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The mechanobiology of cancellous bone structural adaptation

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Abstract—The distinguishing morphological feature of cancellous bone is its high level of porosity relative to cortical bone. This porosity leads to more free surfaces and thus to more of the cellular constituents that inhabit those surfaces. As a result, cancellous bone is often more metabolically active and responsive to stimuli than cortical bone. This extends to the relationship between cancellous bone's internal structure and external mechanical loading. Observational investigations established this relationship as early as the late 19th century. These findings point to the interplay between biology and the cellular mechanical environment, forming the underpinnings of the modern term mechanobiology. Interestingly, it has proven to be more straightforward to assay the biological response than to quantify the precise mechanical environment of cancellous bone and the influence of cancellous bone structure. Despite this concern, significant insights into the nature of cancellous bone mechanobiology can be obtained from computational simulations that allow investigators to determine the morphological consequences of quantitative assumptions about cancellous bone mechanobiology. As the power of computers and the sophistication of these modeling techniques continue to grow, we can expect an increased impact in terms of clinical diagnosis and treatment. The next decade will bring improvements in exercise interventions to prevent and reverse bone loss; improved replacement-joint designs, particularly for those joints currently having poor expected outcomes; and an integration of computer simulation technology with clinical scanners.

Key words: *bone adaptation, bone remodeling, cancellous bone, finite element analysis, mechanical properties, mechanobiology.*

INTRODUCTION

The correspondence between cancellous bone structure and the mechanical loads to which it is exposed is at the historical root of the study of tissue adaptation. The drawings of the internal structure of the proximal femur by the Swiss anatomist von Meyer (1) in 1867 marked the beginning of serious research directed at uncovering the influence of the mechanical environment on trabecular structure. These drawings were studied by Culmann, a German civil engineer who had immigrated to Zurich, in what Roesler (2) termed "the first cooperation in the field

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of bone biomechanics." Culmann had developed a technique known as graphical statics for determining the direction of internal forces (or stresses) in complex structures. The mechanical stress patterns in a curved column structure that Culmann had been analyzing (known as a Fairbairn crane, **Figure 1**) were remarkably similar to the patterns of internal trabecular patterns documented by von Myer (3).

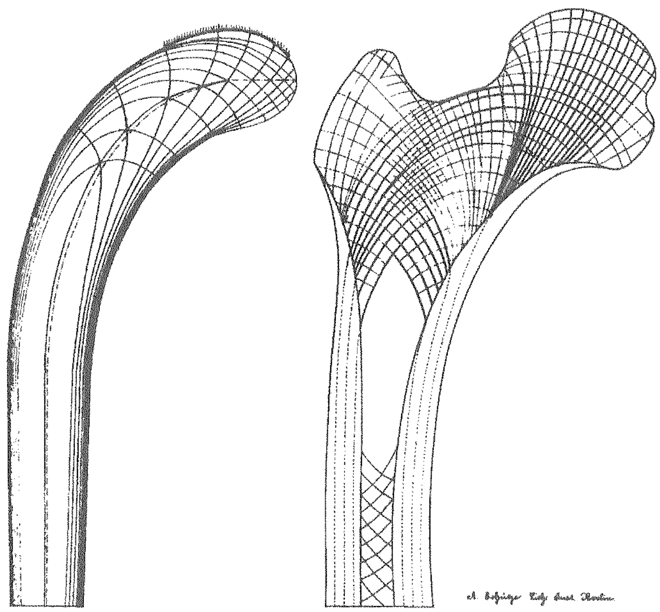

Figure 1.
On the left is Culmann's graphical statics analysis of the patterns of internal mechanical forces (stresses) in a Fairbairn crane. The curved column was under a distributed vertical load from the top. On the right is Wolff's depiction of the trabecular alignment in the proximal femur. Notice that the trabecular trajectories meet at right angles. Adapted from Wolff (32).

Although the work of Culmann and von Myer suggested that trabecular alignment is regulated by internal stress patterns, it was the outspoken support of Wolff (which came just 2 years later) that brought widespread acceptance of the idea. Wolff devoted the bulk of his writings to this subject, which he termed the "Trajectorial Theory" of trabecular alignment. Although sometimes criticized—even by such prominent mechanicians as Mohr (2)—Wolff's hypothesis went largely unquestioned by the scientific community of the time. He is said to have delivered quite passionate lectures to large crowds, where he would present numerous examples, illustrating the reorientation of trabecular alignment following a change in internal stress patterns such as occurs due to a fracture that has healed in malalignment. He is often credited with the discovery of cancellous bone adaptation and clearly made a significant contribution in popularizing the interaction of biology and mechanics, which we now refer to as mechanobiology.

Wolff thought that an implication of the Trajectorial Theory was that trabeculae would always intersect perpendicular to one another (**Figure 1**). This conclusion was based on an established fact in mechanics that internal stress directions must always intersect perpendicularly for any given loading case. Because trabeculae were proposed to align with these stress directions, it followed that cancellous bone architecture must form a network of perpendicular intersections. Wolff criticized the anatomical drawings of von Meyer—which were based solely on observations of cadaveric specimens—for not reflecting this perpendicular architecture. Modern investigations of cancellous bone suggest that in some cases the activities of daily living lead to a dynamic mechanical environment that cannot be supported effectively by a perpendicular trabecular structure. In this regard, Wolff may have been limited by restricting his thinking to the ideal situation of a single or predominant loading environment.

Nonetheless, Wolff firmly established a longstanding scientific interest in the mechanobiology of cancellous bone adaptation. Moreover, he proposed that such behavior would progress beyond his qualitative observations until cancellous bone adaptation could be understood in terms of a "law according to which alterations in the internal architecture clearly observed and followed mathematical rules..." (2). This idea foreshadowed an active area of current research aimed at uncovering just such a set of mathematical rules. Although an accepted "law of bone remodeling" has not been identified, important insights into the character of cancellous bone mechanobiology have been made by utilizing computer simulation to extrapolate the morphological consequences of various proposed relationships between the mechanical environment and the biological response. Furthermore, this research has led to novel technology with the potential to revolutionize clinical treatment by supplying physicians with accurate predictions of the mechanical environment, biologic response, and the ultimate mechanical competence of cancellous bone. Therefore, in the remainder of this article we will review and update advances in modeling of the mechanobiology of cancellous bone.

DISCUSSION

Apparent Level of Mechanobiological Adaptation of Cancellous Bone

The goal of the studies described in this section is to formulate a mathematical description of the interplay between the mechanical and biological behavior of cancellous bone at an apparent level. The foundation of the engineering field of continuum mechanics is the idea of considering the apparent behavior of materials that may have a complex microarchitectural structure. This is one of the most powerful tools available in structural analysis. The apparent level approach to understanding mechanical behavior is analogous to the biological approach of studying the net effect of cellular activity on a tissue without needing to account for each cell individually. Thus, for cancellous bone, one can relate the apparent level mechanics to the apparent level biological response and *vice versa* to arrive at an apparent level description of mechanobiological adaptation. This kind of approach is particularly suited to clinical applications, development of computer-assisted design tools, and establishment of promising directions for future design improvements.

The parallel advances of the high-speed digital computer, coupled with the invention of the finite element (FE) method to numerically analyze structural behavior, have led to dramatic improvements in our ability to determine quantitatively the apparent level mechanical environment of bone. These numerical approaches have improved on the graphical and photoelastic methods employed in prior studies of bone mechanobiology. It is possible to determine not only the predominant directions of internal stress, but also the quantitative mechanical intensity. This has made it feasible to model the implications, in terms of whole bone structure, of potential mathematical relationships describing mechanobiological interactions. These mathematical relationships, foreshadowed by Wolff one century earlier, initially only considered bone to be described by its apparent density. Interestingly, they did not account for the most remarkable feature of cancellous bone suggestive of mechanical-biological interaction, namely trabecular architecture and alignment. Density-based simulation of cancellous bone adaptation has been successfully applied to a number of clinical areas including, for example, the structure of the proximal femur (4–6) and hip joint arthroplasty (7–9). However, an area of research that is receiving increased attention is the reintroduction of the features of trabecular architecture.

The "Adaptive Elasticity" approach of Cowin and Hegedus (10) was an early model of cancellous bone mechanobiology that was capable of accounting for trabecular architecture at the apparent level. This was a mathematical framework that related internal mechanical stress to alterations in the apparent mechanical behavior of the bone. However, the large number of unknown parameters in the model has made it cumbersome to implement and compare with experimental observation. Fyhrie and Carter (11) developed the apparent level mathematical conditions that must be satisfied by the cancellous bone structure for it to be mechanically optimal for a given loading environment. However, the concept was not developed to the point of relating loading to the adaptation process as had been done in the case of bone density.

Jacobs et al. (12) introduced a mathematical approach that was capable of combining any existing rule describing mechanobiologic adaptation of density with an assumption that at each point the cancellous bone is mechanically optimized to support the mechanical load at that particular point. This approach is mathematically similar to the "free material" approach from the field of mechanical optimization. The free material approach is so named because at every point in the structure the material assumes the best possible mechanical behavior, and is in that sense free.

We utilized this approach in an analysis of the structure and function of the subchondral bone plate and how it is related to joint incongruity and cartilage contact pressures. We were motivated by a hypothesis advanced by Pauwels (13) that regions of high subchondral bone plate density occur due to high contact pressures in the adjacent cartilage. Such a correspondence would be very useful clinically, in the context of osteoarthritis, as an indicator of cartilage loading that could be visualized radiographically.

We tested these ideas in the context of the humeroulnar articulation of the human elbow. This joint is normally incongruous in that the trochlear notch of the ulna is deeper than would be required for a congruous fit with the trochlea of the humerus, resulting in a concave incongruity. When the trochlea articulates with the trochlear notch, cartilage-to-cartilage contact occurs initially in two distinct regions, one toward the dorsal aspect of the joint surface and one toward the ventral aspect of the joint surface. Under normal loading conditions these two regions may or may not merge together; but regardless, two points of maximal cartilage contact pressure are observed in what is termed a "bicentric" pressure pattern.

We constructed a FE model of the humeroulnar joint that reflects the anatomic geometry and level of incongruity. Boundary conditions were applied to simulate contraction of the triceps muscle with the joint in a 90º flexed configuration (i.e., resisted extension similar to a slow push-up exercise; 14). The equations for the free material formulation were applied to each element in the model to determine its mechanically optimal material behavior.

As expected, we did indeed observe a bicentric pattern of articular pressure as a result of the incongruous articulation. Furthermore, this did result in a pattern of subchondral bone with two different peaks centered around the middle of the joint (i.e., a bicentric pattern). However, the maximal predicted bone density was not located adjacent to the maximal predicted articular pressure, as would be suggested by Pauwels's hypothesis (13). Rather, the peak contact pressure was found roughly 5 mm toward the joint periphery (i.e., ventral and dorsal) from the peak subchondral bone density. Furthermore, the adaptive material model predicted that the most optimal orientation for subchondral cancellous bone was not perpendicular to the joint surface, as one might expect if the bone was supporting primarily normal pressure in the adjacent cartilage layer (**Figure 2**). Instead, the material model predicted trabecular alignment that followed parallel to the joint surface.

Our results indicate that joint incongruity can indeed lead to a bicentric pattern of articular pressures, which, in turn, brings about a bicentric pattern of subchondral bone density that can be understood as a result of mechanobiological adaptation. However, contrary to Pauwels's proposal (13), this adaptation was predicted to occur due to tensile forces in the subchondral bone (15,16) that come about due to bending and joint spreading caused by joint incongruity rather than the normal compressive stresses found adjacent to regions of articular contact. This interpretation is further supported by our finding of an optimal microstructural architecture oriented parallel to the joint surface. This is a highly mechanically-efficient architecture for supporting bending stresses in the subchondral bone plate. It is also important to note that the computer-predicted microstructure corresponds closely with the trabecular orientation observed in the anatomic specimen from which the model was created (**Figure 3**). With respect to our original hypothesis, we conclude that in incongruous joints the subchondral cancellous bone density patterns do not closely reflect the long-term distribution of contact pressure in the adjacent articular surface, but that the bone is adapted to the bending stresses that occur due to spreading open of the joint. Thus, with such an analysis it may yet be possible to relate subchondral cancellous bone structure to articular cartilage pressure; however, this relationship will not be as simple as once envisioned.

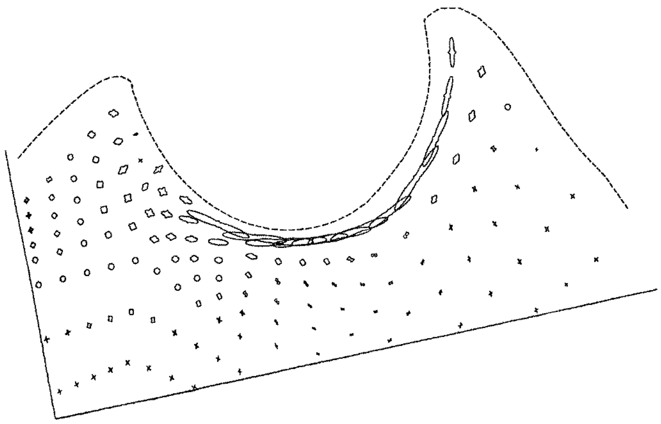

Figure 2.
The trabecular orientation as a function of direction presented as polar plots for selected elements in the model. Note that the olecranon and dorsal aspect of the joint is to the left and the coronoid process and ventral aspect of the joint is to the right. In this depiction, nonaligned trabeculae are represented by circles and progressively aligned trabeculae are represented by progressively eccentric plots. The maximum stiffness of the subchondral bone is oriented parallel to the adjacent articular surface.

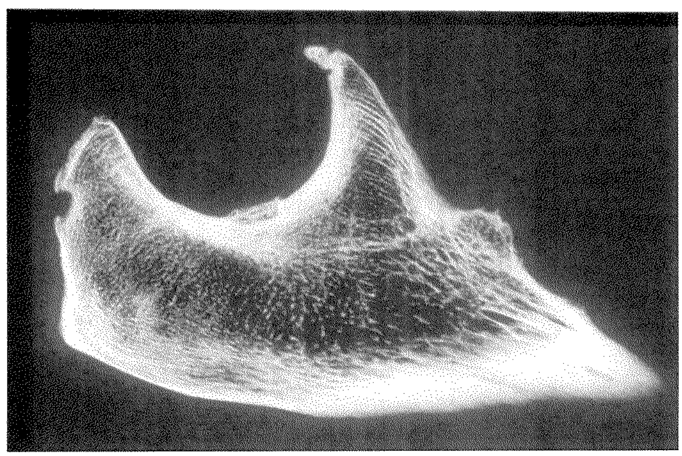

Figure 3.
Trabecular architecture of the trochlear notch obtained from the anatomic specimen that the finite element model was based upon. Note the higher density and increased thickness of the subchondral bone in a bicentric pattern surrounding the center of the joint. Also, the trabeculae in these regions are oriented parallel to the joint surface. Toward the periphery (dorsal and ventral aspects) of the joint, where the articular contract pressures are maximal, the subchondral plate is thinner and the trabeculae are oriented perpendicular to the joint surface.

Integration of Cancellous Bone Microstructure with the Apparent Level Approach

Although the free material approach described above can yield important insights into the mechanobiological nature of cancellous bone in many situations, it suffers from one important practical shortcoming. The free material approach places no limitations on the predicted material properties, except that they are mechanically optimized. In many cases this indeed appears to be the case for cancellous bone. However, as bone densities become very high, the free material approach leads to predictions of extreme orientation, much higher than can be realized with actual bone tissue. Thus, in some cases the free material approach incorporates material behavior that is highly mechanically efficient but cannot be achieved by real bone due to the limitations of the organic construction material.

This concern can be overcome by incorporating microstructural models directly into the formulation. Such an approach was adopted by Fernandes et al. (17). They were motivated by Wolff's Trajectorial Theory to incorporate a trabecular microstructure consisting of many small rectangular-shaped voids that are assumed to be oriented with the internal stress directions at each point in the bone. They applied this approach to a three-dimensional model of the proximal femur and are currently embarking on a comparison of total hip replacement stem designs. One difficulty they discovered with this approach is that it cannot provide optimal trabecular orientations in some cases involving multiple loadings. They found that at a small number of locations in the bone the orientation that was optimal for one loading case, such as stair climbing, was not optimal for another loading case, such as single limb stance. This can occur when the stress directions from two or more load cases are not mutually perpendicular to each other. In this case the most mechanically efficient microstructure will involve trabeculae that do not intersect perpendicularly. Quantitative investigation (18) as well as visual inspection (**Figure 3**) indicate that although a majority of cancellous bone does indeed exhibit perpendicular trabecular intersections, it is not limited to only perpendicular structure. Fernandes et al. (17) conclude that both their mathematical model for cancellous bone and the original ideas of Wolff represent a sufficiently accurate approximation of the adaptive nature of cancellous bone for many applications. However, one is left with the question: Can this nonperpendicular aspect of cancellous bone structure be understood in terms of mechanobiological adaptation?

The shortcomings described above of both the free material approach and the assumption of perpendicular trabecular intersections motivated us to develop an approach that combines the positive aspects of each. Our solution to this problem was to directly model trabecular architectural patterns. This involves creating another FE model for each element in the main or primary FE model. These secondary models are then utilized to determine the optimal mechanical trabecular pattern given the apparent density and internal mechanical stress directions in that particular element (19,20). This is repeated over and over for each element in the primary model (**Figure 4**; 21). In addition to the overall pattern of bone density in the primary model, this approach predicts seemingly reasonable patterns reflecting trabecular architecture at each point in the primary model. Interestingly, it was predicted that most of the cancellous bone structure would include perpendicular intersecting trabeculae, but in some regions the intersections did occur at an oblique angle. This suggests that significant aspects of trabecular microstructure can indeed be understood in terms of biologically mediated adaptation to the mechanical environment. Furthermore, such an approach should

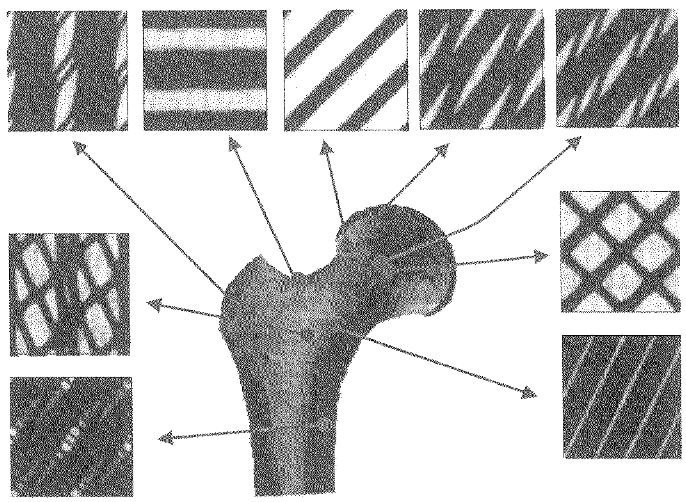

Figure 4.
The predicted density distribution from a 2-D side-plate model of the proximal femur in the coronal plane and optimal trabecular level structure at some selected locations. Notice that many locations have a trabecular morphology adapted to a single predominant loading direction, some are adapted to mutually perpendicular loading directions, and a few are adapted to as many as two or three different nonperpendicular loading directions. Also, although these optimal microstructures seem to reflect some important aspect of in vivo trabecular structure in terms of mechanical performance, they are at best idealizations. This suggests that some additional factors play an important role in determining trabecular morphology such as the process of morphogenesis, nutrient diffusion, or additional cellular or mechanical requirements.

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prove to be a powerful design tool for optimizing surgical interventions in which cancellous bone remodeling plays an important role.

The Direct Microstructural Approach

Techniques of mechanical analysis that have led to insights into the mechanobiologic regulatory mechanisms involved in forming and maintaining cancellous bone structure only recently have begun to be applied to the level of mineralized tissue itself. As described above, traditional modeling considers bone in terms of its average or apparent level behavior, and cannot address the small-scale behavior of individual trabeculae. This approach is built upon the assumption that on the apparent level the behavior of cancellous bone can be approximated by a continuum, also known as the continuum assumption. As such models are refined to smaller and smaller length scales, they eventually break down when the size of a single element approaches that of a single trabecula. Interestingly, the continuum assumption becomes valid again when the element size is much smaller than the size of a single trabecula. I refer to the application of continuum mechanics to cancellous bone on the tissue level (i.e., on a scale small enough to account for individual trabeculae) as direct microstructural modeling.

Direct micromechanical modeling at the tissue level holds the promise of avoiding the simplifying assumptions made in the apparent level approaches described above, thus facilitating the investigation of the relationship between the mechanical environment of individual trabeculae and the resulting biological response. Direct micromechanical modeling has been made feasible by technological advances in the areas of ultra-high-resolution tomographic scanners (22), automatic FE mesh creation algorithms (23), and FE solution procedures for the resulting very large FE models (24,25). Prior to these advances, the extreme geometric complexity of trabecular microarchitecture prohibited a precise determination of quantitative mechanical loading on the level of individual trabeculae. Critical to the acceptance of this technology has been practical validation of its accuracy and establishment of minimum numbers of elements required to achieve accurate solutions (26).

These advances have made it possible to routinely determine the micromechanical environment of cancellous bone in whole small animal specimens (**Figure 5**), and to perform initial analyses of whole human bones (27). In addition, potential cellular response behaviors have been proposed and the resulting mechanobiological consequences determined (28,29). In one example, Huiskes et al. (30) proposed that the stress concentration surrounding osteoclast resorption cavities is responsible for localizing osteoblastic bone formation during infilling of the cavity. They have shown this hypothesis to be consistent with experimental remodeling results on the apparent level. It seems clear that significant future insights into cancellous bone mechanobiology and structure will be made at the microstructural rather than the apparent level. In the coming decade we can anticipate that cancellous bone microstructural models will routinely include as many as 100 million to one billion elements and that radiological advances will lead to higher resolution with lower radiation exposures. The ability to moni-

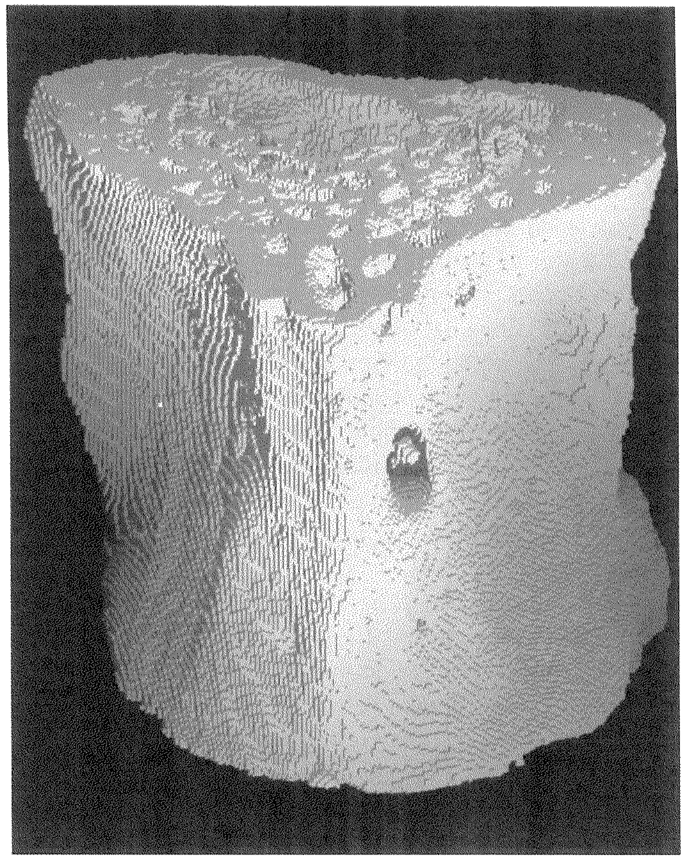

Figure 5.
A direct microstructural model of the lumbar vertebra of a rat containing over one million elements. Each small cube in the picture represents a single element in the finite element model. The upper endplate has been removed to reveal the interior cancellous bone structure. Models of this type are currently solved as a matter of routine and are being scaled up to human size as computer capabilities continue to grow.

tor the fate of individual trabeculae over time will soon be routine (31). Integration of estimates of cancellous bone mechanical competence from microstructural analysis into the standard software of clinical scanners will not be far behind. This development will represent a significant advance in the information available to the practicing physician and will greatly improve the standard of clinical care.

CONCLUSION

In summary, this review describes current advances in our understanding of the mechanobiology of cancellous bone structure made by attempting to identify the quantitative mathematical relationship between the mechanical environment and the biologically mediated processes that are ultimately responsible for trabecular architecture—an approach initially suggested by Wolff in the 19th century. These advances have taken investigators to the level of the micromechanical behavior of individual trabeculae and its relationship to cellular level responses. Simultaneous advances in the areas of cancellous bone experimental mechanics, *in vivo* models, cell biology, and cellular mechanics (not considered in this review) have led to equally significant advances. As the two fields of mechanics and biology continue to converge, we can expect increasing insights into the basic science of cancellous bone structure.

Furthermore, the technology developed by this research has the potential to lead to dramatic improvements in clinical care through improved diagnostic tools and more effective treatment strategies. In the future, computer simulations of the mechanobiologic adaptation of cancellous bone will be employed to evaluate and improve the efficacy of physical loading interventions such as exercise to help protect the elderly from the effects of osteoporosis or to build bone mass in younger people, or standing frame therapy to prevent bone loss in persons with spinal cord injury. In the area of orthopaedic endoprosthesis design, simulation can be utilized as a preclinical evaluation tool to streamline the development process. Accounting for trabecular architecture will play an important role in the next generation of replacement joints for which current designs have only a limited survival rate, such as the elbow. Finally, as computer power continues to grow, it will soon be possible for patient-specific simulations to be provided to clinical decision-makers to facilitate improved outcomes in cases of skeletal disease with a mechanical component.

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REFERENCES

1. von Meyer GH. Die architektur der spongiosa. Arch Anat Physiol Wiss Med. 1867;34:615–28.
2. Roesler H. The history of some fundamental concepts in bone biomechanics. J Biomech 1987;20:1025–34.
3. Thompson DW. On growth and form. New York: Dover Publications, Inc.; 1992.
4. Beaupré GS, Orr TE, Carter DR. An approach for time-dependent bone modeling and remodeling-application: a preliminary remodeling simulation. J Orthop Res 1990;8:662–70.
5. Levenston ME, Beaupré GS, Jacobs CR, Carter DR. The role of loading memory in bone adaptation simulations. Bone 1994;15:177–86.
6. Fischer KJ, Jacobs CR, Levenston ME, Carter DR. Different loads can produce similar bone density distributions. Bone 1996;19:127–35.
7. Huiskes R, Weinans H, Grootenboer HJ, Dalstra M, Fudala B, Slooff TJ. Adaptive bone-remodeling theory applied to prosthetic-design analysis. J Biomech 1987;20:1135–50.
8. Van Rietbergen B, Huiskes R, Weinans H, Sumner DR, Turner TM, Galante JO. ESB Research Award 1992. The mechanism of bone remodeling and resorption around press-fitted THA stems. J Biomech 1993;26:369–82.
9. Kerner J, Huiskes R, van Lenthe GH, Weinans H, van Rietbergen B, Engh CA, et al. Correlation between pre-operative periprosthetic bone density and post-operative bone loss in THA can be explained by strain-adaptive remodeling. J Biomech 1999;32:695–703.
10. Cowin SC, Hegedus DH. Bone remodeling I: a theory of adaptive elasticity. J Elasticity 1976;6:313–26.
11. Fyhrie DP, Carter DR. A unifying principle relating stress to trabecular bone morphology. J Orthop Res 1986;4:304–17.
12. Jacobs CR, Simo JC, Beaupré GS, Carter DR. Adaptive bone remodeling incorporating simultaneous density and anisotropy considerations. J Biomech 1997;30:603–13.
13. Pauwels F. Biomechanics of the locomotor apparatus. Berlin: Springer; 1980.
14. Eckstein F, Merz B, Schon M, Jacobs CR, Putz R. Tension and bending, but not compression alone determine the functional adaptation of subchondral bone in incongruous joints. Anat Embryol (Berl) 1999;199:85–97.
15. Eckstein F, Jacobs CR, Merz BR. Mechanobiological adaptation of subchondral bone as a function of joint incongruity and loading. Med Eng Phys 1997;19:720–8.
16. Jacobs CR, Eckstein F. Computer simulation of subchondral bone adaptation to mechanical loading in an incongruous joint. Anat Rec 1997;249:317–26.
17. Fernandes P, Rodrigues H, Jacobs C. A model of bone adaptation using a global optimisation criterion based on the trajectorial the-

ory of Wolff. Comp Meth Biomech Biomed Eng 1999;2:125–38.

18. Bacon GE, Bacon PJ, Griffiths RK. A neutron diffraction study of the bones of the foot. J Anat 1984;139:265–73.
19. Bendsoe MP. Optimisation of structural topology, shape and material. Amsterdam: Springer-Verlag; 1995.
20. Sigmund O. On the optimality of bone microstructure. Boston: Kluwer Academic Publishers; 1999.
21. Rodrigues H, Jacobs C, Guedes JM, Bendsoe MP. Global and local material optimization models applied to anisotropic bone adaptation. In: Pedersen P, Bendsoe MP, editors. Synthesis in biosolid mechanics; vol 69. Boston: Kluwer Academic Publishers; 1999. p. 209–20.
22. Feldkamp LA, Goldstein SA, Parfitt AM, Jesion G, Kleerekoper M. The direct examination of three-dimensional bone architecture *in vitro* by computed tomography. J Bone Miner Res 1989;4:3–11.
23. Keyak JH, Meagher JM, Sinner HB, Mote CD Jr. Automated three-dimensional finite element modelling of bone: a new method. J Biomed Eng 1990;12:389–97.
24. van Rietbergen B, Weinans H, Polman BJW, Huiskes R. A fast solving method for large-scale FE-models generated from computer images, based on a row-by-row matrix-vector multiplication scheme. ASME CED 1994;6:47–52.
25. Hughes TJR, Levit I, Winget J. An element-by-element solution algorithm for problems of structural and solid mechanics. Comp Meth Appl Mech Eng 1983;36:241–54.
26. Jacobs CR, Davis BR, Rieger CJ, Francis JJ, Saad M, Fyhrie DP. The impact of boundary conditions and mesh size on the accuracy of cancellous bone tissue modulus determination using large-scale finite-element modeling. J Biomech 1999;32:1159–64.
27. Van Rietbergen B, Muller R, Ulrich D, Ruegsegger P, Huiskes R. Tissue stresses and strain in trabeculae of a canine proximal femur can be quantified from computer reconstructions. J Biomech 1999;32:443–51.
28. Mullender MG, Huiskes R, Weinans H. A physiological approach to the simulation of bone remodeling as a self-organizational control process. J Biomech 1994;27:1389–94.
29. Mullender MG, Huiskes R. Proposal for the regulatory mechanism of Wolff's law. J Orthop Res 1995;13:503–12.
30. Huiskes R, Ruimerman R, van Lenthe GH, Janssen JD. Indirect osteoclast-osteoblast coupling through mechanical stress relates trabecular morphogenesis and adaptation to bone turn-over. Bone 1998;23:S344.
31. Ryaby JT, Magee FP, Haupt DL, Kinney JH. Reversal of osteopenia in ovariectomized rats with combined magnetic fields as assessed by x-ray tomographic microscopy. J Bone Miner Res 1996;11:S231.
32. Wolff J. Das Gesetz der transformation der knochem. Berlin: Hirschwald; 1892.