From Broida to Bedside: From Fundamental to Clinical Research on Bone Fracture

Paul Hansma
presenting collaborative work done at

Hospital del Mar-IMIM, Autonomous University of Barcelona
Department of Physics, University of California, Santa Barbara
Active Life Scientific, Inc. Santa Barbara
An Abalone shell is 97% crystalline calcium carbonate

But it is 3000 times more fracture resistant than crystalline calcium carbonate! WHY?
Sacrificial Bonds and Hidden Length in Bone

James B. Thompson, Johannes H. Kindt, Barney Drake, Helen G. Hansma, Daniel E. Morse, and Paul K. Hansma

The sacrificial bond – hidden length mechanism

It takes much more work to stretch hidden length than to break a bond.

sacrificial bond breaks
work \leq 1 \text{ eV} = 23 \text{ kCal/mole}
= 1.6 \times 10^{-19} \text{ J}

hidden length stretched out
work \approx 100 \text{ eV} = 2,300 \text{ kCal/mole}
= 1.6 \times 10^{-17} \text{ J}

Bone consists of mineralized collagen fibrils that are 100 nm in diameter. The insert shows the effects of demineralization.

**Plasticity and toughness in bone**, R. O. Ritchie, M. J. Buehler and P. Hansma, Physics Today 24 (June 2009)

AFM images by Johannes Kindt UCSB
Trabecular Bone

Osteopontin?
This fracture mechanism would be called fiber pullout in a conventional composite material. It would be attributed to bonding failure at the fiber-matrix interface.
What resists the separation of mineralized collagen fibrils?

We believe that it is the glue within our bones.

Cover photo by: Georg Fantner
“The glue within our bones”: Maria Bellantone, Senior Editor, Nature Materials
The glue within our bones appears to resist the separation of mineralized collagen fibrils

Both high resolution SEM (A and B) and AFM (C) show “glue” filaments between mineralized collagen fibrils

Georg Fantner, Tue Hassenkam, Johannes Kindt, James Weaver, Henrik Birkedal, Leonid Pechenik, Jacqueline Cutroni, Geraldo Cidade, Galen Stucky, Daniel Morse, Paul Hansma

Bone medicine today

- Bone loss is quantified with X-rays (DXA). Patients with some bone loss are “osteopenic” with more bone loss are “osteoporotic”.
- Bone loss is treated drugs such as Fosamax, Boniva, Estrogen and Forteo.
- Side effects such as jaw necrosis and atypical femoral fracture are rare, but troubling.
- Fracture risk can be reduced by about 50% for the osteoporotic population.
Practical advice

• If you are under 30, get plenty of calcium and exercise to build up your bone.
• For all ages, have your vitamin D level checked. Aim for greater than 50 and less than 125 nmol/l. For most people this takes between 600 and 2000 IU vitamin D$_3$ daily.
• To do online research on health conditions enter the condition plus “NIH” or “Mayo” or “Johns Hopkins” in the search box.
Why can existing drugs only reduce fracture risk by 50%?

• Perhaps because bone loss is only half the problem!
Demo of good and bad Bone Material Strength
It is not really practical to do three point bending on a patient.

So what can be done?
A short history of the development of Reference Point Indentation
In the beginning.
The resistance to fracture decreases with baking.
The first success.

An automatic center punch makes larger indentations in the Baked bone than in the Control bone.

Hansma 2004
Reference Point Indentation RPI

Test Probe
Reference Probe

Hansma, January 2005
Probe assembly for Reference Point Indentation
The prototypes.


Prototype 19 (2007)

December 2004 to February 2005
From Broida to Bedside
Alex Proctor and Davis Brimer win New Venture Competition.
Dr. Adolfo Diez Perez tests Davis Brimer with Alex Proctor in the background.
Patients with fractures had larger Total Indentation Distances than patients with no fracture.
Image of an indentation compared to a dime

Close up view: indentation does not just compress the bone, it opens small cracks, just as in bone fracture.
Bone fracture begins with the separation of mineralized collagen fibrils.

Fracture resistance depends on the resistance to this separation of mineralized collagen fibrils.
Microindentation for *in vivo* Measurement of Bone Tissue Mechanical Properties in Humans

Adolfo Diez-Perez, Roberto Güerri, Xavier Nogues, Enric Cáceres, María Jesus Peña, Leonardo Mellibovsky, Connor Randall, Daniel Bridges, James C. Weaver, Alexander Proctor, Davis Brimer, Kurt J. Koester, Robert O. Ritchie, Paul K. Hansma

JBMR, 25, 1877-85 (2010)
From here there have been multiple new directions.

• A commercial version of our instrument is now being used in many institutions for basic research.
• A new type of Reference Point Indenter that is easier to use on patients and horses.
• A new, larger clinical study confirmed and extended the original study. Many new studies are already underway. Many more are planned.
• Theoretical work on modeling fracture processes.
• High resolution imaging of fractures and fracture processes.
• Experimental investigations of other tissues.
A commercial version of our instrument is now being used in many institutions for basic research.
A new type of Reference Point Indenter that is easier to use on patients and horses: the Osteoprobe®

Connor Randall holding the Osteoprobe head.
Dan Bridges holding the electronics.
The Osteoprobe® went from a sketch on yellow lined paper to clinical applications in less than one year thanks to the excellence and hard work of Connor Randall and Dan Bridges.

Dr. Roberto Güerri-Fernández training a new operator on himself at Hospital del Mar, Barcelona, Spain

Kevin Hoffseth (one of Chancellor Yang’s graduate students) with Doug Herthel, Alamo Pintado Equine Medical Center, Los Olivos, CA
### Osteoprobe – Potential Research Areas

**Over 100 known diseases that can increase risk of bone fracture**

<table>
<thead>
<tr>
<th>Acromegaly</th>
<th>Dent-Friedman syndrome</th>
<th>Liver disease</th>
<th>Peripheral neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acroosteolysis neurogenic</td>
<td>Dentinogenesis imperfecta, type I</td>
<td>Lobstein disease</td>
<td>Perthes’ disease</td>
</tr>
<tr>
<td>Adrenal Cortex Diseases</td>
<td>Depression</td>
<td>Lupus</td>
<td>Pituitary cancer</td>
</tr>
<tr>
<td>AIDS/HIV</td>
<td>Diabetes</td>
<td>Lymphoma and leukemia</td>
<td>Polio and post-polio syndrome</td>
</tr>
<tr>
<td>Allison atrophy</td>
<td>Dwarfism</td>
<td>Malabsorption syndromes</td>
<td>Poor diet, including malnutrition</td>
</tr>
<tr>
<td>Alpha-Mannosidosis</td>
<td>Dyskeratosis Congenita</td>
<td>Medication induced osteoporosis</td>
<td>Premature menopause</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Eating disorders (esp. anorexia nervosa)</td>
<td>Medullary cystic kidney disease</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Anorexia Nervosa</td>
<td>Familial Expanisite Osteolysis</td>
<td>Megarbane-Jalkh Syndrome</td>
<td>Pseudophosphatasia</td>
</tr>
<tr>
<td>Arterial occlusive disease</td>
<td>Female athlete triad (incl. missing periods)</td>
<td>Metabolic disorders</td>
<td>Renal osteodystrophy</td>
</tr>
<tr>
<td>Autoimmune Lymphoproliferative Syndrome</td>
<td>Fibrous dysplasia</td>
<td>Multiple endocrine neoplasia type 1</td>
<td>Renal rickets</td>
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<tr>
<td>Biliary cirrhosis</td>
<td>Gastrectomy</td>
<td>Multiple Myeloma</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Blood and bone marrow disorders</td>
<td>Gastrointestinal bypass procedures</td>
<td>Multiple pterygium syndrome lethal type</td>
<td>Rickets</td>
</tr>
<tr>
<td>Bone atrophy (from inactivity)</td>
<td>Gaucher Disease</td>
<td>Multiple sclerosis</td>
<td>Salvioli syndrome</td>
</tr>
<tr>
<td>Bone cancer</td>
<td>Gnathodiaphyseal dysplasia</td>
<td>Nephronophthysis, autosomal dominant</td>
<td>Scoliosis</td>
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<tr>
<td>Breast cancer</td>
<td>Grange syndrome</td>
<td>Neuropathy</td>
<td>Secondary Biliary Cirrhosis</td>
</tr>
<tr>
<td>Bruck syndrome 1</td>
<td>Grix-Blankenship-Peterson syndrome</td>
<td>Organ transplants</td>
<td>Secondary hyperparathyroidism</td>
</tr>
<tr>
<td>Bruck syndrome, 2</td>
<td>Hodgkin’s Disease</td>
<td>Osteogenesis imperfecta</td>
<td>Spinal cord injuries</td>
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<tr>
<td>Calcium deficiency</td>
<td>Hyperhomocysteinemia</td>
<td>Osteomalacia</td>
<td>Stroke</td>
</tr>
<tr>
<td>Calvarial doughnut lesions</td>
<td>Hyper-IgE Syndrome</td>
<td>Osteomylelitis</td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Chemical poisoning -- Aluminum</td>
<td>Hyperparathyroidism</td>
<td>Osteopetrosis</td>
<td>Thick skull syndrome</td>
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<tr>
<td>Chemical poisoning -- Ammonium Bifluoride</td>
<td>Hyperthyroidism</td>
<td>Osteopenia</td>
<td>Thyrotoxicosis</td>
</tr>
<tr>
<td>Chitty-Hall-Webb syndrome</td>
<td>Hypervitaminoses A and D</td>
<td>Osteoporosis</td>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td>Christian-Demyer-Franken syndrome</td>
<td>Hypophosphatasia</td>
<td>Paget's disease</td>
<td>Weight loss (incl. surgery like gastric bypass surgery)</td>
</tr>
<tr>
<td>COPD, including emphysema</td>
<td>Hypophosphatemic rickets</td>
<td>Panostotic fibrous dysplasia</td>
<td>Wilson's Disease</td>
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<tr>
<td>Cushing's syndrome</td>
<td>Inflammatory bowel disease (incl. Chron's disease)</td>
<td>Parastremmatic dwarfism</td>
<td></td>
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<tr>
<td>Decreased serum phosphate</td>
<td>Juvenile hyaline fibromatosis</td>
<td>Parkinson's disease</td>
<td></td>
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Also: Over 1,450 drugs with side effects known to increase risk of fracture.
## Current plans for Osteoprobe studies

Osteoprobe Study Proposals Include Researching How Bone Material Strength is Affected By ___:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bone Material Strength Affected By</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-menopausal osteoporosis</td>
<td>Diabetes – Type 1</td>
<td>Myastenia gravis</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Diabetes – Type 2</td>
<td>Chronic obstructive lung disease</td>
</tr>
<tr>
<td>Glucocorticoid steroid induced osteoporosis (GIOP)</td>
<td>Osteomalacia</td>
<td>Zoledronic acid (osteoporosis treatment)</td>
</tr>
<tr>
<td>Atypical femur fracture / long term use of bisphosphonates</td>
<td>Osteoporosis with and without hip fractures</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>Primary hyperparathyroidism</td>
<td>Van-Buchem disease</td>
</tr>
<tr>
<td>Post-organ transplant (kidney, liver)</td>
<td>Hyper- and Hypo-thyroidism</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Men (elder)</td>
<td>Multiple sclerosis</td>
<td>Osteogenesis Imperfecta</td>
</tr>
<tr>
<td>Fibrous dysplasia</td>
<td>Hypophosphatasia</td>
<td>Osteoporosis with and without vertebral fractures</td>
</tr>
<tr>
<td>Parathyroid Hormone (PTH) (osteoporosis treatment)</td>
<td>Vitamin D Deficiency</td>
<td>Weight loss after bariatric surgery</td>
</tr>
<tr>
<td>Obesity</td>
<td>Nutrition</td>
<td>Shoulder surgery/replacement</td>
</tr>
</tbody>
</table>

Davis Brimer, Active Life Scientific, Inc.
Theoretical work on modeling fracture processes: sacrificial bonds and hidden length increase resistance to crack propagation

The “glue” with sacrificial bonds and hidden length increases the flaw tolerance in bone. That is, a larger stress is required to trigger a dynamic crack propagation (i.e. a catastrophic fracture) when the glue is present.

- $a$ is the initial crack length
- $a_o$ is the crack size below which the specimen fails by yielding rather than fracture.
- $\sigma$ is the failure stress.
- $\sigma_y$ is the yield stress.
Theoretical work on modeling fracture: cortical bone plasticity and fracture

Kevin Hoffseth

Henry Yang
High resolution imaging of fractures and fracture processes

- SEM and AFM imaging of fracture process.
- Strong bone showing bridging (left column)
- Diseased bone without bridging (right column)

Connor Randall

Heather Barnard
Experimental investigations of other tissues

Mechanical profiling of intervertebral discs
Journal of Biomechanics 42 (2009) 1154–1157

Azucena Rodriguez & David Schultz
In summary

- Basic research on bone pointed to the need for a new clinical instrument.
- A Reference Point Indentation instrument can assess the contribution of materials properties to whole bone fracture risk in patients.
- Many human diseases are associated with changes in material properties of tissues.
- Now there is hope of measuring these changes in patients.
Acknowledgments

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• NIH Grant RO1 GM 065354

Thanks for your attention!
High resolution imaging of fractures and fracture processes

Indentation by Connor Randall, Collaboration by Alex Proctor and Chris Mazzochi, Active Life Scientific, Inc.

John Jameson
Microtomography Beamline 8.3.2, Advanced Light Source, Lawrence Berkeley National Lab, Berkeley, CA
Orthopaedic & Rehabilitation Engineering Center (OREC), Department of Biomedical Engineering, Marquette University, Milwaukee, WI

Gerald Harris, PhD, PE
Orthopaedic & Rehabilitation Engineering Center (OREC), Department of Biomedical Engineering, Marquette University, Milwaukee, WI
Shriners Hospitals for Children, Chicago, IL
Hip Fracture: a serious problem

A person with a hip fracture has a greater chance of dying within one year than if they had a heart attack.

33% are totally dependent or in a nursing home in the year following a hip fracture
Pass around bone model
A new, larger clinical study that confirmed and extended the original study.