Software for Quantitative Image Assessment of Musculoskeletal Diseases:
(A tasting menu of methodologies)

Jeffrey Duryea
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Software for Quantitative Image Assessment of Musculoskeletal Diseases:
(A tasting menu of methodologies) without wine pairings

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Motivation

• Imaging is widely used to diagnosis and assess several MSK diseases (OA, RA, OP)
• Radiography and MRI are the most common modalities
• Highly useful for clinical trials and other research studies.
• Can be expensive and subjective
• **Reason for talk:** Seeking collaborations.
Knee radiograph
Radiologist: “Tricompartment osteophytes, moderate to severe medial tibiofemoral compartment cartilage space loss, compatible with moderate to severe osteoarthritis.”
Knee radiograph

Radiology researcher: “KL score of 3” *

*KL scoring
Grade 0: no radiographic features of OA are present
Grade 1: doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2: definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4: large osteophytes, marked JSN, severe sclerosis and definite bony deformity
My method: “Medial compartment joint space width (JSW) = 2.94 mm”
Assessment methods for research

• Semi-quantitative methods
  • Atlas-based. Numerical score
  • e.g. K & L, OARSI Atlas, WORMS, BLOKS, MOAKS

• Quantitative methods
  • Use software and digital images to produce quantitative measures (distance, area, volume, gray scale patterns)
  • e.g. Radiographic joint width, cartilage volume, osteophyte area, bone texture.
Motivation for software methods

• Objectivity and speed
• Improved surrogate outcome measures
• Improvements in algorithms and CPU speed
• Clinical Benefit:
  • Short term: Assist in clinical studies
  • Longer term: Single patient evaluation
Feature Extraction Software

• Digital image:
  • Computer file
  • Set of pixels organized in rows and columns.
  • Each pixel assigned a number (gray scale intensity)

• Image processing software: Find an organized pattern in the image

• Our Goal: Extract features that provide objective measurements of structural changes from arthritis
Feature Extraction Software
Osteoarthritis Initiative (OAI)

- Large NIH/industry study of over 4,700 subjects
- 7 time points: BL, 12, 24, 36, 38, 72, and 96mo
- Subjects with established OA and with significant risk factors for OA
- Extensive set of clinical data and images
  - Knee MRI (all visits)
  - Knee radiography (all visits)
  - Hand radiography (BL, 48mo)
  - Hip radiography (BL, 48mo)
Motivation

• Example: ~50,000 Individual knees scanned with MRI.
• Assuming 1 hour/scan, total reader time is 24.0 years!
• Lower the time to 10 minutes/knee... 4 years
• Other large studies: e.g. MOST, Health ABC
• Clinical trials
Location-specific joint space width (JSW)
• Medial compartment JSW: From $x = 0.15 - 0.3$.
• Lateral compartment JSW: From $x = 0.7 - 0.9$. 
Validation study*

- **Radiography**
  - PA bilateral fixed-flexion knee radiographs
  - Use of Synoflexer™ positioning frame
  - Software JSW analysis

- **MRI**
  - Measure cartilage morphometry using segmentation software (independent group)

Validation study

• 150 subjects from the OAI
• Progression Cohort (Data Set 0.1.1 and Image Releases 0.B.1 and 1.B.1)
• Baseline and 12 month follow-up
• Analyze a single indexed knee
• All readings done paired but blinded to time point
• \[ \text{SRM} = \text{Avg}(\Delta X) / \text{SD}(\Delta X) \]
<table>
<thead>
<tr>
<th>Measure</th>
<th>All (n = 150)</th>
<th>K/L scale grade of 2 or 3 (n = 116)</th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline,</td>
<td>Change from model,</td>
<td>SRM for</td>
<td>Baseline,</td>
<td>Change from model,</td>
</tr>
<tr>
<td></td>
<td>mean ± SD</td>
<td>mean ± SD</td>
<td>mean change</td>
<td>mean ± SD</td>
<td>mean ± SD</td>
</tr>
<tr>
<td>Minimum JSW, mm</td>
<td>3.41 ± 1.62</td>
<td>-0.09 ± 0.62</td>
<td>-0.15</td>
<td>3.42 ± 1.40</td>
<td>-0.12 ± 0.64</td>
</tr>
<tr>
<td>JSW (x = 0.250), mm</td>
<td>4.71 ± 1.67</td>
<td>-0.19 ± 0.60</td>
<td>-0.31</td>
<td>4.74 ± 1.41</td>
<td>-0.21 ± 0.60</td>
</tr>
<tr>
<td>JSW (x = 0.275), mm</td>
<td>5.20 ± 1.69</td>
<td>-0.21 ± 0.65</td>
<td>-0.32</td>
<td>5.23 ± 1.41</td>
<td>-0.22 ± 0.67</td>
</tr>
<tr>
<td>JSW (x = 0.300), mm</td>
<td>5.85 ± 1.73</td>
<td>-0.21 ± 0.73</td>
<td>-0.29</td>
<td>5.89 ± 1.44</td>
<td>-0.23 ± 0.74</td>
</tr>
<tr>
<td>JSW (x = 0.700), mm</td>
<td>7.26 ± 1.98</td>
<td>-0.15 ± 0.74</td>
<td>-0.20</td>
<td>7.23 ± 1.99</td>
<td>-0.20 ± 0.73</td>
</tr>
<tr>
<td>JSW (x = 0.725), mm</td>
<td>7.13 ± 1.83</td>
<td>-0.12 ± 0.68</td>
<td>-0.18</td>
<td>7.06 ± 1.84</td>
<td>-0.16 ± 0.69</td>
</tr>
<tr>
<td>JSW (x = 0.750), mm</td>
<td>6.97 ± 1.74</td>
<td>-0.13 ± 0.67</td>
<td>-0.19</td>
<td>6.91 ± 1.73</td>
<td>-0.17 ± 0.67</td>
</tr>
<tr>
<td>MT volume, mm$^3$</td>
<td>1,317.76 ± 508.73</td>
<td>-7.96 ± 83.13</td>
<td>-0.10</td>
<td>1,321.15 ± 457.10</td>
<td>1.78 ± 84</td>
</tr>
<tr>
<td>LT volume, mm$^3$</td>
<td>1,880.00 ± 606.80</td>
<td>-14.89 ± 68.50</td>
<td>-0.22</td>
<td>1,847.78 ± 579.60</td>
<td>-17.69 ± 68.37</td>
</tr>
<tr>
<td>MF volume, mm$^3$</td>
<td>1,504.12 ± 701.52</td>
<td>-37.44 ± 94.92</td>
<td>-0.39</td>
<td>1,519.82 ± 640.89</td>
<td>-33.94 ± 81.42</td>
</tr>
<tr>
<td>LF volume, mm$^3$</td>
<td>1,736.76 ± 558.18</td>
<td>-3.38 ± 58.80</td>
<td>-0.06</td>
<td>1,748.14 ± 525.57</td>
<td>-5.41 ± 58.10</td>
</tr>
<tr>
<td>MT thickness, mm</td>
<td>1.76 ± 0.46</td>
<td>-0.0043 ± 0.098</td>
<td>-0.04</td>
<td>1.79 ± 0.39</td>
<td>0.0057 ± 0.11</td>
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<tr>
<td>LT thickness, mm</td>
<td>2.36 ± 0.51</td>
<td>-0.015 ± 0.071</td>
<td>-0.22</td>
<td>2.33 ± 0.50</td>
<td>-0.017 ± 0.093</td>
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<tr>
<td>MF thickness, mm</td>
<td>1.88 ± 0.69</td>
<td>-0.039 ± 0.12</td>
<td>-0.34</td>
<td>1.89 ± 0.61</td>
<td>-0.035 ± 0.11</td>
</tr>
<tr>
<td>LF thickness, mm</td>
<td>2.25 ± 0.41</td>
<td>-0.0090 ± 0.071</td>
<td>-0.13</td>
<td>2.27 ± 0.40</td>
<td>-0.0094 ± 0.079</td>
</tr>
</tbody>
</table>

* SRM = standardized response mean; K/L = Kellgren/Lawrence; JSW = joint space width; MT = medial tibia; LT = lateral tibia; MF = medial femur; LF = lateral femur.
Compares favorably to MRI (full sub-plate)
Advantages of location Specific JSW

• Consistent definition of space for cross sectional and longitudinal studies
• Look at other structural measures (osteophyte location, ROIs for bone texture measures)
• No need to fully delineate joint margins.
• Has been thoroughly validated
• Over 40,000 OAI knee radiographs evaluated
JSW of the hip joint for OA
Outer edge of the acetabular roof

Hip JSW

JSW1 (10°)  JSW2 (30°)  JSW3 (50°)
Validation Study

• OAI: Nested case/control study
• Select all subjects with a total hip replacement (THR) after the BL visit
• BL and 48 mo. hip radiographs
• Set 1: THR after 48 mo. THR hip. (N = 27)
• Set 2: THR before 48mo. nonTHR hip. (N = 79)
• Age and gender matched controls
• Quantify responsiveness at each location (JSW1, JSW2, JSW3) with standardized response means (SRMs)
## Results

<table>
<thead>
<tr>
<th></th>
<th>Standardized Response Means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JSW1</td>
</tr>
<tr>
<td>THR Cases (n=27)</td>
<td>-1.06</td>
</tr>
<tr>
<td>Controls (n=27)</td>
<td>-0.03</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
</tr>
<tr>
<td>Contralateral Cases (n=79)</td>
<td>-0.34</td>
</tr>
<tr>
<td>Contralateral Controls (n=79)</td>
<td>-0.07</td>
</tr>
<tr>
<td>p-value</td>
<td>0.002</td>
</tr>
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</table>
JSW of the hand joint for OA
JSW Measurement

(Majority of published work for hand RA)

5 Measurement regions: JSW1, JSW2, JSW3, JSW4, JSW5
Central JSW measurement: $JSW_c = (JSW2+JSW3+JSW4)/3$
## Results

<table>
<thead>
<tr>
<th></th>
<th>JSW1</th>
<th>JSW2</th>
<th>JSW3</th>
<th>JSW4</th>
<th>JSW5</th>
<th>JSWc</th>
</tr>
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<tr>
<td>MCP</td>
<td>n.a.</td>
<td>0.083</td>
<td>0.028</td>
<td>0.022</td>
<td>n.a.</td>
<td>0.032</td>
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<tr>
<td>PIP</td>
<td>0.001</td>
<td>0.031</td>
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<td>DIP</td>
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<td>0.024</td>
<td>0.06</td>
<td>0.017</td>
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Table 1. P-values for the difference between the OA and normal subjects.
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# Results

## Table 1: P-values for the difference between the OA and normal subjects.

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Local-area cartilage segmentation (LACS)
Segment cartilage

Time consuming: 100 slices per knee
Location specific MRI

Specify by $z_0$, $\Delta z$, $\theta_0$, and $\Delta \theta$.

$z_0 = 0.8$, $\Delta z = 0.1$

$\theta_0 = 200^\circ$, $\Delta \theta = 50^\circ$
Validation Study

- **122 subjects**: OAI Progression Cohort (Data Set 0.1.1 and Image Releases 0.B.1 and 1.B.1.)
- **Time points**: Baseline and 24 month visits.
- **Pulse sequence**: Siemens Trio 3T scanner using 3D DESS with water excitation
- **Voxel size (reformatted)**: 0.7 mm (slice thickness) $\times 0.37$ mm $\times 0.37$ mm
Validation Study

Responsiveness measures:

- Average volume change ($\Delta V$)
- Standard deviation of volume change (SD)
- Standardized response means
  $\text{SRM} = \frac{\text{Avg}(\Delta V)}{\text{SD}(\Delta V)}$
Results

<table>
<thead>
<tr>
<th>Δz</th>
<th>Δθ</th>
<th>ΔV (mm³)</th>
<th>SD (ΔV) (mm³)</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>100°</td>
<td>-46.2</td>
<td>89.5</td>
<td>-0.52</td>
</tr>
<tr>
<td>0.08</td>
<td>80°</td>
<td>-30.8</td>
<td>62.8</td>
<td>-0.49</td>
</tr>
<tr>
<td>0.06</td>
<td>60°</td>
<td>-17.9</td>
<td>40.6</td>
<td>-0.44</td>
</tr>
<tr>
<td>0.04</td>
<td>40°</td>
<td>-9.2</td>
<td>20.4</td>
<td>-0.45</td>
</tr>
<tr>
<td>0.02</td>
<td>20°</td>
<td>-2.3</td>
<td>7.2</td>
<td>-0.32</td>
</tr>
</tbody>
</table>

\[ z_0 = 0.8, \ \theta_0 = 210°. \]
Results

\[ z_0 = 0.8, \quad \theta_0 = 210^\circ. \]

<table>
<thead>
<tr>
<th>( \Delta z )</th>
<th>( \Delta \theta )</th>
<th>( \Delta V ) (mm(^3))</th>
<th>SD (( \Delta V )) (mm(^3))</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
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</table>

Decreasing area
Discussion points

• Method is fast: < 20 minutes/knee
• Only a sub region requires attention
• Reader only has to segment a small region on a limited number of slices
• Tools are included to automate the process.
• Can be used to quantify additional structures. (e.g. BMLs)

• Limitation: only a single region assessed.
MRI Osteoarthritis Software Score (MOSS)

A computerized semi-automated method for quantitative assessment of morphologic features of knee osteoarthritis
**BONE-MARROW LESION (BML) VOLUME**

**Precision:** Inter/Intra reader ICCs = 0.96/0.97  
**Correlation with WORMS:** Spearman’s correlations (0.72 to 0.88)  
**Correlation with weight-bearing pain:** (p < 0.007)  
**Reader time:** 5 min/knee

**OSTEOPHYTE VOLUME**

**Precision:** Inter/Intra reader ICCs = 0.98/0.97

**Correlation with MOAKS:** Kruskal-Wallis (p < 0.001)

**Responsive (BL-48mo):** SRM = 0.72

**Reader time:** 10 min/knee

**EFFUSION/SYNOVITIS**

Hoffa’s precision: Inter/Intra reader ICCs = 0.82/0.87
Effusion/synovitis precision: Inter/Intra reader ICCs = 0.75/0.90
Correlation with MOAKS: Kruskal-Wallis (p < 0.001)
Reader time: Less than 15 min/knee for both


**MENISCUS**

**Precision:** Inter/Intra reader ICCs = 0.90/0.95

**Repositioning precision:** ICC = 0.86

**Responsiveness (BL-48mo):** SRM = -0.31

**Reader time:** 3 min/knee

Conclusions (MOSS)

- Measurements are reproducible and responsive.
- Increased objectivity and speed
- Clinical validity
- Can begin to address large data issues
Machine Learning
Machine Learning (ML)

- Promising method to increase efficiently (reduce reader time)
- Deep learning (DL), a subclass of ML, is a powerful method for image analysis
  - Takes advantage of high-powered computing (video games)
  - DL algorithms are trained using some sort of gold-standard
  - Requires large amounts of data for success
- OAI data are ideal for this study.
- Segmentations from our studies will be used to train model.
- June 2018 NIH grant submission.
Preliminary Results (BMLs)

- 600 subjects from the OAI
- BL, 12, and 24mo visits.
- BML volume already measured with semi-automated (SA) method
- Train deep learning (DL) algorithm and test (cross validation)
- Compare DL to SA.
Preliminary Results (BMLs)
Preliminary Results (BMLs)
Other Projects

- Erosion healing in hand RA (hand CT)
- Zebrafish vertebral morphometry (microCT)
- Fracture healing in a rat model (radiography and microCT)
Conclusions

• Fully quantitative methods are valuable
• Diverse method and modalities
• Large N is good
• Open to new ideas and methods
• Grant applications
  • e.g. BRI Track B “Collaborative” grant program. $50,000 and no applications yet!
Thank you
Acknowledgements

<table>
<thead>
<tr>
<th>Jamie Collins</th>
<th>Tim McAlindon</th>
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<tbody>
<tr>
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