4.4 Responses of bone to stress: constraints on symmorphosis

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Symmorphosis, the hypothesis that organisms can adapt "economically" to changing functional demands, is not new to bone biology. Meyer first applied an early version of the theory to trabecular bone in 1867, which was later incorporated into Wolff's 1892 Law of Bone Transformation that every change in a bone's function is followed by changes in its internal structure and external conformation. Despite widespread evidence that bones respond dynamically to external stimuli, Wolff's Law remains controversial because the processes by which they adjust to their mechanical environment are poorly understood.

We discuss here, using experimental data, several major processes by which bones respond to mechanical loading and how these processes constrain the optimization of mechanical design. Stress (σ, F/A) generates strain (ε, $\Delta L/L$) that can induce osteogenesis because it potentially damages bone tissue. Frequent, high-strain magnitudes often induce bone growth, whereas low levels lead to resorption. Professional tennis players, for example, develop extreme hypertrophy in their playing arm, while astronauts in the gravity-free environment of space resorb bone systemically. Because bone is a complex tissue with many functions and structures, different types of bone (for example, woven, parallel-fibered, or lamellar) often respond to similar strains differently. For example, chewing elicits comparable strains in the mandibular corpus of the goat and the opossum which have different histologies, but, as we discuss below, only the goat responds with a significant amount of Haversian remodeling, even though remodeling can occur elsewhere in the opossum jaw.

A hierarchical model for bone symmorphosis

A simple model expresses how bones may adapt to mechanical loading:

Structural responses/constraints
Force → Transductional responses/constraints → Adaptation (modeling/remodeling)
Design constraints

Force applied to a bone, measured as stress, generates strain that can vary in magnitude, frequency, predictability, and orientation. Such stimuli can ultimately lead to diverse adaptive responses. Macrostructurally, bones adapt either through *modeling*, the deposition of new bone, or *remodeling*, the resorption and/or replacement of old bone. Bones also adapt microstructurally in terms of collagen organization, mineralization, and so forth.

The intermediate processes and constraints that mediate osteogenic responses to force occur through at least three hierarchical levels: structural, transductional, and design. The most basic level of response is *structural*, the attributes of a bone that determine how a given force elicits strain. These include its macrostructure (size and shape), as well as many microstructural properties (for example, collagen orientation and density, mineralization, lamellar organization). Fibrolamellar bone, for example, has a higher tensile strength than Haversian bone, and young bone is more elastic than old bone. The second, *transductional* level comprises the cellular processes by which bone cells detect and respond to strain. These constraints are incompletely understood, but several factors appear to be critical. Bones may sense strain through nerves in the periosteum, and perhaps through pressure changes in fluid-filled canaliculi of osteocytes and from pieozoelectrical potentials generated by collagen deformation. Vascular supply also limits bone responses to force because bone cells require nutrients. Finally, numerous design constraints operate at different levels involving numerous cell types. Some bones conserve mass, grow to specific dimensions, or have special structural properties. Most bones also perform non-mechanical functions that influence their shape.

Force, in other words, induces modeling and remodeling responses in bone through a series of interrelated, hierarchical processes.

Variations in responses to strain

To examine how the structural, histological, and design levels of osteogenic response mediate the adaptation of bones to environmental

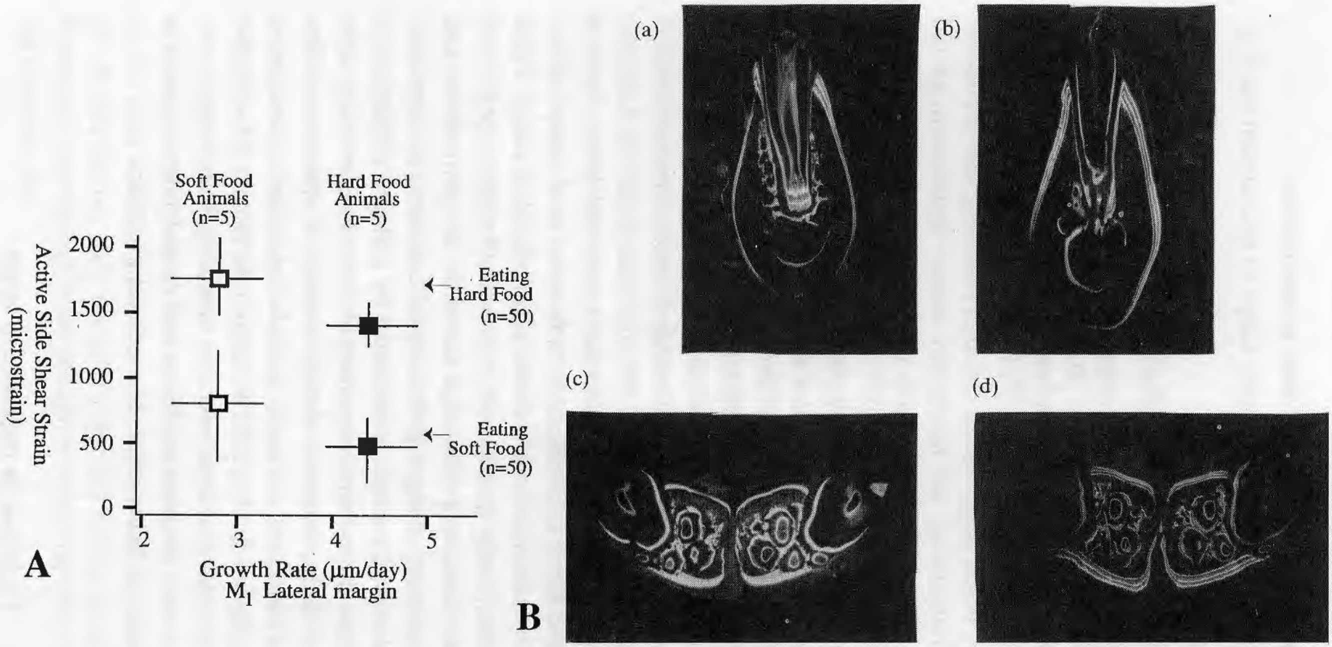

Figure 4.3. Test of the dynamic equilibrium theory in the opossum jaw. (A) Comparison of periosteal growth (µm day^{-1}) at lateral margin of corpus at M_1 with mean active side shear strains (µε) measured at the lateral margin of corpus near ventral margin at M_1. Strains in animals raised on hard food for 12 weeks ($n = 5$) are significantly lower ($p < 0.05$) than those in animals ($n = 5$) raised on soft food because of their faster growth rate ($p < 0.05$). (B) Comparison of growth in mandibular corpus for representative hard food (h) and soft food (s) animal at M_1 (M) and in symphysis (S). Fluorescent dyes (calcein and tetracycline) show that periosteal growth was significantly greater ($p < 0.05$) in the medial and lateral margins of the corpus and in the ventral margin of the symphysis. Note that the only Haversian systems occur along the medial margins of the symphyseal plate.

conditions, we present data from several experiments in which we subjected diverse species to reasonable ("normal") levels of habitual force in the laboratory. These illustrate a wide range of responses to increased levels of force.

Macrostructural responses

If bone tissue is designed to tolerate certain strains, then bones should respond to increased forces structurally by augmenting their mass in their principal planes of deformation, thereby decreasing the level of strain a given force generates. This theory of dynamic strain similarity – formulated by researchers such as Lanyon, Rubin, and Biewener – explains many of the quantitative increases in bone mass at functionally equivalent sites in growing animals. To examine how this optimization process operates on mature animals we divided ten twelve-month-old female opossums (*Didelphis virginia*) into two equal groups that ate nutritionally identical hard and soft food, respectively, for twelve weeks. We labeled newly deposited bone with fluorescent dyes, and placed rosette strain gauges on the lateral surface of each mandible.

The dynamic strain similarity theory predicts that the opossums fed a soft-food diet would experience higher strains when chewing hard food than the opossums raised on hard food. The results (Figure 4.3) agree with the predictions. During the experiment, the hard-food animals deposited periosteal bone more rapidly in their mandibles (Figure 4.3B), particularly on the lateral surface, so that they experienced roughly 25 percent and 68 percent lower shear strains at this location when chewing hard and soft food, respectively (Figure 4.3A). In other words, the opossums adapting to a hard-food diet had lower strains than those who ate soft food because of osteogenic responses to the higher strains they previously encountered.

Microstructural responses

Strains also induce microstructural changes, the most important of which is Haversian remodeling. Several factors, including strain magnitude and frequency, tissue age, and the degree of vascularization, appear to influence Haversian remodeling.

We examined how some of these factors affect Haversian remodeling by comparing mandibular growth in three groups of subadult goats (*Capra hircus*) fed different diets: all ate a hard, nutritionally adequate

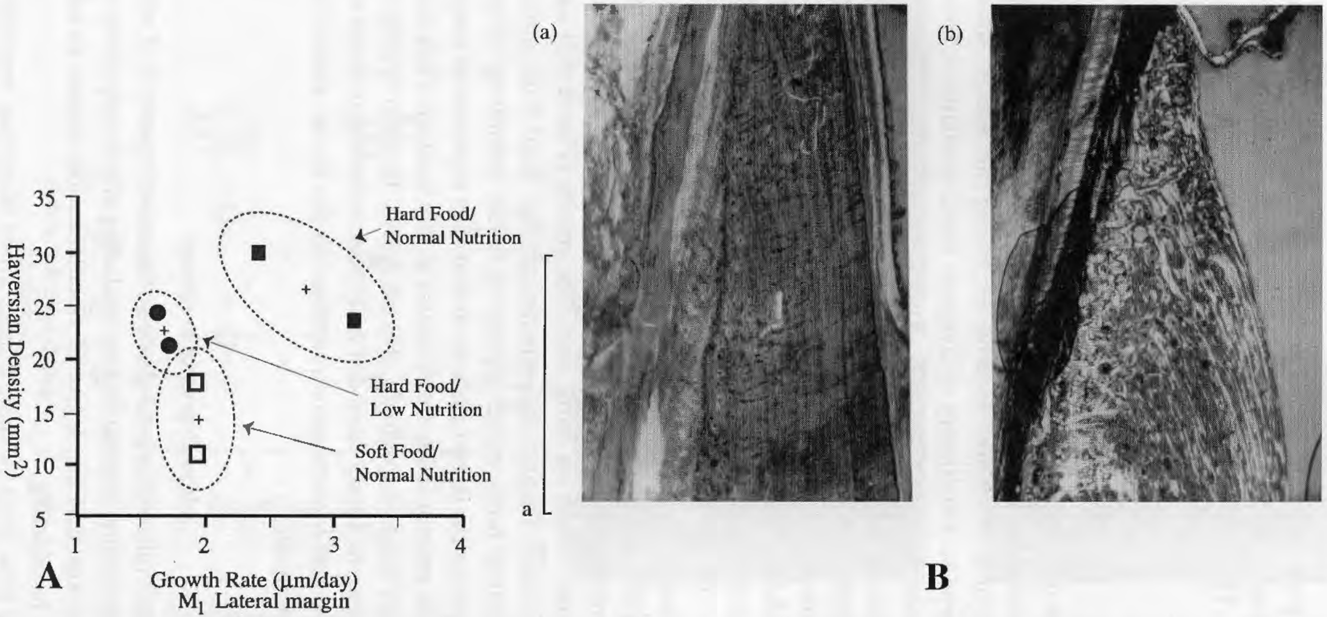

Figure 4.4. Relationship between strain, growth rate, and Haversian remodeling. (A) Relationship between growth rate (µm/day) and Haversian density (mm^2) at the lateral margin of mandibular corpus at M_1 in three groups of goats. The hard food/normal nutrition goats had a significantly faster rate of growth and more dense Haversian bone than either the low nutrition group or the soft food group ($p < 0.05$). (B) Comparison of lateral margin of M_1 (a) goat and (b) opossum, raised on hard food. Note that goat has Haversian remodeling of fibrolamellar bone, whereas opossum has parallel-fibered bone without Haversian systems.

diet during the first and last four months of the experiment; during the middle four months, however, one group ate softened food, and one group ate a hard but nutritionally deficient diet (34 percent lower in protein and 50 percent lower in minerals). Fluorescent dyes were used to label bone growth and remodeling, which Figure 4.4A plots as the periosteal growth rate along the lingual margin of the mandible at M_1 versus Haversian remodeling density in the same region. The goats fed the hard, control diet had a higher rate of periosteal growth than the other goats ($p < 0.05$); and all the goats fed hard food, regardless of nutrient content, had more Haversian remodeling than those who ate soft food ($p < 0.05$). The goats whose jaws grew more slowly from less nutrition remodeled at a higher rate than those whose jaws grew more slowly from a lower strain regime.

These results confirm previous claims by Bouvier, Hylander, and others that strain levels influence both the rate of modeling and the rate of Haversian remodeling. Interestingly, goats' jaws grew significantly ($p < 0.05$) slower ($2.1\,\mu\text{m}\,\text{day}^{-1}$) than the above-discussed opossums ($3.5\,\mu\text{m}\,\text{day}^{-1}$), which were at a developmentally equivalent stage. These rate differences may be reflected histologically (Figure 4.4B). The periosteal bone deposited in the goat mandibular corpus is entirely fibrolamellar, which is more organized and vascular than the parallel-fibered bone deposited in the opossum corpus. Peak strains in the goats and opossums were very similar, however. Peak shear strains on the active side at M_1 was $442.3 \pm 129.2\,\mu\varepsilon$ ($n = 10$) and $484.4 \pm 275.9\,\mu\varepsilon$ ($n = 50$) in the hard-food goats and opossums, respectively.

Design constraints

Bones may adapt diversely to strain through different proportions of modeling and remodeling in order to select for certain properties such as shape, elasticity, density, or mass. Such design constraints occur to some extent through modulations of various cellular responses that regulate modeling and remodeling.

Varying responses to strain can be tested in limbs. In most vertebrates, distal limb bones tend to be thinner and, therefore, weaker than more proximal bones. While a purely structural model for bone optimization predicts that animals will compensate by depositing relatively more bone in their distal than proximal limb elements, natural selection may also favor animals who minimize mass distally to conserve the angular momentum of the limb during deceleration and acceleration (big feet take exponentially more kinetic energy to swing than small feet). Haversian remodeling rates are therefore predicted to increase in proportion to the square of each element's radius of gyration (an approximation of its moment arm) in order to repair the presumably higher rate of damage potentially generated by high forces in more lightly built bones.

We tested the relationships between moment arm length, modeling and remodeling in the limbs of six miniature swine (*Sus scrofa*) between the ages of one and four months. These animals were divided in two groups, of which one ran on a treadmill at $4.8\,\mathrm{km\,h^{-1}}$ twice daily for a total of 60 min. Bone growth was labeled with fluorescent dyes. As predicted above, the runners had significantly more rapid modeling rates at bone midshafts than the controls, but responses to strain differed between elements, suggesting that they have different design constraints. In particular, relative rates of midshaft modeling and remodeling varied inversely between proximal and distal elements in proportion to estimated moment arm length. In the hindlimb, for example, the pigs had a 71-fold higher rate of remodeling in the metatarsals than femur, but a concomitant 5.6-fold decrease in midshaft strength. This trade-off between modeling and remodeling is shown in Figure 4.5, which graphs the percentage of cortical bone modeled and remodeled relative to midshaft cross-sectional area for each element. Distal bones in the limb are weaker than the proximal bones to conserve mass, but appear to maintain this mechanical compromise with higher Haversian remodeling rates. Note that Haversian density is significantly greater for all bones (except the femur, which did not remodel) in runners than in controls, and that the modeling–remodeling trade-off slope differs between the forelimb and hindlimb, presumably because more of a pig's mass is concentrated cranially.

Bones respond to increased mechanical force through diverse optimization processes. However, any simple, direct relationship between exogenously induced strain and endogenous structural and microstructural responses remains elusive.

Discussion

Modeling and remodeling processes coadjust to adapt to force-induced strain as predicted by the theory of symmorphosis, but these responses are varied and sometimes unpredictable. As we have shown, bones sometimes respond purely macrostructurally by altering their shape and size because a given force generates less strain in a more massive bone. In

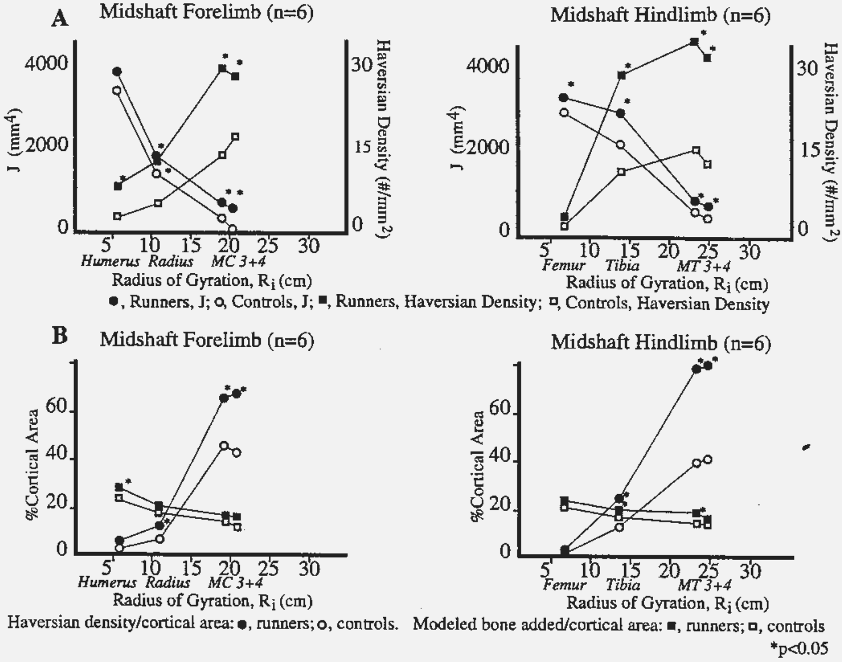

Figure 4.5. (A) Polar moment area, J (mm^4), and density of Haversian remodeling (mm^2) in midshaft of limb bones in pigs versus the estimated radius of gyration (moment arm length). Modeling and remodeling rates are higher in exercised animals; in both groups the distal limb bones are increasingly thinner and weaker, but appear to compensate with a correspondingly higher density of Haversian systems. (B) Evidence for a trade-off between modeling and remodeling; the percentage of modeled versus remodeled bone per cortical area at limb midshafts versus the estimated radius of gyration. Distal elements apparently conserve mass by modeling less and remodeling more; this trade-off is exaggerated in exercised animals.

other bones, intermediate mechanisms appear to preferentially induce Haversian remodeling instead of modeling. Most bones probably adapt to mechanical forces from both processes; in some such cases, the relative degree to which bones change through macrostructural and microstructural responses appears to vary inversely according to design constraints. This trade-off between modeling and remodeling suggests that the primary role of Haversian remodeling is not to recover mineral from bone tissue but instead to repair the fatigue damage induced by strain.

Symmorphosis, therefore, appears to be a real phenomenon in bones; one that we should expect, given the unpredictability of the interactions between an organism and its environment. Since symmorphosis is essentially the result of several hierarchical levels of process (structural responses, transduction, and design constraints), it follows that the history and nature of these processes constrain how bones optimize their mechanical design. Secondary remodeling, for example, requires vascularization, which, in turn, is a consequence to some extent of its rate of growth. Haversian remodeling, therefore, may be less common in active but more slowly growing reptiles than in equally active but more rapidly growing mammals because their bones are less vascularized.

The many functions of bone and the many processes by which it grows, however, confound efforts to construct simple models for the optimization of bone to mechanical demands. Future efforts to understand the adaptations of bones need to focus on the many poorly understood cellular processes that intervene between the proximate action of force on a bone and the ultimate activation of bone cells. More information on these processes will undoubtedly lead to a more satisfying but probably more complicated model of symmorphosis in bone.

Further reading

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