Reviewers' Comments:

Reviewer: 1

Comments to the Author
In this study, the authors have utilized deep learning method to translate H&E images to generate fibrosis map image. Despite interest of the idea, as mentioned by the authors the topic is studied previously and the novelty of the proposed study is not clarified. Also, Mason's trichrome images are used to evaluate the fibrosis tissue evaluation, yet H&E images are used as gold standard which is not judged. Also, it's not clear how the ground-truth images are generated from histology images. Also, the model development and processing steps should be detailed for allowing replication of the results.
1. Please revise the statement expressing the work of Li et al in the second paragraph of page 2.
2. Despite examples of the development of image-to-image translation of pathological data, the physical characteristic of the underlying mechanism is not able to be predicted accurately. Therefore, the acceptance of the learning-based models for generating pathological images will be theoretical. Therefore, "leading to the advent of digital pathology" is a very strong claim without citation of the well-established article.
3. You should use digital not digitalized images for citing the histological images.
4. Please revised the following phrase "standard H&E-stained tissues". Is there any specific H&E staining procedures that you would like to emphasize?
5. Please revise the first statement of the hypothesis paragraph.
6. Please define the abbreviations at first use.
7. Please revise the second statement of section II. A for potential language-related issue.
8. Please clarify "60 cores" from 36 cases. Do you mean 60 histology images from 36 different patients?
9. The following statement is not part of the methods section and is not supported with any evidence, "The network's inclusion of skip connections (Fig. 1C) significantly increased the training accuracy and efficiency."
10. Please express the collagen parameters
11. For a set of 60 samples, 20 neighbors seems to be an extreme value. Have you evaluated the distribution of the feature map?
12. You can describe the ratio of fibrosis versus the whole area within the text, please consider removing the formula.
13. Also, you didn't clarify the need for the dispersion parameter.
14. Please clarify "computationally translated images"
15. The resolution of the histology images are not providing sufficient details for evaluation of the steps.
16. Please revise the first sentence of the second paragraph in page 5. It seems that you used similar statement like the fig 3.
17. Please avoid using subjective terms for assessment of the quality of the results. What was the evaluation criteria thresholds for SSIM e.g. for excellent, good, or bad?
18. Although you claim that Fig 3D shows statistical similarity for the fibrosis orientation, the figure doesn't clearly support it. It just shows that both measurements are similar. However, the overlap of the predicted vs true should be utilized.
19. Also, you're mis-referenced to sub-figures within the manuscript. Please correct it.
20. Again, do you have a quantitative metric for the assessment of bland-altman plot outcome?
21. Please describe Fig 3H. Also, fiber orientation maps visually differ in 3F and G. Assuming this one is the best among 60 samples, the quality of the outcome is concerning.
22. Could you please share the in-plane resolution of the histology images?
23. On page 5, the right column needs your attention which is mis-citing the figure, incomplete statement.
24. Please discuss the need for comparison of fibrosis percentage of the different subject groups and alignment with the hypothesis of the study.
25. the first two sentences of the first paragraph in the right column on page 6 are not part of the results. Please consider moving it.
26. Again, the resolution of the figures is not reasonable. Please correct them.
27. Please check the font of Table 1.
28. Could you please clarify the need for discussing stellate cells in this study?
29. H&E images are very standard in the pathology labs and mostly performed automatically in which similar staining patterns are expected. Also, the straining normalization is not proposed by the recent study and the discussion of this problem here will be confusing the readers.
30. Please revise the following statement for clarity, "The collagen image translated using CNN are capable of detecting the changes in the architecture of the collagen network."
31. Similarly, the following statement please "The collagen image translated using CNN is capable of detecting the changes in the architecture of the collagen network."
32. Despite the disadvantages of the SHG imaging, you used it as ground truth for the fibrosis maps which is also confusing. Please discuss it.
33. The paragraph discussing fibrosis alignment reads as if to be part of the introduction section. Please check it.
34. Could you please clarify the need for discussing stellate cells in this study?
35. You're missing limitations and comparisons with other techniques in the literature.

Reviewer: 2

Comments to the Author

The manuscript presents an approach using a 'U'-shaped neural network to transform standard hematoxylin-and-eosin (H&E) slides of pancreatic tissues into collagen images, offering an alternative to the gold standard, second harmonic generation microscopy, used in stromal-based research analyses. Subsequently, a comprehensive analysis of collagen features in pancreatic lesions（including normal, PDAC, PanIN, and CP）, encompassing parameters such as fiber length, fiber width, Fiber Box Density.

Weaknesses of the Manuscript:
1.It is recommended that the authors clearly delineate the unique contribution of their approach in comparison to existing research.

2.Given the existence of a plethora of state-of-the-art CNN architectures, the rationale behind opting for the UNET as the translation model for converting H&E images to collagen images could be elucidated.

3.In Section III, RESULTS, Subsection A (Performance of Cross-Modality Image Translation), while the manuscript describes the Structural Similarity Index (SSIM) comparison between the proposed model and ground truth, an inclusive evaluation involving multiple SOTA methods is crucial to validate the efficacy of the proposed algorithm.

4.The authors should expound on the rationale for selecting specific features, such as length, width, alignment, density, overall collagen deposition area, and dispersion parameter, for analyzing the collagen images using standard software.

5.In Section II (MATERIALS AND METHODS), Subsection E (Statistical Analysis), while K-Nearest Neighbors (KNN) was employed for neoplastic vs. non-neoplastic tissue discrimination, it is advisable to evaluate several alternative classification techniques for a comprehensive analysis.

6.The image labels ought to be replaced with high-resolution versions to ensure clarity. Furthermore, the manuscript should be carefully reviewed to rectify any typographical errors or symbol inaccuracies.

Reviewer: 3

Comments to the Author
1. At the end of Section I, the authors should provide a list of the contributions of this article instead of merely stating what was computed, extracted, and compared. It should explain why these computations or extractions were conducted and what was gained through the comparisons.
2. In Figure 1 (B), the kernel size of the first layer of the encoder is 4×4, which is unconventional. This is because using an even-sized kernel can potentially introduce spatial positional biases, which may hinder the ability of the convolutional operator to extract local features effectively. Please ask the authors to explain why they chose this design and provide justification for it.
3. In Section II-D, the authors used Otsu's method to suppress background noise. However, it is well known that Otsu's method is a global thresholding technique. Why didn't the authors utilize an adaptive thresholding algorithm to overcome the influence of background noise in this case? Please ask the authors to provide an explanation for their choice and address this concern
4. The authors should introduce a discussion on the limitations of this work in the discussion section and remove redundant statements regarding the significance of the study that has already been addressed earlier.
5. In order to demonstrate the smoothness of the overall algorithm and how the various stages are interconnected, the authors should provide a discussion regarding the integration of multiple processing stages. This would help in highlighting how each stage seamlessly transitions to the next and ensures the coherence of the entire methodology.