Dear Dr. Naylor and Professor Andersson-Engels,

Thank you for reviewing and providing comments for my PhD thesis titled “Detection of joint inflammation in rheumatoid arthritis using multispectral diffuse optical imaging”. I would like to thank both reviewers for taking the time to review the work and thank them for their highly constructive comments. I have addressed these specific queries below and made the appropriate changes within the revised document, with any substantial changes highlighted in red below. I have also made a number of spelling / grammatical corrections throughout the revised version, including those highlighted either in part 4 or annotated in the provided thesis copies.

* List of acronyms and abbreviations is needed (list of figures and tables exists, but not acronyms)

*This has been included with the corresponding acronyms updated throughout for clarity to the reader.*

* Consider removing all acronyms from the abstract and from the conclusion chapter to make the thesis easier to browse.

*Yes I agree and these sections have been altered accordingly.*

* It would be great if you could give a few sentences about the contributions in developing the Lambert-Bouguer Law and Beer-Lambert Law

*Thank you,*

* Please clarify that you mean elastic scattering when you talk about Rayleigh-type scattering

Elastic scattering, Mie where particle greater than wavelength greater than

* Provide a short discussion that your reconstruction is objective in terms of algorithm and initial conditions.

*The following has been added to highlight this point. Chosen the same for consistency during recontruction.*

“These initial conditions and reconstruction parameters we the same for all participants, making the algorithm objective in the sense that all processing was carried out in an automated fashion to produce quantitative image maps that if repeated by multiple users would produce identical outcomes.” Data filtering?

Elements of acquisition were subjective including the joint positioning, image mask definition.

* Correct Figure 3.4(b)

*This figure has been removed, as the data was not correctly calibrated for at the time and its removal is not significantly detrimental to the work.*

* Please explain Eq.5.1 better

*This has been corrected to include the subtraction of the mean, to allow the variance to be accounted for.*

* In the patient chapter you tested many ways to analyse the data in a relatively small data set. I would have preferred you tested all techniques on one dataset and then evaluated on a completely independent set. Please add a small discussion on this.

*The reviewer is correctly identifying the risk of over-fitting for a large number of parameters with the relatively small data set*

“AUC values from ROC analysis provided a degree of inference about the discriminatory values over a range of . Due to the relatively , in future work with this larger cohort of patients, the data should be partitioned appropriately in a machine learning framework, such that a training data set is used to establish optimum thresholds, an independent testing sample partition used and validation sets, with t, to more rigorously test the generalisation of the reported diagnostic accuracies.”

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Comments written from internal examiner

* On request, a number of Figure 1.3 has been reorientated to be made more clear, and a number of Figure captions have been expanded upon in more detail, including Figures 1.1, 1.3, 1.6, 2.7 and Table 1.2
* Format of all references have been standardised to initials only.

Comments written from external examiner

* Pg 20 with decay constant µa known as the absorption coefficient having units mm-1, commonly chosen as such within the literature in place of their SI unit equivalent as they provide a sensible numerical scaling of values.
* Pg 23 Importantly, when bound to oxygen molecules at up to four potential binding sites,
* Pg 26 The later has been commonly implemented in joint imaging, presumably as it should provide a better dynamic range for this application as a result of a smaller variation in the pathlength when considering source-detector pairs for an array of detectors on an opposing boundary of a cylindrical-like object when compared to reflectance mode, when sources and detectors are placed on a common boundary.
* Pg 29 Discuss limits of DA
* Pg 34 Through optimising a wavelength set selecting a combination that simultaneously minimise $\kappa$ and maximumise \textit{R},

To DO:

Comments from Amy Fig 2.12

Expand Fig3.7

Explain 5.6 better

Correct table 5.1

Label 6.16

We hope we have addressed all issues raised by the reviewers and we would like to thank them again for their constructive comments.

Yours faithfully,

Daniel Lighter (on behalf of all authors)