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Marjolein C. H. van der Meulen

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THE ROYAL SOCIETY

Mechanics in skeletal development, adaptation and disease

By Marjolein C. H. van der Meulen[1] and Patrick J. Prendergast[2]

[1]*Sibley School of Mechanical and Aerospace Engineering, Cornell University, Upson Hall, Ithaca, NY 14853, USA* (mcv3@cornell.edu)
[2]*Department of Mechanical Engineering, Trinity College, Dublin 2, Ireland* (pprender@tcd.ie)

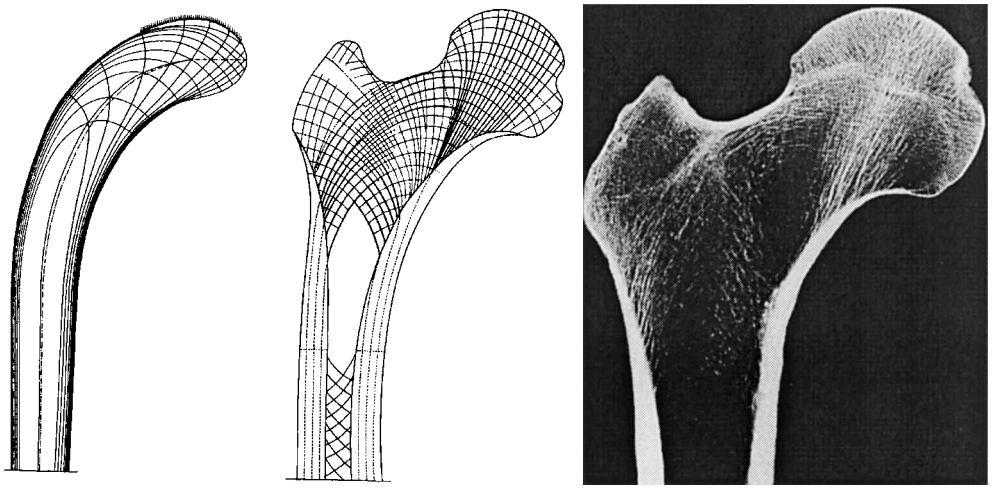
Mechanical loading plays an important role in the development, adaptation and function of the vertebrate skeleton, but our understanding of this role is incomplete. The influence of mechanics initiates during early embryogenesis and continues throughout life, determining the geometric and material characteristics of the skeleton. In this paper, the current understanding of bone mechano-biology will be reviewed, highlighting important open questions. Advancing our knowledge in this field, coupled with important recent biological advances, has exciting potential for orthopaedic methods and treatments in the future.

Keywords: bone; mechanics; computer simulation; adaptation; cell mechanics; imaging

1. Introduction and historical background

The mineralized skeleton of vertebrates serves several important functions, including structural support for the organism; storage of ions, particularly calcium; production of red blood cells; and protection of vital organs such as the heart and lungs. The structural role of the skeleton is particularly interesting to physicists and engineers because bone is an adaptive, living tissue containing cells that respond to their physical environment. Form follows function. Historically, most of our knowledge comes from treating bone as a conventional engineering material, studying bone tissue and whole bones when placed under loads in the laboratory. This approach does not consider that bone is a living tissue nor account for the influence of mechanical loading in regulating the biological processes that occur to form the skeletal structure. Separating the mechanics from the biology is impossible: mechano-biological coupling initiates during early development when the primordial cellular structure first experiences deformations and pressures, and continues throughout the growth, development and ageing of the organism. Understanding the influence of biophysical stimuli on skeletal growth and adaptation is of great recent interest to medicine for diseases such as osteoporosis and osteoarthritis.

The structural adaptation of the skeleton has been one of the most fascinating problems in the history of science. Galileo (1638) observed that longer bones had to be thicker for the same structural strength, and diagrammed the required scaling in his *Discorsi e Dimostrazioni Matematiche intorno a due nuove scienze*. In discussing



(*a*) (*b*) (*c*)

Figure 1. (*a*) Culmann's diagram of the stress trajectories in a crane, (*b*) Wolff's drawing of the trabecular orientation in the upper part of the femur, and (*c*) a photograph of the cross-section of the upper part of the femur.

heritable and acquired traits in *On the origin of species*, Darwin (1859) noted that flying wild ducks have proportionally larger wing bones and smaller leg bones than their non-flying domestic relatives. Many natural philosophers of the 19th century used mechanical principles to explain bone geometry, including, most famously, Wolff (1892) in his *Das Gesetz der Transformation der Knochen*. Wolff examined many pathologically healed bones to argue that bone tissue was distributed within the organ to best resist mechanical forces. A famous exchange between the Swiss engineer Culmann and his colleague von Meyer has become the defining 'eureka' episode of modern biomechanics. The internal architecture of a femur was being demonstrated by von Meyer, and Culmann, who developed the methods of graphic statics, exclaimed 'That's my crane' (figure 1). These concepts were further developed and generalized by D'Arcy Thompson (1917) in his influential work *On growth and form*. The mechanism of bone adaptation was first addressed by the German embryologist Wilhelm Roux (1895), who proposed the controversial hypothesis that bone cells compete for a functional stimulus, *á la* Darwin, and engage in a struggle for survival that leads to *Selbstgestaltung* (self-organization).

Roux and his turn-of-the-century contemporaries were not able to advance much beyond this philosophical and descriptive understanding of the role of mechanics in skeletal growth. As the century progressed, biology increasingly reduced the organism to the molecular level, and the interest in mechanics and other biophysical factors waned. However, in recent years, the emergence of several new technologies has fostered a re-examination of the old questions relating to the mechanical regulation of tissue growth and adaptation. The first of these is computer-based structural modelling, which allows a more valid analysis of effects of physical forces within complex skeletal geometries; the second is molecular biology, which localizes individual gene expression and protein synthesis under different mechanical forces; and the third is the tremendous advances in imaging technologies, which enable scientists to identify

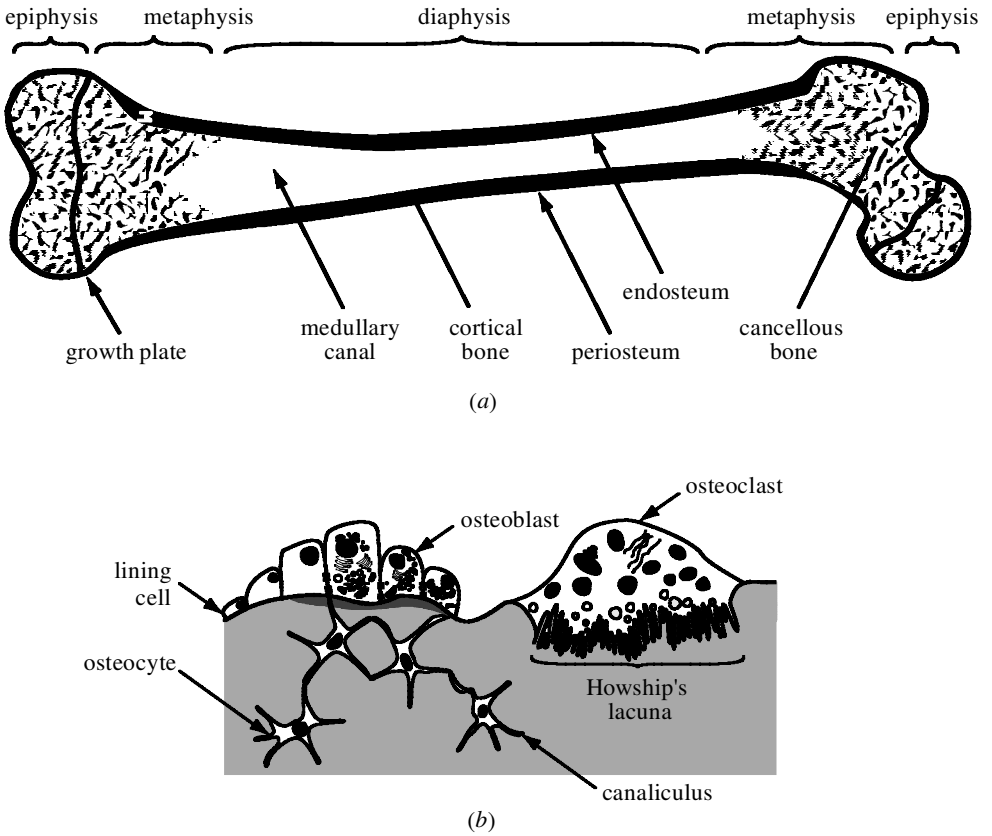


Figure 2. (*a*) The distribution of cortical and cancellous tissue in a long bone, and (*b*) bone cells (osteoblast, osteocyte, and the osteoclast).

microstructural characteristics of tissues and the role of cells in constructing and maintaining skeletal strength. In this paper, our current understanding of the role of mechanical forces in skeletal biology will be used to highlight the interaction between the physical and biological sciences, and motivate important future questions.

2. Form and function in bone

The musculo-skeletal system consists of bones, blood vessels, nerves, ligaments, tendons, muscles and cartilage, which work together to perform the structural and kinematic functions of the organism. These musculoskeletal tissues all have a composite structure of cells embedded in a matrix produced by the cells themselves. While we focus on the skeleton here, analogous organization exists within other organs.

(*a*) *Bone structure*

The geometry and structure of a bone consists of a mineralized tissue populated with cells. This bone tissue has two distinct structural forms: dense cortical bone (apparent density greater than 1.5 g cc^{-1}) and lattice-like cancellous bone (apparent

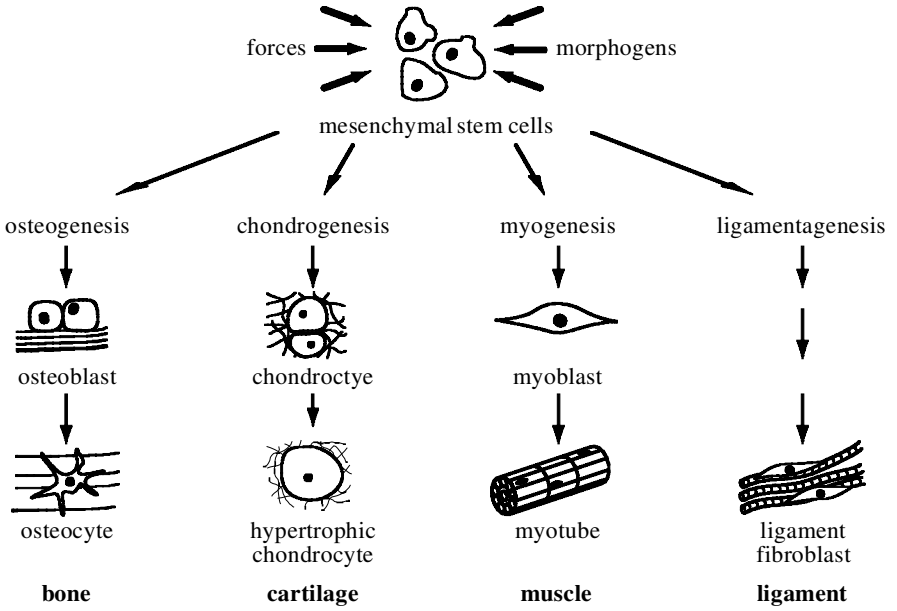


Figure 3. Tissue forming cells differentiate from the mesenchymal cell pool in response to the local mechanical and biochemical stimuli. Adapted from Caplan (1994).

density less than 1.0 g cc^{-1}), see figure 2*a*. Reilly & Burstein (1975) demonstrated that cortical bone is a nearly transversely isotropic material. The structure is made up of osteons, longitudinal cylinders of bone centred around blood vessels. Cancellous bone, on the other hand, is an orthotropic material, with a porous architecture formed by individual struts or trabeculae (Gibson 1985). This high surface area structure represents only 20% of skeletal mass, but has 50% of the metabolic activity. The density of cancellous bone varies significantly, and its mechanical behaviour is influenced by density and architecture. Carter & Hayes (1977) first identified that the modulus and strength of both tissue structures are functions of the apparent density.

(*b*) *Cells and matrix*

The material of cortical and cancellous bone consists of cells in a mineralized matrix. All skeletal cells are known to differentiate from a common precursor cell pool: the mesenchymal stem cells of the embryo (figure 3). Mechanical stimuli considerably influence the stem cell differentiation pathway and the resulting tissue type. Manipulation and control of stem cell differentiation holds considerable tissue engineering promise and has recently been receiving much commercial and ethical attention. In addition to precursor cells, three principal cell types are present in bone: osteoblasts, osteocytes and osteoclasts (figure 2*b*). Osteoblasts are active bone-forming cells. All bone surfaces are covered by a single layer of precursor cells and resting osteoblasts. Upon activitation, osteoblasts secrete osteoid, the organic extracellular matrix into which mineral crystals are deposited. The organic matrix contains 90% collagen and a ground substance consisting of large protein polysaccharides and a variety of matrix proteins. Gaps in the collagen fibrils serve as mineral nucleation sites for calcium phosphate, which forms the inorganic phase. The result

is a composite of a ductile polymeric (collagen) phase and a strong ceramic phase. This combination gives bone its unique mechanical qualities of high strength and toughness (Currey 1984).

Approximately 15% of osteoblasts become entrapped in their own matrix to become osteocytes. Osteocytes have a vast three-dimensional network of cell processes (canaliculi), providing nourishment and cell–cell interactions. Due to their location throughout bone tissue and the extensive canalicular network, osteocytes are assumed to be a vital component of sensing mechanical signals. Nutrients are essential for the vitality of bone tissue and are obtained from the blood supply, limiting most osteocytes to lie within 150 μm of a blood vessel, resulting in a high cellular density: 25 000 osteocytes within 1 mm^2 of bone tissue (Baron 1996). The third cell type, the osteoclast, has a different origin than the other two, and is presumed to arise from the fusion of blood cells. Osteoclasts are large distinctive multinucleated cells that resorb bone. By sealing to a bone surface, the osteoclast forms an acidic cavity, which effectively dissolves the underlying bone (figure 2*b*).

(*c*) *Bone growth and maintenance*

Bone forms by two different developmental processes: endochondral ossification and intramembranous ossification. Endochondral ossification involves an intermediate tissue stage, cartilage, not present in intramembranous formation. The long bones all form endochondrally. In these bones, development begins with the condensation of mesenchymal cells, which differentiate into chondrocytes (figure 3), creating a cartilage prepattern of the skeleton. The first bony tissue, known as the bone collar, appears spontaneously surrounding the midshaft. Thereafter, ossification proceeds axially towards each bone end. An identical temporal sequence of ossification occurs at each location: the cartilage calcifies, blood vessels invade the site, and the cartilage is resorbed and replaced by bone. This sequence is regulated by a cascade of factors including genetic regulatory factors, systemic hormones, growth factors and mechano-biologic effects (Vortkamp *et al*. 1996). The timing of these signals is critical to the outcome. In the developing embryo, the first ossification of cartilage is coincident with the first muscle contractions; if a muscle is immobilized in the embryo, a distorted and disorganized bone forms (Wong *et al*. 1993), demonstrating the link between mechanics and bone tissue formation.

After embryonic bone formation, the skeleton continues to grow in length by dividing and enlarging cartilage cells, which then ossify to form cancellous bone. Growth in bone diameter occurs by direct deposition of bone on existing bone surfaces, accompanied by resorption of outer surfaces. As the skeleton continues to develop, mechanical forces generate an ever increasing influence on the forming bone architectures and geometries. Cellular proliferation increases skeletal size and needs to be exquisitely controlled to maintain form and proportion throughout growth.

Once the skeleton is formed, continual ‘remodelling’ of bone tissue maintains structural integrity and also creates more orderly tissue structures. Remodelling involves coupled resorption and formation on all bone surfaces in a well-defined sequence of events. Frost (1973) described the remodelling sequence as activation of the surface, resorption by osteoclasts, reversal, formation by osteoblasts, and return to quiescence of the surface. In the adult, remodelling serves to repair, renew and adapt bone tissue. A primary function of remodelling is to replace damaged tissue, such as microcracks

resulting from repetitive functional loading (Martin & Burr 1989). Without this continuous repair process, preventing the accumulation of damage would require a much larger skeleton.

Another important mechanically mediated process is bone fracture repair. A fracture initiates a multistage sequence of tissue regeneration, which recapitulates tissue differentiation and development. There is also evidence of this process in individual, fractured trabeculae (Fazzalari 1993). Initially a large granuloma forms containing undifferentiated mesenchymal stem cells whose differentiation is once again regulated by genetic and epigenetic factors. Following this immediate trauma response, the cells differentiate into cartilage to stabilize the fracture. The initial bridging and immobilization are performed by tissues that can tolerate the high strains that preclude bone formation (Perren 1979). Thereafter, endochondral ossification of the cartilage occurs and bone forms. Finally, the new bone is remodelled and integrated into the original structure. The mechanical environment is critical to the tissue regeneration. Fracture immobilization may enhance early healing while stability is critical, but fractured bones that are dynamically loaded during healing regain strength more quickly. However, if the applied strains are too large, cartilage or fibrous tissue forms and a pseudo-joint may develop at the fracture site.

3. Mechanical regulation of bone structure

(*a*) *Adaptation experiments*

The growth and development of organisms living within Earth's gravitational field is intricately linked to mechanical demands. Manipulation of forces in animal experiments has provided insights into the overall nature of the adaptation process. The characteristics of adaptation to increased or decreased *in vivo* loading include the following: changes in bone quantity, not material quality; greater response in immature than mature tissue; and, response to cyclic, not static, loading. These results were elegantly demonstrated in a series of studies by Hert *et al.* (1971) with loads applied to rabbit limbs and have been confirmed by a variety of studies. In the adult, in general, when the loads are increased over normal levels, bone mass is increased, and when the loads are decreased, bone mass is lost. Changes occur in the cross-sectional size and shape of cortical bone and in the apparent density of trabeculae; bone length is seldom significantly affected, but curvature may be altered.

Most experiments examine cortical bone responses, in contrast to the historical interest in trabecular adaptation. Exercise studies often show little or no effect, presumably because the overall activity level is not substantially elevated beyond the normal range. Demonstrating a definitive decrease in physiological loads is more straightforward and has been accomplished by casting, space flight and hindlimb suspension. Hindlimb suspension was developed as a ground-based model for space flight, demonstrating similar skeletal effects. Compared with age-matched controls, suspended growing animals continue to grow, but at a reduced rate, with lower age-related increases in femur strength and cross-sectional area (figure 4). van der Meulen *et al.* (1995) showed the decreased formation occurs on the outer cortical surface, exactly the location of the greatest reduction in mechanical stimulus.

While many experiments have been performed, quantitative relationships between mechanical loads and bone adaptation do not exist yet. *In vivo* strain gauge studies have found a remarkable similarity of peak surface strains: $-2000\mu\epsilon$ at the midshaft

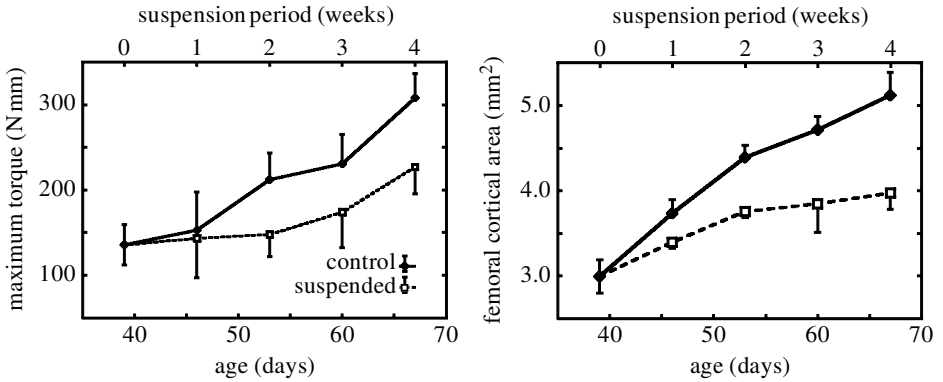


Figure 4. Torque to failure and cross-sectional area of the rat femur following hindlimb suspension.

of different bones across different animals at maximum activity (Rubin & Lanyon 1984). Measuring strains in adaptation studies would allow us to relate *in vivo* load changes to altered surface strains to adapted bone mass and strength.

Applying loads directly to a skeletal site has the advantage of known or controllable load magnitudes, frequency and duration. Loads at sites or in directions that are not normally loaded have been demonstrated to induce a greater response than increasing physiological loads. Recent experimental models for non-invasive, controlled *in vivo* loading have been developed for weight-bearing bones in the rat (Turner *et al.* 1991; Torrance *et al.* 1994). The latter group is one of the few that has integrated these *in vivo* approaches with *in vitro* and *ex vivo* studies to acquire a more complete understanding of load-induced adaptation. These animal models can be used to examine loading parameters, to study gene expression, and to validate computer simulations. The mouse has recently become more relevant; our ability to manipulate the mouse genome has led to the development of mutations and new biological markers and assays. *In vivo* loading of mouse mutants will help identify critical genes and regulatory factors in the mechanical response pathway.

Adaptation around bone implants has received considerable attention clinically and experimentally. When a bone segment is replaced by a stiff metal prosthesis, the implant becomes the primary load bearing structure, reducing the mechanical stimulus to the surrounding bone. Severe bone loss is one of the impediments to the long-term success of orthopaedic joint replacements. Future developments will include active devices that stimulate the surrounding bone and, ultimately, artificial organs engineered in the laboratory.

(*b*) *Modelling*

For a skeletal element to respond to its mechanical environment, the cells within the tissue must regulate their environment in response to the mechanical stimuli they receive. The regulatory process can be thought of as a feedback loop (figure 5), where the osteocyte senses the stimulus and signals the osteoblasts and osteoclasts to either add or resorb tissue to regain the required physiological environment for the cell. We can define a homeostatic mechanical stimulus, S_0, necessary to maintain bone density. Then, if the tissue should be subjected to any other stimulus, S, there

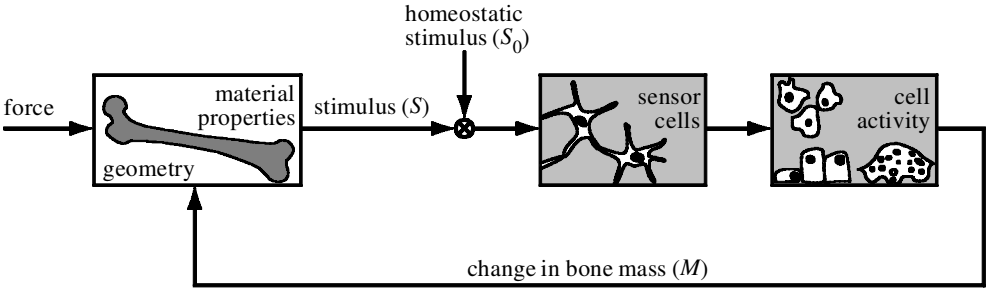


Figure 5. Feedback diagram for skeletal mechanical regulation.

will be a driving signal to adapt the tissue to re-establish the homeostatic equilibrium. The simplest mathematical model for such a mechano-regulatory process is given by

$$\frac{\mathrm{d}M}{\mathrm{d}t} = C(S - S_0), \tag{3.1}$$

where M is the mass of the element, C is a rate constant, and $(S - S_0)$ is the driving signal. Since the sensory cells are distributed throughout the tissue, this model describes a spatially discrete process: each cell will regulate its stimuli by changing the mass or density of its extracellular environment. Many biomechanical stimuli have been proposed, including strain (Cowin & Hegedus 1976), strain energy density (Carter *et al*. 1987; Huiskes *et al*. 1987) or fatigue microdamage (Prendergast & Taylor 1994). These approaches were first coupled to computational stress analysis procedures by Hart *et al*. (1984) and are capable of predicting bone adaptation around implants (van Rietbergen *et al*. 1993) and simulating the influence of mechanics on long bone growth (van der Meulen *et al*. 1993).

Recently, considerable interest has been given to investigations of the nonlinear dynamics of bone adaptation. Finite-element models have been used in iterative computer simulation procedures (Carter *et al*. 1989; Weinans *et al*. 1992; Jacobs *et al*. 1995). To illustrate the dynamics of achieving a homeostatic equilibrium, we can consider a beam of bone in three-point bending. If we choose strain energy per unit mass to be the mechanical stimulus, then $S = U/\rho$, where U is the strain energy density and ρ is the apparent density. Starting with some initial density pattern, the evolution of density can be determined using the known relationship between density and modulus. To obtain a mesh independent solution for equation (3.1), one approach is to integrate the stimulus over an influence region according to

$$\frac{\mathrm{d}M_j}{\mathrm{d}t} = B \sum_{i=1}^{n} f_{ij}(S - S_0), \tag{3.2}$$

where M_j is the mass at position j, B is a rate constant and f_{ij} is a spatial influence function that incorporates the stimulus at position i into the change of mass at position j (Mullender & Huiskes 1995). If a uniform initial density is taken, the simulation proceeds by each element adapting independently; some elements will resorb to zero density and others will achieve the maximum density and the homeostatic equilibrium is a porous 'trabecular' structure, see figure 6*a*. This phenomenon can be viewed as a self-organizational process operating within the bone (Weinans

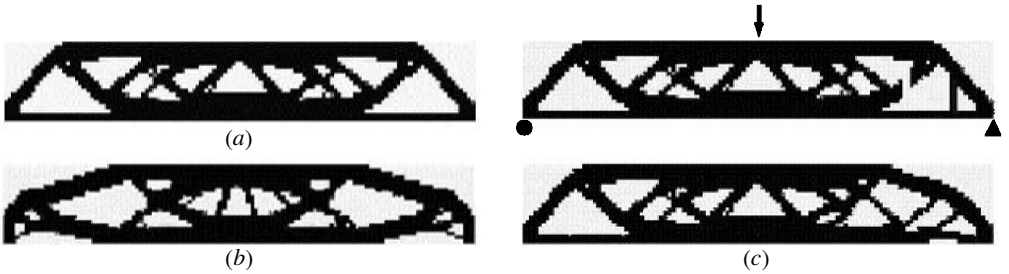


Figure 6. Adaptation of a bone beam subjected to three-point bending, (*a*) starting from a uniform density, (*b*) starting from a non-uniform density, and (*c*) adaptation of structure shown in (*a*) after fracture of a trabecula. Courtesy of Dr Ir. Harrie Weinans, Erasmus Universiteit Rotterdam.

et al. 1992). A different initial density pattern will lead to a different trabecular structure (figure 6*b*), illustrating the nonlinear nature of the adaptation process. Furthermore, the homeostatic equilibria, or end-configurations, may be considered metastable because a perturbation of the structure caused by the fracture of a trabecula, for example, will not be followed by a return to the former equilibrium. However, bone structures are stable in the sense that the inevitable trabecular microfractures that occur in aged osteoporotic bone do not lead to immediate degeneration, rather a completely new equilibrium is sought by the regulatory process; the structure is almost immediately trapped in another metastable equilibrium (figure 6*c*). If this computer simulation does indeed capture the essence of bone adaptation, then adaptation is a far-from-equilibrium process generated by positive feedback whereby elements of tissue compete for mechanical stimulus (Weinans & Prendergast 1996). To date, these approaches have focused attention on the central role of mechanical factors in determining bone structure.

Mechano-biologic concepts have been applied to other skeletal tissues. Differentiation of stem cells to form cartilage, fibrous tissue and bone is central to tissue growth and regeneration. Pauwels (1941) proposed that hydrostatic stresses stimulate differentiation to cartilage cells, whereas distortion stimulates differentiation into fibrous cells (figure 3). Simulations based on Pauwels's ideas have correlated patterns of mechanical stimuli with tissue type during fracture healing (Carter *et al*. 1998). These models suggest that we will be able to simulate skeletal growth, adaptation and degeneration over an individual's lifetime.

(*c*) *Imaging*

A key new tool in the validation of analytical models is high resolution imaging coupled with computer analyses to calculate the material stresses, strains and stimuli within cancellous bone. The average thickness of a trabecula is 100–150 μm, undetectable with conventional computed tomography resolution of 100–200 μm. Micro-computed tomography (microCT) can currently image bone at 17 μm resolution, and the images can be converted directly into large-scale, finite-element models (figure 7). These models can determine bone stiffness and strength without the need for a traditional mechanical test. These 'virtual bone biopsies' (Müller & Rüegsegger 1995) have the potential to revolutionize the clinical assessment of bone health, an increasingly important clinical objective in an ageing population susceptible to osteoporosis.

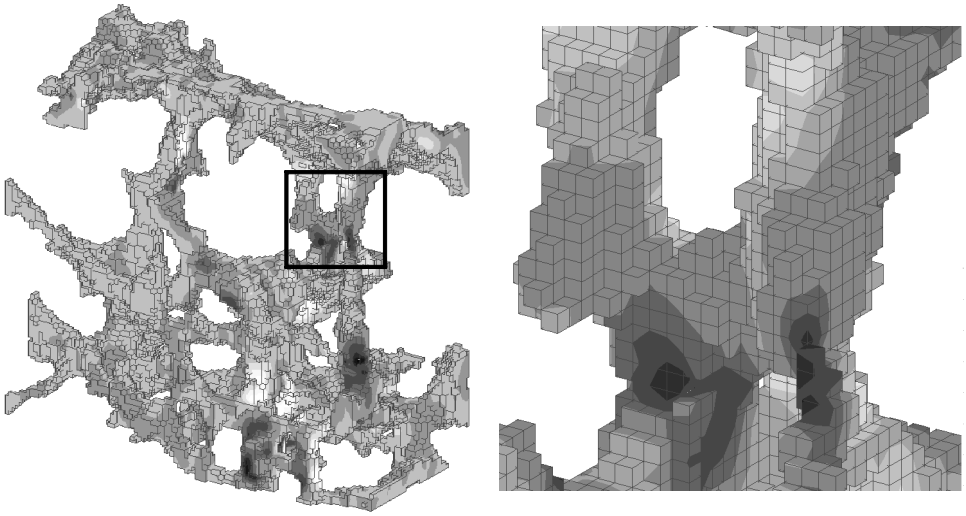


Figure 7. A finite-element model of a cancellous bone specimen generated using microCT scanning. The distribution of tissue level stresses is computed for compression.

Although these microCT-based models simulate the architecture precisely, the magnitude and variation of tissue-level material properties still needs to be determined.

Another imaging development is laser scanning confocal microscopy (LSCM) to image individual living cells non-invasively. The deformation of osteoblasts and chondrocytes has been observed using this method (see, for example, Boyde *et al*. 1995; Guilak *et al*. 1995). LSCM has also been used to image microdamage in bone tissue (see, for example, Zioupos *et al*. 1994) showing modes of microcrack arrest within the complex microstructure of bone tissue.

4. Visions for the future

With these new tools and so many unanswered questions about tissue function and maintenance, the time for mechano-biology has truly arrived. High-resolution imaging systems will allow tissue structures to be determined from the highest hierarchy of the organ to the lowest of the genome. These digital images are ideally suited for analysing physical forces and linking continuum level tissue stresses to deformation-induced gene activation in the DNA molecule. Advances in dynamic systems theory and applied mathematics will play a critical role in explaining the behaviour of otherwise intractable models.

As the complete genomes of organisms become mapped, functional genomics will combine with biomechanics to answer questions such as: What is the regulatory role of mechanics in skeletal gene expression? How would organisms grow in the microgravity environment of space? Can we define the mechanical forces needed to culture complete skeletal organs in the laboratory? Are there genes that code for 'bone strength'? Orthopaedics and reconstructive surgery will be completely revolutionized.

The rapid growth of the field has produced an interdisciplinary community of engineers, biologists, mathematicians and physicians with visions of answering scientific questions of the highest import. These questions will bridge the boundary between

physics and biology, between forces and cells, to understand how organic forms are shaped by the mechanical world and how living systems actually 'extract order from their environment', first posed by Erwin Schrödinger (1945) in his famous lectures *What is life?*

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References

Baron, R. E. 1996 Anatomy and ultrastructure of bone. In *Primer on the metabolic bone diseases and disorders of mineral metabolism*, 3rd edn. (ed. M. J Favus), pp. 3–10. New York: Lippincott-Raven.

Boyde, A., Wolfe, L., Maly, M. & Jones, S. 1995 Vital confocal microscopy in bone. *Scanning* **17**, 72–85.

Caplan, A. I. 1994 The mesengenic process. *Clin. Plast. Surg.* **21**, 429–435.

Carter, D. R. & Hayes, W. C. 1977 Bone as a two phase porous structure. *J. Bone Joint Surg.* A **59**, 954–962.

Carter, D. R., Fyhrie, D. P. & Whalen, R. T. 1987 Trabecular bone density and loading history: regulation of connective tissue biology by mechanical energy. *J. Biomech.* **20**, 785–794.

Carter, D. R., Orr, T. E. & Fyhrie, D. P. 1989 Relationships between loading history and femoral cancellous bone architecture. *J. Biomech.* **22**, 231–244.

Carter, D. R., Beaupré, G. S., Giori, N. J. & Helms, J. A. 1998 Mechanobiology of skeletal regeneration. *Clin. Orthop.* **355**, S41–S55.

Cowin, S. C. & Hegedus, D. H. 1976 Bone remodeling. I. Theory of adaptive elasticity. *J. Elasticity* **6**, 313–325.

Currey, J. D. 1984 *Mechanical adaptations of bones*. Princeton University Press.

Darwin, C. 1859 *On the origin of species by means of natural selection*. London: John Murray.

Fazzalari, N. L. 1993 Trabecular microfracture. *Calcif. Tissue Int.* **53**, S143–S146.

Frost, H. M. 1973 The origin and nature of transients in human bone remodeling dynamics. In *Clinical aspects of metabolic bone disease* (ed. B. Frame, A. M. Parfitt & H. Duncan), pp. 124–137. Amsterdam: Excepta Medica.

Galilei, G. 1638 *Discorsi e dimostrazioni mathematiche intorno à due nuove scienze*. Lieda: Elsevier. (Translated by H. Crew & A. de Salivio (1939) as *Dialogue concerning two new sciences*. Northwestern University Press.)

Gibson, L. J. 1985 The mechanical behavior of cancellous bone. *J. Biomech.* **18**, 317–328.

Guilak, F., Ratcliffe, A. & Mow, V. C. 1995 Chondrocyte deformation and local tissue strain in articular cartilage: a confocal microscopy study. *J. Orthop. Res.* **13**, 410–421.

Hart, R. T., Davy, D. T. & Heiple, K. G. 1984 A computational method for stress analysis of adaptive elastic materials with a view towards applications in strain induced bone remodelling. *J. Biomech. Engng* **106**, 342–350.

Hert, J., Lisková, M. & Landa, J. 1971 Reaction of bone to mechanical stimuli. Part 1. Continuous and intermittent loading of tibia in rabbit. *Folia Morph., Prag.* **19**, 290–300.

Huiskes, R., Weinans, H., Grootenboer, H. J., Dalstra, M., Fudala, B. & Slooff, T. J. 1987 Adaptive bone remodelling theory applied to prosthetic design analysis. *J. Biomech.* **20**, 1135–1150.

Jacobs, C. R., Levenston, M. E., Beaupré, G. S., Simo, J. C. & Carter, D. R. 1995 Numerical instabilities in bone remodeling simulations. The advantages of a node-based finite element approach. *J. Biomech.* **28**, 449–459.

Martin, R. B. & Burr, D. B. 1989 *Structure, function and adaptation of compact bone*. New York: Raven Press.

Mullender, M. G. & Huiskes, R. 1995 A proposal for the regulatory mechanism of Wolff's law. *J. Orthop. Res.* **13**, 503–512.

Müller, R. & Rüegsegger, P. 1995 Three dimensional finite element modelling of non-invasively assessed trabecular bone structures. *Med. Engng Phys.* **17**, 126–133.

Pauwels, F. 1941 Grundrieß einer Biomechanik der Fracturheiling. In *34e Kongress der Deutschen Orthopädischen Gesellschaft*, pp. 464–508. Stuttgart: Ferdinand Engke. (Translated by P. Maquet & R. Furlong (1986) as *Biomechanics of fracture healing*, in *Biomechanics of the locomotor apparatus*, pp. 106–137. Berlin: Springer.)

Perren, S. M. 1979 Physical and biological aspects of fracture healing with special reference to internal fixation. *Clin. Orthop.* **138**, 175–196.

Prendergast, P. J. & Taylor, D. 1994 Prediction of bone adaptation using damage accumulation. *J. Biomech.* **27**, 1067–1076.

Reilly, D. T. & Burstein, A. H. 1975 The elastic and ultimate properties of compact bone tissue. *J. Biomech.* **8**, 393–405.

Roux, W. 1895 *Gesammelte Abhandlungen der Entwicklungsmechanic der Organismen*. Berlin: Wilhelm Englemann.

Rubin, C. T. & Lanyon, L. E. 1984 Dynamic strain similarity in vertebrates: an alternative to allometric limb bone scaling. *J. Theor. Biol.* **107**, 321–327.

Schrödinger, E. 1945 *What is life? The physical aspect of the living cell* (Lectures delivered in Trinity College Dublin in 1943). Cambridge University Press.

Thompson, D'A. W. 1917 *On growth and form*. Cambridge University Press.

Torrance, A. G., Mosley, J. R., Suswillo, R. F. & Lanyon, L. E. 1994 Noninvasive loading of the rat ulna *in vivo* induces a strain-related modeling response uncomplicated by trauma or periosteal pressure. *Calcif. Tissue Int.* **54**, 241–247.

Turner, C. H., Akhter, M. P., Raab, D. M., Kimmel, D. B. & Recker, R. R. 1991 A noninvasive, *in vivo* model for studying strain adaptive bone modeling. *Bone* **12**, 73–79.

van der Meulen, M. C. H., Beaupré, G. S. & Carter, D. R. 1993 Mechanobiologic influences in long bone cross-sectional growth. *Bone* **14**, 635–642.

van der Meulen, M. C. H., Morey-Holton, E. R. & Carter, D. R. 1995 Hindlimb suspension results in diminished femoral growth in the rat. *J. Orthop. Res.* **13**, 700–707.

van Rietbergen, B., Huiskes, R., Weinans, H., Sumner, D. R., Turner, T. M. & Galante, J. O. 1993 The mechanism of remodelling and resorption around press-fitted THA stems. *J. Biomech.* **26**, 369–382.

Vortkamp, A., Lee, K., Lanske, B., Segre, G. V., Kronenberg, H. M. & Tabin, C. J. 1996 Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. *Science* **273**, 613–622.

Weinans, H. & Prendergast, P. J. 1996 Tissue adaptation as a dynamical process far from equilibrium. *Bone* **19**, 143–150.

Weinans, H., Huiskes, R. & Grootenboer, H. J. 1992 The behaviour of adaptive bone remodelling simulation models. *J. Biomech.* **25**, 1425–1441.

Wolff, J. 1892 *Das Gesetz der Transformation der Knochen*. Berlin: Hirschwald. (Translated by P. Maquet & R. Furlong (1986) as *The law of bone remodeling*. Berlin: Springer.)

Wong, M., Germiller, J., Bonadio, J. & Goldstein, S. A. 1993 Neuromuscular atrophy alters collagen gene expression, pattern formation, and mechanical integrity of the chick embryo long bone. *Prog. Clin. Bio. Res.* B **383**, 587–597.

Zioupos, P., Currey, J. D. & Sedman, A. J. 1994 An examination of the micromechanics of failure of bone and antler by acoustic emission tests and laser scanning confocal microscopy. *Med. Engng Phys.* **16**, 203–212.

AUTHOR PROFILES

P. J. Prendergast

Born in Enniscorthy, Ireland, in 1966, Patrick Prendergast studied at Trinity College Dublin (TCD), where he graduated with first class honours in engineering science in 1987, and obtained his PhD in 1991. He was a Council-of-Europe Scholar at the University of Bologna and a Marie Curie Fellow at the University of Nijmegen before being appointed to a Lectureship in TCD in 1995 and elected to Fellowship in 1998. He won the European Society of Biomechanics Research Award in 1996. He is on the editorial board of *Journal of Biomechanics and Clinical Biomechanics*. Scientific interests include computational modelling of tissue adaptation and design of medical devices. Recreation involves occasional games of squash, reading some poetry, and entertaining his daughter, Eimear Wytsche Prendergast (aged 14 months).

M. C. H. van der Meulen

Born in 1965 in Utrecht, The Netherlands, Marjolein van der Meulen received her Bachelors in mechanical engineering from the Massachusetts Institute of Technology in 1987. Thereafter, she received her MS (1989) and PhD (1993) from Stanford University. She spent three years as a Biomedical Engineer at the Rehabilitation R & D Center of the Department of Veterans Affairs in Palo Alto, CA. She received a FIRST Award from the National Institutes of Health in 1995. In 1996, Marjolein joined the faculty of Cornell University as an Assistant Professor in the Sibley School of Mechanical and Aerospace Engineering. She is also an Assistant Scientist at the Hospital for Special Surgery, New York. Scientific interests include bone structural behaviour and skeletal mechano-biology. Recreations include volleyball and travelling.