \in \Lambda} & \text{for } m = 6,\ldots,10, \quad (G_2 \times I_1, \ldots, I_5) \end{cases}$$

Observed processes for individual j:

$$\Phi^o_j = \{g^o_{jt_k}, i^o_{jt_k}\}_{t_k \in \mathcal{T}}$$

Distributional assumptions for individual j in model m:

$$p_m(\Phi^s_{jm} \mid \theta_{jm}) \propto \begin{cases} \nu_j^{|\Lambda|} \exp(-V_m(\Phi^s_{jm}, \theta_{jm})) & \text{for } m = 1,\ldots,5 \\ \nu_j^{3|\Lambda|/2} \exp(-V_m(\Phi^s_{jm}, \theta_{jm})) & \text{for } m = 6,\ldots,10 \end{cases}$$

$$p_m(\Phi^o_j \mid \theta_{jm}, \Phi^s_{jm}) \propto (\nu_{g^o_j} \nu_{i^o_j})^{|\mathcal{T}|/2} \exp(-W(\Phi^o_j, \Phi^s_{jm}, \theta_{jm}))$$

where

$$\theta_{jm} = \begin{cases} (S_{Gj}, S_{Ij}, \varphi_{1j}, b_{3j}, b_{0j}, G_{bj}, I_{bj}, \varphi_{2j}, p_{2j}, h_j, \nu_j, \nu_{g^o_j}, \nu_{i^o_j}) & \text{for } m = \{1,\ldots,9\} \setminus 5 \\ (S_{Gj}, S_{Ij}, \varphi_{1j}, b_{3j}, b_{0j}, G_{bj}, I_{bj}, b_{5j}, \nu_j, \nu_{g^o_j}, \nu_{i^o_j}) & \text{for } m = 5 \text{ and } 10 \end{cases}$$

Population Modelling – cont'd

and

$$V_m(\Phi^s_{jm},\theta_{jm})=\begin{cases}\frac{1}{2}\nu_j\sum_{t_k\in\Lambda}(g^s_{jmt_k}-f^g_{jmt_k})^2+(x^s_{jmt_k}-f^x_{jmt_k})^2+(i^s_{jmt_k}-f^i_{jmt_k})^2 & m=1,\ldots,5\\ \frac{1}{2}\nu_j\sum_{t_k\in\Lambda}(g^s_{jmt_k}-f^g_{jmt_k})^2+(i^s_{jmt_k}-f^i_{jmt_k})^2 & m=6,\ldots,10\end{cases}$$

$$W(\Phi^o_j,\Phi^s_{jm},\theta_{jm})=\frac{1}{2}\sum_{t_k\in\mathcal{T}}\nu_{g^o_j}(g^o_{jt_k}-g^s_{jmt_k})^2+\nu_{i^o_j}(i^o_{jt_k}-i^s_{jmt_k})^2$$

Likelihood for population of L individuals in model m:

$$L(\Psi_m,\theta_m,\Phi^s_m\,|\,\Phi^o)=\prod_{j=1}^{L}p_m(\Phi^o_j\,|\,\theta_{jm},\Phi^s_{jm})p_m(\Phi^s_{jm}\,|\,\theta_{jm})p_m(\theta_{jm}\,|\,\Psi_m)$$

where

$$\begin{aligned}\Phi^s_m &= (\Phi^s_{1m},\Phi^s_{2m},\ldots,\Phi^s_{Lm})\\ \Phi^o &= (\Phi^o_1,\Phi^o_2,\ldots,\Phi^o_L)\\ \theta_m &= (\theta_{1m},\theta_{2m},\ldots,\theta_{Lm})\end{aligned}$$

and $p_m(\theta_{jm}\,|\,\Psi_m)$ is the product of log-normal (for the system parameters) and gamma distributions (for the precisions).

Bayesian Analysis

Posterior Distribution: MCMC Methods (Metropolis-Hastings)

$$\pi(\Psi, \theta, \Phi^s \mid \Phi^o) \propto \prod_{j=1}^{L} p(\Phi_j^o \mid \theta_j, \Phi_j^s) p(\Phi_j^s \mid \theta_j) p(\theta_j \mid \Psi) p(\Psi)$$

where $p(\Psi)$ prior for the population parameters - a product of normal (for the means) and gamma (for the precisions) distributions.

Model Uncertainty: Reversible Jump MCMC

$$\pi(\Psi_m, \theta_m, \Phi_m^s, m \mid \Phi^o) \propto \prod_{j=1}^{L} p_m(\Phi_j^o \mid \theta_{jm}, \Phi_{jm}^s) p_m(\Phi_{jm}^s \mid \theta_{jm}) p_m(\theta_{jm} \mid \Psi_m) p(\Psi_m \mid m) p(m)$$

where $p(m)$ prior for model index - uniform.

Improving Mixing: Simulated Tempering (RJ)MCMC

$$\pi_\tau(\Psi_m, \theta_m, \Phi_m^s, m \mid \Phi^o) \propto \prod_{j=1}^{L} \left(p_{m,\tau}(\Phi_j^o \mid \theta_{jm}, \Phi_{jm}^s) p_{m,\tau}(\Phi_{jm}^s \mid \theta_{jm}) \right)^{s(\tau)} \times p_m(\theta_{jm} \mid \Psi_m) p(\Psi_m \mid m) p(\tau \mid m) p(m)$$

where $p(\tau \mid m)$ prior for temperature τ (coarseness level of discritisation) and

$s(\tau) = 2^{-(\tau-1)n}$ for $n > 0$. Note, $\tau = 1$ provides the posterior.

Results

Posterior Model Probability:

		Posterior model probability									
Population	Coarseness	1	2	3	4	5	6	7	8	9	10
Healthy	1	0.00	0.21	**0.76**	0.03	0.00	0.00	0.00	0.00	0.00	0.00
	2	0.10	0.15	0.23	0.20	0.08	0.02	0.07	0.08	0.05	0.01
	4	0.11	0.13	0.12	0.10	0.10	0.16	0.07	0.05	0.09	0.06
Diabetic	1	0.00	0.00	0.07	0.00	0.01	0.00	0.00	**0.75**	0.00	0.17
	2	0.05	0.09	0.15	0.07	0.08	0.04	0.13	0.20	0.08	0.11
	4	0.13	0.05	0.11	0.10	0.07	0.08	0.14	0.13	0.12	0.09

Results

Simulated values of m and τ:

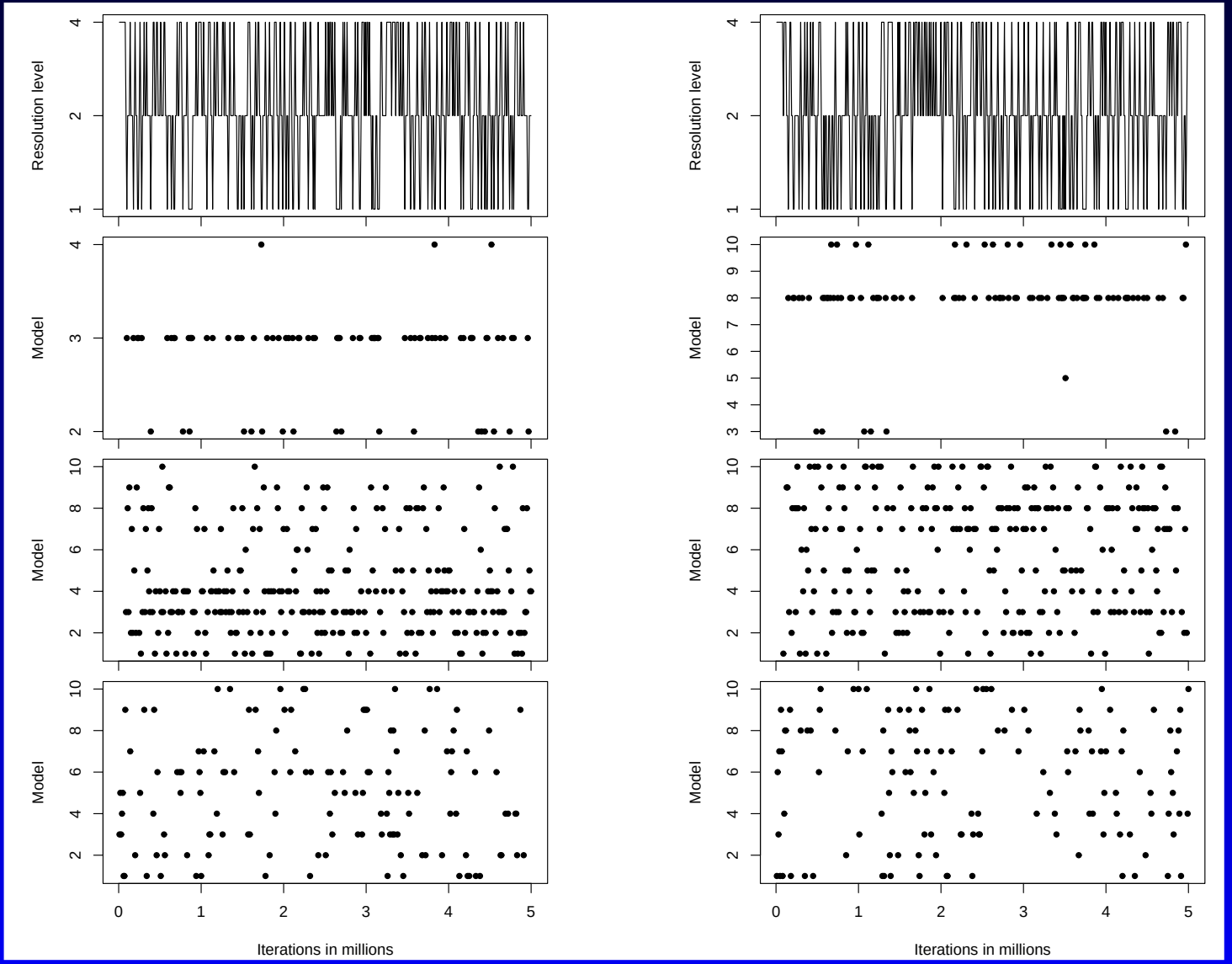
Healthy population | Type II diabetic population

Coarseness

$\tau = 1$

$\tau = 2$

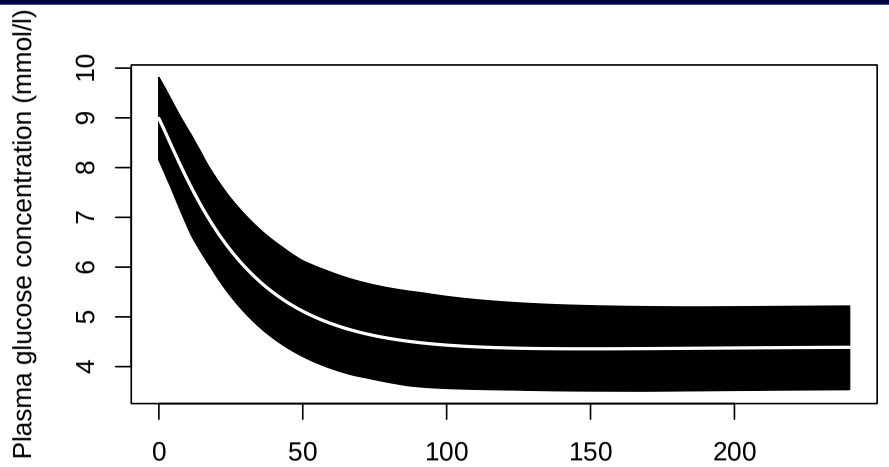
$\tau = 3$

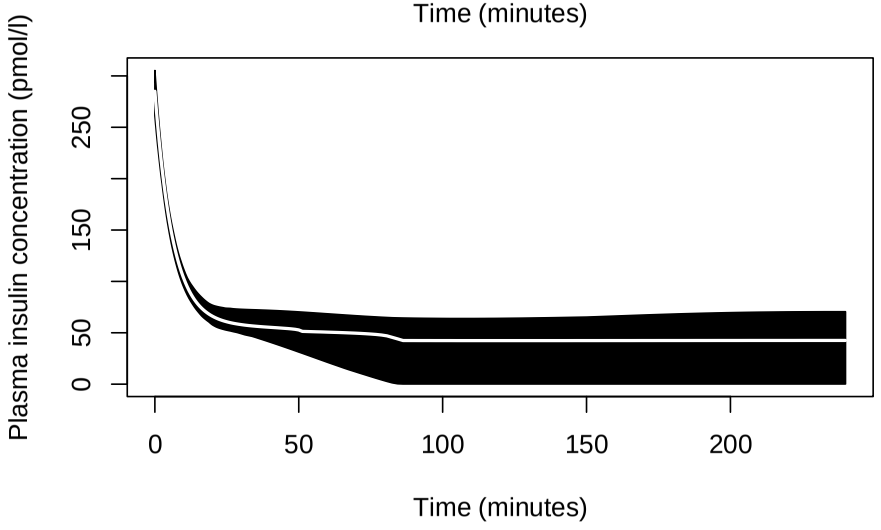


Results

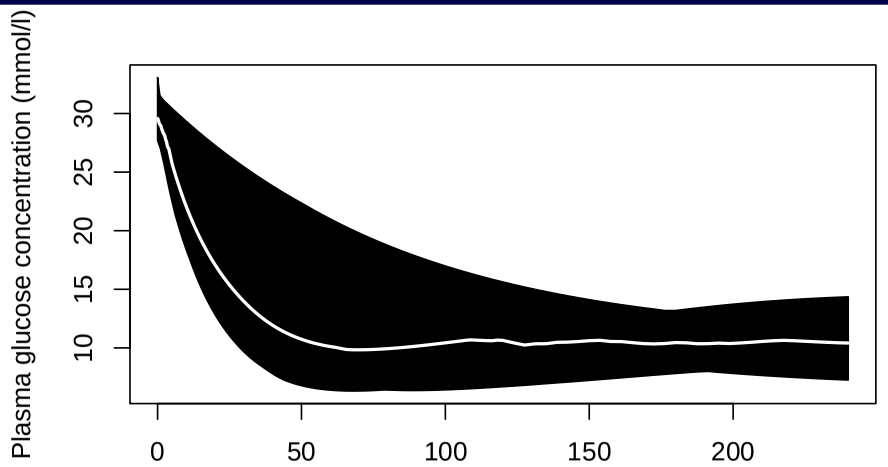
Posterior Population Glucose and Insulin Concentrations:

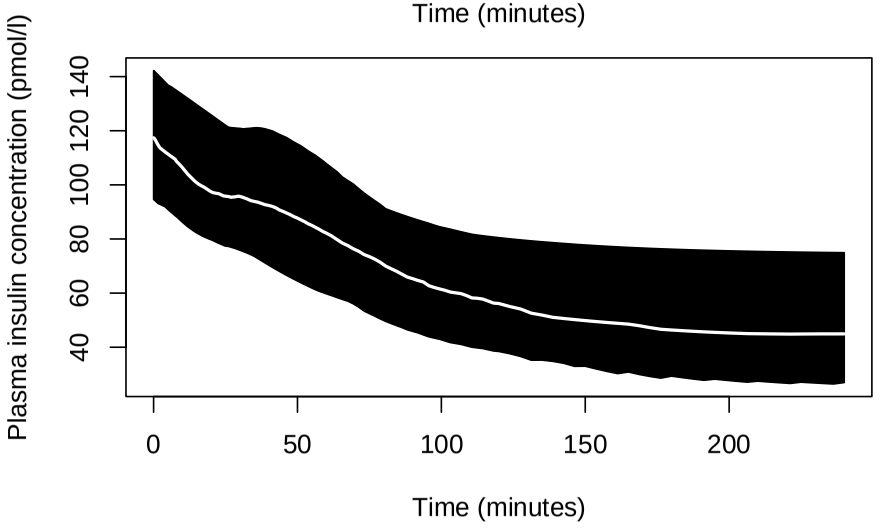
Healthy





Type II diabetic





Discussion

Results:

- Discriminating among 10 glucose and insulin models.

  ↓

  Healthy population: Minimal model with no positive relection (original model)
  Diabetic population: Original insulin minmal model and new glucose model.
- Providing model-averaged inference on parameters of interest.
- Unified systems of both glucose and insulin.
- No $S_I = 0$ problems for diabetic population.
- Possible to estimate φ_1 and φ_2.
- Random errors on system and measurements.
- Population modelling.

For more details see Andersen, Brooks and Højbjerre(2004) - download from

http://www.math.aau.dk/research/reports/R-2004-15.pdf

References

Bergman, R. N., Y. Z. Ider, C. R. Bowden and C. Cobelli (1979), Quantitative estimation of insulin sensitivity. *American Journal of Physiology* **236**, E667 – E677

Toffolo, G., D. R.N. Bergman, C. R. Finegood, Bowden and C. Cobelli (1980), Quantitative estimation of beta cell sensitivity to glucose in the intact organism: a minimal model of insulin kinetics in the dog. *Diabetes* **29**, 979–990

de Gaetano, A. and O. Arino (2000), Mathematical modelling of the intravenous glucose tolerance test. *Journal of Mathematical Biology* **40**, 136 – 168

Andersen, K. E. and M. Højbjerre (2005), A Population based Bayesian Approach to the Minimal Model of Glucose and Insulin Homeostasis. To appear in *Statistics in Medicine*.

Andersen, K. E., Brooks, S. P. and M. Højbjerre (2004), Bayesian Model Discrimination for Glucose-Insulin Homeostasis. Technical Report R-2004-15, Department of Mathematical Sciences, Aalborg University.