QUANTITATIVE IMAGE ANALYTICS FOR STRATIFIED PULMONARY MEDICINE

Sushravya Raghunath[1], *Srinivasan Rajagopalan*[1], *Ronald Karwoski*[1], *Brian Bartholmai*[2], *Richard Robb*[1]

[1]Biomedical Imaging Resource, [2]Dept. of Radiology,
Mayo Clinic College of Medicine, Rochester, MN.

ABSTRACT

Recently we proposed spatio-pathological stratification of lungs from multiple subjects. This enabled a pulmonary disease landscape to objectively diagnose pathology, track progression and assess pharmacologic response within and across patients. Even though the approach based on unsupervised affinity propagation clustering of a symmetric pairwise dissimilarity metric showed strong statistical and clinical correlation, it did not address the possibility of candidates being potential outliers within a cluster and consequently being triaged to suboptimal personalized care. In this paper, we address this limitation through the use of an asymmetric dissimilarity metric and a density-based outlier detection technique to identify the *natural* outliers within the individual clusters. In a database of 370 datasets, 28 outliers were detected among 20 clinically correlated clusters. The proposed quantitative analytics could facilitate an optimized landscape wherein every patient is triaged through the most appropriate individualized pulmonary care.

Index Terms— Stratified medicine, affinity propagation, outlier detection, LOcal Correlation Integral (LOCI), Generalized Extreme Studentized Deviate (GESD) test, parenchymal abnormality, glyphs.

1. INTRODUCTION

Stratified medicine bridges the current empirical medicine and the futuristic personalized medicine by matching a patient with a cohort that exhibits similar diagnosis, therapy response and prognosis. Differential biological mechanisms, multiple treatment options and medically acceptable clinical biomarkers are the necessary requirements for enabling stratified medicine. While the etiology, behavior and therapy response are fairly understood for different parenchymal lung diseases, the existing clinical decision support tools are suboptimal for consistent characterization of the type and extent of disease. This leads to inconsistent diagnosis among *within-* and *across-specialty* physicians from academic and community healthcare centers[1] despite the use of High Resolution CT (HRCT) scans wherein the lung parenchymal diseases are characterized by disease specific spatial distribution of five primal patterns- normal, emphysema, ground glass, honeycombing and reticular. Recently we introduced quantitative analytics to stratify and iconically visualize the parenchymal abnormality landscape[2]. Though this maiden approach yielded stratification that correlated with clinical consensus, it did not incorporate outlier detection within the individual clusters. This could potentially lead to outlier candidates being ascribed to a different disease and treatment pathway. Existing cluster outlier detectors cannot be incorporated *as-is* since they either assume that every cluster has an outlier or require apriori specification of the number of outliers within each cluster.

This paper addresses these limitations by enabling a clinical biomarker that matches a patient-specific lung to a cohort with well characterized biological behavior, therapy response and prognosis. Robustness of the stratification is improved using an asymmetric dissimilarity metric. Outliers within the individual clusters are detected using a judicious combination of local correlation integral[3] and generalized extreme studentized deviate test[4]. The efficacy of stratification and outlier detection was assessed statistically using ANOSIM and clinically using expert review. Our preliminary results provide the significant first step towards a direct improvement of quality and consistency in clinical pulmonary practice.

2. MATERIALS AND METHODS

2.1. Datasets, Classification, Feature Extraction, Visualization

HRCT scans from 370 patients across the diffuse parenchymal disease spectrum were used for this study. The datasets were preprocessed to segment the lungs, airways and vessels; the resultant parenchymal voxels were classified into the five primal patterns using an Earth Mover's Distance (EMD) based supervised classifier as described in [5]. To facilitate pre-attentive holistic visualization of the classified patterns in an individual lung and across a cohort, iconic glyphs capturing the lobar (upper, middle, lower) abnormality distribution were created. The anatomically non-existent left middle lobe was defined by reflection from the right counterpart. Figure 1 shows a representative glyph whose radius is proportional to the lung volume. The glyph is divided into six regions each representing a lung lobe. The asymmetry, if any, between

the left and right lungs can be readily observed in the glyph. The individual lobes span through angles proportional to their respective volumes. Within each lobe, the proportional distribution of the primal patterns is represented by proportionally filled color-coded sectors. The concentric circles are drawn at 20% intervals for enhanced visualization.

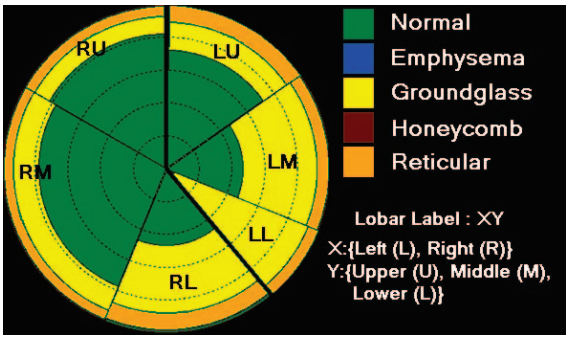


Fig. 1. Iconic glyph enables holistic unambiguous overview of lobar abnormality distribution.

Our previous affinity propagation[6] based stratification [2] used a symmetric metric based on normalized lobar abnormality distributions weighted by the respective mean lobar volumes. The mean lobar volumes were calculated from all the lungs used in the stratification. Such a weighting does not reflect the true dissimilarity between the lungs under paired comparison. The normalized abnormality distribution ignores the lung volume differences. To overcome these limitations, we now propose a modified metric that captures global abnormality (GA), lobar abnormality (LA), and lobar volume differences (LV).The dissimilarity between lungs A and B is defined as,

$$D(A,B) = GA + \sum_{j=1:6} \frac{{}_{Vol}A^{L_j}}{{}_{Vol}A^{G}} \times LV \times LA \tag{1a}$$

$$GA = \sum_{i=1:5} \frac{|{}_{Abn}A_i^G - {}_{Abn}B_i^G|}{max({}_{Abn}A_i^G, {}_{Abn}B_i^G)} \tag{1b}$$

$$LV = 1 + \frac{|{}_{Vol}A^{L_j} - {}_{Vol}B^{L_j}|}{max({}_{Vol}A^{L_j}, {}_{Vol}B^{L_j})} \tag{1c}$$

$$LA = \sum_{i=1:5} \frac{|{}_{Abn}A_i^{L_j} - {}_{Abn}B_i^{L_j}|}{max({}_{Abn}A_i^{L_j}, {}_{Abn}B_i^{L_j})} \tag{1d}$$

where, ${}_{Abn}A_i^G$ and ${}_{Abn}A_i^{L_j}$ are the % abnormality distributions of i^{th} primal pattern in whole of lung A and in j^{th} lobe of lung A, respectively; ${}_{Vol}A^G$ and ${}_{Vol}A^{L_j}$ are the total volume of lung A and of the j^{th} lobar volume of lung A, respectively. $\frac{{}_{Vol}A^{L_j}}{{}_{Vol}A^G}$ is the asymmetric component that weights the lobar dissimilarities proportional to the lobar volumes of lung A. Affinity propagation based on this metric was used to find the natural cluster among the 370 datasets.

Similar to [2], the clusters were categorized automatically into clinical groups using the clinical guidelines[7]. Accordingly, based on the type and extent of abnormality distribution in the individual exemplar, its cluster was labeled as one of the following seven types: (T1) diffuse emphysema (T2) upper-lobe emphysema (T3) mixed disease (T4) probable non-specific interstitial pneumonitis (NSIP), (T5) confident NSIP, (T6) probable usual interstitial pneumonitis (UIP) and (T7) confident UIP.

2.2. Outlier Detection

The clinical goal of the proposed stratification is to ensure that no candidate is anomalously grouped to a cluster and hence triaged to suboptimal personalized care. This requires the detection of *natural* outliers- detections that do not force a fixed number of outliers within a cluster and do not even assume that every cluster has an outlier. We overcome this limitation by judiciously cascading density-based multivariate local correlation integral (LOCI) [3] with univariate generalized extreme studentized deviate (GESD) test [4]. LOCI uses the *within-cluster* pairwise distances to compare the local neighborhood density (number of neighbouring candidates) with multiple scales of extended neighborhood density (average density of the local neighborhoods of candidates within the extended neighborhood) to compute the normalized multi-granularity deviation factor (NMDEF) for each candidate. Candidate that lies deep inside a cluster has a local neighborhood equal to its neighbours and has lower NMDEF; outlier candidates have higher NMDEF. In the original algorithm, the NMDEF values are arbitrarily thresholded to detect outliers. In the proposed approach, the univariate NMDEF values are used to detect outliers, if any, using GESD. Given a univariate data (x1, x2... xr) and the upper bound on the possible number of outliers, which we set to the number of candidates in cluster, GESD performs r separate tests each to identify one, two, ... upto r outliers. The LOCI-GESD cascade was applied to all the natural clusters to detect their respective outliers.

3. RESULTS

Figure 2 shows a mosaic of the glyphs from all the 370 HRCT scans in the database. The glyphs provide a succinct comparative overview of the disease states and lobar distribution of the abnormal tissue. It is easy to visualize the presence of distinct cases with emphysema (blue shades), NSIP- variable amounts of ground glass and reticular distributions, and UIP-extensive reticulation and honeycombing. Lung volume increase associated with emphysema and similar NSIP-, UIP-associated decrease is clearly reflected in the radius of the individual glyphs.

Affinity propagation based stratification of pairwise dissimilarities [Equation 1] yielded 20 natural clusters. The max, min and mean cluster sizes were 40, 6 and 18. The intra-

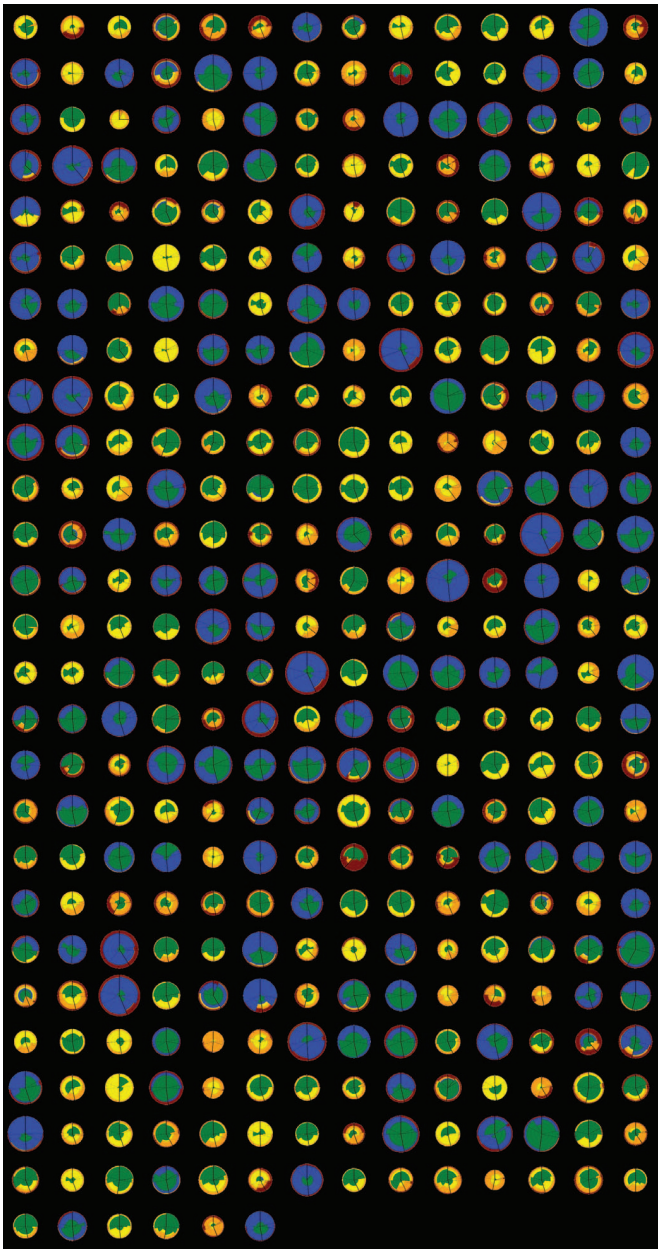


Fig. 2. Mosaic of glyphs of 370 lungs. The glyphs provide a succinct comparative overview of inter-subject distribution of parenchymal abnormalities.

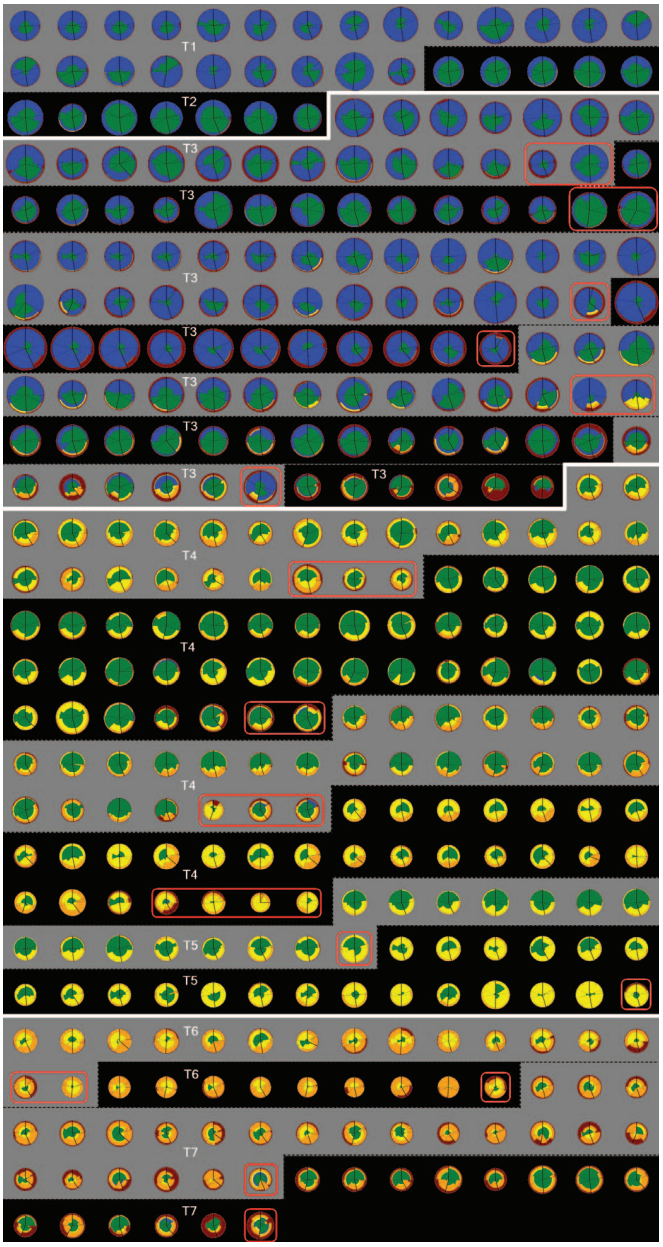


Fig. 3. Mosaic of glyphs in the stratified space. Cluster specific outliers are outlined in red. The efficacy of the stratification can be preattentively gleaned from the mosaic.

cluster pairwise dissimilarities were used to detect the cluster specific outliers. A total of 28 outliers were detected across the 20 clusters. The number of clusters with 0, 1, 2, 3 and 4 outliers were respectively 4, 8, 5, 2 and 1. This suggests that the upper bound specified in GESD test did not overestimate the cluster outliers.

Figure 3 shows the glyphs reordered in the stratified space. Alternate clusters are demarcated with dark and gray background shades. The detected cluster specific outliers are marked with red outlines. The efficacy of the stratification can be preattentively gleaned from the mosaic. The four thick partitions broadly categorize the stratification respectively into emphysematic (types T1,T2), mixed(T3), NSIP (T4,T5) and UIP (T6,T7) categories. The first glyph in each of the 20 clusters represent the cluster exemplar. Figure 4 shows a magnified view of these exemplars and the clinical category of the clusters they represent. While the clinical guidelines specify probable and confident categories, the proposed quantitative

analytics identifies subtypes within and this could reflect the progressive stages within the categories.

Figure 5 shows the candidates in a representative T4 (probable NSIP) cluster along with its outliers. While three of the four outliers are visually obvious, the last outlier could be due to confounding global and regional abnormalities. Nevertheless, it is preferable to err on the side of caution and flag such discrepancies for further expert resolution.

ANOSIM R was used to assess the statistical efficacy of outlier detection. The combined R value for the 20 clusters before and after outlier detection were 0.883 ± 0.185 and 0.909 ± 0.159 ($p < 0.001$ in each case) respectively. It is worth noting that the moderate increase in R pales in comparison with the associated clinical significance wherein 28 patients who showed considerable deviation from their most similar cohort were flagged for closer examination towards providing the best individualized care.

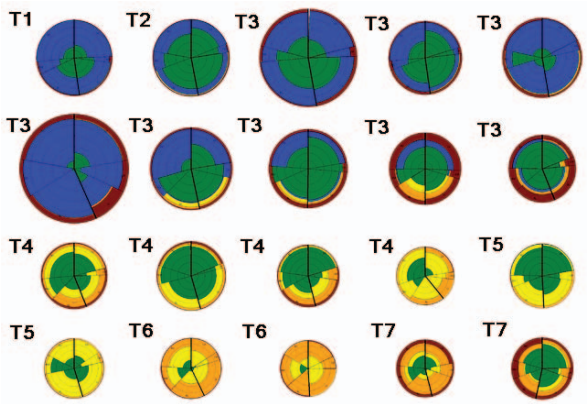


Fig. 4. The glyphs for the 20 natural cluster exemplars along with their respective clinical categories: (T1) diffuse emphysema (T2) upper-lobe emphysema (T3) mixed disease (T4) probable NSIP, (T5) confident NSIP, (T6) probable UIP and (T7) confident UIP.

4. CONCLUSION

A simple Google search for the term *"personalized medicine"* shows 1,760,000 hits which document the unrelenting quest for efficacious, targeted and risk minimizing treatment. However, as William Osler rightly pointed out *"medicine is the science of uncertainty and the art of probability"*. This is especially relevant in the diagnosis of the disorders of the lung- an anatomical bog with very few referential landmarks. Current management of diffuse parenchymal lung disease might best be described as a random walk through therapy space. However, advances in understanding the structural and functional mechanisms underlying diseases, as well as therapy response, are increasingly creating opportunities to match patients with therapies that are more likely to be effective and

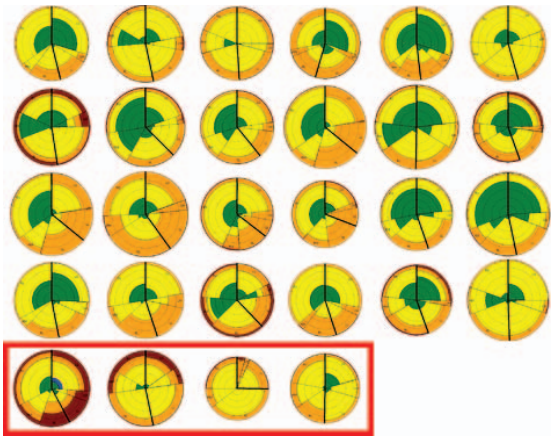


Fig. 5. A representative T4 (probable NSIP) cluster with cluster specific outliers (boxed in red).

safe. Concomitantly, it is crucial to develop robust biomarkers that are effective in reducing uncertainty and competent in addressing it. The efficacy of such a biomarker should transcend through the stratified population precisely to the individual patient in line of therapy. The quantitative image analytics proposed in this paper could serve as a potential biomarker that provides a trustable, verifiable and clinically relevant staging of pulmonary disease, including the extent and character of disease, both within an individual patient and across a cohort of patients.

5. REFERENCES

[1] K. Flaherty, et al., *Am. J of Resp. and Crit. Care Med.*. 175, pp. 1054–1060.

[2] S. Raghunath, et al., "Referenceless Stratification of Parenchymal Lung Abnormalities" in *MICCAI 2011* .Part III, LNCS 6893, 2011, pp. 223–230.

[3] H. Papadmitriou, et al., "LOCI: Fast outlier detection using the local correlation integral" in *Proc 19th Intnl. Conference on Data Engineering*. 2003, pp. 315–326.

[4] B. Rosner, "Percentage Points for a Generalized ESD Many-Outlier procedure" in *Technometrics*. 1983, 23(2), pp. 165–172.

[5] V. Zavaletta, et al., "High Resolution Multi-Detector CT Aided Tissue Analysis and Quantification of Lung Fibrosis" in *Academic Radiology*. 2007, 14(7), pp. 772–787.

[6] B.J. Frey and D. Dueck, "Clustering by Passing Messages Between Data Points" in *Science*. 2007, Vol. 315 no. 5814, pp. 972–976.

[7] M. Akira, et al., "UIP and NSIP with and without concurrent emphysema" in *Radiology*. 2009, 251, pp. 271–279.