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Techniques and Applications of Adaptive Bone Remodeling Concepts

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2.1 Introduction and Synopsis

Despite the apparent inanimate nature of bone, bone is a dynamic living material constantly being renewed and reconstructed throughout the lifetime of an individual. Bone deposition and bone resorption typically occur concurrently, so that bone is remodeled continually. It is this adaptive remodeling process, driven partially in response to functional requirements, that distinguishes living structural materials from other structural solids. As a complex biological phenomenon, adaptive bone remodeling has played a dominant role in the study of bone physiology and biomechanics for over a century, and has been active biologically for as long as there have been vertebrates.

The relationship between the mass and form of a bone to the forces applied to it was appreciated by Galileo,[1] who is credited with being the first to understand the balance of forces in beam bending and applying this understanding to the mechanical analysis of bone. Julius Wolff[2] published his seminal 1892 monograph on bone remodeling; the observation that bone is reshaped in response to the forces acting on it is presently referred to as Wolff's law. Many relevant observations regarding the phenomenology of bone remodeling have been compiled and analyzed by Frost.[3,4] Despite the general acceptance that mechanical stimulation influences bone homeostasis and adaptation, controversy remains as to the governing mechanical stimuli: how mechanical signals are transduced at the cellular and subcellular levels, and whether electrical and molecular phenomena coincident with mechanical stimulation mediate cellular responses.[5]

The development of a theoretical framework for the prediction of bone remodeling and the clinical implementation of this framework are of particular interest. An all-inclusive understanding of bone

remodeling has the following potential in clinical practice: the reduction, treatment, or possible prevention of osteoporotic bone loss; acceleration of fracture healing; and the optimization of implant design. In search of this goal, mechanistic and phenomenological theories of bone remodeling have been proposed.[6-12]

The following sections provide an overview of the methods hypothesized to predict the phenomenon of adaptive bone remodeling. Following a brief review of bone morphology, special emphasis is placed on adaptive remodeling: theoretical and experimental investigations, proposed theoretical models of bone adaptation, and the possible causal mechanisms responsible for the adaptive bone remodeling processes.

2.2 Structure of Bone

The development of bone from embryonic to adult size depends on the orderly processes of mitotic divisions, cellular growth, and structural remodeling. Bone has been recognized as a highly complex system, a multifunctional tissue subjected to a large number of interrelated biochemical, biophysical, and biological processes.[13] In turn, mechanical and geometrical properties of bone have been attributed to these processes.

The sizes, shapes, and structures of human skeletal bones are quite well known. Each bone possesses a characteristic pattern of ossification and growth, a characteristic shape, and features that indicate its functional relationship to other bones, muscles, and to the body structure as a whole. The shape and surface features of each bone are related to its functional role in the skeleton. Long bones, for example, function as levers during body movement. Bones that support the body are massive, with large articulating surfaces and processes for muscular attachment. Because the primary responsibility of the skeleton is structural, bone has acquired the unfortunate reputation of being a simple material.[14]

Histological Organization

The following is a brief discussion with regard to the basic histological organization of bone, for it is with this understanding that the significance of the structure may be assessed. Bone represents a complex, highly organized, connective tissue, characterized physically by its hardness, rigidity, and strength, and microscopically by relatively few cells and considerable intercellular substance, formed of mineralized fibers and cement. It has a rich vascular supply and is the site of considerable metabolic activity. At the lowest level, bone may be categorized as a composite material composed of a fibrous protein, collagen, stiffened by an extremely dense filling of inorganic calcium phosphate (hydroxyapatite). Bone has additional constituents, namely, water and some ill-understood amorphous polysaccharides and proteins which accompany living cells and blood vessels.

Bone Cells

Four types of bone cells are commonly recognized: *osteoblasts, osteocytes, osteoclasts,* and *bone lining cells.*[15] Osteoblasts, osteocytes, and the bone lining cells arise from primitive mesenchymal cells, called osteoprogenitor cells, within the investing connective tissue. Bone formation is carried out by active osteoblasts, which synthesize and secrete the proteins and other organic components of the bone matrix.[16] This process creates an organic matrix known as osteoid, within which calcium and phosphate are subsequently deposited in amorphous masses. The inorganic or mineral phase constitutes approximately 50% of bone by volume and is composed of calcium crystals primarily in the form of hydroxyapatite.[17] Hydroxyapatite crystals precipitate in an orderly fashion around collagen fibers present in the osteoid. The osteoid rapidly calcifies (approximately 70% calcification after a few days), reaching maximal calcification within several months.[18]

As the completely mineralized bone accumulates and surrounds the osteoblast, that cell loses its synthetic activity and becomes an interior osteocyte. Although encased in the mineralized bone matrix, osteocytes maintain contact with other osteocytes, osteoblasts, and bone lining cells via an extensive network of small, fluid-containing canals, or canaliculi. The bone lining cells are resting cells located on inactive bone surfaces which represent more than 80% of the trabecular and endocortical surfaces of

adult bone.[15,19] These cells represent a terminal differentiation of the osteoblasts and are thinly extended over the bone surface. In general, mitotic activity is absent. Upon stimulation, however, the bone lining cells may be activated to form a layer of osteoblasts. Osteoclasts, on the other hand, are multinucleated giant cells with the capability of removing bone tissue in a process referred to as osteoclasis or bone resorption.

Bone Tissue

At the macroscopic level, adult bone tissue is broadly divided into two distinguishable forms: cortical bone, also referred to as *compact* bone, and trabecular bone, also referred to as *spongy* or *cancellous* bone (Fig. 2.1). Trabecular and cortical bone differ in histological structure, gross appearance, location, and function. Dense cortical bone comprises the diaphysis of appendicular long bones while a thin shell encompasses the metaphysis. Cancellous, or trabecular, bone exists as a three-dimensional, interconnected network of rods and plates which delimit a labyrinthine system of intercommunicating spaces that are occupied by bone marrow. This porous, highly vascular tissue reduces the weight of the bone, while providing space for bone marrow where blood cells are produced.

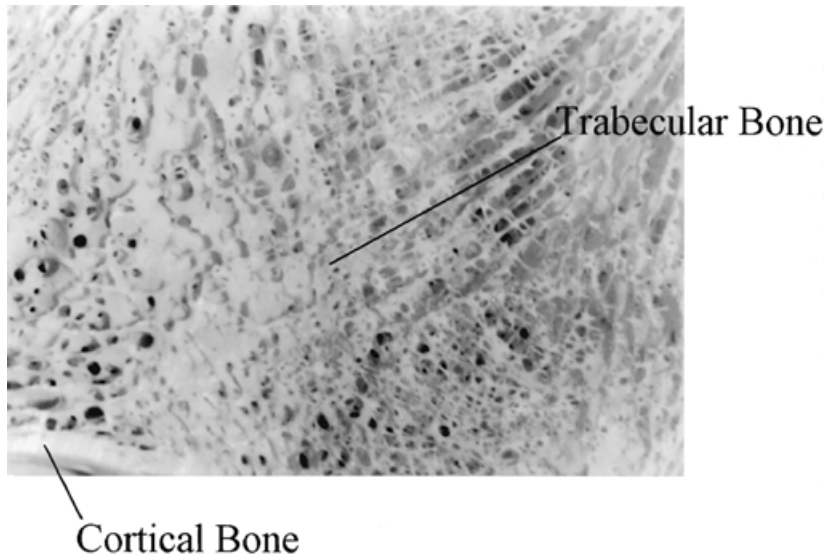

FIGURE 2.1 Lamellar organization — appearance and distribution of trabecular and cortical bone.

Although it constitutes only 20% of the skeleton, trabecular bone has a greater overall surface area than does cortical bone and is considered to possess greater metabolic activity. Relative density (i.e., the ratio of specimen density to that of fully dense cortical bone — usually 1.8 g/cc) provides the criterion upon which the classification of bone tissue as cortical or cancellous is based. The relative density of trabecular bone varies from 0.05 to about 0.7 while that of cortical bone is approximately 0.7 to about 0.95.[20] The external surface of bone is covered by a periosteum consisting of a fibrous connective tissue outer layer and a cellular inner layer. The periosteum not only serves for the attachment of muscles, but aids in protection and provides additional strength to the bone. Moreover, the periosteum provides a route for circulatory and nervous supply, while actively participating in bone growth and repair.[16]

While all bone tissue in mammals contains cells, fibers, and cement, their relative amounts and arrangements vary. Because the chemical, molecular, and cellular components are similar among bone types, the variability in properties of bone has been attributed to the differences in the organization of these elements. In general, bone microstructure can be divided into three broad categories: (1) woven bone; (2) primary bone (primary lamellar, plexiform, primary osteons); and (3) secondary bone.

Woven bone is architecturally arranged as a close network of fine trabeculae. It is nonlamellar and generally less dense than other types of bone. It should be noted that the reduction in density is a function of the loose packing of collagen fibers and large porosities rather than reduced mineralization. The collagen in woven bone has fine fibers, approximating 0.1 μm in diameter, and oriented almost randomly. Consequently, it is difficult to make out any preferred direction over distances in excess of a few micrometers (μm). Typically, woven bone proliferates rapidly, most notably in the fetus and during callus formation in fracture repair. Equally rapid woven bone formation can result from damage to, or tension on, the periosteum.

In contrast to woven bone, primary bone requires a pre-existing substrate for deposition. Consequently, lost trabeculae may not be replaced, unless done so by woven bone, and then remodeled. Furthermore, primary bone is divided into three morphologically distinct categories: primary lamellar, plexiform, and primary osteons.

Lamellar bone is distinguished histologically by its multilayered structure. Primary lamellar bone is arranged circumferentially around the endosteal and periosteal surfaces of whole bones. Primary lamellar bone can become increasingly dense. Compact lamellar bone superficially resembles plywood in section, as if numbers of thin plates were cemented together. A series of concentric plates characterizes the cross-sectional appearance.[21] Cancellous bone is also composed of primary lamellae, with a large surface area intimately contacting marrow. In general, primary lamellar bone exhibits superior mechanical strength.

Like woven bone, plexiform bone is deposited rapidly, but exhibits mechanical qualities superior to those of woven bone. Analogous to primary lamellar bone, plexiform must be deposited on pre-existing surfaces. Structurally, however, plexiform bone resembles highly oriented cancellous bone. Plexiform is predominatly seen in larger, rapidly growing animals such as young cows, and has been observed in growing children.[22]

When the accretion of lamellar bone surrounds a centrally placed blood vessel, a concentrically arranged osseous structure is created. It is this architecture that distinguishes the Haversian system. A set of concentric lamellae (from a few to as many as 20), in conjunction with associated bone cells (osteocytes) and a central vascular channel, constitutes an osteon. Osteons are elongated, almost solid cylinders largely directed in the long axis of the bone.

Osteons are categorized as primary or secondary. Primary osteons are the first to be laid down in early life. Note that primary bone is new bone deposited in a space where bone failed to exist previously, although it may be fabricated on an existing bone surface. By contrast, secondary bone is the product of the resorption of pre-existing bone tissue and the deposition of new bone in its place. In cortical bone, the result of osteoclastic resorption and subsequent osteoblastic formation is a secondary osteon. Consequently, secondary osteons replace primary osteons and are subject to continual resorption and renewal throughout life. The process is referred to as internal remodeling. Primary osteons are relatively small; they have no cement lines; there are no fragments or wedges of interstitial bone between them; and the central canal may contain two or three vessels. In contrast, secondary osteons are generally larger structures. They are surrounded by narrow cement lines and between them reside irregular pieces of lamellar bone (interstitial bone), many of which are remnants of former osteons removed during remodeling.[21] The cement lines bounding secondary osteons tend to be irregular and represent lines of reversal, indicating the change from bone resorption to deposition. The absence of these lines in primary osteons establishes the prominent morphological distinction from secondary osteons. After initial deposition, all types of bone are subject to secondary reconstruction or remodeling.

2.3 Adaptive Remodeling of Bone

Phenomena

Living bone is continually undergoing processes, collectively termed *remodeling*, of deposition and resorption, partially but not totally driven by changes in its mechanical load environment.[15] This dynamic

aspect of bone tissue has the effect of providing strength in direct response to weightbearing stress. Adaptive remodeling may be conveniently recognized as external and internal, although the cellular mechanisms are the same for both and the processes overlap in time.[21] External remodeling is concerned with the architecture of bones (i.e., geometry and form), while internal processes alter the bone structure histologically. Remodeling may replace the matrix material while leaving the bone as a whole unchanged, or may produce alterations in the shape, internal architecture, or mineral content of the bone. Although the general shapes of bones are established genetically, other forces are at play. The actions of muscles, in addition to their places of origin and insertion, introduce important mechanical factors that influence the external shape and internal arrangement of trabeculae. Erect posture, for example, in combination with gravity, greatly influences the internal architecture of the vertebrae of the axial skeleton (Fig. 2.2) and long bones of the appendicular skeleton.

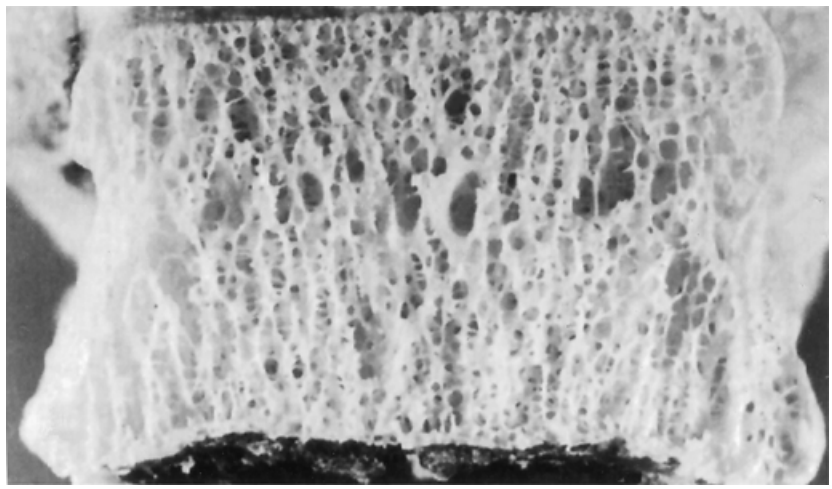

FIGURE 2.2 Longitudinal section through a vertebral body illustrating the trabecular network. *Source*: White and Panjabi, *Clinical Biomechanics of the Spine*, J.B. Lippincott Co., 1990, p. 41. With permission.

General Description and Clinical Observations

In a healthy adult who maintains a consistent level of physical activity, a balance between bone resorption and formation exists so that there is no net change in bone mass. In general, adaptive bone remodeling is acknowledged as error-driven. That is, mechanical loads upon bone must deviate from normal values by a sufficient amount (error signal) to initiate a remodeling response. If the threshold stress is not exceeded, no remodeling response occurs. In addition, saturation limits beyond which bone refrains from adapting are assumed by most theories. The mechanisms for regulation of the remodeling process are largely unknown, but undoubtedly involve local regulatory factors, a combination of physical factors as a result of weightbearing stress, and the effects of calcium-regulating hormones impinging on the different bone cell populations.[22,23] The turnover rate of bone is undeniably high. In a young adult, approximately one-fifth of the skeleton is resorbed and then rebuilt or replaced annually.[16] It should be noted that regional as well as local differences exist in the rate of turnover. As a result, not every part of every bone will be equally affected.

Although the mechanosensory system in bone tissue has not been identified, it appears reasonable to assume that, when living bone is deformed, the mechanical strain signal is transduced to the bone cell population.[15] Mechanical loading has been cited as an important factor shifting the remodeling balance in favor of bone formation in adults. Mechanical factors are responsible for adjusting the strength of bone in response to the demands placed upon it. The greater the physical stress to which the bone is subjected, the greater the rate of bone deposition. On the other hand, loss of bone mass occurs in response

to the removal of mechanical stress, as in persons who undergo prolonged bed confinement or those in prolonged space flight. Such changes in response to altered mechanical loading conditions have significant clinical implications.

At an estimated rate of 600,000 operations yearly, artificial joint replacements constitute one of the major surgical advances of this century, second only to dental reconstruction as an invasive treatment of bodily ailments.[24] Adaptive bone remodeling has been cited as an important factor affecting the long-term post-operative behavior of joint replacements. Clinical, as well as experimental, studies have demonstrated that factors such as prosthesis position, patient activity level, body weight, fixation technique, and component material properties significantly affect the success rate of total joint arthroplasty.[25-27] These factors, whether in conjunction or individually, contribute to the nature of the mechanical environment at the bone-implant interface. The long-term success of any implant is going to be dependent on the biomechanical as well as biochemical compatibility of the implant.[28] For example, a decrease in stress in the proximal femur as a result of load transmission through the implant stem, past the proximal femur, to the midshaft is thought to be a possible explanation for the resorption in the calcar region and subsequent loosening of hip implants.[29] The changes in bone structure following prosthetic joint replacement have been studied extensively, especially for total hip replacements,[30,31] and total knee replacements.[32,33] Advanced stress analysis methods, such as finite element (FE) modeling, have proven to contribute significantly to such research endeavors.

Quantitative Experiments

While clinical inquiries provide the ultimate evaluation of long-term implant-induced remodeling, the cost, duration, and ethical considerations involving human experimentation prolong feedback to the implant designers. The advent of modern computing capabilities, in conjunction with numerical stress analysis techniques, enabled researchers to relate bone mechanics to the observed bone structure. The aforementioned mathematical descriptions have enabled bone modeling and remodeling simulations to be implemented in combination with the finite element method (FEM).[10,11,34-38] Most of these evaluations have sought to procure a characteristic mechanical stimulus, or collection of stimuli which predict most realistically, adaptive remodeling in response to distinct loading modalities.

As previously mentioned, it is common for bone remodeling theories to be coupled with the finite element method. In general, such simulations initiate with a given model geometry, initial density distribution, and a set of selected applied load cases. The remodeling equations are employed to update the internal density distribution and/or external geometry incrementally. The model is considered to have converged once the change in density and/or geometry with each increment is small. Validation studies reveal that these computer simulations enable accurate predictions of long-term formation and resorption of bone around orthopedic implants in animals and in humans. Consequently, the incentive for continued investigations aimed at establishing the specific factors governing the adaptation response of bone is great. To date, the majority of work in this area has focused on the femur, knee, and more recently the spine.

The validity of such finite element models must be assessed by experimental verification. Brown et al.[39] made an attempt to correlate the Rubin-Lanyon turkey ulna model with finite element modeling to establish the mechanical parameters associated with bone remodeling. Functionally isolated turkey ulnae were selected, enabling the loading conditions to be characterized completely while the periosteal adaptive responses were monitored and quantified after four and eight weeks of loading. Subsequently, their three-dimensional FE model of the ulna was validated against a normal strain-gauged turkey ulna under identical loading conditions. Twenty-four mechanical parameters were compared in an attempt to correlate the FE results with those obtained experimentally. The pattern of perisoteal bone remodeling was most highly correlated with strain energy density and longitudinal shear stress. Recently, Adams[5] extended the preliminary work of Brown et al.[39] to 43 candidate mechanical parameters, further investigating whether the initiation of appositional bone formation in the turkey ulna can be predicted by examining changes in mechanical factors associated with controlled loading regimens.

Beaupré et al.[40] combined adaptive remodeling techniques and finite element analyses to forecast the evolution of density in the human proximal femur. A two-dimensional finite element model of the human femur was subjected to three loading conditions to establish the daily tissue stress level stimulus. Representative loads consisted of a single-legged stance and extreme cases of abduction and adduction with respective daily load histories of 6000, 2000, and 2000 cycles. Based on the daily load history, the simulation was used to predict the density evolution from an initial homogeneous state. Density distributions were established after various iterations (i.e., 1, 15, 30) for remodeling with and without the inclusion of a lazy zone (i.e., a certain threshold level in over- or underloading must be exceeded prior to an adaptive response). As the number of time increments exceeded 30, the differences between the two models became more pronounced. The model incorporating the lazy zone showed little change (elemental density changes $< 0.02\ g \cdot cm^{-3}$), while in the absence of a lazy zone, the model continued to change as far as 125 iterations, predicting much higher density gradients. The more realistic density gradients predicted by the lazy zone may warrant attribution to some physiologic counterpart to which it is related. Orr et al.[41,42] embarked on a similar investigation into the bone remodeling induced by a femoral surface prosthesis. The density changes induced by a metal cap, a metal cap and central peg, and an epiphyseal plate surface prostheses were computed. It was assumed that there was total bone ingrowth in the prosthetic device, rigidly bonding the bone and implant.

Huiskes et al.[37] coupled the finite element method with numerical formulations of adaptive bone remodeling to investigate the relation between stress shielding and bone resorption in the femoral cortex around intramedullary prostheses such as those used in total hip arthroplasty (THA). A generalized, simple model of intramedullary fixation was implemented.[43] The FE model consisted of a two-dimensional axisymmetric straight bone and stem. Results indicated that the amount of bone resorption is largely dependent upon the rigidity and bonding properties of the implant; these results are compatible with animal experimental data on similar intramedullary configurations reported in the literature.[44-47]

Huiskes et al.[48] developed a three-dimensional FE model of a finger joint system. FE analysis was carried out to investigate the stress patterns in the structure as a whole and to establish the influences of material and design alternatives on these patterns. A follow-up investigation[49] was aimed at evaluating the aforementioned stress patterns at a local rather than global level, enabling a more detailed comparison with bone adaptive behavior.

Levenston et al.[50] employed computer modeling techniques to examine stress-related bone changes in the peri-acetabular region. They simulated the distribution of bone density throughout the natural pelvis as well as changes in bone density following total hip arthroplasty. The post-surgical models analyzed simulated fully fixed and loose bone-implant interfaces. The geometrical nature of the finite element model was based on a two-dimensional slice through the pelvis, passing through the acetabulum, pubic symphysis, and sacroiliac joint.[50,51] Initiating from a homogeneous bone density distribution, an incremental, time-dependent technique was employed to simulate the bone density distribution of the pelvis.

The average daily loading history was approximated with loads from a number of different activities along with the assumed daily frequencies of each. The simulations progressed until a stable bone density or state of little net bone turnover was achieved. The authors simulated the distribution of bone density in the natural pelvis as well as changes in bone density following total hip arthroplasty (THA). When loads representing multiple activities were incorporated, the predicted bone density for the natural pelvis was in agreement with that of the actual bone density distribution (Fig. 2.3). In contrast, the simulation restricted to a single-limb stance did not generate bone density distribution deemed realistic. This supports the concept that diverse loading plays a dynamic role in the development and maintenance of normal pelvic bone morphology. Utilizing the density distribution predicted of the natural bone, the finite element models were modified to investigate two designs of noncemented, metal-backed acetabular cups. A number of morphologic changes were predicted by these simulations.

The fully ingrown spherical component induced extensive bone resorption medial and inferior to the acetabular dome and bone hypertrophy near the interior rim; the fully loose component induced a lower level of bone loss as well as bone hypertrophy, by comparison. Acetabular components with no ingrowth transferred loads in a more physiologic manner than their fully fixed counterparts. The authors concluded

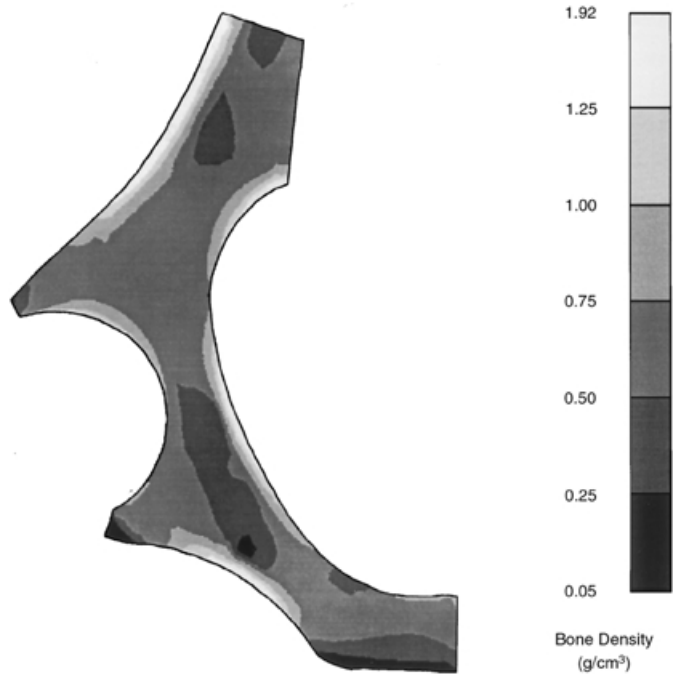

FIGURE 2.3 Predicted density distribution around the natural acetabulum subjected to a varied loading history. *Source*: Levenston, M.E. et al., *J. Arthroplasty*, 8, 595, 1993. With permission.

that an ideal state of complete bony fixation may yield unfavorable adaptive responses; hence, a successful acetabular component design must balance such considerations. It was interesting to note that the overall bone remodeling predicted around the acetabular components is much less destructive than that around the prosthetic femoral components.

A preliminary study by Goel and Seenivasan[52,53] applied a bone-adaptive remodeling theory to a basic ligamentous lumbar spine model. The change in shape of a two-motion segment model in response to axial compression and as a function of injury and stabilization was of primary interest. The vertebral bodies and discs were assumed to be cylindrical and have flat endplates. The simplified cylindrical shape was adopted in the attempt to validate the hypothesis that the bone adaptive remodeling applications yield the actual vertebral configuration. In response to an axially compressive load, the shapes of the remodeled vertebrae closely resembled the shape of an actual vertebral body (Fig. 2.4). The changes in shape observed in response to the fixation device were representative of stress shielding, characteristic of rigid fixation. Although the study demonstrated the feasibility of quantifying changes observed in the spinal segments following surgery, the simplicity of the model entailed limitations. Because spinal structures are inherently complex, the FE model utilized required considerable refinement.

In a follow-up study,[54,55] similar trends were observed in a more detailed model of the spine. An insignificant change in external geometry was not surprising because the models were derived directly from CT scans. As a result, few alterations were necessary. The opposite held true for internal remodeling, however. The internal remodeling algorithm converged for all governing loads, excluding torsion. The total strain energy density (TSED) for cancellous bone decreased as a function of iteration (or time), reaching a minimum at iteration 30 during compression. TSED is defined in the "Strain Energy Density (SED) Theory of Adaptive Bone Remodeling" subsection of the "Empirical Models" section of this chapter.

The elastic modulus distribution in the mid-transverse plane of the L4 vertebral body was higher in the postero- and central regions of the cross-section (Fig. 2.5). In the coronal view, elevated values were predicted centrally and adjacent to the endplates. An approximately uniform distribution of 15 MPa was

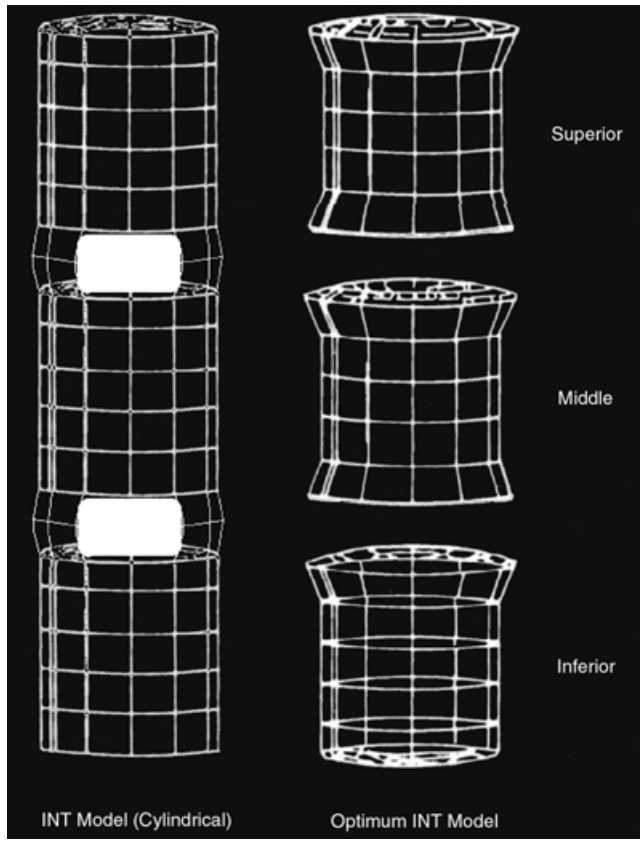

FIGURE 2.4 The optimal vertebral shape predicted via a cylindrical intact (INT) model in response to axial compression.

observed in other loading modes. Deviations from uniformity, however, were observed. For example, during extension, increased elastic moduli were predicted in the anterior and posterior regions of the transverse plane, the central region of the coronal plane, and the posterocentral and anterior inferior-most elements of the midsagittal plane. The distribution for flexion and lateral bending closely resembled that of extension, deviating slightly. The predicted inhomogeneous distribution following the remodeling procedures was in agreement with the experimental data.

In flexion, extension, and lateral bending modes, the cancellous bone region surrounds the neutral axis (bending axis). This is due to the load sharing role of posterior elements (ligaments in flexion, facets and ligaments in extension, and lateral bending modes). Thus, one would expect a smaller role of the stresses/strains in the bone remodeling process of the cancellous bone. Furthermore, in a healthy person, the muscular forces counteract the external bending moments and the ligamentous spine is only subjected to axial compression and small amounts of AP and lateral shear forces. Thus, the contributions of the bending moments toward the inhomogeneity of the cancellous bone should be minimal. The precise cause of nonconvergence in the axial torsional mode is not clear, but the ineffectiveness of torsional loads on the bone remodeling of a vertebral body is in agreement with similar predictions for the long bones.[56] This study has opened up a new research direction in the area of spinal biomechanics.

For example, the use of threaded interbody fusion cages for achieving spinal fusion has the potential to impart increased stability, while simultaneously reducing complications associated with the use of autogenous bone grafts. Interbody fusion devices are designed to facilitate stability as well as restore and maintain disc height. The BAK (BAK Interbody Fusion System, Spine-Tech) implant is a hollow, threaded cylinder accommodating multiple fenestrations to facilitate bone ingrowth and through-growth.

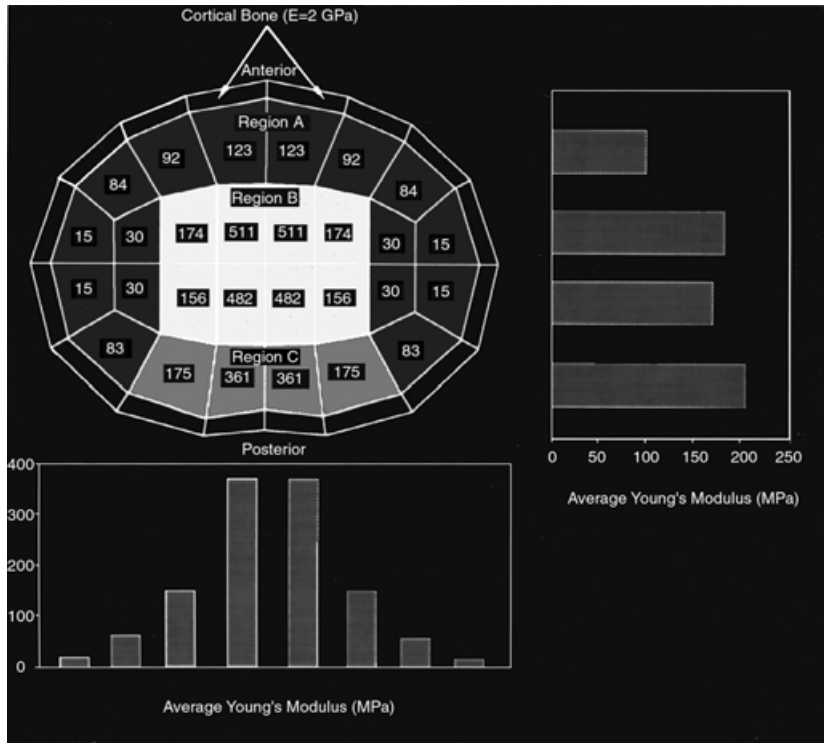

FIGURE 2.5 Predicted average elastic moduli distribution (in MPa, unless noted otherwise) in the transverse plane of the L4 vertebra subjected to 424.7 N axial compression.

Consequently, this device is an ideal candidate for exercising the aforementioned bone remodeling applications in conjunction with a finite element model of the spine.

Grosland et al.[57] are currently in the process of mimicking a spinal fusion, incorporating the BAK Interbody Fusion System in a refined finite element model of the spine (L3-L5). A bilateral anterior surgical approach was assumed. The internal remodeling algorithm utilized was based on a blend of various hypotheses reported in the literature.[37,38,58] A preliminary investigation has predicted a number of morphological alterations in response to the bone remodeling simulations following implantation of the device. During compression, the overlying and underlying bone directly adjacent to the device experienced bone hypertrophy (expressed as a percent change with respect to the intact model), while atrophy was induced laterally (see Fig. 2.6). Bone adjacent to the large holes of the device experienced minimal change. During flexion, extensive bone hypertrophy was induced anteriorly adjacent to the device, while atrophy was predicted posteriorly. The results clearly indicate that the vertebral bone, following cage implantation, undergoes both hypertrophy and atrophy as compared to the optimal intact bone density distribution. Bone growth in the anterior region predicted by the model is in agreement with experimental observations. Thus, the bone is likely to grow in and around the larger size holes of the BAK device, suggesting that in the long run the device will entrench itself into the denser bone.

Empirical Models

Following in the footsteps of Wolff, investigators began experimenting with mathematical descriptions of mechanical bone-mass regulation. Their theories provide a quantitative formulation of Wolff's law which states, qualitatively, that bone is an optimal structure relative to its mechanical requirements and possesses the ability to maintain an optimal configuration in response to a mechanical alteration. As stated originally, Wolff's law was neither quantitative nor mechanistic. The first quantitative demonstration that

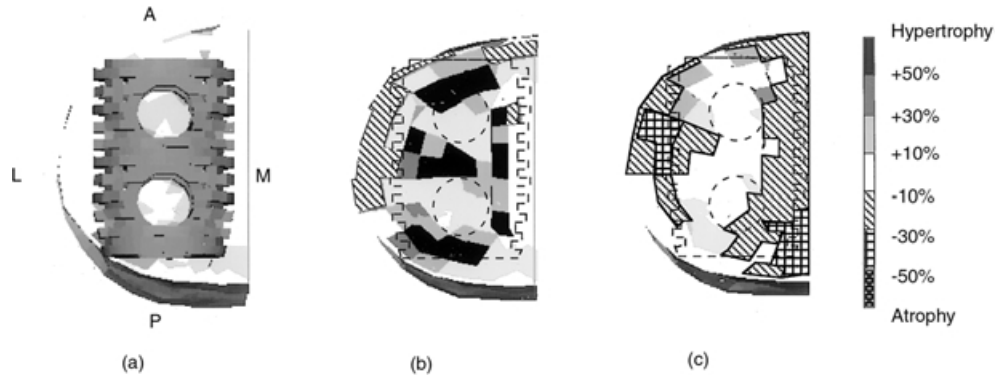

FIGURE 2.6 Interbody fusion system: (a) FE model of the BAK device positioned with respect to the inferior surface of L4 (A = anterior; P = posterior; L = lateral; and M = medial). Percent change in bone density adjacent to the BAK device with respect to the intact model during (b) 400 N compression and (c) 10 Nm flexion and 400 N preload. Dashed line indicates position of the device.

bone responds to its mechanical environment was presented by Koch,[59] although André[60] was the first to suggest that deformation rather than load could govern bone geometry. Martin[22] suggests that the idea may have been conceptualized and stated most clearly by D'arcy-Thompson:

> The origin, or causation, of the phenomenon would seem to lie partly in the tendency of growth to be accelerated under strain and partly in the automatic effects of shearing strain, by which it tends to displace parts which grow obliquely to the direct lines of tension and pressure, while leaving those in place which happen to lie parallel or perpendicular to those lines … accounting therefore for the rearrangement of … the trabeculae within the bone.[61]

Two types of bone mass changes may occur. Remodeling may affect the density of the bone and thereby its elastic moduli (internal remodeling) or its structural behavior (external remodeling). As a result of either remodeling process, the stresses and strains throughout the bone will be altered. That may in turn perpetuate a cascade necessitating further remodeling. The process continues until the remodeled bone density and shape are optimally suited to support the imposed loads. The precise nature of the feedback mechanism is neglected in the modeling of the adaptation process; it is only asserted that such a process exists. For example, numerous biological and biochemical constituents discussed previously are overlooked, or dealt with superficially.

Frost's Flexural Neutralization Theory

The flexural neutralization theory (FNT) of bone remodeling developed by Frost[7] in 1964 became the first mathematical formulation of bone remodeling as a function of mathematical variables. Frost suggested that changes observed in bone curvature, in combination with the polarity of tangential stress, are intimately associated with remodeling responses, namely, an increase in surface convexity favors bone resorption (osteoclastic activity), while bone deposition (osteoblastic activity) is promoted by a decrease in convexity. Initially, Frost theorized that there exists a *minimum effective stress* that must be exceeded to excite an adaptive remodeling response to mechanical overload.[7] In recent years, he has reformulated his theory in terms of strain rather than stress. Instead of speculating that strains below a certain threshold are "trivial" and evoke no adaptive response, Frost suggests that a *range* of strain values elicits no response.[89] Consequently, strains above this threshold evoke a positive adaptive response (i.e., deposition of bone), while those below the threshold induce a negative response (i.e., bone resorption).

The aforementioned FNT proposed by Frost, however, has been criticized on the basis that bones are naturally curved, and need be. It must be kept in mind that Frost's theory concerns load-induced changes in surface curvature rather than absolute curvature. Martin[22] suggests that if Frost originally expressed his theory in terms of a variable more directly related to strain and divorced from notions of local

anatomic conformation, the confusion and debate may have been reduced. All controversy aside, Frost is commonly credited with providing the conceptual framework from which many of the current mechanical theories have been guided.

Pauwels' Stress Magnitude Theory

Pauwels[62] proposed a model for predicting the cortical thickness of diaphyseal bone as a function of the axial stresses due to bending. Accurate predictions were attained with respect to distortions in the cross-sectional geometry of a rachitic femur, through simplified assumptions relating surface remodeling to stress. Simplifying the initial femoral cross-section to a hollow elliptical geometrical configuration, the surface stress, σ_s, was calculated as a function of a simulated hip load. Alterations were made to the cortical thickness (T_c) via the following power function:

$$T_c = a + b\sigma_s^n \tag{2.1}$$

where, *a*, *b*, and *n* are arbitrary constants. A sequence of remodeling steps was established. Following an iterative process, the final stage (considered an equilibrium point) closely resembled the geometrical configuration of the actual bone. The rationale for the algorithm defining his model was not explained in detail; nonetheless, his efforts established the capabilities of a simplistic model to predict generalized adaptive geometries. Kummer[63] advanced a concrete form of Pauwels' theory which has been carefully reviewed by Firoozbakhsh and Cowin.[64] The cubic relationship between bone remodeling and stress is expressed as:

$$U = a[(\sigma_s - \sigma_o)^2 (\sigma_i - \sigma_s) - (\sigma_i - \sigma_s)^3] \tag{2.2}$$

where, *U* is a measure of the bone remodeling (i.e., positive values indicate bone apposition, negative values indicate bone resorption); *a* is a proportionality factor related to the remodeling rate; σ_i is the actual stress; σ_s is the optimal equilibrium stress; and σ_o represents the lowest/highest tolerable bone stress. The cubic relationships developed by Kummer accounted for the adaptive changes associated with pressure necrosis, but neglected those associated with disuse atrophy.

Cowin's Adaptive Elasticity Theory

The mathematically rigorous and potentially powerful theory proposed by Cowin and colleagues,[56,65-67] was developed to describe the physiological adaptive behavior of bone. The basic hypothesis governing the thermomechanical continuum theory of adaptive elasticity is that the load-adapting properties of living bone can be modeled by a chemically reacting porous medium in which the rate of reaction is strain controlled. The objective was to model bone as a porous elastic solid and to model the normal adaptive processes that occur in bone remodeling as strain controlled mass deposition or resorption processes which modify the porosity of the porous elastic solid.[65] An implementation of this model[56] revealed that a nonhomogeneous cylindrical bone would become homogeneous when subjected to uniform stress. In addition, it was shown that remodeling will not occur in a long bone, such as the femur, as a result of a purely torsional load about its long axis.

In the years that followed, Cowin and Firoozbakhsh[68] presented a somewhat less rigorous surface adaptation model in which bone assumed a site-specific homeostatic equilibrium strain state. Control equations, in which the rate of remodeling is proportional to the deviation from a reference (homeostatic) value were developed. Consequently, any aberrant strain state would influence bone remodeling in an attempt to reinstate homeostatic conditions via the following formula:

$$U = C_{ij}\left(e_{ij} - e_{ij}^o\right) \tag{2.3}$$

where *U* represents the rate of deposition or resorption; e_{ij} is the actual strain tensor, and e_{ij}^o is the homeostatic or reference strain tensor. The C_{ij} establishes a generalized matrix of remodeling coefficients. It should

be noted that the authors relied on generality for the choice of C_{ij}, without reference to a biological basis. The values of the remodeling rate coefficients are necessary for a model to prove biologically useful, as the C_{ij} tensors contain coefficients for each component of strain. Experimental procedures indicate that the coefficients vary with each test model, consequently eliminating the ability to describe adaptation in a generalized sense. Cowin and associates[64] performed cubic approximations of the theory of internal remodeling, and performed numerous studies attempting to establish possible values of the remodeling coefficients. Cowin and associates[6] also described a computational approach to the theory of surface remodeling enroute to predicting *in vivo* values for surface remodeling rate coefficients.

Employing the surface remodeling theory established by Cowin and Van Buskirk,[67] Cowin and Firoozbakhsh[68] presented a variety of theoretical predictions of surface remodeling in the diaphysis of long bones. For example, both endosteal and periosteal surfaces can move in either direction, in or out, in the same or opposing directions. It is possible for the medullary canal to fill completely, subsequently causing the endosteal surface to vanish. They proposed that the limitations of Cowin and Van Buskirk[67] were attributable to their assumption that the movement of the periosteal and endosteal surfaces was small.

The Cell Biology-Based Model

Hart et al.[11,69] utilized the adaptive elasticity model proposed by Cowin and co-workers to develop a computational model used to predict strain-history-dependent remodeling in long bones. Rather than follow the mechanical phenomenological approach of the adaptive elasticity theory, the model developed the remodeling rate constants in terms of biological parameters including the number of different cells present and their average daily activity. The basic premise of the model was that since bone is both resorbed and formed by cells that line the bony surfaces, bone remodeling is the manifestation of surface cellular processes. Hart's computational model was constructed around the techniques of the finite element method. The model was extended to incorporate the influence of material maturation (i.e., the material added to the surface of the bone was allowed to mature with time). Results were in agreement with the available analytical results and added to the importance of coupled remodeling effects not examined previously.

Strain Energy Density (SED) Theory of Adaptive Bone Remodeling

Huiskes and co-workers[37] proposed an alternative to the formulation of the theory of adaptive elasticity utilizing the strain energy density function as the remodeling signal rather than the strain tensor. As a scalar, the SED (U) represents the deformational energy available at any point:

$$U = {}^{1}/_{2}\ \varepsilon_{ij}\sigma_{ij} \tag{2.4}$$

where σ_{ij} and ε_{ij} represent the local stress and strain tensors, respectively. The driving mechanism for adaptive activity is assumed to be the aberration between the actual SED (U) and a site-specific homeostatic equilibrium SED, (U_n). Following a suggestion from Carter,[70] Huiskes assumed bone to be "lazy." In effect, he assumed that a certain threshold level, s, in overloading or underloading must be exceeded before bone reacts (Fig. 2.7). Mathematically, the internal remodeling rule becomes:

$$\begin{aligned} dE/dt &= C_e\left(U-(1+s)U_n\right); \quad U>(1+s)U_n \\ &= 0; \qquad\qquad\qquad (1-s)U_n \le U \le (1+s)U_n \\ &= C_e\left(U-(1-s)U_n\right); \quad U<(1-s)U_n \end{aligned} \tag{2.5}$$

where E is the elastic modulus of the element in question and C_e is the internal remodeling rate constant to be determined experimentally. External remodeling is represented by a similar modified formula, such that dx/dt exemplifies the rate of surface growth normal to the surface.

In the absence of a "lazy zone" (i.e., s = 0), internal remodeling is represented by:

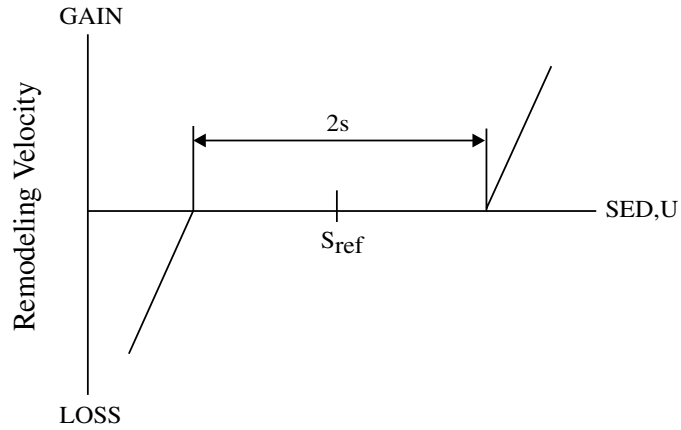

FIGURE 2.7 The adaptive remodeling rate as a function of strain energy density (SED) with threshold (s). (*Source*: Adapted from Huiskes, R. et al., *J. Biomech.*, 20, 1135, 1987. With permission from Elsevier Science.)

$$dE/dt = C_e(U - U_n) \tag{2.6}$$

while the external relocation of surface nodes takes the form:

$$dx/dt = C_x(U - U_n) \tag{2.7}$$

To date, the remodeling rates (i.e., C_e, and C_x) have not been established and are defined arbitrarily. Consequently, only the end result is deemed realistic.

Theory of Self-Optimization or Bone Maintenance

Fyhrie and Carter[10] advanced a theory suitable in principle to describe the self-optimization capabilities of bone Wolff proposed mathematically. They postulated that bone would adapt its apparent density and trabecular orientation locally for any loading environment in order to normalize a predestined effective stress value. The proposed bone remodeling objective was approximated using two independent measures of structural integrity: one based on strain energy; the other based on failure stress. The strain energy density (SED) principle optimized the stiffness while strength was optimized via the failure stress principle. Both measures were capable of predicting the orientation of trabeculae consistent with the trajectory hypotheses of Roux, von Meyer, Culmann, and Wolff and define stress measures that can be used to predict apparent density.[10] Each optimization approach predicted that at equilibrium the apparent density of cancellous bone is related to applied stress via:

$$\rho \propto \sigma_{eff}^{c} \tag{2.8}$$

where σ_{eff} is an effective stress measure. The predicted value of the exponent C depends upon whether stiffness of strength optimization is assumed. Fyhrie and Carter[71] discovered that the apparent density was proportional to the square root of an effective stress ($C \approx 1/2$), when optimizing strength. By contrast, the strain energy density approach or strain energy density principle conveyed an apparent density proportional to the cube root of an effective stress squared ($C \approx 2/3$).

As introduced initially,[10] the SED principle did not optimize the strain energy density of the bone tissue but rather it optimized the apparent strain energy density of the continuum representation of the cancellous bone. The average "true" strain energy density of bone tissue, U_b, was subsequently related to the apparent SED, U, via:[72]

$$U_b = U/\nu \tag{2.9}$$

where ν represents the volume fraction of mineralized bone tissue.[73] The argument for using U_b as the objective function was that "one would expect cellular reactions to stress to be a result of mineralized tissue strain energy only rather than an average of strain energy over mineralized tissue and marrow spaces."[72] Fyhrie and Carter[71] utilized this predictive theory to contrive the bone density distribution concordant with that found in the normal femoral head when a loading condition representing the single limb stance of gait was applied.

Whalen et al.[74] and Carter et al.[72] expanded the single-load approach for predicting bone density to encompass the multiple-loading history of bone over a predefined period. This approach characterized the bone loading histories for an "average day" in terms of stress magnitudes or cyclic strain density and the number of loading cycles. The assumption that bone mass is adjusted in response to strength or energy considerations enabled relationships between the local bone apparent density and loading history to be established.

Beaupré et al.[34] sought to extend the bone maintenance theory developed by Carter and colleagues into a time-dependent modeling/remodeling theory. The daily mechanical stimulus ψ_b was defined as:

$$\psi_b = (\rho_c/\rho)^2\psi \tag{2.10}$$

where ρ_c is the density of cortical bone (assumed to be approximately equal to the density of mineralized tissue); ρ is the apparent density (mineralized tissue mass per total tissue volume); and ψ represents the daily stress stimulus measured at the continuum level. The tissue level remodeling error, e, in the following form, represents the difference between the actual tissue level stress stimulus and the tissue level attractor state stress stimulus:

$$e = \psi_b[\psi - (\rho/\rho_{AS})^2\psi_{AS}]/\psi \tag{2.11}$$

where ρ_{AS} and ψ_{AS} denote the bone density and stress stimulus of the attractor state (AS), respectively. This error constitutes the driving force for bone remodeling.

Intertwining the time-dependent remodeling rules governing the theories of Huiskes, and Beaupré, and the self-optimization or bone maintenance theory,[71] Weinans et al.[38] sought to obtain a better understanding of the behavior of strain-adaptive bone remodeling in combination with FE models. In particular, the stability and convergence behavior of the remodeling rule were investigated in relation to the characteristics of the FE mesh. Hence the remodeling objective took on the following form:

$$\partial\rho/\partial t = B(U_a/\rho - k); \quad 0 < \rho < \rho_{cb} \tag{2.12}$$

where, $\rho = \rho(x, y, z)$ is the apparent density, B and k are constants, and

$$U_a = (1/n)\sum_{i=1}^{n} U_i \tag{2.13}$$

This process was considered to have *converged* when $\partial\rho/\partial t$ attained zero value according to Eq. (2.6) or when the density secured a minimal or maximal value. The stimulus, as a rule, was measured per element. Each element in principle possessed three possible paths of convergence en route to remodeling equilibrium: (1) the bone absorbed completely ($\rho = 0$); (2) the bone became cortical ($\rho = \rho_{cb}$); or (3) the bone remained cancellous with an apparent density satisfying $E = c\rho^{\gamma}$. Based on their results, the following hypotheses were drawn: (1) that bone is indeed a self-optimizing material that produces a self-similar trabecular morphology, a fractal, in a chaotic process of self-organization, whereby uniform SED per unit mass or a similar mechanical signal is an attractor; (2) that the morphology has qualities of

minimal weight; and (3) that its morphological and dimensional characteristics depend on the local loading characteristics, the maximal degree of mineralization, the sensor density, and the attractor value.

It should be noted that these models are empirical, not physiological. They may be used to estimate the outcome of a remodeling process, but provide little or no explanation about the operation of remodeling process. Nonetheless, the aforementioned models provide an evolution of adaptive remodeling techniques.

Unstable Behavior

The literature is scarce regarding the stability of the proposed theoretical bone remodeling simulations. The lack of an analytical solution for stresses, in a medium where material properties vary with position, acts as a limitation to the study of these models. Harrigan and Hamilton[75] sought the origin of unstable bone remodeling simulations mathematically, using strain-energy-based remodeling rules in an attempt to assess whether the unstable behavior was due to the mathematical rules proposed to characterize the process or to the numerical approximations used to exercise the mathematical predictions. The physiologic interpretation indicated that the instabilities that occur in some remodeling simulations are due, at least in part, to the mathematical characterization of bone remodeling. In addition, the behavior of the observed instabilities is not present *in vivo*. Consequently, the cause of this unstable behavior is most likely not attributed to natural remodeling processes.

Carter et al.[35] observed that when their simulation of femoral bone remodeling was allowed to progress past the first few iterations, "The method employed appeared to converge toward a condition in which most elements will either be saturated … or be completely resorbed." Recently, Weinans et al.[38,76] demonstrated, confirmed by others,[75,77] that previous bone remodeling implementations tend toward discontinuous density patterns (Fig. 2.8). In the vicinity of the applied loads, elements predict alternating patterns of high and low density, resembling the pattern of a checkerboard. Jacobs et al.,[77] in an attempt to eliminate the spurious near-field discontinuities, while maintaining anatomically correct far-field discontinuities, implemented a "node-based" technique.

Fyhrie and Schaffler,[78] in the same vein, sought to improve spatial stability via a revised phenomenological theory of bone remodeling. They cite that bone remodeling theories are often based on the common assumption that the changes in bone structure in response to an *error* signal are *adaptive*, and therefore bring about a reduction in error. They criticized that under these assumptions, the basic formulation of the remodeling problem is to adapt the structure to make the error approach zero. Consequently, this formulation will not converge to an optimal bone structure unless the error function is specifically designed to do so. If, however, the optimality is defined as zero signal error at each point in the bone, this formulation does result in an optimal solution. En route to the development of a new remodeling theory, the following distinctions were made. The apparent density was identified as the controlling variable, while the controlled variable was a function of the apparent strain, denoted $M(\mathrm{E})$. The controlling and controlled variables were defined as those which the bone cells can directly modify, and those which measure the ability of bone to adapt to the current need, respectively. Although the precise form of the function $M(\mathrm{E})$ is not known presently, it is considered the homeostatic value of apparent density attained by bone subjected to constant strain. The fact that the function is not necessarily zero as the strain magnitude goes to zero accounts for the biological factors which prevent the total disappearance of bone tissue. The fundamental character of the remodeling equation was exponential, consistent with experimental observations of changes during disuse, after hip replacement surgery, and during growth and aging. Fyhrie and Schaffler were able to demonstrate that the model is stable temporally, and more spatially stable than some models published previously.

Causal Mechanisms

The origin and function of adaptive remodeling have been debated extensively. The feedback mechanism by which bone tissue senses the change in load environment and initiates the deposition or resorption of bone is not understood.[15] Undoubtedly, mechanical factors play an important role in remodeling;

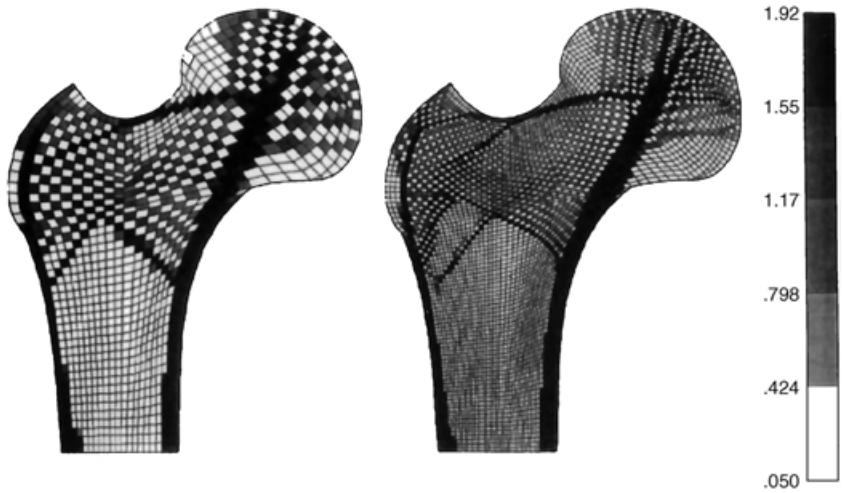

FIGURE 2.8 Predicted checkboard density distribution characteristic of the traditional element-based bone remodeling algorithms. *Source*: Jacobs, C.R. et al., *J. Biomechanics*, 28, 449, 1995. With permission.

inactivity results in widened Haversian canals and porotic bone, while stresses result in a more solid compactum. Recent investigations have explored the biological response of bone to mechanical loading at the cellular level, but the precise mechanosensory system that signals bone cells to deposit or resorb tissue has not been identified.[15]

Numerous recorded observations suggest that bone cells *in situ* are capable of responding to mechanical stimuli and do so in a predictable fashion (i.e., Wolff's law). Experimental limitations often hinder such investigations at the cellular level. A major constraint of *in vitro* organ culture conditions is that the cultured structures are complex and composed of heterogeneous cell populations.[15] Although *in vivo* loading conditions may be approximated, extracting satisfactory information from these models regarding individual cell behaviors is laborious. Nonetheless, experimental procedures have implicated different mechanisms for adaptive bone remodeling.

Debate is ongoing as to the mechanical signal to which bone cells respond. The question with regard to the causation of adaptation — stress or strain? — is intrinsically difficult to answer due to their direct proportionality. Although closely related, their relationship in a nonhomogeneous and anisotropic material such as bone is altogether variable. Stress is an abstract concept, the components of which must be deduced from measurements of load, or from measurements of strain and elastic constants.[22] In addition, stress is defined based solely on its effects. Strain may be measured directly via strain gauges, or calculated from measured displacement fields as the symmetric part of the displacement gradient. Cowin[79] states that the reason bones sense strain rather than stress is that strain is a primary, directly measurable physical quantity, whereas stress is not.

The advent of *in vivo* strain gauging techniques that permit direct measurement of bone deformation prompted a series of experiments to define and quantify the nature of the relationship between mechanical loading and bone remodeling. The results of experiments employing *in vivo* strain gauge techniques spanning a 15-year period have been used to support the contention that bone senses and responds to strain rather than stress.[22] Numerous strain-gauged animal experiments have been performed by Lanyon and Rubin[23,80-82] to assess the relationship between bone tissue response and tissue level strain magnitude. Experimentation has confirmed that bone remodeling is responsive to dynamic strains within the matrix, manifesting a progressively increasing osteogenic response to progressively increased loading.[83] These experiments consisted of depriving a bone of its normal loading *in vivo*, while interrupting the subsequent disuse by daily intermittent loading. Strains of less than 0.001 were associated with the loss of bone, whereas elevated strains resulted in a proportional increase in bone area.

The components of a dynamic strain regime which influence remodeling behavior have yet to be characterized completely. However, they appear to include peak strain magnitude, strain rate, and strain distribution.[82] In combination, these factors play some role in producing an effective strain stimulus. The reader is referred to Burr[84] and Martin and Burr[22] for a complete description of the aforementioned potential mechanical stimuli. Although little hard experimental evidence suggests that strain energy provides the adaptive signal, it is often used theoretically to model the development and adaptation of bone and cartilage.[37,55,74,85] Strain energy is proportional to the product of stress and strain. However, strain energy possesses two characteristics distinguishing it from both stress and strain: (1) it is a scalar rather than a tensor; and (2) it is always positive regardless of whether the loads are tensile or compressive.[22] Consequently, strain energy represents a less complex variable as compared to strain, but more information is needed.[22]

Although the majority of theories emphasize the mechanical aspects of bone adaptation, the process cannot be reduced to a purely mechanical form. It is highly possible that cells are not sensitive to stress or strain, but to another factor (i.e., electrical potential) generated via the stress or strain fields. A number of chemical reactions supplement the bone remodeling process. Although the mechanism responsible for these reactions continues to elude researchers, there are two promising candidates: one electrical, the other chemical.

At the cellular level, stretch-activated ion channels transduce mechanical strain into an ion flux or an electrical response.[86] This mechanism is activated when the cell membrane is strained, thus developing a preferential passageway for the transit of specific ions. The aforementioned cellular-level strains are classified as highly localized at the cell lacunae level; by contrast, tissue level strains represent macroscopic strain averages over a significant volume of bone tissue. In 1953, the work of Fukada and Yasuda[87] led to the hypothesis that strain-related electrical potentials mediate the adaptive response. The aforementioned theory of piezoelectricity in cortical bone led Gjelsvik[88,89] to derive mathematically a theory of mechanically adaptive surface remodeling. This theory proposed that resorption would occur systemically on all bone surfaces, while apposition in proportion to the surface charge counterbalanced this tendency.

Utilizing the constants derived by Fukada and Yasuda,[87] Gjelsvik observed the effects of alterations in mechanical usage, and the classical problem of the flexural neutralization in an angulated bone.[89] As interpreted by Martin,[22] the resulting data implied that the collagen molecules possess a left-hand twist on one side of the body and a right-hand twist on the other. This, however, is not feasible since all naturally occurring collagen has the same direction of twist.[90,91] Consequently, the likelihood of piezoelectricity governing the adaptive response in bone is probably not as great as initially anticipated.

Subsequent investigations suggest that the physiologically significant strain generated potential (SGP) in bone is not piezoelectricity, but electrical potential of electrokinetic origin.[92,93] When pressure differentials between two sites in bone tissue elicit flow of the charged fluid in bone channels, a streaming current which gives rise to SGP is established. The potential difference or streaming potential between the two sites may, in turn, be measured. Hence, transient pressures and fluid flow have been cited as potential candidates governing adaptive bone remodeling. Jendrucko et al.[94] evaluated the relationship between applied compressive stress and the pressure exerted on an osteocyte. Axial compressive loading of an osteon was shown to induce radial flow.[95,96]

2.4 Soft Tissue Remodeling

Brickley-Parsons et al.[97] suggest that while Wolff's law was formulated originally to describe the adaptive response of bone to externally applied mechanical forces, there is no *a priori* reason why the same biological principles do not apply to other skeletal structures whose major functions are also mechanical in nature. Perhaps the most well-known example is the hypertrophy of muscle following athletic training. In contrast to the extensive work on bones, very little has been done on modeling the relationship of stress, strain, and growth in soft tissues. This has been attributed to the fact that soft tissues typically exhibit large elastic deformations under physiological loading.[98] In recent years, however, phenomena suggesting response to the change in mechanical conditions have been observed in soft biological tissues.

Aortic walls in hypertensive rats, for example, increase their thickness as if the hypertrophy maintained the circumferential stress at a similar level to that in normotensive animals.[99-101] At the cellular level, myocardial cells have been shown to atrophy in response to a month-long reduction in cardiac work as the result of an artificial assist device.[102] Matsumoto et al.[103] suggest that dimensional changes such as wall thickening observed in hypertensive aortas and overloaded left ventricles seem to occur to maintain the mechanical stresses developed under *in vivo* conditions, approximating the same level as that in normal tissues and organs.

Inspired by the fact that growth and remodeling in tissues may be modulated by mechanical factors such as stress, Rodriguez et al.[98] proposed a general continuum formulation for finite volumetric growth in soft elastic tissues. The shape change of an unloaded tissue during growth was described by a mapping, analogous to the deformation gradient tensor. This mapping was decomposed into a transformation of the local zero-stress reference state and an accompanying elastic deformation that ensured the compatibility of the total growth deformation. Residual stresses arose from the elastic deformation. With a thick-walled hollow cylinder of incompressible, isotropic hyperelastic material as an example, the mechanics of left ventricular hypertrophy were analyzed. Results indicate that transmurally uniform pure circumferential growth, which may be similar to eccentric ventricular hypertrophy, changes the state of residual stress in the heart wall.

Yamamoto et al.[104] investigated the effects of stress shielding on the mechanical properties of the rabbit patellar tendon. Stress shielding was accomplished by stretching a stainless steel wire installed between the patella and tibial tubercle, thus releasing the tension in the patellar tendon completely. Significant alterations in the mechanical properties of the patellar tendon were observed as the result of stress shielding. It decreased the tangent modulus and tensile strength to 9% of the control values after 3 weeks. There was a 131% increase in the cross-sectional area and a 15% decrease in the tendinous length. Histological studies revealed that the stress shielding increased the number of fibroblasts while decreasing the longitudinally aligned collagen bundles.

2.5 Summary

The skeleton's capacity to withstand external loading is achieved and maintained because the adaptive remodeling of bone tissue is both sensitive and responsive to the functional demands placed upon it. Numerous attempts to quantify the adaptive phenomena of bone have been reported in the literature. Qualitative predictions require that the internal mechanical load on the bone structure be determined accurately in terms of stresses and strains, for which the finite element method (FEM) has proven an effective tool.[38,105] Mathematical bone remodeling theories, in conjunction with finite element models, enable bone formation and resorption patterns in realistic bone structures to be predicted quantitatively.

To date, the precise mechanism underlying the functional adaptation of bone tissue continues to elude researchers. It appears, however, to involve simultaneous cell-controlled mechanical, bioelectric, and biochemical processes.[15] Numerous candidate mechanosensory transduction mechanisms, ranging from mechanical to electrical in nature, have been proposed.

The capability of remodeling algorithms to yield more realistic density distributions and external configurations continues to improve. Undoubtedly, an accurate representation of the bone remodeling process would provide significant clinical benefits. The possibilities for artificial joint replacement, pre- and post-clinical testing, and clinical research generally are endless.

Acknowledgment

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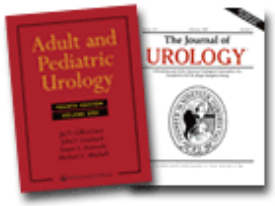

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