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Bayesian Modelling of the Consistency of Symptoms Reported During Hypoglycaemia for Individual Patients

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1. Introduction

Hypoglycaemia is a problem caused by insulin treatment. It can lower the blood glucose level in insulin-treated diabetic patients. It is fundamental for diabetes patients to be able to recognise their own symptoms quickly to prevent more severe problems before restorative action can be taken. Among the most prominent symptoms are sweating, trembling, difficulty concentrating, nervousness and dizziness. Symptoms have also been sub-divided into groups: Hepburn et al. (1992) classified symptoms developed from lack of glucose in brain as neuroglycopenic symptoms and symptoms that happen unconsciously resulting from the nervous system's response to hypoglycaemia as autonomic symptoms. Deary (1993) added a “general malaise” group to the two previous groups. Many studies show that symptoms of hypoglycaemia vary considerably among patients (Cox et al, 1993), but symptom variability for individual patients has attracted less attention.

Zammitt et al. (2011) developed a statistical model quantifying individual differences in symptom reporting and found that adults exhibit distinct intra-individual variability in symptom reporting. This is important in educating patients with diabetes as they should be aware that symptoms vary not only between individuals but also between hypoglycaemic episodes of an individual.

In this paper we build on work in Zammitt et al. (2011) to allow for different forms of symptom experiencing thresholds and consider between-group variability when symptoms are classified in groups. We also extend the investigation of the impact of patient-specific factors on symptom consistency by including certain interactions among these factors, and determine the best predictive model by performing variable selection.

2. Data

Data were collected during a study conducted in several health centres in the UK. The data were collected from 381 participants, aged between 17-75 years old and this study involved adult participants with age range, 22-74 years.Provided information includes all hypoglycaemic episodes experienced (see Table 1) with time, date, duration, symptoms, treatment received (oral or injection) and concurrent blood glucose. Episodes occurring within 24 hours of the preceding episode are considered to have diminished intensity. Thus, those episodes were excluded from the present work.

The analysis includes 59 subjects as we only included subjects who experienced at least two hypoglycaemic episodes per month. Therefore, only patients with 19 or more episodes were considered for further analysis. The study also collected information on the following 10 patient-specific factors: age, gender, body mass index (BMI), type of diabetes, duration of diabetes, retinopathy, awareness of hypoglycaemia, stimulated C-peptide, hemoglobin A1c, and serum angiotensin converting enzyme activity (ACE). Retinopathy is an eye disease in the retina which acts as a marker for lack of glucose. C-peptide is a protein that acts as insulin precursor and links directly with insulin secretion. Therefore, by measuring the amount of C-peptide in blood, we will also know the insulin level of a patient. HaemoglobinA1c measures how much sugar is bound to haemoglobin, and high haemoglobinA1c test indicates high glucose level. Diabetic patients have higher than normal serum angiotensin converting enzyme level. This protein relates to blood pressure control.

TABLE 1: List of Symptoms on Patients' Report Form and The Group Categorisation

No.	Symptom	Group	No.	Symptom	Group
1	Confussion	Neuroglycopenic	14	Blurred vision	Neuroglycopenic
2	Sweating	Autonomic	15	Hunger	Autonomic
3	Drowsiness	Neuroglycopenic	16	Thirst	Autonomic
4	Weakness	Neuroglycopenic	17	Nausea	General Malaise
5	Dizziness	Neuroglycopenic	18	Anxiety	Autonomic
6	Feeling warm	Autonomic/Neurogly copenic	19	Tiredness	Neuroglycopenic
7	Difficulty speaking	Neuroglycopenic	20	Tingling	Autonomic
8	Pounding heart	Autonomic	21	Trembling	Autonomic
9	Impaired concentration	Neuroglycopenic	22	Headache	General Malaise
10	Shivering	Autonomic	23	Malaise	General Malaise
11	Unsteady	Neuroglycopenic	24	Irritability	Autonomic/Neuroglycop enic
12	Nonspecific awareness	Other	25	Other	Other
13	Double vision	Neuroglycopenic	26	None	No symptoms

3. Model For Patient Consistency

Following Zammitt et al. (2011), we model the intra-individual consistency using a logistic-type latent variable model. Latent variables are used to represent the propensity of symptoms and intensity of episodes as these cannot be observed directly and need to be estimated through observation of symptoms and episodes of hypoglycaemia.

To assess consistent reporting across episodes for each subject, we present the symptoms and episodes of the patient in a matrix form with $J \times K$ dimension, where J = number of symptoms and K = number of episodes. This is illustrated in Figure 1, where the frequency of a symptom reported by a patient represents the symptom's propensity and the intensity of an episode is represented by the number of symptoms occurring during that particular episode.

We consider the random indicator variable, $Y_{ijk} \sim Bernoulli(p_{ijk})$taking value 1 for patient i reporting symptom j at episode k (and 0 otherwise), where p_{ijk} is the corresponding probability of "success". Patient i reports symptom j at episode k when $h(\alpha_{ij},\beta_{ik})$ exceeds a random threshold assigned to each patient, where α_{ij} represents the propensity of symptom j for individual i, β_{ik} represents the intensity of episode k for individual $i$and $h()$ is an appropriate functional form. The propensity of a symptom refers to the tendency for a patient to report that particular symptom, whereas intensity of an episode corresponds to how intense the episode is, with more symptoms experienced in an episode implying higher intensity. The random threshold

assigned to each patient, denoted by τ_{ijk} is assumed to follow a log-normal distribution, i.e. $\tau_{ijk} \sim N(0, \sigma_i^2)$. Thus, the probability of patient i reporting symptom j in episode k, is given by

$$p_{ijk} = \Pr(\tau_{ijk} \leq h(\alpha_{ij}, \beta_{ik})) = \Phi\left(\frac{\log\{h(\alpha_{ij}, \beta_{ik})\}}{\sigma_i}\right)$$

where $\Phi()$ is the cumulative distribution function of a standard normal variable. Under a Bayesian framework, we also specify appropriate prior distributions for the model parameters α_{ij}, β_{ik} and σ_i. In this analysis, we assume independent priors for the latent variables with $\alpha_{ij} \sim Gamma(a_\alpha, b_\alpha)$ and $\beta_{ik} \sim Gamma(a_\beta, b_\beta)$ where $a_\alpha = a_\beta = 1$ and $b_\alpha = b_\beta = 0.1$. We also assign a relatively vague inverse-gamma prior distribution to the variance parameter, $\sigma_i^2 \sim Inv\text{-}Gamma(\gamma_\sigma, \delta_\sigma)$ for $i=1,\ldots,59$ where $\gamma_\sigma = 1$ and $\delta_\sigma = 0.1$.

Parameter σ_i measures the symptom-reporting consistency of a patient. A rescaled consistency parameter is used for easier interpretation, given as $c_i = 100/(1+\sigma_i^2)$ where $c_i \in (0,100]$. A large c_i value indicates high consistency. Note that for large c_i (small σ_i^2) the thresholds τ_{ijk} get highly concentrated around a value representing reporting of symptoms associated with latent symptom propensity α_{ij} and episode intensity β_{ik} such that $h(\alpha_{ij}, \beta_{ik}) > \tau^*_i$ with τ^*_i approaching a constant value as σ_i tends to zero.

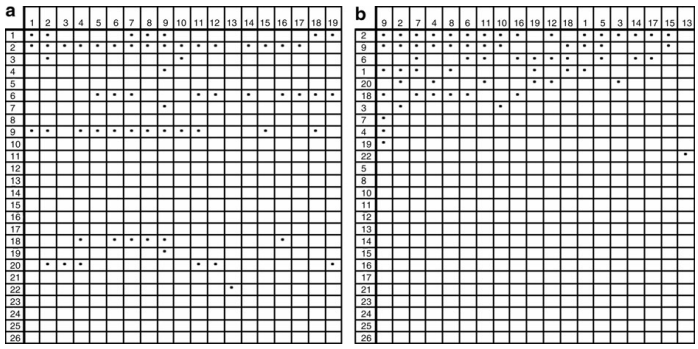

Figure 1: (a) Example of a $J \times K$ symptom matrix (J = number of symptoms; K = number of episodes) for subject 6010 with symptoms 1-26 listed vertically and hypoglycaemic episodes listed horizontally. Each reported symptom is marked with a square. (b) Rearrangement of the matrix rows and columns so that rows now appear according to frequency with which symptoms are experienced and columns according to the number of symptoms per episode (both following a descending order from the top-left corner)

We use a Bayesian approach (Berger, 1985) to estimate the posterior distribution of the unobserved latent factors and the variability of the thresholds. Posterior distributions of the latent variables are obtained using Markov chain Monte Carlo simulation techniques (Arminger and Muthen, 1998).

3.1 Thresholds in Model for Intra-Individual Consistency

In earlier work (Zammitt et al, 2011) a multiplicative threshold form $h(\alpha_{ij},\beta_{ik}) = \alpha_{ij}\beta_{ik}$ was assumed with individual *i*experiencing symptom *j* at episode *k* when $\tau_{ijk} \leq h(\alpha_{ij},\beta_{ik}) = \alpha_{ij}\beta_{ik}$. In this paper, we also explore two other different thresholds to fit to this model. They are: (i) $h(\alpha_{ij},\beta_{ik}) = \alpha_{ij} + \beta_i$, and (ii) $h(\alpha_{ij},\beta_{ik}) = \alpha_{ij} + \beta_{ik} + \alpha_{ij}\beta_{ik}$. The most appropriate threshold for the data in this analysis is chosen using the Deviance Information Criterion value of the corresponding model (Spiegelhalter et al., 2002).

3.2 Grouped Symptoms

To allow for an additional source of variation in the precision parameter, σ_i^{-2} we categorised the symptoms into six distinct groups, three of which are discussed earlier (autonomic, neuroglycopenic, and general malaise). The three additional groups are: "autonomic/neuroglycopenic" for symptoms that are debatable as to which category they belong; "other symptoms" for symptoms that were not specified by patients in the report form; and "no symptom" when patients reported hypoglycaemia without experiencing any particular symptom. The group categorisation is shown in Table 1. This categorisation provides us with an additional source of variation that may arise from inherent differences between symptoms in different groups.

To allow for group effects, the change made to the model presented in Section 3 relates to the prior for α_{ij} which corresponds to propensity of symptom *j* for patient *i*. Now, with each symptom being assigned to a specific group, we have α_{ijl} where l =1,…,6 indicates group, and we assume the following hierarchical prior:

$$\alpha_{ijl} \sim Gamma\left(\theta, \frac{\theta}{u_l}\right), l = 1, \ldots, 6$$

$$\text{giving } E\left(\alpha_{ijl}\right) = u_l, \text{ and } Var\left(\alpha_{ijl}\right) = \frac{u_l^2}{\theta}, l = 1, \ldots, 6$$

The prior for u_l is chosen to be relatively non-informative:

$u_l \sim Gamma(\alpha_{ul},\beta_{ul})$ with $\alpha_{ul}= 1$ and $\beta_{ul}= 1$. To facilitate the convergence of the MCMC algorithm, we set θ to 1, but a non-informative prior $\theta \sim Gamma(\alpha_\theta,\beta_\theta)$ may also be assumed.

3.3 Patient Consistency Results

Threshold $\tau_{ijk} \leq \alpha_{ij}\beta_{ik}$ gives the lowest DIC value (DIC = 29003.1) indicating that it is the most suitable threshold to fit the consistency model. Therefore, all results discussed here are based on this threshold. Analysing the episodes of hypoglycaemia with the symptoms being grouped gives slightly different consistency estimates for some of the subjects, as compared to the analysis in Zammitt et al (2011). With grouped symptoms, the consistency values estimated from this model range from 16.15 (subject 2013) to 95.35 (subject 1028) with standard deviation 2.055 and 2.407 respectively. The distribution of the mean consistency estimates under the two models is shown in Figure 2.

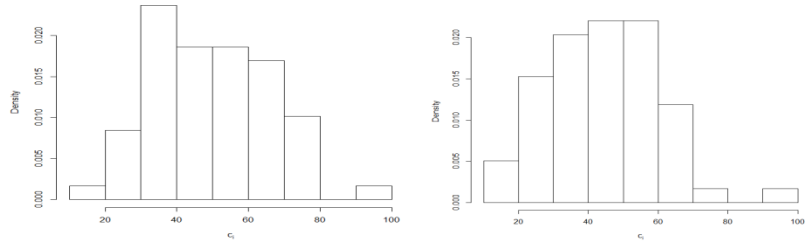

Figure 2: Histogram of estimated consistency parameter $\tilde{c}_i^2 = 100/(1+\sigma_i^2)$for model without grouped-symptoms (left), and for model with grouped-symptoms (right).

Figure 3 (Left) shows the ranking of patients' consistency with the grouped symptoms model (Section 3.2) versus their ranking with the model not using grouping (Section 3). Patients are ranked in descending order based on their consistency estimates starting from the highest estimates to the lowest. It is noticeable that a number of subjects have obvious changes in their ranking. Under the grouped symptoms model, patients 6018 and 5009 have increased consistency estimates (from low consistency rank 53 and 56, to higher rank 33 and 26 respectively). Similarly considerable changes are observed in patients' 4008 and 6002 ranking, while patient 6065 appears to move towards the opposite direction with the grouped-symptoms model resulting in lower consistency.

Figure 3 (Right) shows the posterior densities of mean propensity for each group,u_l. These densities demonstrate that groups have distinct propensity mean. The "No symptom" group shows highest variability since it is less frequently reported by patients in this study.

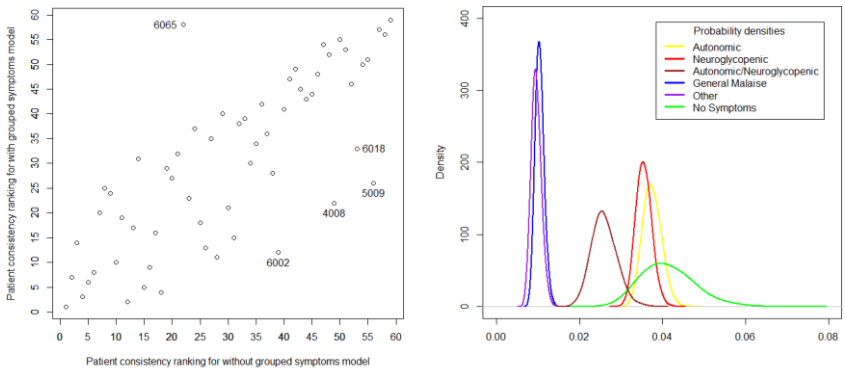

Figure 3: (Left) Graph shows descending order for ranking of consistency estimates, $\bar{c}_i$ of 59 patients for model with grouped symptoms versus model without grouped symptoms. (Right) Distributions of posterior group propensity, u_l

4. Association Between Consistency and Patient-Specific Covariates

We now investigate the effect of ten patient-specific covariates on patients' symptom reporting consistency. Zammit et al. (2011) explored the main effects of such covariates, and we extend this by also considering a number of interactions between them. The 10 covariates described in Section 2 are used in the analysis. Type of diabetes (1 or 2) and retinopathy (no retinopathy RET1, background retinopathy RET2 and proliferative retinopathy RET3) are considered as categorical while other covariates are in numerical form. Hypoglycaemiais measured on a scale 1 to 7, with higher scores corresponding to weaker awareness of hypoglycaemia.

Aiming to establish whether or not the effect on consistency of one factor is the same at all levels of other factors, we also consider the following possible interactions between covariates: interactions of gender with type of diabetes, duration, awareness, BMI, and retinopathy; interactions of C-peptide with duration and type of diabetes; interactions of awareness with age, duration, and type, and interaction between duration and retinopathy. These specific interactions were suggested as the most

meaningful combinations based on anecdotal evidence in the area. In a GLM setting we assume

$$\widetilde{w}_i \sim Gamma\left(\lambda, \frac{\lambda}{m_i}\right) \text{for} i = 1, \ldots, 59$$

so we have $E(\widetilde{w}_i) = m_i$ and $var(\widetilde{w}_i) = \frac{m_i^2}{\lambda}$. Parameter m_i is the mean consistency response and linked to all patient-specific covariates through function $m_i = exp(x_i^T, b)$ where i=1,2,…,I and $b = (b_0, b_1, \ldots, b_p)^T$ is a vector of coefficient corresponding to the vector of covariates $x_i^T = (1, x_{1,i}, x_{2,i}, \ldots, x_{p,i})$, as shown in detail in the linear predictor equation below:

$$\begin{aligned}
\log\{E(m_i)\} = b_0 &+ b_{gen}GEN_i + b_{age}AGE_i + b_{type}TYPE_i + b_{dur}DUR_i \\
&+ b_{ret1}RET1_i + b_{ret2}RET2_i + b_{ret3}RET3_i + b_{awar}AWAR_i \\
&+ b_{bmi}BMI_i + b_{cpep}CPEP_i + b_{hba}HBA_i + b_{ace}ACE_i \\
&+ b_{genXtype}(GEN.TYPE)_i + b_{genXdur}(GEN.DUR)_i \\
&+ b_{genXawar}(GEN.AWAR)_i + b_{genXbmi}(GEN.BMI)_i \\
&+ b_{cpepXdur}(CPEP.DUR)_i + b_{cpepXtype}(CPEP.TYPE)_i \\
&+ b_{awarXage}(AWAR.AGE)_i + b_{awarXdur}(AWAR.DUR)_i \\
&+ b_{awarXtype}(AWAR.TYPE)_i + b_{durXret1}(DUR.RET1)_i \\
&+ b_{durXret2}(DUR.RET2)_i + b_{durXret3}(DUR.RET3)_i \\
&+ b_{genXret1}(GEN.RET1)_i + b_{genXret2}(GEN.RET2)_i \\
&+ b_{genXret3}(GEN.RET3)_i
\end{aligned}$$

where GEN represents gender, DUR represents duration, RET1 represents no retinopathy, RET2 represents background retinopathy, RET3 represents proliferative retinopathy, AWAR represents awareness of hypoglycaemia, BMI represents body mass index, CPEP represents C-peptide, HBA represents haemoglobin A1c, and ACE represents angiotensin converting enzyme.

All b = 1,…,p are assumed to have normal distribution priors and the prior for λ is inverse-gamma:

$$b_p \sim Normal\left(\mu_{b_p}, \sigma_{b_p}\right) \text{where} \mu_{b_p} = 0,\ \sigma_{b_p} = 10^4$$
$$\lambda \sim Inverse - gamma(\gamma_\lambda, \delta_\lambda) \text{where}\ \gamma_\lambda = \delta_\lambda = 10^{-3}$$

4.1 Results on patients characteristics effects

Figure 4 summaries the Bayesian estimation for all coefficients in the model without grouped symptoms (left) and in the model with grouped symptoms (right). When symptoms are not grouped, the Bayesian intervals for b_{gen} and b_{awar} exclude zero indicating that these two covariates have significant effects on consistency. The estimate of b_{awar} is 0.1362 implying that subjects with lower awareness recorded lower variability in their symptoms than those with higher awareness. With grouped symptoms, gender is the only factor affecting consistency of symptom reporting (gender was coded as males = 0, females = 1). Female subjects appear to have lower consistency than their opposite gender, with b_{gen} = −0.7986 (95% Bayesian interval −1.264, −0.3354).

Examination on what effect covariates and their interactions have on consistency estimates (Figure 5) reveals that female subjects are less consistent than male subjects. Although the mean for gender coefficient was positive, b_{gen} = 0.7855 (95% BI 0.0894, 1.479), if we take into account the overall effect of gender, the consistency of female patients (mean = 0.6488, 95% BI 0.3325, 1.2761) is significantly lower than that of male patients (mean = 5.2331, 95% BI 2.2412, 12.025). The ratio of female to male consistency is 0.14 (95% BI 0.0449, 0.3366).

The posterior mean of the coefficients for type and age are b_{type} = −1.159 (95% BI −2.616,−1.0715) and b_{age} = 0.6291 (95% BI 0.1921, 1.1100) respectively, indicating that patients with diabetes Type 2 are less consistent than Type 1 patients (type was coded as type 1 = 0, type 2 = 1), and older subjects are more consistent than younger subjects. C-peptide is another factor that appears to have a systematic negative effect on consistency.

The analysis also suggests a number of significant interactions on the effect of patient characteristics on their symptom consistency. These include the interactions of awareness with age, duration and type, meaning that when patients with different level of awareness have different profiles regarding age, duration or type of diabetes, their consistency when reporting hypoglycaemia symptoms vary. The mean of the coefficient for interaction between awareness and type of diabetes is $b_{awarXtype}$ = 0.8105 suggesting that as the awareness score increases (implying impaired awareness), diabetes Type 1 patients have lower consistency while for patients with diabetes Type 2, consistency increases as awareness score increases.

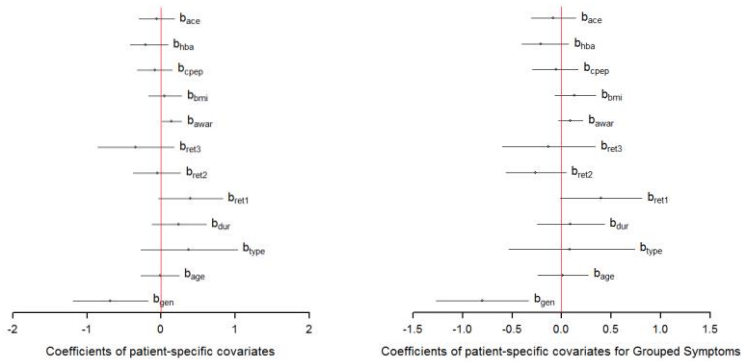

Figure 4: Posterior means (bullets) and 95% equal-tailed Bayesian intervals (bars) for standardised coefficients of patients-specific covariates for model without grouped-symptoms (left); and for model with grouped-symptoms (right).

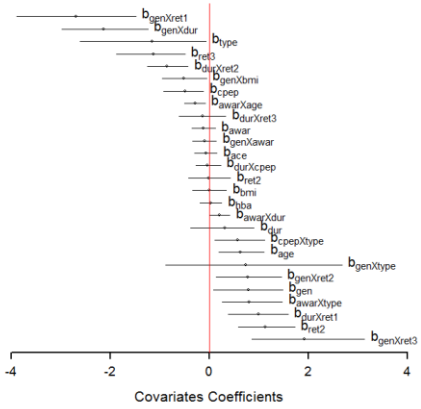

Figure 5: Posterior means (bullets) and 95% equal-tailed Bayesian intervals (bars) for standardised coefficients of patient-specific covariates and their interaction terms for model without groupedsymptoms.

5. Predictive Model

We apply variable selection through stepwise regression to determine which covariates are important and should be included in a predictive model. Stepwise regression will add or remove one variable at a time, given that the variable meets a selection criterion for entry or removal, until a stable set is obtained. The selection criterion used in this analysis is the Deviance Information Criterion (DIC). To run the procedure, we incorporate a binary vector $\gamma = (\gamma_1, \gamma_2,\ldots,\gamma_p)$, where p is number of covariates, to the linear predictor. We have $w_i = \sigma_i^{-2}$ and

$$w_i \sim Gamma\left(\lambda, \frac{\lambda}{m_i}\right), \quad \text{for } i = 1, \ldots, 59$$
$$\log(m_i) = \beta_0 + \beta_1\gamma_1 X_1 + \beta_2\gamma_2 X_2 + \cdots + \beta_p\gamma_p X_p.$$

In each step, we fit p models and estimate DIC values. The procedure is terminated when the selected model is the same as the one indicated in the previous cycle of procedure (Ntzoufras, 2011).

5.1 Variable selection results

Stepwise regression for the model without grouped-symptoms containing ten covariates gives a predictive model which includes covariates gender, retinopathy, duration, haemoglobin A1c, and awareness of hypoglycaemia (DIC=151.40). When we also consider interactions between covariates, the best predictive model (DIC=134.213) includes covariates gender, duration of diabetes, retinopathy, C-peptide, haemoglobin A1c and awareness,and interactions between gender × duration, gender × awareness, gender × retinopathy, C-peptide × duration, C-peptide × type, awareness × type, and awareness × duration.

6. Conclusions

The analysis in this paper extends previous research on individual consistency of hypoglycaemic symptom reporting by considering different functional forms of symptom experiencing thresholds, allowing for additional variation arising from grouping of symptoms, and performing variable selection to determine a predictive model for the effect of patient characteristics and their interactions on symptom consistency. Although this is not a large-scale study, the results provide useful insight on the consistency of individuals when reporting hypoglycaemic symptoms throughout a series of episodes.

Our work shows that a multiplicative form of symptom propensity and episode intensity provides the most suitable symptom experiencing threshold for the data in this study. Allowing additional variation in the model, by considering symptoms grouped in six categories based mainly on their physiological features, reveals that groups of symptoms show distinct propensity and that subjects' gender has significant impact on the consistency of symptom reporting. This agrees with earlier findings where gender and awareness appear to significantly affect symptom variability.

Variable selection was performed on the model without grouped symptoms model, since this appeared to fit the data better, based on a lower DIC value. When we consider the interactions between covariates, the variable selection results suggest that gender, C-peptide and retinopathy which are statistically significant characteristics should be in our predictive model. The predictive model also includes interactions between gender and duration, awareness and retinopathy.

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