**SDI Review Form 1.6**

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| Journal Name: | Asian Journal of Probability and Statistics |
| Manuscript Number: | **Ms_AJPAS_44107** |
| Title of the Manuscript: | **Computational Generalization of Mixed Models on Large-Scale Data with Applications to Genetic Studies** |
| Type of the Article | **Original Research Article** |

**General guideline for Peer Review process:**

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty'**, provided the manuscript is scientifically robust and technically sound.
To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(http://www.sciencedomain.org/page.php?id=sdi-general-editorial-policy#Peer-Review-Guideline)

**PART 1: Review Comments**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
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| **Compulsory** REVISION comments | | The abstract has been written as per the reviewer's comment and results discussed |
| **Minor** REVISION comments | L24: (LMM) in singular<br>L28: please check if Z is in majuscule or miniscule like the formula!!!<br>L29: similarly, you have to correct the letter "u" with the symbol "μ" like the formula!!!<br>L30: in the reference of "Golan and Rosset", date (year) is needed. Also, please add a space after "et al.,"<br>L33: add a comma and space after "Thompson"<br>L65: Linkage disequilibrium (LD). Why did you put this full stop (point), it is not a sentence? Does it a title of a new subsection?!! If not, it is better to write "Linkage disequilibrium (LD) is defined as.."<br>L67: I guess that "Heritability" is a title of a new subsection, please check and if so put it in a new line!!<br>L70: the closed parenthesis in ($\sigma_P^2$) should not be in superscript!! Please correct it.<br>L71: please rewrite the formula with P, G and e (miniscule letter) in subscript and 2 in superscript.<br>L76: is defined as<br>L78: please put a point after "variance" instead of a comma, and put the formula with its number (1.2.2) in a new line.<br>L79: I guess that "Genotypes-Phenotypes" is a title of a new subsection, please check and if so put it in a new line!!<br>L82-83: year is needed in the reference of "Golan and Rosset"<br>Footnotes of Page 2 (definitions): please start all sentences with capital letters and put a full stop (point) at the end of each sentence. Thanks.<br>L92: the symbol "ϵ" is needed before "$_{ij}$" to define the sum of random environmental factors affecting animal *i* as "$\epsilon_{ij}$" according to the formula (1.2.3)<br>L92-93: please put "Single Nucleotide Polymorphisms (SNPs)" in a new line, I guess that is the title of a new subsection!!<br>L93: SNP (remove the miniscule letter "s" referring to a plural, it is not the case here)<br>L94: "Lääperi", please correct this author name in the whole text even in the references list!<br>L109: add a space after "with"<br>L111: add a space after "into"<br>L123: please put "Genome wide association studies (GWAS)" in a new line, I guess that is | All the mentioned corrections have been corrected as per the reviewer's comments |

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| | the title of a new subsection!!<br>Figure 1.3: please mention (a) and (b) in the figure as it is mentioned in the title. Also, try to check the sentence after “step 2”: information, not extracted for case and control (remove the point and “mation”) and please rephrase it...<br>L156: it is difficult to<br>L158: remove the space between the closed parenthesis of the reference (Frazer et al., 2009) and the point.<br>L163: please put “Genetic relatedness (kinship) matrix” in a new line, I guess that is the title of a new subsection!!<br>L178: (Kang et al., 2008; Kang et al., 2010)<br>L186: please remove this title it is already written after<br>L190: please put “The statistical method currently used in LMM” in a new line, I guess that is the title of a new subsection!!<br>L192: year is needed in the reference of “Golan and Rosset”<br>L208: remove one “of”<br>L210: assume<br>L225-226: please remove the “Section 1.4. Current Challenges in Mixed Models in GWAS”<br>L232: please identify the abbreviation of “GRM” in its first call in the text, then you could use just the abbreviation in the text.<br>L260-261: please remove the “Section 1.4. Current Challenges in Mixed Models in GWAS”<br>L279-280: (Guo and Hankey, 2009; Fusi et al., 2014).<br>L305: rephrase the sentence beginning from “Loh et al. (2015)...efficient ???), it is not clear the idea, sentence must to be continued!!!!<br>L306: contain<br>L316: please rewrite the formula (2.1.1) correctly because X and β are not clear<br>L318: q × 1 vector of random (remove “is” after “1”)<br>L319: please add “ϵ”: “and ϵ is the error vector.”<br>L232: within cluster (add a space to separate the two words)<br>L325: please add “ϵ”: the vectors u and ϵ are also....<br>L334: 12 ????<br>L339: vector u and what???<br>L345: 2.1.1??? please check the number of the section, we could not move from 1.4.6 to 2.1.1. Where are the section 2 and section 2.1 ???<br>L347: put a point instead of a comma to have (2.1.1).<br>L350: please write the “y” letter in majuscule according to the formula (2.1.5)<br>L351: please check the number of the section 2.2.<br>L358: remove one “the”<br>L362: please check $W^0$ or W’ (as in the formula 2.2.2)?<br>L364: please rewrite correctly the formula (2.2.3), some terms are not clear<br>L365: maximize<br>L366: equation<br>L368: try to put exactly the ^ on β symbol, not close!!<br>L369: please rewrite correctly the formula (2.2.5), some terms are not clear<br>L370: please check the number of the section 2.2.1<br>L374: remove “the” after “how”: how to obtain....<br>L393: please try to put β correctly in the formula!!<br>L401: add “and” before TASSEL<br>L403: please check the number of the section 2.2.2<br>L421-425: please rewrite it correctly !!<br>L439: please check the number of the section 2.3<br>L443: please rewrite correctly the formula (2.3.1), some terms are not clear<br>L446: please add “ϵ”: and ϵ is....<br>L451: equation<br>Footnote of page 12 ($^8$ Handy-Weinberg principle states...)<br>L459: Please check $r_i$ or $r_{ij}$?<br>L465: and TASSEL | |

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| | L466: please check the number of the section 2.3.1<br>L481: please check the number of the section 2.3.2<br>L489: please rewrite correctly the formula (2.3.2), some terms are not clear<br>L492: please add a comma after SNPs<br>L493: please add “ϵ”: and ϵ is the error term.<br>L502: please rewrite correctly the formula (2.3.3), some terms are not clear<br>L505: remove the comma just before “=” and put it in the end of the line just before<br>L507: equation<br>L510: please try to put “β” correctly in the formula (2.3.4)<br>L517: please try to put “β” correctly in the formula<br>L522: add follow the line L521 in presenting the terms with adding a space before “at” to have “at causal...” together, similarly put $\Lambda_{mean}$ in the beginning of the line.<br>L527: and TASSEL<br>L528: please check the number of the section 2.3.3<br>L529: equation<br>L529-531: please rewrite correctly the formula (2.3.5 and 2.3.6), some terms are not clear and put their numbers correctly close them<br>L533: please rewrite correctly the formula (2.3.7), some terms are not clear<br>L536: is defined by<br>L538: please rewrite correctly the formula, some terms are not clear<br>L540-542: please try to reorganize your writing of the formula!!!<br>L544: remove space after ”tools”<br>L551: I guess that “Causal markers” should be in the first column ($M_c$) of the “Type of markers”, please check and correct it!!<br>L554: please check the number of the section 2.3.4<br>L554-555: put “Table 2.2:...” in a new line<br>Table 2.2: Approach (not all the word in majuscule letters)<br>L556-558: please define also “BAYES” as you have done for “ST” and “LRT”!!!<br>L568: According to...<br>L584: complete linkage<br>L587: identical-by-state<br>L598: at stage 2<br>L602: consist of a total...<br>L607: add a space after “0,” in order to have “1” as a numeric score apart !!<br>L622: remove one “component”<br>L630: the presence<br>L636: presence<br>L642: Results and discussion, until discussion section does not figure in the manuscript, also you should discuss more your results and compare them with others recent studies!!!<br>L647: significant<br>L648: equation<br>L652: move (3.4) to the line 651 after “Table”<br>L653-654: please put the lines of the Table 3.1 at the same level (particularly the two first lines)<br>Please remove “References” from the header of the pages 20, 21, 22, 23 and 24<br>Why the text lines are not numbered from the page 20????!!!<br>Table 3.2: please include a key after this table defining the CHR and BP abbreviations...<br>The paragraph after the Table 3.2: equation 1.2.2<br>Table 3.3: Summary<br>The 3rd line in the Table 3.3: write the ratio correctly, some terms are not clear!!!<br>Paragraph after the Table 3.3: The gray line represents....<br>Paragraph after the Figure 3.2: In addition,....suggests the presence of.....<br>(adjusted genetic association): remove the space before the closed parenthesis<br>Key of the Table 3.4: please include in this key, the definition of CHR abbreviation...<br>Conclusion: “no presence” instead of “no presences”, in the last paragraph: ...to assess...which poses.... | |

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| | Please try to shorten the conclusion, it is too long and includes results that have already shown and discussed before, so don't repeat what you have said in the previous sections, just a brief summary with perspectives, and in conclusion section, you should not include call for figures or tables!!!!<br>Please check if all references cited in the list are cited in the text and vice versa!!! Thanks.<br>References: write correctly « García-Cortés » instead of "Garc´ıa-Cort´es" and this reference is not cited in the text!!!<br>This reference « D. Golan and S. Rosset. Mixed models for case-control genome-wide association studies: Major challenges and partial solutions » is not written correctly according to the guidelines of the Journal, many details are needed such as year of publication, journal…. | |
| **Optional/General** comments | Well carried out study. Tables and figures essential to understanding the work are given. However, authors have to pay attention when writing the equations because some terms are not clear!!!<br>Also, there is a mixture of American and British English spelling in the whole manuscript, please let all manuscript text be written in only one English spelling!!! For example, some time authors write "to analyze" in L13 (American English), and some others "analysing" in L266 and L570, "to analyse" in L544, "we analyse" in L601 and "analysed" in Conclusion, which are British English spelling words. Others words should be checked (e.g. Generalization in the Title, generalized in L50, recognized in L293, maximizes L365, L367, L394, normalizing in L454, summarised in L178 and L480, to visualize in L582...). So please choose one English spelling in your manuscript, do not mixture between them. | The spelling mistakes and equations have been corrected as per the reviewer's comments |

**PART 2:**

| | **Reviewer's comment** | **Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)* |
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| **Are there ethical issues in this manuscript?** | *(If yes, Kindly please write down the ethical issues here in details)* | No ethical issues because the data used was secondary data |