Reviewer's report

Title: Histological Image Classification Using Biologically Interpretable Shape-Based Features

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Reviewer: Anant Madabhushi

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Summary: The authors present a classification system based on biologically interpretable shape-based features for histological renal tumor images. They provide quantitative results compared to other industry standard approaches.

Major Critiques: However there is no mention previous related medical systems which utilize Fourier Descriptors (see Comaniciu et. al. 1999, Yang et. al. 2009) -> both of these papers use FD on single cells (or nuclei) to distinguish between hematopoietic malignancies subtypes.

The pre-processing steps are poorly described, namely a lack of description of how segmentation of the various biological entities occurs and/or a discussion of the way in which inter sample variance is handled (through lighting/technology/staining differences).

The next step is to extract the contours of the entities, which although in itself is an entire field of study in biomedical imaging, isn’t described in proper detail on how to successfully reproduce the results for the numerous challenging cases which occur (cell overlap, poor focus, broken boundaries, etc etc).

Assuming it is possible to complete the above 2 steps accurately, the paper proceeds by computing Fourier descriptors of the closed contours. What is seemingly novel is that for each co-efficient the magnitude of the major and minor axis is computed for the associated ellipse. Their claim is that a ratio between these magnitudes accurately defines the shapes, where simple shapes have higher order coefficients rapidly approaching zero, while complex shapes do not. After computing these variables for all shapes in the image, a histogram is computing which represents the distribution of these variables across the image. After combining the variables from the 3 masks (where each mask is associated with a specific colored segmented stain), the final dimensionality of the feature vector is 900.

For interpretability only the top 25 features are used to display segmentation effects so that each shape is color coded however classifier results are presented for 900 features. It would be interesting to see the classification results for only the 25 features selected for visualization purposed.

Lastly, a feature selection algorithm was used, mRMR, to select a subset of the overall features.
Overall, the pre-processing steps could have used more accurate description.

Novelty: It would seem there is a novel use of Fourier descriptions for feature generation which is unknown to this reviewer. The quantitative results are sound, and indicate that these new features do indeed operate as expected.

Minor Critiques: I would have liked to see, in addition, a discussion of the computational complexity of the overall approach, as segmentation and contour detection are known to be difficult problems, leading me to question the applicability of this algorithm (which seems highly expensive) in a clinical setting.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.