Analysis of Bone Histomorphometric Information from the Plain Radiograph (in particular fractal signature analysis)

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Disclosure

- **Pfizer (Non Tx progression studies)**
- **David H Murdock Research Institute**
  - Gift to Duke University
  - M.U.R.D.O.C.K. Study (Horizon 1)
  - http://www.dhmri.org/science/murdockstudy.html
  - The **M**easurement to **U**nderstand **R**eclassification of **D**isease **O**f **C**abarrus/**K**annapolis Study

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Texture Analysis of Bone

- Texture Analysis of macroradiographs of OA knees using fractal signature (Lynch, Hawkes, Buckland-Wright 1991) first use of the approach
- Fractal geometry in quantitativeCT of cancellous bone in vitro (Majumdar, Weinstein, Prasad 1993) In-vitro study in 3D
- Fractal nature of trabecular stucture by NMR (Chung, Chu, Underweiser, Wehrli 1994) Similar to the above using MRI
- FSA measures cancellous bone organization (Buckland-Wright et al. 1996) Vertical trabecular stucture by FSA relates to JSW
- FSA vs Bone Mineral Density (BMD) in OA (Messent, Buckland-Wright, Blake 2005) FSA more sensitive marker of disease status than BMD.
- FSA and OA progression (Messent, Ward, Tonkin, Buckland-Wright 2005) FSA is an indicator in slow vs. detectable JSN OA subjects.
- 2 Year longitudinal study of bisphosphonate on subcondral bone loss (FSA) (Buckland-Wright, Messent, Bingham, Ward, Tonkin 2007) Feasibility of FSA for Tx response
- Differences in trabecular bone texture w/ and w/o radiographic OA (FSA)(Podsiadlo, Dahl, Englund, Lohmander, Stachowiak 2008)Validation of the B-W approach with a slightly different algorithm

So what can we get from analysis of a radiograph (using the knee as an example) (Optasia Knee Analyzer)

For Each Image we obtain:

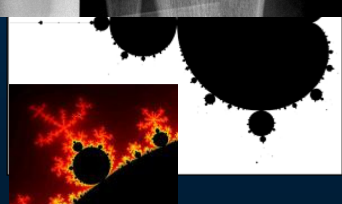
IMD

Calibration (Magnification)

Alignment (Varus/Valgus)	(single variable)
Joint Space Width and Profile	(2D array by compartment)
Joint Surface Model	(2D array by compartment)
mJSW	(single variable by compartment)
Cartilage 'Area'	(single variable by compartment)

Fractal Signature Analysis (Trabecular Complexity)   (2D arrays)

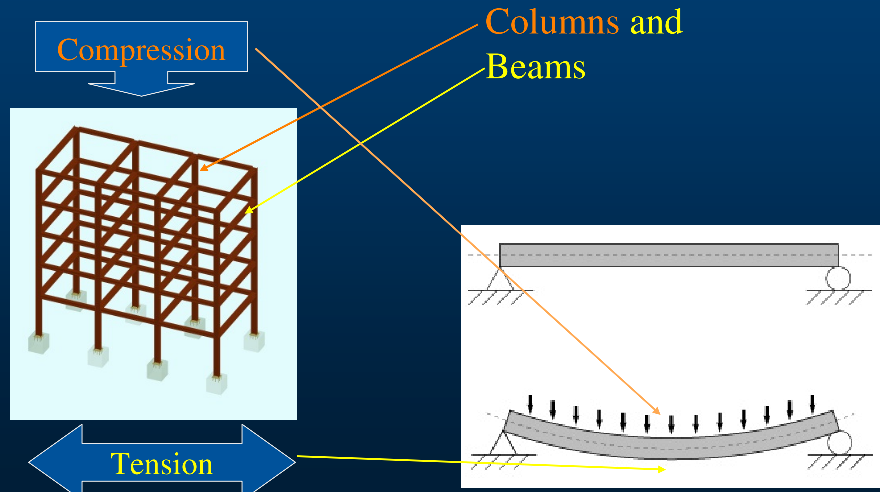
So let's consider 'Fractals'



Some Disclaimers

- Medical Images are not fractal in nature!
- We use Fractal Analysis as a means of extracting texture information at a variety of scales
- This texture is (hopefully) related to some 3 dimensional structural component

The information we are trying to extract relates to trabecular strength when subjected to Compression and Tension



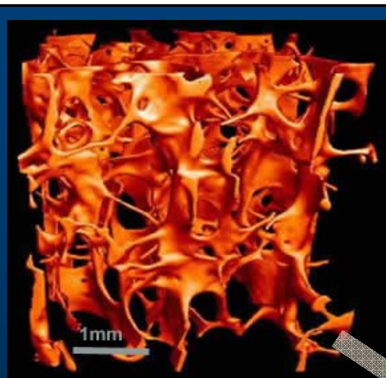
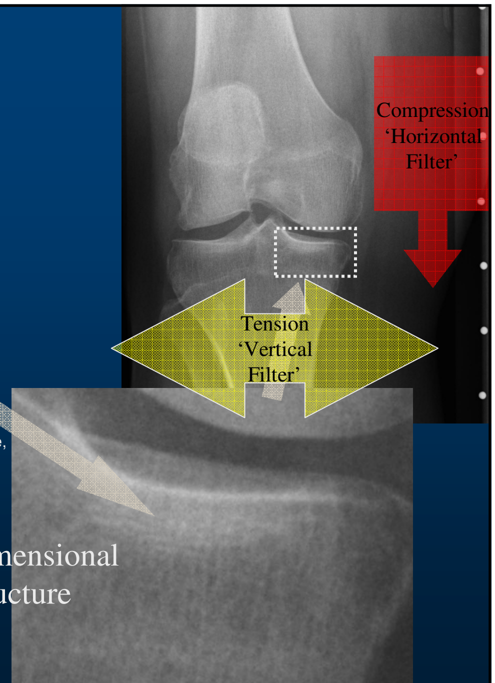


Image of trabecular bone structure in human vertebrae

Kinney, J.H., J.S. Stolken, T.S. Smith, J.T. Ryaby, and N.E. Lane, "An orientation distribution function for trabecular bone," Bone 36(2), 193-201 (2005)



The radiograph gives a two dimensional projection of the trabecular structure

How do we evaluate the "honeycomb" integrity of the trabeculae from a radiograph (Xray)?

- **Evaluate the complexity or heterogenity of the region rather than shape alone**
- **General Fractal Analysis**
  - •Fractal Dimension
  - •Fractal Dimension by 'multiple' scaling rule
  - •$N = A\varepsilon^{-DF}$ or
  - •DF = log N/log ε
    - Where ε is the scale ("ruler") size, N is the 'number' of pieces or the detail and
    - DF is the fractal dimension.

  Or plot DF against scale size

  •SO the Fractal Dimension is a way to evaluate the complexity of the detail of the image (in this case a projection of trabecular integrity)

Study Approach

- Validation Phase: Impact of Digitization
- Validation Phase: Impact of Analyst
- Study Phase: POP Study

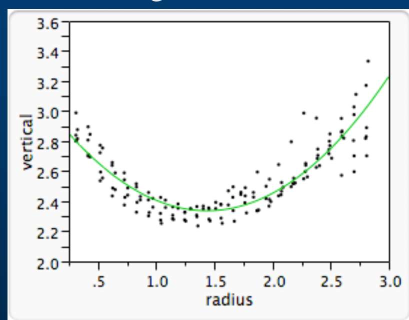
Impact of Digitization

Native Digital	ND to Film then Digitized
0.31	0.46
0.41	0.62
0.52	0.77
0.62	0.92
0.73	1.08
0.83	1.23
0.93	1.38
1.04	1.54
1.14	1.69
1.24	1.85
1.35	2.00
1.45	2.15
1.56	2.31
1.66	2.46
1.76	2.62
1.87	2.77
1.97	
2.07	
2.18	
2.28	
2.39	
2.49	
2.59	
2.70	
2.80	

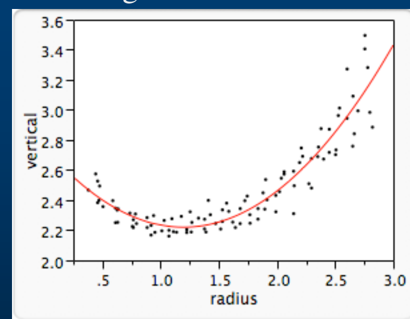
- DF = log N/log ε
  - Where ε is the scale ("ruler") size, N is the 'number' of pieces or the detail and
  - DF is the fractal dimension.
- Mapping Digitized to Native with interpolation gives the following regression
- Digitized = 1.019 Native - 0.029 (r^2 = .998)

Validation Phase: Impact of Digitization

Native Digital

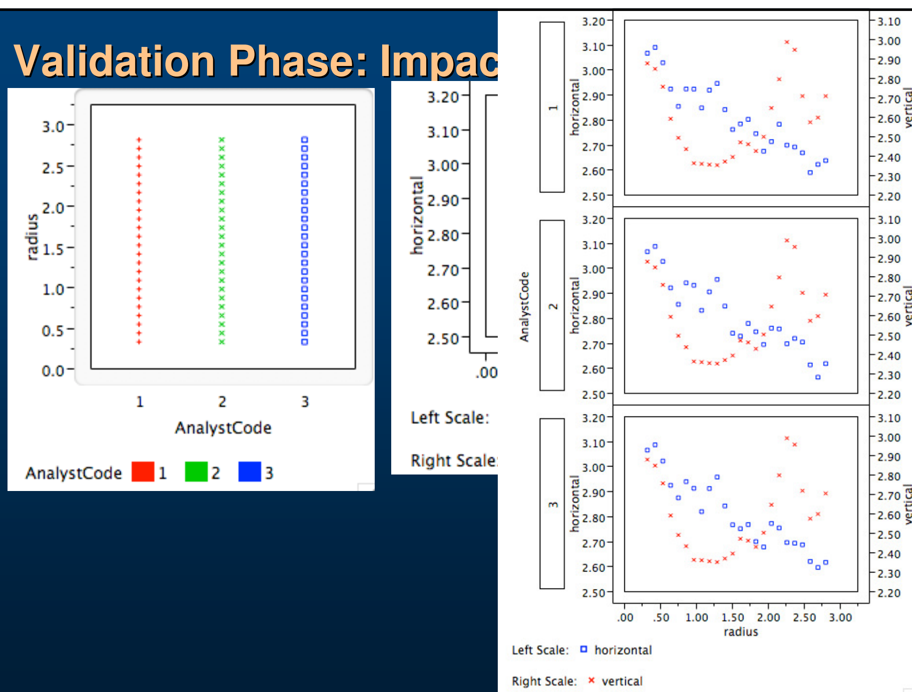


'Digitized'



Note the 'shape' of the distribution of dimensions- Disturbingly quadratic

Validation Phase: Impac



Initial Summary for FSA

- **Impact of Digitization** is ‘small’ and only ‘filters’ for small ε values

  Recall that in this example to test this idea, we took native digital radiographs, created films and redigitized the films using a VIDAR Diagnostic Pro Plus digitizer.

  The effect is likely due to subtle smoothing of detail in the secondary digitization. When working from original film based data, this should not be an issue.

- **Impact of Analyst** is vanishingly small and non-significant

POP Cohort

Prediction of Osteoarthritis Progression

Investigator initiated 2002 (V. Kraus)

NIH funded

Baseline and 3 year follow-up; 89% return rate

159 individuals with symptomatic knee OA

Bilateral knee x-rays

- progressors: 11% by joint space narrowing, 44% by osteophyte (OARSI Criteria)

Whole body and knee bone scans

Long limb xrays for knee alignment

Calcaneal bone density

Biological Samples

- Synovial fluid ~ both knees
- Serum
- Urine
- Blood for DNA
- RNA PAX tube sample

Analysis

- **FSA Analysis: Medial compartment analysis, all subjects, all knees (R,L)**
- **Global Shape Analysis: Reduce FSA to quadratic terms**
- **Statistical Analysis: Model Building**
  1. ***Outcome*: OA severity measures, e.g., JSN, Osteophyte (OARSI Criteria)**
  2. ***Clinical covariates*, e.g., age, gender, BMI, bone mineral content (in future: knee alignment, baseline knee OA severity)**
  3. ***Design parameters*, e.g., Left vs. Right, baseline vs. follow-up**
  4. ***Image data*, FD (H + V), filter radius**
  5. **Correlations and error terms, e.g., within patients, among patients, along the radius**

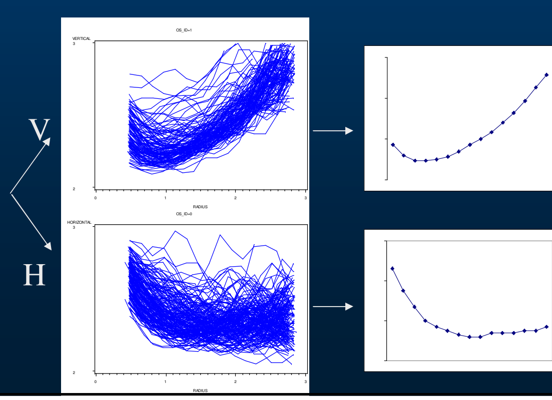
Modeling Strategy

Step 1. To understand FS data by asking:

(1) how to characterize the FD/radius data?

(2) is FD associated with any clinical variables?

Radius	FD(H)	FD(V)
0.48	2.71	2.43
0.64	2.57	2.36
0.80	2.49	2.30
0.96	2.42	2.26
1.12	2.36	2.30
1.28	2.33	2.35
1.44	2.32	2.39
1.60	2.40	2.49
1.76	2.48	2.54
1.92	2.43	2.54
2.08	2.36	2.54
2.24	2.42	2.66
2.40	2.47	2.93
2.56	2.32	3.08
2.72	2.16	2.94



The "global" Shape approach

Curve fitting with 2^{nd} order polynomial regression:

$Y = ax + bx^2 + e$

Step 1. To understand FS data

Approach: ANCOVA w/ Variance Component Model

FD (H,V) = 2^{nd} polynomial fitting over “radius” |OA prog + Clinical covs + Design pars + random effects (Variance Components)

Tension

Effect	P- (OS)	P- (JSN)
OA_progression (by JSN)	0.4219	0.065
radius	<0.0001	<0.0001
Radius*Radius	<0.0001	<0.0001
LeftvsRight	0.7002	0.8982
Radius*OA_prog	0.0022	0.0330
Radius*Radius*OA_prog	<0.0001	0.0222
Gender	0.6310	0.6481
Age	0.3553	0.3358
BMI	0.8683	0.9515
BMC	0.0256	0.0224

Compression

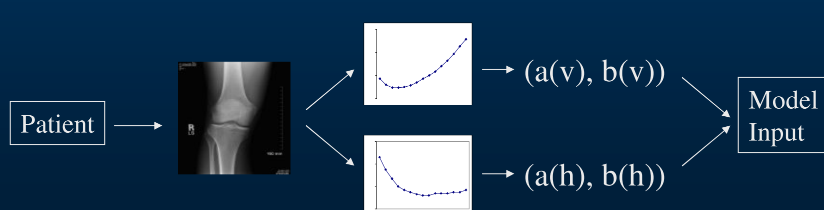
Effect	P-(OS)	P- (JSN)
OA_progression (by JSN)	0.7055	0.1417
radius	<0.0001	<0.0001
Radius*Radius	<0.0001	<0.0001
LeftvsRight	0.2166	0.1201
Radius*OA_prog	0.9433	0.8855
Radius*Radius*OA_prog	0.8743	0.7212
Gender	<0.0001	<0.0001
Age	0.0565	0.0398
BMI	<0.0001	<0.0001
BMC	0.1753	0.2122

Second Modeling Strategy

Step 2. Based on what was learned in step 1, build a prediction model for OA progress

Approach: due to the correlation patterns, we used GLM/GEE {generalized estimating equations} (Dist: Bin; L: logit)

OA prog = FS info (in polynomial parameters) + Clinical covs + Design pars + multiple correlation structures.



Results: p-values in type 3 GEE analysis
(SAS: proc genmod)

Outcome	JSN	JSN_MED	JSN_LAT	OS	OS_MED	OS_LAT
Age	0.42	0.030	0.053	0.21	0.94	0.48
Gender	0.69	0.93	0.28	0.61	0.93	0.79
Left vs. right	0.48	0.56	0.43	0.99	0.84	0.97
BMI	0.38	0.12	0.64	0.09	0.16	0.07
BMC	0.38	0.93	0.27	0.91	0.68	0.85
H_linear	0.028	0.023	0.53	0.47	0.07	0.50
H_quad	0.039	0.028	0.70	0.49	0.10	0.49
V_linear	0.034	0.011	0.75	0.96	0.20	0.46
V_quad	0.065	0.033	0.57	0.70	0.60	0.31

Recall only medial compartment FSA analysis

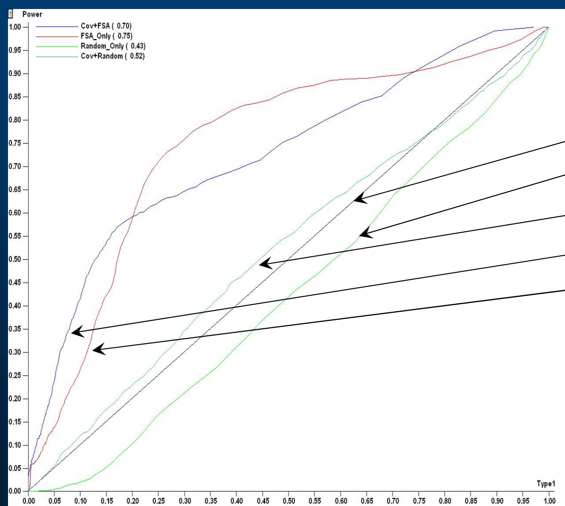
The Prediction Model

For every knee, a score (FS) is computed
e.g., for JSN_MED, knee (i):

FS (i) = – 0.54 + 0.02*age + 0.24*(female) – 0.24*(left knee) – 0.04*BMI – 0.06*BMC

What is the prediction power of this approach?
– The ROC curve

Results: JSN-MED Progress Prediction
5-fold Cross-Validation



	AUC
Null-model:	0.50
4 r.v. :	0.43
Cov+r.v. :	0.52
Cov+FS :	0.70
FS only :	0.75

The Goal of FSA

Generate a biomarker of trabecular integrity that is:

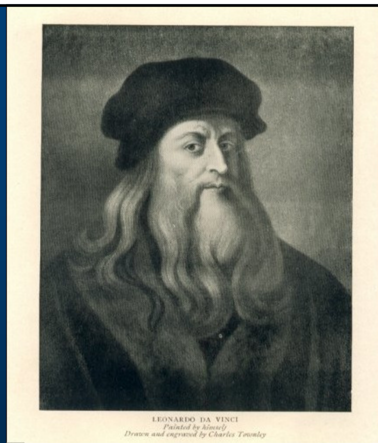
• Less sensitive to image acquisition quality

• Yields information related to 'mechanical/stuctural' integrity of the bone (Strength to Weight)

• Yields a marker of bone remodeling

• Yields a marker of response in a DMOAD trial

• Helps predict progression



In about 1490 Leonardo da Vinci drew plans for a flying machine.