**Required Minor Corrections**

1. **Abstract**: Include an abstract that succinctly summarises the objectives, methodologies, contributions, and key findings of the thesis.
2. **Formatting**: Ensure consistent formatting throughout the document, including chapter headings, subheadings, and figure/table captions.
3. **Language Consistency and Proofreading**:
    - Review the thesis for language consistency, ensuring that English spelling and grammar are used uniformly. There were too many for me to annotate or highlight hence I recommend a thorough proof-reading.
    - Correct typographical errors and grammatical issues.
    - Ensure technical terms and abbreviations are consistently used and defined when first introduced.
4. **Chapter Organisation**: Ensure that each chapter begins on a new page and that transitions between sections are clear and logical.

1. **Generic Questions:**

   a. Briefly talk about the work you have done in this thesis with clear reference to your own original contributions to the field of knowledge.

   b. What motivated you to work on this area of Bio-Medical Engineering? What was that key motivational factor that prompted you to look into this area? What the basis or rationale to develop the algorithmic frameworks you have reported in this thesis. How and why did you arrive at the various variants and models you have presented?

   c. What in your view is/are key reference(s) that marked the turning point in the research in this area and how does your own work compare with this/these contribution(s)?

   d. What are other possible directions and/or applications of this work that you or others can take up in continuation of the work that is reported in the thesis?

2. **Specific Questions:**

a) **Inter-Spectral Relationships and Machine Learning Models**: Can you elaborate on how your machine learning models capture and utilise inter-spectral relationships in MRS data? How do these relationships improve the accuracy of biomarker quantitation compared to traditional curve-fitting methods?

b) **Wavelet-Based Denoising Techniques**: You utilised wavelet transform for multi-scale decomposition and noise removal. Could you explain the specific advantages of wavelet-based denoising over other signal processing techniques in the context of MR spectra?

c) **Macromolecular Baseline Isolation**: Your thesis discusses the challenge of macromolecular baseline overlap. How does your gradient-boosted regression tree ensemble model isolate macromolecular spectra, and what were the key findings in terms of model performance and robustness?

d) **Clinical Application and Future Directions**: Considering the clinical application of your research, what are the potential impacts on diagnostic processes in hospitals? Additionally, what future developments or improvements do you foresee in post-acquisition MRS analysis using advanced machine learning techniques?

Examiner – II

Chapter 1:

This chapter and the thesis as a whole need thorough copyediting. Some of them are pointed below but, there are many such. The scholar needs to go through the thesis carefully.

Page 2: Static magnetic field is referred as $B_0$ (in italic) in equation but not so in text description where it is $B_0$.

Page 3: $M_z$ in equation becomes $M_z$ in text, $M_{xy}$ in equation becomes $M_{xy}$ in text and so on.

Please address such issues in this chapter and in other places of the thesis.

Page 3: T1 and T2 in text should be $T_1$ and $T_2$ as per equation and description at a different place of the thesis e.g. Page 10.

Page 3: Regarding "…and the transverse and longitudinal magnetization were given as …", a diagram with appropriate labelling will make it clearer on what is conveyed here.

Page 3: Regarding "… Hydrogen/Proton (1H), Carbon (13C), Sodium (23Na), and Phosphorous (31P) are prominent []", reference is missing within the square bracket.

Page 4: Regarding "The difference in these resonant frequencies is termed as 'Chemical Shift' [] and", reference is missing within the square bracket.

Please address such issues in this chapter and in other places of the thesis.

Page 4: The equation defining $f_{ppm}$ needs a number. This equation seems to be different from the one given in the reference quoted in this context. That gives chemical shift as,

$$f_{ppm} = (f_{sample} - f_{reference}) \times 10^6 / f_{reference}$$

for which $f_{ppmreference} = 0$ after substitution. This aspect may be looked into.

Page 5: Figure 1.1: What is the source of the data used for plotting these? What are $x$ and $y$ axis? How is fourier transform computed? Assuming $x$-axis of right figure to be frequency, will it not be symmetric about 0 frequency?

Page 9: "ml" abbreviation is used before it is defined few lines later. Please check such issues throughout the thesis.

Page 12: Regarding, "... creating models which are able to learn [***]", it is not clear what is conveyed here using triple star.

Chapter 2

Page 14: There is a mix-up of fonts within equation (1) which needs correction. This equation can be numbered 2.1 following the convention used in Chapter 3 where the first equation is numbered 3.1.

Page 14: $f_k$ is correctly scripted in the text but, $d_k$ is not italicised.

Page 15: $B(t)$ should be corrected as $B(t)$ and similarly other such cases.

Page 15: Regarding "Mathematically, it can be represented as a parametric linear combination model given by" a reference can be provided.

Page 15: Equation (1) is defined one page before in Page 14. It cannot be redefined here. Numbering of equations needs to be properly done.

Page 15: Regarding "$A,B,\varphi,d,f$ are amplitude, phase-shift, damping, and frequency shift of $k^{th}$ metabolite and $m^{th}$ macromolecular component ..", one of the five terms is not defined and "respectively" should be used for defining sequentially. Also, these terms should have appropriate suffix as the definition talks about $k^{th}$ and $m^{th}$.

Page 16: The convention is to use "L1" and "L2" for norms and not "l1" and "l2".

Page 28: Figure 2.1: Regarding "DL Model", DL is not defined before as Deep Learning. There is a reference to ReLU abbreviation before but not that of "relu". There is a mix up of x and X. X is added as F(x) + x. Further, in this figure, X becomes F(x) after 1st weight layer but, there is no change to F(x) when it passes through 2nd weight layer! Why so? It is not clear how "relu" block contributes being alongside the arrow direction.

Page 33: Table 2.1: It is difficult to read a Table which is spread over more than a page in which column headings do not appear in subsequent pages . There is enough scope of making the Table compact by decreasing line space and categorizing the references.

x and y axis
will it not

Chapter 3

Page 38: Fig. 3.1. Font size used inside the figure is too small to read. Instead of two columns, two figures can be placed in two rows. In previous chapter "Figure" was used and not "Fig.". The same convention should be continued with for this and other figures of this chapter.

Page 39: Equation (3.1): There is mix up of fonts. The reference for this equation is missing.

Page 39: Fig. 3.2: Non-uniform fonts in titles and non-uniform boundaries need correction. It is not readable what is written at bottom of Fig.3.2(b).

Page 40: Is it $L_{pq}$ as in equation or $\mathbf{L_{p,q}}$ as in text? Why bold? Mathematical symbols in text needs to be italic.

Page 40: After Equation 3.1 comes 3.2a and then 3.3b? Why are not they simply 3.2 and 3.3?

Page 41: What is "gradient \"?

Page 43: "The method proposed by Srivastava et al" needs a reference number.

Page 44: Regarding "A of each detailed coefficient level is calculated and for level having A > 0.1, the decomposition level is selected", is there any reason for this choice of 0.1? Is it from grid search, energy consideration or any other consideration?

Page 44: "$\alpha_j$ is the level-dependent parameter to adjust threshold values". Is there any specific reason or hypothesis behind this and the way it is defined in equation 3.6?

Page 45-46: Wherefrom the MRS dataset was obtained? It appears that it is not a publicly available dataset since no reference was given. For the uncorrupted 249 – 8 = 241 signals, how many were from normal and how many from tumour? It is mentioned for whole 249 as 211 normal and 38 tumour.

Page 46: Regarding "present method is also applied to the signals acquired from the Raman spectroscopy data bank", details about the databank is needed, including reference.

Page 46: What are $N$, $x_i$ and $\tilde{x}$ in equation 3.8? After equation 3.9, it is written, "In (9) and (10), $x_i$ is the original signal and $\tilde{x}$ is the reconstructed signal after denoising." Wherefrom (9) and (10) come? Assuming these definitions of $x_i$ and $\tilde{x}$ hold true for equation 3.8 and 3.9 then why is there no subscript $i$ for $\tilde{x}$ ? Next, in equation 3.8 denominator, $(x_i - \tilde{x})$ appears to represents noise. Is it reconstruction noise? Is there a different formula used for SNR calculation when noise (e.g. additive white Gaussian noise) is added to the signal?

Page 47: Are the corrupted signals used in this study? It seems so as all 249 MRS signals are considered. Will it affect the conclusion?

Page 48: Regarding "Figure 3 (a-d) clearly shows that the present method can remove the echo component more effectively compared to the other methods." it can be commented if there is an possibility of a nearby valid peak getting suppressed.

Page 49: In Table 3.2, for DDDT-DWT, SNR shows improvement but RMSE and SSIM deteriorate. Is it expected?

Page 49: Regarding "The complete dataset of 219 MR signals was used in this study" there is more confusion. Is it a subset of original dataset? If so, which subset and why? Or is it a typo error? If it is 249 then why 8 corrupted signals were said to be not used?

Page 49: Regarding "In the following table, the mean amplitude of 38 signals with the tumor cases has been shown", there is no such table presented after this. Also, a table number can be used to avoid such disconnect.

Page 50-51: Figure and figure caption should be presented together in one page.

Page 51: It is mentioned, "For this study, denoising was performed on the complete dataset of 219 signals (7 spurious echoes containing signals as well)." The number 219 came again in presentation of result. In page 52, it is mentioned, "The calculated standard deviations of these indices for 219 signals are …" Was then the database size of 249 mentioned in the description of database wrong?

Chapter 4

Page 56: Regarding "Distinct baseline spectra were simulated by summing individual macromolecule peak of Voigt lineshape generated using parameters given in Table 1." there is no Table 1. There is a Table 4.1 six pages later which should be close to where it is referred first. That table can be compacted to fit into one page. Also, some description of Voight lineshape and its generation can be given as it is an important part of simulated data generation and on which results are presented. Later, in equation 4.1b, Gaussian basis is used for macromolecular components – are these two related?

Page 57: Presentation of mathematical symbols needs a careful check. Regarding "$A,B,\varphi,d,f$ are amplitude, phase-shift, damping, and frequency shift of $k^{th}$ metabolite and $m^{th}$ macromolecular component ..", one of the five terms is not defined and "respectively" should be used for defining sequentially. Also, these terms should have appropriate suffix as the definition talks about $k^{th}$ and $m^{th}$.

Page 59: Bold mathematical variable has a different use which does not seem to fit here. Please look into. Text description of mathematical representations needs correction as before.

Page 60: Regarding "Variation in individual MM components, with amplitude range in ±15%, and linewidth within ±20% range", was there any statistical method followed? How was it varied?

Page 63: Regarding "A set of 500 spectra was generated by varying overall linewidths and noise content of the spectra using method as described in steps 3 and 4." where are steps 3 and 4? Regarding "to create a regression model for spectral fitting (Figure 2)", there is no Figure 2 – is it Fig. 4.2?

Page 63: Regarding "Secondly, to encapsulate local variabilities, we took inspiration from traditional window-based time-series methods" a reference can be given and the method can be described in brief since it constitutes an important part of the model development.

Page 65: Regarding Fig. 4.2 model, when validation data / test data is sent, is ground truth sent alongside? Is that appropriate? What is the data flow for a validation / test data?

Page 67: Table 4.3 should not be split into two pages. Same is suggested for Table 4.4 appearing in Page 70.

Chapter 5

Page 80: Step 9: Is random noise added to ground truth too which is a simulated data?

Page 84: It is not clear what is meant by "it was trained in a supervised manner with simulated degraded training data set and concatenated ground truth metabolite-MM spectra as validation and test sets." Why ground truth will be considered as validation / test data?

Page 88: Why 70/15/15 ratio was not considered like before? Why noisy spectra were not considered?

Page 91: The plots presented here needs discussion.

Chapter 6 and 7

They can be combined with Future Scope coming as a section. This will avoid a one page Chapter 7 as in Page 101 where "Chapter highlights" has no content.