Reviewer’s report

Title: A semi-parametric mixed models for longitudinally measured fasting blood sugar level of adult diabetic patients

Version: 0 Date: 10 Aug 2018

Reviewer: Abbas Bahrampour

Reviewer's report:

The manuscript analyzed the fasting glucose data over 27 months follow-up for diabetic patients using linear mixed models with random intercepts and slopes and quadratic terms as well as semi-parametric spline models where the spline coefficients are also random. I have the following comments -

1. What is the optimization criterion in estimating the penalized splines? How are the random coefficients for the splines estimated? Please give explicit formula instead of the names of the package (gamm/glimmix) which includes tons of options and we don't know exactly what you did.

2. Page 7, "Assuming the vector of contrasts have approximately multivariate distributions with mean vector 0 and variance-covariance matrix (C'R-1C+B)-1" Do you have proof for the multivariate normal distribution?

3. Model Selection: The -2logL of M4 cannot be found in Table 4. More importantly, the decrease in -2logL from 50542.51 in M3 to 50538.54 in M5 is trivial given the sample size of 534. The choice of penalized spline model is not justifiable. Especially when parameter estimates are similar, it is natural to choose the simpler model. Not sure why when the spline coefficients are all zero or variance of b_1 is zero, the splines reduce to the quadratic term with random coefficients. Also the mixed chi-square distribution for sigma_b2 square is based on the normal assumption of sigma_b2_hat/estimate, which is not proved.

4. What kind of improvement do the terms with the random effects (random intercept, random slopes, random quadratic, random spline coefficients, et cl) provide in terms of clinical interpretation or prediction? I totally don't see the value of the much more complicated models for clinicians.
Are the methods appropriate and well described?  
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?  
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?  
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Yes

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I am able to assess the statistics

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