Automatic Pathology Software for Diagnosis of Non-Alcoholic Fatty Liver Disease

(OTT ID 1236)

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Shortfalls of current liver pathology assessment

Problems/Unmet Needs:

• Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common liver disease in the U.S.
• Accurate distinction of mild vs. severe phenotypes is essential and liver biopsy is the only way to accurately diagnose and stage NAFLD
• Current NAFLD scoring method relies on manual pathologist assessment and grading of histological features
• Studies demonstrate substantial pathologist disagreement and inter-observer error (Gawrieh, S., Knoedler, 2011. 15: 19-24.)
• Poor reproducibility; intra-observer error
• Does not reflect the true continuous nature of “scoring” lesions

Technological Solution:

• The inventors have utilized a supervised machine learning technique for identification of white regions in liver biopsies with 92% accuracy (based on results from 47 patients)
• This is the first work to identify white regions using machine learning and automatically quantify lobular inflammation and hepatocyte ballooning
• This technology is automatic, faster, and more accurate than human pathologists
• Applications include diagnosis of NAFLD, assessment of candidate liver donors for transplants, and biopsy index database searching
Market

- The global market for liver disease treatments was $400 million in 2009 and expected to increase to more than $700 million by 2014.

- Computer aided detection and diagnosis (CAD), originally used in image analysis and the development of algorithms for image recognition, has evolved to offer full workflow management packages for a range of healthcare conditions.

- Use of CAD can provide a more economically viable proposition for busy, cost-focused healthcare providers; CAD allows physicians to deal with enormous data sets more efficiently, making their job easier and in turn making physicians more accurate.

Intellectual Property

- Copyrighted Software

Partnering

- We are looking for a partner to license the algorithm and software and to develop the technology into a final product for use by pathologists or other end users.
Liver Anatomy-Lobule

- The bile duct, portal artery and vein, and central vein are some of the white regions that must be distinguished from the fatty white regions in a liver lobule.
Liver Biopsies for Pathological Assessment

- Biopsy sections are cut into different planes for staining

- White regions are identified from the stained biopsy sections from a patient
Pathologists use the NAFLD Activity Score (NAS)

- State-of-the-art scoring system for NAFLD (Kleiner et al., 2005)

- Based on 3 key histological features:
  - Steatosis [0-3]
  - Lobular Inflammation [0-3]
  - Hepatocyte Ballooning [0-2]

- NAS = Steatosis + Lobular Inflammation + Hepatocyte Ballooning
Examples of Histological Legions

- Steatosis
- Lobular Inflammation
- Hepatocyte Ballooning
Approach for Machine Learning

Study Patients

H&E Stained Images

TC Stained Images

Pathologist Annotations

Fibrosis Classifier

Lobular Inflammation Classifier

White Region Classifier

Ballooning Classifier

Image\textsubscript{HE}

Image\textsubscript{TC}

Portal Triad Identification Heuristic

Ballooning Calculator

Steatosis Calculator

Lobular Inflammation Calculator

Fibrosis Calculator

\(B_P\)

\(S_P\)

\(L_P\)

\(F_P\)
• **Motivation**
  
  – Classifying all white regions provides a direct method for quantifying steatosis
  
  – Many anatomical landmarks manifest as white or with a white center. This is useful for other tasks
Hypothesis:

- Comparing previous methods that use hand crafted rules based purely on morphology, to a supervised machine learning approach that uses a richer feature vector representation
- Richer feature vector representations lead to more accurate classifications than ones based purely on morphology
  - We compare 2 representations:
    1. Morphology Only
    2. Advanced feature set

Approach

- Represent each white region by a fixed length feature vector
- 10 fold cross validation
Results of White Region Classification

**Accuracy**

<table>
<thead>
<tr>
<th>Model</th>
<th>Overall Accuracy</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>74.8%</td>
<td></td>
</tr>
<tr>
<td>Advanced feature set</td>
<td>92.1%</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

**Supervised Machine Learning Results**

The results show that the algorithm is predicting the white regions with very high accuracy.
Results of White Region Classification-Cont’d

<table>
<thead>
<tr>
<th>Feature</th>
<th>Precision</th>
<th>Recall</th>
<th>ROC Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile Duct</td>
<td>0.900</td>
<td>0.849</td>
<td>0.981</td>
</tr>
<tr>
<td>Central Vein</td>
<td>0.732</td>
<td>0.788</td>
<td>0.938</td>
</tr>
<tr>
<td>Macro Steatosis</td>
<td>0.954</td>
<td>0.974</td>
<td>0.980</td>
</tr>
<tr>
<td>Micro Steatosis</td>
<td>0.930</td>
<td>0.927</td>
<td>0.967</td>
</tr>
<tr>
<td>Other</td>
<td>1.000</td>
<td>0.857</td>
<td>0.994</td>
</tr>
<tr>
<td>Portal Artery</td>
<td>0.786</td>
<td>0.767</td>
<td>0.973</td>
</tr>
<tr>
<td>Portal Vein</td>
<td>0.901</td>
<td>0.880</td>
<td>0.976</td>
</tr>
<tr>
<td>Sinusoid</td>
<td>0.924</td>
<td>0.899</td>
<td>0.982</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td><strong>0.921</strong></td>
<td><strong>0.921</strong></td>
<td><strong>0.974</strong></td>
</tr>
</tbody>
</table>

- Results again show that the algorithm is classifying white regions with very high accuracy. Of particular interest is how well it performs for macro and micro steatosis (fat)
• Percent Steatosis = total steatosis area / total tissue area
• Learn a different model for each patient using a leave one out approach
• The model is able to correlate best with the average grade

Correlation of Computed Percentage Steatosis with Pathologist Grade

![Graph showing correlation between model percent steatosis and pathologist grade](image1)

Relationship of Computed Percentage Steatosis with Pathologist Grade

![Graph showing relationship between pathologist grade and model percent steatosis](image2)

\[
y = 0.0252x^2 + 0.0067x + 0.003
\]

\[R^2 = 0.9392\]
Hypothesis/Approach:

• Lobular inflammation classification can be performed by supervised machine learning
• Provide a representative quantification for actual lobular inflammation regions
• Use a feature vector very similar to the one used for white regions
• 10 fold cross validation
Approach for Lobular Inflammation Classification:
95.6% accuracy (vs. 94.0% baseline)

<table>
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<th>Feature</th>
<th>Precision</th>
<th>Recall</th>
<th>ROC Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular Inflammation</td>
<td>0.696</td>
<td>0.489</td>
<td>0.946</td>
</tr>
<tr>
<td>Not-Lobular Inflammation</td>
<td>0.968</td>
<td>0.986</td>
<td>0.946</td>
</tr>
<tr>
<td><strong>OVERALL</strong></td>
<td><strong>0.952</strong></td>
<td><strong>0.956</strong></td>
<td><strong>0.946</strong></td>
</tr>
</tbody>
</table>

![Precision vs. Recall Curve](image1.png)

![Receiver Operating Characteristics](image2.png)
Hepatocyte Ballooning: Classification Results

- 98.9% accuracy (vs. 97.9% baseline)

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<th>Recall</th>
<th>ROC Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocyte Ballooning</td>
<td>0.912</td>
<td>0.542</td>
<td>0.983</td>
</tr>
<tr>
<td>Not-Hepatocyte Ballooning</td>
<td>0.990</td>
<td>0.999</td>
<td>0.983</td>
</tr>
<tr>
<td>OVERALL</td>
<td>0.989</td>
<td>0.989</td>
<td>0.983</td>
</tr>
</tbody>
</table>

![Precision vs. Recall Curve](image1)

![Receiver Operating Characteristics](image2)
Overall Results for NAFLD Activity Score (NAS)

- 73.8% Correlation with Pathologists

\[ y = 0.7624x + 0.4561 \]
\[ R^2 = 0.6532 \]

Comparison of Computed NAS with Average Pathologist NAS

- Circled region accounts for diagnosis by software of a worse case than that predicted by pathologist
• Computer imaging techniques can effectively be used as a diagnostic aid for NAFLD / NASH

• Supervised learning techniques are superior to hand crafted computational rules

• Steatosis grading accurate enough for clinical use

• Next Steps
  – Additional data to study lobular inflammation and ballooning
  – Model refinement, tile size, etc.
  – Features in other domains (FFT, Wavelets, etc)
  – Impact of magnification of scan
Next Steps: Product Development

• Company must convert Matlab algorithms into a production software environment for commercial use

• Estimated 500 hours of development to move this technology into production
31B Treats Ovarian Cancer in Mice

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